A Phase 1-2 clinical trial of EO1001, a novel irreversible pan-ErbB inhibitor with promising brain penetration

Helen Wheeler[1], Jeffrey Bacha[2], Sarath Kanekal[2], Ian Nisbet[3], Harry Pedersen[4], Neil Sankar[2], Wang Shen[2,5], Kathy Skoff[3], Wang Zhen Zhong[6], Dennis M. Brown[2,5]

[1]University of New South Wales, Northern Sydney Cancer Centre; [2]Edison Oncology Holding Corp.; [3]Senz Oncology; [4]NewGen Therapeutics, Inc.; [5]Valent Technologies LLC; [6]Jangsu Kanion Pharmaceutical Co. Ltd.

Background: CNS metastasis has become a prominent driver of morbidity and mortality in recent years as new targeted therapies have improved systemic outcomes. Mutations in the ErbB family of kinases are known oncodrivers in many of these cancers. ErbB family member "crosstalk" is associated with rapid development of acquired resistance to ErbB TKIs. The development of agents targeting multiple ErbB receptors has shown promise but has been limited by toxicity and poor brain penetration. **EO1001 is a first-in-class, oral, brain penetrating, irreversible pan-ErbB inhibitor with superior CNS penetration targeting ErbB1, ErbB2 and ErbB4. Preclinical data suggests a favorable pharmacokinetic and safety profile and promising activity against ErbB-driven cancers in patient-derived xenograft models.**

Table 1. EO1001 exhibits potent balanced activity against important ErbB targets, with high specificity vs. off-target receptors

Target	IC_{50} nM	Target	IC_{50} nM
ErbB1/EGFR	0.40	ABL1	113.80
ErbB2/HER2	4.18	BLK	21.43
ErbB4/HER4	2.08	JAK3	133.20
EGFR (d746-750)	2.62	LCK	45.40
EGFR (L858R)	0.39		
EGFR (T790M)	4.35		
EGFR (L858R/T790M)	7.42		

Fig1.Following oral administration, EO1001 treatment-resulted in a statistically significant improvement in outcomes compared to positive and negative controls in erbB-positive mouse orthotopic models of systemic and CNS tumors

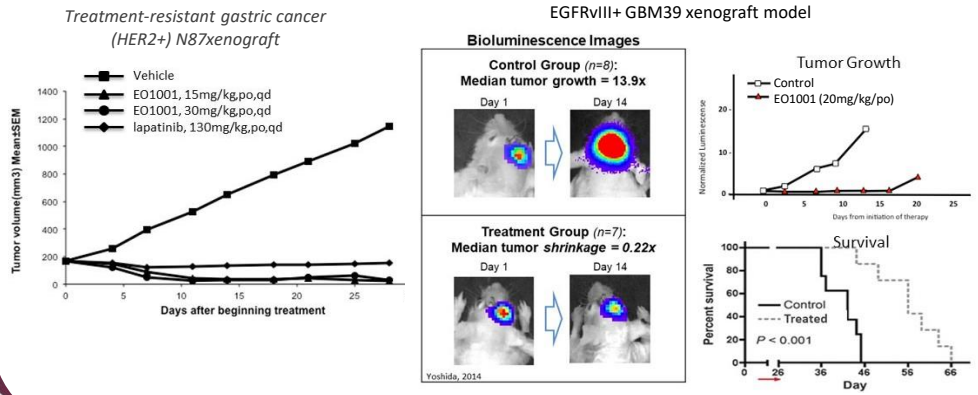
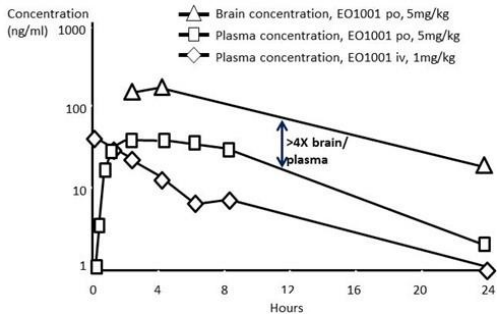


Table 2/Fig2. EO1001 rapidly enters the CNS following 5mg/kg dosing in rats and enters brain tumor tissue with long observed exposure vs. plasma



Concentration of EO1001 in GBM12 xenografts vs. plasma exposure following 5mg/kg daily oral dosing

Days post dosing	Concentration (ng/mL) Brain Exposure tumor	adjacent	Plasma Exposure
Day 33	***673***	*247*	468
Day 43	***216***	*187*	128
Day 57	***107***	*60*	92

Summary of repeat dose toxicity studies

(multiple ascending daily dose)

Observations in rat (14d dosing)

- No observed adverse event level (NOAEL): 5 mg/kg/day
- MTD: >5, <15 mg/kg/day
  - Mortality observed at 15 & 30 mg/kg/day
- Clinical observations at 15 & 30 mg/kg/day: Watery feces (diarrhea), ocular discharge (red), swollen (lip, nose), material around eyes and nose (red), emaciated, posture hunched & decreased activity.

