nivolumab showed clinical benefit. Here, we present long-term follow-up results from CheckMate 459.

Methods: In CheckMate 459, 743 systemic therapy—naive patients ≥ 18 years of age with aHCC and Child-Pugh A liver function were randomized 1:1 to nivolumab (240 mg intravenous every 2 weeks; n = 371) or sorafenib (400 mg oral twice daily; n = 372). The primary endpoint was OS. Secondary endpoints were objective response rate and progression-free survival by blinded independent central review per Response Evaluation Criteria in Solid Tumors v1.1; efficacy by programmed death ligand 1 (PD-L1) tumor cell expression; and safety.

Results: At a minimum follow-up of 33.6 months, nivolumab demonstrated a clinically meaningful improvement in OS versus sorafenib (median OS, 16.4 months [95% CI, 14.0—18.5] vs 14.8 months [95% CI, 12.1—17.3], respectively; hazard ratio [HR], 0.85 [95% CI, 0.72—1.00]; nominal *P* value = 0.0522). The 33-month OS rates for nivolumab and sorafenib were 29% (95% CI, 25—34) and 21% (95% CI, 17—25), respectively. A consistent benefit was observed with nivolumab regardless of baseline PD-L1 expression (PD-L1 ≥ 1% HR, 0.80 [95% CI, 0.54—1.17]; PD-L1 < 1% HR, 0.84 [95% CI, 0.70—1.01]). Median OS (mOS) in patients with PD-L1 ≥ 1% was longer with nivolumab versus sorafenib (16.1 months [95% CI, 8.4—22.3] vs 8.6 months [95% CI, 5.7—16.3], respectively). Among patients with hepatitis C virus (HCV) and hepatitis B virus (HBV) etiology, mOS was numerically longer with nivolumab versus sorafenib (17.5 vs 12.7 months; HR, 0.72 [95% CI, 0.51—1.02] for HCV and 16.1 vs 10.4 months; HR 0.79 [95% CI, 0.59—1.07] for HBV, respectively). Nivolumab demonstrated greater liver function preservation over time than sorafenib as evidenced by albumin-bilirubin levels and Child-Pugh scores. Seven patients (2%) in the nivolumab arm and 77 patients (21%) in the sorafenib arm received subsequent immuno-oncology therapy. Nivolumab demonstrated a more favorable safety profile compared with sorafenib, with grade 3—4 treatment-related adverse events occurring in 82 patients (22.3%) and 180 patients (49.6%), respectively.

Conclusion: At a minimum follow-up of 33.6 months, 1L nivolumab monotherapy continued to demonstrate clinically meaningful survival benefit in aHCC. Nivolumab had a more favorable and manageable safety profile and greater preservation of liver function over time compared with sorafenib, consistent with previous reports, with no new or unexpected safety signals observed.

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LBA-4 Updated analysis of DELIVER trial (JACCRO GC-08): A large observational/translational study of nivolumab treatment in advanced gastric cancer

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Background: Nivolumab (Nivo) demonstrated survival benefit in previously treated gastric cancer patients (pts), with a response rate (RR) of 11% and a disease control rate (DCR) of 40% in a phase III trial (ATTRACTION-2: AT-2)(Kang YK, et al. *Lancet* 2017). Alternatively, about 60% of the pts did not respond to Nivo, and it has been demonstrated that some tumors grow rapidly after Nivo treatment, but the proportion is uncertain. There are few real-world data of Nivo, and its predictive markers are needed in gastric cancer. Several studies revealed that the efficacy of anti-PD-1-based immunotherapy was associated with composition of gut microbiome in various types of cancers. We therefore investigated clinical outcomes of Nivo in clinical practice and whether host-related immune-factors will serve as predictors for Nivo in advanced gastric cancer.

Methods: DELIVER trial was a prospective, multicenter, observational/translational study which assessed pts with advanced gastric or gastroesophageal junction adenocarcinoma treated with Nivo alone and ECOG Performance Status (PS) 0-2 (UMIN000030850). The aims were to evaluate the efficacy and safety of Nivo treatment in real world, and to discover novel host-related immune-biomarkers using fecal and blood samples which were collected before and after treatment with Nivo. The RR, DCR, progression-free survival (PFS), overall survival (OS), and tumor growth rate (TGR) were estimated as the efficacy. Novel biomarkers to predict clinical outcomes of Nivo will be explored in the first 200 pts and then validated in the last 300 pts from host-related factors (gut microbiome, genetic polymorphism, gene expression, and metabolome). The tumor response was evaluated based on RECIST version 1.1.

