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SUMMURY

SEASONS OF SURVIVORSHIP

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Cancer changes people's lives, starting with diagnosis and continuing through and beyond treatment. The expression 'cancer survivor' was coined in 1985 by physician and cancer patient Dr. Fitzhugh Mullan to describe the multiple medical and psychosocial needs and concerns, as well as the shifts in interpersonal roles and dynamics that accompany cancer patients and their loved ones for the rest of their lives. (1,2) Mullan's definition was adopted by the National Coalition for Cancer Survivors in 1986 and later extended to 'everyone who has been touched by cancer. (3) Subsequently endorsed by all major cancer organizations in the United States, including the American Society of Clinical Oncology (ASCO), this definition is widely appreciated and shared in the United States where the term 'survivor' carries a positive connotation related to resilience. In other countries and cultures, however, 'survivor' is rather perceived as an unwelcome label equating a person's identity with her illness. (4,5) Furthermore, even within Anglo-American countries, patients and professionals do not fully embrace the original definition of 'cancer survivor' for multiple reasons, including its 'murkiness', or failure to capture or reflect the individual experiences of cancer survivors, some who have been disease-free for many years and wish to put their past history of cancer behind, and others whose life keeps fluctuating between phases of remission and relapse requiring constant or repeat treatments. (6-9)

Long-term cancer survivors reflect on how cancer has effected or changed them in relation to their age, diagnosis, treatment, personal history and priorities, attitudes and beliefs.

The existential issues for cancer survivors may be quite profound during any of the seasons of survivorship. Fear, uncertainty, and loss caused by cancer may inspire a search for deeper meaning and a fresh perspective on old problems. As a result, many survivors report that

their life after diagnosis is characterized by new emotional depth that was previously lacking, and is richer because of the experience of cancer (10).

For the purpose of developing optimal survivorship care models and guidelines, while continuing to embrace the NCCS definition of 'survivor', in 2013 ASCO adopted a 'functional definition' of long-term survivorship as 'individuals who have successfully completed curative treatment or . . . transitioned to maintenance or prophylactic therapy. . .' (11) A similar definition was applied by ASCO to 'long-term survivors' in need for more research on the 64% of current survivors, 67% of whom received a diagnosis as adults and 80% of whom received a diagnosis as children, who survive ≥ 5 years after diagnosis. (12) The need to use a stricter 'functional' definition, while considering as survivor any person touched by cancer from the time of diagnosis to end of life, arises from the recognition that not all survivors are alike for the purpose of communication, clinical management or modalities of survivorship care delivery.

Original definition of 'cancer survivor' and of 'seasons of survivorship'

In 1985, Dr. Fitzhugh Mullan, young physician who had become a cancer patient, published an often cited article, "Seasons of Survival: Reflections of a Physician with Cancer" in the *New England Journal of Medicine*. (1) Dr. Mullan, after complaining of a relentless cough, referred himself for a chest x-ray. He "recoiled" when he looked at his own x-ray and recognized a huge mediastinal mass, then diagnosed as extragonadal seminoma. (1,2) After the diagnosis, he wrote, "I was, in fact, surviving, struggling physically and mentally with the cancer, the therapy, and the large-scale disruption of my life. Survival, however, was not one condition but many. It was desperate days of nausea and depression. It was the elation at the birth of a daughter in the midst of treatment. It was the anxiety of my monthly chest x-rays." … "It was survival, an absolutely predictable but ill-defined condition that all cancer patients pass through as they struggle with their illness".

Dr. Mullan defined three seasons of survival, a medical continuum in the new path of life of people who had received a diagnosis of cancer stage starting at cancer diagnosis. The first was 'Acute Survival', a medical stage including the time of diagnosis and initial, often acute, therapy. The second was 'Extended Survival', a time of watchful waiting with celebration,

uncertainty, and transition. Finally, the third was 'Permanent Survival', a time when a gradual sense of confidence develops as the risk of recurrence decreases, and the chance of long-term survival is medically high. (1)

Seasons of survival: evolution and new meaning.

Though the notion of different seasons of survival defined by Dr. Fitzhugh Mullan has not changed and carries a profound truth, those seasons have changed, according to the improved survival and quality of life (QoL) of many cancer patients, especially in western countries. Specifically, there is a larger group of cancer survivors who are living with advanced cancer for long periods of time, or who are in a remission that is dependent on the use of new targeted therapies. Furthermore, permanent survival defines a large and heterogeneous group of survivors, some who have moved beyond cancer and are healthy; some who are living with the "fall-out" of the cancer experience, including psycho-social consequences involving their health, sexuality, career, and insurability; and some who re-enter the system year later with a second cancer that is related to or unrelated to their previous cancer and its treatment.

Accordingly, some Authors have analyzed a new conception of the "Seasons of Survivorship" that includes 'Transition Survival' when the cancer is not cured but will continue to be a significant problem. This period of transition leads to physical, psychological, social, and financial readjustment for the survivor in the context of their family, social environment, job, and community. Finally, some patients in 'Extended Survival' receiving ongoing therapy may experience few, moderate, or more significant side effects. Overall, they must balance the everyday challenges of "regular life" and the "ups and downs" of living with cancer and its treatment. Their family and caregivers are living in this same way with what one survivor describes as a "sense of fear and impermanence mixed with healthy denial, a focus on the present and even confidence." (13)

Those survivors who are 'cancer-free and free of cancer' include a large group who may have had early stage cancers that were surgically cured, did not require any postoperative therapy, and required little or no monitoring, as well as survivors with advanced cancer that responded complete to aggressive multimodality therapy and who then lead their life without significant physical or emotional "fall-out." Some of these survivors have the "that's life" approach where cancer becomes part of their past medical history. (13)

How categorization of cancer survivorship can improve our care and survivors' QoL.

The original definition of cancer survivor by Dr. Mullan and the NCCS captures a deep truth about all persons who have been diagnosed with cancer, no matter how small or with positive expected outcomes: despite the progresses of medical, radiological and surgical oncology and the constant development of new immunotherapies and targeted drugs, caner still carries a metaphorical meaning and it changes the life of both patients and their family and loved ones. It therefore remains most valuable for taking into account the changes that occur in the lives of 'all people touched by cancer' and it helps viewing cancer as a whole disease process that deserves a continuum of care, research and funding from diagnosis through its varied outcomes.

Yet during the last decade, the study and practice of survivorship care has also evolved and it is now possible to better distinguish among highly heterogeneous forms of cancer and their clinical courses (14) This would lead to categorization of cancer survivorship, through the proper categorization of persons now broadly defined as 'cancer survivors', not to deny the deep of their own experience of cancer, which can be very traumatic or considered as a life occasion to re-evaluate one's own priorities in life, but rather to improve survivorship care through risk-based assessment based on evolving new methodologies, new clinical and organizational approaches, improved follow-up and surveillance recommendation and guidelines.

Under the broad definition of 'survivors' there are patients who live with chronic disease characterized by alternating remission and relapse; whose cancer progresses slowly, often accompanied by acceptable quality of life as in other chronic illnesses such as some cardiovascular diseases; who after years of being disease-free can be declared 'cured' when their life expectancy equals that of gender- and age-matched members of the general population, such as many patients with early stage thyroid, cervix, testicular or colon cancer (16) and those who are in clinical remission for long periods of time or for their entire life, usually referred to as 'long term survivors.' (4,11) Long-term survivors most often resume their usual life and jobs, yet remain at risk for oncologic, medical, rehabilitation and psychosocial needs and issues. (11,16)

As cancer is characterized by a fluid rather than flat chronic course, it may also involve the possibility of 'cure' as we described in a recent paper on the why is categorization of cancer survivors useful and needed. (17-20)

The current lack of distinction among survivors, in fact, might negatively affects communication with our patients and families, patients' adherence to clinical recommendations, and effectiveness of survivorship care in different delivery contexts. By contrast, the study and clinical application of categories of survivorship might help us avoid inflicting on some of our patients the psychological burdens of over-medicalization and potential social stigmatization, while fostering adequate follow-up, surveillance and global care for others. (17)

Conclusion: is a cancer survivor ever 'cured'?

Many long-term cancer survivors would like to think of themselves as cured from the initial cancer, and would like to be declared 'cured' by their oncologists. The debate over the possible use of the term 'cured' is expanding among patients and oncologists through social media and medical blogs in the United States and other countries. (18-20) Attitudes toward this issue vary with individual and cultural beliefs and preferences, of both patients and professionals involved in survivorship care. Still most oncologists prefer to use "long-term survivor" instead of "cured," even when patients prefer go be declared "cured" because of the uncertainty that exists in oncology, as in life itself, and not to risk to reassure their former patients in such way that they would no longer continue their follow-up over time, or properly care for their general health.

Several Authors, including our group in Siracusa, Italy, have analyzed the meaning of 'cure' in oncology and the possibility to apply it in the clinic and say the word 'cured' to a few selected group of cancer survivors. (21, 22) In cancer patients, the risk for death from a specific neoplasm is highest in the initial years after diagnosis; it decreases progressively thereafter, until a time at which the risk becomes negligible, and surviving patients reach a life expectancy that matches that of a sex- and age-matched general population. (22) Conditional relative survival—the probability of a patient surviving an additional 5 or 10 years after already surviving a given number of years—is a clinically relevant measure of long-term excess mortality in a cohort of cancer patients. (22-24) As a result, there is agreement on: 1) the statistical definition of 'cured' refers to a population of long-term cancer survivors whose risk of mortality is no greater than that of the general age- and gender-matched population; 2) 'cured' patients are exposed to the risk of other cancers as are members of the general population, and should therefore undergo routine surveillance. For example,

thyroid cancer and germinal testicular cancer have a cure rate, according to the prior definition, higher then 90%. Colo-rectal, gastric, cervical cancer and Hodgkin disease reach a conditional relative survival (CRS) >95% of 5 to 10 years in less than 10 years. In patients with Hodgkin's disease, recurrences tend to occur in the first two years, treatment-related second cancers can occur twenty years later, and their oncologic follow-up should therefore continue even if the patient can be considered 'cured' from the initial disease. (17)

In conclusion, the actual number of cancer survivors that may appropriately be defined 'cured' is limited. Yet we could now confidently apply this category to specific clinical cases, as well as in organizational settings and policy-making, with potential positive reverberations in the social and relational dimensions of the lives of 'cured' survivors.

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WHAT IS ON THE RESEARCH AGENDA?

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When we look at the research agenda for oncology much effort is used to develop new drugs, new understanding of mechanisms causing cancer, mechanisms making metastasis possible and personalizing treatment to the highest degree possible. All this is admirable and valued by all levels in society from the politicians, hospital administrators, health professionals and citizens. We cannot accept that cancer is a disease for which we do not have a cure in all cases but have to provide treatment, that we know do not cure but probably prolong length of life. The incidence of cancer world-wide is still rising but on the other hand, one of the measurable successes is the increasing number of cancer survivors in all industrialized parts of the world. Millions of our fellow citizens have been treated for cancer, at least one time in their life and we now have cancer survivors among us, who have lived more than 60 years following a cancer treatment (Hovaldt et al., 2015).

However, the positive aspects of the combined efforts across the entire specter of cancer treatment also have some untold or rather not acknowledged problems. When we highlight the increasing number of survivors, the improved survival curves, we tend to forget, that across all cancer sites, survival is becoming better among the well educate, those who have a job, the affluent – we are simply missing the fact that our success has not reached out to those most in need for improvements in survival (Dalton et al., 2008).

Even in the Scandinavian societies (Denmark, Finland, Iceland Norway and Sweden) having some 22 million citizens and characterized by a public, tax-paid health sector, having free access to cancer treatment at all levels and no limitations in medical or radio-therapeutic interventions as

no insurance company can add more benefits to one citizen compared to another with regard to the cancer treatment provided – we observe social differences in survival, no matter how we measure the social component. It can be school education, education as such, income, fortune, square meters in your dwelling, owing or renting the place where you live, or family structure (married, having children), early retirement or early pensioning – it all ends up in one conclusion: The social factor chosen plays a significant role for both 1-year and 5-year survival (Dalton et al., 2008). And do not forget that this overall observation seems to be the case for all cancers. Of course, the gap between high and low varies but in principle the same pattern is observed.

A short summary of a large nationwide and population based study, which we carried out in 2007 illustrates this point. From the paper I quote the following: The purpose of this register-based study was to describe variations in cancer incidence and survival by social position Denmark, on the basis of a range of socioeconomic, demographic and health-related indicators. Our study population comprised all 3.22 million Danish residents born in 1925-1973 and aged >or=30 years, who were followed up for cancer incidence in 1994-2003 and for survival in 1994-2006, yielding 147,973 cancers. The incidence increased with lower education and income, especially for tobacco- and other lifestyle-related cancers, although for cancers of the breast and prostate and malignant melanoma the association was inverse. Conversely there was a general increase in incidence among early retirement pensioners, persons living in rented housing and those living in the smallest dwellings. Also incidence rates were generally higher in persons living alone compared to those living with a partner and in the capital area compared to the rural areas. Social inequality in the prognosis of most cancers was observed, despite the equal access to health care in Denmark, with poorer relative survival related to fewer advantages, regardless of how they were measured, often most pronounced in the first year after diagnosis. Also living alone and having somatic or psychiatric comorbidity negatively impacted the relative survival after most cancers. Our study shows that inequalities in cancer incidence and survival must be addressed in all aspects of public health, with interventions both to reduce incidence and to prolong survival (Dalton et al., 2008).

In my view you cannot have more strong data supporting the notion, that

the primary focus on our agenda for research is to investigate how we can support these fellow citizens in our population in order to achieve a low incidence of cancer and also the same survival probability as more affluent citizens. This is, almost never mentioned from the podium of large international cancer congresses, this is not a part of the vocabulary in the cancer world and does not play a part, a role in the decisions taken about organization of care for cancer patients at all levels in the system having responsibility for cancer care (diagnostics, treatment, rehabilitation, follow-up, psychosocial care, late effect prevention, detection and treatment, palliation and so on). We are simply observing a huge difference in both incidences for some cancers and a difference in survival for all cancers. We are not acting.

If we then move to the aftermath of cancer and not only focus on survival but investigate some serious aspects or consequences of being diagnosed and treated for this devastating disease, we observe that social factors also seem to play a role in the incidence of these later effects of a cancer disease. Just as an example we investigated the risk for use of antidepressant medications by linking various registries that are accessible in Scandinavia, especially so in Denmark (population 5.6 million people), e.g., the Danish national registries were used to identify 1,997,669 women with no diagnosis of cancer or a major psychiatric disorder. This cohort was followed from 1998 to 2011 for a diagnosis of breast cancer and for the two outcomes, hospital contact for depression and redeemed prescriptions for antidepressants. Rate ratios for incident hospital contacts for depression and incident use of antidepressants were estimated with Poisson regression models. Multivariable Cox regression was used to evaluate factors associated with the two outcomes among patients with breast cancer. In this study we identified 44,494 women with breast cancer. In the first year after diagnosis, the rate ratio for a hospital contact for depression was 1.70 (95% CI 1.41 to 2.05) and that for use of antidepressants was 3.09 (95% CI 2.95 to 3.22); these rate ratios were significantly increased after 3 and 8 years, respectively. Comorbidity, node-positive disease, older age, basic and vocational educational levels, and living alone were associated with use of antidepressants. We concluded that women with breast cancer are at long-term increased risk for first depression, including both severe episodes leading to hospital contact and use of antidepressants. Clinicians should be aware that the risk is highest in women with comorbid conditions, node-positive disease, and age of 70 years or more. We found no

clear association between type of surgery or adjuvant treatment and risk for depression (Suppli et al., 2014)

This risk for depression and subsequent also a worse outcome, as indicated by data we have under review based on the same data set, illustrate how important the psychological effects are when diagnosed and undergoing treatment for a cancer disease. But not only social and psychological factors are of importance, there is also a need to change the paradigm of cancer treatment with regard to the existence of other major diseases at time of diagnosis. Today each disease is, in principle, treated by a specialist. The consequence for the citizen is that having three diseases at hand, i.e., diabetes, hypertension and prostate cancer requires three different schedules, follow-up programs, appointments and health professionals. Polypharmacy and multi-morbidity is a new player in the overall picture of what a cancer patient is, as the generations of cancer survivors to come will change disease phenotype - in a metaphoric way.

Cancer treatment not only influence the organ or tissue area hosting the tumor, it affects nearby organs and areas and the entire body. In many European countries, the US and Australia cardiovascular diseases, diabetes and lung diseases are the three most prevalent diseases in the populations diagnosed with cancer. The pharmaceuticals prescribed for the treatment of these diseases as well as the physiological function of these organs may highly impact the probability that a newly diagnosed cancer patient may receive the optimal treatment for the cancer in terms of radiation dose and volume as well as chemotherapy dose and intervals. To disentangle this problem two alleys of research has been conducted. One direction has shown that comorbidity severely influence survival in cancer patients (Ref), while another tradition has shown how polypharmacy, besides the drugs used for treatment of cancer, influences prognosis negatively. This effect is ascribed both to the changed or even reduced function of the organs that 'host' the comorbidity, e.g., heart, lung or thyroid gland and the medications used for treatment of the diseases. Several studies have shown how more than one disease significantly reduce survival, increase the use of health services and reduce the quality of life. Some studies have estimated the prevalence of comorbidity in prostate or breast cancer patients to be 30 % when aged 65 or more. With regard to colorectal cancer this is 44 % and for lung cancer patients 53 %. Further this burden of comorbidity has a social bias and is more prevalent among socially disadvantaged cancer patients.

Polypharmacy, which is defined as daily use of five or more drugs for the treatment of chronic conditions, may not always present a problem for cancer patients. This will depend on the exact drug and drug combination as well as drug-drug interaction. This equation include the treatment suggested to be part of the cancer treatment and the medications used for treatment of the comorbid conditions. No matter how the relationship is, then this problem of potential interaction between treatments prescribed for several chronic diseases including cancer present an increasing dilemma for oncologists, when deciding on the treatment plan for patients exhibiting comorbidity. It has been shown how the benefit/risk ratio is reduced when patients, across diagnoses, in treatment are older, have a high number of comorbidities, evaluated as frail and have a limited prognosis. This is also true for cancer patients, as illustrated by a medium sized study of 248 elderly cancer patients (mean 80 years of age), who on average used nine different drugs and of these 40 % was evaluated as unnecessary (Nightingale et al., JCO 2015).

Besides the entire change in the disease universe of cancer patients arise the risk for other late effects than depression. For many cancers we have established knowledge about the risk for late effects but for others it is now the time to conduct research in order to specify and define which conditions patients may be at risk for in the aftermath of cancer. With regard to lymphoma, a cancer that only accounts for a small part of all cancers there are now options to get a clearer picture of what patients may be prepared to when treatments are over. The annual incidence of lymphoma is approximately 1150 new case diagnosed in Denmark, and between 130-150 of these patients are in the Hodgkin Lymphoma (HL) group having the best five-year survival rate of 85 % when comparing various types of lymphomas.
Across all types of this cancer, the survival rate is 60 %. The treatment protocols for different histology's varies but mostly consist of a combination of radiation and chemotherapy. For some patient's immune therapy is part of the standard treatment procedures provided as well. Today approximately 16,000 Danes are lymphoma survivors equivalent to 7 % of the total cancer survivor population (Hovaldt et al, 2015).
A considerable proportion of these survivor's experience late morbidities. The heart is one of the organs most often affected and several cohort studies across the industrialized world has shown an excess mortality and morbidity from heart diseases, especially in HL (Maraldo et al. 2015; Nim-

wegen et al., 2015, 2016). In a meta-analysis of 21 studies the relative risk (RR) of second lung cancer in HL patients was 4.6 (95 % CI, 3.2-6.7) with the highest risk in patients below the age of 24, in the time span of 10 to 14 years after the diagnosis and with the highest risk estimate among patients in chemotherapy (RR, 5.2; 95 % CI, 4.1-6.5; Ibrahim et al., 2013). These findings were confirmed in a large Dutch study showing a standardized incidence ratio of 4.6 (95 % CI, 4.3-4.9) for second cancers in five-year survivors of HL (Schaapveld et al, 2015). Early studies investigating quality of life utilized data based on drug testing randomized trials, showing impaired quality of life and an increase in fatigue after years of follow-up (Ganz et al, 2003). More recent quality of life studies using the same approach and having 10-years of follow-up show that HL patients experience strain and limitations in all domains of the quality of life and that fatigue at the end of treatment predict this outcome even at 10-years follow-up (Heutte et al, 2009). In a systematic review of the impact of treatment, socio-demographic and clinical characteristics on quality of life among both HL and non-HL lymphoma survivors HL survivors showed the most problems, while non-HL survivors showed most problems in physical functioning, loss of appetite, vitality and financial problems (Oerlemans et al, 2011). But also endocrine, pulmonary diseases and nonfatal second malignancies are often reported in lymphoma survivors (Gebauer et al., 2015; Mols et al., 2013) In addition anxiety and depression present a large clinical problem in lymphoma survivors (Oeerlemans et al., 2014; Mols et 8 of 33).

There is a need for studies that investigate the etiology and course of physical, psychological and social late effects following treatment of lymphoma. Well-designed studies in the area are sparse, and the science conducted so far is characterized by cross-sectional design, small sample sizes, loss to and short follow-up time. Besides these methodological shortcomings no studies, to the best of my knowledge, has integrated the rich population based and non-biased data sources applied in a dynamic time depending and analytic approach.

These considerations about lymphoma patients may also be true for other cancers and much knowledge is already established within different cancers. On the research agenda of today is more detailed research diving into the possible mechanisms explaining the observations of a higher risk for certain conditions in cancer patients.

The research agenda is full of themes and several issues are open for further investigation, especially in the light of the growing number of cancer survivors. There is a need for more cross-disciplinary research within the clinical, social and psychological problems that cancer survivors face and we both have an obligation to carry out observational studies of the epidemiology of late effects in terms of the occurrence, severity and probabilities of prevention by identifying patient groups at the highest risk. Much can be done by register based research in countries that have access to such data sources. However, there is also a great need for well conducted clinical studies linking the treatment data with outcomes of interest. In this context patient reported outcomes (PRO) is gradually becoming standard of the daily clinical work and these data seem to have great impact on the overall picture of what cancer patients experience when undergoing treatment of their disease.

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MODELS OF SURVIVORSHIP CARE: OPPORTUNITIES AND CHALLENGES

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The number of individuals living after a diagnosis of cancer is increasing rapidly due to advances in early detection, treatment and supportive care. In the United States (US) and many European countries, the 5-year survival rates have increased to 50% or more for individuals diagnosed with adult-onset cancers and 83% for childhood cancers. There are currently 17.5 million cancer survivors in Europe (diagnosed within 10 years), 15.5 million cancer survivors in the US and 32.6 million people living with a diagnosis of cancer as of 2012 worldwide. Since Fitzhugh Mullan published his seminal 1985 article in the New England Journal of Medicine about the Seasons of Survival, incredible progress has been made in assuring that individuals who have been diagnosed and treated for cancer will have both Extended Survival and Permanent Survival. Scientific advancements have resulted in better treatments and improved diagnostic tools at the same time oncology research has broadened to focus on the patient as a whole person with an emphasis on psychosocial, as well as medical needs. However, along with these successes come substantial risks for morbidity, reduced quality of life and premature mortality. It is an important time to ask the questions: How can long-term and late effects be identified early? How can they, once identified, be efficiently and effectively managed and by whom? What can be done to preserve health? Adding specificity to the identified needs of this growing community of survivors also highlights the importance of the development and evaluation of survivorship care delivery models that allow us to "maximize the cure, minimize the cost." Because of the heterogeneity of cancer and the growing number of interventions to treat these diseases, the sequelae of cancer treatments are quite variable requiring an approach to follow-up care that is, by necessity, risk-based as proposed by the 2005 Institute of Medicine report, "From Cancer Patient to Cancer Survivor." Follow-up care is important, but not

as a set of generic services that are offered to all survivors without regard to the survivor's unique health risks predisposed by the cancer treatment, genetic and familial factors, comorbid health conditions and lifestyle behaviors. Rather, a risk-based approach is needed with a focus on the treatments received, the anticipated future health problems and interventions to maximize health and well being. According to Oeffinger, the key components of optimum risk-based survivorship care include the provision of care that integrates the cancer and survivorship experience into the overall health needs of the individual. Such an approach is ideal and is dependent not only on knowledge about survivor risks, but also is dependent on the communication of these risks among the health care providers, in particular between the oncologist and the primary care physician (PCP). To date, knowledge transfer and communication between and among providers can be difficult and here lies the challenge in assuring quality care for long term survivors. Clearly, a risk-based approach to care is needed.

As part of the equation of applying a risk-based approach to the set of services needed by cancer survivors, a variety of care models have been developed internationally that are based on the type of care provider, the survivor population, site of care and the capacity to deliver the desired services. In addition, the design of the health care system and payment mechanism for services also greatly influence the type of survivorship care model(s) within a country. This paper will briefly highlight four types of models being used internationally. First, one of the most widely promoted models of care includes a focus on the PCP as having an active role in the follow-up care of the cancer survivor. Although surveys conducted in the US describe skepticism that the PCP is prepared to take on this role, the PCPs identify that lack of communication by the oncologist is the major barrier to their assuming survivorship care responsibilities. In contrast, countries with a strong PCP community utilize the PCP as central to the provision of post-treatment care. For example, in Canada the pan-Canadian Guideline for Survivorship Services recommends that the PCP be integrated early into survivorship services. To date, studies demonstrate the ability of the PCP to provide care equivalent to that provided by the oncologist, using metrics such as evaluation for cancer recurrence and management of late effects. Although the number of these studies is limited and often have small sample sizes, larger randomized studies comparing PCP and oncologist care are ongoing.

Second, as groups begin to evaluate the types of providers capable of providing survivorship care, there is focus on the role of the nurse, especially the nurse practitioner (NP) as a health care professional who can assume care during the post-treatment period. Studies to date demonstrate equivalence with services provided by the oncologist. How this NP role is actualized can be done is a variety of ways. For example, Watts and colleagues published a paper highlighting how Wagner's chronic care model can be implemented by nurses either through shared visits (both the specialist and generalist are involved in care) or in group visits. This model is very applicable to oncology after care, especially as we have a larger population of elderly cancer survivors internationally. In Australia as well as in the US, nurse-led survivorship care is being provided, and to a limited extent, evaluated. Researchers at the Peter MacCallum Cancer Centre in Australia have evaluated a nurse-led consultation model that includes a tailored education package, a psychosocial assessment and the provision of a tailored survivorship care plan for long-term survivor of Hodgkin lymphoma. In the United Kingdom, a nurse-led service model has been successfully implemented for men who have been treated for prostate cancer with 90% of the men using the recommended services.

A third type of follow-up care is one focused on a rehabilitation model. In Europe, rehabilitation is well established and survivorship programs may be imbedded within a rehabilitation program providing services, such as psychological care and exercise. In Germany, rehabilitation after illness has long been established within the health care system and the intention is to enhance recovery after an acute illness through vocational rehabilitation to promote a return to employment. In Italy, rehabilitation centers focus on diagnostic groups other than cancer, as do many other countries, but there are now efforts for wider use within cancer services, especially after surgery. In contrast, similar models are not well developed in the US, in part because rehabilitation is often quite separate from survivorship, although this is changing as the concept of "prehabilition" is growing. The philosophy of this approach is that rehabilitation is a service to be offered at diagnosis with the goal of preventing problems before they occur. Although rehabilitation isn't a new recommendation for some groups of patients, such as women with breast cancer who have been treated with surgery and the head and neck cancer patient who has had an extensive neck dissection, it is novel to consider rehabilitation more generally in terms of overall recovery for the cancer survivor. Broadening the applica-

tion of rehabilitation and evaluation of its effectiveness remain one of the important challenges for survivorship programs going forward.

A fourth model of care is self management which has been shown to improve health in chronic diseases such as arthritis, diabetes, heart disease and lung disease. In cancer patients, this interactive process promotes skills to manage the physical and psychosocial consequences of treatment through problem solving, decision-making, timely communication with health professionals and taking action when needed. In the US, the model has been used successfully to promote lifestyle change and psychosocial health. Self management has been promoted in the UK Department of Health through their Expert Patient Programmes for patients with long term health problems and there is an interest in applying the same principles to the cancer survivor.

Universal health care, which exists in most European countries, is one of the most important facilitators of survivorship care since it provides services free of charge thus making the services available to all citizens. This is in contrast to the US where health care coverage, although greatly expanded under the Affordable Care Act, is still not available to all individuals. Although the financial support of the health care system is a basic facilitator of survivorship care, there is the additional requirement for a commitment to the provision of services during the post-treatment period. Such formal commitments are most often reflected within the national health care plans of the nation. One important effort is the EU Joint Action in Comprehensive Cancer Control under the auspices of the Association of European Cancer Leagues. Although not focused on Survivorship, the Cancer Control Joint Action (CanCon) includes survivorship and rehabilitation as one of the core work packages. Even greater national facilitators are the health plans where the presentation of survivorship is central to the policy document. One such example stands out - the UK National Cancer Survivorship Initiative launched in 2008. This landmark report not only called for the transformation of medical care for survivors, but also outlined the need to develop and test models for efficient and cost-effective models of survivorship care. This is an exemplar of a strong collaboration between the Department of Health and a major UK charity, Macmillan Cancer Support. In addition, the Health Council in the Netherlands has also promoted a national approach for survivorship specific services: the development and use of Survivorship Care Plans along with cancer rehabilitation services. Professional societies can also

be strong facilitators of survivorship. For example, the American Society of Clinical Oncology has a Survivorship Committee that includes international members and is focused on: 1) guideline development; 2) highlighting survivorship research at its annual meeting; and 3) supporting education initiatives such as the ASCO annual Cancer Survivorship Symposium. Likewise, the European Society for Medical Oncology (ESMO) and European Society for Therapeutic Radiology and Oncology (ESTRO) have each included sessions focused on cancer survivorship in their annual meetings. Facilitating survivorship services for pediatric and young adolescents has been facilitated by the European Society of Pediatric Oncology (SIOPE). One additional facilitator of survivorship services is the existence of a strong PCP group within the health care system, such as Canada. Because the PCP is central to the follow-up care of survivors in Canada, many of the studies looking at models of survivorship care have been conducted here to evaluate the quality of care with the important endpoints of recurrence and identification of late effects.

One of the most important issues to be addressed in survivorship care going forward is the need to understand the significant challenges that exist in making this a formal period of care with evidence-based services accessible across populations. Although the number of survivors has increased significantly across the globe and survivorship research has grown exponentially, limited evidence exists regarding the best practices for survivorship care. To date, significant elements in the growing number of survivorship guidelines remain consensus-based because the evidence is still limited. In addition, the assessments evaluating models of survivorship care have applied different end points so they cannot be compared and important metrics, such as long term health outcomes and costs, are lacking. A second major barrier to the development and broad dissemination of survivorship programs and services is the lack of a trained survivorship work force. This deficit is true for both the PCP who may be caring for the cancer survivor and for oncology providers who would be ideal to follow survivors in need of services. This may be a problem due, in part, to the oncologist's lack of confidence in the PCPs ability to identify disease recurrence and manage late effects. Future efforts may well follow the activities in Italy where Numico reports that only 55% and 30% of oncologists follow breast cancer survivors and colorectal cancer survivors indefinitely. Finally, there are health delivery challenges that exist even in countries with national health care. Financial barriers exist when there

are out-of-pocket expenses for services, concerns about employment and time away from work when dealing with post-treatment problems. There are also the challenges of variable access to survivorship services because of geographic location or economic disparities despite their availability within a country. This challenge is a part of the larger concern about health disparities in vulnerable populations.

Although much has been accomplished in survivorship internationally, significant work remains to be done. This brief review highlights the progress to date in the development and implementation of survivorship programs and highlights the challenges that remain in assuring that an evidence-based set of services are available to all survivors. Increasingly, research results demonstrate that survivorship services are best focused on recovery and based on need using a risk-based approach to care. This information is essential in developing successful models of care even as they continue to evolve reflecting the needs of the specific survivor population, available professional and financial resources, and the overall organization and priorities of the health care system. Going forward, evaluation of these models is necessary as we determine the type most effective in achieving the goals of care. Thus, the most important next steps for cancer survivorship include: continuing to develop the evidence base for practice; development and assessment of care coordination between oncology specialists and PCP generalists; application of metrics for care models that include outcomes in addition to process measures; and sharing of knowledge between international survivorship experts in order to accelerate progress. Continuing to move forward with survivorship as a patient-centered endeavor will assure that we meet our goal of assuring that cancer survivors have the highest quality of life possible.

LATE EFFECTS OF SURGERY

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Breast cancer is the most common cancer in women in the United States and Europe and the second leading cause of death from malignancy in women. The effect of breast cancer on U.S. society, however, exceeds even those impressive numbers in that this disease has had dramatic social, psychological, cultural, and even political consequences. Recent cancer statistics show the good news that in the 1990s death rates from breast cancer have been decreasing in the United States and the United Kingdom, despite the increasing incidence of breast cancer during this period. However, the magnitude of the decrease in death rates in African Americans and other minority groups has not been as great. The most likely cause is lack of access to early-detection programs and treatment services, although biologic differences have not been excluded.

Certain key factors led to changes in the management of breast cancer and ultimately improvement in death rates. These factors include incremental improvements in the screening and early diagnosis of breast cancer throughout the last century as well as improvements, refinements, and innovations in surgery and radiation therapy. Other factors include new adjuvant endocrine therapies, cytotoxic drugs, biologic therapies, and combinations of these treatments, as well as a vigorous patient advocacy movement that not only has facilitated and accelerated research efforts, but also has made therapy more accessible to the U.S. population. The marked increase in the understanding of the molecular and cellular biology of breast cancer is also beginning to yield new molecularly targeted diagnostic and therapeutic approaches, and progress in prevention is also being made. This chapter reviews the epidemiologic and biologic basis of the current understanding of breast cancer, and emphasizes the collaborative, multidisciplinary, preventive, diagnostic, treatment, and supportive care approaches that are required to continue making significant progress against this disease. Particular attention has to be focus now on quality of life of survivers from breast cancer with improvement of surgical, radiation and aduvant therapy.

Recently proposed procedures, the sentinel node biopsy, for example, were quite uniformly accepted as routine management only a few years after the

first consistent preliminary results were published (Fischer B et al. 2002; Veronesi U et al. 2001). The sentinel node procedure is only one example of the several proposed procedures during the last 5 years; others include intraoperative radiation therapy (Schwartz GF et al. 2002), new localization techniques on non palpable breast lesions , nipple sparing mastectomy (Veronesi U et al. 1997), all procedures to improve quality of life of surgical patients.
The management of early invasive breast cancer is multidisciplinary. Patients should be evaluated by a team of breast cancer specialists representing the subspecialties of breast imaging, surgical oncology, radiation oncology, and medical oncology. Approximately 75% of patients with newly diagnosed breast cancer have tumors less than 5cm in diameter. Patients with stage I and II disease usually have two options: breast conservation with radiation, and mastectomy with or without reconstruction. Careful clinical, Imaging and histologic assessment of the tumor, with particular attention to size, histologic margins, and histologic features, is important for the decision. It is important to determine the patient's needs, expectations, and understanding of available therapeutic options. The goal of breast conservation is an acceptable cosmetic outcome without sacrificing disease-free survival and overall survival. Most patients with stage I or II breast cancer can be managed well with breast conservation. If the size or location of the tumor relative to the size of the breast suggests that resection of the tumor would cause significant distortion of the breast, induction (preoperative chemotherapy) accomplishes two goals. Eighty percent of breast cancers are reduced in diameter by more than 50% after induction chemotherapy. This reduction may allow a considerably improved cosmetic result. lumpectomy and radiation. Approximately 5% to 20% of patients have measurable arm edema. Factors associated with edema include the extent of axillary dissection, postoperative wound complications, and the use of direct axillary radiation.(Giuliano AE et al. 1997).
In the NCI series, the rate of arm edema in the lumpectomy group was identical to the rate after mastectomy. This implies that the axillary dissection performed in both sets of patients, rather than the specific treatment to the breast, is likely responsible for the arm edema.
Rib fractures are seen in approximately 2% to 5% of patients treated with radiation. In this setting, most rib fractures are asymptomatic and are detected on a bone scan or chest x-ray that is performed for other reasons.
Rib fracture should always be included in the differential diagnosis of a previously irradiated patient with breast cancer who has chest wall or rib

tenderness and whose bone scan shows an area of tracer uptake in the ribs of the treated chest wall. No specific therapy is indicated for these rib fractures, and they heal spontaneously.

Approximately 1% or fewer of patients treated with radiation have symptomatic radiation pneumonitis. This complication is more frequent in patients who have received chemotherapy and radiation that included a field to the supraclavicular lymph nodes. In almost all patients, pneumonitis resolves either spontaneously or with a short course of steroid therapy, and no long-term sequelae occur. In some patients, radiation causes scarring in the small rim of lung treated in the tangential fields.

This scarring can appear as a density in the lung field underlying the treated breast on routine chest radiograph. The diagnosis of radiation-induced scarring can be made with a computed tomography scan that shows lung changes confined to the area of high-dose irradiation just underneath the anterior chest wall. These patients usually need no specific therapy, and lung biopsy is not needed.

Rarely, breast irradiation leads to late cardiac damage. Much of this information comes from treatment of the post mastectomy chest wall, especially when radiation was directed specifically at the internal mammary nodes. Recent studies suggest that few patients have sufficient cardiac volume within the radiation port to place them at risk for later damage and that these patients can be recognized in advance. With sophisticated treatment planning, these complications can be avoided. A supraclavicular portal sometimes results in brachial plexus injury, greatly increasing in frequency if large daily dose fractions are used. In rare cases, years later, radiation results in a soft tissue sarcoma within the radiation portal. The incidence of this extremely serious complication is approximately 0.1%. Add risk of lung cancer in smokers.

In the early 1990s, the introduction of the sentinel lymph node (SLN) concept revolutionized the management of axillary surgery in breast cancer (Krag DN et al. 1993). Prior to this, all patients with invasive breast cancer had a complete axillary lymph node dissection (ALND). Now, patients with a negative or partially positive (micrometastasis or less than 3 lymph-nodes involved) SLN can avoid an unnecessary ALND and its attendant morbidity (Veronesi U. et al. 2001). More recently, data from the Z0011 trial (American College of Surgeons Oncology Group) have challenged the role of ALND in patients with a positive SLN undergoing breast-conserving surgery (BCS) followed by radiotherapy (RT).This

study observed no statistically significant difference in local recurrence in patients randomized to SLN and ALND or just SLN alone in patients receiving BCS and RT with a follow-up of 6.3 years. The obvious progression from this practice-altering trial is to question and re-evaluate the role of ALND in the modern management of breast cancer. What additional information does it provide, can this information be reliably obtained by other means, and how does an ALND alter the patients' management or outcome? In this article, the authors evaluate the changing role of ALND in the modern era of breast cancer management.

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LATE EFFECTS OF RADIOTHERAPY

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The increasing number of radiation treatments and cancer survivors suggest a higher attention for late adverse effects from radiation therapy. Radiation dermatitis often needs topical steroids and emollient creams. Radiation esophagitis is treated with dietary modification, proton pump inhibitors, promotility agents, and also topical anaesthetics. In patients who receive radiation therapy on the thoracic region, radiation fibrosis treatment is aimed at relief of symptoms with steroids and, in severe cases, oxygen for dyspnoea. Chronic enteritis is managed with a low¬ residue diet, stool softeners, and loperamide administration. Treatments for chronic radiation cystitis are represented by anticholinergic agents and phenazopyridine. Erectile dysfunction and vaginal stenosis benefit from phosphodiesterase type 5 inhibitors and vaginal dilators, respectively. Finally, in cases showing depressive status, serotonin reuptake inhibitors may improve symptoms.

Radiation therapy is performed through external beam or brachiterapy techniques and exhibits curative, palliative or prophylactic purposes, on the basis of the type, status and localization of cancer. Radiation therapy acts by damaging neoplastic cells and inhibiting their ability to reproduce, whereas non-neoplastic cells tends to recover. Nowadays, treatment planning is delineated to limit radiation exposure of non-affected tissues and critical structures (such as airways, bone marrow and cardiovascular ones), for limiting also adverse effects. Adverse effects from radiation therapy are classified as "early" or "late". Early adverse effects occur during treatment or immediately after its completion, and tends to resolve within six weeks. On the other hand, late adverse effects occur months to years after treatment completion and tend to become permanent. Secondary malignancies from radiation therapy may present 10 to 15 years after treatment and show a positive correlation with the radiation dose and a negative correlation to the age at which the radiation was received (American Cancer Society 2016).

Radiation dermatitis is common and its onset is related mainly with radiation treatment of breast, prostate, perineal, and head and neck cancers. Late cutaneous effects of RT may develop months to years following treatment and vary considerably in severity, course, and prognosis: they include pigmentation changes, telangiectasias, hair loss, atrophy, fibrosis, ulceration and cutaneous malignancies. Risk factors for dermatitis are represented by obesity, concurrent chemotherapy, and high body mass index (Roy I et al., 2001; Wells M et al., 2004). Telangiectasia is related to acute radiation injury and boost dosing (Turesson I et al., 1996; Bentzen SM et al.,.1994). Small arteries and arterioles predisposed to thrombosis or obstruction may lead to skin breakdown and ulceration (Hymes SR et al.,.2006; Mendelsohn FA et al.,.2002). Moreover, damaged skin slow to heal (Hymes SR et al.,.2006;8 Harper JL et al.,.2004). Severe cutaneous injury is responsible for loss of nail and skin appendages together with absence of hair follicles and sebaceous glands conducting to alopecia (Hymes SR et al., 2006). Finally, risk for skin cancers is dose-related, and increases over the patient's lifespan (Shore RE 2001; Perkins JL et al., 2005; Ron E et al., 1991). Radiation recall is a phenomenon of rapid onset skin erythema in a previously radiated field usually after chemotherapy agents, but also after non-chemioterapic drugs (Sindoni A et al., 2016)
Topical steroids and emollients are often used for treatment of radiation dermatitis. Skin can be washed with a mild and unscented soap (Roy I et al., 2001). Patients undergoing radiation therapy should avoid swimming in chlorinated or hot water and applying adhesive solutions on irradiated skin (BC Cancer Agency 2016). Soft tissue radionecrosis benefits from traditional wound care techniques and, in severe conditions, hyperbaric oxygen therapy (Bui QC et al., 2004). Stem cell treatments to replace necrotic tissue and high-grade radiation dermatitis may be available options in the future.
Cardiovascular disease, pericarditis and lung injury secondary to radiation therapy affect mainly patients receiving radiation therapy on thoracic region. Estimated relative risk of fatal cardiovascular events after mediastinal radiation ranges from 2.2 to 7.2 for Hodgkin lymphoma and 1 .0 to 2.2 for left¬ breast cancer (Adams MJ 2003), which increases in patients who are in a younger age at treatment and if a high radiation dose is delivered (Adams MJ et al., 2003). Various dosimetric parameters have been assessed as predictors for the development of pulmonary radiation damage such as the mean lung dose (MLD), the volume of lungs receiving a

specified dose, and normal tissue complication probability (NTCP). RT is responsible for a rapid cascade of genetic and molecular events, involving a variety of cytokines (eg, interleukin [IL]-1, tumor necrosis factor-, platelet-derived growth factor, and transforming growth factor [TGF-]), cell types (such as macrophages, epithelial cells, pneumocytes and fibroblasts) and gene products (such as egr-1, NF-k, cjun, c-fos) (Vujaskovic Z et al., 2000), in a condition which can be worsened by hypoxia. RT-induced fibrosis is a condition of progressive chronic dyspnoea associated with scarring of the irradiated lung. This condition may result in pulmonary hypertension and cor pulmonale. Treatment is aimed at symptom relief, with steroids, and, in severe cases, oxygen. High doses of RT (70 Gy) may be associated with bronchial stenosis, bronchomalacia, and mediastinal fibrosis with secondary recurrent laryngeal nerve injury (Maguire PD et al., 2001; Dechambre Sv et al., 1998).

