Gastrointestinal Cancers: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner

Nina N. Grenon, DNP, AGCNP-BC, AOCN®, of Dana-Farber Cancer Institute, evaluates data on single and dual immunotherapy for advanced esophageal squamous cell carcinoma; maintenance therapy for metastatic colorectal cancer; a HER2-targeted therapy for colorectal cancer; adjuvant therapy for resected esophageal cancer and gastroesophageal junction cancer; and standard of care for patients with advanced biliary tract cancer.

Abstract LBA4001

Nivolumab Plus Chemotherapy and Nivolumab Plus Ipilimumab as First-Line Treatment for Patients With Advanced Esophageal Cancer

By Jo Cavallo

Visit https://meetinglibrary.asco.org/record/195919/abstract to read the full abstract and view author disclosures.

The first results from the phase III CheckMate 648 study represent significant progress in the treatment of patients with advanced esophageal squamous cell carcinoma. The trial evaluated first-line treatment with nivolumab plus chemotherapy or nivolumab plus ipilimumab in patients with advanced disease. The findings show that both treatments demonstrated superior overall survival compared with chemotherapy alone; the combination therapies also demonstrated a significant durable objective response benefit and an acceptable safety profile. These results were presented by Ian Chau, MD, and colleagues at the 2021 ASCO Annual Meeting (Abstract LBA4001).

Esophageal cancer is the sixth most common cause of cancer-related deaths and the eighth most common cancer worldwide, with a 5-year survival rate of less than 25%. Each year, about 19,260 people in the United States are diagnosed with esophageal cancer and over 15,000 die from the disease. The most common subtype of esophageal cancer is squamous cell carcinoma, which accounts for 90% of all esophageal cancers each year.

Study Methodology

The researchers enrolled 970 adults with previously untreated, unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma, regardless of tumor cell PD-L1 expression. The patients were randomly assigned to nivolumab plus fluorouracil and cisplatin chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone.

The primary endpoints for both comparisons were overall survival and progression-free survival per blinded independent center review in patients with tumor cell PD-L1 ≥ 1%. Hierarchically

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tested secondary endpoints included overall survival and progression-free survival in all randomly assigned patients.

CheckMate 648 Results

The researchers found with 13 months minimum follow-up, nivolumab plus chemotherapy and nivolumab plus ipilimumab led to a statistically significant improvement in overall survival vs chemotherapy in patients with tumor cell PD-L1 ≥ 1% and all randomly assigned patients.

A statistically significant progression-free survival benefit was also observed for nivolumab and chemotherapy vs chemotherapy alone (hazard ratio = 0.65, 98.5% confidence interval = 0.46–0.92, *P* = .0023) in patients with tumor cell PD-L1 ≥ 1%. Progression-free survival with nivolumab plus ipilimumab vs chemotherapy in patients with tumor cell PD-L1 ≥1% did not meet the prespecified boundary for significance.

The objective response rate (per blinded independent central review) was 53% (nivolumab/chemotherapy), 35% (nivolumab/ipilimumab), and 20% (chemotherapy) in patients with tumor cell PD-L1 ≥ 1%. In all randomly assigned patients, rates were 47%, 28%, and 27%, respectively. Longer median (95% confidence interval) duration of response was observed vs chemotherapy for patients with tumor cell PD-L1 ≥ 1%: 8.4 (6.9–12.4), 11.8 (7.1–27.4), and 5.7 (4.4–8.7) months, and for all randomly assigned patients, 8.2 (6.9–9.7), 11.1 (8.3–14.0), and 7.1 (5.7–8.2) months, respectively. No new safety signals were identified.

Clinical Significance

"Nivolumab plus chemotherapy and nivolumab plus ipilimumab both demonstrated superior overall survival vs chemotherapy, along with durable objective responses and acceptable safety, in patients with advanced esophageal squamous cell carcinoma, and each represents a potential new first-line treatment option," concluded the study authors.

