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Clinical Trial Protocol

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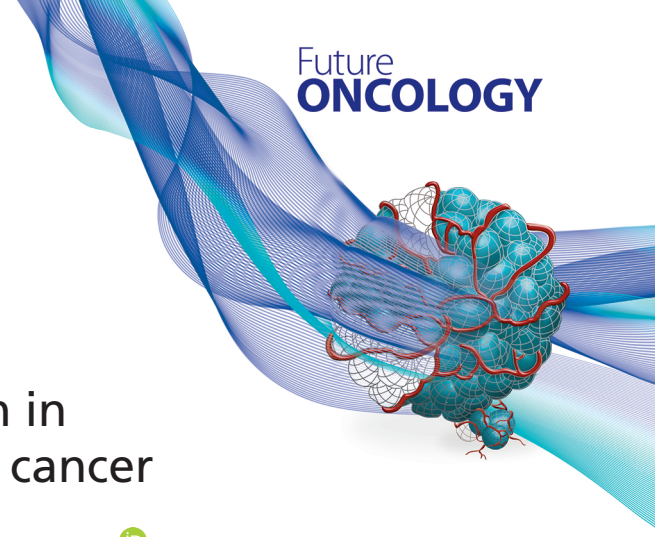

KEYSTEP-008: phase II trial of pembrolizumab-based combination in MSI-H/dMMR metastatic colorectal cancer

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Robust clinical activity has been observed with the immune checkpoint inhibitor pembrolizumab in patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). However, given the response rate of 45% and a median progression-free survival of 16.5 months with first-line pembrolizumab demonstrated in KEYNOTE-177, there is room for improvement. Targeting a second immune receptor, such as CTLA-4, LAG-3, TIGIT, or ILT-4 may improve efficacy of PD-1 inhibition. Here we describe the design and rationale for the open-label, randomized, phase II KEYSTEP-008 trial, which will evaluate the efficacy and safety of pembrolizumab-based combination therapy compared with pembrolizumab monotherapy in chemotherapy-refractory (cohort A) or previously untreated (cohort B) MSI-H/dMMR mCRC.

Clinical Trial Registration: NCT04895722 (ClinicalTrials.gov)

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Keywords: favezelimab • MK-4830 • MSI-H/dMMR colorectal cancer • pembrolizumab • quavonlimab • vibostolimab

In 2020, colorectal cancer (CRC) was the third most prevalent cancer, accounting for 10% of new cases, and the second most common cause of cancer-related mortality [1]. The incidence of CRC has been steadily rising in many formerly low-risk and lower Human Development Index countries in Eastern Europe, South Eastern and South Central Asia and South America, likely due to changes in lifestyle factors and diet [1,2]. In contrast, in many previously high-incidence countries, including the USA, Canada and Australia, a decline in overall incidence has been observed. However, this decline has been limited to adults aged ≥50 years, whereas the rate of early-onset CRC (aged <50 years at diagnosis) has increased [1,2]. Approximately 21% of CRCs are metastatic at diagnosis and have a lower 5-year survival rate of 15% compared with 91% for localized CRC and 72% for regional CRC.

Fewer than 5% of metastatic CRC (mCRC) is microsatellite instability-high (MSI-H) and/or mismatch repair-deficient (dMMR) [3]. Historically, patients with MSI-H/dMMR tumors treated with chemotherapy with or

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without targeted therapy have had significantly worse clinical outcomes compared with patients with mismatch repair-proficient tumors; however, MSI-H status is now considered a predictor of sensitivity to immune checkpoint inhibitors [3–5]. The emergence of effective immune checkpoint inhibitor therapies offers patients with MSI-H/dMMR mCRC an initial prognostic advantage; however, some patients do not respond to these therapies and some experience disease progression after an initial response. Despite recent advances in the treatment of MSI-H/dMMR mCRC, there remains a need for additional therapies for this subset of patients.

