Clinical Trial Protocol

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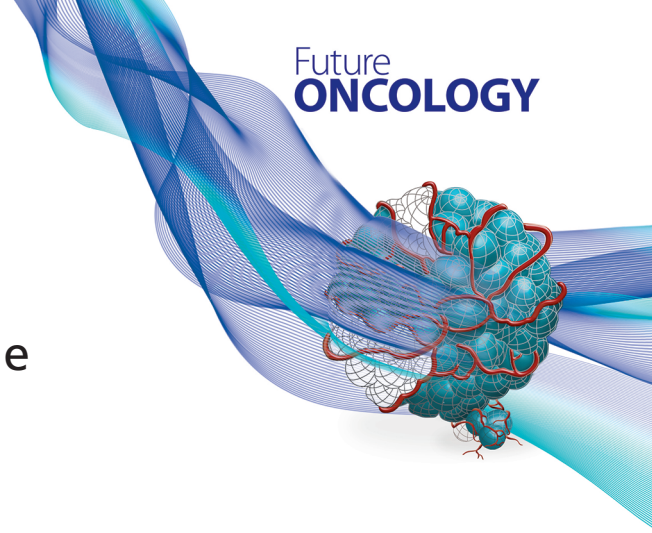

SEAMARK: phase II study of first-line encorafenib and cetuximab plus pembrolizumab for MSI-H/dMMR *BRAF*V600E-mutant mCRC

Elena Elez[1], Scott Kopetz[2], Josep Tabernero[3], Tanios Bekaii-Saab[4], Julien Taieb[5], Takayuki Yoshino[6], Gulam Manji[7], Kathrine Fernandez[8], Antonello Abbattista[9], Xiaosong Zhang[10] & Van K Morris*[,2]

[1]Vall d'Hebron Hospital Campus & Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain
[2]University of Texas MD Anderson Cancer Center, Houston, TX, USA
[3]Vall d'Hebron Hospital Campus & Vall d'Hebron Institute of Oncology, Universitat de Vic - Universitat Central de Catalunya, Barcelona, Spain
[4]Mayo Clinic, Phoenix, AZ, USA
[5]Georges Pompidou European Hospital, Université de Paris, Paris, France
[6]National Cancer Center Hospital East, Kashiwa, Japan
[7]Columbia University Irving Medical Center & NewYork-Presbyterian Hospital, New York, NY, USA
[8]Pfizer Global Product Development-Oncology, Cambridge, MA, USA
[9]Pfizer Global Product Development-Oncology, Milan, Italy
[10]Pfizer, New York, NY, USA
*Author for correspondence: Tel.: +1 713 792 2828; VKMorris@mdanderson.org

Patients with both *BRAF* V600E mutations and microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC) have poor prognosis. Currently, there are no specifically targeted first-line treatment options indicated for patients with mCRC whose tumors harbor both molecular aberrations. Pembrolizumab is a checkpoint inhibitor approved for the treatment of MSI-H/dMMR mCRC, and the BRAF inhibitor encorafenib, in combination with cetuximab, is approved for previously treated *BRAF* V600E-mutant mCRC. Combination of pembrolizumab with encorafenib and cetuximab may synergistically enhance antitumor activity in patients with *BRAF* V600E-mutant, MSI-H/dMMR mCRC. SEAMARK is a randomized phase II study comparing the efficacy of the combination of pembrolizumab with encorafenib and cetuximab versus pembrolizumab alone in patients with previously untreated *BRAF* V600E-mutant, MSI-H/dMMR mCRC.

