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BIOPHARMACEUTICALS

Biosimilars: A New Kind Of Innovation

For several recent entrants, the biosimilars game isn't just about creating copies; it's about promoting and branding a new kind of hybrid proposition where the innovation isn't in the molecule, but in how you make it, position it, and support it. In this sense biosimilars reflect the broader payor-driven push away from scientific novelty toward a focus on value.

BY MELANIE SENIOR

NEXT-GENERATION Combination Therapy In Oncology

The explosion in knowledge tied to both the genetics and molecular biology of cancer has resulted in limited clinical success, largely because the complexity of most cancers defies novel single-target approaches. Major advances in the future of cancer therapy will only result from the development of rational combinations of targeted therapeutics, a reality that presents industry players with both opportunities and challenges.

BY AIDAN FINLEY AND VIVEK MITTAL

- Traditional cancer development focused on individual druggable targets and combinations were developed empirically post-approval.
- Drug developers need to focus on combinations early, and the FDA is helping to enable this transition with new guidance.
- While new guidance on combination products is essential, cancer drug development must evolve further, with an emphasis on collaborations between drug developers, improved clinical trial regimens, and better use of biomarkers.
- The recent launches of *Xalkori* and *Zelboraf* demonstrate the real world benefits of companion diagnostics, and clinicians are already working on slotting these agents into combinations to address resistance and improve clinical outcomes.

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Prior to the 1970s, therapeutic regimens for oncology consisted largely of surgery, radiation, and the use of non-specific, combination chemotherapy. Working in cooperative groups organized through the **National Institutes of Health's National Cancer Institute**, oncologists sought to refine combination regimens for both hematological malignancies and solid tumors. By the 1970s and 1980s, these same oncologists had optimized empiric combinations, offering clinically beneficial and cost-effective cancer treatment in many hematological indications. Multi-drug regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), introduced in the late 1980s, induced 45%-55% complete remissions and 30%-35% cures in non-Hodgkin patients, while refinements to treatment protocols for Hodgkin lymphoma resulted in more dramatic cure rates around 70%. Although these accomplishments are impressive, therapeutic advances have been more muted in solid tumors. Relative success stories like the use of tamoxifen to treat estrogen-responsive breast cancer have been outweighed by the lack of progress against lung and colorectal cancer.

Moreover, for novel oncology therapies, FDA approval is no longer sufficient to ensure market adoption, especially if pricing is seen as incommensurate with clinical benefit. The

rapid success of recently approved agents like **Bristol-Myers Squibb Co.'s Yervoy** (ipilimumab), which had \$95 million in sales in its launch quarter, illustrate the tangible rewards achievable when a product demonstrates robust clinical benefit in a poorly treated cancer like metastatic melanoma. (With a \$120,000 price tag, it seems likely some concessions on price will be necessary for adoption in the UK and Europe.) On the other hand, payor pushback and physician skepticism over a modest four-month survival benefit has resulted in only modest growth for **Dendreon Corp.'s** \$93,000-a-year therapy *Provenge* (sipuleucel-T) and investors have punished the biotech for the lackluster commercial performance. The same is true for recently approved agents such as *Arzerra* (ofatumumab), *Istodax* (romidepsin), and *Folotyn* (pralatrexate), which offer only incremental improvements in clinical outcomes but cost vastly more than their generic combination competition. In an increasingly cost-constrained global economy, developers can no longer trust that independent single agents will be able to deliver the significant survival improvements that physicians and payors demand. (See "What New Cancer Pathways Programs Mean For The Drug Industry," *IN VIVO*, May 2011.)

However, the problem lies not entirely with the agents themselves, but more in

the manner in which they were developed. As the standard-of-care improves in many cancer indications, achieving a clinically and financially meaningful difference becomes more difficult. Companies will need to develop novel combinations of molecularly targeted therapies to successfully compete with existing efficacious combinations of chemotherapies and single targeted therapies. A combination therapy that offers 6, 8, or even 12 months of survival benefit at \$100,000/year (\$50,000 per drug) is vastly more attractive to clinicians, patients, and payors than a single agent that provides 3 months of clinical benefit for \$80,000.

