Name of Sponsor:
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Name of finished product:
VLX1570

Name of active ingredient:
(3E,5E)-3,5-bis[(4-fluoro-3-nitrophenyl)methylidene]-1-(prop-2-enoyl)azepan-4-one

Title of the study:
VLX1570 and Low-Dose Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma: A Clinical and Correlative Phase 1/2 Study (Protocol No. V14-11056)

Investigators and study centers:
Principal Investigator: Ola Landgren, MD, PhD, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065 USA (212) 639-5153 [Site 001]

Other Investigators and study centers that enrolled patients:

- Site 002: Paul Richardson, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, Massachusetts 02446 USA
- Site 004: Agne Paner, MD, Rush University Cancer Center, 1725 West Harrison Street, Chicago, Illinois, 60612 USA
- Site 005: Jesus G. Berdeja, MD, Sarah Cannon Research Institute, 250 25th Avenue North, Suite 412, Nashville, Tennessee 37203 USA
- Site 006: Kimmo Porkka, MD, PhD, Helsinki University Hospital Comprehensive Cancer, Department of Hematology, P.O. Box 372, 00029 HUCH, Helsinki, Finland

Study period (years): 2015 - 2017
First patient enrolled: 07 April 2015
Last patient completed: 24 May 2017

Clinical phase: Phase 1/2

Objectives:
Phase 1 Component
Primary Objective:

- To determine the maximum tolerated dose (MTD) of VLX1570 when used with low dose dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma (RRMM).

Secondary Objectives:

- To determine the frequency and severity of adverse events associated with the combination of VLX1570 and low dose dexamethasone.
- To evaluate the clinical pharmacokinetics of VLX1570.
- To investigate if VLX1570 treatment at any dose results in objective response per International Myeloma Working Group (IMWG) criteria.

Phase 2 Component
Primary Objective:

- To evaluate the clinical benefit rate (≥ minimal response, MR) of VLX1570 with low dose dexamethasone in RRMM.

Secondary Objectives:

- To further characterize the toxicities associated with VLX1570 with low dose dexamethasone.
- To determine the overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS) with this therapy.

- To further evaluate the clinical pharmacokinetics of VLX1570.

Exploratory Objectives Phase 1 and Phase 2

Bone marrow samples, blood, plasmacytoma and other tumor tissues collected during the study will be used for biomarker and mechanism of action studies to support planned clinical trials of VLX1570 in plasma cell disorder indications. The in vitro biomarker analysis from MM tissues and blood may include examination of gene expression, proteomics and functional analysis of proteasomes, proteasomal subunits and associated enzymes.

Methodology:

The study was planned as a Phase 1/2, multi-center, non-randomized, open label study to determine the safety and efficacy of VLX1570 intravenous (IV) infusion administered with low dose dexamethasone in patients with RRMM. VLX1570 treatment was administered on Days 1, 2, 8, 9, 15, 16 of 28-day cycles in combination with dexamethasone on those days. On VLX1570 treatment days patients also received an H1/H2 antagonist premedication regimen.

The Phase 1 starting dose of VLX1570 was 0.05 mg/kg/day administered as a 10 minute (± 2 minutes). The study design used an Initial Accelerated Titration design to be followed by a traditional "3+3" cohort design to establish the MTD and RPTD for the Phase 2 portion of the study. If at any point during the Initial Accelerated Titration cohorts any ≥ grade 2 VLX1570 related or possibly related adverse events (AEs) were observed, the study would revert to a traditional "3+3" design and a new cohort of patients enrolled at that dose level. Six additional patients were to be enrolled at the MTD to further evaluate tolerability and antitumor activity.

Number of patients:

Planned enrollment was 12-36 patients in Phase 1 and 22-26 patients in Phase 2.

Following the deaths of the first 2 patients treated at the 1.2 mg/kg/day dose level (Cohort 3), The Food and Drug Administration (FDA) placed the study on full clinical hold on May 9, 2017. Subsequently, Vivolux AB terminated the study.

