Evaluate Vantage

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Esmo 2018 – Without overwhelming efficacy the me-too PD-1 chase is futile

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Results from Tesaro, Sanofi, Novartis, Merck KGaA and others have come in thick and fast, but can any beat the entrenched leaders?

Anyone doubting the seriousness of the effort to develop follow-on anti-PD-(L)1 drugs should look at the timelines for spartalizumab and Libtayo. The respective Novartis and Sanofi/Regeneron assets quickly recruited vast numbers of trial subjects, and the latter was approved just over three years after first entering the clinic.

The question, however, is what these and other competitors are fighting for; the stranglehold of first-generation drugs like Keytruda will prove hard to break. The weekend's Esmo conference showed plenty of work among the me-too camp, but in many cases the best these drugs could show was efficacy in line with the leaders – something that will cut little ice in the real world.

A case in point was camrelizumab, a Jiangsu Hengrui Medicine asset that until recently had been licensed to Incyte. At Esmo data in Chinese second-line liver cancer patients were damned by the discussant, Gustave Roussy's Dr Michel Ducreux, who said camrelizumab was "probably an interesting drug that is working, but it doesn't bring anything major".

This study also highlighted an adverse event, a skin reddening called reactive cutaneous capillary endothelial proliferation, possibly related to camrelizumab reactivating an immune response. Perhaps such factors explain why Incyte gave up on the asset in favour of Macrogenics' MGA012.

Selected anti-PD-1 data presented at Esmo 2018			
Project	**Company**	**Esmo highlight**	**Cross-trial comparison?**
TSR-042	Tesaro	MSI-H endometrial cancer, ORR 48%	ORR 36% for Keytruda
Libtayo (cemiplimab)	Sanofi/Regeneron	Liver cancer, ORR 20%	ORR 15% for Opdivo, 17% for Keytruda
Libtayo (cemiplimab)	Sanofi/Regeneron	Head & neck cancer, ORR 7%	ORR 13% for Opdivo, 16% for Keytruda
Camrelizumab (INCSHR1210)	Jiangsu Hengrui Medicine	2L liver cancer, ORR 14%	ORR 15% for Opdivo, 17% for Keytruda
Spartalizumab (PDR001)	Novartis	Thoracic NETs, ORR 20%	Case reports
Toripalimab (JS001)	Shanghai Junshi Biosciences	Advanced NETs, ORR 20%	ORR 6% for Keytruda, plus case reports
M7824	Merck KGaA	HPV+ve head & neck cancer, ORR 50%	ORR 21% for Keytruda
Source: Esmo 2018. NETs=neuroendocrine tumours. ORR=overall remission rate, confirmed by RECIST where available. MSI-H=miscrosatellite instability-high.			

Camrelizumab's remaining potential lies in China, and this is also the plan seemingly being pursued by Shanghai Junshi Biosciences with toripalimab, which has been filed locally for melanoma. However, this country has already seen the approval of Opdivo, for lung cancer, and likely carries far worse economics than the West.

Toripalimab is an example of how some me-too players are chasing very small indications – early remissions in neuroendocrine tumours, just presented at Esmo, look impressive – just to get a shot at approval. This way Sanofi/Regeneron's Libtayo last month became the first US-approved treatment for the rare cancer cutaneous squamous cell carcinoma.

Sanofi/Regeneron will have to work hard to advance beyond this setting, however: at Esmo Libtayo was shown to have "evidence of activity" in relapsed hepatocellular carcinoma, where Opdivo is already approved, while in the tough indication of head and neck cancer it "did not demonstrate efficacy above what could be achieved with other PD-1 inhibitor monotherapies", said the study authors.

Novartis's spartalizumab is similar to Libtayo in that it only entered the clinic in 2015. The Swiss firm has felt sufficiently confident to pinpoint it as the cornerstone of its immuno-oncology combination strategy, with a US filing planned for next year.

While spartalizumab's efficacy at Esmo in neuroendocrine tumours of thoracic origin looked promising, Novartis is thinking bigger, and its US filing is to be in melanoma, using spartalizumab in combination with Tafinlar and Mekinist.

Think big or go home

Indeed, such is this market that only bold bets might have a chance of success. Three years after clinical work began, the planned study enrolment totals for Libtayo and spartalizumab stand at an incredible 5,075 and 6,447 patients respectively.

Such numbers overshadow the 1,316 subjects intended to be enrolled into trials of Merck KGaA's M7824, though this asset is no less noteworthy. It is not just an anti-PD-L1, but rather a fusion protein with activity against PD-L1 as well as acting as a trap for TGF-beta.

The German company says it is its most promising R&D asset, and hopes that it can blow market-leading anti-PD-1s and its own Bavencio out of the water. The Esmo data with M7824 were extremely early, but promising: in an expansion cohort of eight head and neck cancer patients who were positive for HPV, a known cause of the disease, four responded.

HPV-positivity is known to lead to high tumour burden, and there is an additional scientific rationale in that the TGF-beta receptor is frequently mutated in HPV-positive head and neck tumours. Still, the late-stage focus for M7824 will be the rare disease cholangiocarcinoma, and the highly competitive lung cancer setting, Luciano Rossetti, Merck KGaA's head of R&D, told *Vantage*.

How bold is the bet? While some companies continue comparing data against historical controls, Merck KGaA recently detailed on Clinicaltrials.gov a study of M7824 head to head against Keytruda in first-line NSCLC, a move that looks like a bid for death or glory.

“We believe in truth-seeking behaviour,” said Mr Rossetti. “[The move] is gutsy, less irrational than you might think, and it’s looking for a big effect. What else would you do? I didn’t see any other alternative.”

Is the aim for M7824, on the primary progression-free survival measure, to beat Keytruda? “Yes.” Other PD-(L)1 wannabes should take note.

This story has been amended to correct some of the data comparisons.