(19.4%) bleeding (mayor or fatal bleeding 4 patients). Median survival was 20.86 months for non-VTE patients and 11.30 months for VTE patients (hazard-ratio [HR] 2.13; CI 95% 1.38-3.28; p=0.001).

Conclusions: VTE is associated with increased morbidity and mortality in patients with BRAF-mutated CRC.

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P-12 A phase 3 study of nivolumab (NIVO), NIVO + ipilimumab (IPI), or chemotherapy for microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): CheckMate 8HW

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Background: Patients with MSI-H/dMMR mCRC treated with chemotherapy have poorer outcomes than patients with microsatellite stable/MMR proficient mCRC. Pembrolizumab monotherapy is approved in multiple countries as first-line therapy for patients with MSI-H/dMMR mCRC; however, despite observed clinical benefit vs chemotherapy, the 24-month progression-free survival (PFS) rate was 48% (Andre et al. NEJM 2020). NIVO (anti−programmed death 1 [PD-1]) and IPI (anti−cytotoxic T lymphocyte antigen-4 [CTLA-4]) are immune checkpoint inhibitors with distinct but complementary mechanisms. NIVO±IPI is approved in previously treated patients with MSI-H/dMMR mCRC in the US, EU, and Japan, based on findings from the phase 2, non-randomized, multicohort CheckMate 142 study. Indirect comparisons suggest that NIVO (3 mg/kg) + IPI (1 mg/kg) provides improved clinical benefit vs NIVO (investigator-assessed [INV] objective response rate [ORR] 55% vs 31%; 12-month INV PFS rate 71% vs 50%; 12-month overall survival [OS] rate 85% vs 73%) with a favorable benefit-risk profile for previously treated MSI-H/dMMR mCRC (Overman et al. JCO 2018). NIVO+IPI also demonstrated robust and durable clinical benefit and was well tolerated for the first-line treatment of MSI-H/dMMR mCRC (INV ORR 69%; 24-month INV PFS rate 74%; 24-month OS rate 79%; Lenz et al. JCO 2022). To date, no prospective phase 3 studies have reported results for anti−PD-1 + anti−CTLA-4 vs chemotherapy or anti−PD-1/programmed death ligand 1 (PD-L1) monotherapy in MSI-H/dMMR mCRC. CheckMate 8HW (NCT04008030) is an international, multicenter, open-label, randomized, phase 3 study designed to compare the efficacy and safety of NIVO+IPI to chemotherapy or NIVO in patients with MSI-H/dMMR mCRC.

Trial design: Approximately 748 patients across 23 countries aged ≥18 years with histologically confirmed recurrent or mCRC that is not amenable to surgery, irrespective of prior treatment with chemotherapy and/or targeted agents, with known tumor MSI-H or dMMR status and ECOG performance status ≤1 will be randomized to receive NIVO, NIVO+IPI, or investigator's choice chemotherapy (patients in the chemotherapy arm can receive NIVO+IPI upon progression). The dual primary endpoints are PFS, assessed by blinded independent central review (BICR), for NIVO+IPI vs NIVO across all lines and NIVO+IPI vs chemotherapy in the first-line setting in patients with centrally confirmed MSI-H/dMMR mCRC. Other key endpoints include PFS by BICR for NIVO+IPI vs NIVO in the first-line setting, PFS by INV, ORR by BICR, OS, and safety. Recruitment of patients in the first-line setting is ongoing.

Clinical trial identification: NCT04008030.

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P-14 Safety and short-term efficacy of preoperative FOLFOX therapy for patients with resectable esophageal squamous cell carcinoma who are not candidates for cisplatin

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Background: The standard treatment for resectable locally advanced esophageal squamous cell cancer (LAESCC) in Japan is a preoperative cisplatin (CDDP)-containing chemotherapy followed by surgery. However, patients with renal or cardiac dysfunction and elderly patients are not candidates for CDDP because of renal toxicity and the need to ensure adequate hydration. Oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) therapy, which causes less renal toxicity than CDDP-containing regimens and does not require hydration, has efficacy comparable with that of CDDP plus 5-fluorouracil as part of definitive chemoradiotherapy or palliative chemotherapy. However, data on the safety and efficacy of preoperative FOLFOX therapy in patients who are unsuitable for CDDP remains unknown.

Methods: Patients who received preoperative FOLFOX therapy at our hospital between 2019 and 2021 were enrolled in this retrospective study. The main selection criteria were as follows: histologically proven squamous cell carcinoma; cT1N1-3M0, cT2-3N0-3M0, cT1-3N0-3M1, or M1 disease limited to supraclavicular lymph node metastasis (UICC TNM 8th edition); age ≥75 years or renal dysfunction (creatinine clearance < 60 mL/min) or cardiac dysfunction (ejection fraction ≤45% on cardiac ultrasound, past history of heart failure, ischemic heart disease, or poorly controlled arrhythmia); and no history of therapy for esophageal cancer. Preoperative FOLFOX therapy (oxaliplatin 85 mg/m2, leucovorin 200 mg/m2, and 5-fluorouracil 400 mg/m2 [bolus] plus 2400 mg/m2 [continuous] every 2 weeks) was administered for 3 or 4 courses. We evaluated adverse events during preoperative chemotherapy (CTCAE version 5.0) and the relative dose intensity, complete resection rate, and histopathological response.

Results: Thirty-five patients were eligible for inclusion in the study (median age 77 years [range, 65−89]; performance status 0/1, 40%/60%; clinical stage I/II/III/IVB, 11%/29%/57%/3%). The reasons for selecting FOLFOX were renal dysfunction (74%), age ≥75 years (69%), and cardiac dysfunction (17%). The median creatinine clearance in patients with renal dysfunction was 45.0 mg/dL (range, 26.4−56.1). Four patients (11.4%) discontinued chemotherapy because of progression (n=2), febrile neutropenia (n=1), or neutropenia (n=1). The relative dose intensity was 78.9% for 5-fluorouracil and 85.2% for oxaliplatin. The most common grade ≥3 adverse events were neutropenia (60%) and leucopenia (29%). Two patients (6%) developed febrile neutropenia and pneumonia. Granulocyte colony-stimulating factor was used as secondary prophylaxis in 9 patients (26%). Grade ≥3 loss of appetite and nausea were observed in only 1 patient (3%). Mild elevation of creatinine was seen in 2 patients (6%). Of the 35 patients, 4 did not proceed to surgery (patient declined, n=3; pneumonia, n=1). Finally, 31 patients underwent surgery. The complete resection rate was 87% (27/31) and the pathological complete resection rate was 16% (5/31). There were no treatment-related deaths.

Conclusions: Preoperative FOLFOX therapy was well tolerated and showed promising short-term efficacy in patients with resectable LAESCC who were not candidates for CDDP.

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