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STK11 and *KEAP1* mutations as prognostic biomarkers in an observational real-world lung adenocarcinoma cohort

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Study Summary

Context:

- Previous high-profile reports of *STK11* / *KEAP1* as ICB-specific negative biomarkers
- Most of those studies don't include non-ICB arms

Challenge:

- With a ~20% mutation prevalence and modest effect size (HR), assessing the treatment-specific effect requires a large cohort
- Challenging to do using clinical trial data
- Flatiron/FMI CGDB data allow us to compare associations in ICB and non-ICB

Key Questions:

- Are *STK11* and/or *KEAP1* mutations associated with poor outcomes across all 1L treatment paradigms?
- Is there a synergistic effect of *STK11* + *KEAP1* mutations on outcomes?

Recent reports focus on *STK11* and checkpoint inhibitors

Fail to demonstrate whether association is specific to ICB

Paper/abstract	Sample size	Treatments	Results	Notes
Biton et al. 2018, <i>Clinical Cancer Research</i>	<ul style="list-style-type: none"> • 32 adv-stage LUAD • 31 from Ritzi et al. 	<ul style="list-style-type: none"> • nivolumab 	TP53mut/ EGFR-STK11-WT have better outcomes than TP53-EGFR-STK11-WT or EGFRorSTK11-mut groups	<ul style="list-style-type: none"> • No comparator arm • Small n
Skoulidis et al. 2018, <i>Cancer Discovery</i> (BMS)	<ul style="list-style-type: none"> • 174 LUAD SU2C (KRAS-mut) • 44 CM057 (KRAS-mut) 	<ul style="list-style-type: none"> • PD-1 inh. mono (165/174, 95%) or PD-1 & CTLA-4 blockade (9/174, 5%) • Nivolumab (24) or docetaxel (20) 	KRAS/STK11-mut have worse outcomes than KRAS-mut/STK11-WT tumors. “Given the relatively small numbers within subgroups, it cannot be determined whether STK11/LKB1 mutation is prognostic or predictive of treatment outcomes in the CM-057 dataset”	<ul style="list-style-type: none"> • No comparator arm for SU2C cohort • Small sample size for docetaxel treated (20)
Jure-Kunkel et al., ASCO abstract 2018 (AstraZeneca)	<ul style="list-style-type: none"> • 119 CP1108 • 63 ATLANTIC • 120 D4190C00006 	<ul style="list-style-type: none"> • Durvalumab • Durvalumab • Durv & Trem 	“ reduced ORR and shorter survival were observed in Non-SQ NSCLC pts harboring STK11 non-synonymous mutant tumors compared to pts harboring STK11 wild type (wt) tumors “	No non-IO comparison
Ross et al., ESMO 2017 (Flatiron/Foundation Medicine)	<ul style="list-style-type: none"> • 37 in FMI cohort • ?? In FH-FMI 	<ul style="list-style-type: none"> • Checkpoint inhibitors • nivolumab 	“preliminary analyses suggest correlation with negative ICPI treatment outcome ”	No non-IO comparison
Murugesan et al., ESMO 2018 (Flatiron/Foundation Medicine)	<ul style="list-style-type: none"> • 1310 NSCLC 	<ul style="list-style-type: none"> • Checkpoint inhibitors 	“Patients with STK11 loss had reduced mPFS (wt 3.1 mo vs mut 2.5 mo, P = 0.01)”	No non-IO comparison

ASCO 2020 - the debate continues!!

Modulating tumor immune microenvironment by the **STK11/LKB1 signaling** in breast cancer.

HP Hsu, CY Wang, YL Kuo, KT Lee, PS Chen... - 2020 - [ascopubs.org](#)

... Modulating tumor immune microenvironment by the **STK11/LKB1** signaling in breast cancer ... Liver kinase B1 (LKB1) protein (**STK11** gene) is the upstream of AMP activated Protein Kinase (AMPK)/mammalian Target of Rapamycin Complex 1 (mTORC1) signaling pathway ...

☆ 📄

Clinically aggressive malignancies associated with **STK11** germline mutations (**STK11GCa**): A comprehensive genomic profiling (CGP) study.

E Sokol, N Danziger, D Pavlick, JA Elvin, JA Vergilio... - 2020 - [ascopubs.org](#)

... DOI: 10.1200/JCO.2020.38.15_suppl.3558 Journal of Clinical Oncology - published online before print May 25, 2020. Clinically aggressive malignancies associated with **STK11** germline mutations (**STK11GCa**): A comprehensive genomic profiling (CGP) study ...

