A Year in Review
Groundbreaking Research Improves Care for Patients With Gastrointestinal Cancers

By David H. Ilson, MD, PhD March 25, 2022 - Supplement: Gastrointestinal Oncology Almanac

The past year has seen unprecedented progress across the spectrum of gastrointestinal malignances, including the advancement of immunotherapy and targeted molecular agents and the refinement of adjuvant therapy using novel as well as existing therapies. Three themes emerging from these reports are: (1) the key role of next-generation sequencing and biomarker testing to identify treatable patient subsets; (2) the advancement of immunotherapy agents in earlier-line treatment of gastrointestinal cancers; and (3) the validation of optimal adjuvant and neoadjuvant therapy strategies.

Treatment Advances in Colorectal Cancer

Total neoadjuvant therapy in rectal cancer—to improve therapy tolerance, potentially improve overall survival, and increase organ preservation—gained support with the publication of the UNICANCER-PRODIGE 23 trial. This trial compared conventional capecitabine/radiation followed by surgery and adjuvant chemotherapy, to preoperative chemotherapy with FOLFIRINOX (leucovorin, fluorouracil [5-FU], irinotecan, and oxaliplatin) followed by capecitabine plus radiation, surgery, and adjuvant chemotherapy. Neoadjuvant FOLFIRINOX followed by capecitabine/radiation achieved a higher rate of pathologic complete response at surgery and superior 3-year disease-free and metastasis-free survival compared to conventional capecitabine/radiation. The higher rate of pathologic complete response may translate into the greater potential for nonoperative management in these patients.

The IDEA collaboration pooling results of six trials comparing 3 vs 6 months of adjuvant therapy in stage III colon cancer previously reported that a shorter 3-month duration of capecitabine/oxaliplatin should be given to nearly all patients with stage III disease. An updated analysis now reports no survival benefit for extending therapy with oxaliplatin beyond 3 months, regardless of high- or low-risk stage III status or receipt of either FOLFOX (leucovorin, 5-FU, and oxaliplatin) or capecitabine/oxaliplatin. There may be modest benefit in high-risk stage III patients for extending the fluorinated pyrimidine component beyond 3 months. These potentially practice-changing results support treating

all stage III colon cancers with only 3 months of oxaliplatin, with an individualized decision to extend the fluorinated pyrimidine beyond 3 months.

Provocative data are now emerging regarding the use of checkpoint inhibitors as initial therapy in locally advanced microsatellite instability (MSI)–high rectal cancer. Investigators recently reported preliminary results of a pilot trial of the anti–PD-1 agent dostarlimab as initial therapy in MSI-high or DNA mismatch repair protein–deficient rectal cancer. In the first 11 patients treated, 100% achieved a clinical complete response to therapy with dostarlimab without planned chemotherapy, radiation therapy, or surgery. This striking early result may lead to consideration of a new treatment paradigm in patients with MSI-high rectal cancer: the potential avoidance of chemoradiotherapy and surgery dependent on response to initial immune checkpoint inhibitor therapy. Other pilot trials of single-agent and combination immunotherapy are ongoing.

Targetable molecular subsets in colorectal cancer beyond *RAS* wild-type and MSI-high cancers now include patients with *BRAF* V600E mutation, *KRAS* G12C mutation, and *HER2*. The U.S Food & Drug Administration (FDA) approval for the combination of cetuximab and encorafenib as later-line treatment in *BRAF* V600E–mutant colon cancers has led to augmenting this therapy with other agents. A recent report combined nivolumab with cetuximab and encorafenib, given the potential for *BRAF* V600E–mutant tumors to harbor a higher tumor mutational burden and potentially greater immune activation. In this phase I/II trial of 22 patients, a response rate of 50% with both a promising progression-free and overall survival were observed. A randomized trial adding nivolumab to encorafenib/cetuximab in *BRAF* V600E–mutant patients is planned. Study of earlier-line use of BRAF V600E–targeted agents compared to conventional chemotherapy is ongoing, and trials are moving forward to evaluate BRAF V600E–targeted therapy in the adjuvant setting.

KRAS G12C mutations also now appear targetable by small-molecule inhibitors including sotorasib and adagrasib. In a recent phase II trial of sotorasib in 62 patients with *KRAS* G12C–mutant colorectal cancer, a signal of activity was observed with a response rate of 9%. Further study of these agents and potentially adding other drugs targeting resistance mechanisms are planned.

