2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Gastrointestinal Cancer

Using coverage from *The ASCO Post* of the ASCO Annual Meeting, **Carolyn Grande, CRNP, AOCNP®,** of the University of Pennsylvania Health System evaluates study findings in gastrointestinal cancer and discusses what advanced practitioners should take away from these results.

Abstract 3501

IDEA Collaboration Turns to Duration of Adjuvant Treatment in Stage II Colon Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/171153/abstract to read the full abstract and view author disclosures.

The findings of the landmark IDEA trial in stage III colorectal cancer, presented at the 2017 ASCO Annual Meeting and subsequently published in *The New England Journal of Medicine* (Grothey et al., 2018), were upheld by a subsequent analysis by the same group, the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration—this time, in the high-risk stage II subset (Iveson et al., 2019). The results of this recent pooled analysis of the four IDEA studies in patients with stage II disease were presented at the 2019 ASCO Annual Meeting.

In patients with high-risk stage II colorectal cancer, 3 months of adjuvant capecitabine plus oxaliplatin (CAPOX) were as beneficial as 6 months, with considerably less toxicity. By contrast, 6 months of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) yielded better efficacy than 3 months of FOLFOX, albeit with significantly more toxicity than the shorter duration of treatment, according to Timothy Iveson, MD, of the University Hospital Southampton (England) NHS Foundation Trust.

"We now have good data on both the efficacy and also toxicity of the regimens according to the duration of treatment," said Dr. Iveson. "That should allow us to recommend both the chemotherapy regimen and the duration of treatment to our patients."

The results of the primary IDEA analysis triggered a more nuanced algorithm for treating stage III disease. Although the study did not confirm the noninferiority of 3 vs 6 months of adjuvant FOLFOX or CAPOX in the overall population, it did find that 3 months of CAPOX, especially in lower-risk patients, was sufficient.

Turning to Patients With Stage II Disease

Questions were then raised as to whether the results could be extrapolated to stage II disease. In the IDEA Collaboration's recent prospective, preplanned analysis, the investigators zeroed in on 3,273 patients with high-risk stage II disease

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drawn from the SCOT, TOSCA, ACHIEVE-2, and HORG trials, of whom 2,019 received CAPOX and 1,254 received FOLFOX. "High risk" was defined as one or more T4 tumors, inadequate nodal harvest, poorly differentiated tumors, obstruction, perforation, or vascular/perineural/lymphatic invasion.

Clinically meaningful inferiority was a hazard ratio of at least 1.2, corresponding to a 3.1% reduction in 5-year disease-free survival with 3 months vs 6 months of treatment. This was different from the upper limit (1.12) in patients with stage III disease. Clinically meaningful inferiority was a hazard ratio of at least 1.12, corresponding to a 3.1% reduction in 5-year disease-free survival with 3 months vs 6 months of treatment. This was different from the upper limit (1.12) in patients with stage III disease.

Regimens Differed

The overall analysis could not demonstrate the noninferiority of 3 vs 6 months of treatment in terms of efficacy—similar to that of the primary IDEA analysis. By regimen, however, CAPOX proved noninferior to FOLFOX, with 5-year disease-free survival rates of 81.7% for 3 months of treatment and 82.0% for 6 months. By contrast, with FOLFOX, these rates were 79.2% vs 86.5%—an absolute 7.3% difference in favor of a longer treatment duration.

"These data strongly suggest noninferiority of 3 months of CAPOX vs 6 months but equally suggest inferiority of 3 months of FOLFOX vs 6 months," Dr. Iveson said.

The rates of grade ≥ 2 neuropathy were 36% for 6 months of treatment and 13% for 3 months of treatment; for grade 3 or 4 neuropathy, these rates were 8% and 1%, respectively ($P < .0001$). Six months of FOLFOX was associated with a 51% rate of grade 3 to 5 adverse events.

