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A SPECIAL MEETING REVIEW EDITION

Highlights in Colorectal Cancer From the 2021 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2021 ASCO Annual Meeting • June 4-8, 2021

Special Reporting on:

- Final Overall Survival for the Phase III KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability–High/Mismatch Repair Deficient Metastatic Colorectal Cancer
- Single-Arm, Phase 2 Study of Regorafenib Plus Nivolumab in Patients With Mismatch Repair Proficient/Microsatellite Stable Colorectal Cancer
- Phase 1b/2 Open-Label, Randomized Evaluation of Atezolizumab + Imprime PGG + Bevacizumab vs Regorafenib in MORPHEUS: Microsatellite-Stable Metastatic Colorectal Cancer
- LEAP-005: A Phase 2 Multicohort Study of Lenvatinib Plus Pembrolizumab in Patients With Previously Treated Selected Solid Tumors—Results From the Colorectal Cancer Cohort
- Regorafenib Combined With PD-1 Inhibition as Salvage Treatment and in a Real-World Study of Patients with Metastatic Colorectal Cancer
- Preliminary Results of a Phase 1b Study of Fruquintinib Plus Sintilimab in Advanced Colorectal Cancer
- The TRUSTY Study: A Randomized Phase 2/3 Study of Trifluridine/Tipiracil Plus Bevacizumab Versus Irinotecan and Fluoropyrimidine Plus Bevacizumab as Second-Line Treatment in Patients With Metastatic Colorectal Cancer
- Regorafenib in Patients With Relapsed Advanced or Metastatic Colorectal Cancer

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Tanios S. Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Consultant, Mayo Clinic
Phoenix, Arizona

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Final Overall Survival for the Phase III KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability–High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Pembrolizumab is a monoclonal antibody that binds to programmed death 1 (PD-1). This agent has demonstrated activity among patients with colorectal cancer (CRC) and other tumor types that are microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR).[1,2] The open-label phase 3 KEYNOTE-177 trial compared pembrolizumab vs chemotherapy as first-line therapy in 307 patients with MSI-H/dMMR stage IV CRC.[3-5] Pembrolizumab was administered at 200 mg every 3 weeks for up to 35 cycles. Chemotherapy consisted of the investigator's choice of leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) or leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI), plus bevacizumab or cetuximab, administered in 2-week cycles. Patients in the chemotherapy arm had the option to cross over to the pembrolizumab arm upon centrally verified disease progression. The trial had 2 primary endpoints: progression-free survival (PFS) and overall survival (OS). Blinded independent central reviewers evaluated outcomes using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[6]

Patient characteristics in the 2 arms were well balanced. The patients' median age was 63 years (range, 24-93). Approximately half of the patients had recurrent disease, and more than one-third had liver metastases. Approximately two-thirds of the patients had right-sided tumors, 23% had received prior adjuvant therapy exclusively, and 73% had received no prior therapy.

In the final analysis, the median PFS was 16.5 months with pembrolizumab vs 8.2 months with chemotherapy (hazard ratio [HR], 0.59; 95% CI, 0.45-0.79; *P*=.0002; Figure 1).[4] The 3-year PFS rate was 42% with pembrolizumab vs 11% with chemotherapy. The objective response rate (ORR) was 45.1% with pembrolizumab vs 33.1% with chemotherapy, and the complete response (CR) rate was 13.1% vs 3.9%, respectively. The median duration of response was not reached (range, 2.3+ to 53.5+ months) in the pembrolizumab arm vs 10.6 months (range, 2.8-48.3+) in the chemotherapy arm. The proportions of patients with a duration of response lasting at least 24 months

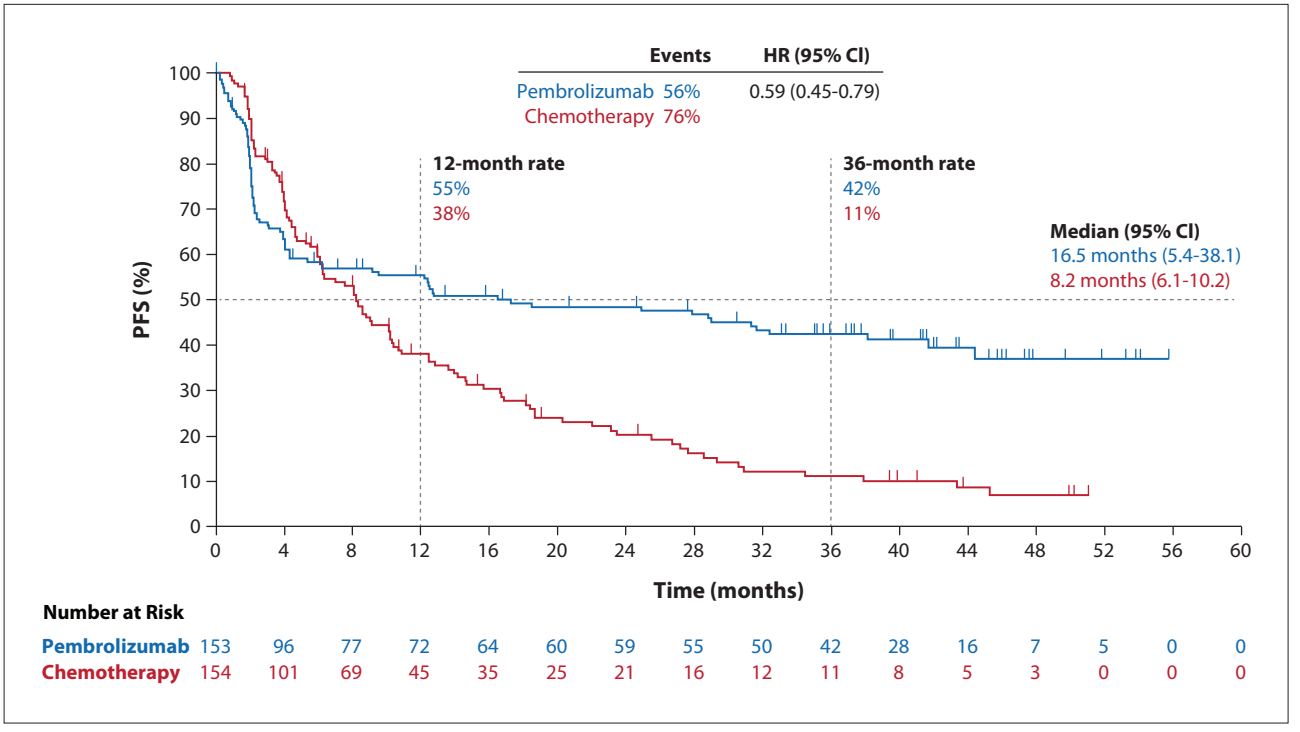

Figure 1. Progression-free survival in the phase 3 KEYNOTE-177 trial, which compared pembrolizumab vs chemotherapy as first-line therapy in patients with microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer. HR, hazard ratio; PFS, progression-free survival. Adapted from André T et al. ASCO abstract 3500. *J Clin Oncol*. 2021;39(15 suppl).[4]

were 83.5% and 33.6%, respectively. In the chemotherapy arm, 56 patients (36%) crossed over to the pembrolizumab arm after disease progression, and an additional 37 patients (24%) received PD-1 or programmed death ligand 1 (PD-L1) inhibitors outside of the study, resulting in an effective crossover rate of 60% in the intention-to-treat population.

The median OS was not reached in the pembrolizumab arm (95% CI, 49.2 months to not reached) vs 36.7 months in the chemotherapy arm (95% CI, 27.6 months to not reached; HR, 0.74; 95% CI, 0.53-1.03; *P*=.0359). The trial did not meet the prespecified threshold of *P*=.0246 for the superiority of pembrolizumab vs chemotherapy in terms of OS. OS was generally superior in the pembrolizumab arm vs the chemotherapy arm for most subgroups.

Patients in the chemotherapy arm were less likely than those in the pembrolizumab arm to develop treatment-related adverse events (AEs) of any grade (79.7% vs 98.6%) or treatment-related AEs of grade 3 or higher (21.6% vs 66.4%). Immune-mediated AEs and infusion reactions were more common in the pembrolizumab arm.

