Drug Development: Portals of Discovery
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Abstract
A British humorist said, "There is much to be said for failure. It is much more interesting than success." This CCR Focus section is aimed at identifying lessons to be learned from difficulties encountered in recent years during development of anticancer agents. Clearly, we have not found a silver bullet tyrosine kinase inhibitor against solid tumors comparable with imatinib in chronic myelogenous leukemia. Although vemurafenib for B-Raf–mutated melanoma and crizotinib for non–small cell lung cancers with echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) rearrangements were developed rapidly and offer hope for individualized targeted therapies, the development of agents targeting a number of other pathways has been slower and less successful. These agents include drugs for blocking the insulin-like growth factor I/insulin receptor pathways, mitotic kinase inhibitors, and Hsp90 antagonists. Several potentially useful, if not groundbreaking, agents have had setbacks in clinical development, including trastuzumab emtansine, gemtuzumab ozogamicin, and satraplatin. From experience, we have learned the following: (i) not every altered protein or pathway is a valid anticancer target; (ii) drugs must effectively engage the target; (iii) the biology of the systems we use must be very well understood; and (iv) clinical trials must be designed to assess whether the drug reached and impaired the target. It is also important that we improve the drug development enterprise to enhance enrollment, streamline clinical trials, reduce financial risk, and encourage the development of agents for niche indications. Such enormous challenges are offset by potentially tremendous gains in our understanding and treatment of cancer.

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Introduction
This CCR Focus series is not about the latest hot topic in drug development or the most exciting idea on the horizon. Rather, this series is about difficulties that have been encountered, and sometimes solved, on the road toward the development of personalized therapy for cancer. Considerable literature can be found on the subject of learning from experience and how success often springs from prior failure.

A man of genius makes no mistakes. His errors are volitional and are the portals to discovery.
—James Joyce, Ulysses, Chapter 9: Scylla and Charybdis, 1922

There is much to be said for failure. It is much more interesting than success.
—Max Beerbohm, Mainly on the Air, 1946

Sometimes failure in science comes from errors in our underlying assumptions, and we discover that we must change those assumptions.

If at first you don’t succeed, redefine what you did as success.
—Stephen Colbert

When the history of cancer therapy in the first decades of the twenty-first century is written, it very possibly could point to the great success in chronic myelogenous leukemia (CML) treatment as having set cancer therapeutics on an unwinnable path for a time. The discovery of imatinib and its excellent activity against the Bcr-Abl fusion protein in CML led to the hope that all tumors could be equally targeted. The "silver bullet" image was widely cited in the lay press and in review articles, and indeed for CML, imatinib was the silver bullet. Current estimates of progression-free survival (PFS) and overall survival rates are 96% to 99% at 2 years (1). The activity in CML was soon followed by reports of activity in gastrointestinal stromal tumor, with its oncogenesis mediated by mutations in c-Kit kinase, containing an ATP-binding site similar, but not identical to, that of the Abl kinase (2). This research led to a long list of small-molecule kinase inhibitors targeting epidermal growth factor receptor (EGFR), HER2, insulin-like growth factor I receptor (IGF-IR), platelet-derived growth factor receptor (PDGFR), B-Raf, and the anaplastic lymphoma kinase (ALK). Along the way, another treatment paradigm emerged that cancer could be managed as a chronic disease.
and that tumor shrinkage need not be observed. This paradigm held that tumors could be controlled by kinase inhibitors that could slow cancer cell growth. Although termed cytostatic, a better descriptor would be cytolytic, a cell-slowing agent (3).

However, attempts to replicate the success of imatinib with other kinase inhibitors in other tumor types have been far less successful, and no truly cytostatic drugs have achieved regulatory approval. In solid tumors, it became apparent that targeted therapies led to tumor shrinkage followed by recurrence as drug resistance emerged (e.g., a 31% objective response rate for sunitinib in renal cell carcinoma; refs. 4, 5). It also became apparent that development of tyrosine kinase inhibitors (TKI) for solid tumors would be more difficult than expected, and hope for both the silver bullet and the cytostatic treatment paradigm faded. Nonetheless, the armamentarium expanded, although often the margin of benefit was small, making the Stephen Colbert quote applicable, its irony notwithstanding.