Xerostomia is a common late effect of salivary gland that consists in both the subjective sensation of oral dryness and the objective reduction in salivary function; it follows irradiation of the head and neck region, and is more severe if radiotherapy is performed simultaneously with chemotherapy. Oral dryness impacts the ability to eat, sleep, speak, and swallow, whereas reduction in salivary function is responsible for poor dentition, oral infections, sleep disturbances, oral pain, and difficulty in talking, chewing and swallowing. It is treated with saliva substitutes and/or stimulants. Pilocarpine is an effective but not immediate approach to resolve this condition. Amifostine give benefits, but it is not employed in mucositis and esophagitis (Hensley ML et al., 2009).

Esophagus is frequently exposed to radiation during treatment of oesophagus, lung and breast cancers. Radiation esophagitis is responsible for pain, dysphagia and odynophagia. These symptoms occur with dosages exceeding 30 Gy (Trowers E et al., 1994). Esophageal dysmotility may be due to radiation-induced damage of the Auerbach plexus. Risk factors are represented by increased age, higher nodal stage, and fractionation and radiation dose (Ahn S et al., 2005). Proton pump inhibitors, promotility agents and topical anaesthetics may provide relief of symptoms (Coia LR et al., 1995). Medical treatment has to be associated with dietary modification which consist mainly in avoiding alcohol, coffee and acid foods (Sasso FS et al., 2001). Enteritis occurrence increases linearly with radiation dose; abdominal surgery, pelvic inflammatory disease, hypertension and diabetes mellitus represent relative additional risk factors (Coia LR et al.,

1995). Symptoms of chronic enteritis are managed with a low¬ residue diet, stool softeners and loperamide (Coia LR et al., 1995).

Radiation proctitis is seen in radiation treatments of lower abdomen and pelvic cancers. It is generally classified as acute or chronic: acute radiation proctitis is defined as an inflammatory process involving only the superficial mucosa that occurs almost immediately after the initiation of therapy or up to 3 months after the onset of therapy, whereas in chronic one symptoms may not appear until months to years later after the end of therapy. Risk factors include medical history of inflammatory bowel disease, radiation dose and concurrent chemotherapy (Willett CG et al., 2000). Oral sulfasalazine and sucralfate enemas are effective approaches in the prevention/treatment of proctitis in all patients receiving pelvic radiation (Kiliç D et al., 2000). Refractory disease may benefit from hyperbaric oxygen (Clarke RE et al., 2008).

Pelvic radiation is performed by external beam and/or brachytherapy techniques. Technical and software solutions offer the possibility to delineate the dose intensity pattern that will best conform to the tumour shape, such as intensity modulated radiation therapy (IMRT) and 3-D/4-D imaging for dose calculations, to deliver a higher radiation dose to the tumour while minimizing the dose to surrounding normal critical structures. The accumulated radiation dose to the pelvic organs is important for acute bowel, bladder, and genital toxicity.

Sexual dysfunction and impotence follow radiation therapy in patients affected by prostate cancer and, less frequently, colorectal malignancies. Estimation of their incidence is difficult due to comorbidities often found in older patients. Erectile dysfunction is more frequently seen after brachytherapy than external beam radiation therapy (Catalona WJ et al., 2006]. Association with androgen ablation drugs is an additional risk factor. Erectile impairment usually occurs 1 to 2 years after treatment (38% and 59% after 1 or 2 years, respectively) (Turner SL et al., 1999) in cases with normal pre-treatment function, with increased frequency if there was pre-treatment erectile dysfunction. Phosphodiesterase type 5 inhibitors are effective for radiation--associated erectile dysfunction (Incrocci L et al., 2003; Incrocci L et al., 2007; Incrocci L et al., 2006,).

On the other hand, in the female gender adverse effects include decreased sexual interest and dissatisfaction, vaginal dryness, stenosis and dyspareunia, mainly after radiation therapy for cervical and endometrial cancer (Jensen PT et al., 2003). Vaginal wall thinning, adhesions, atrophia and

fibrosis may result in decreased vaginal elasticity and stenosis (Jensen PT et al., 2003; Bergmark K et al., 1999; Bergmark K et al., 2002; Denton AS et al., 2003; Jensen PT et al., 1998; Schover LR et al., 1989). Additionally, radiation-induced endarteritis ischemia may give rise to bleeding. Similar effects are observed in the bladder and rectum resulting in late effects as urgency, haemorrhagic cystitis, tenesmi and fecal incontinence (Andreyev HJ 2007;„Andreyev J, 2007; Majewski W et al., 2009; Marks LB et al., 1995; Parkin DE et al., 1987). The use of vaginal lubricating creams and mucosal protecting ovules may provide relief of symptoms. To prevent stenosis, the American Cancer Society recommends intercourse or use of a vaginal dilator three times per week (American Cancer Society 2016). The couple may benefit from referral to a sex therapist or support group. Sperm or egg preservation should be discussed with patients in cases who wish post treatment pregnancy.
Radiation cystitis is usually due to radiation because of prostate, colorectal, bladder, and pelvic cancers. Radiation cystitis is classified as acute or late: acute radiation cystitis occurs during or soon after radiation treatment, whereas late radiation cystitis can develop from 6 months to 20 years after radiation therapy. For patients who experience haematuria, intravenous fluid replacement, blood transfusion if indicated and transurethral catheterization with bladder washout and irrigation are indicated in severe manifestations. Moreover, oral or parenteral drugs used to treat haematuria include conjugated estrogens, pentosan polysulfate or WF10 (Smit SG et al., 2010). Chronic medical therapy is administered to relief symptoms: in particular, phenazopyridine is indicated for dysuria, oxybutynin for urinary urgency and flavoxate for bladder spasm (Marks LB et al., 1995).

The prevalence of depression varies among patients, with higher rates in patients with family history of depression (Jenkins C et al., 1998). Patients affected by malignancies can undergo to combined treatment regimens, so it is difficult to assess relationship of radiation with depression. Moreover, diagnosis may be more difficult because of the onset of fatigue, and radiation-¬related fatigue occurs in 80 percent of patients acutely and 30 percent chronically (Jereczek-Fossa BA et al., 2002): it is more frequent in patients with low Karnofsky performance score, female sex, and higher tumor burden (Armstrong TS et al., 2016). Serotonin reuptake inhibitors appear to improve depressive status, even if these drugs exert no effect on fatigue (Morrow GR et al., 2003, Roscoe JA et al., 2005), for which

exercise, adequate sleep, stress reduction and relaxation therapies may be beneficial (Monga U et al., 2007; Portenoy RK, et al., 1999). Psychostimulants are mandatory in cases in severe condition.

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INITIAL SURVIVORSHIP AFTER TREATMENT IN UROLOGICAL NEOPLASIA AND MULTIDIMENSIONAL GERIATRIC EVALUATION: A COOPERATIVE PROSPECTIVE STUDY

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In older patients with prostate ,kidney and bladder cancer a Multidimensional Geriatric Evaluation (MGE) could be proven of value to study the geriatric care needs after initial treatment the but also the age associated conditions play a role on the choice of initial treatment

To determine in patients with urological neoplasia immediately after primary treatment the percentage of vulnerable and frail patients and the consequent implications for their follow up(to make a comparison between the real follow up with that recommended also with the involvement of a Geriatrician)

From November 2012 to May 2013 to all patients older than 70 years operated on or treated with radical Radiotherapy at the main departments of Urology and of Radiotherapy of Milan after initial treatment, in the framework of a study supported by the Italian Ministry of Health was offered an MGE. After informed consent patient to entered in a prospective study aiming at examining the geriatric care needs after initial treatment. The MGE was carried out by 2 specially trained evaluators and results supervised by a Geriatrician to subdivide patients in fit, frail and vulnerable according to the classical Balducci' definition . Information about healthcare pathways was collected through phone calls at 6 and 12 months, from the 2 trained evaluators.

An MGE could be carried out in 143,while 27 refused to be examined. A prostatic carcinoma was observed in 83 patients, while 49 had bladder cancer and 11 a kidney tumor. Patients with prostatic carcinoma had a median age of 75 years , with bladder carcinoma 76 , 9 females and 41 males. Patients with kidney carcinoma had a median age of 77 , 3 females and 9 males.

The distribution of fit, frail and vulnerable patients in the various tumor

types was the following:

Patients	Prostate ca.	Bladder ca.	Kidney ca.	Total
Fit	39	11	2	52
Vulnerable	23	16	2	41
Frail	17	23	5	45

Data on health care provided (for comorbidity and functional deficits) collected at 6 and 12 months will be presented.

PHYSICAL AND PSYCHOLOGICAL SPECIFIC NEEDS BY THE VOICE OF PATIENTS

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The Association "Noi e il Cancro – Volontà di Vivere" (We and Cancer – Will to live) was born in Padova in 1979 as physical and psychological rehabilitation centre of oncological patients, in particular of breast operated women, and of their families; it has been founded thanks to a group of women who wanted to get over the solitude and pessimism that at that time surrounded cancer, in order to create a point of reference where it was possible to re-elaborate the past and participate in support activities.
"Personally I would have really wanted to meet a cured and free of cancer woman so that to have a positive model which could help me to hope again, allowing me to project myself into the future. "
These are the words of Caterina Tanzella, who has been the president of the Association for more than 30 years, which represent pefectly how Cancer was meant at the end of the 80's and which emphasize the importance of associations of patients, also from an emotional point of view, because they offer first of all a comparison with people who have suffered from the same illness and who have got over it. This helps patients to live the acute phase – where patients feel observed by everybody - like a facable and managable period, supported also by the various services answering to physical and psychologycal problems.
Infact since its constitution, the mission of the Association has been oriented in helping cancer patients in transforming a negative experience – if this is ignored, it could develop into a tragedy for the whole person – into an improvement of the psycho-physical balance in general and then of life quality, both personal and familiar.
Volontà di Vivere has always been oriented towards a patient global care (bio-psycho-social approach) which favors a higher life quality level in every illness phases, both for the ill person and for the caregiver.
In these last years we have met many people and heard their needs, so that we could activate the right services to offer them an immediate, concrete and focused help: manual lymphatic drainage, psychological support, sport activity, relax techniques, creative activities and more.
Cancer patients have to face many problems, that occur and change in the

various phases of the illness and of the treatment. These are psycological, social, physical, economical and concrete problems in general that influence in a negative way the patient life quality and of the caregivers.
The physical problems of the patients can be distinguished in needs of the immediate post-operatory period and needs linked to a permanent recovery of the functions.
These problems are linked to the more serious and fearsome complication of the surgical operation, which is the post-operatory lymphedema, that is often underestimated and barely considered, also treated with unsuitable techniques. The unique treatment which is considered valid is the manual lymphatic drainage and by the Association operate professionists who can treat this complication in a very competent way.
Immediatly after the post-operating the aim is to restore and maintain the freedom of movment of the crawler humeral bachelor; with the manual lymphatic drainage it is possible to operate to drain the edema, keeping in this way the limb free and light.
We encourage the patient to recognize the signals of her own body, as for example the symptoms of the lymph stasis, that is the classic sensation of "small pins" or the sensation to have a pillow near the scapula.
In the meantime the therapists aim at reassuring carefully women about the secondary effects of the operation they had, as for example the reduction of skin sensitivity, which is a normal sensation due to the operation.
Since an early rehabilitative intervention plays a fundamental role to obtain a good functional recovery, it is important that the patient receives immediately a correct postural education and knows which movements must be avoided and which have to be done; during the rehabilitative process the diet has a very important role that must be underlined.
The manual lymphatic drainage service results to be particularly appreciated, also because it becomes a moment of personal contact and dialogue with professionists who can go beyond the concrete intervention , putting themselves at disposal of the patients as "human beings".
The intelligence of our physiotherapists' hands amazes us: before the patient is aware of having a painful point, they are able to find in women body those critical points where there could be an energetic or lymphatic stagnation and they unblock the situation. In particular they are able to go beyond the registers, since they don't practice the same massage to everybody, but they adapt it to the particular needs of each single person. In this way the massage results beneficial since in a fitter body the mood

improves, the tensions unbend and a person has the feeling to begin and go on better with the everyday life.
This testimony demonstrates how rehabilitation gets a way to become reconciled with the body, as a mean to nose around in life, to learn, feel joy and not only to get ill, finding also pleasure again.
Concerning the psychological aspect, the first and absolutely necessary need of a cancer patient is information.
A patient tells:
What they told me was not enough to understand what I was going to face and mostly what was going to happen to me. I had no other alternatives. They proposed me only one solution.
On the contrary, the patient and her family need clear and precise information to understand better the illness, the consequences it will have in their lives and the available options for the cure.
People giving these information have absolutely to respect the comprehension capabilities and the integration and elaboration time of the news received by the patients.
Only if patients receive appropriate and clear information and there is a good communication and therapeutic relationship, they can be active participants in the clinic process; among the most urgent needs, they look for keeping their own dignity and self-determination, participating in the therapeutic choices and not depending only from decisions of other people.
Information is the right mean to face the shock of the diagnosis, which causes in the patient emotional answers like crying, fear, anger and disorientation; if the patient is correctly informed about the characteristics of the illness and of the clinical treatments, he can get over confusion. It is important to add information about the available services, local organizations and concrete helps.
Since the adaptation of cancer patients improves with the family's and partner's support, it is important to take care also about them (partners, children, parents, friends) into a psycho-social care route.
The psychological problems that patients have to face concern: worry for body's look, sexual problems, interpersonal difficulties, or big problems as anxiety, depression, stress post-traumatic troubles, fear and/or worries linked to surviving and to relapses. Psychological problems could be underestimated or not so much known, even if they are very frequent in oncological patients. Actually health inspectors and doctors should give great importance to these problems of adaptation and patient functionality, and give all useful indications and information, addressing the patient and her

family to specialized services as soon as possible.
Concerning the physical aspects of the illness, information is fundamental as well: patients have to know exactly which effects the illness will have on their body, following operations and/or therapies (nausea, vomit, fatigue, pain, fertility, lymphedema, changements of look and functionality, cognitive and nutrition problems and so on….)
Patients have often to face practical problems and high expenses (for screenings, doctor's procedures, support therapies, prosthesis, travels, movements, baby-sitting, house assistance, difficulties in house-keeping or in self-care and so on …). Moreover patients have to face changements in their work status, job and financial (changements in the job relationships, in credit access, life insurance and so on…) therefore it is important to give them correct answers and information about these aspects, in order to influence in a positive way their treatment and their weel-being.
It is extremely important to inform the patient correctly about his rights and to address him to the available judirical guardianships, benefits and services, both financial and job.
Many years after therapies, fatigue is one of the elements that mostly interfere with the patient everyday life, but it is unluckly systematically underestimated. Moreover, when a person survives cancer, he doesn't stop needing psycho-social assistance. Patients and their families need to have the possibility, also after a long time, to enter specialized structures that can offer in the various phases of the illness welcome, information, hearing, support and specific psycho-social interventions. For this reason it is important that also doctors and politicians are aware of patients' psycho-social needs, in order to promote global and integrated cure programs, that could give concrete and effective answers to the psycho-social and bio-medic problems which the oncologic pathology imposes.

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LOSING MYSELF
RETURN TO WORK

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The words 'brain tumour' tend to evoke thoughts of ending, dying and the absence of a life. Yet, for thousands of people across the UK a brain tumour is a part of living — an aspect of their present and future. Life with a brain tumour means going on, though often in dramatically altered circumstances. In this ground-breaking research project over a thousand people shared their stories of what it is to live with a brain tumour. People recounted a loss of identity due to personality changes, cognitive and communicative impairment and being forced to abandon or change career. The decline in one's own physical or mental functions can feel like betrayal, obliging a person to rely on the care and support of others, and denying them the independence of adult life they once enjoyed. No longer being able to work and provide for the family, to socialise, or even help around the house, can have a devastating effect on relationships with loved ones. Living with a brain tumour also means coping with the dread of decline, fear of death, and anxiety about the wellbeing of those left behind. The stories we've shared in this report illustrate the real-life needs, harms and hopes underpinning our goals to double survival within 10 years and halve the negative impact that brain tumours have on quality of life

The Life with a Brain Tumour project was conducted by The Brain Tumour Charity in partnership with Alterline, an independent research agency. In total 1,004 people completed the study questionnaire between 13 February and 13 March, 2015. Following the survey, 15 people took part in in-depth, face-to-face interviews and a further 25 kept reflective diaries over seven days. The questionnaire used to collect the large-scale data was directly advertised to subscribers of The Charity's e-newsletter. It was also promoted on The Charity's website and other communication channels, and by The Charity's volunteer and healthcare professional networks. The majority of respondents accessed the questionnaire online, with a small number completing it over the phone. Alterline also publicised the questionnaire on mainstream social media websites to reach people living with a brain tumour who had no association with The Charity. Developed by

Alterline alongside The Charity, the questionnaire covered many aspects of people's lives, reflecting experiences recounted in pre-survey scoping interviews with people with a brain tumour.
There were seven key areas that came out of this project and which we use to help shape our services, policy work and direct our research.

Losing self-identity
A fundamental difference between a brain tumour and a tumour in other parts of the body is the effect it can have on the mind and interaction with other people. Brain tumours frequently lead to the loss of the characteristics and faculties that make us who we are as individuals: personality, memories, cognition and the ability to communicate with others.
Our key findings included:
28% experience personality changes
1 in 2 experience memory loss
1 in 4 experience cognitive problems
Struggling with physical challenges
Brain tumours may occur in any part of the brain and can therefore affect the full range of physical functions. The majority of people with brain tumours experience physical symptoms of some sort, such as mobility problems, fatigue, pain, sensory impairment or seizures. Brain tumours limit the control people have over their body, reducing their capacity to function normally and live life to the full.
Our key findings included:
29% have mobility problems
80% of those with mobility problems have them moderately or severely
3 in 5 people experience fatigue

Losing independence
Whilst the effects of a brain tumour vary in range and severity, the net result for many is a loss of the autonomy that defines a person as a fully independent adult. The personal toll of adapting to a new way of living, dependent on the support of others, can be high indeed. Loss of one's driving licence leads to an increased reliance on others that can feel frustrating and burdensome for all involved. Those who find they require assistance with personal care may feel their dignity and self-respect has been undermined by their condition.
Our key findings included:

3 in 4 lose their driving licence at some point
61% have difficulty with domestic chores
2 in 5 have difficulty with personal care

Struggling to return to employment

The negative effects of a brain tumour on employment and career prospects are often far-reaching and profound, affecting individuals, their partners and families. Many people find they have to give up work entirely, change job, or reduce their hours and duties. If a partner acts as a carer, their career may also be affected. Financial difficulties as a result are common, adding to the stress and vulnerability of illness. The loss of identity and purpose provided by work can also have a deeper emotional impact, undermining self-worth and hope for the future.

Our key findings included:
3 in 4 have had their partners working life affected
28% have had to give up work entirely
1 in 2 experience financial difficulty

The impact on family and friends

The negative effects of a brain tumour on employment and career prospects are often far-reaching and profound, affecting individuals, their partners and families. Many people find they have to give up work entirely, change job, or reduce their hours and duties. If a partner acts as a carer, their career may also be affected. Financial difficulties as a result are common, adding to the stress and vulnerability of illness. The loss of identity and purpose provided by work can also have a deeper emotional impact, undermining self-worth and hope for the future.

Our key findings included:
2 in 3 people have seen a negative impact on relationships
72% have had physical intimacy affected
1 in 2 are playing with children less or have stopped entirely

I've become isolated

A brain tumour diagnosis, and the ensuing symptoms can cause lasting damage to the social fabric of a person's life in a way that reflects the unique impact of brain tumours. Fear and incomprehension of changes to the individual and the poor probability of their recovery may lead friends and acquaintances to withdraw. Meanwhile the person living with the tumour may retreat from social and leisure activity due to mobility

problems, fatigue, pain and difficulties with cognition or communication. The resulting loneliness or boredom can markedly diminish quality of life.
Our key findings included:
70% feel awkward in social situations
61% participate in less social activity
29% are severely isolated

I'm scared of dying

The low survival rate of those diagnosed with a brain tumour compared to other cancers makes fear of dying a key consideration in understanding the reality of life with a brain tumour, crossing the boundaries of tumour type, grade and terminal or non-terminal prognosis. The chronic and life-changing nature of symptoms and the lack of control that people feel over their condition may heighten awareness of bodily fragility and their mortality in a way that can be difficult to articulate. Anxiety about physical and mental decline and the uncertainty of the timeframe of a terminal prognosis can place individuals and their loved ones under enormous strain.
Our key findings included:
58% are scared of dying
1 in 5 survey respondents had a terminal prognosis
55% who have a terminal diagnosis haven't been given a choice about end of life options

THE RELEVANCE OF TRAINING AND EDUCATION

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The importance of quality in surgical training and medical education are still today important topics in modern medicine because health care quality (Rose GL et al., 2015), efficiency and safety of medical-surgical protocols and their application in daily practice mostly depend on the above mentioned factors (Steinhausen S et al.,2014). Of these aspects the motivation of medical students to embark on a surgical career seems to be one of the most important factors for a successful communication with patients. Furthermore, mentoring has been considered a core component of the duties of the medical school faculty to facilitate successful fulfillment of this academic mission (Healy NA et al.,2012). Despite this, which factors are influencing vocations to surgery, quality of educational programs and satisfaction of scholars remain a matter of debate. The aim of this paper is to review the main problems related to the current vocation to a surgical career and the impact of different factors on such a choice by doctors in developed countries.

A pubmed search was conducted using the key words: "surgical education, importance of surgical training, mentorship in surgery, surgical residency programs, medical education" and after that, only papers judged relevant for the topic were selected and filtered. Papers published only during last 10 years were taken into consideration for our study. The first endpoint of the search was to analyze which factors were judged to be important or relevant, having an impact on choosing a surgical career by prospective medical students; the second endpoint was to analyze the importance of education, mentorship and surgical training on such a choice.
We found 172 papers with the above mentioned key words. Among those, only 73 papers were judged to be relevant for our study related to specific problems of training and education in general surgery during residency programs.
The problems extracted and analyzed from the selected studies were: role

of mentorship, factors influencing student motivation, results of residency programs on education to an academically oriented career.

Looking at the number of publications of the last 10 years related to the topic of our review, it appears very clear that many schools of medicine are feeling the problem of surgical career vocations, mentorship, quality of residency programs and their relation to academic careers.
From the analysis of the literature and available studies, the importance of training and education in medical faculties seems to be related mostly not only to the modernity of facilities, logistics, up-to-date knowledge of faculty members, new modern tools for access to knowledge (multimedia libraries, availability of online tutorials, online accounts for administrative problems etc) (Tahir M et al.,2014; Stjulien J et al.,2016), but also to some human factors that cannot be scientifically measured. On the other hand, ranking programs of medical faculties depending on many of above mentioned factors were also judged to be not consistent with their objectives (Wilson AB et al., 2015). As already referred some human and psychological factors are important and have an influence on students, for example the quality of mentorship (Sambunijah D1 et al.,2006; Stagg P et al.,2012) and the relationship between mentor and mentee that could positively influence the choice of medical students and the grade of satisfaction of scholars after a training program (Schmidt LE et al.,2016; Marshall DC et al.,2015; Grigg M et al.,2014). Perceived importance of mentorship was related to career satisfaction(Sciscione AC et al.,1998). These aspects also reflect on the productivity of scholars during residency programs, related to the choice to be enrolled and engaged in an academic career. Of course, financial aspects must also be taken into account and a generous availability of grants should be considered the basis for a successful clinical research-oriented academic career.
Also original programs of research involving local teaching hospitals under the coordination of academic centers were proposed in a "work in progress" model, to improve the quality of training programs (Patel H et al.,2016). Personal motivation seems to be the first factor, but the kind of enrollment also depends on the organization and direction of each residency program with differences among specialties (Cullej DJ et al.,2014). If we consider that residency programs and the education level of medical schools have to balance the needs of education with the duties of doctors in health systems (Quinn A et al.,2009; Kennedy GD et al.,2014), we could

understand how important the grade of satisfaction of scholars is during training and education programs positively impacting also on emotional status and positive predisposition to patients. In fact, empathy is intended to be an important factor influencing the quality of patient assessment and treatment (Steinhausen S et al.,2014; Steinhausen S et al.,2014). Furthermore, educational and training programs will, in the future, deal more and more with the increasing problem of resident "burn-out" especially in surgery due to stress, long learning curve, amount of duties and hours of work and level of knowledge expected from health systems (Elmore LC et al.,2016).

The importance of training and education is still today, despite all the technologies and progress mainly related to human factors such as quality of mentors, type of relationship between mentors and mentees, first experiences of clerkship, fellowship and scholarship before accessing residency programs. Satisfaction of scholars will consequently impact on the quality of patient treatment. Much effort is being made by many schools of medicine all over the world to improve educational programs and residency courses, even if there is a lack of evidence and it is difficult to demonstrate in an evidence based manner, "Mentoring" is perceived as an important part of academic medicine.

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MOST FREQUENT TOXICITY AND NEW SIDE EFFECTS OF NOVEL DRUGS AND TREATMENTS IN BREAST CANCER

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Introduction

With an estimated 1.67 million of new cancer cases diagnosed in 2012 (25% of all cancers), breast cancer (BC) represents the second most common cancer in the world and, by far, the most frequent cancer among women (1). Due to early detection and improved adjuvant therapies (2), BC mortality has declined over the past years (3-4). Furthermore, improvements in treatment for metastatic disease have significantly prolonged survival and extended the period of medical intervention (5,6).
Therefore, it is extremely important for the clinicians to pay attention to quality of life (QOL) of BC patients with advanced disease, also in relation to potential toxicities of anticancer treatments (7-9).
On the other hand, in the adjuvant setting, the main concern is the long-term toxicity related to the different therapeutic strategies (i.e. chemotherapy, endocrine therapy, anti-HER2 agents) (10-15).
Research is currently driven by the precepts of precision medicine (i.e. to maximize the efficacy and to minimize the toxicity) but new therapeutic agents are not free of side effects. Indeed, new toxicity profiles that characterize novel anticancer agents need to be known in order to optimize prevention and management of adverse events. The present manuscript describes incidence and management of some of the most relevant drugs or therapeutic strategies that are expected to dominate the clinical scenario in the next few years.

Palbociclib

Hormone receptor-positive phenotype accounts for approximately 75% of all BC and endocrine agents represent the cornerstone of treatment

(16). However, due to primary and secondary resistance, patients may not respond to a first-line endocrine therapy or experience progression after initial response (17,18).
Trying to overcome mechanisms of resistance, new potential targets have been identified (19). Several studied investigated cyclin-dependent kinase 4 and 6 (CDK4/6) that play a key role in the cell-cycle regulatory machinery. In particular, CDK4/6 regulate the transition from G1 to S phase (20) and are critical drivers of oncogenesis (21). Moreover, resistance to endocrine therapy was observed to be linked with genes that are regulated through cyclin D–CDK–Rb pathway (22).
Palbociclib is the first-in-class selective CDK4/6 inhibitor (21). Preclinical studies have demonstrated that luminal estrogen receptor (ER)-positive or HER2-amplified cell lines subtypes were most sensitive to palbociclib (23). Phase I studies have shown that palbociclib is well tolerated, with neutropenia being the most significant and dose-limiting toxicity (24,25). Despite single-agent activity has been observed (26), palbociclib determined significant improvement in progression-free survival (PFS) when combined with endocrine agents such as letrozole or fulvestrant. On the basis of results from randomized phase II trial PALOMA-1, palbociclib plus letrozole combination obtained accelerated Food and Drug Administration (FDA) approval in February 2015 for the treatment of postmenopausal women with ER-positive, HER2-negative advanced BC as initial endocrine-based therapy for metastatic disease (27,28). The recommended schedule of palbociclib is 125 mg daily for 21 consecutive days followed by 7 days of rest, with letrozole 2.5 mg daily continuously throughout the 28-day cycle.
In PALOMA-1 the most common adverse events reported for the palbociclib plus letrozole group were neutropenia, leucopenia, and fatigue. All 83 patients who received palbociclib plus letrozole had at least one adverse event. Despite the increase in all grades of neutropenia (74%) and leucopenia (43%) with palbociclib plus letrozole, no cases of febrile neutropenia were reported. Other adverse events (of any cause) that were increased in the palbociclib plus letrozole group included anemia, nausea, arthralgia, and alopecia, but most of these were mild. Of these adverse events, the difference between treatment groups was significant only for anemia and alopecia. Overall, 33% of patients in the palbociclib plus letrozole had dose interruptions because of adverse events. In the combination group, 45% of patients required a delay in the start of a subsequent treatment cy-

cle because of an adverse event and 40% of patients had a dose reduction. However, the mean relative dose intensity for palbociclib in the combination group was 94% (27).

Since the exploratory assessment of pain can provide additional meaningful information on the overall clinical benefit of a new treatment, one of the secondary objectives of the PALOMA-1 study was to assess the impact of adding palbociclib to letrozole on pain severity and pain interference with daily activities. The evaluation of pain was measured using the Brief Pain Inventory patient-reported outcome tool, which was administered at baseline and on day 1 of every cycle thereafter until disease progression and/or treatment discontinuation. Results from this study demonstrated that the addition of palbociclib to letrozole did not significantly alter pain severity or pain interference with daily activities. These findings are significant for patient care, especially in the metastatic setting, where the goal of treatment is to control disease progression while maintaining functional status and QOL (29).

Results of PALOMA-2, a phase III trial that mirrored the design of PALOMA-1, were recently presented at the 2016 Annual Meeting of the American Society of Clinical Oncology (ASCO). PALOMA-2 expanded and confirmed the significant clinical benefit and safety of observed in PALOMA-1. In particular, a median PFS of 24.8 months was observed for the combination palbociclib+letrozole vs. 14.5 months of the placebo arm (HR=0.58 [0.46–0.72], $p<0.000001$). Common adverse events of all grades with palbociclib plus letrozole vs. placebo plus letrozole were neutropenia (79.5% vs. 6.3%), fatigue (37.4% vs. 27.5%), nausea (35.1% vs. 26.1%), arthralgia (33.3% vs. 33.8%) and alopecia (32.9% vs. 15.8%). Febrile neutropenia was seen only with palbociclib plus letrozole (2.5%) (30).

The efficacy of palbociclib in combination with endocrine therapy was confirmed also by PALOMA-3, a multicenter, double-blind, randomized phase III trial that investigated the value of palbociclib plus fulvestrant combination in women with hormone receptor-positive, HER2-negative metastatic BC that had progressed on previous endocrine therapy. Again, the main toxicity observed with palbociclib was neutropenia. Namely, 81% of patients who received at least one dose of study drug experienced neutropenia of all grades, whereas grade 3 or 4 neutropenia was reported in 65% of patients receiving fulvestrant plus palbociclib; febrile neutropenia was uncommon in both groups. Leucopenia of all grades was also substantially more common in the palbociclib arm. Infections, fatigue,

nausea, anemia, thrombocytopenia, alopecia, rash, and stomatitis, among others, were also more common in the palbociclib group. Of note, 54% of patients in the fulvestrant plus palbociclib group had a dose interruption because of an adverse event, 36% had a cycle delay, 34% had at least one dose reduction, and 4% discontinued treatment because of adverse events (31).
Neutropenia is therefore the most common adverse event associated with palbociclib. Although this hematological toxicity could make palbociclib similar to chemotherapy, the incidence of febrile neutropenia is very rare. Accordingly, compared with chemotherapy, palbociclib results more manageable and safer.

Anti-HER2 therapy in metastatic breast cancer: pertuzumab and T-DM1

Human epidermal growth factor receptor 2 (HER2)-neu, a member of the epidermal growth factor receptor (EGFR) family, is a proto-oncogene located on chromosome 17q21 and its amplification drives cellular proliferation and angiogenesis (32). HER2-neu amplification and/or HER2 protein overexpression occur in approximately 20-25% of BC and are associated with more aggressive tumor behavior and poor prognosis (33,34). The introduction of trastuzumab, an anti-HER2 humanized monoclonal antibody, has changed natural history of HER2-positive BC with significant advantages in terms of patients' survival (35).
Despite the proven efficacy of trastuzumab plus chemotherapy (36), some patients with HER2-positive BC do not respond, and the majority of metastatic BC patients progress within 1 year (37). Trying to overcome primary or acquired drug resistance, novel anti-HER2 drugs have been developed, such as pertuzumab and T-DM1.
Pertuzumab is a recombinant humanized monoclonal antibody directed against the extracellular dimerization domain (subdomain II) of HER2 and it is used in combination with trastuzumab. As resistance to trastuzumab develops, there is an upregulation of other members of the HER family in order to compensate for the lack of HER2 ligand-independent signaling. Pertuzumab blocks the ability of HER2 to heterodimerize with other members of the HER family and initiate HER2 ligand-dependent signaling. The HER2/HER3 dimer is thought to be the most potent in terms of interaction strength and amplification of downstream signaling (38,39).
Efficacy and safety of pertuzumab have been evaluated in several trials.

Two phase II studies (the BO179292 and TOC3487 trials) (40,41) and the phase III CLEOPATRA trial (pertuzumab/trastuzumab plus docetaxel in experimental arm vs. placebo/trastuzumab plus docetaxel) (42) demonstrated the efficacy and safety of pertuzumab in metastatic BC. Other two studies (NeoSphere and TRYPHAENA trials) evaluated the pharmacologic combination of trastuzumab and pertuzumab with or without chemotherapy in neoadjuvant setting (43,44).

The PERUSE trial investigated the efficacy and safety of the combination of pertuzumab with trastuzumab associated with three different taxanes (docetaxel, paclitaxel, and nab-paclitaxel) for HER2-positive locally recurrent/metastatic BC. Preliminary data suggested a good toxicity profile of the double blockade associated with paclitaxel or nab-paclitaxel (45). The APHINITY study (NCT01358877), an ongoing trial, compared pertuzumab, trastuzumab and chemotherapy to trastuzumab and chemotherapy in the adjuvant setting.

HER2 plays an important role in cardiac development and in maintaining the physiologic function of an adult heart. A lot of preclinical data suggested that HER2 is implicated in embryogenesis of heart and the absence of HER2 is associated with myofibrils damage. All anti-HER2 drugs might lead to cardiac toxicity in the form of either congestive heart failure or asymptomatic left ventricular dysfunction, which is characterized by echocardiographic finding of a reduction of a value ≥10 points from baseline or in absolute terms, of a value <50% left ventricular ejection fraction (LVEF). For this reason, all patients treated with anti-HER2 therapy must be evaluated with an echocardiogram at baseline and then every 3 cycles. For cardiotoxicity no dose reduction is permitted, but only temporary or permanent discontinuation of the drug (46).

In the NeoSphere study, there was no significant increase in left ventricular dysfunction with the addition of pertuzumab to trastuzumab; indeed, the prevalence of 10-15% decline in LVEF from baseline as well as new LVEF <50% was not statistically significant (43). In the CLEOPATRA trial, the incidence of cardiac adverse events was slightly lower in the pertuzumab arm (14.5%) than in the control-placebo arm (16.4%); accordingly, the number of events reported as grade 3 or higher (among which left ventricular systolic dysfunction was the most common) was lower in the experimental arm compared with the placebo arm (1.5 vs. 3.8%, respectively) (42). An important aspect emerged from CLEOPATRA study is that pertuzumab/trastuzumab combination did not increase the tox-

icity of cardiac events, even in the subgroup of patients with ≥65 years (42). Additionally, a large database analysis of 598 patients treated with pertuzumab was done to review the incidence of asymptomatic LVEF dysfunction and symptomatic heart failure. Overall, 331 patients received pertuzumab alone, 93 patients received pertuzumab and trastuzumab, and 175 received pertuzumab in combination with a non anthracycline-based regimen. Of note, 23 patients (6.9%) in the pertuzumab alone group developed asymptomatic LVEF dysfunction and only 1 patient (0.3%) developed symptomatic heart failure. In the dual-blockade group, 6 patients (6.5%) developed asymptomatic LVEF dysfunction and 1 patient (1.1%) developed symptomatic heart failure. Lastly, in the pertuzumab-non anthracycline-based chemotherapy group, 6 patients (3.4%) developed asymptomatic LVEF dysfunction and 2 patients (1.1%) developed symptomatic heart failure (47).
In the CLEOPATRA study, diarrhea occurred in 66.8% of patients treated with pertuzumab and in 46.3% of patients treated with placebo. Most events were of mild to moderate severity and occurred in combination therapy with docetaxel. Grade 3-4 diarrhea was reported in 7.9% of patients in the experimental arm and in 5% of patients in the control arm. All cases of diarrhea have been successfully treated according to the existing guidelines. Rash occurred more frequently in patients treated with pertuzumab; the majority of events were mild, early-onset, and responsive to standard therapies (42). Patients who received pertuzumab, trastuzumab and docetaxel were at increased risk of developing febrile neutropenia compared to placebo-treated patients (trastuzumab and docetaxel). Since the neutrophil count nadir was similar in the two groups, probably the higher incidence of febrile neutropenia in the experimental arm may be associated with higher incidence of mucositis and diarrhea. The incidence of grade 3-4 febrile neutropenia was 13.8% in patients treated with pertuzumab and 7.6% in the control arm (42).

After progression to trastuzumab, another targeted therapy available for HER2-positive metastatic BC is represented by trastuzumab emtansine (T-DM1), an immunoconjugate consisting of 3.5 molecules of DM1 linked to lysine residues of 1 molecule of trastuzumab. When T-DM1 binds HER2, with subsequently receptor-mediated internalization, the complex undergoes a proteolytic degradation, resulting in release of active metabolite containing cytotoxic DM1 (48).

This drug has a double mechanism of action. On one side, it is a proper targeted therapy, binding HER2 extracellular domain and mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (49). On the other, once into cytoplasm, DM1 binds tubulin and inhibits its polymerization with subsequent mitotic arrest. Both effects induce an arrest of cell cycle in G2/M phase, resulting in cell apoptosis (50,51).

Many clinical phase Ib and II studies have shown efficacy, safety and tolerability of T-DM1 in HER2-positive BC. The first phase III study, EMILIA trial, evaluating efficacy and safety of T-DM1 compared to capecitabine plus lapatinib, showed that T-DM1 improves PFS and overall survival (OS) with good tolerability in locally advanced or metastatic BC (52). Based on these data, FDA approved this treatment on February 2013 for HER2-positive metastatic BC patients that were pretreated with trastuzumab. Notably, the TH3RESA trial subsequently demonstrated that T-DM1 has a positive impact on PFS and OS in patients treated with at least two anti-HER2 lines (53). More recently, the MARIANNE trial compared treatment with trastuzumab and a taxane, T-DM1 plus placebo or T-DM1 plus pertuzumab in first-line setting. Data showed no superiority and no differences in OS and response rate of the experimental arms compared to trastuzumab and taxane. However, patients treated with T-DM1 presented a more acceptable tolerability profile (50).

In general, treatment with T-DM1 is well tolerated and severe toxicities are rare. Indeed, trastuzumab emtansine is a zwitterion, thus it is less soluble in organic solvent and concentrates mainly in cancer cells. This is demonstrated by the detection of very low levels of free DM1 in plasma (49).

The most common adverse events reported in clinical trials were thrombocytopenia, elevated serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), fatigue, hypokalemia, vomiting, and anemia. A pooled analysis of 882 patients, enrolled in 7 clinical trials until 2013, reported thrombocytopenia as the most frequent adverse event during treatment with T-DM1 (28.7%). Grade 3 or 4 thrombocytopenia generally occurred within cycles 1 and 2 (54). This condition is rapidly reversible, but not in all patients, who had to reduce the dose. Platelet count can be reduced from 24 hours after drug's infusion, with a nadir around day 8 and a recover from day 15. Thrombocytopenia has been rarely associated with major bleeding events, in particular there was no temporal association between grade 3 bleeding events and grade 3 thrombocytopenia (51).

In the EMILIA study, 12.9% of patients receiving T-DM1 has developed a grade 3 and 4 thrombocytopenia and 2% of patients had to discontinue treatment for this complication. Furthermore, bleeding events were more frequent in the experimental arm than in the control arm (29.8% with T-DM1 vs. 15.8% with lapatinib plus capecitabine), but grade 3 and 4 bleedings were 1.4% and 0.8%, respectively (52).
In more recent phase III trials, Th3RESA and MARIANNE, thrombocytopenia grade 3 was very frequent. In the first, grade 3 thrombocytopenia had a higher incidence in the T-DM1 group than in the control group (5% vs. 2%, respectively) (55). Also in the MARIANNE trial grade 3 and 4 thrombocytopenia was observed more frequently in patients treated with T-DM1 than in controls (7.5% vs. 1.5%, respectively) (56). The etiology of this adverse event is not well defined, but in vitro studies showed interference at the level of the microtubules with subsequently destruction. Therefore, megakaryocytes lose their ability to release the pro-platelets with consequent arrest of platelets formation (49).
T-DM1 can induce serum transaminases alterations, usually transient. It was observed a cumulative effect of T-DM1 on transaminases, resolved with dose modification or treatment discontinuation. In the pooled analysis, a grade >3 elevation of serum concentrations of AST and ALT was observed in approximately 5% of patients. Out of 882 patients, 3 cases of biopsy-confirmed nodular regenerative hyperplasia were recorded; these patients had clinical or radiographic signs of non-cirrhotic portal hypertension (51,54). In the EMILIA trial, hepatic toxicity was similar to other phase I and II studies. Furthermore, patients with grade 3 or 4 hepatic function alterations could continue treatment with T-DM1. Instead, hyperbilirubinemia was more frequent in the lapatinib plus capecitabine arm than in the T-DM1 arm (8.2% vs. 1.2%, respectively) (52). The hepatic toxicity profile was similar also in the TH3RESA trial (55). Instead, in the MARIANNE study, AST and ALT alterations of grade 3 and 4 were more frequent in T-DM1 group than in the previous trial (ALT 4.5% and AST 7.5% with T-DM1 vs. ALT and AST 0% with trastuzumab plus docetaxel arm) (56). Furthermore, in all studies, ALT plasma levels were higher than AST plasma levels, indicating a greater hepatotoxic effect of T-DM1. Liver toxicity can be explained by the release of immune-conjugate in systemic circulation with activation of Kupffer cells, responsible of IgG immunoglobulins clearance (49).
Fatigue was one of the most common adverse events associated with

T-DM1, occurring in about 1-3% of patients (54). Nevertheless, in the EMILIA study, T-DM1 was less associated to fatigue of grade 3 and 4 than in the control arm with lapatinib plus capecitabine (2.4% vs. 3.5%, respectively), while in the MARIANNE trial, incidence of fatigue of grade 3/4 was not reported in both arms and grade 1/2 events were similar in both groups (52,56).
T-DM1, such as trastuzumab, may be responsible of cardiotoxicity, but this is a rare adverse event. Left ventricular dysfunction has been reported in 2% of patients involved in clinical trials. However, most events consisted in an asymptomatic grade 1 or 2 reduction of LVEF value (46).
In the EMILIA study, only 8 patients (1.7%) developed a LVEF less than 50% and the TH3RESA study confirmed the low incidence of cardiac events (52,55).

