Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies

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Dose-finding:-To determine the adult equivalent exposure/MTD/recommended Phase II pediatric dose of durvalumab monotherapy and durvalumab in combination with tremelimumab-To determine the safety profile of durvalumab monotherapy, or durvalumab in...

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

Summary

ID

NL-OMON55864

Source
ToetsingOnline

Brief title
D419EC00001

Condition

- Other condition

Synonym

advance solid tumours and blood cancer

Health condition

Advanced Solid Tumors and Hematological Malignancies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: monotherapy or combination, Open-Label, Pediatric

Outcome measures

Primary outcome

Dose-finding:

1. Based on PK parameters (including Cmax, Cmin, AUC, and others), identify the adult equivalent exposure/MTD of durvalumab monotherapy and durvalumab in combination with tremelimumab among children and young adults from birth to <18 years of age with advanced solid tumors and non-Hodgkin lymphoma, using a q4w dosing schedule.

2. Identify the safety and tolerability of durvalumab monotherapy and durvalumab in combination with tremelimumab at the adult equivalent exposure/MTD among children and young adults from birth to <18 years of age with advanced solid tumors and non-Hodgkin lymphoma, using a q4w dosing schedule. Endpoints include AEs, vital signs, physical examinations, ECGs, and laboratory evaluations.

Dose-expansion:

3. Objective response rate as determined by the Investigator assessed RECIST 1.1 or alternative pre-specified tumor-specific response rates for different scoring systems.

-Assessment of antitumor activity will be specific to tumor cohort, eg, Investigator assessed RECIST 1.1 and Cheson criteria (other malignancies will be analyzed based on the best response assessed by the Investigator).

4. Additional efficacy endpoints that will be collected include DoR, BoR, DCR, PFS, APF12, and APF18 based on RECIST 1.1, Cheson criteria, Wayne criteria, or INRC assessed by the Investigator, and OS, OS12, and OS24 as appropriate to each individual cohort.

Secondary outcome

5. Individual durvalumab and tremelimumab concentrations in serum, and PK parameters including Cmax, Cmin, AUC.

6. Number and percentage of patients who develop detectable ADAs.

7. Individual antibody titer measurements before and after planned routine immunization during treatment and Cycle 4 or follow-up, whichever is earlier.

8. Flow cytometry for CD4, CD8, B and NK cells, including T-cell activation with Ki67

Study description

Background summary

Standard therapy for solid and hematological pediatric tumors includes various combinations of surgery, cytotoxic chemotherapy, and radiation. These treatments can have detrimental consequences to a developing child, and many survivors carry a substantial burden of long-term

morbidities. With improved survival rates, children with cancer are likely to live longer, with the risk of long-term toxicity being an important crucial factor. In addition, there is an overall unmet medical need for more effective therapies for pediatric patients who have relapsed/refractory disease. Attractive alternatives would include biological agents that do not include toxic chemotherapy and target alternative carcinogenesis pathways that may have acquired resistance from the previous therapies. Immune checkpoint inhibitors may be such candidates, with promising and positive outcomes in adults with melanoma, lung cancer, bladder cancer, gastric cancer, microsatellite instability in colorectal cancer, and other malignancies.

Study objective

Dose-finding:
-To determine the adult equivalent exposure/MTD/recommended Phase II pediatric dose of durvalumab monotherapy and durvalumab in combination with tremelimumab
-To determine the safety profile of durvalumab monotherapy, or durvalumab in combination with tremelimumab.
Dose-expansion:
To determine the preliminary antitumor activity of durvalumab monotherapy and durvalumab in combination with tremelimumab at the recommended dose, using cohort-specific response criteria (eg, Cheson criteria and RECIST 1.1).

Study design

Open-label, non-randomized, international, multicenter study investigating durvalumab in combination with tremelimumab (q4w for 4 cycles only) followed by durvalumab monotherapy (q4w) in pediatric patients from birth to <18 years of age with relapsed or refractory malignant solid tumors and hematological malignancies. Durvalumab in combination with tremelimumab will be examined in all solid malignant tumors (except primary central nervous system tumors) and hematological malignancies (with the exception of patients with Hodgkin lymphoma [HL], who will receive treatment with durvalumab only).
The study will be conducted in 2 sequential phases: a dose-finding phase, followed by a dose-expansion phase.

