JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

# Highlights from ASCO Gastrointestinal Cancers Symposium 2023

Irina Mihaela Cazacu[1,2]

[1] *Department of Oncology, Fundeni Clinical Institute, Bucharest, Romania*
[2] *Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

**Corresponding author**: Irina Mihaela Cazacu; **e-mail:** irina.cazacu89@gmail.com

**Abstract**

On January 19-21, 2023, approximately 4000 international gastrointestinal (GI) cancer specialists gathered in San Francisco for the ASCO Gastrointestinal (GI) Cancers Symposium to celebrate a 20-year milestone and to discuss the latest research and treatment advances in the field. The multidisciplinary experts put the science into context and the attendees were provided with a truly comprehensive view of the latest innovations in GI oncology.

The current article highlights some of the most clinically relevant presentations from ASCO GI 2023 Symposium.

**Keywords:** *gastrointestinal cancers, gastric cancer, colorectal cancer, pancreatic cancer, biliary tract cancer, hepatocellular carcinoma*

Reviews

## 1. Gastric/Gastroesophageal Junction (GEJ) Cancer

According to the results of a phase 3 clinical trial presented at the meeting, regorafenib may emerge as new treatment option for refractory gastric/GEJ cancer. The INTEGRATE IIa trial included 251 patients with advanced gastric/GEJ adenocarcinoma who had received at least two prior lines of chemotherapy and were randomized to received regorafenib versus placebo(1). The primary endpoint of overall survival (OS) was superior in the regorafenib arm compared to placebo (4.5 vs 4.0 months; HR, 0.70; $p$=0.011). Progression-free survival (PFS) was also improved with regorafenib (median, 1.8 vs. 1.6 months; HR, 0.52; $p$<0.001). No new safety signals were observed. The most common grade 3-4 AEs with regorafenib were palmar-plantar erythrodysesthesia syndrome, fatigue, and hypertension. Thus, the addition of regorafenib as a late-line therapy option minimally improves outcomes in patients with advanced, refractory gastric/GEJ adenocarcinoma.

First-line zolbetuximab plus chemotherapy may represent a new standard for advanced gastric/GEJ adenocarcinoma overexpressing claudin-18.2. The results from the global phase 3 SPOTLIGHT trial were presented during the 2023 ASCO GI Symposium (2). The trial evaluated the addition of zolbetuximab to first-line

https://doi.org/10.53011/JMRO.2023.01.04

chemotherapy with leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6) in patients with Claudin18.2 (CLDN18.2)-positive, HER2-negative, locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma. Zolbetuximab is an investigational monoclonal antibody that targets CLDN18.2, a protein that is expressed on malignant gastric epithelial cells.

The study included 565 patients who were randomized to receive frontline zolbetuximab plus chemotherapy versus placebo plus chemotherapy. The primary endpoint of PFS was significantly improved with the addition of zolbetuximab compared with placebo — 10.61 months and 8.67 months, respectively (HR, 0.75; *p*=.0066). The median OS was significantly longer with zolbetuximab than with placebo as well —18.23 months versus 15.54 months, respectively (HR, 0.750; *p*=.0053). It is important to note that the median OS of 18 months is rare for a global trial in cancer gastric patient population.

The most common treatment-related adverse events in the zolbetuximab plus chemotherapy group were nausea, vomiting and decreased appetite. The rates of serious adverse events were similar in both treatment groups.

Zolbetuximab is the first targeted therapy, besides immune checkpoint inhibitors, to show a statistically significant survival benefit in the first-line treatment of advanced gastric and GEJ cancer since trastuzumab over a decade ago.

Another study presented at ASCO GI 2023 showed that frontline tislelizumab plus chemotherapy improves survival in PD-L1 positive, advanced gastric/GEJ adenocarcinoma (3). The phase 3 RATIONALE 305 trial enrolled 546 patients with PD-L1 positive, HER2-negative, locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma. Patients were randomized to receive first-line tislelizumab (anti PD-1 antibody) plus investigator's choice of chemotherapy (cisplatin/fluorouracil or oxaliplatin/capecitabine) *versus* placebo plus chemotherapy. The median OS was found to be superior with tislelizumab plus chemotherapy compared with placebo plus chemotherapy (17.2 vs 12.5 month; HR, 0.74; *p*=.0056). The median PFS was 7.2 months in the tislelizumab arm and 5.9 months in the placebo arm (HR, 0.67). Tislelizumab plus chemotherapy had a manageable safety profile in this patient population, with no new safety signals identified.