Commenting on this study's findings during an ASCO press briefing, Julie R. Gralow, MD, FACP, FASCO, ASCO Chief Medical Officer and Executive Vice President, said, "The CheckMate 648 study found two regimens that improved overall survival beyond the current standard of care, which is chemotherapy alone for recurrent or metastatic esophageal cancers, particularly those that express PD-L1, which was found in about half of the tumors. The addition of the PD-1 immune checkpoint inhibitor nivolumab with chemotherapy, as well as the combination of two immune checkpoint inhibitors without chemotherapy, nivolumab and ipilimumab, a CTLA-4 inhibitor, both significantly extended survival and should be considered superior treatment as first-line treatment of esophageal squamous cell carcinoma. This dual immunotherapy combination without chemotherapy is the first chemotherapy-free first-line treatment showing benefit for these patients."

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Esophageal cancer (EC) is known for its high rate of cancer-related deaths. Globally, the disease is notorious for a large burden of symptoms. The 5-year survival rate is less than 25%. The most common subtype of EC is squamous cell carcinoma, accounting for 90% of cases each year. Until recently, first-line treatment with chemotherapy for advanced esophageal cancer yielded poor prognosis, with a median survival of 10 months. CheckMate 648 is the first and largest randomized phase III clinical trial to show the addition of nivolumab (Opdivo) to chemotherapy or ipilimumab (Yervoy) significantly increased overall survival (OS) in previously untreated patients. Patients with PD-L1 expression of 1% or greater showed the greatest OS benefits and longer progression-free survival.

This study confirms the addition of checkpoint inhibitors to chemotherapy as an innovative approach to a first-line treatment option for appropriate patients with advanced metastatic esophageal squamous cell carcinoma, and as such, will become a new standard of care for this patient population. The combination of two immune checkpoint inhibitors without chemotherapy (nivolumab and ipilimumab) significantly extended OS. The results from this study illus-

trate significant progress in the treatment of these patients.

Future research should focus on better predictive biomarkers and the latest immunotherapy combinations in order to overcome mechanisms of immune resistance.

Disclosure: Dr. Grenon has no conflicts of interest to disclose.

Abstract 3504

Capecitabine Maintenance for Patients With Metastatic Colorectal Cancer

By JADPRO Staff

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Oral capecitabine maintenance therapy led to prolonged progression-free survival but had no effect on overall survival compared with active monitoring in patients with metastatic colorectal cancer, according to findings from the FOCUS4-N trial.

Presented at the 2021 ASCO Annual Meeting by Richard Adams, MD, of Cardiff University in the United Kingdom, the study results support the use of treatment breaks in metastatic colorectal cancer in order to limit toxicity.

From March 2014 to March 2020, the FOCUS4-N trial randomized 254 patients to receive either capecitabine (n = 127) or active monitoring (n = 127) after induction. The primary endpoint was progression-free survival. Secondary endpoints included overall survival (OS), toxicity, and quality of life assessment. The median progression-free survival with capecitabine maintenance was doubled (3.88 months vs. 1.87 months) compared with active monitoring (HR, 0.38). The median OS was 14.8 months in the capecitabine arm and 15.2 months in the active monitoring arm (HR, 0.93).

"Capecitabine maintenance strategy is a reasonable option for clinicians to discuss with their patient at the end of their first-line induction chemotherapy," said Richard Adams, MD. "[Capecitabine] essentially doubles the time until patients need to return to full-dose, induction systemic anticancer therapy."

Safety data showed grade ≥ 2 fatigue (25% vs. 12%), diarrhea (23% vs. 13%), and hand-foot syndrome (26% vs. 3%). There was no statistically significant difference in quality of life between the two arms.

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From 2014 to 2020, the FOCUS4-N trial randomized 254 patients who had stable disease following 16 weeks of first-line chemotherapy, in unblinded fashion, to either active monitoring or maintenance capecitabine (1,250 mg/m^2 twice daily, 2 weeks on followed by 1 week off). The primary endpoint was progression-free survival (PFS), with overall survival and quality of life (QOL) as secondary endpoints.

