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RECENT EVOLUTIONS ON CANCER CLINICAL ASPECTS AND THERAPEUTICS APPROACH *NAPLES (ITALY) 11-12 JULY 2016*

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INTRODUCTION

In the 3rd Millennium the clinical medicine has evolved into a multifaceted technology-driven activity whose major purpose are diagnosed and screening for disease, monitoring health and therapeutic response, and gauging deviations from ordinary physiology in humans. Advances in diagnostic medicine, have been achieved during the application of science and technology as result of a synergic effort among universities, industries, governments and private institutions.

We are now entering in the "Era" of personalized medicine, which is bringing forth the newest and most powerful science and technology available for the modern-day practice of diagnostic-based medicine.

To date new oncologic challenges are represented by: a) the advent of anticancer target therapy; b) immunotherapy-era; c) a new patient population, constantly growing, so called "cancer survivors"; d) virus-related tumors; and finally, e) the enormous cost to support all these aspects on cancer approach and treatment.

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To better understand these "new" entities it is necessary to make some considerations on these different but "accomplices" features.

Here, we've highlighted the most relevant discussion presented by speakers in the conference "Recent evolutions on cancer clinical aspects and therapeutics approach" held in Naples on 11-12 July 2016.

DIAGNOSTIC SESSION

Function imaging to assess preoperative neoadjuvant therapy in locally advanced rectal cancer

Antonella Petrillo, MD

Morphological Magnetic Resonance Imaging (MRI) evaluation is still considered the best available tool for locally advanced rectal cancer (LARC) staging, allowing an accurate evaluation of the disease extent, up to, beyond and over the mesorectal fascia, and of the lymph node involvement. However, there are some limitations in depicting changes after neoadjuvant chemoradiotherapy (CRT) through morphological MRI alone. A favorable tumor response may not correspond to an appreciable tumor size reduction and it is difficult to differentiate between post-radiation fibrosis and fibrosis containing viable tumor remnant. To overcome this limitation, functional approaches aiming to assess tissue "viability" through different imaging modalities such as Position Emission Tomography (PET), Dynamic Contrast MRI (DCE-MRI), Diffusion Weighted Imaging (DWI) are being actively investigated. Actually, PET/CT evaluation is considered the best technique to predict pathologic tumor response and outcome after preoperative CRT in LARC patients, suggesting its great potential in assisting physicians on individualized management decisions in this disease. In scientific literature it has been reported that early changes of the Standardized Uptake Value (SUV) of PET are predictive of pathological response with an optimal threshold value of -42.0% and an accuracy of 93.0%. However, the findings obtained from late PET scans, performed before surgery, have shown lower accuracy in predicting pathologic response.

Moreover, several study have reported the value of apparent diffusion coefficient (ADC) of DWI compared to SUV of PET/CT in evaluation of post-treated locally advanced rectal cancer showing that, up to now, both DWI and PET/CT provide good prognostic indicators (ADC and SUV) in early treatment assessment but that these are not accurate enough in pre-surgical phase to safely select patients for organ-sparing strategies.

In the recent literature, some attention has been posed on the identification of functional parameters by DCE-MRI[1]. These results are provocative since identification of significant and complete respondent patients may prompt conservative strategies or a "wait and see" policy.

DCE-MRI techniques inform on tissue perfusion and vascular leakage. The most commonly used approach for analyzing DCE-MRI data is visual inspection of Time Intensity Curve (TIC)[2]. Petrillo et al[1] used TIC visual inspection to assess CRT response in LARC. According their study, when patients with a partial or complete response to CRT are included, a sensitivity, specificity and an accuracy respectively of 79%, 76% and 78% is obtained; while, considering the performance of qualitative MRI evaluation in complete responders a sensitivity, a specificity and an accuracy respectively of 94%, 76% and 84% is reached. Moreover, Petrillo et al[3] have investigated also a semi-quantitative analysis of DCE-MRI, finding the best combination, called Standardized Index of Shape (SIS), that identifies the linear classifier of the percentage differences Δ of Maximum Signal Difference (MSD) and of Wash-Out Slope (WOS); SIS is able to discriminate responders by non responder patient after CRT with a sensitivity and specificity of 93.5% and 82.1%, respectively[3]. SIS is an objective quantitative method, easily transferable to clinical routine by means of a user friendly software application, able to assess tumor response to CRT through a reproducible semi-quantitative estimation of tumor blood perfusion. SIS percentage change could play a relevant role in LARC management helping to identify significant pathological response allowing to adopt conservative strategies and complete pathological response allowing to adopt a "wait and see" policy, reducing significant morbidity and functional complications of total mesorectal excision.

Predictive and prognostic biomarkers

Renato Franco, MD

The identification of biomarkers is a crucial step in oncology since it aids to optimize diagnostic tests and therapeutic decisions. As well as biomarkers suggest possible targets for novel therapies, they could be used as prognostic or predictive indicators among the most common tumor histotypes such as breast cancer, bladder cancer, lung cancer and melanoma[4]. Molecular diagnostic is highly effective in detecting biomarkers, indeed it is able

to provide the molecular characterization of cancer signatures and information for personalized treatment also helpful in avoiding the toxicity of standard drug therapies (such as chemotherapy)[5]. The main methods used to evaluate the biomarkers are real-time PCR (RT-PCR), fluorescent *in situ* hybridization (FISH), immunohistochemistry (IHC)[5]. Moreover, the development of high-throughput technologies, such as microarrays, new generation sequencing methods and mass spectrometry, allows the use of a growing range of DNA biomarker analyses[5]. The identification of predictive biomarkers can be relatively simple if treatment goals are the cancer driver; nevertheless they may appear several challenges, including the heterogeneity of the tumor and changes of tumor features over time. A number of cancer driver genes responsible of abnormalities and/or required for cancer cells survival have been identified[4]. In addition, examples of analysis as predictive biomarkers are: DNA methilation, circulating tumor cells in the peripheral blood, mutations and polymorphisms and RNA expression analysis. It is possible to observe satisfactory result using predictive biomarkers in lung cancer therapy with drug targeting anaplastic lymphoma kinase (ALK), proving the critical role of predictive biomarkers in anticancer drug development[6]. Moreover, the detection of MYC protein expression in follicular lymphoma (using IHC) might be useful to predict more aggressive clinical course[7]. In the field of immunotherapy the PD-1/PD-L1 axis is playing a promising role in understanding more about the host immune system, favoring the introduction of specific immunomodulators into the cancer therapy[8].

Role of genetics and molecular biology in the diagnosis and therapy of thyroid tumors

Gennaro Chiappetta, MD

Thyroid cancer is the most common malignant tumor of the endocrine system and the majority of thyroid cancers derives from thyroid follicular cells and includes both well-differentiated forms as papillary and follicular carcinomas (PTC and FTC, respectively) and poorly differentiated forms such as anaplastic carcinoma (ATC)[9]. Notably, 5-10% of all thyroid cancers are medullary (MTC) thyroid cancers that arise from parafollicular or C cells.

Among the molecular features found in papillary thyroid carcinoma (up to 45% of cases) there is the activating point mutation (most often V600E) in B-RAF and the gene rearrangements of RET[10].

RET gene encodes the tyrosine kinase (TK) membrane receptor for glial cell line-derived neurotrophic factors. In PTC (2.5-40% of the cases), chromosomal inversions or translocations at 10q11.2 lead to the fusion of the RET TK domain to heterologous genes (RET/PTC oncogenes) and consequently to the activation of its signaling and transforming properties. RET/PTC1 (H4-RET) and RET/PTC3 (RFG-RET) are the most prevalent variants.

Together with RET, B-RAF functions in the mitogen-activated protein kinase (MAPK) pathway. RET, by promoting GTP loading on RAS, stimulates RAF family kinases, which leads to the phosphorylation of MEK (MAP kinase or ERK) and ERK (extracellular signal-regulated kinases or MAPK) mediates the firing of this cascade. The high prevalence of BRAF mutation in lymph node-metastasized PTC tissues from BRAF mutation-positive primary tumors is consistent with a role of BRAF mutation in facilitating the metastasis and progression of PTC in lymph nodes[11].

Follicular thyroid carcinomas are positive (20-50%) for RAS mutations. The N-RAS mutation in codon 61 is the most frequent RAS mutation in FTC and it is more frequent in malignant than in benign thyroid tumors. Our studies in transgenic mice in which a human N-RAS (Gln61Lys) oncogene (Tg-N-RAS) is expressed in the thyroid follicular cells have shown that mutated RAS oncogenes could be able to drive the formation of thyroid tumors that can progress to poorly differentiated and metastatic carcinomas.

Medullary thyroid cancers are 75% sporadic and 25% hereditary. The inherited form of medullary thyroid cancer is transmitted as an autosomal dominant trait due to a germline mutation of the *RET* proto-oncogene, but these mutations occur also in some sporadic cases.

The most frequent initial manifestation of thyroid cancer is the appearance of a nodule. In almost all cases, these nodules are benign; less than 5% are malignant. However, some cases are misdiagnosed, and many patients are subjected to unnecessary surgery. Therefore, it is important that patients undergo an accurate pre-surgery evaluation.

The majority of diagnostic test for thyroid nodules is fine needle aspiration cytology, which accurately distinguishes between a benign and malignant lesion in most cases. However, cytological discrimination between malignant and benign follicular cancer can be difficult because of poor quality samples and many thyroid FNAs are called "indeterminate". In these cases molecular testing has improved the management of patients. Thanks to genetic testing, treatment can be customized for each patient even in inconclusive cases, and surgery can be reserved for malignant cases

with a consequent substantial saving in terms of health care costs. Moreover an understanding of the alterations in different molecular pathways of thyroid cancer is a prerequisite for the development of new targeted drugs.

In recent years, the unraveling of the genetic mechanisms and the identification of molecular alterations involved in thyroid pathology have resulted in a rationale for the management and use of new therapeutic agents that have changed and will continue to change the treatment of thyroid cancer.

BRCAness in patients with ovarian carcinoma and triple-negative breast cancer

Giuseppe Palmieri, MD, PhD

During the last decade, genome-wide association studies (GWAS)[12] have identified several (>70) loci associated with breast cancer susceptibility. A limited amount of them (<15) acts as high- or medium-risk genes for breast and ovarian cancers, usually involved in DNA repair and carrying mutations in coding regions. Almost all the associations identified through GWAS are found in noncoding regions and are likely to involve regulation of genes in multiple pathways.

In recent past years, next-generation sequencing (NGS) has opened up new scenarios through the detailed characterization of the cancer genome and epigenome in a large variety of cancer types. In particular, the whole-exome sequencing (WES) analysis at somatic level has allowed identification of genomic alterations and sequence variations in coding regions of candidate cancer genes. The most common gene alterations are detected by WES analysis in the following genes: *TP53* and *PIK3CA* mutations (25-30% of cases); *CCND1*, *FGFR1*, *MYC*, and *HER2/ERBB2* amplifications (5-10%); *PTEN* loss or mutations (5-7%); *AKT1*, *BRCA1/2*, *RB1*, *HER2/ERBB2*, *GATA3*, *CDH1*, *CDKN2A*, *FGFR3*, and *NF1* mutations (1-4%); *EGFR* and *FGFR2* amplification (1-2%). At germline level, WES studies have confirmed the presence of mutations in driver genes previously implicated in breast cancer susceptibility, such as *BRCA1/2*, *AKT1*, *CDH1*, and *GATA3*. Overall, *BRCA1/2* mutations present a prevalence of about 5% in the general population and about 25% in the families with history of breast-ovarian cancer. Triple-negative breast cancer (TNBC) cases – classified as a patients' subgroup with breast cancer negative for ER (estrogen receptor), PR (progesterone receptor), and HER2 expression, accounting for 15% to 20% of all breast cancer cases and presenting a higher risk of relapse and a relatively poor outcome – have been described to carry *BRCA1* germline mutations up to one third of TNBC patients (mainly, among those with age at diagnosis younger than 50 years). As a confirmation of this relationship, TNBC represents the predominant breast cancer subtype (>60% of cases) among *BRCA1* mutation carriers.

