PD(L)1 + CTLA-4 FOR NSCLC: DATA + HOW I USE IT

Hossein Borghaei, DO, MS, Fox Chase Cancer Center, Philadelphia

@hosseinborghaei

April 2024

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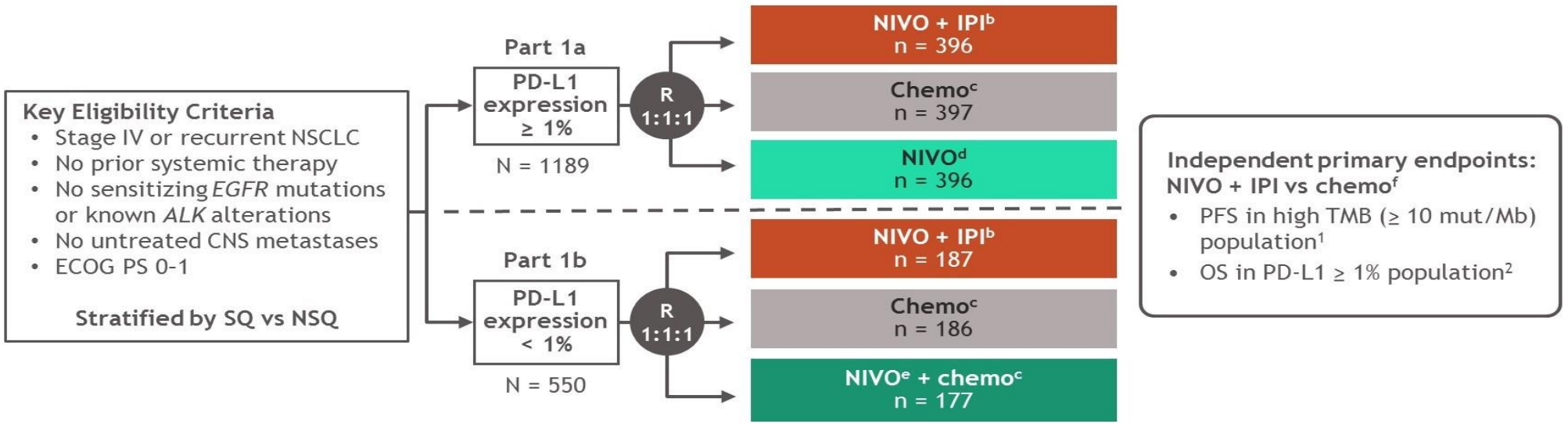
CheckMate 227[a] Part 1 study design