New adjuvant endocrine therapy strategies in early-breast cancer: tolerability and toxicities

Approximately 75% of BC are hormone-receptor positive and endocrine therapy plays a key role for the treatment of these subtypes (57). Adjuvant treatment with tamoxifen has been the mainstay of endocrine therapy for decades, but now various therapeutic options are available, with different side effects and tolerability profiles. Current options include 5-10 years of adjuvant tamoxifen or aromatase inhibitors (AIs). In addition, in premenopausal women, the addition of ovarian function suppression (OFS) by luteinizing hormone-releasing hormones (LHRH) agonists or surgical/radiation ablation may improve efficacy.

Ovarian suppression plus exemestane in premenopausal early breast cancer.

Recently, the SOFT and TEXT trials have tried to clarify the role of OFS in addition to standard tamoxifen or AIs in premenopausal women with early BC. Patients were randomized to receive exemestane plus OFS, tamoxifen plus OFS or tamoxifen alone for 5 years (58,59). The joint analyses of the two trials combined data from 4690 patients after a follow up of 68 months, showing a significant gain in terms of disease free survival (DFS) at 5 years in the exemestane-OFS group compared to the tamoxifen-OFS arm (91.1% vs. 87.3%, hazard ratio 0.72, $p<0.001$) (59). More interestingly, Regan et al. adopted a composite risk score to quantify the absolute treatment effect in both SOFT and TEXT trials. They observed

an improvement of 10% to 15% of the 5-year breast cancer-free interval (BCFI) with exemestane-OFS compared with tamoxifen-OFS or tamoxifen alone for patients at high risk of recurrence (age <35, grade 2-3 tumors, high Ki-67, more than 4 nodes involved, adjuvant chemotherapy), but a lower or minimal benefit for patients at intermediate or minimal risk (5% and <3%, respectively) (60). The clinical relevance of these data rapidly led to a practice change, further defining high-risk premenopausal patients as the most likely to benefit from OFS addition to standard adjuvant endocrine therapy, as reported in a prompt update of the ASCO guideline recommendations (61).

Regarding treatment toxicities, in the SOFT trial it has been observed an increase of climacteric symptoms when adding OFS to tamoxifen, such as hot flushes (93.4% vs. 79.8%), musculoskeletal disorders (75.1% vs. 69%) sweating (61.8% vs. 48.3%), insomnia (57.2% vs. 46.3%), depression (51.9% vs. 46.6%), vaginal dryness (49.8% vs. 41.8%), decreased libido (47.5% vs. 42.2%), osteoporosis (20% vs. 12.3%), and G3-4 adverse events (31.3% vs. 23.7%) (58). Moreover, according to SOFT and TEXT data, when using OFS plus exemestane instead of OFS plus tamoxifen, there was an increment of sexual dysfunction with more severe vaginal dryness (52.4% vs. 47.4%), decreased libido (45% vs. 40.9%) and dyspareunia (30.5% vs. 25.8%) and an higher incidence of osteoporosis (13.2% vs. 6.4%), fractures (6.8% vs. 5.2%) and other musculoskeletal symptoms (88.7% vs. 76%), whereas hot flushes (91.7% vs. 93.3%), sweating (54.5% vs. 59%), thromboembolic events (1% vs. 2.2%) and urinary incontinence (13.1% vs. 17.8%) were reported more frequently when the tamoxifen plus OFS regimen was chosen (59).

As reported above, the frequency of side effects was relevant in both arms, although the changes in QOL compared to baseline was small and similar in all treatments groups, except for the addition of OFS to tamoxifen in the SOFT trial (worse endocrine symptoms and sexual functioning during the first 2 years of treatment) (62,63). Interestingly, a sub-study of the SOFT trial evaluated cognitive dysfunctions as a potential side effect of the overall treatment, providing no evidence that the addition of OFS to adjuvant endocrine therapy affects global cognitive function (64). The higher incidence of bone loss and osteoporosis in the exemestane-OFS group compared to the tamoxifen-OFS group (13.2% vs. 6.4%), represents a real concern for premenopausal women, even considering the premature menopause induced by OFS (59). Therefore, patients who are candidate

to OFS should receive a baseline assessment of bone mineral density and calcium/vitamin-D supplementation if needed, while bisphosphonates should be recommended only in patients with osteoporosis (T-score less than -2.5). Taking into consideration potential long-term cardiovascular toxicities, most of data refers to prospective trials comparing adjuvant AIs to tamoxifen in post-menopausal women. A large pooled analyses of 7 trials, collecting data from 30,023 postmenopausal patients who received AIs or tamoxifen, showed a higher incidence of cardiovascular events in the AIs group when compared to tamoxifen, with an increased relative risk of 26% (OR 1.26, $p<0.001$) and an higher incidence of hypercholesterolemia (OR 2.36, $P<0.001$) (65). It is hard to apply these results directly to the premenopausal setting, but at least they are useful to better plan an effective prevention by monitoring serum lipid levels and other cardiovascular risk factors.

10-year extended adjuvant therapy with aromatase inhibitors

The randomized, placebo-controlled MA.17R trial assessed the efficacy and safety of extending adjuvant letrozole in postmenopausal women who previously received 4.5 to 6 years of adjuvant therapy with an AI. After a median follow-up of 6.3 years and 165 events involving disease recurrence (67 with letrozole and 98 with placebo, respectively), it has been shown a gain in 5-year DFS favoring the letrozole arm (95% vs. 91%, hazard ratio for disease recurrence 0.66, $p=0.01$), but no differences in terms of OS (66). Comparable results were observed in the ABCSG6a trial, in which 856 postmenopausal patients were randomly assigned to 3-year extended treatment with anastrozole or nothing (67).

Toxic effects were similar in the two groups in the MA.17R trial, with the most common adverse events represented by arthralgia, hot flushes, fatigue, arthritis, insomnia, and myalgia (in about 50%, 40%, 35%, 33%, 30% and 30% of patients, respectively). Only bone-related adverse events were more common in the letrozole group, with a higher incidence of bone pain (18% vs. 14%, $p=0.01$), bone fractures (14% vs. 9%, $p=0.001$) and new-onset osteoporosis (11% vs. 6%, $p<0.001$), highlighting the importance of bone loss prevention among these women (66). The impact of extended therapy on QOL was assessed in a sub-study, with no significant differences shown between the two groups. Small (<0.2 standard deviations) but statistically significant differences in mean change scores were seen for physical functioning, bodily pain, vitality, vasomotor and

sexual domains, even if authors denied an adverse impact of letrozole on QOL (68).
In conclusion, when defining the best treatment for a given patient, clinicians have to balance risk of recurrence with expected toxicities, fertility issues and patient preferences, since the tolerability of the treatment is crucial for a good compliance, especially for long-lasting treatments. Notably, in large retrospective studies it has been estimated that only 50% of BC patients completed the entire 5-year adjuvant treatment (69,70), with 35% of patients younger than 40 deciding for an earlier discontinuation (69). Therefore, it is important for physicians to be familiar with the impact of these new therapeutic strategies on QOL and their safety profile, in order to improve the full adherence to endocrine therapy and prevent toxicities.

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THE LONG TERM EFFECTS OF CANCER AND CANCER TREATMENT: RESEARCH AT THE AMERICAN CANCER SOCIETY

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Introduction

The number of long-term cancer survivors in the United States is increasing due to a combination of rising cancer incidence rates and improving survival rates. As the absolute size and proportion of the US population that is over the age of 65 continues to grow, the number of people being diagnosed with cancer will also continue to rise. In addition, advances in cancer screening, early detection, and treatment strategies have resulted in the 5-year survival rate for all cancers combined rising from approximately 50% in the 1970s to more than 67% today.1 Together, these population changes and cancer advances have led to a steady increase in the number of cancer survivors in the US. Indeed, it is estimated that there are now more than 15 million Americans living with a history of cancer and this number is expected to reach 18 million by the year 2022.1

The American Cancer Society has set ambitious goals to improve the quality of life (QoL) of cancer survivors. In line with the Society's mission, the ACS implemented several studies that address the quality of life of cancer survivors. The largest activity is the Studies of Cancer Survivors (SCS). The SCS encompass three separate but interrelated studies. The ACS has more recently initiated two new research projects, the Patient Reported Outcomes Symptom Surveillance Study (PROSSES) and the Cancer Survivor Transition Study. Finally, the ACS has collaborated with the National Cancer Institute (NCI) to conduct the Survey of Physician Attitudes Regarding the Care of Cancer Survivors (SPARCCS). Each of these activities, and their products, are described below.

Projects

The Study of Cancer Survivors-I (SCS-I)

SCS-I is a population-based longitudinal study of the quality of life, psychosocial functioning, and health behaviors of a national population-based

sample of cancer survivors. The population of inference is adult citizens of the United States diagnosed with one of the following ten types of cancer: breast, prostate, colorectal, lung, bladder, kidney, ovarian, non-Hodgkin' lymphoma, skin melanoma, or uterine cancer. Cancer survivors were identified and sampled from SEER and NPCR population-based cancer registries in 11 states (Alabama, Connecticut, Idaho, Minnesota, New Jersey, Ohio, Pennsylvania, Rhode Island, South Carolina, and Wyoming). Stratification of the sample by type of cancer, age (<55, 55+), and race/ethnicity was used to provide an adequate number of cases in each strata. Recruitment of cases was conducted in collaboration with the cancer registry in each participating state. Data collection was conducted via a combination of mailed questionnaires and telephone surveys, the details of which are presented in two previous publications.2, 3 Enrollment of a cohort of 6,309 cancer survivors was completed during the years 2000-2003. The SCS-I baseline questionnaire (Qx1) was administered when survivors were approximately 1 year after their initial cancer diagnosis. The second questionnaire (Qx2) was administered 1 year later (at approximately 2-years post-diagnosis) and was completed by 5,110 survivors (retention rate of 80.1%). The third questionnaire (Qx3) was administered roughly 5 years after Qx2 and was timed to coincide with the 8th anniversary of survivors' diagnosis. A total of 3,138 survivors completed Qx3 (61.4% retention rate).

The Study of Cancer Survivors-II (SCS-II)

The second component of the SCS program of research is the SCS-II, a cross-sectional study of 9,170 cancer survivors who were 2, 5, or 10-years post-diagnosis who had been randomly selected from the population-based cancer registries in 14 different US states. Survivors of 6 different cancers were included in each of the 3 time-since-diagnosis cohorts. These cancers overlap with the cancer sites included in SCS-I; however, survivors of the 4 cancers with the poorest survival rates (lung, ovarian, kidney, and NHL) were not included in SCS-II, as it would have been difficult to find sizable numbers of 10-year survivors for each of these cancers.

The National Quality of Life Survey for Caregivers

The third component of the SCS program of research is the National Quality of Life Survey for Caregivers, which includes a cohort of approximately 1,635 family caregivers of participants in SCS-I, and is one of the largest cohort studies of family caregivers of cancer survivors in

existence.4 Caregivers were nominated by SCS-I participants as part of the baseline survey. Like SCS-I, this project is a longitudinal study with multiple assessments (i.e., baseline: 2-years post-diagnosis; follow-ups: 5- and 8-years post-diagnosis). The most recent assessment coincides with the third data collection point for the SCS-I participants (i.e., Qx3) to provide dyadic data on both the survivor and their nominated family caregiver when both individuals are approximately 8 years from the survivor's original cancer diagnosis. The caregiver survey examines the impact of cancer on the quality of life of family members and close friends of those who provide care for the cancer survivor. Dyadic data (survivor-caregiver) is available on overall quality of life measures (i.e., mental/physical functioning, spiritual well-being, emotional and psychological functioning), social support, global mood disturbance, fear of recurrence, and life satisfaction.

The Patient Reported Outcomes Symptoms and Side-Effects Study (PROSSES)

Symptom control is an important aspect of cancer care known to have major impact on quality of life (QoL), return to usual activities, disability, and completion of treatment; yet, symptoms are often under assessed and undertreated. Systematic, representative data on symptom severity, symptom management, and barriers to symptom care could play an important role in quality control, benchmarking, and scientific understanding. Regrettably, no system currently exists for systematically collecting symptom-related data at the national level, nor is there a well-established procedure for doing so at the health system level. The development of a Symptom Surveillance system could catalyze clinicians, patients, health systems, payers, regulators, and legislators to take action to lessen the burden of cancer-related symptoms. PROSSES is a study of breast and colon cancer patient symptom experience with 2 aims: 1) piloting a method of collecting patient reported outcomes that could be used for surveillance and developing prevalence estimates at institutional and, in the future, population levels. 2) Increasing understanding of patient perceptions of symptom care. 3) Developing actionable quality improvement reports from patient reported data. PROSSES is an ACS-led collaboration with the National Cancer Institute, the Commission on Cancer, and 17 community cancer centers across the U.S. Patients were sampled 4-12 months from diagnosis with loco regional breast/colon cancer. PROSSES closed recruitment in August of 2013 with complete surveys from 2,517 patients (response rate=60%).

B.5 The Cancer Survivor Transition Study

Relatively few studies have attempted to identify who is/is not prepared for the transition out of treatment, how this influences their overall perceived competency for the transition and what influence these factors have on a survivor's long term outcomes and ability to manage cancer as a chronic illness.5, 6 Further, as concluded by Park and Gaffney (2007)7, few studies have examined theoretical models of cancer survivors' health behavior change or attempted to determine the potentially complex relationships of psychosocial variables (i.e., preparedness) in predicting behavioral outcomes following the transition out of treatment. This study,which is being conducted in collaboration with the ACS Health Promotions Department, examines the "re-entry" phase from the perspective of social cognitive theory. In 2011, nine focus groups were conducted with 45 cancer survivors to examine this topic and to inform the development of a theoretical model. Based on those qualitative results, the scientific literature, and social cognitive theory, a model was developed describing how key predictor variables might impact the quality of a cancer patient's transition out of treatment in terms of health behaviors (e.g., energy balance, doctor visits) and health outcomes. Examples of key personal and environmental predictor variables in the model include the needs of cancer survivors during and right after "re-entry", how prepared they feel for the transition, and indicators of access to care. This model is now being tested with questionnaire data collected at two time points in this study. The study is designed to inform interventions by ACS and others by describing the issues 1,240 cancer survivors (418 breast, 452 colorectal, 370 prostate) continue to face after their treatment ends, the key variables interventions should target, and the best time to intervene.

B.6 The Survey of Physician Attitudes Regarding the Care of Cancer Survivors (SPARCCS) SPARCCS is a collaboration between ACS and NCI assessing physicians' knowledge, attitudes and behaviors regarding post-curative care of colorectal and breast cancer survivors. A national sample of primary care physicians and medical oncologists was randomly selected and surveyed. Papers from SPARCCS inform efforts to improve the post-treatment follow-up care of cancer survivors by providing essential descriptions of physician knowledge, attitudes and practices regarding care for cancer survivors, physician and patient barriers to optimal care.

Scientific product

Symptoms and Overall Quality of Life (QoL)

ACS researchers seek to improve understanding of the sequelae of cancer and cancer treatment, as well as the health and well-being of cancer survivors through investigations in the area of QoL. Quality of life is a broad concept covering constructs as broad as satisfaction-with-life and as narrow as pain. Understanding the health issues faced by cancer survivors is the first step towards designing interventions and policies to improve their lives. An early publication from SCS data reported the prevalence of numerous problems reported by cancer survivors.8 Specifically, emotional problems - mostly around fears of cancer recurrence and physical problems - predominately fatigue/sleep issues, were cited most by study participants. More recently, SCS results have demonstrated that more than 1 in 4 cancer survivors had high symptom burden 1 year after diagnosis and that symptom burden was related to Health-Related Quality of Life (HRQoL)9. Similarly, SCS papers have found that among cancer survivors 2-10 years from diagnosis, symptom bother and comorbidities were strongly associated with lower physical function.10, 11 Another publication explored the medical and psychosocial factors associated with body image dissatisfaction among male and female cancer survivors who participated in SCS-II. Female survivors with more advanced disease had the highest levels of body image dissatisfaction, whereas a diagnosis of prostate cancer survivor predicted less body image dissatisfaction among male survivors.12 Our research has also shown that perceived role in medical decision making is associated with HRQoL among short and long-term survivors.13 Specifically, we found that survivors who played their preferred role in medical decision making had higher QoL.13 Our group has also collaborated with researchers at the Fred Hutchinson Cancer Center to publish two papers using SCS data from cancer survivors from Washington. The first investigated long-term breast cancer survivors' search for meaning and its associations with QoL14; the second paper studied the impact of different levels of involvement in decision-making in breast cancer survivors QoL.15 While many survivors return to normative levels of overall HRQoL, these publications show that cancer survivors face persistent, specific health issues and have a need for continued symptom monitoring and management. Yet, often such problems are not adequately addressed. A publication based on SCS-II data demonstrate that more than 40% of SCS participants indicated that their doctor did not provide

clear instructions for managing side effects.16 This paper examined SCS participants' perceptions regarding the quality of cancer-related information they received during treatment. Survivors rated the information they received as being of good quality, but also identified a number of barriers, including not knowing where to find information (>25%), needing to exert too much effort to obtain information (>25%), and finding cancer information difficult to understand (>30%).

Spirituality

SCS-I Qx1, SCS-I Qx2, and Qx3 as well as SCS-II all included the FACIT-Sp17, a measure of spiritual well-being with two sub-scales, Meaning/Peace and Faith. The ACS, in collaboration with spirituality researchers at the Rush University Department of Religion, Health, and Human Values, has produced 2 peer-reviewed publications regarding spirituality issues among cancer survivors. The first paper, published in Psycho-Oncology, describes a factor analysis of the FACIT-Sp indicating that a 3-factor solution, in which the Meaning/Peace factor separates into two distinct factors, provides a better fit to the data than the traditional 2-factor solution.18 Building on this analysis, the other publication focused on different domains of spirituality as they vary with cancer survivors' medical and demographic characteristics. Specifically, these results suggest that levels of Meaning, Peace, and Faith do not vary with time since diagnosis and that black survivors and, in some cases, Hispanic survivors have higher levels of Meaning, Peace, and Faith than white survivors. Another paper examined the relationship between spirituality, social support, and life satisfaction among Hispanic cancer survivors in SCS-II.19 Compared to more acculturated Hispanics, those who were determined to be less acculturated (as assessed by questionnaire language completion) reported higher life satisfaction, despite having lower income, less education and more co-morbidities. Spirituality and social support appeared to mediate the relationship between acculturation and life satisfaction. That is, the less acculturated Hispanic survivors reported higher levels of social support and spirituality, which accounted for their higher life satisfaction.

Nutrition and Physical Activity

Lifestyle and health behaviors are important issues for cancer survivors, and both SCS-I and SCS-II have included questions about cancer survivors' nutrition and physical activity (NuPA). An important publication by our group

demonstrated that cancer survivors were generally not compliant with ACS guidelines in the areas of nutrition and physical activity, but were compliant with the recommendation to avoid tobacco.20 While 80-90% indicated that they did not smoke, less than half of the survivors reported meeting the physical activity recommendation and only 20% met the nutritional recommendation to eat at least 5 servings of fruits and vegetables day. This paper, published in the Journal of Clinical Oncology, also demonstrated a cumulative effect of compliance with ACS guidelines, such that those who were compliant with none of the recommendations had the lowest overall QoL whereas those meeting all 3 recommendations had the highest QoL. The two other categories (meeting 1 or 2 recommendations) fell in between, in the expected order. This manuscript elicited a letter to the editor asking about the potential predictors and implications of such non-compliance, to which our group provided a reply, both of which were also published in JCO.21

Another paper investigated the correlates of both positive (healthy) and negative (unhealthy) behavior change among survivors.22 Interestingly, different variables predicted positive and negative behavior change. Negative behavior change was associated with poorer physical and emotional health, while positive behavior change was related to fear of cancer recurrence and spirituality. These psychosocial predictors remained significant even after controlling for relevant medical and demographic characteristics that were significant at the univariate level.

Complementary and Alternative Medicine (CAM)

Several manuscripts based on SCS data have documented the prevalence and correlates of CAM use among SCS participants. A paper published in Cancer identified the medical and demographic correlates of CAM use and how they varied across the 10 cancer types in SCS-I.23 An additional manuscript, also published in Cancer also identified a number of psychosocial factors associated with CAM use among colorectal cancer survivors in SCS-I.24 Another publication, which was produced in collaboration with researchers at Yale University, focused on the identification of factors related to the use of dietary supplements in SCS-I participants.25 Yet another paper examined the relationship between different domains of survivors' spiritual functioning (faith, meaning, and peace) and use of CAM, with results indicating that while meaning and faith were positively associated with CAM use, peace was negatively associated.26

Continuing Care

Continuing care is the newest area of work for the ACSC. Collaborative work with NCI colleagues has led to five co-authored publications between 2011 and 2013 using SPARCCS data. A paper published in JNCI showed that almost half of oncologists reported providing treatment summaries compared to only 20% providing survivorship care plans (SCPs). Further, the study demonstrated that fewer PCPs reported receiving treatment summaries and SCPs than oncologists claimed to provide.27 Another SPARCCS paper found that approximately two-thirds of oncologists discuss survivorship care recommendations with their patients, but only one-third of oncologists discuss who their patients should see for ongoing cancer-related and other follow-up care.28 Other papers have examined whether oncologists or PCPs feel they provide psychosocial support42 and cancer-related follow-up care29 to cancer survivors. Due to the growing need for additional research in this area, the ACS has engaged in two recent activities. First, continuing care focused questions were added to the SCS-1 (Qx3) survey [e.g., Survivorship Care Expectations: degree of responsibility the PCP and Cancer Doctor should assume in your care44; Discussions with PCP and Cancer Doctor regarding role in care; Primary Care Delivery of Survivorship Care Scale.30 Second, the ACS initiated the Cancer Survivor Transition Study which focuses on identifying survivor needs during the transition from acute treatment to post-treatment care.

CONCLUSIONS

The American Cancer Society's cancer survivorship and quality of life research has contributed greatly to our understanding of the long-term effects of cancer and its treatment on the quality of life and functioning of cancer survivors and their caregivers. Through continued research and, importantly, application of this research via informational and supportive programs, the American Cancer Society aims to identify the factors that negatively affect survivors' quality of life and provide resources for cancer survivors and their loved ones to cope effectively with the challenges of this disease.

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PROSTATE: CURRENT TREATMENT AND NEW APPROACH

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In Western countries prostatic carcinoma represents among males the second most common neoplasm and the second cause of death from cancer (Siegel et al., 2015).
Androgen deprivation therapy is the mainstay of treatment for patients with metastatic disease because androgen receptor pathway has a fundamental role in tumour development and progression (Damber et al., 2005).
Androgen deprivation therapy is able to reduce serum testosterone levels leading serological and clinical response in the major part of patients (Damber et al., 2005). Unfortunately, despite initial excellent responses, many patients progress to the castration resistant phase of disease (Damber et al., 2005).
Recently the approval of highly effective therapeutic agents has significantly modified the natural history of metastatic castration resistant prostate cancer (mCRPC) with an increase in overall survival from 9-18 months to approximately 30 months (Tucci et al., 2015).
This amazing new therapeutic landscape is the result of the evidence that castration resistance does not necessarily imply resistance to hormonal manipulations and that many CRPCs remain dependent on androgen receptor pathway (Tucci et al., 2015).
Literature data has been accumulated showing that serum and intra-prostatic androgens remain high despite the significant reduction of serum testosterone levels (Labrie et al., 2009). This indicates that recurrence is not due to true androgen independence, but rather to functional adaptation that allows response in presence of low levels of circulating testosterone (Tucci et al., 2015).
Several mechanisms have been identified to explain this phenomenon: androgen receptor gene overexpression and mutation (Tucci et al., 2015; Chen et al., 2004; Debes et al., 2004), androgen receptor splice variants expression (Tucci et al., 2015) and up-regulation of enzymes involved in synthesis of androgens, as cytochrome P450 17 alpha-hydroxylase and C17-20-lyase (CYP17) (Chen et al., 2004; Debes et al., 2004).

The best knowledge of disease progression biological mechanisms led to development of innovative new generation hormonal treatments as abiraterone and enzalutamide (Tucci et al., 2015).
Abiraterone acetate is an oral agent able to suppress the activity of CYP17A1 enzyme leading to the reduction of testosterone synthesis in testis, adrenal glands and prostatic cancer cells (Agarwal et al., 2010).
Enzalutamide is an oral androgen receptor antagonist more potent than bicalutamide and able to inhibit androgen receptor nuclear translocation and binding to DNA (Scher et al., 2010).
Two phase III studies enrolling CRPC patients progressing during or after docetaxel, COU-AA-301 and AFFIRM, showed an overall survival improvement with abiraterone (median OS 14.8 vs 10.9 months; hazard ratio [HR] 0.65, 95% CI, 0.54–0.77; $p < 0.001$) (De Bono et al., 2011) and enzalutamide (median OS 18.4 vs 13.6 months; HR 0.63, 95% CI, 0.53–0.75; $p < 0.001$) (Scher et al., 2012), respectively.
Recently the COU-AA-302 trial showed the efficacy of Abiraterone in improving overall survival of asymptomatic and mildly symptomatic chemotherapy-naive metastatic CRPC patients (16.5 vs 8.3 months; HR: 0.53, 95% CI, 0.45-0.62; $p<0.001$) (Ryan et al., 2015) and in the PREVAIL trial, enzalutamide demonstrated a statistically significant 29% reduction in the risk of death (HR 0.70, 95% CI, 0.59–0.83; $p = 0.0001$) (Beer et al., 2014).
Additionally, in 2010 cabazitaxel, a new taxane, showed its efficacy in terms of overall survival, compared to mitoxantrone, in mCRPC patients progressing on or after being treated with docetaxel (15.1 vs 12.7 months; HR 0.70, 95% CI, 0.59–0.83; $p < 0.001$) (de Bono et al., 2010). The IMPACT phase III trial also demonstrated the efficacy of Sipuleucel-T, an immunotherapeutic agent, in improving overall survival in asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC patients (25.8 vs 21.7 months; HR: 0.78; 95% CI, 0.61-0.98; $p = 0.03$) (Kantoff et al., 2010).
Finally, in 2013 the ALSYMPCA phase III study demonstrated, in CRPC patients with symptomatic bone metastases, the efficacy of radium 223, a α-emitting radium isotope, in improving overall survival (14.9 months vs 11.3 months; HR = 0.70; 95% CI, 0.58 to 0.830; $P<0.001$) and delaying time to first skeletal symptomatic event (Parker et al., 2013).
Considering this evolving therapeutic landscape, oncologists today face several therapeutic challenges in CRPC.
One of these challenges is the choice of the most efficacious sequence. Indeed, there are no head-to-head studies comparing the various treat-

ments nor large prospective sequencing trials (Tucci et al., 2015).
Another important challenge is the best knowledge of resistance mechanisms to new therapeutic agents. In particular, we known that approximately one third of patients treated with abiraterone and 25% of those treated with enzalutamide show primary resistance to these agents (Buttigliero et al., 2015).
Therefore, there is an urgent need to find predictive factors of response to each available drug in order to personalize treatment and to maximize benefits (Tucci et al., 2015; Buttigliero et al., 2015).

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MOST FREQUENT TOXICITY AND NEW SIDE EFFECTS OF NOVEL DRUGS AND/OR TREATMENTS OF PROSTATE CANCER

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The treatment of castration-resistant metastatic prostate cancer (mCRPC) has evolved considerably over the last decade.
In 2004, two phase III trials demonstrated that the combination of docetaxel and prednisone significantly prolonged survival in comparison with mitoxantrone plus prednisone, thus making it the new reference first-line therapy [Tannock et al, 2004; Petrylak et al., 2004] More recently abiraterone acetate (a new agent targeting CYP17, which plays a central role in steroidogenesis) and enzalutamide (a new drug targeting the androgen receptor machinery) have demonstrated a survival gain as first- and second-line therapy during the castration resistance phase of the disease [de Bono et al, 2011; Scher et al., 2012; Ryan et al., 2013; Beer et al., 2014; Ryan et al., 2015], and cabazitaxel (a new molecule belonging to the taxane family) has significantly increased the overall survival of mCRPC patients received first-line Docetaxel [de Bono et al., 2010]. Moreover radium 223, an alpha-emitter that acts as a bone-seeking agent, showed a significant improvement in overall survival compared to placebo [Parker et al., 2013]. The different toxicity profile of the available new agents has to be factored in the decision making process, mainly considering that patients with mCRPC are usually elderly or very elderly.

a) Docetaxel

Myelosuppression is the most frequent adverse event category associated with the use of docetaxel. The incidence of grade 3-4 neutropenia in TAX 327 trial was significantly higher in docetaxel group compared to mitoxantrone group (32 vs 22%), while the other hematological toxicities (febrile neutropenia, anemia and thrombocytopenia) were similar [Tannock et al, 2004]. It is noteworthy that the weekly schedule, which failed to demonstrate a survival benefit compared to mitoxantrone, had a lower rate of hematological side effects than the 3-week schedule. Among non hematological toxicities, docetaxel administration may produce alopecia (65%),

nausea and/or vomiting (42%), diarrhea (32%), nail changes (30%), sensory neuropathy (30%), and stomatitis (20%).

b) Cabazitaxel

Neutropenia is the most frequent side effect associated with cabazitaxel administration: in the pivotal TROPIC trial the rate of grade 3-4 neutropenia was 82% [de Bono et al., 2010]. It is clear that this finding may reflect a more advanced disease and may depend by the extent of prior therapy in the first line as confirmed by the relevant difference in the incidence of grade 3 or 4 neutropenia observed in the control group of the TAX 327 and TROPIC trials, both treated with mitoxantrone and prednisone (22% vs 58%,respectively). It is noteworthy that in the TROPIC trial, primary prophylaxis with granulocyte-colony-stimulating factor (G-CSF) was not allowed in the first cycle, but G-CSF use was permitted after a first occurrence of neutropenia. An adequate prophylaxis of neutropenia with G-CSF may significantly reduce the incidence and severity of cabazitaxel-associated neutropenia as demonstrated by the outcomes of several expanded and compassionate use programs [Wissing et al., 2013; Heidenreich et al., 2013; Bracarda et al., 2014; Castellano et al., 2014] . Among the non-hematological side effects of cabazitaxel, the most relevant is diarrhea which occurred in 46% of the patients enrolled in the TROPIC trial (6% grade 3-4) .

The TROPIC trial included 139 patients aged >75 years: 69 (18%) in the cabazitaxel group and 70 (19 %) in the mitoxantrone group. In these patients, the adverse events rates were greater than in the younger population in terms of diarrhea and neutropenia (55.7% and 24.2% vs 44.5% and 17.6%).

The standard dose of cabazitaxel is 25 mg/m2 every three weeks but, as requested by FDA, a reduced dose of 20 mg/ m2 was tested in the PROSELICA trial and the same reduced dose was also tested in the cabazitaxel first-line pivotal FIRSTANA trial. Recently available preliminary results of these trials suggested that the drug administered at 20 mg/ m2 may be better tolerated [De Bono et al., 2016; Sartor et al., 2016].

c) Abiraterone Acetate

Abiraterone exerts its antitumor effects mainly by a selective cytochrome P450 (CYP17A1) inhibition, blocking the synthesis of androgens, leading to an effective systemic and intra-tumoural suppression of androgen

production. The block of cytochrome CYP17 is associated with increased mineralocorticoid levels that result in hypokalemia, fluid retention, hypertension and cardiac disorders. These side effects are largely reduced by the concomitant administration of low-dose glucocorticoids.
In the pivotal trial leading to the drug approval in post-docetaxel setting [3] the most frequent grade 3-4 side effects associated to the abiraterone administration were hypokalemia (2%), fluid retention/edema (1%), hypertension (5%), cardiac disorders (8%), and hepatotoxicity (8%).
A post hoc analysis of the COU-AA-301 trial by Mulders et al. confirmed the abiraterone efficacy also in in patients ≥ 75 years and showed that the drug's safety profile in the elderly patients were similar to those recorded in the overall patient population [Mulders et al., 2014]. In the elderly subgroup treated with abiraterone, the authors observed a slightly higher incidence of cardiac disorders (particularly atrial fibrillation and tachycardia) than in those receiving prednisone, but without a significant increase in treatment interruptions, treatment discontinuations or the incidence of adverse events leading to death.
In the COU-AA-302 trial which led to the approval of abiraterone in the first-line setting [Ryan et al., 2015] , the most frequent grade 3-4 side effects associated to the abiraterone administration were hypokalemia (4%), fluid retention/edema (3%), hypertension (1%), cardiac disorders (5%), and hepatotoxicity (4%).
The efficacy and safety of AA in elderly chemo-naïve patients has been evaluated in a post hoc analysis of 350 patients aged >75 years enrolled in the COU-AA-302 trial [Smith et al., 2015]: a higher rate of abiraterone discontinuations due to adverse events was observed in the elderly patients than in those aged <75 years (15% vs 5%). The safety profile was similar in both groups with a higher incidence of grade 3-4 AEs (57% vs 40%) and peripheral edema.

d) Enzalutamide

In AFFIRM trial, which led to the approval of enzalutamide in the post-docetaxel setting, the enzalutamide administration produced fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache [Scher et al., 2012]. Hypertension was observed slightly more often in the enzalutamide group compared to placebo (6.6 versus 3.3%).
In AFFIRM trial, five cases of seizures were reported in the enzalutamide group. Most of these cases were transient and did not recur after the

drug discontinuation. Moreover, the relationship between the seizure occurrence and enzalutamide administration was unclear: two patients had known brain metastases, one received intravenous lidocaine immediately before the seizure, and one patient had a history of alcohol abuse and brain atrophy and the final event was reported as syncope, but had features suggestive of a seizure.
The published results of a post hoc subgroup analysis of the AFFIRM trial revealed comparable clinical outcomes and toxicities in mCRPC patients aged <75 and >75 years treated with enzalutamide after docetaxel failure, and showed that the tolerability of the drug in the elderly patients were consistent with those observed in the pivotal clinical trial as a whole [Sternberg et al., 2014].
In the PREVAIL study, the pivotal trial in first line setting, the most common adverse events in the enzalutamide group were fatigue, back pain, constipation and arthralgia [Beer et al., 2014]. One case of seizure was observed in the enzalutamide arm but also in placebo arm one case of seizure was observed.
Graff et al. reported a pre-planned subgroup analysis of the chemo-naïve enzalutamide-treated patients aged >75 years treated in the PREVAIL trial [Graff et al., 2016]. The elderly patients in either treatment group had a higher incidence of any grade >3 adverse events, falls, fractures, decreased appetite and asthenia than the patients aged <75 years, and the adverse event rate was higher in the elderly in the enzalutamide arm than those in the placebo arm, but only the incidence of falls remained higher in the enzalutamide -treated patients after adjusting for the length of treatment exposure. The authors concluded that enzalutamide is safe and well tolerated in the elderly.

e) Radium 223

Radium-223 is a radioactive isotope of the radium which, chemically similar to calcium, is able to form complexes with bone mineral hydroxyapatite in areas of active bone remodeling, as occurs at skeletal metastases. Radium-223 is an α-emitter which induces non-repairable double-stranded DNA breaks. Compared to the α-emitters, the range of α particles emitted by radium-223 is much shorter, producing its cytotoxic effect in a small area, with a limited damage to surrounding tissue. In the ALSYMPCA pivotal trial observed grade ≥ 3 side effects were: neutropenia (3%), thrombocytopenia (6%) and anemia (13%) [Parker et al., 2013]. The incidence

of non hematological side effects was very low and probably not related to the drug administration: fatigue (5%) and bone pain (21%).

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PROSTATE: TAKE HOME MESSAGE

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Prostate cancer is common in men > 50 years. There is no consensus regarding optimum management of best sequence treatment in metastatic prostate cancer.
New drugs were approved recently for the treatment of metastatic prostate cancer.
The phase III CHAARTED trial found that docetaxel improved overall survival compared to ADT (androgen deprivation therapy) alone in metastatic hormone naive disease.
The COU-302 trial demonstrated that abiraterone acetate plus prednisone improved overall survival in men with chemotherapy naive, asymptomatic or mildly symptomatic metastatic castrate resistant prostate cancer. The main specific side effect reported were hypertension, edema, hypokalaemia and cardiac events.
Enzalutamide was tested versus placebo in the same setting in the PREVAIL phase III trial. Enzalutamide improved overall survival and the main side-effects reported of Enzalutamide were fatigue, asthenia and hypertension.
The bone targeted alpha emitter Radium-223 was tested versus placebo in patients with mainly bone symptomatic metastatic castration resistant prostate cancer. Radium 223 improved overall survival and time to first symptomatic skeletal event. The main toxicities of radium—223 were diarrhoea and thrombocytopenia.
Docetaxel has demonstrated in phase III trial to improve overall survival compared to mitoxantrone in men with metastatic CRPC, the side-effects of docetaxel were fatigue, alopecia, myelosuppression, diarrhea, neuropathy and peripheral edema.
The optimal sequence of abiraterone, enzalutamide, radium-223 or docetaxel as first line in metastatic castration resistant prostate cancer is unknown. The patients should be informed of the potential benefit and side-effects of the different optional. The sequence decision should also make according the patients co-morbidities.
Cabazitaxel was tested against mitoxantrone in phase III TROPIC trial in

post-docetaxel setting; it improved overall survival but was associated with febrile neutropenia and diarrhea.
In the COU-301 trial, Abiraterone acetate plus prednisone versus placebo plus prednisone improved overall survival in post docetaxel setting.
In the AFFIRM phase III trial, Enzalutamide has shown to improve overall survival, compared to placebo in post docetaxel setting in men with metastatic CRPC.
In conclusion, abiraterone or enzalutamide should be recommended in asymptomatic or mildly symptomatic patients with chemotherapy naive metastatic CRPC; radium-223 should be recommended for patients with bone-symptomatic metastatic CRPC without visceral disease. Docetaxel should be recommended for patients with metastatic CRPC.
In the post-docetaxel setting, abiraterone, enzalutamide, cabazitaxel and radium-223 are recommended options in metastatic CRPC according preference and co-morbidities of the patients.

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THE RELATIONSHIP COUPLE IMPLICATIONS

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Abstract
Sexuality is correlated to the quality of a patient's life in the sense that a negative alteration to one's sexuality inevitably manifests into a decline in their quality of life. Therefore, targeted intervention practices to balance a patient's sexuality, by means of correcting a given state of abnormality, universally affects the patient as it increases their quality of life.
Interventional practices to correct the sexual state of abnormality begin with listening to the suffering patient, and continue by addressing the physical and psychological problems present. Working together to set a prompt and correct approach should be the basis of the doctor-patient relationship, for it covers all components of the health sector.
The diagnosis of cancer is widely met with devastation by those diagnosed and their loved ones. Furthermore, if the diagnosis regards an important sphere of the person's sexuality or sexual identity, the emotional distress can be even more devastating. Prostate cancer, for example, creates physical complications such as erectile dysfunction and urinary incontinence that are associated with psychological problems such as anxiety, denial, social unrest depression. In this manuscript we will address the problems that often occur when we are faced with a patient who has prostate cancer, underwent treatment of sexual dysfunction, and yet still deals with complications. We will provide guidelines on possible strategies to manage the conflicts that arise due to psychophysical implications.

Introduction
Cancer diagnosis inevitably leads to immediate thoughts of survival, so the patient's attention focuses on treatments required to achieve this, and their consequences.
The diagnosis of prostate cancer brings a number of possible emotional difficulties connected on one end to the choice of treatment, and secondly to the preservation of self - image including the level of body perception, and the management of social and relational life.
According to medical literature in Europe, prostate cancer kills at least one

man every 6 minutes, resulting in more than 90,000 deaths every year [1]
The treatment of prostate cancer causes specific symptoms that affect sexual function and thus, the patient's partner.
Questions that often meet the patient are:

- How will my life be moving forward?
- Can I ever return to the person I was before?
- How will this disease affect my sexual life?
- Will my partner leave me because of this disease?

The individual during treatments is overcome by a whirlwind of feelings, thoughts and sexual desires, especially at the end of treatment. The individual often experiences a drop in libido, and in this period the patient needs to have a partner who loves him, even though it lives some discomfort due to the fear of losing their "masculinity." The individual can be reluctant to openly share information about his sexuality. This closure affects the couple's relationship, as it creates a strong discomfort for the patient, who may develop a defensive attitude. Therefore, the relationship evolves in a polluted manner by a lack of communication and expression. It is evident that erectile dysfunction declines the quality of life of the affected patients. This is because of the negative effects erectile dysfunction has on psychological and marital aspects for the patient and their partner [2,3,4,5.]

The couple

After the illness and subsequent treatments, the couple's relationship undergoes a considerable change. The consequences depend on the nature of the couple's relationship prior to the disease, for there needs to be an understanding of what kind of relationship the couple had before. According to this relationship, one can better evaluate the presence of dialogue, psychological resources of the couple, conflict management, the relationship within a social context, presence of children etc. It should also be considered whether or not the couple talked about sexuality before the illness.
It should also be made an assessment of the functionality of the previous couple to the disease. The disease can fortify in some cases the couple or crush definitely. A strong relationship is very important.
Communication issues may be a cause of conflict. For example, in the case of a couple with poor communication, if there is difficulty on the part of the woman to have an appropriate attitude, in these cases there is a misunderstanding, the male is fear of being rejected, starts to move away due to a strong incomprehension.

Bigger is the uncomfortable if she wants sexual contact and the man does not have the desire, there is in him a conflict between the desire and the dysfunctional thought of having to satisfy his partner.
You cannot separate the notion of sexuality from the psyche, as psychological impairment is affected by different emotions. An emotion that often manifests itself within the pair is the sense of loneliness, as no communication and therefore a lack of clarity strains the relationships and isolates the pair. The first step is to become aware of the presence of this issue.
Ages influences a person's sexuality, as over the years sexual desire can decrease due to the changes in our bodies. The man at this stage needs more than of affectivity and sexuality, the partner is not always able to read the needs of the patient. The unspoken creates a number of misunderstandings as to further deteriorate the relationship. As part of man that happens feels more fragile, erectile dysfunction makes him feel less of a man less powerful begins to take a marginal attitude to the tiles and below the family
A recurring question that the spouses of prostate cancer patients often ask is:
"How can I help him? I do not know how he is feeling because he doesn't express these feelings with me. So, I can not accommodate his needs."
Because of strains put on their relationship due to the cancer, the women tend to lose the desire for intimacy upon itself .[6,7]

Sexuality
The notions that come to mind when thinking about sexuality often include the desire to experience pleasure and togetherness, to manifest one's attraction for another person, to express our drives and desire, etc. Compared to the woman, the man sees sex not necessarily related to procreation but goes further. Each person lives their sexuality in a personal way, both from the point of view of the frequency of sexual activity choice in itself. Each applies its own way, and pattern, but it is also true that sometimes the individual allow themselves to schemes already established. In the expression of our sexuality affects a lot our affective education, the way our parents taught us. We are all influenced by external behavioral patterns, by others' expectations of us, and by societal rules we believe we must abide by. Without ignoring the role that the media covering messages about sex education. Sexuality has, therefore, aspects

and physical values, relational and social factors that include the whole person in its integrity, and any sexual problem results in an attack on the whole person and to esteem. A sexuality fully shake, through the sexual gratification process strengthens the identity, while its failure generates a spiral of events, which ultimately undermine deeply the basics.

Anxiety, failure, various attempts to try again constitute the initial moments of a sexuality dysfunctional. Follow the fear and avoidance, sometimes it occurs a final attempt, with outcome, for the most part, in a depressive framework in which the identity of torque changes in a depressive attitude, sometimes up to the dissolution of the union.

Every sexual disorder deprives the person of its pleasure and can lead to a stress personal, psychological and somatic subtle, but significant, with development of similar feelings in men and women: despair, frustration, embarrassment, fear of failure, anger, guilt and shame, fear of rejection, self-guilt, depression, grief and loss, betrayal, fear abandonment. All these aspects must be taken into account both in the study of "normal" sexuality, both a description of sexual problems.[8]

Oftentimes after a patient undergoes a cancer treatment path for prostate cancer, the so-called "performance anxiety," evolves, as a series of doubts arise regarding the probability of achieving a complete sexual encounter. Sexual dysfunction also may be associated with depression, anxiety, relationship conflict, and loss of self-esteem.

