UROLOGICAL CANCER

Neoadjuvant pembrolizumab shows promise

Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) is the standard-of-care approach for patients with muscle-invasive bladder cancer (MIBC); however, this approach is rarely used owing to poor tolerability. Now, new data from the PURE-01 study demonstrate the potential of the anti-PD-1 antibody pembrolizumab as an alternative to chemotherapy in this setting.

In a single-arm, window-of-opportunity trial, 50 patients with a confirmed diagnosis of MIBC requiring RC received three courses of pembrolizumab before surgery, with a prespecified primary end point of T0 disease on examination of the RC specimen. All patients underwent RC as planned and 21 patients (42%) had T0 disease. A further 6 patients had incomplete responses, resulting in 27 patients (68.2%) being downstaged to non-muscle-invasive disease. Four patients discontinued pembrolizumab owing to lack of response on MRI and subsequently received neoadjuvant chemotherapy, as permitted by the trial design.

Three patients had a grade ≥3 adverse event, of which one resulted in treatment discontinuation. Thyroid dysfunctions were the most common adverse events of any grade, occurring in 18% of patients.

The majority of patients in the cohort (35) had PD-L1-positive tumours before treatment (defined as PD-L1 expression on >10% of tumour or immune cells, also referred to as combined-positive score; CPS) and had better rates of downstaging to T0 (54.3%) than those with PD-L1-negative (CPS <10%) tumours (13.3%). Examinations of pretreatment tumour mutational burden (TMB) revealed a positive nonlinear correlation with T0 response, and the authors suggested a cut-off of 15 mutations per megabase as a predictor of clinical benefit.

These findings suggest that pembrolizumab provides a more effective alternative to cisplatin in the neoadjuvant setting; data from longer-term follow-up monitoring are eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLE Necci, A. et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.18.01148 (2018)

HAEMATOLOGICAL CANCER

Reduced MHCII levels in relapsed AML

Patients with acute myeloid leukaemia (AML) can derive benefit from allogeneic stem cell transplantation, but many patients ultimately relapse. The results of a study led by Timothy Ley and John DiPersio now provide insights into a potentially actionable mechanism of relapse after transplantation.

In a cohort of 15 patients with disease relapse after transplantation and 20 patients with relapse after consolidation chemotherapy, "we first looked for mutations that could potentially provide a mechanism, but did not find any that were unique to post-transplantation relapses," explains Ley. The authors then analysed AML cells from 7 patients with post-transplantation relapse and 9 patients with post-chemotherapy relapse using RNA sequencing. "We saw a big difference in the expression of a number of genes that are important in immune cell recognition and function — and most of these changes were restricted to the post-transplantation relapse samples," Ley describes. In 6 of 7 patients with post-transplantation relapse, the expression of 4 major histocompatibility complex class II (MHCII) genes and of several genes involved in antigen processing and presentation by MHCII molecules was significantly downregulated. Flow cytometry and immunohistochemistry were used to confirm this downregulation at the protein level and to validate the result in samples from an additional 27 patients.

"We could rapidly reverse this change in AML blasts by treating them with IFNγ [known to upregulate MHCII expression in several cell types] in vitro, suggesting that the mechanism is epigenetic," comments Ley. He adds: "downregulation of MHCII expression can easily be screened for in all patients with relapsed AML after transplantation. We are very interested in studying whether the administration of IFNγ (or an agonist of IFNγ signalling) could potentially resensitize the AML blasts of these patients — who have very limited therapeutic options — to the graft-versus-leukaemia effect that is essential for the success of allogeneic transplantation."

Diana Romero

ORIGINAL ARTICLE Christopher, M. J. et al. Immune escape of relapsed AML cells after allogeneic transplantation. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1808777 (2018)

SKIN CANCER

Long-term benefits in COMBI-AD

Initial data from the COMBI-AD trial suggested promising benefits of adjuvant dabrafenib plus trametinib (D + T) for patients with high-risk, stage III, *BRAF*$^{V600E/K}$-mutant melanoma. Now, extended follow-up data from the trial confirm these benefits.

As Georgina Long explains, "the Kaplan–Meier curves remained separated at 4 years, with D + T significantly improving relapse-free survival (RFS; median not reached versus 16.6 months with placebo; HR 0.49, 95% CI 0.40–0.59, equating to a 51% reduction in the risk of recurrence)." Notably, the RFS benefits were similar irrespective of disease stage, nodal metastatic burden or ulceration. "Using a cure rate model, we estimate that 54% of the D + T group will remain relapse-free in the long-term, compared with only 37% of the placebo group — a 17% absolute difference," Long adds.

At the ESMO 2018 Congress, Long also reported biomarker data from COMBI-AD, which revealed that MAPK pathway aberrations previously associated with resistance to targeted therapy had no effect on RFS in either arm. By contrast, an IFNγ gene expression signature was highly prognostic, with an IFNγ-high status correlating with better RFS in both arms. Interestingly, a high tumour mutation burden (TMB) had added prognostic value among the IFNγ-high group of the placebo arm but not of the D + T arm. "Apart from the group with IFNγ-low/TMB-high tumours that presumably have many drug resistance mechanisms and insufficient immunogenicity, all subgroups benefit from D + T, including the worst prognosis, IFNγ-low/TMB-low group."

"We might cure a large proportion of patients using adjuvant D + T, including those with the worst prognosis (IFNγ low/TMB low) who presumably have a low chance of responding to immunotherapy; however, this remains to be confirmed," Long concludes. Indeed, these findings might form a framework for patient selection in future trials of adjuvant targeted therapy and/or immunotherapy.

David Killock

ORIGINAL ARTICLES Hauschild, A. et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected *BRAF* V600-mutant stage III melanoma. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.18.01219 (2018) | Long, G. V. et al. Updated relapse-free survival (RFS) and biomarker analysis in the COMBI-AD trial of adjuvant dabrafenib + trametinib (D + T) in patients (pts) with resected BRAF V600–mutant stage III melanoma. *Ann. Oncol.* **29** (Suppl. 8), mdy424.053 (2018)