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Efficacy and Safety Assessment of Oral LBH589 in Adult Patients With Advanced Soft TIssue Sarcoma After Pre-treatment Failure (ESTIM-LBH)

ClinicalTrials.gov Identifier: NCT01136499

Recruitment Status : Completed
First Posted : June 3, 2010
Last Update Posted : March 6, 2013

Sponsor:
Centre Leon Berard

Information provided by (Responsible Party):
Centre Leon Berard

Study Description

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Brief Summary:

The purpose of this study is to assess efficacy and safety of LBH589 - Panobinostat®, a potent HDACi, in patients with advanced STS who experiment disease progression after or during first-line chemotherapy. The rational is based on the observation of activity of deacetylase inhibitor (DACi) in several pre-clinical models of STS including Synovial sarcoma and Ewing sarcoma.

Condition or disease	Intervention/treatment	Phase
Soft Tissue Sarcoma	Drug: LBH589 (Panobinostat®)	Phase 2

Detailed Description:

Despite surgical excision and radiation therapy, approximately 50% of patients treated for localised STS will experience local or distant relapse.

Recurrent STS : current therapeutic strategies Although some patients may be salvaged with surgery, chemotherapy using doxorubicin-based regimens is in most cases indicated for patients with recurrent STS. Progression-free survival (PFS) is in most cases less than or equal to 6 months. Most patients die of their disease within 12-15 months following the diagnosis of advanced disease. Doxorubicin is considered as the standard of care in the first line setting for patients with locally advanced unresectable or metastatic STS. However, only 15-25% of these patients exhibit objective response following this chemotherapy while 30-35% experiment rapid disease progression. Doxorubicin-based combinations have resulted in an inconsistent increase in response rate but no survival advantage versus single-agent doxorubicin. After doxorubicin-based regimens failure, most agents, including other agents approved for the treatment of STS such as dacarbazine, ifosfamide and trabectedin, have shown very low response rates and short PFS. The only approved agent in this setting is trabectedin, which has shown prolonged stabilization in approximately 20% of patients at 6 months in several phase II trials. Gemcitabine-docetaxel combination, although not approved for the treatment of STS has shown interesting response rates in leiomyosarcomas, as well as other STS subtypes . Mechanisms of chemoresistance are poorly understood.

Place of LBH589:

LBH589 is postulated to have activity in sarcomas by being able to arrest gene transcription through the inhibition of HDAC, to cause the misfolding of important proteins

for sarcoma biology such as fusion proteins or overexpressed genes (HDM2, cdk4, AKT…) via the disruption of HSP90 functioning . Some mechanisms similar to leukemia-associated fusion proteins, which have been shown to recruit HDAC to repress hematopoietic differentiation, might be involved by some translocation-associated sarcomas. The SYT portion of the synovial sarcoma oncoprotein SYT-SSX interacts with trithorax-group proteins and binds directly to the mSin3A HDAC component. SSX associates with polycomb-group proteins, which involve HDAC activity to mediate transcriptional repression; thus, aberrant epigenetic changes in gene expression seem to be a central effect of the fusion oncoprotein in this disease. HDAC inhibitors have been effective against both synovial sarcoma and Ewing sarcoma in preclinical studies . Evidence has also been presented for growth inhibition and induction of differentiation in clear cell sarcoma (Nielsen TO, Vancouver Coastal Health Research Institute, Vancouver, Canada, unpublished data) and chondrosarcoma by HDACi.

Data from the phase I study involving patients with advanced solid tumors indicate that the MWF every week schedule of LBH589 is pharmacodynamically and clinically active. Histone acetylation was detected in peripheral blood cells for up to 72 hours (the maximum duration between doses on the MWF every week schedule) in 50% of patients at the 20 mg and 30 mg doses and CR and PR were observed in two and three patients respectively, with cutaneous T-cell lymphoma. Grade 3 fatigue was the dose-limiting toxicity (DLT) in 2 patients treated at the 40 mg level and 1 patient treated at the 60 mg level. The 40 mg level seem to be tolerable and is felt to be the most likely to have activity in solid tumors.