Plain language summary – SEAMARK study: encorafenib & cetuximab plus pembrolizumab for people with BRAF V600E-mutant & DNA repair-deficient colorectal cancer: Colorectal cancer (CRC) occurs when there is an abnormal growth of cells (known as a tumor) in the colon or rectum. Some people with CRC have changes in their tumor genes (known as gene mutations). A gene is a piece of DNA that tells the cell to make specific molecules, such as proteins. Mutations in a gene called *BRAF* can turn on signals that help the cancer cells grow. Gene mutations that impair DNA repair mechanisms can also make the cancer cells grow more quickly and allow the immune system to detect the cancer cells as being foreign to the body. Targeted therapy is a type of cancer treatment that turns off specific genes and proteins involved in cancer cell survival and growth. BRAF and EGFR inhibitors are targeted therapies that work well together in treating people with *BRAF*-mutant CRC. BRAF proteins can help cancer cells grow, and BRAF inhibitors block these proteins to prevent, slow, or stop the growth of the cancer cells. Immunotherapy is a type of cancer treatment that helps a person's immune system fight cancer. Immunotherapy is effective for treating CRC that has mutations in the DNA repair mechanisms. By combining targeted therapy and immunotherapy, patients may be able to live longer without their disease getting worse. In the SEAMARK study, we will use a treatment combination including a BRAF inhibitor (encorafenib), an EGFR inhibitor (cetuximab) and an immunotherapy (pembrolizumab) in patients with CRC who have a *BRAF* mutation and deficiencies in the DNA repair mechanism.

Clinical Trial Registration: NCT05217446 (ClinicalTrials.gov), 2021-003715-26 (EudraCT)

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Tweetable abstract: SEAMARK (NCT05217446) is a phase II study investigating the efficacy of pembrolizumab with encorafenib and cetuximab in patients with *BRAF* V600E-mutant, MSI-H/dMMR metastatic colorectal cancer.

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Keywords: *BRAF* V600 • cetuximab • dMMR • encorafenib • immunotherapy • metastatic colorectal cancer • MSI-H • pembrolizumab • targeted therapy • triplet combination therapy

MSI-H/dMMR mCRC & pembrolizumab as first-line treatment

Colorectal cancer (CRC) is a life-threatening disease and the second and third most commonly diagnosed cancer in women and men, respectively [1]. Among patients with CRC, approximately 25% present with metastases at initial presentation and 50% eventually develop metastatic CRC (mCRC) [2]. Approximately 5% of patients with mCRC have high microsatellite instability (MSI-H) or mismatch repair-deficient (dMMR) tumors [3]. Accumulation of DNA mutations can occur in MSI-H/dMMR tumor cells, resulting in increased generation of tumor neoantigens that enhance immunogenicity. This in turn induces a more potent T-cell–mediated tumor immune response, which can be regulated *via* the PD-1 pathway [4–6].

The PD-1 pathway plays a major role as an immune checkpoint, which attenuates the host immune response to tumor cells [7]. Pembrolizumab is a potent humanized IgG4 monoclonal antibody that binds to the PD-1 receptor with high specificity, thus inhibiting the receptor's binding to its ligands, PD-L1 and PD-L2 [8]. This inhibition enhances T-cell responses to promote immune-mediated tumor regression [9]. Pembrolizumab has a favorable clinical safety profile and is an immunotherapy indicated for the treatment of patients with advanced malignancies and in the adjuvant setting for some malignancies [10–12].

Pembrolizumab was approved for the treatment of patients with MSI-H/dMMR mCRC in the USA and in the EU, based on the results of the KEYNOTE-164 and KEYNOTE-177 trials [13–16]. In the phase III KEYNOTE-177 study, pembrolizumab as first-line therapy of MSI-H/dMMR mCRC led to a statistically significant and clinically meaningful improvement in the median progression-free survival (PFS) compared with standard-of-care (SOC) chemotherapy (median PFS: 16.5 vs. 8.2 months; hazard ratio: 0.60; 95% CI: 0.45 to 0.80; p = 0.0002) [17]. In a subgroup analysis of this study, patients with mCRC harboring a *BRAF* V600E mutation benefited from pembrolizumab treatment compared with SOC chemotherapy [13]. However, approximately 40% of the patients treated with pembrolizumab did not have sustained disease control [13]. Therefore, novel therapeutic approaches are needed to improve the survival outcomes of patients with MSI-H/dMMR mCRC.

