Metabolic profile and therapeutic vulnerabilities of multi-omic characterization of *KRAS/STK11/KEAP1* co-mutant non–small cell lung cancer (NSCLC).

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THE SEN LAB

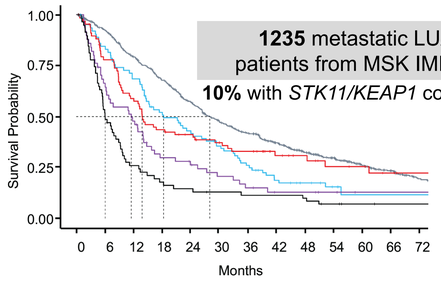
Abstract #8576

Icahn School of Medicine at Mount Sinai

CARIS PRECISION ONCOLOGY ALLIANCE

Background

- *KRAS*-mutant NSCLC with co-occurring loss-of-function mutations in *STK11* and *KEAP1* are remarkably aggressive, have poor prognosis **(Figure. 1)** and unresponsive to chemo- and immunotherapy.
- Novel therapeutic strategies are urgently needed to improve outcomes for patients with *KRAS/STK11/KEAP1* (KSK) co-mutant NSCLC.
- We interrogated the transcriptomic landscape using a large real-world (RW) dataset of NSCLC to identify therapeutic vulnerabilities that may help guide treatment selections in KSK.



1235 metastatic LUAD patients from MSK IMPACT

10% with *STK11/KEAP1* co-mutation

Genotype	Median Months Survival
STK11/KEAP1 WT	26.41
STK11 Mutant	18.23
KEAP1 Mutant	13.77
STK11/KEAP1	11.50
KRAS/STK11/KEAP1	6.50

Wohlhieter, et al. Cell reports (2020).

Figure 1: Patients with *KRAS/STK11/KEAP1* co-mutation have shorter overall survival.

Methods

- *KRAS* mutant NSCLC clinical samples (N=7210) tested with NextGen Sequencing of DNA (592-gene panel or WES) & RNA (Caris Life Sciences).
- Specimens stratified into $KRAS^{MUT}/STK11^{MUT}/KEAP1^{MUT}$ (KSK; N=698), $KRAS^{MUT}/STK11^{MUT}/KEAP1^{WT}$ (KS; N=786), $KRAS^{MUT}/STK11^{WT}/KEAP1^{MUT}$ (KK; N=466), and $KRAS^{MUT}/STK11^{WT}/KEAP1^{WT}$ (K; N=4536) (Figure. 2).
- Overall survival was extracted from insurance claims data and calculated from the time of tissue collection (OS) or initiation of Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab or Ipilimumab treatment (IO-OS) to the last contact, using Kaplan Meier estimates. Pembro-time on treatment (TOT) was similarly calculated from initiation to termination of Pembro treatment.
- Additionally, an *in vitro* bulk RNA sequencing, and phospho-kinase arrays were performed in *KSK*, single mutant, and wild-type cell lines.

Figure.2: Patient characteristics of the CARIS dataset.

Cohort Characteristics	$KRAS^{MUT}/STK11^{MUT}/KEAP1^{MUT}$ (n=698)	$KRAS^{MUT}/STK11^{MUT}/KEAP1^{WT}$ (n=786)	$KRAS^{MUT}/STK11^{WT}/KEAP1^{MUT}$ (n=466)	$KRAS^{MUT}/STK11^{WT}/KEAP1^{WT}$ (n=4536)	q-value
Median Age [range] (N)	67 [35 - 89] (698)	67 [27 - >89] (786)	66 [37 - >89] (466)	70 [24 - >89] (4536)	6.50E-27
Female	50.0% (349/698)	57.0% (448/786)	53.2% (248/466)	59.1% (2679/4536)	4.69E-05
Male	50.0% (349/698)	43.0% (338/786)	46.8% (218/466)	40.9% (1857/4536)	
Smoker	100.0% (205/205)	98.5% (203/206)	100.0% (133/133)	98.3% (1222/1243)	0.12294057
Non-smoker	0.0% (0/205)	1.5% (3/206)	0.0% (0/133)	1.7% (21/1243)	
Adenocarcinoma	83.7% (584/698)	83.7% (658/786)	75.8% (353/466)	80.8% (3664/4536)	0.00066633
Squamous Carcinoma	1.3% (9/698)	1.1% (9/786)	3.9% (18/466)	3.8% (171/4536)	
Adenosquamous Carcinoma	0.1% (1/698)	0.6% (5/786)	0.9% (4/466)	0.7% (34/4536)	
Sarcomatoid	0.0% (0/698)	0.4% (3/786)	0.6% (3/466)	1.3% (57/4536)	
Large Cell Carcinoma	0.0% (0/698)	0.0% (0/786)	0.4% (2/466)	0.2% (10/4536)	
Other/Unclear Histology	14.9% (104/698)	14.1% (111/786)	18.5% (86/466)	13.2% (600/4536)	

Our study highlights the importance of the *SCD1-SLC7A11* axis which regulates unique metabolic and ferroptosis evasion pathways in *KRAS/STK11/KEAP1* co-mutant NSCLCs.

The study demonstrates the potential to translate SCD1 inhibitors and ferroptosis inducers in NSCLC clinical trials.