Thus, drugmakers need to move away from single-agent development to looking for combinations early and often. The FDA is committed to lowering regulatory hurdles for combination development, which will make combination trials easier, especially for agents with additive value in combination but not single-agent approvable. Business development efforts should also be focused on partnerships and licensing activity that can bolster and enrich the

power of the pipeline. The recent \$713 million deal between **Roche/Genentech Inc.** and **Array BioPharma Inc.** is especially promising in this regard, as it intends to marry ARRY-575, the small biotech's preclinical checkpoint kinase 1 (ChK-1) program with GDC-0425, a Phase I ChK-1 program. These agents will be advanced into trials together to test the hypothesis that dual kinase inhibitors of the DNA damage pathway will sensitize tumors to chemotherapy. Not only does this type of strategic dealmaking require close cooperation between development teams and business development professionals, but an organizational commitment to developing and commercializing combination cancer therapy. (See Exhibit 1.)

How can we ensure that deals like that between Genentech and Array, aimed at delivering intelligent and rational combination therapy, our best chance at improving outcomes in oncology, become the norm and not the exception?

In addition to better-credentialed agents targeting fundamental pathways on which cancer cells rely, companies

and trialists must focus on three elements: more creative trial design, increased collaboration, and better diagnostics. Indeed, oncology, with its exquisitely targeted pipeline, is routinely lauded for the development of agents like *Gleevec* (imatinib), *Herceptin* (trastuzumab), or *Xalkori* (crizotinib), which were launched in indications with prospectively defined patient populations. Typically lacking this type of definition, many sponsors still try to develop drugs for the broadest possible market and ignore or neglect addressable subsets. Even Genentech did not invest significant effort looking for *Avastin* (bevacizumab) biomarkers until it was facing marketing withdrawal from the EMEA and FDA for metastatic breast cancer. Only now is the company pursuing a trial to confirm the correlation of VEGF-A levels with therapeutic response and benefit. In order to see substantial gains in performance, companies need to accept biomarkers and biomarker-driven strategies from the get-go, measuring responses in Phase I and Phase II POC trials, enabling prospective identification

Exhibit 1

Recent Cancer Developer Collaborations

PARTNERS	DEAL OBJECTIVE	TERMS	TUMOR TYPE	YEAR
Merck AstraZeneca	Early (Phase I) Collaborative Development	Partners form alliance to conduct Phase I trials of ARRY-886 (MEK inhibitor) and MK-2206 (AKT inhibitor)	Likely development in colorectal and lung cancer	2009
Array Genentech	Early (Phase I) Strategic Licensing	Genentech to develop and commercialize CHK-1 kinase programs GDC-0425 (internal) and ARRY-575 (in-licensed)	Solid tumors or lymphoma (in combination with chemotherapy)	2011
Roche Bristol-Myers Squibb	Lifecycle Management	Partners form alliance to conduct Phase I/II study of vemuafenib and ipilimumab in melanoma to determine safety and efficacy of combination	Metastatic melanoma	2011
Merck Serono Sanofi Aventis	Early (Phase I) Collaborative Development	Partners form alliance to conduct combination Phase I dose escalation trials of Merck's MSC1936369B (MEK inhibitor), Sanofi Aventis' SAR245409 (PI3K/mTOR inhibitor) and SAR245408 (class I PI3K inhibitor) Sanofi will perform a study with its PI3k inhibitor and Merck's MEK inhibitor, and Merck will perform a study with its MEK inhibitor and Sanofi's PI3k/mTOR inhibitor	Solid tumors	2010

SOURCE: Health Advances; Elsevier's *Strategic Transactions*

of patients in pivotal trials, and provide a framework for future decisionmaking.

The future of oncology therapy depends on reinvigorating combination therapy, but doing so in a rational, sophisticated, and targeted manner. If the industry can develop and adopt best practices in trial design and on the diagnostic front, success rates should go up, development times down, and all parties are likely to benefit in terms of an improved cost/benefit ratio.

It will not be easy. Collaboration among competitors, complex trial designs, stricter regulatory policy and emerging payor sensitivity to high-priced therapies all pose systematic challenges to overcome. However, companies that can work together today to develop combination strategies will drive the next sea change in oncology treatment and reap the commercial benefits.

LEARNING FROM SUCCESSES IN ANTI-RETROVIRAL THERAPY FOR HIV/AIDS

As a model for combination therapy, perhaps there is none better than HIV/AIDS. Evolving from its single agent roots, HIV/AIDS therapy has developed into what we believe is the potential future paradigm for oncology: a diagnostic-driven, combination therapy market with a deep armamentarium of medicines that elicit durable responses.

