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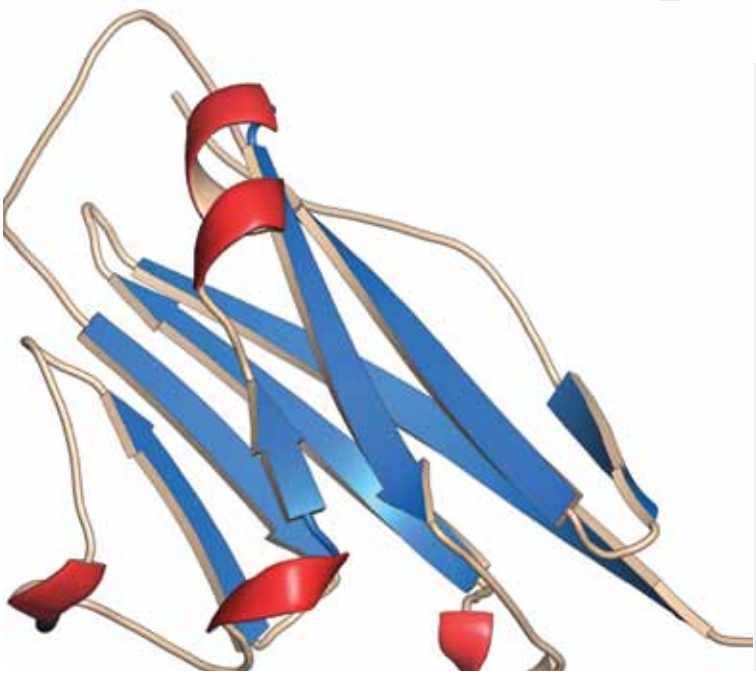
How Immuno-Oncology Is Turning Biomarker Development On Its Head



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Immuno-oncology's challenge is to orchestrate a biomarker program in a highly competitive drug development landscape knowing that prior to having significant clinical experience, the program is unlikely to yield the kinds of binary measurements used to define and select a patient population for a targeted therapy.

BY OLIVIER LESUEUR, RACHEL LAING AND MARK RATNER

With so much opportunity staring them in the face, IO companies are not waiting for biomarkers to emerge to commercialize their drugs.

Neither the content nor the platform(s) for measuring IO biomarkers is as yet determined.

But fitting a considerable biomarker research component into the IO discovery/development process may well be a key element of product differentiation, which is especially important for small companies seeking to enter the market in a niche indication.

The information taken from clinical testing will be the basis for the retrospective identification and validation of predictive markers. This requires a higher biomarker-related spend than has been needed for other molecular therapies, even if their application as a diagnostic is problematic.

For more than a decade, the marching order for drug developers has been that every drug candidate proceeding beyond a proof-of-concept study should be accompanied by a biomarker. Immuno-oncology (IO) is turning that notion of biomarker development on its head. In IO, the role of a biomarker goes well beyond identifying whether the drug target (usually a genetic mutation or rearrangement, in the case of a targeted therapy) is present in a given patient and whether the drug candidate can be delivered at a dose that allows for effective modulation of that target. The challenge in IO – especially for the current wave of drug development programs that look to combine PD-1/PD-L1 targeting agents with drugs that modulate additional targets, IO or otherwise – is in how to orchestrate a program efficiently in a highly competitive landscape without the benefit of the kind of binary measurement that is used prospectively to define and select a patient population for a targeted therapy. In IO, predictive tests will only be identified retrospectively after much guesswork around choosing the combinations to test: the tail will be wagging the dog. To paraphrase from the realm of political investigation, discussions about a successful biomarker development path in IO will turn on questions of what did you know and when did you know it.

