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STK11, *KEAP1* and *TP53* as co-mutations with bad prognosis – is there a predictive role?

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Masters in Thoracic Oncology Summit

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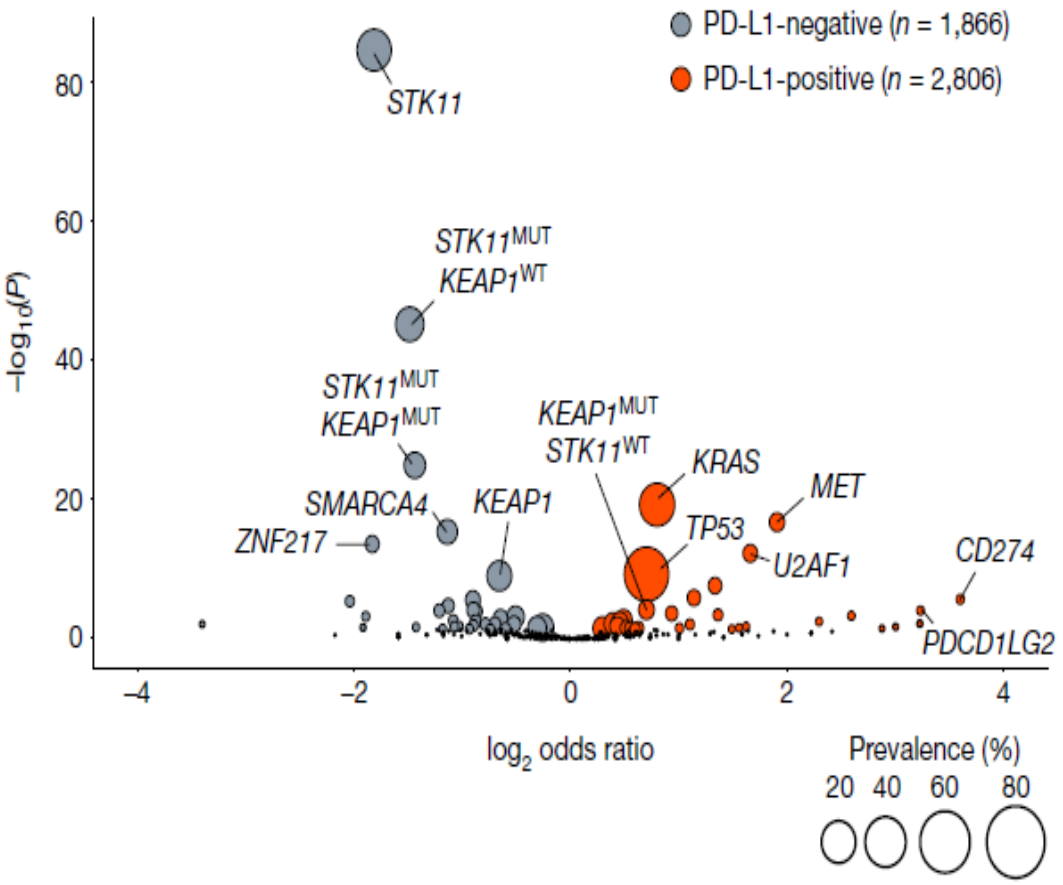
Disclosures

Ferdinandos Skoulidis reports:

- Consulting fees from Amgen Inc., Revolution Medicines, Novartis, BridgeBio, Beigene, BergenBio, Astra Zeneca, Guardant Health Inc., Calithera Biosciences, Tango Therapeutics, Merck Sharp & Dohme, Roche, Novocure, Hookipa Pharma
- Honoraria/Lecture fees from ESMO, AACR, IASLC, Japanese Lung Cancer Society, Medscape LLC, Intellisphere LLC, VSPO McGill Université de Montreal, MJH Life Sciences, IDEOlogy Health, MI&T, PER LLC, CURIO LLC, DAVA Oncology, BMS and RV Mais Promocao Eventos LTDS
- Fees for travel, food and beverage from DAVA Oncology, Tango Therapeutics, AstraZeneca Pharmaceuticals, and Amgen Inc., AACR, IASLC, MJH Life Sciences, IDEOlogy Health, MI&T, PER LLC, CURIO LLC
- Stock or stock options in BioNTech SE and Moderna Inc.
- Research grants (to institution) from Amgen, Revolution Medicines, Mirati Therapeutics, Boehringer Ingelheim, Merck & Co, and Novartis.
- Study Chair funds (to institution) from Pfizer
- Research grants (spouse, to institution) from Almmune, Genentech
- Consulting fees (spouse) from Genentech, Novartis

STK11 alterations represent the most prevalent genomic driver of the cold TIME in ns-NSCLC

A.



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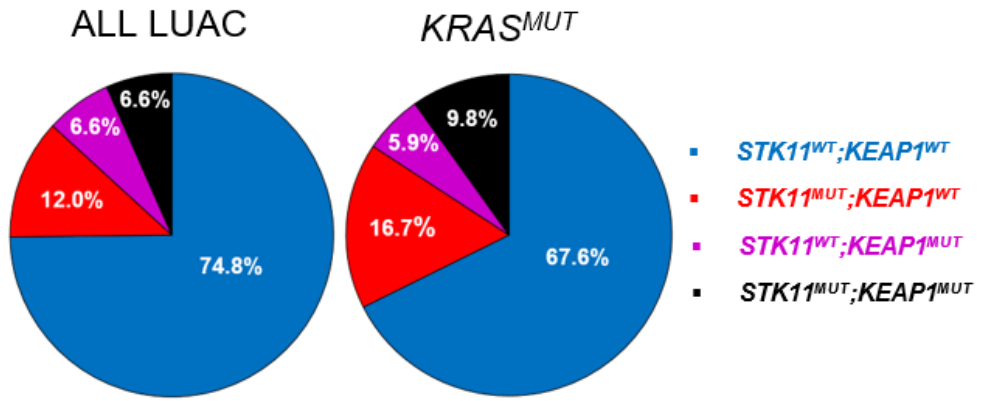

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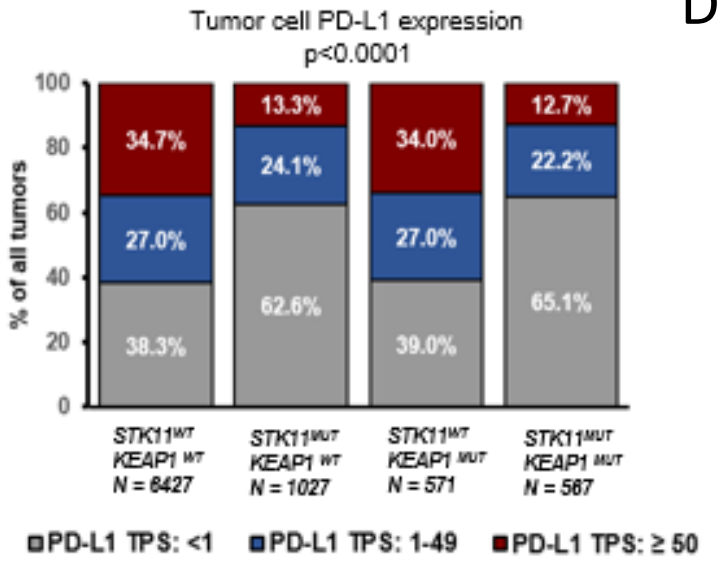

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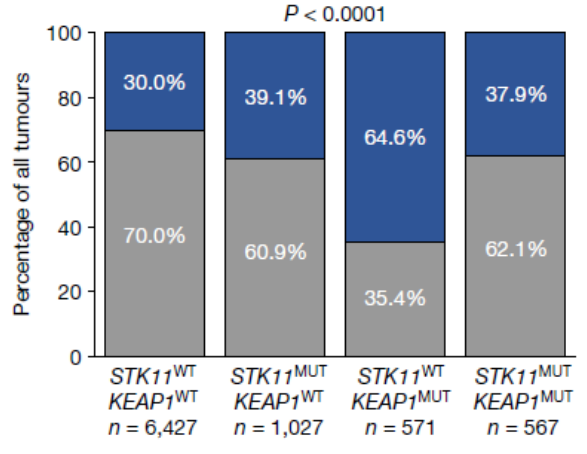


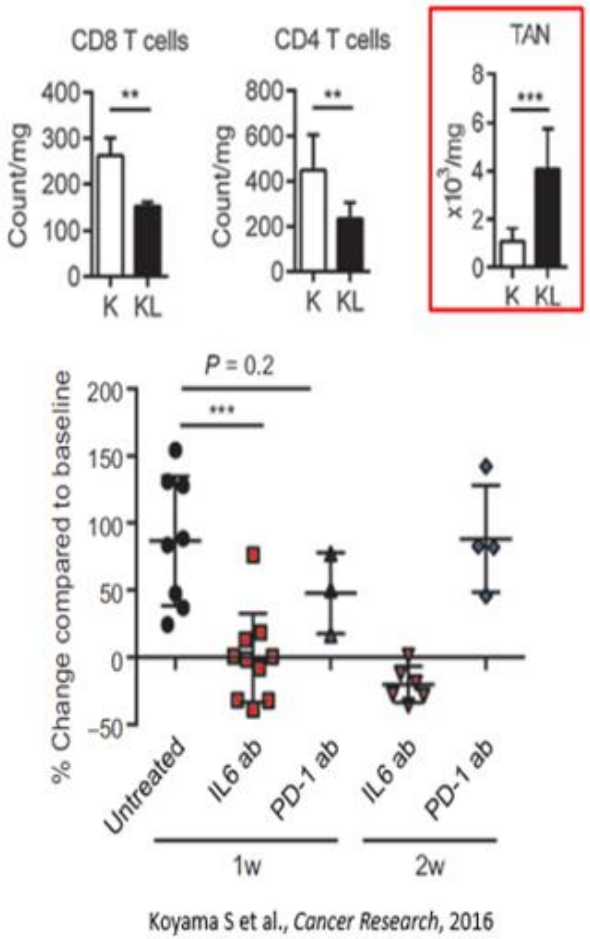
Median TMB (mutations per Mb)

$STK11^{WT}$ $KEAP1^{WT}$	$STK11^{MUT}$ $KEAP1^{WT}$	$STK11^{WT}$ $KEAP1^{MUT}$	$STK11^{MUT}$ $KEAP1^{MUT}$
5.22	7.83	13.05	7.83

Skoulidis F et al., *Nature*, 2024

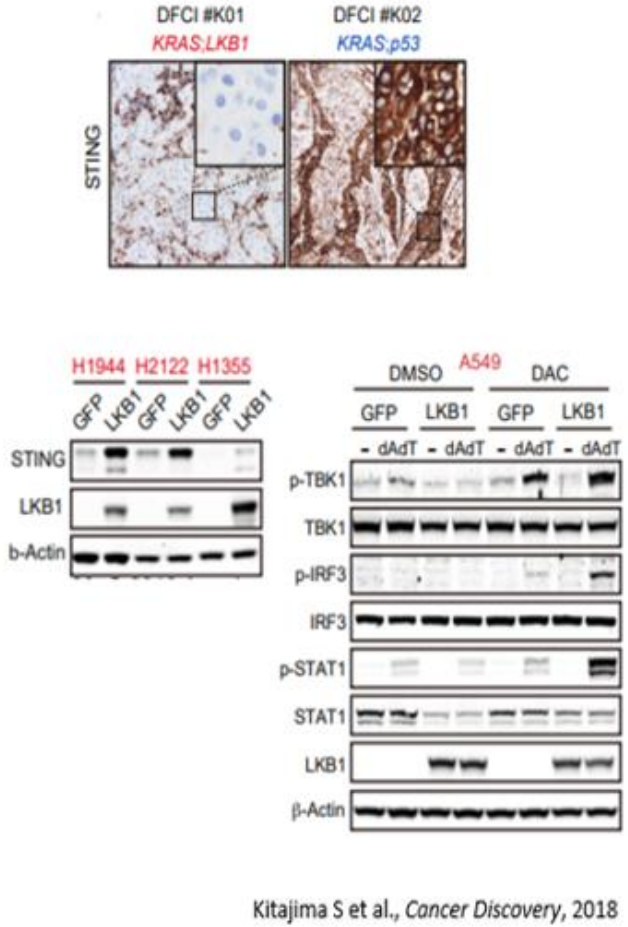
Mechanisms of *STK11* and *KEAP1* loss-mediated immune escape

Recruitment of MDSCs



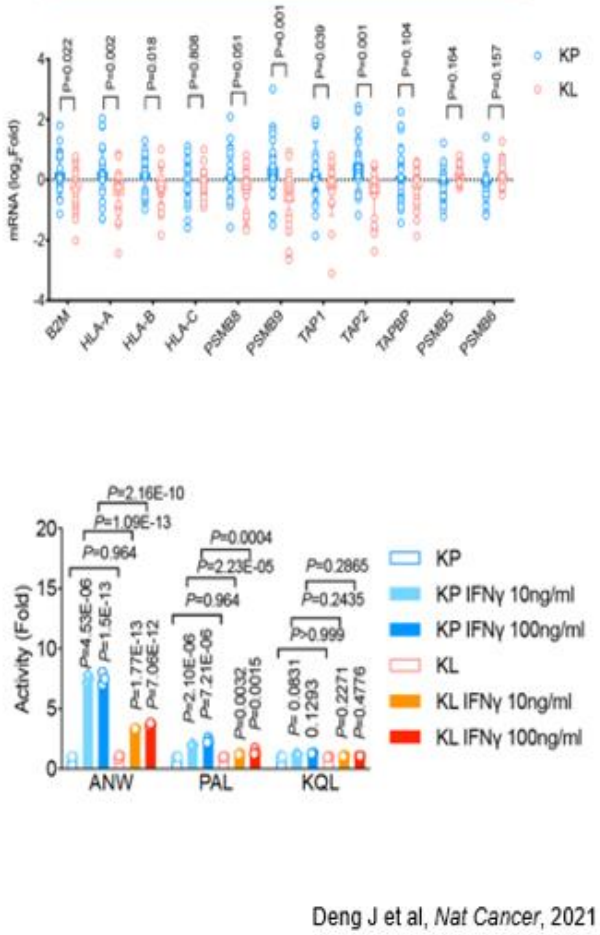
Koyama S et al., *Cancer Research*, 2016

Repression of STING



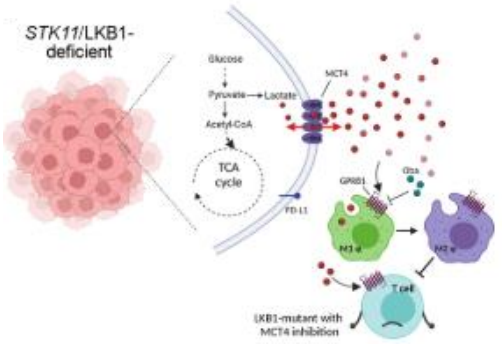
Kitajima S et al., *Cancer Discovery*, 2018

Impaired antigen presentation

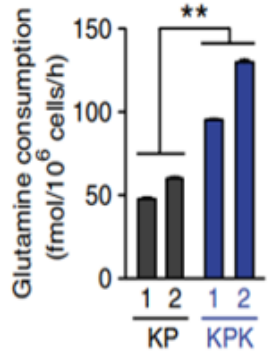


Deng J et al, *Nat Cancer*, 2021

Metabolically adverse TME



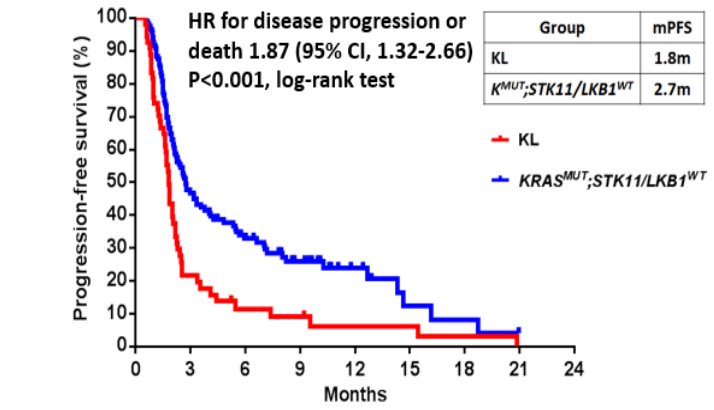
Qian et al., *Cancer Cell*, 2023

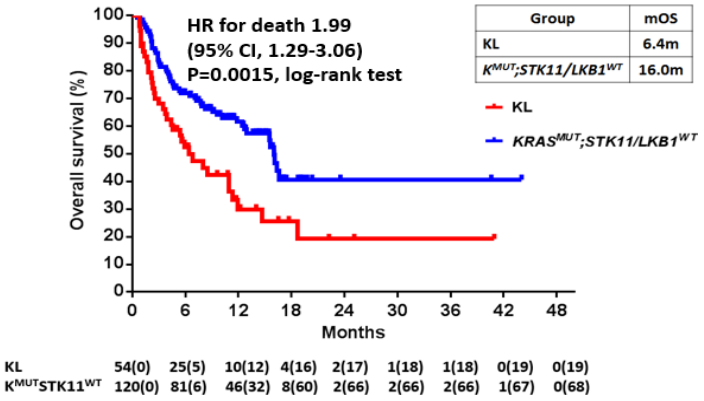


Romero et al, *Nat Med*, 2017

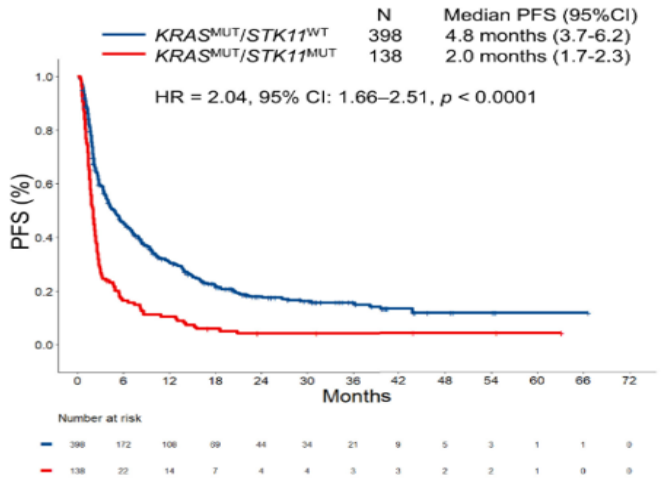
STK11 and *KEAP1* alterations drive inferior clinical outcomes with PD-1 axis inhibitor monotherapy in *KRAS*-mutant NSCLC

