Evaluate Vantage

November 23, 2015

Merck & Co shows the way in immuno-oncology combinations

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Immuno-oncology has proved to be nothing short of a revolution, but already work has advanced to counteract one of its main shortcomings – the fact that most patients still do not respond to treatment.

One approach seeks to find biomarkers as predictors of response, but just as important is combinatorial therapy; and over the weekend Merck & Co showed that such combinations might indeed dial up responses with no concession to adverse events. As a recent *EP Vantage* report points out, there is no stopping the immuno-oncology bandwagon, and the Merck data will not dampen enthusiasm.

Indeed, as of late September Merck & Co's anti-PD-1 MAb Keytruda was in clinical studies with no fewer than nine other MAbs, as well as seven cancer vaccines, three cell/oncolytic virus therapies, 23 small molecules and numerous established cancer drugs and chemotherapies, the *EP Vantage* report found.

Limited arsenal

But, relative to its peers Bristol-Myers Squibb and AstraZeneca, Merck has a limited in-house arsenal of immuno-oncology agents, and collaborations are the basis for all three Keytruda combos highlighted at the Society for Melanoma Research meeting on Saturday.

Merck, for instance, is one of four big pharma groups with non-exclusive rights to Incyte's IDO inhibitor epacadostat. When combined with Keytruda in 19 advanced melanoma patients Keytruda plus epacadostat yielded an overall response rate of 53%, the New Jersey-based group said.

Meanwhile, a Keytruda combo with Amgen's recently approved oncolytic virus Imlygic (T-Vec) gave a 56% ORR. The key comparator here is Keytruda monotherapy data – for instance in the Keynote-002 trial in advanced melanoma, where ORR was only 25%, though this did translate into a 43% improvement in progression-free survival versus chemo.

Thus, while the data are very early, the Incyte and Amgen combos appear to double the response rate – with a safety profile similar to Keytruda alone. Only larger trials will determine the extent to which they improve survival, and Merck is planning a phase III study of Keytruda plus epacadostat.

The rationale behind combinations centres on certain tumours' lack of immunogenicity, as well as the possible presence of additional blocking checkpoints. Thus it is possible that hitting two targets could overcome resistance to one, as well as driving the tumour into a more immunogenic state.

The latter is postulated also to be true for combinations involving oncolytic viruses, which are thought to have extremely limited standalone potential. These viruses might also increase neoantigen exposure to the T-cell based immune system, acting in a manner similar to a vaccine to boost the tumour's susceptibility to immunotherapy.

The importance of Yervoy

The *EP Vantage* report also reveals that Bristol's anti-CTLA4 MAb Yervoy is one of the most widely studied combo agents, appearing in 21 trials with the group's own PD-1 MAb, Opdivo, for instance.

The third study Merck reported concerned Keytruda plus Yervoy, and yielded a 56% ORR. However, Yervoy is a highly toxic agent, and in this study there was a price to pay: 93% of patients reported treatment-related adverse events, 36% suffering grade 3/4 toxicity.

The relevance of a combo containing a CTLA4 agent is commercial, in that only two big pharmas have this in house: Bristol, and Astra with tremelimumab. This could have cost implications, since an in-house combo could be priced more competitively than one relying on a partnership.

A similar case could be made with IDO inhibitors, where the only exclusive alliance struck so far concerns Newlink's NLG919, licensed to Roche. As such, the key beneficiary of the success with epacadostat might not

be Merck and Incyte, but Roche and Newlink.

Selected Keytruda combination studies			
Combination agent	**Study**	**Detail**	**Trial ID**
Epacadostat	Keynote-037	53% ORR, 3/19 CRs and 7/19 PRs.	NCT02178722
Imlygic (T-Vec)	Masterkey-265	56% ORR, 2/16 CRs and 7/16 PRs.	NCT02263508
Yervoy	Keynote-029	56% ORR, 3/72 CRs and 37/72 PRs; 93% treatment-related AEs.	NCT02089685

EP Vantage has published a broad overview of the current landscape for anti-PD-1/PD-L1 combination therapeutics. A free copy of the report is available by download.

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