As the initial wave of checkpoint blockade drugs establish themselves, led by the first PD-1/PD-L1's *Opdivo* (nivolumab, from **Bristol-Myers Squibb Co.**), *Keytruda* (**Merck & Co. Inc.**'s pembrolizumab) and most recently *Tecentriq* (atezolizumab, from the **Roche** unit **Genentech Inc.**), the landscape for oncology drug development is changing rapidly. The chances of enrolling a pure population of IO drug-naïve patients for clinical trials has already diminished for any drug because of the opportunity for greatly increased survival that IO treatments offer, even if for a small proportion of patients. Would-be entrants have quickly pivoted toward establishing the effectiveness of combination therapies that include a checkpoint blocker in more carefully defined subpopulations as the means for gaining a competitive edge. Because there appear few obvious ways to differentiate the PD-1's based on mechanism of action alone, homing in on an indica-

tion and a specified subgroup of patients becomes even more important to be able to establish a first-mover advantage that is more than a short-lived blip.

How, then, to accomplish this when biological understanding, if rapidly evolving, is early and when the tools for elucidating the complexities of the interplay between tumor and immune system are not yet in hand? The makeup of a tumor, priming of a patient's immune system, tumor microenvironment, degree of lymphocyte infiltration, and presence and release of neoantigens are all potential considerations when choosing an indication for IO drug therapy.

With an abundance of potential disease targets and approaches comes the potential for product differentiation. An oncology drug developer will be able to benefit from the relatively early science in that there are more chances to grab a piece of the pie, even if a smallish one. The hundreds of clinical trials of IO agents across tumor types and disease stages, in almost any combination imaginable (with and without another IO drug), suggest that companies are looking for any and every way to show that the efficacy of a combination approach is higher than that of an IO monotherapy.

Without a differentiated product, it's unrealistic to assume a new entrant will be able to seize a competitive advantage for long: companies all want a unique combination that they can bundle versus a commodity backbone monotherapy. Fitting a considerable additional biomarker research component into the IO discovery/development process may well be a key element of differentiating a drug, be it through parallel introduction of a companion or complementary diagnostic, or by showing that such a tool is not needed (an element of confusion the market is already experiencing among the approved PD-1/PD-L1 agents). "The challenge is to turn immunotherapy back into a biomarker-driven therapy," says Roy Herbst, MD, PhD, chief of medical oncology at the **Yale Cancer Center**.

The PD-1 class of drugs, including antibodies that target PD-1 itself or its main binding partner, PD-L1, as well as Bristol-Myers' *Yervoy* (ipilimumab), which targets CTLA4, are the first generation of IO agents aimed at unlocking the immune system's ability to identify and destroy tumor cells. PD-1's are similar to targeted therapies in that they have a binary biomarker associated with them: PD-L1 protein expression, the first and to date the only IO biomarker. But PD-L1 is a relatively poor marker for several reasons. Its expression levels do not clearly correlate with response, those levels change over time, and they may vary depending on exposure to therapy. Beyond PD-L1, getting one's arms around IO biomarkers becomes even more complicated because the function of IO drugs, presumably used in combinations, will rely on stimulating other properties of the immune system. "Biomarkers will be important, but the nature of those biomarkers and the types of biomarkers will be extraordinarily complex," says Kapil Dhingra, MD, principal at KAPital Consulting and former VP and head of oncology clinical development at Roche's Hofmann-LaRoche division.

> *"In 18 to 24 months, companies will probably be asking why so many of the combinations that made theoretical sense haven't worked. In particular, they will be wondering whether they used biomarkers properly to guide the best selection of patients toward the best combinations for them."*
>
> *– Kapil Dhingra, MD, KAPital Consulting*

Working Backwards

Targeted drugs against defined genetic alterations directly inhibit cancer cells. Therefore, markers to predict sensitivity to these drugs are largely found in the cancer cells and can generally be hypothesized intuitively. This molecular drug development strategy changed with the launch of *Avastin* (bevacizumab), a drug that targets angiogenesis (blood vessel formation) to block a tumor's blood supply, in 2004. The biomarker challenge further accelerated with the dawn of the immune-oncology era.

"Especially with IO agents against targets other than PD-1/PD-L1, you are getting into a much more dynamic environment," Dhingra says. The genetic makeup of cancer cells, their immunosuppressive capabilities including presentation of decoy surface receptors and the need to combine a variety of drugs modulating different cellular components of the immune system are all relevant considerations in IO drug development. "There is much more complexity in terms of the interplay of the tumor cells, the microenvironment and systemic immune parameters," he says. "We need to triangulate these in order to come up with useful biomarkers to guide optimal treatment."