It can happen that the sexual dysfunction manifested by man is conditioned by a psychological component. We return to performance anxiety, and the fear of failure. It is evident that the situation will not be resolved by the individual if he feels rejection, and this is why open communication is very important for cancer patients, also inside the relationship with his partner. The long-term emotional impact of being unable to have a child after cancer can be extremely distressing. Advances in knowledge about how cancer treatments may damage fertility, as well as newer techniques to preserve fertility, offer hope to patients who have not achieved their desire to bear children prior to their cancer diagnosis. Unfortunately, many cancer patients are still not informed about potential changes to their sexual function or fertility, and all modalities of fertility preservation remain underutilized. After their treatment, many patients continue to have unmet needs regarding information about restoring sexual function or becoming a parent.

What actions to resolve the conflict?

If there is a refusal to accept the disease, problems with sexuality may only worsen. The first step is undoubtedly to accept the illness, although this is not immediate, it is a crucial step in moving forward psychologically. It is also very important that the patients makes accurate assessments of the principal variables in their lives, including relationships, intimacy, their body, their partners, their family and social environment.

Reactions can range from rejection and social withdrawl, the need for acceptance and need for sexual intimacy. The man usually feels a need to express himself physically and sexually, proving he is capable.

It becomes necessary at this stage to talk with partners and to express their feelings.

In cases where the patient can not recover his previous sexual patterns, then it would be desirable to consult a specialist. It is recommended that both the patient and their spouse or partner consult a sex therapist. In cases where the patient has a deeper psychological disturbance, they should consult a psychotherapist and embark on a path to recovery from the psychological damage provided by the cancer.

The sex therapist provides support and concrete practices so that the patient can perform targeted exercises at home, alone or with their sexual partners. During the sessions with the therapist, it is important for the patient to discuss their own past experiences and feelings. The story of the patient's life, including their current situation and relationships, are important to discuss also, but by staying within the parameters of solving the sexual problem. Psychotherapy instead focuses on the psychological life of the subject, on conflicts and the fears that can adversely affect the sexual sphere. The success of therapy is largely based on a therapeutic relationship characterized by respect, understanding and human warmth between the various parts involved. Men who have erectile problems after cancer treatments often lose the ability to control the moment of orgasm. In many cases the problem can be solved by learning to control his arousal. It is crucial that we reject the fear of seeking the help of a figure like a sexologist and psychologist who, in addition to accepting the patient's feelings and emotions, can allow the patient to develop, accept, learn an alternative to their sexuality. After a diagnosis of cancer that involves the sexual sphere, many men, in fact, live feelings of anger, rejection and self-reproach which can then lead to anxiety or depression. Seeking professional help can allow the patient to confront and control their fears.

You can ask for psychological support discussions and individual or group psychotherapy.
A patient's sex life does not end in the operating room.
The following are some guidelines provided by the American Society of Sexology to reflect on their lives of the first report, during and after the disease.
There are no fixed rules to living a happy sex life. Starting from the idea that sex is not limited to sexual intercourse will help you discover (or rediscover) other forms of intimate, emotional relationships.
Recognize the couple requirements. Seek out dialogue and collaboration with your partner by talking to each other about fears and desires.
Compare the past and present. How was the patient's sexuality before cancer? Was it satisfactory? Did the couple speak of their physical relationship and its quality? Has anything changed in the perception of one's body after the illness? Are relationship problems arising solely from sexual difficulties?
Cultivating the relationship. Do not only focus on the sexual act. It may be nice to rediscover everyday life: pay attention to small details, mutual surprises, experiences that unite one another.
Research on interventions to improve the sexual function and satisfaction in cancer patients and survivors suggests that a multidisciplinary approach, combining medical and psychosocial care, is the most effective strategy. [9,10,11]
An approach that is taking more and more space is the narrative medicine. The narrative, which is the cornerstone of Narrative Medicine, is the fundamental means by which people identify the meaning of their experiences, and above all those painful, for cope with "the attack identity" that often the disease represents.[12] What happens if it's a man the partner ? The reaction of the partners is the same? There are precautions that physicians should follow. These is another reason of the importance of medicine narrative.
In conclusion, it can be safely said that in order to prevent psychological consequences related to subsequent sexual, physical problems due to treatment, it is very important that patients are supported along with partners from the time of diagnosis. A psycho-educational path that eliminates doubt and instead clarifies, they can learn problem solving strategies on stress management. But above all, it is important that the doctor devotes time to developing a trusted relationship with the patient in order to accommodate for their needs narration. These important factors

will not only improve collaboration between doctor and patient, but they mainly serve to improve the quality of care and life for both the patient and their partner. Because it is important that the Quality of Life (Quality of Life, QoL) is related to physical functioning, cognitive and social relations functions, to the perception of general health, mood, to pain, vitality, the global life satisfaction, the Sexual Life Quality is related anxiety in starting a sexual relationship, insecurity for the provision, to the satisfaction this and the sexual life, sexual boredom, satisfaction for a treatment of a sexual dysfunction. The quality of couple life is related to satisfaction in the report by the partners, the feelings toward the partner, the ability to developing intimacy, physical and sexual, to the partner's satisfaction with sex life. Alteration of sexuality is not a problem that concerns only the individual affected in their roots identity, but correspondences in relational context and often even social (relations with the world of work, friends, etc.).[13,14,15]

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CURRENT TREATMENT AND NEW APPROACHES IN GERM CELL TUMORS

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Germ cell tumors represent the 1% of all male tumors and the most frequent male tumor between 15 and 40 years of age. More than 99% of patients with stage I and 80% of patients with metastatic germ cell tumors at diagnosis can be cured with orchiectomy, chemotherapy and radiotherapy or further surgical approaches when needed. Patients treated with first-salvage chemotherapy can be cured in 50% of cases. The main clinical objective in early stages and in good prognosis patients has changed in the last years, and it has become of major importance to reduce treatment-related burden maintaining the efficacy of treatment without compromising the excellent long-term survival rate. In poor prognosis patients, there is the necessity to improve clinical outcome with more intensified treatments, but new approaches are needed in cases not curable with available treatments. This review article summarizes the current treatment and new approaches for patients with germ cell tumors.

Germ cell tumors (GCTs) are highly curable diseases due to the exquisite chemo-sensitivity (Beyer et al., 2013; Gori et al., 2005). GCT are derived from testis in 90-95%of cases and from extra-gonadal origin in the last 5-10% mainly retroperitoneum and mediastinum (De Giorgi et al., 2008). The incidence of GCT/testicular cancer is 3 to 6 new cases per 100,000 males / per year, with an increased incidence observed over the last 10-20 years.

Testicular GCT is usually suspected at clinical examination, but a scrotal ultrasound is required to confirm the diagnosis. The results of tumor marker determination should be available at the time of orchiectomy and have to be reevaluated thereafter. Staging should be completed with computerized tomography (CT) scan of the chest, abdomen and pelvis (chest X-ray sufficient for stage I seminoma only). About 40% of GCTs are seminoma, while 60% are mixed or non-seminomatous tumors. Semen anal-

ysis should be recommended in these patients. Semen cryopreservation should be better discussed with patients before orchiectomy (De Giorgi et al., 2008; Oldenburg et al.,2015).
More than 99% of patients with l stage I and 80% of patients with metastatic testicular GCTs are cured with current standard treatments (De Giorgi et al., 2008). Two main options can be considered in stage I seminoma after orchiectomy: surveillance and one single cycle of chemotherapy with carboplatin AUC 7 with cure rates close to 100% in both cases. Radiotherapy is reserved to selected elderly cases only due to the potential impact of secondary tumors. In stage I non-seminoma, patients can be stratified according to presence of vascular invasion. In cases without vascular invasion, surveillance is the main option, whereas one cycle of chemotherapy with PEB (cisplatin, etoposide or bleomycin) is reserved to selected cases mainly those unsuitable for surveillance. In patients with stage I non-seminoma with vascular invasion one cycle of PEB is suggested, and also retroperitoneal lymphadenectomy can be considered in selected centers with high expertise for this surgical approach; surveillance is an alternative option for these patients with a risk of recurrence of 40-50% (Kollmannsberger et al., 2015; Daugaard et al., 2014).
The availability of highly effective chemotherapeutic regimens led to the development of a risk-based stratification system for patients with metastatic GCT. The risk-based system was developed by the International Germ Cell Cancer Collaborative Group (IGCCCG), and published in '90s (International Germ Cell Consensus Classification, 1997). In 2017 a new version of this classification will be available. The histology (non-seminoma vs seminoma), the primary and metastatic visceral sites, and the level of tumor markers: alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (betaHCG) and lactate dehydrogenase (LDH) contribute to this classification of prognostic groups of advanced GCT (International Germ Cell Consensus Classification, 1997). In particular, primary madiastinal nonseminoma has a poor prognosis independently from other factors with resistance to chemotherapy (Bokemeyer et al., 2002; Banna et al., 2006; Albany et al., 2013). Pulmonary metastases do not deserve a poor prognostic impact in these patients, so the definition of visceral metastases include only brain, bone or liver metastases (International Germ Cell Consensus Classification, 1997). Based upon these factors, in the IGCCCG classification, patients were divided into good, intermediate, and poor prognosis groups (International Germ Cell Consensus Classifi-

cation, 1997). A recent analysis of the five-year survival rate for the good- and intermediate-prognosis groups subsets appeared similar to those seen in the IGCCCG study in '90s, (90% and 75%, respectively), but there was a 5-year overall survival rate of 71% versus 48% for poor-risk patients (Sonneveld et al., 2001). Best supportive care including the use of granulocyte-colony stimulating factors (G-CSF) have allowed a correct dose intensity in poor prognosis patients ameliorating survival rates in the last 10-20 years (Tanaka et al., 2013). In addition, the increase the cure rates have been done also to the better management of post-chemotherapy residual masses with improved surgical resection (Fizazi et al., 2001; De Giorgi et al., 2005; Beck et al., 2005). Finally, the improved outcomes in poor-prognosis patients are related to the better management of salvage treatments including the use of multi-cycle high-dose chemotherapy in these patients, and the use of newer chemotherapeutic agents (De Giorgi et al., 2002; Kopf et al., 2006; Rosti et al., 2002; Pedrazzoli et al., 2003; Einhorn et al., 2007; Lorch et al., 2011; De Giorgi et al., Ann Oncol 2005; De Giorgi et al., Br J Cancer 2005). In patients progressing or relapsing after first-line chemotherapy, a new scoring system has been recently validated [24]. According to this prognostic score visceral metastases on brain, bone or liver deserves a poor prognosis even in that setting, even if, mediastinal primary GCT presents the poorest outcome in spite of the support of intensified chemotherapy (International Prognostic Factors Study Group, 2010).

Cisplatin-based combination salvage chemotherapy produces long-term remissions for about 60-80% of seminoma patients who relapse after first-line chemotherapy, and 40-60% of non-seminoma patients, depending on risk factors. Good prognostic factors are considered low markers and/or tumor volume, a complete remission after first-line chemotherapy, gonadal primary and the absence of visceral metastases. Poor prognostic factors are an incomplete response, high markers and/or tumor volume, mediastinal primary tumor, the presence of visceral metastases and late relapse (International Prognostic Factors Study Group, 2010). Standard regimens for relapsed disease are: PEI (cisplatin, etoposide, ifosfamide), VeIP (vinblastin, ifosfamide, cisplatin), or TIP (paclitaxel, ifosfamide, cisplatin). High-dose chemotherapy (HDC) has been largely investigated in GCT. HDC is an option as second-line treatment and is a referring option in third-line or later therapy and in cisplatin-refractory patients, two or three courses of high-doses of carboplatin and etoposide (tandem HDCT) seemed a possible option, with long-term remissions achieved

in 45% of the patients (Lorch et al., 2011; De Giorgi et al., Ann Oncol 2005). The prognosis of patients with absolutely refractory GCT is very dismal, with cisplatin-based regimens inducing long-term remissions in less than 5% of cases. In these patients, clinical trials or treatment with agents such as gemcitabine, paclitaxel and oxaliplatin have been tested. For patients with a good performance status and adequate bone marrow function, combination regimens of two of these agents (e.g., gemcitabine plus oxaliplatin, gemcitabine plus paclitaxel and oxaliplatin) could be suggested, since at least a small percentage (5-15%) of patients may again reach long-lasting remissions (De Giorgi et al., 2006; Kollmannsberger et al., 2004; Oechsle et al., 2011). Residual tumors after salvage chemotherapy should be resected especially after marker normalization or when a marker plateau is reached (Eggener et al., 2007). In the case of marker progression after salvage treatment and the lack of other chemotherapeutic options, resection of residual tumors should be considered if complete resection of all tumor seems feasible (about 25% long-term survival may be achieved). Several new agents and targeted therapies have been tested in the last years, including imatinib, trastuzumab, gefitinib, sunitinib, pazopanib, everolimus with no promising results. Immuno-oncological drugs as immune-checkpoint inhibitors are in development even in these tumors (Feldman et al., 2014).

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GERM CELL TESTIS TUMORS MOST FREQUENT TOXICITY AND NEW SIDE EFFECTS OF NOVEL DRUGS AND/OR TREATMENTS

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Germ cell tumors (GCT) account for approximately 1-1.5% of all malignancies in men. In Italy tumors of the testis are the most common malignancy in young males between 15 and 40 years of age. The incidence of testicular cancer is 3-6 new cases per year with an increase in incidence observed over the last 30 years. GCTs are among a unique numbers of neoplasms where biochemical markers play a critical role. Finally, it is a model of curable cancer. About 95% or so are primary tumors of the testis, while 5% of cases there is a primary extragonadal, most frequently in the mediastinum and retroperitoneum. In 40% of cases it is pure seminoma, while about 60% are non-seminomatous or mixed tumors. Testicular cancer is usually suspected on clinical examination. A testicular ultrasound is needed to confirm the clinical suspicion. The histological diagnosis is based on the surgical removal of the testicle with inguinal orchiectomy. In patients who present with primitive extragonadal disease is necessary to perform a biopsy of the lesion, with less invasive procedure. In metastatic patients initially with poor prognosis, in which chemotherapy should be initiated as soon as possible, it may be necessary to postpone the intervention of orchiectomy after the first cycle or after the end of chemotherapy. The results of the assay of tumor markers alpha-fetoprotein and beta gonadotropin chorionic must be available before orchiectomy and reassessed after surgery. After complete excision of the tumor dell' alpha-fetoprotein values and beta chorionic gonadotropin normalize after 5-7 days and 2 days respectively. Staging must be completed with computed tomography of the chest and the entire abdomen.

In general, patients presenting with testicular cancer are divided into seminoma or non-seminomatous germ cell tumors (NSGCT). Management is based on volume of disease assessed using radiological staging and tumor marker level after orchiectomy. In low volume disease the goal is to decrease treatment related morbidity while maintaining a high cure rate. In

patients presenting with advanced disease, especially those belonging to the intermediate and poor risk category, the goal of treatment is to improve response to chemotherapy with acceptable patient morbidity.

The prognosis for this stage is great with a survival rate close to 100%. The three treatment options after orchiectomy are chemotherapy or radiation or surveillance.

Radiation. The most important prospective studies in this setting showed that 20 Gy in 2 Gy daily fractions is ideal, though, carboplatin has an equivalent curing effect.

Surveillance. Surveillance of seminoma patients in stage I is now increasingly preformed. Disease relapse while on surveillance is seen in 15–20%, and is confined mainly to the retroperitoneum. Some groups tried to use a model based on high risk for relapse (primary testis tumor >4 cm and rete testis involvement) to direct management to radiation or carboplatin. Nonetheless, using this approach is not sufficiently accurate and 65% of patients may receive unnecessary treatment.

Chemotherapy. Single agent carboplatin is the accepted alternative to radiation and surveillance. One or two cycles of carboplatin have reported relapse rates of 1.8–8.6%.

Management of Relapse. Low volume retroperitoneal disease (i.e., less than 5 cm) may be cured by radiation. Large bulky disease or involvement of other organs is better treated by chemotherapy. Most cases may be cured by three courses of bleomycin, etoposide and cispatin (BEP) or four courses of EP. Rare cases of failure of primary chemo may be salvaged by local radiation or second line chemo therapy.

Data accumulated in studies managing stage II seminoma show that for tumor size up to 5 cm radiation is an acceptable treatment modality with a 5-year relapse rate of up to 9%. Bulkier disease is best treated by chemotherapy with relapse rates of 6–13.5%. Recent studies as in SWENOTECA have shown the superiority of chemotherapy also in lower stages—seminoma IIa/b. The primary consideration for choice of therapy is chemotoxicity in older age patients where radiation may have fewer side effects. Radiation fields in this setting are similar to stage I, limiting pelvic radiation to the level of the acetabulum.

A residual mass after radiation or chemotherapy is a unique challenge. In contrast to NSGCT post-chemotherapy residual disease where teratoma or cancer may be frequently found, most residual seminoma masses harbor fibrosis or necrosis. PET- CT may reliably indicate the presence of

active tumor; therefore a negative PET-CT may allow observation even in large redial masses. Some centers advocate resection of all masses larger than 3 cm, though, this may be a difficult undertaking due to the desmoplastic reaction and adherence to the main blood vessels.

It is long known that the risk of occult metastatic disease (not identified on imaging) is dependent on the presence of lymphovascular invasion (LVI) in the tumor. LVI is present in about 30% of cases and the risk of recurrence is about 50% with LVI versus 15–20% without LVI. Another less accepted risk factor is embryonal predominance, with controversial data among different studies. Recurrences occur most commonly in the retroperitoneum, with the majority diagnosed within 2 years of orchiectomy. Management options for CSI NSGCT include surveillance, RPLND, and adjuvant chemotherapy.

Surveillance. The rationale for surveillance among patients with NSGCT is that studies have shown that approximately one in four patients will recur and require salvage treatment. When studies revealed the importance of LVI as a prognostic factor for recurrence, risk-adapted approaches with surveillance or adjuvant treatment were implemented. At present, some centers advocate surveillance for all NSGCT, consequently no patient will be treated unnecessarily; however, 50% of those with LVI and 15% of the patients without LVI will later need salvage treatment.

RPLND. Although not frequently used today, the advantage of RPLND is that it represents both a diagnostic and a therapeutic procedure. RPLND remains the most accurate means of staging patients with CSI NSGCT; roughly 50% to 70% will be pathologic stage I. In these patients, RPLND is purely diagnostic with the added benefit of a simpler follow up. Because retroperitoneal recurrence is rare with properly performed RPLND, abdominal CT scan may be omitted after negative RPLND. In the case of pathologic stage II disease RPLND is curative in 50% to 90% of patients, thus selected patients may avoid adjuvant chemotherapy.

Adjuvant Chemotherapy. As noted previously, 50% of LVI positive patients will relapse, therefore adjuvant treatment would spare half of this group from a recurrence requiring three to four courses of chemotherapy and possibly post- chemotherapy surgery (PCS) for a residual tumor. Conversely, the other half would receive adjuvant chemotherapy 'unnecessarily'. The main argument against adjuvant chemotherapy is its lack of improved overall survival and its association with long-term side effects including infertility, secondary malignancies, and increased risk for car-

diovascular disease, impaired kidney function, hearing impairment, and peripheral neuropathy. The optimal treatment strategy for NSGCT is controversial. To date, there are no randomized trials that demonstrate superiority of surveillance or adjuvant treatment. Further, cure approaches 100% regardless of treatment strategy. Thus the main issue is how to best minimize treatment related toxicity. For stage I NSGCT, results from the SWENOTECA study show that adjuvant therapy can be safely reduced to just one course of BEP, resulting in a reduction in relapse rate of 90–95%. This lower dose of chemotherapy may mitigate many of the long-term consequences of therapy.

Clinical Stage II and III. In metastatic NSGCT, the degree of marker elevation before chemotherapy correlates with prognosis. The International Germ Cell Cancer Collaborative Group (IGCCCG) has incorporated serum concentrations of human chorionic gonadotrophin (hCG), AFP, and lactic dehydrogenase (LDH) into a prognostic classification system with high, intermediate, and low risk disease and treatment is tailored according to the risk assignment. Systemic therapy for metastatic GCT consists of cisplatin-based chemotherapy. For good risk disease, the accepted standard is three courses of BEP or four courses of EP. Standard therapy for intermediate and poor risk disease remains four courses of BEP. Depending upon the patient population selected, roughly 70% of patients treated with first line chemotherapy will have complete radiographic and biochemical response. In the remaining 30% a residual mass will persist after chemotherapy, most commonly in the retroperitoneum. These patients will then undergo post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) because of possible residual teratoma (40%) or active cancer (10%).

Controversies in PC-RPLND. The excision of all masses after chemotherapy, within and outside the boundaries of the retroperitoneum, is integral to the cure of NSGCT. It is well recognized that incomplete resection or surveillance of a residual mass after chemotherapy risks relapse. Therefore, any patient who has a mass larger than 1 cm in the retroperitoneum should undergo surgery. The proper extent of PCS resection and the need for PC-RPLND in patients achieving complete remission remains controversial. At most centers, the management of patients achieving a complete radiographic response to systemic chemotherapy is observation. However, studies have documented the incidence of residual teratoma in sub-centimeter retroperitoneal nodes following chemotherapy to be 20–

30%. Therefore, some institutions have adopted a policy of PC-RPLND in all patients, including those achieving complete radiographic response. The current European and Canadian guidelines endorse this data and favor observation for patients achieving complete radiographic remission, whereas in the NCCN guidelines either immediate PC-RPLND or observation are appropriate.

There is a relationship between long-term Pt exposure in testicular cancer survivors and known late effects, such as persistent paraesthesia, hypogonadism, hypercholesterolaemia and increased blood pressure. This association between healthy tissue damage in cancer survivors and long-term Pt exposure should be considered during treatment decisions and follow-up care in testicular cancer patients. Hence, further research on healthy tissue damage caused by long-term Pt exposure is needed.

Cisplatin-related hearing loss

A study published in JCO June 27 of this year showed that many adult survivors of testicular cancer have significant cisplatin-related hearing loss, and about 40% also experience tinnitus . The study is the most comprehensive on cisplatin-related hearing loss in adult cancer and the first to show definitively that cisplatin-related hearing loss is over and above age-related hearing loss, the authors note.

Testicular Prostheses in Patients With Testicular Cancer

More than one quarter of GCT patients wish to have a testicular prosthesis. Over-all satisfaction with implants is high in more than 80% of patients. Thus, all patients undergoing surgery for GCT should be offered a testicular prosthesis. However, surgeons should be aware of specific items of dis-satisfaction, particularly shape, size and consistency of the implant and inconvenient high position of the implant within the scrotum. Appropriate preoperative counselling is paramount.

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Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus After Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer ASCO 2016.

CARDIAC: LATE EFFECTS

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Cardiac late effects of antineoplastic therapies can be a direct, delayed, cardiotoxicity of the treatment (anthracyclines, for example), a secondary effect on other organs/systems (as endocrine changes) and a combination of the two (Ferri et al., 2013). In 2007, the "Multiple-Hit" hypothesis has been suggested to explain the risk of cardovascular diseases (CVD) in women diagnosed with early breast cancer and treated with adiuvant therapies. The authors suggested that the series of sequential or concurrent cardiovascular insults coupled with lifestyle perturbations that collectively leave patients with overt or sub clinical CVD. At a minimum, these insults enhance susceptibility to further cardiovascular injury and, ultimately, risk of premature CVD mortality (Jones et al., 2007). This fascinating and very reasonable hypothesis may be logically applied to other cancers and treatments.

A) **Cardiotoxic therapies**

- Anthracyclines have been well known for years as cardiotoxic agents causing left ventricular dysfunction (LVD) and eventually congestive heart failure (CHF); the cardiotoxic effect is usually evident during therapy or shortly after its completion and the risk is proportional to the cumulative dose. Clearance of anthracyclines from cardiac cells should avoid late effects, but toxic metabolites, as doxorubicinol, may be entrapped in the cells and become a toxic reservoir; doxorubicinol formation may be enhanced by the association with taxanes (Salvatorelli et al., 2006). An increased rate of CHF has been observed at 10 years follow-up of elderly women with breast cancer treated with anthracycline regimen compared to women who received non-anthracycline or no chemotherapy ($P < 0.001$ for each) (Pinder et al.,2007).
- Platinum. Cisplatin-based chemotherapy is associated with endothelial dysfunction, which represents a possible predisposing factor to atherosclerosis; hyperlipidemia and the metabolic syndrome have been reported in 80% of a group of survivors of testicular cancer (Vaughn et al.,2008; Meinardi et al., 2000; Haugnes et al.,2007). Cisplatin is detect-

able in serum several years after administration and may continuously stimulate the endothelium. In a long-term follow-up study (median 18.4 years), a moderately increased risk of coronary artery disease (CAD) in 5-year testicular cancer (TC) survivors compared with the general population was found. Remarkably, non-seminoma patients were at particularly high risk of developing an MI at a young age, as illustrated by an approximately two-fold increased risk in patients with attained ages of younger than 45 years (van den Belt-Dusebout et al., 2006). In another long-term follow-up study after treatment for testicular carcinoma, also etoposide was associated with an increased risk for CAD in age-adjusted Cox regression analyses. Elevated risks for atherosclerotic disease were observed with increasing cisplatin ($P = .04$) and etoposide doses ($P < .001$) but not with bleomycin or vinblastine doses. However, in a more recent population-based study the excess cardiovascular mortality was limited to the first year after treatment (Fung et al., 2015).

- Radiotherapy (RT). Radiation-induced heart disease (RIHD) is a typical late effect, with the incidence increasing progressively over time (Galper et al., 2011; Darby et al., 2013; Adams et al., 2003). The most frequent cardiac problems are CHD, LVD, valvular disease, pericardial constriction and arrhythmias. The risk of death due to acute myocardial infarction (AMI) is up to 7-fold higher in patients treated for Hodgkin lymphoma compared with age-matched controls (Swerdlow et al., 2007) The mechanism involved in plaque formation is thought to mirror spontaneous atherosclerosis; however, plaques in irradiated patients have been found to be more fibrous with decreased lipid content, and the lesions more proximal, and longer. Valvular heart disease ranges from sclerosis to calcific valvular stenosis and/or regurgitation. It is more common after mediastinal RT in comparison to chest wall RT. Among breast cancer patients, it is more common after left-sided RT in comparison to right sided RT (McGale et al.,2011). Patients undergone mediastinal irradiation developed asymptomatic valvular defects in 32% of cases at a six years follow-up (Cella et al., 2011). Both bradycardia and tachycardia have been observed arrhythmias as a consequence of RT. Inappropriate sinus tachycardia, both at rest and during effort, is common after thoracic RT and is felt to be a consequence of autonomic dysfunction (Slama et al.,1991). Various degrees of atrioventricular block, including complete heart block, and sick sinus syndrome, may be observed (Slama et al.,1991; Orzan et al., 1993)

. Most of the pancreatic gland is included in the standard dog-leg and para-aortic fields. Thus, radiation injury of the pancreatic function, including diabetes, is a possible long-term complication after infra-diaphragmatic RT (Levy et al., 1993; van Nimwegen et al., 2014). Cranial radiotherapy (CRT) is an important risk factor for cardio-metabolic disease among leukemia survivors; those treated with ≥ 20 Gy CRT had an increased chance of being obese (odds ratio [OR], 2.59 for females $P < .001$; and OR, 1.86 for males, $P < .001$) compared with sibling controls. Female survivors treated before the age of 5 and with ≥ 20 Gy CRT were at highest risk (OR, 3.81, $P < .001$) compared with sibling controls. CRT also increases the risk of a diagnosis of DM; the OR for a diagnosis of DM among male and female ALL survivors in the CCSS with a history of CRT compared with sibling controls was 1.8 (95% CI, 1.2–2.8; $P < .01$) (Oeffinger et al., 2003).

B) **Indirect effects**

- Androgen deprivation therapy (ADT) increases obesity, decreases insulin sensitivity and adversely alters lipid profiles. It may be associated with a greater incidence of diabetes and cardiovascular disease; however, an increased rate of cardiovascular deaths has not been reported (Saylor et al., 2013; Nguyen et al., 2011].
- Endogenous estrogens in younger women are known to prevent CHD in that population; breast cancer patients with treatment-related early menopause may be at higher risk for heart disease than age-matched women in the general population (Barton et al., 2013). Aromatase inhibitors (AI) can raise cholesterol levels and the risk of diabetes; they attain a marked reduction in serum estrogen and -in comparison with tamoxifen- AIs have been associated with more cardiovascular events although the incidence of thromboembolic events was significantly lower (Bell et al., 2012; Mouridsen et al., 2009). Breast cancer patients treated with adjuvant chemoendocrine therapy may show a significant reduction in exercise cardiovascular function secondary to impairments in cardiac reserve; the greatest impairment in observed in women with the worse CVD risk profile (Jones et al., 2007).

Some groups are more at risk of late effects: children, elderlies and patients with concurrent cardiovascular disease.

a) **Children and teen-agers.** Among childhood cancer survivors who

were diagnosed and treated between 1962 and 2001, 57% of those who were exposed to potentially cardiotoxic therapies experienced cardiac abnormalities (Miller et al., 2016). Survivors treated with both anthracyclines and radiotherapy have the highest risk; after 30 years, one in eight will develop severe heart disease (van der Pal et al., 2012). A recent study compared a young (median 33 years) cohort of childhood cancer survivors with siblings. The cumulative incidence of grade 3 to 5 cardiac events by 45 years of age in cancer survivors was 5.3% for coronary artery disease, 4.8% for heart failure, 1.5% for valvular disease, and 1.3% for arrhythmia; among siblings, cardiac events were uncommon with cumulative incidences by age 45 years of 0.9% for coronary artery disease, 0.3% for heart failure, 0.1% for valvular disease, and 0.4% for arrhythmia. The cumulative incidence of cardiac events in cancer survivors was associated both with exposure to cardiotoxic therapies ($P < .001$) and to the presence of other cardiovascular risk factors (P for trend < .001 for all cardiac events), which were more common: in fact, two or more cardiovascular risk factors were reported by 10.3% of survivors and 7.9% of siblings. Potential mechanisms for the observed increase in risk include alterations in leptin and adiponectin, pancreatic insufficiency, poor dietary habits, sedentary lifestyle, and perhaps changes in the composition of the gut microbiota, many of which could be the consequence of RT (Barnea et al., 2015). With aging, the prevalence of cardiovascular risk factors increased among survivors and was statistically significantly greater than that for siblings at age 50 years for hypertension (40.2% v 25.5%; $P <0.001$) (Armstrong et al., 2013). In other studies, after an average follow-up of 27 years, childhood cancer survivors have an overall standardized mortality ratio (SMR) 8.3 to 11-fold higher in relation to the general populations; the risk of dying as a result of cardiac diseases was significantly higher in individuals who had received a cumulative anthracycline dose greater than 360 mg/m(2) and in individuals who received an average radiation dose that exceeded 5 Gy to the heart (Tukenova et al., 2010; Reulen et al., 2010]. Alterations in leptin and adiponectin may contribute to obesity and metabolic disease among childhood cancer survivors (Tonorezos et al., 2012).

b) **Elderlies**. Elderly patients are at higher risk of both early and late cardiotoxicity because the side-effects of the antineoplastic therapies are often superimposed to other cardiovascular risk factors, as hypertension, dyslipidemia, diabetes, or to coronary, valvular or arrhythmic heart disease (Pinder et al., 2007; Hershman et al., 2008; Accordino et al., 2014). The

multiple-hit hypothesis above mentioned might explain this observation. Comorbidities are associated with survival to the extent that patients with these comorbid conditions diagnosed with early-stage breast cancer have survival similar to or worse than that of patients with no comorbidities diagnosed with later-stage tumors (Patnaik et al., 2011).

Practical implications

In long-term cancer survivors the prevention, early and aggressive treatment of cardiovascular risk factors may be relevant in reducing the cardiovascular sequelae of both cancer and therapies. The mainstay of intervention for obesity and metabolic disease in the general population is diet and exercise. There is growing evidence that exercise may be efficacious in lowering both recurrence and CVD risk in cancer patients (Scott et al., 2013). In a study on Hodgkin disease survivors, Cumulative incidence of cardiovascuar events was 12.2% at 10 years for survivors reporting 0 metabolic equivalent (MET) hours/week(-1) compared with 5.2% for those reporting ≥ 9 MET hours/week(-1). In multivariable analyses, the incidence of any CV event decreased across increasing MET categories (Ptrend = .002) (Jones et al., 2014). Diet and exercise training programs - tested in different cancer survivors cohorts- were effective in improving the cardiovascular profile (Sturgeon et al., 2014; Giallauria et al., 2015; Christensen et al., 2015; Mishra et al., 2012; Giallauria et al., 2016).

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CERVIX
CURRENT TREATMENT AND NEW APPROACH

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Cervical cancer is actually the second most common cancer in women worldwide. Almost 80% of cases occur in developed countries. Stage at diagnosis is the best predictor of prognosis.
About 12.200 new cases of cervical cancer diagnosed in the United States in 2010, with 4210 deaths. More than 1800 of these patients will be under the age of 40 years and potentially desire fertility preservation.
The standard surgical treatment for patients with International Federation of Gynecology and Obstetrics (FIGO) stage I-IIA cervical cancer is radical hysterectomy. However, selected patients with early-stage squamous cell carcinoma of the cervix may be potential candidates for fertility preserving surgical interventions. Microinvasion (**FIGO stage IA1**), defined as less than 3 mm of stromal invasion, may be safely managed with cervical conization or large loop excision of the transformation zone (LLETZ). These patients have a 0.8% risk of lymph node metastasis in the absence of lymph vascular space invasion (LVSI).
The recommended criteria for conservative management based on review of the literature include:
1. a negative endocervical curettage at completion of the procedure;
2. absence of LVSI (the risk of tumor recurrence increases from 3.2% to 9.7% with LVSI);
3. a negative endocervical margin, given 10% risk of more extensive disease in individuals with positive margins at completion of biopsy.
In patients who meet the above criteria, the risk of disease recurrence is less than 0.5%. Unlike squamous cell lesions, adenocarcinoma is a glandular lesion and is considered multifocal, with up to 13% of patients having foci of disease separated by 2 mm of stromal mucosa. Furthermore, the complex architecture of endocervical glands, with invagination, branching, and tunnel formation makes determination of depth of invasion problematic. If fertility preserving options are used in patients with squamous lesions or adenocarcinoma, it is essential to have satisfactory

margins free of disease. Patients who undergo a cervical cone biopsy or LLETZ for fertility preserving purposes should understand the potential attendant obstetric risk of preterm delivery.
Patients with greater than 3 mm of stromal invasion, defined as having FI**GO stage IA2-IB1** disease, have a 7% risk of nodal metastasis, and definitive surgical treatment includes pelvic lymphadenectomy. For this group of patients, the fertility preserving option is a radical trachelectomy (RT), which includes resection of the entire cervix and surrounding parametria, and can be performed vaginally, abdominally, laparoscopically, and robotic assisted.
It is recommended that all patients offered this intervention satisfy 5 main criteria:
1. desiring preservation of fertility;
2. compliant with follow-up;
3. squamous cell carcinoma or adenocarcinoma with exclusion of undifferentiated and clear cell histologies;
4. FIGO stage IA1 with LVSI or stage IA2-IB1 lesion <2 cm;
5. no evidence of pelvic lymph node metastasis.

Locally advanced cervical cancer (**FIGO stage IIB–IVA**) accounts for almost 32% of all stages with an overall 5-year survival rates of 40–62% when conventional treatments are used.
Actually standard of care for locally advanced cervical cancer is concomitant use of radiotherapy and chemotherapy. Encouraging results are emerging from neo-adjuvant chemotherapy followed by radical surgery in stage IB2-IIB. Reports from these studies indicated an operability rate ranging from 48 to 100% after neo-adjuvant chemotherapy, with no relevant surgery-related morbidity, and objective responses with about 20% complete and 60% partial responses and 5-year survival rate of about 83% for stage IB2–IIB with a statistically significant improvement of about 10-15%, in front of 5 year survival in control arm (radiotherapy). Our group have evaluated three courses of neo-adjuvant chemotherapy regimen (paclitaxel, ifosfamide and cisplatin) followed by surgery in 136 patients with FIGO stage IB2–IVA cervical cancer, with objective response rate of 80% and resection rate of 93%. A new strategy with dose dense administration of neoadjuvant chemotherapy probably will improve better selection of patients to treat with subsequent surgery or radiotherapy.
Further phase III studies to compare neo-adjuvant chemotherapy followed by surgery compared to concomitant chemo-radiation are warranted. The

EORTC gynaecologic oncology group have recently close a randomized study (EORTC 55994) with this design that will better clarify this issue.

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Efficacy and tolerability of paclitaxel, ifosfamide, and cisplatin as a neoadjuvant chemotherapy in locallyadvanced cervical carcinoma Giuseppa Scandurra, Giuseppe Scibilia, Giuseppe Luigi Banna, Gabriella D'Agate, Helga Lipari, Stefania Gieri, Paolo Scollo; J Gynecol Oncol Vol. 26, 2:118-124.

TOXICITY OF NEW DRUG IN CERVICAL CANCER TREATMENT

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Around 500 000 new cases of cervical cancer and 250 000 cervical cancer-related deaths occur worldwide every year(Tewari K et al, 2012). Although screening with cytology and high-risk human papillomavirus DNA testing have reduced the incidence and mortality of this disease, women who do not have access to health care and those living in resource-poor areas remain at high risk of death from cervical cancer. Although early-stage disease can be cured by radical surgery and locally advanced disease by chemoradiotherapy, women with metastatic and non-operable recurrent disease have previously had few treatment options. Platinum-based chemotherapy in this setting is palliative and is associated with median overall survival of 8–12 months.(Monk BJ et al, 2009).

Vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target in many solid tumours (Moreira IS et al, 2007)). Gynecologic Oncology Group (GOG) protocol 240 (GOG 240) was a randomized phase 3 clinical trial that showed that, compared with chemotherapy alone, chemotherapy plus bevacizumab (a monoclonal antibody that binds VEGF) significantly increased overall survival from 13•3 months to 17•0 months (hazard ratio [HR] 0•71 [98% CI 0•54–0•95], p=0•004) in patients with advanced cervical cancer (Tewari KS et al, 2014). The triplet regimens used in the study (cisplatin, paclitaxel and bevacizumab, and topotecan, paclitaxel and bevacizumab) were quite well tolerated but were both associated with a 6% incidence of fistula and 8% incidence of thromboembolism (compared with fistula <1% and thromboembolism 1% for either chemotherapy regimen alone without bevacizumab). On Aug 14, 2014, under the US Food and Drug Administration's (FDA) Priority Review programme (which makes promising therapies rapidly available to patients), both of these bevacizumab-containing triplet regimens were approved for the treatment of advanced cervical cancer. Other reported Grade 3 and 4 toxicities were: hypertension (15.2%), thromboembolism (10.87%), GI (8.69%), anemia (4.35%), other cardiovascular (4.35%), vaginal bleeding (2.17%), neutropenia (2.17%), leukopenia (2.17%), coagulation (2.17%), constitutional (4.35%), metabolic

(2.17%), pain (13.04%), pulmonary (2.17%).
In the advanced cervical cancer setting, quality of life must be measured to balance potential toxicities with treatment efficacy; before GOG 240, progression-free and overall survival increases in cervical cancer treatments were modest, with little benefit or difference in health-related quality of life (Cella D et al, 2010; Monk BJ et al, 2005) The GOG 240 study showed that a significant improvements in overall survival, progression free survival, and the proportion of patients achieving an objective response conferred by the addition of bevacizumab to chemotherapy did not come at the cost of a concomitant deterioration of health-related quality of life as defined by the FACT-Cx TOI (Richard TP et al, 2015). The 2•1-points lower FACT-Cx TOI measured in the cisplatin–paclitaxel–bevacizumab group than in the cisplatin–paclitaxel alone group after adjustment for baseline score and patients' characteristics could be regarded as an improvement, although it did not reach our prespecified 5•8 points for clinically significant improvement for the FACT-Cx TOI. This could be interpreted as encouraging for the development of combination of bevacizumab with the less toxic and equally effective carboplatin–paclitaxel combination.
The favourable side-effect and quality-of-life profile of bevacizumab suggests it is one of the better novel biologics to use to achieve clinical benefit. Ongoing analyses are assessing whether or not it is possible to predict which patients are at risk of fistula or gastro intestinal perforation, and whether these adverse events can be avoided.
Another aspect that should be taken into account is cardiovascular toxicity: treatment with Bevacizumab increases the incidence of hypertension when compared to patients treated with chemotherapy alone (15.2% versus 2.3%) (gog 240). Hypertension associated with bevacizumab is likely related to VEGF inhibition, which decreases endothelial nitric oxide production.
In patients treated with bevacizumab, another clinically significant side effect is thrombosis, in both the venous and the arterial territory (Kabbinavar F et al, 2003; Chen HX et al, 2006). The GOG conducted a phase II trial to assess the efficacy and tolerability of bevacizumab, eligible patients had recurrent cervical cancer. Treatment consisted of bevacizumab 15 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity. Primary end points were progression-free survival at 6 months and toxicities. 46 patients were enrolled; 38 patients (82.6%) received prior radiation as well as either one (n = 34) or two (n = 12) pri-

or cytotoxic regimens for recurrent disease. Grade 3 or 4 adverse events at least possibly related to bevacizumab included hypertension (n = 7), thrombo-embolism (n = 5), GI (n = 4), anemia (n = 2), other cardiovascular (n = 2), vaginal bleeding (n = 1), neutropenia (n = 1), and fistula (n = 1). One grade 5 infection was observed. Eleven patients (23.9%; two-sided 90% CI, 14% to 37%) survived progression free for at least 6 months, and five patients (10.9%; two-sided 90% CI, 4% to 22%) had partial responses (Monk BJ et al, 2009).

Jing Yu et al (Jing YU et al, 2014) reported a pooled analysis of 4 clinical studies including 282 patients with advanced cancer (gliomas, cervical, breast and ovarian cancer) suggesting that in bevacizumab based regimens, hypertension and thrombo-embolism occurred in 2.5% of patients and only 3 patients reported cardiovascular events (1.1%). The authors concluded that bevacizumab based regimens are associated with reasonable and accepted cardiovascular toxicity.

No other targeted drug has been licensed for cervical cancer until now although other antiangiogenic agents have been evaluated in advanced cervical cancer.

The activity of pazopanib was compared against lapatinib (an HER1/HER2 tyrosine kinase inhibitor) and against the combination of both drugs in 230 patients with pretreated advanced cervical cancer. The combination was discontinued due to toxicity and the final analysis was done only in those patients treated with either lapatinib or pazopanib. Pazopanib was well tolerated and resulted in improved PFS – the endpoint of the study (HR 0.66; 90% CI 0.48–0.91; P=0.013) and OS (HR 0.67; 90% CI 0.46–0.99; P=0.045). Response rates were 9% and 5% for pazopanib and lapatinib, respectively (Monk BJ et al, 2010). Although this study was not powered for OS, an updated publication on this trial reported a median OS of 44.1 weeks for lapatinib and one of 49.7 weeks for patients who received pazopanib (HR 0.96; 90% CI 0.71–1.30; P=0.407) (Monk BJ et al, 2011). Grade 3 and 4 toxicity of pazopanib were: diarrhea (11%), nausea (1%), anorexia (3%), vomiting (1%), asthenia (1%), fatigue (1%), anemia (3%), back pain (1%), urinary tract infection (1%), abdominal pain (5%), abdominal pain upper (1%), pain in extremity (2%), vaginal hemorrhage (2%), neutropenia (3%), alkaline phosphatase (5%), ALT (3%), AST (3%), total bilirubin (1%), groin pain (1%), small bowel obstruction (1%). Grade 3 and 4 toxicities of lapatinib were: diarrhea (13%), anorexia (1%), rash (1%), asthenia (1%), fatigue (5%), anemia (5%), back pain (4%),

dyspnea (6%), proteinuria (1%), abdominal pain (3%), pain in extremity (4%), alkaline phosphatase (1%), intestinal obstruction (1%), peripheral edema (1%), hypercalcemia (1%), hypoglycemia (1%), bone pain (1%), tumor pain (1%).

