UROLOGICAL CANCER

Atezolizumab improves outcomes in mUC

Platinum-based combination chemotherapy is currently the preferred first-line treatment for patients with metastatic urothelial cancer (mUC); however, this standard of care has not changed dramatically for the past 30 years. Now, data from the phase III IMvigor130 trial show that the addition of the anti-PD-L1 antibody atezolizumab improves outcomes of patients with mUC receiving platinum-based chemotherapy.

In IMvigor130, patients with locally advanced or mUC were randomly allocated to receive atezolizumab plus chemotherapy (group A; $n=451$), atezolizumab only (group B; $n=362$) or placebo plus chemotherapy (group C; $n=400$). This trial was originally designed to randomly assign cisplatin-ineligible patients 2:1 to groups A and C; however, the protocol was amended to include group B and include patients deemed cisplatin eligible with 1:1:1 randomization.

At a median follow-up of 11.8 months, median progression-free survival durations were longer in group A than C: 8.2 months versus 6.3 months (HR 0.82, 95% CI 0.7–0.96; $P=0.007$). When compared to group C (median overall survival (OS) 13.4 months), median OS durations were significantly longer in group A (16.0 months; HR 0.83, 95% CI 0.69–1.00; $P=0.027$), but not in group B (15.7 months; HR 1.02, CI 0.83–1.24). The objective response rate was 47%, 23% and 44% in groups A, B and C, respectively, with complete responses in 13%, 6% and 7%.

The safety profiles were comparable to those of each individual agent. The rate of grade 3–4 adverse events (AEs) was 85%, 42% and 86% in groups A, B and C, respectively, and that of grade 5 AEs was 6%, 8% and 5%.

In summary, IMvigor130 established the benefits of adding atezolizumab to standard first-line platinum-based chemotherapy in patients with mUC, with the potential role of atezolizumab monotherapy in selected patients.

Linda Gummlich, Editor,
BMC Cancer

ORIGINAL ARTICLE Galsky, M. D. et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placeobo-controlled phase 3 trial. *Lancet* **395**, 1547–1557 (2020)

GASTROINTESTINAL CANCER

Trastuzumab deruxtecan improves survival

Around 20% of advanced-stage gastric cancers express HER2, and the HER2-targeted therapy trastuzumab, plus chemotherapy, is an approved first-line therapy in this setting. However, other HER2-targeted therapies (including pertuzumab, lapatinib and trastuzumab emtansine) are ineffective following disease progression on trastuzumab. Now, data from the DESTINY-Gastric01 trial demonstrate that the antibody–drug conjugate trastuzumab deruxtecan (T-DXd) is superior to chemotherapy in this setting.

In this phase II trial, investigators randomized 187 patients with HER2$^+$, locally advanced or metastatic gastric or gastroesophageal junction cancer with disease progression on ≥2 prior lines of therapy, including trastuzumab in all patients, (2:1) to receive either T-DXd or chemotherapy with irinotecan or paclitaxel. Objective response was the primary outcome.

Patients receiving T-DXd had significantly improved confirmed objective response rates (ORRs), as determined by independent central review, compared with those receiving chemotherapy (51% versus 14%; $P<0.001$). T-DXd also resulted in longer median duration of response (11.3 months versus 3.9 months) among those with objective responses lasting ≥4 weeks. These improvements in ORR and duration of response are reflected in a significant improvement in the median overall survival duration: 12.5 months versus 8.4 months (HR 0.59, 95% CI 0.39– 0.88; $P=0.01$).

Patients receiving T-DXd had a higher risk of grade ≥3 adverse events, including reduced neutrophil counts (51% versus 24%), anaemia (38% versus 23%) and reductions in white blood cell count (21% versus 11%). A higher percentage of patients receiving T-DXd discontinued treatment owing to adverse events (15% versus 6%).

These findings support T-DXd as a new targeted approach for patients with HER2$^+$ advanced-stage gastric cancer. Nonetheless, this approach is more toxic than chemotherapy, and adverse events remain an important consideration.

Peter Sidaway

ORIGINAL ARTICLE Shitara, K. et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2004413 (2020)

HAEMATOLOGICAL CANCER

Rituximab for paediatric NHL

Children and adolescents with mature B cell non-Hodgkin lymphomas (NHL) generally have good treatment outcomes. Nonetheless, those with high-risk disease continue to have worse outcomes, indicating a need for treatment intensification in this poor-prognosis subgroup. Now, data from a phase III trial demonstrate that adding the anti-CD20 antibody rituximab to the standard-of-care lymphomes malins B (LMB) regimen improves event-free survival (EFS) in this setting.

A total of 328 patients between 6 months and 18 years of age with newly diagnosed high-risk mature B cell neoplasms (of whom 85.7% had Burkitt lymphoma) were randomly assigned (1:1) to receive LMB chemotherapy either with or without rituximab. All patients received prephase chemotherapy, consisting of cyclophosphamide, vincristine and prednisone. The intensity of chemotherapy in both groups was then stratified based on the presence or absence of CNS-positive disease and/or extensive bone-marrow involvement (≥25%). EFS was the primary end point of this trial.

At a median follow-up duration of ~40 months in both arms, patients receiving rituximab plus chemotherapy had a significantly improved 3-year EFS rate (93.9% versus 82.3%, HR 0.32, 95% CI 0.15–0.66; $P=0.00096$). Overall survival (OS) was also improved in patients receiving rituximab plus chemotherapy at this time point (HR for death 0.36, 95% CI 0.16–0.82).

Patients in the rituximab group had a significantly increased risk of adverse events, including acute rituximab-related infusion reactions in 33.3%, of which 4.3% were grade 3 in severity. Following completion of prephase chemotherapy, patients in the rituximab plus chemotherapy group had a higher, albeit statistically insignificant, risk of grade ≥4 adverse events (33.3% versus 24.2%; $P=0.07$). Three patients in each group died of treatment-related adverse events.

These findings provide robust evidence that the addition of rituximab to chemotherapy improves EFS in children or adolescents with high-risk mature B cell neoplasms. Longer-term follow-up data are required to assess the extent to which this approach improves OS and the possibility of late-onset toxicities.

Peter Sidaway

ORIGINAL ARTICLE Minard-Colin, V. et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. *N. Engl. J. Med.* **382**, 2207–2219 (2020)