Preclinical models have generally not proven to be good predictors of clinical

Exhibit 1
Selected IO/Dx Partnerships

PHARMA/DX PARTNERS	DEAL TERMS
Merck & Co./Nanostring Technologies	Merck is sending samples from patients treated with Keytruda off to collaborator Nanostring, which is compiling a mountain of Big Data embracing that treatment population based on a gene signature Merck discovered and is moving forward to commercialization
Genentech/Foundation Medicine	Roche/Genentech expects to be able to use the Foundation Medicine platform to sequence DNA and RNA and measure T effector cell signatures, mutation burden and driver mutations, at the same time, in time leading to a universal IO diagnostic test
HalioDx/Nanostring Technologies	Nanostring is providing nCounter to HalioDx to enable the latter's development of a gene expression signature based on quantifying the number of tumor infiltrating lymphocytes (CD8 and CD3 cells) on the surface of tumor cells, as a prognostic tool for early-stage colon cancer and to help predict response to IO therapies
Bristol-Myers Squibb/ HTG Molecular Diagnostics	BMS will use HTG's EdgeSeq NGS platform to profile tumors as part of the big pharma's immuno-oncology translational research
Merck KGAA & Pfizer/Dako AS	Expanding upon an existing agreement, Merck KGAA and Pfizer have enlisted the help of Agilent Technologies' Dako AS to develop a companion diagnostic for avelumab

SOURCE: Strategic Transactions | Pharma Intelligence, 2016

efficacy, especially for treatments targeting the immune system. This makes discovery of predictive biomarkers extremely challenging prior to exposing patients to a drug candidate during a clinical trial. Given the complexities of the dynamism between tumor and surrounding environment, the lack of good preclinical models and limited efficacy of IO drugs as monotherapies, "it's reasonable to assume that a lot of combination successes will come from serendipity," Dhingra says. And with the natural impulse for companies to combine IO with what's already in their portfolios, there will be an abundance of novel combinations – a phenomenon already in evidence among the market leaders. (*Also see "Bristol Pushes Pedal To Metal In Immuno-Oncology Combo Testing"* – Scrip, *July 4, 2016.*) (*Also see "Roche's Guide To Success In Oncology"* – Pink Sheet *June 27, 2016*.)

Unfortunately, as data come out, reality will set in. "In 18 to 24 months, companies will probably be asking why so many of the combinations that made theoretical sense haven't worked," Dhingra predicts. In particular, they will be wondering whether they used biomarkers properly to guide the best selection of patients toward the best combinations for them, he says.

"If you are going to be competitive in the space you have to understand the biology of the compound: it will help you define and prioritize your next set of targets for combinations," says Stanley Frankel, MD, corporate VP and head, immuno-oncology clinical R&D at **Celgene Corp.** Hence the need for exploratory biomarkers.

In developing molecular therapies, clinicians want to limit the patient population to those expressing the drug target, and perhaps also avoid situations where a mechanism of resistance or a compensatory mechanism exists. In IO, however, when perturbing one part of the immune system with the promise of therapeutic activity, the compensatory mechanisms that may exist in the patient are unknown. The challenge is not just understanding whether the drug works, but also what happens as a consequence if there is clinical activity when a pathway is blocked. "This is fundamental to finding the next generation of IO therapies," Frankel says, including defining and prioritizing your next set of targets for combinations. The process is especially difficult because "we don't have all the drugs developed that hit the alternative ways in which a cell may be either seen or hidden from the immune system," he says.

That many patients will have already received a PD-1 drug further complicates matters. "The idea that you are going to see, by luck, a very large signal – either response rate or time to progression – in patients who have already seen a PD-1 or PD-L1 inhibitor seems overly optimistic," Frankel adds. In particular, he says, biomarkers could play a significant role retrospectively in trials that enroll all comers, with drug developers later figuring out how to characterize the responding patients.