In ovarian cancer, mean age at diagnosis for the mutation groups appears to be younger (43 and 47 years for *BRCA1* and *BRCA2* mutation carriers, respectively) as compared with non-carriers (49 years). Among such patients, *BRCA2* mutation carriers are associated with even better overall survival (OS) than non-carriers. Indeed, a meta-analysis of 26 studies has indicated the following 5-year survival rates: 36% for non-carriers, 44% for *BRCA1* mutation carriers, and 52% for *BRCA2* mutation carriers[13]. The *BRCA1/2* mutations (mostly, at germline level) are associated with generally favorable response to platin-based chemotherapy, independent of class stratification, as compared with mutation-negative patients. The significant activity of poly-ADP-ribose polymerase (PARP) inhibitors in *BRCA1/2* mutation carriers has focused the attention on *BRCA* genetic testing in early disease management. On this regard, changes in the guidelines for stably including the evaluation of the *BRCA1/2* mutation status in all invasive ovarian cancer patients seem to be mandatory. Moreover, the *BRCA* genetic testing should be consistently integrated into clinical trial designs as a major stratification factor.

In breast cancer, again *BRCA* mutation carriers are comparatively younger in age (52 and 54 years for *BRCA1* and *BRCA2* mutation carriers, respectively) as compared with non-carriers (58 years). Furthermore, *BRCA1* mutation carriers are more likely to be ER- and PR-negative, to have lower histologic grade, and to result responsive to DNA-damaging chemotherapy. In contrast with ovarian cancer data, a recent meta-analysis comparing breast cancer OS between *BRCA* mutation carriers and non-carriers showed no association between mutation occurrence and OS[14].

THERAPEUTIC SESSION

Therapeutic response evaluation in oncology

Alessandro Bertolini, MD

The criteria of response in oncology are chanced in the last forty years, depending from the development of new e more active therapies. One

time the Oncologists lived in a world done by measures. We needed to have response parameters because we rarely use symptomatic drugs. The first step of oncologic therapy has been to defeat the cell cycle and measures are the level of victory. Chemotherapy drugs worked and work using the cell cycle as target. These were the arms used during last century. Fighting the cell cycle we obtained reduction of tumor volume. During the last 30 years of 20th century we developed diagnostic instruments to establish a response rate. Using radiology (CT, US and MNR) WHO and RECIST criteria[15] have transformed in objective results the efficacy of chemotherapy. The second step of oncology was the target therapy that works against the tumor cell without interfere with cellular cycle. The diagnostic methods that we use now to verify a response rate are similar: the radiologic instruments. WHO and RECIST criteria are also used in this step; however, sometime in clinical practice, we don't leave target therapy because one metastasis appears. On the contrary, the target therapy continues even if a new metastasis appears. Clinical benefit and not a volume is the model to follow in clinical practice. In the third step of cure, called as modern checkpoint inhibitors of immune activity, the response is not measured by RECIST criteria but as benefit and we accept also a bigger volume as favorable response. We came back to early oncologic time. In the 1970s, the patients that appeared in progression were also treated with chemotherapy (5FU), thinking that by chemotherapy we could reduce cancer growth. The practice in oncologic history has changed again.

Maintenance therapy in metastatic colorectal cancer (MCRC)

Carmela Romano, MD, Ph.D

Maintaining patients on chemotherapy until disease progression or unacceptable toxicity has been routine in clinical practice and in clinical trials in MCRC[16]. The dangers of continuing cytotoxic therapy, specifically oxaliplatin-containing therapy, as cumulative toxicity often occurs before clinical progression and there is limited evidence supporting the prolongation of first-line treatment beyond 4 to 6 months. Modern trials suggest avoiding treatment continuance beyond 6 months[17]. At the time of tumor reassessment, if the disease is stable or it has even shrunk yet remains unresectable, patients might be considered for maintenance therapy[18].

Several different strategies may be considered: pre-planned drug holidays or clinically driven treatment breaks or a depotentiated combination of the upfront therapy or a completely different compound to which the patient has not previously been exposed. Optimal candidates must have experienced disease control with the induction therapy namely, a response, or at least disease stabilization[19].

The OPTIMOX1 trial[20] and OPTIMOX2 trial[21] compared the fluoropyrimidine-based maintenance strategy with an intermittent approach or a "chemotherapy-free interval" after FOLFOX induction; the COIN study compared continuous *versus* intermittent oxaliplatin-based therapy[22]. A phase 3 Italian trial[23] compared continuous *versus* intermittent irinotecan-based therapy suggesting that both strategies can be used.

The greatest experience of maintenance therapy achieved so far is with antiangiogenic agents because strong biologic and clinical rationales suggest the use of bevacizumab until (and perhaps beyond) disease progression[24].

The first indirect demonstration of the benefit of the use of bevacizumab until disease progression came from the NO16966 study, in which PFS was longer when the antiangiogenic treatment was maintained until disease progression[25].

In the Macro-TTD trial[26] the patients were randomized to receive either XELOX and bevacizumab until progression or unacceptable toxicity, and 6 cycles of the same regimen followed by bevacizumab alone. The SAKK-41/06 trial[27] compared maintenance bevacizumab versus observation after 4 to 6 months of standard first-line chemotherapy plus bevacizumab.

More recently, CAIRO3[28] and AIO KRK 0207[29], 2 North European randomized studies, have set the standard for maintenance therapy with bevacizumab. These studies are summarized in Table 1.

Tamburrini and collaborators have evaluated all randomized phase III trials comparing bevacizumab-based maintenance therapy (MB) with complete stop therapy (ST) or with continuous therapy (CT). This meta-analysis has suggested that the use of MB approach increases Time to Failure Strategies (TFS) and PFS compared to ST. MB should be considered the standard regimen in patients with stage IV CRC after first line induction therapy[30].

In ESMO consensus guidelines, the optimal maintenance treatment is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab as monotherapy is not recommended. Initial induction therapy (as long as no relevant residual toxicity is present), or second-line therapy, has to be reintroduced at either radiological or first signs of symptomatic progression[31].

TABLE 1. Clinical trials about maintenance therapy in MCRC according to different strategies.

Drugs	*Study*	*Induction regimen*	*Maintenance*	*PFS (months)*	*OS (months)*	*HR; p*
Fluoropyrimidine	OPTIMOX1	FOLFOX	Continuing	9.0	19.3	HR 0.93 p =.49
			FU alone	8.7	21.2	
Fluoropyrimidine	OPTIMOX2	FOLFOX	FU alone	8.6	23.8	HR 0.88
			Discontinuing	6.6	19.5	
	COIN	Oxaliplatin-based	Continuing	NR	15.8	HR 1.08 p = NR
			Discontinuing	NR	14.4	
On-off	LABIANCA	FOLFIRI	Continuing	6	18	HR 0.88 p = NR
			2 months on 2 months off	6	17	
Bev	MACRO	XELOX/Bev	Continuing	10.3	20.0	HR 1.05; p = .38
			Bev	9.7	23.2	
Bev	SAKK 41/06	CT/bev	Bev	4.1	25	HR 0.83 p = .22
			Discontinuing	2.9	22.8	
Cape/Bev	CAIRO 3	XELOX/Bev	Metronomic Cape/Bev	8.5	21.6	HR 0.89; p = .22
			Discontinuing	4.1	18.1	
FU/bev	AIO KRK 020774	Oxaliplatin-based CT/Bev	FUFA Bev	6.8	23.8	p = NS
			Bev alone	6.5	26.2	
			Discontinuing	6.1	23.1	

Abbreviations: 5-FU = 5-fluorouracil; Bev = bevacizumab; CT = chemotherapy; Cape = Capecitabine
HR = hazard ratio; NR = not reported; NS = not significant; OS = overall survival; PFS = progression-free survival.

The biologic rationale and the clinical evidence for using EGFR inhibitors as maintenance are less convincing[32] and some studies are ongoing[33]. However, a more accurate molecular selection of patients with disease that has a greater chance of responding might support future studies. Novel compounds are currently tested as maintenance agents, thus enriching the future available options ([18]). For the time being, maintenance therapy should be considered a valuable option for selected patients rather than a standard of care.

Role of regorafenib in the treatment of colorectal cancer: an updated

Anna Nappi, MD

In the last few years, new drugs have been included in the treatment of MCRC that have contributed to improve survival of our patients especially in the early lines of treatment. Regorafenib can be used beyond progression to standard therapies. Regorafenib has been shown to improve OS and PFS in this setting of patients. Regorafenib is an orally available multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis, oncogenesis and the tumor microenvironment. The efficacy of Regorafenib has been evaluated in several studies. The most important is CORRECT trial[34]. CORRECT is a phase III trial; it is an international, multicentre randomized trial, involving 114 centers in 16 countries in North America, Europe, Asia and Australia. In the CORRECT trial, patients with MCRC have been recruited. All patients have received previous therapies with a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab for patients who had K-RAS wt tumors. Patients have been randomly assigned 2:1 ratio to Regorafenib or placebo. All patients have been randomized to receive oral Regorafenib 160 mg or matching placebo once daily for the first 3 weeks of each 4 week cycle until disease progression, death or unacceptable toxic effect. Results. Between April 2010 and March 2011, 760 patients have been randomized. Median overall survival has been 6.4 months in the Regorafenib

group and 5 months in the placebo group; Hazard ratio has been 0.77% and the reduction in the risk of death has been 23%. For OS, Regorafenib has shown the same result in all sub groups analyses. Secondary endpoint has been PFS. Median PFS has been 1.9 months in the Regorafenib group and 1.7 months in the placebo group. Also in this case, the difference has been statistically significant. This significance is reported in all subgroups. The most frequent adverse events of any grade in the Regorafenib group have been fatigue, HFSR, diarrhea and hypertension. Most adverse events have occurred early in the course of treatment, during cycle 1 or 2. This result suggested that the patients' monitoring should be more frequent during the first few cycle of treatment. Based on the results of this trial, Regorafenib has been approved by FDA and EMEA for the treatment of adult patients with mCRC who have previously progressed to available therapies.

CONCUR trial is another phase III trial, whose design is partially overlapping to CORRECT trial[35]. CONCUR trial is a randomized double blind placebo controlled phase III trial carried out with patients affected by MCRC. Twenty-five centers distributed in China, Taiwan, Korea, Vietnam took part to the trial. When comparing the two studies, some important differences exist. First: the number of patients. 760 patients have been enrolled in the CORRECT trial, while only 200 in the CONCUR trial. In the CORRECT trial, before recruitment all patients have received bevacizumab and only in case of K-Ras WT cetuxumab or panitumumab. In the CONCUR trial, only 60% of patients have received a previous treatment with target therapy.

Median OS has been 8.8 months in the Regorafenib arm and 6.3 months in the placebo arm, HR has been 55%, the reduction in risk of death has been 45%. Median PFS has been 3.2 months with Regorafenib and 1.7 months with placebo. Both CONCUR and CORRECT trial have shown a significant improvement in OS and PFS with Regorafenib over placebo. Mean duration of treatment has been 7.3 weeks in the CORRECT trial and 10.6 weeks in the CONCUR trial. The most commonly adverse events have been HFSR and hypertension, these results are consistent with other trials with Regorafenib. The CONCUR trial has not revealed any new unexpected adverse events.

On April 2012 the CONSIGN trial, EAP based on CORRECT trial's results, has began[36]. This trial is a prospective, open-label, single arm study involving 134 centers across 24 countries in the world. More than 3000 patients have been enrolled all around the world and 25% of them have been enrolled in Italy. Italy in fact has been the top recruiter country. The first six centers that have enrolled the largest number of patients are Italian. The results of CONSIGN trial are similar to those emerged from CORRECT and CONCUR trial.

Using Regorafenib, fatigue is a very common adverse effect. Recently, the results of the study showed that the evening intake of Regorafenib can reduce incidence of fatigue.

Observing CORRECT and CONCUR trials' curves, we note that they present similar trends; at the beginning they are not detached. They have the similar trend to curves of first trials with cetuximab or panitumumab in non selected patients. Only in case we analyze curves of selected patients, based on the RAS status, we note that these are separated from the beginning. In the CORRECT trial, different subgroups of patients might have differential responses to Regorafenib treatment. Future research should aim to identify these subgroups. RAS mutational status seems to have no interference with Regorafenib's activity.

At the current state of the art, available data strongly support the idea that Regorafenib can be a useful treatment for pre-treated MCRC patients. This evidence is included in the AIOM, ESMO and ASCO guidelines who recommend Regorafenib as a new standard option in pre-treated MCRC patients.

