PD-L1: The Story So Far

The twists and turns of a new biomarker

Diaceutics

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Introduction

We are witnessing the start of a new era in which the old and well-known 'one-size-fits-all' approach to therapy is overtaken by the precision medicine concept of targeted therapies. It is an era in which the integration of diagnostics and biomarker detection on the treatment pathway is not an option, but mandatory.

One of the most talked about biomarkers in the context of precision medicine targeted therapy has been PD-L1. Diaceutics' real-time observation of PD-L1 reveals many issues of novel biomarker integration into treatment pathways and drug launch programs. Precision medicine continues to progress yet it still suffers from the lack of pre-launch market development of critical biomarkers, even though most of the issues surrounding PD-L1 testing have been seen before.

This Ebook tracks the story of PD-L1 through a series of Expert Insights written from 2015 to 2017, and examines topics including test availability, integration alongside more established biomarkers, complementary testing and how a suboptimal PD-L1 diagnostic marketplace can lead to lost treatment opportunities. In addition, it includes a concluding article about the FDA approval of Keytruda for specific biomarkers, to show the promise of a mechanism that allows for a broader, generic make-up.

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Diaceutics is a global group of experts from the laboratory, diagnostic and pharmaceutical industries. Our goal is to help pharmaceutical companies to integrate diagnostic testing into their treatment pathways. We are empowered through a real-time flow of testing data from our worldwide laboratory network which we use to help our pharma clients understand and leverage the diagnostic landscape.

Test availability at launch can be underestimated, under-budgeted and under-resourced: An example using real-time, real world analysis of PD-L1

Diaceutics gave a presentation at TriCON 2017 discussing how biomarkers and diagnostics are still falling short at launch, even though the industry is no longer in its infancy. Here, Jordan Clark, Managing Director with Diaceutics, reports on how we can track the real-time, real world development of PD-L1 in NSCLC and highlights the differences in the test's availability, budgeting and resourcing.

The dynamic PD-L1 space provides opportunities to undertake real-time market analysis and improve our understanding of novel biomarker adoption. It's an interesting space, too, seeing as in the first 18 months since launch over 70 US labs are using the test, indicating PD-L1 testing has a fast-track pattern of uptake in parallel with treatment recommendations. It's also in line with ALK and EGFRm - 75% of all NSCLC trials for five PD-1/PD-L1 therapies are likely to require known PD-L1 status, bringing PD-L1 in line with ALK and EGFRm as key disease-based biomarkers. When we combine these facts with the knowledge that the anti PD-1 therapy class of drugs is slated to achieve $33 billion, it is worrying that the PD-L1 testing market is still underdeveloped.

There is an increasing interdependency between therapy and diagnostic that is likely to continue as regulatory authorities around the world encourage joint submissions for approval and support simultaneous launches. In the US we observe that:

- $200bn of therapy revenue is already dependent upon the diagnostic ecosystem (42% of all therapy revenue) at each disease level[1].
- 70% of future therapy launches (2020+) will incorporate a diagnostic, making the link with diagnostics a predominant feature of the pharma commercial model[1].
- Already some $3m per day is being spent across the industry on diagnostic investments to optimize treatment[1].
- There has been a dramatic increase in biomarker-targeted drug development programs: 5% of new drug approvals were for targeted therapies in the early 1990s rising to 45% in 2013[2].

PD-L1 testing is a dynamic market that has given Diaceutics a unique opportunity to analyse the availability and adoption of PD-L1 in NSCLC as a real-time, real world example. What we mean by availability is having nearby, trusted laboratories to run the chosen test. Analysis of the PD-L1 market reveals that in less than three years there have been three new entities, six indications, over 16 approvals and more than three tests, and this list was expanded in March 2017 with the approval of Keytruda for cHL and Bevencio for Mercel cell carcinoma.

Within NSCLC, PD-L1 status reveals a competitive component given that around 40 per cent of all NSCLC trials, regardless of the phase (I-IV), require determination of PD-L1 status. However, despite therapy/diagnostic dependency and expected PD-L1 integration, barriers

to availability and adoption persist. This is a concern because we know that unaddressed diagnostic need leads ultimately to the loss of potential patients eligible for targeted therapy.

What are the factors affecting availability in the US?
Various factors can affect availability including confusion over testing options, interpretation and reporting of results. Our analysis of PD-L1 testing in the US reveals these are some of the questions raised:

- Do labs require multiple platforms and could they possibly know what clinicians want to order?
- Is PD-L1 comparable between clones?
- How shall PD-L1 staining be interpreted and reported?
- Should immune cell staining be reported?
- Which expression level is meaningful?
- Do clinicians need PD-L1 tested?
- Do these decisions impact payer decisions to cover testing and a therapeutic?

Another factor affecting availability here is the significant role LDTs play in the provision of PD-L1 testing. Around 50% of labs have only an LDT option, but LDTs are less well-defined with the Ab being used and cut-off values in place. Often labs will offer both LDT and kits but there is no suggestion that LDTs are preferred.

Even though availability of PD-L1 testing has increased since companion diagnostic approval it has always lagged behind. Diaceutics began tracking PD-L1 testing in 2015 and found that test availability already lagged behind 2014 approvals. 2016 saw strong availability of PD-L1 testing but we may also have reached a testing plateau at the end of 2016 in the US, with broad adoption in key laboratories.

Does Europe experience similar issues on availability?
The Diaceutics global network of laboratories has enabled us to track particular markets in relation to PD-L1 testing and a focus on Germany and Italy for PD-L1 in NSCLC has provided some contrasting data on availability and investment in these countries[3].

- **Germany**: There are ten different antibody clones available for testing here, but early harmonization, driven by pathologists, made the choice of antibodies easier, with heavy adoption of one antibody.
- Due to EU legislation, German labs used the harmonization results to improve the availability independently of the platform.
- Over 30 training sessions were held in 2016, educating and aiding labs on the validation, interpretation of the results and reporting.
- Diagnostic reimbursement was incorporated into the existing system.
- **Italy**: There are four different antibody clones available for testing here and there is still lack of consensus on which should be used; harmonization studies started later.
- There is a tendency to adopt the kit corresponding to the existing platform and test adoption is pushed by clinicians.
- Fewer than five training sessions were conducted in 2016, mostly based on the platform rather than the test.

- Reimbursement coverage is poor and an anatomical pathology lab is necessary to claim reimbursement for PD-L1.

Comparison of PD-L1 testing in practice	Germany	Italy
Top volume NSCLC laboratories performing PD-L1 testing	93%	8%
All NSCLC samples tested for PD-L1	44%	2%

How do availability issues impact physicians?
We recognise that availability and adoption - the adoption of the test by physicians for use with recommended patients (as described in guidelines) - can be interdependent. The test needs to be available in labs to facilitate physicians' choice on testing but if they adopt a particular test above others the availability of other tests can be reduced. Understanding around test differences is improving but prescribers remain unclear and this creates uncertainty for prescribers and impacts their confidence in testing[4]. Furthermore, pharma companies are sending out different messages, with the 22C3 companion diagnostic being promoted with Keytruda and 28-8 complementary diagnostics promoted with Opdivo.