Certain characteristics, such as left-sided tumors, *PIK3CA* wild type, no PTEN loss, and no prior EGRF inhibitor exposure, appeared to predict improved PFS survival with the maintenance approach. Overall survival was not significantly improved with the maintenance approach. The median PFS in this trial extended from 1.9 months with active monitoring to 3.9 months with capecitabine in the maintenance group in patients with targetable tumor mutations who responded or had stable disease after first-line chemotherapy.

Although toxicities were mild to moderate (grade 1 and 2), the maintenance approach had more toxicities, including more diarrhea, fatigue, nausea, and hand-foot syndrome. Additionally, there was no significant difference in QOL between the two groups.

For patients with metastatic colorectal cancer who achieve control and stable disease as best response after initial chemotherapy, maintenance chemotherapy is an option to be considered. In patients who achieved a response, perhaps less is more as these patients are likely to harbor a more favorable tumor biology. To help and inform the discussion with

patients following first-line chemotherapy, clinicians can discuss capecitabine maintenance chemotherapy as a reasonable option strategy, as it can essentially double the time until they will need to return to full-dose regimen standard chemotherapy. This trial lays out choices between increased toxicities and progression-free survival.

Disclosure: Dr. Grenon has no conflicts of interest to disclose.

Abstract 3505

Trastuzumab Deruxtecan Shows Activity in Patients With Advanced HER2-Expressing Metastatic Colorectal Cancer

By JADPRO Staff

Visit https://meetinglibrary.asco.org/record/201555/abstract to read the full abstract and view author disclosures.

Trastuzumab deruxtecan (Enhertu) demonstrated clinically meaningful activity and a manageable safety profile in patients with HER2-expressing unresectable and/or metastatic colorectal cancer who received at least two prior lines of standard treatment. Trastuzumab deruxtecan has already demonstrated clinical activity in four different cancer settings, and shows potential to improve patient outcomes in a number of HER2-targetable tumors.

In the phase II DESTINY-CRC01 trial, patients had centrally confirmed HER2-expressing, *RAS* wild-type metastatic colorectal cancer that progressed after two or more prior regimens. 6.4 mg/kg of trastuzumab deruxtecan was administered every 3 weeks in three cohorts (A: HER2 IHC3+ or IHC2+/ISH+; B: IHC2+/ISH−; C: IHC1+). The primary endpoint was confirmed objective response rate (ORR) by independent central review in cohort A. Secondary endpoints were disease control rate (complete response + partial response + stable disease), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Data from a cohort of 53 patients with HER2-positive metastatic colorectal cancer showed confirmed ORR was 45.3%, disease control rate was 83.0%, median duration of response was 7.0 months, median PFS was 6.9 months with 37 (69.8%) PFS events, and median OS was 15.5 months with 36 (67.9%) OS events.

Salvatore Siena, MD, of Università degli Studi di Milano, and Niguarda Cancer Center, Milan, Italy and principal investigator of the DESTINY-CRC01 trial, said "Understanding new ways we can treat patients with colorectal cancer, such as targeting HER2, is critical as patients have few remaining treatment options once progression occurs in the advanced disease setting. The results from DESTINY-CRC01 in patients with HER2-positive advanced colorectal cancer are striking and warrant further research, especially considering many of these patients have had numerous prior therapies."

Treatment-emergent adverse events (TEAEs) of grade ≥ 3 occurred in 65.1% of patients; the most common TEAEs were hematologic and gastrointestinal. Treatment-emergent adverse events leading to drug discontinuation occurred in 13 patients (15.1%). Notably, 8 patients (9.3%) had interstitial lung disease, which continues to be recognized as an important identified risk that requires careful monitoring and intervention as needed.

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Approximately 3% to 5% of colorectal cancers have amplification of the HER2 oncogene or overexpress its protein product, HER2. Accumulating data provide proof-of-principle support for the potential benefit of HER2-targeted therapies (e.g., trastuzumab plus pertuzumab or lapatinib, fam-trastuzumab deruxtecan) in these patients.

At present, there are no approved HER2-targeted therapies for HER2-positive metastatic colorectal cancer. Recommended therapies based on guidelines include regorafenib or trifluridine/tipiracil as third line or later treatment with little effect on objective response.