As a result, the drug-diagnostic co-development path is far from straightforward. "I don't think it is reasonable to expect, as the FDA initially wanted, that there would be a companion diagnostic

for Phase I for everything you are going to do," Frankel says. Technology has been advancing way too fast to lock that in when contemplating a three- to five-year development program, even under an accelerated regime to approval. "It's hard to lock down a diagnostic," he states, as evidenced by the multiple immunohistochemistry (IHC) tests available for PD-L1 and the Blueprint program aimed at making that testing more uniform. (*Also see "Industry, Cancer Groups Draft Blueprint For PD-1 Companion Dx Approvals"* – Medtech Insight, *March 27, 2015.*) And that's for measuring a single analyte.

Blueprint was necessitated because the PD-1 field was moving so fast that each company commissioned its own test, with different specifications. That led to different tests yielding different results in the same patient and the same tumor. "We should be creating biomarker tools, immune biomarkers that can be tested using the same assay (probably in array format) at the same time," says Axel Hoos, MD, PhD, VP, oncology R&D at **GlaxoSmithKline PLC.** "You might then get a platform for biomarkers that together may be relevant for identifying a certain patient," he says.

Taking serial biopsies and developing the right panel of tests to understand what's happening in responders and non-responders will be essential. "It's critical to understand what happens once a target is engaged," Frankel says. "We know there are going to be compensatory responses." Although much has been said about the ability of liquid biopsy to enable such testing, the technology remains aspirational. Other tools – multiplex IHC assays and next-gen DNA and RNA sequencing in particular – will maintain their place in the diagnostic armamentarium. Sequencing and RNA-based expression is relatively straightforward for a large number of targets using small quantities of material. Flow cytometry will be relevant, as will the continued use of IHC, despite the latter's inconsistencies depending on the antibody used and observer bias. IHC will also become more sophisticated in time, with multicolor staining to more carefully see what cell expresses the target, not just whether the target is present.

Real-time imaging of markers in blood or bodily fluids could also be used for monitoring in IO. But with imaging, even relatively straightforward strategies like using antibodies that target known markers such as Her2 or EGFr and imaging those markers throughout the body have not been made to work. "To think we can [develop a] real-time imaging modality that can somehow assess macrophages, tumor cells, lymphocytes all in metastatic lesions doesn't seem feasible in a 10- to 15-year time frame," acknowledges Dhingra.

Beyond PD-L1

Several factors limit the use of PD-L1 expression as a predictive biomarker and explain why expression of the protein does not tightly correlate with response. PD-L1 can be induced by various therapies, stress or lymphocytic infiltrate. A PD-1 drug may work in patients with low PD-L1 expression because the test was run on an archival specimen not representative of what is going on in the tumor at the time a patient started on drug. When looking at the effects of checkpoint blockers in combination with other IO drugs, targeted agents or even chemotherapy, PD-L1 expression becomes even less predictive.

Looking at biopsies or samples during the course of therapy to gauge the therapy's pharmacodynamic effect and compensatory changes is very different than the application of a companion diagnostic, which will only tell you what to do at the beginning of treatment. Drug developers need additional markers such as those that measure genetic instability, basic characterization of lymphocytic response, and if the technology can be validated, liquid biopsy to monitor PD-L1 or other relevant markers over time.

The IO leaders are already enlisting diagnostics companies in this endeavor: Merck is now sending samples from patients treated with Keytruda off to collaborator **Nanostring Technologies Inc.**, which is compiling a mountain of Big Data embracing that treatment population based on a gene signature Merck discovered and is moving forward to commercialization. Roche/Genentech, via its relationship with **Foundation Medicine Inc.** (FMI), expects to be able to use the Foundation Medicine platform to sequence DNA and RNA and measure T effector cell signatures, mutation burden and driver mutations, at the same time, in time leading to a universal IO diagnostic test. (*Also see "Which Path Forward For Foundation Medicine?"* – In Vivo, *June 2015.*) Genentech's biomarker plan for Tecentriq leading to its approval in bladder cancer shows how even at this early stage, biomarker considerations can influence a trial, an approval and initial market penetration. (*See sidebar, "A Lesson From Tecentriq's Development."*)

Having in hand large clinical data sets will refine patient populations and indications and also inform combinations: once a data set for monotherapy is in hand, it will be possible to query patients who have failed their first line of IO to determine whether to enroll them in Phase I/II trials of a new agent or rapidly go to a combination to see if that changes response. The future lies in this dynamic process of testing that looks at multiple variables, then overlaying the results of clinical trials to define which set of patients to pursue.

