# AN EARLY PHASE, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS

Published: 11-08-2015
Last updated: 15-04-2024

Safety ObjectiveThe safety objective for this study is as follows:* To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on the nature, frequency, and severity of serious and non-serious adverse...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Lymphomas Hodgkin's disease |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47877

**Source**
ToetsingOnline

**Brief title**
GO29664

### Condition

- Lymphomas Hodgkin's disease
- Miscellaneous and site unspecified neoplasms benign

**Synonym**
Solide tumors and lymphoma's

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** F. Hoffmann-La Roche Ltd.
**Source(s) of monetary or material Support:** F. Hoffmann-La Roche Ltd

## Intervention

**Keyword:** MPDL3280A, PDL1, Pediatrics, Relapsed/Refractory tumor

## Outcome measures

### Primary outcome

The primary efficacy outcome measures for this study are as follows:

* Objective response, defined as a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non-measurable but evaluable disease at baseline (except patients with neuroblastoma) on two consecutive occasions * 4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors, mINRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non Hodgkin's lymphoma, and RANO criteria for patients with ATRT.
* Clinical benefit response, defined as objective response or stable disease for at least 6 months, as determined by RECIST v1.1 for patients with osteosarcoma
* PFS, defined as the time from initiation of study drug to the first documented occurrence of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors, mINRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients

with Hodgkin's lymphoma or non Hodgkin*s lymphoma, and RANO criteria for patients with ATRT, or death from any cause, whichever occurs first

**Secondary outcome**

The secondary efficacy outcome measures for this study are as follows:

* DOR, defined as the time from the first tumor assessment that supports the patient*s objective response to the time of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors, mINRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non Hodgkin's lymphoma, and RANO criteria for patients with ATRT, or death from any cause, whichever occurs first
* OS, defined as the time from initiation of study drug to death from any cause
* ORR, PFS, and DOR as determined by the investigator using immune modified RECIST v1.1 for patients with other solid tumors and immune related response criteria for patients with neuroblastoma, Hodgkin's lymphoma, or non Hodgkin's lymphoma

# Study description

**Background summary**

See protocol version 5 dated 21 October 2016 - Section 1:3 Study rationale and benefit -risk assessment on page 44 & 45

**Study objective**

Safety Objective
The safety objective for this study is as follows:
* To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values

and vital signs
Pharmacokinetic Objective
The pharmacokinetic (PK) objective for this study is as follows:
* To characterize the pharmacokinetics of atezolizumab
Immunogenicity Objective
The immunogenicity objective for this study is as follows:
* To evaluate the immune response to atezolizumab on the basis of the incidence of anti therapeutic antibodies (ATAs)
Efficacy Objectives
The efficacy objectives for this study are as follows:
* To evaluate the anti-cancer activity of atezolizumab, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and clinical benefit response rate (only for osteosarcoma).
* To evaluate the anti-cancer activity of atezolizumab, as measured by overall survival (OS)
Dose Assessment Objective
The dose assessment objective for this study is as follows:
* To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures

**Study design**

The study is an early phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients with solid tumors with known or expected PD L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options exist.

Approximately 100 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America. Of those who are enrolled at least 20 patients 18 years of age will be treated with study drug, and at least 40 patients across all tumor type cohorts will be treated and available for response assessment.

**Intervention**

Patients will receive atezolizumab by intravenous (IV) infusion on Day 1 of each 3 week cycle. The dosing regimen in this study aims to achieve similar atezolizumab exposures in children and adolescents (18 years) to those of adults receiving the recommended Phase II/III dose of 1200 mg every 3 weeks. Patients who are 18 years old will receive 15 mg/kg atezolizumab (maximum dose 1200 mg) every 3 weeks. Dose adjustments may be made, if necessary to achieve exposures corresponding to those measured in adult patients and if the safety profile is acceptable. Patients 18 years old who are enrolled will receive a

flat dose of 1200 mg atezolizumab.

**Study burden and risks**

An overview of the risks can be found in the informed consent, Annex 5
Study procedures can be found in the informed consent, on page 2 under header How will the study be carried out and in the protocol under Study procedures.

## Contacts

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Basel 4070
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**Scientific**
F. Hoffmann-La Roche Ltd.