References

Grothey, A., Sobrero, A. F., Shields, A. F., Yoshino, T., Paul, J., Taieb, J.,...Iveson, T. (2018). Duration of adjuvant chemotherapy for stage III colon cancer. *New England Journal of Medicine, 378*, 1177–1188. https://doi.org/10.1056/NEJMoa1713709

Iveson, T., Sobrero, A. F., Yoshino, T., Sougklakos, I., Ou, F.-S., Meyeres, J. P.,...Paul, J. (2019). Prospective pooled analysis of four randomized trials investigating duration of adjuvant oxaliplatin-based therapy (3 vs 6 months) for patients with high-risk stage II colorectal cancer [Abstract 3501]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.3501

The Advanced Practitioner Perspective

Carolyn Grande, CRNP, AOCNP®
University of Pennsylvania Health System

For decades, adjuvant treatment for stage II colorectal cancer has been controversial. The focus on decision-making has been through stratifying stage II patients into low- and high-risk groups. The low-risk patients are in the stage IIA category, while those considered high risk are stage IIB or IIC, portending poor prognostic features.

Considerations for Advanced Practitioners

Advanced practitioners are on the front lines of educating, assessing, and managing disease- and treatment-related symptomatology. The neuropathic toxicities of oxaliplatin are well documented. Unfortunately, prophylactic and on-treatment interventions have fallen short. The reality is that the majority of patients cannot withstand full-dose oxaliplatin for 6 months, related in part to grade and debilitation from their neuropathy. This side effect has not only impacted quality of life during and after treatment, but also influenced dose reductions of oxaliplatin with a perception of treatment outcome impact.

The results of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration enhance communication points between advanced practitioners and patients as well as caregivers when making treatment decisions for adjuvant stage II colorectal cancer. In 2019, due to multifaceted progress through research, the conversation has expanded not only based on factors influencing low- vs. high-risk patients, but also in terms of the optimal treatment combination and duration of therapy. For stage II colorectal cancer patients, this broadening discussion can guide them to the least toxic and most efficacious path when making decisions.

Disclosure: Ms. Grande has served as a consultant for AstraZeneca and Pfizer.

Abstract 3507

Targeting FOLFOXIRI/Bevacizumab to a Metastatic Colorectal Cancer Subset

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/171164/abstract to read the full abstract and view author disclosures.

In a population of patients with metastatic colorectal cancer deemed to be at high risk by the presence of circulating tumor cells (CTCs), first-line treatment with FOLFOXIRI (fluorouracil [5-FU], leucovorin, irinotecan, oxaliplatin) plus bevacizumab improved progression-free survival by about 3 months, compared with modified FOLFOX plus bevacizumab, although patients experienced more side effects (Sastre et al., 2019).

"This study suggests that FOLFOXIRI plus bevacizumab could be considered an adequate treatment option for patients with metastatic colorectal cancer and three or more CTCs," said Javier Sastre, MD, PhD, of Hospital Clínico San Carlos, Spain, reporting the results of the phase III VISNU-1 trial at the 2019 ASCO Annual Meeting in Chicago.

VISNU-1 is the first study in metastatic colorectal cancer performed in a population selected by baseline CTC count. Although FOLFOXIRI plus bevacizumab has been shown to produce better outcomes than FOLFOX (5-FU, leucovorin, oxaliplatin) plus bevacizumab, the regimen is not routinely recommended because of toxicity. The investigators hoped to optimize the patient population who might benefit most from the more intensive regimen.

Key Points

- The phase III VISNU-1 trial evaluated the first-line treatment of patients with metastatic colorectal cancer deemed at high risk by the presence of circulating tumor cells.
- Patients were randomly assigned to FOLFOXIRI or FOLFOX, both with bevacizumab.
- FOLFOXIRI/bevacizumab improved progression-free survival by about 3 months (hazard ratio = 0.64; P = .0006).
- The regimen was associated with significantly more grade ≥ 3 diarrhea.

