AstraZeneca's Imfinzi-Treme Checkpoint Inhibitor Combination Fails Again In NSCLC

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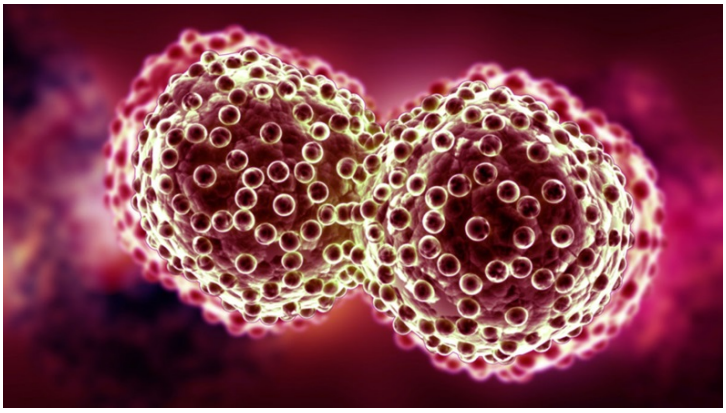
Executive Summary

The Phase III NEPTUNE lung cancer trial found the combination of Imfinzi and tremelimumab was no better than chemotherapy at extending overall survival. After repeat setbacks, AstraZeneca is now running out of opportunities to show its dual checkpoint blockade is effective in NSCLC.



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AstraZeneca PLC's Imfinzi-tremelimumab combination has failed to improve overall survival in metastatic non-small cell lung cancer (NSCLC) patients, dealing another blow to the company's push to establish its anti-CTLA4 antibody as part of the immuno-oncology treatment toolkit.

The analysis of the NEPTUNE trial centered on first-line patients with a high tumor mutational burden (TMB), defined by AstraZeneca for this study as 20 or more mutations per megabase. AstraZeneca, like Bristol-Myers Squibb Co. before it, focused on TMB-high patients in the belief the larger numbers of neoantigens associated with their cancer cells could fuel a stronger antitumor immune response.

AstraZeneca's NEPTUNE results raise further doubts about that theory. The top-line finding is that the combination of anti-PD-L1 antibody Imfinzi and anti-CTLA4 antibody tremelimumab failed to better the overall survival achieved by chemotherapy. Observers were braced for the failure.

"Expectations for first-line NSCLC are low after the MYSTIC failure. We are cautious on Imfinzi+treme combo arms in Phase III NEPTUNE and POSEIDON given prior setbacks," analysts at Jefferies wrote in a note to

investors last month. The high bar set by Merck's checkpoint inhibitor Keytruda in NSCLC means even a moderate clinical success may have mattered little commercially.

Researchers at AstraZeneca are still analyzing the clinical and biomarker data generated in the trial with a view to presenting the full results at an upcoming medical meeting. The lack of data available publicly today make a deep analysis of the trial and its implications for AstraZeneca impossible, but the top-line findings and their concurrence with other studies provide some pointers.

As the Jefferies analysts referenced last month, the Imfinzi-tremelimumab combination has been tarnished by earlier clinical failures. Tremelimumab failed its first Phase III back in 2008, three years before AstraZeneca picked up rights to the CTLA-4 drug from Pfizer, and has been involved in a series of weak clinical readouts over the past two years.

AstraZeneca's MYSTIC, the company's big hope of making up lost ground in immuno-oncology, found the Imfinzi-tremelimumab combination failed to improve progression-free survival in first-line NSCLC in 2017. The following year, AstraZeneca reported the trial also failed to improve overall survival.

In between those readouts, AstraZeneca identified TMB-high patients as a subpopulation that could increase the likelihood of NEPTUNE generating better results than MYSTIC. A subsequent post hoc analysis of MYSTIC data showed overall survival was longer in TMB-high patients, in that case defined as above 16 mutations per megabase. By then, AstraZeneca had already expanded NEPTUNE to gain the option to look at TMB-high patients.

BMS, an early mover in TMB, has also faced setbacks in its efforts to turn the idea into a commercial opportunity. BMS filed for FDA approval of its checkpoint inhibitor combination – anti-PD-1 antibody Opdivo and anti-CTLA-4 antibody Yervoy – in advanced NSCLC patients with TMBs above 10 mutations per megabase last year, only to withdraw the filing in January.

BMS withdrew the filing after talks with the FDA led it to conclude it would need "further evidence on the relationship between TMB and PD-L1" to show the impact of its combination. As the required data was not available at that time, it pulled the submission. The comany has since reported that its combination improved overall survival in first-line NSCLC.

Analysts asked AstraZeneca last month about the potential readthrough from the BMS's data for NEPTUNE's prospects but management declined to offer an opinion.

"What we're learning is that these immuno-oncology studies have a degree of inconsistency," José Baselga, head of oncology R&D at AstraZeneca, said on the quarterly results conference call.

The failure of NEPTUNE leaves AstraZeneca reliant on the ongoing POSEIDON trial for evidence of the efficacy of its immuno-oncology combination in NSCLC. That Phase III trial is also looking at Imfinzi in combination with chemotherapy. POSEIDON is due to readout by the end of the year.