New Challenges in Translational Medicine

Translating basic research in cancer patient care

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Summary. With the advent of molecular targeted therapies and the development of high-throughput biotechnologies, it has become evident that progress in cancer research is largely due to the creation of multidisciplinary teams able to plan clinical trials supported by appropriate molecular hypotheses. These efforts have culminated in the identification and validation of biomarkers predictive of response, as well as in the generation of more accurate prognostic tools. The identification of cancer stem cells has provided further insights into mechanisms of cancer, and many studies have tried to translate this biological notion into prognostic and predictive information. In this regard, new agents targeting key stemness-related pathways have entered the clinical development, and preliminary data suggested an encouraging antitumor activity.

Key words: translational research, cancer stem cells, biomarkers, biotechnologies, adaptive trial designs.

INTRODUCTION

More than twelve million of new cases of cancer are diagnosed yearly, and a large percentage of cancer patients will die despite multimodal treatment including radical surgery, radiotherapy, systemic chemotherapy and targeted agents. Moreover, an increase in the number of new cancer diagnoses and a growing number of cancer survivors are expected in forthcoming years. As a result, it is estimated that cancer will exceed cardiovascular disease as the primary cause of mortality in Western Countries within the next decade, despite efforts in tobacco control and the widespread adoption of screening programs. Both the aging of the population and lifestyle factors will contribute to the overall increase in cancer incidence. With the global burden of the problem in mind, it is evident that additional human and financial resources must be brought into play in the fight against cancer. In the past, cancer research has been broken into two categories, basic and clinical. Even though basic research has broadened our knowledge in cancer biology, both some degree of experimental artifacts and the intrinsic complexity of many biotechnologies have limited the translation of preclinical findings into clinical studies. Clinical research, on the other hand, has traditionally focused on the evaluation of new treatment modalities, with little or no attention to molecular mechanisms of cancer. In recent years, it has become evident that the interaction between basic researchers and physicians can provide a more concrete way to really improve patients’ outcomes. Thus, the “translational research”, consisting in the integration of advancements in cancer molecular biology into clinical trials, by taking advantage of innovative technologies such as microarrays, genome sequencing and proteomic...
analysis, has gained identity (Figure 1). Although at early stage, this constant feedback has led to the identification of predictive biomarkers, new targets for anticancer drug development and new prognostic tools based on microarray technology. In this article are discussed the most relevant advances in cancer biology and treatment, resulting from “the bench to the bedside and back again” philosophy.

**CANCER STEM CELLS: TARGETING THE ROOTS OF CANCER**

More than a century ago Cohnheim and Durante postulated the “embryonal rest theory”, according to which adult tissues contain dormant embryonic remnants that, when activated, give rise to a tumor. This original view has been recently updated with the “cancer stem cell (CSC) hypothesis”, which implies that a stem cell is the initial target of the oncogenic process. Considering the high proliferative potential and the long life-span of stem cells, it is reasonable to assume that stem cells are more likely to undergo and accumulate genetic alterations than their differentiated progeny. The identification of stem cell-like, tumor-initiating cells led to the formulation of the “hierarchical model” of cancer in which, like in a normal tissue, undifferentiated cells are positioned at the apex of the pyramid. This model largely replaced the “clonal evolution model”, consisting in different dominant mutant clones endowed of self-renewal ability which compete with each other, according to darwinian principles, for vital resources. The CSC hypothesis has taken more concrete shape following the seminal paper of D. Bonnet and J. Dick, who prospectively isolated leukemia-initiating stem cells in the peripheral blood of acute myeloid leukemia patients [1]. Ever since, putative CSCs have been isolated from many solid tumors including colorectal cancer (CRC) [2], non-small cell lung cancer (NSCLC) [3] and glioblastoma multiforme (GBM) [4]. Operative properties of CSCs include a distinctive repertoire of cell surface markers, ability to grow as tumorspheres in suspension culture, tumorigenic capacity in immunocompromised mice and ability to generate a tumor closely resembling the parental one. From a functional point of view, CSCs share the general hallmarks of normal stem cells, including extensive proliferation, self-renewal ability and capability to differentiate into multiple lineages. Mounting evidences support the notion that these tumor-initiating cells hijack physiological stem cell signaling and, like its normal counterpart, require specialized microenvironments, named niches, which provide physical anchorage and govern the stem cell fate by controlling the self-renewal program. Thus, the current paradigm is that CSCs aberrantly use developmental regulatory molecules and pathways orchestrating the self-renewal program such as Wingless-type-β-catenin, Notch-Jagged, Hedgehog-Patched-Smoothened and Bone Morphogenetic Proteins. In line with this belief, the hedgehog pathway, for example, has been found to be reactivated in basal-cell tumor [5] and medulloblastoma [6]. The constitutive activation of this pathway is due to activating mutations in the positive regulator Smoothened homologue (SMO), or inactivating mutations in the negative regulator Patched homologue 1 (PTCH1). In a similar manner, the activation of the Wnt-β-catenin axis has been associated with hyperproliferation of intestinal crypt pro-