"We considered that it would be of interest to explore the role of this combination in a subgroup of patients with poor prognostic factors," Dr. Sastre said. Higher CTC levels have been shown to be a poor prognostic factor for survival. VISNU-1 considered CTC counts ≥ 3 as the cutoff for high risk.

VISNU-1 Details and Results

VISNU-1 is an open, multicenter, randomized phase III trial that enrolled 349 patients up to 70 years of age with a good performance status. Patients with at least 3 CTCs were randomly assigned to modified FOLFOX or FOLFOXIRI, both with bevacizumab, until disease progression. After accrual of 63 patients, the protocol was changed to recommend the use of granulocyte colony-stimulating factor in the FOLFOXIRI arm due to a high rate of neutropenia.

The median progression-free survival was significantly longer with FOLFOXIRI/bevacizumab: 12.4 months vs 9.3 months with FOLFOX/bevacizumab (hazard ratio [HR] = 0.64; P = .0006). Its superiority was shown in virtually all subgroups except for patients with *P13K* mutations. The benefit appeared to be greatest for patients with left-sided primary tumors and wild-type *RAS/BRAF* tumors, Dr. Sastre reported.

In the multivariate analysis, treatment with FOLFOXIRI/bevacizumab, *BRAF* and *RAS* wild-type status, CTC counts > 20, and an Eastern Cooperative Oncology Group performance status of 1 were independent predictors for progression-free survival.

At a median follow-up of 50.7 months, the overall survival analysis is not mature, but survival was also numerically prolonged with FOLFOXIRI/bevacizumab (22.3 months) vs FOLFOX/bevacizumab (17.6 months; HR = 0.84; P = .1407).

There was no statistically significant difference between the two arms in terms of objective response rate or duration of response in the intent-to-treat analysis. However, in patients evaluated for response, 69% responded to FOLFOXIRI/bevacizumab, compared with 57% who responded to FOLFOX/bevacizumab (HR = 0.61; P = .0381), with this arm showing a longer duration of response (9.9 vs 8.1 months; HR = 1.786; P = .0010). The rate of R0 resections was similar, around 93%,

as was the total use of subsequent lines of treatment, though there were some differences in the use of specific drugs.

As expected, FOLFOXIRI/bevacizumab was associated with more grade ≥ 3 toxicities, 78% vs 67% (P = .022), especially asthenia (16% vs 7%; P = .007), diarrhea (21% vs 6%; P < .001), and febrile neutropenia (9% vs 2%; P = .004). ●

Reference

Sastre, J., Vieitez, J. M., Gomez-España, M. A., Calle, S. G., Salvia, A. S., Suárez, B. G.,...Díaz-Rubio, E. (2019). Randomized phase III study comparing FOLFOX + bevacizumab versus FOLFOXIRI + bevacizumab as first line treatment in patients with metastatic colorectal cancer with ≥ 3 baseline circulating tumor cells [Abstract 3507]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.3507

The Advanced Practitioner Perspective

Carolyn Grande, CRNP, AOCNP®
University of Pennsylvania Health System

Patients diagnosed with stage IV colorectal cancer (CRC) have a wide array of systemic treatment options with diverse mechanisms of action afforded to them. Several of these systemic options have been studied to determine which subset of patients will derive any or the most benefit. In some instances, this was done retrospectively.

The combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) is a challenging regimen wrought with an extensive toxicity profile, including but not limited to neutropenia, peripheral neuropathy, and diarrhea. The degree and severity of these toxicities alone and combined limit the pool of patients who could be considered to receive or tolerate it for the prescribed duration. Hence, identifying those who may derive the most benefit can narrow the at-risk pool.