CheckMate-227, Five Year OS

Figure 4. OS in patients with tumor PD-L1 ≥ 1% by histology

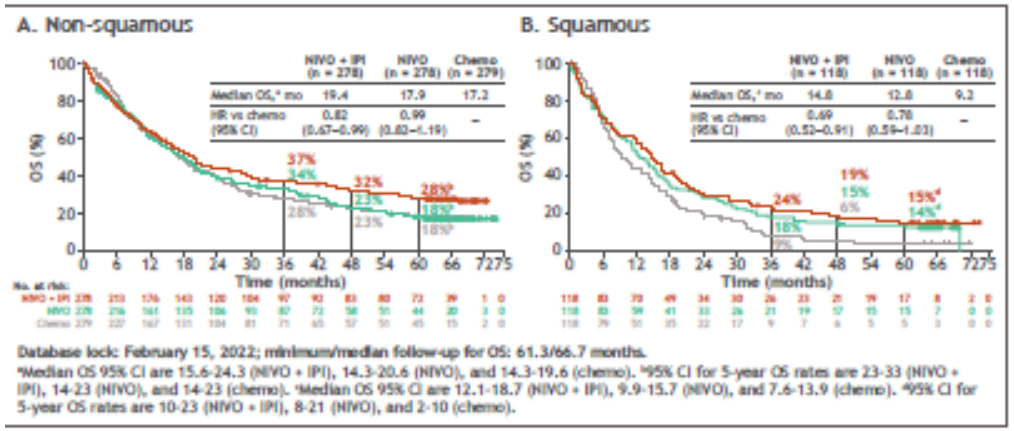


Figure 5. OS in patients with tumor PD-L1 < 1% by histology

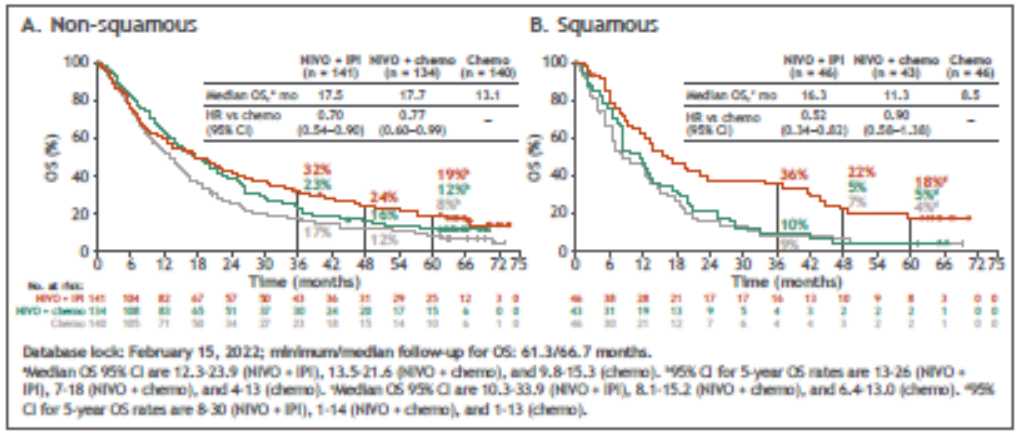
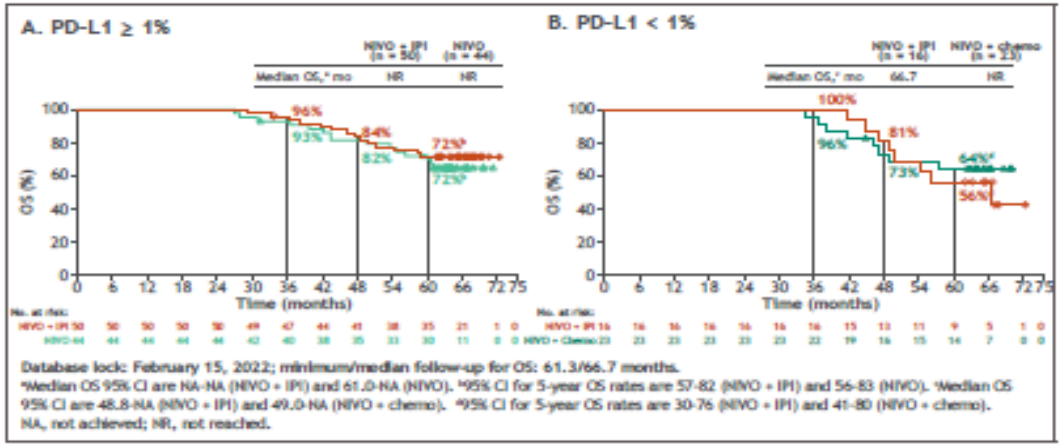


Figure 6. OS in patients who completed 2 years of immunotherapy

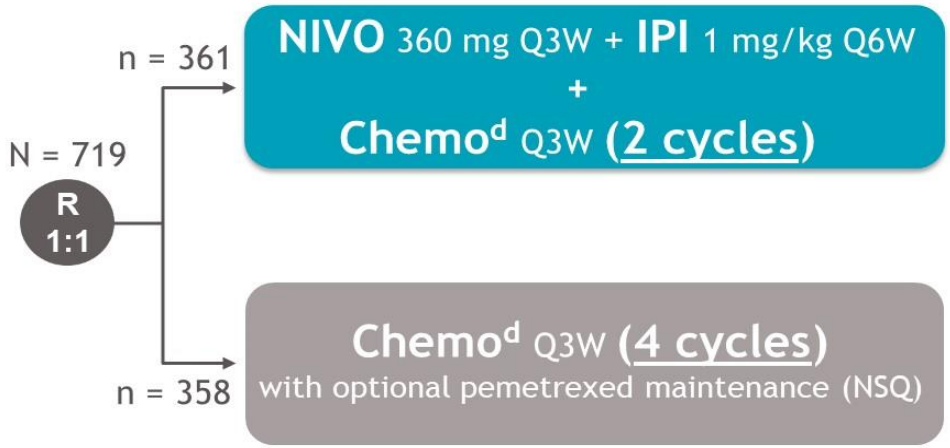


Borghaei, NACLC, Chicago, 2022, Brahmer, JCO, 2022

CheckMate 9LA study design[a]

Key eligibility criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



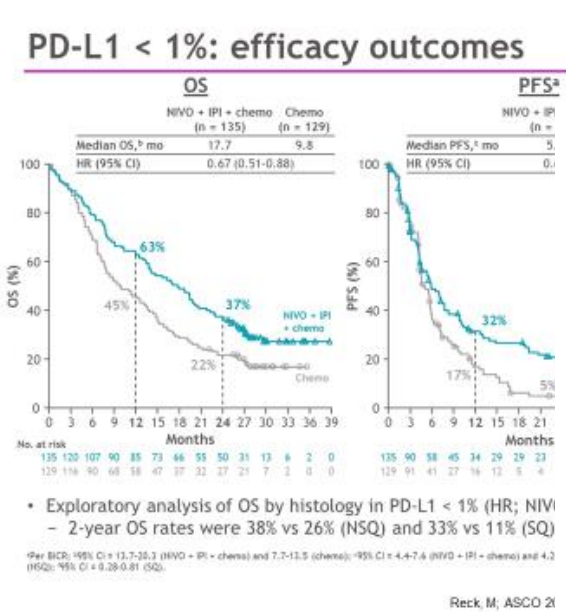
Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