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**Fig. 1** The aim of translational research is to generate hypotheses for personalized anticancer medicine through a continuous interface between basic scientists and physicians. The creation of tissue banks and the functional characterization of human tumors through innovative animal models (cancer stem cell-derived xenografts) and high-throughput technologies permit to understand molecular forces governing a tumor, thus fostering optimal preclinical testing of pathway-targeted inhibitors. The identification of molecular parameters of response can be exploited for biomarker-driven clinical trials, thus allowing to test a given drug only in selected patients populations.
genitor cells, leading to colonic polyps [7]. In order to connect the biology of CSCs to the clinical course of tumors, some considerations have to be done. First, since circulating tumor cells in the peripheral blood and disseminated tumor cells in the bone marrow of early-stage cancer patients are often detectable, it is reasonable to assume that the acquisition of pro-metastatic traits is a more precocious event than thought in the recent past. Second, the pattern and the time of recurrence of many tumors, often in the order of years after the primary treatment, can be explained with a phenomenon known as “tumor dormancy”, consisting in the ability of disseminated cancer cells to remain in a quiescent state. Third, the failure of (neo)adjuvant chemotherapy and/or radiotherapy in eradicating minimal residual disease implies that a fraction of residual cancer cell is intrinsically resistant to radiotherapy- and chemotherapy-induced cell death. Biological properties of CSCs can explain, at least in part, both the early micro-dissemination of cancer cells and the failure of a multimodal therapeutic strategy. Cancer cells that undergo epithelial-to-mesenchymal transition (EMT) gain motility and metastatic proclivity in consequence of a drastic cytoskeletal rearrangement. The acquisition of this mesenchymal-like phenotype has been found to be associated with an increased ability to form spheres in suspension culture, an hallmark of CSCs [8]. Global gene expression profiling revealed that pathways correlated with the induction of the EMT, such as the transforming growth factor-β (TGF-β) pathway, are selectively deregulated in CSCs isolated from breast cancer (BC) but not in non-tumorigenic cells. Moreover, micrometastases from BC have been found to be enriched of CSCs, compared with the primary tumor [9]. These observations, together with the speculation that, like normal stem cells, CSCs could remain dormant within a protective microenvironment, enforce the assumption that a CSC is not only the tumor-initiating cell, but can also initiate a metastatic lesion and then thrive in a tumor-hostile microenvironment. With regard to anticancer therapy, the CSC pool is often enriched following exposure to different chemotherapeutic agents. Since chemotherapy is effective against active cycling cells, the capability of CSCs to remain in a quiescent state protect them against cytotoxic effects of antiblastic therapy. Moreover, additional mechanisms conferring chemoresistance have been described. Among these, the increased expression of multidrug-resistance proteins, an efficient DNA repair machinery and, finally, a proclivity towards an anti-apoptotic state [10]. Although resistant to current treatments, recent advances in CSCs biology have allowed a first wave of clinical trials with innovative pathway-targeted inhibitors targeting stemness-related signalings. GDC-0449 is a small-molecule inhibitor of SMØ, a key member of the hedgehog signaling pathway. Preliminary clinical data revealed an encouraging antitumor activity in locally advanced or metastatic basal-cell carcinoma [11] and in medulloblastoma. At the moment, GDC-0449 is undergoing Phase II studies in different solid malignancies, such as pancreatic adenocarcinoma (PAC) and GBM. As previously mentioned, the Notch-Jagged pathway is thought to be one of the major determinants in stemness maintenance. Gamma-secretase inhibitors act by blocking nuclear translocation of Notch receptors by preventing their gamma-secretase-mediated proteolytic cleavage and activation. Due to antitumor activity reported in preclinical model, gamma-secretase inhibitors are under clinical development. A first Phase II trials aiming at evaluating the gamma-secretase inhibitor MK-0752 as neoadjuvant therapy in combination with tamoxifen or the aromatase inhibitor letrozole has been started for treating patients with early, estrogen receptor- (ER) positive BC. A second investigational gamma-secretase inhibitor, RO4929097, is under clinical evaluation as a single agent in patients with recurrent or refractory NSCLC. Further clinical trials have been planned with the rationale to restore or improve chemosensitiveness. A Phase II study with XR9576, a selective multidrug resistance protein 1 (MRP1) inhibitor, aims at evaluating the ability of XR9576 to restore primary doxorubicin and taxane resistance in advanced BC. It is evident, however, that clinical trials assessing the efficacy of novel agents require optimal preclinical testing. The identification of CSCs able to reproduce the original tumor in immunocompromised mice might represent a stable system to investigate the efficacy of new compounds on a close simulation of a given patient tumor. Our preliminary results (unpublished data) suggest that CSC-derived xenografts faithfully replicate the patient tumor at signal transduction level. Notably, CSC-derived xenografts were more similar to human tumors than commercial cell line-derived xenografts. By way of summary, although CSCs are, probably, responsible for distant recurrence and the failure of systemic therapy, different pharmacological strategies including agents inhibiting stemness-associated pathways, agents able to restore sensitivity to chemotherapy and differentiation-inducing drugs might pave the way for an effective eradication of CSCs.

