A Phase II Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab plus Olaparib Combination Therapy Compared with Durvalumab Monotherapy as Maintenance Therapy in Patients whose Disease has not Progressed Following Standard of Care Platinum-Based Chemotherapy with Durvalumab in First Line Stage IV Non Small Cell Lung Cancer (ORION)

Published: 05-12-2018
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Primary objective:-To assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed)Secondary objectives:- To further assess the efficacy of durvalumab plus olaparib…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52731

Source
ToetsingOnline

Brief title
ORION

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Durvalumab, non-small cell lung cancer, Olaparib, Orion

Outcome measures

Primary outcome

Endpoint Primary objective:

PFS: Time from date of randomization until the date of objective radiological

disease progression according to Investigator assessment using RECIST 1.1 or

death (by any cause in the absence of progression)

Statistical considerations can be found in the protocol summary

Secondary outcome

Endpoints secondary objectives

a) OS: Time from date of randomization until the date of death by any cause

ORR: Percentage of patients with an Investigator-assessed response of CR or PR

after Randomization

DoR: Time from the date of first documented response following randomization until the first date of documented progression or death in the absence of disease progression

b) PFS: Time from date of randomization until the date of objective radiological disease progression according to Investigator assessment in HRRm population using RECIST 1.1 or death (by any cause in the absence of progression)

c) Concentration of durvalumab

d) Change from baseline and time to deterioration (for maintenance phase) in EORTC QLQ-C30 and EORTC QLQ-LC13

e) Presence of ADAs for durvalumab

Endpoints safety objective

AEs, physical examinations, laboratory findings, and vital signs

Endpoints exploratory objectives

- Biomarkers (eg, TMB, alterations in HRR and other relevant gene variants, protein expression detected by IHC, blood ctDNA, tumor and blood mRNA expression, and PD-L1 expression) correlating with clinical response
- The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
- Change in specific treatment-related symptoms
- Proportion of patients assessing current symptom severity
- Health care resource use will be captured, including inpatient admissions,

intensive care unit admissions, and length of stay in hospital

Statistical considerations can be found in the protocol summary

Study description

Background summary

Rationale:
Current SoC therapies for metastatic non-small cell lung cancer (NSCLC) have mixed outcomes with responses to systemic chemotherapy in the first-line setting of approximately 20% to 40% and a median overall survival (OS) of approximately 11 to 14 months (Breslow 1974, Carbone et al 2017, Paz-Ares et al 2013, Socinski et al 2018, Gandhi et al 2018). Treatments are associated with a variety of significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia (Sandler et al 2006, Scagliotti et al 2008). The KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407 studies, along with the IMpower131 and IMpower150 studies, have shown that immunotherapy alone or in combination with chemotherapy can be effective first-line treatment for patients with metastatic NSCLC (Gandhi et al 2018, Jotte et al 2018, Lopes et al 2018, Paz-Ares et al 2018, Reck et al 2016, Socinski et al 2018). Results from these studies have been encouraging and represent a substantive advance, but further improvement is needed. All of the aforementioned studies yielded a median progression-free survival (PFS) of <1 year. Furthermore, there are no approved maintenance immunotherapy-based combination regimens for patients with squamous histology. Increased DNA damage triggered through polyadenosine 5*diphosphoribose [poly (ADP ribose)] polymerase (PARP) inhibition has the potential to not only provide antitumor activity but also modify tumor immunogenicity and sensitize tumors to immune checkpoint inhibition, promoting a more durable antitumor response. Therefore, in this Phase II study, the combination of durvalumab plus olaparib will be investigated to determine if this combination can prolong PFS in the maintenance setting in patients whose Stage IV NSCLC has not progressed following SoC platinum-based chemotherapy with durvalumab.