The DESTINY-CRC01 trial showed promising and durable activity in HER2-positive metastatic colorectal cancer refractory to standard treatment. Patients in this trial had regression of target lesions and lasting responses, resulting in PFS and OS benefits.

In this trial, treatment-related adverse events needing monitoring include interstitial lung disease, which was managed with systemic corticosteroids. Recommendations include close monitoring of patients with symptoms such as fever, cough, and dyspnea. Treatment with trastuzumab deruxtecan should be interrupted in the setting of grade 1 interstitial lung disease and discontinued for grade 2, with further evaluation and consultation with pulmonary medicine. An evaluation should include bronchoscopy with broncho-alveolar lavage, pulse oximetry, and arterial blood gases. Predisposing factors, which could increase the likelihood of interstitial lung disease, should be identified.

Given the promising results of this study, further research in a larger population of patients with HER2-positive metastatic colorectal cancer needs to be considered.

Disclosure: Dr. Grenon has no conflicts of interest to disclose.

Abstract 4003

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

By JADPRO Staff

Visit https://meetinglibrary.asco.org/record/195939/abstract to read the full abstract and view author disclosures.

Nivolumab in the adjuvant setting led to improved disease-free survival compared with placebo in patients with resected stage 2/3 esophageal cancer or gastroesophageal junction (GEJ) cancer who received neoadjuvant chemoradiation therapy and had residual disease, according to results from the CheckMate 577 trial presented at the 2021 ASCO Annual Meeting.

Presented by Ronan Joseph Kelly, MD, MBA, of Baylor University Medical Center, CheckMate 577 is a phase III randomized, multi-center, double-blind study evaluating nivolumab as adjuvant therapy in patients with resected esophageal or GEJ cancer who have received neoadjuvant chemoradiation therapy and have not achieved a pathologic complete response.

794 patients were randomized 2:1 to receive nivolumab 240 mg or placebo every 2 weeks for 16 weeks, followed by nivolumab 480 mg or placebo every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint of the trial was disease-free survival, and the secondary endpoint was overall survival. Median distant metastasis-free survival was 28.3 months with nivolumab vs. 17.6 months with placebo (HR, 0.74). Median progression-free survival 2 (PFS2; time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier) was not reached with nivolumab vs. 32.1 months with placebo (HR, 0.77).

Safety was a key measure in the study, and the results highlight the tolerability of nivolumab in the adjuvant setting. No unexpected adverse effects were observed. Most adverse events were grade 1 or 2; however, any grade 3 or 4 treatment-related adverse events occurred in 13% of patients with nivolumab and 6% with placebo. In addition, serious treatment-related adverse events were observed in 5% and 1% of patients, respectively.

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Esophageal cancer is a leading cause of cancer-related illness and death throughout the world. Because there is no effective screening or early detection, most patients present with locally advanced or overt metastatic disease. Esophageal cancer is known to cause significant mortality. Until recently, no adjuvant

therapy was available for patients with resected esophageal cancer and gastroesophageal junction cancer (EC/GEJC) who received adjuvant chemoradiotherapy.

Data from the CheckMate 577 trial included adjuvant nivolumab for patients with resected esophageal cancer. Kelly and colleagues presented an update on the trial, which demonstrated persistent efficacy, tolerable toxicity, and no difference in quality of life in the treatment group vs. the placebo group. Overall, 794 patients were randomized. Distant recurrence was reported for 29% vs. 39% and locoregional recurrence for 12% vs. 17% of patients in the nivolumab and placebo groups, respectively. Median distant metastasis-free survival was 28.3 vs. 17.6 months with nivolumab vs. placebo. Toxicities, mainly immune related, were as expected. These data provide additional support for the use of adjuvant nivolumab as a new standard of care for patients who remain at high risk with residual disease following neoadjuvant chemoradiotherapy.

In patients who received nivolumab, the magnitude of benefit with respect to disease-free survival was greater for those in whom nivolumab was initiated at least 10 weeks after surgery than for those in whom nivolumab was initiated less than 10 weeks after surgery. This finding suggests that a prolonged recovery may be needed after intensive preoperative therapy followed by surgery, especially esophagectomy. This trial is ongoing, and an analysis of the secondary endpoint of overall survival is planned.

