The role of co-mutations in immunotherapy response in NSCLC

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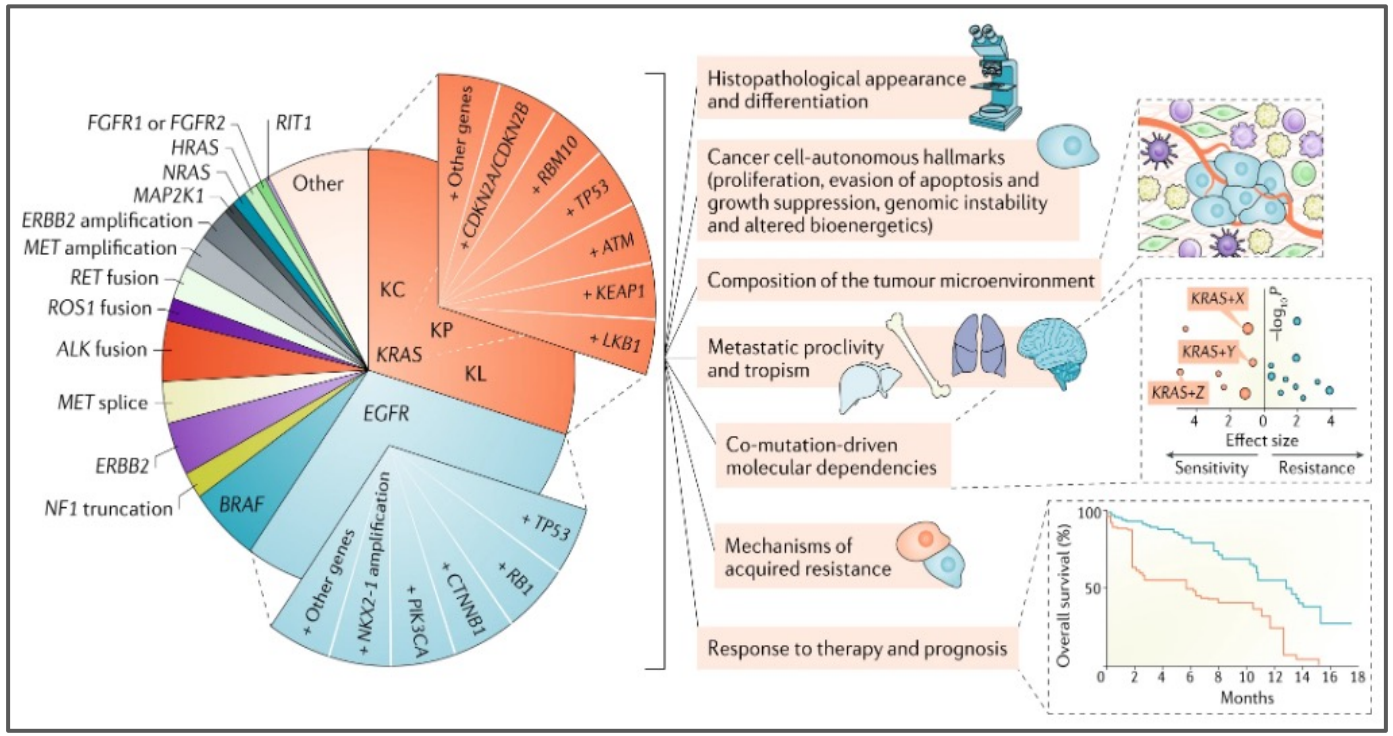
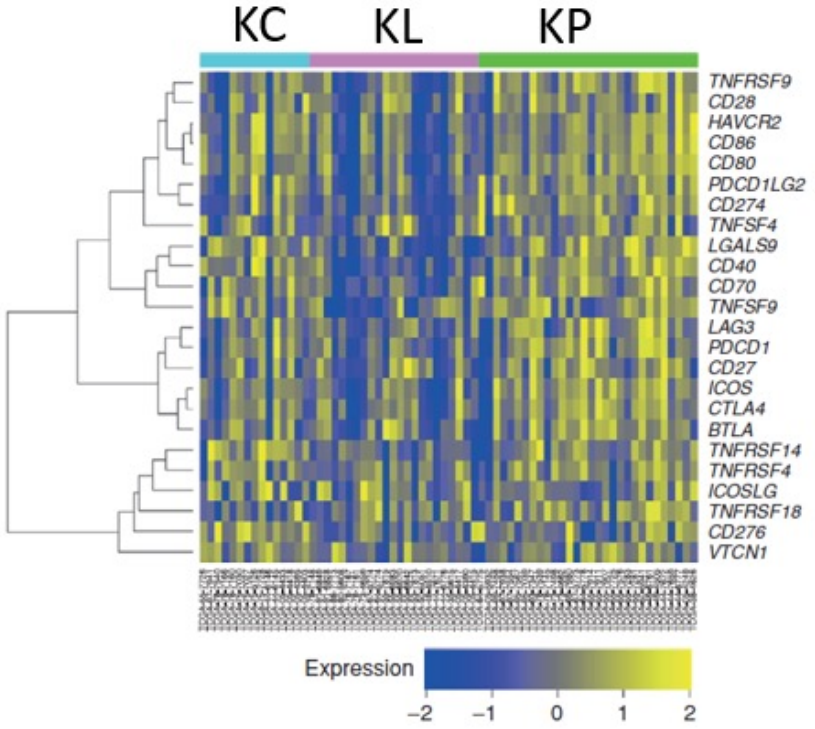
Oncogenic drivers and co-alterations collectively impact both tumor cell-intrinsic and non-tumor cell autonomous cancer hallmark traits

A.



Skoulidis F and Heymach JV, *Nat Rev Cancer*, 2019

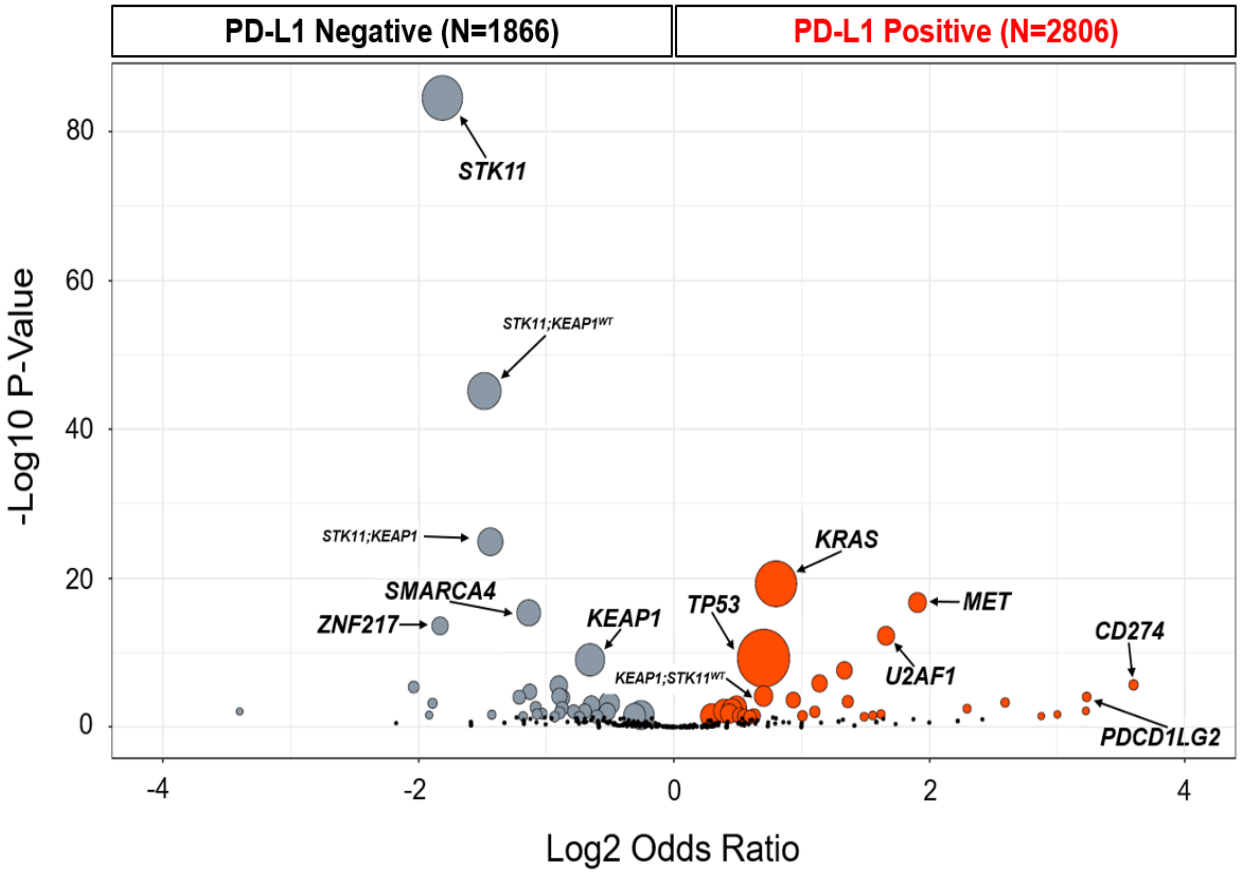
B.



Skoulidis F et al., *Cancer Discovery*, 2015

Oncogenotype and tumor cell PD-L1 expression in lung adenocarcinoma

A.



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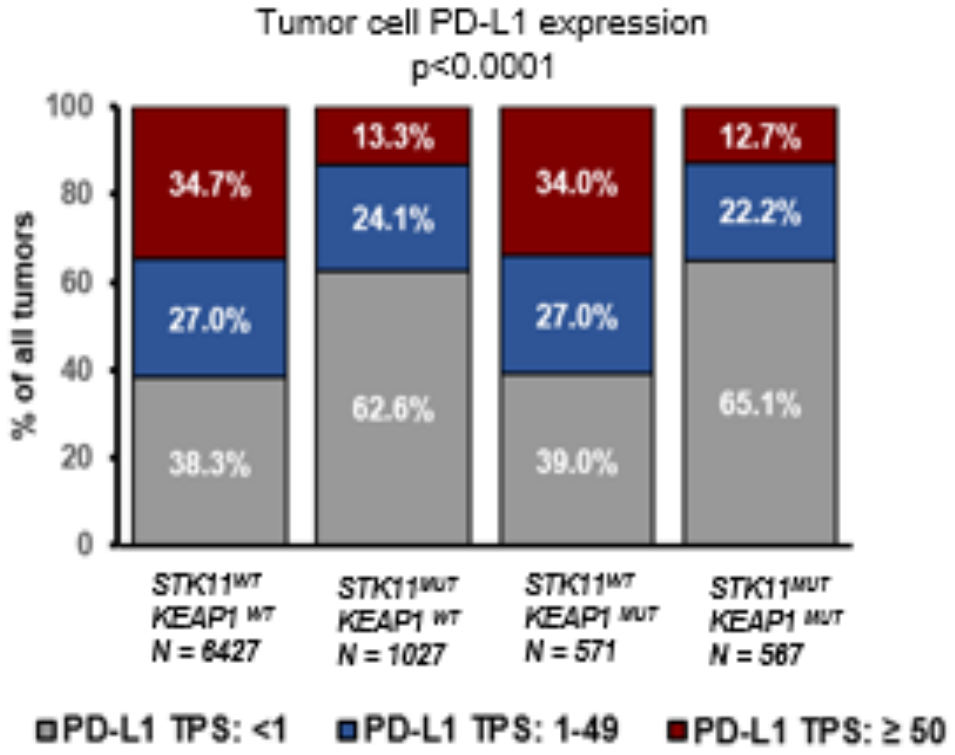
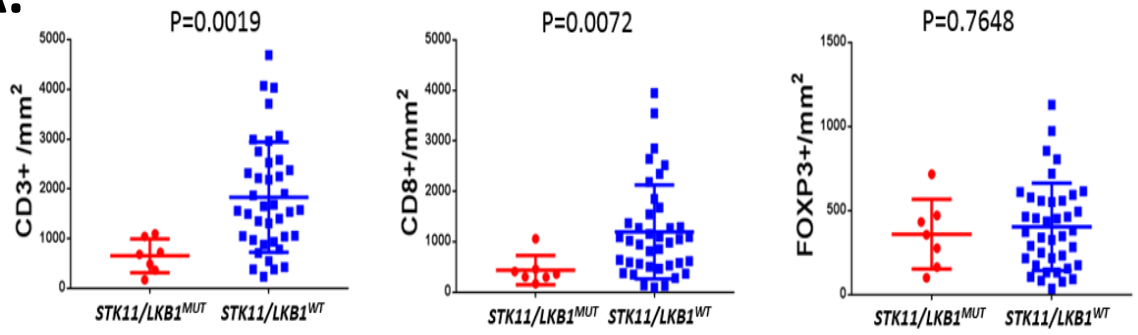


Skoulidis F et al., under review
Collaboration with Lee Albacker, FMI

Somatic mutations in *STK11/LKB1* (KL) promote establishment of a T-cell depleted and suppressive myeloid cell –enriched TIME in NSCLC

A.



