Abstract # 3579: A Phase 1b Study of Oral Chk1 Inhibitor LY2880070 as Monotherapy in Patients with Advanced or Metastatic Cancer

Wilson H. Miller, Jr.,[1] Quincy Chu,[2] Nathaniel Bouganim,[3] Derek Jonker,[4] Gerald Batist,[1] Najwa Buhlaiga,[3] Stephanie Lheureux,[5] Jennifer Spratlin,[6] Thierry Alcindor,[3] Patricia S. Smith,[7] Joel Owen,[8] Sara Zaknoen,[9] John R. Stille,[7] Caroline Fortier,[10] Darcy Vincett,[11] and Amit Oza[5]

For questions: caroline.fortier@esperasinc.com

Background

In the context of DNA damage, Checkpoint Kinase 1 (Chk1) mediates a checkpoint response which arrests the cell cycle and allows the cell to complete DNA repair and replication. LY2880070 (LY) is a selective adenosine triphosphate-competitive inhibitor of Chk1. Chk1 overexpression has been found in a variety of cancers. The safety of patients who are CYP2D6 poor metabolizers is an important consideration.

Objectives

Primary:

To determine the maximum tolerated dose (MTD) for multiple escalating oral doses of LY2880070 (LY) in patients with advanced or metastatic cancer.

Secondary:

To characterize the dose-limiting toxicities (DLTs), overall safety profile, pharmacokinetics (PK), and efficacy for LY.

Overall Study Design

This 3+3, 2-part, open-label, multi-center study explored the safety, PK, PD, and efficacy of LY in patients with advanced or metastatic cancers.

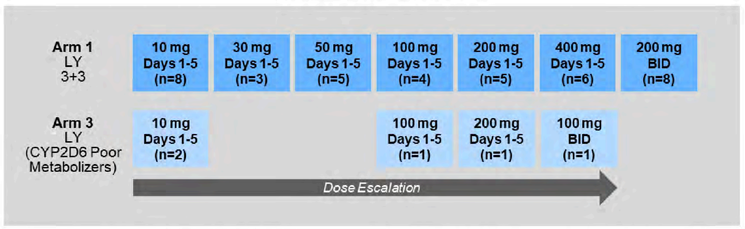
Part A: Patients receive LY in 21-day cycles in several multiple ascending dose (MAD) treatment arms:
- Arm 1: Dose (MAD) escalation of LY2880070
- Arm 2: Dose escalation of LY2880070 in combination with gemcitabine
- Arm 3: Dose escalation of LY2880070 in CYP2D6 poor metabolizers

Part B: Dose Confirmation in ovarian and pancreatic cancer patients
- LY2880070 in combination with gemcitabine

Tumor response was measured using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Patients continued receiving study treatments in 21-day cycles until disease progression, death, unacceptable toxicity, or start of a new anticancer treatment.

This poster describes the results from the Part A monotherapy treatment Arms 1 and 3.

Part A: Dose Escalation



Part B will begin after the LY+GEM recommended Phase 2 dose is established in Part A and will be conducted in patients with ovarian (N=15) and pancreatic (N=15) cancers.

Patient Population

44 patients with advanced or metastatic cancer (solid tumors) were enrolled. Median age was 61.0 years, 61.4% were female, 81.8% had an ECOG status of 1, and 63.6% had received ≥3 lines of prior therapy.

Results

Safety Evaluation

- All patients experienced at least one treatment emergent adverse event (TEAE). The most common TEAEs were: vomiting (65.9%), nausea (61.4%), fatigue (43.2%), decreased appetite (38.6%), constipation (36.4%), and diarrhoea (29.5%).
- 29.5% of patients experienced at least one treatment emergent serious adverse event (TESAE). The most common TESAEs were: pulmonary embolism (4.5%), sepsis (4.5%), and vomiting (4.5%).
- Dose limiting toxicities included supraventricular tachycardia (n=1; 10 mg, Days 1-5) and decreased platelet count (n=1; 200 mg, BID).

Summary

- Apparent linear pharmacokinetic parameters are observed over the dose range of 10 mg - 400 mg.
- $T_{1/2}$ for the median profile was found to be 5.35 ± 2.3 hours.
- Low accumulation is observed at steady-state, based on AUC and C_{max}.
  - Twice daily dosing achieved similar overall exposure ($AUC_{0\text{-}24h}$) with lower C_{max} as single daily equivalent dose.
- LY2880070 monotherapy appears safe and tolerable up to doses of 200 mg BID (MTD) with exposures exceeding the IC_{80} for ~6 hours and the IC_{50} for ~12 hours.
- Although the data are limited, the exposures in patients with CYP2D6 poor metabolizer status are consistent with those in patients with normal or intermediate metabolizer status.
- LY2880070 was well tolerated; most common adverse events were nausea, vomiting, and fatigue.
  - Nausea and vomiting were controlled with use of anti-emetics.
- The maximum tolerated dose for monotherapy was 200 mg LY2880070, BID, daily.

Conclusions

- LY was tolerated in a daily BID schedule.
- The toxicity profile can be modulated by changing the dosing frequency from QD to BID while administering the same daily dose.
- LY may be a potential combination therapy with DNA damaging agents.
- Oral formulation and short half-life allow customization of dose regimen.

