Evaluate Vantage

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Bavencio’s gastric failure calls into question rival approvals

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No doubt Bavencio’s failure in Merck KGaA’s Javelin Gastric 300 study will prompt further suggestions that underlying mechanistic properties are causing some anti-PD-(L)1 agents to do better in trials than others. For regulators, however, the truth might be more embarrassing.

The latest trial had pitted Bavencio against chemo – a higher bar than competitors had beaten to secure regulatory green lights. Historic data for third-line gastric cancer chemotherapy suggest that checkpoint inhibition might be a non-starter – providing an obvious reason for Bavencio’s failure, as well as calling into question recent approvals of Keytruda and Opdivo.

The setback highlights the difficulty of being a market latecomer, and Merck KGaA and its Bavencio partner, Pfizer, might as well accept that being first in immuno-oncology brings special perks. Not only did they need to study Bavencio against active chemo they of course had to try and demonstrate efficacy on the gold standard of overall survival, and yesterday said Javelin Gastric 300 failed.

Easy target

But the fact that Keytruda and Opdivo got over the regulatory finish line so easily – when historical data suggest that third-line patients might do just as well on chemo – should give pause.

Keytruda’s US approval came on an accelerated basis based on the single-arm Keynote-059 trial, which showed a 13.3% overall remission rate; Opdivo, approved in Japan, did extend survival, but only versus a placebo comparator. The survival benefit for each drug, around 5.5 months, is in line with historic studies of paclitaxel and irinotecan, which are frequently used in this setting in the US.

The most logical explanation for Bavencio’s failure is therefore that the Merck KGaA/Pfizer drug resulted in similar survival, and that subjects given chemo lived as long as historic data suggest. Asked by *EP Vantage*, Merck KGaA would not reveal whether Javelin Gastric 300 allowed patient crossover, or whether there might have been a benefit in PD-L1-high patients.

Selected gastric cancer studies

		Median OS		
Study	**Drug**	**Active**	**Control**	**Trial ID**
Attraction-2*	Opdivo	5.3 mth	4.1 mth (placebo)	NCT02267343
Keynote-059**	Keytruda	5.6 mth	None	NCT02335411
Retrospecive Japanese analysis	Paclitaxel	6.7 mth	None	–
33-patient Italian study	Irinotecan	7.5 mth	None	–
Javelin Gastric 300	Bavencio	Study failed, OS not disclosed	Not disclosed (chemo)	NCT02625623
Keynote-061^	Keytruda	Yet to report	Yet to report (chemo)	NCT02370498

*Source: company reports, Pubmed. All studies third-line, except Keynote-061, which is second-line. Notes: *basis for Japan approval; **basis for US accelerated apoproval, in PD-L1-high patients; ^PD-L1-positive patients.*

The imminent readout of Keytruda's Keynote-061 study should further elucidate the potential of checkpoint blockade in gastric cancer – this does use a chemo comparator, but tests second-line, PD-L1-positive subjects.

Still, the chances of the US FDA revoking an accelerated approval like Keytruda's are vanishingly small, considering the failed confirmatory studies of Keytruda in head and neck cancer and Tecentriq in bladder cancer; both remain on the market in these cancer types.

Bristol-Myers Squibb's US gastric cancer strategy is interesting: the group is using chemo comparators in the first-line Checkmate-649 trial and Fraction-GC, a study in advanced subjects, but – perhaps mindful of how high a bar chemo is – combinines Opdivo with Yervoy or the anti-Lag3 MAb BMS-986016 to improve chances of success.

It had boasted that Opdivo's placebo-controlled Attraction-2 trial, in Asian patients, was the first to show a statistically significant overall survival benefit in third-line gastric cancer. For Roche's Tecentriq, meanwhile, gastric cancer does not even seem to be a major focus, given the lack of advanced studies under way (*Asco-GI – Opdivo heads close pack of anti-PD-1s in gastric cancer, January 20, 2017*).

It cannot be denied that Bavencio is coming very late to the checkpoint inhibitor party. But it should not be written off just yet, at least not on the basis of Javelin Gastric 300.

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