INFORM2 NivEnt

INFORM2 Study Uses Nivolumab and Entinostat in Children and Adolescents With High-risk Refractory Malignancies

NCT-Nummer:
NCT03838042

Studienbeginn:
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Wirkstoff:
Nivolumab and Entinostat
Indikation (Clinical Trials):
Neoplasms, Central Nervous System Neoplasms

Geschlecht:
Alle

Altersgruppe:
Alle

Phase:
-

Sponsor:
University Hospital Heidelberg

Collaborator:
German Cancer Research Center

Studien-Informationen

Detailed Description:

Compared to adult cancers, most pediatric cancers carry a relatively low mutational burden. However, a small fraction of pediatric tumors in the INFORM registry cohort display a higher mutational burden. Truly hypermutated tumors, e.g. in the context of rare cancer

predisposition syndromes, are reported to respond well to immune checkpoint inhibition. In addition to hypermutation, increased PD-L1 expression is associated with clinical responses to checkpoint inhibition. Increased PD-L1 mRNA expression is observed in a small fraction of pediatric patients in the INFORM registry cohort independent from mutational load. We hypothesize that pediatric tumors with a high mutational burden and/or high PD-L1 expression will respond to checkpoint inhibition.

HDAC inhibition (HDACi) modifies T-cell regulation and can augment response to checkpoint inhibition by reducing the number of myeloid-derived suppressor cells and creating an immunogenic tumor microenvironment including induction of MHCI and neo-antigens. In vitro and in vivo models showed enhanced anti-tumor activity of the combination of checkpoint inhibition and HDACi compared to either agent alone. This provides a strong rationale to combine these drug classes.

Furthermore, MYC- or NMYC-driven (referred to as MYC(N)) malignancies like very high-risk medulloblastomas or very high-risk neuroblastomas still have a dismal outcome. MYC is not only reported to upregulate PD-L1 and thereby a possible biomarker for checkpoint inhibition but also very compelling recent preclinical data strongly suggests that HDAC inhibitors are active against MYC amplified medulloblastoma in vitro and in vivo. In NMYC amplified neuroblastoma cell lines similar observations were made in vitro. Taken together, our results suggest that MYC(N)-driven tumors depend on HDAC and we hypothesize that MYC(N) status can serve as a biomarker for response prediction to a combinatorial treatment of checkpoint inhibition and HDAC inhibition.

Pediatric patients aged 6-21 years with refractory/relapsed/progressive high-risk malignancies with a high mutational load (group A), with high PD-L1 mRNA expression (group B), with MYC(N) amplification (group C) and with a low mutational load, low PD-L1 mRNA expression and no MYC(N) amplification (Biomarker low group D) are eligible for this trial.

Phase I determines the recommended phase 2 dose (RP2D) for the combination of the HDACi entinostat and the checkpoint inhibitor nivolumab for the age groups 6-11 and 12-21 years,

respectively. Phase II investigates activity in 4 groups A, B, C, D. The duration of treatment is 12 cycles (1 cycle = 28 days), preceded by 1 priming week.

In addition, a comprehensive accompanying research program investigates PD biomarkers for immune checkpoint and HDAC inhibition.

Clinical trials investigating the combination of nivolumab and entinostat in children have not been reported so far.

Ein-/Ausschlusskriterien

Inclusion Criteria:

- Children and adolescents with refractory/relapsed/progressive high-risk
- CNS tumors: medulloblastoma, ependymoma, ATRT, ETMR, pediatric high grade glioma (including DIPG) or other pediatric embryonal CNS tumors OR
- solid tumors: neuroblastoma, nephroblastoma, rhabdoid tumor, embryonal or alveolar rhabdomyosarcoma or other embryonal small round blue cell tumors including pediatric type (bone) sarcoma OR
- Children and adolescents with newly diagnosed high grade glioma (HGG) in the context of a constitutional mismatch repair deficiency syndrome after maximum safe surgical resection with no established standard of care treatment option with curative intention available
- No standard of care treatment available
- Age at registration ≥ 6 to ≤ 21 years
- Molecular analysis for biomarker identification (SNV load, PDL1 mRNA expression, 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), RNA-sequencing (PDL1 mRNA expression) and whole genome 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 ≤ 12 weeks

- Disease that is measurable as defined by RANO criteria or RECIST v1.1 (as appropriate).

- Life expectancy > 3 months, sufficient general condition score (Lansky ≥ 70 or Karnofsky ≥ 70). Transient states like infections can be accepted, and also stable disabilities resulting from disease/surgery (hemiparesis, amputations etc.) can be accepted and will not be considered for Lansky/Karnofsky assessments.

- Laboratory requirements:

- Hematology: absolute granulocytes ≥ 1.0 × 109/l (unsupported) platelets ≥ 100 × 109/l hemoglobin ≥ 8 g/dl or ≥ 5,6 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

- Patient is able to swallow oral study medication

- Ability of patient and/or legal representative(s) to understand the character and individual consequences of clinical trial

- Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to initiation of treatment. Sexually active women of childbearing potential must agree to use acceptable and appropriate contraception during the study and for at least 6 months after the last study treatment administration. Sexually active male patients must agree to use a condom during the study and for at least 7 months after the last study treatment administration.