Study objective

Primary objective:
-To assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed)

Secondary objectives:

- To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS, ORR, and DoR
- To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed) in the HRRm population
- To assess the PK of durvalumab in combination with Olaparib
- To assess disease-related symptoms and HRQoL in patients treated with durvalumab plus olaparib combination therapy compared with durvalumab monotherapy
- To investigate the immunogenicity of durvalumab

Safety objective:
To assess the safety and tolerability profile of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy

Exploratory objectives:
- To assess blood and tissue samples at baseline (for initial therapy and maintenance phases) and/or on-treatment for immune-related markers, mRNA/protein signatures, and DNA mutations/signatures that are predictive of clinical benefit to durvalumab plus olaparib combination therapy compared with durvalumab monotherapy.
- To explore the impact of treatment and disease state on health utility using the EQ-5D-5L
- To assess treatment-related side effects using PROCTCAE
- To assess the patient*s overall impression of the severity of their cancer symptoms using PGIS
- To explore the impact of treatment and disease on health care resource use

Study design

Overall design:
This is a Phase II randomized, multi-center, double-blind, global study to determine the efficacy and safety of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy as maintenance therapy in patients whose disease has not progressed following SoC platinum-based chemotherapy with durvalumab in first-line Stage IV NSCLC. There will be approximately 80 sites in the study. During the initial therapy phase, approximately 350 to 400 patients will receive treatment with durvalumab, along with the Investigator*s choice of platinum-based doublet therapy for squamous NSCLC (nanoparticle albumin-bound [nab]-paclitaxel plus carboplatin or gemcitabine plus carboplatin/cisplatin) and nonsquamous NSCLC (nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin/cisplatin) for 4 cycles.

It is estimated that approximately 350 to 400 patients will be enrolled in the initial therapy phase in order for approximately 250 patients who have not progressed (ie, maintained complete response [CR], partial response [PR], or stable disease [SD] throughout the initial therapy phase according to

Investigator-assessed RECIST 1.1) to be randomized into the maintenance phase of the study (patients completing the initial therapy phase who are not randomized cannot continue durvalumab). Patients will be randomized 1:1 to receive either durvalumab plus placebo or durvalumab plus olaparib maintenance therapy. Randomization will be stratified by histologic subtype (squamous or nonsquamous) and objective response (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) during the initial therapy phase.

Confirmation of eligibility criteria for randomization (eligibility scan and other specific criteria; see Sections 5.1 and 5.2 for criteria that must be met at randomization) will take place 14 to 28 days after Cycle 4 Day 1 of the initial therapy phase. Laboratory assessments for eligibility should be taken after the last dose of chemotherapy in the initial therapy phase. If determined eligible, patients will be randomized within 5 weeks after Cycle 4 Day 1 of the initial therapy phase; every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. Patients will receive maintenance treatment until specific discontinuation criteria are met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent. Note that crossover within the study will not be permitted.

Intervention

Treatments and treatment duration:

Durvalumab (MEDI4736) and platinum-based chemotherapy (initial therapy phase)
During the initial therapy phase, all patients will receive durvalumab 1500 mg via intravenous (IV) infusion q3w for 4 cycles, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met. If a patient*s WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q3w after consultation between Investigator and Study Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w. If there is a dosing delay during the treatment schedule for durvalumab, all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. The standard infusion time is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

In addition to durvalumab, patients in the initial therapy phase will also receive 1 of the following SoC regimens as part of their treatment regimen (durvalumab will be infused first,followed by the SoC chemotherapy regimen):
-Nab-paclitaxel plus carboplatin (squamous and nonsquamous patients):
Nab-paclitaxel 100 mg/m2 via IV infusion on Days 1, 8, and 15 of each 3-week cycle and carboplatin area under the concentration-time curve (AUC) 5 or 6 via

IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 2).
-Gemcitabine plus carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 3-week cycle and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3).
-Gemcitabine plus cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 3-week cycle and cisplatin 75 mg/m2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3)
-Pemetrexed plus carboplatin (nonsquamous patients only): Pemetrexed 500 mg/m2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.
- Pemetrexed plus cisplatin (nonsquamous patients only): Pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.

In the event that SoC is delayed during the initial therapy phase, durvalumab administration must also be delayed.
In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point during the study.

Durvalumab monotherapy and durvalumab plus olaparib combination therapy (maintenance phase)
During the maintenance phase, all patients will receive durvalumab 1500 mg via IV infusion every 4 weeks (q4w). Patients will also receive 300 mg oral olaparib (durvalumab plus olaparib treatment arm) or its matching placebo (durvalumab plus placebo treatment arm) BID continually until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD (Figure 5 and Figure 6), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.
Before commencing olaparib/placebo treatment, patients must first meet the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days.

If a patient*s WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w. If there is a dosing delay during the treatment schedule for durvalumab, subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days; olaparib/placebo administration may continue as scheduled if durvalumab is delayed. The standard infusion time for durvalumab is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.
See Section 7.1 for details about discontinuation of either durvalumab or olaparib/placebo in the maintenance phase.

