A phase IB study of crizotinib in pediatric malignancies

Gepubliceerd: 06-01-2016 Laatst bijgewerkt: 18-08-2022

Objectives: • To determine the RP2D of crizotinib in combination with vinblastine • To determine the RP2D of crizotinib in combination with temsirolimus • To determine the safety and preliminary activity of single-agent crizotinib in ALK, MET…

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24969

Bron
NTR

Verkorte titel
CRISP

Aandoening

children, cancer, pediatric malignancies, ALK positive tumors, ROS1 positive tumors, MET positive tumors
kinderen, kanker, pediatrische maligniteiten, tumoren positief voor ALK, ROS1, MET afwijkingen

Ondersteuning

Primaire sponsor: University Medical Center Erasmus Medical Center Rotterdam The Netherlands
Overige ondersteuning: • Pfizer
• Go4Children

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

• Dose Limiting Toxicities (DLT) during the first cycle of crizotinib, in combination with either vinblastine, temsirolimus for stratum 1 and 2.
• Overall response rate (descriptive) for stratum 3.

Toelichting onderzoek

Achtergrond van het onderzoek

Crizotinib is a ALK, MET and ROS1 inhibitor that has proven to be effective and is registered for ALK positive non-small cell lung carcinoma in adults. In children, various tumors harbour ALK/MET/ROS1 aberrations, and children with these tumours may potentially benefit from treatment with crizotinib. Crizotinib as single-agent in the pediatric phase I dose-escalation study showed favorable results in terms of toxicity, but variable results in terms of efficacy, despite dose-escalation to much higher dosages than used in adults. Very promising results were obtained in a small cohort of patients with ALCL, although not all patients responded. Especially in patients with neuroblastoma and ALK point-mutations responses were less promising than was anticipated, but preclinical in-vitro and in-vivo studies have suggested that this may be overcome with the combined use of crizotinib with a TORC 1/2 inhibitor.

In this study we therefore aim to evaluate combination therapy for different strata. For strata 1 we will combine crizotinib with vinblastine, based one earlier studies showing efficacy of vinblastine in the group of relapsed, ALK positive ALCL patients (stratum 1). For stratum 2 a combination of crizotinib with temsirolimus will be given to patients with relapsed, ALK positive neuroblastoma and rhabdomyosarcoma (stratum 2). Children who have other ALK-ROS or MET positive tumors and who have no other treatment options, will be enrolled in a separate stratum with crizotinib only (stratum 3).

Doel van het onderzoek

Objectives:

• To determine the RP2D of crizotinib in combination with vinblastine

• To determine the RP2D of crizotinib in combination with temsirolimus

• To determine the safety and preliminary activity of single-agent crizotinib in ALK, MET or ROS1 positive tumors

Onderzoeksopzet

Baseline, end of cycle 2, 4, 8, 12, 18, 24 (=End of study)

Onderzoeksproduct en/of interventie

Stratum 1: 12 cycles of 28 days Crizotinib daily and Vinblastine weekly, followed by 12 cycles of 28 days Crizotinib daily only.

Stratum 2: max 8 cycles of 28 days Crizotinib daily and Temsirolimus weekly

Stratum 3: Crizotinib daily for 12 cycles of 28 days

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Inclusion criteria stratum 1

• Histologically or cytologically confirmed diagnosis of ALCL

• Age at diagnosis ≥1 year of age and ≤ 21 years

• Lansky play score > 60%; or Karnofsky performance status > 60%.