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

## Inclusion criteria

Patients must meet the following criteria for study entry:
* Histologically or cytologically confirmed solid tumor of a type listed below (tumor types with known or expected PD L1 pathway involvement) (including Hodgkin*s and Non Hodgkin*s lymphoma), for which prior treatment had proven to be ineffective (i.e., relapsed or refractory) or intolerable
Patients must have had histologic or cytologic confirmation of malignancy at the time of diagnosis or relapse.
Neuroblastoma
Rhabdomyosarcoma
Non-rhabdomyosarcoma soft tissue sarcoma
Osteosarcoma
Ewing sarcoma
Wilms tumor
Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Rhabdoid tumor
Note: Patients who have synchronous rhabdoid tumor and atypical teratoid rhabdoid tumor (ATRT) with no clear primary should be enrolled into the rhabdoid tumor cohort, and they should complete the additional assessments scheduled for patients with ATRT.
ATRT
Other tumor types not included in the list above with documented expression of PD L1 on either tumor cells or immune infiltrating cells with approval of the medical monitor
Other tumor types not included in the list above without documented expression of PD-L1 can be included with approval of the medical monitor and should not exceed 20% of the total sample size
* Signed Informed Consent Form
* Signed Child's or Young Adult*s Assent Form when appropriate, as determined by patient's age and individual site and country standards
* Age at study entry < 30 years
The first 5 patients must be *2 years of age (i.e., patients must have reached their 2nd birthday) to ensure safety and tolerability before patients <2 years of age receive their first dose of study drug. These first 5 patients must be followed for either two cycles of treatment or until drug discontinuation, whichever is shorter, prior to enrolling younger patients.
The Sponsor may decide to stop enrollment of patients who are * 18 years old at any time during the study to ensure adequate enrollment of patients < 18 years old.
Patients who are * 18 years old and are eligible for an adult PD L1 treatment protocol will be preferentially enrolled onto those adult studies.
* In exceptional cases of relapsed pediatric tumors in patients * 30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric specific diseases (i.e., neuroblastoma), for whom clinical trials are unlikely to be available, and will not be extended to patients with tumors that typically occur both in children and adults (i.e., high grade glioma).
* Able to comply with the study protocol, in the investigator*s judgment
* Weight * 3 kg

* Disease that is measurable as defined by Response Evaluation Criteria in Solid Tumors Version 1.1(RECIST v1.1), modified International Neuroblastoma Response Criteria (mINRC), Revised Response Criteria for Malignant Lymphoma, or Response Assessment in Neuro-Oncology (RANO) criteria (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
* Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission, or willingness to undergo a core or excisional biopsy prior to enrollment (fine needle aspiration, brush biopsy and lavage samples are not acceptable)
Patients with fewer than 15 slides available may be eligible for study entry following discussion with the Medical Monitor.
* Lansky Performance Status (patients < 16 years old) or Karnofsky Performance Status (patients * 16 years old) * 50
* Life expectancy * 3 months, in the investigator's judgment
* For patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 5 months after the last dose of study drug
Examples of contraceptive methods with a failure rate of <1% per year include established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
Barrier methods must always be supplemented with the use of a spermicide.;* Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:
* ANC * 0.75 x 109/L (unsupported)
* Platelet count * 75 x 109/L (unsupported)
* Hemoglobin * 8 g/dL (transfusion permitted)
* Bilirubin * 1.5 x upper limit of normal (ULN) for age
* AST and ALT * 2.5 x ULN for age
* Serum creatinine * 1.5 x ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m2
* INR and aPTT * 1.5 institutional ULN for age
Patients receiving therapeutic anticoagulants are excluded from the study.
* Fractional shortening * 30% or left ventricular ejection fraction * 50% at baseline, as determined by echocardiography or multigated acquisition scan within 28 days prior to initiation of study drug

## Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
* Known primary CNS malignancy or symptomatic CNS metastases, except ATRT
Patients with ATRT must not have tumor brainstem involvement or tumors within 10 mm of

