Checking in on Checkpoint Inhibitors

Expert insights into future opportunities in immuno-oncology

It is widely accepted that the use of immunotherapy agents has been one of the major advances in oncology over recent years.

But what further changes can we expect as the area develops in the next few years, and what does that mean for pharma? To look further into these important questions, Beyond Blue conducted self-funded research with 5 global KOLs[1] to understand these future perspectives and the opportunities for new checkpoint inhibitors and costimulatory agonists. Their views, and their implications, are discussed here.

PD-1/L1-inhibitors are here to stay, but the role of CTLA4 inhibitors is less certain, even with new developments

Unsurprisingly, our experts confirm that PD-1/L1 inhibitors have made a significant impact on treatment of a range of cancer indications. There is consensus that these agents will continue to play a pivotal role in the future, with the potential to expand their role into new settings, new combinations, and retreatment, with the obvious caveat that this must be supported by robust trial data.

"Every time you have a randomized PD-1 or PD-L1 inhibitor, plus or minus a CTLA-4 inhibitor, the results are negative, including for Keynote-598. My view is that the approach for ipilimumab plus nivolumab (Opdivo), is that they never compare it to nivolumab alone, the comparator is always something else. And so for me, the Keynote- 598 data is just very consistent with the idea that there is no efficacy role. There clearly is toxicity added. My view is that there is no efficacy there."

In contrast, there is less enthusiasm for the CTLA4 inhibitor ipilimumab (Yervoy). For some, its use is constrained by its toxicity profile, and there are also questions regarding the additional benefit vs. PD-1/PD-L1 inhibitors.

- In melanoma, KOLs have been left wondering regarding the long-term survival benefit, due to the lack of direct head-to-head comparisons with PD-1/L1 inhibitor monotherapy.
- The negative Keynote-598 data in 1L PD-L1 high NSCLC, which combined ipilimumab with pembrolizumab, and demonstrated a lack of improved outcomes, has reinforced perceptions that there is limited benefit in NSCLC (despite of a current indication for the nivolumab/ipilimumab combination).
- New CTLA-4 inhibitors are anticipated to show an improved toxicity profile, but it remains to be seen how well, if at all, they address current uncertainties regarding efficacy.

[1] KOLs were selected on the basis of being actively engaged in clinical trials for checkpoint inhibitors. The focus of the KOLs' clinical practice was predominantly melanoma or lung cancer.

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Emerging targets are interesting... but some are more interesting than others

01

TIGIT

TIGIT has attracted a lot of attention, largely because of the positive efficacy of tiragolumab + atezolizumab (Tecentriq) seen in 1L PD-L1+ NSCLC. However, some felt the atezolizumab comparator arm performed poorly in the CITYSCAPE trial, potentially biasing the findings. Our experts were keen to see data for other anti-TIGITs, notably vibostolimab (Merck), to see what TIGIT-targeting can add over and above pembrolizumab.

02

LAG-3

The KOLs are more cautious around the potential of LAG3-directed therapies, noting the protracted development time and limited data released for the lead therapy, relatlimab, though they are still looking forward to the upcoming ASCO presentation on this[2].

03

co-stimulatory agonists

There is also less enthusiasm for co-stimulatory approaches and little surprise among some KOLs over the recently reported failures of ICOS. They also comment on the poor predictability from pre-clinical findings in this area.

> *"ICOS is not a good target and that was well known before and the fact GSK were looking into it surprised people. GITR has been negative, 41BB not very exciting, OX-40 not highly exciting and not highly likely to change, but there are still some studies ongoing in this space. It doesn't look like an exciting area right now"*

> *"Maybe the only one which may have some potential, [though it's] still up in the air, may be CD40. But all the others, OX40, GITR, now ICOS – there was great pre-clinical data, but major failure in the clinical arena. So ICOS is the last victim. So the question is really, is there a future for agnostic antibody in humans, and the answer seems to be no for now."*

[2] This research was completed following the press release reporting positive PFS data from RELATIVITY-047 but prior to the release of ASCO abstracts, therefore the magnitude of the benefit achieved by relatlimab was unknown at the time of the research

