A Phase 3 Randomized, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants with Advanced and/or Unresectable Biliary Tract Carcinoma (KEYNOTE 966)

Published: 07-08-2019
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-506657-38-00 check the CTIS register for the current data. To compare pembrolizumab plus gemcitabine plus cisplatin to placebo plus gemcitabine plus cisplatin with respect to overall survival (OS...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52576

Source
ToetsingOnline

Brief title
MK3475-966

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Advanced and/or Unresectable Biliary Tract Carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Biliary Tract Carcinoma, Gemcitabine/Cisplatin, Pembrolizumab, Unresectable

Outcome measures

Primary outcome

To evaluate:

- Overal survival (OS)

Secondary outcome

- Progression-free survival (PFS)

- Objective response rate (ORR)

- Duration of response, DOR

- Safety and tolerability

Study description

Background summary

Biliary tract cancer is a rare but aggressive malignancy with limited treatment options. The majority of patients present with advanced or unresectable disease and undergo systemic chemotherapy. Patients presenting with earlier stage disease may undergo curative surgical resection but have a high rate of recurrence and metastases. Poor prognosis and limited treatment options in this challenging cancer highlight the unmet medical need for more effective therapies for those with advanced disease. Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell

death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications.The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.The PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in BTC.

Study objective

This study has been transitioned to CTIS with ID 2023-506657-38-00 check the CTIS register for the current data.

To compare pembrolizumab plus gemcitabine plus cisplatin to placebo plus gemcitabine plus cisplatin with respect to overall survival (OS) and progression free survival (PFS).

Study design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of pembrolizumab plus gemcitabine/cisplatin versus placebo plus gemcitabine/cisplatin in participants with advanced (metastatic) and/or unresectable (locally advanced) biliary tract carcinoma (intra- or extrahepatic cholangiocarcinoma or gallbladder). Participants must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, as determined by investigator/site radiologist. Lesions situated in a previously irradiated area by either radiotherapy, photodynamic therapy, or arterial embolization are considered measurable if progression has been shown in such lesions.
Approximately 1048 participants are expected to be randomized 1:1 into 1 of the 2 treatment arms:
- Arm 1:
Pembrolizumab 200 mg IV on Day 1 Q3W + gemcitabine 1000 mg/m2 IV and cisplatin 25
mg/m2 IV on Day 1 and Day 8 Q3W.

- Arm 2:
Placebo (saline) IV on Day 1 Q3W + gemcitabine 1000 mg/m2 IV and cisplatin 25 mg/m2 IV
on Day 1 and Day 8 Q3W.

Eligible participants will be stratified by 1) Region (Region 1: Asia versus

Region 2: Non-
Asia), 2) locally advanced versus metastatic, and 3) site of origin
(gallbladder, intrahepatic,
or extrahepatic).

Intervention

Group 1:
Pembrolizumab 200mg (IV) on day 1 of each cycle (3 weeks) and Cisplatin 25mg/m2 (IV) on day 1 and 8 of each cycle and gemcitabine 1000mg/m2 (IV) on day 1 and 8 of each cycle.

Group 2:
Placebo (Saline) (IV) on day 1 of each cycle (3 weeks) and Cisplatin 25mg/m2 (IV) on day 1 and 8 of each cycle and gemcitabine 1000mg/m2 (IV) on day 1 and 8 of each cycle.

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, IV line insertion, CT-MRI or bone
scans, physical exams, possibly confrontational questionnaires, and patients will be asked to visit the hospital regularly.
Patients will be administered with pembrolizumab or placebo through an IV line, during three-week cycles, up to a
maximum of 35 treatments.
It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.
Pembrolizumab has been administered in a large number of cancer participants with a well characterized safety profile and has received regulatory approval for multiple malignancies. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W).
Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Has histologically confirmed diagnosis of advanced (metastatic) and/or unresectable
(locally advanced) biliary tract cancer (intra-or extrahepatic cholangiocarcinoma or
gallbladder cancer).
2. Have measurable disease based on RECIST 1.1, as determined by the site investigator.
Lesions situated in a previously treated area by either radiotherapy, photodynamic
therapy, or arterial embolization are considered measurable if progression has been
shown in such lesions and they meet criteria for measurable disease per RECIST 1.1.
3. Participants with past or ongoing HCV infection are eligible for the study. Treated
participants must have completed their treatment at least 1 month prior to starting study
intervention. Untreated or incompletely treated HCV participants may initiate anti-viral
therapy for HCV if liver function remains stable for at least 3 months on study

