Evaluate Vantage

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Neptune leaves Astra at sea

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The Neptune lung cancer study fails, denting yet further Astrazeneca and Bristol-Myers Squibb's chances of challenging Merck & Co's Keytruda on the basis of tumour mutation burden.

With the post-hoc re-analysis of its failed Mystic study last year Astrazeneca set the stage for Neptune, a trial in a similar first-line lung cancer population, to be analysed prospectively in patients with high tumour mutation burden (TMB). Today's failure of Neptune therefore puts the company back to square one.

The setback is also yet another black mark against tremelimumab, the CTLA-4 inhibitor Astra licensed from Pfizer that seems to doom every study in which it is tested. And, if Astra has just shown that not enough is known about TMB for this biomarker to be the basis for filing, that spells yet more bad news for Bristol-Myers Squibb.

It was Bristol, after all, that had first suggested TMB-high patients as the relevant population for Opdivo plus Yervoy in Checkmate-227, its extensively overhauled first-line NSCLC trial. But, even if there had been mileage in the theory, an FDA request for more data prompted Bristol to pull its filing, and the company was likely awaiting further events before deciding on a path forward.

If the readout of Neptune was one of these events then today Bristol will be disappointed. Astra, a relatively recent convert to the relevance of TMB, says that in Neptune its combo of Imfinzi and tremelimumab failed to prolong overall survival of TMB-high patients versus standard chemo alone, the study's primary endpoint.

As a reminder, last year Neptune had been upsized to give Astra what it called the "flexibility" to look at TMB, before a post-hoc reanalysis of Mystic, the group's failed NSCLC trial, suggested that there was indeed mileage in this biomarker in front-line NSCLC.

Spanner in the works

Apart from putting another spanner in this theory, Neptune's failure casts yet more doubt on the viability of tremelimumab, Astra's competitor to Yervoy. Mystic's primary analysis hinted at a numerical benefit with Imfinzi monotherapy but not with the combo; similarly, in the Caspian SCLC trial it was the Imfinzi-only cohort that yielded a hit.

If treme is inert that is one thing, but it is more concerning if the project's toxicity is causing patients to drop out of studies, or even contributing to their deaths – which could explain why numerically Imfinzi has been seen to be more effective without treme than in combination with it.

To the extent that it is still possible to challenge Keytruda's stranglehold on first-line NSCLC this is important to bear in mind when betting on Astra's two other front-line trials, Poseidon and Pearl: both test Imfinzi alone plus chemo, though the former also has a treme combo arm, and the latter is effectively an Asia-focused study.

The next to read out will be Poseidon, in the second half of this year, though it is unclear whether it will be cut by subjects' TMB status. Its clinicaltrials.gov entry mentions TMB as a keyword; as *Vantage* went to press Astra had not responded to a request for clarification.

For its part, Bristol has said nothing about its plan to refile Opdivo plus Yervoy in first-line NSCLC since deciding to pull the TMB-based application in January. Next year the Checkmate-9LA trial of Opdivo, Yervoy and chemo reads out, but nothing has been said about how it will be analysed.

Selected first-line metastatic NSCLC trials				
Study	**Active treatment**	**Population**	**Trial ID**	**Result**
Mystic	Imfinzi +/- tremelimumab	PD-L1 ≥25%	NCT02453282	Miss; post-hoc benefit suggested in TMB high (≥16mut/Mb) subjects
Checkmate-227 part 1	Opdivo + Yervoy	TMB high (≥10mut/Mb)	NCT02477826	Unclear*
Checkmate-227 part 1a	Opdivo + Yervoy	PD-L1 ≥1%		Hit
Checkmate-227 part 2	Opdivo + chemo	Non-squamous all-comers		Miss
Neptune	Imfinzi + tremelimumab	TMB high (≥20mut/Mb)	NCT02542293	Miss
Poseidon	Imfinzi + chemo +/- tremelimumab	All-comers	NCT03164616	Data H2 2019
Checkmate-9LA	Opdivo + Yervoy + chemo	All-comers	NCT03215706	Data H1 2020
Pearl	Imfinzi + chemo	PD-L1 high	NCT03003962	Data H1 2021 (Asia-focused study)
*Notes: *called into question by a similar result in TMB low subjects and the FDA's request for more data.*				

One sign of how unclear TMB still is as a putative biomarker is the different cutoffs being used: Checkmate-227 used ≥10mut/Mb to define the TMB-high population, while the Mystic reanalysis set ≥16mut/Mb and in Neptune the cutoff was ≥20mut/Mb.

True, with Poseidon Astra has another outside chance of success. But perhaps its best bets in lung cancer are to focus on the stage III setting where Imfinzi is carving out a niche thanks to Pacific, to try and steal a march on Roche's Tecentriq in SCLC thanks to Caspian, and to hope for the best in Asia from Pearl.