Mature results favor pembrolizumab as second-line treatment for bladder cancer

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Mature results from the KEYNOTE-045 trial to be presented today at the ESMO 2017 Congress in Madrid (1) have confirmed significantly longer survival in patients with advanced urothelial cancer who receive the checkpoint inhibitor pembrolizumab after initial chemotherapy, compared to an alternative chemotherapy regimen.

The new data back up interim figures published earlier this year (2) and are "striking in the setting of urothelial cancer, which is highly lethal in the metastatic state," said study investigator Dr Ronald de Wit, from Erasmus University Medical Center in Rotterdam, the Netherlands.

"Pembrolizumab is the first agent to improve survival over chemotherapy in the second-line setting. Not all patients benefit from checkpoint inhibition, but a sizeable proportion of patients who respond have very durable responses, even well over one year," noted de Wit.

The phase 3 study randomly assigned patients whose urothelial cancer had recurred or progressed after platinum-based chemotherapy, to either pembrolizumab (n=272) or the investigator's choice of paclitaxel, docetaxel, or vinflunine chemotherapy (n=270).

Results now out after 22.5 months of follow-up show an approximately three month advantage in overall survival (OS) in the pembrolizumab-treated patients compared to those receiving a second-line of chemotherapy (median 10.3 months vs. 7.4 months), with a further improvement in the hazard ratio [HR] from 0.73 to 0.70 (P = 0.0003)

since the interim analysis, he said.

Median progression-free survival (PFS) was not significantly different (2.1 months for pembrolizumab vs 3.3; HR, 0.96; P = 0.32).

"Some patients also benefit from second line chemotherapy, but these responses tend to be short-lived and toxicity typically prevents prolonged treatment, whereas pembrolizumab is well tolerated," de Wit said, adding that treatment-related adverse events of any grade occurred in 62.0% of pembrolizumab-treated patients compared to 90.6% of those treated with chemotherapy.

In addition, quality of life (QOL), measured at week 15 and reported earlier this year, showed better results in the pembrolizumab arm. "Overall, the superior survival, better adverse event profile, and better QOL render pembrolizumab a new standard of care in the second line treatment of urothelial cell cancer," he concluded.

Commenting on the study, Dr Maria De Santis, from the University of Warwick, Coventry, and Queen Elizabeth Hospital, Cancer Centre, in Birmingham, UK, said: "These updated KEYNOTE-045 results are important as they confirm the overall survival benefit of pembrolizumab compared to chemotherapy (investigator's choice) in platinum-pretreated patients. This is particularly important as the progression-free survival was not superior with pembrolizumab. The PFS curve in this trial diverges late but then, after 6 months, it was again in favour of pembrolizumab. As PFS does not seem to be a good surrogate endpoint with pembrolizumab, a confirmed, robust OS benefit as shown in this updated analysis becomes increasingly important. The robustness of the OS benefit is confirmed by the even better HR of 0.70 in this update, compared to 0.73 at the first presentation of the data last year."

De Santis added that specific properties of this immunotherapy include

"a superior duration of response in the 20% of patients who do respond and a favourable safety profile with a lower rate of severe side effects, compared to chemotherapy. Fewer patients on pembrolizumab had to discontinue treatment because of side effects compared to those on chemotherapy. Severe immune related side effects were rare. This is of special importance as patients with urothelial cancer are usually older with multiple comorbidities."

More information: 1 Abstract LBA37_PR 'Pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine for recurrent, advanced urothelial cancer (UC): mature results from the phase 3 KEYNOTE-045 trial' will be presented by Dr Ronald de Wit during Poster Discussion Session 'Genitourinary tumours, non-prostate' on Sunday,10.09.2017, 14:45 - 16:15 (CEST), Cordoba Auditorium

2 *N Engl J Med* 2017;376:1015-26

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