PHASE 1/2 STUDY TO EVALUATE PALBOCICLIB (IBRANCE®) IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE AND/OR IN COMBINATION WITH TOPOTECAN AND CYCLOPHOSPHAMIDE IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

Published: 09-08-2022
Last updated: 07-04-2024

Primary: To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS.Secundary: To further compare the efficacy...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Skeletal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56430

Source
ToetsingOnline

Brief title
A5481092

Condition

- Skeletal neoplasms malignant and unspecified

Synonym
Bone tumor, cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: Combination therapy, Ewing sarcoma, Palbociclib, pediatric

Outcome measures

Primary outcome

Event-free survival (EFS) based on investigator assessment. Assessment of response in phase 2 of the study in Ewing sarcoma patients will be made using RECIST 1.1 criteria as per Appendix 5. The primary outcome measure of event-free survival (EFS) is defined in the Protocol (section 9.6.1) as the time from randomization until first event (ie, progression, recurrence following response, second malignancy or death without progression or recurrence. RECIST 1.1 criteria will be applied to define progression and/or recurrence following response.

Secondary outcome

* Event-free survival (EFS) assessed by an independent review committee.

* Objective response (OR), as assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

* PET-CT response after cycle 4 compared to objective response on MRI/CT.

* Progression free survival (PFS) based on investigator assessment

* Overall survival (OS).

* Adverse Events (AEs) as graded by National Cancer Institute [NCI] Common

Terminology Criteria for Adverse events [CTCAE] version 4.03)

* Pharmacokinetic parameters of palbociclib, TMZ, IRN:

- Palbociclib PK: MD (assuming steady state is achieved) - Css,max, Tmax,

AUCss, Css,trough, and CL/F, as data permit.

- TMZ PK: MD - Css,max, Tmax, AUCss,*, Css,trough, and CL/F, as data

permit.

- IRN (and active metabolite, SN-38) PK: MD - Css,max, Tmax, AUCss,*,

Css,trough, and CL/F, as data permit.

* QoL reported by patient at baseline and after 2 and 4 cycles using

age-appropriate tools.

* Days of hospitalization.

Study description

Background summary

Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. CDKs are important regulatory enzymes that mediate cell cycle control by regulating and promoting transition through the cell cycle. While a number of various CDK enzymes are recognized, in complex organisms the control over cell cycle entry is regulated at the level of CDK4 and CDK6. As cancer represents a process of uncontrolled cell division and proliferation, CDKs represent potential therapeutic targets Palbociclib (IBRANCE®) is approved for the treatment of patients with hormone

receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or in combination with fulvestrant in patients with disease progression following endocrine therapy.
Curative options for pediatric, adolescent or young adult patients with relapsed or refractory solid tumors are limited, and outcomes are poor. TMZ and IRN are used frequently in clinical practice for many recurrent pediatric cancers, including recurrent EWS. In several pediatric case series and Phase 2 clinical trials, IRN, and TMZ given alone or in combination with other agents such as vincristine or temsirolimus have been associated with response rates of up to 68% in patients with recurrent EWS, with some patients maintaining a response for >14 cycles of therapy. New agents have been combined with this backbone in pediatric clinical trials.

The multicenter, open-label, randomized Phase 2 portion of the study will compare the efficacy of the combination of palbociclib with IRN and TMZ versus IRN and TMZ alone in the treatment of children, adolescents and young adults with recurrent or refractory EWS for whom no standard therapy is available.

Study objective

Primary: To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS.

Secundary: To further compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone.

To characterize the toxicity and safety of the combination of TMZ and IRN plus or minus palbociclib.

To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory EWS when given in combination.

To assess the impact of the combination of palbociclib with TMZ and IRN treatment on the quality of life (QoL) of patients with refractory or recurrent EWS.

Study design

This is a Phase 2, randomized, open-label study

Intervention

Combination of 75mg/m2 palbociclib with 2 chemotherapy agents,50mg/m2

irinotecan (IRN) and 100mg/m2 temozolomide (TMZ) in comparison to treatment with 50mg/m2 IRN and 100mg/m2 TMZ alone.

Study burden and risks

The study treatment is broken up into *cycles* with each cycle defined as 21 days in length. After the first two cycles (7 visits total), each cycle there will be 1 visit to the hospital. For a treatment period of 18 weeks there will be 6 cycles with 12 visits to site in total. Patients will need to keep a medication diary and complete 2 questionnaires 3-4 times. A physical examination will be done once per cycle. The following blood draws are extra for this study: for PK, TK and biomarkers, for younger children who are less than Tanner 4 stage additional samples are taken for hormonal and bone metabolite assessments in, Approximately 8- 10 times for a treatment period of 18 weeks.

