research partnership

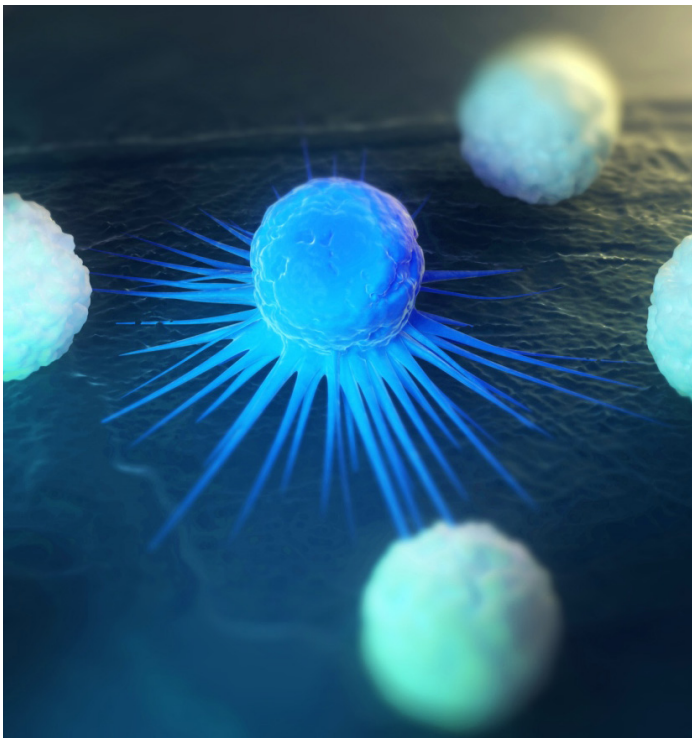
Free Thinking

Issue 10

Part 1: The US Situation

From promise to practice: immuno-oncology in action

Immuno-oncology therapies that harness the body's own defences to fight off tumours are widely acknowledged as the new frontier in cancer treatment.



Clinical trials of emerging products, both alone and in combination, have delivered impressive evidence of improvements in durability and endpoints such as progression-free survival, and even overall survival. R&D pipelines are stuffed with immuno-oncology prospects across a wide range of indications.

To date, only a few immuno-oncology products have actually reached the market though. Two of them target the anti PD-1/PD-L1 pathway where much of the interest in immuno-oncology is currently invested.

We spoke to key opinion leaders and payers in the US and EU to find out how the new immunotherapy products are faring clinically and financially.

In the first of this 3 part series, we will take a look at the current situation in the US, where immuno-oncology therapies are becoming more established, having been approved for a longer period.

In Part 2, we will look at how things are shaping up in the EU and in Part 3, we will investigate the prospects for PD-1/PD-L1 inhibitors in emerging markets, where the burden of cancer is fast increasing but self-pay arrangements are far more dominant.

Contributors

Dr. Richard Joseph is a medical oncologist at Mayo Clinic in Jacksonville Florida. He completed his fellowship in Medical Oncology at the University of Texas M.D. Anderson Center, and Residency in Internal Medicine at Weill Cornell Medical College and New York Presbyterian Hospital. He was awarded the ASCO Young Investigator Award in 2010 and the AACR Career Development Award in 2012. His research interest is novel combinations of immune and targeted therapy and his clinical focus is on the treatment of melanoma, renal cell carcinoma, bladder cancer, and prostate cancer.

Sue Marett is a Director at Research Partnership and has over 18 years of pharmaceutical market research experience, having begun her career at UCB and Bayer. Sue has led many oncology projects working across a number of areas including prostate, pancreatic NET, breast, colo-rectal and mRCC.

Claire Aubignat is a Research Manager at Research Partnership. In the last six years she has built up expertise in global pharmaceutical projects across a range of therapy areas, including oncology and its latest developments.

Brett Gardiner is an Associate Director at Access Partnership. He specialises in helping his clients develop payer value strategies in order to achieve commercial success for their innovations.

The anti PD-1 products currently available are:

– Bristol-Myers Squibb's (BMS) Opdivo (nivolumab), approved in the US and the EU for the treatment of metastatic melanoma and advanced squamous non-small cell lung cancer (NSCLC), and more recently in the US for advanced non-squamous NSCLC; and advanced renal cell carcinoma (RCC)

– Merck's Keytruda (pembrolizumab), approved in the US and EU for advanced melanoma and in the US for both non-squamous and squamous NSCLC, along with a companion diagnostic, in patients expressing high levels of the PD-L1 protein.

Also available in both the US and EU for advanced melanoma is BMS's Yervoy (ipilimumab), which activates the immune system by targeting the CTLA-4 protein receptor.