BRAF V600E-mutant mCRC & encorafenib with cetuximab as treatment

BRAF mutations occur in approximately 8 to 10% of patients with CRC. These mutations are usually (>95%) located at the V600E codon and have been consistently associated with a poor prognosis [18–21]. Among patients with *BRAF* V600E-mutant mCRC, approximately 20 to 25% also have MSI-H/dMMR [13,21]. The combined presence of both *BRAF* mutations and MSI-H/dMMR is associated with poor prognosis in patients with mCRC, which is thought to be primarily driven by the *BRAF* mutation [21].

The RAF/MEK/ERK pathway regulates cell proliferation and survival, and *BRAF* mutations activate this pathway to create an immunosuppressive environment to allow uncontrolled tumor cell growth [22]. Encorafenib is a highly selective, ATP-competitive small-molecule BRAF kinase inhibitor that suppresses the RAF/MEK/ERK pathway in tumor cells harboring *BRAF* V600E mutations to inhibit tumor cell proliferation [23]. BRAF inhibition alone is ineffective in treating CRC, as the inhibition causes a rapid feedback activation of EGFR, which supports continued tumor cell proliferation; this can be overcome with combination therapy targeting both BRAF and EGFR pathways [24–27]. Cetuximab is an anti-EGFR antibody that specifically binds to the EGFR with high affinity to block the EGFR/MAPK signaling pathway and inhibit tumor cell proliferation [28].

Currently, there are no specifically targeted first-line treatments indicated for patients with *BRAF* V600E-mutant mCRC. Thus, patients usually receive systemic therapy that is recommended for non-molecularly selected mCRC [29]. Encorafenib in combination with cetuximab was recently approved in the USA and the EU for the treatment of patients with previously treated mCRC harboring a *BRAF* V600E mutation based on the results from the phase III BEACON CRC trial [30,31]. In this study, patients with *BRAF* V600E-mutant mCRC who were treated