How do availability issues impact testing and ROI?
The availability issues clearly impact return on investment and timely investment will boost the returns. When Diaceutics analysed the differences between the German and Italian markets for the webinar What are the major differences in biomarker test adoption in European countries? An analysis of PD–L1 testing in Italy and Germany, it revealed surprising statistics about Italy in relation to PD-L1 testing:

- Loss of treatment opportunities: 1,775 patients NOT treated
- Lost revenue opportunity: $194m
- Diagnostic investment required: $2m
- ROI for every $1 diagnostic investment: $97m

This one example demonstrates that despite prescribing's increasing dependency on PD-L1 testing, issues of availability and adoption persist. Crucially, 20 years on from Herceptin we still observe the absence of attention to pre-launch market development for critical biomarkers and patients are being missed. (More information will be made available after our bottom up analysis of patients lost to anti PD-1 treatment directly caused by testing issues is completed in May 2017.)

Summary
An increasing requisite for PD-L1 status knowledge prior to prescribing will drive increased outcomes and response rates with PD-L1 therapies but guidelines clarifying PD-L1 testing and reporting are lagging behind the dynamic testing landscape. Several factors however, including early physician confusion and a lack of standardization in testing and reporting, will continue to hinder test availability. A comprehensive biomarker strategy is key to a successful therapeutic launch and increasingly impacts return on investment but current

planning and implementation on the majority of biomarkers is underestimated, under-budgeted and under-resourced

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2. FDA Review Process for Companion Diagnostic Devices (Soma Ghosh, Tri-Con presentation 2017)

3. Diaceutics webinar February 2017, What are the major differences in biomarker test adoption in European countries? An analysis of PD–L1 testing in Italy and Germany

4. Diaceutics' Longitudinal Panel of PD-L1 Testing Behaviour Among Prescribers. (This panel leverages an analysis of the same 20 Opdivo/Keytruda prescribers in NSCLC to track shifting perceptions over time.)

Originally published at Diaceutics.com, 25 May 2017

PD-L1: A chance to get things right?

Peter Keeling, CEO of Diaceutics, examines the dynamic PD-L1 testing landscape and assesses what the future holds for this biomarker and its role in precision medicine.

The extraordinarily dynamic PD-L1 testing and anti-PD-1 therapy space allows, for the first time, a real-time analysis of a truly competitive personalized medicine market, giving us the chance to analyse in detail the PD-L1 testing market's trajectory and ultimately improve our understanding of novel biomarker adoption in our increasingly dynamic and competitive landscape. Despite the uncertainties hanging over the first generation of PD-L1 tests, our data point to the fact that the space will require ever more PD-L1 testing and that by 2018 PD-L1 will become a hyperconnected oncology biomarker led by NSCLC.

In short, the data suggest a rapid integration of PD-L1 testing despite its uncertain molecular interpretation. One year after launch, PD-L1 already appears to be more integrated into oncology clinical trials than other biomarkers were 18 months post-launch. Use in over 70 US labs shows PD-L1 testing has a fast track pattern of uptake in parallel with treatment recommendations. This is all very encouraging, but there are issues including:

- Of the 70-plus US labs that have adopted PD-L1 testing, the majority have opted to make an LDT available. Kits are important in priming the market but, as with other biomarkers, labs decide on the best test going forward, so their impact in the space should be not be ignored. This appears at odds with FDA attempts to de-limit LDT use, although with a changing US administration this may be binned.
- Test availability can impact prescribing choices and the way labs offer a test could be a disruptive factor for pharma. Our research shows if only one PD-L1 test is offered by a lab it appears to limit prescriber choices.
- PD-L1 biology of expression determines that late disease is likely to reveal higher levels of PD-L1 expression whereas pre-treatment can also interfere with PD-L1 levels, so a patient's position in the diagnostic journey may be key to segmentation. This is not well articulated in clinical guidance.

Clinical trials for immuno-oncology therapies in NSCLC reveal that PD-L1 will need to be integrated alongside more established biomarkers like ALK and EGFRm as part of future patient segmentation strategies. Testing guidelines are constantly lagging behind biomarker launches and this is likely to be increasingly so in the PD-L1 space. This inevitably limits direct-to-patient communication and prevents patients' easy understanding of the space. PD-L1 is unlikely, therefore, to be patient led, as HER2 is today.

Our real-time observation of PD-L1 reveals many issues of novel biomarker integration into treatment pathways and drug launch programs. Precision medicine continues to progress yet we still suffer from the lack of pre-launch market development of critical biomarkers, even though most of the PD-L1 issues have been seen before. Optimizing the potential of a still underdeveloped PD-L1 testing market could help to realise the $32bn per annum in

expected drug revenues, but learning from it could shape hundreds of billions of dollars in future dependent therapy revenues.

Originally published in Diaceutics' Pharma Readiness for Diagnostic Integration 2017

Diagnostics ignored in targeted therapy pricing, access and value

Peter Keeling, CEO of Diaceutics, provides insight on the role precision medicine can play, specifically the diagnostic, in adding value to a therapy and why pricing models need to be reviewed to reflect the value that complementary and companion diagnostics can have on the overall targeted therapy value.

There is a rising storm of debate around 'excessive' therapy prices on one side and, on the other, the exploration of 'new models' to articulate the positive impact which the pharma industry's 10 per cent of the health cost pie has on the other 90 per cent of healthcare spend.

At one end of the spectrum, payers are seeking and getting steep discounts from launch onwards for new therapies[1]. (*This combative approach is surely equivalent of Tesla launching their new people's car with 30 per cent off from day one!*) Payers' empowerment comes from the arrival in the US of cost-effectiveness groups like the non-profit Institute for Clinical and Economic Review (ICER), whose methods closely resemble those of NICE, the successful gatekeeper to therapy pricing in the UK[2]. Whether we agree with the methods deployed by ICER in terms of their inclusiveness or not, they are getting the ear of Medicare and presidential hopefuls and will serve to intensify the pricing debate[3].

Does personalized medicine help or hinder the debate?

Of course, not all of the therapies under pricing scrutiny are personalized with the use of biomarkers. It does seem as if the pharma industry has, by implication, leveraged its existing Health Economic Assessment (HEA) models to consistently cross the $100,000 per patient barrier in return for dramatically improved outcomes in smaller patient segments targeted with the use of biomarkers. It is a pity then that the diagnostics at the heart of this segmentation are so ignored.

Our observation here is a simple one. Current HEA models which focus on therapy pricing generally ignore the value of the diagnostic in two ways:

1. Diagnostic value is seldom expressed in its own right despite its huge impact on improving therapy value. As recently reported in GenomeWeb from the American Society of Clinical Oncology's annual meeting, "researchers presented data from a cost-effectiveness analysis of Opdivo and Keytruda when administered with PD-L1 testing and without. In studies of patients who had non-squamous cell tumors with PD-L1 expression in 1 percent or more of cells, the cost per QALY gained decreased from $176,000 to $105,000. For Keytruda, when patients had PD-L1 expression in 50 percent of more cells, the cost per QALY gained dipped from $163,000 to $138,000"[4].
2. The financial and clinical promise of personalized medicine is NOT optimally delivered in the premium pricing of late stage therapies (despite their clinical impact on outcomes), but rather in integrating diagnostics and therapy ever earlier into the treatment pathway. Diaceutics has already published on the opportunity to harness personalized medicine to strike a more balanced value for all stakeholders[5]. Indeed to give this balanced value model a chance to breathe, we, along with a group of

physician, pharma, laboratory and diagnostic stakeholders, have established a unique not-for-profit initiative (pmconnective.org) to get specific with the value equation at a disease level. This pre-competitive initiative has already started to identify the barriers to a balanced value approach with the goal of developing a collaborative (versus combative) model.

