Highlights in Colorectal Cancer

Commentary by Tanios S. Bekaii-Saab, MD

Neoadjuvant Chemotherapy Allows Most Patients With Locally Advanced Rectal Cancer to Skip Pelvic Chemoradiation

The phase 3 PROSPECT trial found that the addition of neoadjuvant chemotherapy to treatment for patients with locally advanced rectal cancer (LARC) allowed for selective use of chemoradiation rather than universal chemoradiation.

The trial, which was presented by Dr Deborah Schrag, enrolled 1194 patients (mean age, 57 years) with LARC from 264 centers in the United States, Canada, and Switzerland from June 2012 to December 2018. Eligible patients had cT2N+, cT3N–, and cT3N+ rectal cancers and were deemed appropriate for neoadjuvant therapy prior to low anterior resection with total mesorectal excision, and high-risk patients were excluded.

Patients were randomly assigned without blinding to receive either fluoropyrimidine-based chemoradiation with 5040 cGy over 5.5 weeks (control group, n=585) or 6 cycles of neoadjuvant chemotherapy with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) followed by restaging (intervention group, n=543). Patients in the intervention group received chemoradiation if they did not experience tumor regression of at least 20% or did not tolerate at least 5 cycles of FOLFOX. The primary endpoint was disease-free survival (DFS). Only 53 (9%) patients in the intervention group received chemoradiation.

After a median follow-up of 58 months, DFS in the intervention group was noninferior to that in the control group, at 80.8% vs 78.6%, respectively (hazard ratio [HR], 0.92; 95% CI, 0.74-1.14). Overall survival (OS) in the intervention group also was noninferior to that in the control group, at 89.5% vs 90.2%, respectively (HR, 1.04; 95% CI, 0.74-1.44). During neoadjuvant treatment, patients in the intervention group were more likely to report appetite loss, constipation, fatigue, nausea, and neuropathy, whereas those in the control group were more likely to experience diarrhea. Most patients (82% in the intervention group and 83% in the control group) received chemotherapy after surgery.

Dr Schrag concluded that "neoadjuvant FOLFOX, with only the selective use of pelvic chemoradiation, is a safe and effective treatment option for patients with cT2N+, cT3N–, or cT3N+ rectal cancer."

Schrag D, Shi Q, Martin WR, et al. PROSPECT: a randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision (TME) for treatment of locally advanced rectal cancer (LARC) (Alliance N1048) [ASCO abstract LBA2]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: PROSPECT, a culmination of more than 10 years of research, challenges the assumption that all patients with early-stage rectal cancer require all treatment modalities for the best chance at a cure. It turns out that patients who achieve more than a 20% response to chemotherapy may not need radiation prior to surgery, with comparable survival rates and improved quality of life. The evolving field of rectal cancer treatment suggests that radiation can be omitted for most patients with cT2N+, cT3N–, and cT3N+ disease; surgery can be skipped for select patients with low rectal cancer; and immune therapy may provide a curative option in the presence of microsatellite instability–high disease. These findings mark a significant shift in the standard of care, emphasizing the success of a more personalized approach for patients with early-stage rectal cancer.

Lower Dose of Trastuzumab Deruxtecan Improves Benefit-Risk Profile in HER2+ mCRC

The DESTINY-CRC01 trial demonstrated antitumor activity with trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic colorectal cancer (mCRC) at a dose of 6.4 mg/kg every 3 weeks. Now, the primary results of the DESTINY-CRC02 trial suggest that the 5.4-mg/kg dose of T-DXd has a better benefit-risk profile than the 6.4-mg/kg dose.

Dr Kanwal Raghav presented the results of the phase 2 study, which enrolled 80 patients with centrally confirmed HER2+ mCRC, defined as immunochemistry (IHC) 3+ or IHC 2+/in situ hybridization (ISH)+. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and wild-type *BRAF; RAS* could be wild-type or mutated. In stage 1 of the trial, 80 patients were randomly assigned in a 1:1 ratio to receive T-DXd at either 5.4 mg/kg or 6.4 mg/kg every 3 weeks. In stage 2, an additional 42 patients received T-DXd at 5.4 mg/kg. All patients received systemic chemotherapy. The primary endpoint was confirmed objective response rate (cORR) assessed by blinded independent central review.