The phase 2 INFINITY trial (4) showed promising data for patients with gastric cancer in the neoadjuvant setting. The study evaluated the use of a neoadjuvant combination of immune checkpoint inhibitors (durvalumab plus tremelimumab) for patients with MSI-H resectable gastric/GEJ junction adenocarcinoma. Patients were treated with the STRIDE regimen: single high dose tremelimumab 300 mg plus durvalumab 1500mg, for 3 doses every 4 weeks followed by surgery.

The INFINITY trial was a small proof-of-concept study that included 18 patients; one patient withdrew informed consent after first cycle, and two patients refused surgery because of a complete clinical response. Among 15 evaluable patients, one had disease progression and 14 underwent surgery. The pathologic complete response rate was 60%. Grade 3 or higher immune treatment-related serious adverse events occurred in three patients and were treated with high-dose steroids.

Patients with resectable gastric/GEJ cancer with microsatellite instability have a better prognosis and may not benefit from chemotherapy. Microsatellite instability is also a strong predictor of the success of immunotherapy. Immune checkpoint inhibitors may eliminate the need for additional treatments like chemotherapy, radiation therapy, or surgery in the early stages of a disease.

**2. Colorectal cancer**

Bevacizumab plus triflurifine/tipiracil represents a new standard of care for patients with refractory metastatic colorectal cancer (CRC), according to a study presented at ASCO GI 2023 meeting. (5).

The phase 3 SUNLIGHT trial enrolled 492 patients with metastatic CRC who had received at least two prior treatment regimens. Patients were randomized to receive triflurifine/tipiracil and bevacizumab versus triflurifine/tipiracil alone.

The primary endpoint of OS was superior with the addition of bevacizumab (median, 10.8 vs. 7.5 months; HR, 0.61; P<0.001). PFS was also improved (median, 5.6 vs. 2.4 months; HR,

0.44; P<0.001). Grade 3 adverse events were reported in 70% of patients in the control arm and 72% in the bevacizumab arm.

The combination of bevacizumab with trifluridine/tipiracil represents a new standard of care for colorectal cancer, and this trial provides support for the continuation of bevacizumab in subsequent lines of chemotherapy.

### 3. Pancreatic Cancer

The phase 3 NAPOLI-3 trial (6) presented at the meeting compared first-line gemcitabine/nab-paclitaxel with liposomal irinotecan, 5-fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). The study included 770 PDAC patients who were randomized to receive NALIRIFOX or gemcitabine/nab-paclitaxel until disease progression or unacceptable toxicity.

The primary endpoint of median OS was 11.1 months in the NALIRIFOX arm and 9.2 months in the gemcitabine/nab-paclitaxel arm (HR, 0.83; p =.04). The median PFS was 7.4 months and 5.6 months, respectively (HR, 0.69; p <.0001). Grade 3/4 treatment-related adverse events that were more frequent with NALIRIFOX included diarrhea and nausea. Grade ¾ anemia and neutropenia were more common the gemcitabine/nab-paclitaxel arm.

This was the first study to compare two-drug versus three-drug therapy in metastatic PDAC and supports the use of NALIRIFOX as the preferred first-line regimen for patients who are candidates for three-drug therapy.

### 4. Biliary Tract Cancer

According to a study presented at the meeting, adding nab-paclitaxel to standard care chemotherapy does not improve outcomes in biliary tract cancers. The phase 3 SWOG 1815 trial (7) enrolled patients with advanced cholangiocarcinoma or gallbladder cancer who were randomly assigned to receive first-line nab-paclitaxel, gemcitabine, and cisplatin (294 patients) or gemcitabine and cisplatin (147 patients).

The primary endpoint was median OS. There was no statistically significant difference in OS with the triplet chemotherapy versus standard of care (median, 14.0 and 12.7 months; HR, 0.93; P=0.58). Other efficacy endpoints, including PFS and overall response rate were also numerically improved in the triplet chemotherapy arm, but not statistically significant. However, an exploratory analysis indicated potential survival benefits in patients with locally advanced versus metastatic disease and in the small subset of patients with gallbladder primary tumors. The rate of grade 3/4 hematologic toxicity was higher with nab-paclitaxel, gemcitabine and cisplatin (60% vs. 45%).