**EMERGING ROLE OF PREDICTIVE BIOMARKERS IN THE TARGETED THERAPY ERA**

Chemotherapy was the only therapeutic option for treating advanced/metastatic cancer patients for many decades. Despite the rapid increase of chemotherapeutic agents that have entered the therapeutic armamentarium, such as DNA-damaging agents, mitotic spindle poisons, anti-metabolites and oral agents, has allowed the introduction into the daily clinical practice of more effective and tolerated combinations, a “chemotherapy efficacy plateau” has been reached for many tumors. Advances in cancer biology clarified how tumor relies on peculiar mechanisms to survive, grow and metastasize in a foreign
soil. Neoangiogenesis, activation of mitogenic growth factor pathways and evasion of programmed cell death are among these. Such findings represented the rationale for the development of targeted agents able to specifically block one or more processes associated with cancer aggressiveness, thus representing a paradigmatic example of translating basic research into clinical practice. Most compounds are small molecule inhibitors or monoclonal antibodies which act by binding the tyrosine kinase domain of transmembrane receptors or their extracellular region, respectively. Receptors of the ErbB family, such as the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2/neu, also known as ErbB-2), currently represent the most characterized druggable targets. Among molecular targeted agents acting on ErbB family members are the anti-HER2 monoclonal antibody trastuzumab, approved for the treatment of BC patients [12], the anti-EGFR monoclonal antibodies cetuximab [13] and panitumumab [14] used for metastatic CRC (mCRC) and the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib [15] and gefitinib [16] for treating NSCLC patients. Targeting the tumor-supportive microenvironment has emerged as a key strategy for the development of anticancer therapy, as well. Neoangiogenesis, for example, is a critical process for survival and proliferation of primary tumors and metastases. Through neoangiogenesis cancer cells gain access to oxygen and nutrients and can enter the systemic blood circulation. This process is mainly sustained by the vascular endothelial growth factor (VEGF) and its cognate receptors (VEGFR), which trigger a multitude of proangiogenic activities ranging from endothelial cell survival to recruitment of endothelial progenitor cells from the bone marrow. The anti-VEGF monoclonal antibody bevacizumab is the antiangiogenic agent at the most advanced stage of clinical development, and it is routinely used for treating mCRC [17], BC [18], renal cell carcinoma (RCC) [19] and NSCLC [20]. Furthermore, dual or multiple kinase inhibitors such as lapatinib [21], sorafenib [22] and sunitinib [23] have entered the clinical practice, and many others are under late phases of clinical development. Finally, with the elucidation of the intracellular networks activated by transmembrane receptors, agents direct against intracellular effectors, such as the mammalian target of rapamycin (mTOR) inhibitors everolimus [24] and temsirolimus [25], have been recently approved by regulatory agencies for treating advanced or metastatic RCC. With the experience gained with the routinely use of targeted agents, oncologists have learned how these agents are effective only in a percentage of patients. In fact, although this remarkable progress has expanded the continuum of care concept, many patients fail to obtain a meaningful clinical benefit from targeted therapies despite the non-negligible risk of treatment-related adverse events. As a result, how to pinpoint the most appropriate treatment has become a significant effort has been devoted
FOLFIRI significantly increased response rate (59% vs 40%), progression-free survival (9.9 months vs 7.6 months), resectability of liver metastases and resulted in a trend towards a prolonged overall survival in patients with the wild-type gene compared with patients with mutated KRAS. Similarly, two randomized Phase III trials evaluating single-agent panitumumab or cetuximab versus best supportive care in chemorefractory mCRC patients demonstrated an advantage for anti-EGFR therapy exclusively in the non-mutant KRAS setting [31, 32]. Moreover, activating mutations in genes encoding BRAF and PI3K, key intracellular crossroads of the EGFR pathway, seem to be correlated with intrinsic resistance to anti-EGFR monoclonal antibodies. It is worth noting that predicting therapy-related side effects is as important as predicting its activity. Systemic therapy is often burdened by severe treatment-related adverse events, thereby jeopardizing patient adherence to medical therapy. If many patients, in fact, experience moderate side effects, a minority develops severe drug toxicity which can result even in cessation of treatment. In the FOCUS trial (Fluorouracil, Oxaliplatin, CPT-11: Use and Sequencing) authors also assessed putative pharmacogenetic biomarkers of toxicity [33]. Even if results do not support their routine use, also including the UDP glucuronyltransferase polymorphism UGT1A1*28 previously associated with severe irinotecan-related toxicity, this study provided a proof-of-concept for the introduction into clinical studies of biomarkers of toxicity. Considering the mounting enthusiasm regarding targeted agents and the need to overcome the “biomarker barrier”, innovative statistical designs within a framework consisting in high throughput technologies for biomarkers identification and validation have been recently proposed. These clinical trials are discussed in next paragraphs.