References

1. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413.
2. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
3. André T, Amonkar M, Norquist JM, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(5):665-677.
4. André T, Shiu KK, Kim TW, et al. Final overall survival for the phase III KN177 study: pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer [ASCO abstract 3500]. *J Clin Oncol*. 2021;39(15 suppl).
5. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218.
6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Single-Arm, Phase 2 Study of Regorafenib Plus Nivolumab in Patients With Mismatch Repair Proficient/Microsatellite Stable Colorectal Cancer

A single-arm phase 1b study conducted in Japan evaluated the combination of regorafenib and nivolumab in 24 patients with microsatellite-stable (MSS)/mismatch repair–proficient (pMMR) CRC.[1] The study demonstrated an acceptable safety profile for the 2-drug combination and yielded an ORR of 33% in this patient population. An open-label, single-arm phase 2 study conducted in North America investigated the safety and efficacy of regorafenib plus nivolumab in patients with MSS/pMMR CRC.[2] Prior lines of therapy had to include fluoropyrimidines, irinotecan, oxaliplatin, vascular endothelial growth factor (VEGF) inhibitors, and, for patients with extended *RAS* wild-type disease, endothelial growth factor receptor (EGFR) inhibitors. Patients with *RAS*-mutant disease had received up to 2 prior lines of therapy, and those with *RAS* wild-type disease had received up to 3 prior lines of therapy. *RAS* status was assessed based on extended testing. Regorafenib was administered according to a schedule of 3 weeks on followed by 1 week off. The dose was initiated at 80 mg daily and escalated to 120 mg daily. Nivolumab was administered at 480 mg every 4 weeks. The primary endpoint was the ORR according to RECIST 1.1, as assessed by the investigators.[3]

The phase 2 study enrolled 70 patients, whose median age was 57 years (range, 34-85).[2] The site of the primary cancer was the right side of the colon in 36%, the left side of the colon in 47%, and the rectum in 17%. In 93% of patients, the histology was adenocarcinoma, not otherwise specified. At baseline, 67% of patients had liver metastases and 73% had lung metastases. The *KRAS* or *NRAS* mutation was present in 61% of patients, and the *BRAF* mutation was reported in 4%. *KRAS*, *NRAS*, and *BRAF* were wild type in 31% of patients. More than half of the patients had received 3 or more prior lines of therapy. The median time from diagnosis was 24 months (range, 1-141).

The median duration of treatment was 2.2 months for regorafenib (range, 0.7-11.7) and 1.9 months for nivolumab (range, 0.03-11.1).[2] No patient achieved a CR. A partial response (PR) was reported in 5 patients, all without liver metastases, yielding an ORR of 7% for the entire study population. Among the 23 patients without liver metastases, the ORR was 22%, and 22 of the patients (31%) achieved stable disease. Among the 70 patients, the median OS was 11.9 months (95% CI, 7.0 months to not evaluable). Changes in tumor size in patients without or with liver metastases at baseline are shown in Figures 2 and 3. The median OS was 11.0 months (95% CI, 7.9-11.9) among patients without liver metastases vs 10.7 months (95% CI, 6.1 months to

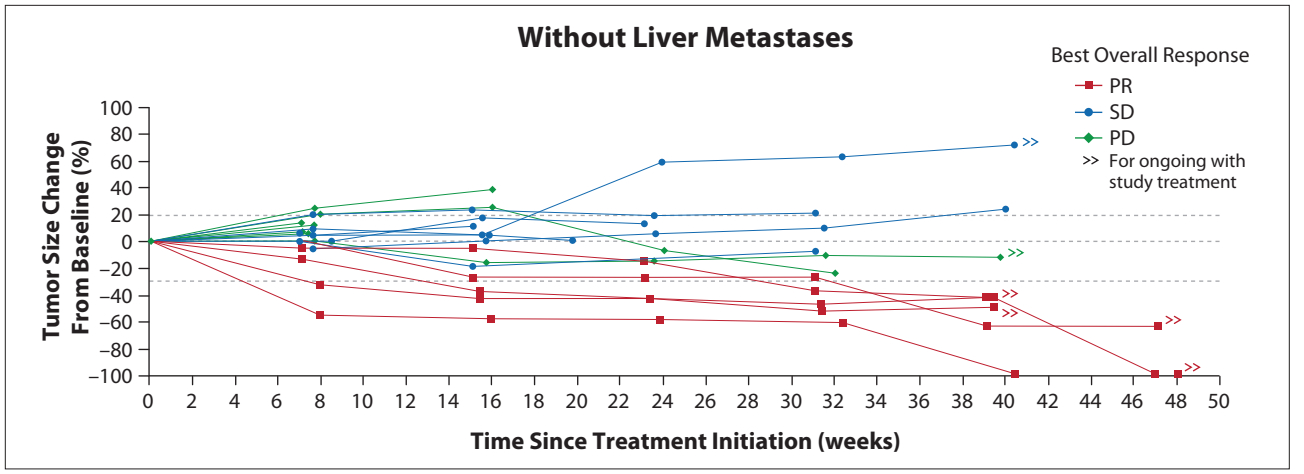

Figure 2. Changes in tumor size among patients with mismatch repair–proficient/microsatellite-stable colorectal cancer, without liver metastases, in a phase 2 study of regorafenib plus nivolumab. PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Fakih M et al. ASCO abstract 3560. *J Clin Oncol*. 2021;39(15 suppl).[2]

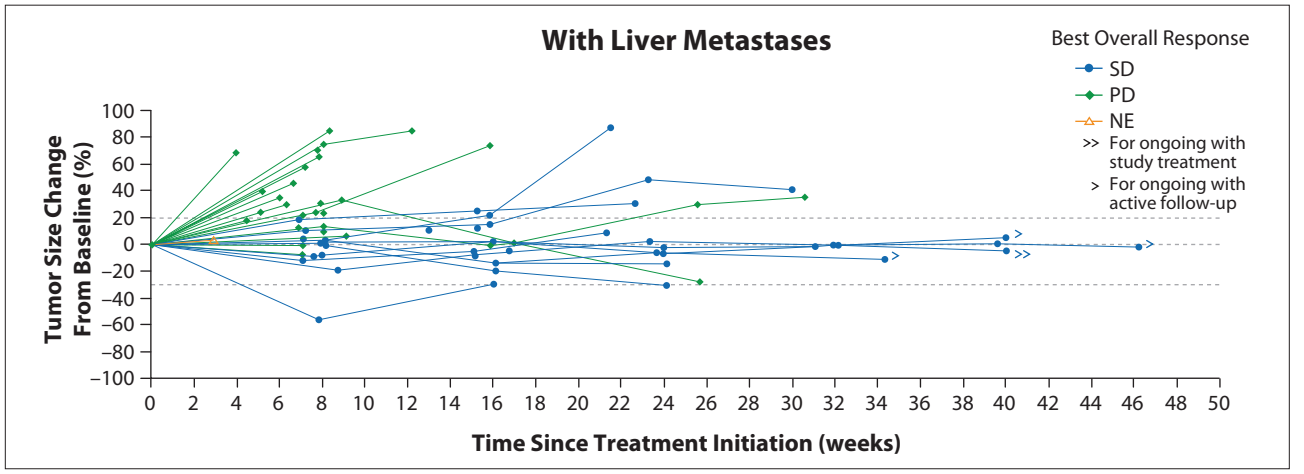

Figure 3. Changes in tumor size among patients with mismatch repair–proficient/microsatellite-stable colorectal cancer, with liver metastases, in a phase 2 study of regorafenib plus nivolumab. NE, not evaluable; PD, progressive disease; SD, stable disease. Adapted from Fakih M et al. ASCO abstract 3560. *J Clin Oncol*. 2021;39(15 suppl).[2]

not evaluable) among those with liver metastases.

Biomarker analyses were conducted in 40 patients with baseline tumor samples.[2] Clinical benefit corresponded with higher baseline expression of cytotoxic T cells ($CD3^+/CD8^+$/granzyme B^+; Figure 4), regulatory T cells ($FoxP3^+$), and macrophages ($CD68^+$).

Drug-related, treatment-emergent AEs of grade 3 or 4 were observed in 40% and 3% of patients, respectively. Grade 5 AEs occurred in 2 patients (3%). Drug-related, treatment-emergent AEs required dose interruption of regorafenib in 46% of patients and of nivolumab in 11% of patients. The most common grade 3/4 drug-related, treatment-emergent AEs were maculopapular rash (14%, all grade 3), fatigue (7%, all grade 3), pneumonia (4%, grade 3; 1%, grade 4), and increases in blood levels of bilirubin (3%, grade 3; 3%, grade 4).

Final results from a phase 1/1b study of regorafenib and nivolumab in MMR-proficient advanced refractory CRC were reported at the 2021 European Society for Medical Oncology World Congress on Gastrointestinal Cancer.[4] The primary objectives were to evaluate the safety and tolerability, describe the dose-limiting toxicities, and identify the maximum tolerated dose of regorafenib in combination with nivolumab. Among 52 enrolled patients, 51 received at least 1 dose of study treatment, and 40 were evaluable for response with imaging. The patients' median age was 56 years, and they had received a median of