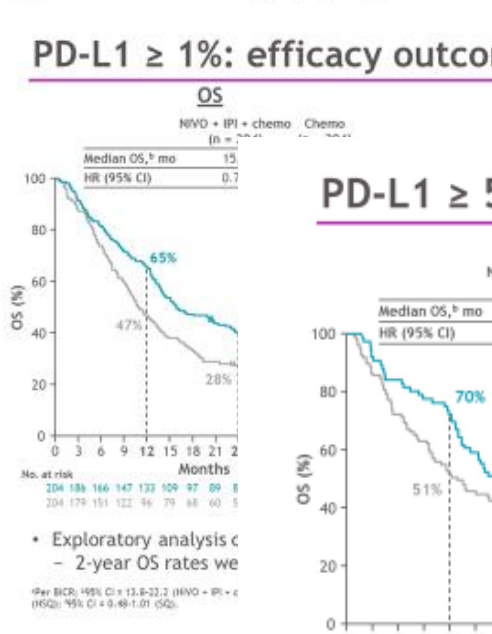
Primary endpoint
- OS

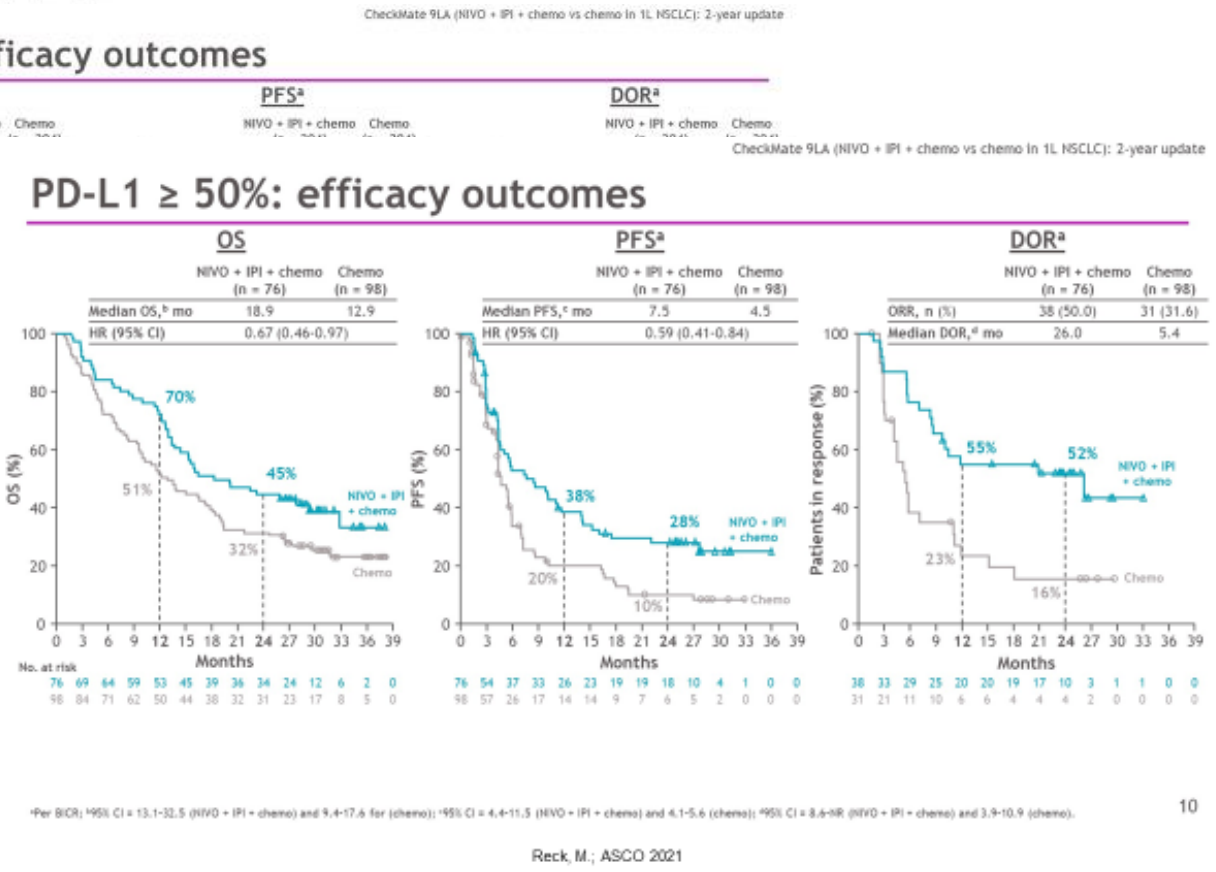
Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

CheckMate-9LA



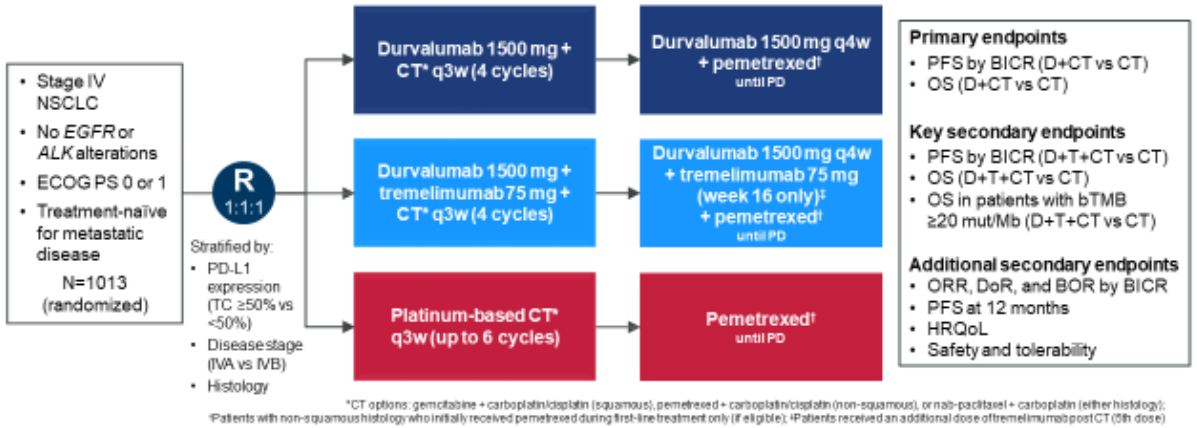




POSEIDON

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology); †Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