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

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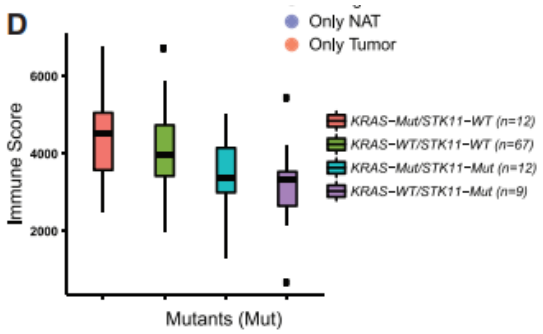

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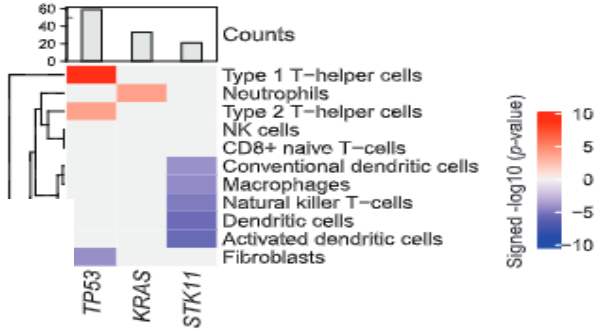
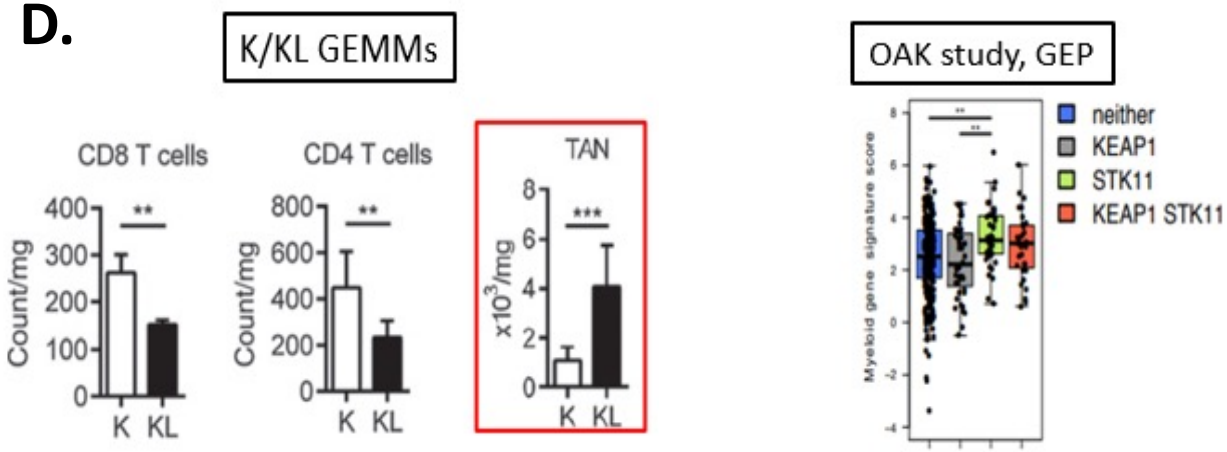


Gillette MA et al., *Cell*, 2020

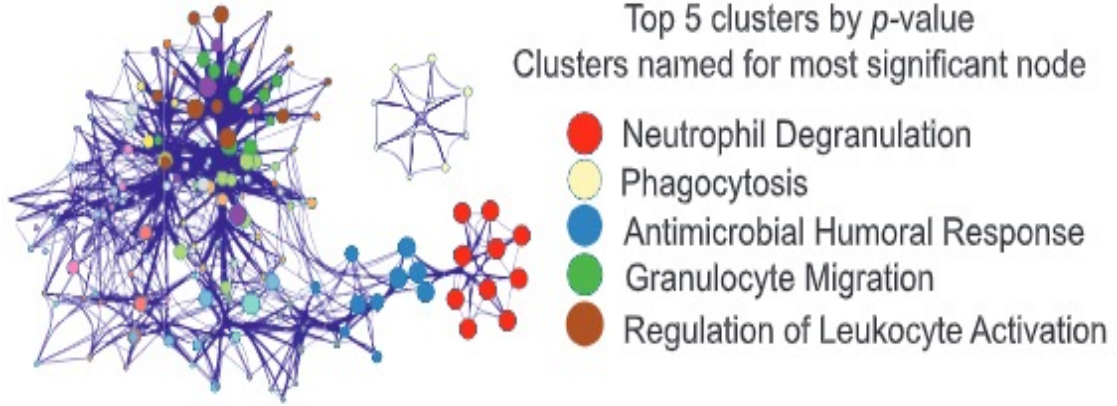
D.



Koyama S et al, *Cancer Research*, 2016

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

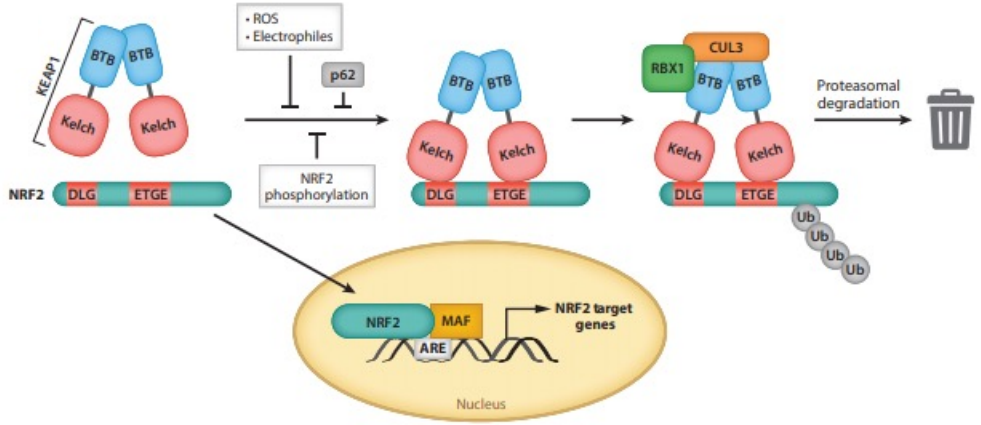
E.



Gillette MA et al., *Cell*, 2020

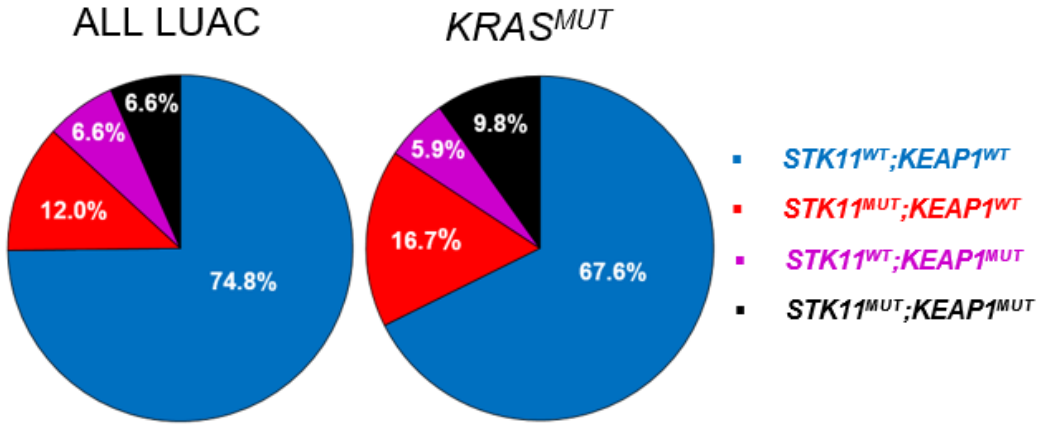
KEAP1 inactivation is also associated with an altered NSCLC TIME

A.



Wu WL, Papagiannakopoulos T, 2021

B.



Collaboration with Lee Albacker, FMI

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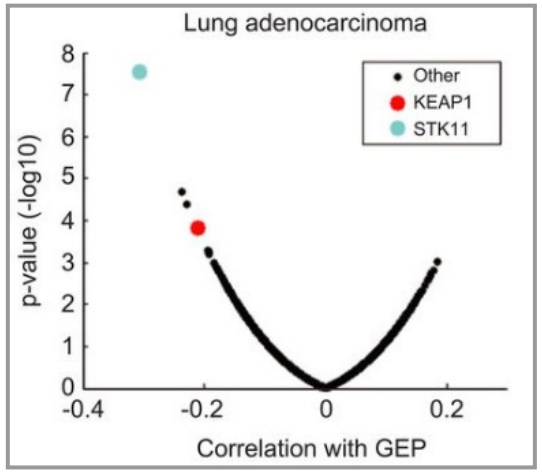

Cristescu R et al, *Science*, 2018

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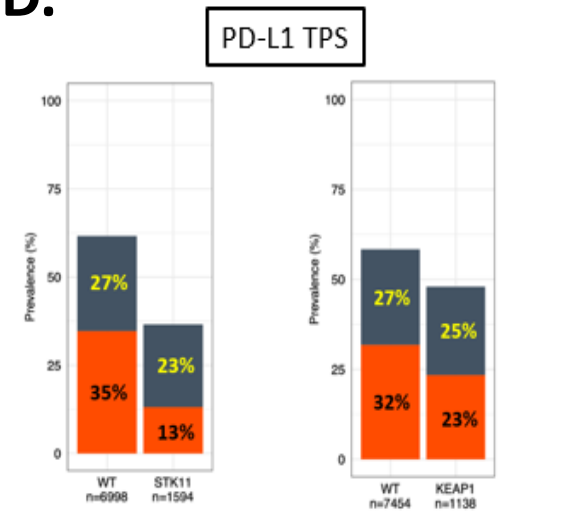
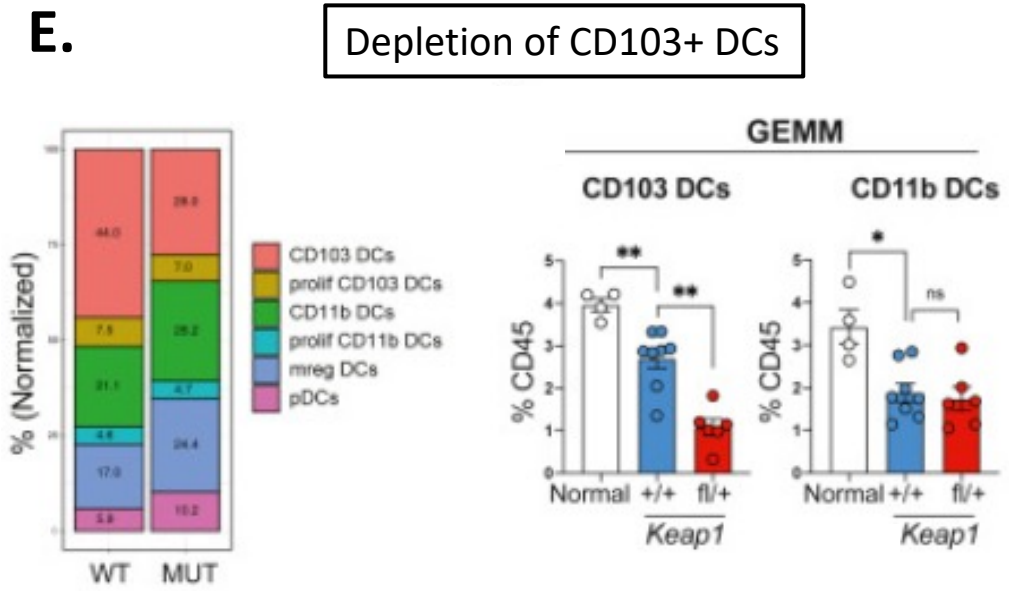


Skoulidis F et al, EON meeting, 2020
Collaboration with Dr Albacker, Foundation Medicine

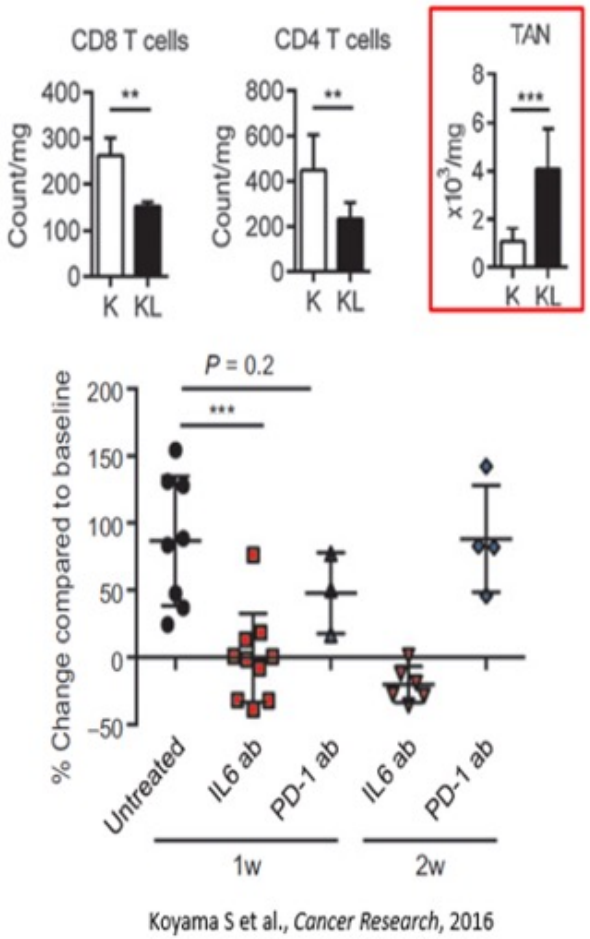
E.



Zavitsanou AM et al., *Cell Reports*, 2023

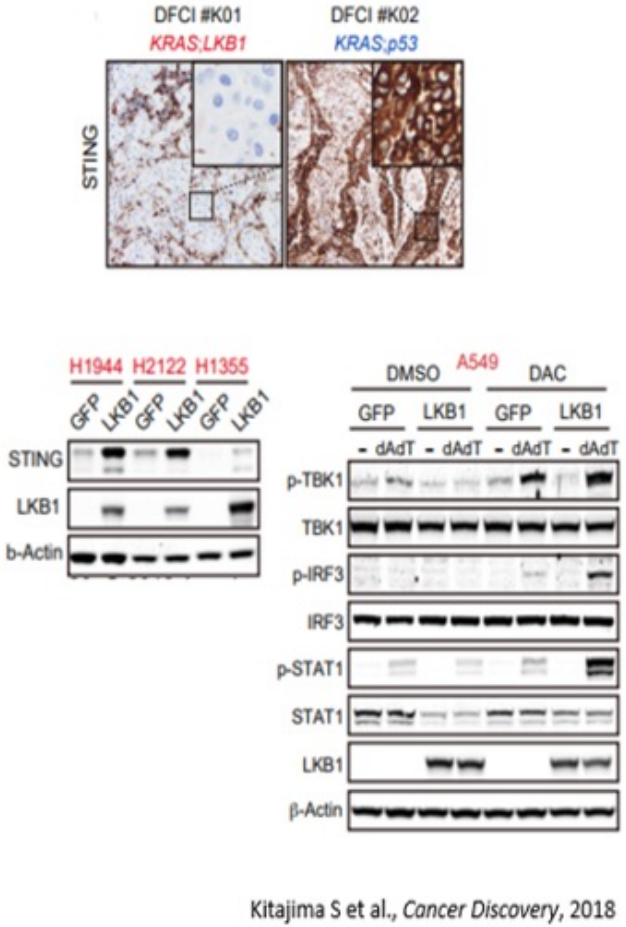
Mechanisms of *STK11* and *KEAP1* loss-mediated immune escape