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Outcomes of patients with stage III non-small cell lung cancer (NSCLC) that harbor a **STK11** mutation.

J An, M Yan, N Yu, A Chennamadhavuni, M Furqan... - 2020 - [ascopubs.org](#)

... Outcomes of patients with stage III non-small cell lung cancer (NSCLC) that harbor a **STK11** mutation ... 9033. Background: **STK11** mutation (**STK11 m**) in patients with stage IV NSCLC is associated with inferior survival and poor response to immune check point inhibitors (ICI) ...

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Alterations in **STK11** to limit response to immune checkpoint inhibitors in lung cancer.

J Fricke, I Mambetsariev, R Pharaon, AR Baroz, D Zhao... - 2020 - [ascopubs.org](#)

... Alterations in **STK11** to limit response to immune checkpoint inhibitors in lung cancer ... **STK11** mutated patients represent a subgroup of lung cancer patients with diminished outcomes when given ICIs, with some of these patients developing hyperprogressive disease (HPD) ...

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Association of a **STK11/KEAP1**-mutation gene expression signature in lung adenocarcinoma with immune desertion in squamous cell carcinomas and mediation by ...

DT Rieke, KF Klinghammer, B Obermayer, E Blanc... - 2020 - [ascopubs.org](#)

... May 25, 2020. Association of a **STK11/KEAP1**-mutation gene expression signature in lung adenocarcinoma with immune desertion in squamous cell carcinomas and mediation by NFE2L2 deregulation. Damian Tobias Rieke ...

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The association between **STK11/LKB1** and/or **KEAP1** mutations and resp PD-1/PD-L1 inhibitors in patients with advanced non-small cell lung cancer (NSCLC) ...

ME Miller, M Patel, SK Althouse, NH Hanna... - 2020 - [ascopubs.org](#)

... lung cancer (NSCLC) patients with tumors harboring **STK11/LKB1** or **KEAP1** mutations have inferior treatment outcomes when treated with PD-1/PD-L1 blockade, regardless of KRAS status, PD-L1 score, or TMB score (Skoulidis et al, Cancer Discovery 2018, **ASCO** abstract 102 ...

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STK11/LKB1 revisited: A prognostic rather than predictive biomarker for immunotherapy in **EGFR/ALK^{WT}** nonsquamous non-small cell lung cancer

H Zhao, N Qi, D Chen, D Li, Y Fu, Y Xu, G Wang, Y Bai... - 2020 - [ascopubs.org](#)

... online before print May 25, 2020. **STK11/LKB1** revisited: A prognostic rather than predictive biomarker for immune checkpoint inhibitor in **EGFR/ALK WT** nonsquamous non-small cell lung cancer (NSCLC). Hui Zhao x Hui Zhao ...

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Impact of **STK11** and **KRAS** co-mutations on outcomes with immunotherapy in non-small cell lung cancer.

F Basher, D Saravia, D Fanfan, JA Cotta, G Lopes - 2020 - [ascopubs.org](#)

... No companion articles. ARTICLE CITATION. DOI: 10.1200/JCO.2020.38.15_suppl.e15135 Journal of Clinical Oncology - published online before print May 25, 2020. Impact of **STK11** and **KRAS** co-mutations on outcomes with immunotherapy in non-small cell lung cancer ...

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Effect of **STK11** mutations on efficacy of PD-1 inhibition in non-small cell lung cancer (NSCLC) and dependence on **KRAS** mutation status.

B Ricciuti, KC Arbour, JJ Lin, N Vokes... - 2020 - [ascopubs.org](#)

... Effect of **STK11** mutations on efficacy of PD-1 inhibition in non-small cell lung cancer (NSCLC) and dependence on **KRAS** mutation status ... e15113. Background: **STK11** mutations (**STK11m**) have been associated with resistance to ICI in **KRAS**-mutant (**KRASm**) NSCLC ...

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Serine/threonine kinase 11 (**STK11**) mutations and immunotherapy resistance in patients with non-small cell lung cancer.

R Uba, LE Raez, K Dumais, F Gentile, HW Powery... - 2020 - [ascopubs.org](#)

... Serine/threonine kinase 11 (**STK11**) mutations and immunotherapy resistance in patients with non-small cell lung cancer ... We investigated the role of **STK11** and **KRAS** mut as markers of poor response to CPI in patients (pts) with non-small cell lung cancer (NSCLC) ...

