An Open-Label, Multi-Center, Global Study to Evaluate Long Term Safety and Efficacy in Patients Who are Receiving or Who Previously Received Durvalumab in Other Protocols (WAVE)

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Primary Objective: To monitor long-term safety of durvalumab (allcohorts)Secondary Objectives: To assess the efficacy of durvalumab in terms of ORR and DOR in patients who undergoretreatment with durvalumab (Cohort 2 only)Secondary ObjectivesTo...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52594

Source
ToetsingOnline

Brief title
WAVE D910FC00001

Condition

- Other condition

Synonym
Advanced solid tumors

Health condition

Advanced stages Gastric adenocarcinoma, Urothelial cancer, non small cell lung cancer, Squamous cell carcinoma of the head and neck, hepatocellular carcinoma, biliarytract

cancers

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Durvalumab, Efficacy, Open-label, Safety

Outcome measures

Primary outcome

Endpoints/Variables:

• All SAEs

• Non-serious AEs that lead to dose modification,

drug discontinuation, or withdrawal from the study

• All Grade 3 and Grade 4 AEs

• Grade 2 AEs that affect vital organs (eg, heart, liver)

• Immune-mediated AEs

• Laboratory findings qualifying as an SAE/AE (endpoints defined above) up

until 90 days after the last dose of durvalumab in all patients

Secondary outcome

Endpoints/Variables:

• ORR: Number (%) of patients with a confirmed response of CR or PR.

• DOR: Time from first documented CR or PR to time of first documented disease

progression or death in the absence of disease progression

• OS: Time from date of randomization/enrollment in the parent clinical study

until the date of death by any cause AE adverse event; CR complete response;

DOR duration of response; ORR overall response rate; OS overall survival; PR

partial response; SAE serious adverse event.

Study description

Background summary

2.1 Study rationale
This is a multicenter, open-label, global study that will enroll patients who are currently receiving durvalumab monotherapy, or have previously received durvalumab as monotherapy or in combination with any other approved or investigational anticancer agents, in an eligible AstraZeneca/MedImmune-sponsored clinical study (herein referred to as a parent clinical study).
The aims of the study are the following:
• To collect long-term safety and survival data from patients who received durvalumab monotherapy and/or durvalumab in combination with any other approved or investigational anticancer agents.
• To provide continued access to durvalumab monotherapy until confirmed progressive disease (PD) to patients currently receiving treatment.
• To allow for future retreatment with durvalumab monotherapy upon disease progression in patients who previously benefited from treatment with durvalumab as monotherapy, and/or durvalumab in combination with any other approved or investigational anticancer agents and experienced disease progression after completion of planned treatment.
The primary aim of this study is to monitor the long-term safety of durvalumab. Extensive safety-related data are being collected throughout the course of drug development, and knowledge about a drug*s safety profile continually evolves as safety data accumulate. This study is aligned with the growing interest in larger, simpler trials to obtain outcome data,
including long-term effects of drugs and comparative effectiveness and safety.

2.2 Background
A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the Investigator*s Brochure (IB).
2.2.1 Immunotherapies
It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).
Programmed death ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T cell activation. The programmed cell

death protein 1 (PD-1) receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016).

Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous antitumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells (IC). This activity overcomes PD-L1-mediated inhibition of antitumor immunity.

While functional blockade of PD-L1 results in T cell reactivation, this mechanism of action (MOA) is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer.

Results of preclinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Preclinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and

atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies, including metastatic melanoma, squamous and non-squamous cell non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on IC. It is being developed by AstraZeneca/MedImmune, for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The propose MOA for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD- 1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient*s antitumor immune response by binding to PD-L1 and by shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies, either as monotherapy or in combination with any other approved or investigational anticancer agents.

Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1.1 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Durvalumab administered either as a single agent or in combination continues to be evaluated in multiple immuno-oncology clinical studies. To date, several different doses and schedules have been evaluated in multiple indications, including administration for a fixed duration.

Durvalumab has been administered intravenously (IV) in multiple clinical studies for up to 12 months or until PD, whichever occurs earlier. After the completion of therapy in these ongoing clinical studies, patients are followed with regular tumor assessments to continue monitoring the clinical activity of durvalumab. Emerging data from these ongoing studies
suggest that some patients lose clinical benefit after completing 12 months of therapy, eg, HAWK (NCT02207530) and ATLANTIC (NCT02087423) studies. Patients treated with chemotherapy alone are generally unlikely to respond to re-challenge with the same agent upon progression. In contrast, responses have been observed upon retreatment with immunotherapies (Santini 2018). Several

potential mechanisms of resistance to immunotherapy exist, including loss of T cell *memory* or recurrence of immune escape, which suggest that retreatment for patients who initially respond or demonstrate stable disease (SD) merits further study. Preliminary data in patients previously treated with immunotherapies suggest that responses are similar to those observed following initial treatment (Forde et al 2014, Hodi et al 2010).
Therefore, AstraZeneca has modified the durvalumab treatment regimen in specific indications, to allow patients to continue treatment until confirmed PD, rather than requiring treatment discontinuation at 12 months. Treatment until progression is consistent with the approved agents with a similar MOA to durvalumab, such as PD-1 targeting antibodies nivolumab and pembrolizumab, which are used to treat patients in a number of indications, including but not limited to melanoma, NSCLC, urothelial cancer, and renal cell carcinoma.