Study Drug Risks (Palbociclib)
Palbociclib has been given to approximately 1842 patients with breast cancer who received palbociclib together with hormonal treatment in Pfizer sponsored clinical trials.

The following side effects have been reported:
30% or more: decreases in neutrophil blood cells (may increase the risk for infection), decreases in white blood cells (infection fighting cells), infections, fatigue.
10 to <30%: decreases in hemoglobin (may cause weakness), decreases in platelets (may cause bleeding and/or bruising), inflammation of the mouth, diarrhea, constipation, nausea, vomiting, joint pain, back pain, pain in hands and feet, hair loss, rash, cough, shortness of breath, headache, dizziness, decreased appetite, hot flush, insomnia (inability to sleep), fever, common cold, increases in blood liver markers that may indicate liver damage
5 to <10%: abdominal pain, indigestion, asthenia (general weakness), swelling of hands and feet, irritation or sores in the lining of hollow organs like mouth, throat, stomach, bowels ; pain, influenza (flu) like illness, muscle pain, pain in the muscles and bone including around the chest and neck, muscle cramps, dry skin, itching, mouth/throat pain, nosebleed, depression, fall, increased blood pressure, acid reflux (heartburn), increased creatinine level (may indicate abnormal kidney function).

The following side effects have been reported in <5% of the patients but are still deemed important:
• fever associated with dangerously low levels of a type of white blood cells (neutrophils)
• blurred vision
• increased tearing and/or dry eye
• impaired sense of taste
• In addition, interstitial lung disease (an inflammation of the lungs which

can cause cough and shortness of breath) can occur.

Serious and life-threatening infections have been observed in some patients treated with palbociclib.
Palbociclib is also being evaluated in a number of adult and pediatric clinical trials run in a variety of tumor types given alone or together with other drugs. The side effects reported in these studies to date are similar to those mentioned above.

Please see protocol page 48- 52 for a risk benefit assessment.

Contacts

Public
Pfizer

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United States NY 10001
US
Scientific
Pfizer

Hudson Boulevard East 66
United States NY 10001
US

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)

Inclusion criteria

1. Histologically confirmed relapsed or refractory solid tumor as follows:
• For randomized Phase 2 part: Histologically confirmed Ewing sarcoma at diagnosis or at relapse, with presence of EWSR1-ETS or FUS-ETS rearrangement. Histopathology confirmation of both EWSR1-ETS or FUSETS rearrangement partners is required OR availability of formalin fixed paraffin embedded (FFPE) tumor tissue sample for central testing. Patient must have relapsed or have refractory disease and at least evaluable disease in at least one site other than bone marrow that can be followed by imaging.
2. Age >=2 and <21 years at the time of study entry. Refer to Section 4.3 for reproductive criteria for male and female participants.
3. Lansky performance status >=50% for patients <=16 years of age, or Eastern Cooperative Oncology Group (ECOG) 0, 1 or 2 for patients >16 years of age.
4. Adequate bone marrow function.
• Absolute neutrophil count >=1000/mm3;
• Platelet count >=75,000/mm3 (transfusion independent, no platelet transfusion in past 7 days prior study entry);
• Hemoglobin >=8.5 g/dL (transfusion allowed).
5. Adequate renal function: Serum creatinine level based on age/gender must be less than or equal to the following maximum upper limits
6. Adequate liver function, including:
•Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2.5 × upper limit of normal (ULN) or <=5 × ULN for age, if attributable to disease involvement of the liver;
•Total bilirubin <=1.5 × ULN for age unless the patient has documented Gilbert's syndrome. Patients with documented Gilbert's syndrome are eligible if direct bilirubin is within normal ranges (<=ULN).
7. Patients enrolled to Phase 1 portion of the study and tumor specific cohorts must have measurable disease as defined by RECIST version 1.1 or modified RANO criteria for CNS disease or at least evaluable disease by INRC for neuroblastoma.
The eligible patients with neuroblastoma must have at least one of the following at the time of study entry:
•Measurable tumor by CT or MRI that is avid on MIBG scan or demonstrates increased FDG uptake on PET scan;
•Avid lesion on MIBG scan with positive uptake at a minimum of one site;
•For disease that is not avid by MIBG-scan, at least one lesion that demonstrates increased FDG uptake on PET scan AND viable neuroblastoma confirmed by current or prior biopsy;
•bone marrow involvement with more than 5% neuroblastoma cells in at least one sample from bilateral bone marrow biopsies;
•In non MIBG-avid refractory soft tissue disease that does not demonstrate increased FDG uptake; lesion biopsy is required to document the presence of viable neuroblastoma, unless patient has a
new soft tissue lesion (radiographic evidence of disease progression). Patients

