

<u>TYPE OF CANCER:</u>	Prostate Cancer
<u>TYPE OF TRIAL:</u>	Phase IB
<u>TRIAL SPONSOR:</u>	Novartis
<u>PRINCIPAL INVESTIGATOR:</u>	Nicholas Vogelzang, M.D.
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STUDY SUMMARY

An open label, single arm, Phase Ib dose finding study of I.V. panobinostat (LBH589) with docetaxel & prednisone in patients with hormone refractory prostate cancer

TREATMENT OVERVIEW

The study will evaluate escalating doses of i.v. panobinostat (LBH589) administered on days 1 and 8 in combination with docetaxel given i.v. on day 1 and with oral prednisone given as 5 mg bid every day, with cycles of treatment repeated every 21 days.

PRETREATMENT ASSESMENT

- Demography/Informed consent
- Inclusion/exclusion criteria
- Relevant Medical history/current medical conditions
- Diagnosis and extent of prostate cancer
- Prior antineoplastic therapy
- Physical Examination
- Vital signs (height, weight, ECOG)
- Tumor Evaluation
- EKG/ECG
- Hematology
- Biochemistry
- Urinalysis
- Coagulation
- PSA
- Serum testosterone test
- Thyroid function test
- Cardiac Imaging (MUGA/ ECHO)
- Pharmacogenetics blood sample (optional)
- Tumor biopsies (optional)
- Blood for circulating tumor cells
- Blood for bone markers

- Urine for bone markers
- Prior/ Concomitant medications
- Adverse events

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion Criteria

- Histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate
- HRPC patients:
 - During dose escalation: patients who are chemo-naïve or have tolerated previous docetaxel treatments (have had no docetaxel reductions or treatment delays) will be enrolled
 - During dose expansion: patients who have had no prior chemotherapy treatment will be enrolled
- Evidence of disease progression as defined by at least one of the following:
 - New lesions on bone scan OR
 - Progressive measurable disease per RECIST criteria OR
Two documented consecutive increases in PSA over a previous reference value (first increase at least 1 week after reference value). The second documented increase must be ≥ 1 week after the first documented increase. If the second increase is not above the first increase then a third PSA must be provided. The third PSA should be greater than the first documented increase. The increasing PSA should have a value of at least
 - 2 ng/mL if rising PSA is the only evidence of progressive disease.
 - Most recent PSA level must be obtained within the past 2 weeks
- Disease progression after prior anti-androgen withdrawal must be confirmed by a rising PSA after the 4-6 week washout period (e.g., PSA level higher than the last PSA obtained while on anti-androgen therapy)
 - Flutamide must be discontinued for ≥ 4 weeks, and bicalutamide, megestrol acetate, cyproterone acetate or nilutamide must be discontinued for ≥ 6 weeks prior to study entry.
- Patients who have undergone medical castration must continue LHRH agonist or antagonist therapy during study treatment
- Patients who have not received prior surgical castration must have a serum testosterone level < 50 ng/mL with continuation of LHRH agonist/antagonist therapy
- ECOG performance status 0-1

- Patients must have the following laboratory values
- ANC \geq 1500/mm³ [SI units 1.5×10^9 /L], Platelet \geq 150K/mm³ [SI units 125×10^9 /L],
- Hgb \geq 10 g/dL [SI units 100 g/L]
- Creatinine \leq 1.5 x ULN
- Bilirubin WNL, AST and ALT \leq 1.5 x ULN
- Serum K, Mg, P, Ca (total, corrected for albumin) or ionized Ca within normal limits (WNL). Note: Potassium, calcium, magnesium, and/or phosphorus supplements may be given to correct values that are $<$ LLN, but these must be documented as corrected prior to patients being enrolled on the study. \geq LLN.
- Albumin $>$ 3.0g/dL [SI units 30 g/L]
- Normal thyroid function (TSH and free T4). Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.
- Patients with elevated alkaline phosphatase secondary to bony metastases may be enrolled
- Concurrent bisphosphonates allowed if initiated at least 4 weeks prior to study entry
- Sexually active subjects with partners of childbearing potential must be willing to use a condom as primary method of contraception (even if surgically sterile) throughout the study and for 12 weeks after study completion

Exclusion Criteria

- Patients with active CNS disease or brain metastases (Note: patients who have received prior treatment for the CNS disease and are stable without any steroid treatment for at least 2 months are eligible)
- Patients with a history of invasive malignancies other than adequately treated nonmelanoma skin cancer or other solid tumors curatively treated with no evidence of disease for $>$ 5 years
- Prior radiotherapy \leq 3 weeks prior to study treatment
- Prior radiopharmaceuticals (strontium, samarium)
- Prior biologic therapy \leq 28 days prior to study treatment

- Prior therapy with a DAC inhibitor for treatment of cancer
- Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first LBH589 treatment
- Impaired cardiac function, including any one of the following:
 - Cardiac - LVEF < the lower limit of institutional norm as determined by baseline ECHO or MUGA
 - Complete Left Bundle Branch Block, obligate use of a cardiac pacemaker, congenital long QT syndrome, history or presence of ventricular tachyarrhythmias, clinically significant resting bradycardia (< 50 beats per minute), QTcF > 450 msec on screening ECG, or Right Bundle Branch block + left anterior hemiblock (bifascicular block)
 - Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation are allowed in the study provided they do not meet the other cardiac exclusion criteria
 - History of unstable angina pectoris or acute MI within 6 months of study entry
 - New York Heart Association functional classification III-IV
- Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy, cardiac artery disease, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Acute or chronic liver or renal disease with impaired hepatic or renal functions
- Peripheral neuropathy ≥ CTCAE grade 2
- Diarrhea ≥ CTCAE grade 2
- Clinically significant third space fluid accumulation
- Symptomatic pleural effusion
- Concomitant use of drugs that have a risk of prolonging the QT interval or causing torsades de pointes
- Concomitant use of CYP3A4/5 inhibitors or inducers, where the treatment cannot be discontinued or switched to a different medication prior to starting study treatment
- History of allergic reaction attributed to compounds of similar chemical composition as docetaxel/polysorbate 80