# A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)

Published: 13-01-2016
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Primary Objective & HypothesisIn subjects with first line (1L) stage IV MSI-H or dMMR CRC treated with first line (1L) pembrolizumab (MK-3475) versus SOC chemotherapies,Objective: To compare Progression Free Survival (PFS) per RECIST 1.1 by...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54608

**Source**
ToetsingOnline

**Brief title**
MK3475-177

### Condition

- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
colon cancer; rectum cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Merck Sharp & Dohme (MSD)
**Source(s) of monetary or material Support:** Industrie

## Intervention

**Keyword:** Colorectal Carcinoma, Micosatalite Instability High, Pembrolizumab

## Outcome measures

### Primary outcome

This study will use PFS as the primary endpoint. PFS is an acceptable measure

of clinical benefit for a randomized phase III trial that demonstrates

superiority of a new antineoplastic therapy, especially if the magnitude of

effect is large and the therapy has an acceptable risk-benefit profile.

### Secondary outcome

ORR per RECIST 1.1 by central imaging vendor

# Study description

### Background summary

In the United States (US), CRC is the third most common diagnosed cancer and the third leading cause of cancer death in both men and women. The American Cancer Society estimated that 132,640 people will be diagnosed with CRC and 49,700 people will die from the disease in 2015. Approximately 4.5 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime.

Colorectal cancers (CRCs) may be divided via molecular phenotyping into tumors with normal DNA mismatch repair (MMR) function and those with DNA MMR deficiency (MMR-D). Tumors showing the presence of MSI are classified as MSI-H (high) depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS). The prevalence estimates of MSI-H in all CRC patients were similar across studies, ranging between 14-16%. In one population-based study included 2,080 persons diagnosed with incident invasive CRC between January, 1998 and

June, 2002, residing in one of the 3 counties of Washington State, US, approximately 16% of all the cases had tumors that were MSI-H.

Germline mutations in MMR genes cause a cancer susceptibility syndrome called Lynch syndrome. Germline mutations in the MMR genes MLH1, MSH2, MSH6 and/or PMS2 or EpCAM are found in individuals with Lynch syndrome, which is responsible for 2% - 4% of colon cancer cases. Many studies have found that some CRCs occurred in non-Lynch syndrome patients also showed MSI (sporadic CRCs with MSI) and CRCs with MSI showed different clinical-pathological features, prognosis and response to chemotherapeutic agents comparing to microsatellite-stable CRCs.

MSI-H CRC comprises approximately 15% of sporadic CRC and 5% of Stage IV CRC, whereas MSS CRC comprises the remainder. The estimates for MSI-H CRC in stage IV patients range from ~3.5%-5%.

A recent study reported that once the disease recurs the prognostic advantage of MSI-H CRC is lost as the median OS after recurrence in stage II disease is 1.6 versus 2.2 years (MSI-H CRC vs MSS CRC, respectively; hazard ratio (HR) 1.00, 95% confidence interval (CI), 0.68-1.48; $p > 0.99$) and after stage III disease is 1.2 versus 1.6 years (MSI-H CRC versus MSS CRC, respectively; HR 1.00, 95% CI, 0.85-1.17; $p > 0.99$). The same group reported that there is actually a disadvantage in having MSI-H status in advanced disease. Five percent of the primary tumors of 3,063 patients, pooled from four phase III first-line studies in CRC, were found to be MSI-H. The median PFS and OS were significantly worse for patients with MSI-H CRC compared with proficient MSS tumors (PFS: 6.2 vs 7.6 months; HR 1.33, 95% CI, 1.12-1.57; $p = 0.001$; OS: 13.6 vs 16.8; HR 1.35, 95% CI, 1.13-1.61; $p =0.001$). These data emphasize that the prognosis for patients with metastatic MSI-H CRC is poor despite the current treatment options. Therefore, advanced or metastatic MSI-H CRC patients represent a group of patients with high unmet medical need.

**Study objective**

Primary Objective & Hypothesis

In subjects with first line (1L) stage IV MSI-H or dMMR CRC treated with first line (1L) pembrolizumab (MK-3475) versus SOC chemotherapies,
Objective: To compare Progression Free Survival (PFS) per RECIST 1.1 by central imaging vendor.
Hypothesis (H1): Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by central imaging vendor compared to SOC chemotherapies.

Objective: To compare Overall Survival (OS).
Hypothesis (H2): Pembrolizumab (MK-3475) prolongs OS compared to SOC chemotherapies.

Secondary Objective(s) & Hypothesis(es)
In subjects with 1L stage IV MSI-H or dMMR CRC treated with pembrolizumab (MK-3475) versus SOC chemotherapies,
1) Objective: To compare Overall Response Rate (ORR) per RECIST 1.1 by central imaging vendor.
Hypothesis (H3): Pembrolizumab (MK-3475) improves ORR compared to SOC chemotherapies
2) Objective: To evaluate the safety and tolerability profiles.