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... (NGS) in advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with immune checkpoint inhibitors (ICIs): Impact of **STK11** and TP53 mutations on ...

A Pavan, E Zulato, L Calvetti, A Ferro, G Nardo... - 2020 - [ascopubs.org](#)

... 25, 2020. Plasma next-generation sequencing (NGS) in advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with immune checkpoint inhibitors (ICIs): Impact of **STK11** and TP53 mutations on outcome. Alberto ...

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Therapeutic impact of mutation subtypes and concomitant **STK11** mutations in **KRAS**-mutated non-small cell lung cancer (NSCLC): A result of nationwide genomic ...

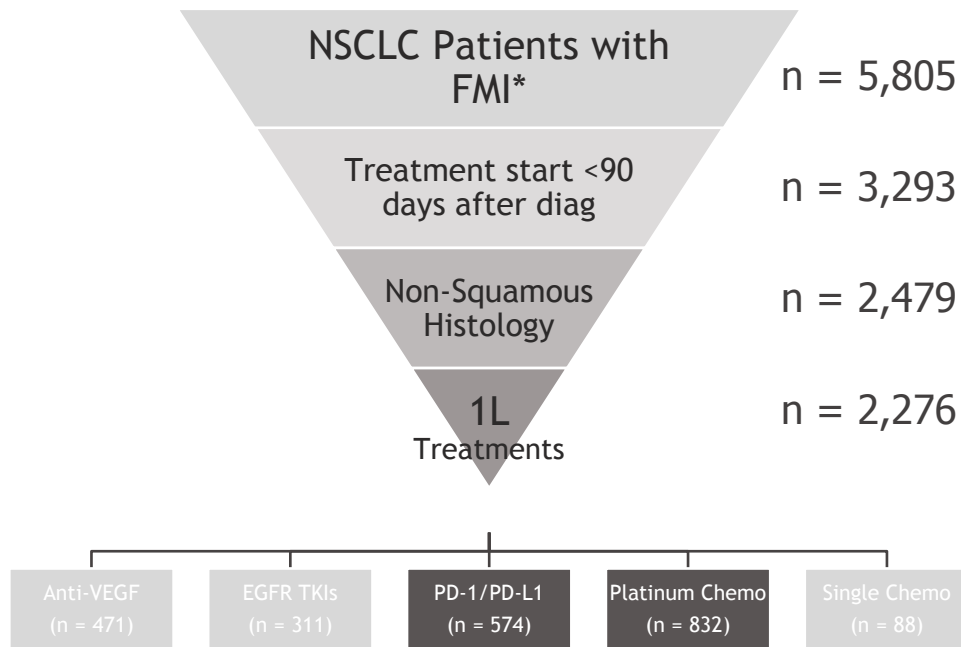
Y Tamiya, Y Zenke, S Matsumoto, N Furuya... - 2020 - [ascopubs.org](#)

... 25, 2020. Therapeutic impact of mutation subtypes and concomitant **STK11** mutations in **KRAS**-mutated non-small cell lung cancer (NSCLC): A result of nationwide genomic screening project (LC-SCRUM-Japan). Yutaro Tamiya ...