Among the multitargeted tyrosine kinases inhibitors , imatinib (BCR-ABL, c-KIT, PDGFR) and sunitinib (PDGFRa, PDGFRb, VEGFR1, VEGFR2, c-kit, and FLT3) have been evaluated in the advanced disease setting. No evidence of response nor suggestion of increased stabilization of disease were observed (Candelaria M et al, 2009; Mackay HJ et al, 2010) at the prize of the typical toxicity of TKIs. Additionally, in the sunitinib trial, a higher rate of fistula formation (26.3%) was observed than expected and is of concern (Mackay HJ et al, 2010). Fatigue is the dominant symptom in patients with cancer (Farley J et al, 2011). Achievement of antiangiogenic blockade with tyrosine kinase inhibitors is associated with more fatigue than is reported with bevacizumab.

Cediranib – another orally bioavailable small molecule inhibitor of VEGFR-1, 2, and 3 is under evaluation in a randomized Phase II trial comparing carboplatin paclitaxel with or without cediranib in advanced cervical cancer (NCT01229930).

The availability of agents against EGFR, either monoclonal antibodies or small molecule inhibitors, and their success in lung and colorectal cancer among others, prompted evaluation of these agents in cervical cancer. None of these agents have progressed to Phase III trials. There were 4 studies with cetuximab retrieved (128 patients) (Santin AD et al, 2011; Kurtz JE et al, 2009; Hertlein L et al, 2011; Butt Z et al, 2008) all conducted in recurrent metastatic or refractory disease. Clinical data concerning cetuximab have presented modest results, with an ORR ranging between 0% and 32%, and median OS between 6.7 and 8.77 months. Grade 3 and 4 reported toxicities were: metabolic (23.19%), dermatologic (11.59%), fatigue (8.69%), anemia (8.69%), gastrointestinal (8.69%), nausea/vomiting (8.69%), infection (7.25%), allergy (5.79%), leucopenia (5.79%), genitourinary/renal (4.35%), neutropenia (4.35%), musculoskeletal (1.45%), vascular (1.45%).

Erlotinib has been tested in combination with cisplatin and radiotherapy for untreated patients with locally advanced squamous cell cervical cancer, with promising results (Nogueira-Rodrigues A et al, 2008; Schilder RJ et al, 2009; Ferreira CG et al, 2008). In a phase II trial, Ferreira et al. evaluated the combination of erlotinib, cisplatin and radiotherapy in 37

patients with locally advanced squamous cell cervical cancer (FIGO Stages IIB: 47.8%, IIIA: 4.3% and IIIB: 47.8%). During a median follow-up of 9 (3–25) months, none of the patients progressed; 91.3% of patients presented CR and 8.7% presented partial response. The combination was well-tolerated; significant grade 3 toxicities included diarrhea (12%) and skin rash (20%). Hence, it seems that this combination leads to high CR (91.3%) compared to historical chemoradiation data (38–75%) and merits further evaluation (Ferreira CG et al, 2008).

Characterization of the mutational landscape of cervical cancer has already been initiated, indicating that, for now, few of these targetable alterations match with available agents. Progress in both the mutational landscape knowledge and developments of novel targeted therapies may result in more effective and individualized treatments for cervical cancer. Concerns about toxicity of these drugs exist and should be taken into account.

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LATE EFFECTS FERTILITY

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Although the incidence of cancer increases with age and has a peak after the age of 50, a large amount of young women and men are diagnosed with cancer (Siegel RL et al, 2016).
Nowadays, considering the improvement of cancer prognosis, more attention is given to late effects of treatment, especially fertility issues.
One of the most common sequelae that could disrupt the psychosocial aspects of life for adult cancer survivors after anticancer treatment is represented by infertility. Understanding the effects of the disease and/or treatment on fertility has become increasingly important over time, since women are having children later in life (Johnson JA et al, 2012) and many patients have not yet started or completed their families at the time of cancer diagnosis.
As with the other potential complications of cancer treatment, international guidelines recommend that oncologists inform and discuss with patients the risks of potential treatment related infertility and about fertility preservation options prior to treatment (Peccatori FA et al, 2013; Lambertini M et al 2016).
In the present manuscript I will try to summarize the up-to-date knowledge on main field of fertility and fertility- preservation techniques in young patients with cancer. In particular, I will focus on the following topics:
1. Factors that provoke and are related to gonadal toxicities;
2. Markers of gonadal toxicity;
3. Fertility preservations methods;
4. Main debatable issues;
5. Focus on fertility preservations strategies in cervical cancer.

Infertility is functionally defined as the inability to conceive after 1 year of intercourse without contraception.
Risk of infertility or compromised fertility is related to different factors. The effects of chemotherapy and/or radiations therapy depend on: the drug, size/location of the radiations field, dose, dose-intensity, method of administration, disease, age, sex, and pre-treatment fertility of the patient

(Lee SJ et al, 2006).
The level of risk of each anticancer treatment with relation to the dose and to the radiation field is illustrated in Table 1.

Male fertility may be affected by: the disease itself (testicular cancer and Hodgkin's lymphoma are more at risk); anatomic problems (retrograde ejaculation or anejaculation), primary or secondary hormonal insufficiency, or damage or depletion of germinal stem cells (Lee SJ et al, 2006).
Female fertility may be influenced by any treatment that decreases the number of primordial follicles, affects hormonal balance, interferes with ovaries, fallopian tubes, uterus, or cervix function (Lee SJ et al, 2006).

Natural conception may be hindered by any anatomic or vascular changes of the uterus, ovaries of fallopian tube caused from surgery or radiation (Lee SJ et al, 2006).
Five different risk categories are defined from the American Society of Clinical Oncology (Lambertini M et al, 2016):
High Risk: > 80% risk of permanent amenorrhea in women; prolonged azoospermia in men.
Intermediate Risk: 40-60% risk of permanent amenorrhoea in women; likelihood of azoospermia in men especially when given with other sterilizing agents.
Low Risk: < 20% risk of permanent amenorrhea in women; only temporary reductions in sperm counts in men particularly when not given with other sterilizing agents.
Very low or no risk: risk of permanent amenorrhea in women; temporary reductions in sperm count in men but additive effects are possible.
Unknown risk: risk of permanent amenorrhea in women; effect on sperm production in men.

Tab.1 Risk of treatment-related infertility with the main anticancer therapies (from Lambertini , BMC 2016)

Level of risk	**Type of anticancer treatment**	
	Women	**Men**
High risk	-HSC transplantation with cyclophosphamide/TBI or cyclophosphamide/busulfan; -External beam radiation to a field that includes the ovaries; -CMF, CEF, CAF, TAC x 6 (>40 years)	Radiation > 25 Gy to testis -Chlorambucil (1.4 g/m2) -Cyclophosphamide (19 g/m2) -Procarbazine (4g/m2) -Melphalan (140 mg/m2) -Cisplatin (500mg/m2) -BCNU (1g/m2
Intermediate risk	-BEACOPP -CMF, CEF, CAF, TAC x 6 (30-39) -AC x 4 (> years) -AC or EC x 4 followed by Taxanes	Busulfan (600 mg/kg) -Ifosfamide (42 g/m2) -BCNU (300 mg/m2) -Nitrogen mustard -Actinomycin D
Low risk	-ABVD (≥ 32 years) -CHOP x 4-6 -CVP -AML therapy -ALL therapy -CMF, CEF, CAF, TAC x 6 (≤ 30 years) -AC x 4 (≤ 40 years)	-Carboplain (2 g/m2) - Doxorubicin (770 mg/m2) - Thiotepa (400 mg/m2) - Cytosine arabinoside (1 g/m2) - Vinblastine (50 g/m2) - Vincristine (8 g/m2)
Very low or no risk	-ABVD (< 32 years) -Methotrexate -Fluorouracil -Vincristine -Tamoxifen	-Amsacrine -Bleomycin -Dacarbazine -Daunorubicin -Epirubicin -Etoposide -Fludarabine -Fluorouracil -6-mercaptopurine -Methotrexate -Mitoxantrone -Thioguanine -Prednisone -Interferon-α
Unknown risk	-Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab) -Tyrosine kinase inhibitors (erlotinib, imatinib)	-Oxaliplatin -Irinotecan -Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab) -Tyrosine kinase inhibitors (erlotinib, imatinib) -Taxanes

Abbreviations: HSC hematopoietic stem cell, TBI total body irradiation, CMF cyclofosfamide, methotrexate, fluouracil, CEF cyclophosphamide, epirubicin, fluouracil, CAF cyclophosphamide, doxorubicin, fluorouracil, TAC docetaxel, doxorubicin, cyclophosphamide, BEACOPP doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, procarbazine, BCNU carmustine, CCNU lomustine, AC doxorubicin, cyclophosphamide, EC epirubicin, cyclophosphamide, ABVD doxorubicin, bleomycin, vinblastin, dacarbazine, CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, CVP cyclophosphamide, vincristine, prednisone, AML acute myeloid leukemia, ALL acute lymphocytic leukemia

Several factors (environmental, therapeutic, genetic, occupational, etc.) are responsible for male reproductive failure. These factors primarily affect the hypothalamic-pituitary-gonadal axis, which results in hormonal imbalance and testicular damage causing reproductive failure and infertility. The evaluation of male gonadal function mainly includes: endocrine function and semen analysis.

A complete evaluation of an infertile men should check: (1) an abnormal testicular size and/or pathology; (2) abnormal semen parameters; (3) impaired sexual function; (4) other clinical findings suggestive of a specific endocrinopathy. Initial evaluation should include levels of serum testosterone (T), luteinizing hormone (LH), follicular stimulating hormone (FSH), inhibin and also prolactin (if erectile dysfunction is suspected).

If the T level is low, a repeat measurement of total and free/bioavailable T and serum LH is important. A normal serum FSH level does not guarantee the presence of intact spermatogenesis. Abnormal serum FSH and inhibin are indicative of impaired spermatogenesis.

The World Health Organization (WHO) manual for the evaluation of semen has been the core of andrology and fertility evaluation. These include the physical appearance of the ejaculate, assessments of sperm count, motility, vitality, morphology, and functional aspects of the sperm and semen sample. These tests also include biochemical evaluation of the semen, detection of antisperm antibodies in serum, the use of computer-aided sperm analysis (CASA), sperm DNA integrity, and its damage due to oxidative stress (Sikka SC et al, 2016)

Summing up, the best and suggested way to evaluate male reproductive function is to combine semen analysis and dosage of FSH, inhibin B and Testosterone (Peccatori FA et al, 2013).

Most of the available literature quantifying chemotherapy-induced ovarian toxicity reports rates of chemotherapy induced amenorrhea, though this

is only a surrogate and imprecise measure of premature ovarian failure and infertility.
Hormonal measurements to assess the ovarian reserve have been evaluated: follicle stimulating hormone (FSH) and estradiol (E2) measured on day 3 of the menstrual cycle reflect the population of maturing follicles and are indirectly associated with ovarian reserve; inhibin-b is directly associated with the loss of oocytes (it is secreted by the granulosa cells lining the follicles) but the assay is not very reliable. AMH, secreted by the granulosa cells of follicles, varies relatively little through the menstrual cycle and can thus be measured at any time. AMH has been established in various trials as a reliable marker of chemotherapy-induced ovarian toxicity and had been accepted as a standard measure of ovarian reserve post chemotherapy (La Marca A et al, 2009; Kelsey TW et al, 2011; Nelson SM et al, 2011; Shuhui Loh J et al, 2011; Neugebauer JK et al, 2011).
The best way to measure ovarian function is to perform both antral follicles count and hormonal dosage (E2, FSH, AMH) carried out in the first part of menstrual cycle (Peccatori FA et al, 2012).
Oligo-azoospermia can result from the damage of the germinal epithelium caused by anticancer treatment. In fact, a large proportion of patients treated for cancer have lower sperm concentrations than matched controls. Some data suggest that cancer itself can influence spermatogenesis. However, no correlation between semen alterations and cancer stage or associated symptoms has been reported.
Sperm cryopreservation before gonado-toxic therapies is the standard strategy for fertility preservation in adult. Sperm banking should be planned before treatment initiation with collection of one to three samples recommended. It has to be considered that a large amount of patients maintains a level of spermatogenesis adequate to obtain spontaneous conception. Cancer survivors who don't recover spermatogenesis nor had their semen cryopreserved before cytotoxic therapy may need Assisted Reproductive Technology (ART), and specifically intracytoplasmatic sperm injection (ICSI).
Nevertheless, while cryopreservation of mature sperm cells is a well-established technique, preserving fertility from testicular tissue of pre-pubertal male children in whom only spermatogonial stem cells are available is still under investigation. Micro-surgical testicular sperm extraction (TESE) is still considered as an experimental technique (Peccatori FA et al, 2013; Lambertini M et al, 2016).

To preserve fertility of young women and pre-pubertal girls undergoing gonado-toxic treatments, several options and strategies can be offered according to recent guideline, including (Salama M et al, 2016):
1. Established options such as embryo freezing and egg freezing;
2. Experimental options such as ovarian tissue freezing and autotransplantation and in vitro maturation;
3. Debatable options such as ovarian protection techniques
Embryo or oocyte cryopreservation are the main standard method to preserve female fertility.
Cryopreservation of embryos: standardly available with a 20-30% pregnancy rate per transfer of 2-3 embryos. This technique have some limitations such as require medical stability, time, partner/sperm, adequate ovarian reserve. It also requires ovarian stimulation prior to systemic breast cancer treatment and it is a matter of concern in patients with hormone-sensitive cancer (Jain JK et al, 2006)
Cryopreservation of oocyte: The review of Jain et al reported the outcomes of cryopreservations and data showed a gradual improvement in oocyte efficiency over time, with live-births rates increasing from 21.6% per transfer between 1996 and 2004 to 32.4% between 2002 and 2004. The spontaneous-abortion rate after oocyte cryopreservation initially appeared to be quite high. However in the review of Okey et al the overall abortion rate was of 20% which may be potentially subject to publication bias but it's comparable to the 25% loss rate after spontaneous pregnancies (Jain JK et al, 2006).
Both the methodologies have good reproductive outcomes with limited invasiveness. The possible cons are the possible delay in chemotherapy start (14-35 Days) and high estrogen level for a short time (3-7 days).
Ovarian tissue freezing and autotransplantation:
This method involves surgical ovarian tissue extraction, freezing/thawing and transplantation back into the same patient. According to the most recent female fertility preservation guidelines, ovarian tissue freezing and autotransplantation is still considered experimental. In prepuberal girls, it is recommended to extract half or one ovary via laparoscopy or mini-laparotomy before starting chemotherapy or radiotherapy. If the risk of gonadal toxicity is minimal, extraction of less than half an ovary may be enough. After surgical extraction, ovarian cortex that contains the vast majority of oocytes is separated from medulla and further cut into pieces or strips as a preparation step for freezing. By freezing cortical ovarian

tissue, most of oocytes are preserved as well as the reproductive potential. Nowadays the standard method for cortical ovarian tissue freezing is low freezing.

When the girl gets cured from cancer, her stored ovarian tissue can be transplanted back to her after the age of puberty. Autotransplantation of frozen ovarian tissue can be either orthotopic or heterotopic.

Ortothotopic: 2 to 9 months after successful transplantation, ovarian function can resume allowing spontaneous pregnancy. We have to consider the limited evidence of this technique worldwide that has resulted in around 40 healthy lifeborns. This results confirms the feasibility of this technique for preserving the reproductive potential of prepubertal girls with cancer. In comparison to other options, this option does not delay cancer treatment considering that it does not need any ovarian stimulation. Moreover, this option can also restore both endocrine and reproductive ovarian functions for some years. Despite these advantages, this option has two major disadvantages: 1. Risk of reintroducing malignant cells; 2. The relatively short lifespan of ovarian tissue transplants. To avoid the reintroduction of malignant cells some precautions should be taken into consideration: histological examination, immunohistochemistry, and DNA analysis of ovarian tissue to exclude malignancy; to contraindicate the procedure in case of ovarian cancer or malignancies that can metastasize in ovaries. To overcome the short lifespan of ovarian tissue the following measures can be attempted: use of angiogenic factors, gonadotropins, antioxidants, antiapoptotics to the host and grafted tissue; vascular grafting or whole ovary autotransplantation.

Heterotopic: consists in retransplantation of the frozen ovarian tissue back to the same girl after the age of puberty into extra pelvic sites such as the subcutaneous space of the forearm or abdominal wall. This technique has the same risk of introducing malignant cells but it is surgically easier and it may be used when ortotopic is not possible due to radiotherapy induced pelvic adhesions. Whit this method pregnancy is possible only after ovarian pick up and in vitro fertilization. Worldwide only two healthy babies after heterotopic transplantation are described (Salama M et al, 2016)

It consists in the surgical transposition of the ovaries away from the irradiation field and it may be used when abdominal irradiation is planned. When the anticancer therapy is terminated, the ovaries may be surgically placed back into their normal anatomical sites to allow future spontaneous pregnancy. According to the most recent guidelines, oophorexy is consid-

ered debatable and it is not feasible when chemotherapy is used. However, for adult women undergoing pelvic or abdominal irradiation without chemotherapy, offering this technique should be taken into account (Salama M et al, 2016).

Theoretically, GnRH analogues inhibit hypothalamic-pituitary-ovarian axis and hence make ovaries suppressed and therefore less sensitive to gonadotoxic agents.

The concomitant use of GnRH agonists during the course of chemotherapy as a mean of preserving fertility has been investigated in several phase III studies leading to conflicting results. Some studies have shown higher rates of menses recovery using GnRH, but others didn't reproduce the same results. Major limitations of these studies were: the lack of the same patient population; their primary end points were defined differently across the different studies. Moreover, most of these studies reported on menstrual rather than an ovarian function. For these reasons the use of GnRH analogues concomitantly should not be considered as a reliable means to preserve fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted (Peccatori FA et al, 2013).

1. Should all patients be referred to a fertility unit before initiating anticancer treatments?

According to the international recommendation, all patients with potential interest in keeping their fertility should be referred to fertility unit for adequate determination of risk of infertility, chances of future conception and how to preserve it. However, we have to consider that some patients will not require the help of a fertility clinic after cancer treatment. Since several patients-and treatment related factors are associated with the risk of developing infertility, the oncofertility counseling should be tailored to the individual patients' needs. Specifically, type of treatment and patients' age are the most important factors to be taken into account when counseling the patient (Lambertini M et al, 2016).

2. Are cryopreservations strategies accepted by young cancer patients?

In men sperm cryopreservation is a widely available option in more than 95%of patients and should be encouraged for those who want to preserve fertility.

A recent review showed that only a minority of patients (8%) uses the frozen sperm. On the basis of these considerations the need to investigate the economic implications of male cancer sperm banking programs is

emerging as an important issue (Ferrari S et al, 2016).
Considering female data, from 2% to 65% of women undergo to one of the available preservation options: oncologist should discuss fertility issues and refer them to appropriate cancer centers (Lambertini M et al, 2016).
3. Which are the safety of ART of male patients previously treated with chemotherapy?
Although most of the published data are reassuring on fatherhood after cancer, the amount of evidence is still scarce. In fact, some recent published studies suggest a potential increased risk of birth defects particularly among the children born closer to a paternal cancer diagnosis and caution should be taken in counseling these patients (Lambertini M et al, 2016).
4. Is it safe to perform a controlled ovarian stimulation (COS) in female cancer patients?
The current limited data suggest the safety of COS in cancer patients. Letrozole (or tamoxifene) should be incorporated in protocol for COS in cancer patients with hormone-responsive tumors (Lambertini M et al, 2016).
5. Focus on fertility preservation strategies on cervical cancer.
Nowadays, the standard surgical procedure for patients with early stage cervical cancer is radical hysterectomy and pelvic lymphadenectomy but this technique does not preserve fertility. The radical trachelectomy came in clinical practice more than three decades ago but the oncological outcomes were still uncertain. Six different types of fertility sparing surgery are appropriate to treat stage IB1 cervical cancer:
- Simple trachelectomy or cone resection
- Neoadjuvant chemotherapy plus conservative surgery
- Abdominal radical trachelectomy : lapatotomic, laparoscopic, robot-assisted
Selection of approach depends mainly on tumor size and lymphovascular space involvement status.
Beyond considering the oncological outcomes, the oncologist should discuss with the patient to find out the best balance between the risk of recurrence, the best chance for cure, and the best fertility results. Four ongoing observational studies are investigating the various strategies (Bentivegna E et al, 2016).

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ADVANCED MELANOMA
CURRENT TREATMENT AND NEW APPROACH

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In the treatment of metastatic melanoma, the use of chemotherapy was previously generally considered as being merely palliative in intent given the disappointing results that had been achieved. For example, the well known meta-analysis by Korn et al.(Korn EL et al., 2008) reported that chemotherapy, either single agent or combination, was associated with a median survival of 6.2 months, a median progression free survival (PFS) of 1.7 months, and a 1-year overall survival (OS) rate of 25.5%.
However, since 2010, the development of novel drugs has revolutionized the prognosis of patients with a melanoma. There are currently two major classes of drugs in the therapeutic landscape for advanced melanoma: monoclonal antibodies directed against specific immune cell receptors (immunomodulating antibodies) and small molecule inhibitors (targeted therapy). Both these groups of drugs have been shown to improve PFS and OS beyond what was previously achieved with chemotherapy. As a result, the use of chemotherapy has been largely superceded by the use of targeted therapies (e.g. BRAF inhibitors) and/or immunomodulatory monoclonal antibodies (anti-CTLA-4 and anti-PD-1 antibodies). Today's challenge is to optimally combine or sequence these two distinct classes of drugs in order to further improve the survival of patients while avoiding intolerable toxicity.

Cutaneous melanoma has always been considered an immune-sensitive cancer, as evidenced by the huge number of scientific studies on immunotherapy in both the adjuvant and the metastatic settings. Unfortunately, initial cancer vaccine studies showed a low response rate and no clear survival benefit. How do we explain this failure? Melanoma cells, as with cancer cells in general, can evade the common mechanisms of immune response. In particular, activation of the immune system involves antigen presentation to and recognition by T and B lymphocytes. T cells are activated when the T cell receptor (TCR) binds the antigen being presented by the major histocompatibility complex (MHC). T cells then proliferate and

migrate into the tumor site, where they exert their anti-cancer effect. The interaction between T cells and tumor antigens is mediated by receptors and other co-stimulatory and co-inhibitors receptors which act as 'checkpoints'. An example of immune response mediated by co-stimulatory molecules is the binding between CD28 on T cells and B7 on antigen-presenting cells. This binding induces the co-stimulation signal required for the final activation of the T cell after binding to the TCR-MHC-antigen complex. Tumor cells can inhibit the T cell response through the expression of various ligands that interact with inhibitor receptors on T cells, such as cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1). To counter these immune-evasive mechanisms, monoclonal antibodies targeting these receptors have been developed (O'Day SJ et al., 2007).

CTLA-4 is a receptor upregulated on activated cytotoxic T lymphocytes that inhibits the T cell mediated immune response by competing with CD28 for binding to CD80 (B-7) and CD86 on antigen-presenting cells, with a consequent inhibition of T cell proliferation (O'Day SJ et al., 2007). Ipilimumab (Yervoy®, Bristol-Myers Squibb) is a human IgG1 monoclonal antibody that binds to CTLA-4, thereby preventing binding between CTLA-4 and B7 and leading to the activation and proliferation of T lymphocytes. Phase I-II studies have demonstrated the efficacy and safety of this drug in metastatic melanoma at various doses. In a randomized double-blind study, a dose-dependent effect was observed with 0.3, 3 and 10 mg/kg doses, with the best response rate (BORR) obtained with the dose of 10 mg /kg (11.1%; 95% CI: 4.9-20.7) (Wolchok Jd et al., 2010). In another phase II single-arm study with ipilimumab 10 mg/kg, a median survival of 10.2 months and a survival rate of 47.2% at 1 year were achieved (O'Day SJ et al., 2010). This study also showed that the use of immune-related response criteria allows the identification of patients who, although considered to have disease progression according to WHO criteria, obtained a survival benefit with treatment.((O'Day SJ et al., 2010; Wolchok Jd et al., 2009).
A randomized, 3-arm phase III study with 676 pretreated patients compared ipilimumab (n=137) with the combination of ipilimumab and a vaccine, GP100 (n=403), and vaccine alone (n=136 patients). Ipilimumab was administered at a dose of 3 mg/kg every 3 weeks and the primary endpoint of the study was OS. Patients treated with ipilimumab monotherapy

achieved a median survival of 10.1 months compared to 6.4 months in patients treated with the vaccine (hazard ratio [HR] 0.66, p=0.0026). No difference was observed between ipilimumab alone and in combination with the vaccine (HR 1.04, p=0.76). Approximately 20% of patients were alive after more than 2 years of follow-up and without the appearance of new adverse events (Hodi FS et al., 2010). In another randomized phase III trial (BMS CA184-024, NCT00324155) conducted in 502 patients with previously untreated metastatic melanoma, OS was higher in patients treated with combined ipilimumab 10 mg/kg and dacarbazine than in those receiving dacarbazine alone (11.2 vs. 9.1 months, HR 0.72, p<0.001) (Robert C et al., 2011). These phase III studies led to the registration of ipilimumab for the treatment of metastatic melanoma in 2011 in the US and Europe (2013 in Italy). A subsequent meta-analysis that included more than 4800 patients enrolled and treated with ipilimumab in different studies showed an OS rate at 3 years of 22% (95% CI: 20-24%), with 20% of patients still alive at 10 years (Schadendorf D et al., 2015) . More than 80% of patients treated with ipilimumab experienced immune-related adverse reactions, with colitis, hepatitis and dermatitis the most frequent. Serious adverse reactions occured in 10-26% of patients; however, these were mostly reversible and could be managed if detected early and treated according to immune-related toxicity management algorithms.

PD-1 is a transmembrane protein type I receptor expressed on activated CD4 and CD8 T lymphocytes that modulates the immune response by triggering a negative signal (immunosuppression). Once the receptor is activated by its ligand, PD-L1, it induces the reduction of T cell proliferation and the release of interleukin (IL)-2 and reduces T cell survival through dephosphorylation. Expression of PD-L1 on tumor cells is able to activate the PD-1 pathway (Swanson MS et al., 2015). PD-L1 is constitutively expressed on macrophages and can be rapidly upregulated by different tissues and tumors in response to interferon-gamma and other inflammatory mediators. In addition to binding to PD-1, PD-L1 can also bind CD80 on activated T cells. This binding may explain the differences in terms of clinical activity and toxicity between anti-PD-1 and anti-PD-L1 agents. Another ligand of PD-1 is PD-L2, which is expressed on macrophages and dendritic cells, although its impact on the control of the immune response is less well understood. Tumor expression of PD-L2 could be a further potential immunoevasive mechanism.

Pembrolizumab is an anti-PD-1 IgG4 type human monoclonal antibody. In a phase I study, 135 patients with advanced melanoma were treated with pembrolizumab 10 mg/kg every two weeks, 10 mg/kg every three weeks, or 2 mg/kg every three weeks (Hamid O et al., 2013). The rate of response in all patients was 38% (95% CI: 25-44), with the highest observed response rate at a dose of 10 mg/kg every 2 weeks (52%, 95% CI: 38-66). Responses were long-lasting in most patients and, at a median follow up of 11 months, 81% of patients in response (42 of 52) were still receiving treatment. The median PFS was 7 months. In a recent update of this study, at a median follow-up of 14.8 months among 655 patients with measurable disease, the ORR according to RECIST criteria was 38% in patients not pretreated with ipilimumab and 29% in those who were pretreated.11 Responses were durable, with 80% still ongoing at the the time of analysis. The median PFS was 5.5 months in ipilimumab-naïve patients and 4.9 months in pretreated patients. The median OS was not reached, with an OS of 67% at 1 year and 50% at 2 years. Overall, 12% of patients experienced grade 3-4 adverse events and 4% discontinued treatment due to toxicity. The most common toxicities were fatigue (36%), itching (24%), rash (20%), diarrhea and arthralgia (both 16%). There were no deaths related to the drug. The expression of PD-L1 in the tumor was assessed as a predictive marker for response to pembrolizumab and, although a positive PD-L1 status was correlated with a greater response, the absence of PD-L1 expression did not preclude a clinical response (Daud A et al., 2015).
Based on these results, two additional randomized trials were conducted, one in ipilimumab-pretreated patients and one in ipilimumab-naïve patients. In the KEYNOTE-002 study, 540 patients with advanced melanoma refractory to ipilimumab were randomized to pembrolizumab 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks or chemotherapy (Ribas A et al.,2015). Both PFS, which was the primary endpoint of the study, and ORR were significantly higher in the two pembrolizumab groups than with chemotherapy. Treatment was well tolerated, with adverse events of grade 3-5 reported in 11% and 14% of patients in the pembrolizumab groups and 26% of chemotherapy-treated patients. Pembrolizumab also showed superiority in terms of BORR, PFS and OS versus ipilimumab in non pretreated patients in the randomized phase III KEYNOTE-006 trial (Robert C et al.,2015). The final OS survival analysis presented at ASCO 2016 showed that, at a follow up of ≥21 months, median OS was not reached for pembrolizumab compared with 16.0 months for ipilimumab,

while 2-year OS rates were 55% and 43% respectively (Adil Daud et al., 2016).

Nivolumab is another IgG4 type human monoclonal antibody that targets the PD-1 protein. In a phase I study, 107 patients were treated with increasing nivolumab dosage and achieved a median OS of 17 months, and survival rates at 1, 2, 3, and 4 years of 63%, 48%, 42% and 32%, respectively (41% at the 3 mg/kg dose used for the phase III studies) (Hodi FS et al., 2015). The response rate observed was 32%. In 21 patients, treatment was discontinued for reasons other than disease progression and 67% of these patients continued to be progression-free. The expression of PD-L1 by the tumor appeared to be predictive of response to treatment. On the basis of these results, randomized phase III trials with nivolumab were conducted in different subgroups of patients. In the Checkmate 066 study (NCT01721772), 418 ipilimumab-naive BRAF wild type patients were randomized to double-blind treatment with nivolumab or dacarbazine (Robert C et al., 2015). OS was significantly higher in the group treated with nivolumab, with a survival rate at one year of 73% versus 42% (HR 0.42 99.8% CI: 0.25-0.73). PFS was superior in the nivolumab arm (5.1 versus. 2.2 months), as was the ORR (40% versus 14%). In the Checkmate 037 study (NCT01721746), patients previously treated with ipilimumab were randomized to treatment with nivolumab or chemotherapy (Weber JS et al., 2015). A planned interim analysis at 6-months follow-up included 167 patients (nivolumab, n=120; chemotherapy, n=47) and showed superiority of nivolumab. The response rate in patients treated with nivolumab was 32% (95% CI: 23.5-40.8) compared to 10% (95% CI: 3.5-23.1) with chemotherapy while median duration of response was also higher in patients treated with nivolumab with median not reached (36/38 patients [87%] still in remission) compared to a median of 3.5 months for chemotherapy patients. Although a greater number of responses to nivolumab were observed in PD-L1-positive patients, some patients with negative PD-L1 status also responded to treatment. These studies led to approval of nivolumab for the treatment of advanced melanoma by the USA and Europe.

In recent years, the use of combined anti-PD1 and CTLA-4 therapy has become a topic of increasing attention. The efficacy of the combination of nivolumab and ipilimumab was reported in phase I and II randomized studies, both of which showed an increase in objective response and PFS (Wolchok JD et al., 2013; Postow MA et al., 2015). In a phase III double-blind trial (Checkmate 067, NCT01844505), 945 treatment-naïve

patients were randomized to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone (Larkin J et al., 2015). At a 9-month median follow-up, median PFS was higher with the combination treatment and with nivolumab monotherapy versus ipilimumab alone (11.5 versus. 2.9 months, HR 0.42 [95% CI: 0.31-0.57] and 6.9 versus 2.9 months, HR 0.57 [95% CI: 0.43-0.76], respectively). However, the study was not designed to compare the combination of ipilimumab plus nivolumab with nivolumab monotherapy, although PFS in the combination arm was superior to nivolumab monotherapy (median PFS 11.9 versus 6.9 months, HR 0.74 [95% CI: 0.60-0.92]). The ORR for the combination, nivolumab alone and ipilimumab alone was 58%, 44% and 19%, respectively. Complete response rates were 11.5%, 8.9% and 2.2%, respectively. Grade 3-4 adverse events were reported in 55% of patients treated with combination, 16% with nivolumab alone and 27% with ipilimumab alone. Median PFS for patients with positive expression of PD-L1 was 14 months for both the combination and nivolumab monotherapy and 4 months for ipilimumab monotherapy; however, the median PFS for patients who were PD-L1 negative was 11.5, 5.3 and 3 months respectively. ORR for PD-L1 positive patients was 72%, 58% and 21% and 55%, 44% and 18%, for PD-L1 negative patients receiving combination, nivolumab or ipilimumab, respectivley. In September 2015, the FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

Another group of checkpoint inhibitor drugs being developed for the treatment of melanoma are the anti-PD-L1 antibodies. One of these, atezolizumab (MPDL3280A), showed an ORR of 29% with 43% of patients progression-free at 24 weeks in a phase I dose escalation study that enrolled 45 patients with advanced melanoma (Hamid O et al.,2013). Additional data will be available with the expansion phase of the study.

Another anti-PD-L1 is durvalumab (MEDI4736), an IgG1κ human monoclonal antibody that has high affinity and selectivity for PD-L1 and is designed to eliminate cell-mediated antibody-dependent cytotoxicity. The dose selected for clinical development is 10 mg/kg every 2 weeks. Phase I trials both as monotherapy and in combination are ongoing in many solid tumors and melanoma. In melanoma, durvalumab is being tested in combination with MEK inhibitors and BRAF inhibitors. Durvalumab is also undergoing clinical development in non-small cell lung cancer (NSCLC) (Ibrahim R et al., 2015).

The identification of the MAPK-pathway and the development of selective BRAF inhibitors were milestones in the history of the treatment of advanced melanoma. RAS was one of the first oncogenes identified in the carcinogenesis of human cancers and the hyperactivation of the MAPK pathway induced by RAS is one of the most frequent events in the development of tumors (Malumbres M et al., 2003). Mutations of NRAS activating the proliferation of melanoma were identified for the first time in the 1970s, but the real importance of the MAPK pathway involved the identification of mutations in the protein kinases of RAF (Davies et al., 2002). BRAF mutations are present in about 45% of cutaneous melanomas, whereas mutations in NRAS represent about 15-25% (Hocker T et al., 2007). BRAF mutations significantly increase the catalytic activity of the BRAF protein, leading to activation and constitutive phosphorylation of the MERK and ERK signaling cascade inside the RAS-RAF-MAPK(Davies et al., 2014). In recent years, drugs have been selectively developed that target the mutated form of BRAF or MEK, which inhibit the signal transduction of the MAPK pathway.

Vemurafenib was the first inhibitor of BRAF registered by the FDA in 2011, based on the results of a clinical phase III study (BRIM-3) that showed a statistically significant benefit in terms of PFS (5.3 versus 1.6 months) and OS (13.6 versus 9.7 months) versus dacarbazine in patients with treatment-naïve BRAF-mutated metastatic melanoma(Chapman et al., 2011). Dabrafenib, another inhibitor of BRAF, was also compared with dacarbazine in a clinical phase III study (BREAK-3) and showed similar results to vemurafenib in terms of PFS (5.1 versus 2.7 months) and OS (Hauschild et al., 2012). This led to the approval of dabrafenib by the FDA in 2013. The response rates and PFS of patients with BRAF mutation V600K were significantly lower than those of patients with mutation V600E(Falchook et al., 2012). The action of both BRAF inhibitors is characterized by a rapid response, with rapid improvement of the symptoms related to the disease and performance status, especially in patients in very poor clinical condition (the so-called 'Lazarus Effect'). These improvements are achieved thanks to rapid metabolic shutdown of the disease, with slower volume reduction of metastatic lesions.

The toxicity profile of both BRAF inhibitors is similar, characterized by rash, fatigue and joint pain as the most common side effects, while the difference between the two drugs is in the greater occurrence of photosensitivity with vemurafenib and more frequent fever with dabrafenib. Both

BRAF inhibitors induce the development of squamous cell carcinomas of the skin (SCC) and keratoacanthoma (KA) as frequent side effects, as observed in 14% of patients treated with dabrafenib and 26% of patients treated with vemurafenib. The development of these tumors occur in the first two months therapy (Sosman et al.,2012; Larkin et al.,2014). This type of toxicity seems to be secondary to paradoxical activation of the MAPK pathway in keratinocytes concurrent with the activation of the signal mediated by mutations of RAS (Oberholzer et al.,2012; Su et al., 2012). The combination of a MEK inhibitor with an inhibitor of BRAF can avoid this type of hyperactivity. In fact, as observed in early clinical trials, the rate of cutaneous SCC is significantly lower (5.1% versus 15-20%) when the two inhibitors are administered concomitantly. Another highly selective inhibitor of BRAF is encorafenib (LGX818), which showed greater antiproliferative activity of melanoma cells at the preclinical stage compared with vemurafenib and dabrafenib and is currently in clinical development. Since their discovery, the MEK inhibitors have been considered especially promising because they are able to inhibit melanoma cell lines with NRAS mutations as well as those with BRAF mutations (Joseph EW et al., 2010). Trametinib was the first MEK inhibitor approved by the FDA in 2014 on the basis of positive results from the phase III METRIC study that showed a higher PFS versus chemotherapy in patients with BRAF-mutated advanced melanoma. Cobimetinib is another MEK inhibitor that has shown clinical activity in patients with solid tumors (Hoeflich KP et al., 2012). Another potent, highly selective inhibitor of MEK is binimetinib (MEK162, ARRY-438162), which has shown a significant antiproliferative activity in NRAS-mutated and BRAF-mutated melanoma cell lines in in vivo and in vitro preclinical models (Winski et al., 2010). Recently, data from the NEMO trial in patients with NRAS-mutated metastatic melanoma were reported with binimetinib showing improvements over dacarbazine in several clinically relevant endpoints including PFS, ORR and disease control rate with a manageable toxicity profile (Reinhard D et al., 2016).

The majority of patients treated with BRAF inhibitors undergo disease progression after an average of 6-7 months, with this attributed to the onset of secondary resistance mechanisms. In some patients, this resistance is 'MEK dependent'. Thus, concomitant inhibition of MEK and BRAF may show a greater response rate and prolonged duration of response

compared with BRAF inhibitor monotherapy. In a phase III clinical trial (COMBI-D)comparing the combination of dabrafenib and trametinib versus dabrafenib monotherapy, the median PFS of the combination was 11.0 months versus 8.8 months with monotherapy (HR 0.67; 95% CI: 0.53-0.84; p<0.001) (Long et al.,2015). The response rate was 69% for the combination and 53% for dabrafenib alone (p=0.002). The HR for death was 0.71 (95% CI: 0.55-0.92; p=0.02). The toxicity profile was similar in both cohorts, but the incidence of SCC was higher in the dabrafenib treatment arm (9% versus 28%). Moreover, survival rate in the combination group was consistent with that of the phase I /II study, with 74% of patients alive at 12 months and 51% at 24 months. The combination of dabrafenib and trametinib was also compared with vemurafenib monotherapy in the COMBI-V phase III clinical trial (Robert C et al., 2015). The HR for death was 0.69 (95% CI: 0.53-0.89; p=0.005) and the median PFS was 11.4 months for the combination therapy versus 7.3 months for vemurafenib alone (HR 0.56; 95% CI:0.46-0.69; p<0.001). The response rate was 64% (95% CI: 59-69) in the dabrafenib plus trametinib combination group and 51% (95% CI: 46-57) in the monotherapy group. In another phase III study, the combination of vemurafenib and cobimetinib was compared with vemurafenib monotherapy (Larkin J et al.,2014). This trial met its primary endpoint, PFS, which was 9.9 months with vemurafenib plus cobimetinib versus 6.2 months with vemurafenib alone (HR for death or progression: 0.51; p<0.001). An update of this study showed a PFS of 12.3 months for the combination arm compared with 7.2 months for monotherapy and a response rate of 69.6% compared to 50%. The majority of toxicities observed with vemurafenib and cobimetinib in combination were mild or moderate (grade 1 or 2), with 49% of patients in both treatment arms having grade 3 adverse events. Encouraging results have also been reported with the combination of encorafenib and binimetinib in a phase I/II study in patients with BRAF-mutated solid tumors(Kefford R et al., 2013). A phase III study, the COLUMBUS trial, comparing this combination with encorafenib monotherapy and vemurafenib monotherapy is ongoing.

Immune-checkpoint inhibitors have been shown to help provide an effective immune response against melanoma, although their use can be associated with immune-related side effects. As of now, the anti PD-1 antibodies, pembrolizumab and nivolumab, should be the first choice therapeutic approach in patients with advanced melanoma. Ipilimumab is likely to

retain a role in combined or sequential use with anti-PD-1 agents. However, the optimal combination and/or sequencing of various treatments, especially in patients with mutations suitable for targeted therapy as well as immunotherapy, is yet to be defined and clinical studies to investigate such questions are being conducted.

In an effort to combine the speed of response of targeted therapy with the long-term efficacy of immunotherapy, and given the immune-modulating effect of targeted therapy on the tumor microenvironment, various combination studies have been conducted. However, the first combined ipilimumab and vemurafenib experience was unsuccesful due to excessive grade 3 liver toxicity. The other inhibitor of BRAF, dabrafenib, may be combined with ipilimumab with acceptable tolerability, as demonstrated in a phase I clinical trial. However, treatment with the triple combination of dabrafenib, trametinib and ipilimumab was stopped early due to a high rate of intestinal perforations.

The combination of dabrafenib and trametinib has also been assessed in combination with durvalumab in a phase I study that enrolled both BRAF-mutated and wild-type patients. Activation of the immune system with increased lymphocytic infiltrate and increase in levels of interferon gamma was greatest in the triple combination arm, which achieved a response rate of 69% and a disease control rate of 100%. Responses were rapid, as observed frequently during treatment with BRAF inhibitors with or without MEK inhibition, and durable, as is often observed with immunotherapy. The safety profile was particularly favorable and phase II studies to evaluate the activiy of this triple combination are already planned (Gordon M et al., 2014). The most innovative clinical trials are currently investigating triple combination approaches and another open-label, multicentre clinical trial currently underway is evaluating the activity and safety of a triple immuno-target association, combining dabrafenib, trametinib and pembrolizumab (NCT02130466). Another example is the multicentre phase II clinical trial (NCT01820364) that is studying the activity and safety profile of the combination of encorafenib, binimetinib and LEE-011 (ribociclib), an inhibitor of cyclin-dependent kinase (CDK) that targets the pathway of cyclin D1/CDK4 and D3/CDK6.

Another important consideration is that the lack of biomarkers makes the selection of patients for treatment difficult, in particular combined or sequential treatment approaches. This is especially so given that PD-L1 cannot today be used as a predictive marker for response to treatment

with anti-PD-1 or PD-L1 drugs. Future research on the identification of effective biomarkers is essential to help guide therapy.