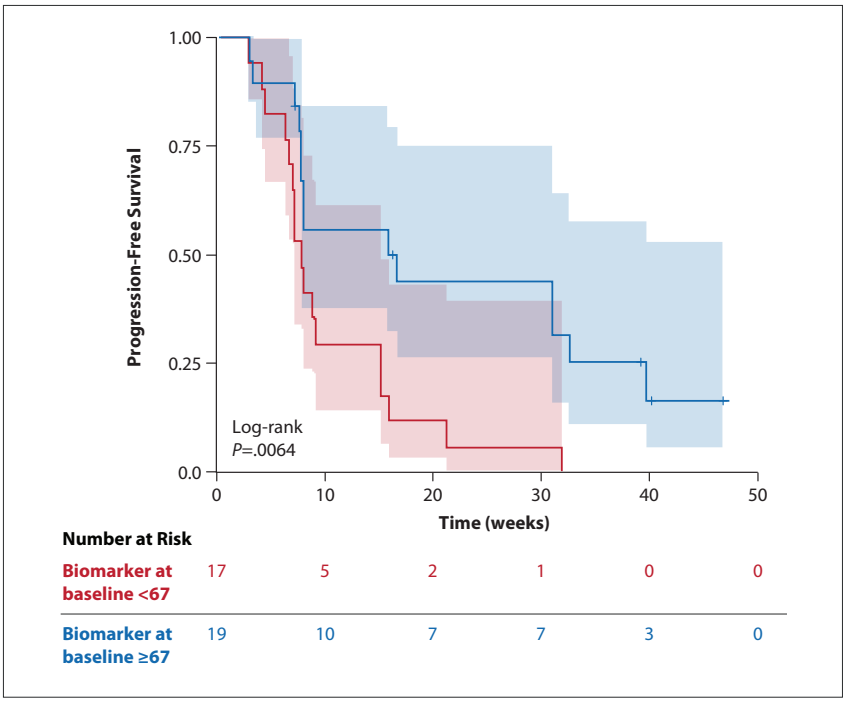

Figure 4. Clinical benefit corresponded to higher baseline expression of cytotoxic T cells (CD3+/CD8+/granzyme B+) in a single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair–proficient/microsatellite-stable colorectal cancer. Adapted from Fakih M et al. ASCO abstract 3560. *J Clin Oncol.* 2021;39(15 suppl).[2]

2 lines of prior therapy. After two 28-day cycles, response was evaluated using RECIST guidelines among 12 patients in the phase 1 cohort. For the expanded cohort of 40 patients, the recommended dose of regorafenib was 80 mg. For nivolumab, the recommended dose was 240 mg administered intravenously every 2 weeks. Among the 40 patients evaluable for response, 10% had a PR (including 1 unconfirmed case), and 53% had stable disease. Among all 51 patients, the median PFS was 4.3 months (95% CI, 1.6-7.0), and the median OS was 11.1 months (95% CI, 7.7-14.5).

Forty-eight patients discontinued treatment, for reasons such as progressive disease (n=28), clinical progression (n=9), AEs (n=7), and withdrawal of consent (n=4). The most common grade 3 or higher AE was hypertension (26%). The study investigators are performing correlative research to identify any predictive biomarkers.

References

1. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). *J Clin Oncol.* 2020;38(18):2053-2061.
2. Fakih M, Raghav KPS, Chang DZ, et al. Single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair proficient/microsatellite stable colorectal cancer [ASCO abstract 3560]. *J Clin Oncol.* 2021;39(15 suppl).
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
4. Kim R, Imanirad I, Strosberg J, Carballido E, Kim D. Final result of phase IB study of regorafenib and nivolumab in mismatch repair proficient advanced refractory colorectal cancer [ESMO GI abstract PD-2]. *Ann Oncol.* 2021;32(suppl 3).

Phase 1b/2 Open-Label, Randomized Evaluation of Atezolizumab + Imprime PGG + Bevacizumab vs Regorafenib in MORPHEUS: Microsatellite-Stable Metastatic Colorectal Cancer

The MORPHEUS platform includes several early-stage clinical trials that are comparing multiple therapies simultaneously against a single control arm, to allow for the early assessment of the safety and efficacy of chemoimmunotherapy treatments.[1,2] The MORPHEUS-CRC trial investigated the combination of atezolizumab (an anti–PD-L1 antibody), Imprime PGG (which activates the innate immune system), and bevacizumab among patients with refractory metastatic CRC.[3] Patients in the control arm received regorafenib. The study enrolled patients with histologically confirmed metastatic adenocarcinoma, with disease that had progressed during or after a maximum of 2 lines of treatment for metastatic CRC. Patients with the *BRAF* mutation were

ABSTRACT SUMMARY Maintenance Therapy With 5-Fluorouracil/Leucovorin Plus Panitumumab or 5FU/LV Alone in *RAS* Wild-Type Metastatic Colorectal Cancer—the PANAMA Trial (AIO KRK 0212)

The PANAMA trial investigated 5-fluorouracil plus leucovorin, with or without panitumumab, as maintenance therapy after 6 cycles of FOLFOX plus panitumumab in patients with previously untreated *RAS* wild-type metastatic CRC (Abstract 3503). The primary endpoint was PFS. The full analysis set of patients included 125 randomly assigned to receive 5-fluorouracil, leucovorin, and panitumumab and 123 randomly assigned to the control arm. After induction therapy, the ORR was 80.8% in the panitumumab arm vs 80.5% in the control arm, and rates of stable disease were 19.2% vs 19.5%. The median PFS was prolonged with the inclusion of panitumumab as maintenance therapy (8.8 vs 5.7 months; HR, 0.72; 80% CI, 0.60-0.85; *P*=.014). The median OS was similar in the 2 arms (*P*=.32). The trial met its primary endpoint, yielding an ORR of 40.8% with panitumumab vs 26.0% without panitumumab (odds ratio, 1.96; 95% CI, 1.14-3.36; *P*=.02). No new safety signals were observed.

excluded. Treatment in the experimental arm consisted of atezolizumab (1200 mg every 3 weeks), Imprime (4 mg/kg on days 1, 8, and 15 of each 21-day cycle), and bevacizumab (7.5 mg/kg every 3 weeks). Patients in the control arm received regorafenib (escalated up to 160 mg during the first cycle). The primary endpoint was investigator-assessed ORR.

The trial randomly assigned 15 patients to the experimental arm of atezolizumab, Imprime, and bevacizumab and 13 patients to the control arm of regorafenib.[3]

The ORR was 0% in each arm.[3] Stable disease occurred in 33.3% of patients in the atezolizumab combination arm and in 61.5% of patients in the regorafenib arm. The median PFS was 1.5 months with the atezolizumab regimen vs 2.8 months with regorafenib, and the median OS was 5.7 months vs 10.2 months, respectively.

Serious AEs occurred in 6.7% of the atezolizumab combination arm vs 23.1% of the control arm. Grade 3/4 AEs occurred in 20.0% vs 61.5%, respectively. Treatment-related AEs required dose modification or interruption in 33.3% vs 53.8% of patients, respectively. In the atezolizumab arm, the most common treatment-related AEs, occurring in at least 20% of patients, were infusion-related reaction, diarrhea, fatigue, and hypertension.

References

1. Desai J, Kortmansky JS, Segal NH, et al. MORPHEUS: a phase Ib/II study platform evaluating the safety and clinical efficacy of cancer immunotherapy (CIT)–based combinations in gastrointestinal (GI) cancers [ASCO GI abstract TPS4670]. *J Clin Oncol*. 2019;37(4 suppl).
2. Oh DY, Al-Batran SE, Chung HC, et al. MORPHEUS: a phase Ib/II trial platform evaluating the safety and efficacy of multiple cancer immunotherapy (CIT) combinations in patients (pts) with gastric or pancreatic cancer [ASCO abstract TPS4134]. *J Clin Oncol*. 2018;36(15 suppl).
3. Fakih M, Cleary JM, Hong YS, et al. Phase 1b/2 open-label, randomized evaluation of atezolizumab + Imprime PGG + bevacizumab vs regorafenib in MORPHEUS: microsatellite-stable metastatic colorectal cancer [ASCO abstract 3559]. *J Clin Oncol*. 2021;39(15 suppl).

LEAP-005: A Phase 2 Multicohort Study of Lenvatinib Plus Pembrolizumab in Patients With Previously Treated Selected Solid Tumors—Results From the Colorectal Cancer Cohort

Lenvatinib is a multitarget tyrosine kinase inhibitor that has demonstrated antitumor activity in CRC xenografts and in patients with refractory metastatic CRC.[1,2] In the phase 2 LEAP-005 study, lenvatinib was investigated in combination with pembrolizumab in patients with advanced CRC that was not MSI-H or pMMR.[3] The trial enrolled 32 patients, who had received 2 prior lines of therapy that included oxaliplatin and irinotecan in separate regimens. The treatment consisted of pembrolizumab (200 mg every 3 weeks) plus lenvatinib (20 mg daily) for up to 35 cycles. The primary endpoint was the ORR according to RECIST 1.1[4] and evaluated by blinded central review.

The confirmed ORR was 22% (95% CI, 9%-40%), and the disease control rate was 47% (95% CI, 29%-65%).[3] There were no CRs. PRs were reported in 7 patients (22%), and 8 patients (25%) had stable disease. The percent change from baseline in target lesion size is shown in Figure 5. The median duration of response was not reached (range, 2.1+ to 10.4+ months). The median PFS was 2.3 months (95% CI, 2.0-5.2), and the 6-month PFS rate was 31%. The median OS was 7.5 months (95% CI, 3.9 months to not reached), and the 6-month OS rate was 62%. Treatment was discontinued by 75% of patients, including by 56% after disease progression.

Grade 3/4 treatment-related AEs were observed in 47% of patients.[3] Treatment-related AEs included hypertension (44%) and decreased appetite (31%). The most common AEs of any grade that were considered related to treatment with lenvatinib were hypertension (47%), hepatotoxicity (34%), and proteinuria (34%). The trial will expand enrollment in the CRC cohort to 100 patients.