The Food and Drug Administration (FDA) has also cleared a combination of Yervoy and Opdivo for BRAF V600 wild-type unresectable or metastatic melanoma. This was the first approval anywhere for two immuno-oncology products taken together. It came with a daunting price tag of around $256,000 for the first year of combination therapy.

The market potential

One factor driving the development of combination products is the need to broaden the patient population for immuno-oncology therapies beyond the 20-30% who respond to these drugs in monotherapy at present. Novel ways of stimulating tumour immunogenicity to help kick-start the immune response may help to spread the net wider.

Moreover, existing marketing approvals for PD-1 inhibitors in melanoma and lung cancer are just the tip of the iceberg.

The expansive development programmes for the new wave of cancer therapies reflect both the diversity of immune regulation, offering numerous targets for therapeutic intervention, and potential communalities of response across indications to strategies such as PD-1 receptor blockage.

Given this potential scope, and expectations that immuno-oncology products will eventually form the backbone of cancer therapy, some analysts see annual sales going as high as US$40 billion within a decade.

Market forecasts vary considerably, though. Estimates of the potential for PD-1/PD-L1 inhibitors alone range from US$10 billion to US$30 billion a year.

Whatever the therapeutic gains already made by PD-1/PD-L1 inhibitors, and those anticipated from other immuno-oncology products as they feed through development pipelines, high treatment costs will inevitably complicate market access.

These issues are already coming to a head as the first PD-1/PD-L1 inhibitors start to enter the major markets of North America and Europe.

"I would say five-year overall survival in metastatic melanoma was approximately 5% before these drugs. Now [for patients who are responsive to these immunotherapies] that number has probably moved up to somewhere around 30-40%."

Significant strides

One powerful incentive for uptake, whatever the market, is acknowledgment that PD-1/PD-L1 inhibitors represent a leap forward in cancer therapy, even following the advances made by precision oncology medicines targeting cellular abnormalities.

I would say five-year overall survival in metastatic melanoma was approximately 5% before these drugs," states Dr. Richard Joseph, medical oncologist at Mayo Clinic in Jacksonville Florida. "Now [for patients who are responsive to these immunotherapies] that number has probably moved up to somewhere around 30-40%."

The toxicity-to-efficacy ratio of the new immunotherapies is "probably one of the best in all oncology", he adds. That is particularly important when the PD-1/PD-L1 inhibitors are providing durable survival benefits and are taken long-term.

"Some of the targeted therapies have improved median survival, but I'm not sure they have improved the number of people who are alive at five years, which for me is the most important thing," Dr. Joseph comments. "We want people with durable remissions and durable survival."

Patient segmentation

Less clear is where the available products sit in the clinical pathway, and what the real points of differentiation are. As things stand, KOLs and payers alike see little to choose between Opdivo and Keytruda in terms of basic safety, efficacy and cost.

Once combination products are established, toxicity may become a more discriminating factor, particularly in patients with poor performance status. Younger, stronger patients may benefit more from combination therapy.

The availability of standardised biomarker assays to sift out the most receptive patients – measuring PD-L1 expression, for example – should help to provide a rational basis for these decisions.

"[For melanoma patients who have a low-volume disease, or a very slow-growing tumour], I would certainly consider a PD-1," Dr. Joseph says. "I don't think very old patients or ones who are very sick can can tolerate the combination. [For] patients who are maybe less toxic, have less burden of the disease and are less healthy, I would consider using the single agents rather than the combination."

All of this suggests that product choices will be shaped largely by patient segmentation within available indications, as well as dosing schedules and, especially where payers are concerned, costs.

In this last respect, the PD-1/PD-L1 inhibitors are likely to have an easier ride in the US than in Europe, where in a number of important markets (such as Germany, France and the UK), positive cost-benefit assessments are the gateway to market access and/or high entry prices.

That is notwithstanding the trend in the US for payers to push back strongly on prices, negotiating exclusive access to expensive new drugs in return for deep discounting. Even US oncologists are now refusing to prescribe some new cancer drugs if they do not see marginal benefits justifying high treatment costs.

For the PD-1/PD-L1 inhibitors, with their compelling safety and efficacy profile, this does not yet appear to be a significant barrier to uptake. That may change as new indications pile up and more products targeting the same immune-system pathway enter the US market.

Certainly comparative costs have not been ignored. FDA approval may guarantee a place for the PD-1/PD-L1 inhibitors on health-insurance formularies, but the way those formularies structure patient access is by no means cost-neutral.

Mainstay therapy

In the meantime, clinicians will be eager to move the PD-1/PD-L1 inhibitors up the therapeutic cascade.

In Dr. Joseph's view, these products will "probably remain the mainstay therapy for melanoma for many years to come", with product labelling just recently endorsing first-line use.