**Study design**

This is a two arm, multicenter, international, randomized, open label, controlled trial of pembrolizumab (MK-3475) monotherapy versus standard chemotherapy in subjects who have stage IV Microsatellite instability high (MSI-H) or Mismatch Repair Deficient (dMMR) colorectal carcinoma (CRC)

**Intervention**

Arm 1: Pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W)

OR

Arm 2: Standard of Care (SOC): Investigator*s choice of the following:
mFOLFOX6, or
mFOLFOX6 + bevacizumab, or
mFOLFOX6+ cetuximab, or
FOLFIRI, or
FOLFIRI+ bevacizumab, or
FOLFIRI+ cetuximab

**Study burden and risks**

The patient will receive the study drug every 3 weeks. The patient will visit the doctor every week or every 3 weeks. The first visit a tumor biopsy will take place (if necessary). Each visit, a physical examination will be performed, and blood samples will be taken. The patient will also fill in three questionnaires each visit concerning the quality of life, namely the EORTC QLQ-C30, de EORTC QLQ-CR29, de EQ5D-3L.

The patient may experience physical and I or psychological discomfort with some of the procedures performed during a visit, such as blood sampling, the IV line, ECG, CT scan, MRI and tumor biopsy.

The main side effect reported with the use of MK3475 are fatigue, itching, rash, frequent or excessive bowel movements, joint pain and nausea.

# Contacts

**Public**
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
**Scientific**
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Provide documented informed consent for the study.
2. Be male or female who is >= 18 years of age on the date of signing informed consent.
3. Have locally confirmed MMR deficient (dMMR) or microsatellite instability high (MSI-H) stage IV colorectal carcinoma
4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 10 days prior to treatment initiation.
5. Have life expectancy of at least 3 months
6. Have measurable disease at baseline based on RECIST 1.1 as determined by the local site Investigator/radiology assessment.
7. Female subjects of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study

medication.
8. Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the study starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm and 120 days for pembrolizumab arm, whichever is later.
9. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm (no contraception requirement for pembrolizumab MK-3475 arm).
10. Demonstrate adequate organ function. All screening laboratory assessment should be performed within 10 days prior to treatment initiation.

## Exclusion criteria

1. Has received prior systemic therapy for stage IV CRC. Subjects may have received prior adjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to randomization.
2. Is currently participating and receiving study medication in another study, or has participated in a study of an investigational agent and received study medication, or used an investigational device within 4 weeks of randomization.
3. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.
5. Has had radiation therapy within 4 weeks prior to randomization of study medication and who has not recovered to baseline from adverse events due to radiation therapy. Subjects who have been given palliative radiotherapy to peripheral sites (e.g., bone metastasis) may enter the study before 4 weeks have elapsed but must have recovered from any acute adverse effects.
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases [without evidence of progression by imaging as confirmed by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging] at least four weeks prior to the first dose of study medication; also, any neurologic symptoms must have returned to baseline], and have not used steroids for brain metastases for at least 28 days prior to trial initiation. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical

stability.
7. Has had major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization.
8. Has received prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or anti-CTLA-4 agent, etc).
9. Has another malignancy that is progressing or requires active treatment. Exceptions include non-melanomatous skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma.
10. Has received a live vaccine within 30 days of planned start of study medication.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject*s participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
12. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
13. Has known history of, or any evidence of interstitial lung disease or active, non-infectious pneumonitis.
14. Has a known history of active tuberculosis.
15. Has an active infection requiring systemic therapy.
16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study medication for SOC (applicable for male and female subjects) or 120 days after the last dose of study medication (MK-3475) arm. (applicable for female subjects only).

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 10-06-2016 |
| Enrollment: | 15 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Erbitux |
| Generic name: | Cetuximab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Keytruda |
| Generic name: | Pembrolizumab |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | NA |
| Generic name: | Calcium Folinate |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | NA |
| Generic name: | Irinotecan |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | NA |
| Generic name: | Oxaliplatin |
| Registration: | Yes - NL intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 13-01-2016 |
| Application type: | First submission |

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| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-05-2016 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-07-2016 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-11-2016 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-01-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 01-03-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-03-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-03-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 29-06-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-10-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-12-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-01-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-05-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-08-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-01-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-09-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

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| | (Assen) |
| Approved WMO Date: | 18-11-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-01-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 22-04-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-07-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-07-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-01-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-08-2021 |

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| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-10-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 31-01-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-09-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-02-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 20-02-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-002024-89-NL |
| CCMO | NL56051.056.15 |