INFORM2 exploratory multinational phase I/II combination study of Nivolumab and Entinostat in children and adolescents with refractory high-risk malignancies

Published: 28-02-2019
Last updated: 30-01-2025

This study has been transitioned to CTIS with ID 2024-514409-78-01 check the CTIS register for the current data. Primary objectivePhase I (Phase I of the younger cohort was concluded in May 2023): To determine the recommended phase II dose (RP2D) of…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55442

Source
ToetsingOnline

Brief title
INFORM2 NivEnt

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
refractory or progressive high-risk solide tumors or CNS tmors

Research involving
Human

Sponsors and support

Primary sponsor: Heidelberg University Hospital, Hopp Children's Cancer Center Heidelberg (KiTZ)
Source(s) of monetary or material Support: bijdrage vanuit Heidelberg University Hospital;eigen fondsen

Intervention

Keyword: entinostat, fase I/II, high risk malignancies, nivolumab

Outcome measures

Primary outcome

Phase 1:Dose Limiting Toxicity (DLT) of the combination treatment.

Phase 2: Best response (CR or PR) will be based on RANO criteria for all

primary CNS tumors and RECIST for non-CSN tumors, defined for each patient as

the best response under study combination therapy during the first 6 cycles.

Calcified or intra-osseous (osteo)sarcoma target lesions which were progressive

before initiation of treatment and show SD on response evaluation (confirmation

through a subsequent scan at least 4 weeks later) will be considered as a

responder

Secondary outcome

Duration of Response (DOR)

Disease Control Rate (DCR)

Stabel disease (SD)

Progression-free survival (PFS)

Time to Response (TTR)

Overall survival (OS)

Immune related Response Rate (RR) measured by iRECIST criteria and iRANO

criteria

Entinostat plasma PK

Study description

Background summary

Children and adolescents with relapsed or refractory malignant disease of a high-risk entity have a particularly poor prognosis and well-established treatment protocols are rare in this setting. Survival rates of less than 20% after recurrence imply an urgent need for innovative treatment strategies for these patients. The aim of the INFORM (INdividualized Therapy FOr Relapsed Malignancies in Childhood) program is to translate next generation molecular diagnostics into a personalized, biomarker driven treatment strategy for this patient cohort. The program consists of two major foundations: the INFORM2 series of biomarker driven phase I/II trials within a common framework and the INFORM registry [http://www.dkfz.de/en/inform] providing a molecular screening platform (Worst et al., 2016).
The current trial is based on the rationale that tumors with high mutational load or high PD-L1 expression are susceptible to treatment with immune checkpoint inhibition, which can be augmented by HDAC inhibition (HDACi) through induction of an immunogenic tumor microenvironment.

However, and in contrast to our assumption at the start of this study, in the meantime it has become clear that PD-L1 mRNA expression is no longer considered a consistent predictive biomarker for tumor response to immune checkpoint based therapy.

Checkpoint inhibition results in activation of tumor-associated T cells. It is now becoming increasingly evident that patients with tumors with a high number of tumor infiltrating T cells at baseline show an increased response rate. Additionally, recent clinical data on immune checkpoint inhibition (ICI) for melanoma patients detected tertiary lymphoid structures (TLS) as indicators of an activated adaptive immune response. Their presence has been linked to objective treatment responses in patients with different cancer entities receiving ICI.

Furthermore, recent preclinical data strongly show that HDAC inhibitors show activity in MYC amplified medulloblastoma in vitro and in vivo which is the rationale to explore the combination of nivolumab and entinostat in patients with MYC(N) driven tumors. Lastly, because of the potential immune priming

effect of HDAC-inhibitors, efficacy of the combination treatment in patients with low mutational burden and PD-L1 expression and no MYC(N) amplification will also be explored.

Study objective

This study has been transitioned to CTIS with ID 2024-514409-78-01 check the CTIS register for the current data.

Primary objective
Phase I (Phase I of the younger cohort was concluded in May 2023): To determine the recommended phase II dose (RP2D) of the combination treatment with nivolumab and entinostat administered to adolescents 12-21 years with progressive, relapsed , refractory high-risk solid tumors and CNS tumors.
To determine the recommended phase II dose (RP2D) of the combination treatment with nivolumab and entinostat administered to children 6-11 years with progressive, relapsed , refractory high-risk solid tumors and CNS tumors.

