Agnostic-Histology Approval of New Drugs in Oncology: Are We Already There?
Cinta Hierro1,2, Ignacio Matos1,2, Juan Martin-Liberal2,3, Maria Ochoa de Olza1,2, and Elena Garralda1,2

Abstract

Over the last several years, several molecular aberrations have been unevenly described across cancers, although the distinct functional relevance in each biological context is not yet fully understood. Novel discoveries have led to the development of drugs tailored to the molecular profile of patients, thus increasing the likelihood of response among biomarker-selected patients. In this context, there has been a progressive redefinition of a precision medicine framework where evidence-based development and earlier approvals might now be driven by this molecular information. Innovative trial designs have greatly facilitated the evaluation and approval of new drugs in small cohorts of orphan cancers in which histology-dependent molecularly defined trials might be logistically difficult. However, accelerated approvals based on this agnostic-histology development model have brought new clinical, regulatory, and reimbursement challenges. In this article, we will highlight many of the biologic issues and clinical trial design challenges characterizing the development of tissue-agnostic compounds. Also, we will review some of the key factors involved in the development of pembrolizumab and larotrectinib, the first two drugs that have been approved by the U.S. Food and Drug Administration in an histology-agnostic manner. Because we anticipate that agnostic-histology approvals will continue to grow, we aim to provide insight into the current panorama of targeted drugs that are following this strategy and some premises to take into consideration. Clinicians and regulators should be prepared to overcome the associated potential hurdles, ensuring that uncertainties are dealt with properly and allowing new, promising agents to arrive faster to the market.

Introduction

In recent years, advances in high-throughput technologies have yielded impressive insights into the molecular biology behind cancers. Novel discoveries have resulted in the development of several innovative drugs, representing a paradigm shift in the oncology early drug development panorama (1, 2). Cancer-omics have become a powerful ally for applying biomarkers and focusing clinical development in molecularly selected populations, although they have also brought another layer of complexity (3).

In consequence, we are witnessing the emergence of a new era characterized by the recognition of tumors as genetic diseases, accelerating the development timings from the molecular aberration discovery to the approval of new drugs (Fig. 1; ref. 4). Although more clinical evidence-based information is gathered, several classifications have been developed to guide clinicians to prioritize molecular biomarkers to tailor patients with the most appropriate targeted agents [e.g., European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT); ref. 5]. In this context, histology-agnostic trials might represent the ideal scenario for gaining a better understanding of the functional relevance of a certain molecular aberration across multiple tumor types (6).

In this article, we will review the clinical development of a number of compounds that were early assessed in anagistic-histology trials and which lessons were learnt from these initial studies. Moreover, we will then depict the key factors involved in the development of pembrolizumab and larotrectinib, the first drugs approved by the U.S. Food and Drug Administration (FDA) in an histology-agnostic manner, although not yet by the European Medicines Agency. Finally, we aim to provide insight into the current panorama of promising drugs that are following this strategy and its associated potential hurdles.

Where Do We Come From?

The biological relevance of molecular aberrations and the response to targeted agents can substantially differ depending on tumor type (7). Two of the most illustrative cases are the development of the v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) and the HER2 inhibitors.

The BRAF inhibitor (BRAFinh) vemurafenib, showed encouraging efficacy among patients with melanoma enrolled in a phase I trial (81% complete or partial response; ref. 8). Posterior identification of reactivation of the mitogen-activated protein kinase (MAPK) pathway as an escape mechanism led to the approval of an evidence-based combination strategy of BRAFinh and mitogen-activated extracellular signal-related kinase (MEK) inhibitors for BRAF mutant (BRAFmut) patients with melanoma (9). This combined approach drastically changed the outcome...
of this disease. However, only 5% of BRAFmut patients with colon cancer responded to BRAFinh monotherapy, translating the heterogeneous pattern of BRAF activation within this histology (10). Further preclinical insights evidenced that the BRAFinh effect could be rapidly bypassed by ERK reactivation through an EGFR-mediated activation of RAS and C-RAF (11, 12). Unfortunately, triple strategies of BRAF/MEK/EGFR inhibition have not paralleled the efficacy reached in melanoma, mainly due to the continued adaptive feedback reactivation of the MAPK signaling in the colorectal cancer context (13).