Recruitment of MDSCs



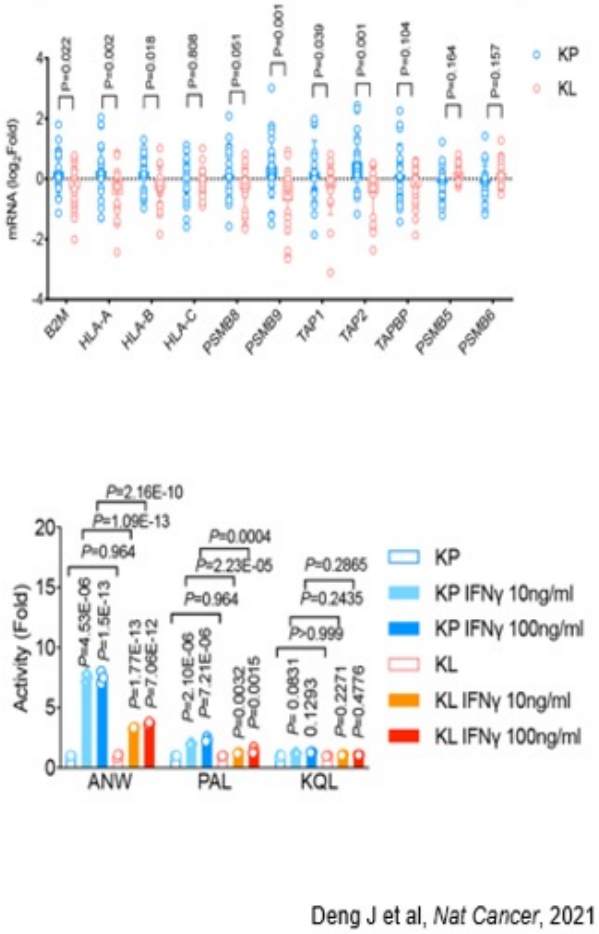
Koyama S et al., *Cancer Research*, 2016

Repression of STING



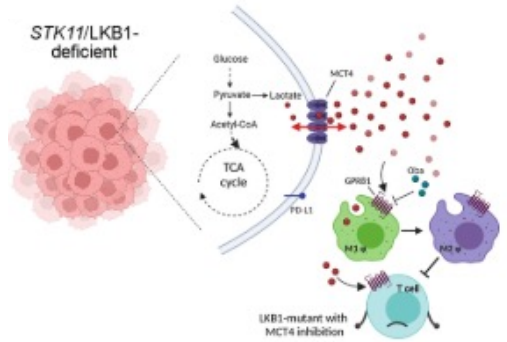
Kitajima S et al., *Cancer Discovery*, 2018

Impaired antigen presentation

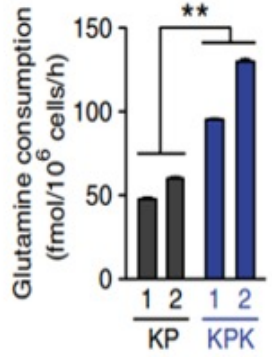


Deng J et al, *Nat Cancer*, 2021

Metabolically adverse TME

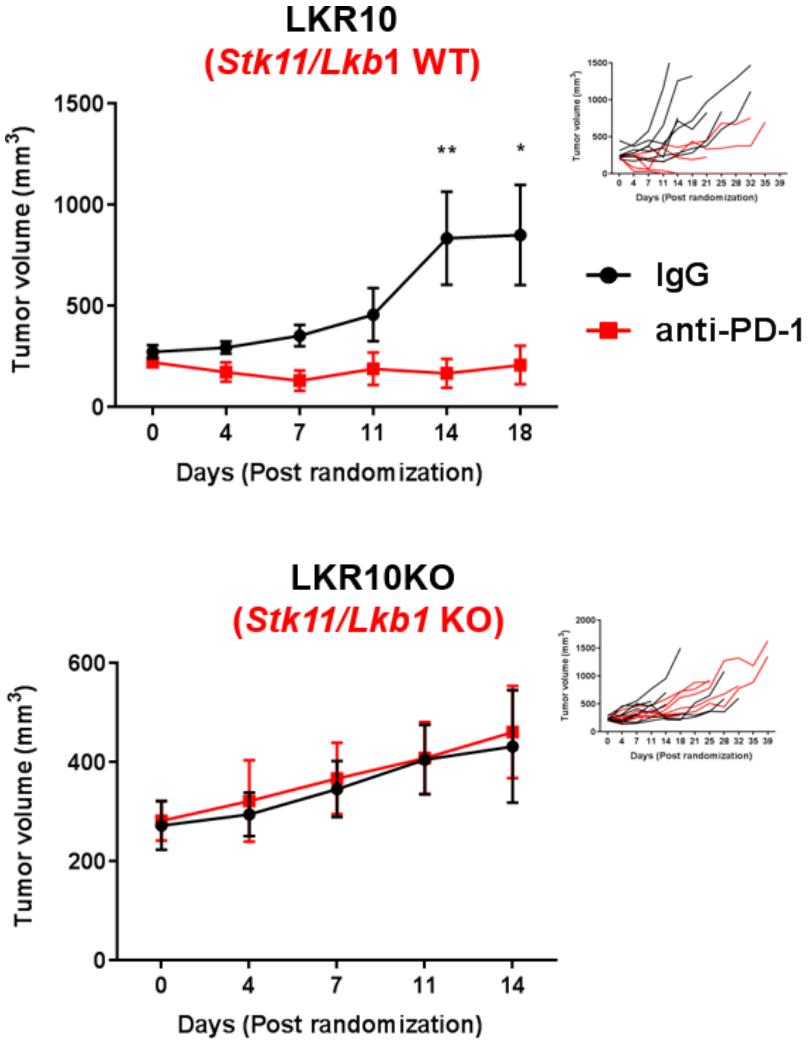


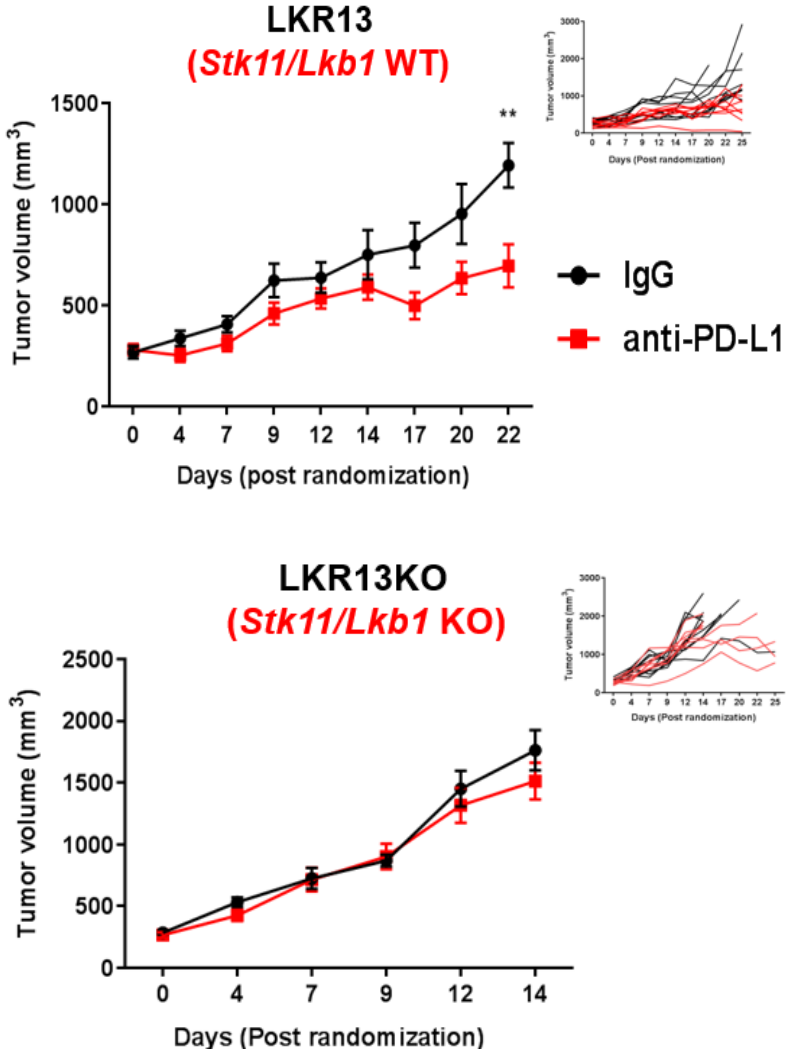
Qian et al., *Cancer Cell*, 2023



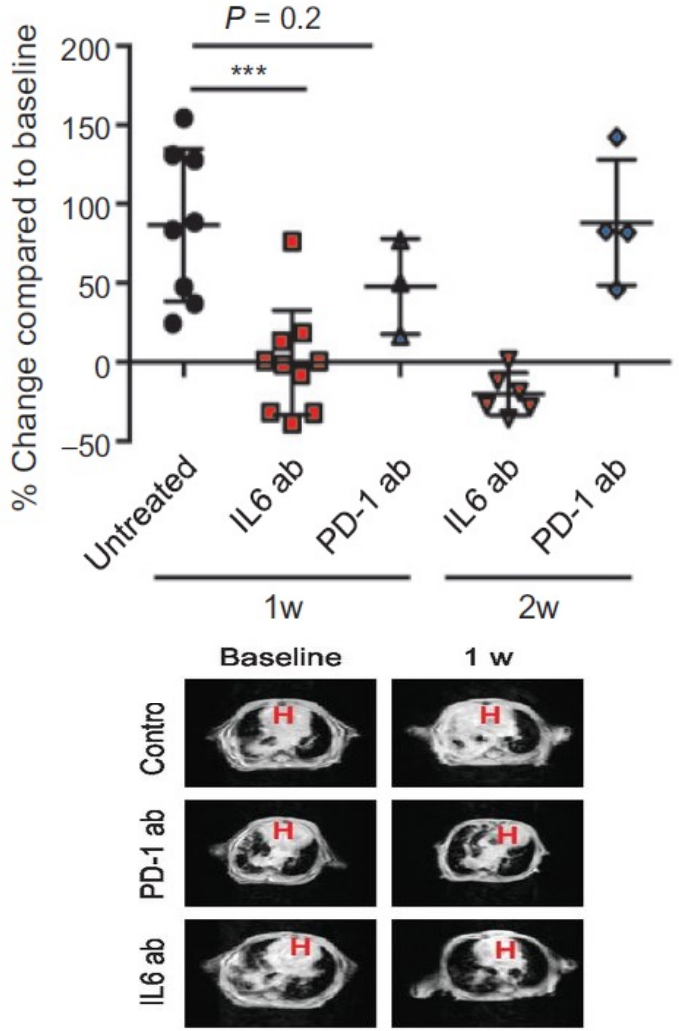
Romero et al, *Nat Med*, 2017

Stk11/Lkb1 loss promotes primary resistance to PD-1/PD-L1 blockade in immune-competent models of *Kras*-mutant LUAC





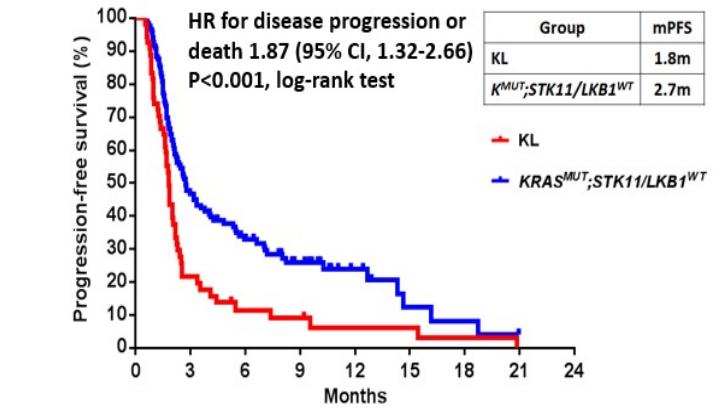
Skoulidis F et al, *Cancer Discovery*, 2018

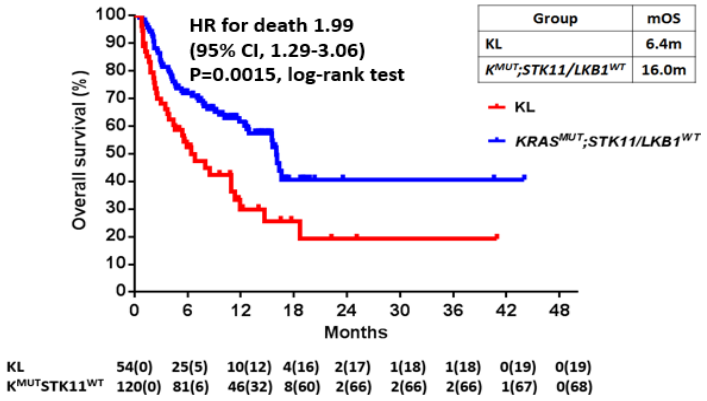


Koyama S et al, *Cancer Research*, 2016

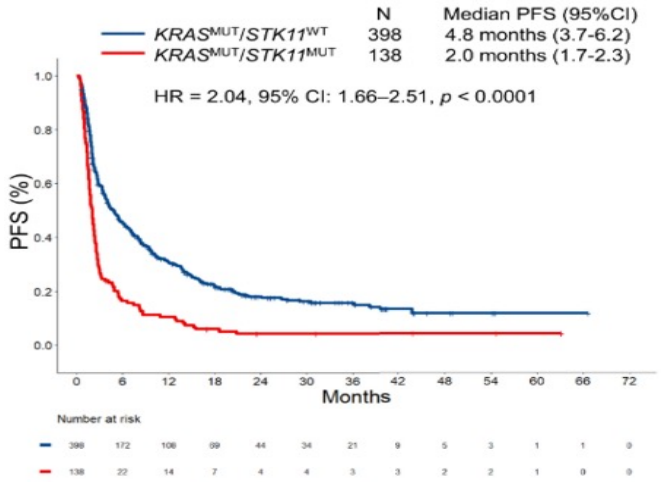
STK11 and *KEAP1* alterations drive inferior clinical outcomes with PD-1 axis inhibitor monotherapy in *KRAS*-mutant NSCLC

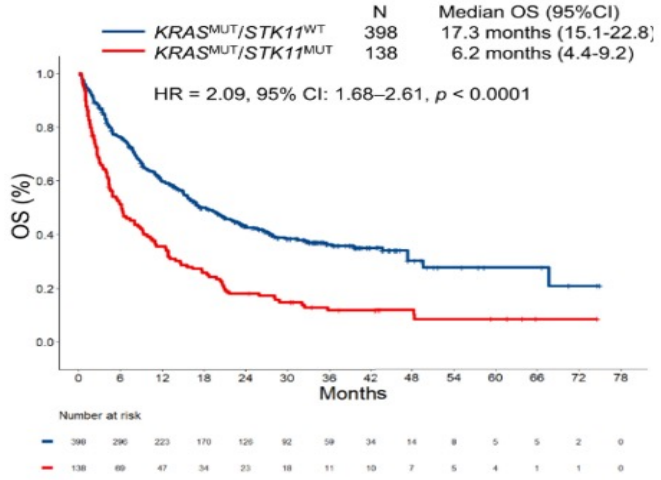
Skoulidis F et al., *Cancer Discov*, 2018



