Evaluate Vantage

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Tumour mutational burden, and other tricks up Astra's Imfinzi sleeve

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Failure of the first analysis of Imfinzi's Mystic trial might have put the Astrazeneca drug seriously behind Merck & Co's Keytruda in first-line lung cancer, but Astra reckons it still has a couple of tricks up its sleeve.

Judging by comments on this morning's first-quarter call, for instance, the Neptune study could be modified to look at tumour mutational burden – the focus of Bristol-Myers Squibb's controversially overhauled Checkmate-227 trial – and a handy delay beyond the next Mystic readout could have strategic importance. Astra has a plan to make the most of its first-mover advantage in earlier, stage III disease too.

That advantage, in a relatively untapped niche, came courtesy of the Pacific study that read out positively for progression-free survival and ensured US approval in February. Overall survival data are due next year.

But stage III disease is something of a mystery, and Astra reckons that only 20% of NSCLC patients are diagnosed this early. At diagnosis 50% already have stage IV, metastatic disease – the setting for trials like Mystic and Neptune, and the one in which Keytruda is approved first-line.

Education

Dave Fredrickson, head of Astra's oncology unit, said after the Pacific success initial efforts had focused on educating doctors about the availability of a therapy before progression on chemoradiotherapy, a setting where until now the standard was watchful waiting.

While stopping short of suggesting new screening efforts, he suggested that Astra would do more to ensure that stage III NSCLC patients who are candidates for chemoradiotherapy know about Imfinzi.

"Education around the availability of the Pacific regimen is certainly creating a greater awareness around the need to make sure that patients are identified as early as possible," he said today. "We're focused on those efforts right now."

Since the drug has only just been launched the precise market potential is unclear, but it will not go unnoticed that for Astra stage III disease represents an open goal. The competition is focused on stage IV NSCLC – where Astra's Mystic trial of Imfinzi plus tremelimumab failed its first PFS analysis last summer.

That effectively put Astra out of the running to catch up with Keytruda, and fearing a similar fate Bristol redesigned its Checkmate-227 trial of Opdivo plus Yervoy to look at patients with high tumour mutational burden (TMB) – and claimed a win (*Bristol-Myers turns alchemist to get lung cancer win, February 5, 2018*).

TMB again?

Today Astra said it might follow suit – not with Mystic but with Neptune, a sister study that has a greater focus on South America and Asia than western markets.

Astra's chief medical officer, Sean Bohen, confirmed that the statistical analysis plan for Mystic was locked, and that after the PFS failure most of its powering was allocated to the OS analysis by PD-L1 expression cuts.

But he added: "Neptune does retain flexibility with regard to using different patient selection criteria or looking at a subset such as TMB. We'll look at what we'd like to apply later, and have the opportunity to change Neptune to reflect that."

Last year Neptune was expanded, though Astra still hoped for OS readout in the second half of 2018. Today it said this would now take place in 2019.

The delay could be strategically beneficial, as it would put Neptune's readout after that of Mystic. This would mean that a post-hoc analysis of Mystic could potentially look at TMB, and be used to inform the final analysis of Neptune.

A separate consideration is what cuts of TMB might be used, and indeed whether TMB is even relevant. At last

month’s AACR meeting experts were split, one calling TMB an independent and reliable biomarker, but another saying it should not be relied on alone; particularly worrying is that it does not seem to correlate with survival.

Still, with investors falling out of love with PD-(L)1 and CTLA4 combinations, Astra, like Bristol, seems willing to give anything a shot.

A 1st-line lung cancer plan for Imfinzi			
Study	**Setting**	**Data**	**Trial ID**
Cementing a lead in non-metastatic NSCLC…			
Pacific	Imfinzi after chemo/radio (pre progression) in stage III	US-approved on PFS data; OS readout 2019	NCT02125461
Adjuvant	Imfinzi after complete resection of stage Ib-IIIa disease	Disease-free survival data ~2020	NCT02273375 (IST)
…and a final hope in later-stage, metastatic stage IV disease			
Mystic	Imfinzi +/- tremelimumab, vs chemo	PFS analysis failed; OS readout H2 2018	NCT02453282
Neptune	Imfinzi + tremelimumab, vs chemo	OS readout (possible focus on TMB) 2019	NCT02542293
Source: Clinicaltrials.gov and company materials.			