Oncology Information Group

ARTICLE SUMMARIES

UROTHELIAL CARCINOMA

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

Bellmunt J et al., N Engl J Med. 2017 Mar 16;376(11): 1015-1026

BACKGROUND

- Platinum-refractory patients with advanced or metastatic urothelial carcinoma treated in the second-line setting have a poor prognosis. Immunotherapy checkpoint inhibitors have shown promising response rates.

- Study objective: Within the second-line treatment of patients with advanced urothelial carcinoma previously progressed during or after platinum-based chemotherapy, pembrolizumab was compared with investigator's choice of chemotherapy.

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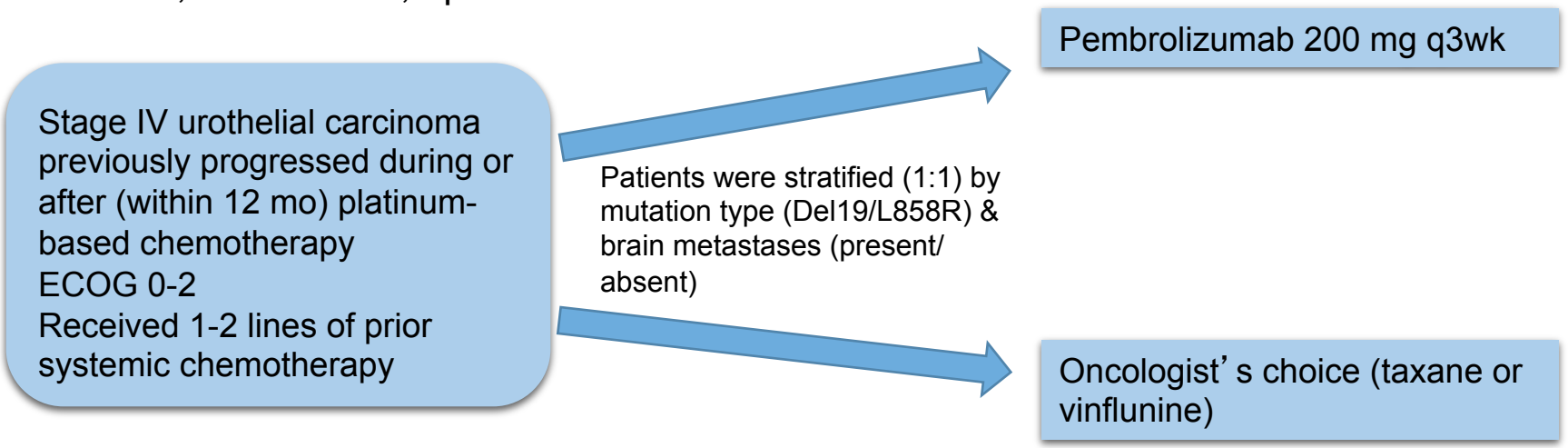
KEYNOTE-045 STUDY DESIGN

Phase III, randomized, open-label trial



Treatment beyond progression allowed if deemed beneficial by investigator. RECIST (V1.1).

Endpoints:
Primary: Overall Survival (OS), Progression Free Survival (PFS)
Secondary: Overall Response Rate (ORR), duration of response (DOR), time to response, safety
PDL1 testing compared patients expressing PDL1 < 10% vs PDL1 ≥ 10%

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STUDY DESIGN - CONTINUED

- Study Conduct: 120 sites and 29 countries.
- Recruitment: November 2014 – 2015. Median follow-up: 14.1 mo.
- Statistical design: Sample size was based on one-sided alpha 2.5%, power 88% to show hazard ratio (HR) 0.781, and power 86% to show HR 0.625. Calculated enrollment of 470 patients.
- OS, PFS, and DoR estimated using the Kaplan–Meier method.
- OS and PFS between-group differences calculated with the stratified log-rank test.
- HR's and 95% confidence intervals calculated using stratified Cox proportional-hazards model and Efron's method.
- Intention to treat analysis applied.

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RESULTS

- 542 randomized to pembrolizumab (P) (270) or oncologists'-choice chemotherapy (C) (272)

- Balanced baseline patient characteristics:
  - Age - median 67 YO (P) vs 65 YO (C)
  - ECOG 0 slightly more in P: ECOG 0- 44% (P) vs 39%(C)
  - PDL1≥10%: 68.9% (P) vs 73% (C)
  - Liver metastases: 33.7% (P) vs 35.1% (C)
  - Hb < 10 g/dL: 16.4 % (P) vs 16.5% (C)

- Study found pembrolizumab significantly improved OS (HR 0.73; 95% CI, 0.59–0.91; p = 0.002) and ORR (21.1% in P and 11.4% in C, p = 0.001), compared to oncologists' choice chemotherapy. Median OS 10.3 mo (P) vs 7.4 mo (C).

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RESULTS

- No significant difference in PFS between P vs C (HR 0.89; 95% CI, 0.61 to 1.28; P=0.24)

- Pembrolizumab consistently better OS than chemotherapy for all subgroups, including all PDL1 groups.

- ORR was observed significantly higher in 21.1 % of patients treated with P (95% CI, 16.4% - 26.5 %), compared to only 11.4% treated with C (95% CI, 7.9 to 15.8) (P=0.001).

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RESULTS – ADVERSE EVENTS

	Pembrolizumab	Chemotherapy
Most common grade 3 AEs	Overall 15.0% •Pneumonitis 6 (2.3%) •Colitis 3 (1.1%)	Overall 49.4% •Neutropenia 31 (12.2%) •Anemia 20 (7.8%)
Most common Drug-related grade 3 AEs leading to treatment discontinuation	Overall 5.6% •Pneumonitis death 1 (0.4%) •Urinary obstruction 1 (0.4%)	Overall 11.0% •Sepsis 2 (0.4%) •Septic shock 1 (0.4%)

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DISCUSSION

- Pembrolizumab significantly improves OS, in contrast to oncologists' choice chemotherapy, regardless of PDL1 status.
- PDL1 testing currently does not allow for the prediction of who will respond to pembrolizumab or checkpoint inhibitors.
- PFS was not significantly different in patients treated with pembrolizumab, in comparison to chemotherapy. This is a trend seen in several other tumor groups treated with checkpoint inhibitors, suggesting that PFS is not an accurate reflection of the effectiveness of these treatments.
- The safety profile of pembrolizumab is tolerable and as expected. Overall treatment related adverse events were lower in pembrolizumab, in contrast to chemotherapy.

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