Increased Preclinical Activity by KEAP1/NRF2 mutations are associated with enhanced sensitivity to telaglenastat.

**BACKGROUND**

- Mutational activation of the KEAP1-NRF2 pathway occurs in >20% of NSCLC patients.
- In non-squamous NSCLC patients receiving standard-of-care (SOC; pembrolizumab/platinum/pemetrexed), KEAP1 mutations were associated with poor outcomes (median OS: 7.8 vs. 20.4 months for KEAP1+, P=0.0021).
- KEAP1/NRF2 activation protects tumors from oxidative stress and promotes tumor growth/survival (Fig. 1).
- Upregulated NRF2 in these tumors results in increased dependence on glutamine (GLS) conversion of glutamate to glutathione due to expression of genes required for glutathione metabolism and transport.

**RATIONALE FOR TELAGLENASTAT IN KEAP1/NRF2-MUTATED NSCLC**

- Telaglenastat is an investigational, first-in-class, potent, oral GLS inhibitor that has shown encouraging efficacy and activity in several cancers when combined with targeted agents, checkpoint inhibitors, and chemotherapy.

**Methods**

- Telaglenastat is active against many NSCLC cell lines, particularly those bearing KEAP1 or NRF2 mutations (Fig. 2A), selectively inhibits KEAP1+ tumor growth in vivo (Fig. 2B), and synergizes with anti-PD-1 inhibition.

**Figure 1. KEAP1/NRF2 mutations are associated with enhanced sensitivity to telaglenastat.**

**Figure 2. KEAP1/NRF2 mutations are associated with enhanced sensitivity to telaglenastat**

**Figure 3. KEAPSAKE Study Design**

**KEY ELIGIBILITY CRITERIA**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td><strong>Screening</strong></td>
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<tr>
<td>• Documented histological or cytological diagnosis of nonsquamous NSCLC</td>
<td>• Squamous cell histology and mixed histology tumors with any small cell component</td>
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<td>• Stage IV (M1a, M1b, M1c) disease not previously treated with systemic therapy for metastatic NSCLC</td>
<td>• Active concomitant disease requiring systemic treatment in last 2 years and/or history of significant untreated disease within past 3 years</td>
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<td>• ECOG PS 0-1</td>
<td>• Radiation therapy to the lung &gt;30 Gy within 6 months of randomization</td>
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<td>• No known actionable mutation in EGFR, ALK, ROS1, BRAF, NTRK, or other known actionable mutation for which there is approved therapy</td>
<td>• Concurrent chronic systemic steroid use (&gt;10 mg equivalent of prednisone) or other immunosuppressive drug</td>
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<td>• Measurable disease (RECIST v1.1)</td>
<td>• Pump inhibitor (mechanism) within 3 days of randomization</td>
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<td>• Enroll in KEAP1 or NRF2 mutations from a COP-accredited and/or CLIA-certified laboratory and STK11/LKB1 mutation status is known for the purpose of stratification</td>
<td>• Major surgery within 3 weeks or 2 days before withdrawal of SOC therapy</td>
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<td>• Adequate hepatic, renal, cardiac, and hematologic function</td>
<td>• Prior severe hypersensitivity reaction to other monoclonal antibody</td>
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<td>• No history of other malignancy (other than nonmelanoma skin cancer)</td>
<td>• Active and/or untreated CMS metastasis</td>
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**SUMMARY**

- Telaglenastat is an investigational, first-to-class, potent, oral inhibitor of glutaminase (GLS, responsible for controlling glutamine utilization) that has shown encouraging activity and manageable tolerability across many cancer types in combination with multiple agents.
- KEAP1 mutations are associated with reduced survival and poor outcomes in patients with nonsquamous NSCLC treated with standard-of-care therapy
- The KEAPSAKE Study is a randomized controlled phase 2 clinical trial
  - Telaglenastat (or placebo) in combination with pembrolizumab, carboplatin, and pemetrexed
  - First-line therapy for patients with KEAP1- or NRF2 mutated, non-squamous metastatic NSCLC
- Primary endpoint: Safety and Investigator-assessed PFS
- Study will open to enrollment in July 2020

**Findings of this novel NGS biomarker-selected study will inform the efficacy and safety profile of telaglenastat + standard-of-care chemoimmunotherapy for 1L treatment of metastatic KEAP1/NRF2-mutated, non-squamous NSCLC

**REFERENCES:**


**ACKNOWLEDGMENTS:** We thank the patients and families for their contributions, and coordination for participation in the study. The authors thank Calithera Biosciences for financial support.