When Roche’s Zelboraf (vemurafenib) and Pfizer Inc.'s Xalkori (crizotinib) were cleared by FDA, they were heralded as the first in a wave of next-generation personalized cancer drugs, therapies approved in tandem with a companion diagnostic to identify the patients most likely to respond to treatment. But while they are clear medical and regulatory wins, the experience from the first year of marketing suggests that commercial success may be harder to achieve.

Zelboraf and Xalkori are both great success stories. They sailed through development and regulatory approval (Zelboraf was approved by FDA in 3.6 months and Xalkori in less than five); have been welcomed on the market by patients, physicians and even payers, despite their high cost; and represent a significant advance in the treatment of two of the deadliest cancers. Both drugs offer a survival advantage over the former standard of care – but only in a subset of patients whose tumors present with certain gene mutations. Zelboraf helps metastatic melanoma patients with tumors expressing the V600 BRAF mutation and Xalkori helps non-small cell lung cancer patients with tumors expressing the EML4-ALK mutation. The two drugs were approved in August 2011, Zelboraf first followed by Xalkori (“Zelboraf Approval Hastened By FDA Officials Impressed With Early Efficacy” — “The Pink Sheet,” Aug. 22, 2011 and “Pfizer’s Crizotinib Eases Past FDA With Targeted Population” — “The Pink Sheet,” Aug. 29, 2011).

The two drugs have been viewed as poster children for personalized medicine, examples of pharmaceutical manufacturers identifying biomarkers early on in drug development to target the patients most likely to benefit from treatment and avoid unnecessary exposure if patients are unlikely to respond. There have been few such examples in the history of drug development with such prospective planning for biomarkers, Novartis AG’s Gleevec (imatinib) for Philadelphia chromosome-positive chronic myeloid leukemia and Roche/Genentech Inc.’s Herceptin (trastuzumab) in HER2 positive breast cancer – both decade-old drugs – being the most notable. Often, biomarkers are discovered in hindsight or because sponsors were pushed to find them to keep a troubled drug on the market.

Excluding Patients, Limiting Sales

When it comes to commercializing targeted cancer drugs, the business model is chockfull of pitfalls, the most inherent of which is the fact that large groups of patients – often the vast majority – do not respond to treatment. That in turn raises the importance of finding those patients in which the therapy will work. The launches of Zelboraf and Xalkori highlight those challenges and suggest it could take years for some targeted drugs to generate the kind of sales big pharma relies on to recoup return on investment.

Early on in the era of personalized medicine, industry did the math on limiting patient populations – determining that the benefits afforded by specification outweighed an all-comers approach. Some of that advantage comes from the ability to command a premium price; personalized cancer therapies, including Zelboraf at $9,400/month and Xalkori at $9,600/month, have blown past the six-figure mark in the last couple years (“Pfizer’s Xalkori Joins The Six-Figure Oncology Drug Club” – “The Pink Sheet,” Sep. 5, 2011). But a cost-benefit analysis out of Eli Lilly & Co. comparing the traditional blockbuster model to what was just starting to be called personalized medicine found that the higher response rates reached with targeted therapies can produce a sufficient market share that even at the same price, the targeted therapy yields higher sales (“Better, Faster, Smaller: Personalized Medicine Could Bring R&D Savings” – “The Pink Sheet,” Mar. 3, 2008).

But sales of Zelboraf and Xalkori in the first six months of the year have come in below non-targeted oncology drug launches. Zelboraf generated sales of $96 million (CHF92) in the first half of the year. Pfizer has so far declined to break out sales of Xalkori – generally a sign a drug did not contribute meaningfully to the top line.

In comparison, Johnson & Johnson’s Zytiga (abiraterone), approved in May 2011 for metastatic castration-resistant
prostate cancer, generated $432 million in sales the first six months of the year. Bristol-Myers Squibb Co.'s Yervoy (ipilimumab), a drug that does not work in every patient but does not have a biomarker for identifying appropriate patients, was approved for metastatic melanoma just ahead of Zelboraf in March 2011. Yervoy generated more than three times the sales of Zelboraf in the first half of 2012, bringing in $316 million for Roche.

During Pfizer's second quarter sales and earnings call July 31, CEO Ian Read admitted the launch of Xalkori has faced more challenges than expected. “I think the issue on Xalkori is we’re changing medical practice,” he said. “We need to get doctors to have the tests done to identify the specific need for Xalkori. It’s frankly slower than we expected to achieve the changes.”

For Xalkori, Testing Proves Challenging

It’s still very early in the launch trajectory to label either of these drugs disappointments. But the slower-than-expected uptake suggests targeted therapies linked closely to companion diagnostics face distinct commercial risks.

Xalkori faces the highest hurdle commercially of any targeted cancer therapy to reach the market because the ALK mutation is present in only about 5% of NSCLC patients. Getting physicians to commence routine testing of the vast NSCLC patient population for such a small subset of patients presents a specific challenge for Pfizer, especially given how difficult it is to extract sufficient tissue samples from lung tumors. Samples are generally extracted through a needle aspiration procedure, which results in samples that are limited in quantity and often limited in quality.