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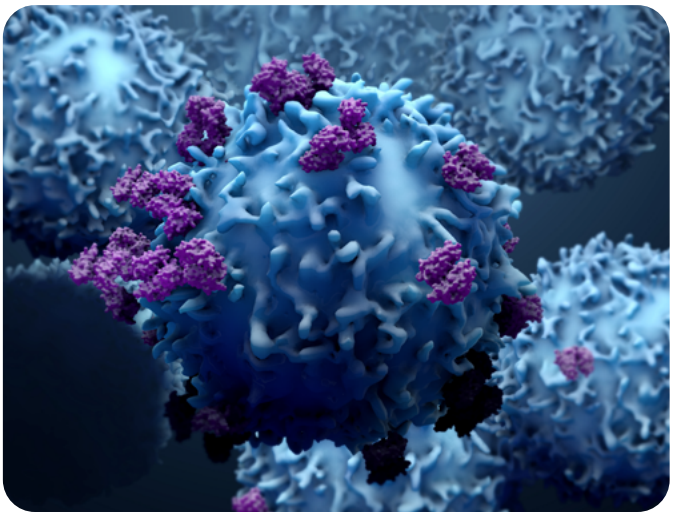

With multiple assets in development across TIGIT, LAG-3 and TIM-3, where is the opportunity for differentiation?

Currently, KOLs interested to explore the impact of molecules with enhanced Fc binding fragments (in the context of TIGIT) and bifunctional therapies as potential strategies for differentiation. In contrast, there is less excitement for co-formulated biologics, which are seen as having limited clinical benefit.

> *"I am very interested looking at this new TIGIT antibody [Genentech and Merck], which has some significant differences in terms of design, and to see if this translates into better activity. So, beside the IgG1 which combines to Fc receptors, there are some other ones which seem to have an even higher Fc binding capability and some even show depletion activity in vitro like the Seattle Genetics agent. So I am looking forward to seeing what these TIGIT antibodies are going to do in the clinic."*

Emerging data may increase the use of less established PD-1/L1 Inhibitors

KOLs believe that rigorous positive data for novel combinations will help drive use of therapies which currently have fewer approvals and lower market share. For example, the potential for the tiragolumab combination could help drive use - and sales - of atezolizumab (Tecentriq).

> *"If the atezolizumab plus tiragolumab trial were to show superiority across the board, I think that is a place where you would start to see pembrolizumab be supplanted by the atezolizumab combination"*

However, perhaps because all drugs in this class are considered fairly similar, there is low enthusiasm for new entries to the PD-1 market, such as GSK's dostarlimab (Jemperli), unless they are strongly competitive on cost or offer other benefits.

> *"I don't know that if your GSK PD-1 inhibitor that gets approved just in a rare gynecologic malignancy, where there are already approved PD-1 agents - do people ever start using it? I think there is a dip in enthusiasm for even recruiting clinical trials for new PD-1 inhibitors, where others are already approved. That may not be important in some parts of the world, where enrolling on study is the only way to access these agents, that group of patients are not going to care what the PD-1 inhibitor is, but in the US people will care"*

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What does this mean for Pharma?

The "high frontier" days of just a few years ago, when the availability of PD-1/L-1 inhibitors was in itself exciting, have passed. Now the territory has been mapped out in broad terms, with the role and value of PD-1/PD-l1 inhibitors well-established, Oncologists are looking for more detailed maps of specific areas within the overall territory, in terms of ever-more precise information on developments with checkpoint inhibition. *Thus, they want to know more about*

- Rational novel combinations are seen as a way of optimising outcomes and prescribing
- New classes are more interesting than new PD-1/L-1s
- Careful patient selection, perhaps in very specific sub-indications, and different comparator arms from those seen in older studies, are likely to be of most interest to physicians

For both established companies and newer organisations just moving into the oncology field, this looks to be a key area for development, especially once most indications and settings have been explored for monotherapy and/or pairing with chemotherapy.

and what's next?

ASCO 2021 highlights the continued investment and development in the area, notably:

01 Differentiation among PD-1 inhibitors; emerging evidence suggesting balstilimab exhibits a differentiated activity profile compared to currently approved anti-PD-1 agents

02 Further interest and investment in TIGIT; with Beigene reporting the design for 2 trials with their FC-competent anti-TIGIT antibody (ociperlimab) in combination with tislelizumab in previously treated R/M cervical cancer and PD-L1 selected NSCLC

03 Data from two LAG-3 antibodies in malignant melanoma: primary phase III from RELATIVITY-047 providing tangible evidence for the potential of relatlimab in combination with nivolumab, and fianlimab (Regeneron) in combination with cemiplimab

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