Similarly, the VE-Basket trial testing vemurafenib in BRAFmut V600 non-melanoma cancers, reported isolated responses among a myriad of tumor types (14). Non–small cell lung cancer (NSCLC) cases and patients with Erdheim-Chester disease (ECD) seemed to retain clear oncogene-addiction to BRAFmut, achieving an overall response rate (ORR) of 42% [95% confidence interval (CI), 20–67] and 43% [95% CI, 18–71], respectively. Remarkably, the results of this study led to the FDA approval for vemurafenib in ECD in 2017 (15). Furthermore, the study highlighted that BRAFinh would not act homogenously across histologies, since depending on the biological role of BRAF, distinct resistance mechanisms might develop.

Another example worth mentioning is the case of HER2 inhibitors (HER2inh). Trastuzumab, the first humanized HER2-directed monoclonal antibody (mAb), received FDA approval after demonstrating survival benefit for patients with HER2-amplified (HER2amp) metastatic breast cancer (16). In 2010, trastuzumab also showed increased overall survival (OS) from...
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11.1 to 13.8 months [hazard ratio (HR) for death 0.74; 95% CI, 0.60–0.91; P = 0.0046] in patients with HER2amp gastroesophageal cancer (GE) in the ToGA trial (17). The HERACLES study demonstrated that the combination of lapatinib plus trastuzumab was active in a subset of HER2amp patients with refractory colorectal cancer (5%), achieving an ORR of 30% (95% CI, 14–50; ref. 18). Noteworthy, low prevalence of HER2amp has also been reported among other miscellaneous tumor types, thus encouraging the research of novel HER2inh beyond the classical indications. ZW25, a bispecific antibody targeting EC22–EC24 HER2 domains, showed a disease control rate (DCR) of 33% in non-breast/GE tumors overexpressing HER2 (19). Also, trials testing different antibody–drug conjugates, such as ado-trastuzumab emtansine (T-DM1; ref. 20) and trastuzumab deruxtecan (DS-8201a; ref. 21), have confirmed clinical activity of the HER2 blockade among other HER2-expressing cancers (e.g., salivary gland).

Lately, rising evidence of mutations in HER2 (HER2mut) widened further exploration of anti-HER2 therapies (22). The MOSCATO-01/02 trials showed that the clinical benefit rate (CBR) to HER2 blockade for HER2amp patients was significantly higher (CBR 64%) compared with those HER2mut (CBR 25%; ref. 23). In the SUMMIT trial, patients with HER2/3mut across 21 tumor types were treated with neratinib, a pan-HER multitarget kinase inhibitor. No activity was observed in the HER3mut cohort. On the contrary, among HER2mut patients (n = 124), responses were reported among NSCLC, breast, biliary, salivary and cervical cancers, with the greatest activity being seen in kinase domain missense mutations. To date, this study has provided the most comprehensive data that exist on the differential clinical actionability of HER2/3mut (24).

Several concepts were learnt from these initial trials developing BRAFinh and HER2inh. First, it became clear that the molecular status alone is not enough to predict response, as the signaling pathway might play different roles in each specific histologic context, where different mechanistic explanations could mediate resistances. Second, the results revealed that efficacy might be influenced by the class of molecular alteration (amp > mut), the involved gene (HER2 > HER3) or, the type of allele (mut in the kinase domain > frameshifts in receptor domain). Finally, these studies demonstrated that molecularly guided trials could be used to refine our biological understanding of targets, and that conventional cancer therapy should not be solely replaced by the molecular findings. Investigators should be careful when extrapolating the outcomes seen with one drug from one cancer to another, keeping in mind that significant differences exist between different histologies, and profound heterogeneity has been observed even within one same cancer type.