KEYSTEP-008 study

Here we describe the design and rationale of the open-label, randomized, multicenter, multi-arm, phase II KEYSTEP-008 trial (NCT04895722), which will assess the efficacy and safety of pembrolizumab-based combinations versus pembrolizumab monotherapy in MSI-H/dMMR mCRC.

Background & rationale

Pembrolizumab is a highly selective humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2, and thereby restores host antitumor activity [6]. Pembrolizumab has demonstrated robust clinical activity in MSI-H/dMMR solid tumors, including mCRC. Results from the phase II KEYNOTE-164 trial showed that pembrolizumab monotherapy had clinical activity in patients with mCRC who had been treated with ≥2 prior lines of standard therapy and in patients who had received ≥1 prior line of therapy (objective response rate [ORR], 33% each) [7]. Further, in the randomized phase III KEYNOTE-177 trial in patients with previously untreated MSI-H/dMMR mCRC, pembrolizumab monotherapy led to significantly longer progression-free survival (PFS) compared with chemotherapy (median, 16.5 months vs 8.2 months; HR: 0.60; 95% CI: 0.45–0.80; p = 0.0002) [8]. Although a trend toward improved overall survival (OS) was observed with pembrolizumab, the improvement did not reach statistical significance, likely due to the high effective crossover (60%) of patients from the chemotherapy treatment arm to receive treatment with pembrolizumab [9]. However, the response rate of 45% and the estimated 36-month OS rate of 61.4% with first-line pembrolizumab and the response rate of 33% with second-line or later pembrolizumab suggest there is room for improvement [7,9].

The addition of a second immune checkpoint inhibitor targeting a different immune inhibitory pathway such as CTLA-4, LAG-3, TIGIT and ILT-4 enhances host immunologic activity against tumors and further improves the efficacy of PD-1 inhibitors [10–12]. Additionally, compared with sequential administration, coformulated combination therapy may offer more convenience for patients and healthcare providers and reduce medication errors while maintaining a similar pharmacokinetic and safety profile [13]. This may be particularly relevant in our study as dosing of each drug does not change with body surface area or body weight. This approach is endorsed by the WHO [14]. Moreover, the agents being tested in this study have shown promising efficacy when combined with pembrolizumab and were not intended to be administered as monotherapy.

Quavonlimab is a novel humanized IgG1 monoclonal antibody that binds CTLA-4 and blocks the interaction with its ligands, CD80 and CD86 [15]. In a phase I study, first-line quavonlimab plus pembrolizumab showed antitumor activity (ORR, 37.5%) with a tolerable safety profile (grade 3–5 treatment-related adverse event [AE] rate, 30%) at the recommended phase II dose of quavonlimab 25 mg every 6 weeks (Q6W) in non-small-cell lung cancer [15]. Combination therapy with another PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab has also shown durable clinical benefit as first-line or later in patients with MSI-H/dMMR mCRC in the phase II CheckMate 142 study and is currently being evaluated in a phase III study (CheckMate 8HW) [16–21].

Favezelimab is a humanized IgG4 monoclonal antibody that binds to LAG-3 expressed on tumor-infiltrating lymphocytes and blocks interaction with major histocompatibility complex class II molecules on tumor cells. Tolerable safety has been observed with favezelimab in combination with pembrolizumab (grade 3–5 treatment-related AE rate, 20%) [22].

Vibostolimab is a humanized monoclonal antibody that blocks the interaction between the immune inhibitory receptor TIGIT and its ligands, CD112 and CD155 [23]. TIGIT is highly co-expressed with PD-1 in cancer, and, therefore, combination therapy with the anti–TIGIT antibody vibostolimab and pembrolizumab offers an attractive option for these patients [10,23]. In a first-in-human phase I trial, vibostolimab plus pembrolizumab demonstrated promising antitumor activity in patients with advanced solid tumors, including CRC and non-small-cell lung cancer, and particularly in patients who had PD-1/L1 inhibitor–naive tumors with PD-L1 tumor proportion score ≥1% (ORR, 33%) [23]. Vibostolimab plus pembrolizumab also had a tolerable safety profile (grade 3–5 treatment-related AE rate, 15%) [23].