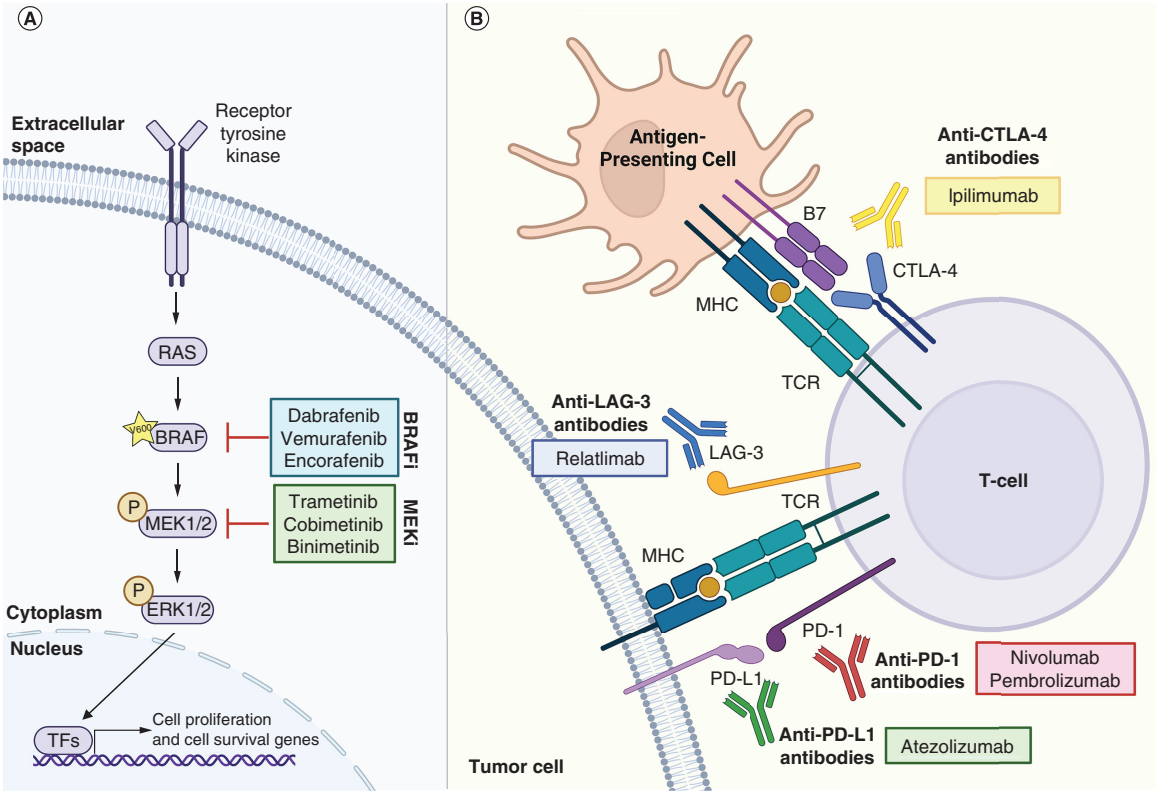

Figure 1. Rationale for pembrolizumab with encorafenib and cetuximab combination therapy. (A) MAPK pathway inhibitors. **(B)** Immune checkpoint inhibitors.

with encorafenib (300 mg daily) and cetuximab (400 mg/m^2 as an initial dose, followed by 250 mg/m^2 weekly) had statistically significant improvements in overall response rate (ORR), PFS and overall survival compared with those who were treated with irinotecan-based chemotherapy [32]. The combined therapy of encorafenib and cetuximab also demonstrated a manageable safety profile in patients with *BRAF* V600E-mutant mCRC. Currently, an ongoing phase III study, BREAKWATER, aims to evaluate the clinical outcomes of encorafenib and cetuximab in combination with SOC chemotherapy in patients with previously untreated *BRAF* V600E-mutant, microsatellite stable mCRC [33,34].

Rationale for pembrolizumab with encorafenib & cetuximab combination therapy

Tumor progression in patients with *BRAF* V600E-mutant, MSI-H/dMMR mCRC is hypothesized to be driven by both the genomic instability reflected by the MSI-H/dMMR state, as well as the deregulated MAPK pathway signaling resulting from the *BRAF* mutation. Translational studies demonstrated that the activated BRAF-MAPK signaling pathway creates an immunosuppressive environment and that inhibiting BRAF leads to increased tumor antigen presentation, T-cell infiltration and activation and PD-L1 expression, while preserving T-cell function and inducing antitumor activity [35–40]. Furthermore, studies have also shown that BRAF inhibition is enhanced when combined with immune checkpoint blockade through immunomodulation [41]. The results of these studies suggest that combining BRAF inhibitors with immune checkpoint inhibitors could produce additional clinical benefit in patients with *BRAF* mutations, and the combination of pembrolizumab with encorafenib and cetuximab is hypothesized to have greater antitumor activity in patients with *BRAF* V600E-mutant, MSI-H/dMMR mCRC compared with pembrolizumab alone (Figure 1). The potential synergistic effect of pembrolizumab with encorafenib and cetuximab in patients with previously untreated *BRAF* V600E-mutant, MSI-H/dMMR mCRC will be explored in the SEAMARK study.