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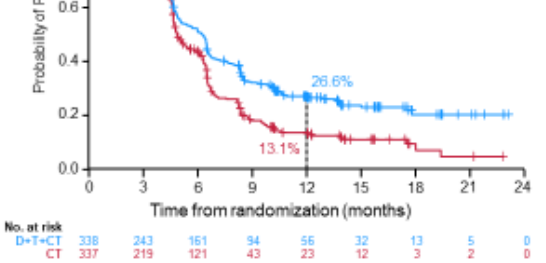
BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

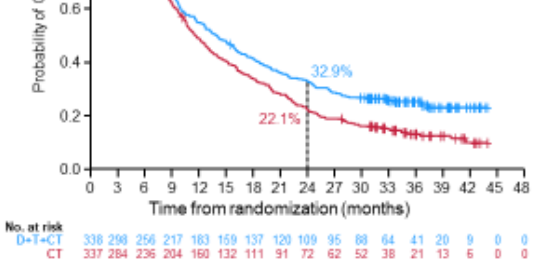
	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	



• Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



• Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

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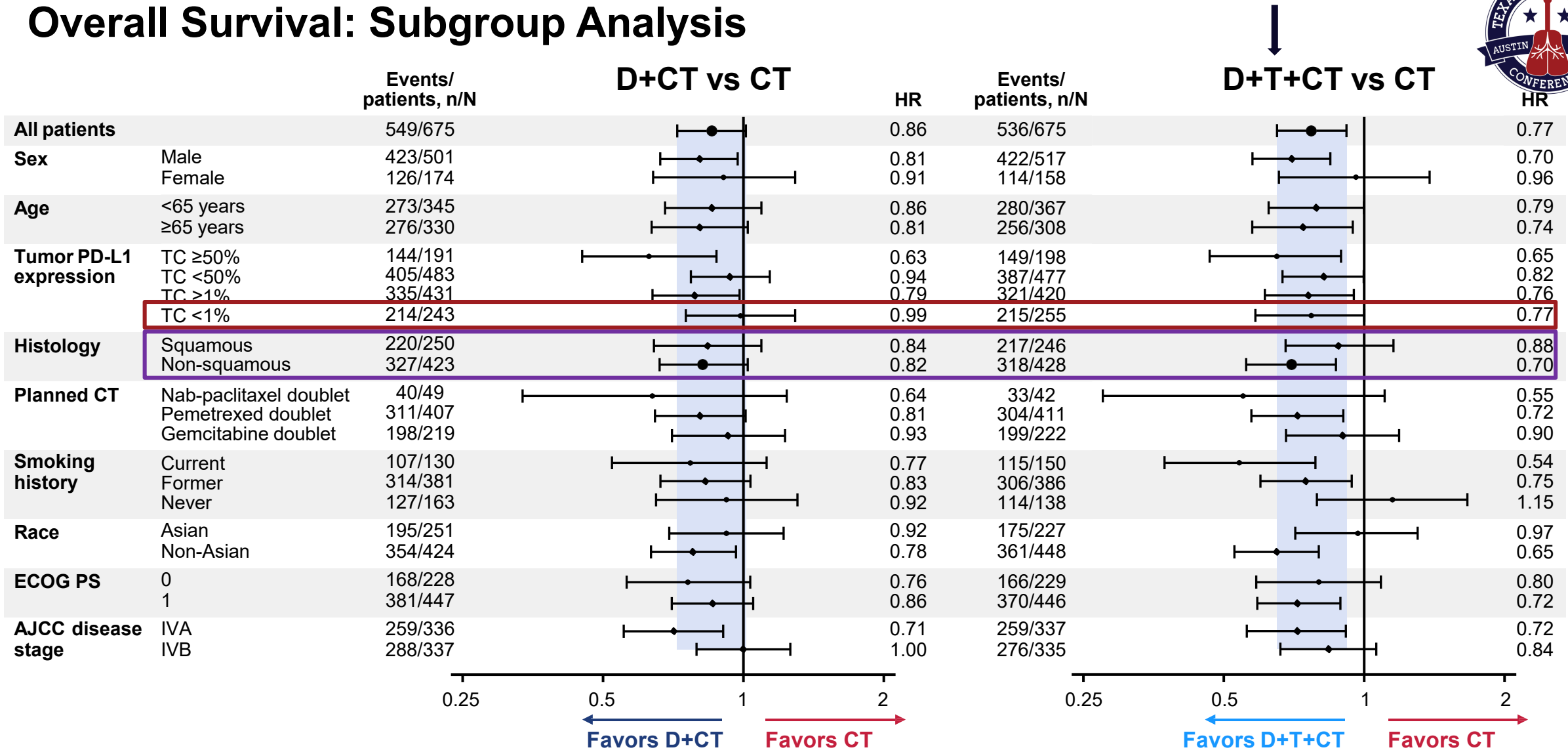
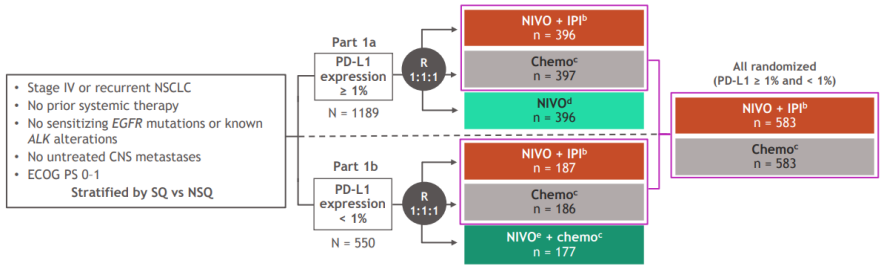
DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Melissa Johnson, 2021