**ADDING “-OMICS” TO CLINICAL TRIALS**

In the past 10 years, the introduction of whole genome profiling technologies has greatly expanded our knowledge of genetic changes occurring in cancer and, more recently, commercialized multigene prognostic tests have provided a way to improve risk stratification of cancer patients. In such a scenario, early BC represents a working model for identification and validation of these prognostic and predictive tools. Traditionally, prognosis and treatment of early-stage BC are dependent on well-known clinical and pathological features, that have been combined in both the St. Gallen and National Institutes of Health (NIH) clinical guidelines, as well as in mathematical prediction models such as the Nottingham Prognostic Index and the Adjuvant! Online algorithm. Survival data, however, revealed a wide variability in BC course suggesting that molecular differences are responsible for such heterogeneity. This clinical heterogeneity was elucidated at the molecular level by Perou and coworkers through cDNA microarray analysis, who provided a “molecular portraits of BC” [34]. Hierarchical cluster analysis revealed the existence of four different molecular entities named luminal, normal breast-like, HER2 and basal-like, according to the resemblance between the genetic profiles of normal and neoplastic breast epithelial and mioepithelial cells. Thus, it is widely accepted that BC is constituted by different neoplastic diseases affecting the same anatomical region. Beside this molecular taxonomy, “gene signatures” are currently being assessed in large, prospective trials aiming at evaluating their contribution in the decision-making process. The MammaPrint® was the first BC prognostic signature described. This 70-gene signature is currently being assessed in a prospective, Phase III clinical trial named MINDACT (Microarray In Node negative Disease may Avoid ChemoTherapy) [35]. The MINDACT trial, sponsored by the European Organization for Research and Treatment of Cancer, is designed to compare the accuracy of the molecular test with that of the mathematical prediction model Adjuvant! Online in identifying low-risk patients who can be spared from chemotherapy. The Oncotype DX®, consisting in a panel of 21 genes, was validated in two prospective clinical trials (NSABP B-20 and B-14). The expression of these 21 genes is presented as a tripartite Recurrence Score (RS) predicting the risk of 10-year distant recurrence in ER-positive, lymph node-negative patients (low RS < 18, intermediate RS 18-31 and high RS ≥ 31). It is worth noting, however, that despite the Oncotype DX® has been included in both the American Society of Clinical Oncology (ASCO) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines for BC treatment, it should be used complementary to, and not instead of, clinical-pathological features. In addition, the management of patients with intermediate RS represents the main limitation of the Oncotype DX®. To assess the accuracy of the RS in this subset of patients, a large clinical trials named TAILORx (Trial Assigning Individualized Options for Treatment) has been started [36]. The TAILORx aims at evaluating whether intermediate risk, ER-positive patients benefit from adjuvant cytotoxic therapy or not. Next, given that the major implication of the CSC theory is that pathways controlling normal stem cells are deregulated in their malignant counterpart, high-throughput technologies might capture a snapshot of deregulated stemness-associated genes. The invasiveness gene signature (IGS) is a prognostic assay consisting of 186 differentially expressed genes in BC tumor-initiating cells compared with normal breast epithelium [37]. Designed for both node-negative and node-positive and both ER-negative and ER-positive patients, the IGS was significantly associated with overall and metastasis-free survival and, moreover, it seems to predict prognosis also in lung and prostate cancers. It is important to mention, however, that cancer relies on a supportive microenvironment, consisting in a variety of mesenchymal and inflammatory cells, to survive and grow. As a result of the constant cancer-stroma interplay...