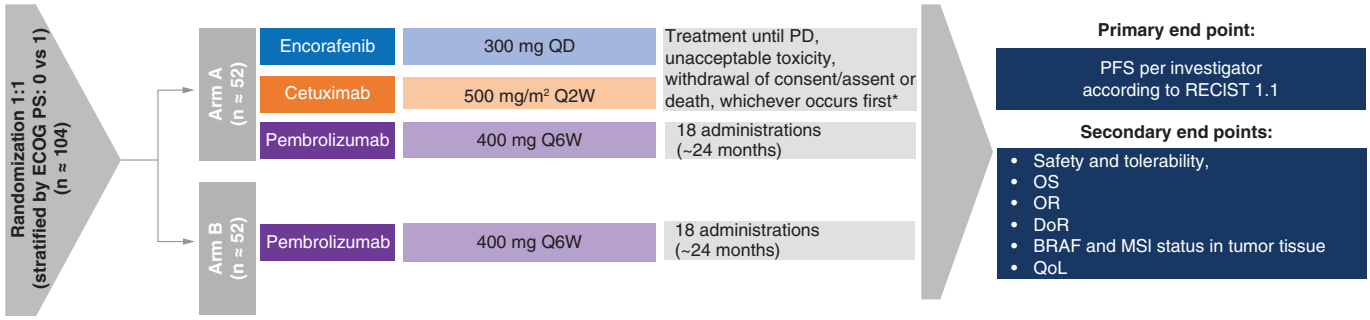

Figure 2. Study design.
DOR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; MSI: Microsatellite instability; OR: Objective response; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; QD: Daily; Q2W: Every 2 weeks; Q6W: Every 6 weeks; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors.

Design

Study design

SEAMARK is an open-label, multicenter, randomized phase II study evaluating the safety and efficacy of pembrolizumab with encorafenib and cetuximab (arm A) compared with pembrolizumab alone (arm B) in patients with previously untreated *BRAF* V600E-mutant, MSI-H/dMMR mCRC.

Approximately 104 eligible patients will be randomized in a 1:1 ratio to arm A or B, with approximately 52 patients per arm, assigned using an Interactive Response Technology (Figure 2). Randomization will be stratified by Eastern Cooperative Oncology Group performance status (0 vs 1). Patients in arm B are not eligible for crossover to arm A. Patients in arm A will receive pembrolizumab with encorafenib and cetuximab. Patients in arm B will receive pembrolizumab. In this open-label study, investigators will not be blinded to treatment allocation. Study intervention will be administered until progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The duration of pembrolizumab treatment will not exceed 18 administrations (≈24 months) in both treatment arms, and the duration of encorafenib and cetuximab in arm A will continue until progressive disease per RECIST 1.1. After discontinuation of all study intervention, patients will be followed for safety, disease status, subsequent anticancer therapy and survival status until withdrawal of consent or assent, the patient is lost to follow-up, death, or the defined end of study, whichever occurs first.

In arm A, encorafenib is administered at 300 mg orally once daily and cetuximab at 500 mg/m^2 intravenously every 2 weeks. Pembrolizumab in both arms A and B is administered at 400 mg intravenously every 6 weeks [42–44].

An external data monitoring committee will review all accumulated safety data to confirm that the combination of pembrolizumab with encorafenib and cetuximab is acceptable for continued use in arm A and will either confirm the safety and tolerability of the combination or make recommendations for dose adjustments or discontinuation of the study. Criteria for treatment dose modification or study termination include, but are not limited to, significant number of serious adverse events or deaths reported during study treatment. An initial safety assessment will be conducted after the first 20 to 24 patients have received at least one dose of study intervention and have been followed for at least 42 days.

The study centers are located in the USA, Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, The Netherlands, Norway, Poland, Slovakia, Spain, Sweden and the UK.

Eligibility criteria

The study population consists of patients aged ≥16 years or ≥18 years per country-specific regulations, with metastatic stage IV colorectal adenocarcinoma, and dMMR/MSI-H disease and *BRAF* V600E mutation in their tumor tissue or blood (i.e., circulating tumor DNA; Table 1). Patients must not have received prior systemic regimens for metastatic disease.

Exclusion criteria include the presence or unknown status of a *RAS* mutation (Table 1). Patients must not have previous treatment with any BRAF, EGFR, or immune checkpoint inhibitor. The key inclusion and exclusion criteria are listed in Table 1.

Table 1. Eligibility criteria.