VISNU-1

The VISNU-1 trial uniquely selected a subset of metastatic CRC patients considered high risk by the presence of circulating tumor cells (CTC) to ascertain their response to FOLFOXIRI or modified fluorouracil, leucovorin, and oxaliplatin (FOLFOX), both with bevacizumab. The prospective approach, combined with further extrapolation based on diagnostic features and genetic mutation to elucidate the margin of patients to receive greatest benefit, was optimized. While the results are meaningful and applicable, what is more intriguing are the precision and predictive elements incorporated. It is not particularly surprising that the FOLFOXIRI + bevacizumab arm showed a significantly longer progression-free survival of 12.4 months vs. 9.3 months in the modified FOLFOX + bevacizumab arm. In this instance, "more is better," based on the numbers. What stands out is the further investigation of patient subgroups likely to benefit from the more toxic FOLFOXIRI regimen, identifying that the benefit appeared greater in left-sided primary tumors and wild-type *RAS/BRAF* tumors.

As the landscape for cancer therapies continues to expand and diversify through research, the cost of therapy is consistently being scrutinized. The debates continue on how to quantify the worth of individual longevity in dollars and cents. Examining who will benefit most from the outset may assist in honing in on that value.

Disclosure: Ms. Grande has served as a consultant for AstraZeneca and Pfizer.

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Abstract 3504

Study Supports Neoadjuvant Chemotherapy in Operable Colon Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/171160/abstract to read the full abstract and view author disclosures.

For patients with operable colon cancer, neoadjuvant chemotherapy resulted in numerous benefits in the FOxTROT trial but did not reach target significance for the primary endpoint. The study was presented at the 2019 ASCO Annual Meeting by Matthew T. Seymour, MD, of the University of Leeds School of Medicine and the National Institute for Health Research Clinical Research Network (Seymour & Morton, 2019).

"There was a trend toward an improved 2-year relapse rate with neoadjuvant chemotherapy that reached the target hazard ratio (0.75) but not the predetermined significance (P = .08)," Dr. Seymour said, explaining that the control arm achieved better outcomes than expected. "Moving 6 weeks of chemotherapy ahead of surgery, without major additions to the cost or patient burden of treatment, was safe, with less major postoperative morbidity. It significantly downstaged tumors and reduced incomplete resections. And it trended toward improved 2-year cancer control...We believe that neoadjuvant chemotherapy can be considered a new therapeutic option for locally advanced operable colon cancer."

Key Points

- The FOxTROT trial randomly assigned 1,052 patients with resectable colon cancer to neoadjuvant chemotherapy or surgery first, followed by chemotherapy.
- The neoadjuvant approach reduced the risk of relapse at 2 years by 25%, but possibly due to a good-performing control arm, it missed statistical significance.
- Neoadjuvant chemotherapy resulted in greater receipt of chemotherapy, more downstaging of tumors, fewer incomplete resections, greater ability to receive chemotherapy as planned, and fewer surgical complications than upfront surgery.
- Neoadjuvant chemotherapy may prove to be an option in operable colon cancer.

FOxTROT Details

The FOxTROT trial randomly assigned 1,052 patients with operable, nonobstructed radiologically staged T3 or T4 (N0–2, M0) colon cancer to neoadjuvant chemotherapy or surgery, followed by postoperative chemotherapy, as follows:

- Neoadjuvant arm: 6 weeks of modified FOLFOX (fluorouracil, leucovorin, oxaliplatin; 72%) or capecitabine/oxalipatin (XELOX; 28%) followed by surgery and 18 weeks of oxaliplatin/fluoropyrimidine. Patients with KRAS wild-type tumors could opt to be randomly assigned to panitumumab (or not) during preoperative treatment.
- Surgery arm: Surgery followed by 24 weeks of FOLFOX (94%) or 12 weeks of the same (6%)
- Patients with KRAS wild-type tumors allocated to the neoadjuvant arm could opt to be randomly assigned 1:1 to panitumumab (or not) during the neoadjuvant chemotherapy phase.
- Older or low-risk patients had the option of 12 weeks rather than 24 weeks of chemotherapy (6% did so), and patients had the option to choose XELOX rather than FOLFOX (28% did so).