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MOST FREQUENT TOXICITIES AND NEW SIDE EFFECTS OF NOVEL DRUGS AND/OR TREATMENTS

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The therapeutic armamentarium for metastatic melanoma has been evolving rapidly, with a plethora of drugs showing effectiveness in several large, well-conducted phase 3 trials (Vennepureddy A et al., 2016). In the past 5 years, 7 novel agents have received FDA approval: MAP-kinase inhibitors (vemurafenib, dabrafenib, trametinib and cobimetinib) and immunologic checkpoint blockade antibodies (ipilimumab, nivolumab and pembrolizumab). Although these targeted agents are thought to be more specific and less toxic then traditional chemotherapy, they are associated with a variety of side effects. Most of these toxicites are directly related to the specific molecular target in normal tissues inhibited or modulated by the specific drug. Such toxicities are termed mechanism-based toxicities. Other toxic effects are instead related to individual drugs.
Prompt and active toxicity management is important to ensure maximum treatment benefit and avoid unnecessary treatment discontinuation. For this purpose it is essential the collaboration with a team of subspecialists (gastroenterologists, hepatologists, endocrinologists, neurologists, ophthalmologists, dermatologists, rheumatologists, infectious disease specialists, and possibly others). Subspecialists may have no knowledge of the recommended treatment algorithms for toxic effects of targeted agents. Presentations and discussions at tumor boards and staff meetings may to facilitate collaboration and patient care. Good communication between patient and health care providers also contributes to successful and safe treatment with these drugs.

The Ras/Raf/MEK/ERK pathway, also known as the MAPK (mitogen-activated protein kinase) pathway, is a signal transduction cascade relaying extracellular signals from plasma membrane to nucleus via an ordered series of consecutive phosphorylation events (Garnett MJ et

al., 2004). In response to a variety of cellular stimuli, including growth factor-mediated activation of receptor tyrosine kinases (RTKs), Ras assumes an activated, GTP-bound state, leading to recruitment of Raf from the cytosol to the cell membrane where it becomes activated, likely via an Src-family tyrosine kinase (Minden A et al.,1994; Lange-Carter CA et al.,1994; Marais R et al., 1995). Activated Raf causes the phosphorylation and activation of MAP kinase extracellular signal regulated kinases 1 and 2 (MEK1/MEK2), which in turn phosphorylate and activate extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2) at specific Thr and Tyr residues (Marais R et al.,1997; Mason CS et al., 1999; Xu S et al., 1995). Activated ERK translocate to the nucleus and phosphorylate several nuclear transcription factors (Elk-1, Myc, CREB, Fos and others) which bind promoters of many genes, including growth factor and cytokine genes that are important for stimulating the cellular proliferation, differentiation, and survival of multiple cell types (Deng T et al.,1994; Davis RJ 1995; Robinson MJ et al., 1998; Aplin A E et al., 2001; Tresini M et al., 2001; Adachi T et al., 2002; Troppmair J et al., 2003).
About 50% of melanomas hold an activating mutation in BRAF, the most common being BRAF V600E, which renders the kinase constitutively active (Davies H et al., 2002; Solus Jf et al., 2013; Lito P et al., 2013). The discovery of this mutation allowed the development of two potent tyrosine kinase inhibitors of the BRAF(V600E) kinase, vemurafenib and dabrafenib, which significantly improved the outcome of metastatic melanoma (Chapman P et al.,2011; Hauschild A et al.,2012). However tumor resistance to BRAF inhibitors after a certain period of treatment has limited their clinical benefit. The reactivation of the MAPK pathway is the most frequent cause of acquired/secondary resistance; it may be driven by events that occur upstream (upregulation and activation of the RTK, NRAS activating mutations) or downstream (activating MEK1/2 mutation, or at the level of BRAF) (Spagnolo F et al.,2015); this discovery led to development of two MEK inhibitors, trametinib and cobimetinib, and to explore the efficacy of their combination with a BRAF inhibitor in order to bypass tumor resistance (Flaherty K et al., 2012; Long G et al., 2014; Grob JJ et al., 2015; Larkin J et al., 2014).

The most common adverse effects related to BRAFi are dermatologic events, such as rash, pruritus, photosensitivity, alopecia, hand-foot skin reactions, hyperkeratosis, keratoacanthoma and cutaneous squamous cell

carcinoma (SCC) (Chapman P et al.,2011; Hauschild A et al.,2012). However the prevalence of these cutaneous toxic effects differs among vemurafenib and dabrafenib; for example, photosensitivity and cutaneous squamous cell carcinoma are more frequent during therapy with vemurafenib compared to dabrafenib.

Photosensitivity is related to the drug's chemical structure and sun exposure (Dummer R et al., 2012). Therefore, patients should avoid prolonged sun exposure and use protective barriers (e.g., long sleeves, hat, sunglasses and sunscreens) when exposed to the sun. Photosensitive skin reactions develop within days of drug initiation and could insist during treatment, compromising patients' quality of life and their compliance to therapy (Lacouture ME et al., 2013; Welsh SJ et al., 2015). In these cases, dabrafenib may be considered an appropriate alternative treatment option for patients who are intolerant to vemurafenib due to photosensivity.

SCC occurs in 14–26% of patients treated with a BRAF inhibitor, usually within 2–3 months of starting therapy (Sosman JA et al., 2012; Larkin J et al., 2014); this toxicity has been attributed predominantly to "paradoxical ERK activation," or the ability of BRAFi to stimulate RAF signaling in BRAF wild-type cells, hyperactivating ERK and driving oncogenesis (Hatzivassiliou G et al., 2010; Poulikakos PI et al., 2010; Heidorn SJ et al., 2010; Halaban R et al., 2010; Karreth FA et al., 2009). It has been shown vemurafenib, but not dabrafenib, suppress apoptosis through the inhibition of multiple off-target kinases upstream of c-Jun N-terminal kinase (JNK). NK signaling is suppressed in multiple contexts, including in SCC of vemurafenib-treated patients, as well as in mice (Vin H et al., 2013). Therefore suppression of JNK-dependent apoptosis is a significant, independent mechanism that cooperates with paradoxical ERK activation to induce SCC. This might account for the relatively high rate of SCC induction with vemurafenib relative to dabrafenib.

The treatment of SCC and keratoacanthoma is a simple surgical resection without dose interruptions or reductions. For patients with multiple SCCs/KAs, multiple excisions may not be feasible; alternative surgical procedures (e.g., saucerization), non-surgical modalities (e.g., curettage, electrodessication, cryosurgery,photodynamic therapy), and other medical therapies (e.g., topical fluorouracil, systemic acitretin) have been reported (Alloo A et al., 2012; Anforth R et al., 2012) and can be considered; however, there are no conclusive data on the safety of these treatments.

Radiotherapy and psoriasis are two conditions in which concomitant

BRAF inhibitor therapy is feasible with an acceptable increase in cutaneous toxicity (Anker CJ et al., 2016; Pulvirenti T et al., 2016; Fawaz B et al., 2016). Other frequent toxicities of BRAFi are arthralgia, fatigue, nausea, diarrhea, headache and vomiting (Chapman P et al., 2011; Hauschild A et al., 2012). The incidence and severity of arthralgia is probably higher with vemurafenib compared with dabrafenib. Any joints may also be affected and the pain may be intermittent or constant. Arthralgia can regress and be less problematic after the first few months. Pyrexia and chills are common with dabrafenib but rare with vemurafenib. Fever can usually be managed with paracetamol, steroids and/or temporary drug dose interruption.

BRAFi are associated with increased risk of QTc prolongation. It has been proposed a mechanism through which BRAF inhibitors may determine their cardiotoxic effect (Bronte E et al., 2015). A recent study has shown that BRAF is a powerful regulator of hERG K+ channels, which have a critical role in the repolarization process of the action potential in cardiomyocytes. Cells treated with the BRAF inhibitor PLX-4720 highlighted a down-regulation of hERG channel protein quantity and activity. Hence, it is possible to consider that BRAF inhibitors down-regulating hERG channels protein quantity and down-regulating their activity. This event determines a slowdown in repolarization, which leads lastly to QT prolongation (Pakladok T et al., 2014; Jonsson MK et al., 2012). Treatment with BRAFi is therefore not recommended in patients with uncorrectable electrolyte abnormalities (including low magnesium), long QT syndrome or those who are taking medicinal products known to prolong the QT interval. Initiation of treatment with dabrafenib or vemurafenib is also not recommended in patients with QTc greater than 500 ms.

A number of ophthalmologic complications have been rarely observed during treatment with BRAF targeted agents; the most common ocular toxicity is uveitis. When it occurs, it tends to develop over weeks and months of drug exposure. In general it is easily managed with temporary dose interruption, ophthalmology review, a course of topical steroids and in most cases a dose reduction.

With the increasingly extensive use of BRAFi, literature is being enriched with case reports that describe new and rare cutaneous and non-cutaneous toxicities related to the use of these agents (Jhaveri KD et al., 2015; Wanchoo R et al., 2016; Keating M et al., 2016; Munch M et al.,2016; Ramani NS et al., 2015; Maldonado-Seral C et al., 2013; Bellòn T et al., 2016). Rare/emergent side effects due to BRAFi are shown in table 1.

The most common adverse effects with MEKi are rash, fatigue, diarrhea, peripheral edema, hypertension and acneiform dermatitis (Falchook GS et al., 2012; Kim KB et al., 2013; Flaherty KT et al., 2012; Rosen L et al., 2011). Secondary skin neoplasms do not occur with the MEKi. Decrease in left ventricular ejection fraction (LVEF) or ventricular dysfunction, ocular toxicities and interstitial lung disease (ILD) or pneumonitis are less commonly observed events and likely are class effects of MEK inhibition (Falchook GS et al., 2012; Rosen L et al., 2011).

Skin reactions occur within days after the treatment starts. The nature of the rash observed with MEKi is papulopustular, and different to the hyperkeratotic maculopapular rash caused by vemurafenib. Another skin toxicity triggered by MEKi is acneiform eruption that tends to appear on the face, chest and back (Anforth R et al., 2014).

LVEF should be assessed prior to initiating treatment with MEKi, a month after the start of therapy and thereafter at intervals of about 3 months during treatment. MEK inhibitor should be discontinued for up to 4 weeks in patients who have asymptomatic, absolute decrease in LVEF <10% or ≥ 10-20% from baseline and the ejection fraction below the lower limit of normal (LLN). If LVEF improves to near normal value, treatment can be resumed at lower dose level; if it doesn't improve to normal value after two dose reductions, treatment must be permanently discontinue. In the presence of symptomatic reducted ejection fraction or absolute decrease in LVEF >20% from baseline that is below LLN, MEK inhibitor must be permanently discontinued.

ILD or pneumonitis occurred in 2.4% of patients treated with trametinib monotherapy (Fla herty KT et al., 2012). The patients who develop cough, shortness of breath, or abnormal chest signs during MEKi therapy should be investigated with plain chest X-ray or chest computed tomography scan, and treatment should be halted at least temporarily if pneumonitis is suspected. MEK inhibitor must be permanently discontinued in patients with certain diagnosis of ILD or pneumonitis.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachments (RPEDs) rarely occur during MEKi therapy. These ocular toxicities usually present acutely within the first week of the first dose. The clinical presentation is always bilateral and often symmetrical. Mild cases of RPEDs are usually characterized by a single serous retinal detachment that may be accompanied by minimal or more substantial subretinal fluid. In moderate cases, multifocal serous retinal detachments can be seen involving the fo-

vea and peripheral macular area. More severe cases may develop intraretinal cysts and/or a disarrangement of the outer retinal layers (Stjepanovic N et al., 2016). The protective function of MEK on the retinal pigment epithelium against oxidative stress, light-induced damage and inflammation could explain the pathophysiological mechanism of MEKi retinopathy (Jiang Q et al., 2009; Huang W et al., 2009).
Before initiating MEKi treatment, an ophthalmologic assessment with documentation of baseline visual acuity should be performed and treatment avoided in patients with preexisting ocular conditions such as glaucoma. Cases of MEKi retinopathy are often mild and frequently they resolve rapidly without treatment interruption or dose modification (Urner-Bloch u et al., 2014). Patients describing more clinically significant visual symptoms, such as blurred vision, altered color perception, shadows, light sensitivity, metamorphopsia and glare, should stop the therapy, undergo urgent ophthalmologic review, and if symptoms resolve, they can be retreated with a lower drug dose. If ocular symptoms do not improve within three weeks or in the presence of RVO, MEK inhibitor must be permanently discontinued. Rare/emergent side effects due to MEKi are shown in table 1. Class effects of BRAF and MEK inhibition are listed in Table 2.

Melanoma is considered an highly immunogenic tumor (Soengas MS et al., 2003; Mukherji B et al., 2013), a theory supported by several observations such as the presence of lymphoid infiltrates at the site of primary melanoma associated with pathologic evidence of tumor regression (Bulkley GB et al., 1975; Lowes MA et al., 1997; Wenzel J et al., 2005), melanoma with better outcome in patients who develop autoimmune events (e.g., vitiligo) (Quaglino P et al., 2010) and worse outcome in patients with immunodeficiency (Vajdic CM et al., 2009; Frankenthaler A et al.,2010; Dillon P et al., 2011).
Cancer, including melanoma, bypasses immune surveillance by expressing ligands that engage inhibitory receptors inducing tolerance among tumor specific T cells (Mellman Iet al., 2011). Immune checkpoints cytotoxicT-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) are involved in regulation of immunological tolerance in order to prevent autoimmunity. CTLA-4 is a transmembrane inhibitory receptor expressed on activated T lymphocytes. Upon binding to B7.1 or B7.2, CTLA-4 down-regulates T cell activation by inducing cell cycle arrest, inhibiting IL-2 secretion, and by down regulating T-cell cytokine receptors (O'Day SJ et al., 2007). Treatment with ipilimumab (anti-CTLA-4 antibody) blocks

this negative signal resulting in increased T-cell proliferation and promoting the generation of effector T cells (Peggs KS et al., 2006). Programmed cell death 1 (PD-1) is a receptor expressed by activated T and B cells. Its binding with programmed cell death ligand 1 (PD-L1) and PD-L2, expressed on antigen-presenting cells and on cancer cells and tumor-infiltrative macrophages, delivers a negative signal to lymphocytes (Iwai Y et al., 2002; Dong H et al., 2002). As with anti-CTLA-4 therapy, antibodies against both PD-1 (nivolumab and pembrolizumab) and PDL1 inhibit this down-regulatory pathway, enhancing anti-tumor immune responses.

As CTLA-4 acts as a negative T-cell co-stimulatory signal, maintaining the peripheral T-cell homeostasis and tolerance to self or environmental antigens, CTLA-4 blockade with ipilimumab can result in an autoimmune damage of various organ systems, leading to immune-related adverse events (IrAEs) (Thumar JR et al.,2010; Di Giacomo AM et al.,2010; Kaehler KC et al., 2010). They appear to be dose-related and typically low-moderate grade and manageable, but can also be serious and life threatening if not recognized early and treated with appropriate measures (Vosken CJ et al., 2013). The skin and gastrointestinal tracts are most frequently involved, while hepatic, endocrine, and neurologic events are less common (Weber JS et al., 2012). The time to onset of irAEs varies according to the organ system affected. Dermatologic irAEs are often evident after 2 to 3 weeks, gastro-intestinal and hepatic AEs after 6 to 7 weeks, and endocrinologic AEs only after an average of 9 weeks (Weber JS et al., 2012; Lebb'e C et al., 2008). In addition as irAEs could occur even after drug treatment is ended, it is critical to have an adequate time for their follow-up.
A maculopapular, erythematous rash, often accompanied by pruritus, is more frequent Ipilimumab-induced cutaneous reaction. It usually is well tolerated and limited. It is mainly localized at proximal extensor surfaces of the limbs, trunk, and distal extremities. Other reported dermatologic reactions include acneiform rash, lichenoid exanthema, pyoderma gangrenosum-like ulcerations, skin toxicity in the irradiated area, photosensitivity and vitiligo (Voskens CJ et al., 2010). Interestingly, the occurrence of spontaneous vitiligo has been postulated to be a positive prognostic sign in patients with melanoma as it signals an immune attack on melanocytes (Quaglino P et al., 2010), but it is not known whether the ipilimumab-induced vitiligo produces the same benefit.
The second most commonly reported irAE is diarrhea. Abdominal pain,

or an increase in the number of bowel movements, hematochezia, nausea, and vomiting have been also reported (Andrews S et al., 2012). Endoscopic biopsies obtained after the onset of diarrhea often reveal features of diffuse active colitis with infiltrates of neutrophils, lymphocytes, and plasma cells in the lamina propria, together with crypt abscesses and mucosal ulcerations (Beck KE et al., 2006; Berman D et al., 2010; Oble DA et al., 2008). Rarely, diarrhea and/or colitis can become life threatening (Hersh EM et al., 2011; Phan GQ et al., 2008; Freeman HJ et al., 2012; Thumar JR et al.,2010; Beck KE et al., 2006), leading to fatal bowel perforation and sepsis (Hersh EM et al., 2011; Phan GQ et al., 2008; Smith FO et al., 2010).

The most common endocrinopathy reported with ipilimumab is hypophysitis (Thumar JR et al., 2010). It is presumed to be secondary to a lymphocytic infiltration of the pituitary leading to enlargement of the gland, followed by damage to the pituitary cells with hypofunction of ACTH, TSH, and other secreting cells leading to secondary adrenal insufficiency and hypothyroidism. The imaging characteristics of hypophysitis are also non-specific and, on the basis of imaging alone, often cannot be differentiated from other causes, including metastasis. Clinically, affected patients usually present with non-specific symptoms such as headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills (Yang JC et al., 2007; Dillard T et al., 2010). Levels of ACTH, cortisol, TSH and/or free T4, GH, prolactin, insulin-like growth factor I, follicle-stimulating hormone, luteinizing hormone, and testosterone are variably altered, indicating different degrees of hypopituitarism. Hypopituitarism is the only potentially irreversible irAE induced by anti–CTLA-4 mAbs.

Others ipilimumab induced endocrinopathies have been observed, including hypothyroidism and hyperthyroidism secondary to thyroiditis, adrenal insufficiency and hypogonadism (Lemech C et al., 2012).

Immune-related hepatotoxicity has been observed in 3% to 9% of patients receiving ipilimuab. It consists in serum liver transaminases and bilirubin increase and inflammatory hepatitis (Hodi FS et al 2010; O'Day SJ et al., 2010; Wolchok JD et al., 2010). Ocular events that have been reported with ipilimumab include conjunctivitis, scleritis, uveitis, and Graves' ophthalmopathy (Thumar JR et al., 2010; Min L et al., 2011).

The correct clinical management of irAEs requires prompt medical at-

tention and a local network of organs'specialists. The primary treatment for most low-grade irAEs is supportive care. For patients with moderate (grade 2) immune-mediated toxicities, treatment should be withheld and should not be resumed until symptoms resolve. Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) should be started if symptoms do not resolve in a week. For patients with severe or life-threatening AEs, treatment should be stopped permanently and high-dose systemic corticosteroids (prednisone 1-2 mg/kg/day or equivalent) should be given. If symptoms do not improve after 3 days of treatment with intravenous steroids, next step is to administer infliximab (5 mg/kg). Endocrinopathies are also treated with hormone substitution. Importantly, the treatment of irAEs with corticosteroids, does not appear to negatively impact the efficacy of ipilimumab (Amin A et al., 2009; Harmankaya K et al 2011).

In general, toxicities with anti-PD-1/PD-L1 mAbs appear to be less frequent and less severe when compared with ipilimumab (Weber Js et al., 2015). The most common adverse events observed with these agents are low grade fatigue, diarrhea, nausea, maculopapular rash, pruritus (Topalian SL et al., 2012; Hamid O et al., 2013). Of note, a direct comparison of pembrolizumab with ipilimumab demonstrated a higher incidence of vitiligo of approximately 10% in pembrolizumab-treated patients, versus 2% in ipilimumab-treated patients (Robert C et al., 2015). Myalgia, arthralgia, oral mucositis, elevated AST and ALT levels, hypothyroidism and hypophysitis have been also reported (Topalian SL et al., 2012; Hamid O et al., 2013).
The most serious toxicity related with anti-PD-1/PD-L1 mAbs is interstitial pneumonia, described in less than 10% of patients (Brahamer J et al., 2015 ; Garon EB et al., 2015). This toxicity led to three treatment-related deaths in an early phase study of nivolumab (Topalian SL et al., 2012). Therefore a close monitoring for pneumonitis is critical during the treatment with anti PD-1/PDL-1 antibodies. Rare/emergent side effects due to immune checkpoint antibodies are shown in Tables 1.

Combining BRAF and MEK inhibitors to mitigate drug resistance and combining MAP-kinase inhibitors with immunotherapy has yielded further improvement in outcomes for melanoma metastatic patients (Menzies AM et al., 2012; Wolchok J et al., 2013; Postow MA et al., 2015; Larkin J et al., 2015).
In combinated therapy BRAFi/MEKi, if pyrexia, uveitis, cutaneous squa-

mous cell carcinomas or QT prolongation occur, only BRAFi must be reduced in dosage, interrupted or suspended according to the degree of severity; while if reduced LVEF, OVR, RPED or ILD/pneumonitis occur, only MEKi treatment must be changed. The addition of trametinib to dabrafenib changes the adverse event profile: in fact, it makes hyperkeratosis and cutaneous squamous cell carcinomas less common, increasing however side effects such as fever and nausea. The combination of cobimetinib and vemurafenib seems to be more toxic than the combination therapy dabrafenib and trametinib even if these four drugs have never been compared in a randomized trial.

In the phase III study CheckMate 067, treatment-related grade 3/4 AEs were more common with NIVO+IPI (55%) than with NIVO (16%) or IPI (27%) and no patients died from treatment-related toxicity in the combination arm (Larkin J et al., 2015). These data are consistent with those observed in another study of combined nivolumab and ipilimumab therapy (CheckMate 069).

(Postow MA et al., 2015). One important characteristic of the immuno-related toxicity associated with the combination was the involvement of more than one organ, which is rare with monotherapy. However, new safety signals were not reported for the combination, with adverse events affecting the same organs as typically seen with monotherapy (i.e. the skin, gastrointestinal tract, liver, endocrine system, lungs). Phase I data showed that combined vemurafenib and ipilimumab increases liver toxicity (although this was not reported with dabrafenib plus ipilimumab) (Puzanov I et al., 2014), while the triple combination of ipilimumab plus dabrafenib and trametinib has reported to increase the risk of bowel perforation (Minor DR et al., 2015). Recent experimental evidence suggests that BRAF inhibitors may promote T-cell activation mediated by paradoxical activation of the MAP kinase pathway, leading investigators to postulate a risk of increased toxicity in patients receiving concurrent ipilimumab (Callahan MK et al., 2014). An alternative hypothesis is that the potential for an increased infiltration of activated T cells is due to a decrease in immunosuppressive cytokines such as CCL2 and VEGF mediated by inhibition of the MAPK pathway in BRAF V600E/K-mutated melanoma metastases (Sumimoto H et al.,2006).

Rare/emergent side effects due combination therapy are listed in Table 1.

The mortality rate for malignant melanoma is higher in elderly patients aged

75 years or more, with over 25% of melanomas being diagnosed in this population. However, the knowledge about efficacy and toxicity of innovative therapies in this specific population is limited, as most of the studies have involved a low number of older patients. In clinic practice vemurafenib appears safe and active in elderly patients (Del Vecchio M et al., 2015). Age does not appear to impact tolerance or efficacy of ipilimumab and it has been administered safely to elderly pts, including those over age 75 (ASCO ANNUAL MEETING ABSTRACT; 2016). Current literature does not allow one to draw definitive conclusions regarding the role of others immune checkpoint inhibitors and combination therapies in elderly patients.

Molecularly targeted and immune-modulating agents are now available in routine practice for metastatic melanoma. These biological therapies have a distinct spectrum toxicity and requires a management strategy. Educating patients and maintaining close communication with them is essential. Assembling a multidisciplinary team prior to treating patients with these molecular therapies will foster collaboration and facilitate their future care and management.

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Table 1: rare adverse events observed during treatment with novel drugs for metastatic melanoma

Rare adverse events	Targeted agents and immunotherapy
Toxic epidermal necrolysis	
Stevens-Johnson syndrome	BRAFi ICI
	BRAFi ICI
Dress syndrome	
Acute interstitial nephritis	BRAFi, MEKi
Panniculitis	BRAFi
Rhabdomyolysis	MEKi
Pancreatitis	BRAFi MEKi
Guillain-Barre´ syndrome, severe motor neuropathy or myasthenia gravis	ICI
Intracranial Hemorrhage	BRAFi+MEKi
Acute encephalopathy	BRAFi+MEKi
Granulomatous nephritis	BRAFi+MEKi
Alveolitis, sarcoidosis	ICI

Table 2: class effects of BRAF and MEK inhibition

class effects BRAFi	class effects MEKi
secondary skin neoplasms	decreased left ventricular ejection fraction (LVEF) or ventricular dysfunction
uveitis	retinal vein occlusion
QTc prolongation	retinal pigment epithelial detachments
pyrexia (dabrafenib)	ILD or pneumonitis

CANCER AND SLEEP DISORDERS

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This paper represents an expert point of view on sleep disorders in cancer patients with the aim to provide clinically useful information to the readers. There are several categories of sleep disorders, such as insomnia, hypersomnia, and sleep-related movement disorders that can accompany medical conditions such as cancer and/or be determined/influenced by its different treatments. The most important and frequent sleep disorder reported by cancer patients is insomnia; however several other disorders, such sleep-related movement disorders and disordered breathing can be associated with cancer. All sleep disorders, if correctly identified and characterized, can be treated, with subsequent significant beneficial effects for the patients.

There are several categories of sleep disorders, such as insomnia, hypersomnia, and sleep-related movement disorders that can accompany medical conditions such as cancer and/or be determined/influenced by its different treatments (American Academy of Sleep Medicine 2014). We discuss here some of them that we felt worth mentioning, based on our own clinical experience with patients with sleep disorders. Thus, this paper does not want to be an exhaustive review of the literature on this topic but rather represents an expert point of view with the aim to provide clinically useful information to the readers.

In a multicentre study on the association between sleep disordered breathing (SDB) and cutaneous malignant melanoma (CMM) aggressiveness (Martinez-Garcia MA et al.,2014), patients diagnosed with cutaneous malignant melanoma underwent respiratory sleep monitoring with a subsequent assessment of the relationship between SDB severity such as apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) and measures of CMM aggressiveness. This study showed a positive and inde-

pendent association between AHI e ODI and melanoma growth rate, as well as a positive association with other makers of CMM aggressiveness, such as Breslow index, the presence of ulceration, the mitotic index and the melanoma stage. This seems to support the hypothesis that intermittent hypoxemia caused by SDB may promote faster cancer growth or aggressiveness in patients suffering from CMM.

Restless legs syndrome (RLS) is a neurological disorder characterized by an irresistible urge to move the legs especially at rest; symptoms worsen in the evening and night and improve with activity such as walking (Allen RP et al.,2014). RLS may be secondary to, or exacerbated by, a number of conditions that include iron deficiency, pregnancy, end-stage renal disease, diabetes and rheumatoid arthritis, or with neurological disorders such as peripheral neuropathy.
Aricò et al.(Aricò D et al.,2013) reported a case of RLS due to iron deficiency in the setting of a multiple myeloma (MM), a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow and, usually, the presence of a monoclonal immunoglobulin in the blood and/or urine. A 78-year-old woman with an 8-month history of severe RLS which caused insomnia underwent polysomnography (PSG) that showed an abnormally high number of periodic leg movements during sleep (PLMS) (PLMS index 80.9/h). The blood analyses showed low levels of hemoglobin and ferritin. Serum protein electrophoresis showed a peak in the gamma zone. Bone marrow biopsy showed monoclonal plasma cells. All these results allowed to reach the diagnosis of multiple myeloma in this patient, who was referred to a hematology clinic. The patient went back to the sleep lab for a follow-up visit when the treatment of iron deficiency had resolved the anemia, and reported a notable reduction of RLS symptoms. Gabapentin and pramipexole were also regularly and continuously taken. A second PSG was carried out and the resulting hypnogram appeared to be significantly improved and practically normalized, with a clear decrease of PLMS number (PLMS index 0.13/h). The first important consideration from this case report is that the patient was referred to the sleep center because of her severe RLS symptoms dramatically reducing her quality of life. However, the clinical study clearly demonstrated that RLS was not the primary disease but was most probably secondary to a series of factors known to cause it. In this patient, radiculopathy was likely present before the onset of RLS and MM;

conversely, iron deficiency and severe bone pain probably started with MM and induced the appearance of severe and apparently dopamine agonist-resistant RLS symptoms. RLS symptoms can sometimes be the sign of a life-threatening condition that should be suspected if symptoms do not respond promptly to dopamine agonists; if so, careful and complete collection of clinical and laboratory data should be carried out. In particular, if RLS onset coincides with pruritus and bone pain, a complete blood count should be checked along with ferritin and iron studies; if anemia is found, serum protein electrophoresis should then be checked.

Insomnia is defined by the International Classification of Sleep Disorders, third edition(American Academy of Sleep Medicine 2014) as "a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment". Insomnia is characterized by subjective complaints about dissatisfaction with sleep quality or duration, difficulty falling asleep at bedtime, waking up too early in the morning or in the middle of the night, or non-restorative or poor quality sleep. Insomnia also involves subjective reports of daytime symptoms such as fatigue or low energy, difficulties with cognitive functions (for instance attention, concentration, and memory), and mood disturbances including irritability and dysphoria, all of which can produce functional impairment and are often the primary concerns pushing patients to seek for treatment.
Insomnia seems to be determined by predisposing, precipitating and perpetuating factors (Spielman AJ et al.,1987; Bastien CH et al.,2004; American Psychiatric Association, 1994). Predisposing factors can be several such as gender, older age, hyperarousability as a trait, personal or family history, mood or trait anxiety, predisposition to rumination; precipitating factors consist of diagnosis of cancer, severity of disease, cancer treatment that alter the levels of inflammatory cytokines or disrupt circadian rhythms or sleep-wake-cycles, side effects of cancer treatment, menopausal symptoms including pain or fatigue, and medications used to treat side effects such as corticosteroids. Moreover, perpetuating behavioral factors such as long term use of medications or use of inappropriate medications, and maladaptive coping, i.e. inaccurate appraisal of sleep difficulties and quality (Bastien CH et al.,2004; American Psychiatric Association, 1994).
Insomnia associated with cancer is most likely multifaceted. Although it is conceivable that other mechanisms are involved (immune response, psy-

chological reaction, personality, changes in the circadian rhythms), recent findings suggest a mediating role for the somatic symptoms due to chemotherapy and radiotherapy side effects, such as headache, nausea and digestive symptoms, urination and night sweats (Savard J et al.,2015). Several studies on cancer patients showed that chemotherapy and radiotherapy were associated with worsening of insomnia (Palesh O et al.,2012; Costa AR et al.,2014; Thomas KS et al.,2010; Savard J et al.,2001). Chemotherapy seems to have an important concurrent effect on sleep dysfunction, significantly mediated by urinary symptoms, nausea, night sweats, digestive symptoms and dyspnea. The radiotherapy has a concurrent effect on insomnia symptoms, significantly mediated by dyspnea and night sweats (Savard J et al.,2015).

Interesting findings about breast cancer and sleep disorders, especially insomnia, can be found in the literature. Patients with the diagnosis of breast cancer report very often insomnia (Ohayon MM,2002) furthermore it is estimated that in older adults (>65 years of age) with cancer the prevalence of insomnia is 19-60% (Loh KP et al.,2016). Insomnia can occur on its own, although it is often present in a cluster of symptoms along with pain, fatigue, distress, depression and anxiety. The relationship and interactions among these symptoms are complex; they can exacerbate each other and have synergistic effects on the functional performance of patients with cancer. A study by Garrett et al.(Garrett K et al.,2011), showed that, based on self-report, patients with breast cancer experience sleep disturbance more frequently and with greater severity than patients with prostate cancer while objective measures of sleep disturbance suggest that prostate cancer patients have more severe sleep disturbance than breast cancer patients. All of the patients experienced poor sleep quality and fatigue which suggests that oncology patients need to be assessed for these symptoms.
The prevalence of insomnia in the general population is estimated to be up to 20%, increasing to more than half of patients with cancer. The complaint of cancer-related fatigue is reported in nearly 80% of oncology patients. It has been estimated that approximately 30-60% of breast cancer women experience insomnia and the prevalence is higher than in non-cancer patients (Savard J et al.,2009; Palesh OG et al.,2010) .
Insomnia has a high prevalence in women with breast cancer for several reasons, such as a general increase in psychological distress after the cancer

diagnosis and disruption of sleep due to increased frequency and severity of hot flushes caused by menopause, often induced by the chemotherapy (Fiorentino L et al.,2010).
A recent study (Ratcliff CG et al.,2014) examined sleep before and during chemotherapy for BCS and suggested that subjectively disturbed sleep, during chemotherapy infusion, is associated with greater fatigue, and more negative and anxious thoughts. It is probable that improving sleep in these patients might improve their mood and, consequently, quality of life. Psychological problems such as depression, anxiety and intrusive thoughts were found to be common among breast cancer patients. Jassim et al (Jassim et al.,2015) reviewed the effects of cognitive behavioral therapy on depression, anxiety and mood disturbances in 28 randomized controlled trials which included a total of 3,940 non-metastatic BCS. CBT was associated with decreased levels of depression, anxiety, with concomitant improvement in quality of life, when compared to the control groups.
It is also important to notice that fatigue is one of the most common symptoms of any neoplastic condition. Very often, cancer-related fatigue is more severe and more enduring than that of patients without cancer(Poulson MJ, 2011).
Although in the majority of cases the etiology of fatigue is unknown and the complex relationship between fatigue and sleep remains not clearly established, behavioral and psychosocial interventions were shown to be efficacious to improving cancer-related fatigue. This is important because, notwithstanding that fatigue is a symptom common to many pathologies, in the particular clinical picture of breast cancer comorbid with insomnia, it can contribute to a mutual auto-reinforced relationship between these two conditions.

Recently, Aricò et al.(Aricò D et al.,2016) reviewed the literature on cognitive behavioral therapy for insomnia (CBT-I) in women treated for breast cancer and evaluated the efficacy of this intervention on sleep, mood and psychological outcomes. CBT-I is a brief, sleep-focused, multimodal intervention (Morin CM, 2003; Edinger JDet al.,2008). CBT-I is considered to be the gold standard treatment for primary and comorbid insomnia in young and older adults (Morin CM et al.,2012). The most common approach includes a behavioral component (stimulus control, sleep restriction, relaxation) combined with a cognitive and an educational component (sleep hygiene). Each of these therapies can be used alone or in com-

bination; however, the combined approach is preferred because several dimensions of insomnia can be addressed at the same time. An increasing number of studies have supported the efficacy of CBT-I in patients with cancer(Garland SN et al.,2014). Overall, results have been quite consistent in showing that CBT-I is associated not only with improved sleep but also with a reduction of psychological distress and improved quality of life. All of the studies included reported a clear efficacy of CBT-I in BCS. The efficacy covers several aspects including sleep, fatigue, menopausal symptoms, mood, pain, quality of life and, importantly, immunological function. The improvements associated to CBT-I were clinically and statistically significant for both subjective (sleep dairies and questionnaires) and objective measures (PSG and actigraphy). The results of the study by Aricò et al.(Aricò D et al.,2016) are in agreement with the conclusions reported by Garland et al.(Garland SN et al.,2014) in their systematic review of CBT-I, in patients with different and heterogeneous types of cancer (including BCS) and based on only 12 controlled and uncontrolled trials.
CBT-I was reported to have durable effects by most of the studies, in agreement with Morin & Benca (Morin CM et al.,2012), who reported that CBT-I in chronic insomnia is usually followed by a persistent therapeutic effect over time, whereas patients taking only drugs tend to relapse after discontinuation.
CBT-I might trigger a virtuous cycle by improving sleep quality which, in turn, might improve mood; mood improvement could possibly be associated with better treatment adherence and reduced intake of medication for sleep disorders, reduced anxiety and, finally with better sleep.

As seen above, sleep disorders occur often in cancer patients as a direct consequence of the presence of the neoplastic condition or as an undesired effect of its different treatments. It should not be forgotten that, given their high prevalence in the general population, sleep disorder can predate the occurrence of cancer and their course can be aggravated or they can add negative influence on the physical, cognitive and emotional status of patients, contributing to their quality of life impairment. The most important and frequent sleep disorder reported by cancer patients is insomnia; however several other disorder, such sleep-related movement disorders and disordered breathing can be associated with cancer. All sleep disorders can be treated, with subsequent significant beneficial effects for the patients.

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THE PHENOMENON OF PROLONGATION OF SURVIVAL OF METASTATIC COLORECTAL CANCER PATIENTS: POOLED ANALYSIS OF PATIENTS TREATED WITH DRUGGABLE ONCOGENIC DRIVERS AT NIGUARDA CANCER CENTER

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Backround

In the landscape of cancer as a chronic disease with raising numbers of living persons previously treated or being treated with oncologic therapies, it should be considered that in the western world overall colorectal cancer (CRC) incidence has dropped by almost 40% since 1975 and by more than 45% since its peak in the mid-1980s (Welch HG et al, 2016). Moreover, CRC mortality has fallen by more than half (Figure 1). These trends are often attributed to screening, but the magnitude of the changes alone suggests that other factors must be involved. In fact, none of the trials of colorectal cancer screening has shown a 50% reduction in mortality, nor have trials of screening for any type of cancer. Besides, the timing of the trends isn't consistent with the slow uptake of screening and its expected delayed effect on mortality. A plausible explanation of the decrease in colorectal cancer mortality is the evolution of treatment options, included the resection of distant metastases in the oligometastatic disease and the availability of clinical trials with targeted therapies to oncogenic drivers. To support the last hypothesis we have assessed clinical results of administering tumor targeted therapies based on the presence of a matched molecular alteration within phase I-II studies in a mono-institutional series of metastatic CRC patients in advanced line at Niguarda Cancer Center (NCC), Milan, Italy.

Patients and methods

We retrospectively analyzed data of patients with metastatic CRC resistant to standard therapies treated at NCC during the last five years with chemotherapy or targeted agents in phase I-II clinical studies based on the presence of a druggable oncogenic driver or context of susceptibility as

per inclusion criteria. Objective tumor response, progression-free survival (PFS) and overall survival (OS) were evaluated.

Results

From June 2011 to May 2016, 2044 patients with mCRC were referred to NCC for molecular screening within phase I-II trials encompassing targeting of actionable molecular alterations or exploiting molecular contexts of susceptibility. 80 patients (3.9%) were enrolled in ad hoc studies; median age was 60 years (range 36-86), median number of previous treatment lines 5 (range 2-8). Studies included therapies based on MGMT promoter hypermethylation (49%), HER2 amplification (28.5%), BRAF V600E mutation (20%), gene fusions involving ALK or TRKA (2.5%) (Figure 2). Among the whole cohort, any KRAS (exon 2) mutation was found in 38.5% of patients. According to RECIST criteria, 14 patients (17.5%) had partial response (PR), and 28 (35%) stable disease (SD) (Figure 3). Median PFS was 2.8 months (range 2.63 – 3.83), with 24% of patients displaying PFS > 5 months (Figure 4A and 4B). Median OS was 7.83 months (range 7.17 – 9.33). Among the 78 patients with known KRAS status, wild type tumors had longer PFS than mutated (3.8 vs 2.1 months respectively; $p < 0.001$) and longer OS than mutated (7.83 vs 7.18 months respectively; $p = 0.06$) (Figure 5A and 5B).

CONCLUSIONS: This Niguarda Cancer Center case series indicates that, in a heavily pretreated population, about 4% of mCRC tumors display a potential actionable molecular context suitable for therapeutic intervention. Application of molecular selection is challenging and improves clinical outcome even in later lines of treatment (Amatu A et al, 2016; Sartore-Bianchi A et al, 2016; Amatu A et al, 2015; Sartore-Bianchi A et al, 2015; Bardelli A et al, 2010; Sartore-Bianchi A et al, 2016; Leone F et al, 2016) with an estimation of 5% of patients achieving long term survival. Overall this information contributes to support the epidemiological evidences that prolongation of survival of mCRC granted also by modern targeted therapies renders this disease a chronic disease with increasing responsabilities for health care systems.

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COLORECTAL CANCER: TAKE HOME MESSAGE

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The medical treatment of colorectal cancer (CRC) is undoubtedly one of the areas of oncology in which in the recent years it has been observed a growth of scientific knowledge and clinical progress.
If you think, in fact, that some fifteen years ago everyone was talking about whether to treat or not to treat the patients with metastatic CRC (m-CRC), with the few resources available, the results obtained today, with treatment regimens and with their optimization, appear even more surprising and gratifying.
The significant increase in objective response (OR) rates obtained with the new generation regimens, compared to those obtained with regimens based only on fluoropyrimidine, has allowed an increase in the percentage of curative surgical resection.
We can say that we are experiencing a real cultural revolution in the therapeutic approach to CRC, that, by orphan disease, it is now becoming an important paradigm of scientific innovations and concepts.
CRC is the third tumor incidence in the world with over 940,000 new cases and nearly 500,000 deaths annually worldwide [Berretta M et al, 2011; Berretta M et al, 2014). About 50% of CRC patients has, diagnosis, distant metastases, and overall survival (OS) does not exceed two years (Rosen SA et al, 2000; De Vitidis C et al, 2015).
The significant increase in OR rates is the result of the introduction, in the nineties, of the new chemotherapy (oxaliplatin and irinotecan essentially); above all, the use of molecular targeted drugs has allowed to overcome the psychological boundary of the 20-month median survival and the 50% of overall OR (De Vitis et al, 2014).
Another element of fundamental importance in the approach to innovative CRC in the era of targeted therapies is the personalization of treatments based on the identification of markers with prognostic and predictive value.
The analysis of prognostic and predictive factors, in fact, is now a crucial moment in the planning of the therapeutic strategy to be adopted both, in the treatment of patients with colorectal cancer diagnosed at an early

stage, and in the treatment of metastatic colorectal cancer. Furthermore, this analysis allows to obtain important information about the results obtained with certain therapies in the various categories of patients and offers as well, more generally, new tools to be able to estimate the probability of recovery of these patients (Pritchard CC et al, 2011).

Therefore, the promise of personalized medicine in the treatment of m-CRC is becoming a reality thanks to new knowledge of genetics that, some times, have changed the clinical practice.

The availability of biologics drugs, (together with the identification of RAS mutation status as predictive testing of response to the monoclonal antibodied anti-epidermal growth factor receptor such as cetuximab and panitumumab), associated to chemotherapy, have increased the overall survival (OS) of the patients with m-CRC to more than 24 months of median (Asghar U et al, 2010) (Table 1). All this, as expected, has been achieved at the cost of specific toxicity and with a significant economic weight; these events that will be increasingly limited and contained only if it will seek an attentat selection of patients to be treated with such drugs (Di Martino S et al, 2015).

Until the nineties the only active drug in the treatment of this disease was 5-fluorouracil (5-FU), which guaranteed control of disease limited to 3-4 months and a survival of only 6-9 months. Subsequently, the evidence of effectiveness of oxaliplatin and irinotecan in combination with 5-FU, led to a better control of the disease, delaying time to progression (TTP, 6.7 months) and prolonging survival (14-16 months). The therapeutic efficacy of these drugs (in terms of reduction of tumor volume) has had an important impacted on prognosis, providing the possibility of a radical surgery of metastatic lesions initially inoperable, modifying the natural history of the disease (Asghar U et al, 2010). It was discussed on what regime would be more appropriate to use in the first or second line.