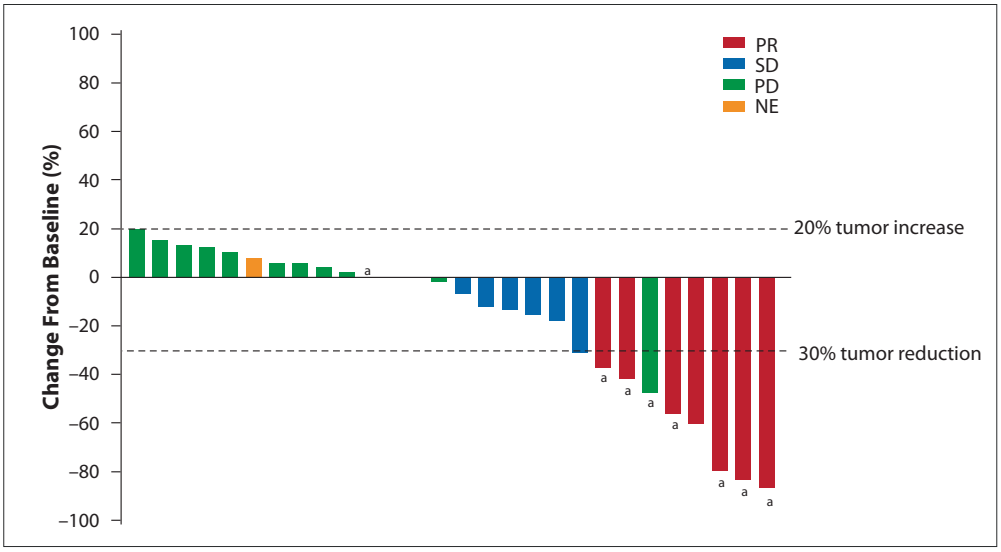

Figure 5. Changes in target lesion size among patients with previously treated colorectal cancer in the phase 2 LEAP-005 trial, which evaluated lenvatinib plus pembrolizumab. All responders had a programmed death ligand 1 Combined Positive Score of ≥1. [a]Patients with treatment ongoing. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Gomez-Roca C et al. ASCO abstract 3564. *J Clin Oncol.* 2021;39(15 suppl).[3]

References

1. Iwasa S, Okita N, Kuchiba A, et al. Phase II study of lenvatinib for metastatic colorectal cancer refractory to standard chemotherapy: the LEMON study (NCCH1503). *ESMO Open*. 2020;5(4):e000776.
2. Wiegering A, Korb D, Thalheimer A, et al. E7080 (lenvatinib), a multi-targeted tyrosine kinase inhibitor, demonstrates antitumor activities against colorectal cancer xenografts. *Neoplasia*. 2014;16(11):972-981.
3. Gomez-Roca C, Yanez E, Im SA, et al. LEAP-005: a phase 2 multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—results from the colorectal cancer cohort [ASCO abstract 3564]. *J Clin Oncol.* 2021;39(15 suppl).
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Regorafenib Combined With PD-1 Inhibition as Salvage Treatment and in a Real-World Study of Patients with Metastatic Colorectal Cancer

A prospective, open-label, single-arm study investigated the combination of regorafenib (80 mg daily) plus sintilimab (200 mg every 3 weeks) in patients with non–MSI-H metastatic CRC.[1] The primary endpoint was the ORR. The study enrolled 24 patients. Half had wild-type *RAS*. Most patients (83.3%) had received 2 prior lines of treatment, and 58.3% had liver metastases.

The best response consisted of stable disease in 6 patients (25%) and progressive disease in 4 patients (16.7%).[1] (Nine patients had not been evaluated at the time of the analysis.) Among the 15 evaluable patients, the ORR was 33.3% and the disease control rate was 73.3%. Among the 10 evaluable patients with liver metastases, the ORR was 30% and the disease control rate was 80%. In 9 evaluable patients with wild-type *KRAS*, the ORR was 44.4% and the disease control rate was 66.7%. The median PFS was 4.2 months, and the median OS was not reached. The 2-drug combination was generally well tolerated.

The combination of regorafenib plus nivolumab was evaluated in a retrospective, real-world study of Chinese patients with MSS/pMMR metastatic CRC.[2] The primary endpoint was OS. Among the 52 patients, 35 (67%) had liver metastases. Regorafenib plus a PD-1 inhibitor was administered to 48 patients (92%) as third-line or later treatment; 11 patients (21%) were receiving treatment at the time of the report. Reasons for cessation of treatment included progressive disease (45%), treatment-related AEs (14%), and death unrelated to treatment (6%).

After a median follow-up of 4.9 months, the median OS was 17.3 months (95% CI, 10.2 months to not reached) and the median PFS was 3.1 months (95% CI, 2.5-5.0 months).[2] Among patients with liver metastases at baseline, the median PFS was 2.7 months. The median PFS was 6.3 months in those without liver metastases at baseline (P<.05). The median OS was 17.3 months in patients with liver metastases at baseline vs not reached in those without, a difference that did not reach statistical significance (P=.6). Among 38 evaluable patients, 2 patients (5%) had a PR and 17 patients (45%) had stable disease. Among the 52 enrolled patients, grade 3/4 treatment-emergent AEs occurred in 8 patients (15%).

References

1. Liu R, Wang X, Deng T, et al. A single-arm study on the efficacy and safety of regorafenib plus sintilimab as salvage-line treatments in non-MSI-H metastatic colorectal cancer [ASCO abstract e15560]. *J Clin Oncol.* 2021;39(15 suppl).
2. Yang K, Han L, Zhao YB, et al. Regorafenib plus PD-1 inhibitors in Chinese patients with microsatellite stable/mismatch repair proficient metastatic colorectal cancer: a real-world study [ASCO abstract e15585]. *J Clin Oncol.* 2021;39(15 suppl).

Preliminary Results of a Phase 1b Study of Fruquintinib Plus Sintilimab in Advanced Colorectal Cancer

Fruquintinib is an orally available inhibitor of the VEGF receptor.[1] Sintilimab is a human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor with high selectivity.[2,3] A phase 1b trial investigated the combination of fruquintinib and sintilimab in patients with refractory metastatic CRC or other solid tumors.[4] The study enrolled 44 patients with metastatic CRC, all of whom required treatment after receiving at least 2 prior lines of therapy that contained a fluoropyrimidine, oxaliplatin, or irinotecan. The dose of fruquintinib was initiated at 3 mg/day on a schedule of 3 weeks on, 1 week off. The dose was then escalated to 5 mg daily on a schedule of 2 weeks on, 1 week off. In the dose-expansion phase, fruquintinib was administered following the 5-mg intermittent regimen in 22 patients and at a continuous dose of 3 mg daily in 22 patients. Sintilimab was initiated at 200 mg every 4 weeks and then escalated to 200 mg every 3 weeks. The primary endpoints were safety, tolerability, and the recommended phase 2 dose.

The patients' median age was 56 years (range, 27-72).[4] All of the patients had stage IV disease at screening. In the intention-to-treat population, the ORR was 22.7% (95% CI, 11.5%-37.8%), and the disease control rate was 86.4% (95% CI, 72.6%-94.8%). Changes in tumor size are shown in Figure 6. After a median follow-up of 11.3 months (range, 9.8-11.7), the median PFS was 5.6 months (95% CI, 4.3-7.5), and the median OS was 11.8 months (95% CI, 8.2 months to not evaluable). In the cohort of 22 patients who received fruquintinib in the 5-mg intermittent regimen, the ORR was 27.3% (95% CI, 10.7%-50.2%), and the median PFS was 6.9 months (95% CI, 5.4-8.3). The 5-mg intermittent dose was chosen as the recommended phase 2 dose for use in combination with sintilimab (200 mg every 3 weeks).

All patients developed treatment-emergent AEs, most commonly proteinuria (52.3%), increased levels of aspartate aminotransferase (45.5%), and palmar-plantar erythrodysesthesia syndrome (45.5%). Serious AEs were observed in 52.3% of the patients.

References

1. Li J, Cai Y, Deng Y. Selection of oral therapeutics in China for the treatment of colorectal cancer. *Curr Treat Options Oncol*. 2021;22(7):55.
2. Liu X, Yi Y. Recent updates on sintilimab in solid tumor immunotherapy. *Biomark Res*. 2020;8(1):69.
3. Zhang L, Mai W, Jiang W, Geng Q. Sintilimab: a promising anti-tumor PD-1 antibody. *Front Oncol*. 2020;10:594558.
4. Guo Y, Zhang W, Ying J, et al. Preliminary results of a phase 1b study of fruquintinib plus sintilimab in advanced colorectal cancer [ASCO abstract 2514]. *J Clin Oncol*. 2021;39(15 suppl).