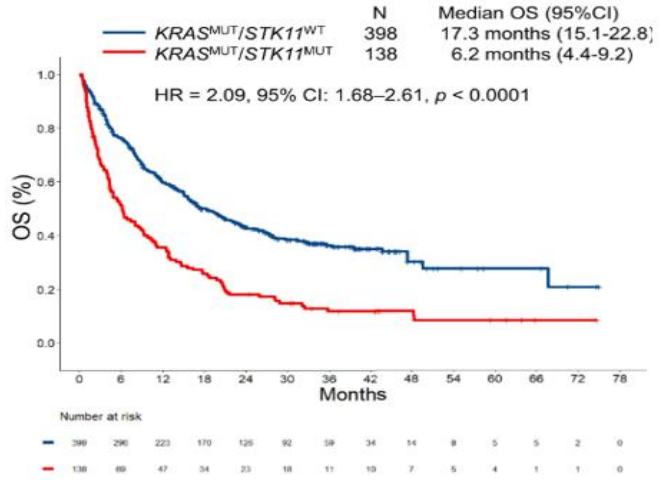
Skoulidis F et al., *Cancer Discov*, 2018



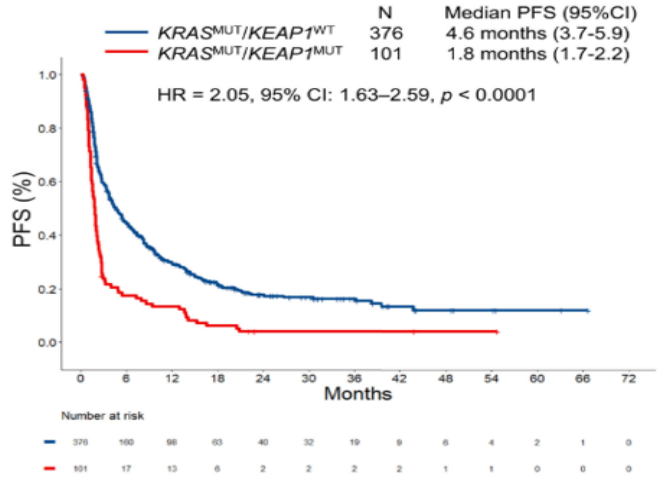


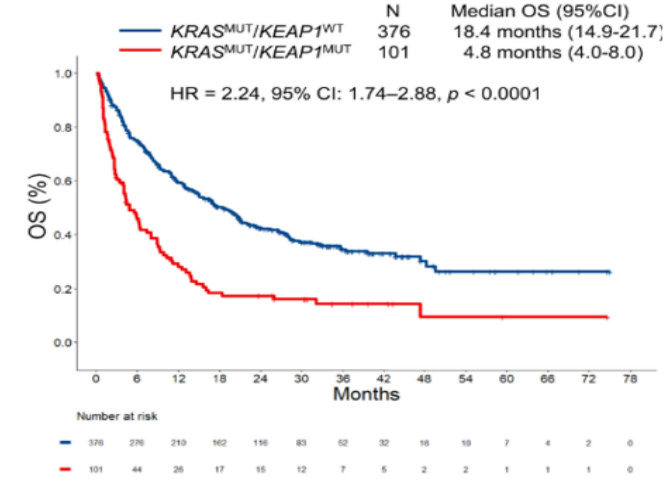
Ricciuti B et al., *JTO*, 2021



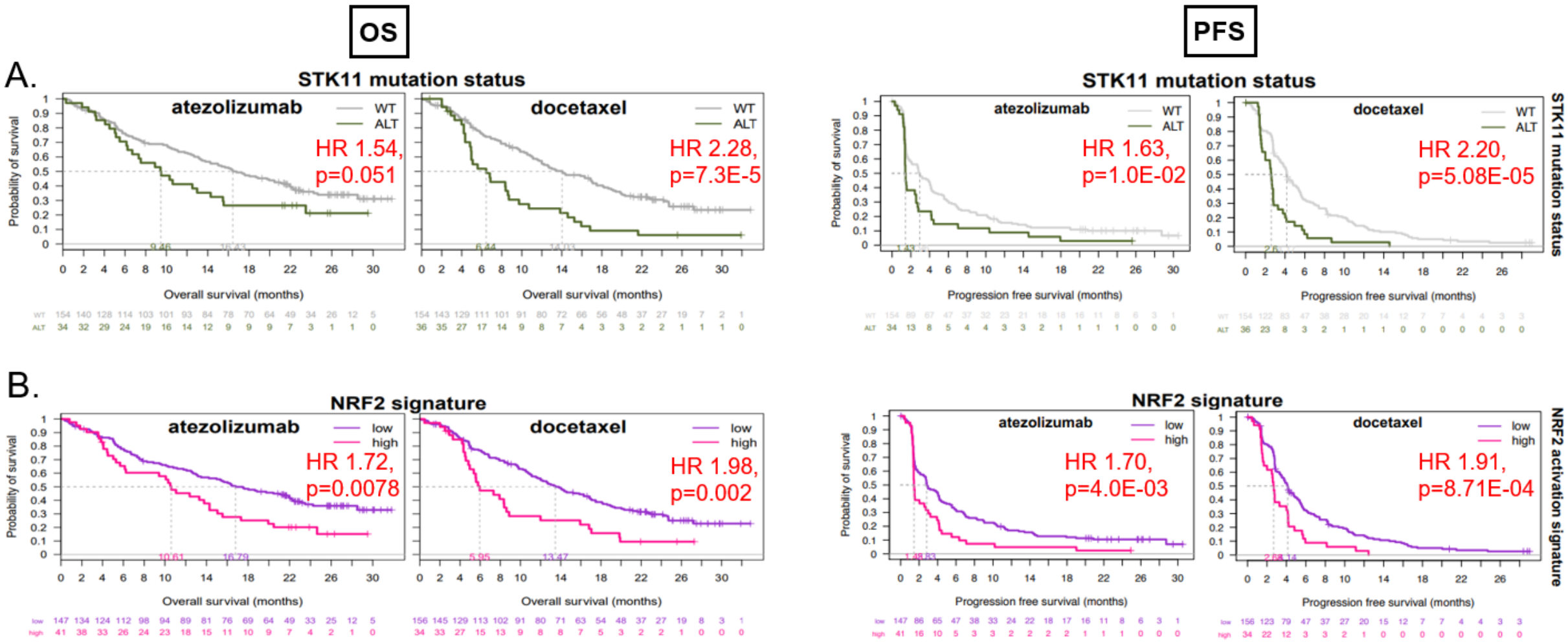


Ricciuti B et al., *J TO*, 2021





STK11 alterations and NRF2 activation are associated with worse clinical outcomes with either atezolizumab or docetaxel in the OAK Phase 3 clinical RCT

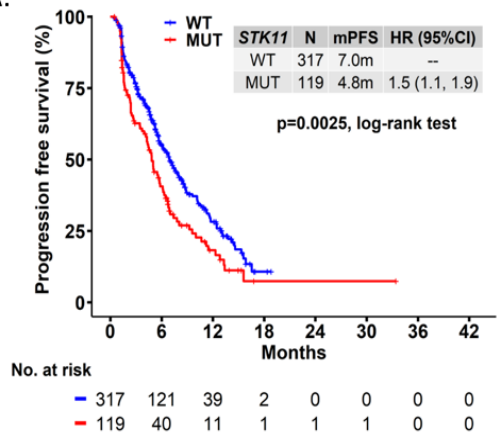


Singh A et al., *Clin Cancer Res*, 2020

STK11 and *KEAP1* alterations and clinical outcomes with first-line PCP chemoIO (platinum, pemetrexed, pembrolizumab)

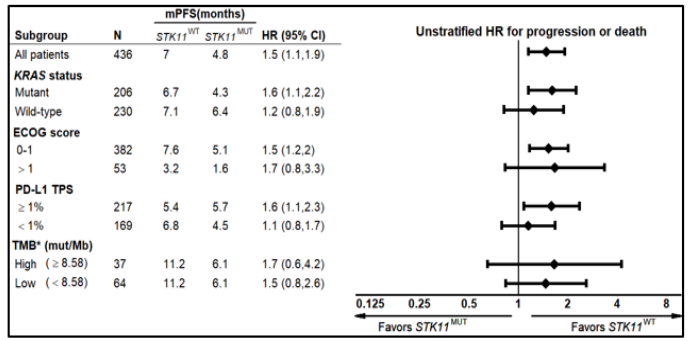
STK11

A.



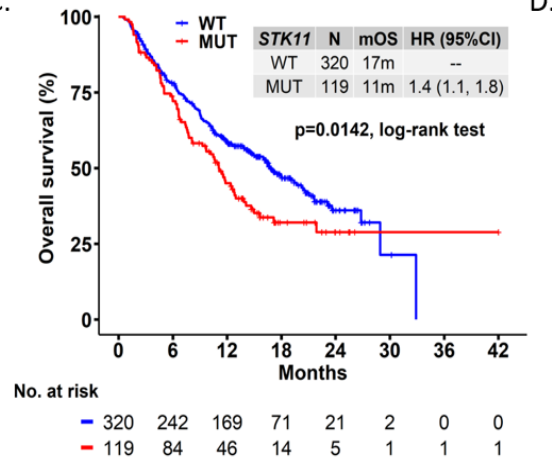
STK11	N	mPFS	HR (95%CI)
WT	317	7.0m	--
MUT	119	4.8m	1.5 (1.1, 1.9)

B.



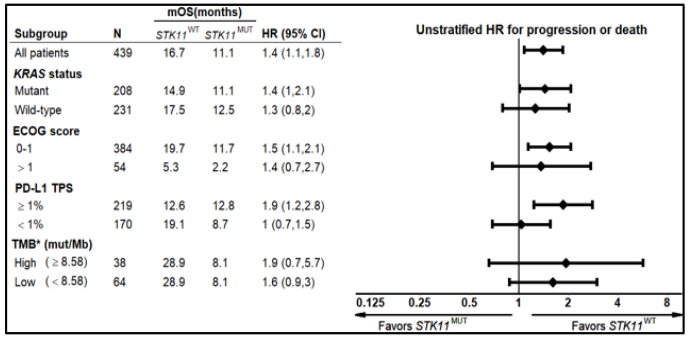
Subgroup	N	mPFS(months) *STK11*^{WT}	mPFS(months) *STK11*^{MUT}	HR (95% CI)
All patients	436	7	4.8	1.5 (1.1,1.9)
***KRAS* status**				
Mutant	206	6.7	4.3	1.6 (1.1,2.2)
Wild-type	230	7.1	6.4	1.2 (0.8,1.9)
ECOG score				
0-1	382	7.6	5.1	1.5 (1.2,2)
>1	53	3.2	1.6	1.7 (0.8,3.3)
PD-L1 TPS				
≥1%	217	5.4	5.7	1.6 (1.1,2.3)
<1%	169	6.8	4.5	1.1 (0.8,1.7)
TMB* (mut/Mb)				
High (≥8.58)	37	11.2	6.1	1.7 (0.6,4.2)
Low (<8.58)	64	11.2	6.1	1.5 (0.8,2.6)

C.



STK11	N	mOS	HR (95%CI)
WT	320	17m	--
MUT	119	11m	1.4 (1.1, 1.8)

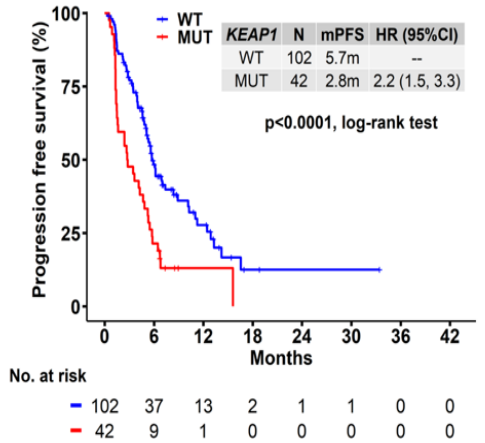
D.



Subgroup	N	mOS(months) *STK11*^{WT}	mOS(months) *STK11*^{MUT}	HR (95% CI)
All patients	439	16.7	11.1	1.4 (1.1,1.8)
***KRAS* status**				
Mutant	208	14.9	11.1	1.4 (1,2.1)
Wild-type	231	17.5	12.5	1.3 (0.8,2)
ECOG score				
0-1	384	19.7	11.7	1.5 (1.1,2.1)
>1	54	5.3	2.2	1.4 (0.7,2.7)
PD-L1 TPS				
≥1%	219	12.6	12.8	1.9 (1.2,2.8)
<1%	170	19.1	8.7	1 (0.7,1.5)
TMB* (mut/Mb)				
High (≥8.58)	38	28.9	8.1	1.9 (0.7,5.7)
Low (<8.58)	64	28.9	8.1	1.6 (0.9,3)

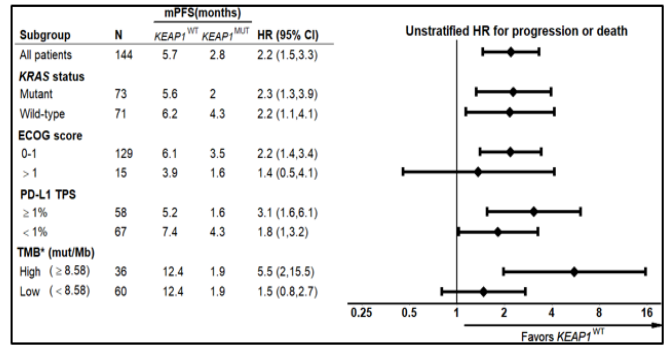
KEAP1

A.



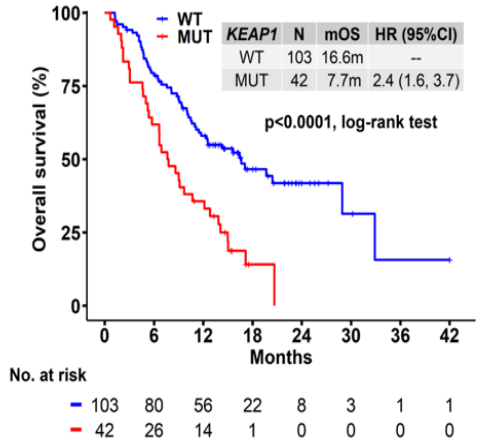
KEAP1	N	mPFS	HR (95%CI)
WT	102	5.7m	--
MUT	42	2.8m	2.2 (1.5, 3.3)

B.



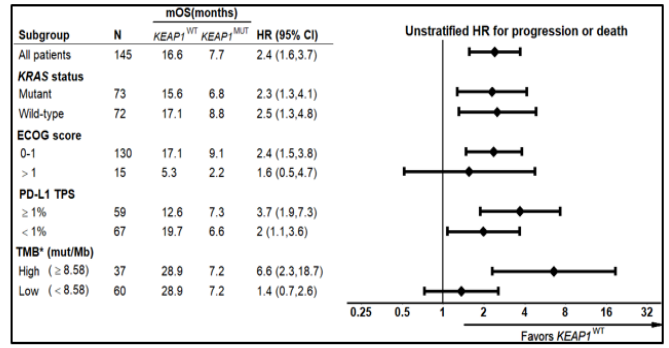
Subgroup	N	mPFS(months) *KEAP1*^{WT}	mPFS(months) *KEAP1*^{MUT}	HR (95% CI)
All patients	144	5.7	2.8	2.2 (1.5,3.3)
***KRAS* status**				
Mutant	73	5.6	2	2.3 (1.3,3.9)
Wild-type	71	6.2	4.3	2.2 (1.1,4.1)
ECOG score				
0-1	129	6.1	3.5	2.2 (1.4,3.4)
>1	15	3.9	1.6	1.4 (0.5,4.1)
PD-L1 TPS				
≥1%	58	5.2	1.6	3.1 (1.6,6.1)
<1%	67	7.4	4.3	1.8 (1,3.2)
TMB* (mut/Mb)				
High (≥8.58)	36	12.4	1.9	5.5 (2,15.5)
Low (<8.58)	60	12.4	1.9	1.5 (0.8,2.7)

C.



KEAP1	N	mOS	HR (95%CI)
WT	103	16.6m	--
MUT	42	7.7m	2.4 (1.6, 3.7)

D.



