Imfinzi demonstrates clinical activity in Stage IV, 1st-line non-small cell lung cancer in Phase III MYSTIC trial

The first Phase III data on blood TMB in this setting show an association between high TMB and overall survival benefit with immunotherapy

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AstraZeneca and MedImmune, its global biologics research and development arm, have presented overall survival (OS) and progression-free survival (PFS) data from the Phase III MYSTIC trial at the European Society for Medical Oncology (ESMO) Immuno-Oncology 2018 Congress in Geneva, Switzerland. The MYSTIC trial evaluated *Imfinzi* (durvalumab) monotherapy and the combination of *Imfinzi* plus tremelimumab, an anti-CTLA4 antibody, versus standard-of-care (SoC) platinum-based chemotherapy in previously-untreated patients with Stage IV (metastatic) non-small cell lung cancer (NSCLC).[1]

Results show that *Imfinzi* monotherapy demonstrated clinical activity with an OS hazard ratio (HR) of 0.76 (97.54% CI 0.564-1.019; nominal p=0.036) in the primary analysis population of patients whose tumours express PD-L1 on 25% or more of their cancer cells, **but this result did not meet statistical significance**. After two years of follow-up, the OS rate for treatment with *Imfinzi* monotherapy was 38.3% vs. 22.7% with SoC. This difference was observed despite a group of patients in the SoC arm (39.5%) that received subsequent immunotherapy following chemotherapy treatment. **The combination of *Imfinzi* plus tremelimumab did not meet the PFS or OS primary endpoints.** A summary of these data are included below.

Summary of primary endpoints

	Durvalumab (n=163)	**Chemotherapy (n=162)**
OS (primary endpoint) in PD-L1 TC ≥25%[i]		
Number of deaths (%)	108 (66.3%)	128 (79.0%)
Hazard ratio	0.76 (0.564, 1.019)	

	Durvalumab (n=163)	**Chemotherapy (n=162)**
(97.54% CI)[ii,iii]		
p-value[ii,iv]	0.036	
Median in months	16.3	12.9
(95% CI)	(12.2, 20.8)	(10.5, 15.0)
24-month OS rate	38.3%	22.7%
	Durvalumab + tremelimumab (n=163)	**Chemotherapy (n=162)**
OS (primary endpoint) in PD-L1 TC ≥25%[i]		
Number (%) of patients with event	113 (69.3%)	128 (79.0%)
Hazard ratio	0.85 (0.611, 1.173)	
(98.77% CI)[ii,iii]		
p-value[ii,iv]	0.202	
Median in months	11.9	12.9
(95% CI)	(9.0, 17.7)	(10.5, 15.0)
24-month OS rate	35.4%	22.7%
PFS (primary endpoint) in PD-L1 TC ≥25%[i]		
Number (%) of patients with event	118 (72.4%)	112 (69.1%)
Hazard ratio	1.05 (0.722, 1.534)	
(99.5% CI)[ii,iii]		
p-value	0.705	
Median in months	3.9	5.4
(95% CI)	(2.8, 5.0)	(4.6, 5.8)
12-month PFS rate	25.8%	14.3%

[i]The data cut-off date was 4 October 2018 (OS and safety) and 1 June 2017 (PFS).

[ii]Stratified by histology.

[iii]Confidence interval adjusted for interim analysis.

[iv]Criteria for statistical significance at the final analysis of OS was p-value ≤ 0.0246 for durvalumab vs chemotherapy and p-value ≤ 0.0123 for durvalumab + tremelimumab vs chemotherapy (using Lan DeMets spending function approximating O'Brien Fleming boundary).

Exploratory analysis using a novel biomarker

A prespecified exploratory analysis of blood tumour mutational burden (bTMB) showed that high bTMB, defined as ≥16 mutations per megabase, was associated with better OS in patients treated with *Imfinzi* monotherapy and the *Imfinzi* plus tremelimumab combination. In high bTMB patients, combination therapy reduced the risk of death by 38% compared to SoC (HR 0.62, CI 0.451-0.855) and the monotherapy arm had an OS HR of 0.80 compared to SoC (CI 0.588-1.077). These preliminary data included 809 samples representing 72.4% of patients. The analysis used a plasma-based TMB score generated from a minimally-invasive diagnostic test from Guardant Health recently granted breakthrough device designation by the US Food and Drug Administration for patients with NSCLC.[2] Additional bTMB analyses will be presented at a forthcoming medical meeting.

The safety and tolerability profiles for *Imfinzi* and the *Imfinzi* plus tremelimumab combination in the MYSTIC trial were consistent with previous experience. Among patients receiving *Imfinzi,* 40.4% of patients experienced a grade 3 or 4 adverse event (AE) vs. 47.7% with the *Imfinzi* plus tremelimumab combination and 46.0% with chemotherapy. 5.4% of patients discontinued *Imfinzi* due to treatment-related AEs vs. 13.2% with the combination and 9.4% on chemotherapy.

Imfinzi is approved for unresectable, Stage III NSCLC in more than 40 countries, including the US, EU and Japan, based on the Phase III PACIFIC trial.[3-8] *Imfinzi* is currently being tested in a range of Phase III trials for Stage IV NSCLC.[8,9]

Immuno-oncology Phase III trials in Stage IV, 1st-line NSCLC[8,9]

PEARL	SoC chemotherapy vs. durvalumab monotherapy
NEPTUNE	SoC chemotherapy vs. durvalumab + tremelimumab
POSEIDON	SoC chemotherapy vs. SoC + durvalumab or SoC + durvalumab + tremelimumab

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