Immunotherapy in colorectal cancer

Guglielmo Nasti, MD

Immunotherapy is a hot topic in oncology at present and immune-checkpoint blockade using programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) antibodies appears to be one of the most promising immunotherapy approaches. Immunotherapy differs from conventional cancer treatment because of its ability to produce durable responses in some patients.

Preclinical studies demonstrated that blockade of this interaction, using anti-PD-1 or anti-PD-L1 antibodies, can restore T-cell activity against tumors cells thereby preventing cancer metastasis and reducing tumor volume. Exciting results have been seen in tumor groups with limited therapeutic options such as melanoma and NSCLC (for which nivolumab has recently been licensed).

PD-1 and PD-L1 blockades in Gastrointestinal (GI) cancers are currently the subject of numerous clinical trials.

PD-1 and PD-L1 blockade are being exploited as single-agents, combinations with chemotherapy, radiotherapy, targeted agents, and other immune-modulatory drugs and in the maintenance setting. Results are expected to be avail-

able within the next few years and may lead to modifications in the treatment paradigm for GI cancers[37]. As regards CRC, recently, MSI status was found to be predictive of the benefit of immune checkpoint blockade in advanced CRC, corroborating the value of integrating knowledge of the underlying biology with drug development strategies[38].

In reports of the effects of PD-1 blockade in human tumors, only 1 of 33 patients with CRC had a response to this treat had a response to this treatment, in contrast to substantial fractions of patients with melanomas, renal-cell cancers, and lung tumors who have a response. What was different about this single patient? The authors hypothesized that this patient had mismatch-repair deficiency, because mismatch-repair deficiency occurs in a small fraction of advanced CRCs.

The hypothesis was correct: the tumor of the single patient with CRC who had a response to PD-1 blockade was mismatched repair-deficient. Therefore, the authors hypothesized that mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors and initiated a phase 2 clinical trial to evaluate immune checkpoint blockade in patients whose tumors had or did not have mismatch-repair deficiency. The immune-related objective response rate and immune-related PFS rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair-deficient CRCs and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair–proficient CRCs. The median PFS and OS were not reached in the cohort with mismatch repair-deficient CRC but were 2.2 and 5.0 months, respectively, in the cohort with mismatch repair-proficient CRC (hazard ratio for disease progression or death, 0.10p<0.001, and hazard ratio for death, 0.22p=0.05. This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab.

Further studies are warranted to establish whether the response rate in non-Lynch syndrome MSI CRC patients differs from Lynch syndrome MSI CRC patients. Within the MSS cohort of CRC patients, it remains to be seen whether patients can be sub-typed by gene significance or immunoscore (e.g., Inflammatory subtype), and whether any additional subtypes are immunosensitive.

Further studies are specifically evaluating PD-L1 blockade in immunological subsets of CRC. In particular, a phase Ib trial evaluating the association of atezolizumab and cobimetinib has shown encouraging preliminary results in MMS patients with chemo refractory CRC[39].

Cobimetinib is a MEK inhibitor and can promote intratumoral T-cell accumulation and MHC I up regulation and synergize with an anti-PDL-1 agent. The combination resulted in a higher clinical response rate in MSS patients than expected from either cobimetinib or atezolizumab alone. An ORR of 17% and 6-month OS of 72% represent clinical improvements over a historical 1% ORR and 6-month median survival for standard of care in this setting. These results suggest that cobimetinib can sensitize tumors to atezolizumab by increasing MHC I expression on tumor cells and promoting intratumoral CD 8 T cell accumulation. On the bases of these encouraging results, the expansion of this phase Ib study in ongoing in mCRC.

CONCLUSIONS

- Trials are ongoing in mCRC
- CRC probably less easy than others
- MSI-H tumors: a good target
- Others may be: MSS with immune infiltrates
- Combination with targeted agents:
  + chemotherapy, sequence?
  + radiotherapy?
  + targeted agents: anti-angiogenics, MEK…?

New therapeutic strategies in the treatment of gastrointestinal neuroendocrine tumors

Salvatore Tafuto, MD

Neuroendocrine tumors of the gastrointestinal tract (GEP-NET), traditionally considered as rare diseases, have become topic of great interest in the last few years. The new evidence in the field of histological classification, the identification of nosographic criteria related clinical aggressiveness, and the new knowledge of molecular biology have made the neuroendocrine tumors object of great ferment both for basic research, that for clinical studies. Currently, the landscape of therapeutic drugs available has greatly expanded thanks to several phase III studies which led to the registration of new drugs that have proven effective for the treatment of neuroendocrine tumors. Somatostatin analogues (SSA) are analogues of the native somatostatin. Over 80% of GEP-NET expresses on the surface of its membrane cell the "SSTR receptors", in particular the low-grade forms. The SSA-approved and used in our country are the octreotide and lanreotide. They are able to produce an improvement of the clinical symptoms in more than 60% of the cases, a stabilization of tumor growth in the 30-50% of

cases. The antiproliferative activity of the SSA has been assessed recently with two clinical studies of equal importance, the study PROMID[40] and the study CLARINET[41]. Both are randomized prospective studies have demonstrated the antiproliferative activity of these molecules *in vivo*. To date we can say that, thanks to these studies, which definitely shown critical issues and limitations, we have seen a change in terms of perception of the two drugs, which by pure drug palliation care should be understood now as drugs to antiproliferative activity and able to impact positively on PFS of patients with GEP-NETs. The therapeutic approach to the GEP-NETs, has certainly revolutionized by the use of molecular targeted drugs such as everolimus, an inhibitor of mammalian target of rapamycin (mTOR) and sunitinib, an inhibitor of tyrosine kinase. Everolimus is a selective inhibitor of mTOR, a serine-threonine kinase whose activity is known to be involved in a several human cancers, and is a potent inhibitor of the growth and proliferation of tumor cells. Everolimus is indicated for the treatment of neuroendocrine tumors of pancreatic origin, well or moderately differentiated, inoperable or in metastatic stage, at a dose of 10 mg daily. Recently, the results of the study RADIANT 4[42] (RAD001 in Advanced Neuroendocrine Tumors) demonstrated that the patients treated with everolimus showed a prolonged median PFS compared to those treated with placebo (11.0 *versus*. 3.9 months, HR 00:48; 95% CI 0.35 to 0, 67; p <0.00001). At the time of the interim analysis of OS it was observed a trend toward improved survivalHR = 0.64; 95% CI, 0.40 to 1.05; p = 0.037, with a total of 70 deaths recorded at the time of data cutoff42 (20.5%) in the everolimus arm and 28 (28.6%) in the placebo arm. The result was not statistically significant, as the significance threshold interim analysis was p = 0.000213. Even Sunitinib[43], a biologic inhibitor of tyrosine kinase associated with the receptor, it is indicated for the treatment of pancreatic neuroendocrine tumors (pNET) well differentiated, inoperable or metastatic disease (median PFS was 11.4 months with sunitinib arm compared to 5.5 months in the placebo armhazard ratio: 0.418 (95% CI 0.263, 0.662), p-value = 0.0001). The pivotal study with sunitinib in pNET was terminated prematurely, and the primary endpoint of the drug evaluation was based on investigator assessment: both conditions may have affected the estimate of the treatment. Chemotherapy has been for years, the only therapeutic option for the treatment of metastatic pNET and GEP-NET, with very various results. Therefore, the regimen with cisplatin and etoposide is usually the preferred treatment schedule for the treatment of poorly differentiated neuroendocrine tumors. Even if such platinum-based treatment scheme has historically shown interesting results in terms of response rate on undifferentiated forms[44], the impact on OS is minimal, so these results remain controversial and the question of what is the best treatment scheme to use for these forms is still debated. The traditional use of this scheme comes from old studies, with little statistical evidence because of the small number of patients enrolled in clinical trials. Also other drugs such as gemcitabine, oxaliplatin, or temozolomide (TMZ) streptozotocin (STZ) can be evaluated in the treatment of NET The activity of TMZ in patients with metastatic neuroendocrine tumors has been evaluated in several studies[42-44] that showed interesting activity by the overall response rate (ORR) point of view, ranging from 25% to 70%. TMZ has shown good activity in patients with NET was taken alone or in combination with other anticancer drugs such as capecitabine, bevacizumab, or thalidomide. The first randomized Phase III study that included the use of chemotherapy in pNETs was performed by Moertel in 1980 that compared the combination of STZ and 5-FU versus STZ as a single agent. The combination arm showed results superior to those of the treatment arm monotherapy in terms of ORR (63% *versus*. 36%, respectively) and median OS (26 *versus*. 16.5 months), even if the difference of OS was not statistically significant. The disparity of these results may be related to several factors: the lack of standardization in order to assess the response in previous studies, the heterogeneity of these tumors in terms of biological behavior and the consequent different response to chemotherapy. In order to clarify the most appropriate place in the therapeutic planning of the STZ associated with 5-FU in the treatment of pNET advanced stage, an international multicenter randomized phase III trial (study SEQTOR) is ongoing. This trial, which is currently active at our Institute, comparing the efficacy and safety of everolimus followed by chemotherapy with STZ and 5-FU until progression in reverse order (chemotherapy with STZ and 5-FU until progression or unacceptable toxicity, followed by everolimus progression). Immunotherapy has recently found a new field of application. Antibodies directed against the checkpoints PD-1/PD-L1 showed tumor regressions and lasting dynamics, suggesting a re-balancing of host-tumor interaction. Pembrolizumab showed a promising anti-tumor activity (objective response rate of 56%) also in the treatment of Merkel cell carcinoma[45,46], which is an aggressive neuroendocrine carcinoma of the

skin (which can be distinguished from other malignant tumors for the expression of cytokeratin 20). These preliminary results leave assume a hypothetical and future role of immunotherapy in the treatment of other neuroendocrine tumors.

Radiation treatment with Cyberknife in 100 prostate cancer patients

Paolo Muto, MD

Prostate cancer (PC) is the second most common cause of cancer worldwide[47]. It is estimated that more than 29.000 men will die from metastatic PC in 2014 in the Unites States[48].

The majority of PC is localized, and various curative treatment options have aimed to improve the oncologic and functional outcomes of these patients; radical prostatectomy and/or external beam radiation therapy (EBRT) is the conventional treatment option for localized PC. Regarding radiotherapy (RT), many treatment options are available for patients treated with RT, ranging from fractionated external beam RT (with different fractionation schedules) to brachytherapy (high dose rate or low dose rate). None of them has shown superiority in terms of efficacy compared to radical prostatectomy. Conventional RT (CRT) as primary treatment for PC is usually protracted over 7-9 weeks, according to different protocols in different centers. Hypo fractionated RT can reduce overall treatment time and result particularly promising in PC for radiobiological considerations. Radiobiologically, slowly growing PC cells are thought to have a low a/b ratio consistently less than 3[49-51], this suggests that PC cells are highly sensitive to dose per fraction, which means that a hypo fractionated radiation therapy with a large radiation dose delivered in a smaller number of fractions may be advantageous. Considering this low ratio and assuming an α/β ratio for early-responding tissues (like skin or mucosa) of 10 and for late-responding tissues (like bladder/rectal mucosa and muscle) of 3[52,53] hypo fractionated RT should reduce the normal tissue complication probability for bladder and bowel[53] compared to conventional schedules. This translates in an increase of the therapeutic index, allowing a dose escalation to the target with a good toxicity profile. CyberKnife is a treatment device used to deliver high-dose hypo fractionated stereotactic body radiation therapy using a robotic arm in combination with intrafraction prostatic motion tracking[54]. It can facilitate delivery of an optimal therapeutic dose to the prostate with a rapid dose falloff near the targeted lesion, resulting in potentially better local control. CyberKnife was used for PC for the first time by King et al[55] and many moderately hypo fractionated schedules for PC have been used in recent years in most RT facilities with promising results[56,57]. A new issue to be addressed is if a more pronounced hypo fractionation, i.e. RT in four or five fractions, can be at least as active, effective, and nontoxic as conventional or moderately hypo fractionated regimens for patients with early-stage organ confined PC. The NCCN guidelines consider CyberKnife technique an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. This modality can be considered an alternative at clinics with appropriate technology, physics and clinical expertise[58].