- 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 according to ICH/GCP, and national/local regulations.
- No prior therapy with the combination of immune checkpoint inhibitors and HDACi
- BSA ≥ 0.9m2
- Phase I: molecular analysis performed and biomarker status known (mutational load, PD-L1 mRNA expression AND MYC(N) amplification status).
- Phase II: molecular analysis performed, biomarker status known (mutational load, PD-L1 mRNA expression 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: 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 genome sequencing OR
- Group D: Patients with biomarker low tumors according to the definitions of group A-C.

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 CNS tumor on imaging are ineligible; bulky tumor is defined as:
- Tumor with any evidence of uncal herniation or severe midline shift
- Tumor with diameter of > 6 cm in one dimension on contrast-enhanced MRI

- Tumor that in the opinion of the investigator, shows significant mass effect

- 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 (e.g., hepatitis B surface antigen-reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative]). Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to study treatment. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- 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 (e.g., chemotherapy, HDACi (including valproic acid), DNA methyltransferase inhibitors, other immunotherapy, targeted therapy, biological response modifiers, endocrine anticancer therapy or radiotherapy) within 4 weeks or at least 5 half-lives (whichever is longer) of study drug administration.

- Radiologically confirmed radiotherapy induced pseudoprogression in CNS tumors

- 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. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. For information on CYP substrates and P-gp inhibitors or inducers see section 5.8.

- 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 (e.g. gastrointestinal disorders or electrolyte disturbances) 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 combined 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.

No patient will be allowed to enroll in this trial more than once.

Studien-Rationale

Primary outcome:

1. Phase I: Dose Limiting Toxicity (DLT) of the combination treatment. (Time Frame - 5 weeks): *A dose limiting toxicity (DLT) is defined as any AE according to the definitions and exceptions listed below that is related to the administration of the combination of investigational agents occurring during the priming week and first cycle of combination treatment (first 5 weeks) in phase I of the trial. A study participant will be considered evaluable for a DLT if at least 2 doses of nivolumab and 4 doses of entinostat were administered during the first 5 weeks (5 weeks normally incorporate the priming week and 1 cycle of planned combination treatment).*

Participants who discontinue treatment or have treatment delays preventing them from receiving the above defined minimal amount of treatment in the first cycle of combination treatment for reasons unrelated to study drug toxicity, are not evaluable for DLT and will be replaced in enrollment (maximum number of replacement subjects will be 3 per dose level).

2. Phase II: Best response (CR or PR) (Time Frame - Change in 24 weeks):
Best response (CR or PR) will be based on RANO criteria for all primary CNS tumors and RECIST for non-CNS tumors, defined for each patient as the best response under study combination therapy during the first 6 cycles (assessment every 2 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:

1. Duration of Response (DOR) (Time Frame - Phase II: maximum of 48 weeks):
DOR will be evaluated for all patients who experienced (confirmed) response. Starting time point will be the time when best response was determined.

2. Disease Control Rate (DCR) (Time Frame - Phase II: maximum of 48 weeks):
DCR will be evaluated in addition, also using iRECIST and iRANO.

3. Stable disease (SD) (Time Frame - Phase II: maximum of 12 cycles (each cycle is 28 days)):
SD will be evaluated in addition, also using iRECIST and iRANO.

4. Progression-free survival (PFS) (Time Frame - 4 years):
The event-time endpoint PFS will be estimated using the Kaplan-Meier method, considering all the patients who started the treatment, whatever their compliance to treatment, including if the treatment was stopped prematurely for a reason other than disease progression. 95%-Confidence intervals will be provided for the Kaplan-Meier estimates.

5. Time to Response (TTR) (Time Frame - Phase II: maximum of 12 cycles (each cycle is 28 days)):
The event-time endpoint TTR will be estimated using the Kaplan-Meier method, considering all the patients who started the treatment, whatever their compliance to treatment, including if the treatment was stopped prematurely for a reason other than disease progression. 95%-Confidence intervals will be provided for the Kaplan-Meier estimates.

6. Overall Survival (OS) (Time Frame - Phase II: maximum of 48 weeks):
The event-time endpoint OS will be estimated using the Kaplan-Meier method, considering all the patients who started the treatment, whatever their compliance to treatment, including if the treatment was stopped prematurely for a reason other than disease progression. 95%-Confidence intervals will be provided for the Kaplan-Meier estimates.

7. Immune related Response Rate (RR) measured by iRECIST criteria and iRANO criteria (Time Frame - Phase II: maximum of 48 weeks):
As a secondary endpoint for patients who continued treatment beyond progression in case of clinical benefit, response as assessed by iRECIST or iRANO will be performed.

8. Maximum Plasma Time (Tmax) (Time Frame - one week):

Time to reach the maximum concentration (hr).

9. Maximum Plasma Concentration (Cmax) (Time Frame - one week):
The peak plasma concentration of a drug after Administration (ng/mL)

10. Half-life (Time Frame - one week):
The time required for the concentration of the drug to reach half of its original value (hr)

11. Area under the curve (AUC) (Time Frame - one week):
The integral of the concentration-time curve (ng/mL·hr)

12. total Clearance (Cl/F) (Time Frame - one week):
The total body clearance will be equal to the renal clearance + hepatic clearance + lung clearance (L/h/m²)

Geprüfte Regime

- Nivolumab and Entinostat:
  Patients entering phase I will receive one week entinostat without nivolumab (priming phase) before receiving the combination treatment of nivolumab and entinostat.

Kontakt

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Perth Children's Hospital
6009 Nedlands
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Status: Rekrutierend

St. Anna Children's Hospital
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Quelle: ClinicalTrials.gov