Actual enrollment was 15 patients enrolled in the Phase 1 study; the Phase 2 portion of the study was not conducted.

Diagnosis and main criteria for inclusion:

Patients had to meet all of the following criteria for inclusion into the study:

1. Diagnosis of relapsed or relapsed and refractory multiple myeloma, or intolerant to established therapy following at least 2 prior therapies. Prior therapies had to include at least one immunomodulatory drug (e.g., thalidomide, lenalidomide or pomalidomide) and one proteasome inhibitor (e.g., bortezomib or carfilzomib); i.e., regimens known to provide clinical benefits.
2. Measurable disease defined by 1 or more of the following:
   a. Serum monoclonal protein ≥ 0.5 g/dL
   b. Urine monoclonal protein >200 mg/24 hour
   c. Serum immunoglobulin free light chain >10 mg/dL AND abnormal kappa/lambda ratio (reference 0.26-1.65)
3. Estimated glomerular filtration rate (GFR) ≥30 mL/min as assessed by CKD-epi, MDRD, or the Cockcroft-Gault Equation.
4. Age ≥18 years.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
6. Females of child-bearing potential* had to have a negative pregnancy test.
   *A female of childbearing potential (FCBP) was a sexually mature female who: 1) had not undergone a hysterectomy or bilateral oophorectomy; or 2) had not been naturally postmenopausal for at least 24 consecutive months (i.e., had menses at any time in the preceding 24 consecutive months).
7. Males and females of childbearing potential had to be willing to use an effective form of contraception (as specified in the protocol) during chemotherapy treatment and for at least six months thereafter.
8. Absolute neutrophil count (ANC) ≥1.0 x 10^9 /L, hemoglobin ≥8 g/dL (transfusion permitted provided the anemia was judged to be disease related), and platelet count ≥ 75 x 10^9/L.
9. Adequate hepatic function, with bilirubin < 1.5 x the ULN, and AST and ALT < 2.5 x ULN.
10. Patient had or was willing to have a central venous catheter (e.g., PICC, Port-A-Cath®, Hickman® catheter) for drug administration.

Exclusion criteria:

Patients were not eligible for the study if they fulfilled one or more of the following criteria:

1. Any concurrent treatment that would compromise the study including but not limited to:
   a. Planned concurrent treatment for multiple myeloma other than bisphosphonates
   b. Ongoing corticosteroids for indications other than multiple myeloma allowed as long as the dose did not exceed 10 mg of prednisone per day or equivalent
   c. Persisting effects of any previous or ongoing treatment ≥ Grade 1 that might compromise delivery of study treatment or assessment of adverse events (except alopecia or neuropathy ≤ Grade 2 without pain)
2. Any cytotoxic or biologic therapy less than 2 weeks prior to initiation of therapy.
3. Pregnant or breast feeding females.
4. Hypertension or diabetes not adequately controlled with current medication, defined as a need for dose adjustment or implementation of new or additional drugs as judged by the Investigator.
5. Known active hepatitis B or C infection or HIV infection.
6. Significant cardiovascular disease with NYHA Class III or IV symptoms, or hypertrophic cardiomegaly, or restrictive cardiomegaly, or myocardial infarction within 6 months prior to enrollment, or unstable angina, or unstable arrhythmia.
7. QTc interval >460 msec (males) or >470 msec (females); or repeated demonstration of a QTc interval >450 msec.
8. A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT syndrome).
9. The use of concomitant medications that prolonged QT/QTc interval.
10. Uncontrolled intercurrent illness including but not limited to psychiatric illness/social situations that, in the opinion of the Investigator, would compromise compliance with study requirements or put the patient at unacceptable risk.
11. Active infection requiring systemic treatment within one week prior to first dose.
12. Major surgery within 1 month prior to enrollment.
13. Use of any investigational agent within the last 28 days. For classes of investigational agents that were not known to have prolonged toxicities the wash-out time could be decreased to 14 days after agreement with the Medical Monitor.
14. History of other malignancy (apart from basal cell carcinoma of the skin, or in situ cervix carcinoma) except if the patient had been free of symptoms and without active therapy for at least 2 years.
15. Known intolerance to steroids or H1/H2-antagonists.
16. Serum calcium (corrected for albumin) level above the ULN range (treatment of hypercalcemia was allowed and the subject could enroll if hypercalcemia returned to normal with standard treatment).
17. Diagnosed with plasma cell leukemia, POEMS syndrome or amyloidosis.
18. Patients with a history of central nervous system (CNS) myeloma or other CNS malignancy.

