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Drug combination improves progression-free survival in melanoma patients

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Patients with advanced melanoma skin cancer survive for longer without their disease progressing if they have been treated with a combination of two drugs, nivolumab and ipilimumab, than with either of these drugs alone. New results show that these patients also do better regardless of their age, stage of disease and whether or not they have a cancer-driving mutation in the BRAF gene.

Dr James Larkin, a Consultant Medical Oncologist at The Royal Marsden, London, UK, told the 2015 European Cancer Congress, that results from the CheckMate 067 phase III clinical trial had already shown that the combination of the two drugs, which target two different pathways that regulate the immune system, improved the progression-free survival in patients with melanoma who had not received any other treatment. However, until now it was not known whether this remained the case when the results were analysed according to genetic status, age and how advanced was their disease.

Nivolumab is an inhibitor of the programmed cell death protein 1 (known as PD-1), which functions as an immune checkpoint, playing an important role in the immune system. Ipilimumab inhibits the CTLA-4 checkpoint, which also plays a role in the immune system.

Dr Larkin said: "Results from our large analysis of pre-defined sub-groups of patients with advanced melanoma provide evidence that suggests the combination of the two drugs consistently improves progression-free survival across a range of sub-groups, including patients

with poor prognostic factors, when compared with either nivolumab or ipilimumab alone."

Out of a total of 945 patients in 20 different countries who were randomised to receive the combination therapy or one of the drugs alone, those on the combination therapy survived for an average of 11.5 months without their disease progressing, compared, to 6.9 months for patients on nivolumab alone and 2.9 months for those on ipilimumab alone.

When the researchers looked at progression-free survival times among patients with and without the V600 type of mutation of the BRAF gene, the average for patients taking both drugs without the mutation was 11.2 months, and it was 11.7 months for those with the mutation. This compared with 7.9 months and 5.6 months respectively for patients on nivolumab alone and 2.8 months and four months respectively for those on ipilimumab alone.

"These results provide evidence that the efficacy of the combination therapy is similar whether or not the tumours harbour BRAF mutations. This has important practical implications for clinicians treating patients with melanoma," said Dr Larkin.

The same pattern was seen when the researchers looked at groups of patients according to the extent of the spread of the disease to other parts of the body (metastases), and whether the patients were aged less that 65, between 65 and 75, and 75 and older (older patients can often be less able to cope with the side effects of treatments).

Among patients with metastatic melanomas with the worst prognosis (stage M1c), the average progression-free survival times were 8.5 months for the combination treatment, 5.4 months for nivolumab alone and 2.8 months for ipilimumab alone.

Patients younger than 65 years, had average progression-free survival times of 11.7 months (combination), 5.5 months (nivolumab) and 2.8 months (ipilimumab), while the 262 patients aged between 65 and 75 had average progression-free survival times of 11.1 months, 12.7 months and 2.9 months respectively. For those aged 75 and over (118 patients), the average progression-free survival time for those on the combination treatment could not be calculated as the patients' disease had not progressed yet; it was 5.3 months for those on nivolumab alone and four months for those on ipilimumab alone.

Dr Larkin said: "The sub-groups included in these analyses are those of particular interest to melanoma clinicians, such as patients aged 75 and over. We believe that the data will give confidence to patients and their healthcare providers that the combination of nivolumab and ipilimumab will be effective regardless of advanced age, the presence of a BRAF mutation, or poor prognostic factors."

Overall, significant (grade 3-4) side effects related to treatment occurred in 55%, 16% and 27% of patients in the combination, nivolumab and ipilimumab groups respectively. A similar pattern was seen in the sub-groups of patients; for instance, in patients aged 75 and over, significant side effects occurred in 48%, 21% and 36% respectively, and in patients with stage M1c disease, they occurred in 54%, 14% and 25% respectively.

The most common side effects were those that related to the way the drugs affect the functioning of the immune system, such as diarrhoea, colitis (inflammation of the lining of the colon) and raised levels of alanine aminotransferase (an enzyme, raised levels of which can indicate liver damage).

The CheckMate 067 trial started in May 2013, recruitment of patients ceased in 2014, and the next significant milestone will be when the

researchers report results on overall survival.

Professor Peter Naredi, the ECCO scientific co-chair of the Congress, who was not involved in the research, commented: "Although the CheckMate 067 study has already reported that a combination of two checkpoint inhibitors, nivolumab and ipilimumab, is superior to either drug alone, the results presented here in Vienna have important clinical implications. These drugs come with a substantial frequency of adverse effects for the patients and it is important to spare patients who will not benefit from the treatment. What Dr Larkin and co-authors show is that bad prognostic indicators, such as BRAF mutations, metastatic pattern or increased age, do not negatively influence progression-free survival. Therefore, more patients can be considered for treatment, and tolerance to the treatment becomes a more important factor."

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