

Gastrointestinal Cancers: ASCO₂₀ Virtual Scientific Program Highlights for the Advanced Practitioner



Using coverage from *The ASCO Post*, **Nina N. Grenon, DNP, AGC-NP-BC, AOCN®**, of Dana-Farber Cancer Institute, evaluates findings from two phase III trials, reviews takeaways from the final results of the IDEA study, and discusses what was learned about PARP inhibitor therapy from the TAPUR basket trial.

Abstract LBA4

Rates of Progression-Free Survival in MSI-H/dMMR Metastatic Colorectal Cancer Doubled by Pembrolizumab

By *The ASCO Post Staff*

Visit <https://meetinglibrary.asco.org/record/186928/abstract> to read the full abstract and view author disclosures.

Upfront treatment with immunotherapy not only improved results in a subset of patients with metastatic colorectal cancer, it doubled the rates of median progression-free survival. These findings—the first of their kind—arose from the interim analysis of the randomized open-label phase III KEYNOTE-177 trial, which compared the PD-1 antibody pembrolizumab with standard-of-care chemotherapy.

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In KEYNOTE-177, patients receiving pembrolizumab had a median progression-free survival of 16.5 months vs 8.2 months with chemotherapy (hazard ratio [HR] = 0.60; $P = .0002$). The study, therefore, met one of its two co-primary endpoints, as reported at the Plenary Session of the ASCO₂₀ Virtual Scientific Program by Thierry André, MD, of Sorbonne University and Saint-Antoine Hospital, Paris.¹

“Pembrolizumab provided a clinically meaningful and statistically significant improvement in progression-free survival vs chemotherapy in patients with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) tumors, with fewer treatment-related adverse events, and it should be considered a new standard of care as first-line therapy in these patients,” Dr. André said.

MSI-H/dMMR tumors constitute about 5% of metastatic colorectal cancers and have proved responsive to PD-1 inhibitors in later treatment lines. Pembrolizumab was approved in previously treated MSI-H/dMMR malignancies regardless of the tumor site of origin.

KEYNOTE-177 Details

The study enrolled 307 previously untreated patients with MSI-H/dMMR metastatic colorectal cancer, randomly assigning them to first-line pembrolizumab at 200 mg every 3 weeks for up to 2 years or investigator’s choice of modified FOLFOX6 (fluorouracil [5-FU], leucovorin, and oxaliplatin) or FOLFIRI (5-FU, leucovorin, and irinotecan) every 2 weeks, with or without bevacizumab or cetux-

imab. Treatment was continued until progressive disease, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35 cycles of pembrolizumab. Patients receiving chemotherapy could cross over to pembrolizumab for up to 35 cycles after confirmation of progressive disease.

The study had two co-primary endpoints: progression-free survival by Response Evaluation Criteria in Solid Tumors (RECIST) and central review, and overall survival. Objective response by central review was a key secondary endpoint. “The study was considered successful if pembrolizumab was superior to chemotherapy for either primary endpoint,” Dr. André said.

The data cutoff date for this interim analysis was February 19, 2020. The study is ongoing, and overall survival data will be presented later. The median study follow-up (time from randomization to data cutoff) was 32.4 months (range = 24.0–48.3 months).

Notable Difference in Progression-Free Survival

Pembrolizumab proved to be superior to chemotherapy by demonstrating a 40% reduction in the risk of disease progression ($P = .0002$). Progression-free survival rates were 55% with pembrolizumab vs 37% with chemotherapy at 12 months and 48% vs 19%, respectively, at 24 months, Dr. André reported.

The confirmed objective response rates were 43.8% and 33.1%, respectively, with the median

duration of response not reached with pembrolizumab (2.3–41.4 months) vs 10.6 months for chemotherapy (2.8–37.5 months). Complete responses were achieved in 11.1% and 3.9%, respectively, and partial responses, in 32.7% vs 29.2%. Best response was stable disease in 30.9% and 42.2% and progressive disease in 29.4% and 12.3%, respectively. At 24 months and beyond, 83% of pembrolizumab responders were still responding, compared with just 35% of the chemotherapy arm.

The ASCO Post asked Dr. André about the 30% of the pembrolizumab arm with progressive disease as the best response. He speculated that the principal cause was primary resistance to pembrolizumab. Alternatively, he suggested, “RECIST version 1.1 criteria may not have been the optimal measure of response, with some pseudoprogression (counting as an event in the progression-free survival curve) and some rare misdiagnosis of MSI-H/dMMR (ie, patients may be proficient).”

Grade 3 to 5 treatment-related adverse events were observed in 22% of the pembrolizumab arm and 66% of the chemotherapy arm. One patient in the chemotherapy arm died due to a treatment-related adverse event. ●

Reference

1. André T, Shiu K-K, Kim TW, et al: Pembrolizumab vs chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 study. ASCO20 Virtual Scientific Program. Abstract LBA4.