We are conflating access with value

We will be the first to decry the lack of reimbursement infrastructure which dogs new companion and complementary diagnostic launches across the leading healthcare markets. We continue to encourage our clients to invest time to navigate this neglected field[6].

However, we must not confuse the access barriers to optimal testing (a pain to manage though they are) with the need to articulate the profound impact which diagnostics can have on the value of targeted therapy. We laud the three year journey which EPEMED and the Office of Health Economics (OHE) have been on to argue for a new evaluation framework dedicated to diagnostics. EPEMED and OHE have proposed "a broader framework for considering the value contribution of complementary diagnostics and provides policy recommendations to support the implementation of this comprehensive framework for assessing their potential value contribution."[7]

Frankly, the inclusion and articulation of diagnostic value needs to be elevated alongside the articulation of the targeted therapy and it is no more acceptable to talk about personalized medicine value only for therapies, than it is to describe the value of a new car without its tyres.

As we all search for new models which collaborate to unlock value rather than battle to protect historic turf, we encourage access and reimbursement experts everywhere to better understand the heroic power of diagnostics to reshape the debate.

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Originally published at Diaceutics.com, 7 July 2016

Complementary testing in PD-L1 – a groundbreaking concept?

The FDA's decision to approve what it terms a complementary diagnostic may not have been a ground-breaking event after all. In fact, it might make the testing landscape even more complex to navigate. Ewelina Golebiewska, Associate Director, Diaceutics asks who, if anyone, will be motivated to drive us towards 'complementary Dx' adoption. More importantly, is this 'new' concept just an unnecessary complication?

In October 2015, the FDA approved the first drug with what it termed a complementary diagnostic in the label. It was Dako's PD-L1 IHC 28-8 IVD test kit that underwent the same rigorous regulatory and review process as companion diagnostic, the difference being that it is not essential for determining which patients should receive the drug. Rather, it can help predict the response to a therapy, in this case Opdivo. In May 2016, another such pairing was approved - Genentech's Tecentriq with Ventana's PD-L1 SP142 Assay. These approvals, together with the announced plans to bring that 'new' category of tests under FDA regulation, are seen as part of the agency's increasing efforts to keep pace with the scientific advancements in an area that is already developing beyond the existing guidelines. But was it really such a ground-breaking event? And isn't the FDA a bit late to the party anyway?

Been there before

In 2006, the FDA produced the first list of pharmacogenomics biomarkers in drug labelling, including around 60 drug-biomarker combinations that can affect clinical decision-making. In 2016, more than 130 drugs have actionable biomarkers in their labels[1], adding up to almost 170 unique drug-biomarker combinations, yet only a handful of those are catered for by FDA-approved companion diagnostic devices[2] (Figure 1). In addition, a further 25 labels 'require' genetic testing but the companion tests used are generic LDTs rather than devices[3]. That leaves us with a further 85 drugs that recommend testing with actionable or informative biomarkers that can still guide therapy, but 'are not essential to the safe and effective use of a therapeutic product' (FDA definition of a CDx[4]).

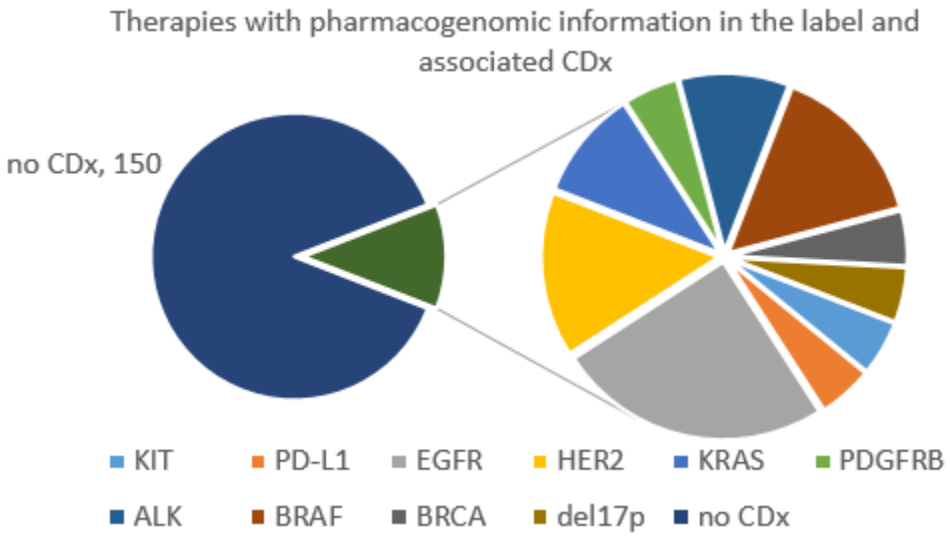

Figure 1. Based on FDA Pharmacogenomics list and Diaceutics Research we identified 169 unique drug-actionable biomarker pairs. Out of these only 20, all of which are oncology therapies, are linked to FDA-approved companion diagnostics (CDx).

And this is where the concept of 'complementary' diagnostics comes in. It is testing that can help to guide therapy but is not *essential* to prescribe the drug, a type of testing that has long been part of therapy labelling (at least implicitly) (Figure 2), and in fact internalised by pharma for at least half a decade. So what is new? There is one key difference, namely the insistence that such testing is now to be regulated alongside, and linked to, the drug.

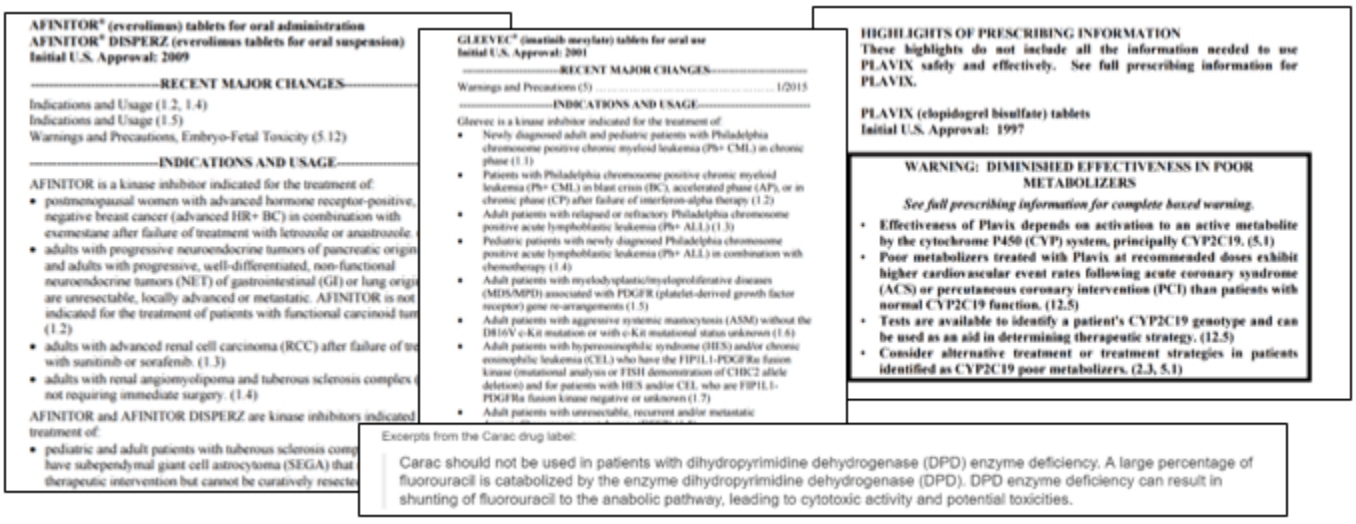

Figure 2. Examples of labels that, implicitly, require testing of patients to determine appropriate dosing or patient population that may benefit from the therapy. None of these therapies is associated with a 'companion diagnostic'.