As of the data cutoff on November 1, 2022, the median cORR was numerically higher in the 5.4-mg/kg arm than in the 6.4-mg/kg arm, at 37.8% (95% CI, 27.3-49.2) vs 27.5% (95% CI, 14.6-43.9), respectively. With the 5.4-mg/kg dose, HER2 IHC 3+ patients (78.0% of the total) had a better ORR compared with HER2 IHC 2+/ISH+ patients (85.0% of the total), at 46.9% vs 5.6%, respectively. Also, with the 5.4-mg/kg dose, antitumor activity was observed in patients with (ORR, 28.6%) and without (ORR, 39.7%) *RAS* mutations, as well as in patients who had previously received anti-HER2 therapy (ORR, 41.2%). The rates of all-grade and grade 3 or higher treatment-related interstitial lung disease/pneumonitis favored the 5.4-mg/kg dose over the higher dose. Grade 3 or higher treatment-emergent adverse events occurred in 49.4% of patients in the 5.4-mg/kg arm and 59.0% of those in the 6.4-mg/kg arm.

Dr Raghav concluded that the results of this trial "support the use of T-DXd at a dose of 5.4 mg/kg, given IV every 3 weeks, as the optimal dose as a single agent in this patient population of HER2-positive mCRC."

Raghav KPS, Siena S, Takashima A, et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study [ASCO abstract 3501]. *J Clin Oncol*. 2023;41(16)(suppl).

Commentary: The DESTINY-CRC02 study builds upon DESTINY-CRC01, which established trastuzumab deruxtecan as a standard treatment option for HER2+ CRC patients. Although response rates were high, the toxicities, particularly interstitial lung disease/pneumonitis, were a concern. The DESTINY-CRC02 study compared 2 doses and concluded that the lower dose of 5.4 mg/kg was as effective as the higher dose of 6.4 mg/kg, with fewer toxicities and slightly higher response rates.

Addition of Atezolizumab to FOLFOXIRI/Bevacizumab Prolongs PFS in mCRC

The addition of atezolizumab (Tecentriq, Genentech) to first-line leucovorin, 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab significantly prolongs progression-free survival (PFS) in molecularly unselected patients with mCRC, according to the results of the AtezoTRIBE trial. The trial also showed a trend toward improved PFS with atezolizumab in patients with mismatch repair–proficient (pMMR) tumors.

The phase 2 trial, which was presented by Dr Carlotta Antoniotti, enrolled 218 patients from 22 Italian sites who had previously untreated, unresectable mCRC and an ECOG performance status of 0 to 2. There was no molecular selection according to *RAS*, *BRAF*, or MMR status. Patients were randomly assigned in a 1:2 ratio to receive first-line FOLFOXIRI plus bevacizumab (control group) or the same regimen plus atezolizumab (experimental group) for up to 8 cycles. Maintenance treatment consisted of 5-FU/leucovorin alone in the control group or with atezolizumab in the experimental group until disease progression. After disease progression, the same agents that were used upfront were reintroduced. The primary endpoint was PFS.

After a median follow-up of 37.0 months, with 80% of PFS events recorded, the median PFS was significantly higher in the experimental group than in the control group, at 13.1 vs 11.5 months, respectively (HR, 0.71; *P*=.015). The response rate was not significantly different between the experimental group and the control group, at 64% vs 59%, respectively (*P*=.21). There were no unexpected grade 3, grade 4, or serious adverse events. There was a trend toward longer median OS in the experimental arm vs the control arm, at 33.0 months vs 27.2 months, but the finding was not statistically significant (HR, 0.81; *P*=.136). Among the 201 patients in the pMMR cohort, there was a trend toward better PFS and OS with the addition of atezolizumab to treatment. Also in the pMMR cohort, the degree of improvement in PFS and OS with atezolizumab was greater in patients with Immunoscore IC (IS IC)-high tumors than in IS IC-low tumors, and greater in tumor mutational burden (TMB)-high tumors than in TMB-low tumors.

Dr Antoniotti said that "based on these results, a confirmatory phase 3 trial will be started soon to investigate the added value of the addition of atezolizumab to first-line FOLFOXIRI plus bevacizumab" in molecularly-selected patients with pMMR and IS IC-high mCRC.