The Advanced Practitioner Perspective

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Microsatellite instability (MSI) is present in approximately 15% of all colorectal cancers (CRC): 3% of these are associated with Lynch syndrome, and the remainder are sporadic. Colorectal tumors with MSI have distinctive features; they tend to be located in the proximal colon, have lymphocytic infiltrate, and have a poorly differentiated, mucinous or signet ring appearance. These CRC tumors are known to have a slightly better prognosis compared to CRC tumors without MSI and do not have the same response to chemotherapy. The presence of MSI in colorectal tumors has in-

creased awareness of the diversity of colorectal cancers and implications for specialized management of patients.

The results of KEYNOTE-177 showed improvement in progression-free survival in patients with MSI-H or mismatch repair deficient (dMMR) CRC receiving pembrolizumab when compared to patients receiving chemotherapy. Today, patients with MSI-H CRC can receive immunotherapy as first-line therapy for metastatic disease. Therefore, patients do not experience the same side effects and toxicity related to chemotherapy. The results from this study have changed standards of care and practice in patients with MSI-H, dMMR colorectal cancer. Also, further exploration of

combination strategies with chemotherapy will hopefully improve efficacy, response, and overall survival.

Treatment with checkpoint inhibitors can cause mild to severe immune-related adverse events. The mechanism of toxicity may be related to a possible release of increased levels of inflammatory cytokines between tumor antigen and healthy tissues. Several organs can

be affected, most commonly gastrointestinal and dermatologic. However, less common reactions can include but are not limited to endocrine, pulmonary, and rarely cardiac and renal toxicity. We are still learning about adverse events as well as potential long-term effects on patients' quality of life.

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

Abstract 4001

Scott Kopetz, MD, PhD, on Colorectal Cancer: Encorafenib Plus Cetuximab With or Without Binimetinib

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/185472/abstract> to read the full abstract and view author disclosures.

Scott Kopetz, MD, PhD, of The University of Texas MD Anderson Cancer Center, discusses phase III results of the BEACON CRC study, which confirmed that, compared with standard chemotherapy, encorafenib plus cetuximab with or without binimetinib improved overall survival and objective response rate in previously treated patients with *BRAF* V600E-mutated metastatic colorectal cancer (Abstract 4001). Below is a transcript of his commentary.

Commentary by Scott Kopetz, MD, PhD

BEACON CRC was a randomized, phase III study looking at patients with *BRAF* V600E metastatic colorectal cancer who were previously treated with 1 or 2 prior lines of therapy. In this study, patients were randomized between a control arm of FOLFIRI and cetuximab or two intervention arms of the *BRAF* inhibitor encorafenib and EGFR inhibitor cetuximab or the triplet of encorafenib, the MEK inhibitor binimetinib, and cetuximab.

The primary endpoint of the study was the *BRAF*, MEK, and EGFR inhibitors compared with the control arm with key secondary of the encorafenib and cetuximab control arm. The premise of this is based on the acknowledgment

that the inhibition of *BRAF* causes compensatory upregulation and activation through EGFR and that the combination of that, including MAP kinase pathway blockade with MEK inhibitor, can improve outcomes. This was an updated overall survival analysis with a total of over 600 patients across multiple international studies.

The updated survival demonstrated a median overall survival of the triplet of 9.3 months compared to the control arm of 5.9 months (hazard ratio: 0.60). Conversely, the doublet arm (encorafenib and cetuximab vs. control) had a numerically identical 9.3 months overall survival compared with the control arm of 5.9 months (hazard ratio: 0.61). This update was different compared to the initial primary endpoint. So, with this mature survival update, what we found was an improvement in the overall survival for the doublet. Progression-free survival in both arms was similar as previously reported: 4.5 months for the triplet, 4.3 for the doublet, and 1.5 for the control arm. The overall response rates, now looking at the totality of all enrolled patients, were 27% for the triplet, 20% for *BRAF* and EGFR alone, and 2% for the control. The safety data here was consistent with the prior safety profile and had a low overall rate of discontinuation due to adverse events.

In conclusion, encorafenib in combination with cetuximab is now FDA approved for use in patients with previously treated *BRAF* V600E metastatic colorectal cancer. It is considered a new standard of care for this population. The addition of a MEK inhibitor, while it improved response rate, did not improve overall survival. As such, building on the doublet of encorafenib and cetuximab with future therapies is warranted and under exploration. ●

The Advanced Practitioner Perspective
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BRAF mutations in metastatic colorectal cancer (mCRC) are present in approximately 10% of colorectal cancers. *BRAF* V600E mutations confer a poor prognosis, resulting in a nearly 2-fold increase in mortality relative to wild-type *BRAF* in the metastatic setting. The *BRAF* V600E mutation in colorectal cancer is associated with a right-sided primary site, advanced age, female sex, high tumor grade, and precursor sessile serrated adenomas.