Key inclusion criteria
• Patients aged ≥16 or ≥18 years (per country-specific regulations)
• Histologically or cytologically confirmed metastatic stage IV colorectal adenocarcinoma
• Locally confirmed MSI-H/dMMR tumor tissue or blood (i.e., ctDNA) as determined by a certified laboratory
• Locally confirmed *BRAF* V600E mutation in tumor tissue or blood (i.e., ctDNA) as determined by a certified laboratory
• Presence of measurable disease per RECIST 1.1, as assessed by investigator and evidenced by available baseline tumor scan
• ECOG PS 0 or 1
• No prior systemic regimen for metastatic disease ◦ Patients with early-stage disease (e.g. stages I–III) treated with surgery followed by chemotherapy (e.g., treatment in the adjuvant setting) or who have received prior systemic neoadjuvant therapy ± radiation who present with new lesions or evidence of disease recurrence ≤6 months from the last dose of chemotherapy would be considered as having received one prior systemic therapy in the metastatic setting
• Adequate bone marrow, hepatic and renal function
• Adequate serum potassium and magnesium levels
Key exclusion criteria
• Colorectal adenocarcinoma with *RAS* mutation or unknown *RAS* status
• Documented clinical disease progression (e.g., worsening of ECOG PS, clinical symptoms, or clinically significant laboratory parameters demonstrating worsening of disease) or radiographic disease progression during the screening period
• Presence of active CNS metastases and/or carcinomatous meningitis, leptomeningeal disease
• Concurrent or previous other malignancy within 2 years of study entry
• Diagnosis of immunodeficiency or active autoimmune disease requiring systemic treatment in the past 2 years
• Presence of acute or chronic pancreatitis, history of chronic inflammatory bowel disease requiring medication within 1 year, or impaired gastrointestinal function or disease
• Clinically significant cardiovascular diseases
• History of pneumonitis or interstitial lung disease that required steroids
• Active and uncontrolled bacterial or viral infection, or active hepatitis B or hepatitis C infection
• Active uncontrolled HIV infection and history of Kaposi sarcoma and/or Castleman disease
• Residual CTCAE grade ≥2 toxicity from any prior anticancer therapy
• Previous treatment with BRAF or EGFR inhibitors, immune checkpoint inhibitors, or agents directed at stimulatory or coinhibitory T-cell receptor
• Concurrent use of a nontopical medication that is a strong or moderate CYP3A inducer within 7 days prior to first dose of study intervention and throughout study duration

CNS: Central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MSI-H/dMMR: Microsatellite instability-high/deficient mismatch repair; RECIST: Response Evaluation Criteria in Solid Tumors.

Study objectives & end points

The primary objective of SEAMARK is to compare the efficacy of pembrolizumab with encorafenib and cetuximab versus pembrolizumab alone, as measured by PFS based on investigator assessment (Table 2). The secondary objectives include comparing the overall safety and tolerability, efficacy and effect of pembrolizumab with encorafenib and cetuximab versus pembrolizumab alone on patient-reported outcomes (PRO), as measured by the adverse events, overall survival, objective response, duration of response, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients – 30 Item Core Questionnaire (EORTC QLQ-C30), EuroQoL-5 Dimensions-5 Level (EQ-5D-5L), Patient Global Impression of Severity (PGIS) score and Patient Global Impression of Change (PGIC). The full list of study objectives and end points is provided in Table 2.

Planned sample size

The ongoing SEAMARK trial will enroll approximately 104 patients (≈52 patients per treatment arm). The final analysis is anticipated to take place approximately 45 months after the first participant is randomized.

Study procedures

Encorafenib and cetuximab in combination with anti-PD-1 therapy (nivolumab) was evaluated previously and was found to have a tolerable safety profile [45]. However, SEAMARK is the first study to combine encorafenib and cetuximab with pembrolizumab. Safety assessment will include a rigorous and continuous monitoring of adverse events, which consists of patient interviews, physical examinations, vital signs, laboratory tests, electrocardiograms and dermatologic examinations for skin malignancies. Tumor response will be assessed throughout the

Table 2. Study objectives and end points.