Interestingly, in HIV, oncologists working with virologists used the painstakingly developed blueprint of combination chemotherapy to achieve a revolution in care. As Siddhartha Mukherjee, MD, PhD, eloquently lays out in his award-winning *The Emperor Of All Maladies: A Biography of Cancer*, the high oncologic burden seen in first-generation AIDS patients (over 60% of patients were presenting with Kaposi sarcoma or lymphomas) ensured oncologists were instrumental in developing early AIDS cocktails and porting multidisciplinary care to AIDS-specific clinics that emerged in San Francisco, New York City and other major cities in the 1980s.

Like cancer, HIV is prone to mutation, and it was quickly recognized that a combination approach would be necessary to effectively treat disease and prevent resistance from developing. Two ideas were critical in making this a reality: improved scientific understanding of the disease and the ability to design treatment regimens that combined complementary mechanisms. HIV care quickly evolved

from monotherapy with AZT to dual, triple, and now quad therapy.

These advances have had a dramatic impact on disease progression and overall survival. Between 1987 and 1994, HIV annual mortality rates spiked, reaching a high of 17 per 100,000; however, by 2003 advances in HIV therapy reduced the mortality rate to around 5 per 100,000, where it has hovered since. A patient diagnosed with HIV today will live an average of 23 years, with a similar survival rate to the general population according to a 2010 study by researchers at the **Centers for Disease Control and Prevention** (part of the **US Department of Health and Human Services**). This success does not end with patients, but extends to drug manufacturers as well. Between 2004 and 2008, **Gilead Sciences Inc.**, the market leader for HIV treatment, saw annual revenue growth of 50% as anti-viral sales grew from \$900 million to \$4.7 billion; this growth compares favorably with the increases seen by Genentech/Roche's Avastin and Herceptin over the same period.

THE FIRST GENERATION OF ONCOLOGY COMBO TRIALS

The mapping of the human genome ushered in an era of optimism and hope for a less complex drug development process; many believed that each cancer could be mapped to a single master gene that would serve as an Achilles' heel to attack with therapeutic approaches. The success of both Gleevec, which specifically targets BCR-ABL, the constitutively active kinase product of the Philadelphia chromosome translocation, and Herceptin, which targets the Her2 receptor overexpressed in aggressive breast cancers, furthered this notion. Unfortunately, the clinical outcomes seen with Gleevec and Herceptin have not been replicated by other targeted therapies such as Avastin or *Erbix* (cetuximab). In fact, recent work from the **Broad Institute** published in *Nature* in 2010 has revealed a striking genetic diversity in many tumors: in certain lung, colorectal, prostate, and brain tumors, for instance, 10 to 15 pathways are consistently mutated, with multiple pathways resulting in uncontrolled cancer growth. As a result, oncology therapy will not be solved by simple, single-gene, single-target approaches, but will require the combination of multiple agents to disrupt the multitude of aberrant signaling pathways active in

most tumor cells.

While hundreds of oncology combination trials are already ongoing, these are unlikely to fulfill the hopes for most patients as most test for only marginal benefit or constitute incremental life-cycle management strategies for already launched agents. For example, a recent analysis of www.clinicaltrials.gov suggests that of the approximately 350 Phase II or III clinical trials evaluating Avastin in oncology, over 40% are testing combinations with other marginally effective agents. Even if some of these combinations prove efficacious, is the scant few months of survival benefit gained with a regimen like Avastin plus *Erbix* really what physicians, patients and payors are looking for?

The need, then, is not just for combination therapy, but combinations designed to combat a specific tumor makeup based on genetic information and validated by companion diagnostics. Only then will combinations provide better outcomes – most importantly increased survival – for patients.

