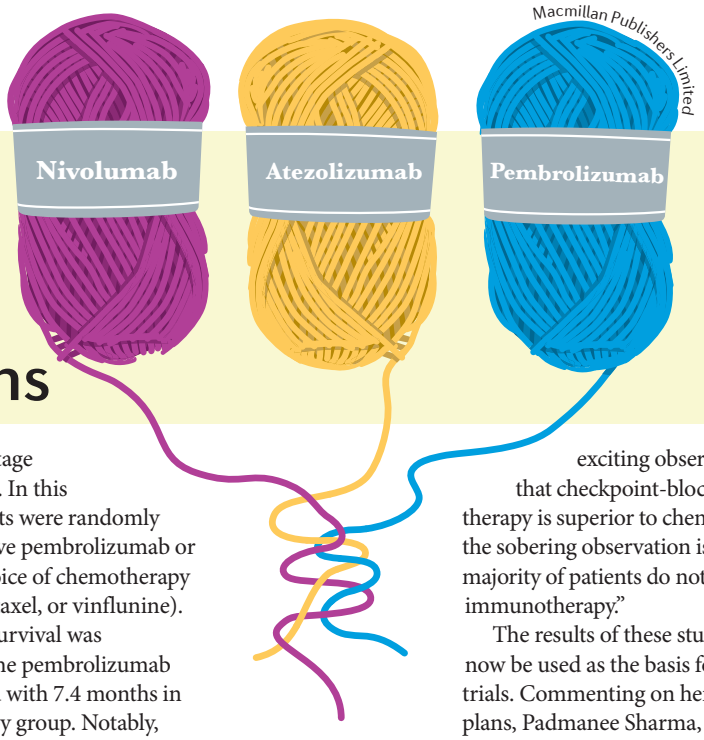
Nature Reviews Clinical Oncology | Published online 20 Mar 2017; doi:10.1038/nrclinonc.2017.38



UROLOGICAL CANCER

Unravelling intertwined second-line options

The standard-of-care treatment for patients with metastatic or unresectable urothelial carcinoma, which is associated with a median overall survival of 12–15 months, is cisplatin-based chemotherapy. For patients with progressive disease after first-line treatment, various chemotherapy regimens can prolong survival for, at best, 6–7 months. The FDA approval of the anti-PD-L1 monoclonal antibody (mAb) atezolizumab in 2016, and the anti-PD-1 mAb nivolumab in 2017 increased the spectrum of therapeutic options available for these patients. Results from the KEYNOTE-045 phase III study, led by Joaquim Bellmunt, now indicate that the anti-PD-1 mAb pembrolizumab might become a new standard of care for patients with advanced-stage urothelial carcinoma.

Both atezolizumab and nivolumab were approved as second-line therapies for patients with bladder cancer on the basis of results from single-arm phase II studies, with objective response as the primary end point. The sizes of the study cohorts were 310 patients and 270 patients for atezolizumab and nivolumab, respectively. In the study that led to the approval of atezolizumab, the objective response rate was 15% for all patients and, importantly, 26% for patients with ≥5% PD-L1-positive tumour cells. The respective percentages were 19.6% and 28.4% in CheckMate 275, the trial that led to the approval of nivolumab.

Thus, KEYNOTE-045 is the first randomized phase III trial comparing an immunotherapeutic agent (pembrolizumab) with chemotherapy for the second-line treatment of patients with advanced-stage urothelial cancer. In this study, 270 patients were randomly assigned to receive pembrolizumab or investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). Median overall survival was 10.3 months in the pembrolizumab group, compared with 7.4 months in the chemotherapy group. Notably, the objective response rate was significantly higher with pembrolizumab than with chemotherapy (21.1% versus 11.4%, $P=0.001$), and the median durations of response were not reached (1.6–15.6 months, ongoing at the time of reporting) versus 4.3 months (1.4–15.4 months). Morever, treatment-related adverse events of any grade were less frequent with pembrolizumab than with chemotherapy (60.9% versus 90.2%), as were grade 3–5 adverse events (15% versus 49.4%).

Samuel Funt, who was not involved in any of the studies discussed, comments "immune-checkpoint blockade of the PD-1/PD-L1 axis has reshaped the therapeutic landscape of metastatic urothelial carcinoma and has led to responses in patients with fatal disease. The results [from KEYNOTE-045] suggest that pembrolizumab may become a standard of care if approved by the FDA." Bellmunt highlights that "longer overall survival, better quality of life and fewer adverse events compared with chemotherapy are excellent news for these patients. The main limitation of these results in urothelial cancer is that a benefit is only observed in 20–24% of patients." Indeed, Funt remarks "despite the exciting observation that checkpoint-blockade therapy is superior to chemotherapy, the sobering observation is that the majority of patients do not respond to immunotherapy."

> "the sobering observation is that the majority of patients do not respond…"

The results of these studies can now be used as the basis for future trials. Commenting on her ongoing plans, Padmanee Sharma, the lead investigator of CheckMate 275, explains "we are conducting studies to understand why some patients responded to therapy while others did not. In addition, we will focus on combination therapies that may provide clinical benefit for a greater number of patients." The future plans of Bellmunt include "to better identify the patients who are going to derive benefit from immunotherapy, and to find the way to make nonresponsive tumours sensitive to immunotherapy." Perhaps the most important question is which immunotherapeutic agent should be the first choice for the second-line treatment of patients with advanced-stage urothelial cancer. Results from studies of these and other investigators addressing this question are eagerly awaited.

Diana Romero

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)
FURTHER READING Sharma, P. *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(17)30065-7 (2017) | Rosenberg, J.E. *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* **387**, 1909–1920 (2016)

© 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.