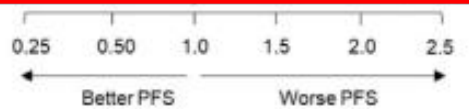
Subgroup	N	mOS(months) *KEAP1*^{WT}	mOS(months) *KEAP1*^{MUT}	HR (95% CI)
All patients	145	16.6	7.7	2.4 (1.6,3.7)
***KRAS* status**				
Mutant	73	15.6	6.8	2.3 (1.3,4.1)
Wild-type	72	17.1	8.8	2.5 (1.3,4.8)
ECOG score				
0-1	130	17.1	9.1	2.4 (1.5,3.8)
>1	15	5.3	2.2	1.6 (0.5,4.7)
PD-L1 TPS				
≥1%	59	12.6	7.3	3.7 (1.9,7.3)
<1%	67	19.7	6.6	2 (1.1,3.6)
TMB* (mut/Mb)				
High (≥8.58)	37	28.9	7.2	6.6 (2.3,18.7)
Low (<8.58)	60	28.9	7.2	1.4 (0.7,2.6)

Skoulidis F et al, *Nature*, 2024

STK11 and *KEAP1* alterations and clinical outcomes with 1st line chemoIO

Forest-plot for progression-free survival (PFS)

Mutation status	N	HR (95%, CI) PFS	*P*-value
$KRAS^{WT}$	560	reference	
$KRAS^{MUT}$	351	1.10 (0.95-1.28)	0.21
$TP53^{WT}$	370	reference	
$TP53^{MUT}$	412	0.83 (0.71-0.97)	0.020
$STK11^{WT}$	516	reference	
$STK11^{MUT}$	191	1.46 (1.22-1.76)	<0.001
$KEAP1^{WT}$	518	reference	
$KEAP1^{MUT}$	189	1.53 (1.28-1.84)	<0.001
$SMARCA4^{WT}$	593	reference	
$SMARCA4^{MUT}$	114	1.62 (1.30-2.02)	<0.001
$KRAS^{WT}$ $TP53^{WT}$	182	reference	
$KRAS^{WT}$ $TP53^{MUT}$	287	0.88 (0.71-1.08)	0.21
$KRAS^{WT}$ $STK11^{WT}$	322	reference	
$KRAS^{WT}$ $STK11^{MUT}$	99	1.19 (0.93-1.54)	0.16
$KRAS^{WT}$ $KEAP1^{WT}$	327	reference	
$KRAS^{WT}$ $KEAP1^{MUT}$	104	1.37 (1.07-1.75)	0.01
$KRAS^{WT}$ $SMARCA4^{WT}$	361	reference	
$KRAS^{WT}$ $SMARCA4^{MUT}$	70	1.36 (1.03-1.81)	<0.001
$KRAS^{MUT}$ $TP53^{WT}$	188	reference	
$KRAS^{MUT}$ $TP53^{MUT}$	125	0.75 (0.58-0.97)	0.027
$KRAS^{MUT}$ $STK11^{WT}$	184	reference	
$KRAS^{MUT}$ $STK11^{MUT}$	92	1.92 (1.46-2.53)	< 0.001
$KRAS^{MUT}$ $KEAP1^{WT}$	191	reference	
$KRAS^{MUT}$ $KEAP1^{MUT}$	85	1.82 (1.38-2.41)	<0.001
$KRAS^{MUT}$ $SMARCA4^{WT}$	232	reference	
$KRAS^{MUT}$ $SMARCA4^{MUT}$	44	2.39 (1.67-3.42)	< 0.001



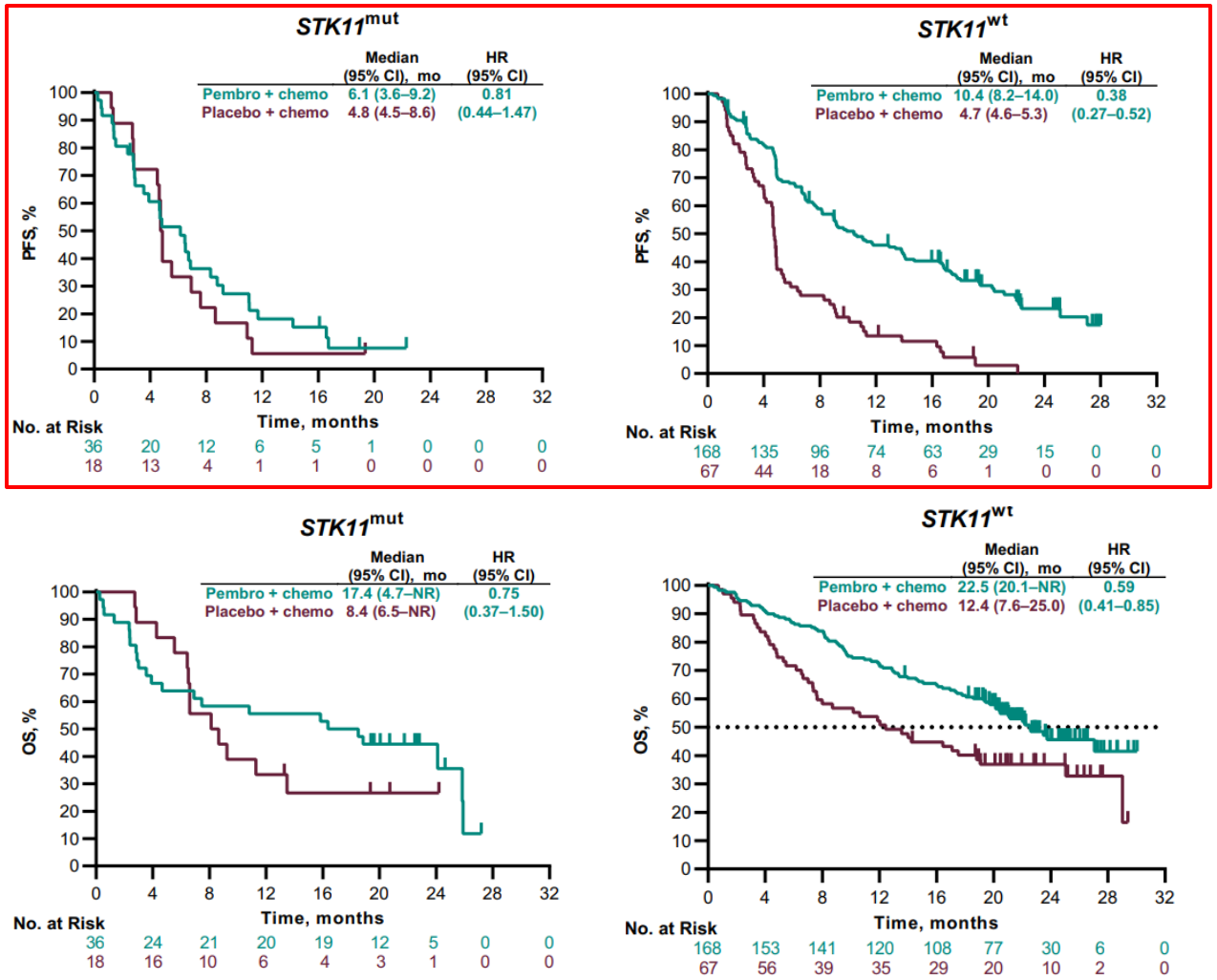
Forest-plot for overall survival (OS)

Mutation status	N	HR (95%, CI) OS	*P*-value
$KRAS^{WT}$	560	reference	
$KRAS^{MUT}$	351	1.07 (0.93-1.28)	0.42
$TP53^{WT}$	370	reference	
$TP53^{MUT}$	412	0.87 (0.73-1.04)	0.13
$STK11^{WT}$	516	reference	
$STK11^{MUT}$	191	1.36 (1.10-1.67)	0.004
$KEAP1^{WT}$	518	reference	
$KEAP1^{MUT}$	189	1.71 (1.40-2.10)	<0.001
$SMARCA4^{WT}$	593	reference	
$SMARCA4^{MUT}$	114	1.70 (1.33-2.17)	<0.001
$KRAS^{WT}$ $TP53^{WT}$	182	reference	
$KRAS^{WT}$ $TP53^{MUT}$	287	0.89 (0.70-1.13)	0.35
$KRAS^{WT}$ $STK11^{WT}$	322	reference	
$KRAS^{WT}$ $STK11^{MUT}$	99	1.14 (0.85-1.53)	0.38
$KRAS^{WT}$ $KEAP1^{WT}$	327	reference	
$KRAS^{WT}$ $KEAP1^{MUT}$	104	1.64 (1.25-2.17)	<0.001
$KRAS^{WT}$ $SMARCA4^{WT}$	361	reference	
$KRAS^{WT}$ $SMARCA4^{MUT}$	70	1.36 (0.98-1.88)	0.06
$KRAS^{MUT}$ $TP53^{WT}$	188	reference	
$KRAS^{MUT}$ $TP53^{MUT}$	125	0.85 (0.63-1.13)	0.27
$KRAS^{MUT}$ $STK11^{WT}$	184	reference	
$KRAS^{MUT}$ $STK11^{MUT}$	92	1.66 (1.22-2.26)	0.001
$KRAS^{MUT}$ $KEAP1^{WT}$	191	reference	
$KRAS^{MUT}$ $KEAP1^{MUT}$	85	1.78 (1.31-2.43)	<0.001
$KRAS^{MUT}$ $SMARCA4^{WT}$	232	reference	
$KRAS^{MUT}$ $SMARCA4^{MUT}$	44	2.52 (1.72-3.68)	<0.001

Alessi JV et al., *JTO,* 2023

Reduced benefit from the addition of pembrolizumab to platinum doublet chemotherapy in patients with *STK11* and *KEAP1*-mutant NSCLC in KEYNOTE-189

A.



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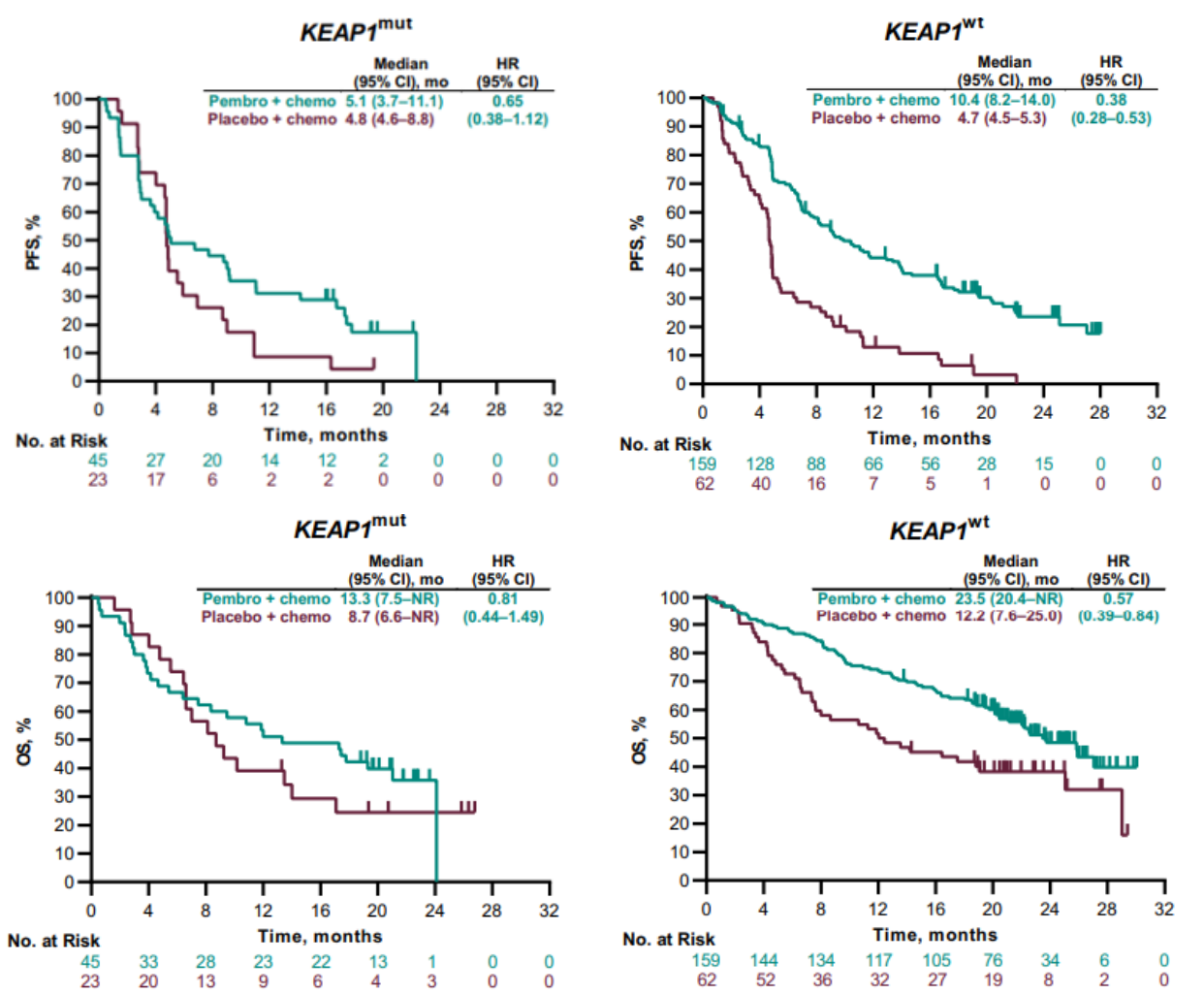
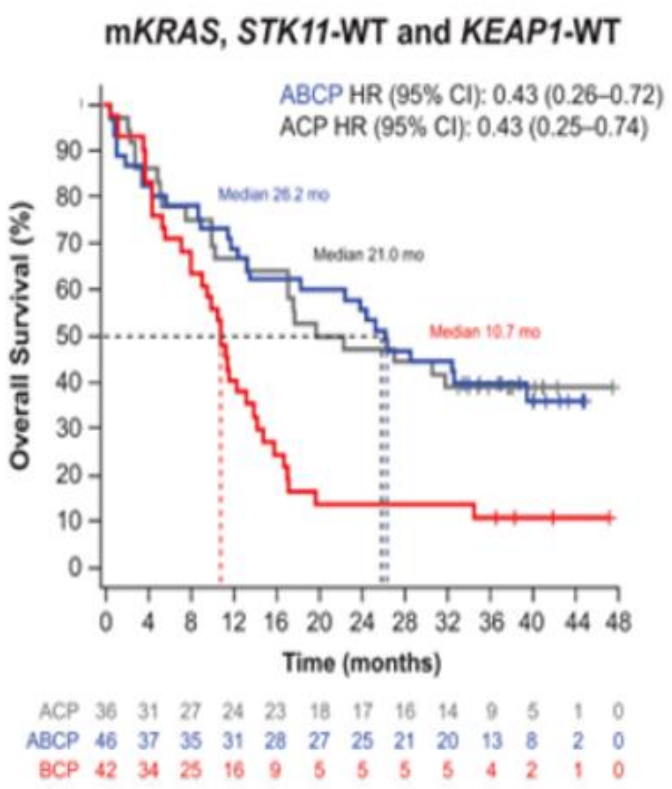
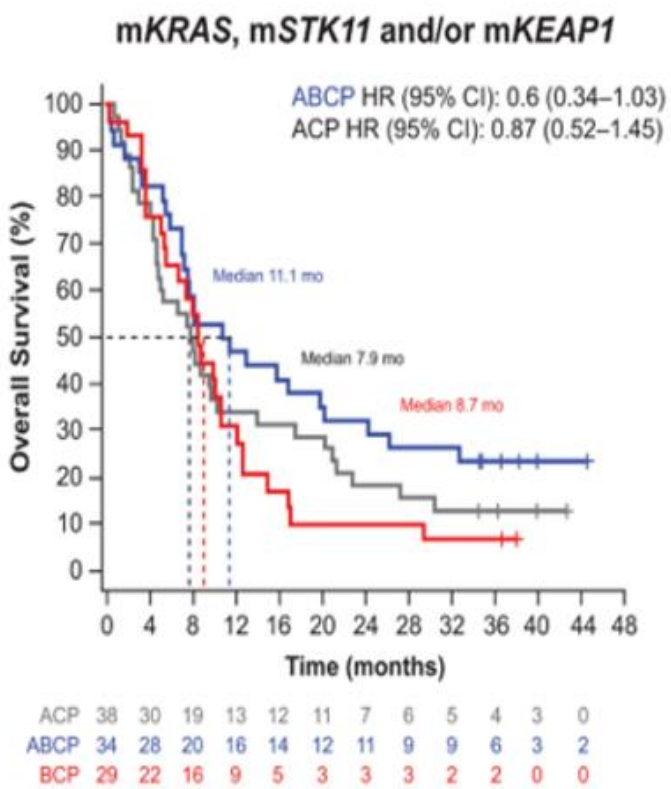
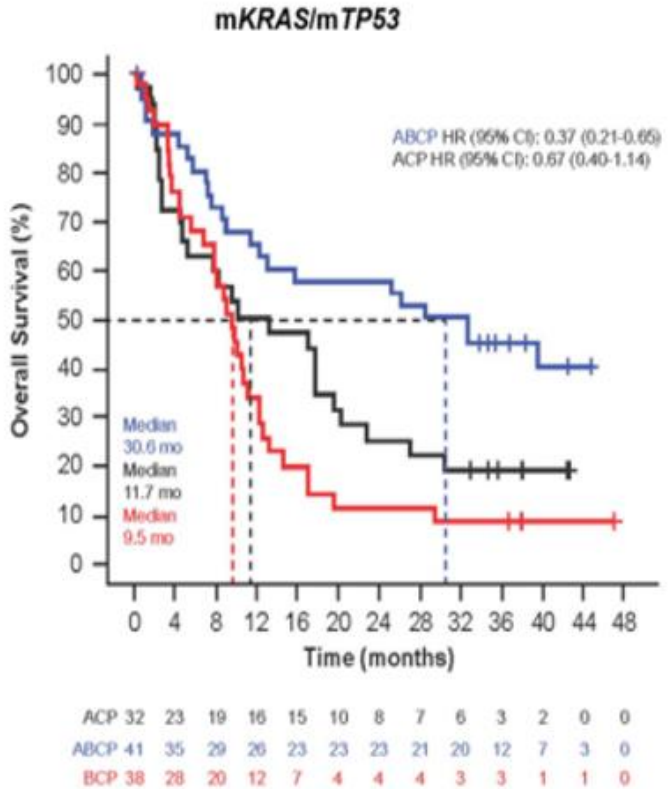