Although the definition of success or failure in drug development is complex, on the simplest level, we can define failure in drug development as the failure to achieve regulatory approval. As the articles in this CCR Focus section describe, there are diverse ways to fail. In the case of B-Raf inhibitors, failure provided a portal to success, whereas with the IGF-IR and Aurora kinase inhibitors and the Hsp90 antagonists, the work is continuing. In the following paragraphs, we discuss these examples in brief and discuss selected compounds from Table 1, which catalogs recent setbacks in clinical drug development. Figure 1 illustrates the range of drug targets that have proved challenging in development, essentially the range of targets that has also proved successful.

One in 4 or 5 compounds entering phase I testing achieves regulatory approval (6), so it is important to understand drug regulatory failures. At times, we have developed the wrong drug for the right target (sorafenib for B-Raf). At other times, we have developed the right drug for the wrong target (mitotic poisons). In some cases, we have developed drugs prematurely, not fully understanding the complexities of the underlying biology, precluding us from selecting patients most likely to benefit [multidrug resistance-1 (MDR-1) and Hsp90 inhibitors]. In some cases, we have failed to heed the lessons of prior clinical experience (satraplatin), whereas in others, the flaw has been poor clinical trial design or poor clinical trial execution. We recognize that, in some cases, these generalizations are part of a much more complex question. However, distilling lessons learned from setbacks in oncology drug development gives us the opportunity to make greater advances in the coming years.

Wrong Drug for the Right Target

When clinical development of an agent does not meet expected endpoints, the community often blames the target, construing treatment failure to mean that the target is not a suitable target for development. The assumption made in this setting is that the target was reached and that treatment failure represents target failure. This assumption was made in several examples. However, proving that a target that has not been validated is at fault requires biomarkers or surrogates that show the drug reached the target, inhibited it as planned, and then failed to cause tumor shrinkage. The case of B-Raf inhibitors in the clinic is a good example. Sorafenib was developed as a B-Raf inhibitor and studied in melanoma, in which 50% to 60% of tumors harbor a B-Raf mutation. However, in phase II and III trials, sorafenib induced minimal objective response (7, 8).

One interpretation was that B-Raf was not a valid target in melanoma, potentially important in oncogenesis, but not a therapeutic target in a well-established tumor. However, as discussed by Marzuka Alcalá and Flaherty, validation of B-Raf as a target was provided by vemurafenib (PLX4032), with its superior inhibition of B-Raf (9). With clinical responses in melanoma observed in phase I, B-Raf was validated as a target. The approval in August 2011 by the U.S. Food and Drug Administration (FDA) of vemurafenib for metastatic or unresectable melanoma harboring a V600E mutation in BRAF was based on a multiinstitutional trial that enrolled 675 patients who had not received prior therapy. The trial was randomized against dacarbazine, and overall survival was the primary endpoint. The median survival in the vemurafenib arm had not been reached at the time of analysis, whereas the median survival in the dacarbazine arm was 8 months (10). As it approved vemurafenib, the FDA also approved a companion diagnostic test, Roche’s cobas® 4800 BRAFV600 Mutation test, which detects the V600E mutation. The approval of this test means that only patients with tumors susceptible to vemurafenib will be treated with this new agent, ensuring that those whose tumors do not harbor the V600E mutation will not be exposed to the expense and toxicity without benefit. Although not the first time that a test has been developed to guide therapy (previous examples include HER2 and estrogen receptor), this was the first time that a drug and a companion diagnostic test have been approved together. This development represents a major step toward personalized therapy and serves as a successful example for other targeted therapy.