After first-line chemotherapy failure, efficacy of therapeutic alternatives is limited. The purpose of this trial is therefore to investigate the efficacy, safety and tolerability of 40 mg of LBH589 given orally on a twice a week.

Study Design

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Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	53 participants
Allocation:	Non-Randomized
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Efficacy and Safety Assessment of Oral **LBH589** in Adult Patients With Advanced Soft Tissue Sarcoma After Pre-treatment Failure: an Open-label, Multicenter Phase II Study
Study Start Date :	January 2010

Actual Primary Completion Date : January 2012
Actual Study Completion Date : January 2013

Resource links provided by the National Library of Medicine

MedlinePlus related topics: Soft Tissue Sarcoma

Drug Information available for: Panobinostat

Genetic and Rare Diseases Information Center resources: Soft Tissue Sarcoma

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: LBH PANOBINOSTAT 40 mg 3 days per week	Drug: LBH589 (Panobinostat®) 40 mg MWF. 40 mg of LBH589, orally administered on Monday, Wednesday and Friday (MWF) on a weekly schedule, until tumor progression or unacceptable toxicity. Other Name: panobinostat

Outcome Measures

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Primary Outcome Measures :

1. 3 months non progression rate [Time Frame: 3 months]

Secondary Outcome Measures :

1. Progression-free survival (PFS) [Time Frame: 6 months after the end of treatment (18 months after the start of treatment)]
2. Time to progression (TTP) [Time Frame: 6 months after the end of treatment (18 months after the start of treatment)]

3. best objective response rate [Time Frame: 6 months after the end of treatment (18 months after the start of treatment)]
4. Safety profile based on incidence, intensity and type of adverse events
   [Time Frame: 6 months after the end of treatment (18 months after the start of treatment)]

   clinically significant changes in patients physical examination findings; vital sign measuremments; and clinical laboratory results will be recorded and monitored.

5. Plasmatic rate of LBH589 [Time Frame: 6 months after the end of treatment (18 months after the start of treatment)]

   assess steady-state pharmacokinetics of the new formulation of LBH589 versus that one used in phase one studies.

Eligibility Criteria

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Information from the National Library of Medicine NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

INCLUSION CRITERIA

- Age ≥ 18 years.
- Histologically proven advanced metastatic or unresectable soft tissue sarcoma, excluding osteosarcoma.
- Prior treatment with a doxorubicin containing regimen whether in the adjuvant setting or for metastatic/advanced disease. If doxorubicin was given as adjuvant therapy

patient may be included if relapse occurs within a year of adjuvant therapy. If relapse occurs more than one year after the completion of adjuvant therapy, the patient must have received one prior regimen for metastatic disease. Patient may have received one or more previous line of therapy. Patients with sex cord tumors may be included after prior treatment with a platinum containing regimen (pretreatment with a doxorubicin containing regimen is not required for this patients subgroup).

- Patient has at least one site of measurable nodal disease at baseline ≥ 2.0 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan can not be performed).
- ECOG performance status (PS) ≤ 2.
- Adequate haematological, liver and renal function:
  - Absolute Neutrophil Count (ANC) ≥ 1.5 G/L,
  - Hemoglobin ≥ 9 g/dL,
  - Platelets ≥ 100 G/L,
  - Total calcium (corrected for serum albumin) ≥ lower limit of normal (LLN) or correctable with supplements,
  - Magnesium ≥ LLN or correctable with supplements,
  - Potassium ≥ LLN or correctable with supplements,
  - Phosphorus ≥ LLN or correctable with supplements,
  - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5.0 x ULN if liver metastasis are present),
  - Serum bilirubin ≤ 1.5 x ULN,
  - Serum creatinine ≤ 1.5 x ULN,
  - If the serum creatinine is ≥ 1.5 x ULN, then a 24-hour creatinine clearance must be conducted and the result must be ≥ 50 mL/min.
- Clinical euthyroidy (patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism).
- Ability to swallow capsules or tablets.
- Life expectancy ≥ 12 weeks.
- Mandatory affiliation with health security insurance.
- Signed written informed consent.