In our Institution, between November 2012 to May 2015, 99 consecutive patients were treated with stereotactic body radiation therapy (SBRT) CyberKnife. Forty-five patients had low risk PC: Clinical stage T1-T2a and Gleason $\leq$ 6 and PSA <10 ng/ml, 49 patients had intermediate risk PC: Clinical stage T2b or T2c, PSA 10-20 ng/ml or Gleason 7 (3+4), and 5 patients presented with recurrent disease. A contrast enhanced CT scan was acquired for planning using a multislice scanner at 1 mm slices thickness. The gross tumor volume was defined on the basis of clinical and radiological findings and for delineator's purpose image fusion of MRI with planning CT was performed. Delineated organs at risk were the rectum, bladder, bowel, femoral heads, penis, testicles, neuro-vascular bundles, skin. All patients were evaluated in terms of biochemical control of the disease, acute and late toxicity and quality of life. CyberKnife treatment was delivered in five fractions of 35 Gy prescribed to 80% isodose line. Fifty-eight patients had a follow up of 12 months with a mean value of PSA of 0.9 ng/ml, and 23 patients had a follow up of 24 months with a mean PSA value of 0.4 ng/ml. In addition, treatment with CyberKnife was well tolerated. The urinary acute toxicity was G1 in 65%, G2 in 2% of patients; the rectal acute toxicity was G1 in 20%; G2 in 9%. The urinary late toxicity was G1 in 22%; G2 in 1%; the late rectal toxicity was G1 in 8% and G1 in 1% of patients.

Immunotherapies in the treatment of NSCLC

Francovito Piantedosi, MD

Lung cancer remains a leading cause of cancer-related mortality worldwide despite improvements in outcomes for patients with advanced non–small cell lung cancer (NSCLC) with platinum-based chemotherapy and molecularly targeted therapies.

TABLE 2. Summarize developing checkpoint inhibitors.

Checkpoint inhibitors Agents	*Mechanism of action*	*NSCLC clinical trial settings (line of therapy)*
CTLA4 blockade		
Ipilimumab	Monoclonal antibody against CTLA4	1st-line, maintenance
Tremelimumab	Monoclonal antibody against CTLA4	1st-line, maintenance, 2nd/3rd-line
PD-blockade		
Nivolumab	Blocks binding of PD-1 to PD-L1 and PD-L2	1st-line, maintenance, 2nd-line, 3rd-line
Pembrolizumab	Blocks binding of PD-1 to PD-L1 and PD-L2	1st-line, 2nd-line, all-lines
Atezolizumab	Blocks binding of PD-L1 to PD-1 and CD80	1st-line, 2nd/3rd-line
Durvalumab (MEDI4736)	Blocks binding of PD-L1 to PD-1 and CD80	Any line, 1st/2nd-line

Immune checkpoint inhibition as a new treatment approach is undergoing extensive investigation in NSCLC and other malignancies[59].

The immune system plays a critical role in identifying and destroying foreign or abnormal cells in the body, including suppressing tumor growth. Tumors utilize several strategies to avoid recognition by the immune system including also induction of T-cell non-responsiveness through modulation of immune checkpoint pathways.

The CTLA-4 and PD-1 immune checkpoint pathways have been the most actively studied pathways in recent times. Both suppress T-cell activity in distinct ways: CTLA-4 regulates T-cell activity at an early stage, whereas PD-1 predominantly regulates later effector T-cell activity within tissues and tumor.

Development of checkpoint inhibitors in lung cancer includes both CTLA4 blockade and PD-blockade**.**

Results from the CheckMate 017 study have shown that Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit *vs.* standard-of-care docetaxel in previously treated patients with advanced SQ NSCLC: (41% reduction in risk of death (HR 0.59; p = 0.00025); 1-yr OS: 42% *vs.* 24%; mOS: 9.2 *vs.* 6.0 mo). Nivolumab benefit is independent of PD-L1 expression and the safety profile of Nivolumab is favorable versus docetaxel.

Checkmate 057 tested Nivolumab versus Docetaxel in advanced non-squamous NSCLC after first line Platinum-based chemotherapy. Primary endpoint has been survival and the study has demonstrated a statistically significant advantage in favor of Nivolumab versus docetaxel: 12.2 months versus 9.4 with HR= 0.73. In comparison with 017, in Checkmate 057 a correlation between OS and expression of PD-L1 has been shown to all cut-offs studied (PD-L1 >1% HR=0.59; >5% HR= 0.43; >10% HR=0.40). In this study also the toxicity profile has been favorable to Nivolumab.

In March 2015 FDA has approved Nivolumab for metastatic SQ-NSCLC with progression after platinum based chemotherapy and in October 2015 has extended the indication to non-squamous NSCLC. In April 2016 EMA has also extended the indication to NSCLC.

In October 2015, also Pembrolizumab has been registered by the FDA for the treatment of pre-treated patients affected by NSCLC, both squamous and non squamous but with expression of PD-L1 on the basis of KEYNOTE-001 study.

In the KEYNOTE-010 study the advantage of Pembrolizumab *vs.* Docetaxel in pre-treated patients has also been shown with expression of PDL-1 >1%. In addition Pembrolizumab has shown efficacy also in the first line (KEYNOTE-024 study) versus dual drugs including platinum in patients expressing PD-L1.

Atezolizumab has shown a statistically significant advantage in OS when compared with docetaxel in pre-treated patients (POPLAR study) hyper expressing PD-L1 on cancer cells as well as lymphocytic infiltrate (HR= 0.49).

According to this evidence Immune checkpoint inhibition represents an important new approach to lung cancer treatment (NSCLC). Future perspectives of immunotherapy treatments include: association with Ipilimumab, with standard chemotherapy, immunotherapy in both adjuvant and neoadjuvant setting.

This new therapeutic approach requires additional assessments in terms of time to treatment response, different pattern of tumor response, different criteria of progression and different toxicity.

MISCELLANEA SESSION

Obesity and cancer

Rosario Vincenzo Iaffaioli, MD

We must remember that the dozens of tons of food that we introduce in our lifetime correspond to innumerable molecular interactions.

These trace the fate of our health as amply demonstrated in large population studies by researchers from around the world, in the wake of Ancel and Margaret Keys and their collaborators (How to eat well and stay well: the Mediterranean way. New York: Doubleday; 1975).

Already in those days they were built certainties about low incidence of coronary heart disease in the population, such as Italy South typical Cilento, metabolic syndrome and related cardiovascular acute conditions. The pathognomonic advantage, confirmed in numerous subsequent studies, still is attributed to the Mediterranean diet and a healthy lifestyle. In recent decades unfortunately those spontaneous rules of life have gone largely disappointed to the point that in Campania, particularly overweight and obesity, affecting much of the population, and especially children and adolescents aged 8 to 14 years (49% of the population!). But throughout Italy, in the North, especially the Triveneto and Liguria, Umbria, and then all the southern regions are strongly affected by the same phenomenon. In Italy more than 1.1 million children are overweight or obese. Obesity is now epidemic disease directly involved in the *"diseases of nutritional well-being."* It is therefore necessary to re-educate a food philosophy, "cibosofia", who prefers biological products, especially by the earth, and replace all foods with low saturated fats in favor of unsaturated and those that determine the prevalence of omega-3 to the omega-6. Certainly we must not forget the pollutants, often with *endocrine interfering effect*. These include: phthalates, perfluorinated, pesticides, flame retardants, many PCB. In thirty years the chemical industry has poured at least 100,000 substances in the environment, of which the WHO has managed to only 900 to test. And we should mention also benzene, resin, glue, lubricants, paints, detergents, etc.

Since 2004, "Appeal of Paris", the precautionary principle has never been applied in the chemical industry. Surely between pollutants will prevail numerous that determine pseudo-estrogenic effects, such as cosmetics.

Many carcinogens are able to accumulate in the fat, with more marked effect for lung, breast, ovaries, prostate, colon and lymphatic system.

And, if you calculate that about 35% of cancers are attributable to smoking, for at least 11 types of cancer is calculated dependence on overweight/obesity: *liver, prostate, ovary, bladder, kidney, colon and rectum, esophagus, breast postmenopausal osteoporosis, pancreas, endometrium, stomach (cardia).*

Furthermore World Cancer Research Fund International has verified a strong link between physical activity and decreased risk for: *post-menopausal breast, colon, and endometrium*. But there is also moderate evidence for these other cancers.

In all studies, collected in recent years, healthy diet and reduced risk of cardiometabolic syndrome, diabetes and cancer mean:

a) Very varied diet characterized by many and various whole grains, legumes, fruits and vegetables;
b) Limit the excessive caloric intake from sugar-rich items especially if refined or fat and avoid excess sugar-sweetened drinks;
c) Avoid preserved meats and limit red meat and foods high in salt as highlighted in studies on diet and gastric cancer (R.R. 1.70).

The IARC monograph of 2015 provides a fairly credible benchmark index between carcinogenicity of certain foods and gastric cancer and CRC[63].

We must also remember that the cardiometabolic syndrome means increase of IGF-1 and IGF-1 free, obesity also means *insulin resistance and/or hyperinsulinemia, increase of free estrogen and cell proliferation*, and that at the global level is demonstrated the increased onset of neoplasms also in correlation with the number of 5 risk factors implicated in the cardiometabolic syndrome.

We must remember the central role of the inflammation and of NFKB as well as on the axis of LPPS gut - liver - fat - obesity and on intestinal permeability with inevitable alteration of the microbiota, from which it could descend chain reactions that allow the passage of toxins and bacterial populations in the circulation.

The overall increased risk of cancer is still studied in relation to BMI, TNF, IL-6 and IL1β, as well as monocyte chemo-attractants of macrophages and adipose tissue (ATM).

Other cytokines involved in these processes are: IL-8, IL-10, IL-12, IL-17, IL-18, IL-22, and IFN-Y.

On top of that we have to consider that the regulatory T cells (Treg), an important anti-inflammatory protective rampart, located in the abdominal deposits, are lost in obesity exacerbating the pro-inflammatory state associated with the increase of BMI.

Obesity and over nutrition stimulate simultaneously and systemically NEFA, insulin, glucose, leptin and inflammatory cytokine reducing the levels of adiponectin, imbalances that can promote the survival of tumor cells and tumor progression. Then in the colon, obesity promotes a change in the microbiota, amplifying the inflammatory phenomena.

The *sequential genetic progression* of neoplasia is well established. *Intestinal adenomas* are considered precursors of cancer and their pre-

valence in the general population is high. As in the pancreas carcinoma the transition is equally influenced by environmental factors.

There are some explanations for the high incidence of gastrointestinal cancers. First, the epithelium contains a much higher number of proliferative activities as the stem cells and progenitor cells compared to other epithelia, including the liver and pancreas, where cell division is mainly evoked in response to injury.

Secondly, the gastrointestinal epithelium is in direct contact with the surrounding environment, whereas the ingested material that may contain substantial traces of toxins and carcinogens.

Finally, the gastrointestinal tract, especially the colon, is home to trillions of microbial diners.

As these microbes are usually well tolerated, some diets including those high in fat content, can lead to dysbiosis and activate the inflammatory response.

Finally, the epithelium serving of barrier and preventing the microbial penetration and disintegration/digestion products (endotoxins, nucleic acids, etc.) can evoke inflammatory responses with neoplastic growth promotion[64].

Also diets low in fiber can alter the microbial diversity by increasing inflammation[65].