A second success followed. On August 26, 2011, the FDA approved crizotinib for the treatment of patients with non–small cell lung cancer (NSCLC) that tested positive for the echinoderm microtubule-associated protein-like 4 (EML4)–ALK fusion gene, which results in an oncogenic-activated tyrosine kinase. FDA approval was based on 2 clinical trials in which patients with this rearrangement had a 50% to 60% overall response rate with median durations of response of 40 to 50 weeks. The FDA simultaneously approved Abbott Molecular’s Vysis ALK Break Apart FISH Probe kit for detection of the rearrangements. Because only 5% of patients with NSCLC have tumors with the rearrangement, it is clear that identifying the target was the critical step in approval of crizotinib (11). In this case, as with
### Table 1. Selected regulatory failures since 2005

<table>
<thead>
<tr>
<th>Agents</th>
<th>Target</th>
<th>Indication</th>
<th>Lessons learned</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin; Roche/Genentech)</td>
<td>VEGFR</td>
<td>Breast cancer</td>
<td>ODAC recommended and FDA withdrew approval on November 18, 2011.</td>
<td>(36, 50)</td>
</tr>
<tr>
<td>Dutasteride (Avodart; GlaxoSmithKline)</td>
<td>5α reductase</td>
<td>Prostate cancer risk reduction</td>
<td>FDA rejected sNDA, January 2011</td>
<td>(51, 52)</td>
</tr>
<tr>
<td>Finasteride (Proscar; Merck)</td>
<td>Type II 5α reductase</td>
<td>Prostate cancer risk reduction</td>
<td>FDA rejected sNDA, January 2011</td>
<td>(53, 54)</td>
</tr>
<tr>
<td>Trastuzumab emtansine (T-DM1; Roche/Genentech)</td>
<td>HER2</td>
<td>Breast cancer</td>
<td>Accelerated approval denied, FDA awaits phase III data, August 2010</td>
<td>(47)</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin (Mylotarg; Pfizer)</td>
<td>CD33</td>
<td>AML</td>
<td>Voluntarily withdrawn from U.S. markets, June 21, 2010</td>
<td>(48, 55)</td>
</tr>
<tr>
<td>Omacetaxine mepesuccinate or homoharringtonine (Omapro; ChemGenex)</td>
<td>BcrAbl T315I mutation</td>
<td>CML</td>
<td>ODAC recommended development of companion diagnostic test for the BcrAbl T315I mutation prior to approval, April 10, 2010</td>
<td>(56, 57)</td>
</tr>
<tr>
<td>Pixantrone Pixantrone, BBR 2778 (Pixuvri; Cell Therapeutics)</td>
<td>Topoisomerase II</td>
<td>Relapsed or refractory NHL</td>
<td>Accelerated approval denied, April 2010</td>
<td>(58)</td>
</tr>
<tr>
<td>Laromustine (Onrigin; Vion)</td>
<td>AML</td>
<td></td>
<td>ODAC recommended and FDA required a randomized study, SPA rejected, September 2009</td>
<td>(59–61)</td>
</tr>
<tr>
<td>Trabectidin, ET-743 (Yondelis; PharmaMar)</td>
<td>DNA</td>
<td>In combination with liposomal doxorubicin in relapsed ovarian cancer</td>
<td>NDA voluntarily withdrawn following a request by the FDA for an additional phase III study, July 2009; approved by EMEA on the basis of same data showing 1.5-month PFS benefit, no OS benefit</td>
<td>(62, 63)</td>
</tr>
<tr>
<td>Satraplatin (Spectrum and GPC Biotech)</td>
<td>DNA</td>
<td>HRPC</td>
<td>GPC Biotech withdrew NDA filed for accelerated approval on the basis of ODAC recommendation that the FDA should wait for the survival analysis of the SPARC trial, July 30, 2007</td>
<td>(44, 64, 65)</td>
</tr>
<tr>
<td>Oblimersen (Genasense; Genta)</td>
<td>Bcl-2 antisense oligodeoxy-nucleotide G3139</td>
<td>In combination with fludarabine and cyclophosphamide for patients with relapsed and/or refractory CLL</td>
<td>ODAC voted no for reasonable likelihood of clinical benefit, the threshold for accelerated approval. FDA recommended that PFS or TTP be used as primary endpoint, rather than response rate, September 25, 2006</td>
<td>(66, 67)</td>
</tr>
</tbody>
</table>

(Continued on following page)
veumafenib, the right target, the right drug, and the right test assured success.