Study objective

Primary Objective: To monitor long-term safety of durvalumab (all cohorts)

Secondary Objectives: To assess the efficacy of durvalumab in terms of ORR and DOR in patients who undergo
retreatment with durvalumab (Cohort 2 only)

Secondary Objectives
To assess the OS of patients (all cohorts)

Study design

This is a multicenter, open-label, global study that will enroll patients who are currently receiving durvalumab monotherapy, or have previously received durvalumab as monotherapy or in combination with any other approved or investigational anticancer agents, in an eligible parent clinical study. The study initially aims to enroll approximately 600 patients; study size may increase as new parent clinical studies are incorporated into this study. Some of these patients will no longer be eligible to receive treatment or retreatment with durvalumab, and will be followed for overall survival (OS).
For patients who are eligible to continue treatment or restart durvalumab, treatment will be administered every 4 weeks (q4w; ±3 days) until PD, unless there is unacceptable toxicity, withdrawal of consent, death, or another discontinuation criterion is met. All patients in the study will be followed for safety for 90 days after the last dose of durvalumab, and every 3 months (±2 weeks) beginning 90 days after the last dose of study drug for OS. For an overview of the study design, see Section 1.3. For details on treatments given during the study, see Section 6.1.
4.2 Scientific rationale for study design

4.2.1 Rationale for retreatment option
In contrast to patients treated with chemotherapy, who are unlikely to respond to re-challenge with the same agent upon progression, responses have been observed upon retreatment with immunotherapies. Several potential mechanisms of resistance to immunotherapy exist, including loss of T cell *memory* or recurrence of immune escape, which suggests that retreatment for patients who initially respond or demonstrate SD is reasonable. Preliminary data in patients previously treated with immunotherapies suggest that responses are similar to those observed
following initial treatment (Forde et al 2014, Hodi et al 2010).
Durvalumab has been administered IV in multiple clinical studies up to 12 months. After the completion of therapy in these ongoing clinical studies, patients are followed with regular tumor assessments to continue monitoring the clinical activity of durvalumab. Emerging data from these ongoing studies suggest that some patients lose clinical benefit after completing 12 months of therapy.

Intervention

4.3 Justification for dose
4.3.1 Durvalumab dose and treatment regimen justification
4.3.1.1 Durvalumab monotherapy dose rationale
A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, preclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).
Pharmacokinetic/Pharmacodynamic data
Based on available PK/pharmacodynamic data from ongoing Study 1108 with dose ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w), durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at >=3 mg/kg q2w, suggesting near complete target saturation (membranebound and soluble PD-L1), and further showed that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses >=3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral soluble PD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed.
No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB.)
A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overallexposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median Ctrough,ss is

expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in the majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibodies impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.
Given the similar area under the serum drug concentration-time curve and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete soluble PD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w
and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.
Clinical data
Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen. The IB reflects the current regimen that is used across the program when durvalumab monotherapy is dosed q4w.
4.3.1.2 Rationale for fixed dosing
A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only a minor impact of body weight (WT) on the PK of durvalumab (coefficient of <=0.5). The impact of body weight (WT)-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.
Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body weight-based dosing perform similarly, with fixed dosing being better for 7 of
12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides, and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community, due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

4.3.1.3 Rationale for duration of treatment
In this study, the duration of treatment was selected to allow eligible patients to continue treatment with durvalumab monotherapy until confirmed PD. Additionally, patients who completed the defined duration of treatment with durvalumab or durvalumab plus any other approved or investigational anticancer agents in a parent clinical study and subsequently experienced confirmed PD, will be permitted

Study burden and risks

2.3 Benefit/risk assessment
More detailed information about the known and expected benefits and risks, and reasonably expected adverse events (AEs) of durvalumab may be found in the IB.

2.3.1 Overall benefits
As is commonly the case for clinical trials with a fixed treatment or study duration, long-term safety and efficacy endpoints often lack feasibility within the time frame permitted by design.
The benefit of this study, which identifies potentially eligible patients from parent clinical studies, allows for the continued access of durvalumab and observation of patients treated with durvalumab. Durvalumab will be provided to eligible, treatment-experienced patients who have been treated for months under parent clinical studies and have demonstrated a response and tolerability to treatment. They will be treated as long as they continue to receive benefit for treatment with durvalumab.
Conducting this study serves the important purpose to better understand the long-term patient safety and survival outcomes across a diverse group of patient population exposed to durvalumab.