Overall Survival: Subgroup Analysis



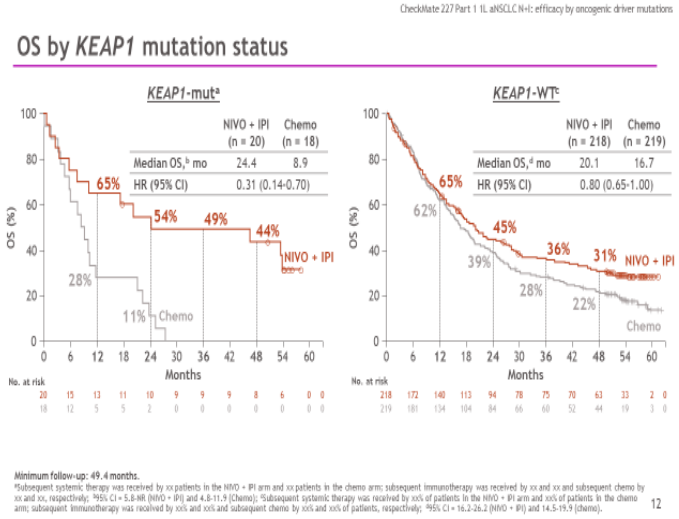
STK11 and *KEAP1* alterations and clinical outcomes with ipi/nivo in Part 1 of CheckMate 227



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

Subgroup, n[b]	4-y PFS rate, %		Median PFS, mo		Unstratified HR	Unstratified HR (95% CI)
	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



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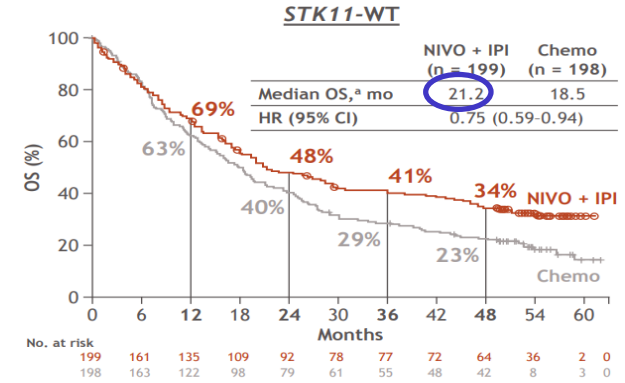
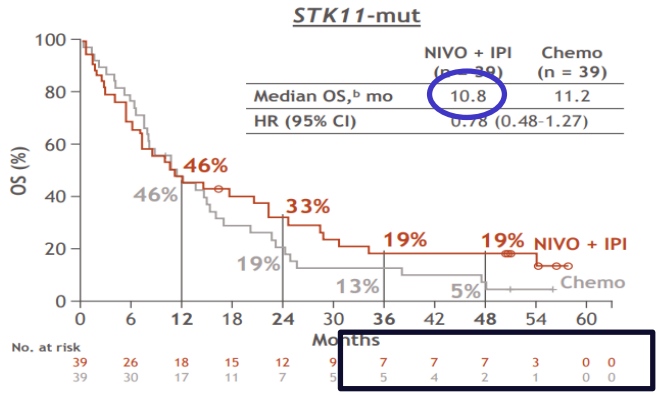
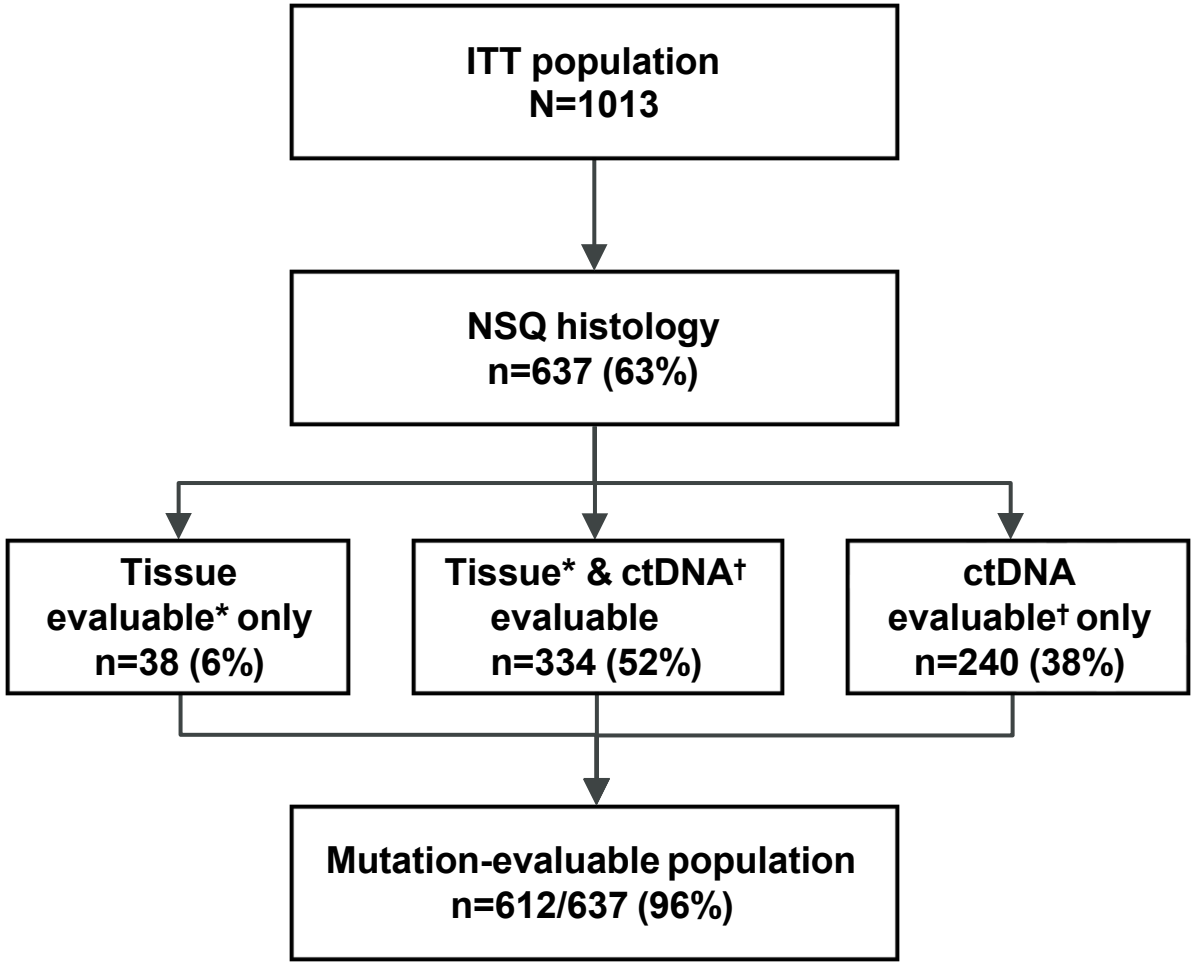


