Phase 1 Dose Escalation of EO1001, an Oral Brain-Penetrating Pan-ErbB Inhibitor, in Advanced Cancer: Preliminary Results from an Ongoing Phase 1–2a Clinical Trial

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BACKGROUND

Central nervous system (CNS) metastases are a major cause of cancer-related morbidity and mortality, particularly as systemic therapies extend survival. Mutations in the ErbB/HER family of kinases are commonly associated with CNS progression in multiple malignancies. EO1001 is a novel, oral, blood brain-penetrating, irreversible pan-ErbB inhibitor targeting EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4). In preclinical models, EO1001 rapidly enters the CNS, achieving concentrations exceeding those in plasma, effectively inhibiting downstream ErbB signaling and improving outcomes compared to controls in orthotopic, ErbB-positive tumor models, including N87 (HER2+), H1975 (EGFR/T790M), GBM12 (EGFR+), and GBM39 (EGFRvIII+). Here, we report initial results from the Phase 1 dose escalation portion of an ongoing Phase 1–2a trial in patients with advanced solid tumors, including those with CNS involvement.

STUDY OBJECTIVES

Primary Objective

- **Evaluate the safety and tolerability** of once-daily EO1001 in patients with advanced or metastatic ErbB-positive solid tumors.

Secondary Objectives

- **Define the Recommended Phase II Dose (RP2D)** based on safety, tolerability, and dose-limiting toxicities.
- **Characterize the pharmacokinetic (PK) profile** of EO1001 following single and multiple dosing.
- **Assess preliminary antitumor activity** using RECIST 1.1 and/or RANO (as appropriate for tumor type).
- **Evaluate exploratory biomarkers** (e.g., EGFR, p-EGFR, HER2, p-MAPK, p-Akt, Ki-67, p27KIP1, Exon20 insertions) in available skin and tumor biopsies (Tier 2) as pharmacodynamic indicators of response.

Exploratory Objectives

- **Explore PK differences across clinical subgroups**, including:
  - East Asian vs. non-East Asian participants
  - Male vs. female participants

STUDY DESIGN

Phase 1–2a, first-in-human, open-label, multi-centre trial evaluating ascending single and multiple doses of **EO1001**, an oral, irreversible pan-ErbB inhibitor with demonstrated CNS penetration.

Two-stage design:

- **Tier 1a — Accelerated Dose Escalation:**
  One patient per cohort until the first ≥Grade 2 treatment-related AE is observed during Cycle 1.
- **Tier 1b — Standard 3+3 Escalation:**
  Transition from accelerated design to 3+3 once a ≥Grade 2 related AE occurs.
  First two patients per cohort are dosed ≥24 hours apart.
  Intra-patient dose escalation allowed after completion of DLT window and SRC approval.
- **Tier 2 — MTD Expansion:**
  Up to **20 patients** treated at the established **MTD/RP2D** for enhanced safety, PK, PD, and early efficacy characterization.

Dosing Schema:

- **Single-dose PK day 1**, followed by **21 days of continuous once-daily dosing** in Cycle 1.
  Subsequent 28-day cycles through Week 24; ongoing treatment allowed via extension protocol if no progression or DLT.
- **Planned Dose Levels:**
  2.5 mg → 10 mg → 20 mg → 30 mg → 50 mg → 70 mg → 90 mg → 120 mg → 160 mg once daily.

Key Assessments:

- **Safety/AE monitoring** and **DLT evaluation** (first 21 days of continuous dosing).
- **Serial PK sampling** after single-dose and multi-dose administration.
- **Radiologic tumor response** at Weeks 8, 16, and 24 (RECIST 1.1 or RANO).
- **Biomarker analyses** (Tier 2), including skin/tumor biopsies and optional CSF sampling to assess CNS penetration.

Target Enrollment:

- Up to **50 evaluable patients** with advanced ErbB-driven cancers (including CNS involvement).