Where Do We Stand Now?

Microsatellite instability-high (MSI-H) tumors can have up to eight times more somatic mutations than microsatellite stable (MSS) cancers, translating into a higher presence of neoantigens able to trigger an immune response (25). Checkpoint blockade with anti-programmed death-1 (PD-1) antibodies was hypothesized to enhance immune responses in MSI-H/deficient mismatch repair (dMMR) tumors, supported by the idea that a higher mutational load was correlated with responses in melanoma (26) and NSCLC (27). All these observations provided the incentive for the development of the KEYNOTE-016 trial, which selectively investigated pembrolizumab in MSI/dMMR patients.

Patients with dMMR colorectal cancer, mismatch repair-proficient (MMR) colorectal cancer, and patients with dMMR non-colorectal cancer refractory cancers were enrolled in the KEYNOTE-016 study. The co-primary endpoints were immune-related objective response rate (irRR) and 20-week immune-related progression free survival (irPFS) rate. irRR were 40% and 71% for patients with dMMR colorectal cancer and dMMR non-colorectal cancer tumors, respectively. The median progression-free survival (mPFS) and mOS were not reached at the time of the report, and the irPFS rates were 78% for the dMMR colorectal cancer cohort and 67% for the dMMR non-colorectal cancer group. Noteworthy, the efficacy among MMR colorectal cancer was meaningless, with 0% irRR, 11% irPFS, and a mOS of 5 months (HR, 0.22; P = 0.05). Whole-exome sequencing (WES) revealed that dMMR tumors presented almost 24 times more somatic mutations compared with MMR ones (P = 0.007). As expected, higher mutation loads were associated with prolonged mPFS (P = 0.02; ref. 28).

In addition to KEYNOTE-016 (n = 58), two subsequent studies also provided robust evidence of antitumor activity of pembrolizumab and durable responses in heavily pretreated dMMR patients. The KEYNOTE-164 trial enrolled patients with MSI-H colorectal cancer who had received at least 2 prior lines of therapy (n = 61), whereas the multi-cohort KEYNOTE-158 study included patients with MSI-H non-colorectal cancer treated with at least one prior regimen (n = 19; refs. 29, 30). Furthermore, patients with PD-L1–positive tumors and MSI-H enrolled in phase 1 studies assessing pembrolizumab were retrospectively identified [KEYNOTE-012, n = 6 (refs. 31–33); KEYNOTE-028, n = 5 (refs. 34–38)].

On May 23, 2017, the FDA granted the accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic refractory MSI-H/dMMR tumors. The first FDA tissue-agnostic approval became a reality, based on 149 patients with MSI-H/dMMR tumors across the five uncontrolled, single-arm trials depicted in Table 1 (ref. 39). ORR was similar irrespective of the origin (36% in colorectal cancer vs. 46% in 14 other cancer types). Despite this accelerated approval, continued approval of pembrolizumab for this indication will rely on the final results of clinical benefit in the ongoing confirmatory trials.

What have we learnt from this historical approval? First, a strong biologic preclinical and clinical rationale was needed, ensuring the homogeneity of effects of this alteration among different tissues. In this case, MSI tumors were found across multiple histologies at varying frequencies (40), sharing common features known to be predictive of response to immunotherapy, such as PD-L1 expression, high tumor mutational burden (TMB) and lymphocyte T infiltration (41). Also, MSI tumors undergo immune-editing processes that provide them with genetic advantages for immune escape, most likely a common resistance trait across MSI cancers (42). Second, it was important to measure the expected efficacy with a reliable endpoint, facilitating the interpretation of results across histologies inside one trial and between studies. Noteworthy, similar ORR and OS/PFS rates were reported in at least 14 tumor types in the pooled analysis for pembrolizumab, with no differential pattern of efficacy indicating a histology qualitative effect (29). Third, a truly agnostic indication would embrace the treatment of both, adult and pediatric patients, ensuring an appropriate formulation for the younger. In fact, the biology of MSI-H/dMMR was expected to be similar in
Table 1. Studies that supported the agnostic-histology approval of pembrolizumab for MSI-H/dMMR solid tumors by the FDA