Acknowledgements

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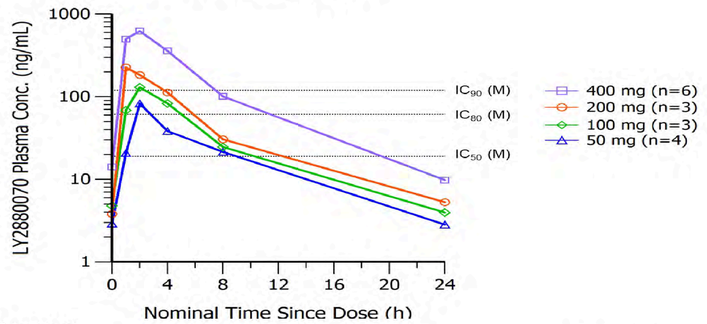
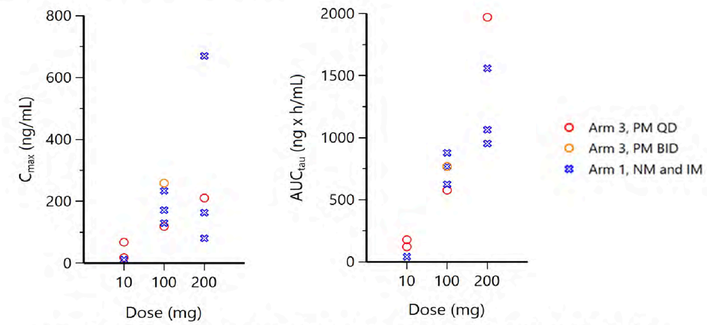
Steady-State Median Exposure Profile on Day 19



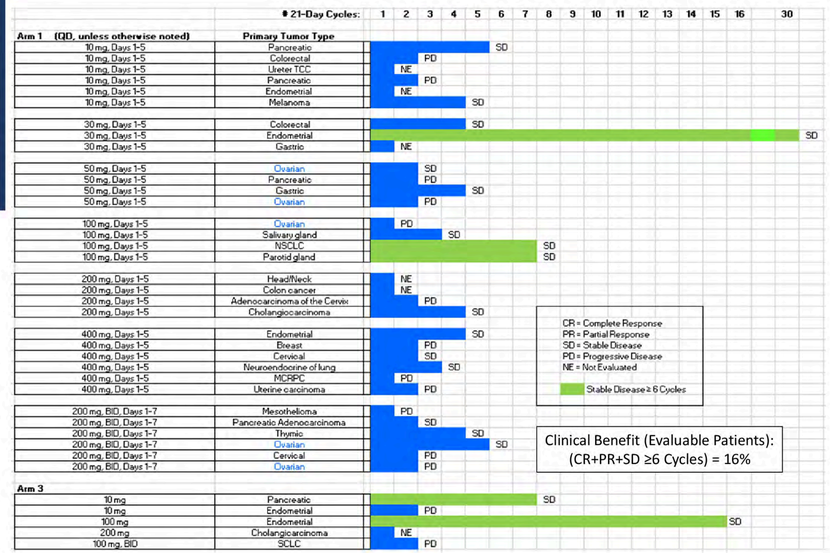
- PK Summary:
  - Apparent linear pharmacokinetics are observed over the dose range of 10 to 400 mg.
  - $T_{1/2}$ for the median profile was 5.35 ± 2.3 hours.
  - Essentially no accumulation upon once-daily multiple dosing.
- At Steady State, the 200 mg dose exceeds the:
  - IC_{80} for ~6 hours; IC_{50} for ~12 hours
- DLTs believed to be related to C_{max}; optimize AUC relative to C_{max} by dosing BID

Day 19 PK According to CYP2D6 Metabolizer Status



AUC_{tau}=area under the plasma concentration-time curve over a dosing interval (0-24h for QD, 0-12h for BID); BID=twice daily; C_{max}=maximum plasma concentration; IM=intermediate metabolizer; NM=normal metabolizer; PM=poor metabolizer; QD=once daily.

- 4 patients with poor metabolizer (PM) status received QD dosing in Arm 3; and one patient received 100 mg BID treatment.
- No apparent trend for clinically greater exposures in patients with PM status compared to patients with normal (NM) or intermediate metabolizer (IM) status.
- Limited PM data were available for assessment.



[1]Segal Cancer Center, Jewish General Hospital, Rossy Cancer Network, McGill University, [2]Cross Cancer Institute, University of Alberta, Edmonton, AB; [3]Department of Medical Oncology, McGill University Health Center, Montreal, QC; [4]Ottawa Hospital Research Institute, Ottawa, ON; [5]University Health Network, Princess Margaret Cancer Centre, Toronto, ON; [6]Alberta Health Services, Edmonton, AB; [7]Eli Lilly and Company, Indianapolis, IN; [8]Cognigen Corporation, Buffalo, NY; [9]Zed Strategic Consulting, Carlsbad, CA; [10]Esperas Pharma Inc, Quebec, Canada; [11]Ozmosis Research, Toronto, ON