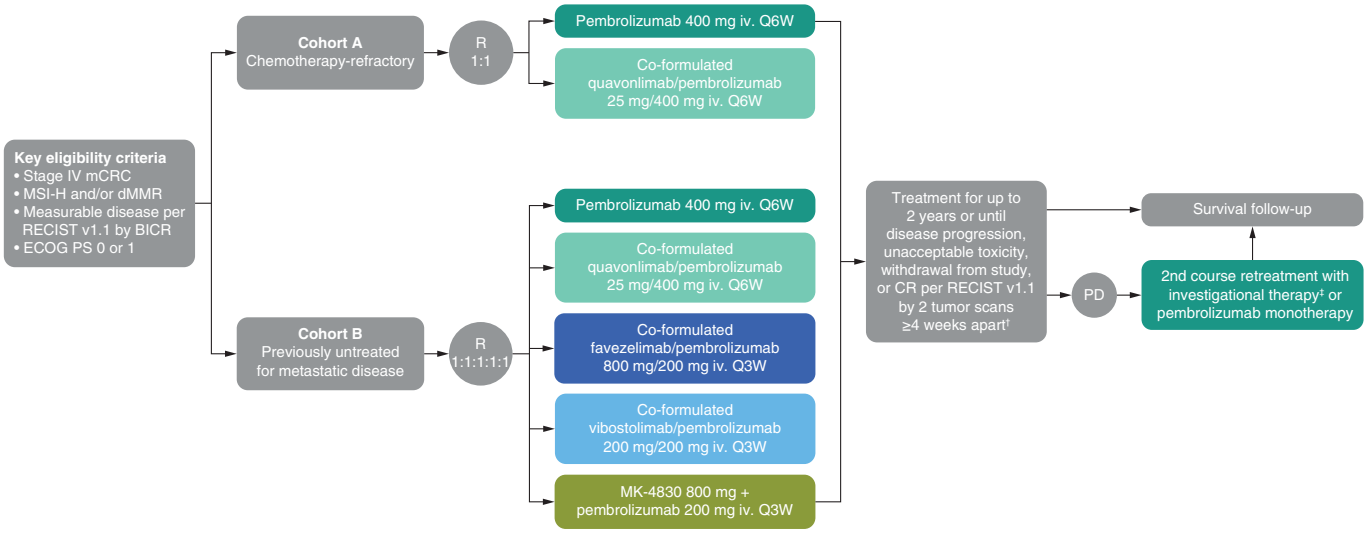

Figure 1. KEYSTEP-008 study design.
†Patients must have received ≥6 months of treatment before discontinuing treatment with ≥6 weeks of treatment beyond CR.
‡Second-course treatment should remain the same as the final treatment used in the first course of treatment.
BICR: Blinded independent central review; CR: Complete response; dMMR: Mismatch repair-deficient; ECOG PS: Eastern Cooperative Oncology Group performance status; iv.: Intravenous; mCRC: Metastatic colorectal cancer; MSI-H: Microsatellite instability-high; PD: Progressive disease; Q3W: Every 3 weeks; Q6W: Every 6 weeks; R: Randomization.

MK-4830 is another novel fully human IgG4 monoclonal antibody that targets ILT-4 and blocks its interaction with human leukocyte antigen G and other ligands [12]. Combination therapy with MK-4830 and pembrolizumab has demonstrated promising antitumor activity (ORR, 24%) in metastatic solid tumors for which no available therapy could convey clinical benefit, including previous use of PD-1/L1 inhibitor therapy [12]. The antitumor activity observed despite prior PD-1/L1 inhibitor therapy suggested that MK-4830 abrogates a PD-1 resistance mechanism [12]. MK-4830 also had a tolerable safety profile when used in combination with pembrolizumab (grade 3–5 treatment-related AE rate, 8%) [12].