These labelling examples illustrate how inconsistent FDA regulation can be. Take fluorouracil, for instance: three to six per cent of people have dihydropyrimidine

dehydrogenase (DPD) deficiency which correlates with very severe, sometimes lethal side effects from fluorouracil and related chemotherapy. The label indicates the drug should not be used in patients with DPD deficiency, but to date the FDA has not actively enforced this. One could argue that for these patients the DPD status is essential information to guide treatment, so should the therapy come with a companion diagnostic? Or would that classify as complementary? Or is it up to someone else to decide?

In these situations to date, the FDA has left the decision to test with physicians, and it is unlikely that the new regulation would deal retrospectively with over a hundred therapies that use genetic and other tests to guide therapy decisions.

For the sake of argument let's forget about those and look to the future. The obvious question is what value does the new category of regulation hold? More importantly, which stakeholders will drive adoption of any newly-regulated complementary testing?

Will pharma drive complementary testing?

There have been instances when pharma has sought to highlight the role of a complementary test, as was the case with Novartis and Gleevec. Novartis launched a campaign in 2011 to standardize monitoring and dosing in AML patients using a BCR-ABL test in collaboration with Asuragen and Cepheid. Better monitoring in that case resulted in a more effective therapy, improved dosing and greater trust in the brand, while at the same time ensuring a growing market for Gleevec's follow-up drug, Tasigna.

Despite the fact that Opdivo was approved with the PD-L1 complementary testing which triggered this dialogue, BMS has sought to emphasize the fact that, as opposed to Keytruda, their therapy *did not* require testing (see the recent Opdivo TV ad here: https://www.ispot.tv/ad/AL_Z/opdivo-longer-life. That message resonated with clinicians, as a recent Diaceutics survey revealed, with a significant percentage indicating they did not see the need to order the test before prescribing Opdivo for NSCLC. Put simply, that means no test sales for Dako.

The situation may be different with the Genentech/Ventana combo as both companies are owned by Roche. Time will tell whether Tecentriq marketing will leverage the clearly informative role of PD-L1 in patient selection to support sales of Ventana's test.

Clearly pharma could drive complementary testing and it will when there is a clear ROI, but Opdivo shows that the complementary label creates plenty of 'wriggle room' to promote or ignore the test .

Will laboratories drive complementary testing?

Perhaps one reason for the FDA's insistence that pharma submits complementary testing for approval is the hope that it will support the shift to regulated diagnostic kits in US Labs. The majority of 'informative' and 'actionable' biomarkers are currently being tested using laboratory developed tests (LDTs), a segment of the IVD market (as of Q2 2016) regulated under CLIA rather than the FDA. In light of this and our observation that already over 70 per

cent of commercial labs offering the PD-L1 test have developed an LDT regardless of companion or complementary test availability, suggests that financial considerations are of equal importance to labs in adopting new tests.

As testing evolves to integrate biomarker panels it is not clear that top-down regulation of complementary testing is the way to go. Commercial labs like Caris Molecular Intelligence and OncoPlexDx are developing biomarker panels driven by bottom-up need, providing physicians with comprehensive information to guide their therapy choice. As NGS technology gets ever cheaper, and the market becomes crowded with panel tests or even DTC pharmacogenomic kits, physicians may opt for a disease-specific or even multi-disease 'complementary' diagnostic that helps them choose between multiple therapies rather than providing a simple 'yes-no' answer for one branded drug before moving on to the next CDx-Rx combo. Would a non-essential, yet expensive (regulated, tied to a therapy) test appeal to the lab manager?

Will physicians drive regulated complementary testing?

In a recent Diaceutics survey of 30 anti-PD-1 prescribing oncologists, 40 per cent admitted to not understanding the nuanced differences between the two approved PD-L1 tests, and even some who claimed to be knowledgeable went on to provide erroneous definitions of 'complementary' and 'companion' diagnostics. With adoption of companion diagnostics still remaining suboptimal, the introduction of even more nuanced labelling for complementary tests is not the way to earn doctors' trust.

Doctors clearly want better testing to aid treatment and patient management. For example, Diaceutics recently asked 20 MS specialists what diagnostic tests would make their life easier. The recurring answers were a call for a test 'that would predict response to all the MS disease-modifying treatment' and 'that would help predict disease progression'. What this says to us is the definition of 'precision' or 'personalized medicine' is migrating from its original context in oncology with the intimate link between disease, driver mutation and therapy, towards more multifaceted diseases and multiple treatment modalities. And in that new domain the 'one drug - one biomarker' model will not fit physician's needs.

Will diagnostic companies drive complementary testing?

The current predominant business model for the diagnostic industry guides it away from making deep financial investment in driving test adoption. Whilst there are exceptions (Genomic Health with CYTYC), it is perceived that the diagnostic company's challenge is to make the test available in a disease area where clinical demand or pharma or payers may drive the test uptake. Diagnostic companies like Dako, Ventana and Abbott have actively participated with pharma in a 'fee for service' model. Here they are funded to develop a regulated test alongside the therapy in the optimum case scenario where therapy and test can then get approved and launched together. Sometimes the diagnostic company also goes on to work with pharma (where funded) to support companion test commercialization since companion status in a label will drive demand. However, without the guarantee that pharma will encourage testing (witnessed already with BMS and Opdivo), the regulated complementary concept is no moneymaker for the diagnostic industry.

Conclusion

We understand why the FDA wants to leverage pharma to support the shift away from LDTs with the regulated complementary labelling. Occasionally in diagnostics the stakeholders can align around new tests and drive rapid change, as seen with BCR-ABL or HLA-B testing in HIV. But the arrival of a regulated complementary label does not appear to have any real stakeholder alignment and we at Diaceutics fear it may complicate rather than simplify clinical decision-making. For this reason we think it does not really further the cause of personalized medicine.

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Originally published at Diaceutics.com, 6 June 2016

The return on investment of better CDx planning based on early PD-L1 observations in NSCLC

Sanna Jousi of Diaceutics assesses the financial benefits of integrating the planning, analytical and action steps for successful development and commercialization of testing into targeted therapies.

The anti PD-1 therapy market promises to be the largest single oncology market, with peak sales projections of $33 billion (http://www.fiercepharmamarketing.com/story/pd-1-wave-report-says-its-33b-tsunami-bms-surfing-first-place/2015-03-04). Five major pharma companies have active asset programs in the space, each leveraging testing in second and first line cancer treatments differently. Merck and BMS have already launched Keytruda and Opdivo. A number of indications and therapy strategies will be specifically interdependent on the efficiency of the PD-L1 testing market so this merits a better understanding of the financial relationship between diagnostic market efficiency and lost therapy revenues.

Current PD-L1 testing options use IHC, the same platform which enabled the HER2 Herceptin franchise but which also took five to seven years to optimize. Retrospective analysis has identified up to $3 billion in lost revenue opportunity for Herceptin due to IHC testing issues.

To help determine the similar readiness of PD-L1 IHC testing to support therapy launches, Diaceutics has tracked key diagnostic drivers in real time and modelled their impact on estimated lost anti PD-1 therapy revenue for one indication only—second line NSCLC—in its first year of launch and over the following four years.

We have used the Diaceutics Financial Planner to reverse-model the current relationship between PD-L1 testing and therapy revenues generated to date. The metrics were used on target population patient penetration, dosing and laboratory adoption observed to date in second line NSCLC (US).