intervention.
4. Participants with controlled hepatitis B are eligible for the study , as long as they meet the
following criteria:
a) Participants with chronic HBV infection, defined as HBsAg positive and/or detectable HBV DNA, must be given antiviral therapy for HBV for at least 4 weeks prior to the first dose of study intervention and HBV viral load must be less
than 100 IU/mL prior to first dose of study treatment. Participants on active HBV
therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention. Antiviral therapy after completion of study intervention should follow local guidelines.
b) Participants with clinically resolved HBV infection, defined as HBsAg negative
and anti-HBc positive, and who have an undetectable HBV viral load at screening should be checked every 6 weeks for HBV viral load and treated for HBV if viral load is over 100 IU/mL. Antiviral therapy after completion of study intervention should follow local guidelines.
5. Is male or female, from at least 18 years of age inclusive, at the time of signing the
informed consent.
6. Male participants are eligible to participate if they agree to the following during the
intervention period and for at least and through 180 days after the last dose of chemotherapy:
a) Refrain from donating sperm
PLUS either:
b) Be abstinent from heterosexual intercourse as their preferred and usual lifestyle
(abstinent on a long term and persistent basis) and agree to remain abstinent
OR
c) Must agree to use contraception unless confirmed to be azoospermic (vasectomized or
secondary to medical cause (Appendix 5), as detailed below:
* Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
d) Male participants must also agree to use a male condom when engaging in any activity
that allows for passage of ejaculate to another person of any sex.
e) Contraceptive use by men should be consistent with local regulations regarding the
methods of contraception for those participating in clinical studies.
7. A female participant is eligible to participate if she is not pregnant or

breastfeeding, and
at least one of the following conditions applies:
- Is not a woman of childbearing potential (WOCBP)
OR
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure
rate of <1% per year), with low user dependency, or be abstinent from heterosexual
intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at
least and through 210 days after the last dose of chemotherapy or through 120 days
after the last dose of pembrolizumab or placebo, whichever is greater, and agrees not
to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose
of reproduction during this period. The investigator should evaluate the potential for
contraceptive method failure (ie, noncompliance, recently initiated) in relationship to
the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as
required by local regulations) within 72 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum
pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
a) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a women with an early undetected pregnancy.
b) Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
8. The participant (or legally acceptable representative, if applicable) provides written
informed consent for the study. The participant may also provide consent for future
biomedical research. However, the participant may enroll in the main study without
participating in future biomedical research.
9. Have a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior
to the first dose of study intervention.
10. Provide archival tumor tissue sample or newly obtained core or excisional

biopsy of a
tumor lesion not previously irradiated (ie, obtained for histological
confirmation) for
biomarker analysis. The tumor tissue must be received by the central vendor and
be
deemed adequate for biomarker analysis evaluation, including but not limited to
PD-L1 and MSI biomarker analysis, prior to participant randomization.
Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides.
Newly
obtained biopsies are preferred to archived tissue. Note: Details pertaining to
tumor tissue submission can be found in the laboratory
manual.
11. Have a life expectancy of greater than 3 months.
12. Have adequate organ function. Specimens
must be collected within 14 days prior to the first dose of study intervention.