The KEYNOTE-164 and KEYNOTE-177 studies demonstrated that pembrolizumab is active in MSI-H/dMMR mCRC, both in the first-line setting and in patients whose disease had been previously treated with chemotherapy [7,8,9]. However, even with the improvement in outcomes from pembrolizumab monotherapy in MSI-H/dMMR mCRC, there remains a need for still more progress. In the KEYNOTE-177 study, approximately 40% of patients treated with pembrolizumab experienced disease progression within 4 months of starting therapy, suggesting that a subgroup of patients with MSI-H tumors is refractory to anti–PD-1 monotherapy [9]. Early clinical data suggest adding a second checkpoint inhibitor that targets a different inhibitory response may potentiate the antitumor activity of pembrolizumab [10,11,12] . KEYSTEP-008 will provide further insight into the clinical utility of pembrolizumab-based immune checkpoint inhibitor combination therapy.

Study design & treatment

Study design

KEYSTEP-008 is an open-label, randomized, multicenter, multi-arm, active-controlled, phase II study of pembrolizumab-based therapy in patients with *de novo* or recurrent MSI-H and/or dMMR mCRC (Figure 1). There will be two cohorts in this study: a chemotherapy-refractory (cohort A) and a previously untreated (cohort B) cohort. Patients in cohort A will be randomly assigned 1:1 to received either co-formulated quavonlimab 25 mg/pembrolizumab 400 mg Q6W intravenously or pembrolizumab 400 mg Q6W intravenously. Patients in cohort B will be randomly assigned 1:1:1:1:1 to receive either co-formulated quavonlimab 25 mg/pembrolizumab 400 mg Q6W, co-formulated favezelimab 800 mg/pembrolizumab 200 mg every 3 weeks (Q3W), co-formulated vibostolimab 200 mg/pembrolizumab 200 mg Q3W, sequentially administered MK-4830 800 mg plus pembrolizumab 200 mg Q3W, or pembrolizumab monotherapy 400 mg Q6W. In both cohorts, treatment will continue for up to approximately 2 years (17 cycles for treatment administered Q6W, or 35 cycles for treatment administered Q3W) or until unacceptable toxicity, confirmed disease progression, or patient or physician decision

Table 1. Eligibility criteria for the KEYSTEP-008 study.

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Histologically confirmed diagnosis of mCRC adenocarcinoma (stage IV per AJCC v8) • Measurable disease per RECIST v1.1 as assessed by investigator and confirmed by BICR • Locally-confirmed MSI-H and/or dMMR tumor status • ECOG PS of 0 or 1 • Available archival or newly obtained tumor tissue sample that has not been previously irradiated • Adequate organ function • Life expectancy ≥3 months Cohort A: • Previously treated and radiographically progressed per RECIST v1.1 on or could not tolerate standard treatment, including all of the following: – Fluoropyrimidine, irinotecan, and oxaliplatin – With or without an anti–VEGF antibody – ≥1 anti–EGFR antibody (cetuximab or panitumumab) for patients with left-sided *RAS* wild-type tumors Cohort B: • Untreated stage IV MSI-H and/or dMMR mCRC with no prior chemotherapy or immunotherapy	• Has received prior therapy with an agent directed to another stimulatory or co-inhibitory T-cell receptor • Received prior systemic anticancer therapy within 4 weeks before first dose of study drug • Received radiotherapy within 2 weeks of first dose of study drug • Immunodeficiency or on chronic systemic corticosteroid therapy (exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before first dose of study drug • Additional malignancy that is progressing or has required active treatment within the past 2 years • Active CNS metastases and/or carcinoma meningitis • Active autoimmune disease that has required systemic treatment in the past 2 years • History of noninfectious pneumonitis that required corticosteroid therapy or has recurrent pneumonitis • History of acute or chronic pancreatitis • Neuromuscular disorders associated with an elevated creatine kinase level • Active infection requiring systemic therapy • Known history of HIV infection • Known active hepatitis B infection • Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from day 1 of study intervention administration or NYHA class III/IV congestive heart failure • Present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks before randomization • Prior allogenic tissue/solid organ transplant