The study of Grootey of 2004, questionable for the methodology used [9], showed that survival correlates with the exposure over time at all three active drugs rather than to the sequence used. Several clinical trials have shown that such schemes as FOLFOX (Berretta M et al, 2012) (5FU, folinic acid and oxaliplatin) or FOLFIRI (5-FU, folinic acid and irinotecan) are to be considered a valid use in first-line treatment of mCRC. A study (Falcone A et al, 2007) of the oncology group of north WEST (Gono) showed for first as the use of the triplet (FOLFOXIRI: 5FU, folinic acid,

oxaliplatin and irinotecan) is more effective than the use of a doublet of drugs (FOLFIRI), in terms response rates (RRs), time to progression and survival, even if such a scheme is to be reserved solely to those patients characterized by good performance status (PS) and without significant comorbidities which could affect the tolerability.
In the last decade the use of inhibitors of growth factor vascular endothelial (Bevacizumab, regorafenib and aflibercept) and EGFR (cetuximab and panitumumab) has brought more benefits than the results of chemotherapy alone: time to progression and OS are in fact increased, respectively, from 8-11 to 20-24 months (Aprile G et al, 2015).

An element of fundamental importance in the innovative approach to cure the metastatic colorectal cancer in the era of targeted therapies is the personalization of treatments based on the identification of markers with prognostic and predictive value, which represents, today, a crucial time in the management of the disease in advanced stage and in the care of the forms in the early stage. Furthermore, the identification of prognostic and predictive facotrs could offer new tools for estimation with respect to the possibility of care. Therefore, the promise of personalized medicine in the treatment of metastatic colorectal cancer is becoming a reality thanks to new knowledge of genetics that have allowed, at times, to change practice. The availability of biologics targeted, together with the identification of RAS mutation status as predictive testing of response to the monoclonal drugs anti-EGFR (cetuximab and panitumumab), associated to chemotherapy, has produced an increase of the OS in patients with metastatic colorectal cancer to more than 24 months of median. All this, as trusted, at the cost of additional specific toxicity and a economic remarkable weight, events that will be ever more content with the "super-selection" of patients.
All this justifies the frantic search for biological markers, prognostic and predictive able to implement the knowledge on the biology of the tumor and guide the clinician in decision making more and more personalized (De Divitiis C et al, 2014). Particularly, in the treatment of metastatic colorectal cancer, first, the proof of the presence of mutations of the KRAS protein in the pathway fo EGFR has changed the therapeutic strategy, from chemotherapy exclusive and "empirical" to a more customized approach that involves the use of monoclonal anti-EGFR drugs.

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OXALIPLATIN INDUCED PERIPHERAL NEUROTOXICITY: WHAT WE KNOW AND WHAT WE NEED

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In last decades, a "new" side effect has become a hot topic in Oncology: Chemotherapy Induced Peripheral Neurotoxicity (CIPN). CIPN is a common adverse event of drugs applied widely to treat the "big killers": breast, colorectal and lung cancer; among these, there are platinum drugs, taxanes, vinca alkaloids, proteasome inhibitors, epothilones and thalidomide (Cavaletti G et al, 2015; Argyriou AA, 2012). Growing awareness of CIPN has promoted its recognition and concerns about its duration. Nowadays, in fact, cancer patients have become a long surviving population, thanks to advances in diagnosis and treatment. Worldwide, it has been estimated there are 28 million cancer survivors. Globally, cancer-related mortality, adjusted for age, decreased both in pediatric, both in adult population in the 1950-2010 period (Cavaletti G, et al, 2015). Chronic or late toxicities are toxic effects persistent more than 12 months or presenting 12 months after the end of chemotherapy (Cavaletti G, et al, 2015).
CIPN is a sensory, length-dependent neuropathy/neuronopathy. Rarely, motor, autonomic impairment or cranial nerve involvement have been observed. Different drugs have a slightly different clinical picture (Cavaletti G et al, 2015; Argyriou AA, 2012; Grisold W et al, 2012). However, some features are quite constant. Sensory alterations can be divided into two main categories. "Negative" signs/symptoms: impairment in touch, pin and vibration perception; if there is a consistent loss of large fiber modalities the patient can develop disability, even though the motor function is preserved, due to sensory ataxia that can cause imbalance and falls (Pachman DR et al, 2012; Bennion AE et al, 2013), and difficulty in manipulating objects (the so called loss of "composite function" (Grisold W et al, 2012)). "Positive" symptoms are instead related to damage of small fibers, with development of paresthesia/dysesthesia and neuropathic pain. Alterations develop initially at limb extremities and then they have a dis-

tal-to-proximal progression, accordingly to the known pathophysiology of a length-dependent neuropathy; the damage is usually dose-dependent. Platinum drugs can manifest a peculiar temporal pattern in neurological deterioration: neuropathy can worsen for a few months after chemotherapy suspension, the so called "coasting phenomenon" (Argyriou AA, 2012). All described manifestations have a negative impact on Quality of Life (QoL) of cancer survivors either causing pain either causing disability. Unfortunately, so far, not a preventive nor a curative strategy has been found as efficacious, as accurately pointed out in a meta-analysis recently published by an American Society for Clinical Oncology (ASCO) (Hershman et al, 2014): only duloxetine has been recognized as moderately efficacious as a symptomatic option (Hershman et al, 2014; Smith EM et al, 2013).
The first application in clinical practice of Oxaliplatin (L-OHP) dates back to 1996 in France; in 1999 it was introduced in whole Europe and in 2002 in the USA, its only indication being metastatic colorectal cancer, extended later to the adjuvant setting, and only in combination with 5-fluorouracil and leucovorin (Chau I et al, 2003). All platinum complexes have a common mechanism of action in cancer cells: they form intra-strand and inter-strand cross-links on DNA, being thus alkylating agents. L-OHP has some features that can explain its unique efficacy and toxicity profile; it has different behavior in: transport and metabolism; effect of DNA platination due to the larger L-OHP size; mechanisms involved in repair of DNA adducts and in sensing DNA damage through the DNA mismatch repair system; in the transduction of DNA damage signals such as activation of apoptosis or immunogenic cell death (Perego P et al, 2016). All platinum drugs, as aforementioned, are associated with peripheral neurotoxicity development, even though some are more neurotoxic than others: cisplatin has been reported to be neurotoxic in about 60% of patients, when receiving at least 225-500 mg/m2; L-OHP have been associated with a rate up to 75% of neurosensory symptoms in patients treated with FOLFOX or XELOX regimen; carboplatin, instead, is significantly less neurotoxic than other two platinum compounds (Argyriou AA, 2012).
The clinical pattern of CIPN due to platinum drugs is dominated by a predominantly distal, symmetric, limb loss of all sensory modalities. Large fibers can be greatly involved, with development of sensory ataxia and gait imbalance. Also small fibers can be damaged and, consequently, neuropathic pain can be present. Motor impairment is quite unusual. Reduction/loss of deep tendon reflexes (DTR) is always seen.

However, L-OHP shows a peculiar and specific neurotoxicity profile; first of all, OIPN is ranked among its major dose-limiting toxicities. From a clinical point of view, it is not associated only with the above mentioned chronic and cumulative peripheral nervous system damage: it is associated with an "acute" and transient toxicity, lasting mainly 24-72 hours after L-OHP i.v. administration; patients experience cold-induced, transient, paresthesia/dysesthesia (located mainly at limb extremities, at pharynx/larynx, and at mouth/lips). Jaw-spasm and camps/muscle spasms have also been described, even if more rarely (Lucchetta M et al, 2012). All these phenomena are compatible with a cold-induced acute neuromyotonia-like syndrome which is characterized by a hallmark of both motor and sensory nerve hyper-excitability. Neuromyotonia is known to be generated by impairment of voltage-gated ion channels (Newsom-Davis J et al, 2007); the acute OIPN clinically resembles neuromyotonia and therefore it could be classified as a channelopathy, because of the interaction between L-OHP with ion channels located in the cellular membrane. There is robust evidence that L-OHP may mostly impair voltage-operated sodium channels (Na+VOC) rather than potassium channels, as demonstrated in vitro studies (Adelsberger H et al, 2000; Krishnan et al, 2005) and clinical studies testing nerve excitability in patients treated with L-OHP (Krishnan et al, 2005; Park SB et al, 2011; Park SB et al, 2012). Most interestingly, it has been suggested that the chronic OIPN may be induced by the decreased cellular metabolism and axoplasmic transport resulting from the accumulation of OXL in dorsal root ganglia (DRG) cells. Nevertheless, the prolonged activation of Na+VOC had been advocated for cellular stress induction, being this an adjunctive mechanisms of damage; this could damage sensory neurons (Grolleau F et al, 2001; Park SB et al, 2009) and further investigations could be useful to determine the potentially critical involvement of Na+VOC in the pathogenesis of both acute and chronic OXLIPN. Evidences in Literature indicate that abnormal kinetics of mutated Na+VOC may lead to various clinical syndromes, known as sodium channelopathies (Catterall WA et al, 2008). Mammalian Na+VOC α-subunits, encoded among others by SCN1A, SCN2A, SCN3A and SCN4A genes are widely expressed in neurons (Catterall WA et al, 2008) and it has previously been reported that missense mutations of the SCNA gene confer liability to cold-induced myotonia as well as also to seizures, likely for its ability to induce sodium channel dysfunction, which may underlie the neuronal hyper-excitability (Sugawara T et al, 2001; Ros-

signol E et al, 2007); thus, acute and chronic OIPN development can be predisposed by polymorphisms in these Na+VOC neuronal genes. In particular, a pharmacogenomics study demonstrated that the overdominant model (CT vs CC1TT) of the skeletal muscle SCN4A-rs2302237 and the tetrodotoxin-resistant SCN10A-rs1263292 polymorphisms emerged as being significantly associated with an increased incidence of acute OIPN. The overdominant model of SCN4A-rs2302237 was also able to predict the severity of acute OXAIPN. A weaker association was found between the overdominant model of SCN4A-rs2302237 and the development of cumulative OXAIPN (Argyriou AA et a, 2013). In any case, the mechanisms underlying the acute and chronic OIPN have not as yet been fully elucidated (Cavaletti G et al, 2015; Cavaletti G et al, 2015).

A longitudinal, observational, non-interventional, international and multicenter trial (Argyriou AA et al, 2012), was held in four centers distributed into three countries in Europe (Italy: Monza and Padua; Greece: Patras; Spain: Barcelona); acute OIPN was reported in 146 of 170 patients (85.9%): the vast majority of these patients manifested cold-induced perioral (95.2%) or pharyngo-laryngeal (91.8%) dysesthesias. The increased number of acute OIPN symptoms was correlated significantly with both the development and the degree of the chronic, cumulative form; so it could be concluded that patients who had a more complex combination of acute phenomena, related to axonal hyper-excitability, were those who eventually develop more severe OIPN (Argyriou AA et al, 2013). The same group demonstrated that patients treated with either FOLFOX-4 or XELOX manifested similar incidence rates and severities of acute OIPN. However, FOLFOX-4 was associated with increased incidence of chronic neurotoxicity, compared with XELOX-treated patients (n = 64/77 versus 44/73; p-value = 0.002), at a very similar L-OHP median cumulative dose during both regimens. Both the NCI-CTCv3.0 and TNSc® demonstrated that the severity of cumulative OIPN in FOLFOX-4-treated patients is higher than in those treated with XELOX (Argyriou AA et al, 2012).

Absence of a treatment for CIPN/OIPN is partly related to the fact that there are still no definite epidemiological data on this condition, being absent a gold standard in its assessment. As a consequence, trials for CIPN treatment/prevention were not based nor on precise prevalence/incidence data, to allow a strong study design, nor on a valid outcome measure could have been elected as an endpoint. So far, the assessment of CIPN was primarily based on clinical examination and quantitative methods, such as

nerve conduction study. Additionally, several comprehensive neurotoxicity grading scales have been used (Cavaletti G et al, 2003; Cavaletti G et al 2006). Many different scales have been proposed in the past to detect and grade CIPN: so far, none was indicated as the ideal one (Cavaletti G et al, 2010). Scales were mainly developed in an oncological setting and do not accurately, and fully, evaluate CIPN; for example, the National Cancer Institute Common Toxicity Criteria (NCI-CTC)(Trotti A et al, 2003) is not based on a neurological examination. Ideally, the gold standard outcome measure should be reliable and valid, but also responsive to modification of neurological examination/symptoms of the patient. The first consistent methodological study designed to address these relevant issues was the CI-PeriNomS study. First validity and reliability findings have been obtained for the selected outcome measures (Cavaletti G et al, 2013). In particular, the Total Neuropathy Score - clinical (TNSc® (Cornblath DR et al, 1999)) scale was found as reliable. This scale, different from NCI-CTC, is based on a formal neurological examination. It cannot be defined as "the" gold standard in CIPN so far, but it is a good basis to start working on. The CI-PeriNomS study gave also a better insight on Patient Reported Outcome Measures (PROs) and QoL. CIPN can greatly impact on QoL, but the exact burden cannot be fully evaluated by the examiner, even if he/she is very careful: the point of view of the patient gives complementary information. So, Patient Reported Outcome measures (PROs) offer adjunctive information, respectively to the neurological examination: they should be integrated in a comprehensive CIPN assessment to fully detect patient condition(Alberti P et al, 2014).

Among reasons for lack of a valuable CIPN treatment, there is also insufficient knowledge of the pathogenesis of cancer treatment-related neurotoxicity. To achieve a better understanding of chemotherapy-induced neurotoxicity, accurate preclinical studies might provide very useful suggestions, but the translation of their results into the clinical setting is sometimes difficult. It is important to carry on preclinical research on a refined and well characterized model. Several in vivo rat models have been established over the past 20 years to reproduce CIPN clinical features and to study the mechanisms responsible for its development (Cavaletti G et al, 1990; Cavaletti G et al, Cavaletti G et al, 2002; Cavaletti G et al, 2001; Authier N et al, 2000; Authier N et al, 2009; Carozzi V et al, 2009; Meregalli C et al, 2010). However, the rat model is now being substituted by a mouse one. Only a few cancer cell lines are able to induce

the development of cancer in immunocompetent rats; so rat models are limited in usefulness for studying, at the same time, antineoplastic activity and neurotoxic effects of a given anticancer compound. Mice models are widely employed in oncological studies to establish the activity of chemotherapy, but their application in CIPN is still not wide, even though in the last few years they have been developed (Verdu' E et al, 1999; Mimura Y et al, 2000; Bruna J et al, 2010)). In this case, it is also possible to go a step further: in immunodeficient mice, the neoplasm can be inoculated in the animal; thus, when testing a compound for CIPN prevention, safety and interaction with chemotherapy can be tested (Meregalli C et al, 2015; Carozzi VA et al, 2016) .
At the moment, the aim of a good model in CIPN/OIPN is to reach a real "chronic" neuropathy induction and the application of formal behavioral, neurophysiological and neuropathological assessment methods, in order to fully characterize neuropathy. But a way to better translate preclinical data into clinical trials is still awaited; neurophysiology could be the answer.

In the last few years, inferences about CIPN and its long-lasting nature have been obtained. Cancer registry were in particular useful for this aim. Patient Reported Outcome Measures (PROs) were widely applied to verify CIPN persistence after treatment; however, different studies were based on different rating instruments making quite difficult to compare overall results. PROFILES Registry (Patient Reported Outcomes Following Initial Treatment and Long Term Evaluation of Survivorship) is a fine example of this (Van de Poll-Franse LV et al, 2011). PROFILES is a large web-based registry; it is directly linked to the Eindhoven Cancer Registry (ECR) that encompass all individuals newly diagnosed with cancer in the southern part of the Netherlands. It is aimed at collecting information on physical and psychosocial impact of cancer and its treatment on long-surviving patients. Analysis of a population of CRC survivors 2 to 11 years after diagnosis (n=1643) demonstrated a persistence of symptoms compatible with CIPN (Mols F et al, 2013). Patients treated with oxaliplatin reported more often symptoms in toes/feet, compared to those who did not received it: tingling in 29% VS 8% (p=0.001); numbness in 17% VS 5% (p=0.0127); burning pain in 13% VS 6% (p=0.03). The analysis of a subset of CRC patients (n=207) evidenced that risk of developing long term CIPN was related to cumulative dose received; delays or decreased

of dose intensity were not found as beneficial (Beijers AJ et al, 2015) . PROFILES registry also gave data about role of comorbidities on CIPN development and persistence; 218 CRC survivors affected by diabetes were compared to 975 CRC survivors who were not affected by diabetes. Survivors with diabetes showed a more pronounced burden of mild to severe neuropathic symptoms, in particular for the following items: tingling fingers or hands (34% vs 25%, p=0.0008), tingling toes or feet (31% vs 22%, p=0.0004), numbness in toes or feet (20% vs 14%, p=0.0002) (Vissers PA et al, 2015).

Also smaller studies are quite important to collect information about CIPN persistence. In particular, if differently from what described so far, neurological examination/nerve conduction studies were performed. A more detailed paper describing a formal neurological assessment monitoring over time was published, describing a prospective study following-up a cohort of colorectal cancer survivors 2 years after discontinuation of oxaliplatin. The neurological examination was formalised through the clinical Total Neuropathy Score© (TNSc©)(Cornblath DR et al, 1999) and nerve conduction studies were also performed. At a median follow-up of 25 months, persistence of neuropathy was present in 61 of 73 patients (84%)(Briani C et al, 2014). Another small study was published on CRC patients (n=24) with a median follow-up of 25 months after CT: 79% of patients had still sensory symptoms; TNSc® score was at least 5 in 38% of patients. rTNS® (which takes into account also nerve conduction studies) score demonstrated the presence a clinically significant neuropathy in 30% of patients (Park SB et al, 2011). The same Group published another small study (Bennett BK et al, 2012) on 20 CRC patients; trough the Patient Neurotoxicity Questionnaire (PNQ) they demonstrated 30% mild persistent toxicity, 40% moderate one, 30% moderate to severe one; NCS confirmed neuropathy burden over time since 85% showed sensory alterations. Padman et al. (Padman S et al, 2015) also conducted a small study on 25 CRC patients, followed up 2 years after treatment; neuropathy was still present in this cohort: the mean mTNSc ® score was 9,5 and EORTC QLQ-CIPN20 mean sensory neuropathy score was 15.4. All this data are consistent with larger trial, such MOSAIC (Andre' T et al, 2009) and NSABP C-07 (Yothers G et al, 2011) in which the burden of neuropathy is still relevant over prolonged time of observation.

In conclusion, OIPN is a highly relevant topic, since it is long-lasting and has no cure. Further studies are warranted both at bench both at bed-side.

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PSYCHOSOCIAL PROBLEMS IN LONGTERM COLO-RECTAL CANCER ELDERLY PATIENTS

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Nowadays growing old is not an extraordinary event. Median life has greatly increased: in Italy the over 65 years are the 20.1%. It has been estimated that in 2035 elderly will be the 28.6% and in 2060 the 32.7% of all Italians. Old age cannot be considered as a homogeneous reality. In fact, if on one hand some people age "successfully", on the other, the condition of many elderly remains of fragility. This is a phase of life in which probably many pathologies and comorbidities are present, many prescription medicines are assumed, and you can find yourself alone (adult children moved from home and widowhood).

Chronological, biological and psychological age are three facets of growing old with many differences and chronological age is just one aspect of this stage of life.

The word old presents, then, with a vaguer connotation than in the past and is inadequate to define the new heterogeneous reality that requires to take into account many peculiarities and differences, as part of the clinical evaluation, even from the psychosocial point of view.

While evaluating the condition of the old person, it should first be considered that at this stage of life psychological, biological and social factors, are closely intertwined and can determine - although not in an inevitable - a mismatch: not excluding ' brain aging, they go by the exhaustion of the productive role (retirement) to the experience of loss (possible departure of the partners and posting of children), by increased dependence to the possible family and social marginality, by the feeling their body is changing to weakening of sexuality, from the difficulty of planning the future to the fear of death.

When it comes to elder, then, some areas where changes may negatively affect the psychosocial well-being, must be addressed.

Retirement is an existential moment of "CRISIS" as an event of sudden transition from active and productive life to an idle state requiring the re-

definition of the self and the social relationships, with the abandonment of some roles and the acquisition of others.
As for the body, in old age it undergoes somatic, functional and psychological transformations (decay of the perceptual apparatus, sensory-motor, and energy reduction). In the case of a "sick" body, it requires attention and energies that are subtracted to "possibilities" and social spaces. The consequences of this are the underrating of body image and the image of oneself, already determined by socio-cultural factors, causing the elderly to gradually continue to retreat from the world.
Other factors that may affect the elder mental well-being, are the psychological dimensions of time and space. With regard to the time, there are dilation of the past, and reduction of future and present; with respect to space, the slowdown of sense-perceptions and motor skills, as well as an actual restriction of the social space reducing the amplitude of life, can be experienced.
In a strictly psychological dimension, the most distinctive aspect of the condition of the aged person seems to be, however, the problem of the progressive shortening of life and the inevitable confrontation with the idea of dying. This awareness, inevitably made even more present with a disease such as cancer, may be the possible introduction of a psychological imbalance and undermine the balance favoring depressive episodes, particularly when this also implies a decrease in social skills.

To study the psycho-social aspects of survivorship to colorectal cancer in the elderly, also means understanding how the psycho-social consequences of the disease and subjective adjustment processes combine with the natural aging process and each individual resources (personal, social) on how to fully live this stage of life that, as such, has its own developments (e.g. Erikson, 1963) and plans opportunities to reward, achievement, and serenity.
Generally, regardless of age, the most common late and/or long-term psychosocial effects of cancer are psychological distress, fear of recurrence, the body image impairment, problems related to intimate and relational spheres, and cognitive limitations; furthermore, for their multidimensional nature, there are also fatigue and pain (Annunziata & Muzzatti, 2014). The type of tumor (site, stage, prognosis), the related treatments (including their side effects), the presence of comorbidities, some socio-demographic variables - among them the age, but also gender, personality and styles

and coping strategies, social support available and perceived, are some of the main factors that interact with these effects.
Concerning colorectal cancer, the most frequent specific long-term effects are abdominal obstructions, hernias in the abdominal wall, and the problems affecting excretory, urinary and sexual functions (Mussa et al., 2002; Ganz, 2007). From a psychological point of view, bowel obstructions are relevant because, in addition to causing pain, they can be a sign of recurrence. The abdominal wall hernias also cause pain, in addition to limitations in daily activities. The impairment of urinary, excretory and sexual functions, however, involve a body image disorder, discomfort for the feeling of loss of personal hygiene, embarrassment and shame for incontinence and the inability to control unpleasant noises and smells, social withdrawal and isolation.
The literature specifically dedicated to the psycho-social aspects of survivorship of colorectal cancer in the elderly is not very rich. However, it can be integrated extrapolating the data on older patients from wider age range studies and/or heterogeneous samples for diagnosis.
The prevalence of cancer in Italy in 2010 amounted to 4.4% (including 45% males, 55% females), increased to approximately 11% in the 60-74 age group and 20% and 13%, respectively, for males and females over seventy (AIRTUM, 2014). Of all diagnoses of cancer, 39% relates to persons included in the age range 60-74 years, 35% in 75 years and beyond (AIRTUM, 2014).
The tumor of the colon-rectum is the second type of tumor in terms of prevalence for both women (12% of all diagnoses) and men (16% of all cancer diagnosis) (AIRTUM, 2014). Among the almost 300,000 Italian patients with a diagnosis of carcinoma of the colo-rectum (51% male), 14% is living 10-15 years after the diagnosis, 16% over 15 years from the diagnosis, with the remainder distributed equally within 2, 2-5 and 5-10 years from diagnosis (AIOM / AIRTUM, 2014). In addition, it is noteworthy that the incidence of colorectal cancer is more than double in persons aged 75+ years, compared with people aged 60-74 years and 8.5 times higher than that of people aged 45- 59 years (AIOM / AIRTUM, 2014).

Jensen et al. (2011) conducted a prospective QoL population-based study in German colon-rectal cancer survivors, administering the EORTC QLQ C30 questionnaire. In their older sub-sample (70+- years old patients at diagnosis) reported comparable or slightly better QoL levels for many

QoL dimensions than controls during the first years after diagnosis but worse or comparable levels after 5 to 10 years. More in detail, these participants reported better physical functioning, role functioning, and global QoL and fewer pain symptoms 3 years after diagnosis. Of the considered dimensions, global QoL and pain level of participants with colorectal cancer were comparable to those of controls after 10 years. In addition , after 10 years, participants reported relevant impairments in role, social, cognitive, and emotional functioning and higher levels of diarrhea, dyspnea symptoms, and financial difficulties. Constipation levels were continuously elevated. After 10 years, detriments were largest for dyspnea, diarrhea and financial difficulties.
These data can be integrated by results provided by another study (Threan-Borowski et al., 2013) involving 832 65+ years-old long-term colon-rectal (5+ years from diagnosis) cancer survivors. According to this latter study, the QoL physical health component was related to physical activity, whereas their QoL mental health component was relate to social participation.

Psychological distress is registered as a unique dimension or considered as composed of both anxiety and depressive states.
In general, anxiety (fear, worry) tend to decline with age, except for concerns related to health.
Deimling et al. (2015), in a study involving 245 patients older than 70 years, long-term cancer survivors of breast, prostate and colorectal cancer report as general health worry and cancer-related worries (that includes fears of recurrence, new cancers, and follow-up testing) are essentially two independent constructs. In addition, they identified the importance of current cancer-related symptoms and comorbidities on cancer-related worry. In additions, they demonstrated the primacy of non-cancer symptoms and general health worry as predictors of anxiety and depression in their sample. The type of cancer and the years since diagnosis were not playing any role in these results.
Data related to depression in the target population, however, can be found in the paper by Clark et al. (2016). They conducted a population-based survey to study depression in patients aged 60 years or older surgically treated for colorectal cancer (CRC). Among the 1785 patients treated, 15.6% were positive for depression screening. Increasing time from diagnosis was associated with a decrease in the prevalence of positive depression screen:

CRC survivors surveyed within 6 months of diagnosis, positive depression screen was 22.9 %; between 7 and 24 months it was 15.1 %; and, in more than 24 months, it was 14.9 %. The strongest predictors of positive depression screen emerged from this study were not tumor-specific factors but higher number of comorbidities and impairment in activities of daily living.
In a study by Moye et al (2014) involving heterogeneous patients for diagnosis (although 50% had a history of colorectal cancer), elderly cancer survivors (65+) compared to non-elderly (<65 years) reported less depression. Serpentini et al. (2011) studied the psychological well-being (i.e. a broader construct than that of psychological distress) in rectal cancer patients through the Psychological General Well-Being Index (PGWBI). In comparison with normative data, the sub-sample 65-74 years (N = 40), reported better scores in all six subscales of the instrument (Anxiety, Depressive mood, Positive well-being, Self-Control, General Health, Vitality) and in the comprehensive Global index, Whereas the sub-sample of participants older than 74 years of age (N = 20), displayed higher scores than controls only at the positive well-being scales.

Pain is a symptom with a strong impact on the perception of well-being and functioning of individuals (e.g., Lowery et al. 2013).
In the already mentioned study involving cancer patients, 50% of whom had a diagnosis of colorectal cancer, the eldest cancer patients (65+ years), compared to the less elderly (<65 years) showed, 6 months after the diagnosis, a lower prevalence (20.5% vs. 42.4%), a lower intensity (2.7 vs. 3.9; range: 0-10), and less pain interference in the activities, work, and enjoyment of life (Moyye et al., 2014). In addition, the pain in older subgroup was associated with comorbidities and depression. However, the study authors couldn't explain if older patients in the study experienced less pain intensity and less impact on function, or if they under-reported them.

Measuring the psychological variables in the elderly is most certainly a challenge, since we do not always have tools specifically adapted for the elderly and without a doubt the subjective perception of emotional states, pain, QoL change over the lifetime. Furthermore, in the elderly, cognitive aspects (decay, memory problems), emotional aspects (depression is more common in old age), cultural aspects (modesty, reticence) an important, but difficult to quantify, role. However, life expectancy gets longer and

today aged people live more active lives than in the past: it is therefore important to study accurately their operation and their welfare.
The psycho-oncological literature on cancer survivorship is itself articulated. Among the various reasons for this phenomenon there is the heterogeneity of definitions of "cancer survivorship" adopted in literature, heterogeneity that makes the interpretation and comparison of data quite difficult.
Nevertheless, in the light of what is available today in the literature, it seems possible to conclude that, from a psychosocial point of view, the experience of the survivorship of the elderly with colorectal cancer does not seem to take particular connotations, since the problems related with age (comorbidity) seem to be more important than those cancer-specific. The elderly survivor of colorectal cancer show, in fact, some psycho-social symptoms, but these are hard to divide into cancer-related symptoms and age-related symptoms (primary and secondary aging). More than ever, then, the psycho-social approach targeting this population should consist in the acceptance and in the treatment of the evolution of bio-psycho-social functioning while aging, of the several health issues (including their effects) and, among them, of the tumor.

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TIROID CANCER
CURRENT TREATMENT AND NEW APPROACH

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Introduction

Thyroid cancer (TC) is the most common endocrine neoplasm, accounting for about 3% of all human malignancies. Its rate of incidence is the fastest among all human cancer with an estimated number of new cases of 64,300 in USA in 2016, thus becoming the eight most common human cancer (1). Despite its frequency and increasing incidence over the years, the mortality rate of this tumor did not increase and is the lowest among the ten most common human malignancies (1).

According to the WHO histological classification, thyroid tumors are classified as papillary (PTC, 75-80%) and follicular thyroid carcinoma (FTC, 5-10%) when originate from the follicular cells and medullary thyroid carcinoma (MTC, 1-2%) when they originate from parafollicular C-cells (2). The latter is sporadic in 70% of cases while in 30% is part of an autosomal dominant inherited disorder such as MEN 2A (Sipple's syndrome), familial MTC (FMTC) and MEN 2B (3). More rare thyroid tumors that likely originate from follicular cells but lose totally or in part the features of the cell of origin are poorly differentiated (PDTC, 3-5%) or anaplastic thyroid carcinoma (ATC, 2-3%) (2).

The different histotype and degree of differentiation affect significantly the survival rates of these patients. In fact, the survival rate is 95% for PTC, 80% for FTC at 35-40 years after the initial diagnosis, 65% for MTC at 10 years, 20% for PDTC at 5 years and less than 10% for ATC at 6 months (3).

Differentiated thyroid cancer (DTC), namely PTC and FTC, maintain the features of the follicular cell such as the ability to take up iodine and produce thyroglobulin (Tg). These features have very important implications in patient's treatment and follow-up, in fact, the ability to take up iodine is the basis for the treatment of these patients with 131-radioiodine while serum Tg measurement allows an accurate management strategy. Similarly to PTC and FTC, MTC has a very sensitive and specific tumor marker,

namely calcitonin (Ct), to guide the management of the disease. In fact, the tumor can remain stable over the years and these markers, both Tg for DTC and Ct for MTC, are useful to assess the intensity of follow-up and to schedule imaging studies.
In the majority of cases DTC are curable by thyroidectomy followed when appropriate by radioiodine treatment. However, in 5-10% of cases the disease is advanced at diagnosis, it is not curable with surgery and do not respond to radioiodine treatment from the beginning or after some radioiodine courses.
Until recently no therapeutic options were available for these patients because advanced thyroid tumors do not respond to classical chemotherapy and radiotherapy that have only a palliative intent. The advances in molecular biology regarding the mutations and activated pathways involved in tumor aggressiveness and the mechanism responsible of disease progression were the basis for the development of new targeted drugs.

Thyroid cancer genetic alterations
In 1986 the first TC genetic alteration, called RET/PTC rearrangement, was reported (4). This rearrangement, that promotes cell proliferation and tumoral transformation through the activation of the mitogen-activated protein kinase (MAPK) pathway in follicular cells, is typical of PTC related to radiation exposure. Since its initial description several other rearrangements of RET gene were described but their cumulative prevalence is low (about 20%).
The most frequent mutation in PTC is BRAFV600E mutation. This mutation accounts for about 40% of all PTC cases and it seems that its prevalence is increasing while the prevalence of RET/PTC rearrangement is apparently decreasing (5). BRAFV600E mutation, is responsible of the hyperactivation of a serine/threonine kinase that promotes the proliferation, tumorigenic effect and dedifferentiation process through MAPK pathway (6). The BRAFV600E mutation is associated to more aggressive phenotype, loss of radioiodine avidity, increased recurrence and mortality rate (7-9). More recently, two point mutations in the TERT gene were reported in ATC and associated with a more aggressive PTC phenotype. Other important but less frequent genetic alterations in PTC are H-, N- and K-RAS that cause the loss of GTPase activity and the constitutive activation of the kinase that promotes carcinogenesis and tumor growth through MAPK and phosphoinositide-3-protein kinase B (PI3K-AKT)

pathway (10). Several other oncogenic alterations have been described in PTC with a lower prevalence; all these alterations are generally mutually exclusive (11).

Mutations in RAS oncogene are the most frequent genetic alterations found in FTC. Other less common genetic alterations in FTC are phosphatase and tensin homolog (PTEN) deletion/mutation, paired box 8-peroxisome proliferator-activated receptor-gamma rearrangement (PAX8/PPARgamma), phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) and isocitrate dehydrogenase 1 (IDH1) mutations.

The most common genetic alterations in PDTC and ATC are H-, N- and K-RAS, tumoral protein 53 gene (p53), BRAFV600E, PIK3CA, PTEN, IDH1, CTNNB1and ALK mutations (12).

The most common and important genetic mutations described up to know in MTC are RET activating mutations. These mutations are present in 95% of hereditary MTC cases, while somatic RET mutations (mainly M918T) were described in 50% of sporadic cases. More recently also H- and K-RAS mutations, were reported in a non-negligible percentage (17%) of RET negative sporadic MTC cases (12). Also RAS and RET are mutually exclusive in MTC tissues. All these genetic alterations were demonstrated to control proliferative and anti-apoptotic signaling in TC mainly through MAPK and PI3K/AKT pathway (12).

Other genetic abnormalities that involve genes encoding tyrosine kinase receptors (TKR) as VEGFR, MET, EGFR, PDGF and KIT are likely responsible of a more aggressive phenotype (14).

Even though it is likely that the most important TC genetic alterations were described, approximately 5-10% of PTC and ATC/PDTC and up to 60 % of MTC are still negative for all genetic abnormalities that were investigated so far (11).

Targeted therapies: tyrosine kinase inhibitors

Until recently, with the exception of doxorubicin, no therapeutic options were available for the treatment of TC patients. This drug was approved in 1974. Due to its scarce efficacy and non-negligible toxicity over the years the combination of different classical chemotherapeutics were investigated. Despite these efforts all these treatments were demonstrated to have low and transient efficacy in controlling tumor growth and significant toxicity. The increasing knowledge in the molecular basis of TC pathogenesis, disease progression and patient's prognosis led to the investigation of new targeted drugs in advanced TC patients. A novel family

of small molecules, tyrosine kinase inhibitors (TKI), was demonstrated to be effective in inhibiting the catalytic activity of several TKR to obtain an anti-proliferative effect. Almost all TKI investigated in TC are multitarget and act on different TKR with different affinity. The most interesting TKI in TC patients were demonstrated to act not only on the product of the gene and activated pathway involved in the pathogenesis of the disease but also against the receptors involved in angiogenesis (VEGFR, FGFR, PDGFR etc). The most interesting and recently approved drugs for the treatment of TC are sorafenib and lenvatinib for advanced radioiodine refractory (RAI-R) DTC and vandetanib and cabozantinib for advanced MTC. A novel drug that seems to be promising in DTC is selumetinib, a selective MEK 1/2 inhibitor that was demonstrated to reverse iodine uptake in RAI-R disease.

Randomized clinical trials evaluating tyrosine kinase inhibitors in thyroid cancer

The first multicenter study investigating a TKI in large cohort of MTC patients was ZETA trial. This randomized phase III study evaluated the efficacy and toxicity of vandetanib versus placebo in locally advanced or metastatic MTC patients. The higher rate of progression free survival (PFS) of patients treated with vandetanib compared to those treated with placebo led to FDA approval of this drug for the treatment of advanced and progressing or symptomatic MTC patients in 2011 (14). Currently, an international, multicenter phase III trial (VERIFY) is exploring the efficacy of this drug in RAI-R DTC. In the same years another TKI, cabozantinib, was investigated in a randomized phase III trial (EXAM) versus placebo in a large cohort of advanced and progressing MTC patients.

In 2012 cabozantinib was demonstrated to prolong the PFS of patients treated with the drug compared to those treated with placebo and was approved for the treatment of these patients (14). Two drugs, sorafenib and lenvatinib, were also investigated for the treatment of advanced and progressive RAI-R DTC patients in two phase III randomized trials versus placebo (DECISION and SELCT trials, respectively). The good results in terms of prolongation of PFS in RAI-R DTC patients treated with sorafenib and lenvatinib in the DECISION and the SELECT trial led to the approval of sorafenib in 2013 and of lenvatinib in 2015.

With the exception of ZETA trial in which symptomatic patients were allowed to enter the trial, in EXAM, DECISION and SELECT trials only

patients with TC showing a progressive disease documented in two CT scans performed within 12-14 months were enrolled.
More recently, a double blind phase III study evaluating the complete remission rate following a 5-week course of selumetinib or placebo and single dose adjuvant radioactive iodine therapy in patients with DTC with intermediate risk of recurrence undergoing thyroid remnant ablation is ongoing but no longer recruiting participants.
An expanded access program with lenvatinib in RAI-R DTC and two phase IV trials investigating if a lower dose of cabozantinib and vandetanib results in similar PFS with fewer adverse events in MTC patients are ongoing.
Despite the large cohort studies performed both in MTC and in RAI-R DTC no robust data are currently available regarding the patient's overall survival (OS) treated with TKI. The only trial in which OS was significantly increased in patients treated with cabozantinib when the analysis was performed in MTC patients with M918T-RET mutation is EXAM trial. In fact, the possibility to "cross-over" and be treated with the drug once the patient experienced progressive disease that was permitted in ZETA, DECISION and SELECT trial but not in EXAM while treated with placebo did not allow the correct interpretation of the data regarding OS. However, when the potential bias of the "cross-over" was considered and a statistical correction method called rank-preserving structural failure time (RPSFT) model was applied to avoid the interference of this confounding factor, an higher and statistically significant OS was observed in patients treated with lenvatinib compared to those treated with placebo (14).

Tyrosine kinase inhibitors: adverse events
Adverse events (AE) in patients treated with TKI are very frequent and expected. In the majority of cases AE are mild but in some cases, particularly if not known, not discussed with the patient and prevented could lead to drug interruption, dose decrease and in case of severe AE to treatment withdrawal. All TKI share the same spectrum of toxicities. The most frequent AE are diarrhea, hand and foot syndrome, hypertension, fatigue, anorexia and weight loss. The majority of these AE could be prevented or treated effectively without affecting the patient's compliance. Serious AE (SAE) are less common and reversible after drug withdrawal even if in some cases they could lead to patient's death or severe disability.
A screening for factors that could represent a potential contraindication to TKI treatment should be done to avoid or decrease the rate of SAE

such as cardio-, hepato-, nephro- and haematological toxicities. Moreover, the possibility to develop these toxicities as well as hypertension, hypothyroidism, pancreatitis, gastrointestinal perforations, hemorrhagic/trombotic events should be carefully monitored during follow-up.

Conclusions

Until recently no effective therapeutic options were available for advanced thyroid cancer patients. The development of TKI and the demonstration that these drugs could prolong PFS opened the era of new targeted drugs for thyroid cancer patients. However, considering that the data regarding OS in these patients are not so robust and that these drugs could affect the patient's quality of life an accurate analysis regarding the risk/benefit ratio should be carefully considered before starting the treatment. Until now, the authors agree that, in the absence of contraindications, the treatment should be started only in patients with radiologically documented progressive disease demonstrated in two CT scans within 12-14 months. An exception could be made in case of symptomatic or threatening disease expected to produce imminent morbidity or mortality (14). It is worth to note that all TKI approved for TC treatment so far are cytostatic drugs and after a variable period of time are no longer able to arrest cancer growth. In fact, tumoral cells develop an "escape" mechanism that leads to disease progression. This "escape" mechanism is different and largely unknown in different tumors. For this reason future basic research should be aimed at defining these mechanisms to develop other drugs able to overcome the escape phenomenon or, even better, to discover novel cytotoxic targeted drugs that could definitively cure these patients.

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THYROID
MOST FREQUENT TOXICITY AND NEW SIDE EFFECTS OF NOVEL DRUGS AND/OR TREATMENTS

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Introduction

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer (85%), generally treated with surgery and radioiodine treatment. A minority of patients (5-15%) becomes radioiodine-refractory. Generally patients have a limited disease and standard treatment includes surgery, followed in case of residual disease by treatment with 131I and suppressive therapy with L-thyroxine. Radioiodine-refractory thyroid cancer is difficult to treat. Chemotherapy and radiotherapy are not associated with good results.

Medullary thyroid carcinoma (MTC) arises from calcitonin-secreting parafollicular cells of the thyroid and accounts for less than 5% of all thyroid cancers.

Target therapy is indicated when there is a progression of disease without iodine uptake (dedifferentiation of tumor); when radioiodine uptake persist, but there is a significant progression of disease; when there is a progression of disease despite maximum cumulative dose of 131I (about 600 mCi).

Tyrosine Kinase Inhibitors (TKIs) constitute a new treatment modality. Their efficacy in prolongation of progression free survival in comparison to placebo has been documented in phase III studies, showing a good specificity and selectivity as mechanism of action.

Sorafenib is the first drug approved by FDA (Food and Drug Administration) for DTC on November 22, 2013 . Decision trial documented a doublet time to progression: mPFS was 10.8 months in patients treated with sorafenib versus 5.8 months in patients treated with placebo. Sorafenib inhibits kinases involved in mechanism of cellular proliferation and neo- angiogenesis as Raf-kinase,VEGFR1, VEGFR2, VEGFR3, PDGFRB, Kit, FLT3, RET.