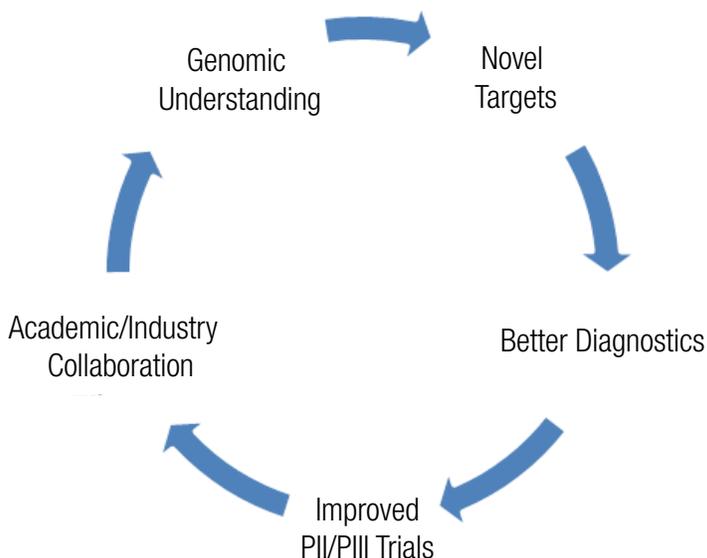
PHASE II DEVELOPMENT STRATEGY

What's needed now are strategies to develop novel oncologics effectively and collaboratively, moving away from the current and largely ineffective single-targeted agent paradigm. (See *Exhibit 2*.)

Perhaps nowhere is the need for improved trial design more apparent than with current Phase II programs. Too focused on reducing time to value-driven milestones, managing cash burn, and minimizing patient numbers, the Phase II trials undertaken by many companies yield only marginal results and bias further development toward pivotal trial failure. A number of late-stage trial failures, including **Sanofi's** iniparib and **Eli Lilly & Co.'s** necitumumab and tasisulam, illustrate the risks of relying too heavily on weak Phase II data. Paul Cuddon, PhD, an analyst at Peel Hunt, noted these development difficulties "reflect a broader problem in cancer drug discovery where Phase II trials are too small and uncontrolled" and fail to "identify specific groups of patients." Nor is this an issue for one or two drugmakers: a 2011 study in *Nature Reviews Drug Discovery* showed that overall Phase III success rates have fallen to only 50% as a consequence of flawed Phase II trials, and two-thirds of these failures were due to efficacy.

Traditional Phase II designs are designed to test toxicity, not efficacy, and are inap-

Exhibit 2

Components Of Next-Generation Oncology

SOURCE: Health Advances

appropriate for new targeted agents, where achieving therapeutic dose – not limiting toxicity – is the key issue. Already studies built on more sophisticated clinical trial designs are underway, but these need to be the rule and not the exception. Indeed, industry must strive to create larger Phase II trials with control groups, while utilizing better surrogate biomarkers and disease progression endpoints. Randomized discontinuation trials (RDT), which have been used in the development of **Onyx Pharmaceuticals Inc./Bayer AG's Nexavar** (sorafenib) and **Exelixis Inc.'s cabozantinib**, identify responders with a run-in period and then randomize patients to stay on or discontinue the agent. These trials may be inherently better for targeted therapeutics because they screen for response, not cell-killing. RDT trials allow increased statistical power and reduced patient numbers, in some cases requiring 20% -50% fewer patients than a classically designed trial. Because such trials enrich the patient population for drug responders, they also have the added advantage of minimizing the number of patients exposed to ineffective drugs.

COLLABORATIVE DRUG DEVELOPMENT

Beyond this, however, there needs to be a major shift in how combinations are devel-

oped, and the expectations on manufacturers in terms of data necessary for approval. Until recently, a classical combination trial would need to consist of four separate arms, one for each individual drug, the combination, and placebo. This type of design is cumbersome and nearly impossible to execute in today's environment. Thankfully, the FDA released draft guidelines in late 2010 for the development of combination therapies that provide increased design flexibility. CDER's guidance provides for testing drugs as multiple active agent combinations, single agents administered separately or sequentially, and even for combinations of one active drug with an independently inactive or minimally active drug that happens to be effective in combination. The FDA will require compelling evidence to allow drugs to be developed through this novel regulatory framework, however. Companies will not only have to provide data showing traditional development would be inappropriate. They must also supply results from novel preclinical experiments that utilize validated biomarkers and stem from data-driven hypotheses to support the use of a combination pathway. Ideally, these requirements will streamline development efforts for combination regimens, as a "minimally active" partner drug would only need independent Phase I safety data. (See Exhibit 3.)

By showing a willingness to engage with manufacturers early in the development process of combination therapy, FDA has put the onus squarely on companies to seek creative solutions to the problem at hand. Frequently that means collaboration.