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Cohort & Approach

Flatiron/FMI NSCLC Cohort Description



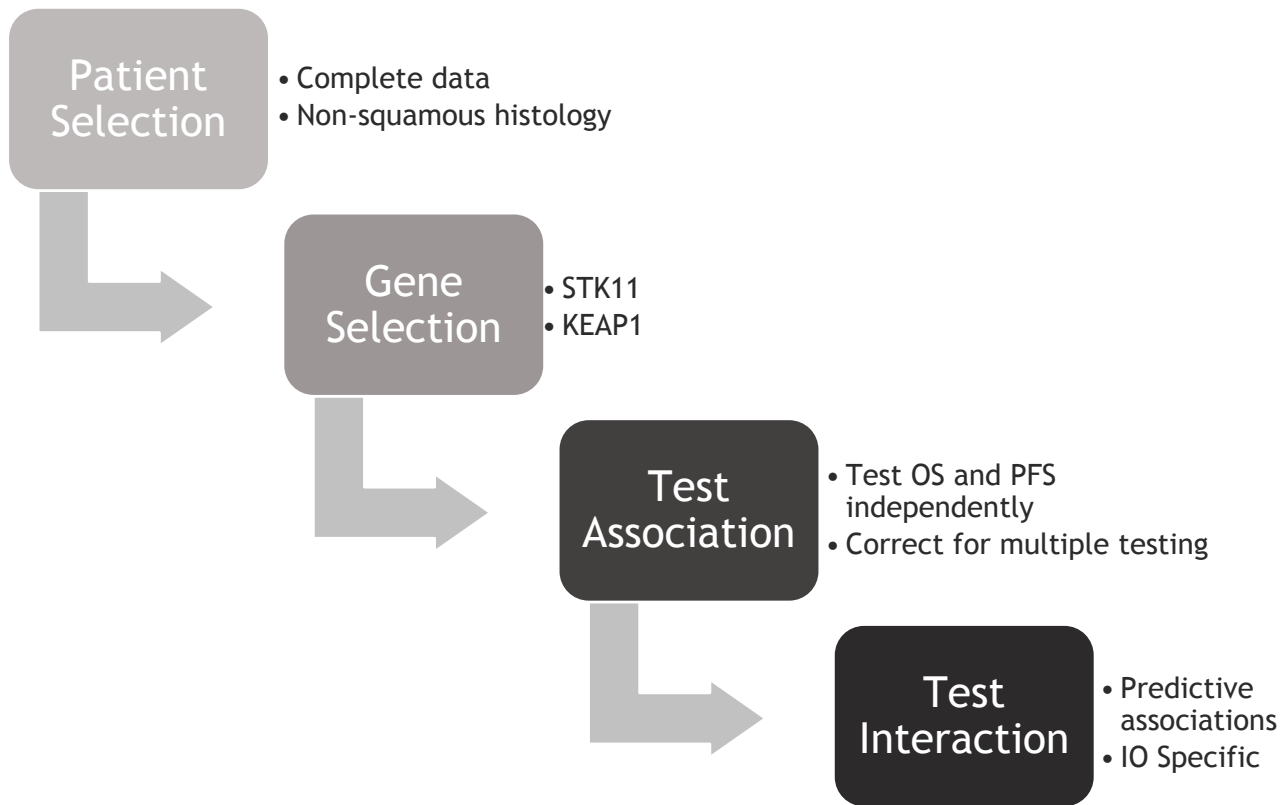
* Tumor FMI genetic testing

Cohort Description

- *STK11-KEAP1* mutated patients are:
 - Enriched in Male patients
 - Younger
 - More likely to be smokers
 - High TMB
 - Not treated with EGFR TKIs
 - *EGFR* and *STK11-KEAP1* mutations are mutually exclusive
 - If we exclude *EGFR*-mutated patients, this enrichment disappears
 - Have lower PD-L1 staining

Characteristic	Mutant (n=674)	Wild-type (n=1602)	P value
Gender, N (%)			<0.001
Female	314 (46.6)	925 (57.7)	
Male	360 (53.4)	677 (42.3)	
Age at advanced diagnosis, median (SD), years	64.9 (9.89)	66.9 (10.5)	<0.001
Smoking, N (%)			<0.001
History of smoking	647 (96.0)	1175 (73.3)	
No history of smoking	26 (3.86)	420 (26.2)	
Unknown/not documented	1 (0.15)	7 (0.44)	
TMB score (SD)	13.1 (11.1)	7.94 (9.69)	<0.001
First-line treatment, N (%)			<0.001
Anti-VEGF-based therapies	154 (22.8)	317 (19.8)	
EGFR TKIs	15 (2.23)	296 (18.5)	
PD-1/PD-L1-based therapies	192 (28.5)	382 (23.8)	
Platinum-based chemotherapy combinations	288 (42.7)	544 (34.0)	
Single-agent chemotherapies	25 (3.71)	63 (3.93)	
PD-L1 status, N (%)			<0.001
Negative	150 (75.8)	279 (60.8)	
Positive	48 (24.2)	180 (39.2)	

