Platinum-based chemotherapy is currently the standard-of-care treatment for patients with advanced-stage urothelial carcinoma; however, no established therapy is available following the failure of this approach. Now, data from the KEYNOTE-045 trial indicate that the anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab is superior to the investigator's choice of chemotherapy, in the absence of an established standard of care in this setting.

In a randomized phase III trial, a total of 542 patients with advanced-stage urothelial carcinoma with disease progression following treatment with platinum-based chemotherapy were randomly assigned to receive either pembrolizumab (200 mg every 3 weeks) or the investigator's choice of chemotherapy (paclitaxel, docetaxel or vinflunine). An open-label design was used owing to differences in the frequency, and route of administration of the treatments under investigation. Patients receiving pembrolizumab had a significantly improved overall survival duration at a median of 14.4 months of follow-up monitoring compared with those treated with chemotherapy (hazard ratio for death 0.73, $P=0.002$), reflecting the improved 12-month survival rates obtained with this agent (43.9% versus 30.7%). Despite this improvement in overall survival, no significant differences in median progression-free survival were observed between groups. Investigators attributed this finding to the fact that only 21.1% of patients had an objective response to pembrolizumab, although this was still superior to the 11.4% response rate in patients who received chemotherapy. Furthermore, the majority of patients with an initial response to pembrolizumab retained this response at the cut-off point for inclusion in the trial report. Patients receiving pembrolizumab had fewer grade ≥ 3 adverse events compared with those in the chemotherapy group (15.0% versus 49.4%), resulting in fewer patients in the pembrolizumab group choosing to discontinue treatment.

These findings indicate that pembrolizumab is safer and more effective than chemotherapy in patients with advanced-stage urothelial carcinoma whose disease has progressed following treatment with platinum-based chemotherapy. Investigators noted that the effects of pembrolizumab were largely independent of the presence of programmed cell death 1 ligand 1 (PD-L1) or immune-cell infiltration, indicating a need for more research into the most effective biomarkers of a response to pembrolizumab and other immune-checkpoint inhibitors. Long-term follow-up data on the outcomes of patients treated with pembrolizumab in this trial are eagerly awaited.

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ORIGINAL ARTICLE Bellmunt, J. et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N. Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1613683> (2017)