Evaluate Vantage

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Esmo-IO 2018 – Astrazeneca plays its tumour mutation burden card

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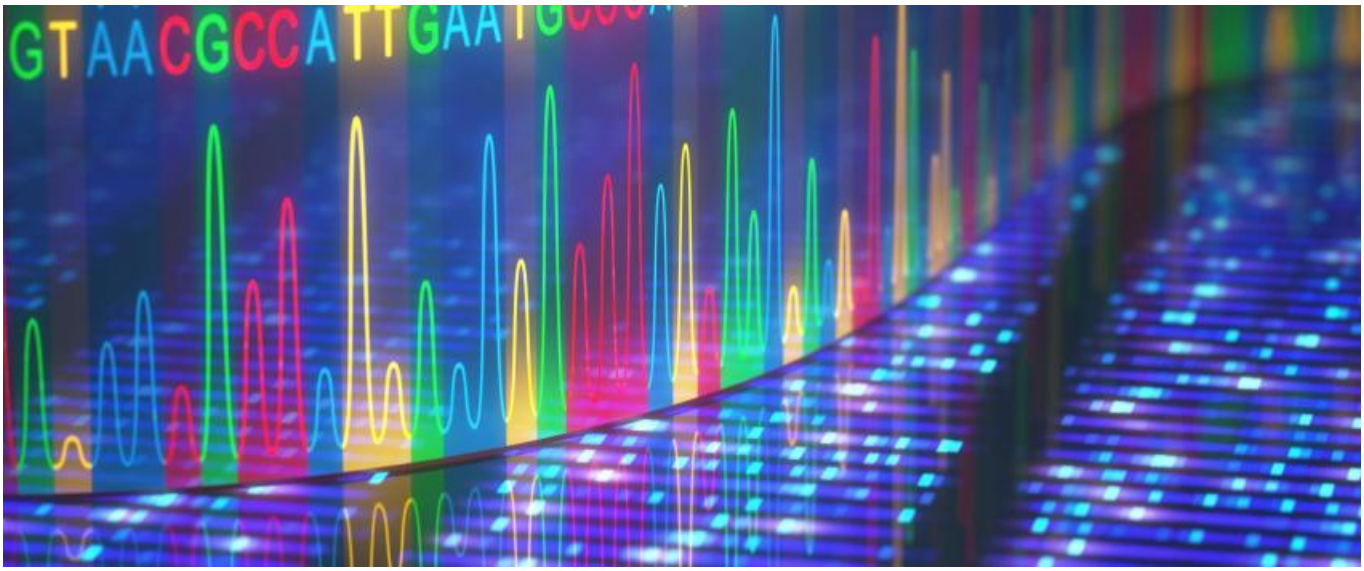

Full results of the Mystic study present a controversial path forward for Imfinzi, and set the stage for the upcoming Neptune trial to be overhauled.

Astrazeneca is not giving up on the first-line treatment of metastatic non-small cell lung cancer with immunotherapy. That much is clear after today's presentation at the Esmo Immono-Oncology conference in Geneva of exploratory analyses from Mystic, its failed study of Imfinzi plus tremelimumab.

Most intriguing is the result the group claims if the data are cut by patients' tumour mutational burden (TMB), a controversial biomarker earlier touted by Bristol-Myers Squibb. The pieces are thus in place to use the Mystic data-dredge to refocus another Astra trial, Neptune, on TMB to try and verify the benefit prospectively.

Neptune also tests Imfinzi plus tremelimumab in first-line NSCLC, and is due to read out early next year. Bristol had earlier overhauled its own Checkmate-227 study to look at TMB-high patients, and the US FDA is to rule on the approvability of Opdivo plus Yervoy in this setting by May 20.

The elephant in the room for both companies is the ready availability of Merck & Co's Keytruda plus chemo in all-comer NSCLC patients.

Primary fail

That Mystic was primarily a bust was no secret. The trial failed its PFS and OS primary endpoints for the Imfinzi plus tremelimumab combo in subjects expressing PD-L1 at 25% or above, representing 488 of the 1,118 total enrolled.

The one glimmer of hope Astra gave in last month's announcement of the OS failure was that Imfinzi monotherapy performed numerically better than chemo, yielding a nominal p value of 0.036.