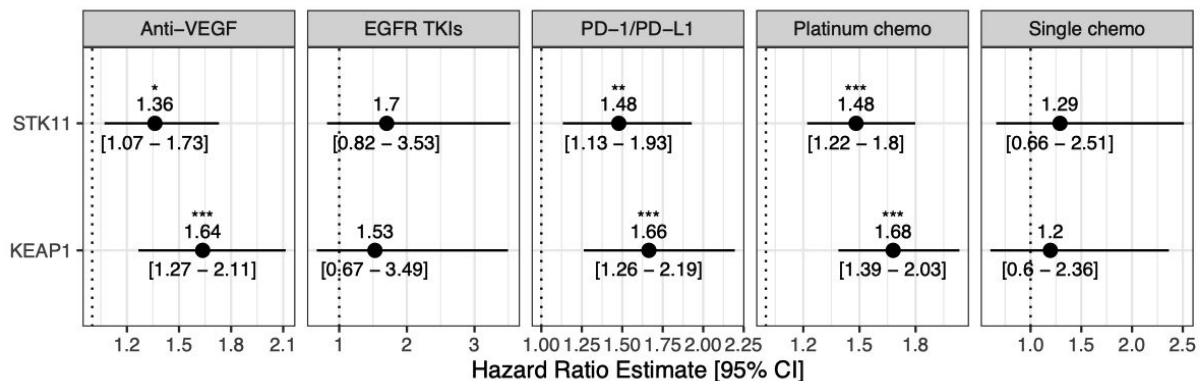
Analysis Flow



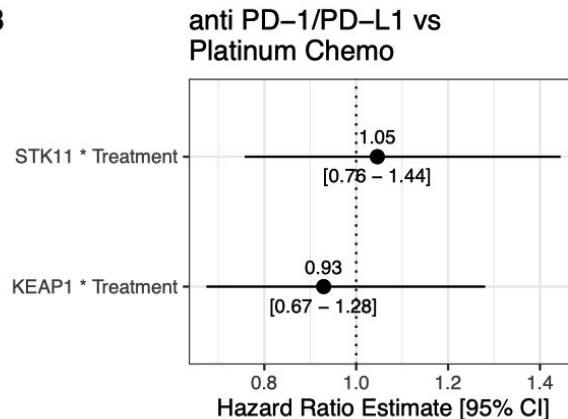
Effect of *STK11-KEAP1* mutations on PFS (rwPFS)

STK11-KEAP1 Mutations are Deleterious Across all Treatments (PFS)