Using this platform we assessed the sensitivity of several drivers. Second line NSCLC drivers modelled:

- Dosing advantage in high expressers
- More accurate test answers
- Greater conversion to therapy from test positives
- Greater test adoption by physicians
- All drivers optimized together

Disclaimer: This is an illustrative model only and is not intended to reflect existing or future therapy forecasts in the anti PD-1 space

The Base Case (Scenario 1) looked at revenues predicted within the model from 2015 to 2019 in second line NSCLC. The projected cumulative base case value for a therapy label dependent upon testing is $1.3 billion in the US market (Figure 1).

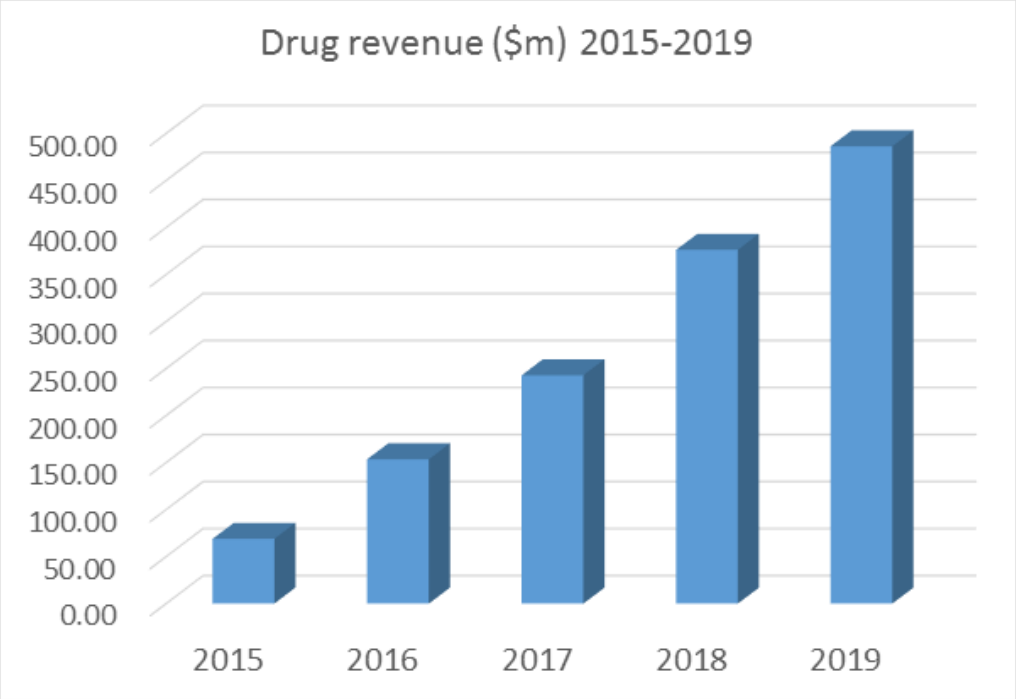

Figure 1. Drug revenue ($m) 2015-2019

Looking at the relative dollar impact of each optimized driver (cumulative five year revenues) revealed that whilst optimized dosing in high expressing PD-L1 patients (>50%) is the biggest single contributor, improving test accuracy and driving greater demand for testing confer significant revenue gains (Figure 2).

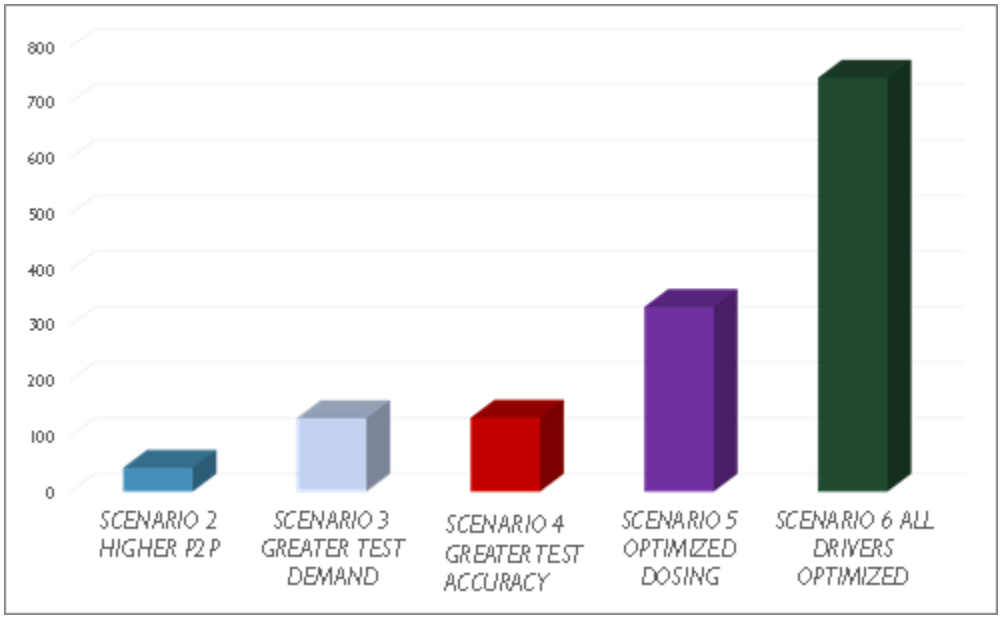

Figure 2. Relative dollar impact of each optimized driver.

Using the model to determine the relative percentage impact of each optimized driver (cumulative five year revenues) showed that having all drivers optimized would confer an additional eight per cent of revenue over the single drivers alone.

Another way to consider this is as year on year lost treatment revenue. The model suggests that therapies have already lost around $40 million in treatment opportunity due to suboptimal testing. This accumulates over five years to $744 million in lost therapy opportunity in second line NSCLC alone, otherwise achieved if all drivers had been optimized (Figure 3).

Finally, when looking at the ROI of diagnostic driver investments expressed in anti PD-1 therapy dollars we saw that investment in greater test accuracy delivers the single greatest dollar for dollar return, but having all drivers optimized provides $24 for every $1 invested in diagnostics for this indication.