Duration of treatment
Unless specific treatment discontinuation criteria are met, treatment during the initial therapy phase will continue for only 4 cycles of durvalumab plus chemotherapy. There is no maximum treatment duration for the maintenance phase; patients will receive maintenance treatment until specific discontinuation criteria are met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent.

Progression during treatment
Patients with clinical disease progression (as assessed by the Investigator), in the initial therapy or maintenance phase of the study, are not eligible for treatment through progression. Patients who are clinically stable with RECIST 1.1-defined radiological PD at Cycle 2 of the initial therapy phase may continue to receive study treatment at the discretion of the Investigator and patient; however, if the patient continues to show a RECIST 1.1-defined radiological PD at Cycle 4, the patient will not be eligible for the maintenance phase of the study. Patients completing the initial therapy phase who are not randomized cannot continue durvalumab.

During the maintenance phase, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix F. Patients with PD in the maintenance phase who continue to receive investigational product (IP) at the discretion of the Investigator and patient (following consultation with AstraZeneca) will have tumor assessments on their regular imaging schedule for the duration of treatment. However, patients will not be permitted to continue immunotherapy or olaparib/placebo if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) in the target lesions (TLs) to either the initial therapy (durvalumab plus chemotherapy) or maintenance treatment (durvalumab or olaparib/placebo) of the study regardless of the appearance of new lesions. Patients who have discontinued durvalumab will not be permitted to be treated with olaparib/placebo monotherapy after progression.

Follow-up of patients post discontinuation of study drug
Patients who have discontinued treatment in the maintenance phase for any reason other than RECIST 1.1-defined radiological PD will be followed up with tumor assessments until RECIST 1.1-defined radiological PD, plus one or more additional follow-up scans if clinically feasible. Patients who discontinue treatment due to RECIST 1.1-defined radiological PD will have one or more additional follow-up scans, if clinically feasible. All patients will be followed for survival. For patients who are not randomized into the maintenance

phase for any reason, follow-up tumor assessments will not be required.

Study burden and risks

- The risks associated with the study medications durvalumab (including iv infusion) and olaparib.
- The risks associated with SOC chemotherapy
- The risks associated with the combination therapy of durvalumab with SOC chemotherapy and the combination of durvalumab with olaparib
- The risk of possible interactions with other medications and grapefruit juice
- The risks linked to blood draws, MRI/CT scans and biopsies

These risks are included in the patient information sheet

Contacts

Public
Astra Zeneca

Building 411A Floor 4
Södertälje SE-151 85
SE

Scientific
Astra Zeneca

Building 411A Floor 4
Södertälje SE-151 85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria
and none of the exclusion criteria apply:
Informed consent
1 Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this
protocol.
2 Provision of signed and dated, written ICF prior to any mandatory study specific
procedures, sampling, and analyses.
3 Provision of signed and dated written informed consent prior to collection of sample for
genetic analysis.
The informed consent process is described in Appendix A 3 (protocol).
Patients must meet the following criteria at screening prior to receiving treatment:
4 Female or male patients aged *18 years. For patients aged <20 years and enrolled in
Japan, a written informed consent should be obtained from the patient and his/her legally
acceptable representative.
5 Histologically or cytologically documented Stage IV NSCLC not amenable to curative
surgery or radiation (according to version 8 of the IASLC Staging Manual in Thoracic
Oncology; IASLC Staging Manual in Thoracic Oncology 2016).
6 Patients must have tumors that lack activating EGFR mutations (eg, exon 19 deletion or
exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and ALK fusions. If a patient has squamous histology or is known to have a tumor with a KRAS
mutation, then EGFR and ALK testing are not required.
7 World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8 No prior chemotherapy or any other systemic therapy for Stage IV NSCLC. Patients who
have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation are eligible, provided that progression has occurred >12 months from end
of last therapy.
9 Life expectancy *12 weeks at screening.
10 Ability to swallow oral medications (capsules and tablets) without chewing, breaking,