HOW TO DO COLLABORATIVE DEVELOPMENT

For obvious reasons, collaboration, ever the backbone of scientific progress, is difficult for companies, and not just in oncology drug development. But it is more important in oncology than other therapeutic segments, not least because of cancer's rapid ability to achieve resistance by subverting parallel or compensatory pathways. As outlined in Exhibit 1, several recently announced partnerships and FDA action suggest that companies are willing to be more creative. The 2009 collaboration between **Merck & Co. Inc.** and **AstraZeneca PLC** seems to be the blueprint for broader industry-wide collaboration. In this case, two manufacturers each had a targeted agent (anti-AKT and anti-MEK) that was likely more valuable in combination than as a single agent. (See "AZ and Merck: Moving Forward Cautiously," IN VIVO, May 2010.) Indeed, recent data published in *PLoS ONE* from a group at the **University of Texas MD Anderson Cancer Center** suggests the combination of these two agents results in a cell killing effect far beyond either agent alone both in vivo and in vitro. Perhaps heartened by these developments, or perhaps seeing the situation for what it is, Sanofi and **Merck KGAA's Merck Serono SA** announced in December 2010 a collaboration to explore combinations of anti-MEK and anti-P13K inhibitors that as single agents might otherwise not achieve clinical efficacy.

Melanoma offers a potent example of a field of development with a wealth of novel targeted therapies in single-agent and combination alternatives. And, melanoma specialists' enthusiasm for significant therapeutic improvement is at an all-time high with the first agents capable of improving survival recently launched. (See "Front-Line Of Melanoma Market Could Be Marketing Battle," "The Pink Sheet," June 13, 2011.) Unfortunately, these agents have flaws. **Zelboraf** (vemurafenib), in a pivotal study published in the *New England Journal of Medicine* in 2011, was only effective for 6-7 months despite its remarkable 48% response rate in a difficult-to-treat patient population. Ipilimumab was trialed in pre-

Exhibit 3

Summary Of FDA Combination Therapy Draft Guidance For Proof-Of-Concept Trials

DEVELOPMENT OPTION	TRIAL DESIGN(S)	ENDPOINTS	ADDITIONAL CONSIDERATIONS
Components not individually administered	Combo v. Standard of Care (SOC) Combo plus SOC v. SOC	Clinical endpoints like overall survival (OS) and progression-free survival (PFS) Pharmacodynamic biomarker or other biomarker (e.g. tumor response) acceptable	Combination should be for treatment of a serious disease or condition Compelling biological rationale for the combination Preclinical (in vivo or in vitro) or short-term clinical study with established biomarker shows "substantial activity" and "greater than additive activity" or a "more durable response"
Components individually administered	Drugs A and B combined v. Drug A v. Drug B v. Standard of Care (SOC) Drugs A and B combined plus SOC v. Drug A plus SOC v. Drug B plus SOC v. SOC Potential for adaptive trial design	Clinical endpoints like overall survival (OS) and progression-free survival (PFS) Pharmacodynamic biomarker or other biomarker (e.g. tumor response) acceptable	Compelling reason why agents can't be developed individually (monotherapy leads to resistance or agents would have limited single agent activity) Biologic rationale, non-clinical safety, and Phase I toxicology and clinical pharmacology required as if drugs are developed independently
One active, one inactive	Drugs A and B combined v. Drug A v. Standard of Care (SOC) Drugs A and B combined plus SOC v. Drug A plus SOC v. SOC	Minimally active drug does not need to advance beyond Phase I safety as single agent Active drug should be in single agent Phase II Pharmacokinetic or dynamic biomarker data useful	

Source: Health Advances; CDER Guidance Document For Industry Codevelopment of Investigational Drugs, December 2010

viously untreated metastatic melanoma and was able to extend overall survival to 11.2 months in combination with dacarbazine, compared to 9.1 months in patients receiving dacarbazine alone. But almost 80% of patients had immune-related adverse events, including 21% with grade 3 or 4 liver function elevations (this study was also published in the *New England Journal of Medicine* in 2011). Unlike CML, which primarily evades Gleevec therapy by mutating the BCR-ABL binding pocket, melanoma rapidly escapes mutant BRAF inhibition through a variety of resistance mechanisms. In fact, recent analysis suggests that over 16 unique resistance mutations can be linked to the resistance seen to vemurafenib after just seven months on therapy.

