# A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma

Published: 10-03-2017
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Objectives: To compare PFS using RECIST 1.1 as assessed by BICR and OS in PD-L1 positive subjects and all subjects between the following treatment comparisons:(a) Pembrolizumab + chemotherapy versus chemotherapy(b) Pembrolizumab versus...

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

## Summary

### ID

NL-OMON45288

**Source**
ToetsingOnline

**Brief title**
MK-3475-361

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
bladder cancer; urothelial cancer

**Research involving**

Human

## Sponsors and support

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

## Intervention

**Keyword:** Advanced or metastatic, pembrolizumab, Urothelial Carcinoma

## Outcome measures

### Primary outcome

The primary endpoints will be progression-free survival (PFS) for compbo vs chemo only in the all-subject population using a blinded independent central review (BICR) and RECIST 1.1 to determine disease progression and overal survival (OS) for combo vs chemo only in the all-subject population and OS for pembro only vs chemo only in the PD-L1 CPS for both the PD-L1 CPS > 10% and all-subject population.

### Secondary outcome

Secondary endpoints will include objective response rates (ORR) and duration of response (DOR) using BICR and RECIST 1.1 to determine disease progression, for both the PD-L1 positive population and the all-subject population. The proportion of subjects who are progression free at specific time points will also be assessed. Exploratory endpoints include health-related quality of life as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and European Quality of Life (EuroQol) EQ-5D*, as well as the relationship between genetic variations and response to treatment.

# Study description

### Background summary

Urothelial (transitional cell) carcinoma describes a range of tumors that arise from the urothelial endothelium, which lines the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually, ranking it as the seventh most common cancer worldwide. Urothelial carcinoma (as distinct from squamous cell or adenocarcinoma) is the predominant histologic type of bladder cancer in the United States (US) and Western Europe, where it accounts for approximately 90% of bladder cancers. In other areas of the world, nonurothelial histologies are more frequent.

Patients with advanced or metastatic urothelial carcinoma present unique challenges. These are clinical scenarios in which patients present with locally advanced disease that cannot be treated with definitive intent or as metastatic disease from the beginning, or with recurrent disease that is inoperable or with metastatic disease that has progressed following initial treatment with definitive intent. Although a variety of chemotherapeutic agents are used in this setting and initially are associated with response, the prognosis for patients is poor - median survival from studies in these setting ranges from 8 to 15 months, and the majority of patients die from complications related to disease. The advanced/metastatic setting represents a clinical area in need of novel therapeutic approaches such as with checkpoint inhibitor therapy with or without chemotherapy.
The primary trial hypothesis is that pembrolizumab-based therapy prolongs PFS and OS as compared with chemotherapy alone in patients with advanced or metastatic urothelial carcinoma.

### Study objective

Objectives: To compare PFS using RECIST 1.1 as assessed by BICR and OS in PD-L1 positive subjects and all subjects between the following treatment comparisons:
(a) Pembrolizumab + chemotherapy versus chemotherapy
(b) Pembrolizumab versus chemotherapy

Secondary Objective(s) & Hypothesis(es) 3.2
1. Objective: To evaluate the safety and tolerability profile in all subjects (PD-L1 positive and negative) in the following treatment groups:
(a) Pembrolizumab (b) Pembrolizumab + chemotherapy (c) Chemotherapy

2. Objective: To compare the ORR using RECIST 1.1 as assessed by BICR between the following treatment comparisons:
(a) Pembrolizumab versus chemotherapy (b) Pembrolizumab + chemotherapy versus chemotherapy

3. Objective: To evaluate the disease control rate (DCR--combined complete response, partial response, and stable disease rates) in all subjects (PD-L1 positive and negative) using RECIST 1.1 as assessed by BICR in the following treatment groups:
(a) Pembrolizumab
(b) Pembrolizumab + chemotherapy
(c) Chemotherapy

4. Objective: To estimate PFS at milestone time points (6 months, 12 months, 18 months, 24 months) in all subjects (PD-L1 positive and negative) using RECIST 1.1 BICR in the following treatment comparisons:
(a) Pembrolizumab (b) Pembrolizumab + chemotherapy (c) Chemotherapy

**Study design**

This is a Phase III randomized, active-controlled, parallel-group, multi-site, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone in subjects with advanced or metastatic urothelial carcinoma (bladder cancer).
there are 3 treatment groups: pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or chemotherapy alone.