Phase II: To evaluate activity of the combination treatment of nivolumab and entionstat in children and adolescents with refractory/relapsed/progressive high-risk solid tumors and CNS tumors in four different groups:
Group A: a high mutational load (> 100 somatic SNVs/exome), Group B (closed per 30 Nov 2023) high PD-L1 mRNA expression (RPKM >3), Group C Focal MYC(N) amplifaction, Group D (closed per 22-01-2024) Patients with biomarker low tumors according to the definitions of group A,C, E.

Secondary objectives:

- Comparison of patient outcomes in group D (biomarker low) with all biomarker positive groups A, B and C (pooled and separately)
- Comparison of patient outcomes in group A-D with matching groups of the INFORM registry (pooled and separately)
- Evaluation of somatic SNV count as a predictive biomarker: relation of patient outcomes to the level of somatic SNVs
- Evaluation of PD-L1 mRNA expression as a predictive biomarker: relation of patient outcomes to the level of PD-L1 mRNA expression
- Evaluation of the level of MYC(N) amplification as a predictive biomarker: relation to patient outcomes
- Evaluate activity using immune related response evaluation methods
- Entinostat plasma PK (CSF if appropriate)

See protocol 2.3 page 33 for exploratory objectives

Study design

INFORM2 NivEnt is an exploratory, nonrandomized, open-label, multinational and

multicenter seamless phase I/II trial of nivolumab and entinostat in children and adolescents with relapsed / refractory or progressive high-risk solid tumors and CNS tumors. Two group phase I evaluating safety profile and determination of RP2D of combination treatment. Four group phase II basket trial evaluating activity of the combination treatment.

The two age cohorts will run independently and follow a 3+3 design with two dose levels. RP2D is the dose at which up to 1 of 6 patients experiences DLT. Patients treated at the RP2D in the Phase I part of the trial will be included for evaluation of activity in Phase II.

A Bayesian adaptive design will be used with the objective of stopping cohorts early which are showing evidence of no activity. Recruitment will not be suspended during the interim analysis.

Intervention

Patients will receive nivolumab 3mg/kg body weight every 2 weeks as a 30-minute IV infusion in both phase I and II of the trial.
Entinostat has 2 dose levels in the phase I part of the trial 2mg/m2 and 4mg/m2. After one priming week with 1 dose of entinostat on day 1, cycles of 4 weeks each will start with entinostat (orally) on day 1, 8, 15 and 22 and intravenous administration of nivolumab on day 1 and 15. Thereafter, every cycle follows the same schedule. There is no pause between cycles. Dose level 2 is the maximum dose level. If an unexpected high level of toxicity is encountered in dose level 2, the sponsor may initiate opening entinostat dose level 1a: 3mg/m2 according to the same regimen and rules as dose levels 1 and 2 following discussion with the DMC.

Study burden and risks

Biopsy/punction or resection needs to be done during screening if it is not been done 12 weeks before registration of the study. A pregnancy test could be seen as a burden. Imaging (MRI/CTscan) needs to be done extra during the study. Patients visit the site every week for the first 2 cycles and after that every other week. Patients receive nivolumab 30 minutes intravenous on day 1 and 15 of every cycle.

Contacts

Public
Heidelberg University Hospital, Hopp Children's Cancer Center Heidelberg (KiTZ)

Im Neuenheimer Feld 672

Heidelberg 69120
DE
Scientific
Heidelberg University Hospital, Hopp Children's Cancer Center Heidelberg (KiTZ)

Im Neuenheimer Feld 672
Heidelberg 69120
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Children and adolescents with refractory/relapsed/progressive high-risk CNS tumors OR solid tumors OR with newly diagnosed high grade glioma. All specified in the protocol.
- No standard of care treatment available
- Age at registration >= 2 to <= 21 years.
- Molecular analysis for biomarker identification (SNV load, high TILs or TLS positive, MYC/N amplification) in laboratories complying with DIN EN ISO/IEC 17025 or similar via INFORM molecular diagnostic platform or equivalently valid molecular pipeline
- Biomarker determined using whole exome sequencing (SNV load), IHC (high TILs or TLS
positive), whole genome- or whole exome sequencing (MYC/N amplification)
- In case molecular analysis was not performed via INFORM Registry molecular pipeline: transfer of molecular data (whole exome and RNA sequencing)
- Time between biopsy/puncture/resection of the current refractory/relapsed/progressive tumor and registration <= 24 weeks. In patients receiving therapy not impacting biomarker stratification, time between biopsy/puncture/resection of the current refractory/relapsed/progressive tumor