Primary objective	Primary end points	Outcome measures
To compare the efficacy per PFS of arm A vs arm B	Investigator-assessed PFS per RECIST 1.1	• Treatment effect, estimated in the analysis population, of arm A on PFS compared with arm B from randomization until PD or death • HR for PFS and corresponding 95% CI • Median PFS and corresponding 95% CI
Secondary objectives	**Secondary end points**	**Outcome measures**
To assess the overall safety and tolerability of arm A vs arm B	AEs	• Incidence and severity of AEs according to the NCI CTCAE v4.03 • Changes in clinical laboratory test parameters, vital signs and ECGs • Incidence of dosing interruptions, dose modifications, and permanent discontinuations associated with AEs
To assess the efficacy per OS and tumor response of arm A vs arm B	OS	• Time from randomization until death • HR for OS and corresponding 95% CI • OS probability estimates at 24 and 36 months and corresponding 95% CIs
	OR	• Confirmed CR or PR based on investigator assessment per RECIST 1.1, from the time of randomization until the first PD, death, or start of new anticancer therapy • ORR and corresponding 95% CI
	DOR	• Time from the first response until PD based on investigator assessment per RECIST 1.1 or death
To confirm the *BRAF* and MSI status in tumor tissue	*BRAF* and MSI status	• Determined by retrospective central testing of baseline tumor tissue
To evaluate the effect on PROs of arm A vs arm B	EORTC QLQ-C30	• Change from baseline in the global health status/QoL, functional and symptom scales, and single items
	EQ-5D-5L	• Change from baseline in the index score and VAS
	PGIS	• Change from baseline in the score
	PGIC score	
Tertiary/exploratory objectives	**Tertiary/exploratory end points**	**Outcome measures**
To understand the relationship between the therapeutic intervention(s) and the biology of the participant's disease	Biomarkers	• Measurements of DNA, RNA, proteins, or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment and/or at end of treatment
To understand the surgical conversion rate of arm A vs arm B	Surgical conversion rate	• Rate of patients who become eligible for surgery and undergo surgery with curative intent as a result of study intervention

AE: Adverse event; CR: Complete response; DOR: Duration of response; ECG: Electrocardiogram; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients – 30 Item Core Questionnaire; EQ-5D-5L: EuroQoL-5D-5L; MSI: Microsatellite instability; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OR: Objective response; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PR: Partial response; PRO: Patient-reported outcome; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; RNA: Ribonucleic acid; VAS: Visual analog scale.

treatment and at follow-up time points (42–49 days and every 6 weeks [±7 days] from the date of randomization for the first 28 months, followed by every 8 weeks [±7 days] thereafter) on all known or suspected disease sites and assessment of response will be made using RECIST 1.1.

Tumor biospecimen will be collected at screening from formalin-fixed paraffin-embedded tissue from tumor resection or biopsy with the intent to analyze candidate nucleic acid and protein biomarkers, or relevant signature of markers (including but not limited to PD-L1). Blood-based samples will be collected from all patients at different timepoints with the intent to analyze genomic and proteomic changes found in peripheral blood following treatment.

These samples and optional on-treatment tumor tissue collected during surgical resection and at progression or end of treatment will be used, with prior consent, to gain insight into the mechanisms that confer sensitivity/resistance to study treatment. These analyses will contribute to the evaluation of the combined therapy of pembrolizumab with encorafenib and cetuximab and identification of patients who are more likely to benefit from treatment with the study drugs.

Statistics

All efficacy analyses will be performed using the full analysis set, defined as all enrolled patients who were randomized, and all safety analyses will be performed using the safety analysis set, defined as all enrolled patients who receive at least one dose of study intervention. For the PROs, change from baseline will be assessed for the EORTC QLQ-C30, EQ-5D-5L, PGIS and PGIC. The EORTC QLQ-C30 and EQ-5D-5L will be scored according to their user guides.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse (NCI-CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events by appropriate MedDRA terms, toxicity grade, seriousness and relationship to study treatment and those leading to death and premature withdrawal from study treatment will be summarized.