Checkpoint Inhibitors in Gastroesophageal Cancer

Studies of immune checkpoint inhibitors in esophagogastric cancers have changed practice, with FDA approval for the first-line use of these agents combined with

chemotherapy in advanced disease. In the practice-changing CheckMate 649 trial, nivolumab was added to first-line FOLFOX in patients with advanced HER2-negative esophagogastric adenocarcinoma. In patients with a combined positive score (CPS) ≥ 5%, the focus of the primary study analysis, nivolumab improved overall and progression-free survival. Response rates were improved across all patient subsets and response duration was also improved. However, in patients with a CPS ≤ 5% or < 1%, there was no clear survival benefit for the addition of nivolumab with hazard ratios for overall survival approaching 1, indicating that the survival benefit may only be for patients with a CPS ≥ 5%. Nivolumab is now approved in combination with first-line chemotherapy for patients with esophagogastric adenocarcinoma irrespective of PD-L1 status.

A second trial, KEYNOTE-590, added pembrolizumab to first-line chemotherapy with 5-FU/cisplatin in esophageal and gastroesophageal junction adenocarcinoma and squamous cancer.[8] In the primary analysis population of patients with a CPS ≥ 10% there were significant improvements in overall survival and progression free survival. Benefits were seen for both adenocarcinoma and squamous cancers, with a diminished overall survival improvement seen in patients with a CPS < 10%. Pembrolizumab is now approved in the United States in combination with first-line chemotherapy in esophageal and gastroesophageal junction adenocarcinoma and squamous cancer irrespective of PD-L1 status. The dependence in survival improvement on CPS score is the subject of ongoing debate for both nivolumab and pembrolizumab.

A third impactful trial was KEYNOTE-811, which led to the approval of pembrolizumab to treat HER2-positive esophagogastric adenocarcinoma in the first-line setting. In this trial, patients received trastuzumab and chemotherapy with or without pembrolizumab. The response rate observed in the planned interim analysis of the first 264 patients improved from 52% to nearly 74% with the addition of pembrolizumab to first-line trastuzumab-based chemotherapy. This improvement may also have some dependence on CPS score, although the vast majority of patients treated on this trial had positive CPS scores.

Another landmark trial for immune checkpoint inhibitor therapy reported in 2021 was CheckMate 577, which evaluated use of adjuvant therapy with nivolumab in patients with esophageal or gastroesophageal junction adenocarcinoma or squamous cancer who received preoperative chemotherapy and radiation therapy and had evidence of residual disease found at surgical resection. Treatment with nivolumab led to a doubling of disease-free survival, the primary trial endpoint, compared to placebo, with improvements in node-positive and -negative patients and patients with adenocarcinoma and squamous

cancer. Although overall survival data are pending, this highly significant improvement in disease-free survival will almost certainly translate into an overall survival benefit. Adjuvant nivolumab is the FDA-approved standard of care adjuvant treatment for these patients, representing the first advance in adjuvant treatment of these cancers in over a decade. The benefit, however, may also depend on CPS score, with a diminished disease-free survival benefit seen in patients with a CPS score < 5%.

Interesting data on neoadjuvant therapy with the combination of ipilimumab and nivolumab in MSI-high esophagogastric adenocarcinoma were recently reported in a pilot trial from France. Recent retrospective series have indicated improved survival with surgery alone for MSI-high gastric cancers, and a potential limited and possible detrimental effect of chemotherapy. In this pilot trial of 32 patients treated with neoadjuvant checkpoint inhibitor therapy followed by planned surgery, the pathologic complete response rate was 59% in the 29 patients who underwent resection; 2 patients achieved clinical complete response without surgery. These results underline the need to evaluate checkpoint inhibitors in locally advanced MSI-high esophagogastric cancers and raise the potential of nonoperative management in patients achieving clinical complete response.

In patients with HER2-positive gastric cancer that has progressed on first-line trastuzumab-based therapy, regulatory approval for the use of the antibody-drug conjugate fam-trastuzumab deruxtecan-nxki was achieved for second- or later-line use based on results of the DESTINY-Gastric01 trial. Updated results from this trial indicated superior response, progression-free, and overall survival for trastuzumab deruxtecan over physician’s choice chemotherapy with a median survival exceeding 12 months. Trials of this agent in earlier-line therapy and in combination with chemotherapy and immunotherapy are ongoing.

Novel Targets and Therapies in Hepatobiliary Cancers

The practice-changing TOPAZ-1 in biliary cancer was recently reported, comparing treatment of advanced biliary cancer with gemcitabine/cisplatin with or without durvalumab. Overall survival was improved with the addition of durvalumab to chemotherapy, as was progression-free survival and response rate, with a suggestion of a greater survival impact in patients with stronger PD-L1 expression. The addition of durvalumab to first-line chemotherapy in biliary cancer will likely become the new standard of care.

Biliary cancers have emerged as clearly targetable by specific molecular agents, underscoring the need to perform next-generation sequencing in all patients with advanced disease. Positive results in the ClarIDHy trial, and a subsequent drug approval, have now been achieved for the IDH1 inhibitor ivosidenib. This updated report of survival results, adjusted to consider crossover of patients from placebo to ivosidenib, indicated a survival benefit for ivosidenib in addition to superior progression-free survival over placebo; this agent largely leads to disease stabilization. Ivosidenib now joins the armamentarium of approved agents for biliary cancer, including the FGFR receptor inhibitors pemigatinib and infigratinib.

