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BOREALIS-1: Phase 1, first-in-human, open-label, multicenter study of ERAS-4001 safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy in patients with advanced solid tumors with KRAS alterations

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Objectives (BOREALIS-1 Part 1)

Primary

- Identify the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of ERAS-4001 monotherapy in adults with advanced solid tumors with RAS/MAPK alterations
- Evaluate the safety and tolerability of ERAS-4001 monotherapy
- Characterize the single-dose and repeat-dose pharmacokinetic (PK) profile of ERAS-4001 monotherapy

Secondary

- Evaluate the preliminary antitumor activity of ERAS-4001 monotherapy

Introduction

- Approximately 18% of all human cancers contain *KRAS* mutations[1]
- Cancers with the greatest prevalence of *KRAS* mutations include:
  - Pancreatic ductal adenocarcinoma (PDAC): 90%
  - Colorectal cancer (CRC): 45%
  - Non-small cell lung cancer (NSCLC): 34%
- The RAS/MAPK pathway (Figure 1) is involved in cell proliferation, migration, and survival[1]
- Aberrant RAS/MAPK signaling is a fundamental mediator of tumor development and progression across human cancer and represents a critical target for precision oncology[1]
- A continued need exists for novel approaches targeting this critical oncogenic pathway

Figure 1. RAS/MAPK Pathway



AE, adverse event; **Chemo**, chemotherapy; **CNS**, central nervous system; **CRC**, colorectal cancer; **CT**, computed tomography; **DLT**, dose-limiting toxicity; **ECOG**, Eastern Cooperative Oncology Group; **G12X-R**, G12X mutations except for G12R; **GAP**, GTPase-activating protein; **GDP**, guanosine diphosphate; **GEF**, guanine nucleotide exchange factor; **gem**, gemcitabine; **GI**, gastrointestinal; **GTP**, guanosine triphosphate; **IO**, immunotherapy; **mets**, metastases; **MRI**, magnetic resonance imaging; **MTD**, maximum tolerated dose; **NA**, not applicable; **NCI CTCAE**, National Cancer Institute Common Terminology Criteria for AEs; **NSCLC**, non-small cell lung cancer; **P**, phosphate; **PDAC**, pancreatic ductal adenocarcinoma; **PET-CT**; positron emission tomography computed tomography; **PK**, pharmacokinetic; **QD**, once daily; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases; **RDE**, recommended dose for expansion; **RECIST**, Response Evaluation Criteria in Solid Tumors; **RTK**, receptor tyrosine kinase; **SHP2**, src homology 2 domain-containing phosphatase 2; **SOC**, standard of care; **SRC**, Safety Review Committee.

References

1. Riedl JM, et al. *Cancer Cell*. 2026;44(3):471-97. **2.** Bae JH, et al. Poster presented at AACR 2025; abstract 4367.

Acknowledgments

Study sponsored by Erasca, Inc.

Writing and editorial assistance was provided by Stephan Lindsey, PhD, of Peloton Advantage, LLC, an OPEN Health company, and was funded by Erasca, Inc.

Disclosures

Shiraj Sen has a consulting or advisory role with Bayer and Guardant Health and received travel, accommodations, or expenses from Bayer and Guardant Health.

Background

- **ERAS-4001 is a novel, orally bioavailable, small-molecule pan-KRAS inhibitor that inhibits KRAS in both the GDP and GTP states**
- **ERAS-4001 selectively inhibits KRAS G12X mutants and wild-type KRAS with single-digit nanomolar potency[2]**
- **Oral administration of ERAS-4001 100 mg/kg twice daily demonstrated significant antitumor activity in KRAS G12D and G12V mutant subcutaneous xenograft models[2]**
- **ERAS-4001 in combination with an anti–PD-1 immune checkpoint inhibitor or cetuximab displayed robust tumor growth inhibition in vivo in KRAS-driven mouse tumor models[2]**
- **BOREALIS-1 (NCT07021898) is a first-in-human, phase 1, open-label, multicenter clinical trial of ERAS-4001 as monotherapy (part 1) and in combination with other cancer therapies (part 2) in adults with advanced solid tumors with RAS/MAPK alterations**

Methods

Endpoints (BOREALIS-1 Part 1)

1 Primary

- Incidence of dose-limiting toxicities (DLTs)
- Incidence of treatment-emergent AEs, treatment-related AEs, and changes from baseline in safety assessments
- Plasma concentrations and derived PK parameters

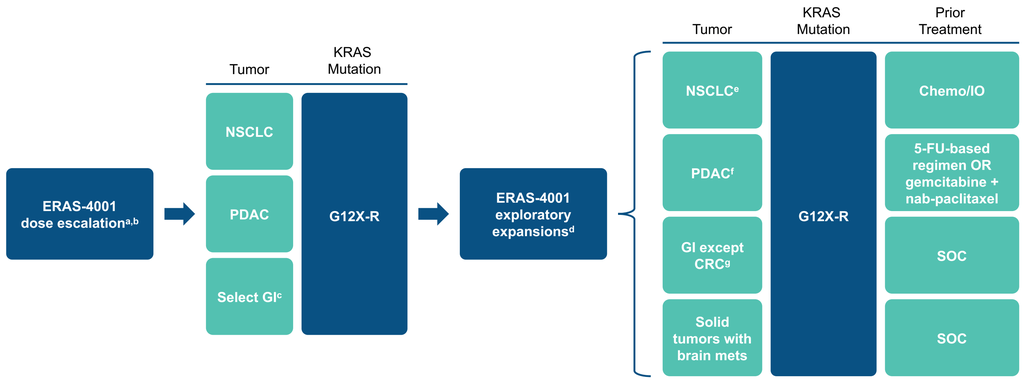
2 Secondary

- Objective response rate
- Duration of response
- Progression-free survival
- Disease control rate
- Time to response