both compartments co-evolve, and cancer cells finally acquire metastatic proclivity. Among cell types co-habitating tumor microenvironment, carcinoma-associated fibroblasts (CAF) are thought to be the main actors. Based on functional analogies described between tumor stroma and the wound healing process, a fibroblast core serum response (CSR) signature was identified. Notably, this “wound-response signature” has been demonstrated to be an independent predictor of metastasis in BC patients, and to improve the risk stratification obtained with the NIH or St. Gallen consensus criteria [38]. Similar to BC, the identification of patients having a high likelihood to experience distant recurrence following radical surgery and adjuvant chemotherapy assumes a dramatic magnitude in stage II and III CRC. Approximately 65% of CRC patients, in fact, present with stage II or III disease at the diagnosis time and, despite an integrated therapeutic approach, the 5-years disease-free survival is in the range of 50-84% depending on disease stage (stage II vs stage III) and type of adjuvant chemotherapy (5-FU/LV vs FOLFOX). Moreover, the net benefit of adjuvant chemotherapy over surgery alone is in the range of 3-7%, and there is no international consensus about the role of adjuvant chemotherapy in stage II disease. The definition of “high risk stage II” is, in fact, largely empiric being dependent on clinical factors including inadequate lymph node sampling, T4 tumor, perforation, poorly differentiated tumor, comorbidities and life expectancy. In order to overcome the drawback of a prognostic judgment exclusively based on clinical and pathological features, a quantitative multigene RT-PCR assay has been prospectively validated in a large clinical study in stage II CRC patients. Results of the study indicated that the “colon cancer recurrence score” is an independent predictor of the recurrence risk [39]. Although microarray analysis of gene expression patterns has gained identity as integral part of clinical trials, these tools offer an incomplete picture of protein-protein interactions. Taking into account that the majority of innovative agents are pathway-targeted inhibitors, transcriptional profiling lacks the accuracy required to identify dysfunctional pathway nodes. In fact, post-translational modifications such as phosphorylation, cleavage and ubiquitination make minimal that absolute correlation between the mRNA expression level and the corresponding protein level. Moreover, it is estimated that the multitude of altered genes found in tumors functionally affect a limited number of signaling pathways. Given this new perspective of cancer as a “pathways disease”, proteomic analysis has recently emerged as an excellent tool to define protein interaction networks. Among technologies developed for this purpose, reverse-phase protein microarrays (RPPM), coupled with laser capture microdissection (LCM), allow to simultaneously map entire protein networks in small-volume samples. Recent studies that adopted a RPPM-based approach to evaluate the activation (phosphorylation) state of signaling pathways have paved the way for a rational use of RPPM in clinical studies. A Phase I/II study named NITMEC (New Individualized Therapy Trial for Metastatic Colorectal Cancer), for example, aims at assessing the efficacy of imatinib mesylate plus panitumumab in KRAS wild-type, chemo-refractory mCRC patients. The study was planned based on the preferential activation of the molecular targets of imatinib mesylate (c-Kit, abl and PDGFR) found in mCRC. Recently, RPPM has been used to dissect the functional role of different phosphorylation sites of EGFR in human NSCLC of known EGFR mutation status [40]. What emerged was that the alteration of multiple phosphorylation sites of EGFR functionally results in activation of the PI3K/AKT/mTOR pathway, altered heterodimerization with HER2 and reduced ubiquitination/degradation of EGFR. Thus, functional proteomic analysis can provide, on the one hand, information about signalings correlated with tumor aggressiveness and, on the other hand, key notions for a rational combination of targeted agents. As a result, proteomic analysis represents a promising tool for identifying mechanisms conferring de novo and acquired resistance to targeted and cytotoxic therapies, as well as for assessing the antineoplastic activity of new agents, as a monotherapy or in combination, in a personalized manner.