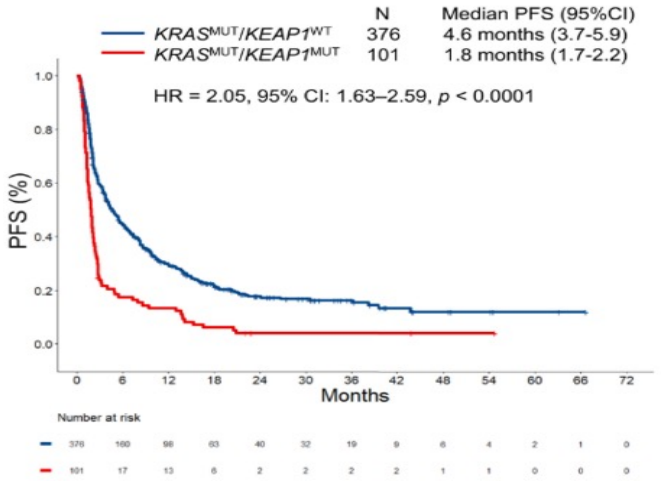


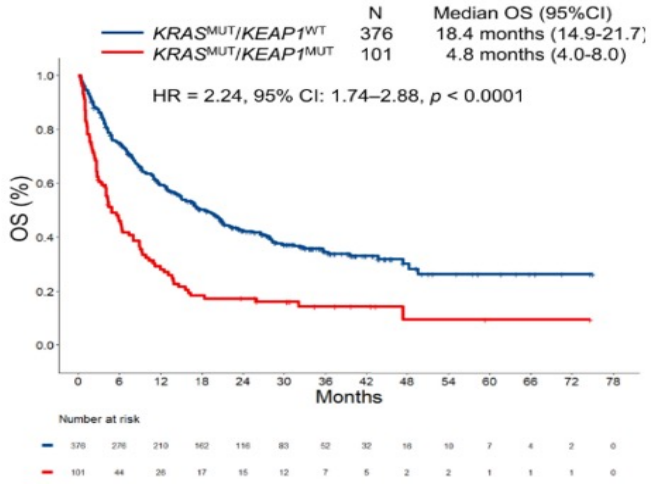
Ricciuti B et al., *JTO*, 2021





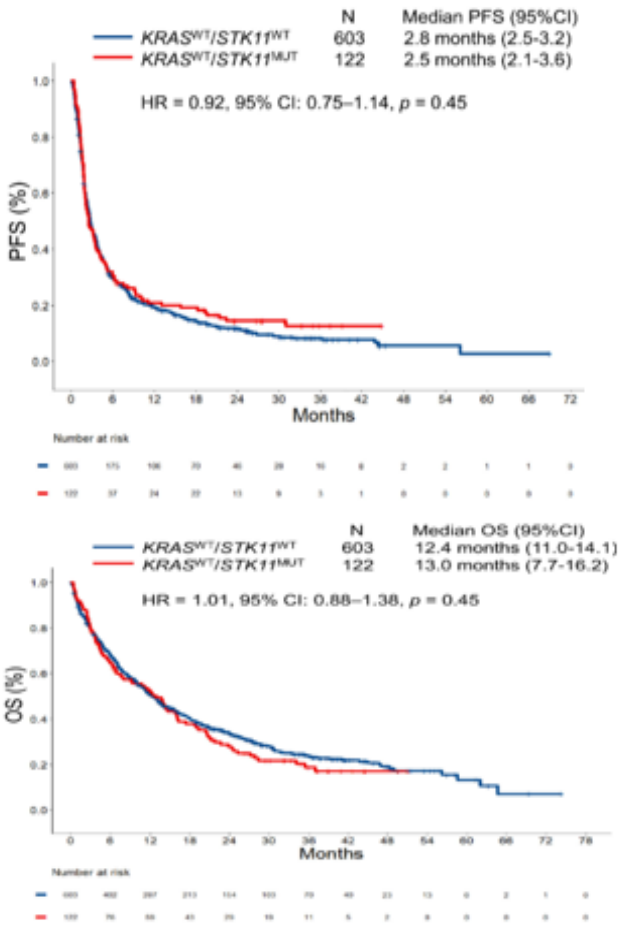
Ricciuti B et al., *J TO*, 2021



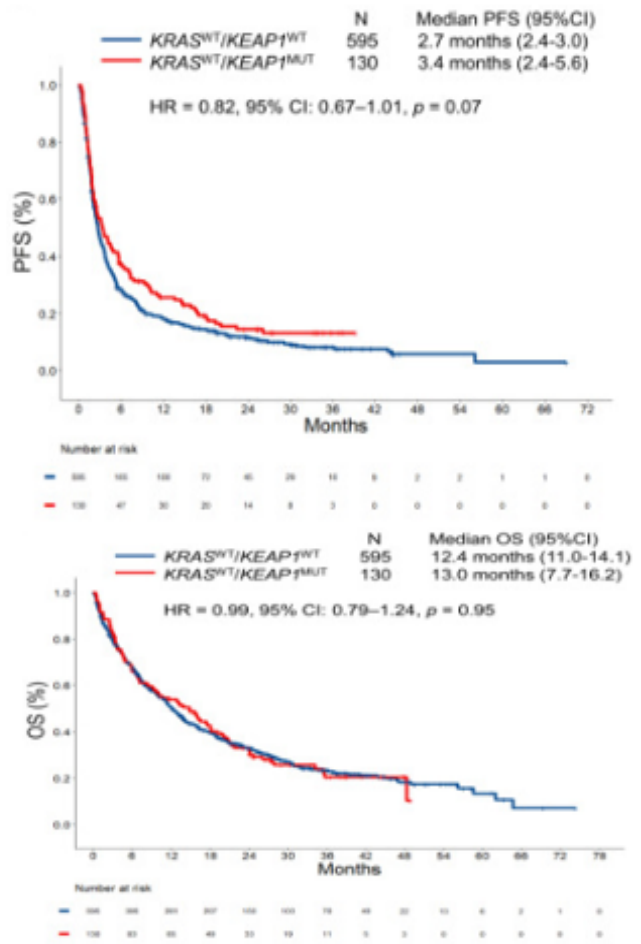


Potential modifiers of the impact of *STK11* and *KEAP1* alterations on IO outcomes : *KRAS* status

$KRAS^{WT}/STK11^{WT}$ vs $KRAS^{WT}/STK11^{MUT}$



$KRAS^{WT}/KEAP1^{WT}$ vs $KRAS^{WT}/KEAP1^{MUT}$

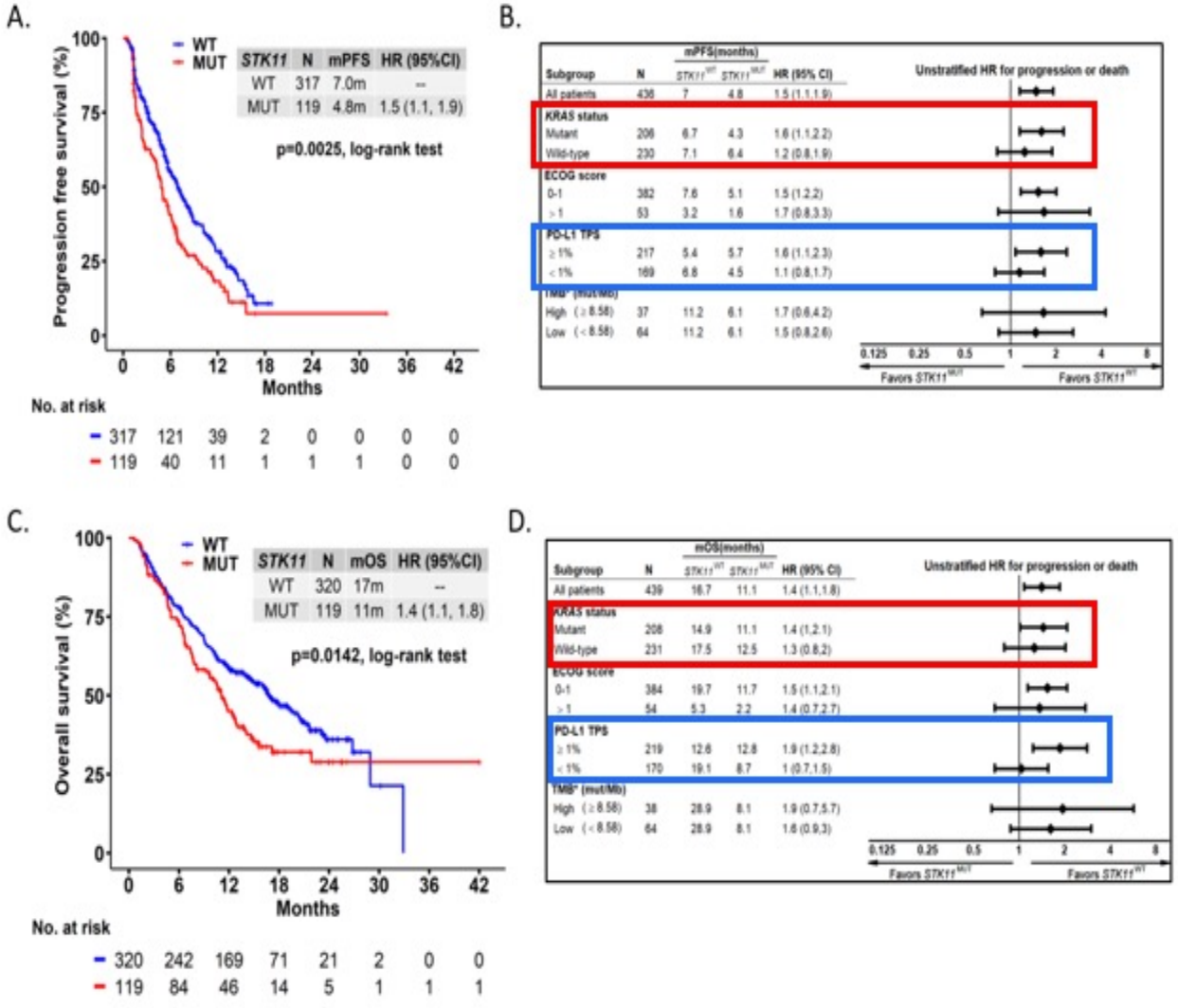


Onco-genotype	mPFS	mOS
$KRAS^{MUT};STK11^{WT}$	4.8m	17.3m
$KRAS^{MUT};STK11^{MUT}$	2.0m	6.2m
$KRAS^{WT};STK11^{WT}$	2.8m	12.4m
$KRAS^{WT};STK11^{MUT}$	2.5m	13.0m
$KRAS^{MUT};KEAP1^{WT}$	4.6m	18.4m
$KRAS^{MUT};KEAP1^{MUT}$	1.8m	4.8m
$KRAS^{WT};KEAP1^{WT}$	2.7m	12.4m
$KRAS^{WT};KEAP1^{MUT}$	3.4m	13.0m

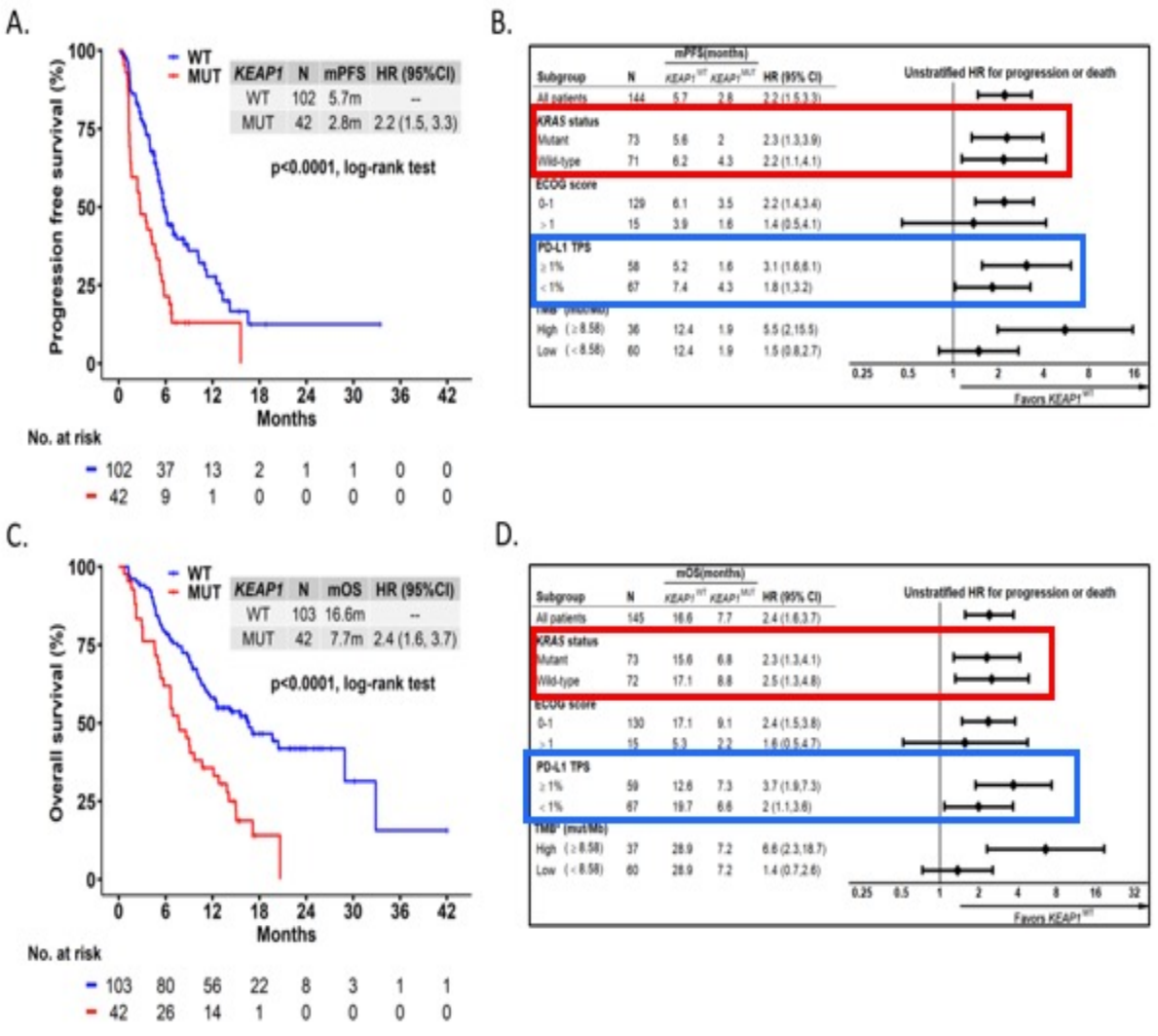
Ricciuti B et al., *JTO,* 2021

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

STK11



KEAP1

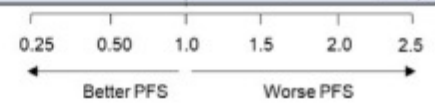


Skoulidis F et al, under review

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

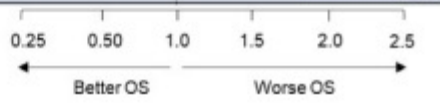
Forest-plot for progression-free survival (PFS)