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Prior therapy</th>
<th>Tumors</th>
<th>N</th>
<th>MSI-H/dMMR testing</th>
<th>Dose</th>
<th>ClinicalTrial.gov ID</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-016</td>
<td>Investigator-initiated ph2 at 6 sites</td>
<td>≥ 2 prior regimen</td>
<td>Multiple</td>
<td>58</td>
<td>Local PCR or IHC</td>
<td>10 mg/kg every 2 weeks</td>
<td>NCT01876511</td>
<td>(28–30)</td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>International and multicenter ph2</td>
<td>≥ 2 prior regimen</td>
<td>CRC</td>
<td>19</td>
<td>Local PCR (central for non-CRC rare tumors) or IHC</td>
<td>200 mg every 3 weeks</td>
<td>NCT02628067</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-164</td>
<td>International and multicenter ph2</td>
<td>≥ 2 prior regimen</td>
<td>CRC</td>
<td>61</td>
<td>Central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>NCT01848834</td>
<td>(31–33)</td>
</tr>
<tr>
<td>KEYNOTE-012</td>
<td>Multicenter ph1b</td>
<td>≥ 2 prior regimen</td>
<td>Gastric, bladder, or TNBC</td>
<td>6</td>
<td>Central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>NCT02054806</td>
<td>(34–38)</td>
</tr>
<tr>
<td>KEYNOTE-028</td>
<td>Multicenter ph1</td>
<td>≥ 2 prior regimen</td>
<td>Esophageal, CRC, breast, endometrial, or biliary</td>
<td>5</td>
<td>Central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>NCT01848834</td>
<td>(34–38)</td>
</tr>
</tbody>
</table>

Where Do We Go?

Pembrolizumab was the first tissue-agnostic drug approved but larotrectinib was the first drug developed with an agnostic-histology indication in mind. The truth is, gene fusions have emerged as an important class of somatic alterations, acting as oncogenic drivers in approximately 16.5% of human cancers (49). It is understandable then that these druggable fusions have focused the attention of the clinical research field.

Pooled data from phase I/II entrectinib trials showed an ORR of 57.4% (95% CI, 43.2–70.8) among NTRKrear adult patients from 19 different histopathologies, also with durable intracranial responses (54.5%; ref. 50). In parallel, the discovery of early acquired mechanisms of resistance, has led the fast development of successful second-generation TRKinhibitors [e.g., lorlatinib (ref. 51), repotrectinib (ref. 52) or merestinib (ref. 53)]. Moreover, debio1347, a selective FGFR1/2/3 inhibitor (FGFRinh), showed promising efficacy among patients harboring fibroblast growth factor receptor (FGFR) fusions. A DCR of 87% was reported in 5 different histologies with FGFRrear (n = 8; ref. 54). In view of these results, other “basket” trials are further developing FGFRinh in this difficult-to-find FGFRrear population (e.g., TAS-120; pediatric tumors (43), and there was an already established dose of pembrolizumab for pediatric Hodgkin lymphoma (KEYNOTE-051 study; ref. 44). Finally, the possibility of identifying those patients whose tumors harbor the predictive biomarker with a validated companion diagnostic is a key limiting factor for ensuring the attrition of patients. In this case, immunohistochemistry (IHC) testing or polymerase chain reaction (PCR)-based assays were commercially available (45).