Conclusion

Patients with both MSI-H/dMMR and *BRAF* V600E-mutant mCRC have poor prognosis, and currently there are no first-line BRAF-targeted treatment options approved. The rationale for pembrolizumab with encorafenib and cetuximab combination therapy is based on encorafenib's properties as a BRAF inhibitor and the ability of cetuximab to block the EGFR/MAPK signaling pathway, which could be enhanced when combined with immune checkpoint blockade *via* pembrolizumab.

This phase II SEAMARK trial will investigate the efficacy and safety of pembrolizumab with encorafenib and cetuximab combination therapy compared with pembrolizumab alone in patients with *BRAF* V600E-mutant, MSI-H/dMMR mCRC. The primary objective is to compare the PFS based on investigator assessment between pembrolizumab with encorafenib and cetuximab versus pembrolizumab alone. The results of this trial will determine whether adding encorafenib and cetuximab to pembrolizumab could be clinically beneficial for patients with *BRAF*-mutant, MSI-H/dMMR mCRC.

Executive summary

Background & rationale

- Patients with both *BRAF* V600E mutations and microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) have poor prognosis, and there are no specifically targeted first-line treatment options indicated for them.
- Pembrolizumab, an immune checkpoint inhibitor that binds PD-1, improved clinical outcomes in patients with MSI-H/dMMR mCRC.
- Combination of the BRAF and EGFR inhibitors, encorafenib and cetuximab, improved patient outcomes for *BRAF* V600E-mutant mCRC.
- Preclinical evidence suggests that BRAF inhibition is enhanced when combined with immune checkpoint blockade through immunomodulation.
- Combination of BRAF inhibitors with immune checkpoint inhibitors could synergistically enhance antitumor effects in patients with *BRAF* V600E-mutant, MSI-H/dMMR mCRC.

Study design & key eligibility criteria

- This is an open-label, multicenter, randomized phase II trial (n≈104 patients) comparing the efficacy of pembrolizumab with encorafenib and cetuximab (arm A) versus pembrolizumab alone (arm B).
- Eligible patients include those aged ≥16 years or ≥18 years (per country-specific regulations) with histologically or cytologically confirmed metastatic stage IV colorectal adenocarcinoma and locally confirmed dMMR/MSI-H disease and *BRAF* V600E mutation in their tumor tissue or blood (i.e., ctDNA).
- Treatment with pembrolizumab will not exceed 18 administrations (≈24 months) and treatment with encorafenib and cetuximab will continue until disease progression, unacceptable toxicity, withdrawal of consent/assent, or death, whichever occurs first.
- Patients in arm B are not able to cross over to arm A.

Outcome measures

- The primary end point of the SEAMARK trial is progression-free survival based on investigator assessment.
- Secondary end points include adverse events, overall survival, objective response, duration of response, *BRAF* and MSI status in tumor tissue and patient-reported outcomes.
- Exploratory end points include the assessment of biomarkers based on analysis of peripheral blood and/or tumor tissue blood and the surgical conversion rate of patients.

Summary

- SEAMARK is an open-label, multicenter, randomized phase II trial designed to compare the efficacy of pembrolizumab with encorafenib and cetuximab versus pembrolizumab alone for the treatment of patients with previously untreated *BRAF* V600E-mutant, MSI-H/dMMR mCRC.
- Results from this trial will establish the potential synergistic and clinical benefits of combining pembrolizumab with encorafenib and cetuximab for patients with *BRAF*-mutant, MSI-H/dMMR mCRC, whose current prognosis remains poor.

Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). All authors contributed substantially to the conception or design of the study, or to the refinement of the study protocol. All authors approved the final manuscript.

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Competing interests disclosure

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Ethical conduct of research

This study is being conducted in compliance with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, and applicable laws and regulations, including applicable privacy laws.

Data sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data.

See www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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