• Target gene aberration as defined as:

- A point mutation in the kinase domain of ALK that results in an amino-acid change, and is not a known polymorphism

- An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells

- A translocation in >15% of the tumor cells (by break apart FISH-assay)

• Life expectancy 12 weeks

• Disease involvement :

- For dose escalation measurable and non measurable disease is allowed

- For does expansion measurable disease is mandated

- Measurable disease is defined as at least one nodule with a longest diameter greater than 1.5 cm (pediatric NHL response criteria) 100, 101

• Any previous systemic anticancer therapy must have been completed at least 3 weeks prior to initiation of study medication. At least 1 week for oral metronomic chemotherapies (e.g. cyclofosphomide or etoposide)

• No treatment with any other investigational drug within the past 3 weeks prior to initiation of study medication

• Major surgery must have been completed at least 3 weeks prior to initiation of study medication (central venous access surgery or a needle biopsy are not considered major surgery)

• No persistence of adverse events, more than grade 2, from prior anti-cancer therapy deemed clinically relevant

• Adequate hematological function, unsupported, last platelet transfusion > 72 hours and off colony stimulating factors:

- ANC ≥0.75x109/L and platelets ≥ 75x109/L for pts without bone marrow involvement.

- Patients with bone marrow involvement will be allowed to enter with ANC ≥0.5x109/L and platelets ≥50x109/L but will not be counted for haematological DLTs.

• Normal renal function defined as ≤1.5 x ULN adjusted for age

• Normal liver function defined as ≤2.5 x ULN for transaminases and ≤1.5 x ULN bilirubin, but ≤5 x ULN (and ≤2.5 x ULN for bilirubin) in case of liver involvement by metastases

• Written informed consent from patients and/or from parents or legal guardians, according to local law and regulations.

• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up

Inclusion criteria stratum 2

• Histologically or cytologically confirmed diagnosis NBL or RMS

• Age at diagnosis ≥1 year of age and ≤21 years

• Lansky play score > 60%; or Karnofsky performance status > 60%.

• Target gene aberration as defined as:

- A point mutation in the kinase domain of ALK that results in an amino-acid change, and is not a known polymorphism

- An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells

- A translocation in >15% of the tumor cells (by break apart FISH-assay)

• Life expectancy 12 weeks

• Disease involvement:

- For dose escalation measurable and non measurable disease is allowed

- For does expansion measurable disease is mandated, except for neuroblastomas where MIBG disease is sufficient

- For RMS: Measurable disease defined as per RECIST 1.1 with a target lesion of at least 10 mm 102

- For NBL: Measurable disease defined as per RECIST 1.1 or evaluable disease (I123 MIBG

uptake with or without bone marrow metastases).

• Any previous systemic anticancer therapy must have been completed at least 3 weeks prior to initiation of study medication. At least 1 week for oral metronomic chemotherapies (e.g. cyclofosphomide or etoposide)

• No treatment with any other investigational drug within the past 3 weeks prior to initiation of study medication

• Major surgery must have been completed at least 3 weeks prior to initiation of study medication (central venous access surgery or a needle biopsy are not considered major surgery).

• No persistence of adverse events, more than grade 2, from prior anti-cancer therapy deemed clinically relevant

• Adequate hematological function, unsupported, last platelet transfusion > 72 hours and off colony stimulating factors:

- ANC ≥0.75x109/L and platelets ≥ 75x109/L for pts without bone marrow involvement.

- Patients with bone marrow involvement will be allowed to enter with ANC ≥0.5x109/L and platelets ≥50x109/L but will not be counted for haematological DLTs.

• Normal renal function defined as ≤1.5 x ULN adjusted for age

• Normal liver function defined as ≤2.5 x ULN for transaminases and ≤1.5 x ULN bilirubin, but ≤5 x ULN (and ≤2.5 x ULN for bilirubin) in case of liver involvement by metastases

• Written informed consent from patients and/or from parents or legal guardians, according to local law and regulations.

• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up

Inclusion criteria stratum 3

• Histologically or cytologically confirmed diagnosis of other solid tumor or lymphomas other than ALCL (at initial diagnosis) that is relapsed or refractory to standard therapy. Or patients with newly diagnosed IMT in whom radical surgery is deemed infeasible or will result in significant morbidity/mutilation

• Age at diagnosis ≥1 year of age and ≤ 21 years

• Lansky play score > 60%; or Karnofsky performance status > 60%.

