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P-81 Phase 3 study of MK4280A (coformulated favezelimab and pembrolizumab) versus standard of care in previously treated PD-L1−positive metastatic colorectal cancer (mCRC)

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Background: Immune checkpoint (IC) inhibitors are effective in mismatch repair-deficient or microsatellite instability-high colorectal cancer (CRC). However, for mismatch repair-proficient (pMMR) mCRC, which account for 95% of mCRC tumors, treatment options are limited. In patients with CRC, LAG-3 is overexpressed on colorectal immune cells and correlated with poor differentiation, advanced stage, lymph node involvement and invasion depth (Chen J, Zihua C. Med Oncol. 2014; 31:82). As such, LAG-3 represents a rational target for IC inhibition in CRC. IC inhibitor combination therapy with MK4280A, a coformulation of anti−LAG3 antibody favezelimab and pembrolizumab, has shown promising antitumor activity and a manageable safety profile in patients with PD-L1 CPS≥1 microsatellite stable mCRC and may be efficacious in pMMR mCRC (Garralda E et al. J Clin Oncol. 2021;39. Abstract 3584). In this ongoing phase 3 study (NCT05064059), we will evaluate the efficacy and safety of MK-4280A in patients with PD-L1−positive pMMR mCRC.

Trial design: The open-label, parallel group, active-controlled study plans to enroll approximately 432 patients aged ≥18 years with histologically confirmed unresectable mCRC, pMMR and PD-L1 CPS ≥1 tumors, and measurable disease per RECIST v1.1 by investigator review. All patients must have experienced progressive disease after: 1) fluoropyrimidine, irinotecan and oxaliplatin, with or without anti-VEGF antibody, anti−EGFR antibody for patients with left-sided tumors that are RAS WT, and 2) RAF inhibitor with or without binimetinib in patients with BRAF v600E mutations. Key eligibility criteria include ECOG status 0 or 1, adequate organ function, and availability of archival or newly obtained tissue sample to assess PD-L1 and MMR status. Patients will be randomly assigned to MK-4280A (coformulated favezelimab 800 mg/pembrolizumab 200 mg; Arm A) IV Q3W or standard of care (Arm B) (regorafenib 160 mg PO Q4W [QD on days 1-21; no dose on days 22-28] or TAS-102 35mg/m^2 PO Q4W [BID on days 1-5 and 8-12; no dose on days 6, 7, and 13-28]). Patients will be stratified by geographic region (Asia Pacific, EMEA/Americas), presence of liver metastases (yes, no) and time from initial diagnosis of mCRC to randomization (≥18 mo, < 18 mo). Treatment will continue for ≤35 cycles of MK-4280A or unacceptable toxicity, disease progression, confirmed CR with MK-4280A must have been treated for ≥8 cycles and have received 2 cycles after the initial CR was observed (Arm A), or withdrawal from study. Disease assessment by CT or MRI will be performed Q9W during the study. Primary end point is overall survival (OS). Secondary end points are progression free survival (PFS), objective response rate (ORR) and duration of response (by blinded independent central review per RECIST v1.1), patient-reported outcomes on health-related quality of life, and safety graded per NCI CTCAE v5.0. OS and PFS will be estimated by Kaplan-Meier methods. ORR with 95% CI will be estimated using the Clopper-Pearson method.

Clinical trial identification: ClinicalTrials.gov, NCT05064059.

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P-82 Evaluation of prognostic tools in locally advanced rectal cancer patients treated with neoadjuvant chemoradiotherapy

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Background: Neoadjuvant chemoradiotherapy (NCR) has become the standard of treatment for patients with locally advanced rectal cancer (LARC). Several prognostic tools such as Neoadjuvant Rectal (NAR) score, Tumor Regression grade (TRG), pathological staging or Downstaging have been developed. However, inconsistent findings among different studies have been shown, therefore their prognostic value has not been validated. Our aim is to find prognostic factors for Overall Survival (OS) and Disease-Free-Survival (DFS) in a cohort of LARC patients.

Methods: A total of 385 LARC patients treated with NCR between 2000 and 2019 were included. Epidemiologic and tumor characteristics were studied. NAR score, TRG and Downstaging were calculated. Kaplan-Meier curves and univariate Cox regression were calculated for both OS and DFS. Finally, multivariate analysis using Cox regression model was performed.

Results: Of the 385 patients, 66.8% were males and median age was 66 years old. The main cT stage was T3 with 88,6% of cases and 41.6% cN2. 90.6% of patients underwent treatment with concomitant radiotherapy and capecitabine. Median follow-up was 79 months. At the time of analysis, 28.8% of patients had died. Median OS was not reached, and median DFS was 178 months. 110, 188 and 85 patients were classified as low, moderate and high-risk NAR group respectively. 10-year-OS rates were 74.9%, 69.9%, and 47.1% in low, moderate and high-risk NAR groups respectively. HR comparing moderate and low group was 1.5 (p=0.13), and 3.05 (p<0.001) between high and low NAR. 10-year-DFS rates were with 72.8%, 60% and 44.4% respectively, with HR 1.85 (p=0.01) and 3.26 (p<0.001) comparing moderate and high with low-risk NAR groups respectively. 10-year-OS rates were 78% in patients with pCR, 65.4% minimal-moderate response and 54.8% if no response was observed. HR comparing pCR and moderate-minimal response was 1.75 (p=0.63) and 2.75 (p=0.003) between pCR and no response. 10-year-DFS rates were 75.1%, 59.1% and 44.9% for pCR, moderate-minimal and no response, HR 1.89 (p=0.019) between moderate-minimal response and pCR and HR 2.85 (p=0.001) between no response and pCR. 10-year-OS rates were 70.6% and 51.9% in patients with positive and negative Downstaging respectively, HR 1.98 (p=0.001). 10-year-DFS rates were 64.9% and 42.2% respectively HR 2.19 (p<0.001). Only age (p < 0,001), NAR group (p < 0.001) and R0 resection (p=0.017) remained as independent prognostic factors for OS at multivariate analysis. Evidence for R0 resection (p < 0.001), Downstaging (p < 0.001), age (p=0.007) and diagnostic CEA levels (p=0.036) as independent prognostic factors for DFS was also proved.

Conclusions: Among all the analyzed tools, only NAR score has shown evidence real prognostic value for OS, as well as Downstaging for DFS. These findings could help oncologists in deciding convenience for further post-resection treatment or stricter follow-up.

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