About 98% of patients had attempted curative resection, with no difference between the arms. However, there was a striking difference between the percentage of patients who did not receive chemotherapy: 4% in the neoadjuvant arm vs 27% in the surgery arm (P < .0001).

Efficacy Analyses

At 2 years, in the intent-to-treat analysis, the 2-year rate of failure (defined as relapse or persistent disease) was 13.6% in the novel arm and 17.2% in the control arm. This result translated to a hazard ratio of 0.75 (95% confidence interval = 0.55–1.04; P = .08).

A sensitivity analysis concluded that adding panitumumab to neoadjuvant chemotherapy did not increase the rate of tumor regression. "The overall effect seen in the primary analysis is not explained by the use of panitumumab," Dr. Seymour said. The investigators are undertaking a full analysis of an enriched biomarker population.

There were 173 patients with tumors demonstrating mismatch repair (MMR) deficiency. In these individuals, neoadjuvant chemotherapy failed to achieve the same effects as seen in MMR-proficient tumors. In MMR-deficient patients, the rate of zero tumor regression was 73.6%, compared with 26.6% in the MMR-proficient patients.

Dr. Seymour cautioned that this was a nonprespecified subgroup analysis that needs validation. However, he said, it suggests the neoadjuvant approach may be ineffective in MMR-deficient patients.

Reference

Seymour, M. T., & Morton, D. (2019). FOxTROT: An international randomized controlled trial in 1,052 patients evaluating neoadjuvant chemotherapy for colon cancer [Abstract 3504]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.3504

The Advanced Practitioner Perspective

Carolyn Grande, CRNP, AOCNP®
University of Pennsylvania Health System

Neoadjuvant therapy (NAT) is an approach utilized in a variety of solid tumors with the intent to enhance surgical resection and improve outcomes. For patients with colorectal cancer, this approach has typically been limited to those with clinical T4b tumors, locally unresectable or medically inoperable tumors, or those with suspected/proven synchronous metastatic adenocarcinoma believed to be convertible for resection.

FOxTROT Trial

The FOxTROT trial failed to reach statistical significance in risk of relapse at 2 years. While this was not reached, the outcomes of this trial are revealing in terms of what has potential feasibility in improving outcomes in this select population.

Histologic regression was seen in 59% of patients after the addition of NAT and a decrease in incomplete surgical resections to 5% in the NAT arm vs. 10% in the control arm. Additionally, a decrease in postoperative complications requiring longer hospital stays was seen—12% in the NAT arm vs. 14% in the control arm. Further, anastomotic leaks were seen 50% less frequently in the NAT group, at 3% vs. 6% in the control group. Interestingly, for patients with mismatch repair (MMR)–deficient tumors who received NAT, the rate of zero progression was significant at 73.6% compared to those with MMR-proficient tumors. Also of interest, in those patients with *KRAS* wild-type tumors who received panitumumab with NAT, there was no increased rate of tumor regression.

The findings of this trial add to the potential armamentarium of treatment options for this traditionally resectable group from the outset. The inability of the FOxTROT results to statistically prove a decrease in 2-year risk of relapse does not dismiss its valuable contribution to a potential new treatment approach. It further elucidates particular subgroups of patients who may be more appropriate for NAT based on MMR status. While this is not practice changing, it certainly has merit for further study.

Disclosure: Ms. Grande has served as a consultant for AstraZeneca and Pfizer.

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Abstract LBA4007

KEYNOTE-062: Pembrolizumab Is a New First-Line Option in Gastric/Gastroesophageal Junction Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/173187/abstract to read the full abstract and view author disclosures.

KEYNOTE-062, a study of first-line treatment in patients with advanced gastric or gastroesophageal junction adenocarcinoma, found pembrolizumab to be noninferior to chemotherapy and perhaps better than chemotherapy in a subgroup of patients. The results were reported at the 2019 ASCO Annual Meeting by Josep Tabernero, MD, PhD, Head of Medical Oncology at the Institute of Oncology at Vall d'Hebron University Hospital, Barcelona (Tabernero et al., 2019).