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



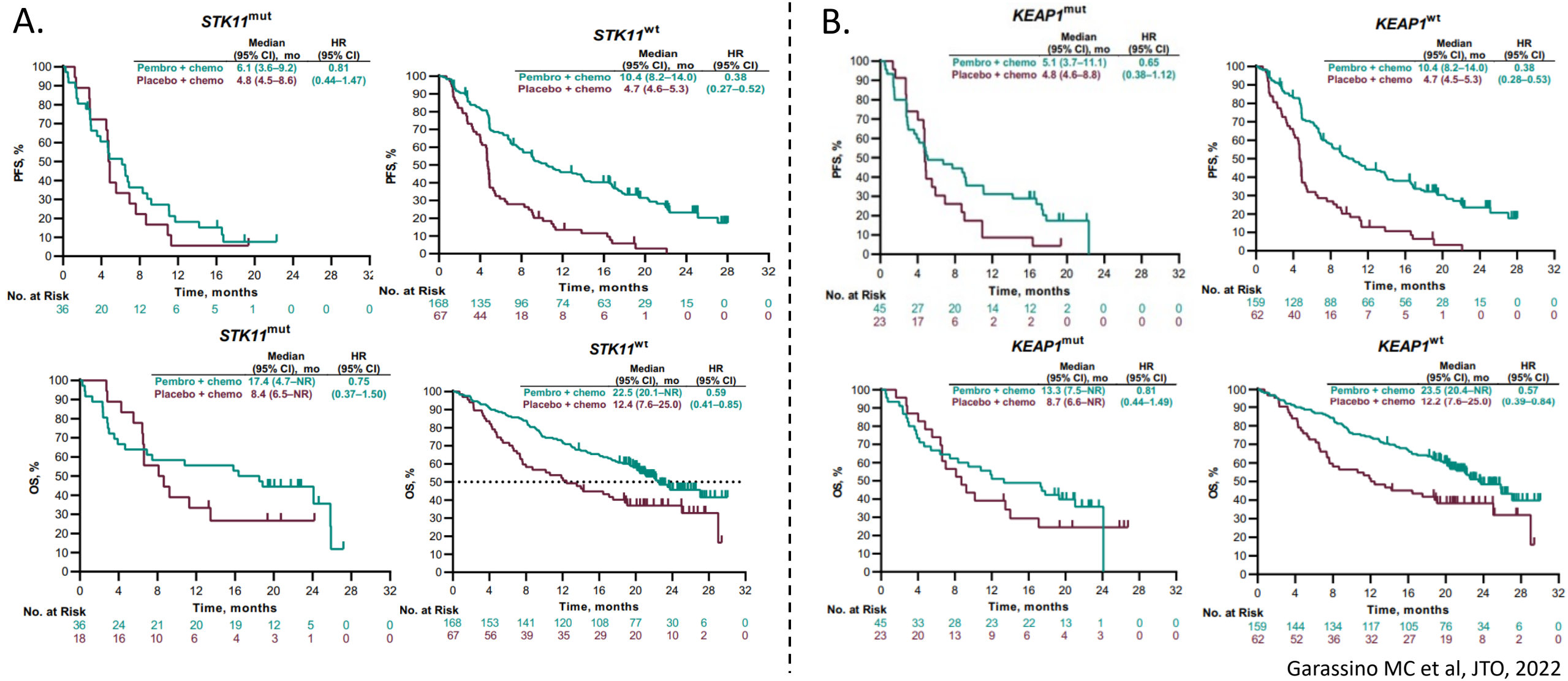
Forest-plot for overall survival (OS)

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



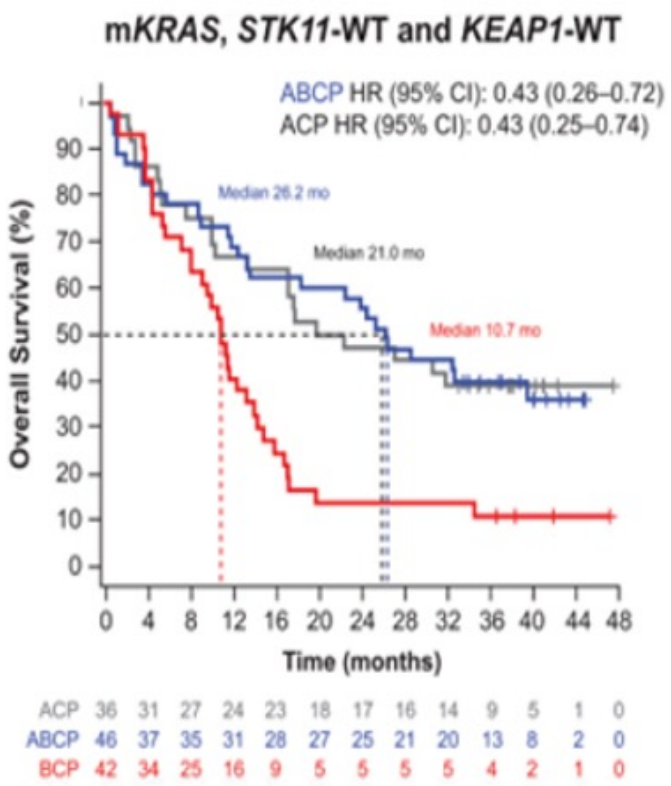
Alessi JV et al., *JTO,* 2023

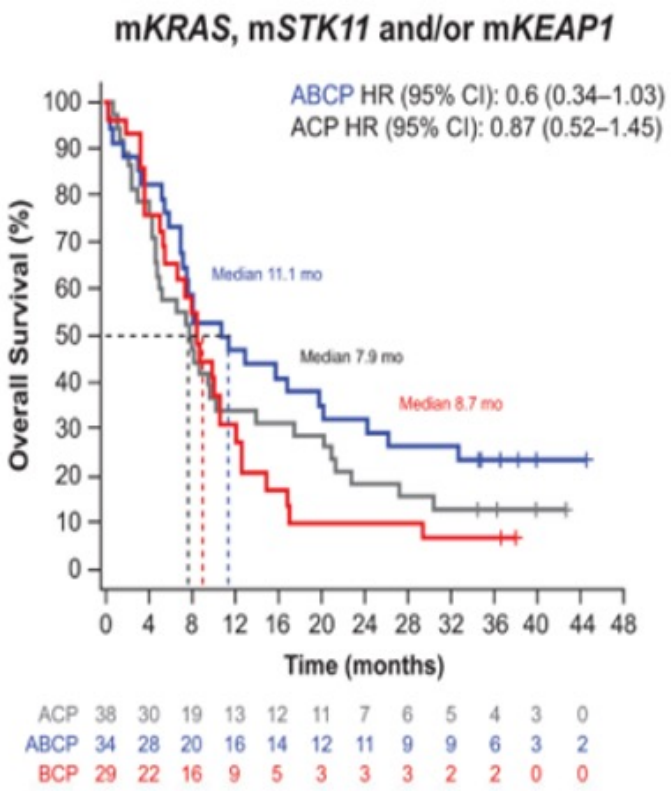
Reduced benefit from the addition of pembrolizumab to platinum doublet chemotherapy in patients with *STK11* and *KEAP1*-mutant NSCLC in KEYNOTE-189

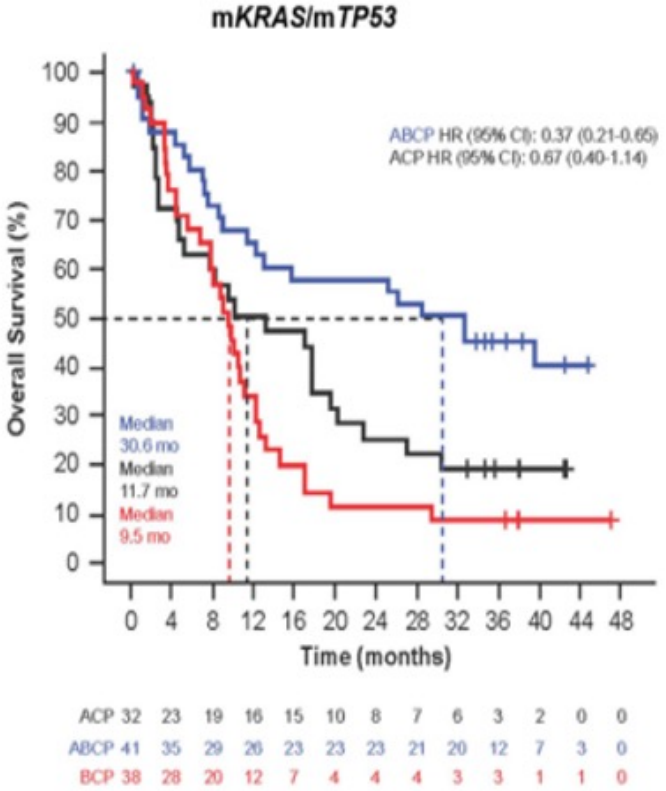


Garassino MC et al, JTO, 2022

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



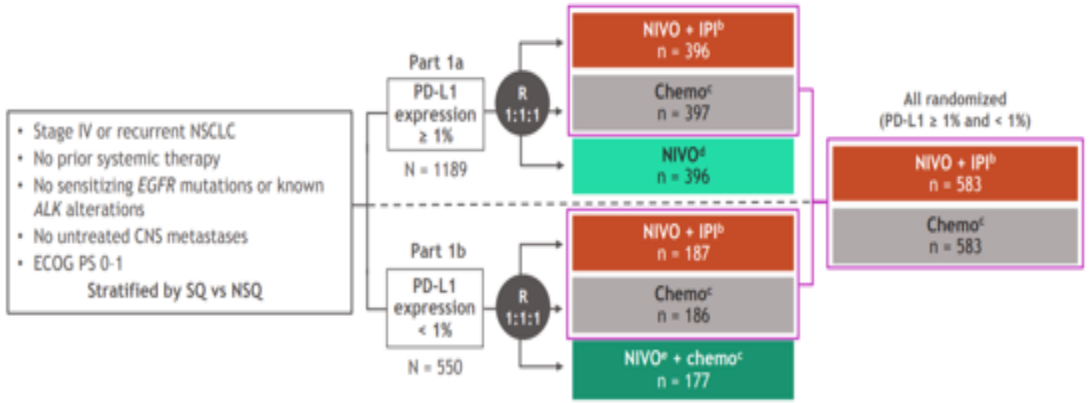




West HJ et al, JITC, 2021

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

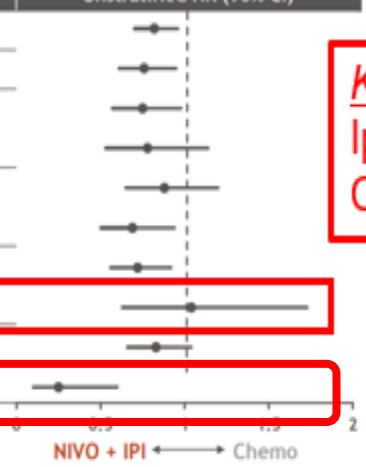
A.



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

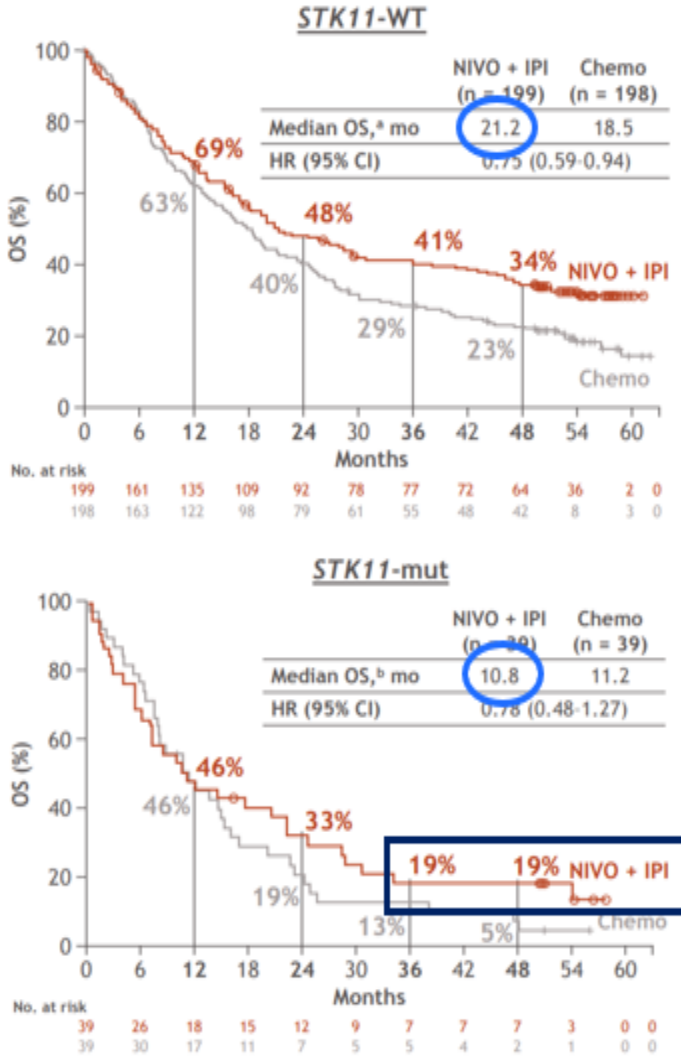
B.