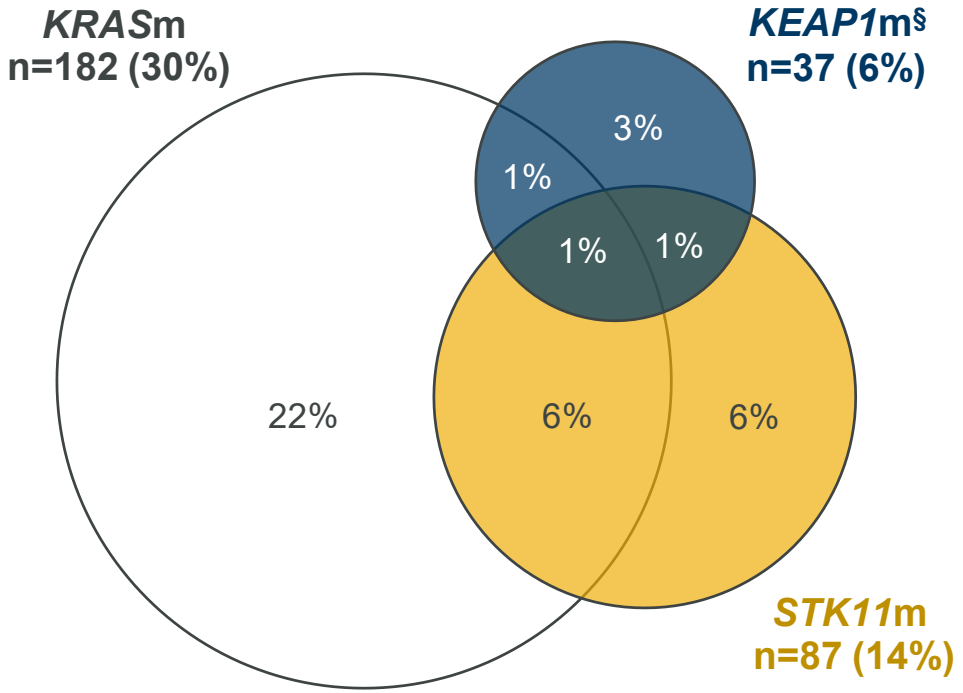


Ramalingam S et al., ESMO Immuno-Oncology Congress,2021
F. Skoulidis, TTLC, 2022

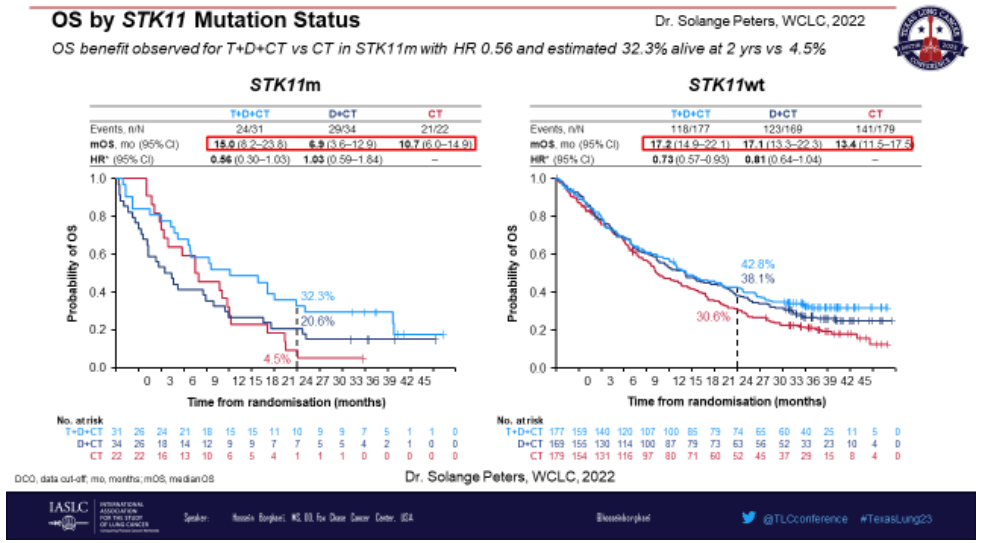
Prevalence of *STK11*, *KEAP1* and *KRAS* Mutations in