the optic chiasm; they must not have a history of intracranial hemorrhage or spinal cord hemorrhage or have had neurosurgical resection, brain biopsy, or radiation to the primary brain tumor within 28 days of Cycle 1, Day 1.
* Patients with asymptomatic untreated CNS metastases may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:
Evaluable or measurable outside the CNS. (Note: this is not required for patients with ATRT).
No metastases to brain stem, midbrain, pons, medulla, or cerebellum or within 10 mm of the optic apparatus (optic nerve or chiasm). (Note: ATRT may have metastases in the cerebellum.)
No history of intracranial hemorrhage or spinal cord hemorrhage
No ongoing requirement for corticosteroids for CNS disease except in ATRT where steroids use is permitted with approval from the Medical Monitor. Patients with ATRT must receive a stable or decreasing dose for * 5 days prior to the baseline magnetic resonance imaging scan and at the time of drug initiation.
Patients taking a stable dose of anticonvulsants are permitted
No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1
* Patients with asymptomatic treated CNS metastases may by enrolled after consultation with the Medical Monitor, provided all the criteria listed above in the above CNS-related exclusion criteria are met as well as the following:
Radiographic demonstration of improvement upon the completion of CNS directed therapy and no evidence of interim progression between the completion of CNS directed therapy and the screening radiographic study
No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1
Screening CNS radiographic study * 4 weeks from completion of radiotherapy and * 2 weeks from discontinuation of corticosteroids
* For patients with lymphoma, known CNS lymphoma or leptomeningeal disease
* Treatment with high-dose chemotherapy and hematopoietic stem-cell rescue within 3 months prior to initiation of study drug
This requirement may be waived at the investigator*s request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
* Prior allogeneic hematopoietic stem cell transplantation or prior solid organ transplantation
* Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within 3 weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug
This requirement may be waived at the investigator*s request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
* Treatment with thoracic or mediastinal radiotherapy within 3 weeks prior to initiation of study drug
* Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, or biologic therapy within 4 weeks or 5 half-lives, whichever is shorter, prior to initiation of study drug.
* This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor

* Treatment with herbal cancer therapy within 1 week prior to initiation of study drug
* Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug. This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
* Treatment with a live vaccine or a live, attenuated vaccine (e.g. nasal spray of live attenuated influenzo vaccine of FluMist®) within 4 weeks prior to initiation of study drug or anticipation that such treatment will be required during the study or within 5 months after the final dose of study drug
* Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibodies
* Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin 2) within 6 weeks or five drug elimination half-lives prior to Day 1 of Cycle 1, whichever is longer
* Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti*tumor necrosis factor agents) at the time of initiation of study drug, or anticipated requirement for systemic immunosuppressive medications during the study
Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor and the ATRT-related exclusion criteria.
* Current treatment with therapeutic anticoagulants
* Any non-hematologic toxicity (excluding alopecia) from prior treatment that has not resolved to Grade * 1 (per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0) at screening
Note: Long-term sequelae of prior treatment (e.g., hearing loss, iatrogenic hypothyroidism, infertility, etc.) are not considered non-hematologic toxicity and instead are considered chronic medical conditions.
* Evidence of progression of neurologic deficit, in the investigator's judgment, within 1 week prior to initiation of study drug
* Major surgical procedure, or significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study
Placement of a vascular access device is permitted if the site has healed prior to initiation of study drug.
Biopsy tissue collections are permitted if all bleeding parameters (including PT/INR and aPTT) are within normal limits and procedure is safe in the judgment of the investigator.
* Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved
* Pregnant or lactating, or intending to become pregnant during the study
Patients of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
* Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
* Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from

treatment complications
* Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator
* History of severe allergic or anaphylactic reaction to monoclonal antibody therapies (or recombinant antibody*related fusion proteins)
* History of clinically significant cardiac or pulmonary dysfunction
* History of any autoimmune disease, including but not limited to Type 1 diabetes mellitus, autoimmune related hypothyroidism, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis, Sjögren*s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
Patients with a history of autoimmune-related hypothyroidism who are receiving a stable dose of thyroid-replacement hormone are eligible for the study.
Patients with controlled Type 1 diabetes mellitus who are receiving a stable dose of insulin regimen are eligible for the study.
* History of severe eczema
* History of Kawasaki disease
* History of Fanconi anemia, Beckwith-Wiedemann, ataxia telangiectasia, or other genetic syndromes that may have immune or hematologic susceptibilities
* History of severe asthma or presence of uncontrolled asthma at time of screening evaluation
Severe asthma is defined as presence of symptoms throughout the day, multiple nighttime awakenings during the week, use of a short*2 agonist several times a day and/or limitations with normal daily activity. In addition, any asthma that does not meet the above definition but is felt to be severe in the eyes of the investigator should also be excluded.
* History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), cystic fibrosis, or evidence of active pneumonitis on screening chest computed tomography scan
* Dyspnea at rest or requirement for supplemental oxygen
* Uncontrolled seizures

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-01-2016 |
| Enrollment: | 2 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | atezolizumab |
| Generic name: | - |

# Ethics review

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|---|---|
| Approved WMO Date: | 11-08-2015 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-12-2015 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-02-2016 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 07-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 24-02-2017 |

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| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 27-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 04-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 18-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 23-11-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 08-01-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 06-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 09-04-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

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| Approved WMO Date: | 03-10-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 16-01-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 21-01-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-02-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 08-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# 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 | EUCTR2014-004697-41-NL |
| CCMO | NL52263.078.15 |