FMI and **Personal Genome Diagnostics Inc.** (PGDx), among others, have plans to introduce tests that measure tumor mutation load – the next piece to be fitted into the IO biomarker puzzle. The increase in mutation rate in certain tumor types, as detected through genetic instability patterns, corresponds to response to PD-1 checkpoint inhibitor monotherapy. Although not specific for all these patients, mutation load could be used to identify those who would not have a significant benefit. "Given that PD-1 is the dominant drug at this point and for the next five-plus years, it is very likely that characterization of genetic instability phenotype will be done in all patients," Dhingra says.

"Mutation load is low-hanging fruit," notes Vincent Miller, chief medical officer at FMI. But it is not something that can be routinely generated by most of the tests that are available commercially, he says. "Measuring tumor mutational burden is the realm of companies doing a well-validated comprehensive genomic profile," Miller explains. "Any of the hot spot tests that have maybe 500 genes on them but only sequence a tiny portion of the gene(s) enriched for the oncogenic variants would not suffice to provide that information."

The vast majority of patients who do not exhibit a genetic instability or actionable mutations will have to be treated

A LESSON FROM TECENTRIQ'S DEVELOPMENT

Roche's Genentech Inc. unit enrolled all comers when it moved into Phase II in bladder cancer, the lead indication for *Tecentriq* (atezolizumab). It chose not to limit enrollment to patients with high levels of PD-L1 expression – unlike **Merck & Co. Inc.**, which did not include low PD-L1 expressers in its *Keytruda* (pembrolizumab) lung cancer trials.

The tactic could have severely hindered Tecentriq's chances, but when low PD-L1 expressers who didn't have the high immune score by their data nonetheless responded, the Food and Drug Administration invoked the relatively new informational term "complementary diagnostic" to advise physicians of the existence of PD-L1 testing without requiring its use (FDA has done the same with indications for **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) in non-squamous non-small cell lung cancer and melanoma). If Merck had included low PD-L1 expressers they might have achieved the same outcome as Genentech, and the test might not be required for a patient to get the drug.

With a complementary diagnostic, information on expression of a recognition marker should be provided to patients and their physicians because that might influence treatment decisions – in this case, advising those with low PD-L1 expression that they may wish to seek another therapy, including perhaps a combination of a checkpoint blocker plus something else. "This is about allowing physicians and patients to make better and more informed choices about what types of therapies to get," says Ira Mellman, PhD, vice president of cancer immunotherapy for Genentech, "and not, as some people say, excluding patients from therapy. When you think about it that way, you have done the best thing for patients; and you wind up getting an all-comers label anyway, which is basically what happened in bladder cancer."

FDA has yet to formally define complementary diagnostic, either in a guidance or through another mechanism: in a case where a drug is approved for an entire population, it is an informational term indicating that use of the diagnostic can help stratify those patients who can probably respond better.

Along with PD-L1, Genentech also included a variety of other biomarkers – mutation load, interferon gamma and TCGA (The Cancer Genome Atlas) status in their Tecentriq program. Both mutation burden and PD-L1 expression correlate with benefit from the drug. But clinical trials have yet to establish what the interplay is between those different features. "Once we understand that, we will have a better understanding of what the diagnostic tools would look like," says Genentech's Garret Hampton, PhD, VP, oncology biomarker development. And the degree to which IHC will be needed will depend on that interplay.

with agents that work at the level of local tumor, to change the microenvironment by causing the release of antigens or to suppress certain macrophages and local cytokines to make the tumor more responsive to PD-1's. Additional tests will therefore need to focus on antigens that the immune system can recognize and to which it can make an immune response. In that scenario, PD-L1 becomes just one component of the checkpoint suppression story, with a whole new angle emerging for the 60% to 70% of cancers where different approaches are needed to get the immune system to recognize them.