EXCLUSION CRITERIA

- Prior treatment with any HDAC or HSP90 inhibitor drug.

- Unresolved toxicities (≥ Grade 1) from prior therapy that would, in the opinion of the investigator, compromise patient safety.
- Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
  - Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
    - Left ventricular systolic function (LVEF) determined by MUGA scan or echocardiogram < center normal value,
    - Complete left bundle branch block,
    - Obligate use of a cardiac pacemaker,
    - Congenital long QT syndrome,
    - History or presence of ventricular tachyarrhythmia,
    - Presence of unstable atrial fibrillation (ventricular response > 100bpm),
    - Clinically significant resting bradycardia (< 50 bpm),
    - Mean corrected QT interval (QTcF - n ≥ 3) ≥ 450 msec on screening ECG,
    - Right bundle branch block + left anterior hemiblock (bifasicular block),
    - Angina pectoris ≤ 3 months prior to starting study drug,
    - Acute myocardial infarction (MI) ≤ 3 months prior to starting study drug,
    - History or presence of acute coronary syndrome,
    - Other clinically significant heart disease (e.g.: Congestive heart failure (CHF), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen),
  - Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LBH589 (e.g.: ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive small bowel resection),
  - Other concurrent severe and/or uncontrolled medical conditions (e.g.: uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease) that could cause unacceptable safety risks or compromise compliance with the protocol.
- Current treatment with any of the medications listed in appendix 04, if the treatment cannot be discontinued or switched to a different medication prior to starting study drug. The medications listed in appendix 04 have a relative risk of prolonging the QT interval, or inducing Torsades de Pointes, or inhibit CYP3A4/5.
- Major surgery ≤ 2 weeks prior starting study drug or who have not recovered from side effects of such therapy.

- History of brain metastases.
- Absence of at least one metastatic lesion greater than or equal to 2cm on pretreatment CT scan or other radiographic imaging as defined in RECIST criteria (appendix 02).
- Systemic treatment with any anti-cancer drug, including any investigational drug that is administered on an intermittent schedule if the last dose has not been administered ≥ 4 weeks ago, or if the patient has not recovered from any ongoing toxicity prior to study enrolment.
- Systemic treatment with any anti-cancer drug, including investigational drug that is administered on a chronic dosing schedule (e.g.: daily dosing, every-other-day dosing, MWF weekly) if ≤ 5 half-lives elapsed since the last dose, or if the patient has not recovered from any ongoing toxicity prior to study enrolment.
- Women who are pregnant or breast feeding.
- Women of childbearing potential (WCBP) are excluded unless they have a negative serum pregnancy test ≤ 48 hours prior starting study treatment. All sexually active WCBP and male patients are excluded unless they agree to use adequate contraceptive methods (injectable or implantable hormonal contraceptive, tubal ligation, intra-uterine device, barrier contraceptive with spermacide, or vasectomized partner) throughout the study. Since the potential of LBH589 to induce CYP3A4 is unknown, patients who are using oral contraceptives should use another effective method of contraception.
- Current immunosuppressive syndrome.
- History of another malignancy that is currently clinically significant or currently requires active intervention.
- Refusal or inability to comply with the protocol or follow the instructions given to them by the clinic staff.

Contacts and Locations Go to ▼

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT01136499***

Locations

France

Centre Léon Berard
Lyon, **France**

Sponsors and Collaborators

Centre Leon Berard

Investigators

Principal Investigator: BLAY PR Jean-Yves Centre Léon Berard

More Information

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Publications:

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Responsible Party: Centre Leon Berard
ClinicalTrials.gov Identifier: NCT01136499 History of Changes

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Additional relevant MeSH terms:

Sarcoma	Antineoplastic Agents
Neoplasms, Connective and Soft Tissue	Histone Deacetylase Inhibitors
Neoplasms by Histologic Type	Enzyme Inhibitors
Neoplasms	Molecular Mechanisms of Pharmacological Action
Panobinostat	