KEAPSAKE Study of Telaglenastat vs Placebo Plus Standard-of-Care in 1L KEAP1/NRF2-Mutated Non-squamous Metastatic NSCLC

David R. Spigel[1], Wallace Akerley[2], Makenzi Evangelist[3], Melissa Johnson[1], Benjamin Levy[4], Taofeek Owonikoko[5], Paul Paik[6], Thales Papagiannakopoulos[7], Karen L. Reckamp[8], Lalith Akella[9], Sacha Holland[9], Yonchu Jenkins[9], Emil Kuriakose[9], Naiyer Rizvi[10]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [2]Huntsman Cancer Institute, Salt Lake City, UT; [3]New York Oncology Hematology, Albany, NY; [4]Johns Hopkins University, Baltimore, MD; [5]Emory University Winship Cancer Institute, Atlanta, GA; [6]Memorial Sloan Kettering Cancer Center, New York City, NY; [7]NYU Langone Health, New York, NY; [8]Cedars-Sinai Medical Center, Los Angeles, CA; [9]Calithera Biosciences, Inc., South San Francisco, CA; [10]Columbia University Irving Medical Center, New York City, NY

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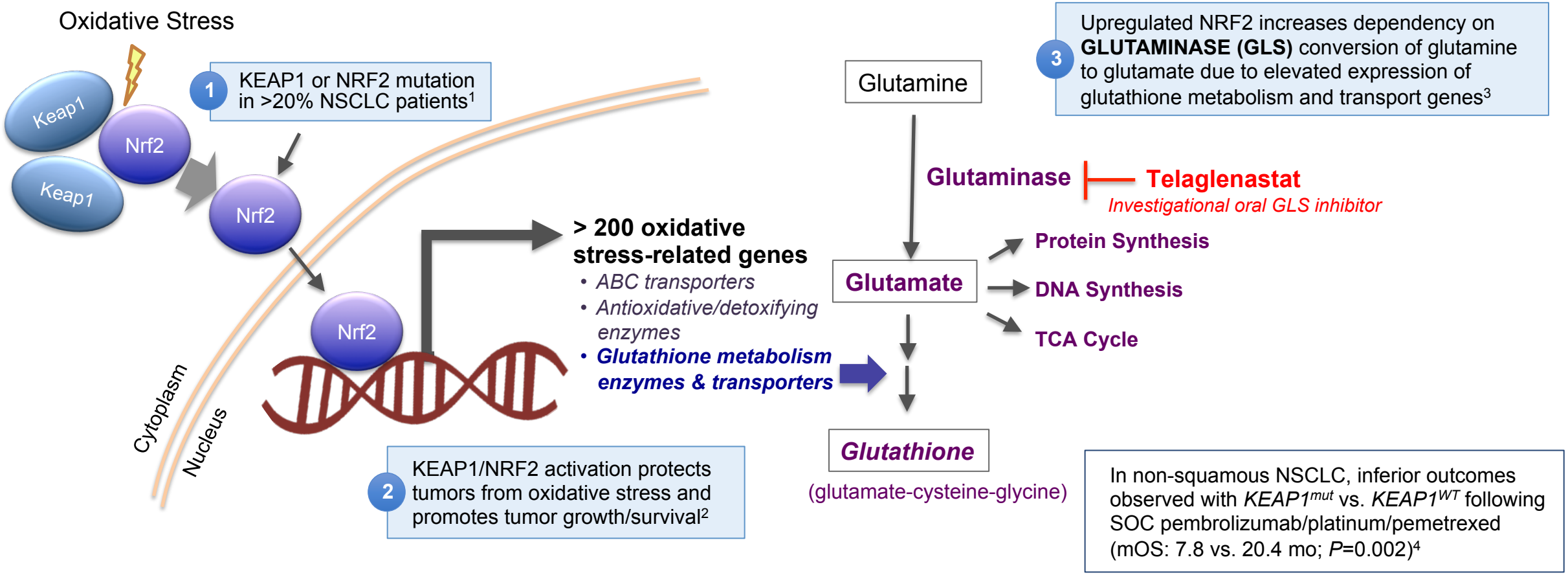
DISCLOSURES FOR DR. SPIGEL