Subgroup, n[b]	4-y PFS rate, % NIVO + IPI	4-y PFS rate, % Chemo	Median PFS, mo NIVO + IPI	Median PFS, mo Chemo	Unstratified HR
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

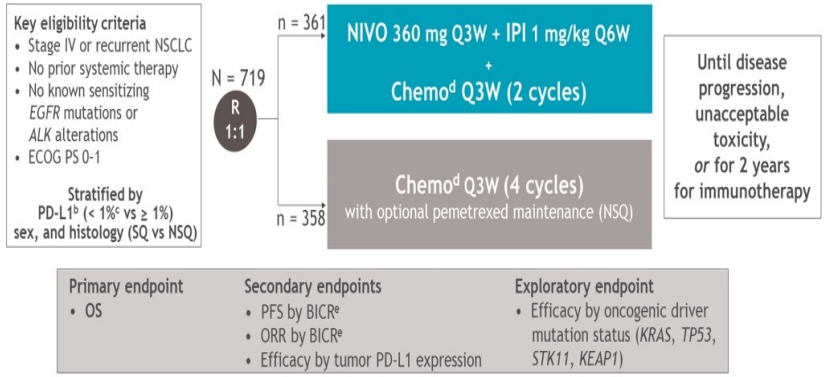
C.



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

Clinical outcomes with the CheckMate 9LA regimen in *STK11*-mutant NSCLC

A.



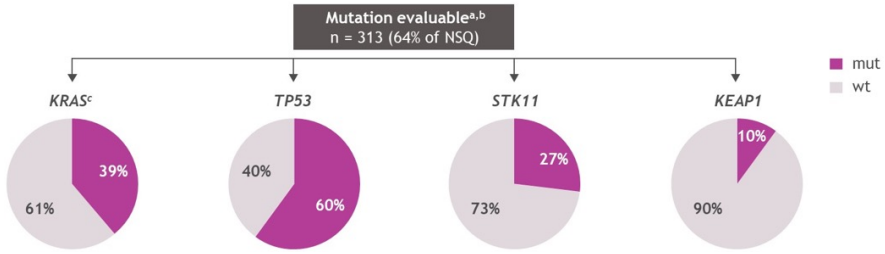
Database lock: February 15, 2022; minimum/median follow-up for OS: 36.1/42.6 months.

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.

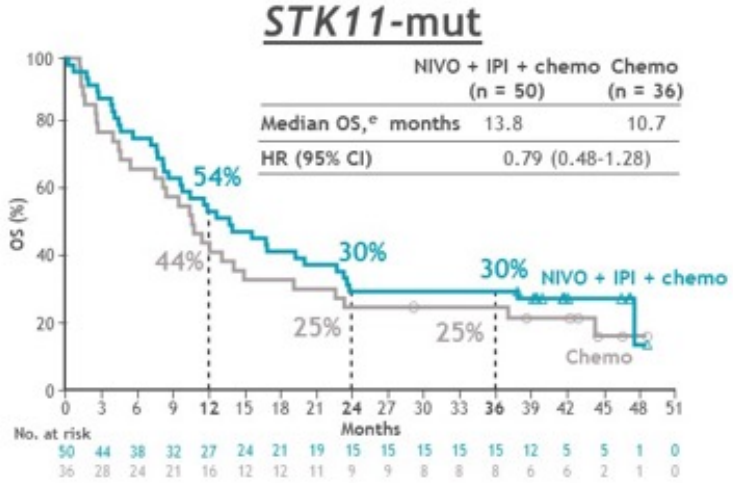
[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

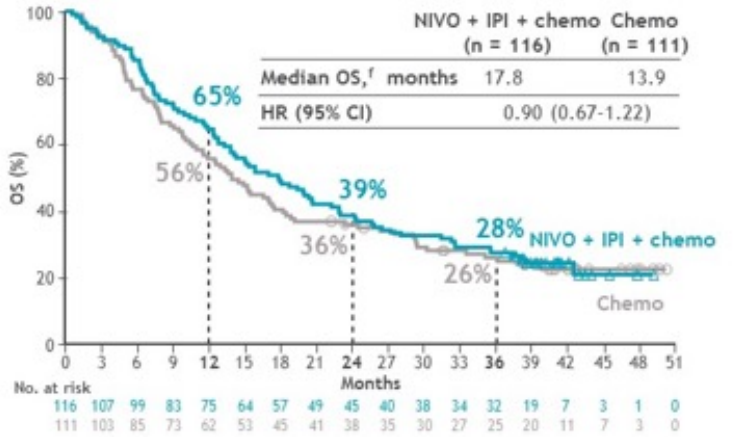
1. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198-211; 2. Reck M, et al. *ESMO Open* 2021;6:100273.

B.

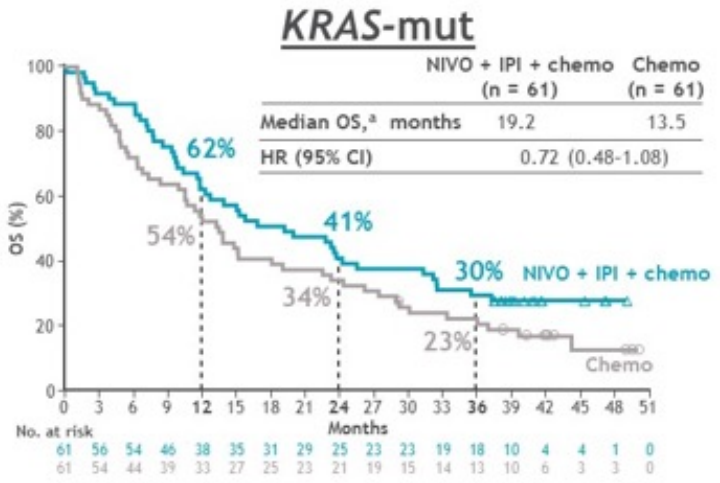


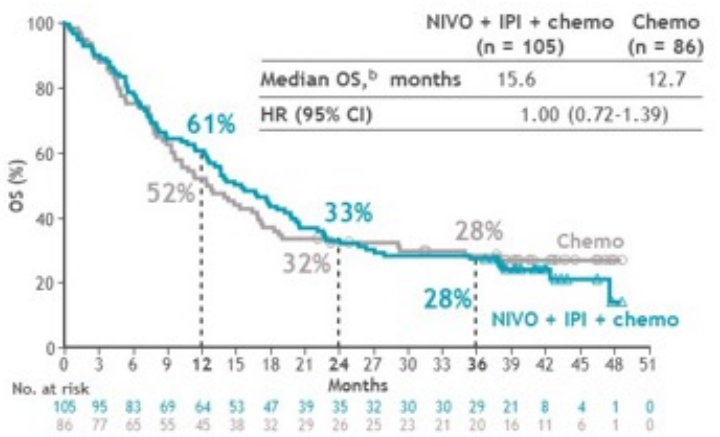
C.





D.





- 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

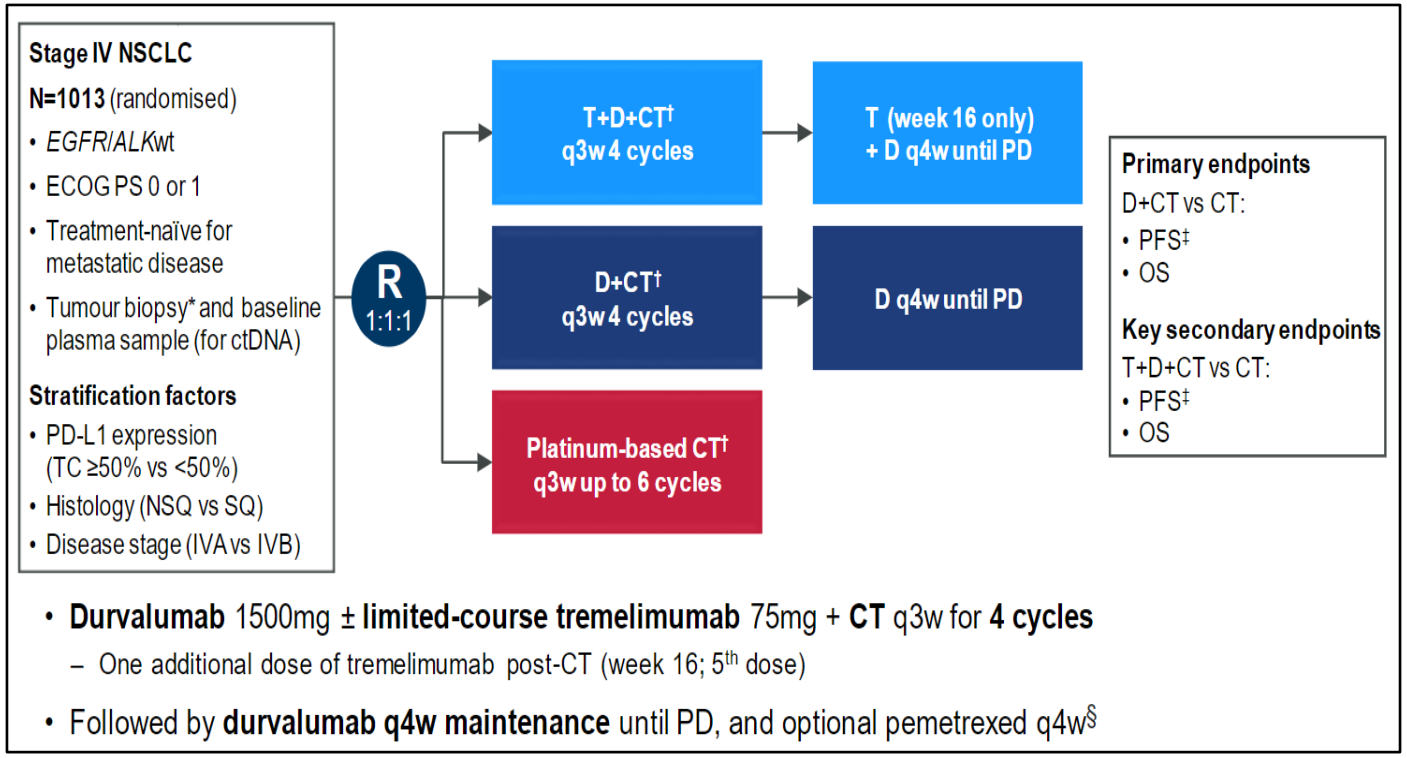
Database lock: February 15, 2022; minimum follow-up: 36.1 months.

[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).

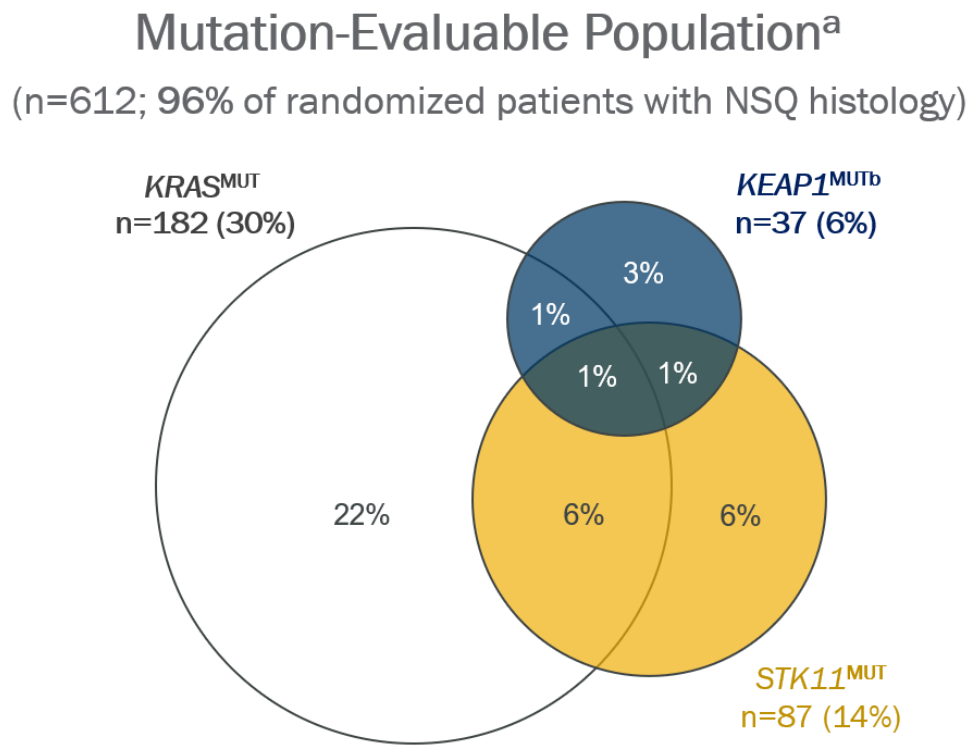
Paz-Ares L et al., ASCO, 2022

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

A.



B.



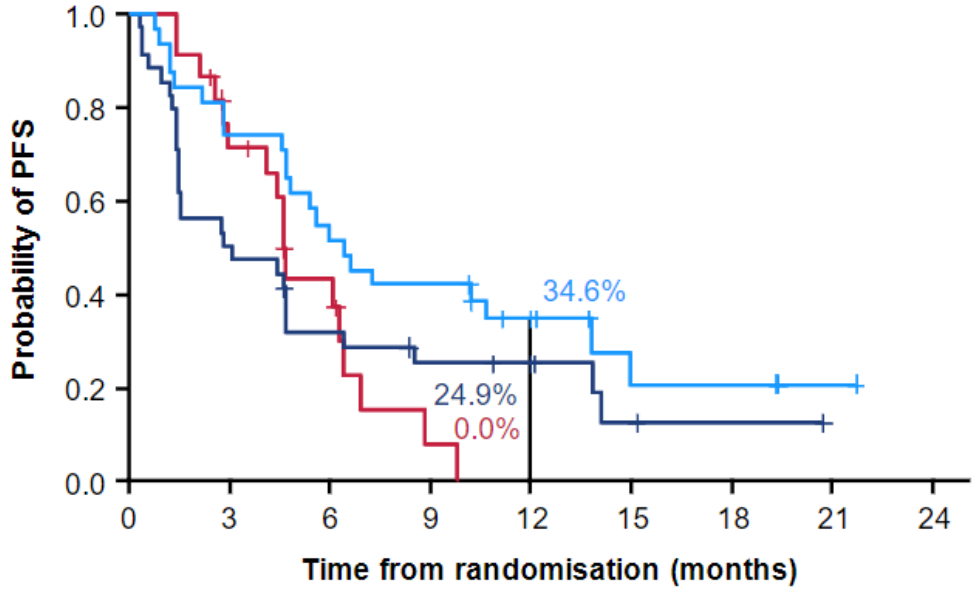
Peters S et al., WCLC, 2022

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

A.