In the adjuvant setting, the ASCOT trial from Japan studied adjuvant therapy with S-1 after resection of biliary cancer. Adjuvant S-1 resulted in significant improvements in overall and relapse-free survival. These positive results reinforce the use of an oral fluorinated pyrimidine as adjuvant therapy after biliary cancer resection and support the current standard of care of adjuvant capecitabine.

Adding to the list of recent practice-changing trials are results recently presented for the HIMALAYA trial in advanced Child-Pugh A hepatocellular cancer, comparing standard first-line sorafenib to single-agent durvalumab or to the combination of a single dose of tremelimumab followed by durvalumab. Tremelimumab/durvalumab achieved superior survival compared to sorafenib, as well as improved progression-free survival and antitumor response. Durvalumab was also shown to be noninferior to sorafenib. Tremelimumab/durvalumab, and potentially single-agent durvalumab will emerge as new first-line therapy options in advanced hepatocellular carcinoma. This therapy may provide an alternative to the current first-line standard of care, atezolizumab plus bevacizumab, particularly in patients with contraindications to receive bevacizumab.

In contrast to HIMALAYA, the COSMIC-312 trial comparing cabozantinib plus atezolizumab to sorafenib failed to achieve superior survival in the first-line setting, despite an improvement in progression free-survival. Trials of other first-line combinations of immune checkpoint inhibitors and other agents are ongoing.

Positive results were also reported for the second-line use of the immune checkpoint inhibitors tislelizumab and pembrolizumab in hepatocellular carcinoma. In a large phase II trial of the anti–PD-1 agent tislelizumab in patients who progressed on prior sorafenib or lenvatinib, encouraging responses and response duration were observed. In the recent phase III KEYNOTE-394trial comparing second-line therapy with pembrolizumab vs placebo in over 450 patients with Child-Pugh A disease, overall survival, progression-free

survival, and antitumor response were all significantly improved with pembrolizumab. With recent and likely additional first-line approval of immune checkpoint inhibitor therapy combinations in hepatocellular carcinoma, how best to sequence these agents with other therapies remains an unanswered question.

Targeting *KRAS* G12C in Pancreatic Cancer

The search for effective targeted agents in pancreatic cancer also yielded recent promising results with the targeting of *KRAS* G12C mutations with the agents sotorasib and adagrasib. In a recent phase I/II trial of sotorasib in advanced pancreatic cancer harboring G12C mutation, in 38 patients a response rate of 21% was observed with encouraging rates of progression-free and overall survival. In another recent phase I/II trial of adagrasib, responses in pancreatic cancer with G12C mutation were seen in 5 of 10 patients, and encouraging rates of response duration were also seen. KRAS G12C has clearly emerged as a targetable pathway, and further study of these agents—as well as combination with other agents—is warranted.

Recent FDA Approvals in Gastrointestinal Cancer

Over the past year, the U.S. Food and Drug Administration granted approval to several novel drugs and new indications for older therapeutic agents used in gastrointestinal oncology.

Cetuximab Plus Encorafenib

On September 28, 2021, cetuximab (Erbitux) was approved in combination with encorafenib (Braftovi) for the treatment of adults with metastatic colorectal cancer and a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy.

Ivosidenib

On August 25, 2021, ivosidenib (Tibsovo) was granted approval for the treatment of adults with previously treated locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (*IDH1*) mutation, as detected by an FDA-approved test.

Infigratinib

On May 28, 2021, the kinase inhibitor infigratinib (Truseltiq) received accelerated approval for adults with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or other rearrangement, as detected by an FDA-approved test.

Nivolumab

On May 20, 2021, nivolumab (Opdivo) was approved for patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

Pembrolizumab Plus Trastuzumab Plus Chemotherapy

On May 5, 2021, pembrolizumab (Keytruda) in combination with trastuzumab (Enhertu, Herceptin) plus fluoropyrimidine- and platinum-containing chemotherapy was approved for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.

Nivolumab Plus Chemotherapy

On April 16, 2021, nivolumab (Opdivo) in combination with fluoropyrimidine- and platinum-containing chemotherapy was approved for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Cetuximab

On April 6, 2021, approval was granted for a new dosage regimen for cetuximab (Erbitux) of 500 mg/m^2 as a 120-minute intravenous infusion every 2 weeks for patients with *KRAS* wild-type, *EGFR*-expressing colorectal cancer or squamous cell carcinoma of the head and neck.

Pembrolizumab Plus Chemotherapy

On March 22, 2021, pembrolizumab (Keytruda) in combination with platinum- and fluoropyrimidine-based chemotherapy was approved for patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1–5 cm above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.