and registration of <= 36 weeks is allowed.
- Disease that is measurable as defined by RANO criteria or RECIST v1.1 (as appropriate).
- Life expectancy > 3 months, Lansky >= 70 or Karnofsky >= 70.
-Laboratory requirements:
- Hematology: absolute granulocytes >= 1.0 × 10^9/l (unsupported)
platelets >= 100 × 10^9/l & stable
hemoglobin >= 8 g/dl or >= 4,96 nmol/L
- Biochemistry: Total bilirubin <= 1.5 x upper limit of normal (ULN)
AST(SGOT) <= 3.0 x ULN
ALT(SGPT) <= 3.0 x ULN
serum creatinine <= 1.5 x ULN for age
ECG: normal QTc interval according to Bazett formula <440ms
- Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to initiation of treatment.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient screening and registration, written informed consent, also concerning data and blood transfer, must be given
- No prior therapy with the combination of immune checkpoint inhibitors and HDACi
- Phase I: molecular analysis performed and biomarker status known (mutational load, high TILs or TLS positive AND MYC(N) amplification status).
- Phase II: molecular analysis performed, biomarker status known (mutational load, high TILs or TLS positive AND MYC(N) amplification status) and stratification according to the following criteria:
- Group A: high mutational load (defined as > 100 somatic SNVs/exome) based on whole exome sequencing
OR
- Group B (enrolment closed): high PD-L1 mRNA expression (defined as reads per million total reads per kilobase of exon model (RPKM) > 3) based on RNA sequencing
OR
- Group C: Focal MYC(N) amplification based on whole exome sequencing or ATRT-MYC subgroup
OR
Group D (enrolment closed): Patients with biomarker low tumors according to the definitions of group A,C,E.
OR
Group E: high TILs or TLS positive (defined as cells per mm2 >600 or prescence of tertiary lymphoid strucure) based on IHC analysis

Exclusion criteria

-Patients with CNS tumors or metastases who are neurologically unstable despite adequate treatment (e.g. convulsions).
- Patients with low-grade gliomas or tumors of unknown malignant potential are not eligible
- Evidence of > Grade 1 recent CNS hemorrhage on the baseline MRI scan.
- Participants with bulky tumor on imaging are ineligible; bulky tumor are defined in the protocol -
- Previous allogeneic bone marrow, stem cell or organ transplantation
- Diagnosis of immunodeficiency
- Diagnosis of prior or active autoimmune disease
- Evidence of interstitial lung disease
- Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.
- Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies). Known active hepatitis B or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection are eligible. Patients positive for hepatitis C antibody ar eliglible only if polymerase chain reaction is negative form HCV RNA. see details in protocol
- Clinically significant, uncontrolled heart disease
- Major surgery within 21 days of the first dose. Gastrostomy, ventriculo-peritoneal shunt, endoscopic ventriculostomy, tumor biopsy and insertion of central venous access devices are not considered major surgery, but for these procedures, a 48 hour interval must be maintained before the first dose of the investigational drug is administered.
- Any anticancer therapy within 2 weeks or at least 5 half-lives (whichever is longer) of study drug administration.
- Confirmed radiotherapy induced pseudoprogression
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity.
- History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form (including benzamide) of the investigational medicinal product
- Participation in other ongoing clinical trials.
- Pregnant or lactating females.
- Presence of underlying medical condition that in the opinion of the Investigator or Sponsor could adversely affect the ability of the subject to comply with or tolerate study procedures and/or study therapy, or confound the ability to interpret the tolerability of combned administration of entinostat and nivolumab in treated subjects.
- Patients receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study

treatment. The use of physiologic doses
of corticosteroids (up to 5 mg/m2/day prednisone equivalent) may be approved
after consultation with the Sponsor.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-07-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Entinostat
Generic name:	NA
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	opdivo
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-02-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	07-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-09-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-11-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EU-CTR	CTIS2024-514409-78-01

Register	ID
EudraCT	EUCTR2018-000127-14-NL
CCMO	NL67122.000.19