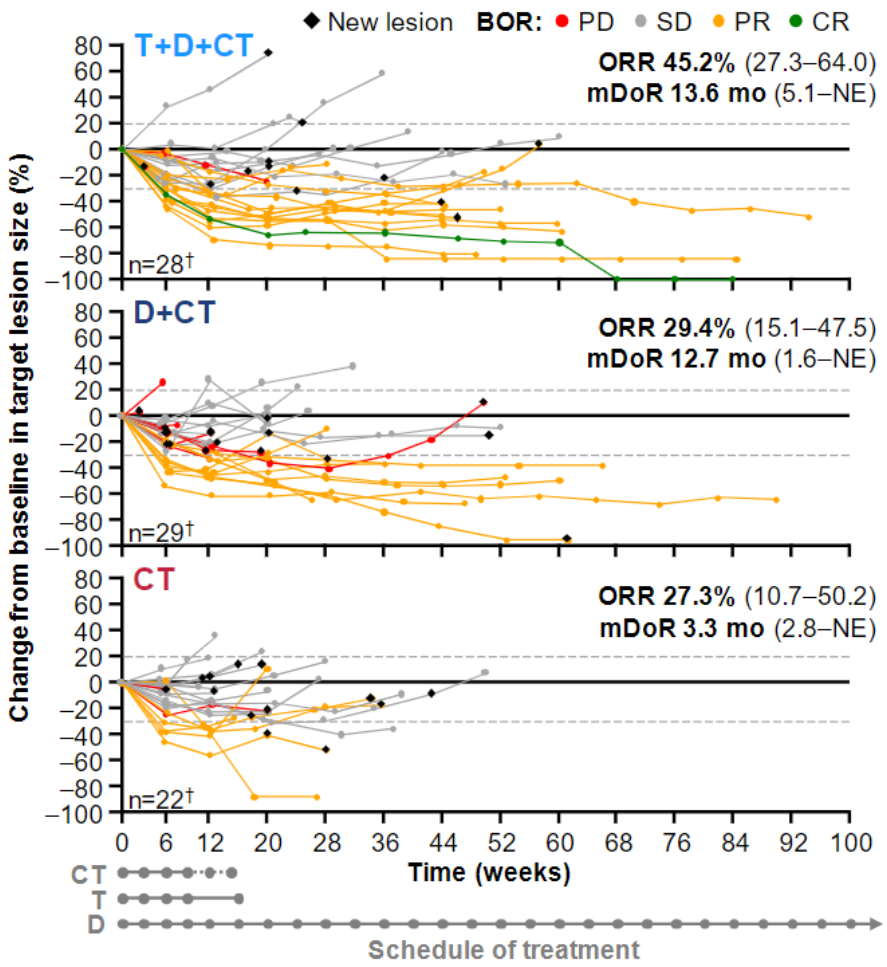
PFS

	T+D+CT	D+CT	CT
Events, n/N	22/31	27/34	17/22
mPFS, mo (95% CI)	**6.4** (4.7–13.8)	**2.9** (1.4–4.7)	**4.6** (2.9–6.4)
HR* (95% CI)	**0.47** (0.23–0.93)	**1.02** (0.55–1.93)	–



No. at risk									
T+D+CT	31	23	16	13	7	3	3	1	0
D+CT	34	17	10	7	5	2	1	0	0
CT	22	14	7	1	0	0	0	0	0

B.

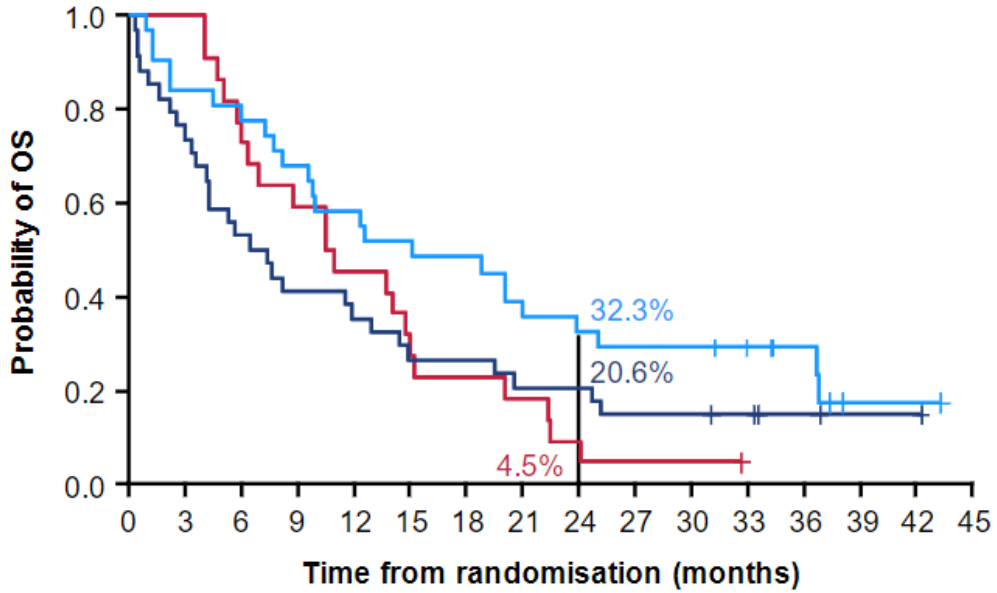


Peters S et al., WCLC, 2022

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

*STK11*m

	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–

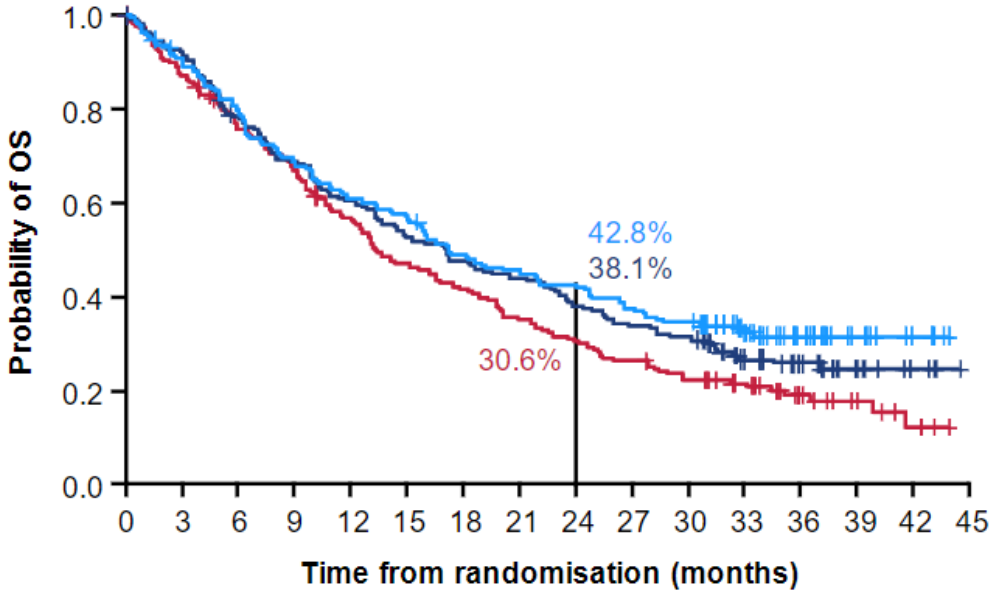


No. at risk

T+D+CT	31	26	24	21	18	15	15	11	10	9	9	7	5	1	1	0
D+CT	34	26	18	14	12	9	9	7	7	5	5	4	2	1	0	0
CT	22	22	16	13	10	6	5	4	1	1	1	0	0	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events, n/N	118/177	123/169	141/179
mOS, mo (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.73** (0.57–0.93)	**0.81** (0.64–1.04)	–



No. at risk

T+D+CT	177	159	140	120	107	100	85	79	74	65	60	40	25	11	5	0
D+CT	169	155	130	114	100	87	79	73	63	56	52	33	23	10	4	0
CT	179	154	131	116	97	80	71	60	52	45	37	29	15	8	4	0

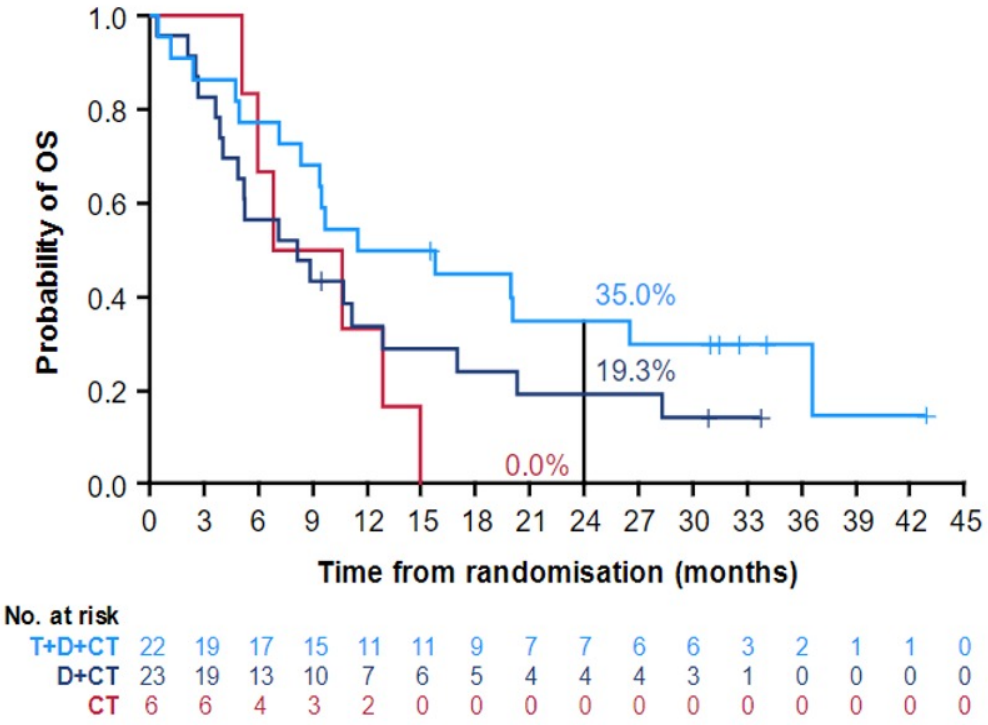
Peters S et al., WCLC, 2022

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

A.

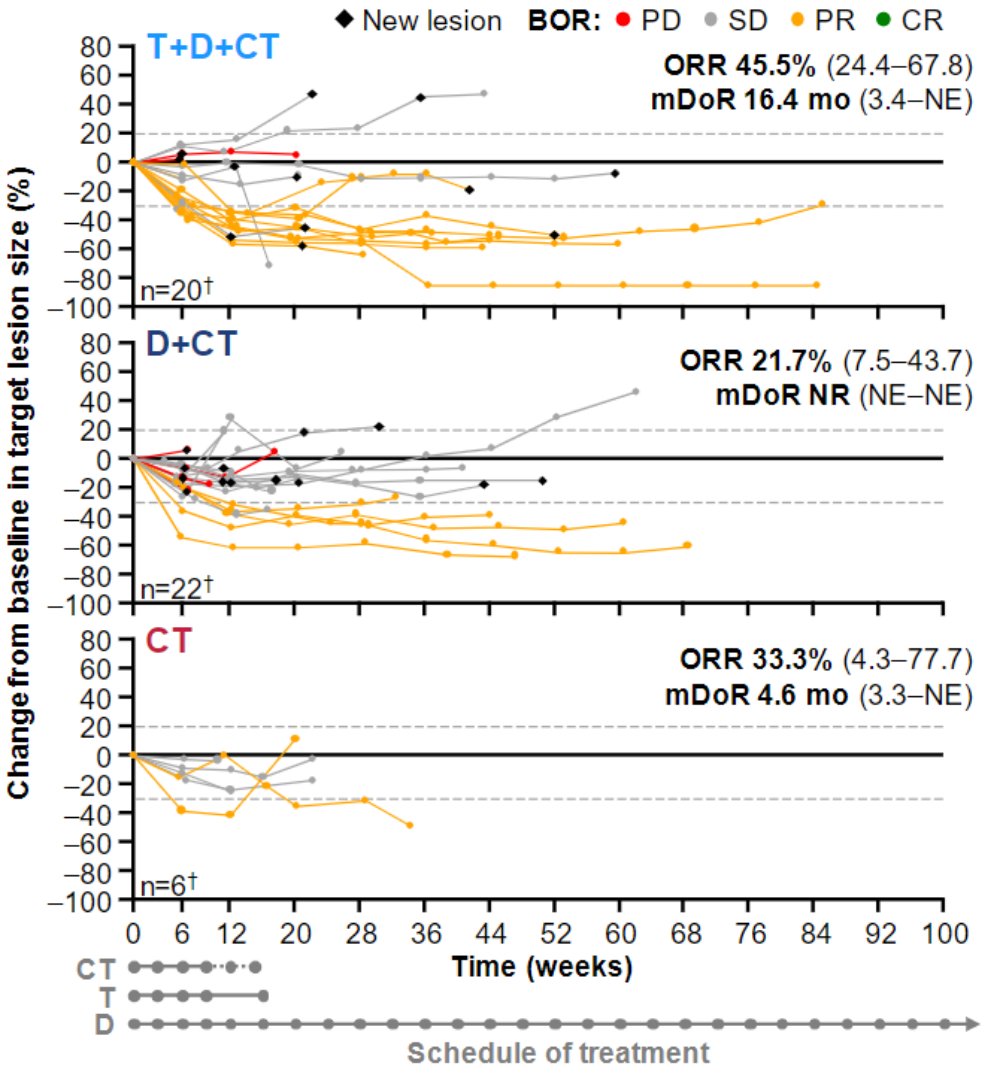
***KEAP1*m**

	T+D+CT	D+CT	CT
Events, n/N	16/22	19/23	6/6
mOS, mo (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–



HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

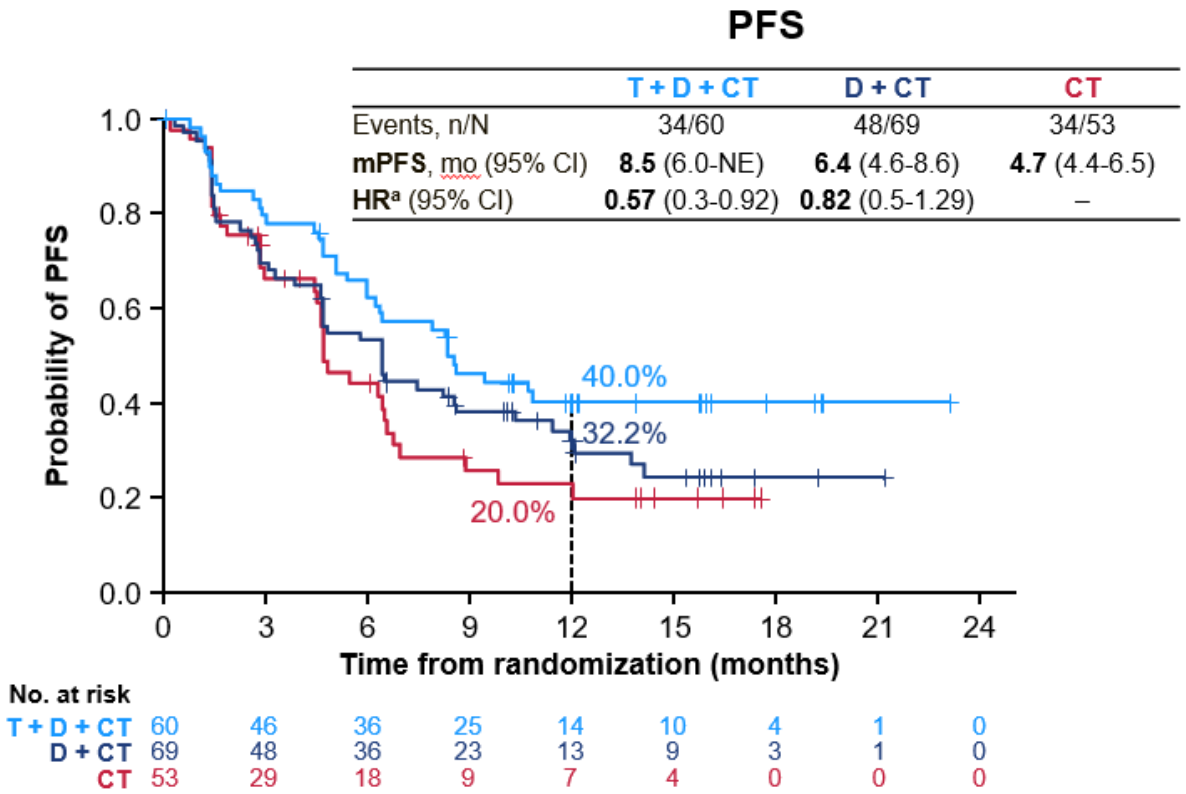
B.



Peters S et al., WCLC, 2022

PFS and ORR with the POSEIDON regimen (D+T+chemo) in *KRAS*-mutant NSCLC (4-year update)

A.



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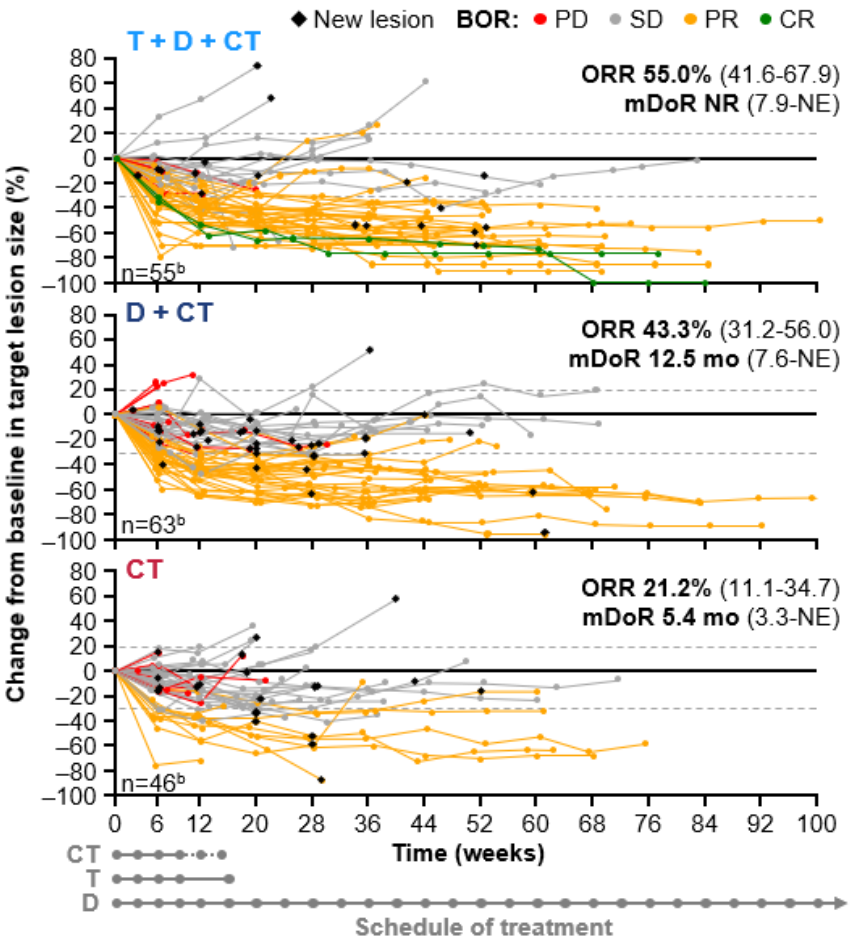
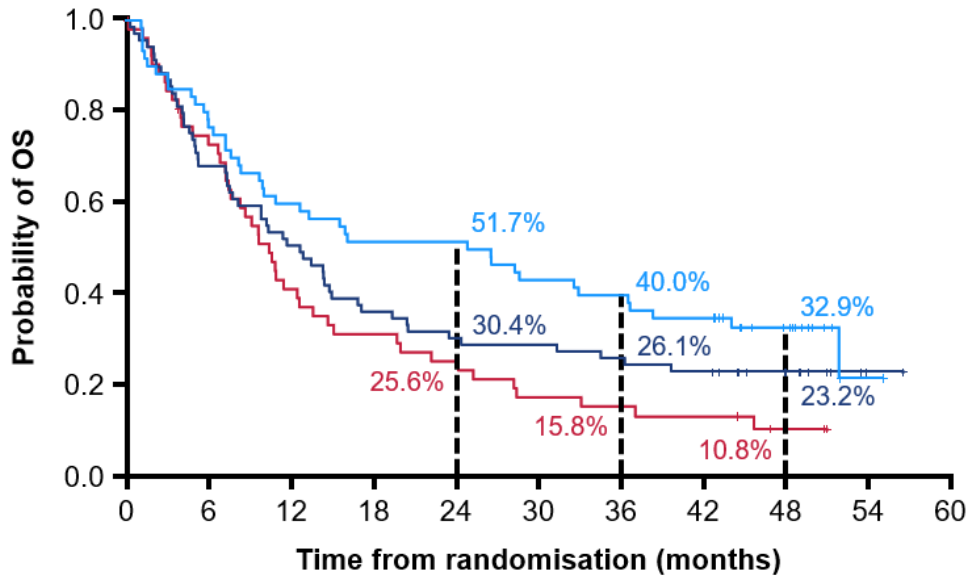


Johnson ML et al., ESMO, 2022

OS with the POSEIDON regimen (D+T+chemo) in *KRAS*-mutant and wild-type NSCLC (4-year update)

*KRAS*m

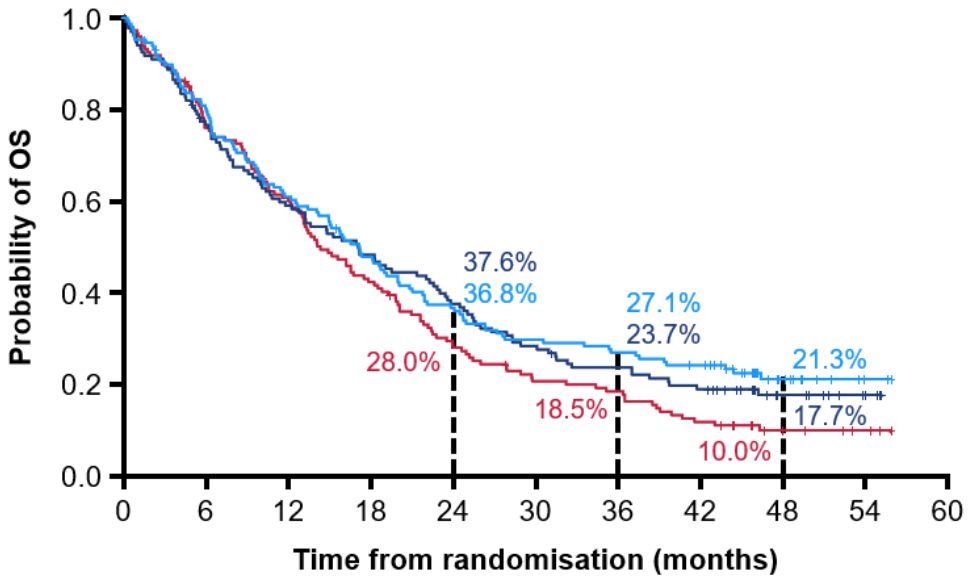
	T+D+CT	D+CT	CT
Events, n/N	41/60	53/69	45/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.55** (0.36–0.85)	**0.78** (0.52–1.16)	–



No. at risk											
T+D+CT	60	46	36	31	31	26	24	21	12	1	0
D+CT	69	47	35	25	21	20	18	16	9	1	0
CT	53	37	21	16	13	9	7	6	2	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events, n/N	113/148	107/134	127/148
mOS, months (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.78** (0.60–1.00)	**0.83** (0.64–1.08)	–

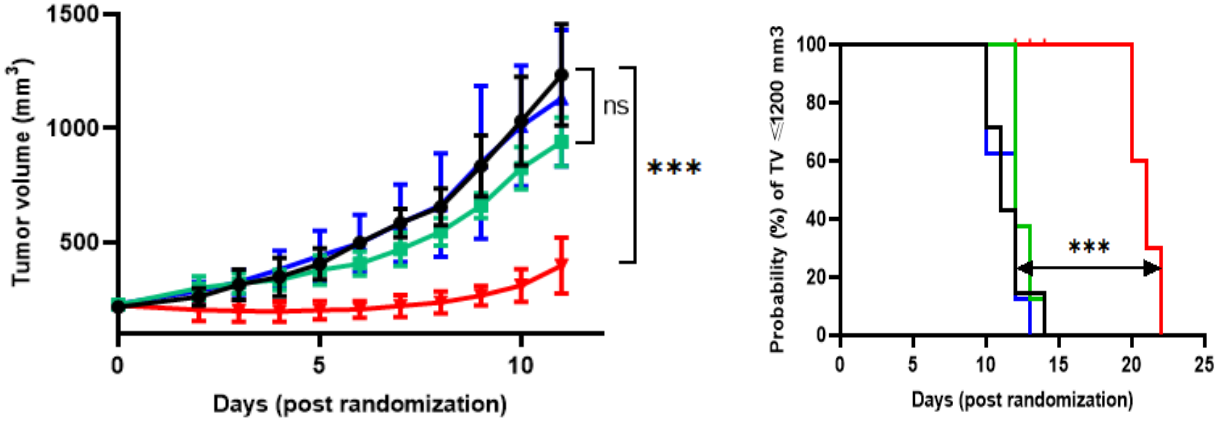


No. at risk											
T+D+CT	148	118	89	69	53	43	39	34	12	2	0
D+CT	134	101	77	63	49	37	30	24	11	3	0
CT	148	110	86	60	39	28	25	16	7	4	0

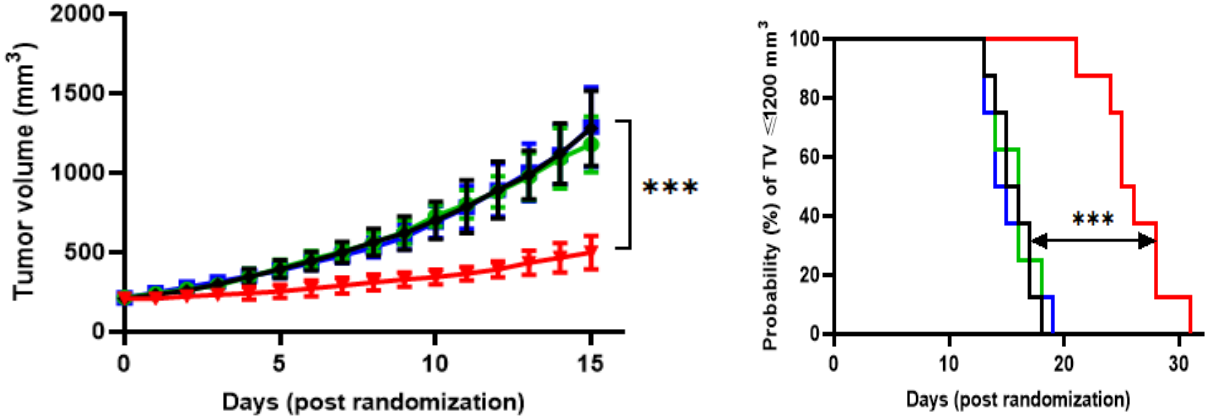
Johnson ML et al., ESMO, 2022

Sensitivity of *Kras^{MUT};Stk11$^{-/-}$* lung adenocarcinomas to dual anti-PD-1/anti-CTLA-4 ICB is recapitulated in syngeneic models

KL2 (Kras^{G12C};Stk11$^{-/-}$)



KL5 (Kras^{G12C};Stk11$^{-/-}$)



IgG control — αPD-1 — αCTLA-4 — αPD-1 + αCTLA-4

Skoulidis F et al., under review

Conclusions

- Co-mutations in key tumor suppressor genes – most prominently *STK11* and *KEAP1* shape the immune contexture of ns-NSCLC.
- *STK11* and *KEAP1* alterations frequently co-occur (and are both enriched in *KRAS*-mutant NSCLC) and loss of both TSGs promotes lung oncogenesis. However, their inactivation imparts both overlapping as well as distinct effects on the TIME.
- Only STK11 alterations are associated with lack of/low PD-L1 expression on tumor cells.
- 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.
- Loss of KEAP1 and/or STK11 may impart selective sensitivity to dual immune checkpoint blockade with anti-PD-(L)1+ anti-CTLA-4.
- 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.
- 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 under development to confirm findings from POSEIDON.
- *STK11*, *KEAP1* represent emerging biomarkers for selection of first-line regimens in advanced NSCLC.
- A number of novel therapeutic strategies to induce/re-invigorate effective anti-tumor immunity in *STK11* and/or *KEAP1*-mutant NSCLC are currently in development.

Thank you !