Pathophysiological and biochemical mechanisms of the metabolic syndrome: implications in oncology

Vincenzo Quagliariello Ph.D

The holistic management of cancer patients includes several areas like medical, nutritional, emotional, behavioral, endocrine and immune. All of these can affect the cytokines, metabolic functions and tumor microenvironment that involves tumor associated macrophages (TAM), adipocytes, and extracellular matrix; all of these have a central role in the onset of metabolic syndrome. Based on the International Diabetes Federation of 2005, a patient with metabolic syndrome has Central obesity (defined as waist circumference ≥94 cm for Europoid men and ≥80 cm for Europoid women) plus any two of the following: raised triglycerides >150 mg/dl, or specific treatment for this lipid abnormality; reduced HDL cholesterol: <40 mg/dl in males, and 50 mg/dl in females, or specific treatment for this lipid abnormality; raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg; raised fasting plasma glucose ≥100 mg/dl, or previously diagnosed diabetes mellitus. Metabolic syndrome is associated with a higher relative risk of developing of level, CRC, pancreas, prostate and breast cancer. Specifically, breast cancer patients with metabolic syndrome and higher levels of testosterone has a relative risk of tumor recurrence of 6,5 times compared to woman without metabolic syndrome and low levels of androgens[66]. Among molecular factors with a key role in the genesis of metabolic syndrome there are D-glucose, Advanced Glycatiion End product (AGE)-Advanced Glycatiion End product receptor (RAGE) axis (because stimulate inflammation), Amadori products, Insulin (trough the insulin resistance), trans unsaturated fatty acids, growth factors, Free fatty acids, with particular attention to intramuscular triglycerides (IMTG), peroxides (with particular attention to MDA-4HNA), animal protein (low levels of hydrogen solforate that decrease butyrate), pro-inflammatory cytokines (especially cytokines produced by adipocytes surrounded by macrophages), neuroendocrine disorders (leptin-adiponectin) due to leptin resistance. Specifically, it is important to understand how leptin resistance and low levels of adiponectin, common in metabolic syndrome patients, can increase cell survival, angiogenesis and drug resistance with possible crucial role in cancer. Specifically, as an example, Leptin stimulates the *in vitro* growth of androgen-insensitive Prostate Cancer cells, and increased serum leptin levels are associated with larger, high-grade, and more advanced tumors. Adiponectin showed antitumor activity via inhibition of angiogenesis, and lower adiponectin serum levels are associated with high-grade and more advanced PC cells. On the basis of these considerations, our research group has conducted several studied based on the use of brown rice extract for CRC treatment; in fact brown rice extract incubated with human CRC cells inhibit cell proliferation and decrease significantly secretion of cytokines that have a key role in metabolic syndrome and cancer progression like IL-8, IL-8, MMP-2 and MMP-9. The same behavior is observed in another research study based on the use of nanotechnology for oral delivery of curcumin in rats pretreated with LPS (molecules that increase inflammation as often happens in patients with metabolic syndrome). Specifically, we have obtained an unprecedented pharmacokinetic profile of curcumin with the best nanoformulation, represented by a combination of the smaller nano-emulsion size (110 nm), co-delivery of curcumin and piperine (weight ratio 100:1) and the highest degree of chitosan thiolation (around 15%). Then, we have assessed its anti-inflammatory properties after oral administration in rats at low doses (≤0.1 times the volume administered in the pharmacokinetic study) compatible with a possible transfer

to humans. Furthermore, the proposed food grade nano-emulsions loaded with curcumin, has not show any cytotoxic effect on normal fibroblasts while they are able to promote death of CRC cells in agreement with common knowledge of curcumin selective action.

Old and new cardioprotective drugs. Which indications?
Nicola Maurea, MD

The cardiotoxic effects of anticancer drugs represent a limit to the treatment of oncological patients. The onset of myocardial damage, with important consequences in terms of morbidity, mortality and strong socio-economic impact, is a particular adverse event considering that the new therapeutic strategies, besides to aim to the patient's healing, try, alternatively, to achieve chronicity of neoplastic disease through a prolonged inhibition of tumor growth.

This results in an increased number of "long term survivors"[67], with respect to the past years, burdened by the onset of chronic or late cardiotoxic effects of anticancer drugs. Unfortunately, to the toxicity of the traditional drugs used in oncology, must be added the less known late consequences of "target therapy", with on-target/off-target important effects against the cardiovascular system. In particular, anthracyclines, drugs used as first-line in many types of cancer, produce a well-known irreversible cardiomyopathy, through multiple mechanisms, which include the generation of ROS and the inhibition of topoisomerase 2 beta (Top2β)[68].

To the anthracycline-related toxicity is added the one of the new biological therapies that, by inhibiting specific proteins involved in tumor growth and homeostasis of cardiovascular system, help to increase the population of cancer survivors who develops a disease following the treatment. Among them, Trastuzumab, a monoclonal antibody founder of ErbB2 inhibitors, has revolutionized the natural history of breast cancer, but is associated with an increased risk of asymptomatic left ventricular systolic dysfunction (3-18%) and heart failure (0-4%)[69].

In real world the incidence of cardiac dysfunction and heart failure in patients treated with anthracyclines and trastuzumab are even higher, in the range of age 65-74 and > 75 years, reaching cardiotoxicity values of 35% and 43%, respectively[70].

Another chapter is represented by the angiogenesis inhibitors. Interfere with angiogenesis is an effective and widely used approach in cancer therapy; unfortunately, the anti-angiogenic therapies can cause significant systemic cardiovascular effects such as hypertension, left ventricular dysfunction, heart failure, ischemic heart disease, myocardial infarction and in some cases QT prolongation[71].

In terms of cardioprotection, after the disappointing conclusions of Prada and Manticore studies, as well as those of other randomized trials of which the preliminary results are known, waiting to resolve doubts on the efficacy of ACE inhibitors, sartans, β-blockers and statins, we wanted to test the effectiveness of Ranolazine. It is a potent inhibitor of the late sodium current (INa) able to effectively counter the dependent accumulation of cytosolic Ca^{2+}/Na^{+}; in normal conditions the membrane sodium calcium exchanger – NCX – allows the entry of extracellular Ca^{2+} exchanging it with the intracellular Na^{+}, with consequent improvement of diastolic relaxation.

In our experimental cardioncology laboratory, we have performed studies on an established animal model, treated with anthracyclines or trastuzumab, the founder of the anti-ErbB2, and we have shown that pre-treatment with Ranolazine or post-treatment with Ranolazine, at the end of antineoplastic treatment, prevents left ventricular dysfunction.

We believe that our animal model is sufficiently valid for the study of anti-neoplastic drugs-related cardiotoxicity as well as to test the cardioprotective effect of any other new molecules with antioxidant action.

In conclusion, considering the increased and widespread use of antineoplastic drugs, especially on patients with advanced age, the side effects are more and more frequents making imperative, in the clinical management of neoplastic patient who develops cardiovascular problems or at risk of developing them, the close interaction between cardiologist and oncologist.

Cancer reprogramming
Michele Libutti, MD

The Neoplastic Tissue is a complex and dynamic entity. It encompasses many cell types (cancer cells, tumor infiltrating lymphocytes, cancer associated fibroblasts, stroma cells, stem cells) in a system rich of molecular crosstalks mediated by cytochines[72]. Depending on the distance from the vascular tree, cells undergo hypoxia, acidosis, and redox changes and oxygen and nutrients shortage too, together with epigenetic and mutational changes. In Mitochondria and in the cytosol we can observe metabolic adaptative changes in the pathways implicated in energy production (aerobic hyperglycolisis, TCA reprogramming,

OxPhos down regulation, alterations in glutamine metabolism) in order to up regulate the membrane lipids and DNA production[73]. Products of such reactions (alfa2-ketoglutarate, lactate, citrate, and pyruvate) and mutated enzymes (FH, IDH, and PDHc) are also inducers of angiogenetic factors (HIF1) and pro-inflammatory cytochines.

They can also induce epigenetic changes. Our aim is to emphasize the importance of the:

- Complex changes in cytosol and mitochondrial environment (Warburg effect, Glutamine and Hydroxibutirate metabolism)[74,75];
- Changes in ASCT and SLC7a5 receptors and transporters;
- Genetic heterogeneity of cancer with modifications in the landscape of pi3k, myc, pTen, p53, bcl2 and cadherins genes;
- Changes in bioenergetics of the cancer cell.

Beyond the metabolic reprogramming (regulated by chemical dissociation k factors of the enzymes implicated and depending on the relative amounts of substrates), a very important role is played by the Microbiota and by immunocompetent cells in the microenvironment[76]. The Study of the genomics and metabolomics of cancer cells will lead to the implementation of a new paradigm in treatment: Glutamin supplementation with carbohydrates restrictions, use of Aminoxyacetic acid, therapy with blockers of Complex1 (Metformin), inhibition of Transporters.

Bone fragility of cancer patient: prevention and treatment

Marco Danova, MD

Osteoporosis is a common condition characterized by bone impairment, in its strength and micro architecture: it represents a risk factor for spontaneous fracture[77]. Anticancer therapies, in particular aromatase inhibitors (AIs), chemotherapy (CT), glucocorticoids and drugs that act on the pituitary gonadotropins (as their analogs), used in breast and prostate cancer patients, may contribute to an enhanced bone remodeling leading to a reduction of mineral density and an increased fracture risk[78]. The five-year survival in breast and prostate cancer has increased respectively 87% and 91%[79]. So, with the increased longevity of the population, even after the diagnosis of malignant disease, it is essential to prevent or to treat all clinical and metabolic effects on bone due to the anticancer therapies.

Breast cancer and osteoporosis: Estrogens are hormones acting on bone by direct and indirect mechanisms, capable of slowing bone resorption: through the estrogen receptor on osteoblasts and on osteoclasts, they determine the suppression of the receptor activator factor kB ligand (RANKL), nuclear inhibition of osteoclastic differentiation and thereby reducing bone remodeling. The risk of osteoporosis is closely related to the age of onset of menopause because estrogen deprivation is certainly the main factor in determining the loss of bone mass and increase the risk of fractures. In postmenopausal the body mass index (BMI) is inversely proportional to the risk of osteoporosis. In this period, most of the androgens are converted into estrogen by the enzyme aromatase in the adipose tissue. Even in absence of bone metastases, other conditions may increase the risk of osteoporosis, producing circulating factors that stimulate bone resorption and hypercalcemia[80-82]. Histochemical studies previously conducted on bone of cancer patients, have shown a higher activity osteoclastic and osteoblastic activity in addition to a reduction of the surface area and volume of osteoid80,83. The mineral depletion is faster and more severe in patients with treatment-induced bone loss in cancer compared to those with natural menopause. Therapies for breast cancer, together with frequent inadequate intake of calcium and vitamin D, induce hypogonadism causing a condition of increate bone fragility[84]. However, several chemotherapeutic agents may have direct effects on bone metabolism beyond hypogonadism[85].

Estrogen receptor modulator drugs and osteoporosis: since 1998 the estrogen receptor modulator drugs (SERMs) tamoxifen (TAM) has become for many years the drug of choice for all cases of tumor with estrogen receptor (ER) positive[86]. The class of drugs effects SERM shows tissue-specific agonist or antagonist to the estrogen receptor: thanks to these properties, TAM may reduce the risk of osteoporosis when used in post-menopausal women[87]. However, the ovarian ablation conducted in premenopausal subjects (drugs that block the gonadotropin releasing hormone (GnRH), causing down regulation of the GnRH) can be associated with decreased bone mass up to 13% in the first year[89,89].

Aromatase inhibitors and osteoporosis: Aromatase inhibitors (AIs) (inhibitors of cytochrome P450 aromatase, an enzyme that catalyzes the conversion of androgens to estrogens) are replacing TAM in the adjuvant hormonal therapy for women after menopause with ER positive early stage breast cancer: in this setting, AIs have been shown to have superior efficacy in reducing the risk of recurrence compared with TAM, and thus have become the preferred choice for this subgroup of patients[90]. However, TAM remains a viable choice for initial hormonal therapy for

those seeking to avoid the musculoskeletal effects of AI. Both the laboratory data that clinical data available suggest that they have a different toxicity profile, in particular for older people who have a low cumulative risk of recurrence but a large number of comorbidities, such as osteoporosis[91]. All subjects treated with AI undergo a block of aromatization and this causes a decrease in bone mineral density (BMD) values. However, the reduction of bone mass is below using steroid AI, because of their androgenic activity that can have a stimulant effect on bone formation. The effects of different AIs on bone can be evacuated quantitatively with the annual rate of fractures per 1,000 women per year. An indirect comparison with the third generation of AI notes that the use of exemestane was associated with a lower incidence of fractures (19.2%) compared to anastrozole and letrozole (21.6% and 22.0%, respectively)[92].

Prostate cancer and osteoporosis: Androgen receptor blocking agents have become an established form of therapy for men with PC spread. Androgen blockade combined in older men with disseminated PC results in high bone turnover with a significant loss of bone[93,94]. The androgen deprivation therapy (ADT) in patients with PC can dramatically affect the BMD, putting patients at risk of serious side effects such as bone fractures. The prevalence of osteoporosis in men with prostate cancer ADT is well documented, so that 53% of men with the disease suffer of osteoporosis. Also, there has been less emphasis on the weight of bone loss in men in the advanced stages of PC, but not subjected to ADT. The prevalence of osteoporosis varies from 4-38% in patients with hormone-naïve prostate, with greater the prevalence of osteoporosis in patients with more advanced disease[93]. This results suggest that all men with PC cancer should have regular monitoring of bone health, regardless of the fact that the start ADT.