Assessments

- MTD and/or RDE identified during dose escalation will be used
  - Not all cohorts will be opened simultaneously
  - Some cohorts may be delayed or stopped prior to ≈20 participants
- RDE-1 and RDE-2 will be evaluated either simultaneously via 1:1 randomization (n≈20/dose/cohort) or sequentially with RDE-1 assessed first and RDE-2 assessed if a signal of potential benefit is found with RDE-1
- Tumor assessments will be performed during screening; on-treatment assessments will be performed every 6 weeks for the first 6 months, every 9 weeks for the rest of year 1, then every 12 weeks thereafter. Participants who discontinue treatment for reasons other than radiographic progression will continue with disease assessments until progression
- All sites of disease will be assessed by imaging (eg, CT, MRI, PET-CT) or measurement (with ruler or calipers) by photographs
- Participants with select tumor types (ie, NSCLC) must have brain imaging (preferably contrast-enhanced MRI) at screening
- RECIST v1.1 will assess sites of disease in all cohorts except the Brain Metastases Exploratory Efficacy Expansion Cohort, for which RANO-BM will assess CNS disease and RECIST v1.1 will assess non-CNS disease

Figure 2. BOREALIS-1 Part 1 Study Design



Part 1 consists of an ERAS-4001 monotherapy dose escalation portion (estimated enrollment, n=130) leading to evaluation of the monotherapy in exploratory efficacy signal–seeking expansion cohorts (estimated enrollment, n=160)

[a]Rolling 6 design, ability to backfill cohorts, ≈20 patients/dose. [b]Exposed to prior SOC or for which no SOC exists. [c]CRC, cholangiocarcinoma, gall bladder carcinoma. [d]≈15-20 patients/cohort. [e]Patients with NSCLC could be pretreated with immune checkpoint inhibitors or platinum-based therapies; some patients were also pretreated with a RAS-G12C inhibitor. [f]Patients could be pretreated with a 5-fluorouracil–based regimen or gemcitabine. [g]Esophageal, gastric, gastroesophageal, small bowel, cholangiocarcinoma, gall bladder, appendiceal, anal.

Table 1. Eligibility Criteria (BOREALIS-1 Part 1)

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Willing and able to provide written informed consent • Pathological documentation of tumor type and mutation prior to first dose of study drug • Locally advanced or metastatic PDAC, CRC, cholangiocarcinoma, gall bladder carcinoma, or NSCLC that has been exposed to SOC therapy or for which no standard therapy exists • Must have a KRAS G12X-R mutation • ECOG performance status 0 or 1 • Presence of ≥1 measurable lesion according to RECIST v1.1 • Adequate bone marrow and organ function	• Prior therapy with a RAS inhibitor • Treatment with the following prior to first dose of study drug (within stated time frames): – Radiation (≤4 weeks) or limited field radiation for palliation (≤2 weeks) – Small-molecule therapies, immunotherapy, chemotherapy, locally directed agents, other investigational agents (≤4 weeks or 5 half-lives) – Cytotoxic agents with delayed toxicity (≤6 weeks) • Interstitial lung disease, history of pneumonitis • Uncontrolled pleural, pericardial effusion; ascites • Impairment of GI function or GI disease • Primary CNS tumor, symptomatic neurologically unstable CNS metastases • Cardiac disease or cardiac repolarization abnormality

Safety and Tolerability

- Participants will be monitored for toxicity while on study treatment
- Toxicity will be assessed using NCI CTCAE v5.0
  - AE reporting will begin on cycle 1 day 1 and continue throughout treatment and up to 30 days after the last dose or until a subsequent anticancer treatment is administered, whichever comes first
- If a participant experiences toxicity, dose administration may be modified (eg, interruption, reduction, permanent discontinuation)
- All concomitant medications and therapies will be documented at screening and every clinic visit

PK Assessment

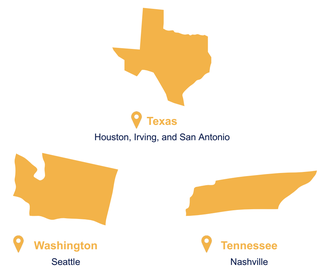
- Blood samples will be collected for PK analysis of ERAS-4001, according to the following PK sampling scheme:
  - Cycle 1 days 1 and 15: Predose and 1, 2, 3, 4, 6, and 8 hours postdose
  - Cycle 1 days 2 and 8: Predose
  - Cycles 2 and 3 days 1 and 15: Predose and 2 hours postdose
- The PK analysis population includes participants who received ≥1 dose of ERAS-4001 and have ≥1 measurable plasma concentration collected postdose

Dose Escalation

- ERAS-4001 will be initially administered once daily in 3-week cycles at a starting dose of 20 mg
- A Rolling 6 design will be used to guide dose escalation

Trial Status and Locations

- BOREALIS-1 is currently active and recruiting patients
- BOREALIS-1 is being conducted at 5 locations in the United States



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Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; October 23–27, 2026; Madrid, Spain