Another study presented at the meeting suggested a possible benefit in adding bevacizumab to atezolizumab/cisplatin/gemcitabine to treat advanced biliary tract cancers. The phase 2 IMbrave1-151trial (8) is the first randomized study to evaluate the inhibition of PD-L1 and VEGF combined with chemotherapy in patients with advanced biliary tract cancers and the results were presented at ASCO GI 2023.

The study included 162 patients who were randomly assigned to atezolizumab z/bevacizumab/cisplatin/gemcitabine or atezolizumab/ placebo/cisplatin/gemcitabine. After a median follow-up of 10.8 months, PFS was 8.3 months for the atezolizumab/ bevacizumab/cisplatin/ gemcitabine arm and 7.9 months for the atezolizumab/placebo/cisplatin/gemcitabine arm (HR 0.76, 95% CI (0.51, 1.14)). The 6-month PFS rate was higher in the bevacizumab arm.

IMbrave151 did not identify a clear winner between the two experimental arms based on median PFS, and longer follow-up is needed to evaluate the overall survival.

### 5. Hepatocellular Carcinoma

Stereotactic body radiation therapy before sorafenib improved outcomes in advanced hepatocellular carcinoma (HCC). The phase 2 NRG/RTOG trial 1112 (9) presented at the meeting, compared sorafenib alone with stereotactic body radiation therapy (SBRT) and sorafenib in patients with advanced HCC. The primary endpoint of OS was improved from a median of 12.3 months in the monotherapy arm to 15.8 months with the addition of SBRT (HR, 0.77; p=0.05). The median PFS and time to pro-

gression were significantly improved with SBRT. Rate of treatment-related adverse events did not differ with and without SBRT.

The results of this trial suggest that adding SBRT to systemic therapy in patients with HCC mainly confined to the liver may improve survival. However, it is necessary to evaluate SBRT with the new standard of care for advanced HCC (atezolizumab/bevacizumab and durvalumab/tremelimumab).

## 6. Conclusions

The ASCO Gastrointestinal Cancers Symposium covered a variety of topics that will shape the future of GI oncology, including screening and diagnosis, drug development, clinical trials, clinical research, and innovations. The symposium demonstrated how the GI specialists community continues to work hard to improve the lives of cancer patients worldwide.

**Abbreviations:**
GI – gastrointestinal
GEJ – Gastroesophageal Junction
OS – overall survival
CLDN18.2 – Claudin18.2
CRC – colorectal cancer
PDAC – pancreatic ductal adenocarcinoma
HCC – hepatocellular carcinoma
SBRT – stereotactic body radiation therapy

**Statements:**
**Author's contributions:** IC gathered the data and wrote the paper.
**Funding:** This study did not receive any specific grant from the funding agencies in the public, commercial, or not-for-profit sector.
**Conflicts of Interest:** The author declares no conflict of interest.

**References:**

1. Pavlakis, N., et al., INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG). Journal of Clinical Oncology, 2023. 41(4_suppl): p. LBA294-LBA294.

2. Shitara, K., et al., Zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients (pts) withclaudin-18.2+ (CLDN18.2+) / HER2− locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary results from phase 3 SPOTLIGHT study. Journal of Clinical Oncology, 2023. 41(4_suppl): p. LBA292-LBA292.

3. Moehler, M.H., et al., Rationale 305: Phase 3 study of tislelizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment (1L) of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC). Journal of Clinical Oncology, 2023. 41(4_suppl): p. 286-286.

4. Pietrantonio, F., et al., INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). Journal of Clinical Oncology, 2023. 41(4_suppl): p. 358-358.

5. Tabernero, J., et al., Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer: The phase 3 randomized SUNLIGHT study. Journal of Clinical Oncology, 2023. 41(4_suppl): p. 4-4.

6. Wainberg, Z.A., et al., NAPOLI-3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Journal of Clinical Oncology, 2023. 41(4_suppl): p. LBA661-LBA661.

7. Shroff, R.T., et al., SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. Journal of Clinical Oncology, 2023. 41(4_suppl): p. LBA490-LBA490.

8. El-Khoueiry, A.B., et al., IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. Journal of Clinical Oncology, 2023. 41(4_suppl): p. 491-491.

9. Dawson, L.A., et al., NRG/RTOG 1112: Randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). Journal of Clinical Oncology, 2023. 41(4_suppl): p. 489-489.