**Right Drug, Right Target in Search of Vulnerable Tumors**

Not all targeted therapies have been able to establish that the intended target is essential. In this CCR Focus section, Pollak discusses lessons learned from the development of both antibodies and receptor TKIs targeting IGF-IR (12). Targeting the insulin and IGF-IR family is supported by clinical and preclinical data showing increased cancer risk and more aggressive cancer biology linked to higher levels of the ligands and impaired cancer cell growth when signaling from the receptors is inhibited. The receptors are commonly expressed in cancer, and at least a dozen agents are in clinical trials, but to date, only limited activity has been observed, and that primarily in Ewing sarcoma (13).

Administration of these agents has resulted in on-target toxicities, including hyperglycemia due to increased growth hormone and insulin resistance. Thus, there is on-target toxicity without on-target efficacy. Pollak considers possible explanations for this and considers how to move forward, rightfully concluding that the most important strategy is to identify patient subgroups in which tumors are particularly susceptible to inhibition of the insulin–IGF-IR pathway. Early data to support the existence of such subgroups include observations in patients with NSCLC enrolled on a phase II trial of the IGF-IR antibody figitumumab (14). Higher PFS probability was observed in patients with higher pretreatment levels of circulating free IGF-I or higher insulin to IGF-binding protein ratios. Similarly, Cao and colleagues had previously shown in preclinical rhabdomyosarcoma models that cells with high levels of receptor were more dependent on IGF-I signaling and more sensitive to the antiproliferative effects of the antibody (15). Pollak concludes that for drugs targeting the IGF-IR pathway, broad-spectrum activity is disproved but that the possibility still exists for specific contexts in which the agents are active (12).

**Right Drug for the Wrong Target**

In contrast to the B-Raf story, mitotic kinase inhibitors have not fared as well. Komlodi-Pasztor and colleagues argue that, in this case, the target is wrong (16). With 1,399 patients treated with a range of mitotic kinase inhibitors and a response rate of 1.6%, they may well be right. Aurora A and B kinases and the Polo-like kinases are integral parts of mitosis. Aurora A, whose expression is largely restricted to mitosis, localizes to the mitotic poles and adjacent spindle microtubules during mitosis. Aurora B localizes to K-fibers, microtubules that connect the kinetochore to spindle fibers, and is involved in chromosome separation. Similarly, Aurora C, polo-like kinases, and the motor protein kinesin spindle protein are all mitotic proteins. Although these proteins would seem at first glance to be ideal cancer drug targets, Komlodi-Pasztor and colleagues argue that, in contrast to frequently dividing bone marrow precursors, cancer cells do not divide often enough to be susceptible to drugs targeting these mitosis-associated proteins. Inhibitors so far in the clinic have caused significant bone marrow suppression, indicating the drugs were potent and hit their target but unfortunately had minimal antitumor activity. In common tumor types, the calculated mean tumor-doubling times in patients range between 114 and 391 days. Thus, compounds targeting these mitotic proteins may fail because their targets are not suitable for anticancer drug development. Exceptions might include rapidly growing malignancies, such as Burkitt lymphoma, and some peripheral T-cell lymphomas. It is also possible, although not yet shown, that there are tumors in which Aurora