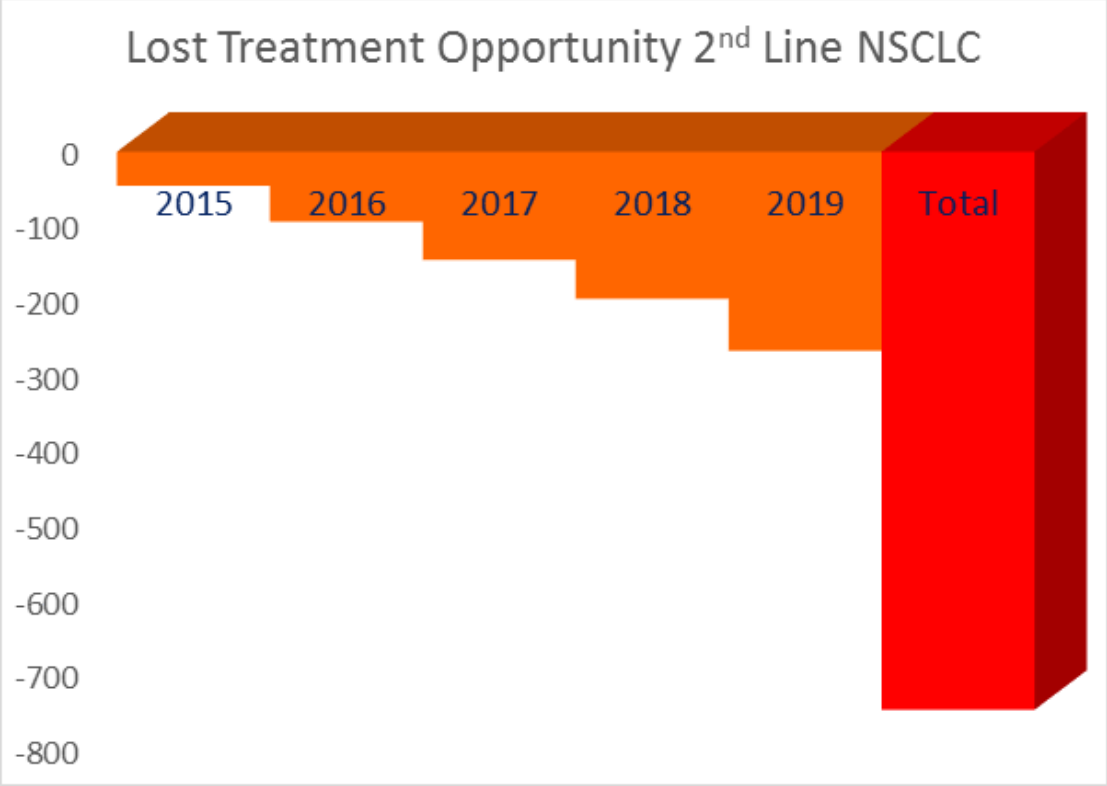

Figure 3. Lost treatment opportunity in second line NSCLC ($m).

Conclusion

A suboptimal PD-L1 diagnostic marketplace is already resulting in lost treatment opportunities. As the dependence upon PD-L1 testing grows over the years and across indications, this is highly likely to magnify.

The Diaceutics model suggests that up to $744 million in lost treatment revenue is at stake in this one indication alone.

Based on this indication, an investment in optimizing the PD-L1 diagnostic marketplace is likely to confer more than $20 additional therapy revenue for every $1 spent on diagnostic investment. Improved quality of testing will deliver the greatest dollar for dollar return and linking higher dosing to high PD-L1 expressing patients should see the single highest dollar amount return.

Pharma asset and management teams are always concerned about the ‘opaque impact’ of investing in diagnostic optimization. By employing real time tracking of the PD-L1 market and reporting this in ‘lost treatment dollars’ it is our intention to highlight the significant financial benefit of earlier and better planning in diagnostic market optimization.

Originally published at Diaceutics.com, 4 April 2016

The Knight's move in PD-L1 chess

What does the future hold for PD-L1? Who will advance or move into the space? Peter Keeling, CEO of Diaceutics offers his insights on this hot topic.

And so it begins, the rolling regulatory approvals of anti PD-1 therapy, an oncology drug class likely to become the biggest in history. Leading oncologists at the American Society of Clinical Oncology and the European Society for Medical Oncology have been highly impressed with the data reported for both Merck's drug Keytruda and BMS's Opdivo. Regardless of which drug they prefer, they are united in one opinion, namely that these drugs will increase patient survival by adding second and first line drug options as monotherapy or in combination with other drugs.

However, look at this from a different angle and the pharmaceutical company strategies used to deploy these new therapies reveal an intriguing set of chess-like moves. Speculation is high among PD-1/PD-L1 watchers as to which opening will take control of the board. Will it be:

- Overall survival data versus progression-free survival data[1]
- The commercial might of Merck squaring up to the oncology boutique of BMS[2]
- Combination cocktails taking on monotherapy approvals[3,4]
- Or PD-L1 as a companion test up against PD-L1 testing as an optional adjunctive aid to treatment?

The truth is we don't yet know, but analogues of previous great drug wars in new categories tell us that competitors tend to benefit from patient share in the first few years, with revenues often neck and neck as the marketplace develops and strategic battles are fought, but there will inevitably be one clear winner. There will be one relative strategic advantage which, in the final analysis, will show how one company gained control. It might be a simple but powerful marketing message, as was seen in the case of Zantac versus Tagamet, or maybe the strength of data in first line and combination versus monotherapy and second line indications, as it was with Erbitux versus Vectibix. It could also be the ability to leverage the testing space, as it was in the beginning with Herceptin versus Tykerb.

Why this particular chess game is so intriguing though is that it could become three-dimensional, directly impacting the PD-L1 or, more correctly, the immuno-oncology business model. In academic medical centres most cancer tumors are being actively genetically profiled, in effect an integration of those mutations currently targeted by approved therapies with other 'likely driver mutations' being explored in clinical trials. So what has historically been a series of guideline-driven treatment choices is rapidly becoming a personalized treatment cocktail based on real time genetic and molecular data.

Consider, for example, the bold, unequivocal and category-shaping announcements of Foundation Medicine[5] (which we were told was acquired by Roche for research purposes) to enable clinical treatment choices (often off label) based on extensive molecular level evidence. Such genetic profiling is no longer confined to organizations like Foundation

Medicine. Instead, the unprecedented uptake of NGS platforms from the likes of Illumina and Life Technologies (our data suggests 65 per cent of leading oncology labs in all the key markets now have access to NGS platforms[6]) is delivering this 'Foundation-like' interpretation capability to oncologists globally.

Diaceutics will be the first to bemoan the lack of infrastructure investment throughout the diagnostic landscape. Our lab data tells us that currently less than 7 per cent of oncology labs globally[7] offer PD-L1 testing despite the likely imminent demand. In short, integrating testing into treatment pathways in line with rapid regulatory approvals is a messy business requiring investment, preparation and deep domain knowledge. However, as we continue to run competitive scenarios on the PD-L1 and immuno-oncology space here at Diaceutics, we come largely to the same conclusion. The therapy company which recognizes immuno-oncology patient profiling as a central communication channel, engineering smart bridges from often incomplete and disruptive testing strategies to truly personalized patient management will, in our view, step over the competition[8]. We call this the Knight's Move and it may be the deciding tactic in the long PD-L1 chess game.

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Originally published at Diaceutics.com, 5 February 2016

How big can Merck's Keytruda be in lung cancer? It's too early to call in the PD-L1 arms race!

Maria Fe Paz and Peter Keeling of Diaceutics discuss the competitiveness of the PD-L1 market and highlight that the key to success, for those in pharma, will be ensuring they leverage all the test adoption drivers to support uptake of the therapy.

Now the PD-L1 arms race draws its first battle lines with Keytruda outperforming Opdivo prescriptions by approximately two to one in the initial melanoma indication. Congratulations must go to Merck for pipping BMS at the post and being first into the market, and also for their nice, clear messaging: My immune system + Keytruda = Help to fight tumors.

However, if there was ever a 'marathon, not a sprint' scenario, it is in the PD-L1 space. Multiple drugs, multiple therapy combinations, multiple pharma marketing teams and, of course, multiple PD-L1 tests, will all have to play out in this space. As the FIRST truly competitive personalized medicine battle, it will be intriguing to observe how the development teams hand over to the commercial and launch teams within Pfizer/Merck KGaG, BMS, AZ and Roche/Genentech and work through this highly complex melange, without further confusing the clinical, laboratory and patient community about best treatment options.

