Advancing precision treatment for GI malignancies

Upper GI

Keynote-811

Since 2009, trastuzumab combined with chemotherapy has been the standard of care for HER2-positive metastatic gastric cancer (mG) and gastroesophageal junction cancer (GEJ), based on the results of the phase 3 ToGA trial (1). In recent years, integrating tumor-specific antibodies with PD-1 inhibitors, has demonstrated enhanced immune infiltration and T-cell response in preclinical studies, effectively countering tolerogenic dendritic cells (2). Clinical translations of this strategy have shown promising outcomes with a regimen of pembrolizumab, trastuzumab, and chemotherapy in patients with HER2- positive gastro-oesophageal cancer.

The KEYNOTE-811 trial (ESMO 2023 Abstract 15110) represents a randomized, double-blinded, placebo-controlled phase 3 study (3). It enrolled 698 treatment-naïve patients with unresectable, HER2-positive mG/GEJ adenocarcinoma, regardless of PD-L1 expression. Participants were allocated in a 1:1 ratio to either pembrolizumab (200 mg intravenously every 3 weeks) or a placebo, in addition to standard chemotherapy and trastuzumab. The randomization process was stratified based on region, PD-L1 status, and chemotherapy regimen. Treatment was administered for a maximum of two years or until disease progression or intolerable toxicity was observed. The dual primary endpoints were progression-free survival (PFS) and overall survival (OS).

At the third interim analysis, conducted at a median of 38.5 months post-randomization, the pembrolizumab combination notably improved PFS (median PFS: 10.0 vs. 8.1 months; HR: 0.73; 95 % CI: 0.61–0.87). In patients with a PD-L1 combined positive score (CPS) ≥ 1, the median PFS was further extended (10.9 vs. 7.3 months; HR: 0.71; 95 % CI: 0.59–0.86). The objective response rate (ORR) at this interim analysis for CPS ≥ 1 was 73 % in the pembrolizumab cohort versus 60 % in the placebo group, with complete responses observed in 17 and 11 % of these groups, respectively. The OS did not yet meet the prespecified significance criterion at this analysis and will be reassessed in the final analysis. The incidence of grade ≥ 3 drug-related adverse events was comparable between the two groups (58 vs. 50 %), without any new safety concerns.

In conclusion, KEYNOTE-811 establishes a new first-line treatment standard for patients with advanced, unresectable or metastatic gastroesophageal cancer exhibiting both HER2 and PD-L1 overexpression. This regimen has already received approval from the European Medicines Agency (EMA), with Swissmedic approval pending. Following the presentation at ESMO, the ESMO clinical practice guidelines were promptly updated to incorporate pembrolizumab for HER2-positive mG/GEJ adenocarcinoma patients with a CPS ≥ 1 in addition to trastuzumab and chemotherapy.

Lower GI

NICHE-3

Immune checkpoint inhibition (ICI) constitutes standard of care for frontline treatment of metastatic colorectal cancer (CRC) with mismatch-repair deficiency (dMMR) based on the KN-177 trial (4). The phase 2 NICHE-2 study, presented at ESMO 2022, demonstrated remarkable efficacy of a 6-week neoadjuvant regimen with ipilimumab and nivolumab in patients with locally advanced dMMR CRC, yielding a major pathological response in 95 % of patients. Similarly, the combination of nivolumab and relatlimab has shown encouraging outcomes and a favorable toxicity profile in melanoma patients in the neoadjuvant setting (5).

The subsequent NICHE-3 study (LB abstract 31), an investigator-initiated, non-randomized, multicenter phase 2 trial, enrolled patients with resectable, locally advanced dMMR CRC (cT3 and/or N+). Participants received two doses of nivolumab and relatlimab (480 mg each) at four-week intervals, followed by surgical intervention within eight weeks of the initial ICI therapy. The primary endpoint was the pathologic response rate, specifically defined as ≤ 50 % residual viable tumor (RVT). The study reported a very high pathological complete response rate (pCR) (79 %; 15/19 patients). A major pathological response (≤ 10 % RVT) was observed in 89 % of patients, and the overall pathologic response rate was 100 % among the 19 participants. Notably, only one patient (5 %) experienced a grade 3 immune-related adverse event (irAE), with no grade 4-5 irAEs reported.

In conclusion, NICHE-3 corroborates the efficacy of a short-course neoadjuvant ICI regimen in resectable, locally advanced dMMR CRC, highlighting its potential for substantial major and complete pathological responses alongside an acceptable safety profile. The findings prompt further investigation into the optimal ICI combination (anti-PD1 with anti-CTLA4 in NICHE-2 vs. anti-LAG3 in NICHE-3) and the possibility of omitting surgical intervention in certain patient subsets.

CodeBreak 300

In metastatic colorectal cancer (mCRC), approximately 3-4 % of patients exhibit a $KRAS^{G12C}$ mutation (6, 7). Monotherapy targeting $KRAS^{G12C}$ has shown limited efficacy and can lead to resistance via reactivation of the RAS-MAPK pathway (8). Combining anti-EGFR therapy with a $KRAS^{G12C}$ inhibitor presents a compelling biological rationale to enhance treatment efficacy.

CodeBreak 300 (LB abstract 10), presented at ESMO 2023, explored this combination in a global, open-label, phase 3 trial (9). The study enrolled 160 patients with chemorefractory KRASG12C-mutated mCRC. These patients were randomized in a 1:1:1 ratio to receive either sotorasib (960 mg daily or 240 mg daily) combined with panitumumab (6 mg/kg IV), or the investigator's choice of TAS-102 or regorafenib as control arm. The primary endpoint was progression-free survival (PFS).

Treatment with sotorasib (both dosages) plus panitumumab significantly improved PFS compared to the control group (median PFS: 5.62 vs. 2.20 months; HR: 0.49; 95 % CI: 0.30–0.80; P = 0.006 for 960 mg dosage, and median PFS: 3.91 vs. 2.20 months; HR: 0.58; 95 % CI: 0.36–0.93; P = 0.03 for 240 mg dosage). Overall survival results were immature at the time of data cutoff. The highest overall response rate (ORR) was observed with the higher dose of sotorasib combined with panitumumab (26 % ORR). The toxicity profile, characterized by acneiform dermatitis, rash, hypomagnesemia, and hematotoxicity, was consistent with expectations from EGFR inhibitors and sotorasib.

In conclusion, CodeBreak 300 indicates a promising new therapeutic avenue for chemorefractory $KRAS^{G12C}$ mutant mCRC with a manageable safety profile. These findings underscore the potential of targeting $KRAS^{G12C}$ mutations in combination with anti-EGFR therapy, paving the way for future research to optimize treatment strategies in this subset of mCRC patients.

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