**INNOVATIVE CLINICAL TRIAL DESIGNS FOR PREDICTIVE BIOMARKERS VALIDATION: TOWARDS PERSONALIZED ONCOLOGY**

With the advent of targeted therapies the identification of predictors of efficacy and safety, based on the genetic asset of tumor and the genotype of the patient, has become an urgent issue for customizing treatment of cancer patients. However, the validation of biomarkers in clinical trials remains a challenge, in large part due to the optimal choice of marker assessment methods and the elucidation of the exact mechanism of action of new drugs. Thus, an essential step towards the goal of personalized oncology is the implementation of trial design strategies which allow a rapid evaluation of biomarker-driven therapy. If retrospective validation may be useful in selected circumstances, randomized controlled trials represent the gold standard for prospective validation of biomarkers. Among different strategies proposed for this purpose, adaptive analysis designs are emerging as innovate clinical trials for a rapid clinical development of new therapies paired with biomarkers identification/validation. In these studies, multiple targeted therapies are studied simultaneously, and patients are assigned to receive a certain agent on the basis of the molecular characteristics found in tumor tissue. The I-SPY 2 study (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis 2), for example, consists in an adaptive, Phase II, neoadjuvant trial for women with locally advanced BC (> 3.0 cm).
Multiple innovative targeted agents will be added to standard therapy, and the pathologic complete response rate of such combinations will be compared with that obtained with standard-of-care therapy consisting in weekly paclitaxel (plus trastuzumab for HER2+ patients) followed by doxorubicin and cyclophosphamide. Among novel drugs, in the I-SPY 2 study will be evaluated inhibitors of insulin growth factor receptor (IGFR), mTOR, cMET, HER2, Hedgehog and Notch. The goal of the study is to test the efficacy of different new regimens according with molecular characteristics of each tumor. Three distinct classes of biomarkers have been considered in the I-SPY2. Standard biomarkers are those accepted and approved by regulatory agencies such as HER2 status, hormone receptor status and MammaPrint. Qualifying biomarkers are those not yet approved but that seem to be promising for measuring treatment response and, finally, exploratory biomarkers are those which are thought to be predictive or prognostic. Among different techniques that will be adopted to validate biomarkers and to determine treatment assignment are microarray analysis, RPPM, microRNAs, single-nucleotide polymorphisms and circulating tumor cells. Thus, the study is designed to “learn” over time which profiles predict the response to each drug. An adaptive randomization scheme has been also used in the BATTLE study (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) in which four treatments, consisting in erlotinib, sorafenib, vandetanib and erlotinib with bexarotene have been planned. In addition to EGFR mutations, KRAS/BRAF mutations, VEGFR-2 expression and RXR/Cyclin D1 expression have been selected as biomarkers for treatment assignment.

CONCLUSIONS
With the increasing complexity of our notions on cancer biology, the advent of targeted therapies and the need to treat each patient according with the molecular asset of tumor, it has become evident that the creation of multidisciplinary teams in which oncologists, basic researchers, biostatisticians and bioinformatics act together has become a priority, as well as the increasing cooperation with the pharmaceutical industry. The identification of cancer-initiating cells, for example, has gone beyond the basic research and it is rapidly becoming a benchmark for many studies of translational oncology, as demonstrated by the validation of CSC-based signatures, the prognostic significance of CSCs detected within the tumor and the growing interest about molecular targeted agents acting on key stem cell pathways, which have recently entered clinical development. In addition, it is worth noting that the advent of molecular targeted agents has been a driving force towards the identification of predictors of response. The most representative examples concern the role of EGFR-activating mutations and the KRAS status. Moreover, if in the recent past the use of high-throughput technologies was limited, nowadays these tools are integral part of clinical trials, as corroborated by the fact that some “signatures” have been approved by the Food and Drug Administration in order to provide, combined with clinical and pathological features, a more accurate prognostic assessment. These collaborative efforts have recently culminated in clinical studies in which, within the framework of innovative technology platforms, multiple molecular targeted agents are tested with the specific aim of identifying biomarkers predictive of response, thus sharpening the potential of established and forthcoming targeted therapies. The advantages of such studies are guessable, since they can allow to administer a certain drug only to patients whose tumors express the molecular target and, at the same time, can significantly shorten the duration of Phase III trials.

Conflict of interest statement
There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Submitted on invitation.
Accepted on 20 September 2010.

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