These data clearly demarcate the outer limits of individual therapy, and in response, developers are embracing combination. Physicians are eagerly awaiting initiation of combination trials with ipili-

mumab and vemurafenib and Bristol and Roche have already announced they will collaborate on a Phase II trial. But doctors would also like the opportunity to explore myriad second line options, including **GlaxoSmithKline PLC's** MEK and mutant BRAF inhibitors, **Novartis AG's** nilotinib, and the eventual use of mTOR and PI3k inhibitors in combination to block MAPKK pathway-driven resistance. GSK is already running a combination pivotal trial with its BRAF and MEK inhibitors, and Roche is using an internally developed MEK inhibitor, GDC-0973, to synergize with vemurafenib. Physicians are collecting germ-line samples from each patient enrolled in current trials to test these samples for mutations. Eventually, this information will allow the rational selection of patients on more than just pathologic criteria or the presence or absence of a particular drug target.

Similar efforts are underway in lung cancer. In a 2010 paper published in

Science Signaling, researchers at the **Fox Chase Cancer Center** identified 61 genes that contribute to EGFR inhibitor drug resistance. This work uncovered clinically relevant, druggable targets for lung cancer that could be exploited in combination with EGFR inhibitors. More efforts focused on entire signaling networks, rather than exploiting single tyrosine kinases, will be required to effectively treat not only primary tumors but also tumor resistance. This is an area of considerable excitement in the field. One thought leader recently interviewed by Health Advances observed that "combining one drug or another for a few days or weeks of benefit" was not a sustainable strategy, and the future lay in combining targeted therapies (creating synergistic anti-tumor effects) based on response and activation of resistance pathways. Targeting a tumor's "vulnerability spectrum" with multiple agents should produce concrete and durable clinical benefit.

GETTING SERIOUS ABOUT BIOMARKERS & DIAGNOSTICS

The third and perhaps most critical element in moving toward better combination therapies is the development and clinical availability of improved biomarkers and diagnostics. In HIV/AIDS treatment, periodic tests give accurate information on the sensitivity and resistance of the individual patient's virus to the available antiretroviral armamentarium. These phenotypic and genotypic tests provide a real-time snapshot of disease and treatment efficacy, allowing clinicians to rationally plan therapy. In the cancer clinic, a focus on single genes and pathways must give way to simultaneous interrogation of complex networks. These monitoring technologies are not yet available commercially, but are already being used in clinical investigations in acute leukemia and myelodysplastic syndrome.

Scientists and clinicians have long realized that the underlying molecular makeup of a tumor is a stronger predictor of response to treatment than the site of disease origination. The BATTLE trial in non-small cell lung cancer deployed a novel trial protocol, testing each of the 255 enrolled patients to obtain a biomarker profile based on a fresh core needle tumor specimen, collecting biomarkers including EGFR mutation status and copy number, KRAS/BRAF mutation status, and VEGF/VEGFR-2 expression. On trial, after an eight-week period of equal randomization in which patients could receive either Tarceva (erlotinib), Zactima (vandetanib), Tarceva and Targretin (erlotinib and bexarotene), or Nexavar, patients were adaptively randomized by their biomarker results to either continue on their existing drug or be randomized to one of the other three treatments. This second treatment was selected by individual biomarker analysis to be the treatment with the greatest potential for efficacy for the patient. This study marks a watershed moment in oncology drug development, not only for the level of collaboration it required among the researchers, but also because of the ability to apply the data generated in the trial on a real-time basis. Published in the inaugural issue of *Cancer Discovery* in 2011, the trial showed an overall 46% eight-week disease control rate and discovered a benefit for Nexavar in KRAS-mutant patients. As the researchers learned more about what worked and what did not work in certain patient

populations, they were able to modify their treatment approach in subsequent treatment strategies. In effect, this was an adaptive trial that leveraged existing biomarkers to improve clinical outcomes with existing agents.

In the cancer clinic, a focus on single genes and pathways must give way to simultaneous interrogation of complex networks.

BATTLE and I-SPY 2 (focused on breast cancer) are both groundbreaking trial designs, but the true legacy of these trials will be only realized if the extraordinary becomes routine, with diagnostics regularly used in patients with diverse tumor types and these results used to guide treatment decisions.

Indeed, manufacturers need to recognize the power of diagnostics to aid patient selection and improve response rates, and be confident they will recognize the market, regulatory, and payor benefits of personalized medicine. Two recently approved compounds, **Plexikon Inc.**'s Zelboraf targeting the V600E mutation of BRAF and **Pfizer Inc.**'s Xalkori targeting mutations in EML4-ALK (reporting an 80% response rate in Phase II trials), are further evidence of the importance of companion diagnostics. Armed with a robust test, the companies were able to accelerate the development of each compound and demonstrate enviable response rates, garnering regulatory approval well ahead of schedule.

