Evaluate Vantage

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Esmo 2020 – more encouraging signs for checkpoint bispecifics

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Promising but early data on PD-1 x CTLA-4 bispecifics from Macrogenics and Akeso add further weight to this approach.

Hitting both PD-(L)1 and CTLA-4 has proven efficacy, as Bristol Myers Squibb has shown with Opdivo plus Yervoy, but toxicities associated with the latter target have capped the potential of the combination. Several other companies are trying to hit both these targets with bispecific antibodies, with the hope of showing similar antitumour activity with better safety.

Early data presented at the virtual Esmo meeting from Macrogenics and Akeso go some way to validating this approach, but with small patient numbers there are still unanswered questions. Macrogenics' MGD019, in particular, was linked with high toxicity; signs from Akeso's AK104 look more promising.

Mesothelioma promise

The data on AK104 came in mesothelioma, a particularly hard-to-treat cancer. Esmo heard details of a 20% overall response rate in 15 immunotherapy-naïve mesothelioma patients in the private Chinese group's phase I study.

The trial found a 17% rate of treatment-related grade 3 or 4 adverse events, lower than the 21% seen in Opdivo/Yervoy's Checkmate-743 mesothelioma study. And only 6% of AK104-treated patients discontinued due to a treatment-related adverse event, compared with 23% with Opdivo/Yervoy in Checkmate-743.

AK104 was specifically designed to be safer than Opdivo/Yervoy. As it only binds to tumour-infiltrating lymphocytes expressing both PD-1 and CTLA-4, its effects could stay localised to the tumour microenvironment, according to Professor Michael Millward of the University of Western Australia, who presented the data at Esmo.

Drawing broad conclusions about safety might be premature: Mizuho analysts noted that later emergence of side effects is not uncommon with checkpoint inhibitors.

Professor Millward concluded that AK104 warrants further study in mesothelioma, adding that a combination with chemo in first-line disease could be particularly attractive. Notably, Akeso is already testing AK104 in combination with chemo in first-line gastric cancers.

Macrogenics looks for sweet spot

Macrogenics, meanwhile, reported a 13% ORR from 30 heavily pretreated patients in a phase I basket study of MGD019, including one complete response.

Encouragingly, the project showed activity in tumour types not typically responsive to checkpoint inhibitors, including microsatellite-stable colorectal cancer and metastatic castration-resistant prostate cancer.

Overall, the side-effect profile looked similar to that of Opdivo/Yervoy, with 33% patients on MGD019 experiencing a grade 3 or greater treatment-emergent adverse event. However, half of these came in the highest dose group, 10mg/kg, which Macrogenics is dropping; only the 6mg/kg will be taken forward.

Macrogenics will hope it has found the sweet spot, and there are reasons for optimism: all four responses came in the 3mg/kg and 6mg/kg groups; and excluding doses lower than 3mg/kg from the analysis gave a more impressive 22% ORR. The group will of course need to replicate this in phase II.

The latest data could have read-across to Xencor's rival bispecific, XmAb20717, which has so far yielded one complete response in a melanoma patient, as reported at this year's Asco. The Mizuho analysts set a 15-20% response rate in checkpoint-experienced patients as a bar for XmAb20717 to beat when the company reports more data from the phase I Duet-2 trial, due within the next 12 months.

Meanwhile, Astrazeneca has pushed ahead with its contender, MEDI5752, with several early-stage trials now under way (*Astra turns to bispecifics to solve the treme problem, February 14, 2020*).

There is some way to go to ascertain whether bispecifics have any edge over Opdivo plus Yervoy. But even a similar efficacy and safety profile could lead to a competitive product, given the likely cost and convenience advantage of a single agent.

Selected PD-1xCTLA-4 bispecifics indevelopment

Project	Company	Setting	Note
MGD019	Macrogenics	Solid tumours inc pancreatic, CRC, ovarian	Esmo 2020: 13% ORR in 30 pts in basket trial
AK104	Akeso	Mesothelioma	Esmo 2020: 20% ORR in 15 mesothelioma pts
XmAb20717	Xencor	Solid tumours	Asco 2020: 1/34 CR in melanoma; ph1 Duet-2 study (NCT03517488) ongoing
KN046	Alphamab	Solid tumours	Asco 2020: 12% ORR in 25 pts progressed after checkpoint blockade; various ph2 trials ongoing
MEDI5752	Astrazeneca	Solid tumours	Ph1 studies ongoing in solid tumours (NCT03530397), NSCLC (NCT03819465), renal (NCT04522323)
CN104974253A	Shanghai CITIC Guojian Pharmaceutical	N/A	Patent only

Source: EvaluatePharma, clinicaltrials.gov.