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**Table 1. Selected regulatory failures since 2005 (Cont’d)**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Target</th>
<th>Indication</th>
<th>Lessons learned</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrasentan (Xinlay; Abbott)</td>
<td>SERA (TM)</td>
<td>HRPC that has spread to the bone</td>
<td>ODAC did not recommend approval of NDA, on the basis of TTP analysis, September</td>
<td>(59, 68–70)</td>
</tr>
<tr>
<td>Geftinib (Iressa; AstraZeneca)</td>
<td>Mutated EGFR</td>
<td>Lung cancer</td>
<td>No survival benefit in unselected patient population. FDA restricted access to gefitinib, June 17, 2005</td>
<td>(71, 72)</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; EMEA, European Medicines Agency; HRPC, hormone-refractory prostate cancer; NHL, non-Hodgkin lymphoma; OS, overall survival; SERA (TM), selective endothelin-A receptor antagonists; sNDA, supplemental New Drug Application; SPA, special protocol assessment; SPARC trial, Satraplatin and Prednisone Against Refractory Cancer; TTP, time to progression; VEGFR, VEGF receptor.
kinase is an oncogenic driver through aberrant or dysregulated off-target expression. At a minimum, increasing our knowledge of the biology of the mitotic kinases may allow the development of rational combinations that could exploit differential expression patterns.

Drug Developed Before the Biology Is Fully Understood

Hsp90 inhibitors may be viewed as agents developed to target a pathway that was not yet fully understood. As discussed by Neckers and Workman, first- and second-generation Hsp90 inhibitors have been tested in the clinic, with modest activity observed (17). However, the development of the early agents has been discontinued. In the case of the first-in-human agent, 17-AAG (tanespimycin), its discontinuation was prompted by a combination of formulation problems, hepatotoxicity, and commercial issues, but this has been criticized (18) in view of the clear activity by RECIST (Response Evaluation Criteria in Solid Tumors) in trastuzumab-refractory breast cancer (19). But Neckers and Workman point out that these early clinical trials provided target validation and that 17 agents targeting this pathway have now entered clinical development. With sufficient effort, it is likely that some agent among these will have an activity and safety profile that will allow it to be moved forward. The authors also note the considerable progress that has been made in understanding Hsp90. We now understand that particular clients of Hsp90 are especially sensitive to its chaperone role, including HER2, ALK, EGFR, and BRAF. Thus, Hsp90 inhibitors would be expected to be more active in diseases in which these proteins mediate the oncogenic phenotype. Further, upregulation of other chaperones in the cell may undermine the efficacy of Hsp90 inhibition. These proteins include Hsp27 and Hsp70, which are activated through an HSF1-mediated mechanism, as well as other Hsp90 isoforms. This redundancy in some cells may prevent Hsp90 inhibitors from having effective antitumor activity. The hope is that a fuller understanding of the biology of this pathway and how it is regulated may allow improved targeting and a better choice of tumor type for clinical testing.

Figure 1. Schematic of drugs and targets that have met challenges in development. RAS, RAF, MAP/ERK kinase (MEK), and extracellular signal-regulated kinase (ERK) are protein kinases. ET1, endothelin 1; ET1R, endothelin receptor type A; Topo-II, topoisomerase II; VEGFR-2, VEGF receptor 2.
Drug Penetration Is Always Assumed but Seldom Proved

When we think about drug development failures, we generally think in terms of either the target or the drug, as illustrated above. However, one assumption that is probably incorrect is that the drug always reaches the target. In fact, very little data have been gathered that prove drugs reach their target. We infer it because we see clinical responses, but we do not know whether, or how often, variable drug penetration can account for treatment failure. Most of the data pertinent to this question are old and most suggest a wide divergence of drug penetration (20–22).

Nonetheless, efforts to improve drug uptake in tumors have so far failed. MDR-1 encodes P-glycoprotein (Pgp), an ABC transporter able to efflux a variety of cancer chemotherapeutics, including taxanes, vinca alkaloids, anthracyclines, podophyllotoxins, and TKIs, including imatinib, dasatinib, and gefitinib. Overexpression of Pgp in tumors, particularly in leukemia, has been consistently associated with poor outcome, implying a role for Pgp in inherent drug resistance. Yet, compounds developed as inhibitors of Pgp-mediated efflux almost uniformly showed no benefit or increased toxicity when they were added to conventional chemotherapy in numerous clinical trials (23). Eventually, assessment of drug accumulation, using the radionuclide-imaging agent 99mTc-Sestamibi as surrogate, showed that tumor uptake was quite variable and that efflux inhibitors increased 99mTc-Sestamibi uptake in some tumors but had no effect in many (24, 25). Although supported science the continued study of transporter inhibitors, it could not drive their development in the setting of the emerging negative clinical trials.