"Certainly, I think response rates are better in the front line than any other lines. The data are now there, at least in melanoma, with anti-PD-1s beating out [Yervoy]"

One sticking point remains the relatively narrow response rate to PD-1/PD-L1 inhibitors. This will likely be addressed from two angles: widening existing applications – for example, through combination products, including those with potential to stimulate immunogenicity; and finding reliable biomarkers to ensure usage is confined to truly responsive patients and indications.
As Dr. Joseph points out, at the moment "every drug company has a different way of assessing PD-L1 and a different interpretation of what is PD-L1-positive or –negative, so it is very challenging to know what is what".

Dosing counts

One area in which payers and clinicians should be able to find common ground on PD-1/PD-L1 inhibitors is dosing, from the perspective both of patient convenience and cost.

Keytruda in melanoma, for example, is given every three weeks. Opdivo infusions are every two weeks, which may entail additional medical visits and associated costs for patients.

On the other hand, there appears to be little distinguishing Opdivo from Keytruda in terms of average monthly costs per patient – estimated at US$12,500 per month or US$150,000 per year for both products in the US, although this does not take into account administration, any discounts or other concessions negotiated with individual PBMs.

Another unanswered question for physicians is optimal duration of therapy with the PD-1/PD-L1 inhibitors, particularly in relation to cost.

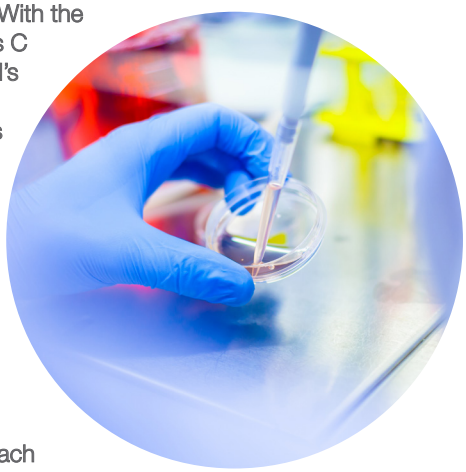
"These drugs are not inexpensive and the problem is, we don't know the optimal duration of therapy," Dr. Joseph observes. As more products enter the market and pressures on costs intensify, this may be something manufacturers or independent researchers need to explore in more detail.

Tentative environment

Without any formal assessment of the relationship between product benefits and costs, and with only a few products currently available for a narrow band of indications, the US payer environment for PD-1/PD-L1 inhibitors remains tentative.

That may reflect the initial positive aura around immuno-oncology products as they enter the market. Payers may be more inclined to rigour as follow-on indications such as NSCLC and expensive combinations like Yervoy/Opdivo begin to eat into healthcare budgets.

Meaningful therapeutic advances can be a double-edged sword. With the next-generation hepatitis C therapies such as Gilead's Harvoni (ledipasvir/sofosbuvir) and AbbVie's Viekiera Pak (ombitasvir, paritaprevir, ritonavir and dasabuvir), and more recently, PCSK9 inhibitors from Amgen (Repatha) and Sanofi/Regeneron (Praluent), US PBMs and health plans tackled escalating demand by pitting manufacturers against each other and extracting substantial discounts in return for exclusive formulary access.



"[PD-1/PD-L1 inhibitors] will probably remain the mainstay therapy for melanoma for many years to come."

"Right now these products are more of a niche therapy", notes a US Pharmacy Director. "With Opdivo, I don't think we are seeing the full impact of this product yet… It is expensive, but they do not use it that much for melanoma, and in non-small cell lung cancer (NSCLC) it's just starting. I think the biggest impact will be when other indications, including wider use in NSCLC, come through."

What US payers are already doing is regulating usage through oncology pathways that may privilege less cost-effective products before qualifying patients can move on to the PD-1/PD-L1 inhibitors.

Higher deductibles or co-payments, particularly in a market where 25-33% of costs are met by patients out of pocket or through co-insurance, may provide another filter to access. In addition, insurers require prior authorisation before physicians can prescribe PD-1 inhibitors in some indications according to the FDA label.

One large payer says he has put Opdivo as first-line therapy for metastatic melanoma, displacing the earlier market entrant Yervoy into second-line or sub-segment usage, while Opdivo is also on second-line NSCLC oncology pathway for squamous type, and Keytruda is not on the pathway at all for either metastatic melanoma or NSCLC.

The emerging picture for US coverage of the PD-1/PD-L1 inhibitors is a mixture of clinical evidence, medical guidelines from organisations such as the NCCN, and cost calculations.

How does the EU market compare?
Find out in Part 2 of this series which will be published in December 2015.

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