Today, at ESMO-IO, the rhetoric went up a gear. Dr Naiyer Rizvi, presenting detailed data on behalf of Columbia University Medical Center, called the survival benefit seen with Imfinzi monotherapy "clinically meaningful".

It is not clear why monotherapy would have performed better than the tremelimumab combo. The added toxicity of tremelimumab could have provided an explanation, but in fact serious adverse events were numerically higher with chemo than with the combination. 39.5% of chemo recipients went on to get immuno-oncology, but if this confounded the data it would have done so for monotherapy too.

That aside, the greatest interest will fall on the TMB analysis. In subjects defined as TMB-high Astra claimed a six-month survival benefit for the combo, which it described as very exciting albeit exploratory.

Speaking to *Vantage* today Mika Sovak, Astra's vice-president of immuno-oncology, stressed that the TMB analysis would need to be confirmed in a future trial. Handily, such a trial is already well under way: Neptune was earlier upsized to give "flexibility" to look at TMB (*Tumour mutational burden, and other tricks up Astra's Imfinzi sleeve, May 18, 2018*).

Ms Sovak confirmed that Astra was still considering such a course of action with Neptune, and would decide after analysing the Mystic data further.

Exploratory analyses of Mystic in subjects assessable for TMB (~783 of 1,118 total enrolled)						
Population	**N**	**Measure**	**Imfi+treme combo**	**Imfi monother**	**Chemo**	**Note**
TMB high*	~313	OS	16.5mth	11.0mth	10.5mth	HR=0.64 for the combo
TMB low**	~470	OS	8.5mth	12.2mth	11.6mth	No effect on OS
*Note: *defined as ≥16mut/Mb; **<16mut/Mb.*						

An obvious question about Mystic is why such a strong OS benefit should have been seen among TMB-high subjects.

One problem with TMB status is that it tends not to correlate with survival, and indeed Bristol's latest analysis of Checkmate-227 revealed no OS difference between TMB-high and TMB-low groups. On this point, Ms Sovak stressed that Mystic represented the "most comprehensive TMB dataset that exists in NSCLC", as defined by percentage of subjects with available blood TMB data from a single study.

Another paradox is that the numerical OS benefit in TMB-high subjects favours the combo, while in PD-L1-highs Imfinzi monotherapy did best. TMB status and PD-L1 expression tend to identify non-overlapping patient populations, however. An analysis of TMB-high patients who were PD-L1-negative has yet to be carried out.

And the sharp-eyed will have noticed that Astra used a different boundary for defining high TMB: 16 mutations per megabase, rather than the 10mut/Mb used by Bristol. This had been prespecified for the Guardant Health blood assay Astra used, said Ms Sovak; Bristol had used Foundation Medicine's tissue-based test.

Still, if TMB is indeed a valid biomarker it is not clear why doctors would carry out such a test for patients who could right now receive Keytruda plus chemo with no need to test at all. And ≥1% PD-L1 expressers could soon have the option of chemo-free Keytruda monotherapy.

Dr Jack West, from the Swedish Cancer Institute, told *Vantage* that, while interest in TMB was building, the latest Mystic results were no better than Keynote plus chemo, adding that the data were not sufficiently superior "to warrant much interest in changing the treatment landscape in first-line advanced NSCLC".

Ms Sovak said getting a blood sample was much easier than doing a tissue biopsy, but accepted that the whole point of a biomarker was to identify patients who could derive "significant benefits above and beyond what currently exists. We have yet to see whether blood TMB can be that biomarker."

Primary analysis of Mystic, in ≥25% PD-L1 subjects (488 of 1,118 total enrolled)				
Study arm	**Primary endpoint**	**Result vs chemo**	**Statistics**	**Stat sig?**
Imfinzi + tremelimumab	PFS	3.9mth vs 5.4mth	HR=1.05, p=0.705	No
Imfinzi + tremelimumab	OS	11.9mth vs 12.9mth	HR=0.85, p=0.202	No
Imfinzi monotherapy	OS	16.3mth vs 12.9mth	HR=0.76, p=0.036	No

This is an updated version of a previous story.

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