The prevention and treatment of osteoporosis in patients with cancer: Besides taking adequate calcium, vitamin D supplements and implementation of regular physical activity, the options for prevention and treatment of osteoporosis in cancer patients include anti-resorptive drug therapies[95-96].

Osteoprotegerin (OPG) acts as a decoy receptor for RANK, interrupting osteoclast activation and bone resorption. Denosumab, a monoclonal antibody of human RANK, acts just like OPG preventing the activation of osteoclast activity and subsequently reducing bone resorption[97]. Subcutaneous administration of the drug in doses of 30 mg every 3 months, or 60 mg every 6 months, determined the reduction of urinary excretion of N-telopeptide[96,98]. In a recent meta-analysis conducted on eleven trials, it was concluded that there was no significant difference in adverse events and deaths between denosumab and control group. Compared to placebo, denosumab significantly reduced the risk of non-vertebral fracture but increased the risk of SAE related to infection in the postmenopausal women with osteoporosis or low BMD. However, there was no difference between the safety of denosumab and bisphosphonates[97]. Smith et al[99] conducted a double-blind, randomized, placebo-controlled study of subjects which for 36 months took on ADT for PC without metastases, who received denosumab at a dose half-year 60 mg subcutaneously and a daily supplement of calcium and of vitamin D. In the group treated with denosumab, biochemical markers of bone turnover were significantly decreased compared with placebo. After 36 months, patients treated with denosumab had a significant reduction in the incidence of new vertebral fractures (1.5%, compared to 3.9% with placebo) (RR, 0.38; 95% CI, 0.19 - 0.78; $p = 0.006$).

Recommendation for maintaining bone health in cancer patients: The available clinical trials reveal that therapies to treat breast and prostate cancer induce significant changes in bone turnover besides BMD and fracture risk: many Authors recommend to all patients undergoing surgical or medical castration, an early assessment of the risk of osteoporosis[85,100]. These subjects should perform an early bone density scan that measures the BMD. In patients with previous osteopenia or osteoporosis, the additional conditions that worsen the bone health (such as vitamin D deficiency, hyperparathyroidism, hyperthyroidism and hypercalciuria) should also be considered as well as coexisting factors of increased risk of fragility fractures, in order to indicate a bisphosphonate or denosumab therapy[101]. To date there hasn't yet been defined the optimal duration of bisphosphonate/denosumab therapy. Surely it is logical to think that this therapy should be conducted at least throughout all anticancer therapy[85].

Super foods and super enzymes: the synergic role of nutraceuticals and onconutraceutical super foods in chemoprevention and chemotherapy

Ileana Parascandolo, MD

Current treatments for cancer including CT, radiotherapy (RT), and biologically based therapies, contribute to unintended side effects and compromise the maintenance of health and well-being nutritional.

The "Nutraceutical" (Nutrition + Pharmaceutical) studies foods or components of the active ingredients present in foods that have a positive impact on wellness and health, including prevention and treatment of diseases[102]. The step from Nutraceutical to Onconutraceutical helps in improving the knowledge of substances with anti-tumor components.

It aims to:

- *Cancer chemoprevention* (primary prevention);
- *Compounds able to bind the cancer therapy* for additive or synergistic action (therapy adjuvant), but also to reduce the concentrations of anticancer drugs and side effects of cancer therapies;
- *Delay the onset of resistance to therapy* (CT, hormone and RT).

Onconutraceutical is always looking for active nutraceuticals in cancer therapy and for technologies to facilitate administration and bioavailability.

Nutraceuticals have the features of:

- *Side effects Decrease of cancer therapies (CT and RT)*
- *Increase of therapy consequences*
- *Improving the quality of life*

The World Cancer Research Fund and the American Institute for Cancer Research have studied for over 12 years, eating habits and lifestyle of about 380 people in 9 European countries. These are the conclusions for the prevention of neoplastic diseases:

- "Superfoods" consumption that enhances the immune system and have an antioxidant activity;
- Increasing "Super Enzymes" intracellular to improve scavenger action of ROS.

Last, there were selected some Superfood and Super Enzymes:

- **Phenol simple:** phenolic acids, coumarins and benzoic acids. Their condensation can let arise to polymers such as lignin;
- **Flavonoids:** flavonoids make up the largest group of natural phenols and all have as an identity 2-phenyl benzopyron or flavonone. Structural changes in the rings allow subdividing the flavonoids in different families: flavonols, flavones, isoflavones, anthocyanins and others.
- **Tannins:** They belong to two categories condensed tannins (proanthocyanidins) (egg, red wine, chestnut) and hydrolysable tannins, heterogeneous polymers containing phenolic acids, e.g., the Gallic acid and simple sugars.
- **Silymarin:** It is a complex of flavolignani consisting of three substances: silybin (also known as silibinin), the silychristin and silydianin. It is found in several plants, especially in thistle[103].
- **Spices:** The chemo preventive properties of spices are mediated by functional bioactive substances that stop the activity of the cytochrome P450 1A1 and CYP isoenzymes, cyclooxygenase-2, reducing activator of transcription-3 (STAT-3) and signal transducer, cell cycle inhibitors.
- **Beans, chickpeas, beans, soybeans, lentils:** each has chemo preventive properties (No GMO)

Conclusions: We improve a synergistic alliance among supportive therapies, natural superfoods, nutraceuticals supplements and pharmacological therapies.

Goals:

- Improvement of Quality of Life (QoL)
- Better cure for cancer patients
- Cancer Pain
- Cancer's related Cachexia
- Fatigue
- Nausea
- Prevention of cancer's therapy related Cystitis
- Prevention and treatment of cancer's therapy related mucositis

Perspectives:

- Constituting a multi-disciplinary team of medical oncology in hospital wards[104];
- Detecting and measuring the parameter Qol and BMI;
- Support therapies in cancer's patients are now realities, but we need a greater commitment by everyone to improve the QoL of the cancer's patients.

^{64}Copper

Francesco Barbato, MD

Copper (Cu) is a transition metal absolutely necessary for the life in an oxygen-rich environment, because of its characteristics as reducing agent. Likewise a regulatory role for Cu and Cu-related proteins in gene expression and cancer cells proliferation has been postulated. According to this premises, the presence of an elevated Cu concentration in cancer cells may be potentially used to differentiate healthy from transformed cells, becoming the target for novel diagnostic and therapeutic agents. Furthermore, in comparison with normal human subjects, significantly higher Cu levels have been measured in serum and tumor cells of patients with cancer because Cu may play a role in the cancer development, acting at different steps, starting from angiogenesis, that is one of the main targets for a Cu-based treatment[105].

Our aim is to demonstrate ^{64}Cu capability to obtain both diagnosis and therapy in PET/CT

imaging for a radiotargeted molecular therapy in patients with tumors. As showed in previous experimental data, tumors need Cu for cellular metabolic activities and ^{64}Cu is able to link DNA and to destroy tumor cells thanks to its Auger effect. In fact, it is characterized by high Linear Energy Transfer (LET) in a small spatial region that can crash the cell[105]. ^{64}Cu is a radio-pharmaceutical used as precursor for the *in vitro* radiolabeling of specific carriers, such as monoclonal antibodies, peptides, aminoacids, hormones and other vectors utilizable for PET imaging and/or for radionuclide therapy. As previously mentioned, it has been amply demonstrated that Cu is required for the tumor angiogenesis process[105]. High Cu levels have been found in many types of human tumors, including prostate, breast and brain cancer; therefore, according to the current literature, we can speculate its theoretical clinical interest mainly for patients with PC to localize recurrence; to evaluate advantages for diagnostic and consequent therapeutic purposes deriving from the use of different ponderal and radioactive doses of the same compound radiolabelled with ^{64}Cu, in particular, in patients with glioblastoma multiform; for receptor imaging and consequent therapeutic purposes in patients with NET.

Use of complementary and alternative medicine (CAM) in cancer patients: an Italian Multicenter Survey

Massimiliano Berretta MD, Ph.D

According to the National Center for Complementary and Integrative Health, USA, the Complementary and Alternative Medicine (CAM), includes a wide range of products, such as herbs (also known as botanicals), vitamins, minerals and probiotics, and medical practices, such as acupuncture or magneto-therapy, which are outside of the mainstream Western medicine. Such practices or substances are defined 'alternative' when they are used *in place of* conventional medicine and 'complementary' when they are used *together with* conventional medicine[106]. Patients with cancer are more likely to resort to CAM, sooner or later in their disease history, for a wide range of reasons. Firstly, the unfavorable outcome in a relevant percentage of cases leads patients to 'leave no stone unturned'; secondly, the heavy toxicities, often associated with the traditional antineoplastic therapies, induce them to look for something different from the prescribed therapy or more simply for substances presumed to reduce the side effects from such therapies[107]. Nevertheless the literature about CAM prevalence in cancer patients is not particularly rich, especially if we consider only the European papers, and the prevalence is probably underestimated. Many patients do not declare that they engage in this practice, on one hand because they undervalue the relevance of the products they take, considering them 'natural', unable to interact with the conventional drugs and devoid of side effects, and, on the other hand, because they are somehow reluctant to admit the use of an unconventional treatment, worrying that such behavior may be interpreted as reflecting a loss of trust in their oncologist and the treatment he/she has prescribed. Furthermore, most clinicians are unfamiliar with these kinds of treatments[108] and hence do not pay enough attention to this aspect of the anamnesis at the time of the visit; usually they do not explicitly ask about this topic, as they do for all other health matters such as comorbidity or conventional drugs[107,109].

The available studies report that the prevalence of CAM use among cancer patients is in the range of 12.5%-73%[110-113]. This enormous variability is, at least partially, justified by the inconsistent definition of CAM, with some authors including only herbal medications, while some others considering also including dietary supplements and unconventional medical practices (massages, acupuncture). The aim of this study was to assess the use of CAM across a number of Italian cancer hospitals, using the same measurement tool and the same definition of CAM and trace the "identikit" of typical cancer patient "CAM-users".

We conducted a descriptive survey in five Italian hospitals involving 468 patients with different malignancies. The survey consisted of a forty-two questions questionnaire, patients were considered eligible if they were Italian-speaking and receiving an anticancer treatment (AT) at the time of the survey or had received an AT no more than three years before participating in the survey. Out of all patients, 48.9% said that they use or have recently used CAM, (supplements and herbals, mainly). The univariate analysis on showed that female gender, high education, receiving treatment at a highly specialized institute and receiving chemotherapy, are associated with CAM use. The multivariate analysis showed that high education (Odds Ratio, (OR): 1.96 95% Confidence Interval, CI, 1.27-3.05) and receiving treatment in a specialized cancer center (OR: 2.75 95% CI, 1.53-4.94) are confirmed as risk factors for CAM use. Roughly half of our patients receiving treatment for cancer used CAM. It is necessary that health professional explore the use of CAM with their cancer patients, educate them about potentially beneficial therapies in light of the limited available evidence of effectiveness, and work towards an integrated model of healthcare provision.

CONCLUSIONS

Cancer represents a model of disease in continuous evolution and to date due to the enormous progress obtained in its diagnosis and the availability of new drugs we are able to obtain encouraging clinical results.

We believe that the right way to obtain better results is based on a multidisciplinary treatment approach and at the same time is important to rationalize the costs of new treatments that are often too expensive respect to results obtained.