AJCC v8: American Joint Committee on Cancer version 8; BICR: Blinded independent central review; CNS: Central nervous system; dMMR: Mismatch repair-deficient; ECOG PS: Eastern Cooperative Oncology Group performance status; mCRC: Metastatic colorectal cancer; MSI-H: Microsatellite instability-high; NYHA: New York Heart Association; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

to withdraw. Treatment can be discontinued if a patient achieves complete response (CR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) confirmed by two tumor scans ≥4 weeks apart and the patient has received ≥6 months of treatment prior to discontinuation with 6 weeks of therapy beyond initial CR. Combination therapy may be de-escalated to pembrolizumab monotherapy based on toxicity.

Patients in each cohort will be stratified by *RAS* tumor mutation status (wild-type vs mutant). No treatment crossover is planned for this study; however, patients who experience centrally-confirmed disease progression after initial response of stable disease or better may receive a second course of the treatment with the same therapy they initially received, or pembrolizumab monotherapy if de-escalation is required. A second course of the treatment will include an additional nine cycles of co-formulated quavonlimab/pembrolizumab or pembrolizumab, or 17 cycles of co-formulated favezelimab/pembrolizumab, co-formulated vibostolimab/pembrolizumab, or sequentially administered MK-4830 plus pembrolizumab.

Eligibility criteria

Eligibility criteria are described in detail in Table 1. In brief, 320 patients aged ≥18 years with measurable disease per RECIST v1.1 confirmed by blinded independent central review (BICR) and an Eastern Cooperative Oncology Group performance status of 0 or 1 will be enrolled. In cohort A, patients who have been previously treated with and experienced disease progression on or after a fluoropyrimidine, irinotecan and oxaliplatin, with or without an anti-vascular endothelial growth factor monoclonal antibody, and ≥1 anti–EGFR for left-sided *RAS* wild-type tumors will be enrolled. In cohort B, patients who have not been previously treated for stage IV disease will be enrolled. The study began in May 2021.

Study procedures

MMR status will be determined by immunohistochemistry and MSI status will be determined by PCR. For MMR/MSI status determined by next generation sequencing, confirmation with immunohistochemistry or PCR will be required. Tumors will be classified as dMMR in the absence of ≥1 of 4 MMR proteins or MSI-H if ≥2 allelic shifts among five analyzed microsatellite loci are detected.

Tumor imaging and disease assessment will be performed using CT, or MRI if CT is contraindicated. MRI is preferred for brain imaging; however, CT scans are acceptable if MRI is contraindicated. Bone scans may also be performed to evaluate bone metastases. Scans will be performed at baseline and every 9 weeks from the date of

allocation until disease progression, as assessed by the site and verified by BICR, initiation of a new anticancer treatment, withdrawal from study, or death.

Safety and tolerability will be assessed throughout the trial, including AEs, serious AEs, AEs leading to death or discontinuation, laboratory test results and vital signs. AEs will be monitored through 30 days after the end of treatment; serious AEs will be monitored for 90 days or 30 days if the patient begins new anticancer therapy after the end of treatment. AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

In cohort A, a health-related quality of life (HRQoL) assessment using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) and EuroQOL-5 dimensions-5 levels (EQ-5D-5L) will be administered prior to treatment administration, AE evaluation and disease status notification at baseline; and Q6W (every cycle) until cycle 4, followed by every 12 weeks (Q12W) until end of treatment or treatment discontinuation, at treatment discontinuation, and 30 days after treatment discontinuation. In cohort B, HRQoL assessment using EORTC QLQ-C30 and EuroQoL EQ-5D-5L will be administered prior to treatment administration, AE evaluation and disease status notification at baseline; Q6W until cycle 17 for treatment administered Q3W or until cycle 9 for treatment administered Q6W, followed by Q12W until end of treatment or treatment discontinuation, at treatment discontinuation and 30 days after treatment discontinuation.