“In the vast majority of cases, diagnosis is made without enough tissue,” said lung cancer specialist Kenneth Algazy, clinical professor of medicine at The University of Pennsylvania School of Medicine. When the tissue sample is insufficient, physicians typically run a test for EGFR first, as the EGFR mutation is more common in lung cancer tumors, around 15% of cases, he said. Roche’s Tarceva (erlotinib) is an EGFR-targeted drug approved for lung cancer. “Chances are you are not going to have enough tissue to do [ALK testing] unless you have actually operated on the patient,” Algazy said. He hasn’t used Xalkori in any patients yet. “I haven’t found anybody who I can use it in,” he said.

Broader adoption of ALK testing in NSCLC may not require physician education as much as advances in biopsy techniques or in testing that allows for the use of limited tissue samples, developments out of the hands of Pfizer’s sales team.

Pfizer R&D President Mikael Dolsten commented on that challenge during the second quarter call. “Currently the diagnostic test is very much one test, one drug, and I would like to see that change,” he said. “It will be a panel of tests for a disease like lung cancer that I think will drive the utilization of the first drug and multiple drugs.”

But BRAF Mutation Testing Becoming Routine

In contrast to the ALK mutation in NSCLC, the BRAF mutation is found in significantly more patients with metastatic melanoma, about 50%. Not surprisingly then, BRAF mutation testing has been adopted more rapidly by oncologists than ALK testing, according to data from the market research firm ImpactRx, which tracks real-time physician action and prescribing patterns using a network of 375 oncologists. It found that between May and July, about 40% of oncologists tested at least half of NSCLC patients for the ALK mutation, while about 80% of oncologists tested at least half their melanoma patients for the BRAF mutation.

Routine testers – defined as those who test at least 80% of their patients – was significantly lower for ALK however, just 15%, compared to almost 70% for BRAF.

Nonetheless, among NSCLC patients who do test positive for the ALK mutation, Xalkori is the treatment of choice. Xalkori has over 70% share of the market for ALK-positive Stage IIIB/IV NSCLC patients across all lines of treatment, and a 90% share among patients receiving first line therapy or those who are new starts, according to ImpactRx. Zelboraf had a 72% share of the market among metastatic melanoma patients who are BRAF mutation-positive across all lines of therapy in the most recent three month period, according to ImpactRx.

Once the appropriate patients are identified, use of the targeted medications in those patients is convincing. “All of these [targeted] drugs, Xalkori, Zelboraf, all of them, have the ability to become blockbusters,” said Ben Bonifant, president of the consulting firm Bonifant Insights Group, who works in the personalized medicine space. “These are absolutely extraordinary drugs but the kinks aren’t worked out yet,” he said. “It’s not as simple as taking a Gleevec uptake curve and applying it to your new category. In every case, there is a drug by drug story that you have to appreciate.”

Gleevec, a blockbuster several times over, is considered a personalized medicine success story, an act other drug makers would be happy to follow. Despite its original approval for a niche indication in 2001, Gleevec has grown into one of Novartis’ top-selling drugs, with sales of $4.66 billion in 2011. Part of Novartis’ success with Gleevec came through expansion of the CML market, but also from expansion of the drug into 10 additional indications.

Pfizer is similarly looking to expand Xalkori into additional indications, testing it in other ALK-positive tumor types like anaplastic large cell lymphoma, inflammatory myofibroblastic tumors and neuroblastoma. The company is also studying it as a c-MET inhibitor, where it could reach a broader patient audience. The drug was originally in development
as a c-MET inhibitor, before Pfizer quickly changed tack and turned the development program to focus on ALK when the target first emerged as a biomarker (“Xalkori And The Art Of Modern Drug Development” – IN VIVO, February 2012).

Another longer term challenge for targeted cancer drugs will be rivals, an issue in any drug category, but one that becomes a greater concern when the patient pool has been thinned down. Zelboraf, for example, soon could face competition from GlaxoSmithKline PLC’s rival BRAF inhibitor dabrafenib. GSK announced the submission on Aug. 3 of an NDA for dabrafenib, along with the MEK inhibitor trametinib. The two drugs are also being studied in combination (“GSK’s Oncology Expansion Heavily Dependent On Dabrafenib, Trametinib” – “The Pink Sheet” DAILY, Aug. 3, 2012).

“Whoever has the better story is going to get the lion’s share of the patients,” said Bonifant, speaking of the competitive dynamics generally. “Very small differences in clinical results may have a huge impact on the market.”

In an area as novel as personalized medicine, the market dynamics will take years to play out. But it’s clear developing a targeted medicine, identifying biomarkers and building a companion diagnostic are just the first leg of the journey. Getting to the final goal of commercial success requires another long road.