Garassino MC et al, JTO, 2022

Clinical outcomes in *KRAS* co-mutational subgroups in IMpower150





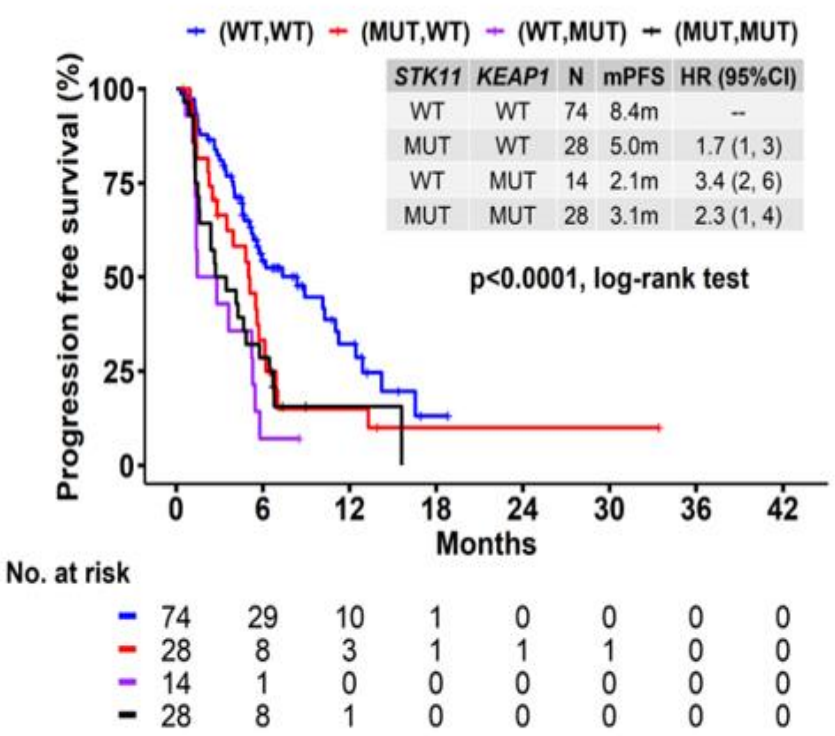


	KRAS^{MUT};*STK11*^{WT};*KEAP1*^{WT}	*KRAS*^{MUT};*TP53*^{MUT}	*KRAS*^{MUT};*STK11*^{MUT} *and/or KEAP1*^{MUT}
ABCP	26.2m	30.6m	11.1m
ACP	21m	11.7m	7.9m

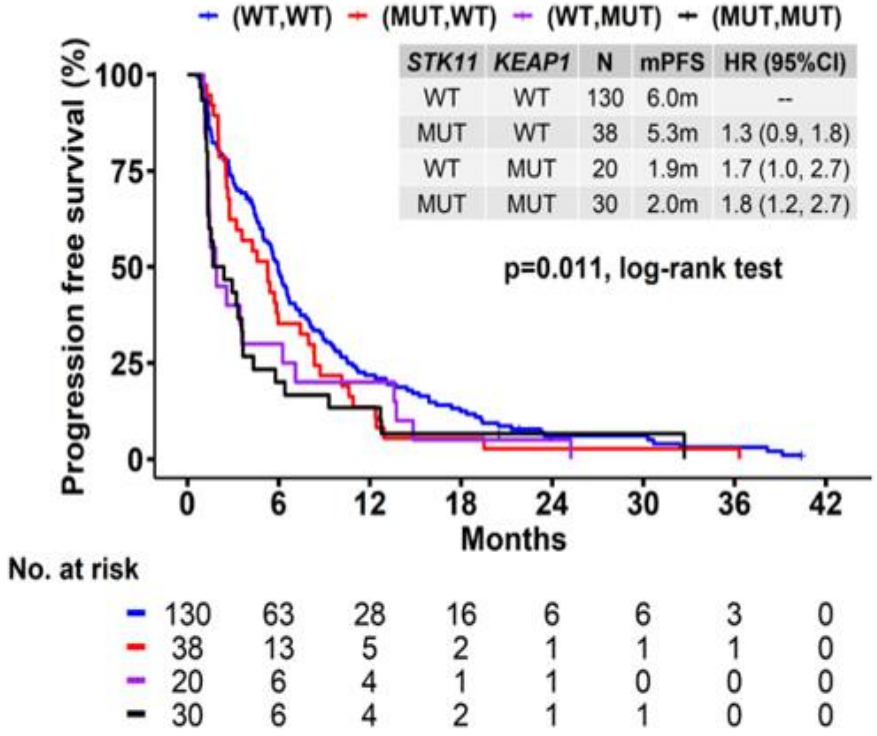
West HJ et al, JITC, 2021

Deconvoluting the impact of *STK11* and *KEAP1* alterations on clinical outcomes with systemic therapies

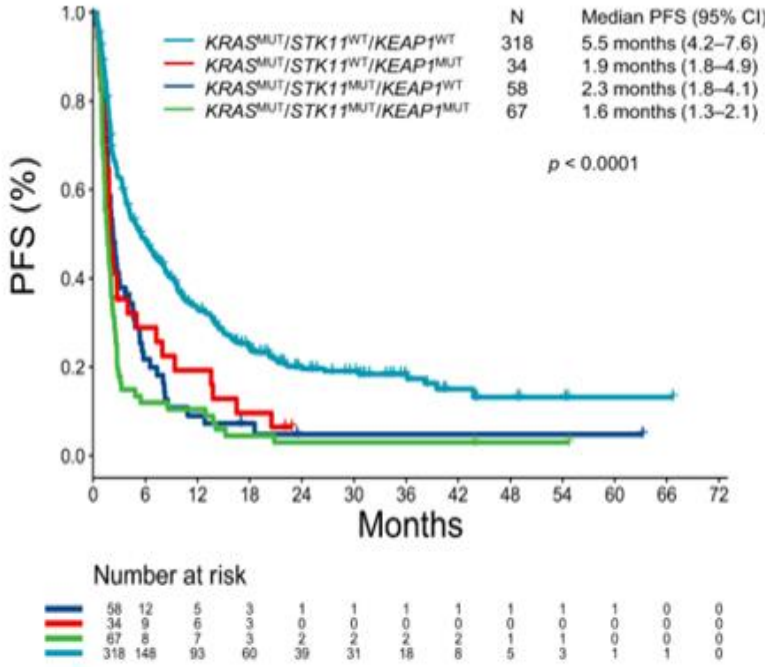
PCP Chemo-IO



Platinum-doublet



PD-(L)1 blockade

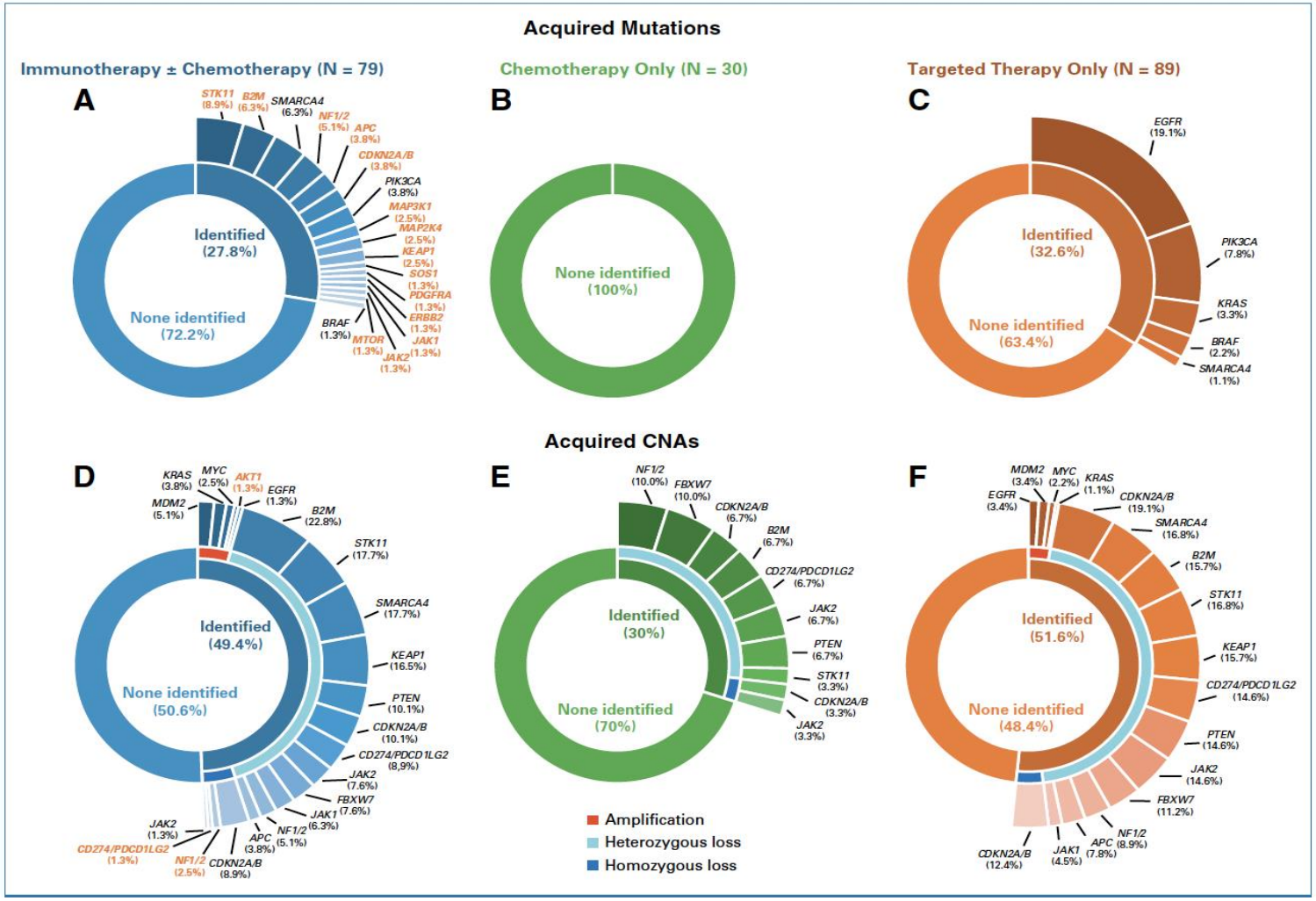


Skoulidis F et al, *Nature*, 2024

Ricciuti B et al., *JTO*, 2021

STK11 predominantly impacts ICB outcomes with single agent anti-PD-(L)1 whereas *KEAP1* alterations drive marked resistance to platinum chemo

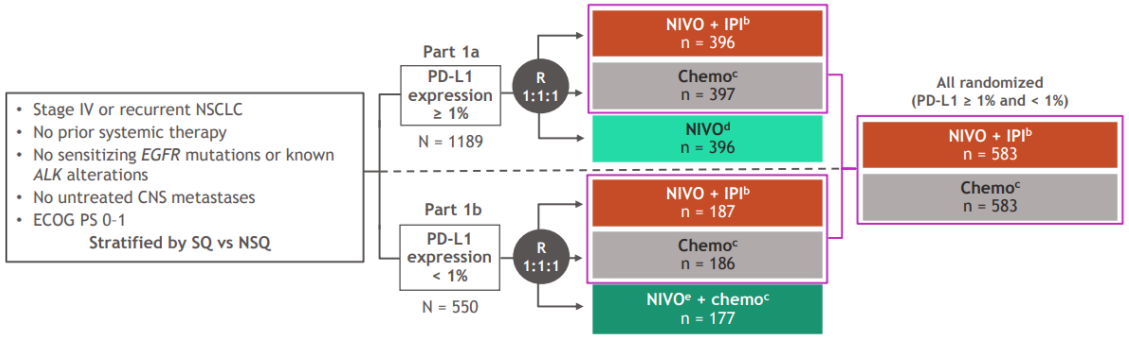
STK11 and *KEAP1* alterations represent putative mechanisms of acquired resistance to PD-1 axis immunotherapy



Ricciuti B et al., J Clin Oncol. 2024:JCO2300580

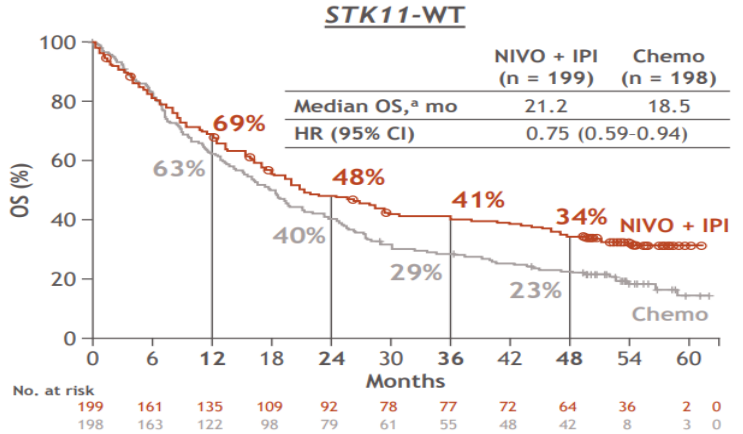
STK11 and *KEAP1* alterations and clinical outcomes with ipi/nivo in Part 1 of CheckMate 227

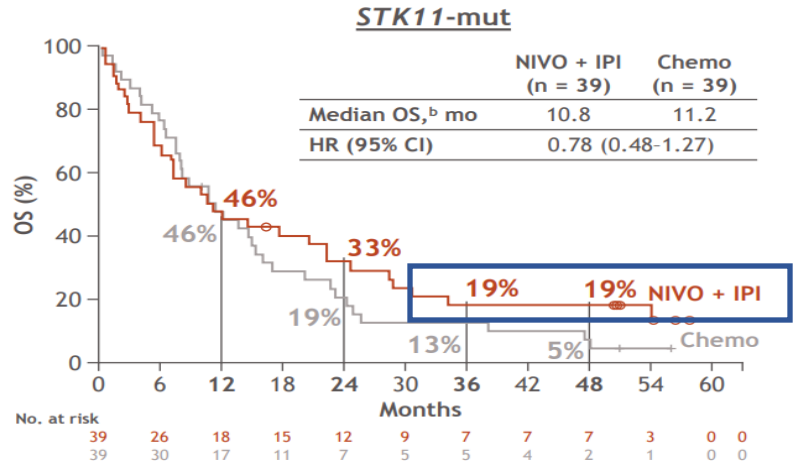
A.



PD-L1 <1% : 29%
PD-L1 ≥1% : 71%
PD-L1 ≥50%: 37%
TMB≥10Mut/Mb : 40%
TMB<10Mut/Mb : 60%

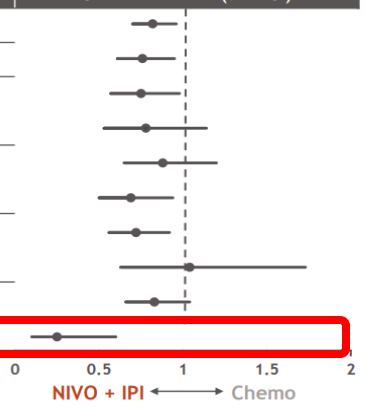
B.





C.

Subgroup, n[b]	4-y PFS rate, %		Median PFS, mo		Unstratified HR
	NIVO + IPI	Chemo	NIVO + IPI	Chemo	
NSQ (n = 419, 419)	14	3	5.2	5.6	0.82
Mut-eval (n = 238, 237)	14	3	5.6	5.6	0.76
KRAS-WT (n = 150, 162)	19	6	5.6	5.6	0.75
KRAS-mut (n = 88, 75)	17	2	5.4	5.8	0.78
TP53-WT (n = 111, 106)	10	5	5.4	5.6	0.88
TP53-mut (n = 127, 131)	24	7	5.8	6.6	0.69
STK11-WT (n = 199, 198)	19	6	8.1	6.1	0.72
STK11-mut (n = 39, 39)	13	0	2.8	4.3	1.04
KEAP1-WT (n = 218, 219)	16	6	5.5	5.8	0.83
KEAP1-mut (n = 20, 18)	41	0	11.1	2.9	0.25

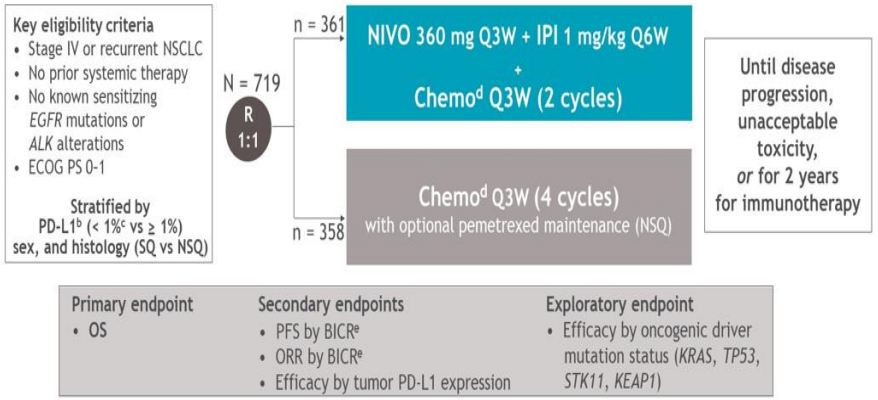


KEAP1^{MUT}(N=38)
Ipi/Nivo: mOS 24.4m
Chemo: mOS 8.9m

Ramalingam S et al., ESMO Immuno-Oncology Congress,2021

Clinical outcomes with the CheckMate 9LA regimen in *STK11*^{MUT} NSCLC

A.



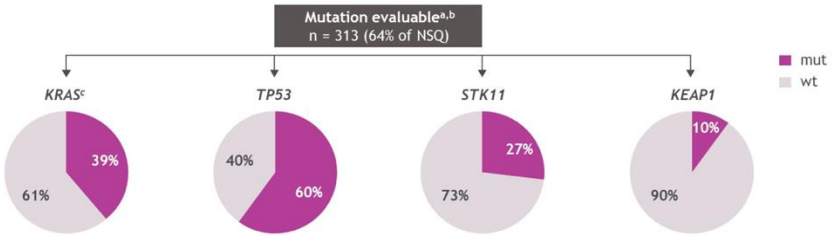
Database lock: February 15, 2022; minimum/median follow-up for OS: 36.1/42.6 months.

