# An Open-label, Multicenter, Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab Plus Lenvatinib in Combination With Belzutifan in Multiple Solid Tumors

Published: 08-06-2021
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2023-503905-12-00 check the CTIS register for the current data. The main objectives for this study are: - To assess the safety and tolerability of the combination of pembrolizumab and lenvatinib and...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Miscellaneous and site unspecified neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54355

**Source**
ToetsingOnline

**Brief title**
MK6482-016

### Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

**Synonym**
Solid tumors

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Combination, Multiple solid tumors, Phase 2

## Outcome measures

### Primary outcome

Primary outcome to asses safety and tolerability

- Dose-limiting toxicity (DLTs) (Safety Lead-in Phase only).

- Adverse events (AEs).

- Study intervention discontinuations due to AEs.

Primary outcome to evaluate ORR

- Objective response (OR): complete response (CR) or partial response (PR)

### Secondary outcome

- DOR: the time from first documented evidence of CR or PR until either disease progression or death due to any cause, whichever occurs first.

- Disease control (DC): best overall response of CR, PR, or stable disease (SD) after >=6 weeks (the start of the window for the first scheduled scan).

- PFS: the time from first day of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.

- OS: the time from first day of study intervention to death due to any cause.

- OR, DOR, DC, and PFS

# Study description

**Background summary**

The immunemodulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. Based on the preclinical findings, pembrolizumab and lenvatinib are being investigated in multiple solid tumors in Phase 2 and Phase 3 clinical studies. This combination has shown clinical efficacy in several tumor types, showed a manageable safety profile, and is currently approved for endometrial cancer (non-MSI-H) under accelerated approval.

The scientific rationale for combining belzutifan with pembrolizumab and lenvatinib stems
from the role of hypoxia signaling and HIF-2α in multiple downstream events. The role of HIF-2α in hypoxia signaling and activation of downstream pathways related to cell survival, angiogenesis, metastases, and tumor progression is relevant in HCC, and a synergistic effect is expected with the addition of belzutifan to the doublet by inhibition of pathogenic angiogenesis, upregulation of immune regulation response by decrease in TAMs, and overcoming resistance to TKIs due to the role of HIF-2α overexpression in mediating resistance to VEGFR TKIs such as sorafenib.

The clinical rationale for studying the triplet of belzutifan, pembrolizumab and lenvatinib in
the proposed indications come from promising doublet (pembrolizumab plus lenvatinib)
antitumor activity and manageable safety profile; the addition of a HIF-2α inhibitor is expected to improve antitumor activity and clinical responses based on
the scientific rationale proposed above.

The tumor types included in this study are Hepatocellular Cancer (HCC), Colorectal Cancer (CRC), Pancreatic Ductal Adenocarcinoma (PDAC), and Biliary Tract Cancer (BTC).
For HCC the importance of angiogenesis pathway, efficacy of immune checkpoint inhibitors, potential for synergism from combination with HIF-2α inhibitor in inhibiting pathogenic angiogenesis, and overcoming resistance to TKIs provides

rationale to study the efficacy and safety of the triplet combination in the 1L setting.
For CRC there is a high unmet need for effective treatment options in metastatic CRC after progressing on at least 2 prior therapies (3L or beyond) especially in non-MSIH/dMMR CRC, and novel treatment combinations are in need.
Overall the benefit for PDAC from later-line therapies after 1L therapy is very limited and most patients die of their disease (the ORR in 2L/3L setting is approximately 15%) [Wang-Gillam, A., et al 2016], hence there is huge unmet need for novel therapies in the 2L or later setting for PDAC.
While there are promising new targeted therapies becoming available for BTC with genomic alterations such as pemigatinib (for FGFR2 alterations), with good antitumor activity in a small subset of patients, a vast majority of patients do not have effective treatment options and hence there is a high unmet medical need for novel treatment combinations in the 2L or later-line treatment setting in advanced BTC.

**Study objective**

This study has been transitioned to CTIS with ID 2023-503905-12-00 check the CTIS register for the current data.

The main objectives for this study are:
- To assess the safety and tolerability of the combination of pembrolizumab and lenvatinib and belzutifan.

- To evaluate the confirmed objective response rate (ORR) per RECIST 1.1 as assessed by blinded independent central review (BICR)

**Study design**

This is a phase 2, nonrandomized, open-label, multisite study of pembrolizumab plus lenvatinib in combination with belzutifan with participant cohorts in CRC (non-MSI-H/dMMR), HCC, PDAC, BTC. esophageal SCC.
Approximately 240 participants (30 per cohort) who meet all inclusion criteria and none of the exclusion criteria will be enrolled (Expansion by up to 70 additional participants per tumor type) including participants from the Safety Lead-in Phase at the chosen dose level.
A Safety Lead-in Phase will be conducted using the mTPI design (target DLT rate of 30%) for:
• HCC participants separately (total N will depend on number of dose levels assessed but should include up to 10 DLT-evaluable participants at Dose Level 0 or a dose level that will be chosen to proceed) and,
• CRC, PDAC or BTC participants (pooled; total N will depend on number of dose levels assessed but should include up to 15 DLT-evaluable participants at Dose Level 0 or a dose level that will be chosen to proceed)

### Intervention

All cohorts will receive: Q6W 400mg Pembrolizumab, daily 20mg Lenvatinib (for HCC, 8mg if <60kg or 12mg if >60kg) and daily 120mg Belzutifan.