Observations in beagle dog (28d dosing)

- No observed adverse event level (NOAEL): 1 mg/kg/day for 28 days
  - Control and low dose well tolerated, clinical signs equivalent between groups
- High Dose: 5mg/kg/day
  - Observed clinical signs included reversible GI tox typical of EGFR-targeting agents
- No observation of dermal toxicity in any group
- No treatment-related changes of organ weights in any group

EO1001 Phase 1/2 clinical trial (ANZCTR #12620000583943)

Male or female adult participants with confirmed ErbB-positive cancer, including patients with CNS involvement, who have progressed after standard of care therapy, with adequate bone marrow, renal and liver function are eligible.

INCLUSION CRITERIA

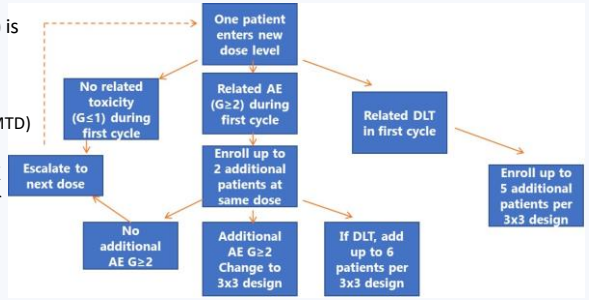
- Adult patients with confirmed ErbB (EGFR, HER2, HER4) positive cancer who have relapsed following approved therapies
- ECOG performance score of 0 or 1
- Measurable disease per RECIST 1.1
- Life expectancy greater than 3 months
- Adequate organ function and baseline hematology measurements
- For patients with CNS metastases: Stable per CT/MRI for a minimum of 4 weeks with stable or declining corticosteroid and/or anticonvulsant dose

EXCLUSION CRITERIA

- Active infection requiring systemic treatment;
- Serious illness or concomitant non-oncological disease
- Untreated or symptomatic brain metastases
- Unresolved adverse reactions to prior treatment
- Currently taking an investigational product or received an investigational product within the longer of 28 days or 5 half-lives
- Significant cardiovascular or other chronic medical risk at the judgment of the investigator

Study employs an accelerated dose-escalation design

- One subject per dose-cohort until drug-related toxicity (≥G2) is observed in the first dosing cycle
  - Minimizes sub-optimal drug exposures
  - Requires fewer subjects
  - Accelerates path to determining optimal dose for further study (MTD)
- Study reverts to 3+3 design after initial toxicity observation
- Each subject in Phase 1 will provide single and multi-dose PK
- Optional biomarker assessments at discretion of investigator



Phase 1: Dose Escalation

Days in a 28-day cycle: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 34 25 26 27 28 → Day 29 +

Day 1: Single Dose
- Baseline (pre-dose) assessments obtained including CNS scan and punch biopsy for base-line biomarker assessment
- Single dose pharmacokinetics

7-day pharmacology and safety monitoring period

Day 8 – 28: Once daily dosing
- First post-treatment radiologic assessment of tumor outcome by RECIST on Day 28
- Multi-dose pharmacokinetic assessment
- Biomarker assessment at day 28
- Safety and adverse events measured by NCI CTCAEv5
- *Enrollment of patients in next higher cohort allowed after day 28*
  - Escalating dose cohorts to determine maximum tolerated dose (MTD)

Day 29 + Continuous dosing in 28-day cycles for up to 24 weeks total
- Continued safety monitoring
- Tumor outcomes measured by RECISTv1.1 every two cycles

Outcome assessments:
- **Toxicity assessed based on NCI CCTCAEv5.**
- **Tumor response assessed by RECIST 1.1**
- **CNS exposure evaluated via CSF collection in subjects with confirmed CNS disease involvement**

Phase 2: Dose Expansion

- Oral EO1001 will be administered once daily at the MTD in continuous 28-day cycles for up to 24 weeks in up to 20 additional subjects