PATIENT POPULATION

Nineteen (19) adult subjects with ErbB expressing cancers having failed at least one prior line of therapy were enrolled in across seven (7) escalating dose cohorts (2.5mg q.d. – 90mg q.d)

Table 1: Patient Demographics

Characteristic	Total (N=19)		
Age, years		**Primary Tumor Type**	
Median (range)	57 (30-80)	GBM	4 (21.0%)
<65	13 (68.4%)	Colorectal	2 (10.5%)
≥65	6 (31.5%)	Ovarian (HGSOC)	2 (10.5%)
Sex		Cervical	2 (10.5%)
Male	10 (52.6%)	Other solid tumor	9 (47.4%)
Female	9 (47.4%)	**ErbB Alteration**	
ECOG Performance Status		EGFR	8 (42.1%)
0	10 (52,6%)	amplification	5 (26.3%)
1	9 (47.4%)	19 del, L858R, etc.	2 (10.5%)
2	0 (0.0%)	EGFR Exon20 ins	1 (5.2%)
		HER2	11 (57.8%)
		HER4	0 (0.0%

SAFETY OBSERVATIONS

- EO1001 was generally well tolerated across 2.5–90 mg q.d., with mostly Grade 1–2 GI and dermatologic AEs, consistent with known class effects of ErbB inhibitors.
- Most common TEAEs: diarrhea (78.9%), rash (63.2%), and fatigue/acneiform rash/constipation (36.8%), largely low grade.
- Dose-limiting toxicity was diarrhea, occurring in 1 patient at 70 mg and 2 patients at 90 mg.
- Grade ≥3 AEs were uncommon, limited to isolated cases of G3 rash, infection, and mucositis at higher doses.
- AEs were generally reversible upon withdrawal of treatment ("drug holidays").

Table 2: Treatment Emergent Adverse Events (TEAE) occurring in ≥20% of enrolled subjects in the dose escalation phase

Observed TEAE	N = 19 total enrolled	Safety Observations Across Escalating Dose Cohorts			
		2.5 – 30 mg q.d. (4 subjects)	**50mg q.d.** (3 subjects)	**70mg q.d.** (10 subjects)	**90 mg q.d.** (2 subjects)
Diarrhoea/loose stool	15 (78.9%)	G1 (N=3)	G1 (N=1); G2 (N=1)	G1 (N=3); G2 (N=3); G3 (N=1); G4* (N=1)	G3* (N=2)
rash	12 (63.2%)	G1 (N=2)	G1 (N=2); G2 (N=1)	G1 (N=6)	G2 (N=1)
acneform rash	7 (36.8%)	G1 (N=1)	G2 (N=1)	G1 (N=1); G2 (N=2): G3 (N=1)	G1 (N=1)
constipation	7 (36.8%)	G1 (N=2)	G1 (N=2)	G1 (N=2)	G1 (N=1)
tired/fatigue/lethargy	7 (36.8%)	G1 (N=2); G2 (N=1)	G2 (N=2)	G1 (N=1)	G1 (N=1)
nausea	5 (26.3%)	G1 (N=1)	G1 (N=1); G2 (N=1)	Nil	G1 (N=2)
infection	4 (21.1%)	G1 (N=1)	G3 (N=1)	G1 (N=1); G2 (N=1)	Nil
mouth ulcers	4 (21.1%)	Nil	Nil	G1 (N=2); G2 (N=1)	G3 (N=1)
mucocitis	4 (21.1%)	nil	Nil	G1 (N=2); G3 (N=1)	G2 (N=1)

**Dose Limiting Toxicity (DLT) per protocol*

PHARMACOKINETICS

- Dose-proportional exposure observed across the escalation range, with EO1001 showing predictable increases in AUC and Cmax with increasing dose.
- Higher-than-projected Cmax values were seen at 70 mg and 90 mg, aligning with emerging toxicity at these dose levels.
- PK exposures at 50 mg q.d. correspond closely with preclinical observations and efficacy targets, supporting 50 mg as a biologically active dose.
- CSF samples were not collected in the dose escalation phase. Samples from the Phase 2 expansion cohort will be analyzed as a surrogate for brain tissue exposure.