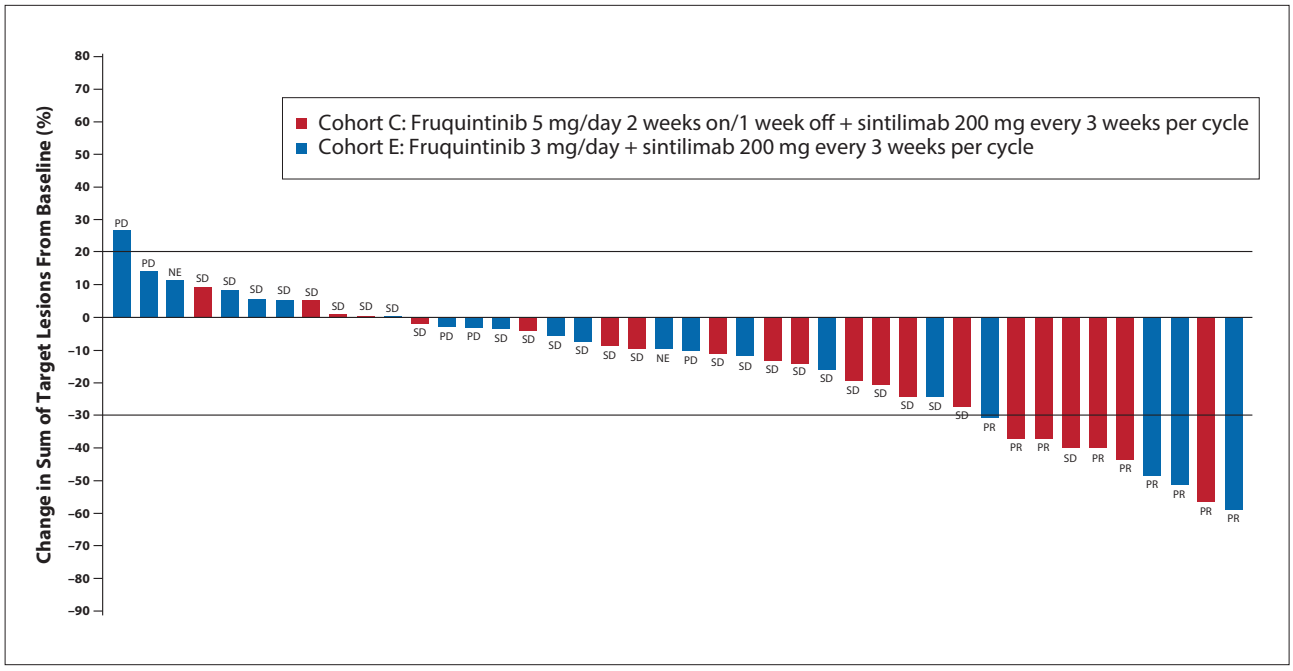

Figure 6. Changes in the sums of target lesions among patients with refractory metastatic colorectal cancer in the intention-to-treat population of a phase 1b study of fruquintinib plus sintilimab. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Guo Y et al. ASCO abstract 2514. *J Clin Oncol*. 2021;39(15 suppl).[4]

The TRUSTY Study: A Randomized Phase 2/3 Study of Trifluridine/Tipiracil Plus Bevacizumab Versus Irinotecan and Fluoropyrimidine Plus Bevacizumab as Second-Line Treatment in Patients With Metastatic Colorectal Cancer

The phase 2/3 TRUSTY study investigated whether trifluridine/tipiracil (FTD/TPI) plus bevacizumab was noninferior to FOLFIRI plus bevacizumab or irinotecan, S-1, and bevacizumab (IRIS-B).[1] The trial enrolled patients with histologically confirmed metastatic CRC who required treatment after first-line doublet chemotherapy that included a fluoropyrimidine and oxaliplatin, plus bevacizumab or an anti-EGFR antibody. The patients were stratified according to *RAS* status, location of the primary tumor, and prior exposure to bevacizumab or an anti-EGFR antibody. Those who were randomly assigned to the control arm received either FOLFIRI plus bevacizumab or IRIS-B according to physician preference. Those who were randomly assigned to the experimental arm received FTD/TPI (25 mg/m^2 twice daily on days 1-5 and days 8-12 every 4 weeks) plus bevacizumab. The primary endpoint was OS.

The study enrolled 199 patients into the control arm and 198 into the FTD/TPI-plus-bevacizumab arm.[3] In the control arm, patients were a median age of 68 years (range, 32-82), and 40% had wild-type *RAS*. The primary tumor was on the right side in 25%, and 59% had 2 or more metastatic lesions. First-line biologic treatment included bevacizumab in 82% and an anti-EGFR antibody in 18%. In the FTD/TPI-plus-bevacizumab arm, patients were a median age of 67 years (range, 26-80), and 40% had wild-type *RAS*. The primary tumor was on the right side in 24% of patients, and 65% had 2 or more metastases. First-line biologic treatment included bevacizumab in 81% and an anti-EGFR antibody in 19%.

After the first interim analysis for futility, the TRUSTY study was terminated.[1] The median OS was 18.1 months (95% CI, 16.0-23.2) in the control arm vs 14.8 months (95% CI, 12.6-19.1) in the FTD/TPI-plus-bevacizumab arm (HR, 1.38; 95% CI, 099-1.93; *P*=.5920 for noninferiority; Figure 7). The median PFS was 6.0 months (95% CI, 5.6-6.7) in the control arm vs 4.5 months (95% CI, 3.8-5.8) in the experimental arm (HR, 1.45; 95% CI, 1.14-1.84). The times to treatment failure were similar in the 2 arms (HR, 1.12; 95% CI, 0.86-1.46). There were no CRs in either treatment arm. PRs were more frequent in the

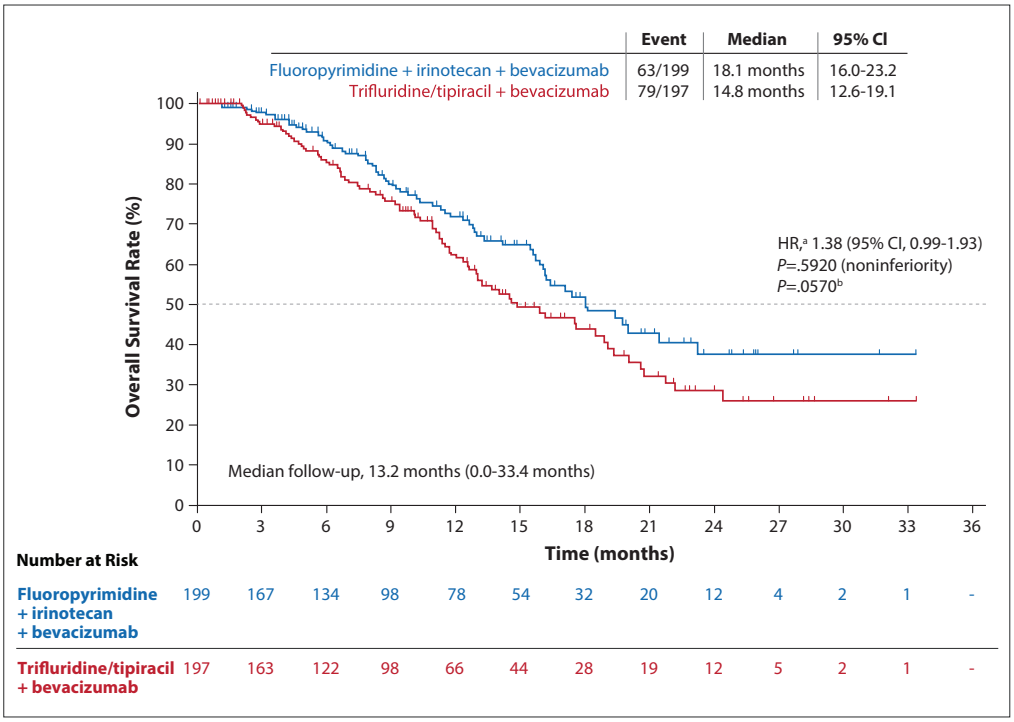

Figure 7. Overall survival in the randomized phase 2/3 TRUSTY study, which compared trifluridine/tipiracil plus bevacizumab vs irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer. [a]Adjusted based on stratification factors. [b]Ad hoc unplanned 2-sided superiority test. HR, hazard ratio. Adapted from Kuboki Y et al. ASCO abstract 3507. *J Clin Oncol.* 2021;39(15 suppl).[3]

control arm vs the experimental arm (7% vs 74%), and more patients in the control arm had stable disease (65% vs 57%). Subgroup analysis underscored the favorable OS outcome with IRIS-B or FOLFIRI plus bevacizumab compared with FTD/TPI plus bevacizumab. A post hoc analysis was conducted in the intention-to-use subgroups in the control arm. In this analysis, the median OS in the FTD/TPI-plus-bevacizumab arm was similar to that in the FOLFIRI-plus-bevacizumab arm (16.4 vs 17.5 months; HR, 1.07; 95% CI, 0.71-1.62), but was inferior to that in the IRIS-B arm (13.2 months vs not reached; HR, 2.14; 95% CI, 1.13-4.05).

No new safety concerns with FTD/TPI plus bevacizumab arose in the second-line setting. Drug-related AEs of grade 3 or higher were observed in 94.4% of the control arm vs 95.9% of the experimental arm. Serious AEs occurred in 23.4% vs 17.3%.