Results: A total of 501 pts was enrolled in this study from Mar 2018 to Aug 2019, and 487 pts were evaluable for analysis (median age 70 years old, 71% male, ECOG PS0/1/2 42%/44%/14%, no. of prior regimen 1/2/≥3 2%/39%/59%, 21% HER2-pos, 42% pts with ascites). The DCR was 39.2% (95%CI 34.9-43.7) in the evaluable pts. In 282 pts with measurable lesions, the RR was 6.7% (95%CI 4.1-10.3) and DCR was 36.5%. Subgroup analysis by patient background indicated that DCR was 41% for PS0, 42% for PS1, and 24% for PS2. In addition, the DCR was lower in pts with ascites compared to those without ascites (28.6% vs. 47.0%, p=0.005). When TGR was calculated as a percentage increase in tumor volume during 1 month, it decreased after introduction of Nivo in 124 (56.6%) of 219 evaluable pts for TGR; however, 20.5% pts were identified as experiencing hyper-progressive disease (HPD) which was defined as a ≥2-fold increase of the TGR before and after Nivo treatment. Preliminary data indicated median PFS of 1.8 months and median OS of 5.9 months in the evaluable pts and common adverse events such as fatigue, decreased appetite, and nausea, were observed more frequently compared to those of the AT-2.

Conclusion: The real-word data of the large observational trial showed comparable clinical outcomes to those of the AT-2 and some pts experiencing rapid tumor growth in advanced gastric cancer treated with Nivo.

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LBA-5 ANCHOR CRC: a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated BRAF V600E-mutant metastatic colorectal cancer

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Background: *BRAF*V600E mutations are identified in 8-15% of metastatic colorectal cancer (mCRC) patients and confer a poor prognosis. In patients with *BRAF*V600E-mutant mCRC, the combination of encorafenib (ENCO) + cetuximab (CETUX) ± binimetinib (BINI) in second- and third-line therapy has demonstrated improved outcomes compared to standard therapies (BEACON CRC study). The ANCHOR CRC study was designed to investigate the triplet combination (ENCO + BINI + CETUX) in the first line setting of this population.

Methods: ANCHOR CRC is an open-label, single arm, two-stage design, phase 2 study in patients with *BRAF*V600E-mutant mCRC who did not receive any prior systemic therapy for metastatic disease. Patients received ENCO 300 mg orally QD + BINI 45 mg orally BID and CETUX IV weekly (250mg/m^2 after a first dose of 400mg/m^2) for the first 28 weeks and then once every two weeks (500mg/m^2). The primary endpoint was confirmed Objective Response Rate (cORR) based on local review; secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. Analysis for Stage 1 was performed after the first 40 evaluable patients with a centrally confirmed *BRAF*V600E mutation had completed four post-baseline tumor assessments or discontinued. At least 12 responses in Stage

1 were needed to initiate Stage 2 and to enroll 50 additional patients to complete the recruitment with a total of 90 patients in the study. Stage 1 analysis results are presented here.

Results: Forty-one *BRAF*V600E-mutant mCRC patients with a median age of 67 years old (61% of the patients were ≥ 65 years old) were enrolled in Stage 1 and received the triplet combination as first line metastatic treatment. At study entry, 56% of patients presented with ECOG PS 1, 78% had metastases to at least 2 organs and 51% had peritoneal metastasis. Forty patients were evaluable for efficacy (*BRAF*V600E mutation was not centrally confirmed for one patient). The investigator assessed cORR was 50% (95% confidence interval [CI], 33.8-66.2) with 85% of patients having a decrease in tumor size. The investigator measured median PFS was 4.9 months (95% CI, 4.4-8.1). Adverse events were consistent with those observed in prior studies with this triplet combination. Grade 3 or higher adverse events were seen in 68% of patients, the most common being: diarrhea (15%), acute kidney injury (12%) and anemia (12%).

Conclusion: The ANCHOR CRC study is the first prospective study using a BRAF inhibitor-based therapy in first line *BRAF*V600E-mutant mCRC. Despite the high risk features of the population enrolled in Stage 1, including high proportion of patients ≥ 65 years old and advanced stage at diagnosis (multiple metastatic sites with frequent peritoneal carcinomatosis), most patients had tumor regression. The safety profile was acceptable and toxicities remained manageable. The Stage 1 analysis exceeded the minimal number of confirmed responses and proceeded to enroll 54 additional patients in Stage 2 to complete the study recruitment.

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LBA-6 Safety, feasibility, tolerability, and preliminary efficacy of perioperative systemic therapy for resectable colorectal peritoneal metastases: Pilot phase of a randomised trial (CAIRO6)

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Background: As CAIRO6 is the first randomized trial investigating perioperative systemic therapy for colorectal peritoneal metastases, this pilot phase was incorporated to assess its feasibility, safety, and tolerability, and response to neoadjuvant treatment.