with EWS enrolled to Phase 2 portion of the study are eligible with at least evaluable disease (eg, bone only disease with no soft tissue component).
8. Recovered to CTCAE Grade <=1, or to baseline, from any non-hematological acute toxicities of prior surgery, chemotherapy, immunotherapy, radiotherapy, differentiation therapy or biologic therapy, with the exception of alopecia.
9. Serum/urine pregnancy test (for all girls >=8 years of age) negative at screening and at the baseline visit.

Exclusion criteria

1. Phase 2 portion: prior treatment with a CDK4/6 inhibitor or progression while on treatment with an IRN-containing or TMZcontaining regimen. Patients who have received IRN and/or TMZ and did not progress while on these medications are eligible.
2. Prior intolerability to IRN and/or TMZ for IRN and TMZ plus/minus palbociclib combinations and prior intolerability to TOPO and/or CTX for TOPO and CTX combination. For patients enrolled in the UK, any contraindication for IRN and/or TMZ treatment, as per the local SmPC.
3. Use of strong cytochrome P450 (CYP) 3A inhibitors or inducers within 12 days of study entry. Patients who are receiving strong uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) inhibitors within 12 days of C1D1 are not eligible for the palbociclib with IRN and TMZ combination. Patients who are receiving strong UGT1A1 inhibitors within 12 days of C1D1 are eligible for the palbociclib with TOPO and CTX combination
4. Systemic anticancer therapy within 2 weeks prior to study entry and 6 weeks for nitrosoureas.
5. Prior irradiation to >50% of the bone marrow (see ATTACHMENTS).
6. Participation in other studies involving investigational drug(s) within 2 weeks or 5 halflives, whichever is longer, prior to study entry.
7. Major surgery within 4 weeks prior to study entry. Surgical biopsies or central line placement are not considered major surgeries.
8. For IRN and TMZ with/without palbociclib combinations: known or suspected hypersensitivity to palbociclib, dacarbazine, IRN and/or TMZ. For combination of palbociclib with TOPO and CTX: known or suspected hypersensitivity to palbociclib, TOPO and/or CTX
9. Patients with known symptomatic brain tumors or brain metastases and require steroids, unless they have been on a stable or on a decreasing steroid dose for >14 days.
10. Patients with previously diagnosed brain metastases are eligible if they have completed their prior treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry for these metastases for at least 14 days postradiation and 4 weeks postsurgery and are neurologically stable.
11. Hereditary bone marrow failure disorder.

12. QTc >470 msec.
13. History of clinically significant or uncontrolled cardiac disease, including:
• History of or active congestive heart failure; if patient had congestive heart failure resolve and >1 year from resolution, patient will be considered eligible;
• Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation or Torsades de Pointes);
• Diagnosed or suspected congenital or acquired prolonged QT syndrome;
• Need for medications known to prolong the QT interval;
• Uncorrected hypomagnesemia or hypokalemia because of potential effects on the QT interval;
• Left ventricular ejection fraction <50% or shortening fraction <28%.
14. Recent or ongoing clinically significant gastrointestinal disorder that may interfere with absorption of orally administered drugs (eg, gastrectomy).
15. Evidence of serious active or uncontrolled bacterial, fungal or viral infection or known history of hepatitis B virus, hepatitis C virus, or human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness. Screening for viral hepatitis and HIV is under discretion of investigator unless required by local regulation.
16. Severe acute or chronic medical or laboratory test abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results, and in the judgment of the Investigator, would make the patient inappropriate for entry into this study.
17. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.
18. Fertile male patients or female patients of childbearing potential who are unwilling or unable to follow contraceptive requirements as detailed in Section 4.3.
19. Pregnant or breastfeeding women.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ibrance
Generic name:	Palbociclib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temodar
Generic name:	Temozolomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-10-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-04-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2023
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	EUCTR2021-003444-25-NL
ClinicalTrials.gov	NCT03709680
CCMO	NL81509.041.22