Following the approval of pembrolizumab, another milestone revolutioned the agnostic-histology scene in 2017. Patients with neurotrophin tropomyosin receptor kinase (NTRK) rearranged (rear) tumor types were prospectively identified and enrolled into the adult phase I (n = 8) or “basket” phase II (n = 35), and the pediatric phase I/II (n = 12) trials evaluating larotrectinib, a first-in-class pan-TRK inhibitor (TRKinh; ref. 46). The ORR was 75% (95% CI, 61–85) among 12 different histologies, ranging in ages from 4 months to 76 years. The most common cancers were salivary gland (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%) and thyroid (9%). Surprisingly, larotrectinib demonstrated clinical benefit regardless of tumor type, NTRK gene, fusion partner or age of the patient. Also, encouraging central nervous system activity was seen in primary malignancies and metastatic lesions, with rapid and prolonged responses. On the basis the results of these 55 patients, on November 26, 2018, the FDA granted accelerated approval of larotrectinib for the treatment of adult and pediatric NTRKrear tumors (47).

Interestingly, the treatment of larotrectinib has been approved based on the presence of a NTRKrear in tumor specimens. However, unlike the approval of pembrolizumab for MSI-H/dMMR tumors, there is not an FDA-approved test for the detection of NTRKrear. Recently, updated results of efficacy with larotrectinib were presented with the expanded 122-patient integrated dataset, showing an ORR of 81% (95% CI, 72–88). Remarkably, 84% of the responding patients and 73% of all patients remained on larotrectinib or underwent surgery with curative intent (48). These highly consistent results might have fostered the approval of larotrectinib, allowing the detection of NTRKrear based on local NGS or FISH.

Are We Ready for Agnostic-Histology Approvals in Oncology?

Abbreviations: Anti-VEGF/EGFR mAb, anti-vascular endothelial growth factor/epidermal growth factor receptor mAb; CRC, colorectal cancer; IHC, immunohistochemistry; N, number of patients enrolled; PCR, polymerase chain reaction; ph1, phase I clinical trial; ph2, phase II clinical trial; Ref, Reference; TNBC, triple-negative breast cancer.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>FDA Status</th>
<th>EMA Status</th>
<th>ClinicalTrial.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debio1347</td>
<td>FGFR1/2/3</td>
<td>Ph1/2</td>
<td>Fast Track designation for tumors with specific FGFR alteration. Orphan Drug designation for BTC.</td>
<td>NCT01948297</td>
</tr>
<tr>
<td>TAS-120</td>
<td>FGFR1/2/3/4</td>
<td>Ph1/2</td>
<td>Orphan Drug designation for iCCA.</td>
<td>NCT02052778</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>TRK</td>
<td>Ph2</td>
<td>Accelerated Approval. Marketing Authorization Application submitted.</td>
<td>NCT02576431</td>
</tr>
<tr>
<td>Entrectinib (RXDX-101)</td>
<td>TRK/ALK/ROS1</td>
<td>Ph2</td>
<td>Orphan Drug designation for adult/children with NTRK rearranged solid tumors. Priority Medicines designation for adult/children with NTRK rearranged solid tumors.</td>
<td>NCT02568267</td>
</tr>
<tr>
<td>Merestinib (LY2801653)</td>
<td>TRK/MET</td>
<td>Ph2 in NSCLC MET exon 14 mut or &quot;basket&quot; for NTRK rearranged solid tumors. Orphan Drug designation for BTC.</td>
<td>NCT02920996</td>
<td></td>
</tr>
<tr>
<td>Repotrectinib (TPX-0005)</td>
<td>TRK/ALK/ROS1</td>
<td>Ph1/2</td>
<td>Orphan Drug designation for NTRK/ALK/ROS1 rearranged NSCLC.</td>
<td>NCT03093116</td>
</tr>
<tr>
<td>Loxo-195</td>
<td>RET</td>
<td>Ph1/2 in adult and children previously treated with NTRK or RET cancer. NDA accepted and granted Priority Review for adults and children with NTRK or RET cancer.</td>
<td>NCT03215511</td>
<td></td>
</tr>
<tr>
<td>Loxo-292</td>
<td>RET</td>
<td>Ph1 in patients with advanced solid tumors. Breakthrough designation for RET rearranged NSCLC and RET mut MTC.</td>
<td>NCT03157128</td>
<td></td>
</tr>
<tr>
<td>Agerafenib (RXDX-105)</td>
<td>RET/BRAF</td>
<td>Ph1/1b</td>
<td></td>
<td>NCT01877811</td>
</tr>
<tr>
<td>BLU-667</td>
<td>RET</td>
<td>Ph1 in RET-altered solid tumors and MTC.</td>
<td>NCT03037385</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; BTC, biliary tract cancers; EMA, European Medicines Agency; iCCA, intrahepatic colangiocarcinoma; MTC, medullary thyroid cancer; mut, mutant; N/E, not evaluated; NDA, New Drug Application; Ph1, phase I clinical trial; Ph2, phase II clinical trial; rear, rearranged.
Later this year, the RET inhibitor (RETinh) loxo-292 showed an encouraging ORR of 77% (95% CI, 61–89) in RETrear evaluable tumors (77% in NSCLC and 78% in other cancers), including intracranial responses in NSCLC (56). Also, many other promising compounds are focusing their development in this small RETrear population [e.g., agerafenib (ref. 57) and BLU-667 (ref. 58)]. With the arrival of these best-in-class molecular targeted agents (MTA), the early drug development panorama is becoming increasingly busy, and what matters most, it seems more promising than ever. Table 2 summarizes the current approval status of some of these MTA.

