Depicting the evolving scenario of translational-guided drug development

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The development process of most important targeted agents currently used in oncologic clinical practice has unveiled the fact that using these types of drugs efficaciously is best supported by the availability of appropriate predictive biomarkers. Conversely, the magnitude of the effect obtained from administering such drugs to patients that respond to them on the basis of known biomarkers is likely to be diluted by concomitantly administering the drugs to an unselected patient population as well. This scenario could compromise the future of bona fide compounds due to the bias of non-selection when measuring drug benefit.

Usually this agent-biomarker matching process and its approval based on positive indications of spent takes in identifying a rational biomarker, and then the back end process of validating the assay used to measure it. In this regard, Bando and collaborators compare, in this issue of the journal, the three methods for determining *KRAS* mutation in colorectal carcinoma with the goal of delineating the best test for this purpose.

The history of the role of *KRAS* mutations in metastatic colorectal carcinoma well illustrates the diverse processes underlying predictive biomarker identification for anti-neoplastic targeted agents during the last 20 years, as reviewed in Table 1.

Mutations in codons 12, 13, 61 and 126 of the *KRAS* protein were accepted as determinants of resistance to treatment with anti-epidermal growth factor receptor monoclonal antibodies (anti-EGFR MoAbs) in colorectal carcinoma, years after cetuximab was first granted approval for its treatment by regulatory agencies [1, 2]. At that time, the development of anti-EGFR MoAbs was focused on EGFR amplification and overexpression as the primary characteristics for selecting patients for clinical trials [3, 4]. The discovery of the role of *KRAS* mutations redirected the development plans for these compounds, causing some ongoing clinical trials to be amended to exclude patients with *KRAS* activating mutations. When this new approach was instituted, clinical endpoints were successfully met, leading these drugs to broad approval in many clinical settings of colorectal carcinoma.

This example and other successes resulting from the correct implementation of translational research data in clinical trials have shifted the panorama of drug development (Table 1). Accordingly, we have witnessed in the last decade clinical and translational research in oncology being brought closer together in a process intended to develop in parallel the best targeted agents and to align them with the best predictive biomarkers to guide their use starting with in early phases of the drug development process. This rapprochement bridging the gap between research and clinical application has modified both arenas. Such alignment is shown not only in the increasing number of research institutes linked to health care facilities but also by the changes that phase 1 clinical trial units have undergone [5].

In keeping with this trend, the search for biomarkers of drug effect (pharmacodynamic markers) and identification of potential target subpopulations of patients that, until recently, has occurred only in the last phases of drug

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Table 1 Approved biomarker-drug pairs used on normal clinical practice in oncology

Biomarker	Assay	Drug	Target	Disease
HER2 expression/amplification	IHC, FISH	Trastuzumab	HER2	Breast carcinoma and gastric adenocarcinoma
Estrogen receptor expression	IHC	Tamoxifen, aromatase inhibitors	Estrogen receptors	Breast cancer
<i>EGFR</i> mutation codon 19, 21	PCR, Sanger	Gefinitinib, erlotinib	EGFR	Lung adenocarcinoma
<i>KRAS</i> mutation codons 12, 13, 61	Sanger, PCR	Cetuximab, panitumumab	EGFR	Colorectal carcinoma
<i>BRAF</i> mutation V600E	PCR	Vemurafenib	BRAF	Melanoma
<i>CKIT</i> mutation	PCR	Imatinib	CKIT	GIST
PDGFR mutation	PCR	Imatinib	PDGFR	GIST
<i>MLL4-ALK</i> translocation	FISH	Crizotinib	ALK	Lung adenocarcinoma

HER2 human epidermal growth factor 2, *EGFR* epithelial growth factor receptor, *KRAS* Kirsten rat antigen sarcoma protein, *PDGFR* platelet-derived growth factor receptor, *MLL4* echinoderm microtubule-associated protein-like 4, *ALK* anaplastic lymphoma kinase, *IHC* immunohistochemistry, *FISH* fluorescence in situ hybridization, *PCR* polymerase chain reaction, *GIST* gastro-intestinal stromal tumor

development, is currently shifting to early clinical trials. Thus, phase 1 studies are progressively occupying a more central role in the development plan of new agents. Recent examples of this evolution are ALK inhibitors in non-small cell lung cancer and BRAF inhibitors in melanoma [6, 7]. Current phase 1 clinical trials are being designed to emulate these successful outcomes, enriching the participant population according to pre-specified exploratory biomarkers to identify trends and signals that can define responding patient populations at the beginning of the early drug development process. This phenomenon requires several decisions to be made. During the trajectory of a given disease when should the patients be screened? Which genetic and epigenetic determinants should be analyzed and which technology is best suited to these purposes? In early drug development, biomarkers are explored as potential predictive markers, leaving the validation of sensitivity, specificity and reproducibility of determination assays for later stages when the relationship between biomarker and response of a given compound has already been determined.

As outlined above, we have transitioned from a clinically directed drug development approach in which responses to drugs in specific tumor types guided the next steps of experimentation to a translational guided scenario in which the predictive biomarkers and drugs are co-developed from the beginning of drug development until drug approval [8]. However, the increasing role translational research has gained toward defining a more extensive characterization of tumors has to be balanced by potential disadvantages to cancer patients that this evaluation process may cause. Institutions dealing with advanced cancer patients must ensure that the patient remains at the center of the stake. It is important not to lose

sight that the fundamental basis driving translational research and drug development is to develop better therapies for patients who are likely to respond to them. What is novel is that emerging new drugs (or revisited old drugs) are enhanced by knowledge of the molecular biology of the disease as well as the capacity to molecularly profile the tumor. These improvements in drug development are increasingly offered to cancer patients who could benefit from them. One of the risks of this approach is to transform the hospitals in basic research institutes. It is the responsibility of the physicians at the helm of these research institutions as well as individual investigators to safeguard patient care and arbitrate in favor of the best interests of the patients they serve.

Conflict of interest None.

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