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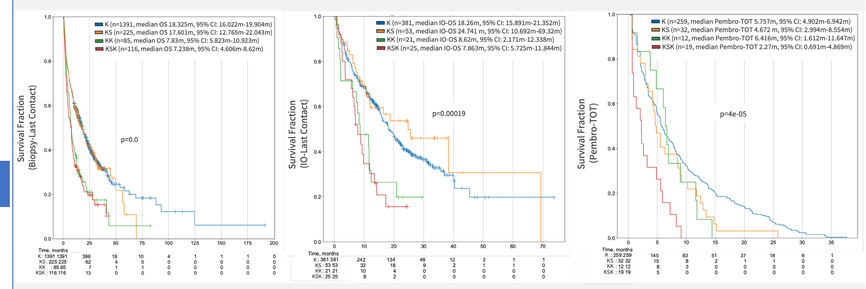
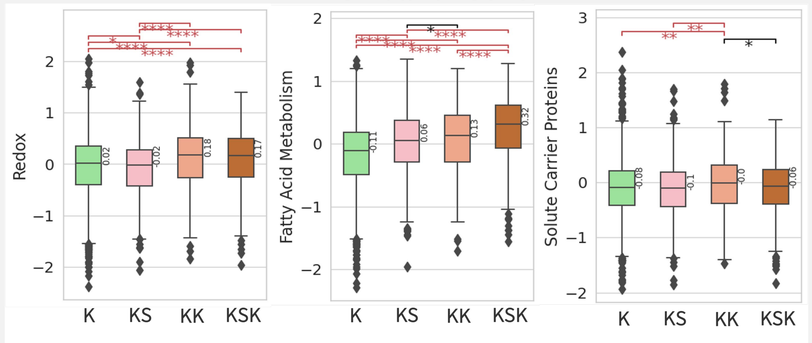
Results

Association of STK11/KEAP1 Mutations with OS, IO-OS and Pembro TOT



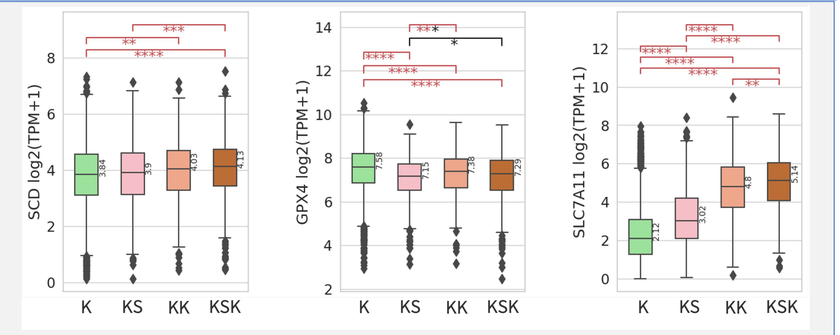
- *KEAP1* mutations more strongly associated with poor OS and poor IO-OS than *STK11* mutations
- $STK11^{MUT}/KEAP1^{MUT}$ were associated with the shortest Pembro TOT compared to either mutation alone

Association of Gene Signature Scores with *STK11/KEAP1* Mutations in *KRAS* mutant-NSCLC



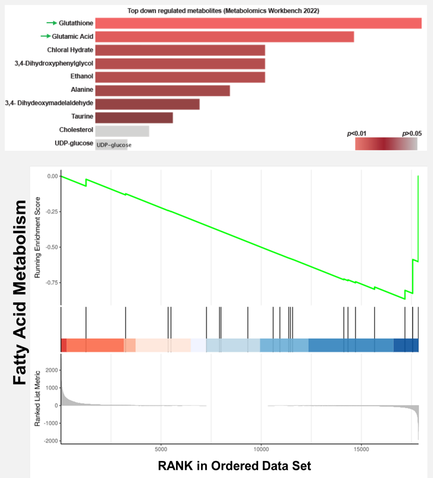
KSK clinical samples had upregulated fatty acid metabolism, solute carrier and redox pathways (z-scores).

Results

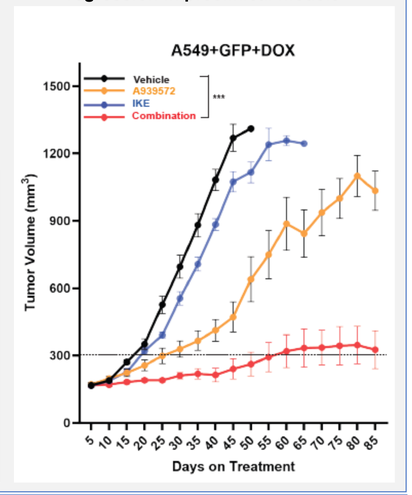


KSK clinical samples had significant overexpression of *SCD1* and *SLC7A11* and reduced expression of *GPX4* genes involved in ferroptosis evasion and metabolism(vs K, all q<0.05).

Pharmacological inhibition of SCD1 significantly reduced Glutathione and Fatty acid metabolism



Inhibition of SCD1 alone or in combination with SLC7A11 inhibition causes tumor regression in preclinical models



Future Directions

- Mechanism of action of SCD1 inhibition and how it uniquely modulates the co-mutant cells for ferroptosis would be worth exploring.
- SLC7A11 inhibitor (Erastin/IKE), SCD1 inhibitor A939572, these agents are safe to use with acceptable toxicity and established doses. Therefore, our study will facilitate and support the translation of ferroptosis inducers or SCD1 inhibitors in clinical trials.

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