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DIGESTIVE ONCOLOGY

Evolving paradigms in digestive oncology: highlights and reflections from ASCO 2025

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Trastuzumab deruxtecan (T-DXd) versus ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): primary analysis of the randomized, phase 3 DESTINY-Gastric04 (DG04) study

DG04, which evaluated T-DXd against the current standard of care combination of RAM and PTX in patients with unresectable or metastatic HER2+ gastric or gastroesophageal junction (GEJ) adenocarcinoma who had progressed on prior trastuzumab-based therapy. T-DXd demonstrated a statistically significant improvement in overall survival and met its primary endpoint, with a reduction of the risk of death of 30% (14.7 vs. 11.4 months; hazard ratio [HR] 0.70; p = 0.0044). This trial highlights the growing relevance of antibody-drug conjugates in gastrointestinal cancers. However, although most of the adverse events related to the treatment were manageable, the 13.9% incidence of interstitial lung disease warrants caution, underscoring the need for close monitoring and patient education. DG04 is a landmark study that will likely influence second-line treatment standards of HER2-positive gastric or GEJA.

Event-free survival (EFS) in MATTERHORN: a randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel chemotherapy (FLOT) in resectable gastric/GEJ cancer (GC/GEJC)

In the early-stage setting, the MATTERHORN trial investigated the addition of durvalumab to the perioperative FLOT regimen in patients with resectable gastric or GEJ adenocarcinoma. Patients in the study arm received neoadjuvant durvalumab (2 cycles) plus FLOT, followed by adjuvant durvalumab (2 cycles) plus FLOT, and then durvalumab monotherapy (10 cycles). The primary endpoint was EFS. At 24 months, 67.4% of the participants in the durvalumab arm remained event-free, compared to 58.5% of the placebo group, with an HR of 0.71 (p < 0.001) and median EFS not yet reached (vs. 32.8 months for the placebo arm). The study suggests meaningful benefit from incorporating immunotherapy in curative-intent treatment. The safety profile of perioperative durvalumab in combination with FLOT was consistent with the known profiles of the individual agents, suggesting that the addition of durvalumab did not exacerbate treatment-related toxicity. As expected, given its mechanism of action, immune-mediated adverse events were more frequent in the durvalumab group than in the placebo group. Importantly, the combination did not impede patients' ability to undergo surgery or receive adjuvant

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Date of reception: 22-07-2025
Date of acceptance: 13-10-2025
DOI: 10.24875/RPO.25000013

Available online: 28-11-2025
Rev. Port. Oncol. 2025;8(4):129-130
www.rponcologia.com

therapy. While overall survival data are still maturing, this trial may pave the way for perioperative immunotherapy to become a standard approach. Nevertheless, the potential for overtreatment underscores the need for precise biomarker-based stratification, and further investigation is warranted to delineate the individual contributions of the neoadjuvant and adjuvant components.

Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/deficient mismatch repair- (MSI-H/dMMR) metastatic colorectal cancer (mCRC): expanded analyses from CheckMate 8HW

The CheckMate 8HW trial was another landmark in the immunotherapy area, specifically for mCRC with dMMR or MSI-H). This study compared NIVO plus IPI to both NIVO monotherapy and chemotherapy in the first-line setting. With a median follow-up of 47 months, the dual checkpoint blockade demonstrated a 72% reduction in the risk of progression or death compared to chemotherapy and a 43% reduction versus monotherapy. In this year's update, an important exploratory endpoint was presented, the progression-free survival 2 (PFS2), defined as the time from randomization to disease progression following subsequent systemic therapy or death, providing a broader assessment of sustained therapeutic benefit beyond initial treatment. In treatment-naïve patients with centrally confirmed MSI-H/dMMR mCRC, the combination of NIVO and IPI led to a median PFS2 that was substantially prolonged with immunotherapy, remaining unreached versus 30.3 months with chemotherapy (HR 0.28). Another important finding was that only 16% of patients treated with first-line NIVO plus IPI required subsequent therapies, compared to 73% of those receiving chemotherapy, highlighting the superior efficacy of the immunotherapy combination in the frontline setting. These findings solidify dual immunotherapy as the preferred frontline strategy for this subgroup of patients.

Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502; ATOMIC)

In the adjuvant setting, the ATOMIC trial examined the efficacy of adding atezolizumab to the standard mFOLFOX6 regimen in patients with stage III dMMR/MSI-H colon cancer. The trial reported a 3-year disease-free survival of 86.4% versus 76.6% (HR 0.50; $p < 0.0001$), representing a 50% reduction in the risk of death. The addition of atezolizumab offers substantial improvements in disease-free survival, representing a major advancement in adjuvant therapy for this subgroup of colon cancer patients. Yet, it remains to be seen whether chemotherapy is a necessary component or if immunotherapy alone could suffice in future protocols. In addition, the absence of mature overall survival data and detailed biomarker analyses, calls for cautious optimism.

First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant mCRC (BREAKWATER): PFS and updated overall survival analyses

The BREAKWATER trial addressed a long-standing clinical challenge: treating BRAF V600E-mutated mCRC, a molecular subgroup historically associated with poor prognosis and limited therapeutic options. This study compared a triplet regimen – encorafenib, cetuximab, and chemotherapy – with the standard chemotherapy plus bevacizumab. The results were compelling, with a PFS of 12.8 months versus 7.1 months (HR 0.53) and an overall survival of 30.3 months versus 15.1 months (HR 0.49), with the triplet regimen resulting in a reduction of the risk of death by 51% compared to standard chemotherapy. The combination regimen had a manageable safety profile, consistent with what is known for each agent. These gains nearly doubled patient survival outcomes and positioned this triplet therapy as the new standard for this molecular subtype.

Conclusion

ASCO 2025 delivered transformative data in digestive oncology. These five trials underscore the promise of precision medicine and immunotherapy in improving patient outcomes across the disease spectrum. The shift toward biomarker-driven, individualized treatment approaches is not only promising but also essential for modern oncology practice. As further data emerge and these findings are integrated into clinical guidelines, multidisciplinary collaboration and real-world evidence will play a critical role in shaping the future of gastrointestinal cancer care.