# First line immunotherapy combination fails to improve overall survival in lung cancer

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Study author Dr Naiyer Rizvi, director of thoracic oncology and immunotherapeutics, Columbia University Medical Center, New York, US. Credit: © European Society for Medical Oncology

First line immunotherapy with durvalumab or the combination of durvalumab and tremelimumab does not improve overall survival in

unselected patients with lung cancer, according to late breaking results from the MYSTIC trial presented at the ESMO Immuno-Oncology Congress.

The combination of immune checkpoint inhibitors and chemotherapy has been successfully tested in different trials as first line therapy for metastatic non-small cell lung cancer (NSCLC) while the use of two immunotherapy drugs without chemotherapy has been addressed in very few studies. Commenting on behalf of ESMO, Dr. Pilar Garrido said: "Some patients are worried about the side effects of chemotherapy and prefer to delay it. Avoiding the use of chemotherapy in the first line setting also leaves an effective rescue option when immunotherapy fails."

The MYSTIC trial enrolled 1,118 patients with metastatic NSCLC who were randomly allocated to durvalumab alone, durvalumab plus tremelimumab, or chemotherapy. The primary endpoints were overall survival for durvalumab versus chemotherapy, and overall survival and progression free survival for durvalumab plus tremelimumab versus chemotherapy in patients with 25% or greater PD-L1 expression in tumour cells.

A total of 488 patients (44%) had PD-L1 expression of 25% or greater. Durvalumab alone or with tremelimumab did not improve overall survival or progression free survival compared to chemotherapy. Study author Dr. Naiyer Rizvi, director of thoracic oncology and immunotherapeutics, Columbia University Medical Center, New York, US, said: "While not reaching statistical significance, durvalumab monotherapy gave a clinically meaningful median overall survival improvement of 16.3 months compared to 12.9 months with chemotherapy in patients with 25% or greater PD-L1 expression."

An exploratory analysis examined survival according to high or low

tumour mutational burden (TMB) in the blood—16 or more mutations per megabase was defined as "high" and less than 16 as "low". TMB evaluation was performed in more than 70% of patients, of whom 40% had high TMB.

In patients with high TMB, overall survival was 16.5 months with durvalumab plus tremelimumab versus 10.5 months with chemotherapy, with a hazard ratio of 0.64. Overall survival with durvalumab alone was 11 months. The proportion of high TMB patients alive at two years was 39% with durvalumab plus tremelimumab, 30% with durvalumab, and 18% with chemotherapy. In those with low TMB, overall survival was 8.5 months with durvalumab plus tremelimumab, 12.2 months with durvalumab, and 11.6 months with chemotherapy.

Rizvi said: "The results of the exploratory analysis need to be validated in a future trial. TMB is measured with a simple blood test and might be an easy way to select patients for this treatment. The CheckMate 227 trial previously showed that first line immunotherapy combinations work best in advanced NSCLC patients with high TMB."

Safety data were consistent with previous studies. The incidence of grade 3/4 treatment-related adverse events was 14.6%, 22.1% and 33.8% with durvalumab, durvalumab plus tremelimumab, and chemotherapy, respectively.

"Immunotherapy has rapidly become a first line treatment option in NSCLC, as shown in the 2018 ESMO Clinical Practice Guidelines for metastatic disease," said Garrido, head of the Thoracic Tumour Section, Medical Oncology Department, Ramón y Cajal University Hospital, Madrid, Spain. "The ESMO Immuno-Oncology Congress showcases cutting edge developments in this fast moving field, such as the highly anticipated MYSTIC trial. The analysis shows that appropriate biomarkers are needed to select the patients most likely to benefit from

combination immunotherapy in first line. The challenge now is to prospectively validate them prior to implementation in clinical practice."

**More information:** 1 Abstract LBA6 'Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC ' will be presented by N. A. Rizvi during Proffered Paper session I on Thursday, 13 December, 18:15 to 19:00 (CET) in Room A. *Annals of Oncology*, Volume 29, 2018 Supplement 10. DOI: 10.1093/annonc/mdy493

2 The tumour mutational burden cut off of 16 mutations per megabase in the blood is equivalent to the cut off used in the CheckMate 227 trial of ten mutations per megabase in the tumour.

3 Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018.;378:2093-2104. DOI: 10.1056/NEJMoa1801946.

4 Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Supplement 4):iv192-iv237. DOI: 10.1093/annonc/mdy275.

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