crushing, opening, or otherwise altering the product formulation. Patients should not have
GI illnesses that would preclude the absorption of olaparib, which is an oral agent.
11 Patients must also have adequate organ and marrow function without blood transfusions
in the past 28 days, defined as follows:
- Hb *10 g/dL
- ANC *1.5 × 109/L
- Platelet count *100 × 109/L
- Serum bilirubin *1.5 × ULN; unless due to Gilbert*s syndrome, in which case patients will be allowed in consultation with their physician and AstraZeneca
- ALT and AST *2.5 × ULN; for patients with hepatic metastases, ALT and AST *5 × ULN
- CrCl *51 mL/min calculated by the investigator or designee using the Cockcroft-Gault equation (using actual body WT) or
measured by 24-hour urine collection
Males:
- CrCl <= WT (kg) × (140 - Age)
(mL/min) 72 × Serum creatinine (mg/dL)
Females:
- CrCl <= WT (kg) × (140 - Age) × 0.85
* (mL/min) 72 × Serum creatinine (mg/dL)
12 Patients must have at least 1 lesion, not previously irradiated, that can be accurately
measured at baseline as *10 mm in the longest diameter (except lymph nodes that must
have a short axis *15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST
1.1 guidelines.
13 All patients must provide a formalin-fixed, paraffin embedded (FFPE) tumor sample for
tissue-based immunohistochemistry (IHC) staining and DNA sequencing to determine PD-L1 expression, HRRm status, and other correlatives; either newly acquired or archival
tumor samples (<3 years old) are acceptable. If available, a newly acquired tumor biopsy,
collected as part of routine clinical practice, is preferred. If not available, an archival
sample taken <3 years prior to screening is acceptable. If both an archival sample and a
fresh tumor biopsy sample are available, both samples should be submitted for analysis and must be submitted as different samples using different accesion numbers. Slides from different blocks cannot be mixed and submitted with the same kit.
14 Tumor lesions used for newly acquired biopsies should not be TLs, unless

there are no
other lesions suitable for biopsy. Samples with limited tumor content and fine needle
aspirate specimens are not acceptable. Specimens from metastatic bone lesions are
typically unacceptable unless there is a significant soft tissue component and should not
be decalcified. For additional details on sample requirements, see Section 8.8.1 (protocol).
15 Body WT >30 kg.
Patients must meet the following criteria to be randomized to maintenance treatment:
16 Patients must have documented radiographic evidence of a timepoint tumor response of
CR, PR, or SD according to Investigator-assessed RECIST 1.1 guidelines following the 4
cycles of platinum-based chemotherapy. An objective response does not have to be confirmed in order for the patient to be randomized.
17 CrCl *51 mL/min calculated by the investigator or designee using the Cockcroft-Gault equation (using actual body WT) or
measured by 24-hour urine collection.
18 Inclusion criterion 10.

Exclusion criteria

Patients must NOT meet the following criteria at screening prior to receiving treatment:
1 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
2 Mixed small-cell lung cancer and sarcomatoid variant NSCLC histology.
3 No radiation therapy is allowed, unless it is 1) definitive radiation that had been
administered at least 12 months prior, 2) palliative radiation to brain, with associated
criteria for stability or lack of symptoms, or 3) palliative radiation to painful bony lesions
(this must comprise less than 30% of the bone marrow).
4 Prior exposure to any chemotherapy agents (with the exception of chemotherapy or
chemoradiation for non-metastatic disease; see inclusion criterion 8 for full details),
PARP therapy, or immune-mediated therapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic

anticancer vaccines and other PARP inhibitors.
5 Any contraindications to platinum-based doublet chemotherapy.
6 Active or prior documented autoimmune or inflammatory disorders (including, but not
limited to, inflammatory bowel disease [eg, colitis or Crohn*s disease], diverticulitis [with
the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome,
Wegener syndrome [granulomatosis with polyangiitis], Graves* disease, rheumatoid
arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion:
- Patients with vitiligo or alopecia
- Any chronic skin condition that does not require systemic therapy
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Patients without active disease in the last 5 years may be included but only after
consultation with AstraZeneca.
- Patients with celiac disease controlled by diet alone may be included but only after
consultation with AstraZeneca.
7 History of another primary malignancy except for:
- Malignancy treated with curative intent and with no known active disease *5 years
before the first dose of IP and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of
disease
- Adequately treated carcinoma in situ without evidence of disease
8 Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone
replacement therapy) is acceptable.
9 Current or prior use of immunosuppressive medication within 14 days before the first
dose of IP. The following are exceptions to this criterion:
- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular
injection)
- Systemic corticosteroids (that are not excluded according to exclusion criterion 10) at
physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
10 Concomitant use of known strong cytochrome P450 (CYP) 3A (CYP3A) inhibitors (eg,

itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or
cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir) or moderate
CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil). The required washout period prior to starting study treatment is 2 weeks.
Concomitant use of known strong (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St. John*s Wort) or
moderate CYP3A inducers (eg, bosentan, efavirenz, dexamethasone, and modafinil). The
required washout period prior to starting study treatment is 5 weeks for enzalutamide or
phenobarbital and 3 weeks for other agents.
11 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first
dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
12 Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged
by the Investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, QT
interval corrected for heart rate using Fridericia*s formula [QTcF] value *470 ms
calculated from 3 ECGs [within 15 minutes at 5 minutes apart], electrolyte disturbances,
etc), or patients with congenital long QT-interval syndrome or congestive heart failure.
13 Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis
identified either on the baseline brain imaging (please see Appendix F [RECIST] for
details on the imaging modality) obtained during the screening period or identified prior
to signing the ICF. Patients whose brain metastases have been treated may participate
provided they show radiographic stability (defined as 2 brain images, both of which are
obtained after treatment to the brain metastases. These imaging scans should both be
obtained at least 4 weeks apart and show no evidence of intracranial progression). In
addition, any neurologic symptoms that developed either as a result of the brain
metastases or their treatment must have resolved or be stable either, without the use of
steroids, or are stable on a steroid dose of *10 mg/day of prednisone or its

equivalent and
anti-convulsants for at least 14 days prior to the start of treatment. Brain metastases will
not be recorded as RECIST TLs at baseline.
14 Uncontrolled intercurrent illness, including, but not limited to, ongoing or active
infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable
angina pectoris, cardiac arrhythmia, ILD, or psychiatric illness, or social situations that
would limit compliance with study requirements, substantially increase the risk of
incurring AEs from IP, or compromise the ability of the patient to give written informed
consent.
15 History of allogenic organ transplantation including umbilical cord blood transplantation.
16 Patients with MDS/acute myeloid leukaemia or with features suggestive of MDS/AML
17 History of leptomeningeal carcinomatosis.
18 History of active primary immunodeficiency.
19 Active infection including tuberculosis (clinical evaluation that includes clinical
history, physical examination and radiographic findings, and tuberculosis testing in line
with local practice), hepatitis B (known positive hepatitis B virus [HBV] surface antigen
[HBsAg] result), hepatitis C, or human immunodeficiency virus (HIV; positive HIV
1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of
hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for
hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is
negative for HCV ribonucleic acid (RNA).
20 Any unresolved toxicity NCI Common Terminology Criteria for Adverse Event
(CTCAE) Grade *2 from previous anticancer therapy with the exception of alopecia,
vitiligo, and the laboratory values defined in the inclusion criteria:
- Patients with Grade *2 neuropathy will be evaluated on a case-by-case basis after
consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by
treatment with durvalumab or olaparib may be included only after consultation with
the Study Physician.

21 Known allergy or hypersensitivity to any of the study drugs or any of the study drug
excipients.
22 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note:
Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days
after the last dose of IP.
23 Participation in another clinical study with an IP administered in the last 12 months.
24 Previous IP assignment in the present study.
25 Prior randomization or treatment in a previous durvalumab (and/or olaparib) clinical
study regardless of treatment arm assignment.
26 Female patients who are pregnant or breastfeeding or male or female patients of
reproductive potential who are not willing to employ effective birth control from
screening to 90 days after the last dose of durvalumab or 30 days after the last dose of
olaparib/placebo, whichever is later.
27 Judgment by the Investigator that the patient should not participate in the study if the
patient is unlikely to comply with study procedures, restrictions, and requirements.
28 Genetics research study (optional):
Exclusion criteria for participation in the optional (DNA) genetics research component of
the study include:
- Previous allogeneic bone marrow transplant
- Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection
Patients must NOT meet the following criterion to be randomized to maintenance treatment:
29 Inability to complete 4 cycles of platinum-based chemotherapy for any reason or
discontinuation of durvalumab during initial therapy. Dose interruptions or delays are not
exclusionary.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2019
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane
Generic name:	Paclitaxel (protein-bound)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	Olaparib / Lynparza and placebo

Generic name:	Olaparib / Lynparza and placebo
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-02-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-06-2022
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
EudraCT	EUCTR2018-003460-30-NL
ClinicalTrials.gov	NCT03775486
CCMO	NL67473.028.18