All patients in the study had a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1. For this population, pembrolizumab outcomes fell within the noninferiority boundary. The greatest benefit, however, was seen in patients with high expression, ie, CPS ≥ 10. In this group, 2-year overall survival was 39% vs 22% for standard chemotherapy, and median survival was 17.4 months vs 10.8 months. Because of the study's hierarchical design, this subgroup was not analyzed for statistical significance.

Survival Improvement in PD-L1 High-Expressers

"We saw a clinically meaningful improvement in overall survival with pembrolizumab vs chemotherapy in the PD-L1 CPS ≥ 10 group. Technically speaking, we could not perform an analysis of statistical significance in this group, but the numbers suggest that pembrolizumab is superior," Dr. Tabernero said.

Similarly, in advanced esophageal carcinoma, KEYNOTE-181 showed that pembrolizumab improved overall survival in patients with a CPS ≥ 10 (hazard ratio [HR] = 0.69; P = .0074), but not in the overall patient population (Kojima et al., 2019).

The current guidelines for gastric or gastroesophageal junction cancer are to treat with a platinum plus a fluoropyrimidine in the first-line setting, and with docetaxel, paclitaxel, irinotecan, and ramucirumab, with or without paclitaxel, in the second-line setting. Pembrolizumab is approved for patients with a CPS ≥ 1 after disease progression on at least two lines of chemotherapy.

'May Well Be Better' Than Chemotherapy

At a press briefing, Richard L. Schilsky, MD, FACP, FSCT, FASCO, Senior Vice President and Chief Medical Officer of ASCO, said that in his experience as a gastrointestinal oncologist, gastric or gastroesophageal junction cancer is "a tough disease to treat." Patients are often frail, elderly, and malnourished—and therefore usually not good candidates for standard cytotoxic chemotherapy.

"This study, demonstrating the potential of immunotherapy to substantially improve outcomes, is important," he told journalists. "The findings fell within the noninferiority boundary, so it's reasonable to conclude that pembrolizumab is not inferior to chemotherapy. In addition, it has a substantially improved safety profile. It's pretty clear to be me that this would be a preferred treatment for this population."

"Also, though not meeting the definition of statistical significance, it's quite clear that pembrolizumab is clinically superior to chemotherapy in the high–biomarker-positive population," Dr. Schilsky continued. "What I take from this study is that for patients with advanced gastric or gastroesophageal junction cancer, pembrolizumab should, in many cases, replace chemotherapy as first-line treatment. It's certainly not worse and may well be better."

KEYNOTE-062 Details

KEYNOTE-062 was a phase III randomized clinical trial of 763 patients with advanced gastric or gastroesophageal junction cancer who were randomly assigned to one of three treatment arms: pembrolizumab at 200 mg every 3 weeks for up to 2 years, pembrolizumab plus chemotherapy (cisplatin and fluorouracil or capecitabine), or placebo plus chemotherapy. All patients had PD-L1 CPS ≥ 1, and 37% had a score ≥ 10.

The study had a complex hierarchic statistical design with four comparisons. The initial hypoth-

eses were tested first, and the remaining hypotheses were tested only after positive results were achieved with the first ones. The initial comparisons and endpoints were:

- Pembrolizumab vs chemotherapy in the CPS ≥ 1 cohort: overall survival, noninferiority
- Pembrolizumab plus chemotherapy vs chemotherapy in the CPS ≥ 10 cohort: overall survival, superiority
- Pembrolizumab plus chemotherapy vs chemotherapy in the CPS ≥ 1 cohort: overall survival, superiority
- Pembrolizumab plus chemotherapy vs chemotherapy in the CPS ≥ 1 cohort: progression-free survival, superiority.

Overall survival differences for pembrolizumab vs chemotherapy in the CPS ≥ 10 cohort could only be determined if superiority was shown for the combination in the CPS ≥ 10 group, and it was not.