BRAF V600E mutations are associated with resistance to *EGFR*-targeted agents, even in the presence of wild-type *RAS*. Monotherapy with *BRAF* inhibitors alone has been proven to lack efficacy. Resistance to *EGFR*-targeted agents in patients harboring mutations in *BRAF* V600E may be overcome with *BRAF* inhibitors in combination with an *EGFR* inhibitor.

Several clinical trials have evaluated *BRAF*, *EGFR* inhibition, and *MEK* inhibitors to achieve greater *MAPK* suppression and improved efficacy patients with *BRAF* V600E colorectal cancer. Findings from these studies have highlighted the *MAPK* pathway as a critical target in *BRAF* V600E mCRC. The phase III BEACON study was one such trial. Although this trial showed the addition of a *MEK* inhibitor produced improved response rate and acceptable tolerability, it did not show greater overall survival. Therefore, second-line therapy in *BRAF* V600E-mutated mCRC standard of care includes encorafenib and cetuximab.

We await the results of the ANCHOR-CRC trial, which looks at the triple combination of encorafenib, binimetinib, and cetuximab in previously untreated *BRAF*-mutant mCRC.

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

Abstract 4004

Alberto F. Sobrero, MD, on Colon Cancer: Adjuvant Oxaliplatin and Fluoropyrimidine-Based Therapy for Stage III Disease

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/185483/abstract> to read the full abstract and view author disclosures.

Alberto F. Sobrero, MD, of the Ospedale San Martino, discusses final results of the IDEA study, which supported the use of 3 months of adjuvant CAPOX, vs 6 months, for most patients with stage III colon cancer. The shorter treatment duration reduced toxicity, inconvenience, and cost (Abstract 4004). Below is a transcript of his commentary.

Commentary by Alberto F. Sobrero, MD

The major findings of this study can be summarized as follows. First, for the first time, at this ASCO meeting, the 5-year overall survival data were presented. It was a secondary and very important endpoint of this study. The two curves of survival of the two arms of the study are superim-

posed. The hazard ratio was 1.02, meaning almost identical results of 5-year overall survival. That is a major finding conveyed by this study.

The second type of information that comes out of this study is equally important. This was a non-inferiority trial. Reducing toxicity by only giving 3 months of treatment was a crucial aspect of this study. And indeed, the overall toxicity went down by 2- to 6-fold according to the type of toxicity. But the most important toxicity as we know with oxaliplatin-containing regimens is neurotoxicity. That dropped from 46% down to 14%, a 3-fold decrease in toxicity.

The third major finding comes from the pre-planned subgroup analysis. Essentially, we found a very important drug regimen effect, meaning that CAPOX at 3 months is as good as 6 months for both lower-risk stage 3 and high-risk patients, whereas when we use FOLFOX, 3 months is acceptable only for low-risk stage 3 patients. For stage 3 high-risk patients, if you use FOLFOX, you need 6 months.

We hope that these clear and straightforward results will settle the debate generated by the initial reporting of the IDEA trial that was published in *The New England Journal of Medicine* 2 years ago. That report reported a sort of

discrepancy between the statistical analysis showing that it could not reject the hypothesis of noninferiority and the clinical interpretation that showed almost identical results of 3-year

disease-free survival. Now that we have these data, we hope that this will clarify how to treat most of our patients with stage 3 colon cancer with just 3 months of chemotherapy. ●

The Advanced Practitioner Perspective

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Approximately 60% of patients with colorectal cancer (CRC) present with locally advanced disease (including stage 2 and 3 disease). The efficacy of adjuvant chemotherapy to eliminate micrometastasis in these patients has been established to improve survival. However, over the past 4 decades, there has been an ongoing debate and examination in prospective and observational studies on the duration of adjuvant chemotherapy. Historically, the recommendation was 12 months of 5-FU and levamisole in stage 3 and selected high-risk patients with stage 2 CRC. Eventually, the treatment was shortened to a 6-month schedule of 5-FU and leucovorin. Over the past decade and half, after the approval of oxaliplatin, FOLFOX (5-FU, leucovorin, and oxaliplatin) became the standard of care.

FOLFOX therapy for 6 months can lead to dose-limiting peripheral neuropathy that can become debilitating and unacceptable to patients. Furthermore, the complexity of administration via continuous infusion pump and cost has led investigators to question whether we were overtreating patients with locally advanced CRC. The take-home message from this abstract is that for stage 3 patients with T4 or N2 disease, 6 months of FOLFOX is recommended. For T1 to T3, N1 disease patients, clinicians should discuss differences in the toxicity and logistics of the two regimens, CAPOX or FOLFOX, and offer 3 months of CAPOX. Using a shared decision-making approach with clear-cut data, patients with less aggressive locally advanced CRC have the same benefit in improvement of survival with less toxicity and time commitment for their adjuvant therapy.