Lenvatinib is a TKI, tested in SELECT trial, able to produce high response rate and delay progression in patients with advanced radioio-

dine-refractory DTC. On February 13, 2015, the U. S. FDA and on June 2015 EMA (European Medicines Agency) approved lenvatinib (Lenvima) for the treatment of patients with locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer. On June 2016 lenvatinib has received registration by AIFA (Agenzia Italiana del Farmaco).
Vandetanib was approved by FDA in 2011, followed by EMA in 2012 and AIFA registering on 2015, based on the ZETA phase 3 clinical trial, for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease. Median progression-free survival was more than 30 months with vandetanib vs 19 months with placebo, and 45% of patients responded to the drug.
Nevertheless tolerabilty represents a problem because these agents have new and unusual side effects such as cardiovascular toxicity (hypertension, prolongation of QT), gastrointestinal toxicity (diarrhea, stomatitis), skin toxicity, endocrine toxicity.
These side effects generally occur as toxicity of grade 1-2 and rarely are letal but have an impact on quality of life .
Their correct management is necessary to maintain patient compliance and avoid potentially life-threatening consequences. (1-6,16-17)

Hypertension
Hypertension is one of the most common adverse effects of therapy with TKI.
TKI cause a reduction of regenerative ability of endothelial cells; alteration of vascular surface area; increase of production of eritropoietin; a decreased production of nitric oxide (NO) in the wall of the vessels. NO is a vasodilator and its low synthesis causes vasoconstriction with increased peripheral resistance and blood pressure. It has been suggested that the mechanism of hypertension is based also on increased fluid retention.
Hypertension can occur anytime after the beginning of treatment and can be managed with oral antihypertensive agents including ACE inhibitors, angiotensin receptor blockers (ARBs) or beta blocker. In the choice of an antihypertensive drug we should consider possible drugs interaction. TKI are metabolized by CYP 450 3A4, so antihypertensive agents, substrates of CYP450, (losartan, calcium channel blockers, doxa-

zosina) should be avoided.
Hypertension should be controlled to a goal of < 140/90 mmHg. Once a TKI is initiated, patients should have the blood pressure monitored within 1 week; if the blood pressure is above goal, antihypertensive therapy should be initiated or adjusted. Patients should continue to check their blood pressure daily and report results on a weekly basis and therapy should be rapidly titrated or new drugs added to the regimen. Blood pressure elevation related to TKI is reversible so discontinuation or dose reduction of TKI can also be used to control hypertension. Discontinuation is useful when the symptom is difficult to control, the therapy should be reinstituted at the same or lower dose once obtained blood pressure control. (7-9,14,16)

Proteinuria
TKIs cause proteinuria because inhibit VEGFR; thrombotic microangiopathy and acute interstitial nephritis are common with sorafenib. The glomerular podocytes express VEGF while glomerular endothelial cells express VEGF–R. The deletion of VEGF allele in podocytes or inhibited VEGF signaling cause proteinuria and capillary endotheliosis. Targeted heterozygous deletion of VEGF in podocytes results in renal pathology manifested by loss of endothelial fenestrations in glomerular capillaries, proliferation of glomerular endothelial cells, loss of podocytes and proteinuria. Inhibition of VEGF dependent interactions between podocytes and glomerular endothelial cells disrupts the filtration barrier, leading to dose dependent proteinuria.
Patients receiving TKI should have a baseline urinalysis and protein to creatinine ratio. A urine protein to creatinine ratio of > 1 or 24 hour urine with > 1 gram /dL/ 24 h of protein should prompt intervention, it could be useful using ACE inhibitors or ARB.(2,6)

Hand-foot syndrome
Hand-foot syndrome or palmar-plantar erythrodysesthesia, is a common side effect of drugs as sorafenib.
It is supposed that these drugs affect the growth of skin cells and capillaries in the hands and feet, tissues are damaged when the drug is out of the vessels.
Symptoms include redness, swelling, tenderness, tightness of the skin. When syndrome is severe, are common peeling skin, ulcers, severe pain

with difficulty walking or using the hands. Generally hand-foot syndrome appears in the first six weeks of treatment.
Prevention measures include limit exposure to hot water, avoid contact with chemicals used in cleaning products, avoid activities that cause friction on the hands or feet.
Treatment consists in use of topical anti-inflammatory medications as corticosteroid creams; topical anesthetics, such as lidocaine, used as a cream or a patch over painful areas in the palms and soles; topical moisturizing exfoliant creams containing urea; pain relievers.
In addition, when syndrome is severe, affecting patient's quality of life, is necessary dose reduction or temporarily drug discontinuation until symptoms of hand-foot syndrome improve.
Sorafenib is associated with hand-foot syndrome in about 30% of patients. In case of grade 1 toxicity is suggested continue sorafenib and use topical therapy. In case of grade 2 toxicity is suggested use topical therapy, if no improvement within 7 days is possible interrumpt treatment until toxicity resolves to grade 0-1. If grade 2 or 3 toxicity recurs , can be useful decrease sorafenib dose by one dose level or in case of 4th occurrence discontinue therapy. (10)

Hypothyroidism
Despite their selectivity, TKIs show variable affinity for different kinase-receptors and none is specific for a single kinase receptor, leading to a variety of toxicities, often unusual, such as those to the endocrine system, mainly including thyroid dysfunction.
TKIs may cause de novo hypothyroidism or hyperthyroidism, or worsen pre-existing hypothyroidism, thus increasing thyroid hormone requirements in patients on levothyroxine (LT4) replacement. When hyperthyroidism occurs, it may represent the transient thyrotoxicosis phase of a destructive thyroiditis, often followed by hypothyroidism.
Several mechanisms have been suggested to explain the onset of thyroid dysfunction in patients under TKI treatment. As thyrotoxicosis in a few cases preceded the development of hypothyroidism and thyroid atrophy, destructive thyroiditis might have triggered both adverse events. Other possible mechanisms include direct toxic effects on thyrocytes, leading to an impaired iodine uptake and a reduced synthesis of thyroid hormones related to inhibition of TPO activity . More likely, the TKI-induced thyroid dysfunction may derive from the inhibition of kinase receptors

of angiogenic pathways, such as VEGF receptors 1–3 and platelet-derived growth factor receptor (PDGFR). TKI-induced regression of thyroid vascular bed with signifi- cant capillary alteration and reduction in density has been demonstrated in experimental animal models. This could cause the reduction of blood flow in the thyroid, an extremely vascular gland. If the thyroid blood flow decreases rapidly, an ischemic thyroiditis could result, leading to transient thyrotoxicosis. If the decreased blood flow develops more slowly, gradual thyroid destruction may occur, resulting in hypothyroidism .
An other hypothesis consists of increased activity of enzyme Deiodinasi D3 causing conversion T4 –T3 and T3-T2 and a decreased activity of Deiodinasi D1 able to convert T4-T3 with subsequent increase of TSH.
A correct and timely identification of thyroid dysfunction induced by anticancer drugs is important despite the recognition of symptoms may be difficult. For example, symptoms such as fatigue and/or constipation may be caused by medications used to control pain or nausea. Similarly, palpitations, weight loss, heat intolerance, tremor, proximal muscle weakness, tachycardia, insomnia, irritability, fever are symptoms of thyrotoxicosis but can be present in case of infection or sepsis. Misunderstanding of thyroid dysfunction induced by TKIs may lead to unjustified dose reduction or treatment withdrawal of the drug. Undetected thyroid diseases can trigger life-threatening consequences, such as cardiac toxicity presenting as complication of TKI-induced hypothyroidism or eventually myxedematous coma
Management of thyroid dysfunction requires assessment of function of the gland at baseline and throughout the treatment and follow-up period.
In thyroidectomized patients under adequate LT4 replacement, pretreatment TSH evaluation, followed by monthly monitoring of TSH, is recommended. In these patients, a substantial increase up to the doubling of the LT4 dose on initiation of TKI should be considered. Once TSH levels are stable, monitoring every 2–3 months is sufficient.
In patients with normal thyroid function, measurement of thyroid function tests before treatment and then measuring TSH on day 1 of every cycle appears appropriate. Elevated TSH levels measured on day 1 of the cycle could indicate clinically relevant thyroid damage requiring further investigation or initiation of substitutive therapy . However measurements of TSH may be empirically advised on day 1 of cycles 1–4,

and then every 2–3 cycles. Patients with overt hypothyroidism (TSH > 10 mIU/L) should receive LT4 with the objective of maintaining TSH within the normal range. This may be achieved by an average starting dose of 1.6 lg/kg/day. The treatment of subclinical hypothyroidism (TSH 5–10 mIU/L with a normal free T4) is questionable in cancer patients. However, LT4 may be offered to cancer patients presenting with TKI-induced subclinical hypothyroidism and TAb, hypercholesterolemia, thyroid nodules, or symptoms, such as fatigue, that may greatly worsen patients' quality of life. (11)

Diarrhea

Diarrhea is a common side effect related to TKIs. Intensity of diarrhea is variable. Generally it is grade 1-2 (grade 1: < 4 episodes die, grade 2: 4-6 episodes die; NCI), appears after 2 days of treatment. It is associated with abdominal pain and needs a tempestive treatment .

It is suggested to take medication with a large meal and water to reduce side effects.

Treatment of diarrhea includes : variation of dose; alimentary intervention; drug intervention

If grade 1 or grade 2 (for less than 48 h) diarrhea occurs, patients should be advised to take loperamide at a dose of 4 mg, followed by 2 mg after each episode of diarrhea, up to a maximum of 16 mg/day. Drinking 1–1.5 l per day of isotonic, oral rehydration salts is recommended; patients should be advised not to drink more than 0.5 l of hypotonic fluids (e.g. water, tea, fruit juice) as this can make the diarrhea worse. Most cases of grade 1 or short duration grade 2 diarrhea resolve quickly. Patients should be advised to inform the medical team if they develop grade 1 or 2 diarrhea that does not resolve within 48 h, or if they develop diarrhea with fever. If the diarrhea persists for 48 h, despite administration of the maximum daily dose of loperamide, or is grade 3–4, the patient's condition should be reviewed and TKI should be discontinued. It could be necessary hospitalise patient, rehydrate with intravenous fluids and use octreotide. If it persists are useful feces examination and antibioticotherapy. (12-14)

Stomatitis

Stomatitis is a common side effect related to TKIs. Patient education about the risk and causes of stomatitis/mucositis is essential before

starting therapy. Maintaining good oral hygiene is essential; non-alcoholic mouthwashes are recommended. It may be necessary to evaluate the use of dental appliances (braces, dentures, retainers, etc.) before therapy begins, as they can aggravate oral mucositis. Patients should be advised to eat food that will not cause oral lesions, i.e. soft, moist, nonirritating food that is easy to chew and swallow. Patients should drink plenty of water and lip balms can help to reduce mouth dryness.
In case of grade 1 stomatitis/mucositis (erythema of the mucosa) patients can usually continue the drug at the current dose. Oral rinses (0.9 % saline or sodium bicarbonate) can soothe the mouth and only nonalcoholic mouthwashes should be used. Prophylaxis against fungal, viral and/or bacterial infections can be considered; infections must be treated as appropriate with topical or systemic antimicrobials.
In case of grade 2 stomatitis/mucositis, it may be necessary to stop the treatment or reduce the dose. TKI should be restarted when the stomatitis/mucositis has improved to grade 1. Topical anaesthetics, mucosal coating agents and/or benzydamine HCl may be administered as needed for pain relief . Infections should be treated with topical or systemic antimicrobials. Obtaining specialist advice should be considered.
In case of grade 3 stomatitis/mucositis, treatment with TKI should be discontinued and the patient is usually hospitalised to receive supportive care . Appropriate pain relief and antimicrobials should be administered . TKI can be restarted, at a lower dose, once the toxicity has resolved to grade 1. If grade 4 stomatitis/mucositis develops, a specialist dermatology assessment should be suggested, TKI therapy should have already been discontinued, and restarting treatment at a reduced dose should only be attempted after complete resolution of toxicity. (12)

QT prolongation

The most important adverse event with vandetanib is QTc prolongation. CTCAE (Common Terminology Criteria for Adverse Events) grade 3 to 4 QT prolongation was reported in 8% of patients. Among patients who experienced QT prolongation, 69% experienced a QT interval Fridericia (QTcF) greater than 450 milliseconds (msec) with 7% having reported a QTcF greater than 500 mse. Management of this toxicity involves Dose Reduction. In event of QTc interval >500 ms, interrupt dosing until <450 ms, then resume at a reduced dose. In the presence of CTCAE grade 3 or greater, interrupt dosing until toxicity resolves or improves to grade 1, then resume at reduced dose. 300 mg daily dose may be reduced

to 200 mg/day and then 100 mg for CTCAE grade 3 or greater.
Before treatment an echocardiogram, ECG, and levels of serum potassium, calcium, and magnesium and TSH should be obtained at baseline. Vandetanib treatment must not be started in patients with QTc 450 ms (US prescribing information); 480 ms in EU summary of product characteristics. Hypocalcemia, hypokalemia, and/or hypomagnesemia must be corrected prior to vandetanib administration.

During treatment an ECG and levels of serum potassium, calcium, and magnesium and TSH should be obtained at 1, 3, 6, and 12 weeks after starting treatment and every 3 months for at least a year thereafter. Serum TSH, serum potassium, serum magnesium, and serum calcium should be kept within normal range. Coadministration of substances known to prolong QTc is contraindicated or not recommended; in particular, the concomitant use of vandetanib with ondansetron is not recommended ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards, with frequent monitoring of the QTc interval. If antiemetic therapy is required, consider palonosetron-based treatment. Additional monitoring of QTc, electrolytes, and renal function is needed in case of diarrhea. If QTc increases markedly but stays below 500 ms, cardiologist advice should be sought. (15,17)

Dermatologic Effects

Very common adverse effects (10% or more) with use of vandetanib are rash (53%); dermatitis acneiform/acne (35%); dry skin (15%); photosensitivity reaction (13%); pruritus (11%).

Types of rash reported included rash (erythematous, generalized, macular, maculopapular, popular, pruritic, and exfoliative), dermatitis, bullous dermatitis, generalized erythema, and eczema. The mechanism of the rash has not been fully elucidated, but most observed rashes, especially those presenting as follicular pustules are probably due to the anti-EGFR action of vandetanib, as antiEGFR agents are associated with acute and subacute folliculitis. It is thought that the ability of vandetanib to block EGFR triggers follicular hyperkeratosis, leading to follicle obstruction and an inflammatory response. There is also a risk of superinfection of these skin lesions.

Before starting vandetanib treatment, it is critical to discuss the potential development of skin reactions with patients, initiate preventive measures, and provide reassurance that these can usually be managed effectively. An evaluation of mucosal and skin surfaces is recommended. Mana-

gement of reactions includes strict photoprotection (e.g. use of a broad-spectrum UVA/UVB sunscreen with a sun protection factor of 30 or higher, avoidance of any sun exposure by cloth protection) and avoidance of products that dry the skin (e.g. soaps, alcohol-based or perfumed products). Early monitoring is essential to capture the emergence of rash, which is generally treatable. Collaboration with a dermatologist may be needed in severe or complicated cases

	Vandetanib	Sorafenib	Lenvatinib
Diarrhea	+++	+++	+
Rash /hand foot syndrome	++	+++	+
Proteinuria	+	++	+
Stomatitis	+	+	+
Hypertension	+	++	+++
QT prolongation	+++	-	+
Hypothyroidism	+	+++	+
Fatigue	+	++	++

Main Side effects of TKI

It can be advisable prophylactic use of hydrating creams all over the body, especially areas of sun-exposed skin and hands and feet; early use of fatty ointments and urea creams. If no improvement, the addition of topical steroids, with or without antibiotics, could be helpful. The oral administration of cloxacillin and anti-histamines also may help.(15)

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NOVEL AGENTS IN LYMPHOMA

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A better understanding of the biologic mechanisms underlying Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) has recently led to the development of a variety of novel therapeutics. In particular, antibodies and antibody-drug conjugates directed against cell surface antigens, agents that block immune checkpoint pathways, and small molecule inhibitors directed against cell signaling pathways have shown significant promise in the relapsed and refractory setting as well as in the setting of frontline therapy.

1. Immune checkpoint inhibitors

In recent years, an improved understanding of the interaction between the immune system and tumors has spawned new and powerful forms of immunotherapy. The recognition that tumors can evade the host immune system by usurping immune checkpoint pathways, such as the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed-death 1 (PD-1) pathways, provided the basis for new strategies in cancer treatment. In fact, tumors can selectively block antitumor immune responses by expressing the ligands of checkpoint receptors, thus downregulating T-cell function. The reversal of this mechanism can be achieved using monoclonal antibodies (mAbs) directed against the receptors or ligands involved in those pathways. Hematologic malignancies (HMs) offer a particularly fertile ground for immunotherapy, as demonstrated by the results of adoptive immunotherapy through allogeneic stem cell transplantation (SCT), which is potentially curative in almost all HMs.[1]

Two phase 1 studies have been conducted testing anti-PD1 antibodies in a broad array of HMs. The first study (NCT01592370) tested the safety and single-agent activity of the anti-PD1 mAb nivolumab in patients with relapsed or refractory (R/R) multiple myeloma (MM), non-HL (NHL), and classical HL.[2] The second study (NCT01953692, KEYNOTE-013) tested another anti-PD-1 mAb, pembrolizumab, as single agent in R/R myelodysplastic

syndromes (MDS), MM, NHL, and HL.[3] In the first study, the response rate was 36%, among patients with DLBCL, and 40% among patients with FL. In HL patients, checkpoint blockade therapy (CBT) with anti-PD-1 mAbs yielded overall response rates of 87% (with a complete response [CR] rate of 17%) and 65% (CR rate 21%) using nivolumab and pembrolizumab, respectively.

These results suggest a strong dependence on the PD-1 pathway for HL survival and reflect the biologic features of Hodgkin Reed-Sternberg (HRS) cells. Indeed, HRS cells harbor alterations in chromosome 9p24.1, which cause overexpression of PD-1 ligands, PD-L1 and PD-L2; furthermore, the extended 9p24.1 amplification region also includes the JAK2 locus and JAK2 amplification, through the JAK2/STAT pathway, increases PD1 ligand expression. In addition, EBV infection also increases PD-1 ligand expression in EBV-positive HL.[4]

The activity of pembrolizumab in myelodysplastic syndromes (MDS) after hypomethylating agent failure was tested in the KEYNOTE-013 trial, while another ongoing trial (NCT02117219) is testing PDL1 blockade in a similar patient population. At this time, results are not yet available for either trial. Multiple myeloma (MM) was also included as an independent expansion arm in the phase 1 studies of nivolumab and pembrolizumab, based on promising preclinical data that demonstrated expression of PD-1 and PD-L1 on MM cells and in the MM microenvironment.[5] Despite this, the results of nivolumab in this disease were disappointing, with no objective response seen among 27 patients treated. However, 18 patients (67%) had stable disease.[6] These results show that this new class of drugs mainly induces a disease control, with few complete responses, highlighting the need for predictive factors and combinations strategies.

There are at least three possible ways to approach combination therapy in this setting, which are being explored in clinical trials. A first option is to combine CBT with conventional cytotoxic agents. The rationale at the basis of this approach is that some cytotoxic therapies can provide "immunogenic apoptosis" by releasing tumor antigens at the site of the tumor and allowing better presentation of tumor antigens by antigen presenting cells (APCs); this could not only provide cytoreduction but also immunologically increase the activity of checkpoint blockade. There is little mature clinical data to date, although many clinical trials are in progress in solid tumors using

chemotherapy and immune checkpoint inhibitors. Several trials are ongoing in HMs combining CBT with other therapies, such as anti-CD20, anti-CD19 mAbs, or lenalidomide (NCT01775631, NCT02036502, NCT02271945, and NCT02077959). In follicular lymphoma (FL), pidilizumab has been combined to rituximab in a phase II trial, showing an objective response in 19/26 patients (66%): complete responses were noted in 15 (52%) patients and partial responses in four (14%).[7] Results are promising, but still preliminary and further studies are needed to clarify the actual synergy between the two drugs. The preliminary results of phase I study KEYNOTE-023 in MM indicate that PD-1 blockade with pembrolizumab in combination with lenalidomide and dexamethasone is associated with a tolerable safety profile and promising antimyeloma activity in heavily pretreated patients. Seventeen patient have been evaluated so far; the ORR was 76%, with 4 patients achieving a very good partial response and 9 patients achieving a partial response. ORR has also been observed in patients with IMiDs-refractory and double refractory disease.[8] A preliminary trial investigated the combination of brentuximab vedotin and ipilimumab in a heavily pretreated HL population, with an outstanding ORR of 67% and CR rate of 42% suggesting a potential deepening of response compared to monotherapy.[9]

The second option is to combine different checkpoint agents in an attempt to enhance immune system disinhibition. There is emerging preclinical evidence of the possible benefit of combined checkpoint blockade both in solid tumors and in HMs. Several trials are underway testing this approach in HMs: for example, a phase 1 study is testing the combination of nivolumab and ipilimumab (NCT01592370), whereas another trial is evaluating the association of nivolumab and urelumab in NHL (NCT02253992). The last option for combination therapy is to combine CBT with other types of immunotherapy, such as chimeric antigen receptor (CAR) T cells, tumor vaccines, or oncolytic viral therapy. Those trials are more complex and therefore will likely require much more time to be launched and completed. Nonetheless, this strategy has already been tested in MM, combining a tumor vaccine with pidilizumab, with interesting preliminary results.[10] In conclusion, immunotherapy is a promising treatment approach that may revolutionize HM therapy, however a lot has still to be studied in terms of response criteria, markers to predict response or resistance and combination therapies, in order to maximize its potential.

2. Brentuximab Vedotin

CD30 is rarely expressed by normal cells and is rapidly internalized upon binding, making it an ideal therapeutic target for monoclonal antibodies and for antibody-drug conjugates in CD30-expressing malignancies [i.e., HL and anaplastic T cell lymphoma (ALCL)]. Brentuximab vedotin (BV) is an anti-CD30 antibody drug conjugate (ADC) which is linked to the antimicrotubule agent monomethyl auristatin E (MMAE). Upon CD30 binding by BV, MMAE is released into the cell resulting in disruption of the microtubule network, cell cycle arrest and apoptosis. BV was found to be effective in pre-clinical mouse xenograft models with ALCL and HL.[11] Phase 1 and 2 trials investigated the safety and activity of BV in heavily pretreated patients with CD30-positive HMs, showing promising results and leading to FDA approval for treatment of patients with HL who have either failed autologous stem cell transplant or two other chemotherapy regimens and are not eligible for transplant as well as for the treatment of relapsed or refractory systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. [12-14] BV has shown remarkable effectiveness in both ALCL (as well as other peripheral T cell lymphomas) and HL. Current phase 3 trials are in progress comparing BV in combination with chemotherapy to conventional chemotherapy both in HL and ALCL, the results of which may dramatically change frontline therapy for both of these agents.

3. Other antibody drug conjugates (ADC)

ADCs are empowered antibodies designed to exploit the targeting ability of mAbs by linking them to cytotoxic agents, giving them higher tumor selectivity, and potentially an increased therapeutic window, as compared with cytotoxic agents alone. Because of the success of BV in treating HL newer ADCs are being investigated. Newer ADCs, such as polatuzumab vedotin (PV, targeting CD79b), pinatuzumab vedotin (PiV, targeting CD22), inotuzumab ozogamicin (INO, targeting CD19), SAR3419 (targeting CD19), IMGN529 (targeting CD37), and SGN-CD19A (targeting CD19 and conjugated with monomethyl auristatin F), have shown promising preclinical and early clinical activity. (**Table 1**)

4. Bispecific T–cell Engagers Antibodies (BiTE)

BiTE antibodies represent a novel class of bispecific mAbs that bind to surface antigens on target cells (e.g., CD19) and recruit/activate effector T-cells within the tumor thereby augmenting the antineoplastic effect. Blinatumomab, the

first-in-class BiTE derived from murine B-cell antibodies, is a 55 kDa single-chain antibody that contains both an anti-CD3 arm and an anti-CD19 arm that are joined by a nonimmunogenic linker. This structure allows a high degree of flexibility needed for simultaneous binding of two cells.[15] A phase 1 study investigated the clinical activity and safety of blinatumomab as a continuous IV infusion over 4–8 weeks in 38 patients with relapsed or refractory B-cell NHL and showed 11 major responses with tumor regression observed in patients with FL, mantle cell lymphoma (MCL), and CLL, with most patients showing durable responses.[16] A phase 2 study evaluating the efficacy of blinatumomab in 25 patients (21 were evaluable) with relapsed/refractory DLBCL showed an ORR of 43%, including CR in 19%.[17] The drug has also shown remarkable activity in acute lymphoblastic leukemia (ALL) with a CR rate of 43% (95% CI, 36% to 50%) in a relapsed/refractory population,[18] leading to FDA accelerated approval for treatment of relapsed/refractory Philadelphia chromosome negative B-cell precursor ALL.

Table 1 – ADC in early phase clinical development

ADC	Study	Phase	Patients, *n*	Disease (Rel/Ref)	Outcomes
PV	Palanca-Wessels et al [19]	III	33	FL, DLBCL, MCL, MZL, tFL, SLL	5 early tumor responses, >50% tumor reduction
PV	Monschhauser et al [20]	II (random to PV+R or PiV+R)	58 (PV arm)	DLBCL, FL	RR-DLBCL: ORR, 51% (CR, 14%; PR, 5%) RR-FL: ORR, 60% (CR, 30%; PR, 30%)
PiV	Monschhauser et al [20]	II (random to PV+R or PiV+R)	63 (PiV arm)	DLBCL, FL	RR-DLBCL: ORR, 54% (CR, 19%; PR, 35%) RR-FL: ORR, 67% (CR, 5%; PR, 62%)
SAR3419	Younes et al [21]	I	39	B-NHL	Tumor reduction in 74% (n=26); 6 patients had PR/CR
INO	Fayad L et al [22]	I/II	118	B-NHL	ORRs 87% in RR FL, 74%. 2-year PFS 42% for RR FL and 42% for RR DLBCL
INO	Wagner-Johnston et al [23]	II (Rituximab + INO)	63	DLBCL after ASCT	ORR 28%
SGN-CD19A	Moskowitz et al [24]	I	21	B-NHL	ORR 40% (CR, 30%; PR, 10%)

5. Signal transduction inhibitors

B-cell receptor (BCR) signaling pathway is important for B cell proliferation, activation and survival and is characterized by complex interactions, involving immunoglobulin heavy (IgH) and light chains (IgL) as well as CD79A/B with downstream signaling via spleen tyrosine kinase (SYK), Bruton's tyrosine kinase (BTK), phosphoinositide-3-kinase (PI3K), and protein kinase C-(PKC). To date, two drugs inhibiting BTK and PI3K within the BCR signaling pathway have been FDA-approved for the treatment of NHL.

Ibrutinib. Ibrutinib is an oral selective irreversible small-molecule BTK inhibitor which inhibits B cell receptor signaling by occupying the active site of BTK. In a phase 1 dose escalation trial, ibrutinib was found to be well tolerated with an ORR of 60%, with the highest response seen in patients with MCL and CLL/SLL.[25] Based on these promising results, a phase 2 trial examined the efficacy of ibrutinib in relapsed and refractory MCL in 111 heavily pre-treated patients who had received a median of three prior therapies.[26] Ibrutinib has also shown to be effective in relapsed/refractory CLL in a phase 2 trial in 85 heavily pre-treated patients with relapsed CLL, with a 71% ORR and a PFS of 75% at 26 months, irrespective of clinical or genetic risk factors (del17p), leading to accelerated FDA approval.[27] Ibrutinib has also shown activity in activated B-cell (ABC) subtype DLBCL, which is known to have a worse outcome compared to germinal center B-cell (GCB) subtype. A phase 1/2 trial investigated the activity of ibrutinib in relapsed/refractory DLBCL comparing its activity both in ABC and GCB subtypes.[28] The ORR was 37% (14/38) patients with ABC DLBCL and only 5% (1/20) in patients with GCB DLBCL. ABC tumors with BCR mutations responded to ibrutinib frequently (5/9; 55%), especially those with concomitant myeloid differentiation primary response 88 (MYD88) mutations (4/5; 80%).[28] Different trials investigating ibrutinib in combination with other drugs are underway in different histologies. Furthermore, other BTK inhibitors are currently being tested in early clinical trials.

Idelalisib. Idelalisib is a first-in-class, delta isoform specific, orally bioavailable, and reversible PI3-kinase inhibitor. In a dose escalation phase I study of oral idelalisib in NHL [29] and CLL,[30] patients were treated at 6 dose levels ranging from 50–350 mg once or twice daily, and remained on contin-

uous therapy while deriving clinical benefit. Diarrhea was one of the most common adverse event that led to idelalisib dose reduction and treatment discontinuation. Serious, including fatal, hepatotoxicity and pneumonitis have occurred in patients treated with idelalisib. A phase 2 trial evaluated the activity of single agent idelalisib in 125 heavily pretreated patients with indolent NHL who had either not had a response to rituximab and an alkylating agent or relapsed within six months of receiving those therapies. ORR was 57% (95% CI, 48% to 66%) with a 6% CR rate and a median duration of response and PFS of 12.5 months and 11 months, respectively.[31] In CLL patients, single-agent idelalisib yielded a 39% ORR according to the 2008 IWCLL criteria.[30] An additional 33% of patients had partial response with lymphocytosis, a class effect which is well described in CLL following treatment with either ibrutinib or idelalisib, due to disease response, rather than disease progression. The median PFS for all CLL patients enrolled was 15.8 months and 32 months for those receiving continuous dosing with idelalisib 150 or more mg twice daily. While patients with del(17p) or a *TP53* mutation responded to treatment, the median PFS of five months was shorter than the 41 months in patients without this abnormality. A randomized phase III placebo-controlled trial comparing rituximab with idelalisib to rituximab with placebo in 220 frail patients with relapsed CLL was stopped early due to excess events in the placebo group.[32] The ORR (all PRs) was 81% in the idelalisib group, as compared with 13% in the placebo group, prompting FDA approval in combination with rituximab for those CLL patients who are too medically frail to undergo standard chemotherapy. Phase III trials investigating the efficacy and safety of idelalisib in combination with rituximab (NCT01732913) and rituximab/bendamustine (NCT01732926) in previously treated indolent NHL are currently in progress. Other PI3K inhibitors, such as duvelisib (gamma/delta isoforms inhibitor), TGR-1202 (selective for isoform delta) and copanlisib (alpha/delta inhibitor) are currently being investigated in clinical trials.

6. New drugs for DLBCL

Despite the proven clinical efficacy of first-line anti-CD20 antibody rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with DLBCL,[33] a consistent percentage of patients eventually relapse after first-line therapy or show refractory disease. Relapsed/refractory disease is associated with poor prognosis, even after sal-

vage therapy followed by autologous stem-cell transplantation (ASCT). [34] High throughput technologies have not only increased our understanding of DLBCL subtypes and the molecular basis of chemotherapy resistance but also led to the identification of novel molecular DLBCL subsets and rational targets for drug interventions that may allow for subtype/subset-specific molecularly targeted precision medicine and personalized combinations to both prevent and treat relapsed/refractory DLBCL. A variety of novel agents including small molecules and mAbs are currently being developed to improve DLBCL treatment, not only in the relapsed/refractory setting but also in the frontline setting. The results of ongoing trials integrated with the genomic-based risk profile of individual patients will significantly impact the treatment of DLBCL.

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LYMPHOPROLIFERATIVE DISEASES MOST FREQUENT TOXICITY AND NEW SIDE EFFECTS OF NOVEL DRUGS AND/OR TREATMENTS

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We are in a very exciting era for treatment of lymphoproliferative diseases, especially for low grade non Hodgkin lymphomas (NHL) and Chronic Lymphocytic Leukemia (CLL). Most of these successes are due to development of a new class of drugs defined as B cell receptor inhibitors. In particular, two drugs are having a widespread use, a BTK inhibitor, Ibrutinib, and a PIK inhibitor, Idelalisib. With these drugs, the scenario of side effects has dramatically changed as compared with side effects induced by chemotherapy and immunotherapy. These toxic effects are usually mild but sometimes can be so intense to induce discontinuation of the drugs.
During phase I trials, Ibrutinib discontinuation was 4% in the 420 mg dose group and 12% in the 820 mg group (Byrd JC, 2013). Adverse events (AE), that occurred mainly during the first year, were responsible for discontinuation in 13% of patients. However, in the phase III trial, AE were responsible only for 4% reduction of the dose and 4% discontinuation of the drug (Byrd JC, 2014). It is also of note that the rate of discontinuation of the drug did not increase when ibrutinib was combined with other drugs. In particular, the combination of ibrutinib and ofatumumab led to a discontinuation in 11% of patients (Jaglowski SM, 2015) while 7% of patients discontinued the combination with bendamustine and rituximab (Brown JR,2015).
One of the most common AE of ibrutinib is diarrhea and it probably depends on the interference with epidermal growth factor receptor (Honigberg LA, 2010). In the follow up of the phase I study, 60% of patients complained at least 1 episode of diarrhea (Byrd JC, 2014), but seldom it was a reason for discontinuation. It is generally less than grade 2 (6 or less bowel movements/day and it occurs within the first month and disappears within 3 weeks).
Fatigue was another common side effect, generally mild and self-resolving. On the contrary, when ibrutinib was combined with rituximab, patients reported improvement of quality of life both after 6 and 12 months of

treatment (Burger JA, 2014).
For Ibrutinib the 5 most common toxicities that has been reported as a reason for discontinuation are: Bleeding, Atrial fibrillation, Infection, Hematologic, and Pneumonitis.
Bleeding has been reported in up to 60% of ibrutinib-treated patients (Byrd JC, 2014). Most events were grade 1 to 2 (spontaneous bruising or petechiae). However, 5% of patients experienced grade 3 or higher after trauma. The phase I/II studies of ibrutinib reported increased bruising in 17% of subjects, and intracranial hemorrhages occurred in 2%, leading to current recommendations for avoidance of concomitant warfarin therapy, and for interruption of ibrutinib for 3–7 days before and after invasive procedures. In a study where ibrutinib was compared with ofatumumab in the treatment of CLL, bleeding-related AE rates were 44% for ibrutinib vs 12% for the control arm, although the rates of serious bleeding were low in both arms (1% vs 2%, respectively). In the study of ibrutinib vs ibrutinib + BR minor bleeding was recorded in 31% and 15% respectively (Chanan-Khan A, 2015) while when ibrutinib was used as first line in elderly patients, severe bleeding was present in 4% of patients and led to discontinuation of treatment in half of them (Burger JA, 2015) Btk has a role in platelets after a stress test and Btk deficient platelets induced by Ibrutinib fail to respond physiological stress test. Ibrutinib treatment also affects collagen and von Willebrand factor-dependent platelet functions and inhibits collagen-mediated but not ADP-mediated platelet aggregation (Levade M, 2014).
Atrial Fibrillation (AF) was observed more frequently in patients receiving ibrutinib vs placebo: 7.7% vs 2.4%. Seven of 22 patients (31.8%) in the ibrutinib arm with AF/atrial flutter interrupted treatment to manage AF, with a median treatment interruption of 7 days (range, 3-65 days). Overall, 1.4% of patients receiving ibrutinib discontinued due to AF. An excess risk of atrial fibrillation (AF) was suggested by the results of early studies of ibrutinib in patients with CLL and mantle cell lymphoma, and was later confirmed in phase III randomized trials. In the phase III trial, the incidence of AF was 3% vs. 0% in patients treated with ibrutinib vs. ofatumumab, respectively (manageable, and led to treatment discontinuation in only one patient). The proportion of patients with a prior history of AF in the study was higher in the ibrutinib arm (5.6%) vs. ofatumumab (2.6%), suggesting that history of AF might be a risk factor for treatment-emergent AF during ibrutinib therapy. Although additional data are needed, these results taken together suggest an increased risk of AF in patients

with CLL treated with ibrutinib. One possible trigger for AF is hypertension, observed in 20% of patients with ibrutinib, particularly after 2 years of therapy. Experimental data indicate that Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling and subsequent effect on Tec kinase (Mcmullen JR, 2015).
The haematological toxicity of ibrutinib is mild. In the pivotal trial grade 3-4 neutropenia was present in 20% of patients and grade 3-4 anemia in just 5 %. These cytopenias tend to be present early during the course of treatment and short-lasting (Byrd JC, 2013).
Infections. The frequency and pattern of infectious complications in patients treated with ibrutinib likely reflect the incidence and clinics usually observed in this patient population, rather than a drug-specific AE profile. Upper respiratory tract infection was the most frequently reported infection across ibrutinib studies and in most cases resolved spontaneously without interrupting treatment. In any case, serious infections occurred early in the course of therapy and the rate declined after the first 6 months. As expected, the frequency of infections was higher in relapsed/refractory patients (51%) than in first-line treatment (13%) with pneumonia being the most common serious infectious AE (Byrd JC, 2015). In the phase III trial, infections were more frequent in the ibrutinib arm (70% vs. 54%) but rate of grade 3-4 infections was not significantly different between the two arms (24% vs. 22%) (Byrd JC, 2014).
As for Idelalisib, in the phase I trial and subsequent extension study, 11 patients died during treatment, all but 1 due to AE (Brown JR, 2014).
The 5 most common toxicities that has been reported as a reason for discontinuation are: Diahhrea/Colitis, Transaminitis, Pneumonitis, Infection, and Rash
Two types of diarrhea were frequently reported: 1) Self-limiting: Typically mild or moderate (grade 1-2) with onset generally within the first 8 weeks of treatment and usually responsive to common antidiarrheal agents 2) Idelalisib-related diarrhea: this can be sudden or gradual in onset, is reported as watery, without cramps, with culture negative and responds poorly to antidiarrheals or empiric antimicrobials but tend to improve after stopping treatment. It occurs usually late with median of 7.1 months (range: 0.5-29.8). Several colonoscopies with biopsies revealed lymphocytic colitis features. Treatment with budesonide and systemic steroids reduces median time to resolution of symptoms: 1-2 weeks with initiation of budesonide and/or systemic corticosteroid vs. approx. 1 month of pure idelalisib (Coutre SE, 2015). In the phase I study, the incidence of

diarrhea of any grade was 30% with 6% grade 3-4.(Byrd JC, 2014) while in the randomized trial, diarrhea occurred in 21% of patients and it was severe in 5% (Furman RR, 2014) More recent studies reported an even higher incidence of this AE. In a phase II study, diarrhea occurred in 64% of patients and it was severe in 42% with severe colitis in 25% of cases (O'Brien SM, 2015) and most authors recommend to permanently discontinue idelalisib in case of grade 4 diarrhea.

Elevation of transaminases (transaminitis) may occur 4-12 weeks after starting idelalisib and it is one of the more common reason for discontinuation of the drug. In most cases it is sufficient withhold the drug and to restart with a lower dose. However, a grade 3-4 of this AE was observed in 14% of patients and was fatal in 1 case (Coutre SE, 2015). This AE led to the recommendation to monitor transaminases in the first 6 months of treatment and to not administer concomitantly drugs potentially hepatotoxic.

Colitis and transaminitis are based on immune-mediated effect. In some cases liver and intestinal biopsies have been performed and they have always shown lymphocytic infiltrates. In addition, a decrease in the PB regulatory T cells have been documented during treatment with idelalisib. These observations confirm that these AE are treatable and preventable with steroids (Coutre SE, 2015).

Both infectious and non-infectious lung involvement has been recorded in idelalisib treated patients. In phase I study the incidence of this AE was 20%, all grade 3-4 and were treated with steroids, allowing to restart therapy after resolution in two cases (Brown JR, 2014). In the phase III trial the incidence was 4% but without grade 3-4 (Furman RR, 2014).

In March 2016 EMA published a recommendation on new safety measures for idelalisib. These measures include close monitoring and use of antibiotics to prevent pneumonia. EMA points were the following:

* Increased rates of serious adverse effects including deaths were seen in 3 clinical trials in the treatment arm evaluating the addition of idelalisib to standard therapy in first-line CLL and relapsed indolent non-Hodgkin lymphoma. Most deaths related to infections such as Pneumocystis jirovecii pneumonia and cytomegalovirus infections.
* As a precaution and while a thorough review is ongoing, idelalisib should not be started as first-line treatment in patients with CLL who have the 17p deletion or TP53 mutation.
* Idelalisib can continue to be used in combination, only with rituximab, in CLL patients who have received at least one prior therapy.

* All patients should receive prophylaxis for Pneumocystis jirovecii pneumonia during idelalisib treatment and should be monitored for respiratory signs and symptoms. Regular clinical and laboratory monitoring for cytomegalovirus infection is also recommended.
Severe neutropenia was reported in 34-43% of idelalisib treated patients while anemia and thrombocytopenia were transient and with tendency to improvement during treatment (Falchi L, 2016).

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POSTER

RELAXATION TECHNIQUES AND CANCER SURVIVORS. GROUP EXPERIENCE AT INTERDISCIPLINARY UNIT FOR SURVIVORS AND CHRONIC CANCER PATIENTS "LIA BUCCHERI E NINO TRALONGO" OF SYRACUSE

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Background

Yoga Nidra, literally "Yoga of Sleep" is an exercise in ancient guided relaxation from which will be born the current biofeedback technique. The session begins with a muscular relaxation and mental proposition (sankalpa), follows the rotation of awareness of their body parts, relaxation in the plane of feelings and emotions, and finally a series of views leading to greater self-awareness and peace mental. To run the Yoga Nidra you need a guiding voice. During practice one remains lying motionless, in a state between sleep and wakefulness, in which consciousness works at a deeper level of awareness.

Methods

At the Interdisciplinary Unit for Lungoviventi Oncology and Chronic "Lia Buccheri and Nino Tralongo" of Siracusa, 5 women were invited to participate in a cancer survivor 3 group meetings cycle, lasting about two hours each. 80% had a previous diagnosis of breast cancer, 20% to the thyroid. All reported anxiety and low mood. The moment of relaxation was preceded by a time of sharing on the part of the group than their lived and ended with a 'interview aimed to investigate the immediate effects of relaxion training.

Results and conclusions

Yoga Nidra is effective. Adequately educated the person uses it whenever he feels the need. Scientific studies have repeatedly shown that it is a valuable aid for those who pass through a cancer journey and the experience described supports the hypothesis that Yoga Nidra is a valuable tool even with cancer survivors.

PAIN, EMOTIONAL STATE AND QUALITY OF LIFE IN CANCER SURVIVORS

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Backgroud

More and more people who, despite all finished cancer treatment for more than 3-5 years, or cancer survivors, living each day with physical problems, such as pain, and / or psychosocial, such as anxiety depression, interpersonal and occupational difficulties difficulties. Inside the RAO (Network of Oncology Care) that operates in Syracuse, it fits the Interdisciplinary Unit for Survivors and Chronic Cancer Patients, RAO, Syracuse "Lia Buccheri and Nino Tralongo", coordinated by medical oncologists and specialists dedicated to various clinical and psychosocial needs.
The aim of this survey is to assess how much pain and emotional state, even years after diagnosis cancer, impact on quality of life cancer survivor.

Methods

Were recruited randomly No. 65 survivors, followed c / o the Interdisciplinary Unit for Survivors and Chronic Cancer Patients, RAO, Syracuse; 16 males and 49 females, aged between 37 and 80 years, in follow-up for more than five years. For the survey was used the 'SF-36 and a socio-data sheet for the collection of clinical and personal data.

Results and conclusions

The investigation shows that 70.31% of cancer survivor while evaluating their overall health status between good and passable only 22.8% has no physical pain, and the remaining 87.2% the 38,59% have a pain between moderate and strong. In 56.89% of cases the pain interferes with normal social and relational activities; 72,41% have been hindered in the ordinary course of business activities, for 63.79% the physical and emotional state health interfered in family and friendships; 40% stated that the pain affects the emotional state for a good portion of time thus manifesting unrest, decline in mood discouragement.
In conclusion, even after overcoming the oncological disease, the pain impacts on physical and emotional health of the survivor impairing their quality of life.

WRITING AND NARRATION WORKSHOP FOR CANCER SURVIVOR PATIENTS. THE EXPERIENCE IN SIRACUSA

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Background
Narrative writing is a scientific method that goes beyond the simple telling about oneself.
The request for communication, social support and relationship of cancer survivors is increasingly widespread .

Methods
The writing workshops, following the epistemology of Gestalt Psychotherapy, are based on group relationships, sharing one's own autobiographical story in which the disease is mentioned as an experience, as far as painful, not able to stop the flow.
The revitalization of the language is the goal through which "the empty words of the patient, plagued by the seeds of verbalization, reacquire light and warmth within the therapeutic relation" .
The data collected in those 2 workshops have been systematized according to qualitative criteria and focus-groups have been created for investigating the level of satisfaction/benefit received by activities and inspirations, related to the given structure and method.

Results
The reality of the disease is highly deconstructing: it affects all fields of one's expression.
The most important rehabilitating step is answering to one question: the search for meaning in what happened. If it is missing, the subjectivity is fragmented and the life of the mind, meant as a system of procedures providing sense to experiences , ceases to be.
The results of the job show a meaningful change on the process of the disease experienced and on the perception of the relational support.

Conclusion

The patient's narration generates value: enhancing the transformational tangles existing in the story from which the strength for changing is withdrawn. People, through their stories, become protagonists of the healing process.

NOTE