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
Aeglea Biotherapeutics, Astellas, AstraZeneca, BIND Therapeutics, Bristol-Myers Squibb, Celgene, Celldex, Clovis, Daiichi Sankyo, Eisai, Lilly, EMD Serono, G1Therapeutics, Roche/Genentech, GlaxoSmithKline, GRAIL, ImClone Systems, ImmunoGen, Ipsen, Janssen, MedImmune, Merck, Molecular Partners, Nektar, Neon, Novartis, Takeda, Tesaro, Transgene, UT Southwestern, Agios, Cyteir Therapeutics, Apollomics	Research Funding (ALL PAYMENTS MADE TO INSTITUTION)
Amgen, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Curio Science, Dracen Pharmaceuticals, EMD Serono, Evelo Biosciences, Exelixis, GlaxoSmithKline, Iksuda Therapeutics, Intellisphere, Illumina, Ipsen Biopharmaceuticals, Janssen, Jazz Pharmaceuticals, Lilly, Merck, Mirati, Molecular Templates, Nektar Therapeutics, Novartis, Novocure, Pfizer, Pharma Mar, Puma Biotechnology, Roche/Genentech, Sanofi-Aventis, Seattle Genetics, Takeda, TRIPTYCH Health Partners, TRM Oncology, Williams and Connolly LLP, and Regeneron Pharmaceuticals	Consulting (ALL PAYMENTS MADE TO INSTITUTION)

BACKGROUND

Mutational activation of the KEAP1-NRF2 pathway protects tumor cells from oxidative stress but increases dependency on glutaminase-dependent pathways[3,4]



In non-squamous NSCLC, inferior outcomes observed with *KEAP1*^{mut} vs. *KEAP1*^{WT} following SOC pembrolizumab/platinum/pemetrexed (mOS: 7.8 vs. 20.4 mo; *P*=0.002)[4]

mOS, median overall survival; NSCLC, non-small cell lung cancer; SOC, standard of care; TCA, tricarboxylic acid

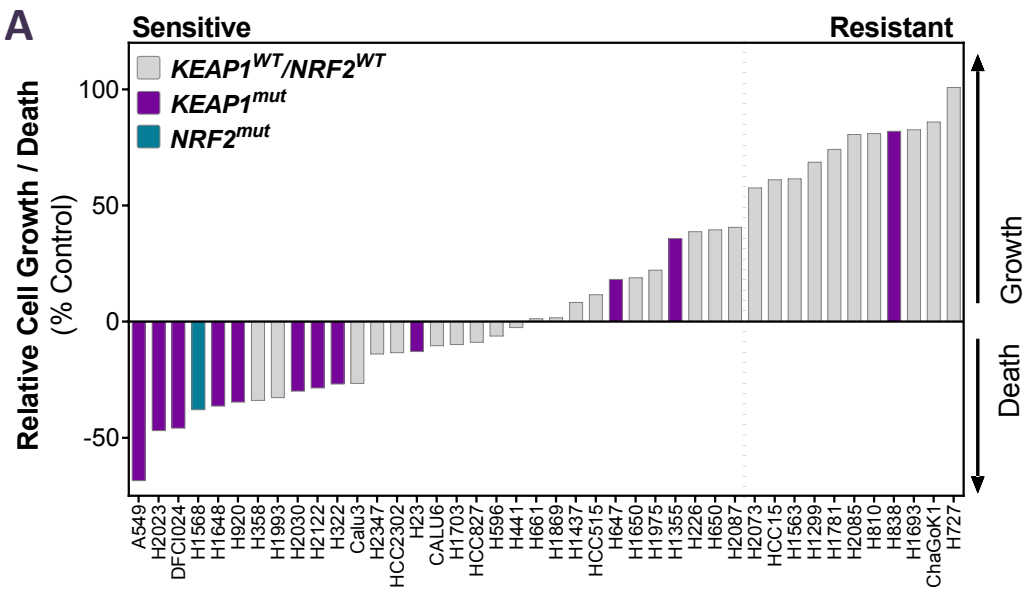
1. Best & Sutherland. Cell Cycle. 2018;17:1696-1707; 2. Hayes & McMahon. Trends Biochem Sci. 2009;34:176-88; 3. Hayes & Dinkova-Kostova. Trends Biochem Sci. 2014;39:199-218. 4. Skoulidis et al. 2019 ASCO Abstr #102.