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

Abstract 4637

Data From TAPUR Study Cohorts on Olaparib for *BRCA*-Mutated Advanced Prostate and Pancreatic Cancers

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/186402/abstract> to read the full abstract and view author disclosures.

Positive results from two cohorts of the Targeted Agent and Profiling Utilization Registry (TAPUR) study provide real-world evidence to support recent clinical trial data that demonstrate a role for olaparib in the treatment of advanced prostate and pancreatic cancers with *BRCA1/2*-inactivating mutations. The findings were presented during the ASCO20 Virtual Scientific Program (Abstract 5567, Abstract 4637).

In two small cohorts, treatment with olaparib resulted in objective responses or stable disease for at least 16 weeks in more than two-thirds (68%) of patients with advanced prostate cancer and *BRCA1/2*-inactivating mutations, and nearly one-third (31%) of patients with advanced pancreatic cancer and *BRCA1/2*-inactivating mutations.

“It makes sense that a targeted therapy that works well and has been approved for one type of cancer with a particular mutation could also be effective for other types of cancer with the same mutation,” said Chief Medical Officer and Executive Vice President of ASCO, Richard L. Schilsky, MD, FACP, FSCT, FASCO. “TAPUR provides data from a broader population of patients and supports olaparib’s safety and effectiveness in patients with extensive prior treatment.”

Prostate Cancer Cohort

The first study included 29 patients with advanced prostate cancer with germline or somatic *BRCA1/2*-

inactivating mutations. Patients had no remaining standard treatment options, measurable disease, adequate organ function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Twice daily, patients received olaparib as either 400-mg capsules or 300-mg tablets. Treatment continued until disease progression.

In the 25 patients evaluable for efficacy, 68% of patients had either an objective response ($n = 9$) or stable disease for at least 4 months ($n = 8$). Three patients had at least one grade 3 adverse or serious adverse event possibly related to olaparib. Reported events were consistent with the drug label.

These data support the recent FDA approval of olaparib for treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (*HRR*) gene–mutated metastatic castration-resistant prostate cancer.

Pancreatic Cancer Cohort

The second cohort included 30 patients with advanced pancreatic cancer and *BRCA1/2*-inactivating mutations previously treated with platinum-based therapy. These patients had no standard treatment options remaining, measurable disease, adequate organ function, and an ECOG performance status of 0–2. Twice daily, patients received either olaparib capsules or tablets until disease progression.

In the 26 patients evaluable for efficacy, 31% of patients had either an objective response (partial response in 1 patient) or stable disease for at least 4 months (7 patients). Four patients had at least one grade 3 adverse or serious adverse event possibly related to olaparib. Reported events were consistent with the drug label.

These findings support the recent FDA approval of olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated metastatic pancreatic adenocarcinoma, and potentially extend its use to patients with more far advanced disease.

More on the TAPUR Study

The TAPUR Study is the first clinical trial conducted by ASCO. Focusing on patients with advanced cancers without remaining treatment options, TAPUR investigates whether specific targeted therapies can benefit patients based on specific genomic profiles of the tumors and lead to more personalized therapies.

TAPUR is a basket trial that groups tumors by specific genomic alterations regardless of the location in the body where the cancer originates. Today, the TAPUR Study has nearly 1,900 patients enrolled at more than 115 participating cancer centers, hospitals, and oncology practices in the United States. TAPUR has served as a model for similar studies around the world. ●

The Advanced Practitioner Perspective Nina N. Grenon, DNP, AGCNP-BC, AOCN® Dana-Farber Cancer Institute

Pancreatic cancer is now the third-leading cause of cancer deaths. However, treatment over the past decade has made significant leaps. In particular, targeted therapy has revolutionized the treatment of pancreatic cancer.

The majority of patients present with advanced disease. Only 9% of patients are alive at 5 years, and the median survival remains 3 months. FOLFIRINOX (5-FU, leucovorin, oxaliplatin, and irinotecan) and gemcitabine/nab-paclitaxel are front-line treatment. Although FOLFIRINOX has an advantage in response rate, disease-free progression, and overall survival, it is a difficult regimen to tolerate and reserved for patients with a very good performance status.

The data from the TAPUR study on patients with germline *BRCA*-mutated advanced pancreatic cancer further support poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy. Germline testing is standard of care for any patient with a confirmed diagnosis of pancreatic cancer. Germline testing is important because pancreatic cancer is associated with numerous hereditary cancer syndromes.

The PARP inhibitor olaparib has been FDA approved in advanced pancreatic cancer patients with no disease progression after receiving up to 6 months of platinum-based therapy. Olaparib is generally well tolerated, with acceptable toxicity. There is a very good possibility this option could be potentially offered in patients in advanced stages of disease.

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