Table 3: Pharmacokinetic Observations

Dose level (No. patient analyzed)	10mg (1)	20mg (1)	30mg (1)	50mg (2)	70mg (6)	90mg (2)
Proportional increase vs. previous level	N/A	2.0x	1.5x	1.67x	1.4x	1.3x
C_{max} Mean (ng/mL)	4.23	6.97	8.58	13.32	25.77	68.15
Increase over previous level[1]	N/A	1.66x	1.23x	1.56x	1.93x	1.75x
AUC_{last} Mean (hr*ng/mL)	50.63	141.41	165.24	229.47	500.96	861.32
Increase over previous level[1]	N/A	2.80x	1.17x	1.34x	2.18x	1.53

Figure 1: *Single-dose Pharmacokinetics*

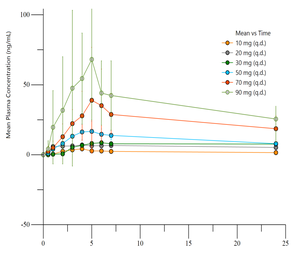


Figure 2: *AUC and Cmax vs. Dose*

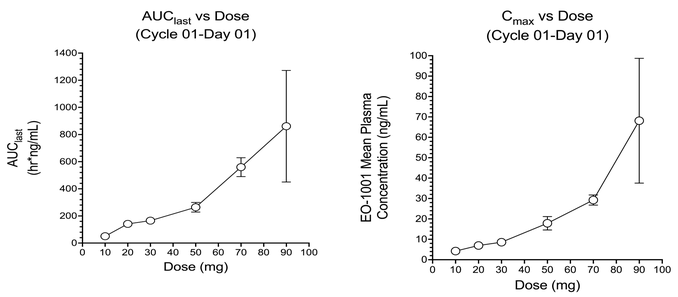


Figure 3: *Plasma/Brain pharmacokinetics after EO1001 single- dose (5mg/kg) oral administration in rat*

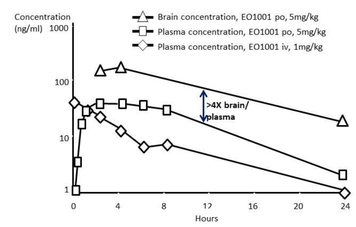
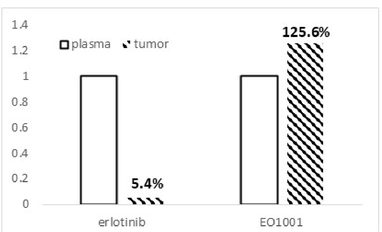


Figure 4: *Relative exposure of erlotinib vs. EO1001 in plasma and brain tumor tissue following daily oral dosing for 3 days*



CNS Exposure (preclinical observations)

Prior nonclinical studies demonstrate that EO1001 achieves rapid and efficient brain penetration, with brain:plasma ratios exceeding 4:1 within hours of oral dosing. In EGFR-positive GBM12 intracranial xenograft models, EO1001 accumulates in tumor tissue at levels >20-fold higher than erlotinib, yielding tumor:plasma exposure of 125% vs. 5.4%, respectively. EO1001 also shows prolonged retention within tumor tissue, maintaining concentrations 2–7× higher than adjacent brain regions for up to 24 days after dosing, supporting durable pharmacologic activity in CNS tumor models.