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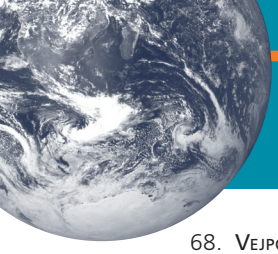
REFERENCES

1. Petrillo M, Fusco R, Catalano O, Sansone M, Avallone A, Delrio P, Pecori B, Tatangelo F, Petrillo A. MRI for Assessing Response to Neoadjuvant Therapy in Locally Advanced Rectal Cancer Using DCE-MR and DW-MR Data Sets: A Preliminary Report. Biomed Res Int 2015; 2015: 514740.
2. Fusco R, Petrillo A, Petrillo M. Use of Tracer Kinetic Models for Selection of Semi-Quantitative Features for DCE-MRI Data Classification. Applied Magnetic Resonance 2013; 44: 1311-1324.
3. Petrillo A, Fusco R, Petrillo M, Granata V, Sansone M, Avallone A, Delrio P, Pecori B, Tatangelo F, Ciliberto G. Standardized Index of Shape (SIS): a quantitative DCE-MRI parameter to discriminate responders by non-responders after neoadjuvant therapy in LARC. Eur Radiol 2015; 25: 1935-1945.
4. Fang B, Mehran RJ, Heymach JV, Swisher SG. 2015. Predictive biomarkers in precision medicine and drug development against lung cancer. Chin J Cancer 2015; 34: 295-309.
5. Nalejska E, Mączyńska, E, Lewandowska MA. Prognostic and predictive biomarkers: tools in personalized oncology. Mol Diagn Ther 2014; 18: 273-284.
6. Pirker, R, Filipits M. Personalized treatment of advanced non-small-cell lung cancer in routine clinical practice. Cancer Metastasis Rev 2016; 35: 141-150.
7. Ichikawa K, Aritaka N, Ogura K, Hosone M, Ota Y, Sato E, Komatsu N, Hirano T. Utility of immunohistochemistry with an antibody against MYC at the initial diagnosis of follicular lymphoma, grade 3A, for predicting a more aggressive clinical course: a case report and review of the literature. Int J Clin Exp Pathol 2015; 8: 7559-7564.
8. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 2015; 14: 847-856.
9. Nikiforov YE, Yip L, Nikiforova MN. New strategies in diagnosing cancer in thyroid nodules: impact of molecular markers. Clin Cancer Res 2013; 19: 2283-2288.
10. Nikiforov YE. Molecular diagnostics of thyroid tumors. Arch Pathol Lab Med 2011; 135: 569-577.
11. Di Martino S, Tomaselli A, Grillo A, Petruzziello A, Di Noto S, Di Biase I, Sangermano A, Lus G, D'Orta A, Berretta M, Pezone A, Di Francia R. Personalized medicine in the clinical practice: the role of functional genomics. WCRJ 2016; 3: e632.
12. Skol AD, Sasaki MM, Onel K. The genetics of breast cancer risk in the post-genome era: thoughts on study design to move past BRCA and towards clinical relevance. Breast Cancer Res 2016; 18: 99.
13. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, Lambrechts D, Despierre E, Barrowdale D, McGuffog L, Healey S, Easton DF, Sinilnikova O, Benítez J, García MJ, Neuhausen S, Gail MH, Hartge P, Peock S, Frost D, Evans DG, Eeles R, Godwin AK, Daly MB, Kwong A, Ma ES, Lázaro C, Blanco I, Montagna M, D'Andrea E, Nicoletto MO, Johnatty SE, Kjær SK, Jensen A, Høgdall E, Goode EL, Fridley BL, Loud JT, Greene MH, Mai PL, Chetrit A, Lubin F, Hirsh-Yechezkel G, Glendon G, Andrulis IL, Toland AE, Senter L, Gore ME, Gourley C, Michie CO, Song H, Tyrer J, Whittemore AS, McGuire V, Sieh W, Kristoffersson U, Olsson H, Borg Å, Levine DA, Steele L, Beattie MS, Chan S, Nussbaum RL, Moysich KB, Gross J, Cass I, Walsh C, Li AJ, Leuchter R, Gordon O, Garcia-Closas M, Gayther SA, Chanock SJ, Antoniou AC, Pharoah PD; EMBRACE.; kConFab Investigators.; Cancer Genome Atlas Research Network. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012; 307: 382-390.
14. Zhong Q, Peng HL, Zhao X, Zhang L, Hwang WT. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. Clin Cancer Res 2015; 21: 211-20.
15. Luersen GF, Wei W, Tamm EP, Bhosale PR, Szklaruk J. Evaluation of Magnetic Resonance (MR) Biomarkers for Assessment of Response With Response Evaluation Criteria in Solid Tumors: Comparison of the Measurements of Neuroendocrine Tumor Liver Metastases (NETLM) With Various MR Sequences and at Multiple Phases of Contrast Administration. J Comput Assist Tomogr 2016; 40: 717-722.
16. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014; 383: 1490-1502.
17. Seymour M. Conceptual approaches to metastatic disease. Ann Oncol 2012; 23(Suppl 10): 77-80.
18. Giuliani F, De Vita F, Colucci G, Pisconti S. Maintenance therapy in colon cancer. Cancer Treat Rev 2010; 36(suppl 3): S42-S45.
19. Aprile G, Giuliani F, Lutrino SE, Mainteinance therapy in Colorectal Cancer: moving the artillery down while keeping an eye on the enemy. Clin Colorectal Cancer 2016; 15: 7-15.
20. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, de Gramont A. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer. A GERCOR study. J Clin Oncol 2006; 24: 394-400.
21. Chibaudel B, Maindrault-Goebel F, Lledo G, Mineur L, André T, Bennamoun M, Mabro M, Artru P, Carola E, Flesch M, Dupuis O, Colin P, Larsen AK, Afchain P, Tournigand C, Louvet C, de Gramont A. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. J Clin Oncol 2009; 27: 5727-5733.
22. Adams RA, Meade AM, Seymour MT, Wilson RH, Madi A, Fisher D, Kenny SL, Kay E, Hodgkinson E, Pope M, Rogers P, Wasan H, Falk S, Gollins S, Hickish T, Bessell EM, Propper D, Kennedy MJ, Kaplan R, Maughan

TS; MRC COIN Trial Investigators. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet Oncol 2011; 12: 642–653.
23. Labianca R, Sobrero A, Isa L Cortesi E, Barni S, Nicolella D, Aglietta M, Lonardi S, Corsi D, Turci D, Beretta GD, Fornarini G, Dapretto E, Floriani I, Zaniboni A; Italian Group for the Study of Gastrointestinal Cancer-GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. Ann Oncol 2011; 22: 1236-1242.
24. Ciombor KK, Berlin J. Targeting metastatic colorectal cancer–present and emerging treatment options. Pharmgenomics Pers Med 2014; 7: 137-144.
25. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008; 26: 2013-2019.
26. Díaz-Rubio E, Gómez-España A, Massutí B, Sastre J, Abad A, Valladares M, Rivera F, Safont MJ, Martínez de Prado P, Gallén M, González E, Marcuello E, Benavides M, Fernández-Martos C, Losa F, Escudero P, Arrivi A, Cervantes A, Dueñas R, López-Ladrón A, Lacasta A, Llanos M, Tabernero JM, Antón A, Aranda E; Spanish Cooperative Group for the Treatment of Digestive Tumors. First-line XELOX plus bevacizumab followes by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist 2012; 17: 15-25.
27. Koeberle D, Betticher DC, von Moos R, Dietrich D, Brauchli P, Baertschi D, Matter K, Winterhalder R, Borner M, Anchisi S, Moosmann P, Kollar A, Saletti P, Roth A, Frueh M, Kueng M, Popescu RA, Schacher S, Hess V, Herrmann R. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). Ann Oncol 2015; 26: 709-714.
28. Simkens LH, van Tinteren H, May A, May A, ten Tije AJ, Creemers GJ, Loosveld OJ, de Jongh FE, Erdkamp FL, Erjavec Z, van der Torren AM, Tol J, Braun HJ, Nieboer P, van der Hoeven JJ, Haasjes JG, Jansen RL, Wals J, Cats A, Derleyn VA, Honkoop AH, Mol L, Punt CJ, Koopman M. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet 2015; 385: 1843-1852.
29. Hegewisch-Becker S, Graeven U, Lerchenmuller CA, Lerchenmüller CA, Killing B, Depenbusch R, Steffens CC, Al-Batran SE, Lange T, Dietrich G, Stoehlmacher J, Tannapfel A, Reinacher-Schick A, Quidde J, Trarbach T, Hinke A, Schmoll HJ, Arnold D. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, openlabel, phase 3 trial. Lancet Oncol 2015; 16: 1355-1369.
30. Tamburini E, Rudnas B, Santelmo C, Drudi F, Gianni L, Nicoletti SV, Ridolfi C, Tassinari D. Maintenance based Bevacizumab versus complete stop or continuous therapy after induction therapy in first line treatment of stage IV colorectal cancer: A meta-analysis of randomized clinical trials. Crit Rev Oncol Hematol 2016; 104: 115-123.
31. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer Ann Oncol 2016; 27: 1386-1422.
32. Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, Sydes B, Madi A, Sizer B, Lowdell C, Middleton G, Butler R, Kaplan R, Maughan T; COIN-B investigators. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. Lancet Oncol 2014; 15: 631-639.
33. ERbitux METastatic colorectal cancer Strategy Study: a phase III randomized two arm study with FOLFIRI þ cetuximab until disease progression compared to FOLFIRI þ cetuximab for 8 cycles followed by cetuximab alone until disease progression in first line treatment of patients with RAS and BRAF wild type metastatic colorectal cancerEudraCT no. 2014-004299-41. Available at: https: //www.clinicaltrialsregister.eu/ctr-search/trial/2014e004299e41/IT.
34. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomized, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303-312.
35. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW; CONCUR Investigators.. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 16: 619-629.
36. Prenen H, Vecchione L, Van Cutsem E. Role of targeted agents in metastatic colorectal cancer. Target Oncol 2013; 8: 83-96.
37. Hazel Lote, Cafferkey C, Chau I. PD-1 and PD-L1 blockade in gastrointestinal malignancies. Cancer Treatment Rev 2015; 41: 893-903.
38. Diaz LA Jr, Le DT. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509-2520.
39. Bendell JC, Rosen LS, Mayer RJ, Goldman JW, Infante JR, Benedetti F, Lin D, Mizuguchi H, Zergebel C, Patel MR. Phase 1 study of oral TAS-102 in patients with refractory metastatic colorectal cancer. Cancer Chemother Pharmacol 2015; 76: 925-932.
40. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol 2009; 27: 4656-4663.