Outcome measures/end points

Primary end points will be ORR, defined as CR or partial response (PR) per RECIST v1.1 as assessed by BICR for cohort A and cohort B.

For both cohorts, secondary efficacy end points will be duration of response per RECIST v1.1 as assessed by BICR and by investigator (defined as time from first documented CR or PR until disease progression or death from any cause), ORR per RECIST v1.1 by investigator assessment, PFS per RECIST v1.1 as assessed by BICR and by investigator (defined as time from randomization to the first documented disease progression, or death), and OS (defined as the time from randomization to death from any cause). Safety and tolerability of all combination therapies compared with pembrolizumab monotherapy will also be assessed as a secondary end point.

Exploratory end points include assessment of HRQoL in both cohorts as assessed by EORTC QLQ-C30 and the EQ-5D-5L scores, pharmacokinetic parameters for all treatments, and molecular (genomic, metabolic and proteomic) biomarkers indicative of response.

Statistics

Efficacy analyses will be performed in the intention-to-treat population consisting of all patients randomly assigned to treatment analyzed by treatment arm. Safety will be assessed in the all-patients-as-treated population consisting of all randomly assigned patients who received $\geq$1 dose of study treatment and will be analyzed by treatment arm. HRQoL will be assessed in all randomly assigned patients who have received at $\geq$1 dose of study treatment and have $\geq$1 HRQoL assessment available.

Conclusion

Results from the randomized phase III KEYNOTE-177 trial demonstrated a statistically significant and clinically meaningful improvement in PFS for pembrolizumab compared with chemotherapy; however, there remains room for improvement [7,8]. Promising antitumor activity has been observed with pembrolizumab-based combination immunotherapy in various settings in previous phase I trials, with a tolerable safety profile [12,15,22,23]. Here, we describe the methodology of the phase II trial that will evaluate the efficacy and safety of pembrolizumab-based combination therapy in patients with MSI-H/dMMR mCRC who were previously treated with and experienced disease progression after fluoropyrimidine-based chemotherapy. This trial will also evaluate the efficacy and safety of pembrolizumab co-formulated with quavonlimab, favezelimab, or vibostolimab, or sequentially administered with MK-4830 in previously untreated patients with MSI-H/dMMR mCRC. The four combination therapies being evaluated in this trial have not been previously studied in this patient population. The results from this study will help define the role of combination therapy in this subset of patients with a poor prognosis.

Executive summary

- Metastatic colorectal cancer (mCRC) has been associated with a lower 5-year survival rate of 15% compared with regional or localized CRC.
- The emergence of effective immune checkpoint inhibitor therapies offers patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) mCRC an initial prognostic advantage; however, this advantage is lost upon disease recurrence. There remains a need for additional therapies in this subset of patients.

Background & rationale

- Pembrolizumab monotherapy has demonstrated improved clinical outcomes as first-line and as second-line or later treatment for MSI-H and/or dMMR mCRC; given the response rate of 45% and an estimated 36-month overall survival rate of 61.4% with first-line pembrolizumab, and a response rate of 33% with second-line or later pembrolizumab monotherapy, there is room for improvement.
- Adding a second immune checkpoint inhibitor targeting a different immune inhibitory pathway may improve PD-1 inhibitor efficacy.
- Early clinical data evaluating combination therapy with pembrolizumab plus quavonlimab, favezelimab, vibostolimab, or MK-4830 have shown promising antitumor activity with a tolerable safety profile, warranting further investigation into their efficacy and safety.