But as with Hsp90 inhibitors, basic and translational science did not stop moving forward when the clinical failures emerged. It became clear that there were many other ABC transporters with efflux capacity and that many other factors affect drug accumulation. Among these, a disordered tumor vasculature and increased interstitial fluid pressure result in a steep gradient in drug concentration from the tumor vasculature (26–29). If these factors are rate limiting for drug penetration into tumor tissue, they may have impacted the penetration of inhibitors as well and together rendered efflux inhibition ineffective.

Among the lessons learned in the development of MDR-1 inhibitors is the importance of understanding the biology, not that of a single protein, and the importance of developing surrogate assays. Knowing whether drug uptake was actually impacted by the inhibitors would have allowed interpretation of clinical trial results much earlier and likely would have argued for investigating the determinants of drug uptake.

Angiogenesis as Ubiquitous Target

One long-studied and long-awaited therapy has been the inhibition of blood vessel growth into tumors, thereby reducing oxygen, nutrients, and promoting cell death. This paradigm was first offered by Judah Folkman, whose vision of tumor angiogenesis as a therapeutic target became a reality with the development of the anti-VEGF antibody bevacizumab (30). In 2004, the FDA approved bevacizumab for first-line treatment of colorectal cancer, in combination with irinotecan, 5-fluorouracil, and leucovorin (31), and in 2006, it extended the indication to include the use of bevacizumab in the second-line colorectal cancer setting in combination with 5-fluorouracil (32). Subsequent approvals included bevacizumab in combination with carboplatin and paclitaxel in first-line treatment of NSCLC in 2006 (33) and in combination with interferon alpha for treatment of metastatic renal cell cancer in 2009 (34). Accelerated approval was given in 2008 for the use of bevacizumab in combination with paclitaxel for the treatment of chemotherapy-naive metastatic HER2-negative breast cancer and for its use as a single agent in glioblastoma in 2009 (35). Against this backdrop of success, in 2011 the Oncology Drugs Advisory Committee (ODAC) recommended that FDA remove the approval for bevacizumab in breast cancer; it was withdrawn in November 2011 after intense debate (36, 37). This recommendation was based on failure to replicate the magnitude of the initial results obtained in the Eastern Cooperative Oncology Group E2100 trial, which had shown a marked improvement in PFS for bevacizumab in combination with paclitaxel compared with paclitaxel alone, 11.3 versus 5.8 months (38, 39). Although considerable effort has been expended to understand the difference between E2100 and the subsequent trials, the inescapable conclusion is that combining bevacizumab with chemotherapy is not a one-size-fits-all treatment. Further, preclinical data suggest all tumor vasculature is not the same and that there are molecular differences in tumor endothelial cells from a variety of tumors (40, 41). The E2100 5.5-month PFS difference most likely was an outlier (42).

Flawed Development Plan

In some cases, potentially useful agents have been rejected because the development plan sought a wider indication than what the drug was capable of delivering. Although personalized therapy based on careful molecular characterization of tumors is an important goal, the downside of this strategy is that costs of development then have the potential to outweigh the financial gain for the pharmaceutical sponsor. This situation has led companies to choose development plans that exceed the scope of the most active niche indication identified in early clinical development.

