KEAPSAKE Trial-in Progress: A Phase 2 Randomized Study of Telaglenastat, a Glutaminase (GLS) Inhibitor, vs. Placebo, in Combination w/ Pembrolizumab (Pembro) and Chemotherapy as First-Line Treatment for KEAP1/NRF2-Mutated Non-Squamous Metastatic Non-Small Cell Lung Cancer (mNSCLC)

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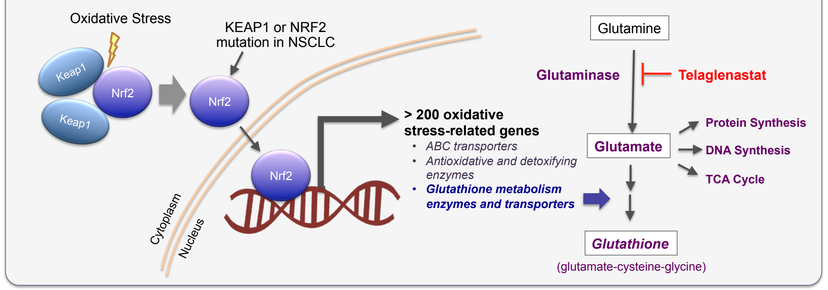
BACKGROUND

Mutational Activation of the KEAP1-NRF2 Pathway in Non-Small Cell Lung Cancer (NSCLC)

- Mutational activation of the KEAP1/NRF2 pathway occurs in >20% of NSCLC patients[1]
- 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^{WT}; *P*=0.002)[2]
- KEAP1/NRF2 activation protects tumors from oxidative stress and promotes tumor growth/survival (**Fig. 1**)[3]
- Upregulated NRF2 in these tumors results in increased dependence on glutaminase (GLS) conversion of glutamine to glutamate due to higher expression of genes required for glutathione metabolism and transport[4]

Figure 1. Mutational activation of the KEAP1-NRF2 pathway protects tumor cells from oxidative stress but have increased dependence on glutaminase-dependent pathways[3,4]

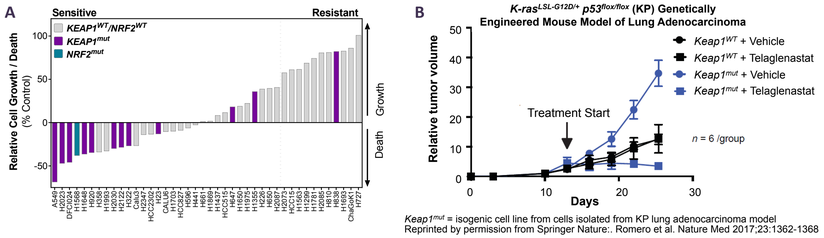


Rationale for Telaglenastat (CB-839) in KEAP1/NRF2-Mutated NSCLC

Increased Preclinical Activity by Telaglenastat in NSCLC Models with KEAP1 or NRF2 Mutations

- Telaglenastat is an investigational, first-in-class, potent, oral GLS inhibitor that has shown encouraging safety and activity in several cancers when combined with targeted agents, checkpoint inhibitors, and chemotherapy[5-9]
- Telaglenastat is active against many NSCLC cell lines, particularly those bearing KEAP1 or NRF2 mutations (**Fig. 2A**), selectively inhibits KEAP1^{mut} tumor growth *in vivo* **(Fig. 2B),** and synergizes with anti-PD-1 inhibition[10,11]

Figure 2. KEAP1/NRF2 mutations are associated with enhanced sensitivity to telaglenastat[10,11]



Keap1^{mut} = isogenic cell line from cells isolated from KP lung adenocarcinoma model
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Clinical Benefit With Telaglenastat + Nivolumab in NSCLC Patients with KEAP1 Mutation

- In an ongoing phase 1/2 study of telaglenastat + nivolumab in patients with late-line NSCLC who progressed on PD-(L)1 inhibitors, *KEAP1* and/or *KRAS* mutations were associated with higher clinical benefit rate and longer median iPFS than those without (**Table 1**)[9,10]