With the increasing evidence of immune-predictive biomarkers commonly displayed by cancers, tissue-agnostic development is focusing on the immune-checkpoint inhibitors arena (59). In

**Figure 2.** Integration of clinical-translational strategies into precision medicine drug development. Sophisticated master protocols are currently being used in the early drug development of new molecularly targeted drugs. "Umbrella" trials serve to study multiple targeted therapies in the context of a single disease (e.g., TRK/FGFR/RETinh in a specific tumor type). “Platform” trials have evolved as a more adaptable design, also aiming to study multiple targeted therapies in the context of a single disease but allowing therapies to enter or leave the platform on the basis of preclinical or clinical data becoming available throughout the study. "Basket" trials test a particular targeted therapy among patients that share a common molecular aberration (colored stars) across multiple cancer types (e.g., TRKinh in multiple histologies). These precision medicine approaches arise as the ideal scenario for implementing smart translational programs, based on the acquisition of biological samples from molecularly selected extraordinary responders. The collection of serial tumor biopsies and plasma samples, allowing the generation of patient-derived xenografts (PDX), has emerged as a powerful tool for integrating a deeper molecular knowledge from a specific target, fine-tuning optimal predictive biomarkers, early discovery of resistance mechanisms, and hypothesis generating of new therapeutic strategies. cfDNA, cell-free DNA.
light that anti–PD-1 therapies have shown efficacy across different cancers, efforts have now focused on the identification of tissue-agnostic immune-biomarkers. In reality, MSI-H might have been a surrogate marker of high TMB (60). Therefore, TMB is emerging as an independent promising biomarker for anti–PD-1/-L1 therapy, and WES methods are investigating its applicability across a full spectrum of tumor types (61).

Although there continues to be an urgent unmet medical need for patients with refractory cancers, the development of new drugs in an agnostic-histology manner will probably increase. However, this model of accelerated drug development, based on unprecedented efficacy coming from single-arm small cohorts of biomarker-selected patients will be an exception rather than a rule.

**Considerations for Agnostic-Histology Approvals**

The increasing evidence of a significant myriad of genomic alterations across different cancers has highlighted that it is getting more difficult to explore rare signatures in one single histology. Tumor agnostic drug development strategies could address this myriad, although improving precision medicine in cancer will certainly require more flexibility from all the participants involved (62).