Future research is focused on whether combining chemoradiotherapy and immune checkpoint inhibitors can induce safe and efficient antitumor immune responses.

Disclosure: Dr. Grenon has no conflicts of interest to disclose.

Abstract 4006

Liposomal Irinotecan With 5-FU and Leucovorin Improves Outcomes for Patients With Biliary Tract Cancer

By JADPRO Staff

Visit https://meetinglibrary.asco.org/record/195927 to read the full abstract and view author disclosures.

Liposomal irinotecan (Onivyde) in combination with 5-FU and leucovorin significantly improved progression-free survival and overall survival for patients with advanced biliary tract cancer who have progressed on first-line gemcitabine and cisplatin.

The NIFTY study is a multicenter, randomized, open-label phase IIb study that randomized patients with disease progression on first-line gemcitabine and cisplatin 1:1 to liposomal irinotecan (70 mg/m^2, 90 minutes) plus 5-FU (2,400 mg/m^2, 46 hours)/leucovorin (400 mg/m^2, 30 min), every 2 weeks or 5-FU/leucovorin, every 2 weeks until disease progression per investigator review or intolerable toxicities. The primary endpoint was progression-free survival (PFS) per blinded independent central review (BICR). Secondary endpoints were PFS per investigator review, overall survival (OS), overall response rates (ORR), and safety.

174 patients were included, and were age > 19 years, ECOG PS 0/1, had histologically confirmed metastatic biliary tract cancer, and had disease progression on first-line gemcitabine and cisplatin. The median PFS per BICR in the liposomal irinotecan plus 5-FU/leucovorin group and 5-FU/leucovorin group was 7.1 months and 1.4 months, respectively (HR, 0.56, P = .0019); median PFS per investigator review was 3.9 months and 1.6 months, respectively (HR, 0.48, P < .0001). Median OS was 8.6 months and 5.5 months, respectively (HR, 0.68, P = .0349). ORR was 14.8% and 5.8% per BICR, respectively (P = .0684) and 19.3% and 2.3% per investigator review, respectively (P = .0002).

"[Liposomal irinotecan] plus 5-FU/LV should be considered as one of the standard treatments for patients with advanced biliary tract cancer [whose disease has progressed] on gemcitabine/cisplatin," Changhoon Yoo, MD, PhD, said in a presentation of the data.

Grade 3 or greater adverse events were reported in 68 patients (77.3%) of liposomal irino-

tecan plus 5-FU/leucovorin group and 27 patients (31.4%) in the 5-FU/leucovorin group. Most common grade 3 or greater adverse events in the liposomal irinotecan plus 5-FU/leucovorin group were neutropenia (n = 21, 23.9%), fatigue (7, 8.0%), and nausea (5, 5.7%).

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Biliary tract cancer includes cancers of the gallbladder and bile ducts (cholangiocarcinoma). These cancers are relatively rare and tend to be diagnosed at an advanced stage. Patients diagnosed with advanced biliary tract cancer often have poor survival, and the optimal approach to treatment remains uncertain. Patients may be treated with chemotherapy, enrolled in a clinical trial, or given best supportive care. In this study, patients with progression of disease after first-line chemotherapy of gemcitabine and cisplatin were enrolled and received either liposomal irinotecan and 5-FU and leucovorin (5-FU/LV) or were treated with 5-FU/LV alone.

According to data from the phase II NIFTY trial, liposomal irinotecan in combination with 5-FU/LV delayed cancer progression and prolonged survival for patients with metastatic biliary tract cancer whose disease had progressed following first-line gemcitabine/cisplatin. Despite the fact that this study was conducted in Korea only, it was appropriately powered to compare the two treatment groups and was designed for meticulous tumor response evaluation. The combination should be considered as a standard of care for second-line therapy in patients with metastatic biliary tract cancers.

Disclosure: Dr. Grenon has no conflicts of interest to disclose.