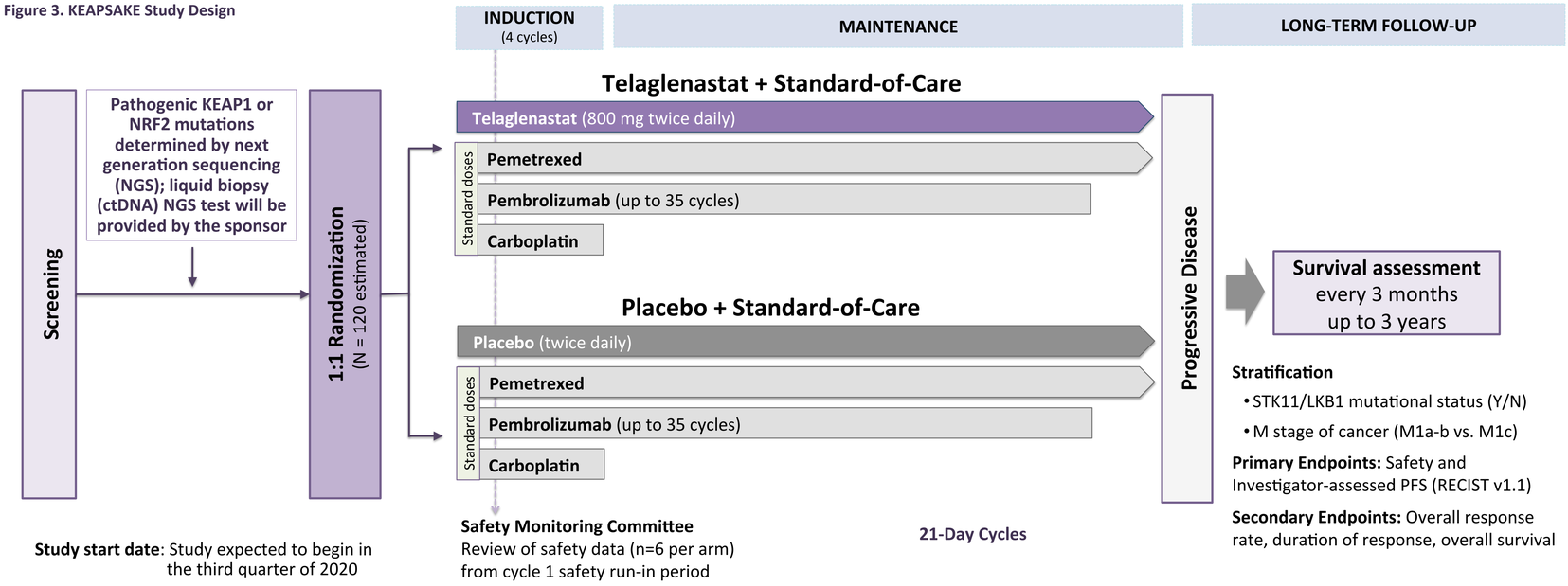
Table 1. *KEAP1^{mut}* associated with improved outcomes

Mutation	Clinical Benefit Rate[a]		Median iPFS[b] (months)	
	Mutation	Wild-type	Mutation	Wild-type
KEAP1	3/4 (75%)	2/13 (15%)	6.4	3.7
KEAP1+KRAS	2/2 (100%)	1/8 (13%)	7.2	3.7
KRAS	3/8 (38%)	2/10 (20%)	4.5	3.7
All Patients	6/22 (22%)		3.7	

[a]CBR = CR + PR + SD per either RECIST or immune RECIST criteria for at least 4 months
[b]Progression-free survival determined using modified RECIST 1.1 for immune-based therapeutics (iRECIST)[12]

KEAPSAKE STUDY DESIGN (NCT04265534)

Figure 3. KEAPSAKE Study Design



KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
Screening	*Screening*
• Documented histological or cytological diagnosis of nonsquamous NSCLC	• Squamous cell histology and mixed histology tumors with any small cell component[b]
• Stage IV (M1a-c, AJCC 8th Edition) disease not previously treated with systemic therapy for metastatic NSCLC[a]	• Active autoimmune disease requiring systemic treatment in past 2 years and/or history of malignancy within past 3 years[c]
• ECOG PS 0-1	• Radiation therapy to the lung >30 Gy within 6 months of randomization
• No known actionable mutation in EGFR, ALK, ROS1, BRAF, NTRK, or other known actionable mutation for which there is approved therapy	• Concurrent chronic systemic steroids (>10 mg equivalent of daily prednisone) or other immunosuppressive drug
• Measurable disease (RECIST v1.1)	• Proton pump inhibitor use within 5 days of randomization
Enrollment	*Enrollment*
• Mutation in KEAP1 or NRF2 documented by NGS from a CAP-accredited and/or CLIA-certified laboratory and STK11/LKB1 mutation status is known for the purpose of stratification	• Major surgery within 3 weeks or radiation therapy within 2 weeks of randomization
• Adequate hepatic, renal, cardiac, and hematologic function	• Prior severe hypersensitivity reaction to other monoclonal antibody
	• Active and/or untreated CNS metastasis[c]

[a]Neo/adjuvant therapy (with or without immunotherapy) for localized NSCLC is allowed if completed within 6 months of development of metastatic disease
[b]Other mixed histology and large cell neuroendocrine histology allowed
[c]Exceptions: definitive treatment with stereotactic radiosurgery (SRS) or surgery to all known CNS lesions; or at least 7 days post SRS and 7 days prior to randomization and 4 weeks post-surgical resection of CNS disease, symptomatically stable, and off steroids before randomization

SUMMARY

- Telaglenastat is an investigational, first-in-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

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