Patients from POSEIDON with NSQ Histology

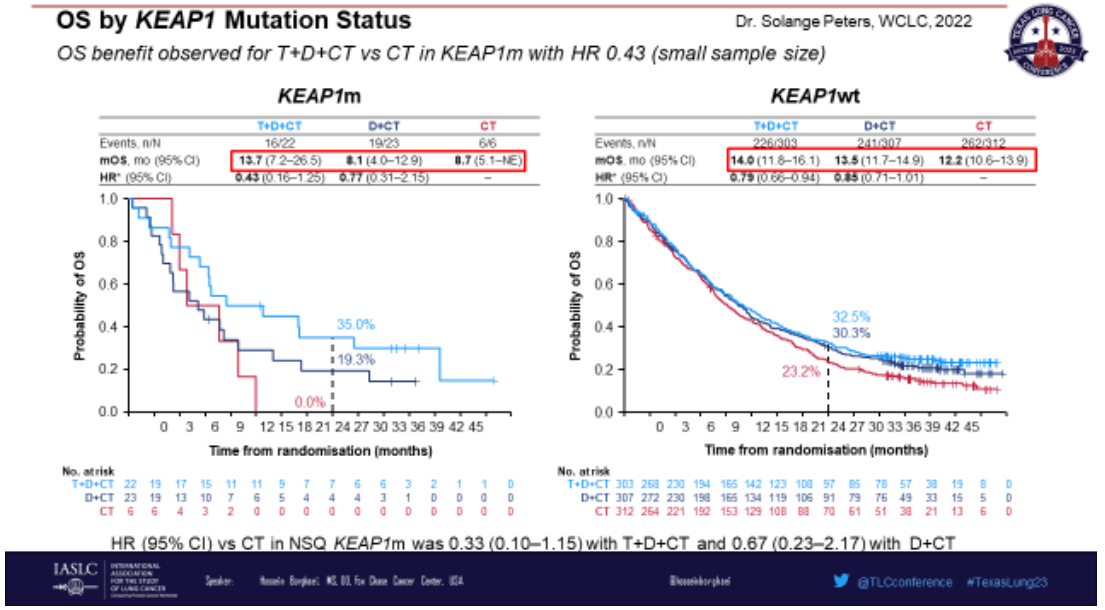


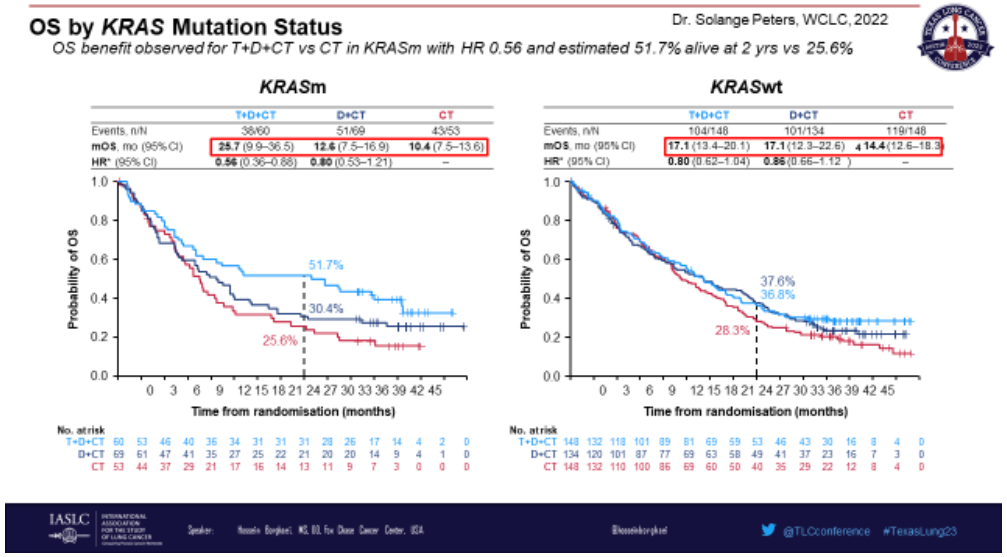
Mutation-evaluable population‡
(n=612; **96%** of randomised patients with NSQ histology)