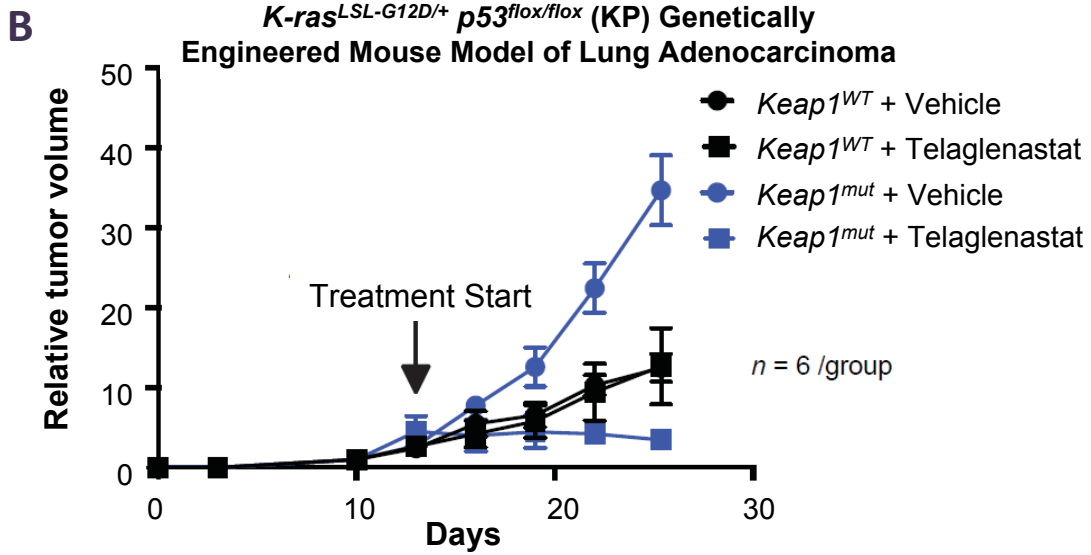
Rationale for Telaglenastat in KEAP1/NRF2-Mutated NSCLC: Preclinical

KEAP1/NRF2 mutations are associated with enhanced sensitivity to telaglenastat

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

- Telaglenastat is an investigational, first-in-class, potent, oral glutaminase inhibitor that has shown encouraging safety and activity in several cancers when combined with targeted agents, checkpoint inhibitors, and chemotherapy[1-5]
- Telaglenastat is active against many NSCLC cell lines, particularly those bearing *KEAP1* or *NRF2* mutations (**Panel A**), selectively inhibits *KEAP1*^{mut} tumor growth *in vivo* **(Panel B),** and synergizes with anti-PD-1 inhibition[6,7]





Keap1^{mut} = isogenic cell line from cells isolated from KP lung adenocarcinoma model
Reprinted by permission from Springer Nature:.Romero et al. Nature Med 2017;23:1362-1368

1. Motzer et al. ESMO 2019. Abstr #811; 2. Meric-Bernstam et al. ASCO-GU 2019. Abstr #549; 3. Vidal et al. SABCS 2018. Abstr #P6-20-07; 4. Eads et al. ASCO 2018. Abstr #2562; 5. Meric-Bernstram et al. SITC 2017. Abstr #016; 6. Calithera Biosciences, Inc., Data on File; 7. Romero et al. Nat Med. 2017;23(11):1362-1368