Ultimately, a biomarker platform for IO will have to look at DNA mutations, RNA expression and perhaps even protein expression to understand the extent of immune system activation and infiltration, as well as look at DNA mutations that drive tumor growth, to know how to combine IO with a targeted therapy. "I think it's too complicated a situation for an academic center to work up a home brew and validate on its own," says Nanostring CEO Brad Gray.

Nanostring is leveraging its gene expression measurement system, *nCounter*, in a variety of ways within IO: in addition to its deal with Merck, Nanostring is providing nCounter to **HalioDx SAS** to enable the latter's development of a gene expression signature based on quantifying the number of tumor infiltrating lymphocytes (CD8 and CD3 cells) on the surface of tumor cells, as a prognostic tool for early-stage colon cancer and to help predict response to IO therapies.

RNA signatures are particularly informative for IO. "When you sample what is going on in a tumor you are capturing both the tumor and the immune cells that are infiltrating the tumor," Gray says. "There are ways to deconvolute the information about what immune cells are there because they exhibit specific markers," he says, making RNA expression extremely important in IO. "It captures in one test both the biology of the tumor and the immune system that is infiltrating the tumor."

A variety of diagnostics tools companies including Nanostring, FMI and PGDx are showcasing their platforms and providing pharma with IO-oriented gene expression testing on a research basis.

In the next three to five years, combina-

tion tests that measure PD-L1 expression, establish a genetic instability phenotype of a tumor and identify the degree of lymphocytic infiltrate will become mainstays for gauging responsiveness in IO. (HalioDx, for example, is also combining CD8 with PD-L1 to improve PD-L1 IHC testing. "Combined with the use of digital pathology, we think we can potentially improve the sensitivity and specificity of a PD-L1 assay to better identify those patients who will benefit from checkpoint inhibitors," says CEO Vincent Fert.)

Farther out will come the time when each patient's tumor is fully profiled at initial diagnosis, including a full transcriptome profile, a selected proteome analysis and a full immune profile including not just lymphocytic infiltrates and expression markers and perhaps a liquid biopsy profile looking at the immune status of the tumor.

The goal is to have a universal test that could encompass all therapies for an indicated patient based on tumor type or stage of treatment. It would look at all possible therapeutic modalities – IO, targeted treatments, chemotherapy – and inform the entire treatment paradigm for that individual patient.

Market Impact

Once companies become systematic about selecting the right markers for cancer patients, they will move away from all comers to more select biomarker-driven patient populations. But that will happen over time.

"You need a lot of data to make a true assessment of whether a biomarker works for selecting patients and differentiating your drug," says Hoos. "With the speed the field moves with now, it's nearly impossible to have all of the data you would like to have before you make a determination on how to use the biomarker. That's what happened with PD-L1. It was meant to be a differentiation factor and got used before they fully knew what it meant." Indeed, with so much competition, the need for differentiation is so great that any emerging marker will likely become a tool for drug differentiation. But with multiple assets against the same target, that element of differentiation will get diluted very quickly. So while offering a potential first-mover advantage, it will be short lived. "The data will limp behind the need to make decisions," Hoos asserts.

> *"There is little choice except to use [a PD-1 drug] and then start to segment the population into patients for whom PD-1 alone is fine, those who need PD-1 plus another checkpoint modulator, then those who need PD-1 plus another antigen disease mechanism or who need PD-1 plus another macrophage suppression mechanism, etc. That is how the segmentation most likely will evolve."*

Following that rationale, we believe that the leading therapy companies will use their markers in drug development, but then only defensively in the commercial realm, suggesting that second-tier players and diagnostics companies will have to lead the way. And should diagnostics companies be collaborating with pharma companies on specific drugs for access to sample sets, they may not be able to use all of that data and those samples. To the extent that holds true, it falls to projects such as Blueprint to validate biomarkers for a broad set of drugs, or for a diagnostics company to work with many different pharma companies with assets in the class.