Reprinted from Lancet Oncology, 22, Paz-Ares L, et al, First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial, 198-211, Copyright 2021, with permission from Elsevier.

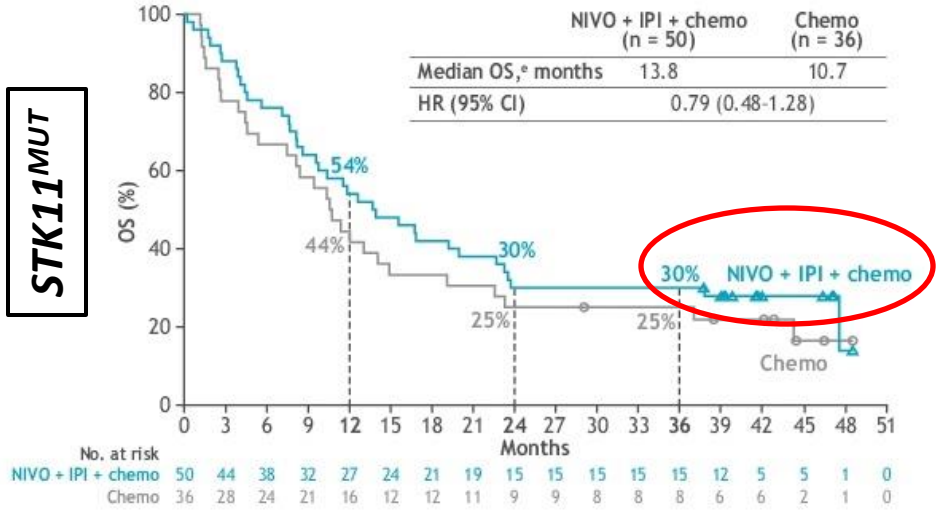
[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

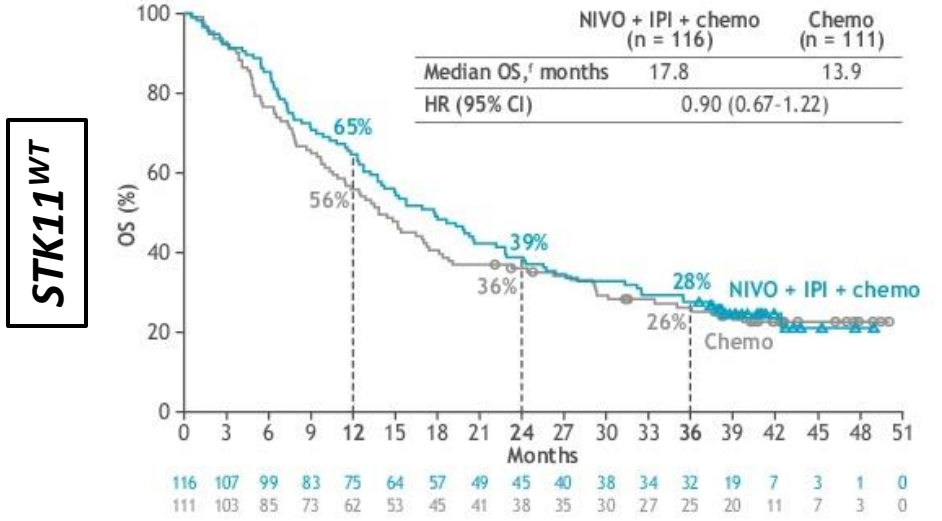
1. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198-211; 2. Reck M, et al. *ESMO Open* 2021;6:100273.

B.



C.





- Similar trend of OS benefit was seen with NIVO + IPI + chemo vs chemo in *KRAS G12C*-mut (n = 50) and *KEAP1*-mut (n = 32) subgroups

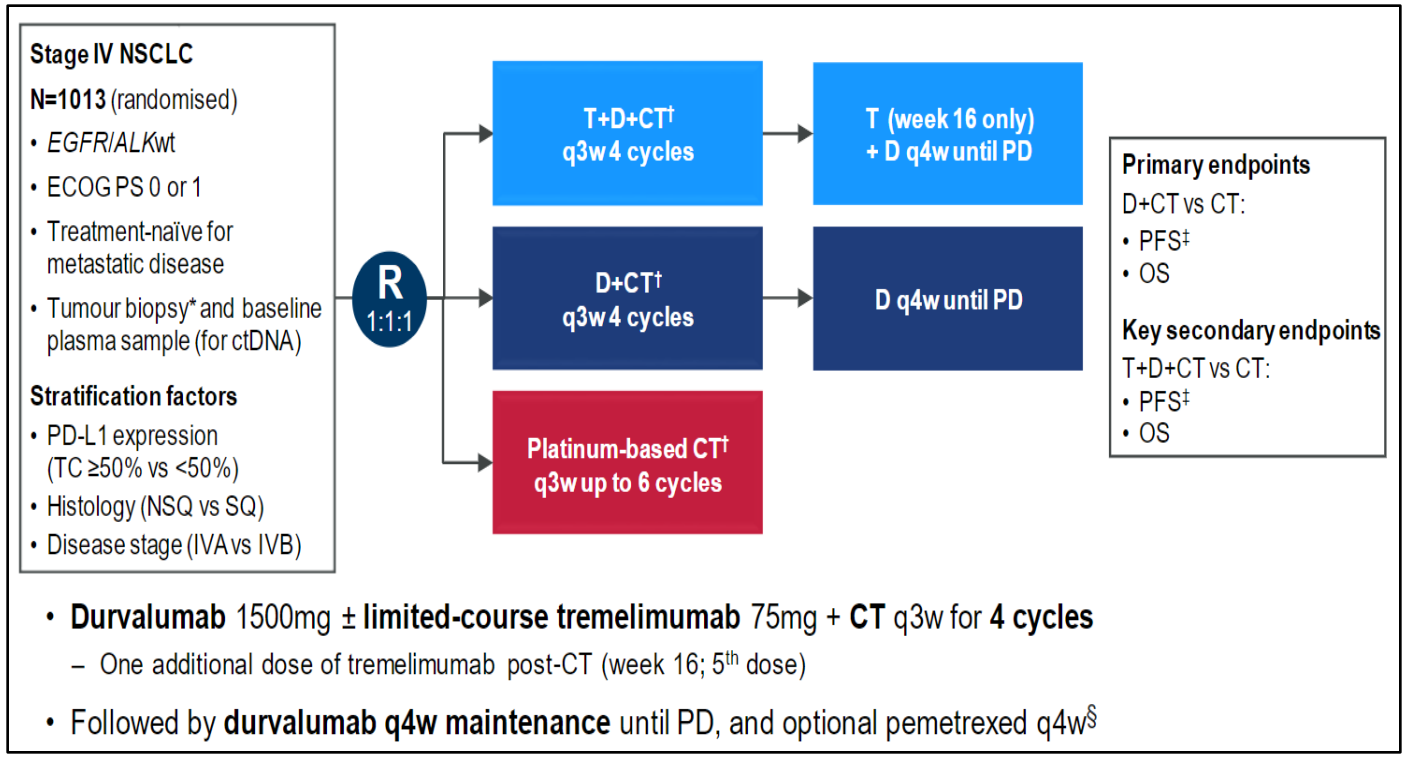
Database lock: February 15, 2022; minimum follow-up: 36.1 months.

[a]95% CI, 11.9-25.5 (NIVO + IPI + chemo) and 10.0-19.1 (chemo); [b]95% CI, 12.3-19.9 (NIVO + IPI + chemo) and 9.5-17.0 (chemo); [c]95% CI, 12.6-22.7 (NIVO + IPI + chemo) and 9.5-15.4 (chemo); [d]95% CI, 10.4-22.9 (NIVO + IPI + chemo) and 9.5-23.3 (chemo); [e]95% CI, 8.6-22.7 (NIVO + IPI + chemo) and 5.4-14.9 (chemo); [f]95% CI, 13.2-22.8 (NIVO + IPI + chemo) and 10.6-17.4 (chemo).

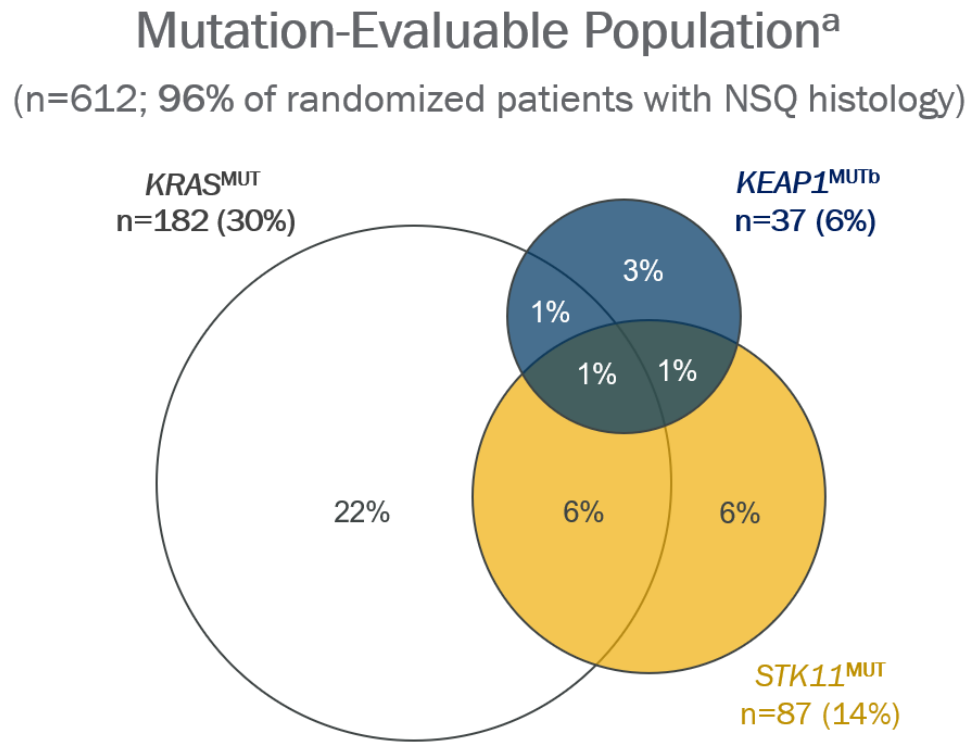
Paz-Ares L et al., ASCO, 2022

POSEIDON Study of Durvalumab+-Tremelimumab+Chemo for the 1st line Treatment of Metastatic NSCLC

A.



B.



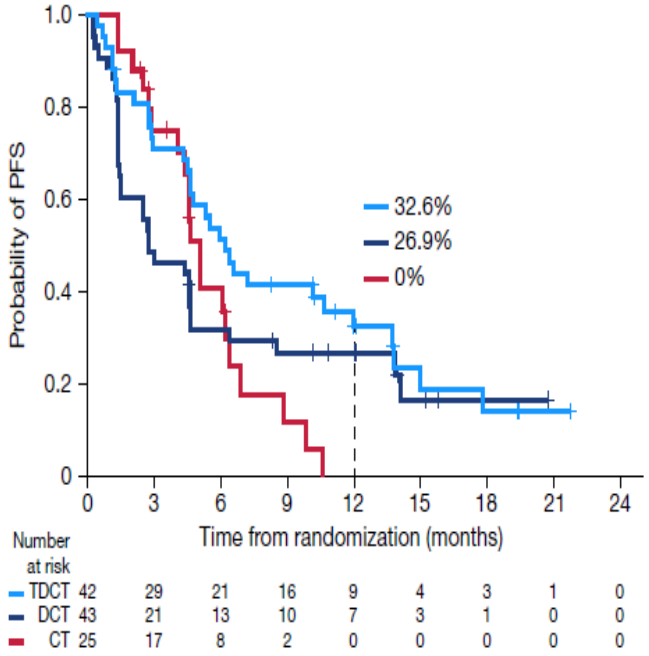
Peters S et al., WCLC, 2022

PFS and ORR with the POSEIDON regimen (D+T+chemo) in *STK11* and/or *KEAP1*-mutant NSCLC

A.

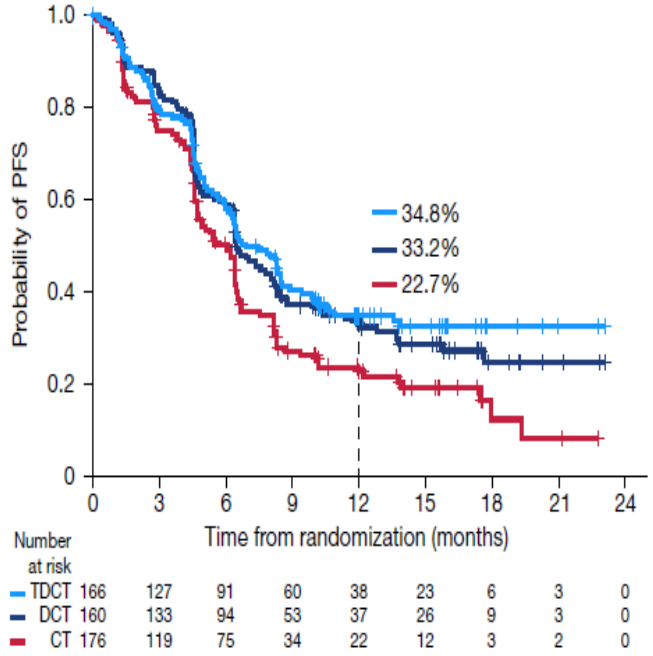
STK11^{MUT} and/or *KEAP1*^{MUT}

	TDCT	DCT	CT
mPFS (months) (95% CI)	6.2 (4.5–12.0)	2.8 (1.5–4.7)	5.1 (4.1–6.4)
HR versus CT (95% CI)	0.52 (0.28–0.95)	1.00 (0.57–1.77)	–
HR versus DCT (95% CI)	0.71 (0.43–1.17)	–	–
ORR (%) (95% CI)	42.9 (27.7–59.0)	30.2 (17.2–46.1)	28.0 (12.1–49.4)

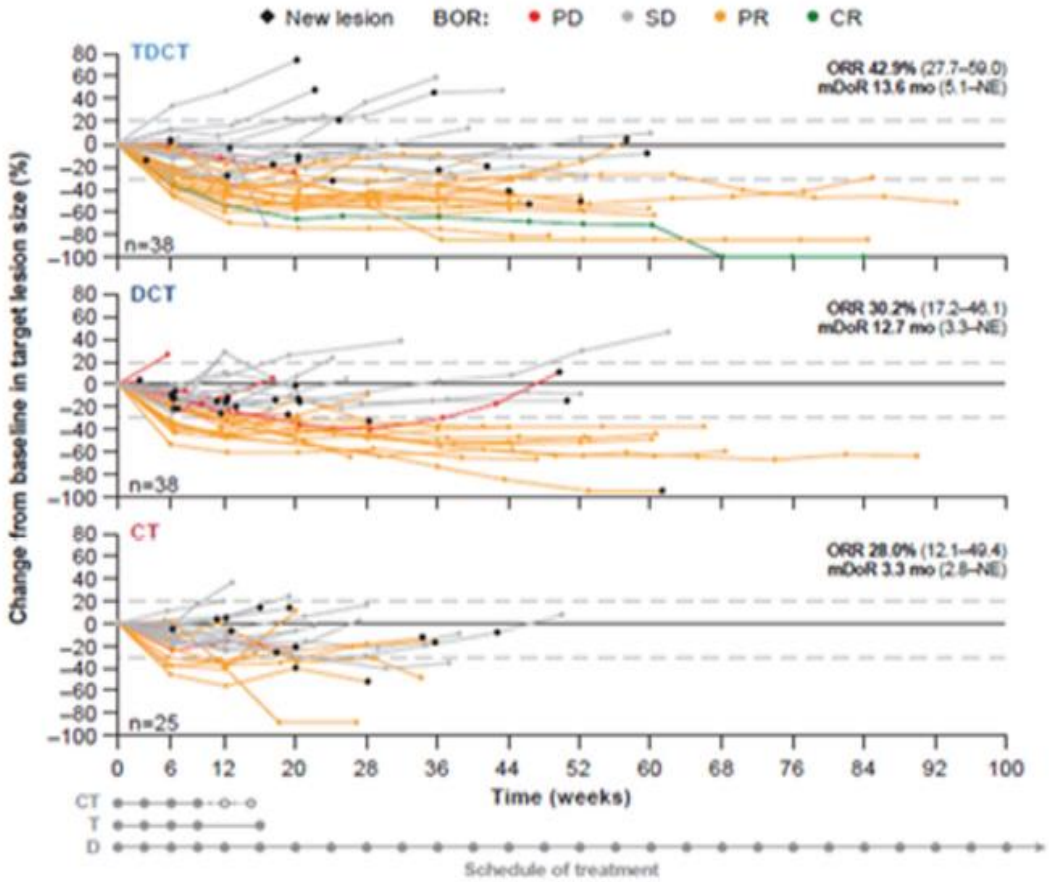


STK11^{WT} and *KEAP1*^{WT}

	TDCT	DCT	CT
mPFS (months) (95% CI)	6.9 (6.1–8.5)	6.5 (6.3–8.2)	6.1 (4.8–6.5)
HR versus CT (95% CI)	0.69 (0.53–0.89)	0.74 (0.57–0.96)	–
HR versus DCT (95% CI)	0.93 (0.71–1.21)	–	–
ORR (%) (95% CI)	47.9 (40.0–55.8)	49.4 (41.2–57.5)	23.6 (17.5–30.6)



B.

