An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies

Published: 16-05-2017
Last updated: 13-04-2024

Main protocol:To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients who are treated with durvalumab and…

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

Summary

ID

NL-OMON48778

Source
ToetsingOnline

Brief title
STRONG

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, Urothelial and NonUrothelial Carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced Solid malignancies, Durvalumab, Open label, Tremelimumab

Outcome measures

Primary outcome

Main protocol:

The common primary objective of all tumor sub-studies is:

1. To collect additional data and assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients with advanced solid malignancies treated with fixed doses of durvalumab and tremelimumab combination therapy or durvalumab monotherapy.

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product. AESIs for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. An immunemediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology.

AESIs observed with durvalumab or tremelimumab include: Diarrhea / Colitis, Pneumonitis / ILD, ALT/AST increases / hepatitis / hepatotoxicity, Neuropathy /

neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis), Endocrinopathies (i.e., events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper-and hypothyroidism and type I diabetes mellitus), Rash / Dermatitis, Nephritis / Blood creatinine increases / Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase). The specific safety objective will be further defined in each tumor specific module.

Module A:

The primary objective is:

1. To collect additional data and assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract (including the urinary bladder, ureter, urethra and renal pelvis) treated with a fixed dose of durvalumab monotherapy.

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product. AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and

where there is no clear alternate aetiology.

AESIs observed with durvalumab include: Diarrhea / Colitis, Pneumonitis / ILD, ALT/AST increases / hepatitis / hepatotoxicity, Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis), Endocrinopathies (i.e., events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper-and hypothyroidism and type I diabetes mellitus), Rash / Dermatitis, Nephritis / Blood creatinine increases, Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase).

Secondary outcome

Main protocol:

The common secondary objectives of all tumor sub-studies are:

1. To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of AEs (including SAEs).
2. To assess the incidence and frequency of durvalumab and tremelimumab (as applicable to each tumor Module) interruption and discontinuation due to treatment-emergent AEs (including SAEs).
3. To assess overall survival (OS).

Additional secondary objectives and exploratory objectives may be added to tumor substudies in each country / region. Additional sub-studies / exploratory studies may be added to the main protocol, in modular fashion.

Module A:

The secondary objectives are:

1. To collect additional data and assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of AEs (including SAEs).

2. To collect additional data and assess the incidence and frequency of durvalumab interruption and discontinuation due to treatment-emergent AEs (including SAEs).

3. To assess overall survival (OS). Patients will be followed for survival for up to 5 years following date of first patient treatment initiation. Patients will be followed to a minimum of 6 months following enrollment of the last patient to the study.

Study description

Background summary

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 a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor (Keir et al 2008) and to CD80 (Butte et al 2007). PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on IC leads to inhibition of T-cell activation (Fife and Bluestone, 2008). Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (eg, IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating immune cells. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination (Zou and Chen 2008). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al 2007; Paterson et al 2011).
In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015).

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types 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 non-clinical 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 e.g., in bladder carcinoma (Alexandrov et al 2013) may contribute to the responses seen with immune therapy.
In contrast to PD-L1, CTLA-4 is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. In addition, blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.
Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was 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 whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition there is data from agents in the anti-PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

There remains a significant unmet medical need for additional treatment options for advanced solid tumors, including bladder, lung, and head and neck. Treatment with agents targeting PD-1/PD-L1 (such as durvalumab) or CTLA-4 (such as tremelimumab) has shown activity in several tumor types in a subset of patients deriving meaningful and durable benefit. Efficacy data for patients treated with durvalumab monotherapy in the bladder cancer, lung cancer, and head and neck squamous cell carcinoma (HNSCC) cohorts have shown some clinical activity. Preliminary data generated from patients with NSCLC treated with durvalumab + tremelimumab combination therapy have shown early signs of clinical activity, and data from competitors indicate that the combination may

act synergistically (Wolchok et al 2013). Thus, these agents may potentially offer benefit to this patient population. The study design aims to minimize potential risks and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the investigational products (IPs; including durvalumab, tremelimumab, and SoC).

Study objective

Main protocol:
To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients who are treated with durvalumab and tremelimumab combination therapy or durvalumab monotherapy, using fixed dosing.