Results:

Fifteen patients were enrolled; 14 patients received VLX1570 study drug and 1 patient did not receive VLX1570 due to unrelated reasons (withdrawn from study prior to receiving first dose due to low ANC). The study utilized anaccelerated titration design which allowed for intrapatient dose escalation (dose increase after the first cycle in the absence of toxicity). Accordingly, 4 patients were treated in the first dose cohort (0.05 mg/kg, 0.15 mg/kg, 0.30 mg/kg); 8 patients were treated in the second dose cohort (0.30 mg/kg, 0.60 mg/kg), and 2 patients were treated in the third dose cohort (1.2 mg/kg). All patients received pretreatment with H1/H2 antagonists.

Doses of VLX1570 ranging from 0.05 to 0.60 mg/kg were well tolerated in patients, but at 1.2 mg/kg (Cohort 3) the first 2 patients treated experienced life-threatening SAEs of respiratory failure and hypoxia, leading to death. The Investigator judged both SAEs to be related to VLX1570. In May 2017, the study was placed on clinical hold by theFDA. Subsequently, the study was closed by the sponsor due to unacceptable toxicity and all patients were taken off study.

Out of 14 safety evaluable patients the most frequently reported study drug related TEAEs were anemia (28.6%) anddyspnea (21.4%). Also reported in 2 (14.3%) patients who were treated at the 1.2 mg/kg dose level were the following study drug related TEAEs: asthenia, pyrexia, hypoxia, respiratory failure, lymphocyte count decrease, platelet count decrease, acidosis, myalgia, acute renal failure. Grade 3 or greater drug related TEAEs (35.7% patients) included anemia (28.6%), dyspnea, hypoxia, respiratory failure, lymphocyte count decrease, platelet count decrease (14.3%).

A preliminary safety analysis by the sponsor after study closure found no pattern of TEAEs or clinical signs at the lower VLX1570 doses suggesting subtle clinical toxicity similar in nature to the severe pulmonary events that occurred at 1.2 mg/kg.

Two patients demonstrated reductions in myeloma proteins in the blood and/or urine:

- A patient treated at the highest dose (1.2 mg/kg), demonstrated a decrease in urinary kappa light chains from 52 mg/dL (pretreatment) to 11.78 mg/dL (day 9), even in the setting of progressively worsening renal dysfunction and respiratory failure. The patient was subsequently discontinued from treatment due to adverse events.

- A patient with progressively worsening manifestations of myeloma, including increasing urinary kappa light chain excretion, demonstrated a modest decrement in urinary kappa light chains (113.90 to 90.8 mg/dL) following one cycle of VLX1570 at the 0.3 mg/kg dose level, which stabilized over the next 4 cycles of treatment. The patient's urinary M protein also decreased from 113.98 mg/dL (pretreatment) to 81 mg/dL (day 1 of cycle 4). These observations were associated with stability of his clinical symptoms indicative of myeloma progression prior to treatment. However, the patient was taken off study when the study was closed due to adverse events at the 1.2 mg/kg dose level.

Conclusions:
The primary objectives were to determine the MTD and clinical benefit rate of the combination of VLX1570 with low dose dexamethasone in patients with refractory or relapsed myeloma. The study was placed on clinical hold and subsequently terminated early due to the development of dose limiting toxicities at 1.2 mg/kg VLX1570. The MTD was unconfirmed. Several patients, including a patient treated at the 1.2 mg/kg dose level, had evidence of clinical and biological activity.