As many of you know, our Diaceutics' particular lens on PD-L1 is about the efficiency of testing and its seamless integration into the treatment pathway. Frankly, we are concerned that the current landscape for seamless clinical testing is more reminiscent of the HER2 testing journey, which took some four to five years to sort out (i.e., make seamless) and which lost Roche/Genentech, by our estimates, at least $3 billion in potential lost revenues[i]. Having said that, we are tracking very closely and will report on any clinical disruption resulting from inadequate marketplace preparation for PD-L1 testing, with a view to articulating gaps and solutions. We also hope to measure the financial impact of any lost treatment opportunity so we can all recognize the return on investment by optimizing clinical testing.

Success for these effective immuno-oncology therapies will be determined not only by the smart design of clinical trials and effective therapy combinations, but also by a simple test-centric axis along which we'll consider points such as what triggers a physician to order a PD-L1 test? Which one will he order? Will the laboratory he normally orders from have the test? How will the laboratory interpret the result? And what percentage of those expressing PD-L1 will he treat?

The pharma company that can join up these dots will have a market advantage, and it is for this reason that it is far too early to call this particular race.

Originally published at Diaceutics.com, 19 May 2015

The PD-L1 case: Immune checkpoint inhibitors and the lack of robust biomarkers

Many experts say that out of all the therapies developed to harness the power of the immune system to fight cancer over the past several decades, PD-1/PD-L1 inhibitors look to be the most promising, even though it is still relatively early days in their development. Maria Fe Paz and Patrick Considine of Diaceutics suggest that there is an urgent need to standardize and harmonize the assays used to evaluate PD-L1 expression, and for integrative initiatives to support the ongoing collaborations amongst the many different key stakeholders.

There is no doubt that immuno-oncology is a paradigm shift holding much promise in cancer treatment. The idea of boosting the immune system to fight against its own malignant cancer cells has provided a strong rationale and focus to researchers for decades, working to translate their studies from the bench to the clinic. Understanding the checkpoints responsible for the immunomodulation was key to facilitating the identification of drug targets, and development of monoclonal antibodies that are showing promising results in the clinical setting.

Not only the medical community, but many other stakeholders, are following with excitement the development of these immune checkpoint inhibitors. Some of the major pharmaceutical companies have initiated clinical trials, using immune checkpoint inhibitors as single therapies or in combination with other therapies for a range of cancers and an increasing scope of indications. The relatively mild safety profile makes them ideal for combinations, and they will very likely become the backbone of most cancer treatment schemes in the next years. Many experts say that out of all of the therapies developed to harness the power of the immune system to fight cancer over the past several decades, PD-1/PD-L1 inhibitors look to be the most promising, even though it is still relatively early days in their development.

Biomarkers of response

In this competitive landscape, in which the market share will be at least partially influenced by the first comers to market, there is a growing need to improve the clinical outcomes to grant faster approvals. A recent Goldman Sachs review[1] suggests some companies with PD-1/PD-L1 inhibitors are betting initially on an ‘all-comers’ strategy, i.e., no requirement to segment patients based on biomarker profile. Such a strategy appears to fit those first into the market with a specific indication such as melanoma and other second line or smaller third indications. BMS have embraced this strategy for Yervoy in melanoma indication and for Opdivo in melanoma indication and third line squamous NSCLC. Merck has adopted the same strategy for Keytruda in melanoma indication and first NSCLC indication. Whilst the early clinical studies may support the ‘no biomarker’ strategy, the move of PD-1/PD-L1 therapies into first line may require the incorporation of a biomarker strategy.

The complexity of the interaction between the immune system and the tumor cells, the role of the microenvironment and other factors yet to be determined, are challenging the application and validation of the one single biomarker of response. Given the scenario in

which many of the indications will require a combination treatment, the validation of a signature of response may be of paramount relevance to guide therapy decisions.

The challenges for PD-L1 diagnostics

Immuno-oncology has been revolutionized with Programmed cell death-1 (PD-1) and its ligand, PD-L1, as the foremost targets of immunotherapies, with more than six of the major pharmaceutical companies involved in the development of antibodies and combinations with them. PD-L1 has been shown to be a potential predictive biomarker in exploratory trials, and has been incorporated as inclusion criteria in the recruitment of patients in an increasing amount of studies. BMS, Merck, Roche/Genentech and AstraZeneca clinical studies have included patient stratification based on PD-L1 status for some NSCLC indications. The application of the PD-L1 diagnostic biomarker as a predictor of therapy response presents a number of technical and clinical utility challenges. There is the unique scenario whereby each PD-1/PD-L1 therapy has its own proprietary PD-L1 CDx test. Independently, each CDx will be technically and clinically validated to achieve regulatory approval. However, there are some technical hurdles with the test and the technology itself. PD-L1 is an inducible biomarker, which is both expressed by tumor cells and also by tumor infiltrating lymphocytes, which are part of the microenvironment of the tumor. Some companies are measuring the staining of PD-L1 just in tumor epithelial cells, whilst others are including tumor infiltrating lymphocytes.

An additional complication is the diverse range of antibody clones used to measure PD-L1. Each assay may have a unique technical performance (sensitivity and specificity) and its own cut-off point to define PD-L1 expression positive. Some companies are considering a tumor as PD-L1 positive when staining more than 50 per cent of the tumor cells, while others are setting a three-score criteria similar to HER2, with different percentages of positivity (1-5 per cent, 5-10 per cent, >10 per cent). Nevertheless, IHC is semi-quantitative and based on subjective assessment, so there might be considerable variability and lack of reproducibility between pathologists. Collectively, the availability of different tests, variability of measurements and cut-offs, the hurdles of the technique itself along with the attempts to make it more accurate, reproducible and quantifiable, are presenting very difficult challenges to pathologists who will be charged with providing quality PD-L1 results to enable therapy decisions. In order to reduce the subjective nature of the assessment, a clear standardized definition of each category should be created and agreed upon. Once the technical standardization has been achieved, interpretative standardization can be addressed to facilitate physicians in their therapeutic decisions.

Clinical relevance of PD-L1 as a companion diagnostic

There is emerging evidence that PD-L1 may not be the ideal companion diagnostic biomarker to predict response to PD-1/PD-L1 therapies. BMS management have stated that clinical experts remain sceptical of PD-L1 status driving decision-making. Many studies do not separate the technical staining component and the interpretative assessment of staining, which can limit the impact of outcomes. Solid tumor tissue is inherently heterogeneous, containing a mixture of healthy and malignant cells in varying proportions. It is common for tumor content to alter between sections from FFPE blocks. The availability of sufficient

homogeneous material may be a stumbling block for PD-L1 characterization. For the same reason, single core biopsy may not be the most adequate sample to determine tumor PD-L1 expression. Furthermore, the correlation of the measurements of PD-L1 in metastatic tissue and matched primary tumor are weak, which means that primary tumor testing may not be the ideal surrogate to determine the expression in metastasis and predicting response in metastatic patients.

There is ever growing evidence of objective and durable responses granting faster approvals of the drugs by regulating agencies, regardless of PD-L1 status. Partly as a consequence of the factors discussed above, but also due to the dynamic inducible nature of the immune response and evolving immunophenotype during the course of the disease and treatment; there is not a robust concordance among PD-L1 positivity and clinical outcomes, especially in some indications. PD-L1 expression as a biomarker seems only moderately useful, and the use as a single biomarker of response may miss patients that would respond despite being negative for the biomarker. There is a higher probability of response to the therapies by those patients expressing higher rates of PD-L1 on tumor cells, but there is still a significant number of negative patients who would respond. The turmoil among physicians is generating an additional layer of confusion to the existing bewilderment among pathologists, who see a complication for physicians to take ‘go/not-go’ therapy decisions given the lack of clear cut binary results on patients' PD-L1 status. And in spite of it all, many physicians would not preclude a negative PD-L1 patient from benefiting from a breakthrough therapy if there are still immeasurable chances of response, or possibilities to synergize the effect with a combination, particularly in patients with limited therapeutic options.