Reference

1. Kuboki Y, Terazawa T, Masuishi T, et al. The TRUSTY study: a randomized phase 2/3 study of trifluridine/tipiracil plus bevacizumab versus irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer [ASCO abstract 3507]. *J Clin Oncol*. 2021;39(15 suppl).

Regorafenib in Patients With Relapsed Advanced or Metastatic Colorectal Cancer

The role of regorafenib in the treatment of advanced or metastatic CRC was evaluated in several studies presented at the 2021 American Society of Clinical Oncology annual meeting.[1-3] A retrospective study investigated the efficacy and tolerability of hepatic arterial infusion chemotherapy combined with regorafenib after 2 or more lines of therapy among patients with advanced CRC and metastases located predominantly in the liver.[1] The median follow-up was 22.2 months for the 47 enrolled patients. The patients received a median of 4 sessions of hepatic arterial infusion chemotherapy (range, 2-8). In 49% of patients, the starting dose of regorafenib was 160 mg daily. The median OS was 22.2 months, and the median PFS was 10.8 months (95% CI, 9.0-13.7). Among 39 patients who were evaluated for response in the liver, the ORR was 51.3% and the disease control rate was 100%. Among 29 patients who were evaluated for tumor response outside the liver, the ORR was 13.8% and the disease control rate was 48.3%. The toxicity profile of regorafenib was consistent with that in prior reports, and only 2 patients discontinued treatment with regorafenib because of an AE.

The phase 3 CORRECT and CONCUR trials investigated 5 dimensions of health-related quality of life (HRQOL).[2,4,5] Both trials randomly assigned patients with previously treated metastatic CRC to treatment with best supportive care plus either regorafenib or placebo. The retrospective study calculated the proportion of patients who reported "no problems" in the 5 dimensions captured by the EuroQol-5 Dimension Questionnaire: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[2] Each dimension has 3 levels: no problems, some problems, and severe problems. The study evaluated data from 760 patients in the intention-to-treat population in the CORRECT trial, of whom 505 were randomly assigned to regorafenib and 255 to placebo. At baseline, patients reported the highest percentage of "no problems" for self-care (87%) and the lowest for pain/discomfort (35%). Questionnaire completion rates decreased with each treatment cycle, as did the proportion of patients reporting "no problems" for each dimension. The declines were more rapid among patients in the placebo arm. After treatment cycle 3, fewer patients in the placebo arm completed the questionnaire and fewer reported "no problems" in each dimension compared with the patients in the regorafenib arm. In summary, treatment with regorafenib appeared better than placebo in terms of enabling patients to maintain mobility, self-care, and usual activities, and the patients treated with regorafenib were more likely to be free of pain and anxiety. Findings were similar for patients in the CONCUR trial.[5]

Immune checkpoint inhibitors combined with regorafenib were investigated as third-line treatment in 23 patients with advanced MSS CRC.[3] Regorafenib was administered at 80 mg daily on days 1 to 21 of 28-day cycles. The median time from diagnosis to initiation of third-line therapy was 31 months. The ORR was 26%, including 1 CR, and the disease control rate was 60%. Among the 6 patients with a response, 5 were male, and 5 had pulmonary metastases. At the time of the report, the response persisted in all 6 patients, who were continuing treatment. The median PFS was 4.8 months (range, 0.69-19.3). The duration of response ranged from 6.4 to 19.4 months.

References

1. Cao G, Zhu X, Yang R, et al. A retrospective pilot study of regorafenib combined with ICIs in the third-line treatment of advanced colorectal cancer [ASCO abstract e15563]. *J Clin Oncol*. 2021;39(15 suppl).
2. Su Y, Ostojic H, Jaeger S, et al. "No problem" health-

related quality of life in patients treated with regorafenib for relapsed metastatic colorectal cancer [ASCO abstract 15593]. *J Clin Oncol*. 2021;39(15 suppl).
3. Zhang H, Zheng Y, Tong Z, et al. A retrospective study of local hepatic artery infusion chemotherapy combined with regorafenib in the treatment of advanced colorectal cancer with predominant liver metastases [ASCO abstract e15582]. *J Clin Oncol*. 2021;39(15 suppl).
4. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
5. Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.

Highlights in Colorectal Cancer From the 2021 American Society of Clinical Oncology Annual Meeting: Commentary

Tanios S. Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Consultant, Mayo Clinic
Phoenix, Arizona

At the 2021 American Society of Clinical Oncology (ASCO) annual meeting, several presentations in colorectal cancer provided insight into management. The studies evaluated treatments such as pembrolizumab, regorafenib, immunotherapies, trifluridine/tipiracil plus bevacizumab, and an antibody-drug conjugate targeting HER2.

Pembrolizumab

The phase 3 KEYNOTE-177 trial is one of the most transformational studies in metastatic colorectal cancer.[1,2] This study enrolled patients with microsatellite instability (MSI)-high disease, who account for approximately 3% to 4% of cases of metastatic colorectal cancer. Studies have shown that the programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab have a high response rate in patients with MSI-high gastrointestinal cancers, such as colon cancer, and in other types of cancers.[3-5] In later lines of therapy, pembrolizumab has led to responses beyond the 5-year mark,[6] which is the relative equivalent of a cure. The KEYNOTE-177 trial compared pembrolizumab with standard chemotherapy in the first-line setting, to assess the possibility of transforming this disease from essentially incurable to curable.[1,2] There were 2 co–primary endpoints: progression-free survival (PFS) and overall survival. An improvement in either endpoint would mean the study was positive. Patients received pembrolizumab for a maximum of 2 years.

The initial report showed that PFS nearly doubled with pembrolizumab vs standard chemotherapy.[1] The update at the 2021 ASCO meeting provided data after a follow-up of nearly 5 years.[2] Approximately 40% of patients still had not developed progressive disease. These patients can be considered cured, and they may never need treatment with chemotherapy. The median overall survival was not yet reached in the pembrolizumab arm vs 36.7 months in the standard-of-care arm, although this difference did not reach statistical significance.

Earlier analyses suggested that approximately 10% of patients progressed somewhat more rapidly during treatment with pembrolizumab vs chemotherapy.[7] These patients were considered to be "hyperprogressors," although this term has no true scientific validity in this setting. What was found in the updated overall survival results is that the improvement in survival associated with pembrolizumab is maintained in patients with more rapid progressive disease. Even with disease progression, overall survival remains longer with pembrolizumab than with chemotherapy. Compared with chemotherapy, pembrolizumab improves PFS, overall survival, and, importantly, quality of life.[1,2] The toxicity profile is better. These benefits make single-agent pembrolizumab the standard of care for patients with MSI-high metastatic colorectal cancer in the first-line setting.

An unanswered question is whether the addition of a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor to a PD-1 inhibitor would improve outcome. Early, ongoing studies with nivolumab plus ipilimumab are showing promise, although they have not impacted clinical practice.[8,9] This regimen is associated with a high risk for toxicity, as well as added costs that are not justifiable in my view, until the results of randomized clinical trials are available. A phase 3 trial is underway.[10]

Immunotherapy Combinations

Immunotherapy is currently an option for approximately 4% of patients with colorectal cancer. In the past few years,

much research has focused on how to bring immunotherapy to the other 96% of patients. Some of the first studies with immunotherapy aimed to make a "cold" tumor "hot." However, these studies were not successful. A phase 1b study of cobimetinib and atezolizumab was promising, with a response rate of 20%.[11] When tested in a phase 3 trial, however, this combination was negative, with hints that it underperforms compared with regorafenib.[12]

In other malignancies, the addition of vascular endothelial growth factor (VEGF) inhibitors to immunotherapy appears favorable.[13,14] In colorectal cancer, some studies have hinted that the addition of VEGF inhibitors or tyrosine kinase inhibitors (TKIs) to immunotherapy may induce some additional responses.[15,16] Several studies presented at the ASCO meeting evaluated this strategy in colorectal cancer settings that were similar, although not identical. The combinations included regorafenib and nivolumab; atezolizumab, bevacizumab, and an agent called Imprime; lenvatinib and pembrolizumab; and fruquintinib and sintilimab.

A phase 2 trial evaluated regorafenib plus nivolumab in patients who had mismatch repair–proficient/microsatellite stable colorectal cancer.[17] A retrospective study of this combination has also been published.[18] Among the entire patient population, the overall response rate was 7%. Interestingly, the response rate increased to 22% among the 23 patients without liver metastases, which reflects findings in the retrospective analysis.[18] The median PFS was 3.5 months in patients without liver metastases vs 1.8 months in those with liver metastases. As a comparison, the median PFS for dose-escalated regorafenib was 9.8 months in the ReDOS trial.[19] Therefore, the median PFS for regorafenib plus nivolumab was unimpressive. An interesting finding in the retrospective analysis is that activity was seen among patients without liver metastases. The biologic reasons for this outcome are unknown. Immunologically, the environment outside of the liver may be more conducive to a response. The premise behind moving immunotherapy to use in patients with microsatellite stable disease is to reproduce the activity seen in MSI-high disease. Unfortunately, the outcomes remain overwhelmingly inferior. Among MSI-high patients, this strategy leads to meaningful outcomes.[1] The responses are durable and prolonged. There are potential cures in patients with stage IV cancer.