Study Outcomes

Compared to chemotherapy, single-agent pembrolizumab was noninferior in the intent-to-treat population and produced a "favorable" effect in the CPS ≥ 10 group (Table 1 online).

Combining pembrolizumab with chemotherapy did not improve outcomes compared with chemotherapy alone, though the trend was favorable. The hazard ratio was 0.85 both for patients with a CPS ≥ 1 and for those with a CPS ≥ 10. The objective response rate was higher for pembrolizumab plus chemotherapy than with chemotherapy alone, but chemotherapy produced more responses than did single-agent pembrolizumab.

Serious adverse events were lowest among patients receiving pembrolizumab alone. "Patients who received pembrolizumab had fewer adverse events and grade 3 to 5 events, and fewer discontinued therapy due to adverse events," Dr. Tabernero reported.

Grade ≥ 3 events occurred in 17% of the pembrolizumab group, 71% of the combination group, and 68% of the chemotherapy group. The safety profile of pembrolizumab was consistent with previous reports.

"This is the first presentation of the results, but other ongoing analyses are being done, especially in the field of biomarkers," Dr. Tabernero added. "Using other biomarkers, perhaps tumor mutational burden, and other CPS cutoffs, we may be able to define other populations who benefit from pembrolizumab."

References

Kojima, T., Muro, K, Francois, E., Hsu, C.-H., Moriwaki, T., Kim, S.-B.,...Metges, J.-P. (2019). Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: The phase 3 KEYNOTE-181 study [Abstract 2]. *Journal of Clinical Oncology, 37*(4_suppl). https://doi.org/10.1200/JCO.2019.37.4_suppl.2

Tabernero, J., Van Cutsem, E., Bang, Y.-J., Fuchs, C. S., Wyrwicz, L., Lee, K. W.,...Shitara, K. (2019). Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction adenocarcinoma: The phase III KEYNOTE-062 study [Abstract LBA4007]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(18_suppl). https://doi.org/10.1200/JCO.2019.37.18_suppl.LBA4007

The Advanced Practitioner Perspective

Carolyn Grande, CRNP, AOCNP®
University of Pennsylvania Health System

KEYNOTE-062 was a first-line phase III trial in patients with advanced gastric or gastroesophageal junction (GEJ) cancer randomly assigned to one of three treatment arms: pembrolizumab at 200 mg every 3 weeks for up to 2 years, pembrolizumab plus chemotherapy (cisplatin and fluorouracil or capecitabine), or placebo plus chemotherapy. All patients had programmed cell death ligand 1 combined positive score (CPS) ≥ 1, and 37% had a score ≥ 10.

The hierarchical design of the study prevented subgroup analysis for statistical significance. While the study showed no benefit in overall survival or progression-free survival, it did clearly show that pembrolizumab was noninferior in those patients with a CPS > 1 and generating a favorable response in those patients with a CPS > 10.

Sixty percent of people diagnosed with advanced gastric or GEJ are older than 64, with the average age being 68. Due to the vague symptoms experienced pre-diagnosis, most diagnoses are made when the cancer is more advanced. At this point, patients present fatigued and frail with nutritional compromise. This clinical presentation can make the toxicity challenges of currently approved first-line

platinum-based cytotoxic chemotherapy difficult to tolerate.

In KEYNOTE-062, patients who received pembrolizumab alone had fewer adverse events and grade 3 to 5 events. To quantify, grade ≥ 3 events occurred in 17% of the pembrolizumab group, 71% of the combination group, and 68% of the chemotherapy group. This study showed that pembrolizumab overall is noninferior. This does not make it better than chemotherapy, but also not worse and with a more tolerable side effect profile. The favorable benefit realized in patients with a CPS ≥ 10 is encouraging and shows enhanced promise for this subgroup of patients.

Disclosure: Ms. Grande has no conflicts of interest to disclose.