Intervention

Durvalumab + tremelimumab combination therapy (dose-finding phase):
• Durvalumab monotherapy q4w will be given via intravenous (IV) infusion at Cycle 1.
Patients will receive durvalumab in combination with tremelimumab via IV infusion q4w, starting on Cycle 2, for up to a maximum of 4 doses/cycles. Four weeks after the last infusion of the combination, durvalumab monotherapy via IV infusion q4w may be given until clinical or confirmed PD, or other

discontinuation criteria is met, whichever comes first.
Durvalumab + tremelimumab combination therapy (dose-expansion phase):
• Durvalumab in combination with tremelimumab via IV infusion q4w will be given for up to a maximum of 4 doses/cycles. Four weeks after the last infusion of the combination, durvalumab monotherapy via IV infusion q4w may be given until clinical or confirmed PD, or other discontinuation criteria is met, whichever comes first.
Durvalumab monotherapy (patients with HL in dose-expansion phase only):
• Durvalumab monotherapy via IV infusion q4w will be given in patients with HL until clinical or confirmed PD, or other discontinuation criteria is met, whichever comes first. Patients will be eligible to receive tremelimumab if they progress on durvalumab monotherapy.

Study burden and 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 in adults 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 hyper-thyroidism. It is still too early to describe the specific toxicity profiles for durvalumab monotherapy and
durvalumab in combination with tremelimumab in pediatric patients. However, data from other immune checkpoint inhibitors and limited data from study D419C00028 (ongoing study evaluating durvalumab monotherapy in pediatrics) has shown safety profiles in pediatric patients
consistent with those observed in adults.
The safety profile of durvalumab and durvalumab in combination with tremelimumab is expected to follow the same pattern as other immune checkpoint inhibitors in regards to imAEs.

Contacts

Public

Astra Zeneca

NA -
Södertälje 151 85
SE
Scientific
Astra Zeneca

NA -
Södertälje 151 85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

• Patients must have pathologically confirmed relapsed or refractory advanced solid tumour malignancy or haematological malignancies including lymphoma and acute leukaemia. Any number of prior treatment regimens allowed. A select group of first-line patients may be eligible for screening and enrolment. These patients will be enrolled based on investigator assessment as patients for whom no curative standard of care treatment options exist or such therapies are not tolerable.
• If available, patients must provide a diagnostic tumor sample taken *3 years prior to screening for evaluation of PD-L1 status.
• Lansky play performance scale >=50 for patients >=1 and <16 years of age and Karnofsky performance status score >=50 for patients >=16 years of age (patients <1 year of age are exempt from this criterion)
• Patients must have measurable/evaluable disease as defined by methods used in

common clinical practice.
• No prior exposure to immune checkpoint inhibitors or genetically engineered cellular therapies including, but not limited to, other anti- CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2 antibodies and antibodies of CAR-T or other cell therapies, excluding therapeutic anticancer vaccines.
Exposure to other investigational agents may be permitted after discussion with the Sponsor or designee.

Exclusion criteria

• History of allogeneic organ transplantation (exceptions may be allowed for HL, NHL, ALL and AML, after discussion with Sponsor or designee). Patients who have previously received an autologous bone marrow transplant may be eligible
• Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis, celiac disease or other serious GI chronic conditions associated with diarrhea, systemic lupus erythematosus, Wegener syndrome; myasthenia gravis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc) autoimmune myocarditis, and autoimmune pneumonitis.
The following are exceptions to this criterion:
* Patients with vitiligo or alopecia
* Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
* Psoriasis that does not require systemic therapy
* Patients with celiac disease controlled by diet alone.
• Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, cardiac arrhythmia, ILD, or psychiatric illness or social situations that would
limit compliance with study requirements, substantially increase risk of incurring AEs from IP, or compromise the ability of the patient to give written informed consent.
• History of primary immunodeficiency.
• Active infection including tuberculosis, hepatitis B, hepatitis C, or HIV.
Patients with a past or resolved HBV infection are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).
• Any unresolved toxicity NCI CTCAE version 5.0 Grade >=2 from previous anticancer therapy with the exception of alopecia, vitiligo, lymphopenia and the laboratory values defined in the inclusion criteria
* Patients with Grade >=2 neuropathy will be evaluated on a case-bycase basis and may be included after consultation with the Study Physician.
* Patients with toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab (eg, hearing loss, gastrostomy tube) may be included after consultation with the Study
Physician.
• Patients with clinically active brain metastases (known or suspected) or

spinal cord compression, and choloromas are excluded, unless these conditions have been previously treated and are considered stable.
• History of leptomeningeal carcinomatosis, or involvement of any other anatomic area that, in the opinion of the Investigator, may cause significant symptoms if an inflammatory reaction occurs.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-03-2019
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Durvalumab
Generic name:	IMFINZI
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tremelimumab
Generic name:	TREMELIMUMAB

Ethics review

Approved WMO

Date:	18-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-09-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	01-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-003118-42-NL
CCMO	NL67429.041.19