**Intervention**

In the pembrolizumab monotherapy arm and pembrolizumab + chemotherapy comparison arm, each subject will receive the following dose of pembrolizumab:
• Pembrolizumab 200 mg every 3 weeks (Q3W) (Day 1 of each 3-week cycle) for a maximum of 35 doses.
In the pembrolizumab + chemotherapy and chemotherapy alone comparison arms, each subject will receive 6 cycles of platinum-based combination chemotherapy as per investigator*s choice (based on clinical factors; refer to Section 4.2.1 for cisplatin ineligibility guidelines) of either:
• Cisplatin intravenous (IV) infusion 70 mg/m2 on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m2 Day 1 and Day 8 of each 3-week cycle
OR (only if ineligible for cisplatin; refer to Section 4.2.1 for cisplatin ineligibility guidelines)
• Carboplatin IV infusion area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m2 Day 1 and Day 8 of each 3-week cycle.

**Study burden and risks**

The patient will approximately be in the study for 2 years if the disease doesn't progress. A treatment cycle consists of approximately 3 weeks. Possibly

the patient needs to go to the hospital more often compare to standard treatment for additional research.
The tests could be uncomfortable, the tests are also applicable for standard care however possibly less frequent. The medication can cause side effects, possibly not all side effects are known yet.

## Contacts

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NL
**Scientific**
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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. Have a histologically or cytologically confirmed diagnosis of advanced/unresectable or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra. Both transitional cell and mixed transitional/nontransitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology.;2. Have measurable disease based on RECIST 1.1 as determined by the local site

investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.;3. Voluntarily agree to participate by providing written informed consent/assent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.;4. Be >=18 years of age on the day of signing informed consent.;5. Have received no prior systemic chemotherapy for advanced or metastatic urothelial carcinoma, with the following exceptions:;a. Neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy is permitted.;b. Adjuvant platinum-based chemotherapy following radical cystectomy with recurrence >12 months from completion of therapy is permitted.;6. Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated from a muscle invasive urothelial carcinoma or a metastatic biopsy, originating from the origingal tumor. A newly obtained biopsy is strongly preferred but not required if archival tissue is evaluable. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. Refer to section 7.1.2.12 in the protocol for an explanation. PD-L1 status (CPS >10%) must be determined by the central laboratory during the screening period prior enrollment. ;7. Have an ECOG PS of 0, 1, or 2.;8. Demonstrate adequate organ function as defined in the protocol;9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.;10. Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment.;11. Male subjects of childbearing potential (section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.2.7 - Contraception, starting with the first dose of trial therapy through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy

## Exclusion criteria

1. Has disease that is suitable for local therapy administered with curative intent.;2. Is currently participating and receiving study therapy.;3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.;4. Has an active autoimmune disease that has required systemic treatment in the past 2 years.;5. Has had a prior anti-cancer mAb for direct anti-neoplastic treatment within 4 weeks prior to the first dose of trial treatment (6 weeks for nitrosoureas or mitomycin C) or who has not recovered (ie, <=Grade 1 or at baseline) from AEs due to mAbs administered more than 4 weeks earlier. ;6. Has not recovered from AEs due to a previously administered agent.;7. Has a known additional malignancy that is progressing or requires active treatment within the past 5 years.;8. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.;9. Has a known history of active tuberculosis (TB) (Bacillus tuberculosis).;10. Has an active infection requiring systemic therapy.;11. Has a history of severe hypersensitivity reaction to pembrolizumab, gemcitabine, carboplatin, or cisplatin or their analogs, and / or to any their excipients.;12.

Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject*s participation.;13. Has known psychiatric or substance abuse disorders.;14. Is pregnant or breastfeeding, or expecting to conceive or father children.;15. Has received prior therapy with an anti-PD-1, or anti-PD-L1, or anti-PD-L2 agent.;16. Has a known history of human immunodeficiency virus.;17. Has known active hepatitis B /C.;18. Has received a live virus vaccine within 30 days of planned start of trial therapy.;19. Has known active CNS metastases and/or carcinomatous meningitis.;20. Has symptomatic ascites or pleural effusion.;21. Has had a prior allogeneic stem cell or bone marrow transplant.

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 14-07-2017 |
| Enrollment: | 20 |
| 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: | N/A |

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|---|---|
| Generic name: | Carboplatin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | N/A |
| Generic name: | Gemcitabine |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Platinol |
| Generic name: | Cisplatin |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 10-03-2017 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-04-2017 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-06-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-10-2017 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-11-2017 |
| Application type: | Amendment |

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| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-03-2018 |
| 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: | 18-12-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-09-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-11-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-12-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-04-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 28-05-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-10-2020 |
| 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: | 30-06-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-09-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-02-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-06-2022 |
| 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 | EUCTR2015-005731-41-NL |
| ClinicalTrials.gov | NCT02853305 |
| CCMO | NL60846.056.17 |