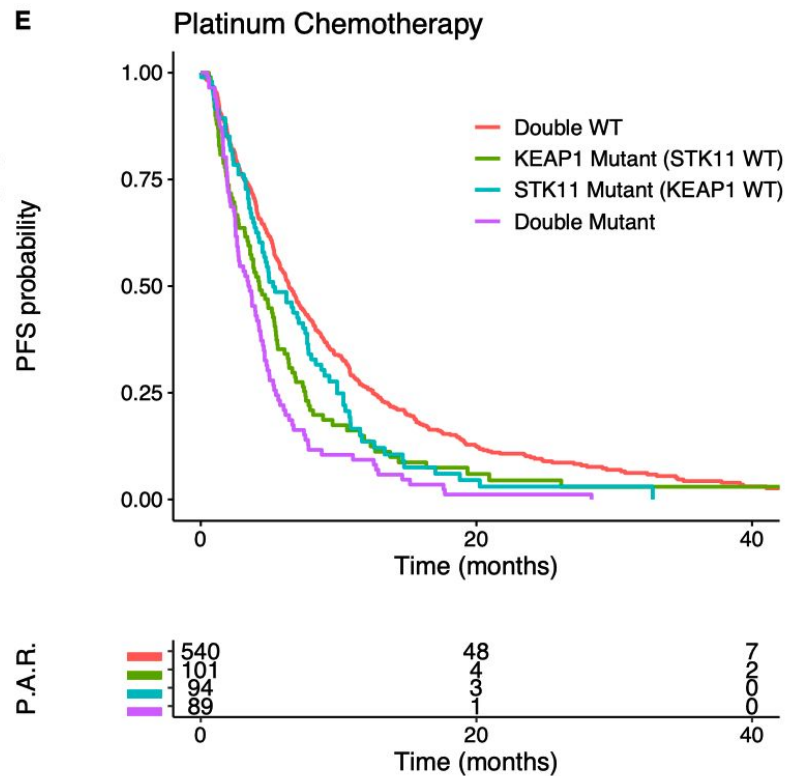
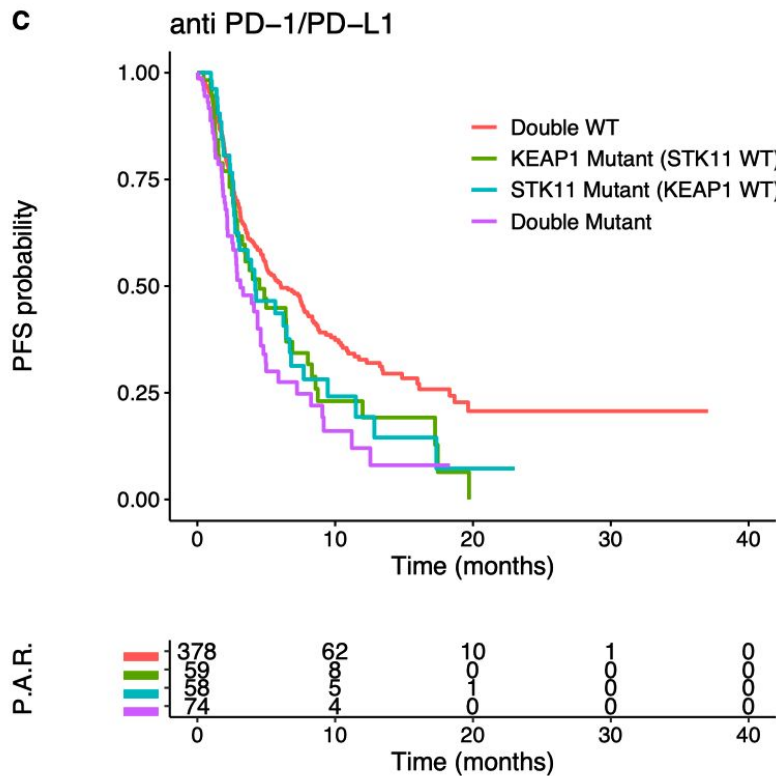
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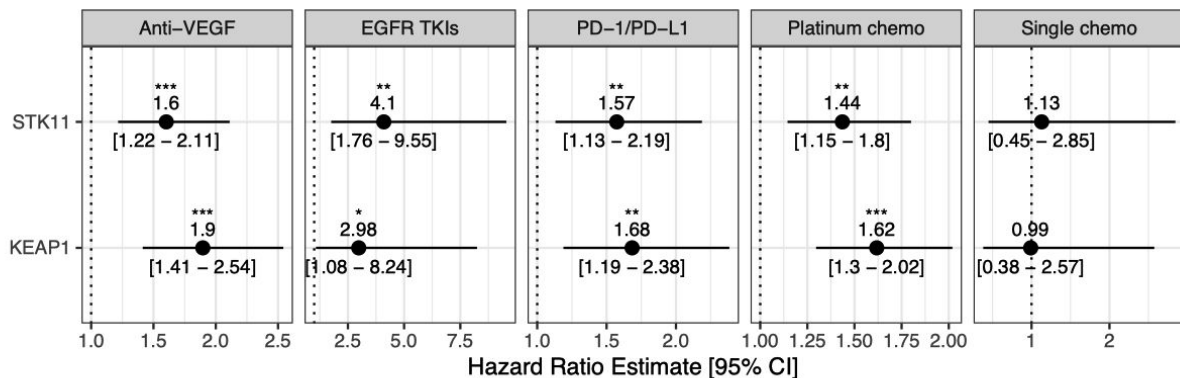
STK11-KEAP1 Mutations Effects are Additive (PFS)



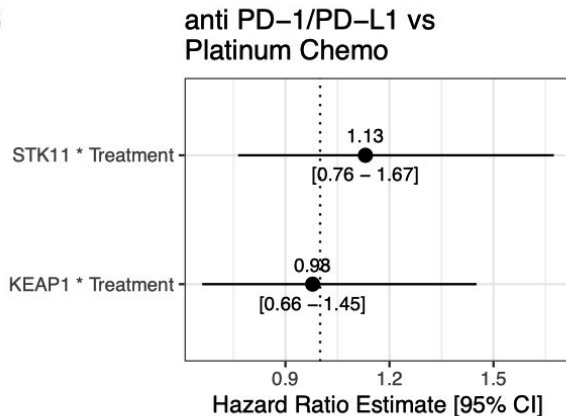
Effect of *STK11-KEAP1* mutations on OS

STK11-KEAP1 Mutations are Deleterious Across all Treatments (OS)