The phase 1b/2 MORPHEUS study evaluated atezolizumab, bevacizumab, and Imprime, which acts as a pathogen-associated molecular platform that typically becomes bound to anti–β glucan antibodies.[20] This process is supposed to further activate the immune system. This trial had a control arm, in which patients received regorafenib. In the MORPHEUS trial, the response rate was 0% for both arms. Stable disease was reported in 33.3% of patients treated with atezolizumab, Imprime, and bevacizumab vs 61.5% of patients treated with regorafenib. The median overall survival was 5.7 months vs 10.2 months, respectively. The median PFS was 1.5 months vs 2.8 months. VEGF inhibition by itself may not be sufficient for treatment, and a multikinase inhibitor, such as regorafenib, may be needed. Overall, however, this remains challenging. Of note, in the phase 2 BACCI study, which was presented at the 2019 European Society for Medical Oncology meeting, the addition of atezolizumab to bevacizumab plus capecitabine improved outcome.[21] In the MORPHEUS trial, the disappointing and adverse outcome in the experimental arm may be attributable to the addition of Imprime, rather than the combination of bevacizumab and atezolizumab.

The phase 2 LEAP-005 trial, which evaluated pembrolizumab and lenvatinib, was a multicohort study that included patients with colorectal cancer.[22] These patients had microsatellite stable disease, and they had received 2 prior lines of therapy. The combination of pembrolizumab and lenvatinib has shown activity in hepatocellular carcinoma, endometrial cancer, and other malignancies.[23-25] Among patients with colorectal cancer, the response rate was 22%. The median PFS was 2.3 months, and the median overall survival was 7.5 months. Again, these rates are no better than those previously reported with regorafenib.[19] Similar to the phase 1b REGONIVO trial of regorafenib plus nivolumab, there were some significant toxicities that can be meaningful to patients.[16] Treatment-related adverse events led 9% of patients to discontinue therapy.

Fruquintinib is a TKI and sintilimab binds to PD-1. A phase 1b study from China evaluated the combination of these 2 agents among patients with advanced colorectal cancer.[26] The overall response rate was 22.7%, the median PFS was 5.6 months, and the median overall survival was 11.8 months. These results fit into similar patterns. The response rate, median PFS, and median overall survival were somewhat higher than those typically seen in studies enrolling Western patients. Approximately 60% of the patients in this study had received prior VEGF therapy. The rate of prior treatment with epidermal growth factor receptor (EGFR) inhibitors was not reported.

Data from the CONCUR trial of regorafenib showed that TKIs improve outcome.[27] Outcome associated with regorafenib was better in the CONCUR trial vs the CORRECT trial, primarily because the CONCUR trial was conducted in Asia and enrolled patients with less preexposure to VEGF therapy and EGFR inhibitors.[27,28] It is difficult to apply results from Asian studies to Western populations. Response rates with regorafenib plus nivolumab were much higher

in the first Japanese study compared with recent reports in Western patient populations.[16,17] There may be some differences between Asian and Western patients in terms of their response to these treatments, and that will need to be accounted for in future studies.

In conclusion, there appear to be hints of response to the combination of a TKI, such as regorafenib, lenvatinib, and fruquintinib, added to a PD-1 or programmed death ligand 1 (PD-L1) inhibitor. A few patients may develop responses, but it is not known how to select for these patients. Toxicity is significantly worsened and has to be accounted for. The Chinese study of fruquintinib appeared to show somewhat better outcomes than the other recent studies.[26] However, it is known that combinations of these agents in Asian studies historically outperform trials conducted in Western populations. Patients enrolled in Asian studies also tend to be less pretreated with other biologics, which may lead to a more favorable outcome.

The finding that patients without liver metastases had a better response to nivolumab and regorafenib parallels data from a retrospective study.[18] There is no clear biologic or immunologic basis for this improvement. Overall, the other outcome parameters do not warrant further development of these regimens. Major drawbacks include lack of meaningful benefit, significant toxicities, and elevated cost. At this time, I am doubtful that "cold" tumors can be made "hot" in microsatellite stable colorectal cancer. This strategy may be an option for "warm" tumors, if it is possible to identify them. Further research is needed to identify these patients, as well as patients who may respond to the combination.

Trifluridine/Tipiracil and Bevacizumab

The randomized phase 2/3 TRUSTY trial compared trifluridine/tipiracil plus bevacizumab vs irinotecan, fluoropyrimidine, and bevacizumab.[29] The study aimed to determine whether trifluridine/tipiracil and bevacizumab could be moved to the second-line setting to replace fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab. Unfortunately, the study failed to meet its primary endpoint of noninferiority for overall survival. In fact, trifluridine/tipiracil plus bevacizumab appeared to be inferior in all outcomes. Toxicities were not reduced with the use of trifluridine/tipiracil plus bevacizumab, with the exception of some gastrointestinal events.

The negative results of this trial were disappointing. The goal is to simplify the treatment regimens. In this instance, however, it seems that patients will still benefit from the combination of FOLFIRI and bevacizumab. Trifluridine/tipiracil remains an agent that is limited to the refractory setting. The question is whether bevacizumab should be added to trifluridine/tipiracil in patients who were refractory or resistant to previous treatment with bevacizumab. Early studies had suggested that trifluridine/tipiracil plus bevacizumab might improve outcome in these patients.[30,31] An ongoing phase 3 trial should help resolve this question.

HER2-Targeted Therapy

Colorectal cancer can be categorized into multiple genomic subgroups. Examples include patients with the *KRAS* or *BRAF* mutation. HER2 has mostly been considered a target in breast cancer and gastric cancer. However, *HER2* amplifications appear to be a major driver in colorectal cancer. The *HER2* amplification is present in 2% to 4% of patients with metastatic colorectal cancer. It is most relevant for targeting in patients without *RAS/BRAF* mutations, meaning in those who are *RAS/BRAF* wild-type. The MAPK pathway is complex, with a variety of interactions. *RAS*-mutated tumors that harbor *HER2* amplifications do not appear to respond to HER2-targeted therapies. Most of the patients with *HER2* amplifications are *RAS* wild-type and *BRAF* wild-type.

Previous phase 2 studies, such as HERACLES and MyPathway, reported response rates of approximately 30% when targeting HER2 in colorectal cancer.[32,33] The highest response rate, 52%, was reported in the phase 2 MOUNTAINEER trial of tucatinib and trastuzumab.[34] The median PFS was 8.1 months, also the highest among these trials. Preclinical data suggested that targeting HER2 with trastuzumab monotherapy did not improve outcome in patient-derived xenograft models.[35] The best responses were observed with combinations of lapatinib plus trastuzumab, rather than either agent alone. Dual targeting appears to be needed.

Antibody-drug conjugates are a relatively recent addition to the treatment armamentarium for cancer. These agents consist of a cytotoxic drug linked to an antibody. T-DM1 was the first antibody-drug conjugate to target HER2. This agent appeared active in breast cancer.[36] However, it was not active in gastric cancer or colon cancer.[37,38] At the ASCO meeting, Dr Takayuki Yoshino presented results from a phase 2 trial evaluating the antibody-drug conjugate trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer.[39] The enrollment criteria permitted prior treatment with other HER2-targeted therapies, which is important to keep in mind when considering the placement of trastuzumab deruxtecan. Trastuzumab deruxtecan is active across several malignancies, and it is already approved for the treatment of breast cancer and gastric cancer.[40,41]

The response rate was approximately 45%, which is similar to that seen in breast cancer, gastric cancer, and other malignancies.[39,40] Some of the responses were durable. The only concern with trastuzumab deruxtecan is the high level of toxicity. In this trial, 10% of patients developed interstitial lung disease, which was fatal for 3

patients and caused debilitating outcomes in all but one patient. During treatment with trastuzumab deruxtecan, patients should be closely monitored for lung toxicity. When suspicion for lung toxicity occurs, clinicians should immediately institute high-dose corticosteroids and stop treatment with trastuzumab deruxtecan.

Prior exposure to HER2-targeted therapies did not impact outcome.[39] This finding makes sense because the activity of trastuzumab deruxtecan depends on one thing: the presence (but less so the activity) of the receptor. It attaches to the receptor, and then releases the linked cytotoxic agent. Previous data have shown that when a patient develops progressive disease after treatment with trastuzumab-based dual HER2 targeting, trastuzumab deruxtecan can be administered as salvage therapy.[42] Therefore, administering trastuzumab deruxtecan following failure of another HER2-targeted therapy makes sense because of the increased risk of toxicity, the mechanism of action, and its maintained level of activity.

For patients with colorectal cancer, the preferred pathway remains dual inhibition with trastuzumab and lapatinib, or preferably enrollment in a clinical trial evaluating agents such as trastuzumab and tucatinib. Patients who develop progressive disease after treatment with these dual agents can then receive treatment with trastuzumab deruxtecan.

