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New results from a trial of an antibody that helps the immune system to recognise and attack cancer cells have shown particularly encouraging responses in patients who are smokers or former smokers.

Presenting the most up-to-date data from 85 patients with non-small cell lung cancer in a large, phase I clinical trial of an experimental drug called MPDL3280A, Professor Jean-Charles Soria told the 2013 European Cancer Congress (ECC2013) [1] today (Sunday): “This is the first study to suggest a potential relationship between smoking history and response to inhibiting the PD-L1/PD-1 pathway – a pathway that is instrumental in enabling cancer cells to escape detection by the immune system. In this study, 26% of smokers responded to treatment, whereas only 10% of never-smokers responded. The fact that smokers seemed to respond better is great news for lung cancer patients, because the majority of them are former or current smokers. Most advances in lung cancer over the last five years have mainly focused in never or light smokers. While the data are preliminary, the trend is potentially promising.”

Lung cancer, which is usually caused by smoking, is extremely difficult to treat successfully and once it has started to spread (metastasise) to other parts of the body it is incurable. The programmed death 1 protein PD-1 and its signalling molecule (or ligand) PD-L1 prevent the body’s immune system from attacking and killing cancer cells and this allows the cancer to spread. However, the anti-PD-L1 monoclonal antibody, MPDL3280A, works by blocking the interaction between PD-L1 and the immune system, thereby boosting a patient’s anti-cancer immune response

Prof Soria, Director of the Site de Recherche Intégrée sur le Cancer (SIRIC) Socrate project at the Institut Gustave Roussy, France, and his colleagues are enrolling patients with metastatic non-small cell lung cancer (NSCLC) who have failed to respond to chemotherapy into the international trial. They are treating them with an intravenous infusion of MPDL3280A once every three weeks. At the ECC2013 congress, they presented efficacy data for 53 NSCLC patients and safety data for 85 NSCLC patients – the largest group of patients to be treated with anti-PD-L1 blockade to date.

“We hypothesised that smoking was associated with tumours that harbour more genetic

mutations and, therefore, the immune systems of these patients might be more likely to respond and attack the tumours once PD-L1 had been blocked," explained Prof Soria. "Our results show that this is likely to be the case because more smokers than non-smokers had a partial response to the therapy."

Although the best results were seen in smokers or former smokers, Prof Soria said that the anti-PD-L1 antibody was also an important strategy for non-smokers. "Some of them benefited from this compound as well."

Among the responding patients, treatment duration ranged from 170 to 534 days. "We observed sustained and rapid responses," said Prof Soria. "Some patients responded to the drug within six weeks, and we can now report for the first time that the median average time to first response is 11.9 weeks." [2]

In addition, the researchers also discovered that there was an increase in response rates in patients who had tumours that had high numbers of cells expressing PD-L1. Patients with higher levels of PD-L1 expression were more likely to respond to anti-PD-L1 blockade than patients with lower levels of PD-L1 expression. Using an immunohistochemistry (IHC) [3] scoring system for PD-L1, with a scale for IHC expression ranging from 0 to 3, patients with IHC 3 had a response rate of 83% and patients with IHC 2/3 had a response rate of 46%.

"The higher the percentage of PD-L1 staining in a tumour, the better the probability a patient will have an objective response with the PD-L1 antibody," explained Prof Soria. [4]

He concluded: "Our results so far demonstrate that the compound is capable of producing striking and durable responses in non-small cell lung cancer patients with metastatic disease who have failed to respond to previous chemotherapy. The study defines a novel approach to identifying the patients most likely to respond to treatment and identifies potential association between smoking and responses to MPDL3280A. A new therapy, with few serious adverse side-effects, that is easy to use – one intravenous infusion every three weeks – and a robust clinical activity as a single agent should soon be available."

The large phase I expansion trial is continuing, but larger phase II/III trials of the drug have already started.

ECCO President, Professor Cornelis van de Velde, commented: “This is an extremely important study for patients with non-small cell lung cancer for whom there are few treatment options that make much impact on their disease. Hundreds of millions of Euros have been spent chasing the dream of immunotherapy for lung cancer patients, but with zero results. These early findings on the effect of the anti-PD-L1 monoclonal antibody, MPDL3280A, suggest that it has the potential to open new therapeutic approaches, particularly for smokers and former smokers."

(ends)

[1] The 2013 European Cancer Congress is the 17th congress of the European CanCer Organisation (ECCO), the 38th congress of the European Society for Medical Oncology (ESMO) and the 32nd congress of European Society for Therapeutic Radiology and Oncology (ESTRO).

[2] The median average is the number separating the higher half of the patient response time from the lower half i.e. the middle number.

[3] Immunohistochemistry is the process of detecting particular proteins (or antigens) in cells in tissue samples in the laboratory.

[4] An objective response is where a tumour shows either a complete or a partial response to treatment.

[5] This study is funded by Genentech Inc.

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