Rationale for Telaglenastat in *KEAP1/NRF2*-Mutated NSCLC: Clinical

Clinical Benefit With Telaglenastat + Nivolumab in NSCLC Patients with KEAP1 Mutation

- In a 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[1,2]

Table 1. *KEAP1*^{mut} associated with improved outcomes, compared with *KEAP1*^{WT} in NSCLC patients treated with telaglenastat + nivolumab

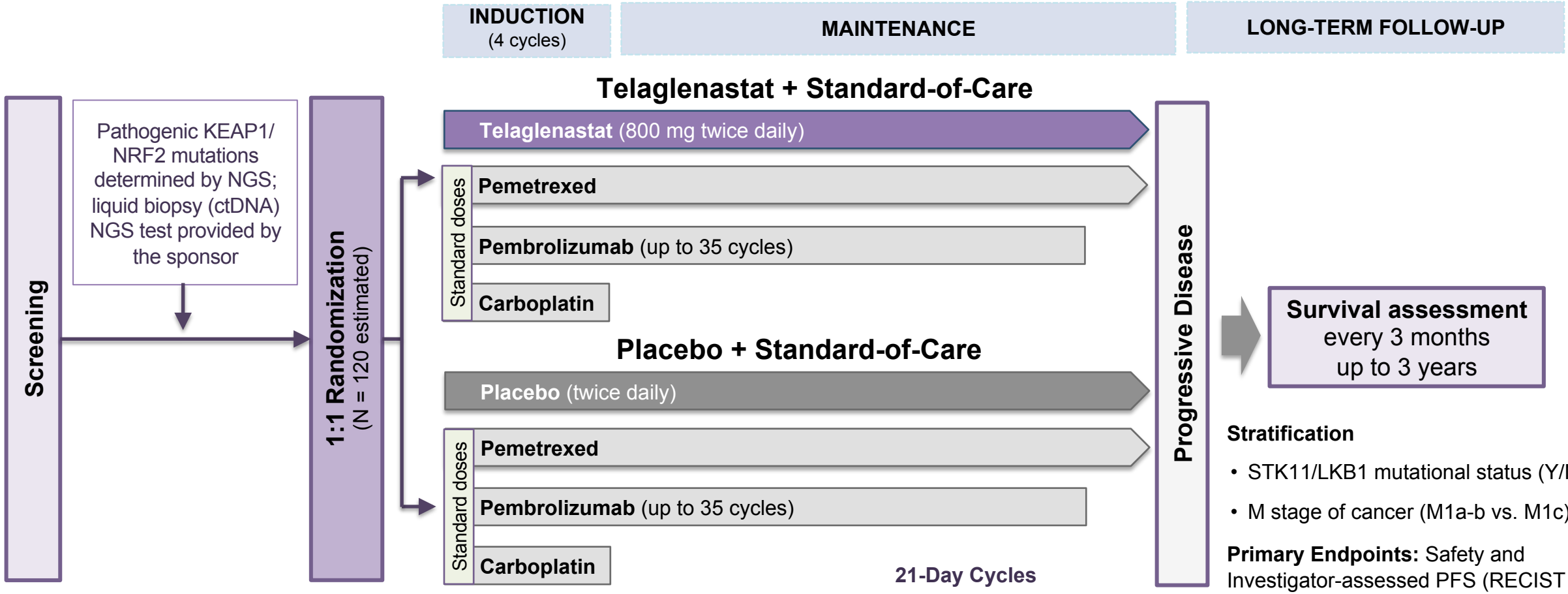
Mutation	Clinical Benefit Rate[a]		Median iPFS[b] (months)	
	Mutation	Wild-type	***Mutation***	Wild-type
KEAP1	***3/4 (75%)***	2/13 (15%)	***6.4***	3.7
KEAP1 + KRAS	***2/2 (100%)***	1/8 (13%)	***7.2***	3.7
KRAS	***3/8 (38%)***	2/10 (20%)	***4.5***	3.7
All Patients	6/22 (22%)		3.7	