Module A:
To collect additional data and assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract (including the urinary bladder, ureter, urethra and renal pelvis) treated with a fixed dose of durvalumab monotherapy

Study design

Main protocol:
This is an open-label, multi-center, study to determine the short and long term safety of fixed doses of durvalumab 1500 mg + tremelimumab 75 mg combination therapy or durvalumab 1500 mg monotherapy in patients with advanced solid malignancies.
This study is modular in design, each tumor specific Module allowing evaluation of the safety, tolerability, and anti-tumor activity of the combination of durvalumab + tremelimumab or durvalumab alone in different solid tumors.
The modules are developed as separate components appended to this protocol. Additional modules may be added as part of this protocol as decisions on additional tumor types and/or exploratory sub-studies are made.
One or more of these modules will be opened in a given country / region based on local patient population prevalence, and results of feasibility studies.
The main protocol (and each tumor specific module) consists of a screening period, a treatment period, a 90 day safety follow-up period*, and a survival follow-up period.
Patients will attend a safety follow-up visit 90 days after study treatment discontinuation. Thereafter, patients will be contacted by phone or electronic communication every 3 months for survival status up to 5 years following date of first patient treatment initiation. All patients will be followed for a minimum of 6 months following enrollment of last patient.

*Any immune-mediated adverse events (imAEs) that are unresolved at the patient*s last visit in the study are followed up by the Investigator for as long as medically indicated and up to 12 months post onset. Non-imAEs are followed to the 90 day visit post treatment discontinuation.

Module A:
This is an open-label, multi-center, study to determine the short and long term safety of fixed dose of durvalumab 1,500 mg in adult patients (age >=18 years) with urothelial and nonurothelial carcinoma of the urinary tract (all histologies e.g.: transitional cell, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, etc.) that has progressed during or after previous platinum based chemotherapy, either for metastatic disease or progressive disease less than 12 months after adjuvant or neo-adjuvant chemotherapy.
The study consists of a screening period, a treatment period, a 90 day safety follow-up period*, and a survival follow-up period.
Patients will attend a safety follow-up visit 90 days after study treatment discontinuation. Thereafter, patients will be contacted by phone or electronic communication every 3 months for survival status up to 5 years following date of first patient treatment initiation. All patients will be followed for a minimum of 6 months following enrollment of last patient.
*Any imAEs that are unresolved at the patient*s last visit in the study are followed up by the Investigator for as long as medically indicated and up to 12 months post onset. Non-imAEs are followed to the 90-day visit post treatment discontinuation.

Intervention

Durvalumab + tremelimumab combination therapy
• Durvalumab 1,500 mg plus tremelimumab 75mg via IV infusion once every 4 weeks (Q4W), starting on Week 0, for up to a maximum of
4 doses (or cycles) followed by:
• Durvalumab monotherapy 1,500 mg via IV infusion Q4W, starting 4 weeks after the last infusion of the combination or discontinuation of tremelimumab.

OR

Durvalumab monotherapy
• Durvalumab 1,500 mg via IV infusion Q4W, starting on Week 0.
Each tumor specific module will specify combination therapy or monotherapy, and will
provide details of infusion duration.

Module A:
Durvalumab monotherapy.

Study burden and risks

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with durvalumab in this tumor type, and the strength of the scientific hypotheses under evaluation, the durvalumab monotherapy and durvalumab + tremelimumab combination therapy proposed in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving quality of life (QoL) and potentially extending survival. Furthermore, preclinical and clinical evidence indicate that the combination of PD 1/PD-L1 and CTLA-4 targeting agents may provide antitumor activity, with additional synergy from the combination (Wolchok et al 2013). Therefore, the investigation of the potential therapeutic efficacy of durvalumab monotherapy and durvalumab + tremelimumab combination therapy in patients with PD-L1-High and PD-L1 Low/Neg tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

Contacts

Public
Astra Zeneca

Forskargatan 18
Södertälje SE 151 85
SE
Scientific
Astra Zeneca

Forskargatan 18
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

- Must have a life expectancy of at least 12 weeks;- Disease not amendable to curative surgery;- Eastern Cooperative Oncology Group (ECOG) performance status as defined in the specific module.;- Body weight >30 kg.;- No prior exposure to anti-PD-1or anti-PD-L1, including on another AstraZeneca study. Exposure to other investigational agents may be permitted after discussion with the Sponsor.;- Adequate organ and marrow function as defined in the protocol

Exclusion criteria

- Any concurrent chemotherapy, investigational agent, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.;- Local treatment of isolated lesions for palliative intent is acceptable (e.g., local surgery or radiotherapy).;- Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of study treatment.;- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.;- 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.;- History of allogenic organ transplantation.;- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal 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;- 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 investigational product (durvalumab + tremelimumab) 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;- History of leptomeningeal carcinomatosis;- Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on baseline brain imaging (please refer to 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 <=10mg/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 Target Lesions at baseline. ;- History of active primary immunodeficiency.;- Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive hepatitis B virus [HBV] surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] 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 RNA.;- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) // Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent;- Active or prior documented autoimmune or inflammatory disorders

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-01-2018
Enrollment:	119
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab

Product type:	Medicine
Brand name:	Tremelimumab
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	16-05-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-05-2018

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-005068-33-NL
ClinicalTrials.gov	NCT03084471
CCMO	NL61095.091.17

Study results

Date completed:	01-11-2018
Actual enrolment:	4