New research in bladder cancer, ASCO 2017

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Immuno-oncology

Already established in melanoma, renal cell carcinoma (RCC) and non-small-cell lung cancer, immuno-oncology is also an emerging area of research in the field of bladder cancer.

The KEYNOTE-045 study was an open-label, phase 3, comparative study of pembrolizumab vs. investigators' choice chemotherapy as second-line therapy after platinum-based chemotherapy for advanced urothelial cancer (UC).[1] Pembrolizumab was administered intravenously at a dose of 200 mg every three weeks. Chemotherapy could be paclitaxel 175 mg/m^2, docetaxel 75 mg/m^2 or vinflunine 320 mg/m^2 every three weeks. The dual primary endpoints were overall survival (OS) and progression-free survival (PFS). In the primary analysis, published in March 2017 in the *New England Journal of Medicine* (median duration of followup 14.1 months), pembrolizumab was associated with a significantly longer OS (median 10.3 months; 95% confidence interval [CI] 8.0–11.8) compared to chemotherapy (median 7.4 months; 95% CI 6.1–8.3). The median PFS, by contrast, was longer with chemotherapy (3.3 months; 95% CI 2.3–3.5) than with pembrolizumab (2.1 months; 95% CI 2.0–2.2).[1]

KEYNOTE-045 was presented at ASCO 2017 with an updated survival analysis with a data cutoff date of January 18, 2017 (median followup 18.5 months).[2] At that time, 33 of the 270 pembrolizumab-treated patients were still being treated, while none of those in the chemotherapy-treated arm (n=272) were receiving chemotherapy on study.

As shown in Fig. 1A, the median OS continued to favour pembrolizumab, with 170 deaths in the pembrolizumab arm and 196 in the chemotherapy arm (hazard ratio [HR] 0.70; 95% CI 0.57–0.86; p=0.0004). Median survival was unchanged from the prior analysis (10.3 vs. 7.4 months). Twelve- and 18-month survival rates were 44.4% and 36.1%, respectively, with pembrolizumab, compared to 30.2% and 20.5%, respectively, with chemotherapy. Subgroup analysis showed that the HRs for OS favoured pembrolizumab across all subgroups studied, including the particular chemotherapy used. In the subgroup of patients with a PD-L1 expression of 10% or greater, the HR for OS was 0.57 (95% CI 0.38–0.86; p=0.0034) in favour of pembrolizumab.

The median PFS remained the same for the updated analysis: 3.3 months for chemotherapy and 2.1 months for

