HAEMATOLOGICAL CANCER

Second elotuzumab triplet efficacious in MM

In 2015, the FDA approved the anti-SLAMF7 antibody elotuzumab, lenalidomide and dexamethasone triplet regimen for the treatment of relapsed and/or refractory multiple myeloma (RRMM) after ≥1 prior line of therapy. Now, data from the randomized, open-label, phase II ELOQUENT-3 trial demonstrate the efficacy of a different elotuzumab-containing triplet in the lenalidomide-refractory setting.

ELOQUENT-3 involved 117 patients with RRMM after ≥2 previous treatments, including a proteasome inhibitor as well as lenalidomide, in a population with a poor prognosis. Indeed, in this trial, control treatment with the FDA-approved pomalidomide and dexamethasone (Pd) regimen resulted in an investigator-assessed overall response rate (ORR) of 26% and median progression-free survival (PFS) of 4.7 months. However, adding elotuzumab to form the EPd triplet increased the ORR to 53% and the median PFS to 10.3 months (HR 0.54, 95% CI 0.34–0.86; $P = 0.008$), and was corroborated upon blinded, independent review. Notably, the PFS benefit of EPd was consistent across key high-risk patient subgroups. At 40% maturity, overall survival data revealed an intriguing trend favouring EPd (HR 0.62, 95% CI 0.30–1.28).

Infection and grade 3–4 adverse events were similarly common with EPd and Pd. Interestingly, however, EPd was associated with lower rates of neutropenia (13% versus 27%), anaemia (10% versus 20%) and treatment discontinuation (18% versus 24%). Only 3 patients had EPd-infusion reactions.

On 6 November 2018, the FDA approved EPd for this indication. Another triplet regimen consisting of the anti-CD38 antibody daratumumab plus Pd is approved in the same setting and has been associated with an ORR of 60% and a median PFS of 8.8 months, suggesting similar efficacy to EPd, but also with high rates of neutropenia (80%) and infusion reactions (50%). Additional trials are needed to compare the safety and efficacy of these triplets.

David Killock

ORIGINAL ARTICLE Dimopoulos, M. A. et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N. Engl. J. Med.* **379**, 1811–1822 (2018)
FURTHER READING Chari, A. et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood* **130**, 974–981 (2018)

LUNG CANCER

Adjuvant TKIs — a long-term matter

Disease relapse is common in patients with non-small-cell lung cancer (NSCLC) after surgery, highlighting the need for treatment optimization in the adjuvant setting. Now, the results of the SELECT trial demonstrate the potential of adjuvant erlotinib, an EGFR tyrosine-kinase inhibitor (TKI), in patients with *EGFR*-mutated NSCLC.

In this study, 100 patients with resected stage IA–IIIA *EGFR*-mutant disease received erlotinib for a median duration of 23 months. 2-year disease-free survival (DFS), the primary end point, was 88% (95% CI 80–93%), a value significantly higher than that of a historical control group of untreated patients (76%; $P = 0.0047$). 5-year DFS was 56%, and 5-year overall survival was 86%.

Disease recurrence occurred in only 4 patients during treatment but in 36 patients after stopping treatment (the median time to recurrence was 25.4 months after cessation). Of these 40 patients, 26 had a new course of erlotinib for a median duration of 13 months; their outcomes were not reported owing to a lack of formal radiographic measurements.

"In this and other studies, very few recurrences occurred during treatment with EGFR TKIs, which is encouraging, but after stopping erlotinib the recurrence rate is similar to what we would expect without adjuvant treatment, only delayed by therapy," explains principal investigator Nathan Pennell, adding "trials testing longer treatment durations, such as the ADAURA trial of osimertinib, are underway."

Dose reductions were required in 40% of patients. No grade 4–5 adverse events were reported; the toxicities observed were those commonly associated with erlotinib (rash, diarrhoea, dry skin or fatigue, among others).

"Ultimately, I believe that adjuvant EGFR-targeted therapy will be the optimal strategy. In the future, we will use more-effective and less-toxic drugs to improve treatment adherence, and we will test both earlier initiation and longer treatment durations," concludes Pennell.

Diana Romero

ORIGINAL ARTICLE Pennell, N. A. et al. SELECT: a phase II trial of adjuvant erlotinib in patients with resected epidermal growth factor receptor–mutant non-small-cell lung cancer. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.18.00131 (2018)

GASTROINTESTINAL CANCER

mCRC: sequencing in REVERCE

The multi-kinase inhibitor regorafenib is approved for the treatment of metastatic colorectal cancer (mCRC) that is refractory to all other standard treatments. Thus, patients with *RAS*-wild-type mCRC are typically treated with regorafenib only after receiving anti-EGFR antibodies, such as cetuximab. Now, data from the phase II REVERCE trial suggest that the reverse sequence is preferable.

In REVERCE, patients with *KRAS*-wild-type mCRC who had treatment failure with fluoropyrimidines, irinotecan and oxaliplatin, most of whom (96–98%) were also refractory to bevacizumab, were randomly assigned to receive regorafenib followed by cetuximab ± irinotecan upon disease progression (R–C; $n = 51$) or the opposite sequence (C–R; $n = 50$). Overall survival (OS) was superior in the R–C arm (17.4 months versus 11.6 months; HR 0.61; $P = 0.0293$), with no difference in quality of life between the arms. Interestingly, the OS benefit seemed to be driven mostly by greater activity of cetuximab than regorafenib as the second treatment: first progression-free survival (PFS1) was 2.4 months in the R–C arm versus 4.2 months in the C–R arm (HR 0.97; $P = 0.91$), whereas PFS2 was 5.2 months versus 1.8 months (HR 0.29; $P < 0.0001$). Notably, the disease-control rate (DCR) was lower when regorafenib was used second rather than first (31% versus 46%). By contrast, the DCR with cetuximab was similar irrespective of sequencing (77% versus 78%).

"Circulating biomarker analyses revealed that, after the first treatment, more patients who had received cetuximab versus regorafenib had new alterations in *RAS*, *BRAF*, *EGFR*, *ERBB2* (*HER2*) and/or *MET* (12 versus 3)," states lead author Kohei Shitara. "Earlier occurrence of these acquired or selected oncogenic alterations might partially explain the worse outcomes when cetuximab is used before regorafenib," he opines. Indeed, these treatment-emergent alterations correlated with shorter OS (HR 2.02; $P = 0.027$).

"This trial included a small number of patients and thus the results are hypothesis-generating: a phase III study is needed to confirm our findings," Shitara concludes.

David Killock

ORIGINAL ARTICLE Shitara, K. et al. REVERCE: a randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for previously treated metastatic colorectal cancer patients. *Ann. Oncol.* https://doi.org/10.1093/annonc/mdy526 (2018)