Hindsight, as the saying goes, is 20–20, and criticizing the development plan of an agent has that implicit flaw. Yet, no lessons will be learned without review and analysis. Satraplatin (JM 216) is a case in point. As an orally bioavailable platinum with similarities to cisplatin and carboplatin, but also with some unique properties, it was thought that satraplatin might be effective in the setting of platinum resistance (43). In a phase II randomized trial in recurrent
Drug Activity Impaired by Drug Resistance in Refractory Tumors

One problem that has not been solved is the need to develop agents in heavily pretreated populations. In fact, to some extent, clinical oncologists are the victims of their own success: the greater the number of therapies that are approved, the less likely patients will be referred for clinical trials early in their disease course. One agent potentially affected by this problem is trastuzumab emtansine (T-DM1), a conjugate of trastuzumab with DM1, a maytansine derivative. Results from a single-arm multi-institutional phase II study (TDM4374g) were submitted to the FDA for consideration of accelerated approval. In 100 women with HER2-positive breast cancer, the overall response rate was 34.5% with no complete responses, a duration of response of 7.2 months, and a PFS of 6.9 months (47). Patients had previously received a median of 8.5 agents, 7 in the metastatic setting, including lapatinib and trastuzumab. The FDA considered that the agent had not met accelerated approval standards because all available approved options had not been exhausted. Although all options were not exhausted, 7 agents in the metastatic setting is a level of drug exposure likely to be associated with resistance in the majority of patients and to have reduced the activity of T-DM1 in the patient population studied. It should be noted that rejection of accelerated approval alone does not truly constitute a drug development failure; the agent continues to be studied, and results of randomized trials in less heavily pretreated populations are awaited. These studies can then be submitted for regular approval.

Clinical Trial Design Failure

Gemtuzumab ozogamicin (GO) may be an example of a failed clinical trial design. GO is an antibody-drug conjugate (48) consisting of a monoclonal antibody recognizing CD33, a ligand on the surface of acute myelogenous leukemia (AML) cells, linked to a calicheamicin derivative. Calicheamicin is released by hydrolysis from the CD33 antibody, which delivers the agent directly to the 90% of AML cells expressing the ligand. GO was initially studied in patients with relapsed or refractory AML. It was granted accelerated approval by the FDA in 2000 based on a 26% complete response rate (including those with incomplete platelet recovery) in 277 patients over age 60 with AML in first relapse (49). The drug was given as monotherapy and was associated with an overall survival of 12.6 months for patients who had response to therapy, compared with 4.2 months for patients without response. However, a different clinical trial design was then chosen to achieve full approval. That design was a randomized study of standard induction chemotherapy with or without GO in a younger population and in the frontline setting. Unfortunately, no difference in response rate or overall survival was found, and increased toxicity in the experimental arm prompted early closure of the study for toxicity. This action led to withdrawal of GO from the market in the United States. Thus, a potentially useful salvage monotherapy for AML that may have provided clinical benefit in a subset of patients went off course. Whether a randomized phase III trial of GO monotherapy would have met response or survival endpoints in the original relapsed setting is a subject for speculation, given the difficulty of identifying an ideal control arm in this setting. GO has full regulatory approval in Japan.

Conclusions

Taken together, the examples above and in Table 1 represent the range of difficulties encountered in drug development. Although we should not redefine clinical measures of success, we should redefine success in drug development. It is lamentable that at times catastrophic financial repercussions follow failure to achieve regulatory approval. Although we can learn from our mistakes and develop the most efficient and effective clinical trials possible, we should also work toward processes that
increase sharing of risk. And we can argue that the number of attempts should exceed the number of successes. DiMasi and Grabowski evaluated 175 agents that were investigated for oncology indications from 1993 to 2002 (6). Of compounds that entered phase I during that time period, 77% transitioned to phase II, and 19% ultimately achieved New Drug Application (NDA) approval. Of those that entered phase III testing, 57% received NDA approval. As in many sports, goals are often scored only after multiple attempts. If we wait until success is guaranteed, we may never succeed. Finally, we should recognize some failures are unavoidable because regulatory agencies, like people, see things differently. For example, in the case of trabectedin, a 1.5-month

observed in advanced ovarian cancer when administered in combination with pegylated liposomal doxorubicin. The FDA said no; the EMA said yes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The opinions expressed in this manuscript are those of the authors and do not necessarily represent those of the National Cancer Institute, the NIH, or the Department of Health and Human Services.

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