[a]CBR = CR + PR + SD per either RECIST or immune RECIST criteria for at least 4 months
[b]Progression-free survival determined using modified RECISTv1.1 for immune-based therapeutics (iRECIST)[3]

iPFS, progression-free survival determined using RECIST 1.1 for immune-based therapeutics (iRECIST); RECIST, Response Evaluation Criteria in Solid Tumors;

1. Calithera Biosciences, Inc., Data on File; 2. Romero et al. Nat Med. 2017;23(11):1362-1368; 3. Seymour et al. Lancet Oncol. 2017;18(3):e143-e152.

KEAPSAKE STUDY DESIGN



Stratification

- STK11/LKB1 mutational status (Y/N)
- M stage of cancer (M1a-b vs. M1c)

Primary Endpoints: Safety and Investigator-assessed PFS (RECIST v1.1)

Secondary Endpoints: Overall response rate, iPFS, duration of response, time to progression, overall survival

Study start date: July 24, 2020

Safety Monitoring Committee
Review of safety data (n=6 per arm) from cycle 1 safety run-in period: Telaglenastat 800 mg BID determined as RP2D in combination with PCP

ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

KEY ELIGIBILITY CRITERIA FOR ENROLLMENT

Inclusion Criteria	Exclusion Criteria
• Documented histological or cytological diagnosis of nonsquamous NSCLC • Stage IV (M1a-c, AJCC 8th Edition) disease not previously treated with systemic therapy for metastatic NSCLC[a] • ECOG PS 0-1 • No known actionable mutation in *EGFR, ALK, ROS1, BRAF, NTRK*, or other known actionable mutation for which there is approved therapy • Measurable disease (RECIST v1.1) • 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 • Adequate hepatic, renal, cardiac, and hematologic function	• Squamous cell histology and mixed histology tumors with any small cell/neuroendocrine component[b] • Active autoimmune disease requiring systemic treatment in past 2 years and/or concurrent malignancy requiring local or systemic therapy • Radiation therapy to the lung >30 Gy within 6 months of randomization • Concurrent chronic systemic steroids (>10 mg equivalent of daily prednisone) • Proton pump inhibitor use within 5 days of randomization • Major surgery within 3 weeks or radiation therapy within 2 weeks of randomization[c] • 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 should be reviewed with the medical monitor for eligibility
[c]Exceptions: definitive treatment with stereotactic radiosurgery (SRS) or surgery to all known CNS lesions; at least 4 weeks post-surgical resection of CNS disease, symptomatically stable, and off steroids before randomization. Pts treated with SRS for brain metastases must be symptomatically stable and off steroids before randomization.

AJCC, American Joint Committee on Cancer; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors;

NGS ELIGIBILITY CRITERIA

- A separate screening protocol (NCT04698681) is also available to assess *KEAP1* or *NRF2* mutational status based on liquid biopsy NGS, which may be used to determine KEAPSAKE trial eligibility of patients whose mutational status is unknown.

NGS Eligibility Criteria

- Biopsy-confirmed OR clinically suspected Stage 4 NSCLC not previously treated with systemic therapy for metastatic disease
- ECOG performance status of 0 or 1
- Age ≥18 on the day of signing informed consent
- Estimated life expectancy of > 3 months
- Measurable disease (RECIST v1.1)
- Clinically eligible to receive standard-of-care combination therapy with pembolizumab + carboplatin + pemetrexed (PCP) assuming Stage 4 disease

ECOG, Eastern Cooperative Oncology Group; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors

SUMMARY

- Telaglenastat is an investigational, first-in-class, potent, oral inhibitor of glutaminase (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 non-squamous 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 opened to enrollment on July 24, 2020
- Safety Monitoring Committee review from safety run-in period led to telaglenastat RP2D selection of 800 mg BID in combination with PCP

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

NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PFS, progression-free survival

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