Further steps

The lack of clinical evidence supporting PD-L1 alone as a single biomarker of response is prompting the clinical research of additional measurements and biomarkers, such as mutation rates, immune scores/cytokine profiling, CD8+ T cell ratios, or neo-epitopes, gene signatures or RNA expression profiles both in the stroma or tumor infiltrating lymphocytes. It may well happen that the signature of response will vary among different indications, as may other tissue-specific or tumor-specific co-stimulatory molecules in the PD-1/PD-L1/PD-L2 pathway that could be influencing the response as well.

Looking to overcome the limitations of PD-L1 as a biomarker, there are many groups looking to develop additional quantitative technologies based on RNA expression of PD-L1, with some groups investigating measurements of biomarkers in liquid biopsies (peripheral blood and serum), to allow for serial analysis during the course of the treatment and disease monitoring. Interestingly, a recent retrospective study[2] found that patients with *NRAS*-mutant melanoma seemed to respond better to immunotherapy compared with patients whose tumors had other genetic subtypes, and this was especially true for patients treated with anti-PD-1/PD-L1 therapies.

There is an urgent need to standardize and harmonize the assays used to evaluate PD-L1 expression, as lack of harmonization will be a barrier to drug/CDx adoption. It could also potentially lead to false negative results which would have a detrimental effect on patient care. PD-L1 is a complex testing landscape and thus laboratories would benefit from a

collaborative study to accelerate the clinical readiness of the test. It is essential to define a reference method/material, or a unified test or algorithm, so as to provide traceability to a reproducible assessment of the threshold. Most importantly, generated data cannot be aggregated to develop guidelines until the results are standardized, and guidelines cannot be issued and implemented until all the methods are harmonized.

Finally, there is an urgent need for integrative initiatives to support the ongoing collaborations amongst the different stakeholders, including academic research institutions and university hospitals, pathologists, physicians, pharmaceutical and diagnostic companies and key bodies.

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Originally published at Diaceutics.com, 16 March 2015

Leave no patient behind: How the FDA approval of Keytruda for specific biomarkers will put laboratory testing in the front line

The FDA approval of Merck's Keytruda (pembrolizumab) "for a specific genetic feature (biomarker)" is leading us into a new era in which the integration of diagnostics and biomarker detection on the treatment pathway is not an option, but mandatory. Marcos Tadeu dos Santos, Senior Director, Merdol Ibrahim, Managing Director and Dawn Wilkinson, Scientific Director, Diaceutics, discuss the ruling and emphasize the importance of test quality, concordance studies, guidelines and education for laboratory best practice.

The recent announcement that the FDA has granted approval to Merck's Keytruda (pembrolizumab) "for patients whose cancers have a specific genetic feature (biomarker)" and not based on the origin of the cancer, is a landmark decision. It is important not only for the way we understand precision medicine and how physicians make treatment decisions, but also for laboratories running the tests. Laboratories, usually the forgotten stakeholder, are now the protagonists in this very promising new direction for diagnostic testing.

We are now witnessing the start of a new era, in which the old and well-known 'one-size-fits-all' approach traditionally used with chemotherapies, is overtaken by the precision medicine concept of targeted therapies. It is an era in which the integration of diagnostics and biomarker detection on the treatment pathway is not an option, but mandatory.

Drug indication according to the biomarker status, regardless of the cancer type, has in fact long been expected as a trend by the scientific community. As far back as the early 19th century, Canadian physician William Osler, said, "It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has". More recently, diagnostic tests have been developed to highlight mutations as potential drug targets and which are not directed against a specific cancer type. Physicians can now see that drugs based on specific targets are a reality and biomarkers are being used to identify both the genotype and phenotype of a disease.

Keytruda's new indication covers any advanced solid tumor identified as microsatellite instability-high (MSI-H) or having a deficient mismatch repair (dMMR) status. The drug produced a complete or partial response in 39.6 per cent of patients across 15 cancer types in five open-label Phase I/II1-5.

Correct identification of the eligible patient

Although these are exciting results, this new era will not become truly revolutionary if we forget that drug efficacy is not the only important parameter to consider. The correct identification of the eligible patient, who could benefit from this impressive efficacy, is now as important as, or maybe more important than, the drug itself. We should keep in mind that Keytruda is now an option for patients with advanced solid tumors who have progressed following prior treatment, and for those who have no satisfactory alternative options - patients in the very late stages of the disease. This may be their last line of attack.

What happens if we do not correctly identify MSI-H or dMMR in these patients? Lack of testing quality at this late stage can have major repercussions for the patient's outcome so there is zero room for error. However, there is no specific companion diagnostic test approved by the FDA to be used alongside Keytruda for this promising new indication. It means that laboratory developed tests (LDTs) are currently the only acceptable means for testing MSI-H and dMMR in these patients. Therefore, standardization and quality control will be extremely important to prevent erroneous results.

Risks associated with laboratory developed tests

Based on the data and experience Diaceutics has accumulated by tracking the MSI and MMR tests provided in the US since 2010, and also by observing results from proficiency testing/external quality assessment (PT/EQA) programs, it is very clear that the quality of these LDTs is a key risk. For instance, they are very sensitive to the quality and quantity of the DNA input. Many other variables, from initial primer design through to the PCR cycling choice, can also influence the quality of results. False negatives are also very common since the analysis is subjective and poorly standardized. It is true that the identification of MSI-high is more robust than the identification of MSI-low, but the threshold separating low from high can vary between labs and also differ greatly from the threshold used in the clinical trials.

Immunohistochemistry (IHC) for dMMR is currently the methodology of choice for most laboratories, and involves the use of four MMR antibodies (MLH1 + PMS2 and MSH2 + MSH6), where loss of expression/staining of either one of the antibodies indicates a potential abnormality in MMR expression. Not only is interpretation of MMR IHC subjective, but there is a major pre-analytical issue with antigenic epitopes for the four anti-MMR antibodies being particularly fixation-sensitive, and as fixation across clinical laboratories is not standardized, this creates uncertainty in the sensitivity and specificity of staining. Furthermore, external quality control data (UK NEQAS, ICC and ISH) also shows an average unacceptable staining rate of 14 per cent, which, if translated into the real world setting, is even more perturbing.

Use of NGS may be more robust, sensitive and less subjective but the current bioinformatics structure required for interpretation is still proving to be a barrier. The long turnaround time associated with NGS is another issue to be considered. However, as all patient samples are subject to the same pre-analytic stages of fixation, its impact on the quality of NGS results still remains to be determined.

Conclusion

The number of MSI tests performed each year is growing fast. From around 1,000 tests performed in 2015 to more than 30,000 predicted for 2017 (US). It shows that the importance of these tests is already being understood by the health system. However, this is based only on colorectal cancer, and the spread to other diseases may be slower, therefore there is a need to educate physicians regarding the clinical utility of this biomarker in other solid tumors. More than ever, we must think how to improve the quality of tests we are offering to patients. Concordance studies, PT/EQA enrolment, international guidelines and

education for laboratory best practice are imperative, and pharma companies must have direct involvement in such initiatives from the start of any drug development strategies.

We cannot let relatively easy to fix testing issues leave any patient behind.

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Originally published at Diaceutics.com, 5 June 2017