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 malignancies.

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

Tumor response was measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 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

Arm 1

- 10 mg Days 1-5 (n=3)
- 30 mg Days 1-5 (n=3)
- 100 mg Days 1-5 (n=3)

Arm 3

- 100 mg Days 1-5 (n=3) in combination with gemcitabine
- 200 mg Days 1-5 (n=3) in combination with gemcitabine
- 400 mg Days 1-5 (n=3) in combination with gemcitabine
- 600 mg Days 1-5 (n=3) in combination with gemcitabine

Dose escalation of LY2880070 in CYP2D6 poor metabolizers

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 (36.5%), and diarrhea (29.5%).
- 49.5% of patients experienced at least one treatment-emergent serious adverse event (TESEA).
- The most common TESEAs were: pulmonary embolism (4.5%), sepsis (4.5%), and vomiting (4.3%).
- Dose-limiting toxicities included supratentorial brain edema (n=3, 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_{DD,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_{50} 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

- It was tolerated in a daily BID schedule.
- The toxicity profile can be modulated by changing the dosage 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

The authors wish to thank the many special patients, families of patients, and the site personnel for their participation in this study. We also acknowledge the contributions of Dr. Inger Darling (Cogignion Corporation) and Dr. John Polzer to the preparation of this poster.

Steady-State Median Exposure Profile on Day 19

Day 19 PK According to CYP2D6 Metabolizer Status

- 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 clinical drug exposures in patients with PM status compared to patients with normal (NM) or intermediate metabolizer (IM) status.
- Limited PM data were available for assessment.

References

1Segal Cancer Center, Jewish General Hospital, Rosy Cancer Network, McGill University, 2Cross Cancer Institute, University of Alberta, Edmonton, AB, 3Department of Medical Oncology, McGill University Health Center, Montreal, QC, Ottawa Hospital Research Institute, Ottawa, ON, 4University Health Network, Princess Margaret Cancer Centre, Toronto, ON, 5Alberta Health Services, Edmonton, AB, 6Lilly and Company, Indianapolis, IN, 7Cogignion Corporation, Buffalo, NY, 8MedStrategic Consulting, Carlbad, CA, 9Espera Pharma Inc, Quebec, Canada, 10Omnis Research, Toronto, ON