

The immunotherapy, pembrolizumab, is active against mucosal melanoma tumors

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Clinical trials of a new immunotherapy, pembrolizumab, have shown that it prolongs life significantly for patients with bladder cancer and is active against a rare sub-type of melanoma, called mucosal melanoma. The findings were presented in two presentations at the European Cancer Congress 2017 today (Sunday).

Until now, mucosal [melanoma](#) has often been excluded from immunotherapy treatments for the disease. Melanoma usually occurs in the skin and is caused by exposure to ultraviolet radiation (such as sunlight). Mucosal melanoma occurs in the moist surfaces that line the body's cavities, such as the airways, digestive tract and genitourinary tracts, and is not caused by UV radiation; there is no known cause. It makes up about one per cent of all melanomas and has a poor prognosis, usually because of late diagnosis - the majority of patients with metastatic disease ([cancer](#) that has spread to other parts of the body) survive for less than a year if they have received conventional treatments.

Reporting the results from three trials of [pembrolizumab](#) for patients with advanced melanoma, Dr Marcus Butler, a medical oncologist at the Princess Margaret Cancer Centre, Toronto, Canada, told ECCO2017 that 84 of the 1567 patients in the KEYNOTE-001, 002 and 006 studies had advanced mucosal melanoma.

"Sixteen of these patients (19%) responded to treatment with pembrolizumab, of whom 12 are still alive without their disease

progressing and, so far, the longest time some of these patients have continued to be successfully treated is more than 27 months," he said.

Of the 1483 patients in these KEYNOTE trials who had other forms of advanced melanoma and who received at least one dose of pembrolizumab, 33% responded to the treatment, 72% were still alive without their disease progressing and the median (average) overall survival time was nearly two years. Median overall survival for patients with mucosal melanoma was 11.3 months.

"Immunotherapy for melanoma has revolutionised treatment of the disease. There are some patients with mucosal melanoma who have had complete responses to pembrolizumab and essentially return to a normal life. Some, of course, have less spectacular responses, but they still benefit from therapy. In earlier studies, mucosal melanoma was excluded since it is a rare subtype. These findings suggest that mucosal melanoma patients should be offered immunotherapy as standard of care and not excluded. Response rates may be a bit lower than for other types of melanoma, so further studies to improve benefit need to be conducted."

Pembrolizumab works by binding to PD-1 and blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocyte cells which may affect both tumour cells and healthy cells. PD-1 (programmed cell death protein 1) is a receptor on the surface of T cells (the white blood cells that are part of the immune system), while PD-L1 (programmed death-ligand 1) is a molecule that binds to PD-1 and is often over-expressed on the surface of cancer cells, enabling them to evade the immune system and allow cancer to grow and spread.

In the KEYNOTE trials, 70% of the mucosal melanoma patients with known PD-L1 status had PD-L1 positive tumours.

"The data presented here are important because they prove that patients

with mucosal melanoma can benefit from anti-PD-1 therapy and should not be excluded from this treatment," said Dr Butler. "At this stage we don't know why some mucosal melanoma patients responded to pembrolizumab, while others did not. This is an important question and research is ongoing."

Ninety per cent of the mucosal melanoma patients had already received at least one prior treatment and 39% of them had received ipilimumab, a type of monoclonal antibody that is already used in the treatment of melanoma. Dr Butler said: "Our results show that patients benefited from pembrolizumab regardless of whether or not they had been pre-treated with ipilimumab."

Patients in the KEYNOTE trials received pembrolizumab intravenously at doses of 2 mg/kg or 10 mg/kg every three weeks, or 10 mg/kg every two weeks.

Chair of the Congress and President of ECCO, Professor Peter Naredi, from the Sahlgrenska Academy, University of Gothenburg, Sweden, who was not involved with the research, commented: "For rare cancer types it is difficult to evaluate new treatments in normal sized trials. But here Butler and colleagues pull three trials together and show that long-lasting responses also occur with pembrolizumab in patients with mucosal melanoma."

In a second, late-breaking presentation, Dr Andrea Necchi, attending physician in the Department of Medical Oncology at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, said results from the phase III KEYNOTE-045 trial showed that treatment with pembrolizumab resulted in longer overall survival with fewer side-effects for patients with previously treated advanced bladder (urothelial) cancer compared with patients given chemotherapy.

He said: "KEYNOTE-045 is a landmark study. It represents a real advance in the second-line treatment of advanced [bladder cancer](#) because pembrolizumab is the first therapy to show a significant survival advantage over chemotherapy for these patients.

"Patients who were treated with pembrolizumab lived significantly longer than patients who were treated with chemotherapy; the median overall survival was 10.3 months with pembrolizumab and 7.4 months with chemotherapy. In addition to helping patients live longer, more patients treated with pembrolizumab responded to treatment and for a longer duration than those treated with chemotherapy; the objective response rate - the percentage of patients whose tumours shrank or disappeared - was almost twice as high with pembrolizumab: 21% compared to 11% on chemotherapy. The median duration of response for patients who responded to pembrolizumab has not been reached, while the median duration of response for patients who responded to chemotherapy was only 4.3 months. We estimate that almost twice as many pembrolizumab responders will respond to the therapy for at least one year: 68% versus 35%."

He said survival and response benefits for pembrolizumab were seen regardless of the levels of PD-L1 expression.

"In addition to the overall survival benefit over chemotherapy, pembrolizumab was also associated with a much lower incidence of treatment-related side effects. This is important because this patient population tends to be mostly elderly patients who have many other illnesses and health conditions as well. These results support the use of pembrolizumab as the new standard of care for advanced bladder cancer," concluded Dr Necchi.

Side effects of any grade of severity were reported in 61% of patients treated with pembrolizumab compared with 90% of patients treated with

chemotherapy, and more severe side effects that were grade 3, 4, or 5 (the most severe grade) were reported in 15% and 49% of patients, respectively.

Bladder (urothelial) cancer is the seventh most common cancer in men and the seventeenth most common in women worldwide. Approximately 430,000 new cases are diagnosed each year worldwide; in the European Union (EU) there are approximately 180,500 new cases each year and 38,200 people die from it.

At present there is no standard second-line therapy for advanced bladder cancer. The chemotherapies paclitaxel, docetaxel and vinflunine are commonly used but provide limited benefit. The KEYNOTE-45 study randomised 542 patients from 29 countries between November 2014 and November 2015 to either pembrolizumab (200 mg, given intravenously once every three weeks for up to 24 months) or one of three chemotherapy options chosen by study investigators. The [patients](#) all had advanced urothelial cancer that had already been treated with platinum-based [chemotherapy](#).

Provided by ECCO-the European CanCer Organisation

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