Antoniotti C, Rossini D, Pietrantonio F, et al. FOLFOXIRI plus bevacizumab and atezolizumab as upfront treatment of unresectable metastatic colorectal cancer (mCRC): updated and overall survival results of the phase II randomized AtezoTRIBE study [ASCO abstract 3500]. *J Clin Oncol*. 2023;41(16)(suppl).

Commentary: The AtezoTRIBE trial explored the effectiveness of combining chemotherapy, the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, and the PD-L1 inhibitor atezolizumab in patients with pMMR tumors. The study found that patients with IS IC–high tumors showed significant improvements in PFS and OS compared with other groups. This suggests that there is significant promise for IS IC–high status to be a predictive biomarker for immunotherapy response. However, further research and the results of the phase 3 trial from the same group (AtezoTRIBE 2) are needed to establish it as a potential standard of care.

Both Tissue- and Blood-Based Assays Can Be Used to Identify Patients With HER2+ mCRC

The results of the MOUNTAINEER study led to the US Food and Drug Administration approval of tucatinib (Tukysa, Seagen) plus trastuzumab in patients with chemotherapy-refractory, HER2+, *RAS* wild-type mCRC. Now, an exploratory analysis of this study shows that both tissue- and blood-based methods of identifying HER2 positivity are effective at identifying patients who may benefit from treatment with this drug combination.

The trial enrolled 114 patients with HER2+ mCRC as detected by at least one local testing platform: (1) IHC/fluorescence ISH (FISH); (2) tissue next-generation sequencing (NGS); or (3) blood NGS. Patients in cohorts A and B received tucatinib and trastuzumab, whereas patients in cohort C received tucatinib monotherapy. The primary endpoint was cORR. For the current analysis, which was presented Dr John H. Strickler, the investigators explored the correlations between tissue and blood-based assays and clinical outcomes among the 86 patients in cohorts A and B. A total of 70 IHC/FISH samples, 50 tissue NGS samples, and 71 blood NGS samples from these patients had evaluable results.

A high level of percent agreement of HER2 status was observed across multiple central HER2 testing modalities. The agreement was 81.0% between blood NGS and tissue NGS, 92.6% between IHC/FISH and tissue NGS, and 79.5% between IHC/FISH and blood NGS. Patients who tested HER2+ by IHC/FISH using a cutoff of IHC3+ had a cORR of 46.7%, a median duration of response (DOR) of 16.4 months, and a median PFS of 10.1 months. Those who tested HER2+ by IHC/FISH using a cutoff of IHC+/ISH+ had a cORR of 20%, which was numerically lower than 46.7% but still clinically relevant, according to Dr Strickler. Patients who tested HER2+ by tissue NGS had a cORR of 47.7%, a median DOR of 15.3 months, and a median PFS of 10.9 months. Patients who tested HER2+ by blood NGS had a cORR of 41.1%, a median DOR of 12.4 months, and a median PFS of 8.1 months.

The study demonstrated that the percent agreement of HER2 status was high across the 3 platforms, with higher agreement between the tissue-based platforms. All 3 platforms were able to predict treatment response to tucatinib and trastuzumab based on HER2 status. Although the detection of *HER2* amplification by blood-based NGS was useful, patients without *HER2* amplification should be confirmed using a tissue-based assay.

Dr Strickler concluded that "these data support the use of tissue- and blood-based methods" to identify HER2+ mCRC patients who may benefit from treatment with tucatinib plus trastuzumab.

Strickler JH, Cercek A, Ng K, et al. HER2 testing in the MOUNTAINEER trial: analysis of treatment response based on central HER2 assessment using IHC/ISH and NGS [ASCO abstract 3528]. *J Clin Oncol.* 2023;41(16)(suppl).

Commentary: The MOUNTAINEER study supports the use of both tissue- and blood-based methods to identify HER2+ mCRC. HER2 testing in the study demonstrated a high level of agreement across different testing modalities, with the strongest correlation observed between tissue- and blood-based assays. Treatment responses appear to be predicted by any test for *HER2* overexpression or amplification using any of the 3 testing platforms. If it is present, a response will be seen in 40% to 50% of the patients. In conclusion, different testing methods, including NGS and IHC, can be used to identify patients eligible for HER2-targeted therapy, with tissue-based testing showing the best correlation.

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