### Study burden and risks

It cannot be guaranteed that participants in clinical studies will directly benefit from
treatment during participation, as clinical studies are designed to provide information about
the safety and effectiveness of an investigational medicine.
As described in the Section 2.1 of the protocol, the combination of pembrolizumab and lenvatinib has shown promising efficacy signals in HCC, CRC (non-MSI-H/dMMR), and BTC patients. The addition of the HIF-2α inhibitor, belzutifan, to improve on the response rates in these high unmet need indications, including PDAC, is justified by the role HIF-2α plays in tumor hypoxia signaling, and downstream effects on promotion of angiogenesis, cell proliferation, metastasis, and a role in conferring resistance to TKIs (eg, HCC). We expect that the novel triple combination of belzutifan, pembrolizumab, and lenvatinib may improve ORR in the tumor types being studied over the pembrolizumab/lenvatinib combination and produce durable clinical benefit. Currently there are no clinical data for the triplet combination of pembrolizumab, lenvatinib, and belzutifan in any tumor type and there are no clinical data for the combination of pembrolizumab plus lenvatinib in PDAC. However, potential risks of this novel combination may be increased toxicity, intolerability, or unanticipated adverse drug reactions. Some of these expected Aes are anemia, hypoxia
and hepatotoxicity. Putative risks associated with combination of pembrolizumab and lenvatinib plus belzutifan, in addition to the known safety profile with each agent alone, may be hypoxia and anemia with increased frequency and/or severity.

## 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)

## Inclusion criteria

1. Diagnosis of one of the following advanced (unresectable and/or metastatic) solid tumors, documented by histopathology or cytopathology:
- HCC
- CRC
- PDAC
- BTC
- ESCC

2. Disease progression on or since the most recent treatment (does not applicable to newly diagnosed unresectable or metastatic HCC).

3. Measurable disease per RECIST v1.1 as assessed locally (by investigator) and verified by BICR.

4. Submission of an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated.

5. Male or female, at least 18 years of age.

6. Male participants are abstinent from heterosecual intercourse or agree to follow contraceptive guidance during and for at least 7 days after last dose of study intervention with belzutifan and lenvatinib.

7. Female participants are not pregnant or breastfeeding, not a woman of child-baering potential (WOCBP) or is a WOCBP and agrees to follow

contraceptive guidance during the intervention period and for at least 120 days after the last dose of pembrolizumab or for at least 30 days after last dose of lenvatinib or belzutifan, whichever occurs last after the last dose of study intervention.

8. ECOG performance status of 0 to 1 within 7 days of before the start of study intervention.

9. Adequate organ function

10. Adequately controlled blood pressure with or without antihypertensive medications.

Additional specific inclusion criteria are applicable per cohort, please refer to the protocol

## Exclusion criteria

1. Unable to swallow orally administered medication or has a significant GI disorder that may affect study intervention absorption.

2. History of a second malignancy that is progressing or has required active treatment within 3 years.

3. A pulse oximeter reading <92% at rest, or requirement of intermittent supplemental oxygen / or requires chronic supplemental oxygen.

4. Presence of Centeral nervous system (CNS) metastases and/or carcinomatous meningitis.

5. Clinically significant cardiovascular disease within 6 months of first dose of study intervention,

6. Prolongation of QTc interval to >480 ms.

7. Urine protein >=1 g/24 hours.

8. Symptomatic pleural effusion unless clinically stable after treatment.

9. Preexisting >= Grade 3 GI or non-GI fistula.

10. Moderate to severe hepatic impairment (Child-Pugh B or C).

11. Clinically significant history of bleeding within 3 months before screening.

12. Presence of serious active nonhealing wound/ulcer/bone fracture

13. Requirement for hemodialysis or peritoneal dialysis

14. Received colony-stimulating factors or transfusion within 28 days before study treatment initiation.

For the complete list, please refer to the protocol.

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 31-08-2021 |
| Enrollment: | 15 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Keytruda |
| Generic name: | Pembrolizumab |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Lenvima |
| Generic name: | Lenvatinib |
| Registration: | Yes - NL outside intended use |

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Welireg |
| Generic name: | Belzutifan |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 08-06-2021 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 10-08-2021 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-08-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 08-09-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 02-10-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 18-10-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 02-12-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 13-12-2021 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 18-07-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 17-11-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 28-11-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 14-01-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-01-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-05-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 26-05-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 16-08-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 25-09-2023 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 |
|---|---|
| EU-CTR | CTIS2023-503905-12-00 |
| EudraCT | EUCTR2020-005-007-4-NL |
| CCMO | NL77365.028.21 |