• Target gene aberration as defined as:

For ALK:

- A point mutation in the kinase domain of ALK that results in an amino-acid change, and is not a known polymorphism

- An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells

- A translocation in >15% of the tumor cells (by break apart FISH-assay)

For ROS1

- A ROS1 rearrangement in > 15% of the tumor cells (by break apart FISH-assay)

For MET

- An amplification of the MET-gene, defined as of ≥5 MET signals per tumor cell (by break apart FISH)

- A MET mutation, defined as the presence of a somatic mutation (Direct, bi-directional sequencing of exon 16-19 of MET)

- TFE3 rearrangement, define as at least 15% of cells rearranged (FISH home-made break-apart TFE3 probe set: RP11-344N17 and RP11-552J9)

• Life expectancy 12 weeks

• Disease involvement:

- Measurable disease according to RECIST 1.1 with a target lesion of at least 10 mm102

- Or, measurable disease as defined as at least one nodule with a longest diameter greater than 1.5 cm (pediatric NHL response criteria)100

• Any previous systemic anticancer therapy must have been completed at least 3 weeks prior to initiation of study medication. At least 1 week for oral metronomic chemotherapies (e.g. cyclofosphomide or etoposide)

• No treatment with any other investigational drug within the past 3 weeks prior to initiation of study medication

• No prior therapy directly targeting ALK or ROS1 or MET

• Major surgery must have been completed at least 3 weeks prior to initiation of study

medication (central venous access surgery or a needle biopsy are not considered major surgery).

• No persistence of adverse events, more than grade 2, from prior anti-cancer therapy deemed clinically relevant

• Adequate hematological function, unsupported, last platelet transfusion > 72 hours and off colony stimulating factors:

- ANC ≥0.75x109/L and platelets ≥ 75x109/L for pts without bone marrow involvement.

- Patients with bone marrow involvement will be allowed to enter with ANC ≥0.5x109/L and platelets ≥50x109/L but will not be counted for haematological DLTs.

• Normal renal function defined as ≤1.5 x ULN adjusted for age

• Normal liver function defined as ≤2.5 x ULN for transaminases and ≤1.5 x ULN bilirubin, but ≤5 x ULN (and ≤2.5 x ULN for bilirubin) in case of liver involvement by metastases

• Written informed consent from patients and/or from parents or legal guardians, according to local law and regulations.

• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Exclusion criteria:

• Other serious illnesses or medical conditions

• Current uncontrolled infection

• History of allergic reactions to the compounds or their solvents

• Patients with known CNS metastases and/or primary CNS tumors and/or meningeal lymphoma involvement, defined as CNS3 status (patients with CNS2 are eligible)

• Concurrent use of drugs or foods that are known potent CYP3A4 inducers or inhibitors as well as medication with known QT-prolongation

• Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of crizotinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)

• Not able to comply with scheduled follow-up and with management of toxicity.

• A cardiac shortening fraction < 29%

• Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTcF interval >470 msec.

• History of extensive disseminated/ bilateral or known presence of grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

• Patients with ALCL and skin lesions only, are excluded

• No evidence of active graft-vs-host disease (GVHD) and at least 3 months post-allogeneic HSCT. Must not receive GVHD prophylaxis.

• For patients with childbearing potential, a negative test for pregnancy and agreement to use effective contraceptive measures is required before entry on study.

Additional exclusion criteria stratum 2

• No evidence of active graft-vs-host disease (GVHD) and at least 3 months post-allogeneic HSCT. Must not receive GVHD prophylaxis.

• Patients with neuroblastoma and bone marrow disease only, are excluded.

Additional exclusion criteria stratum 3

• No evidence of active graft-vs-host disease (GVHD) and at least 3 months post-allogeneic HSCT. Must not receive GVHD prophylaxis.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd

Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-06-2016
Aantal proefpersonen:	82
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	06-01-2016
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4171
NTR-old	NTR5584
Ander register	METC Rotterdam : ITCC-053

Resultaten