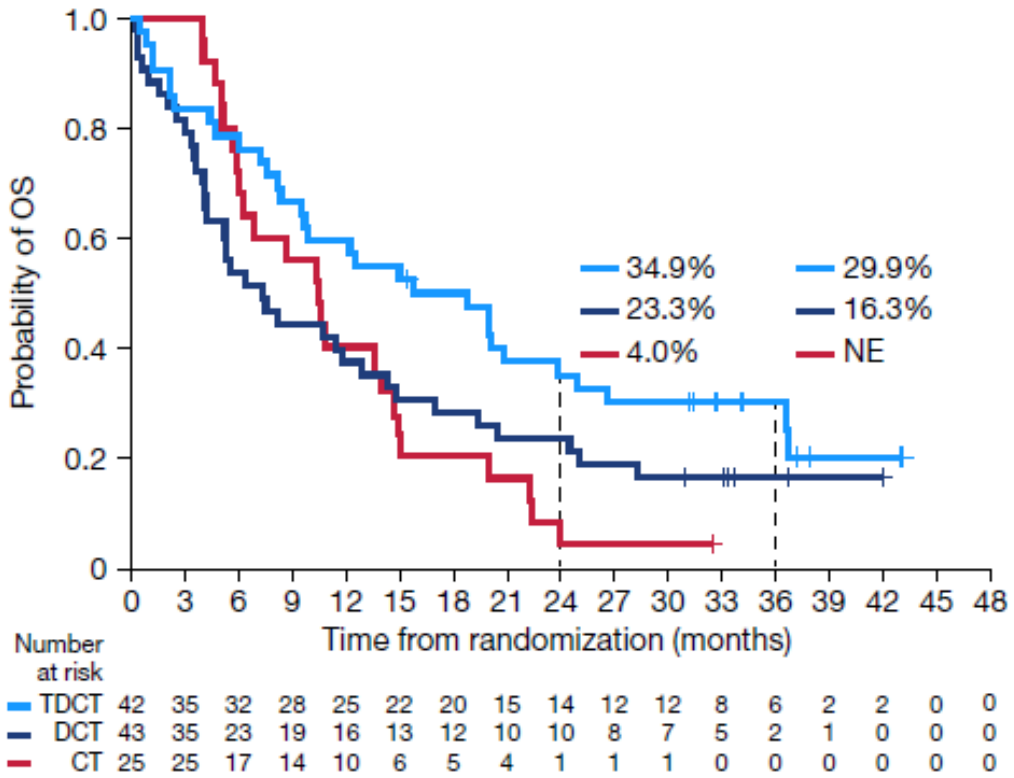


Skoulidis F et al, *Nature*, 2024

OS with the POSEIDON regimen (D+T+chemo) in *STK11* and/or *KEAP1*-mutant NSCLC

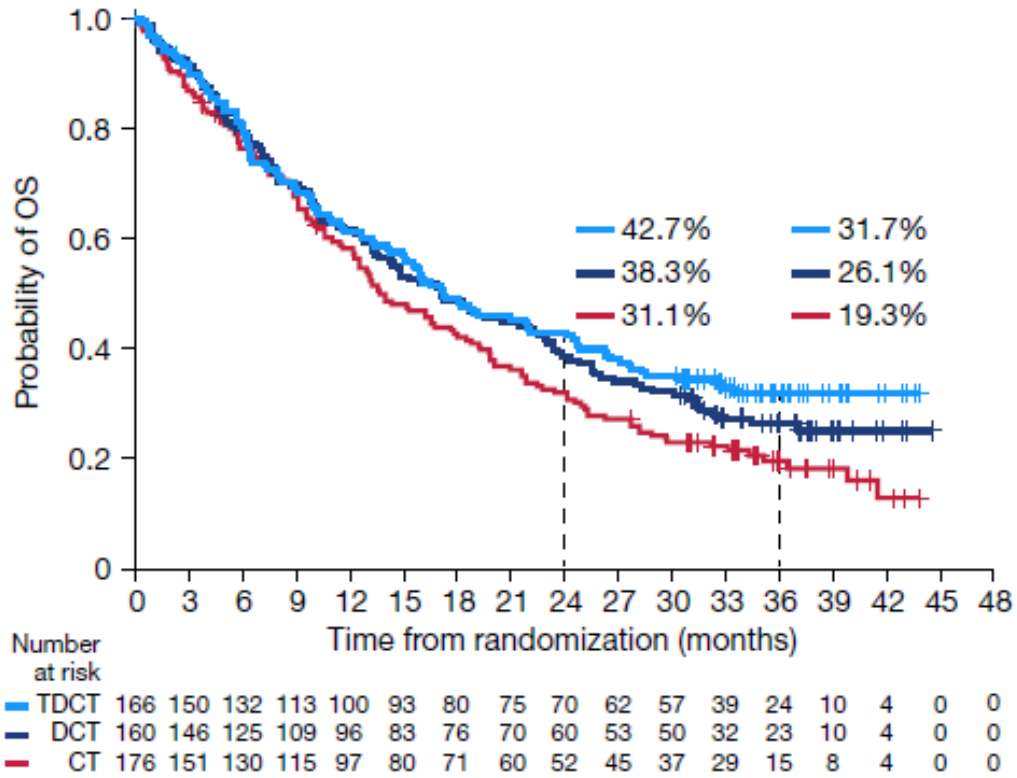
STK11^{MUT} and/or *KEAP1*^{MUT}

	TDCT	DCT	CT
mOS (months) (95% CI)	15.8 (9.5–23.8)	7.3 (4.2–12.9)	10.5 (6.0–14.7)
HR versus CT (95% CI)	0.50 (0.29–0.87)	0.90 (0.53–1.52)	–
HR versus DCT (95% CI)	0.64 (0.40–1.04)	–	–



STK11^{WT} and *KEAP1*^{WT}

	TDCT	DCT	CT
mOS (months) (95% CI)	17.2 (14.2–24.1)	17.1 (13.3–22.6)	13.7 (12.0–17.8)
HR versus CT (95% CI)	0.74 (0.58–0.95)	0.81 (0.63–1.04)	–
HR versus DCT (95% CI)	0.90 (0.69–1.17)	–	–



Skoulidis F et al, *Nature*, 2024

OS in 1st line (chemo)-IO trials in patients with *STK11* and/or *KEAP1*-mutated nsNSCLC

***STK11*^{MUT}**

	KEYNOTE-189	CheckMate 227	CheckMate 9LA	POSEIDON 5y OS update
N	54	78	86	53
Treatment	Pembrolizumab+ CT vs CT	Nivolumab+ipilimumab vs CT	Nivolumab+ipilimumab+CT vs CT	Durvalumab +tremelimumab+CT vs CT
OS HR (95% CI)	**0.75** (0.37-1.50)	**0.78** (0.48-1.27)	**0.79** (0.48-1.28)	**0.57** (0.32-1.04)
OS median (m)	17.0 vs 8.0	10.8 vs 11.2	13.8 vs 10.7	15.0 vs 10.7
3 y OS rate	Not reported	19%	30%	25.8%

***KEAP1*^{MUT}**

	KEYNOTE-189	CheckMate 227	CheckMate 9LA	POSEIDON
N	68	38	32	51*
Treatment	Pembrolizumab+ CT vs CT	Nivolumab+ipilimumab vs CT	Nivolumab+ipilimumab+CT vs CT	Durvalumab +tremelimumab+CT vs CT
OS HR (95% CI)	**0.81** (0.44-1.49)	**0.31** (0.14-0.70)	**0.51** (0.24-1.08)	**0.43** (0.16-1.25)
OS median (m)	13.0 vs 9.0	24.4 vs 8.9	13.2 vs 5.0	13.7 vs 8.7

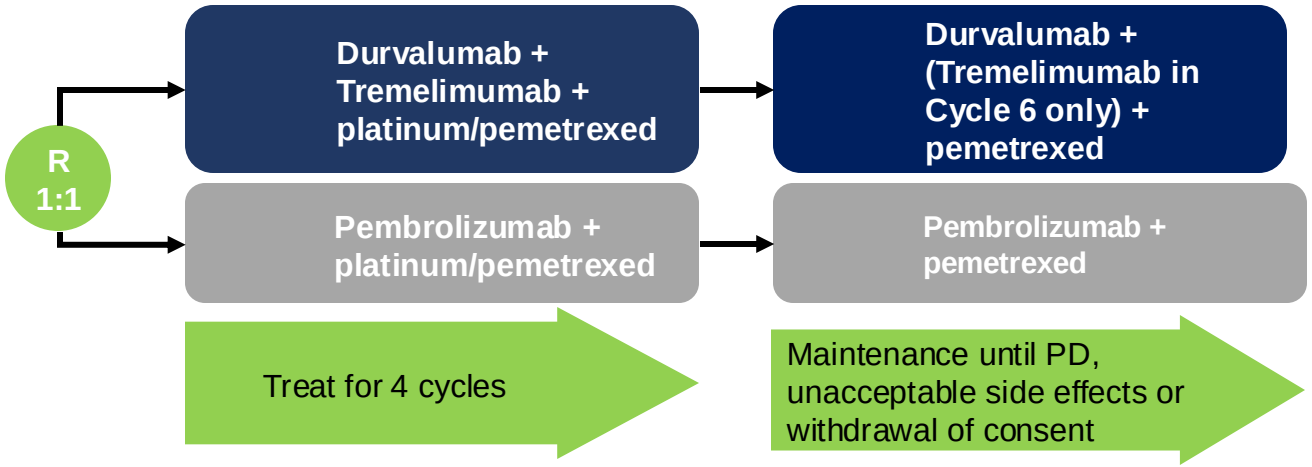
Shown for indicative purposes. Not intended for direct trial-to-trial comparisons.

*includes pts with SCC

Head to head comparison of KEYNOTE 189 and POSEIDON in patients with advanced nsNSCLC and *STK11* and/or *KEAP1* and/or *KRAS* mutations: the TRITON phase IIIB RCT

Study Population

- **N = 280**
- Metastatic **non-squamous** NSCLC with ***STK11* mutations and/or *KEAP1* mutations and/or *KRAS* mutations *** (per local NGS testing)
- No prior systemic treatment for metastatic disease
- No *EGFR* mutations or *ALK* alterations
- ECOG PS 0 or 1

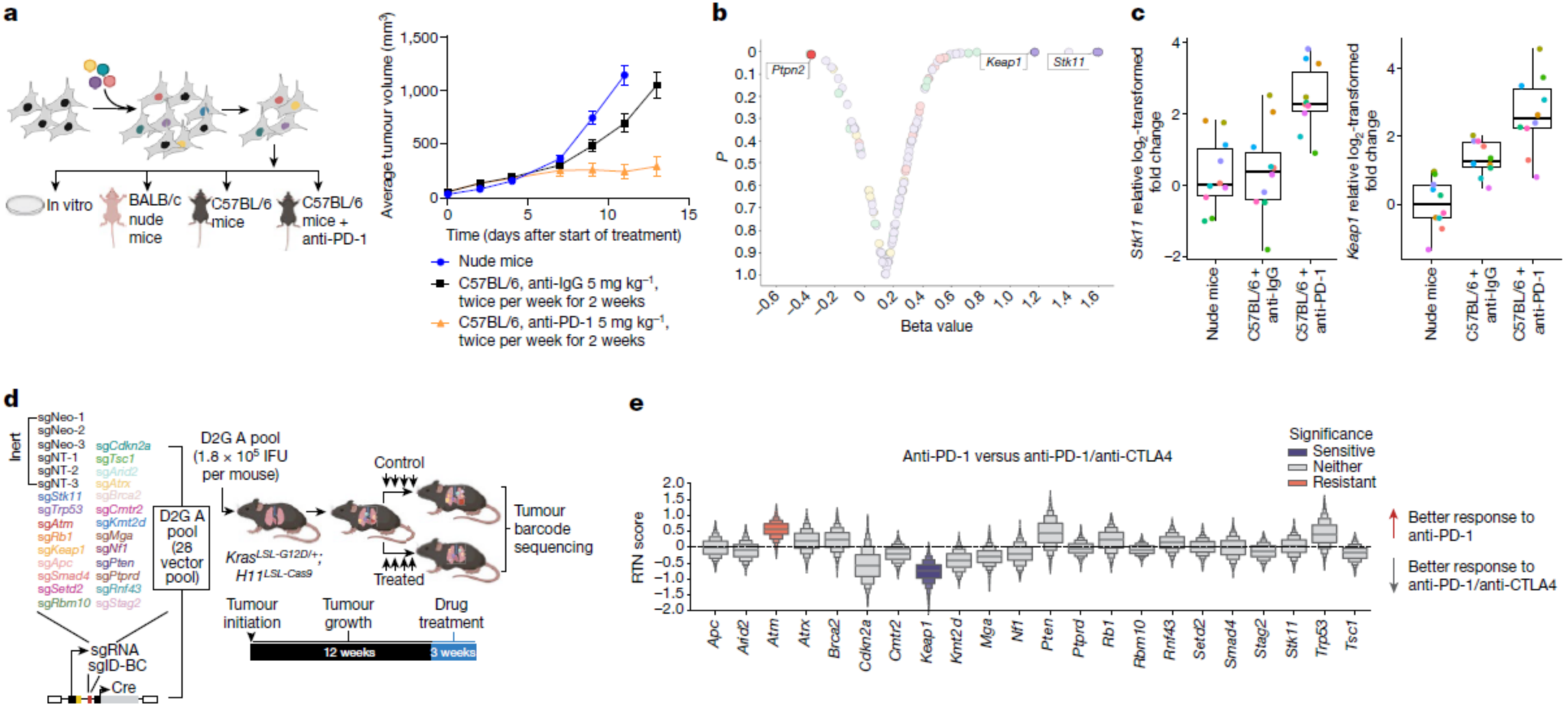


Dual Primary Endpoints

- OS in ITT
- OS in *STK11*m & *KEAP1*m

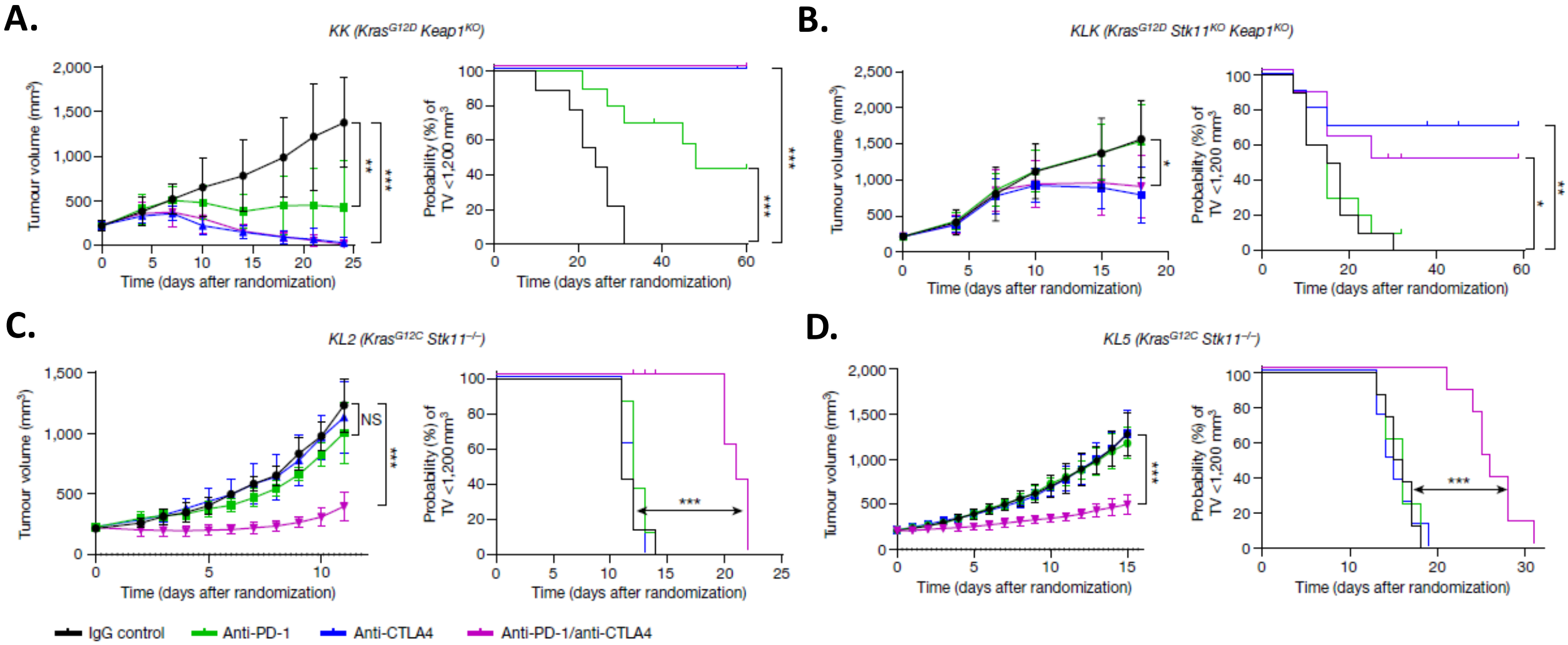
NCT06008093. Open and enrolling. Primary completion date Aug 17, 2027

In vivo CRISPR/Cas9 screens identify selective sensitivity of KEAP1-deficient *Kras*-mutant lung adenocarcinoma to dual ICB