Methods: In the pilot phase of this open-label parallel-group trial in nine Dutch tertiary centers, 80 patients with isolated resectable colorectal peritoneal metastases were randomized (1:1) to perioperative systemic therapy and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) or CRS-IPEC alone. Perioperative systemic therapy comprised either four three-weekly neoadjuvant and adjuvant cycles of CAPOX (capecitabine, oxaliplatin), six two-weekly neoadjuvant and adjuvant cycles of FOLFOX (5-fluorouracil, leucovorin, oxaliplatin), or six two-weekly neoadjuvant cycles of FOLFIRI (5-luorouracil, leucovorin, irinotecan) and either four three-weekly or six two-weekly adjuvant cycles of capecitabine or 5-fluorouracil/leucovorin, respectively. Bevacizumab was added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles. Main outcomes were proportions of complete CRS-HIPEC, major postoperative morbidity, grade ≥3 systemic therapy-related toxicity, and centrally assessed objective radiological and major pathological response to neoadjuvant treatment. Analyses were done modified intention-to-treat in patients starting neoadjuvant treatment (experimental) or undergoing upfront surgery (control).

Results: In 79 analyzed (of 80 randomized) patients, enrolled between June 2017 and January 2019, experimental (n=37) and control (n=42) arms had comparable proportions of complete CRS-HIPEC (33/37 [89%] versus 36/42 [86%], p=0.74) and major postoperative morbidity (8/37 [22%] versus 14/42 [33%], p=0.25). Grade 3-4 systemic therapy-related toxicity was observed in 13/37 (35%) patients. No treatment-related deaths occurred. Objective radiological and major pathological response rates to neoadjuvant treatment were 28% and 37%, respectively.

Conclusion: Perioperative systemic therapy is feasible, safe, tolerable, and able to induce tumor response in patients with isolated resectable colorectal peritoneal metastases.

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LBA-7 Encorafenib plus cetuximab with or without binimetinib for *BRAF*V600E metastatic colorectal cancer (mCRC): Relationship between carcinoembryonic antigen (CEA) and clinical outcomes from BEACON CRC

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Background: In BEACON CRC (NCT02928224), encorafenib plus cetuximab with or without binimetinib improved overall survival (OS) and response rate versus control (irinotecan or FOLFIRI, plus cetuximab) in patients with *BRAF*V600E-mutant mCRC with progression after 1–2 regimens. Elevations in CEA and CA19-9 are linked to poorer prognosis in CRC. We explored relationships between CEA, CA19-9, and clinical outcomes in BEACON CRC.

Methods: Patients were randomized to encorafenib + binimetinib + cetuximab (EBC; n=224), encorafenib + cetuximab (EC; n=220), or control (n=221). Blood samples for CEA and CA19-9 were taken at baseline and Day 1 of subsequent cycles, and end of treatment. Sample analysis and response assessment were conducted centrally. Patients were grouped into tertiles according to their baseline CEA/CA19-9 levels. Associations between baseline CEA/CA19-9 levels and clinical outcomes, and change in CEA/CA19-9 levels from baseline to Cycle 2 and clinical outcomes, were assessed.

Results: The tertile cutoffs for baseline CEA levels were (measured as µg/L): T1: ≤ 8, T2: > 8 to ≤ 66 and T3: > 66. In patients receiving EBC or EC, median OS varied by baseline CEA tertiles: T1: 17.8 mos, T2: 9.5 mos, T3: 7.2 mos (EBC); T1: 17.7 mos, T2: 9.0 mos, T3: 6.1 mos (EC); T1: 9.5 mos, T2: 4.8 mos, T3: 4.8 mos (control). In the experimental arms, CEA reductions were seen at Cycle 2 for patients with T2 and T3 baseline CEA (EBC, T2: 56% improved [shifted to lower tertile group], 32% stayed the same [remained in same tertile group], none worsened [shifted to higher tertile group], 11% discontinued; EBC, T3: 56% improved, 36% stayed the same, 8% discontinued; EC, T2: 60% improved, 28% stayed the same, none worsened, 12% discontinued; EC, T3: 52% improved, 32% stayed the same, 13% discontinued). In the control arm, only 6% of patients with baseline T2 CEA improved, 48% stayed the same, 12% worsened, 35% discontinued; among patients with baseline T3, 1% improved, 61% remained the same, 37% discontinued. In the experimental arms, for patients with T3 baseline CEA, median OS was longer in those with versus without improvement in CEA: 7.4 versus 4.6 mos, respectively (EBC); 7.0 versus 3.7 mos, respectively (EC). There was no statistically significant interaction between treatment and CEA groups for OS. In all arms, patients with larger decreases in CEA from baseline to first tumour assessment were more likely to respond or achieve stable disease; baseline CEA was not associated with overall response. Similar results were observed for CA19-9.

Conclusions: Among patients receiving EBC or EC, lower baseline CEA was associated with longer OS; among patients with the highest baseline CEA, reduction in CEA on treatment was associated with improved OS. Both baseline CEA and early on-treatment changes in CEA and CA19-9 may potentially identify a subgroup of patients with a numerically greater increase in survival and improved clinical outcomes with targeted therapy in *BRAF*V600E-mutant mCRC.

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