There is little evidence of this to date in IO, owing to the fast-moving development pace. But with Blueprint, "the idea of harmonization really is catching on," Hoos says.

Already, PD-1's have found their place as foundational cancer treatments. Even low PD-L1 patients can have some benefit from PD-1's, and given the lack of predictability of preclinical models and the challenges for finding biomarkers, there is little choice except to use one and then start to segment the population into patients for whom PD-1 alone is fine, those who need PD-1 plus another checkpoint modulator, then those who need PD-1 plus another antigen disease mechanism or who need PD-1 plus another macrophage suppression mechanism, etc. That is how the segmentation most likely will evolve. The more the implications of modulating the immune system become clear, the more biomarkers can be applied to figure out where the block in each patient is – at the level of antigen release, antigen presentation, immune response formation or the effector side of the immune response. The timing of that innovation is far from clear, however; we would guess a minimum of five to 10 years.

In the meantime, we foresee tests becoming fairly centralized, particularly in pathology departments of major institutions. Large genomics instrumentation and/or Big Data-focused diagnostics companies – Roche, **Illumina Inc.**, even **Google Inc.**, for example – will also be in a good position to effectively aggregate a variety of tests and platforms: they could take the multiple cell types that are constantly changing along with the choice of dozens of possible drugs, test them together and have the bioinformatics to determine the likelihood of response to certain treatments.

Such a platform must provide results that patient and provider can readily understand: a test will be sent off and come back with a defined set of treatment options, including the risk/benefit profile

of giving a particular drug.

Assuming an approved platform and reagent set and validated data, the interpretation of those data should be able to set the label for a companion diagnostic, either for one drug or for a class of drugs – the latter being the preferred outcome for a diagnostics company if not for a pharma wanting to direct use of its drug.

Payers likely will not proactively push for biomarkers and fund studies absent a clear rationale and expectation that a biomarker would reduce the total system cost of therapy (which is not clear with a complementary diagnostic, for example). Rather, look to collaborative groups and the second-generation IO companies that will want to carve out a subset of patients using biomarkers either based on those who don't respond to PD-1's at all or through identifying higher-responding subsets within the PD-1 population.

Diagnostics companies are limited by access to the sample sets needed to discover and validate biomarkers, says David Brunel, CEO of blood-based immunotherapy diagnostics developer **Biodesix Inc.** "I think it will be the competitive forces in pharma that drive this in the end," he says. "We have explored trying to get payers to take a very different approach than in the past and put some resources behind helping making sure the right drug gets to the right patient. It's been brought up but they scratch their heads."

Where We Stand

It is too much to expect to know the precise role predictive biomarkers will play in IO and the platforms that will be used for testing. But even with uncertainties around the shape of future IO biomarker content, we argue that significant and early investment in biomarkers is essential, especially for second-generation IO companies seeking to identify combination therapies. Diagnostics companies are already out there seeking to work on such programs on a fee-for-service basis. They have much more of an interest in driving the adoption of biomarkers in IO than does big pharma.

The market-leading large pharmas are collecting clinical samples representative of treatment from hundreds of trials using IOs in combination regimens across a broad spectrum of diseases. They have the experimental foundation for conducting retrospective analyses aimed at finding subgroups of responders based on their tumor and immune system profiles. At least for now, however, they are playing a waiting game and not aggressively seeking to commercialize biomarkers representative of those profiles.

The same wait-and-see attitude should not pervade smaller next-generation companies with new IO drugs. Those firms must care more about validating biomarkers to be able to home in on a niche indication where they can run a fast trial and get approval. They will also need a biomarker to differentiate in a crowded indication where current players are taking an all-comers approach. In either case, to be competitive they will need to have exploratory biomarkers embedded in those trials, taking a more aggressive stance in favor of ultimately seeking to validate them in diagnostic form. Otherwise, they are merely taking a shot in the dark hoping to find a strong signal in a crowded field where none have been forthcoming. And if these firms do gain any advantage, chances are it will be short-lived.

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