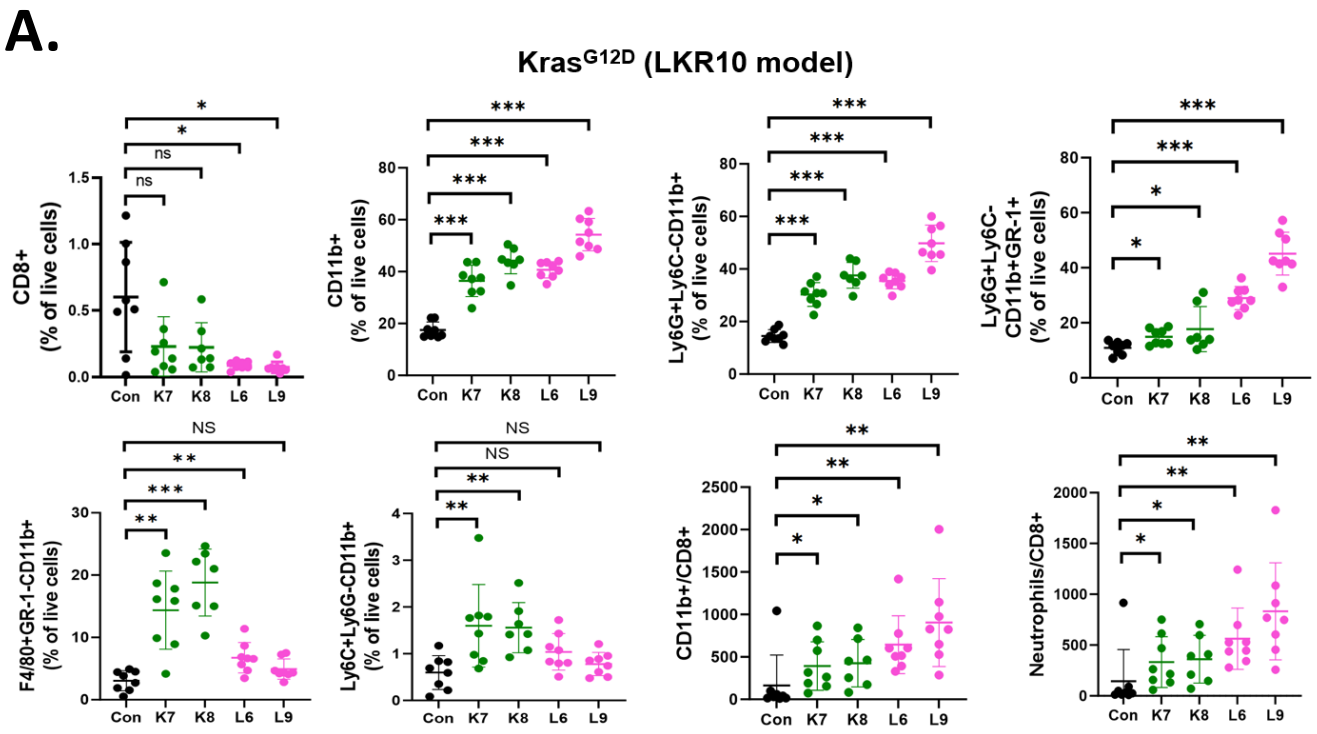
Skoulidis F et al., *Nature,* 2024

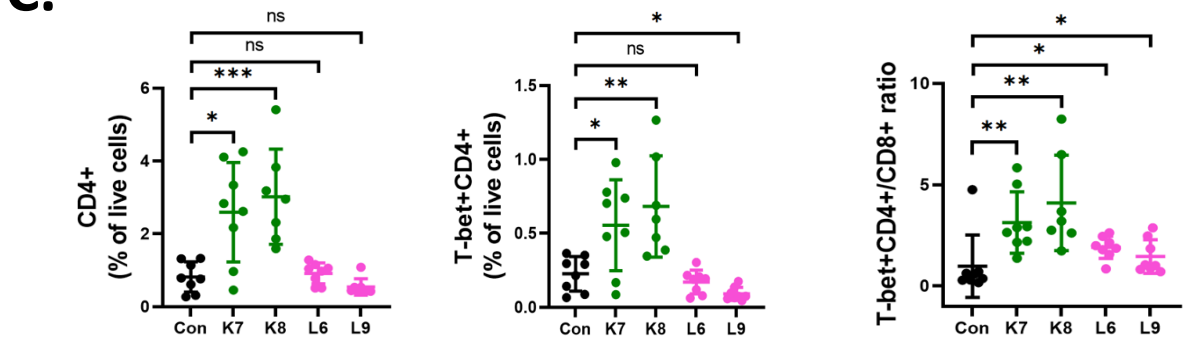
Sensitivity of *Kras^{MUT};Stk11$^{-/-}$ and/or Keap1$^{-/-}$* LUAD to dual αPD-(L)1/αCTLA-4 ICB is recapitulated in syngeneic models

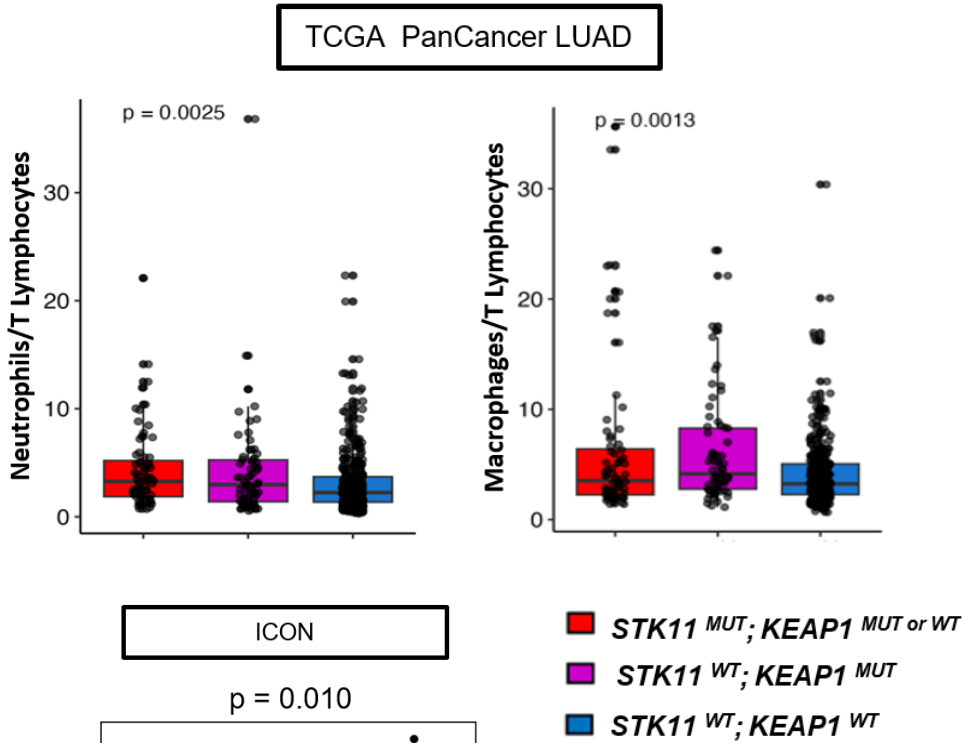


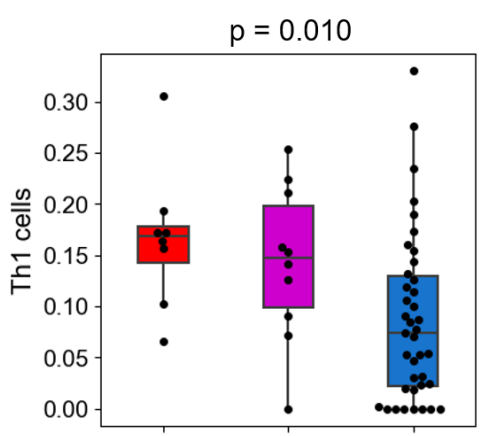
Skoulidis F et al., *Nature,* 2024

Detailed interrogation of the *STK11*^{MUT} or *KEAP1*^{MUT} TIME reveals increased myeloid/CD8+ ratio and relative retention of CD4+ effector cells



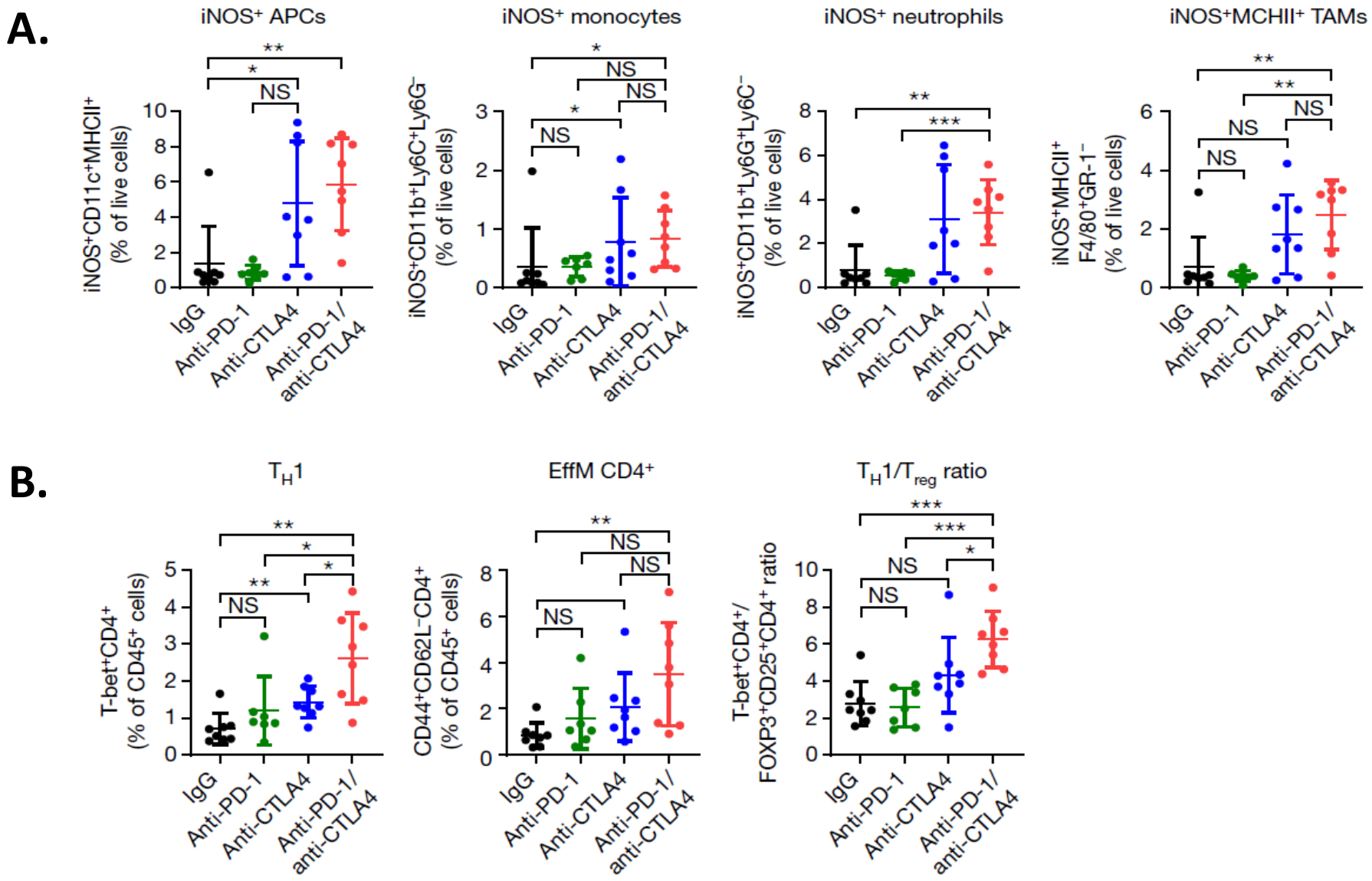






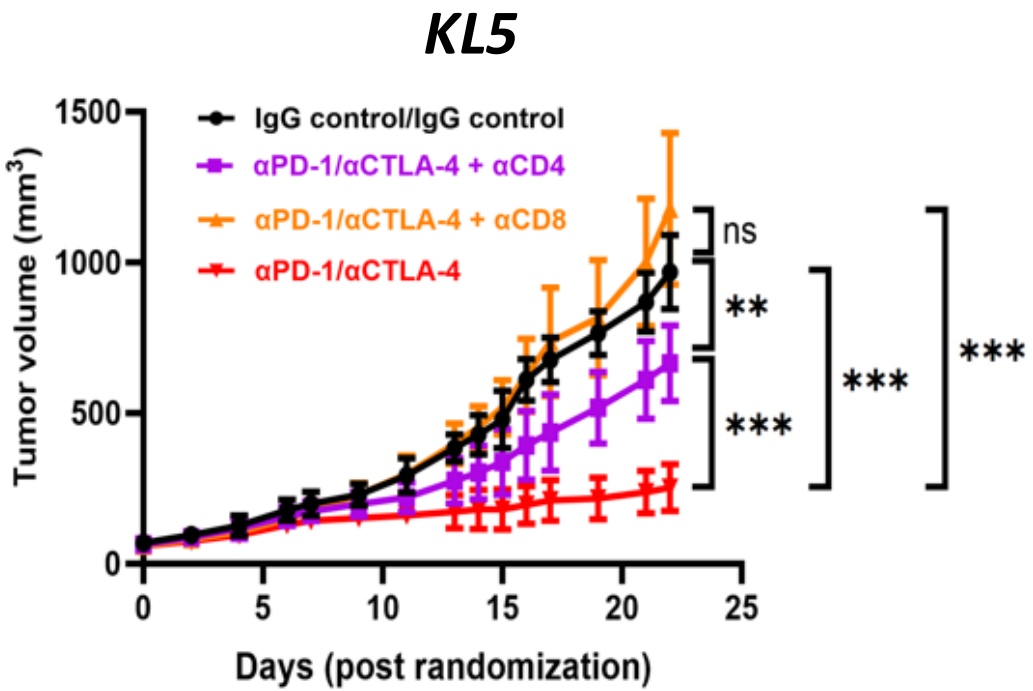
Skoulidis F et al., *Nature*, 2024

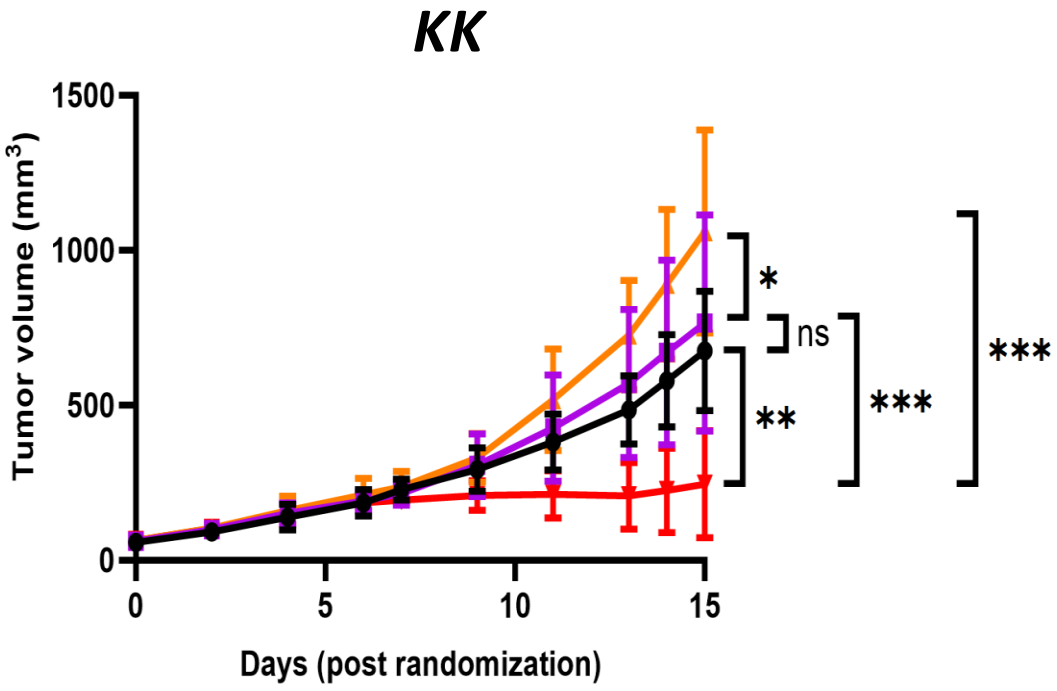
Dual ICB re-programs innate immune cells and engages CD4+ effector T cells in STK11 and/or KEAP1-deficient *KRAS*-mutant NSCLC models



Skoulidis F et al., *Nature*, 2024

The efficacy of dual ICB in STK11 and/or KEAP1-deficient NSCLC models is dependent on both CD8+ and CD4+ TILs