Exclusion criteria

1. Has had previous systemic therapy for advanced (metastatic) or unresectable
(locally
advanced) biliary tract cancer (intra-or extra hepatic cholangiocarcinoma or
gallbladder
cancer), with the exception of adjuvant therapy which is allowed. Adjuvant
therapy
should have been completed at least 6 months prior to diagnosis of advanced
and/or
unresectable disease.
2. Has ampullary cancer.
3. Has small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, mixed tumor
histology and/or mucinous
cystic neoplasms.
4. Has an active autoimmune disease that has required systemic treatment in the
past 2 years
(ie, 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 and is allowed.
5. Has undergone major surgery and has not recovered adequately from the
toxicity to
<=Grade 1 and/or complications from the intervention prior to starting study
intervention.
6. A WOCBP who has a positive urine pregnancy test within 72 hours prior to

administration of study intervention (see Appendix 5). If the urine test is positive or
cannot be confirmed as negative, a serum pregnancy test will be required.
Note: In the event that 24 hours have elapsed between the screening pregnancy test and
the first dose of study intervention, another pregnancy test (urine or serum) must be
performed and must be negative in order for the participant to start receiving study
intervention.
7. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an
agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-
40, CD137).
8. Has received prior anti-cancer therapy for advanced unresectable biliary tract cancer
(intra-or extra hepatic cholangiocarcinoma or gallbladder cancer), including
investigational agents within 4 weeks prior to randomization.
9. Has not recovered (ie, AE <=Grade 1 or baseline) from AEs due to previously
administered chemotherapy. Participants with <=Grade 2 neuropathy may be eligible
based on investigator assessment.
10. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants
must have recovered from all radiation-related toxicities, not require corticosteroids, and
have not had radiation pneumonitis. A 1-week washout is permitted for palliative
radiation (<=2 weeks of radiotherapy) to non-central nervous system (CNS)
disease if deemed safe by the investigator. A 2-weeks washout period is
required for a longer course of radiation (>2 weeks).
11. Has received a live vaccine within 30 days prior to the first dose of study intervention.
Note: Examples of live vaccines include, but are not limited to, the following: measles,
mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-
Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are
generally killed virus vaccines and are allowed; however, intranasal influenza vaccines
(eg, FluMist®) are live attenuated vaccines and are not allowed.
12. Is currently participating in or has participated in a study of an investigational agent or
has used an investigational device within 4 weeks prior to the first dose of study
intervention.
Note: Participants who have entered the follow-up phase of an investigational study may

participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
13. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in
dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.
14. Has a known additional invasive malignancy that is progressing or has required active treatment
within the past 3 years.
Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the
skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have
undergone potentially curative therapy are not excluded.
15. Has severe hypersensitivity (>=Grade 3) to pembrolizumab, gemcitabine, or cisplatin
and/or any of their excipients.
16. Has a history of (non-infectious) pneumonitis that required steroids or has current
pneumonitis.
17. Has an active infection requiring systemic therapy, with the exception of HBV, and HCV.
18. Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry.
19. Has a known history of human immunodeficiency virus (HIV) infection.
Note: No HIV testing is required unless mandated by local health authority.
20. Has known active tuberculosis (TB; Bacillus tuberculosis). Note: No testing for TB is
required unless mandated by local health authority.
21. Has a known history of, or any evidence of, CNS metastases and/or carcinomatous
meningitis, as assessed by local site investigator.
22. Has a history or current evidence of any condition, (eg, hearing impairment, etc.),
therapy, or laboratory abnormality that might confound the results of the study, interfere
with the participant's participation for the full duration of the study, or is not in the best
interest of the participant to participate, in the opinion of the treating investigator.
23. Has a known psychiatric or substance abuse disorder that would interfere with the
participant*s ability to cooperate with the requirements of the study.
24. Is pregnant or breastfeeding or expecting to conceive or father children within the
projected duration of the study, starting with the screening visit through 210

days after
the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab
or placebo, whichever is greater.
25. Has had an allogenic tissue/solid organ transplant.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-02-2020
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatine
Generic name:	Cisplatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	20-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-09-2021
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:	16-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-03-2023
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
EU-CTR	CTIS2023-506657-38-00
EudraCT	EUCTR2019-000944-82-NL
ClinicalTrials.gov	NCT04003636
CCMO	NL70697.056.19