In the case of crizotinib, scientists at **Sugen Inc.** (which was acquired by **Pharmacia** and came to Pfizer via its \$59 billion mega-merger with that company) had in 2004 developed a c-Met tyrosine kinase inhibitor that produced only mediocre results in a population of all-comers with lung cancer. Crizotinib was a drug candidate going to be deprioritized, but fortuity struck in 2007 following the identification and publication in *Nature* of the EML4-ALK fusion protein, present in around 7% of lung cancer patients. Pfizer discovered crizotinib was a potent ALK inhibitor,

and began targeted development in collaboration with **Massachusetts General Hospital**. Pfizer was able to slash its development time on crizotinib with the EML4-ALK biomarker, advancing crizotinib from hypothesis to market in only four years. Ultimately Xalkori was approved with a companion diagnostic ahead of its PDUFA date and on the basis of two multi-center, single-arm studies enrolling just 255 ALK-positive patients.

Unfortunately, as discussed previously, these dramatic initial clinical responses are not durable and researchers are quickly developing a variety of combination strategies to overcome resistance. Notwithstanding front-line successes, the real battles will be developing the combination regimens that can keep tumors at bay for a long time. The key to developing these combinations efficiently is gaining a clear understanding of the unique mechanisms of resistance across patient subtypes. In the case of vemurafenib there are a wide variety of resistance mechanisms that will dictate the optimal combination strategy for each patient. This can only be elucidated through novel complex diagnostics, which are the key to lowering both the risk and overall development cost for combination therapy developers.

For drug developers, the most relevant argument may be a negative one. Neglecting biomarkers is simply not an option in oncology today. Sanofi discovered this through their unselected (and negative) Phase III trial of PARP inhibitor iniparib in triple negative breast cancer. There is still potential for iniparib in refractory triple negative breast cancer, but testing for BRCA1 and 2 in patients could have gotten the drug onto the market today. Even Roche is depending upon a newly identified VEGF-a biomarker to identify patients that will receive benefit from Avastin, hopefully translating into a prospectively selected (and label-saving) trial in metastatic breast cancer.

CONCLUSION

So what does the future look like? A patient presents to a clinic with cancer. The tumor is worked up pathologically, sequenced for key mutations, assayed for sensitivity to chemotherapies and targeted combinations. A rational plan is designed, based on the results of these complex diagnostics. In BRAF-mutated metastatic melanoma, first-line therapy could involve the combination of a BRAF inhibitor with either a MEK inhibitor, a P13K/AKT inhibi-

tor, or an mTOR inhibitor, based on the unique signaling profile of the patient's tumor. This rationally selected combination would then cover the cancer's preferred growth and survival signaling pathways.

For drug developers, the most relevant argument may be a negative one. Neglecting biomarkers is simply not an option in oncology today.

This may sound like science fiction, but many of these targeted molecules are already in the clinic, and the diagnostics are already on the laboratory shelf. The unmet need is combination development, not in the traditional, incremental, laying of new therapies on top of proven ones, but in

combining new targets and quantitative reports of target inhibition in real time.

Oncology has experienced three revolutions in the past century: surgical, chemical, and now informational. By combining agents in an intelligent, fact-based fashion, the field can move from the incremental benefit of additive single-targets to the synergistic benefit of rational combinations. These new combination therapies should be less risky, quicker to develop, and present authentic clinical benefit via gains in overall survival. As Anas Younes, MD, professor of medicine at MD Anderson says, the paradigm has to shift or "we will be stuck with R-CHOP [Rituxan plus chemotherapy] for the next 30 years... [and] stuck with a 45 to 50% cure rate." Without patient identification and new targets, the substantial fraction of patients that do not respond to traditional therapies like R-CHOP will continue to be underserved, and won't have access to rational combinations based on biomarkers and deep tumor understanding.

Companies targeting oncology need to eschew their pursuit of single agents

with marginal benefits and prioritize novel targets and synergistic, biomarker-driven, combinations. By making these critical changes, developers will be able to meet increased regulatory hurdles, will likely garner more approvals, and will provide patients with efficacious therapeutic options.

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