



## The 65th ASH Annual Meeting Abstracts

## ONLINE PUBLICATION ONLY

## 626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

**A First-in-Human, Open-Label, Phase I Dose Escalation Trial of Daily Oral Nmt Inhibitor Zelenirstat in Patients with Relapsed/Refractory B-Cell Lymphomas and Advanced Solid Tumors**

Randeep Sangha, MD<sup>1</sup>, Rahima Jamal, MD<sup>2</sup>, Jennifer Spratlin, MD<sup>1</sup>, John Kuruvilla, MD FRCPC<sup>3</sup>, Laurie H. Sehn, MD MPH<sup>4</sup>, Michael Weickert, PhD<sup>5</sup>, Luc Berthiaume, PhD<sup>6</sup>, John Robert Mackey, MD<sup>5</sup>

<sup>1</sup>Cross Cancer Institute, Edmonton, Canada

<sup>2</sup>Centre Hospitalier de l'Université de Montréal, Montreal, Canada

<sup>3</sup>Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre - University Health Network, Toronto, Canada

<sup>4</sup>BC Cancer Centre for Lymphoid Cancer and The University of British Columbia, Vancouver, Canada

<sup>5</sup>Pacylex Pharmaceuticals, Inc., Edmonton, Canada

<sup>6</sup>University of Alberta and Pacylex Pharmaceuticals, Inc., Edmonton, CAN

**Background**

Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, regulates multiple membrane-bound signal transduction pathways driving cancer cell biology. This modification is catalyzed by two N-myristoyltransferases (NMT), NMT1 and NMT2. Aberrant NMT expression has been identified in cancer cells and inhibition of myristoylation represents a novel anticancer treatment strategy. Zelenirstat (PCLX-001) is an oral, highly bioavailable, small molecule NMT inhibitor with strong affinity for both NMT1 and NMT2 proteins (IC<sub>50</sub> of 5nM and 8nM, respectively). *In vitro* hematologic cancer cell lines were exquisitely sensitive to zelenirstat. Zelenirstat regressed subcutaneous tumors in xenograft models derived from lymphoma cell lines, as well as in a refractory DLBCL patient (pt) derived xenograft model. Zelenirstat also demonstrated anticancer activity in multiple solid tumor xenograft models. Based on pre-clinical data, we conducted a phase I dose escalation trial to determine safety, tolerability, maximum tolerated dose (MTD), and pharmacokinetics (PK) of zelenirstat.

**Methods**

Pts with relapsed/refractory (R/R) B-cell lymphomas and advanced solid tumors were enrolled in a multicenter, open label, standard phase I dose escalation trial of once daily (OD) oral zelenirstat, administered in 28-day cycles until progressive disease or unacceptable toxicity. Seven dose levels were studied: 20 mg, 40 mg, 70 mg, 100 mg, 140 mg, 210 mg, and 280 mg. Dose limiting toxicity (DLT), attributable to zelenirstat during cycle 1, was defined as: grade (Gr) 4 thrombocytopenia, Gr 3 thrombocytopenia with bleeding, Gr 4 neutropenia  $\geq$  7 days, febrile neutropenia, clinically significant > Gr 3 non-hematologic toxicity, or any significant toxicity warranting a hold of zelenirstat. Plasma PK were obtained on C1D1, C1D15, and trough concentrations C1D2, C1D16 and prior to each subsequent cycle. Response assessments occurred every 2 cycles to determine best overall response.

**Results**

Between Sept 2021 and Jul 2023, 21 DLT-evaluable pts [4 R/R B-cell lymphoma (3 DLBCL, 1 FL grade 3b); 17 advanced solid tumor (7 colorectal, 2 pancreas, 2 ovarian, 1 each of sarcoma, NSCLC, pleural mesothelioma, melanoma, CUP, bladder)] received zelenirstat at doses ranging from 20 mg OD to 280 mg OD. Dose escalation occurred without DLT until the 280 mg cohort where two DLTs were reported: a bladder carcinoma pt who developed nausea, vomiting, and drug-induced fever necessitating a hold of zelenirstat and a colorectal cancer (CRC) pt who had Gr 3 dehydration from nausea, vomiting, diarrhea, and oral mucositis. The maximal administered dose was 280 mg OD and the presumptive MTD was 210 mg OD. Drug compliance was high, and of 3 pts within the 210 mg cohort, none required dose reduction. Common treatment-emergent all-grade adverse events (AEs) at doses up to the 210 mg cohort were gastrointestinal and reported in 29% of pts. These were primarily diarrhea, nausea, or vomiting. Gr 2 thrombocytopenia occurred in 17% of patients. No other AEs were seen at a frequency of > 5%. There were no AEs of neuropathy, alopecia, or QT interval prolongation. Noncompartmental PK analyses demonstrated rapid oral absorption, a terminal half-life of approximately 10 hrs, rapid achievement of steady state, and no induction of metabolism. Zelenirstat trough plasma concentrations at 100 mg, 140 mg, and 210 mg doses markedly exceeded the EC<sub>90</sub> required to inhibit cultured cancer cells. Stable disease as best response was seen in five patients (pancreas at 40

mg; CRC at 140 mg; and two ovarian and one CRC at 210 mg). At the 210 mg dose, one of the ovarian cancer pts had a corresponding reduction of CA-125 (20%) while the CRC pt had a reduction in CEA (50%).

### Conclusions

Zelenistat is safe and well tolerated up to the 210 mg OD dose, which we have established as the presumptive MTD. Additional pts, including a phase IIA study in pts with R/R B-cell NHL, are accruing at this dose for further safety and activity exploration. The absence of severe toxicities, attainment of plasma concentrations highly active in preclinical models, and early evidence of antitumor activity support the ongoing development of zelenistat for pts with R/R B-cell lymphomas and advanced solid tumors.

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