First, the clinical framework for drug development will need to adapt accordingly. Sophisticated master protocols, including “umbrella,” “platform,” and “basket” trials, have been designed to answer multiple questions in less time (63). Two examples of these ambitious approaches are the NCI-MATCH trial, which pretends to enroll more than 1,000 all-comer patients in 25 targeted arms (64), or the Basket of Baskets trial, the largest personalized cancer medicine trial in Europe (65). Figure 2 illustrates the integration of these innovative designs with early translational strategies, serving as platforms to advance research (66). Agnostic-histology “baskets” seek the simultaneous detection of early efficacy signals among different histologies, to depict the influence that tumor lineage exerts in drug sensitivity. These studies can serve to interrogate uncharacterized genomic variants and to examine the effects of concurrent genomic alterations, whereas offering a real-time elucidation of acquired resistance mechanisms (67). Also, “basket” trials can unveil the toxicity effects of new drugs across multiple tumor types, allowing the investigators to have well-established safety profiles to support a favorable benefit-risk ratio in biomarker-selected patients. However, the obtained results must be interpreted with caution.
as inferences from small number of patients might not be a secure source to make treatment-decisions.

In this sense, regulatory agencies may have to consider changes in drug approval conditions, to deal with the inevitable degree of uncertainty associated with the efficacy evidence provided from trials lacking randomization, pooling across heterogeneous populations where sometimes there is no standard of care or limited data on prognosis. Accelerated approval translates that the magnitude of benefit-risk assessment performed by regulatory agencies is positive, but clinical evidence is incomplete. Feasible strategies to support these approvals should include temporal approvals or approvals at risk, that can be continuously reviewed once more data from post-authorization studies become available, reflecting the "real-world" data (68). These post-marketing data will be crucial for verifying the real clinical benefit of a new drug, specially when accelerated approvals are based on surrogate or intermediate endpoints, such as ORR instead of OS. Obviously, if benefit from new drugs is not verified when new information arises, indications should be withdrawn or modified accordingly. In parallel, collaborative efforts have focused on developing methods to establish the value of new specific cancer treatments, to support decision-making (69, 70).

Finally, new adaptive reimbursement strategies will need to be considered. Manufacturers could reduce the price of accelerated-approved drugs until robust efficacy confirmation is available. Confirmatory trials should be optimally designed for addressing the uncertainty of the real clinical effect of a new drug and conducted in a timely fashion, or confirmation could be provided from the data of expanded access programs (71). Figure 3 summarizes some of the premises that should be carefully considered when pursuing the agnostic-histology development of new drugs.

Conclusions

Moving away from traditional diagnostic criteria has translated into a new taxonomy of human diseases based on molecular biology. This has offered unique opportunities to more efficiently treat cancer patients, although it has brought several challenges. It seems clear that the positive experience with accelerated approvals in precision medicine will only continue if there is a collaborative effort between government, regulators, pharmaceutical and biotechnology industries, academia and patient groups (72). We anticipate that agnostic-histology approvals will continue to grow and expand the therapeutic options for patients with cancer, because many other candidates are ready-to-go in the pipeline. We just need to be ready for embracing them and to calmly deal with the uncertainties while we try to minimize them.

Disclosure of Potential Conflicts of Interest

C. Hierro reports receiving commercial research grants (to institution) from Bayer, speakers bureau honoraria from Ignyta and Lilly, and travel/accommodation grants from Lilly and Roche. J. Martin-Liberal reports receiving speakers bureau honoraria from Roche, Novartis, MSD, Pfizer, and Bristol-Myers Squibb, and travel grants from Ipsen. E. Garralda reports receiving commercial research grants from Novartis, speakers bureau honoraria from MSD, and is a consultant/advisory board member for Roche, Janssen, Boehinger, NeoMed Therapeutics, and Eliyphes Pharma. No potential conflicts of interest were disclosed by the other authors.

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