41. Chung C. Management of neuroendocrine tumors. Am J Health Syst Pharm 2016; 73: 1729-1744.
42. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Delle Fave G, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Fourth Trial (RADIANT-4) Study Group. Lancet 2016; 387: 968-977.
43. Lahner H, Rinke A, Unger N, Poeppel TD, Kühl H, Lehmann N, Führer D. Sunitinib Efficacy in Patients with Advanced pNET in Clinical Practice. Horm Metab Res 2016; 48: 575-580.
44. Moertel CG, Johnson CM, McKusick MA, Martin JK Jr, Nagorney DM, Kvols LK, Rubin J, Kunselman S. The management of patients with advanced carcinoid tumors and islet cell carcinomas. Ann Intern Med 1994; 120: 302-309.
45. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326: 519-523.
46. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, Berry S, Chartash EK, Daud A, Fling SP, Friedlander PA, Kluger HM, Kohrt HE, Lundgren L, Margolin K, Mitchell A, Olencki T, Pardoll DM, Reddy SA, Shantha EM, Sharfman WH, Sharon E, Shemanski LR, Shinohara MM, Sunshine JC, Taube JM, Thompson JA, Townson SM, Yearley JH, Topalian SL, Cheever MA. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med 2016; 374: 2542-2552.
47. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer Incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374-1403.
48. Siegel R, Fedewa SA, Miller KD, Goding-Sauer A, Pinheiro PS, Martinez-Tyson D, Jemal A. Cancer Statistics, 2014. Ca Cancer J Clin 2014; 64: 9-29.
49. Anwar M, Weinberg V, Chang AJ, Hsu Ic, Roach 3rd M, Gottschalk A. Hypofractionated SBRT versus conventionally fractionated EBRT for Prostate Cancer: Comparison of PSA slope and nadir. Radiat Oncol 2014; 9: 42.
50. Brenner DJ, Hall EJ. Fractionation and protraction for Radiotherapy of Prostate Carcinoma. Int J Radiat Oncol Biol Phys 1999; 43: 1095-1101.
51. Leborgne F, Fowler J, Leborgne Jh, Mezzera J. Later outcomes and Alpha/Beta estimate from Hypofractionated Conformal Three-Dimensional Radiotherapy versus Standard Fractionation for localized Prostate Cancer. Int J Radiat Oncol Biol Phys 2012; 82: 1200-1207.
52. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct Evidence that prostate tumors show high sensitivity to fractionation (low Alpha/Beta ratio), similar to late- responding normal tissue. Int J Radiat Oncol Biol Phys 2002; 52: 6-13.
53. Proust-Lima C, Taylor Jm, S'echer S, Sandler H, Kestin L, Pickles T, Bae K, Allison R, Williams S. Confirmation of a low A/B ratio for Prostate Cancer treated by External Beam Radiation Therapy alone using a post-treatment repeated-measures model for PSA dynamics. Int J Radiat Oncol Biol Phys 2011; 79: 195-201.
54. Seisen T, Drouin SJ, Phé V, Parra J, Mozer P, Bitker MO, Cussenot O, Rouprêt M. Current role of image-guided robotic radiosurgery (Cyberknife(®)) for prostate cancer treatment. BJU Int 2013; 111: 761-766.
55. King Cr, Lehmannj, Adler Jr, Haij. Cyberknife Radiotherapy for Localized Prostate Cancer: Rational and Technical feasibility. Technol Cancer Res Treat 2003; 2: 25-30.
56. Kim H, Kim Jw, Hong Sj, Rha Kh, Lee Cg, Yang Sc, Choi Yd, Suh Co, Cho J. Treatment outcome of Localized Prostate Cancer by 70 Gy Hypofractionated Intensity-Modulated Radiotherapy with a customized rectal balloon. Radiat Oncol J 2014; 32: 187-197.
57. Zilli T, Jorcano S, Escud'e L, Linero D, Rouzaud M, Dubouloz A, Miralbell R. Hypofractionated External Beam Radiotherapy to boost the Prostate with ≥85 Gy/Equivalent Dose for patients with localized disease at high risk of lymph node involvement: feasibility, tolerance and outcome. Clin Oncol (R Coll Radiol) 2014; 26: 316-322.
58. Nccn Guidelines V.1.2016 Prostate Cancer.
59. Facchinetti F, Marabelle A, Rossi G, Soria JC, Besse B, Tiseo M. Moving Immune Checkpoint Blockade in Thoracic Tumors beyond NSCLC. J Thorac Oncol 2016; 11: 1819-1836.
60. Borghaei H, Brahmer J, Horn L, Ready N, Steins M, Felip E, Paz-Ares L, Xx X, Barlesi F, Antonia S, Fayette J, Rizvi N, Crino L, Reck M, Erich Eberhardt WE, Hellmann M, Desai K, Li A, Healey D, Spigel D, Mathias C. P2.35: Nivolumab vs. Docetaxel in Advanced NSCLC: CheckMate 017/057 2-Y Update and Exploratory Cytokine Profile Analysis: Track: Immunotherapy. J Thorac Oncol 2016; 11: S237-S238.
61. Ramalingam S, Hui R, Gandhi L, Carcereny E, Felip E, Ahn MJ, Eder JP, Balmanoukian AS, Leighl N, Aggarwal C, Horn L, Patnaik A, Middleton GW, Gubens M, Hellmann M, Soria JC, Lubiniecki GM, Zhang J, Piperdi B, Garon EB. P2.39: Long-Term OS for Patients With Advanced NSCLC Enrolled in the KEYNOTE-001 Study of Pembrolizumab: Track: Immunotherapy. J Thorac Oncol 2016; 11: S241-S242.
62. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387: 1837-1846.
63. Samet JM. The IARC monographs: critics and controversy. Carcinogenesis 2015; 36: 707-709.
64. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, Taniguchi K, Yu GY, Osterreicher CH, Hung KE, Datz C, Feng Y, Fearon ER, Oukka M, Tessarollo L, Coppola V, Yarovinsky F, Cheroutre H, Eckmann L, Trinchieri G, Karin M. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 2012; 491: 254-258.
65. Poullis A, Foster R, Shetty A, Fagerhol MK, Mendall MA. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2004; 13: 279-284.
66. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: Tumor microenvironment and inflammation. J Clin Oncol 2016; 34: 4270-4276.
67. Tirelli U, Annunziata MA, Spina M, Dal Maso L, Berretta M. Long-term cancer survivorship: a new challenge that requires a new follow-up approach. Eur Rev Med Pharmacol Sci 2011; 15: 725-726.



68. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol 2014; 64: 938.
69. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; Authors/Task Force Members.; ESC Committee for Practice Guidelines (CPG):2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 2768-2801.
70. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012; 104: 1293-1305
71. Maurea N, Spallarossa P, Cadeddu C, Madonna R, Mele D, Monte I, Novo G, Pagliaro P, Pepe A, Tocchetti CG, Zito C, Mercuro G. A recommended practical approach to the management of target therapy and angiogenesis inhibitors cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology. J Cardiovasc Med (Hagerstown) 2016; 17 Suppl 1: e93-e104.
72. Dang CV. Links between metabolism and cancer. Genes Dev 2012; 26: 877-890.
73. Mullen AR, DeBerardinis RJ. Genetically-defined metabolic reprogramming in cancer. Trends Endocrinol Metab 2012; 23: 552-559.
74. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene 2010; 29: 313-324.
75. Medina MA, Sanchez-Jimenez F, Marquez J, Rodriguez Quesada A, Nunez de Castro I. Relevance of glutamine metabolism to tumor cell growth. Mol Cell Biochem 1992; 113: 1-15.
76. Tuan J, Chen YX. Dietary and Lifestyle Factors Associated with Colorectal Cancer Risk and Interactions with Microbiota: Fiber, Red or Processed Meat and Alcoholic Drinks. Gastrointest Tumors 2016; 3: 17-24.
77. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet 2011; 377: 1276-1287.
78. Ottanelli S. Prevention and treatment of bone fragility in cancer patients. Clin Cases Miner Bone Metab 2015; 12: 116-129.
79. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132: 1133-1145.
80. Mundy GR, Eilon G, Orr W, Spiro TP, Yoneda T. Osteoclast activating factor: its role in myeloma and other types of hypercalcemia of malignancy. Metab Bone Dis Relat Res 1980; 2: 173–177.
81. Suva LJ, Winslow GA, Wettenhall RE, Hammonds RG, Moseley JM, Diefenbach-Jagger H, Rodda CP, Kemp BE, Rodriguez H, Chen EY, et al. A parathyroid hormone-related protein implicated in malignant hypercalcemia: Cloning and expression. Science 1987; 237: 893-896.
82. Seyberth HW, Segre GV, Morgan JL, Sweetman BJ, Potts JT, Jr, Oates JA. Prostaglandins as mediators of hypercalcemia associated with certain types of cancer. N Engl J Med 1975; 293: 1278-1283.
83. Stewart AF, Vignery A, Silverglate A, Ravin ND, LiVolsi V, Broadus AE, Baron R. Quantitative bone histomorphometry in humoral hypercalcemia of malignancy: Uncoupling of bone cell activity. J Clin Endocrinol Metab 1982; 55: 219-227.
84. Pfeilschifter J, Diel IJ. Osteoporosis Due to Cancer Treatment: Pathogenesis and Management. J Clin Oncol 2000; 18: 1570-1593.
85. Rozenberg S, Carly B, Liebens F, Antoine C. Risks of osteoporosis associated with breast cancer treatment: the need to access to preventive treatment. Maturitas 2009; 64: 1-3.
86. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998; 351: 1451-1467.
87. McCloskey E. Effects of third-generation aromatase inhibitors on bone. Eur J Cancer 2006; 42: 1044-1051.
88. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol 2001; 19: 3306-3311.
89. Garrett TJ, Vahdat LT, Kinne DW. Systemic adjuvant therapy of breast cancer. J Surg Oncol 1997; 64: 167-172.
90. Coates AS, Keshaviah A, Thürlimann B, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Colleoni M, Láng I, Del Mastro L, Smith I, Chirgwin J, Nogaret JM, Pienkowski T, Wardley A, Jakobsen EH, Price KN, Goldhirsch A. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-reponsive early breast postmenopausal women with endocrine-reponsive early breast cancer: update of study BIG 1–98. J Clin Oncol 2007; 25: 486-492.
91. ATAC Trialists' Group. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completing of 5 years' adjuvant treatment for breast cancer. Lancet 2005; 365: 60-62.
92. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, Jassem J, Van de Velde CJ, Delozier T, Alvarez I, Del Mastro L, Ortmann O, Diedrich K, Coates AS, Bajetta E, Holmberg SB, Dodwell D, Mickiewicz E, Andersen J, Lønning PE, Cocconi G, Forbes J, Castiglione M, Stuart N, Stewart A, Fallowfield LJ, Bertelli G, Hall E, Bogle RG, Carpentieri M, Colajori E, Subar M, Ireland E, Bliss JM; Intergroup Exemestane Study. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007; 369: 559-570.
93. Minana B, Cozar JM, Alcazar A, Morote J, Gomez-Veiga FJ, Solsona E, Rodigruez-Antolin A, Carballido J. Bone health in patients with prostate cancer. Actas Urol Esp 2014; 38: 685-693.
94. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998; 83: 1561-1566.
95. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010; 182: 1864-1873.
96. Farrier AJ, Sanchez-Franco LC, Shoaib A, Gulati V, Johnson N, Uzoigwe CE, Choudhury MZ. New anti-resorptive and antibody mediated antiresorptive therapy. Bone Joint 2016; 98 B: 160-165.

97. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ; AMG 162 Bone Loss Study Group. Denosumab in post-menopausal women with low bone mineral density. N Engl J Med 2006; 354: 821-831.
98. Kiesel L, Kohl A. Role of the RANK/RANKL pathway in breast cancer. Maturitas 2016; 86: 10-16.
99. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C; Denosumab HALT Prostate Cancer Study Group Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009; 361: 745–755.
100. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Annal Oncol 2014; 25: 124-137.
101. Todenhofer T, Stenzl A, Hofbauer LC, Rachner TD. Targeting bone metabolism in patients with advanced prostate cancer: current options and controversies. Int J Endocrinol 2015; 2015: 838202.
102. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in Dietary supplement Use Among US Adults From 1999-2012. JAMA 2016; 316: 1464-1474.
103. Di Francia R, Rinaldi L, Troisi A, Di Benedetto F, Berretta M. Effect of anti-oxidant agents in patients with hepatocellular diseases. Eur Rev Med Pharmacol Sci 2015; 19: 3993-3995.
104. Berretta M, Di Francia R, Tirelli U. Editorial – The new oncologic challenges in the 3RD millennium WCRJ 2014; 1: e133.
105. Roles of Atox1 and p53 in the trafficking of copper-64 to tumor cell nuclei: implications for cancer therapy. J Biol Inorg Chem 2014; 19: 427-438.
106. Definition of Complementary and Alternative Medicine (CAM) according to the National Center for Complementary and Integrative Health, available at: https: // nccih.nih.gov/health/integrative-health
107. Ernst E. Complementary cancer treatment: hope or hazard? Clin Oncol (R Coll Radiol) 1995; 7: 259-263.
108. Newell S, Sanson-Fisher RW. Australian oncologists' self-reported knowledge and attitudes about non-traditional therapies used by cancer patients. Med J Aust 2000; 172: 110-113.
109. Helyer LK, Chin S, Chui BK, Fitzgerald B, Verma S, Rakovitch E, Dranitsaris G, Clemons M. The use of complementary and alternative medicines among patients with locally advanced breast cancer -a descriptive study. BMC Cancer 2006; 6: 39.
110. Maggiore RJ, Gross CP, Togawa K, Tew WP, Mohile SG, OwusuC, Klepin HD, Lichtman SM, Gajra A, Ramani R, Katheria V, Klapper SM, Hansen K, Hurria A; Cancer and Aging Research Group. Use of complementary medications among older adults with cancer. Cancer 2012; 118: 4815-4823.
111. Lichtman SM, Boparai MK. Geriatric medication management: evaluation of pharmacist interventions and potentially inappropriate medication (PIM) use in older (>65 years) cancer patients. J Clin Oncol 2009; 27 (Abstract 9507).
112. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. J Clin Pharm Ther 2007; 32: 169-175.
113. Wyatt GK, Friedman LL, Given CW, Given BA, Beckrow KC. Complementary therapy use e among older cancer patients. Cancer Pract 1999; 7: 136-144.