KEYSTEP-008 study design & eligibility criteria

- KEYSTEP-008 is an open-label, randomized, multicenter, multi-arm, active-controlled, phase II study evaluating the safety and efficacy of pembrolizumab-based combination therapy in patients with histologically confirmed stage IV CRC.
- Eligibility criteria includes patients with histologically confirmed stage IV MSI-H and/or dMMR CRC whose disease has been previously treated with a fluoropyrimidine, irinotecan and oxaliplatin, with or without an anti–vascular endothelial growth factor monoclonal antibody, and at least one anti–epidermal growth factor receptor for left-sided *RAS* wildtype tumors (cohort A) and patients who have not been previously treated (cohort B).

Outcome measures/end points

- The primary end point is objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by blinded independent central review (BICR) in cohorts A and B.
- Secondary end points are duration of response per RECIST v1.1 by investigator assessment and by BICR, objective response rate per RECIST v1.1 by investigator assessment, progression-free survival per RECIST v1.1 by investigator assessment and by BICR, overall survival and safety and tolerability in cohorts A and B.

Conclusion

- The KEYSTEP-008 trial will further define the role of pembrolizumab-based combination therapy in patients with stage IV MSI-H and/or dMMR CRC who have a poor prognosis.

Author contributions

A Avallone, S Yalcin, M Kwiatkowski, J Zolnierek, A Odeleye-Ajakaye, P Leconte, D Fogelman and TW Kim contributed to the conception, design and planning of the study. T André, F Pietrantonio, L Wyrwicz, JG Kim, M Kwiatkowski and S Lonardi acquired the data. S Yalcin, M Kwiatkowski, A Odeleye-Ajakaye and P Leconte analyzed the data. A Avallone, M Gumus, S Yalcin, M Kwiatkowski, S Lonardi, A Odeleye-Ajakaye and P Leconte interpreted the data. S Yalcin, M Kwiatkowski, A Odeleye-Ajakaye P Leconte and TW Kim contributed to drafting of the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content and approved the final version.

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and Amgen. A Avallone reports honoraria from Servier, Bayer, Amgen, Pierre-Fabre, Eli Lilly, MSD, AstraZeneca and Eisai; consulting or advisory roles for Amgen, AstraZeneca, MSD and Servier; research funding from Amgen, Bayer and BMS; and travel or accommodation expenses from Merck-Serono and Amgen. M Gumus reports honoraria from Amgen, Roche, Abdi Ibrahim, Novartis and Bayer; consulting or advisory roles for MSD, Bayer and Gen Drug; speaker bureau for Roche and Amgen; and research funding from Amgen. L Wyrwicz reports research funding from Merck Sharp & Dohme. S Yalcin reports honoraria from Amgen, Roche, Abdi Ibrahim, Novartis, Bayer, Gen Ilac, Eli Lilly, Merck Serono and Eczacibasi; consulting or advisory roles for MSD, Roche, Bayer, Gen Drug, Amgen and Eli Lilly; speaker bureau for Roche, Amgen, Merck, Eli Lilly, Nobel and Roche; stock interests in Curis and travel or accommodation expenses from Gen Ilac and AstraZeneca. MK reports research funding from MSD, AstraZeneca, Roche and BMS. S Lonardi reports consulting or advisory roles for Amgen, Merck Serono, Eli Lilly, AstraZeneca, Incyte, Daiichi-Sankyo, Bristol Myers Squibb, Servier, Merck Sharp & Dohme; speaker bureau for Roche, Eli Lilly, Briston Myers Squibb, Servier, Merck Serono, Pierre Fabre, GlaxoSmithKline, Amgen and AstraZeneca; and research funding from Amgen, Merck Serono, Bayer, Roche, Eli Lilly, AstraZeneca and Bristol Myers Squibb. J Zolnierek reports honoraria and a consulting or advisory role for Merck. A Odeleye-Ajakaye and P Leconte report employment and stock interests at Merck Sharp & Dohme. D Fogelman reports employment at Merck Sharp & Dohme. TW Kim reports research funding from Roche/Genentech. JG Kim has no conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors attest that the study protocol was approved by the appropriate ethics committee or institutional review board at each participating center. The study will be conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. All participants will provide written informed consent before enrollment.

Data sharing statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Open access

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