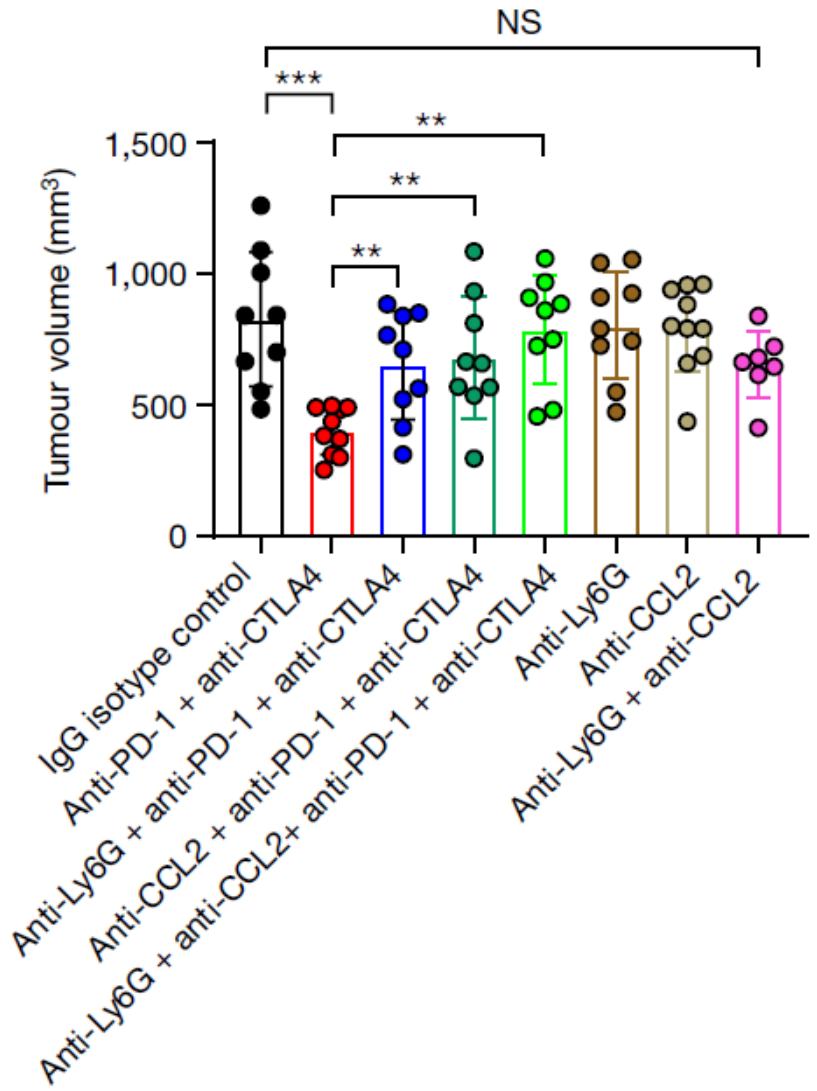


Skoulidis F et al., *Nature*, 2024

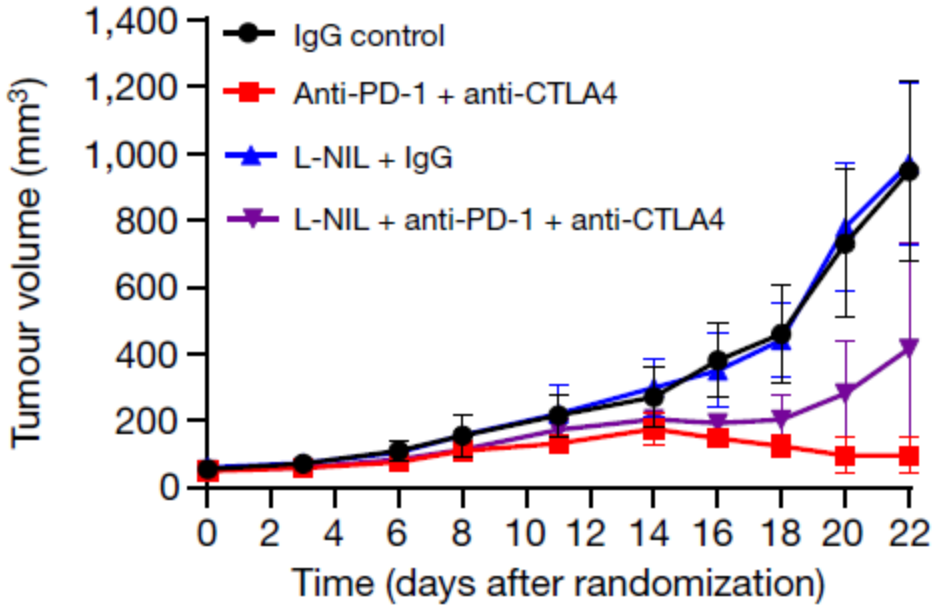
The efficacy of dual ICB in STK11 and/or KEAP1-deficient NSCLC models is partially dependent on myeloid cell subsets

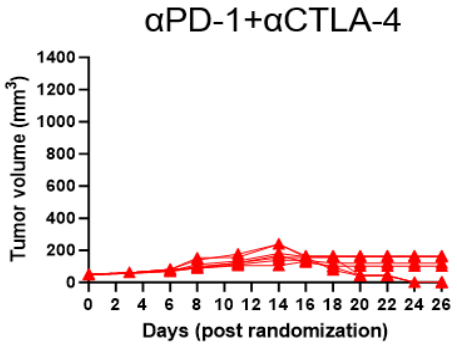
KL5

A.

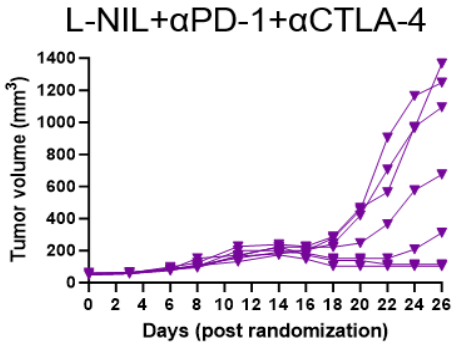


B.





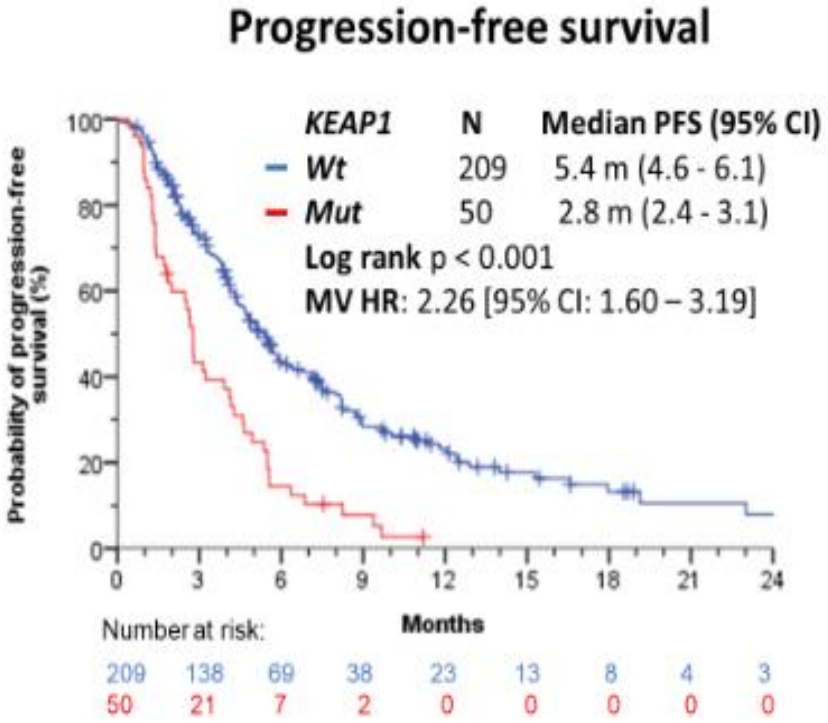
7/7 without outgrowth

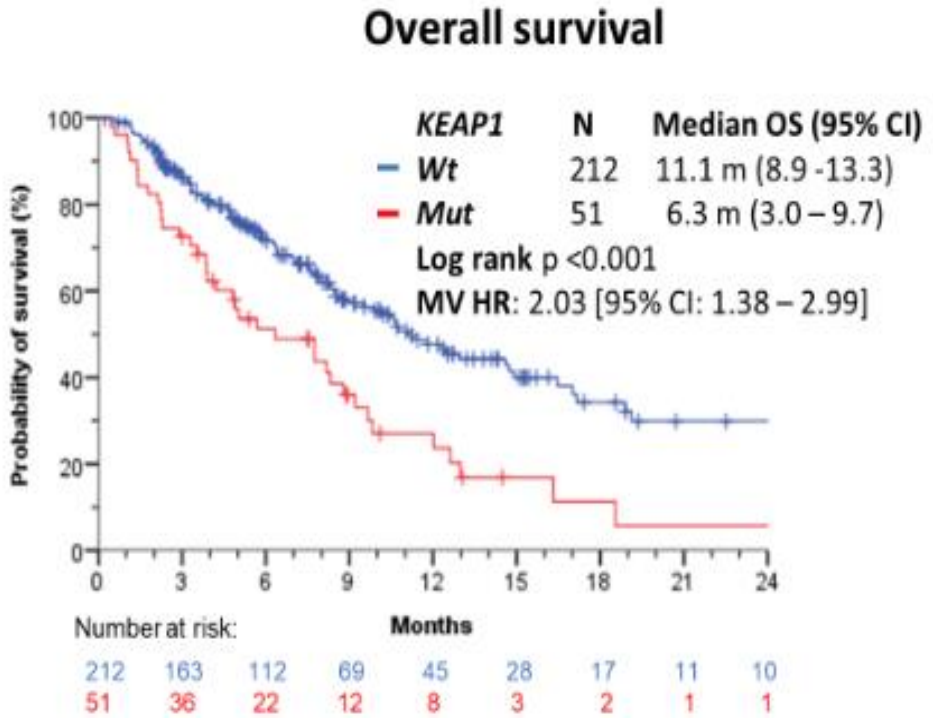


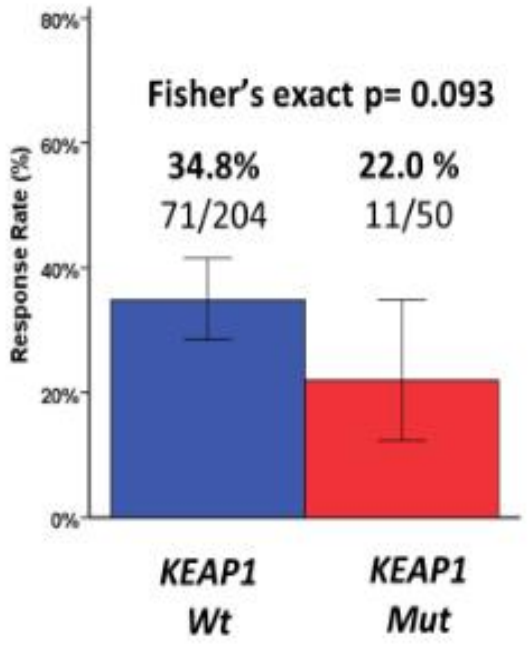
2/7 without outgrowth

Skoulidis F et al., *Nature*, 2024

Patients harboring NSCLC with *KEAP1* co-alterations exhibit inferior PFS and OS with sotorasib and adagrasib

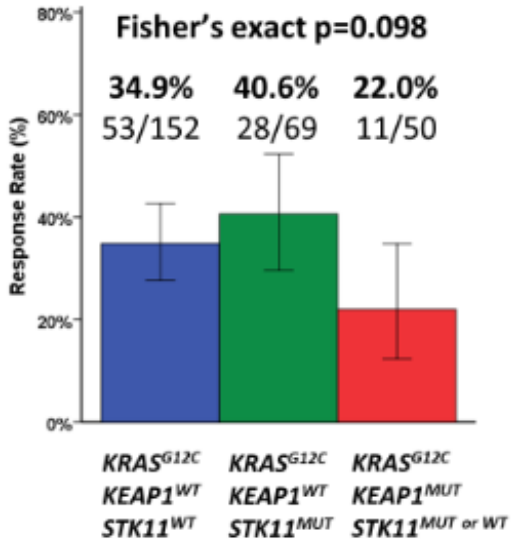


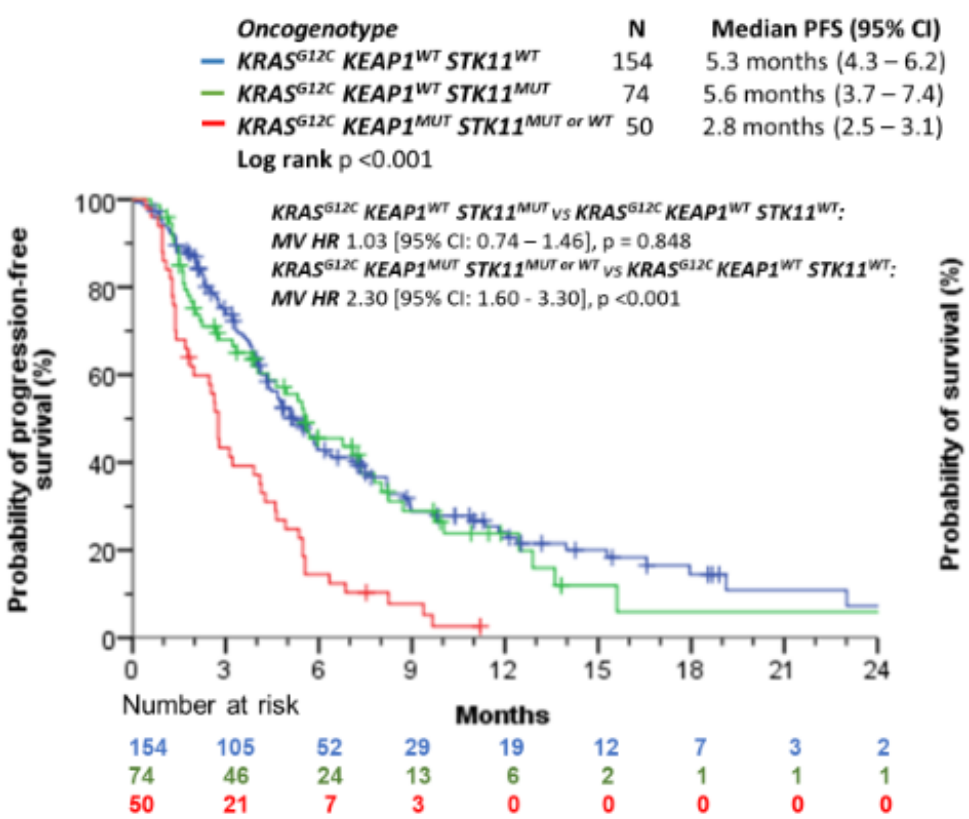


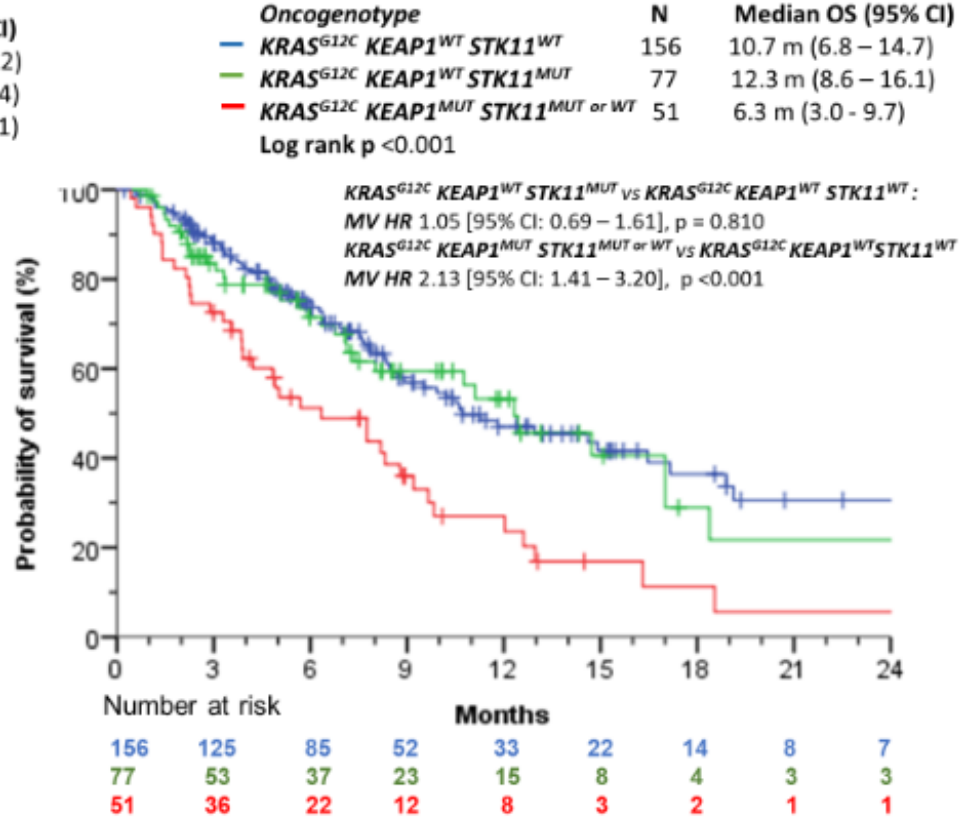


Negrao M*, Araujo H*…… Skoulidis F. *Cancer Discovery*, 2023

STK11 alterations without concurrent *KEAP1* mutations do not appear to impact clinical outcomes with sotorasib and adagrasib







Negrao M*, Araujo H*…… Skoulidis F. *Cancer Discovery*, 2023

Conclusions

- Somatic mutations in *KEAP1* and/or *STK11* identify difficult to treat subgroups of patients with mNSCLC that exhibit poor clinical outcomes with PD-(L)1 inhibitor – based chemo-immunotherapy (such as the KEYNOTE-189 regimen) or PD-(L)1 monotherapy, especially in patients harboring *KRAS*-mutant NSCLC.
- Both prognostic and predictive effects are likely in operation. The adverse impact of *STK11* alterations on clinical outcomes is most notable with regimens that include single agent ICB with anti-PD-(L)1 inhibitors.
- Loss of STK11 and/or KEAP1 establishes an adverse TIME characterized by (a) increased myeloid to CD8+ T cell ratio and (b) profound depletion of CD8+ T cells but relative retention of CD4+ effector cell subsets.
- Preclinical models of *KRAS*-mutant NSCLC with STK11 and/or KEAP1 inactivation exhibit selective sensitivity to dual ICB.
- Mechanistically, dual ICB : (a) reprograms myeloid cells towards tumoricidal phenotypes and (b) engaged CD4+ effector subsets, including T_H1 cells. Myeloid cells as well as CD4+ as well as CD8+ T cells are critical for the anti-tumor efficacy of dual ICB.
- Chemo-IO regimens that incorporate anti-CTLA-4 in addition to anti-PD-(L)1 (such as 9LA and POSEIDON) may represent a preferred approach in *STK11* and/or *KEAP1*-mutated NSCLC with good PS. Data from POSEIDON appear the most robust to date in this patient population.
- *STK11*, *KEAP1* represent emerging biomarkers for selection of first-line regimens in advanced NSCLC.
- A randomized controlled clinical trial (TRITON) (POSEIDON regimen vs KEYNOTE 189) in patients with previously untreated metastatic NSCLC with *STK11*, *KEAP1* or *KRAS* alterations is ongoing to confirm findings from POSEIDON

Thank you !