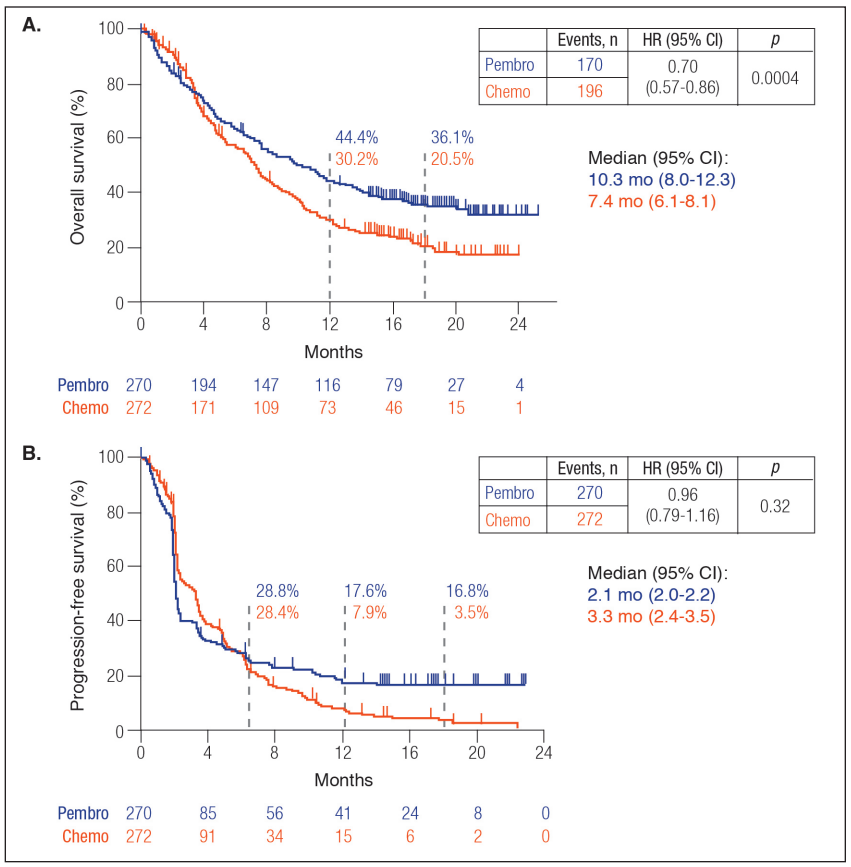

Fig. 1. (A) Overall survival; and ***(B)*** progression-free survival for pembrolizumab vs. chemotherapy in urothelial carcinoma (update of the KEYNOTE-045 trial). CI: confidence interval; HR: hazard ratio.

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pembrolizumab; however, as shown in Fig. 1B, the 12- and 18-month PFS rates were 17.6% and 16.8%, respectively, for pembrolizumab, compared with 7.9% and 3.5%, respectively, for chemotherapy.

Objective response rates remained unchanged from the primary analysis (21.1%, including 7.8% complete response [CR] in the pembrolizumab group and 11.0%, including 2.9% CR in the chemotherapy group). With respect to duration of response, the median for chemotherapy was 4.4 months (range 1.4+ to 20.3+), while the median has not been reached with pembrolizumab (range 1.6+ to 20.7+). Median time to response was identical in both arms, at 2.1 months.

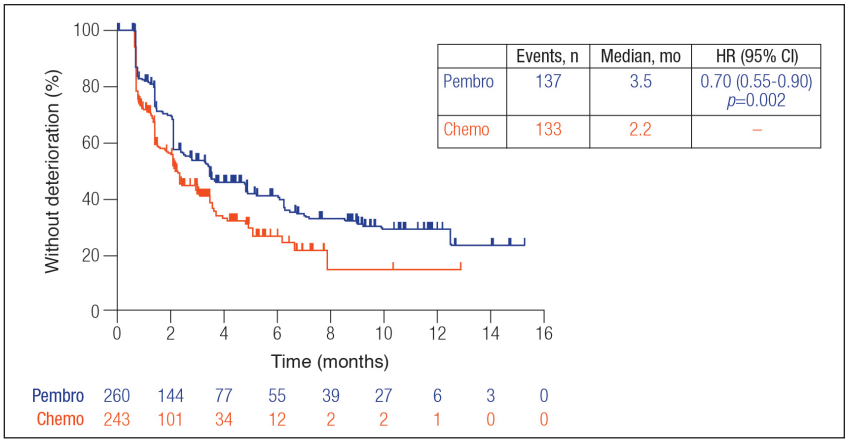

Fig. 2. Time to deterioration in health-related quality of life: Pembrolizumab vs. chemotherapy for second-line treatment of urothelial cancer (KEYNOTE-045). CI: confidence interval; HR: hazard ratio.

Pembrolizumab demonstrated a more favourable safety profile than chemotherapy in this study. For the updated analysis, the rate of treatment-related adverse events (AEs) overall was 61.3% for pembrolizumab compared to 90.2% for chemotherapy. For Grade 3/4 AEs, the rates were 16.5% and 49.8% for pembrolizumab and chemotherapy, respectively.

Importantly, health-related quality of life (HRQoL) was also more favourable in the pembrolizumab arm. A separate analysis presented at ASCO 2017 showed that pembrolizumab significantly prolonged the time to deterioration in HRQoL compared with chemotherapy (Fig. 2).[3]

Pembrolizumab has also been evaluated as a potential first-line therapy in UC for patients who are cisplatin-ineligible. Clinical results for the single-arm KEYNOTE-052 study (n=370) were presented at ASCO 2017, with a median followup of 9.5 months (range 0.1–23 months).[4] Over this time, the objective response rate was 29%, including 7% CR. Median time to response was two months, and the median duration of response had not been reached. Fifty-nine percent of the population experienced a reduction in tumour size.

Immuno-oncological therapy has established a strong foothold within the field of advanced bladder cancer and is now an excellent treatment option in a number of settings, demonstrating clinical efficacy with less toxicity than chemotherapy.

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