PRELIMINARY OBSERVATIONS OF EFFICACY

- Across patients treated at ≥50 mg q.d., 10 of 14 evaluable subjects completing ≥2 cycles achieved stable disease (SD) or partial response (PR), including three PRs, one of which was achieved in a patient treated under the extension protocol, demonstrating consistent early clinical activity.
- Five patients from the dose-escalation phase continued treatment in the extension protocol due to prolonged disease control, highlighting durability of effect in heavily pretreated tumors.
- Objective tumor shrinkage (PR) has been observed at doses ≥50 mg q.d. in multiple ErbB-positive malignancies (e.g., HER2-amplified esophageal cancer, EGFR-driven head & neck cancer), confirming early antitumor activity across tumor types.
- Multiple recurrent glioblastoma (GBM) patients with EGFR extracellular domain (ECD) alterations—including EGFRvIII as well as other common ECD variants such as A289V/D/T—experienced prolonged SD, suggesting CNS penetration (CSF PK analysis ongoing) and intracranial biological activity across a spectrum of EGFR ECD subtypes.
- Several patients demonstrated meaningful clinical benefit beyond radiographic response, including improved cancer-related symptoms and functional status (e.g., wound healing, reduced analgesic requirement), supporting a broader therapeutic effect.
- Evidence of disease control and tumor shrinkage has been observed across diverse ErbB-positive cancers, including gastric, junctional, ovarian, cervical, colorectal, bladder, and GBM, indicating a broad spectrum of activity.

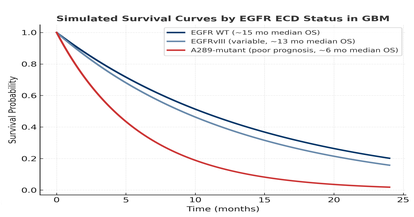
CONCLUSIONS AND NEXT SETPS

- Dose expansion at 50 mg and 70 mg q.d. is ongoing to further define the safety, pharmacokinetics, and antitumor activity of EO1001 at biologically active dose levels.
- EO1001 has demonstrated early clinical benefit (SD and/or PR) across multiple ErbB-positive tumors, including GBM patients with EGFR extracellular domain (ECD) mutations such as A289 variants and EGFRvIII, supporting therapeutic potential in genetically defined CNS malignancies.
- Five patients from the dose-escalation phase continued treatment in the extension protocol, reflecting durable disease control and patient benefit in heavily pretreated cancers.
- Planned translational and non-clinical studies will further characterize EO1001 activity across ErbB molecular subtypes, including GBM-prevalent ECD mutations, and will integrate emerging PK/PD and biopsy-based biomarker data to refine mechanistic understanding and dose selection.

EGFR ECD Mutations are associated with poor patient outcomes in GBM

- Multiple investigators report that specific EGFR ECD missense hotspots—especially A289D/T/V (and, to a lesser extent, R108 and G598)—are associated with shorter overall survival in GBM.
- EGFR ECD variants were observed to be both erlotinib and osimertinib insensitive
- Mechanistically, these ECD variants drive ligand-independent activation and a more invasive phenotype in preclinical models.
- *By contrast, the ECD deletion variant EGFRvIII is not consistently an independent adverse prognostic factor across large IDH-wildtype GBM cohorts.*

Alteration	Reported Clinical Association	Notes
A289D/T/V (ECD missense)	Shorter OS vs ECD-WT	Enriched with EGFR amplification; invasive phenotype in models
R108 / G598 (ECD missense)	Trend toward worse outcomes (cohort-dependent)	Less frequent than A289; activating
EGFRvIII (ECD deletion)	No consistent independent adverse effect	Oncogenic, but prognostic impact varies by cohort



Simulation based on median OS from Binder et al., Cancer Cell 2018; Frontiers in Oncology 2022; TCGA/IDH-wt GBM cohorts.

Selected References
1) Binder ZA et al. Cancer Cell (2018): EGFR ECD A289 hotspot confers invasiveness and associates with worse OS in GBM.
2) T.K.Hayes, et al Nature Communications (2024) 15:2742
3) Frontiers in Oncology (2022) Review of EGFR alterations in GBM, including ECD missense biology.
4) TCGA / IDH-wildtype GBM cohorts (2013–2021) – EGFR landscape; EGFRvIII not consistently independently prognostic.
5) Clinical ctDNA/tissue series summarizing ECD hotspots (A289/R108/G598) and outcome associations

Thank you to our collaborators and the patients and families who have contributed to this work