EGFR Rechallenge

Colon cancer is an exciting field for precision medicine. However, treatment options are limited. Patients are living longer and doing better. The concept of rechallenge, or re-introduction, of chemotherapy was introduced many years ago with mixed enthusiasm. The role of rechallenge with biologic agents is not known. Rechallenge with chemotherapy does not appear beneficial for almost all patients. (Rechallenge might make sense for the very few patients in whom chemotherapy never technically failed.) With biologic agents, it is easier to measure clones that drive resistance to the particular antibodies, such as antibodies to EGFR. This type of resistance is predominantly driven by mutant *RAS* and *EGFR* ectodomain clones. Patients who are *RAS* wild type receive treatment with an EGFR inhibitor. After treatment, analysis of circulating tumor DNA might show the dominance of mutant *RAS* and *EGFR* ectodomain clones, which leads to resistance to the anti-EGFR agents. Preliminary data showed that *EGFR RAS* alleles decreased when treatment with EGFR inhibitors was stopped. This finding appears to indicate that the tumor will regain sensitivity, and it may be possible to use blood-based profiling to reinitiate EGFR inhibitors.

The phase 2 CHRONOS study evaluated anti-EGFR rechallenge with panitumumab in patients who developed progressive disease during previous treatment with EGFR inhibitors.[43] Patients underwent liquid biopsies of circulating tumor DNA. A response to rechallenge was seen in 30% of the patients in whom *RAS* mutant and *EGFR* ectodomain alleles disappeared. It is therefore possible to reuse biologic agents based on rational findings, at least from this small, single-arm study. This treatment strategy has not been compared with other therapies, such as regorafenib or trifluridine/tipiracil. The ongoing randomized phase 2 PULSE trial in the United States is evaluating the same principle of rechallenge with an EGFR inhibitor, but in comparison with a standard treatment arm.[44] Rechallenge with an EGFR inhibitor is not appropriate for all patients. Patients must undergo a liquid biopsy of circulating tumor DNA markers to determine whether treatment might be beneficial. It will be challenging to establish use of this type of testing as a component of standard-of-care treatment. That said, I would encourage all physicians in the United States to consider enrolling suitable patients into the PULSE trial, which will provide randomized data regarding the use of EGFR rechallenge vs the standard of care.

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References

1. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218.

2. André T, Shiu KK, Kim TW, et al. Final overall survival for the phase III KN177 study: pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer [ASCO abstract 3500]. *J Clin Oncol*. 2021;39(15 suppl).

3. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. *J Clin Oncol*. 2020;38(1):11-19.

4. Ott PA, Le DT, Kim JW, et al. Nivolumab (NIVO) in patients (pts) with advanced (adv) chemotherapy-refractory (CT-Rx) esophagogastric (EG) cancer according to microsatellite instability (MSI) status: CHECKMATE 032 [ESMO abstract 674P]. *Ann Oncol*. 2017;28(suppl 5).

5. Azad NS, Gray RJ, Overman MJ, et al. Nivolumab is effective in mismatch repair-deficient noncolorectal cancers: results from arm Z1D-a subprotocol of the NCI-MATCH (EAY131) study. *J Clin Oncol*. 2020;38(3):214-222.

6. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
7. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res*. 2017;23(8):1920-1928.
8. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773-779.
9. Cohen R, Bennouna J, Meurisse A, et al. RECIST and iRECIST criteria for the evaluation of nivolumab plus ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the GERCOR NIPICOL phase II study. *J Immunother Cancer*. 2020;8(2):e001499.
10. ClinicalTrials.gov. A study of nivolumab, nivolumab plus ipilimumab, or investigator's choice chemotherapy for the treatment of participants with deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC) (CheckMate 8HW). https://clinicaltrials.gov/ct2/show/NCT04008030. Identifier: NCT04008030. Accessed July 24, 2021.
11. Hellmann MD, Kim TW, Lee CB, et al. Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors. *Ann Oncol*. 2019;30(7):1134-1142.
12. Eng C, Kim TW, Bendell J, et al; IMblaze370 Investigators. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2019;20(6):849-861.
13. Hato T, Zhu AX, Duda DG. Rationally combining anti-VEGF therapy with checkpoint inhibitors in hepatocellular carcinoma. *Immunotherapy*. 2016;8(3):299-313.
14. Chen DS, Hurwitz H. Combinations of bevacizumab with cancer immunotherapy. *Cancer J*. 2018;24(4):193-204.
15. Lieu CH, Davis SL, Leong S, et al. Results from the safety lead-in for a phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory metastatic colorectal cancer (mCRC) [ASCO abstract 4031]. *J Clin Oncol*. 2020;38(15 suppl).
16. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). *J Clin Oncol*. 2020;38(18):2053-2061.
17. Fakih M, Raghav KP, Chang DZ, et al. Single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair proficient/microsatellite stable colorectal cancer [ASCO abstract 3560]. *J Clin Oncol*. 2021;39(15 suppl).
18. Wang C, Chevalier D, Saluja J, Sandhu J, Lau C, Fakih M. Regorafenib and nivolumab or pembrolizumab combination and circulating tumor DNA response assessment in refractory microsatellite stable colorectal cancer. *Oncologist*. 2020;25(8):e1188-e1194.
19. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019;20(8):1070-1082.
20. Fakih M, Cleary JM, Hong YS, et al. Phase 1b/2 open-label, randomized evaluation of atezolizumab + Imprime PGG + bevacizumab vs regorafenib in MORPHEUS: microsatellite-stable metastatic colorectal cancer [ASCO abstract 3559]. *J Clin Oncol*. 2021;39(15 suppl).
21. Mettu NB, Twohy E, Ou F, et al. BACCI: a phase II randomized, double-blind, multicenter, placebo-controlled study of capecitabine (C) bevacizumab (B) plus atezolizumab (A) or placebo (P) in refractory metastatic colorectal cancer (mCRC): an ACCRU network study [ESMO 3454]. *Ann Oncol*. 2019;30(suppl 5).
22. Gomez-Roca C, Yanez E, Im SA, et al. LEAP-005: a phase 2 multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—results from the colorectal cancer cohort [ASCO abstract 3564]. *J Clin Oncol*. 2021;39(15 suppl).
23. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2020;38(26):2960-2970.
24. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):711-718.
25. Taylor MH, Lee CH, Makker V, et al. Phase Ib/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. *J Clin Oncol*. 2020;38(11):1154-1163.
26. Guo Y, Zhang W, Ying J, et al. Preliminary results of a phase 1b study of fruquintinib plus sintilimab in advanced colorectal cancer [ASCO abstract 2514]. *J Clin Oncol*. 2021;39(15 suppl).
27. Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.
28. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
29. Kuboki Y, Terazawa T, Masuishi T, et al. The TRUSTY study: a randomized phase 2/3 study of trifluridine/tipiracil plus bevacizumab versus irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer [ASCO abstract 3507]. *J Clin Oncol*. 2021;39(15 suppl).
30. Kuboki Y, Nishina T, Shinozaki E, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol*. 2017;18(9):1172-1181.
31. Yoshida Y, Yamada T, Kamiyama H, et al; TAS CC3 Study Group. Combination of TAS-102 and bevacizumab as third-line treatment for metastatic colorectal cancer: TAS-CC3 study. *Int J Clin Oncol*. 2021;26(1):111-117.
32. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(6):738-746.
33. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20(4):518-530.
34. Strickler JH, Zemla T, Ou F, et al. Trastuzumab and tucatinib for the treatment of *HER2* amplified metastatic colorectal cancer (mCRC): initial results from the MOUNTAINEER trial [ESMO abstract 527PD]. *Ann Oncol*. 2019;30(suppl 5).
35. Bertotti A, Migliardi G, Galimi F, et al. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. *Cancer Discov*. 2011;1(6):508-523.
36. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017;18(6):743-754.
37. Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international, randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol*. 2017;18(5)640-653.
38. Sartore-Bianchi A, Martino C, Lonardi S, et al. Phase II study of pertuzumab and trastuzumab-emtansine (T-DM1) in patients with HER2-positive metastatic colorectal cancer: the HERACLES-B (*HER2* amplification for colo-rectal cancer enhanced stratification, cohort B) trial [ESMO abstract 3857]. *Ann Oncol*. 2019;30(suppl 5).
39. Yoshino T, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-expressing metastatic colorectal cancer (mCRC): final results from a phase 2, multicenter, open-label study (DESTINY-CRC01) [ASCO abstract 3505]. *J Clin Oncol*. 2021;39(15 suppl).
40. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
41. Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419-2430.
42. Siena S, Di Bartolomeo M, Raghav K, et al; DESTINY-CRC01 Investigators. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2021;22(6):779-789.
43. Sartore-Bianchi A, Pietrantonio F, Lonardi S, et al. Phase II study of anti-EGFR rechallenge therapy with panitumumab driven by circulating tumor DNA molecular selection in metastatic colorectal cancer: the CHRONOS trial [ASCO abstract 3506]. *J Clin Oncol*. 2021;39(15 suppl).
44. Strickler JH, Ou FS, Bekaii-Saab TS, et al. PULSE: a randomized phase II open label study of panitumumab rechallenge versus standard therapy after progression on anti-EGFR therapy in patients with *RAS* wild-type metastatic colorectal cancer (mCRC) [ASCO GI abstract TPS143]. *J Clin Oncol*. 2021;39(3 suppl).