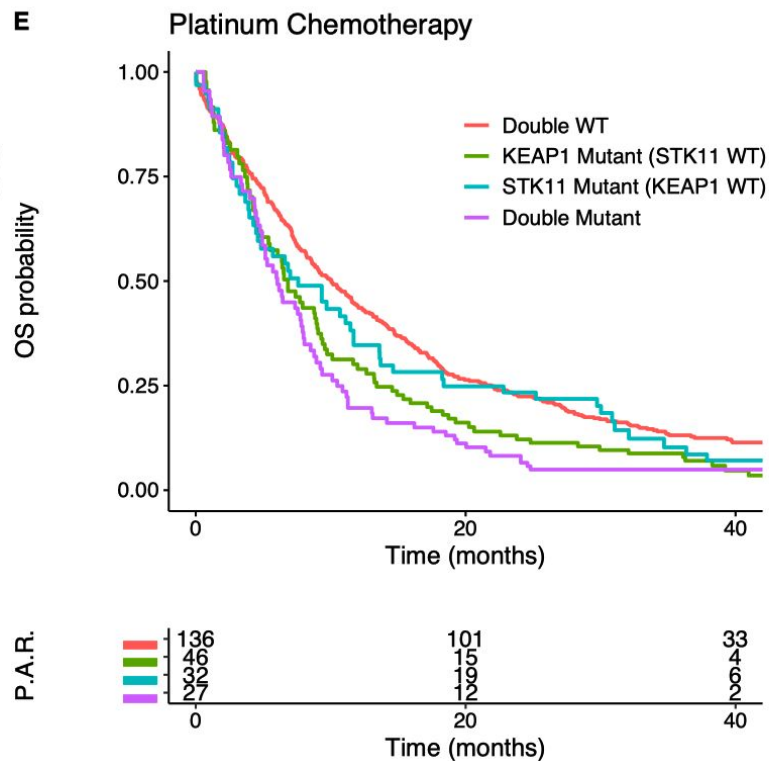
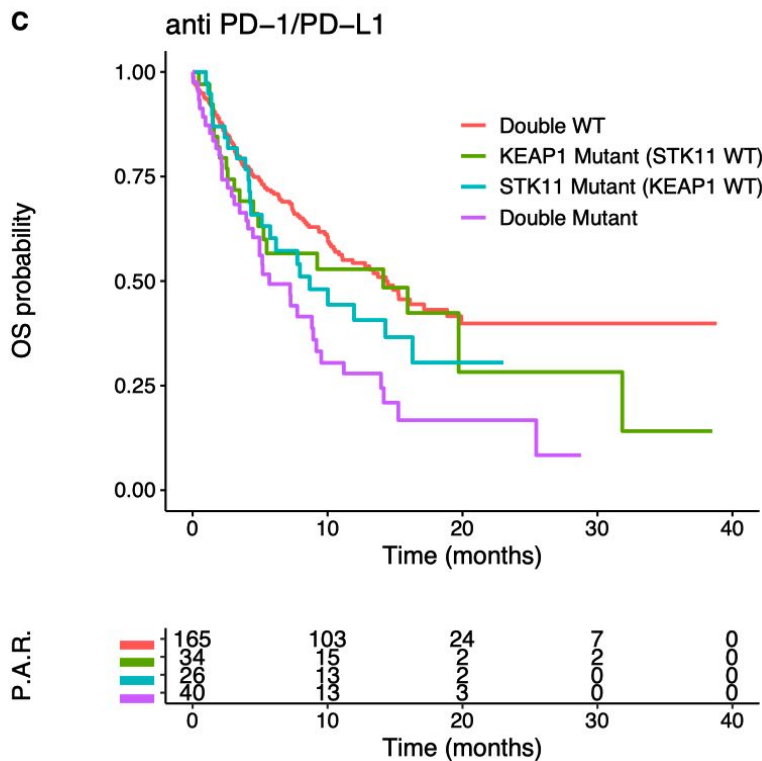
A



B



STK11-KEAP1 Mutations Effects are Additive (OS)



Conclusions

- *STK11* and *KEAP1* mutations are negatively associated with outcomes across all treatment paradigms
- Those results provide evidence against previous reports suggesting that *STK11-KEAP1* mutations are predictive biomarkers for anti-PD-1/PD-L1 therapy
- Our results suggest *STK11/KEAP1* mutation status should not be used as patient selection markers for ICB