2.3.1.1 Benefits of durvalumab as monotherapy
The majority of the safety and efficacy data currently available for durvalumab are based on 5 monotherapy studies (CD-ON-MEDI47361108, ATLANTIC, HAWK, PACIFIC, and D4190C00007) for which efficacy data are available. Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. PACIFIC has shown significant improvements in median progression-free survival with durvalumab treatment compared with placebo for patients with NSCLC (16.8 months [95% confidence interval {CI}: 13.0, 18.1] versus 5.6 months [95% CI: 4.6, 7.8]; stratified hazard ratio for disease progression or death, 0.52; 95% CI: 0.42, 0.65; $p<0.001$). Similar findings in favor of durvalumab compared with placebo were found for duration of response (DOR; 72.8% versus 46.8% of patients had ongoing response at 18 months, respectively) and median time to death or distant metastasis (23.2 months versus 14.6 months, respectively; $p<0.001$).

2.3.2 Overall risks
Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous

immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues. Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or unique interventions, such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal (GI) AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyperthyroidism.

2.3.2.1 Potential risks of durvalumab monotherapy
Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, and type I diabetes mellitus [DM]), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neuromuscular toxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.
For information on all identified and potential risks with durvalumab, please always refer to the current version of the durvalumab IB.
In monotherapy clinical studies, AEs reported an incidence of >=20%, this included events such as fatigue, cough, decreased appetite, dyspnea, and nausea. A total of 5% to 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria Grade 3 to 5 events reported across the durvalumab program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.4).
A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB

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. Patient must be 18 years or older, at the time of signing the ICF. For subjects aged <20 years and enrolled in Japan, a written ICF should be obtained from the subject and his or her legally acceptable representative.
2. Patient received durvalumab monotherapy and/or durvalumab containing combination in an AstraZeneca/MedImmune-sponsored parent clinical study that is approved for enrollment into this study.
3. Patients who received durvalumab in combination with any other approved or investigational anticancer agents in the parent clinical study must have completed or discontinued all other anticancer therapy (beyond durvalumab regimen).
4. Patient must be willing and able to provide written informed consent and to comply with scheduled visits and other study procedures.

Exclusion criteria

The following exclusion criteria apply only to patients receiving treatment or retreatment:
Patients must not enter the study if any of the following key exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

Additional exclusion criteria for Cohort 1 and 2:
2. Currently receiving treatment in another interventional clinical study other than a parent clinical study, or received treatment during the follow-up period before retreatment (Cohort 2 only).
3. Experienced an immune-mediated or non-immune-mediated (hematologic and non-hematologic) toxicity that led to permanent discontinuation of durvalumab in the parent clinical study.
4. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade >=2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
5. Prior treatment with immunotherapy other than durvalumab, or any other approved or investigational anticancer agents other than MedImmune/AstraZeneca*s investigational immunotherapy molecules administered in the parent clinical study.
6. Any concurrent chemotherapy, investigational product (IP), biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn*s disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves* disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
(a) Patients with vitiligo or alopecia.
(b) Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
(c) Any chronic skin condition that does not require systemic therapy.
(d) Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician.
(e) Patients with celiac disease controlled by diet alone.
8. History of allogenic organ transplantation.
9. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic GI conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
10. Documented active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with in line with local practice), hepatitis B virus (HBV) (known positive HBV surface antigen [HbsAg] result), hepatitis C virus (HCV), 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 HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Prior HIV and HBV/HCV testing from the parent clinical study is acceptable documentation and patients will not need to undergo an additional testing prior to Cohort 1 enrollment in this study. For Cohort 2 patients, prior HIV testing from the parent clinical study is acceptable documentation and patients will not need to undergo an additional test prior to retreatment. However, patients will require retesting for HbsAg and HCV within the 28-day window prior to retreatment.
11. Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug in the present study. Note: Patients, if enrolled, should not receive live vaccine while receiving study drug and up to 90 days after the last dose of study drug.
12. 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 monotherapy or 180 days after
the last dose of durvalumab + tremelimumab combination.
* Highly effective methods of contraception are defined as one that results in a low failure rate (eg, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or
female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).
13. For patients randomized to receive Standard of Care (SoC) treatment in parent protocols, follow the local prescribing information relating to contraception, the time limit for such precautions, and any additional restrictions for agents in the SoC treatment regimen.
14. Diagnosis of a new primary malignancy since enrollment into the parent clinical study, with the exception of adequately treated non-melanomatous skin cancer and carcinoma in situ with no evidence of disease.
15. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE >Grade 1, have not experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of
>10 mg prednisone or equivalent per day.
16. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2020
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	durvalumab
Generic name:	IMFINZI
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2023
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	EUCTR2019-001402-20-NL
CCMO	NL70810.056.19