Dr. Solange Peters, WCLC, 2022







D+T+CT vs Chemotherapy alone

	STK11 M	STK11 W	KEAP1 M	KEAP1 W	KRAS M	KRAS W
OS HR v CT	0.57	0.71	0.43	0.76	0.56	0.80
5-yr OS v CT	12.9% 0% with CT	22%	NR	NR	21.7% 8.1% with CT	20.3%

Dr. Solange Peters, WCLC, 2022

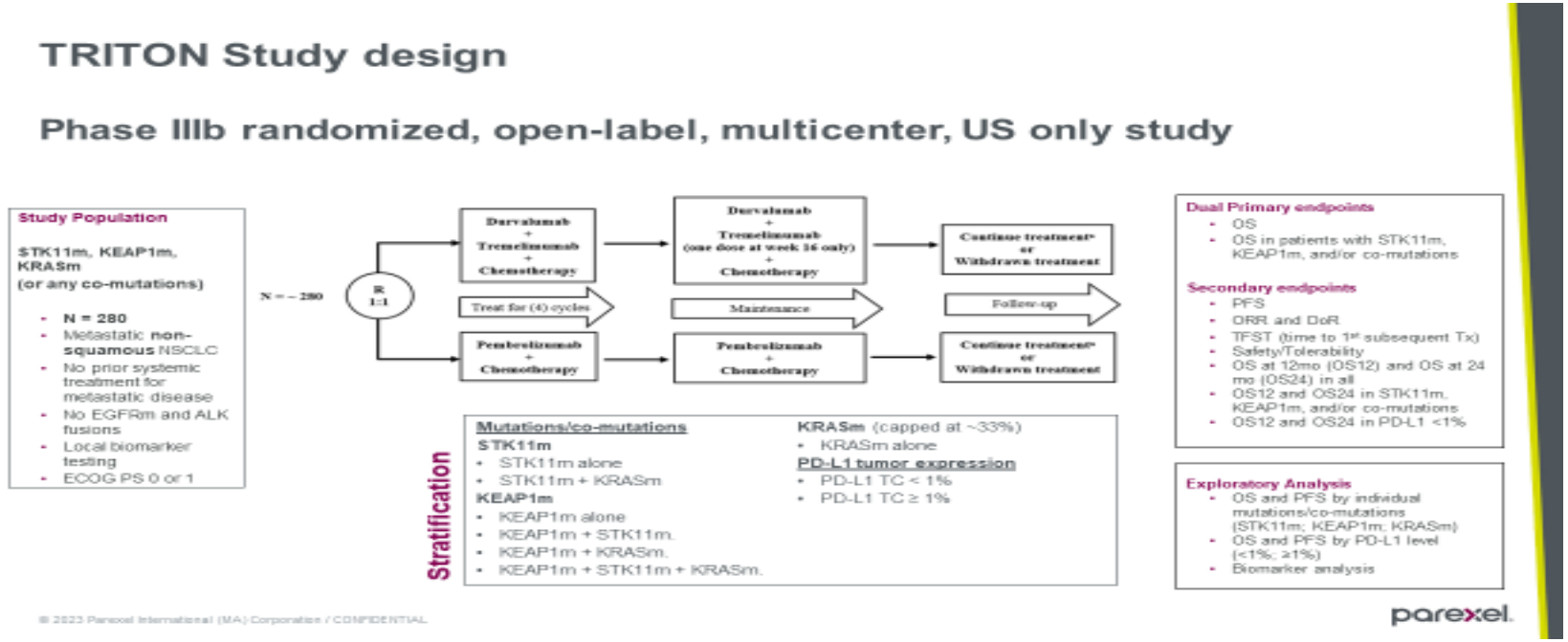
STK11 and *KEAP1* alterations and clinical outcomes in the KEYNOTE-189 Phase III trial

	STK11				*KEAP1*			
	With Mutation		Without Mutation		With Mutation		Without Mutation	
	Pembro + Chemo (n = 36)	Placebo + Chemo (n = 18)	Pembro + Chemo (n = 168)	Placebo + Chemo (n = 67)	Pembro + Chemo (n = 45)	Placebo + Chemo (n = 23)	Pembro + Chemo (n = 159)	Placebo + Chemo (n = 62)
ORR, % (95% CI)	31 (16-48)	17 (4-41)	49 (41-57)	16 (8-27)	36 (22-51)	17 (5-39)	48 (40-56)	16 (8-28)
PFS, median, mo (95% CI)	6 (4-9)	5 (5-9)	10 (8-14)	5 (5-5)	5 (4-11)	5 (5-9)	10 (8-14)	5 (5-5)
PFS, HR (95% CI)	0.81 (0.44-1.47)		0.38 (0.27-0.52)		0.65 (0.38-1.12)		0.38 (0.28-0.53)	
OS, median, mo (95% CI)	17 (5-NR)	8 (7-NR)	23 (20-NR)	12 (8-25)	13 (7-NR)	9 (7-NR)	24 (20-NR)	12 (8-NR)
OS, HR (95% CI)	0.75 (0.37-1.50)		0.59 (0.41-0.85)		0.81 (0.44-1.49)		0.57 (0.39-0.84)	

Gadgeel SM et al, AACR Annual Meeting 2020
F. Skoulidis, TTLC 2022

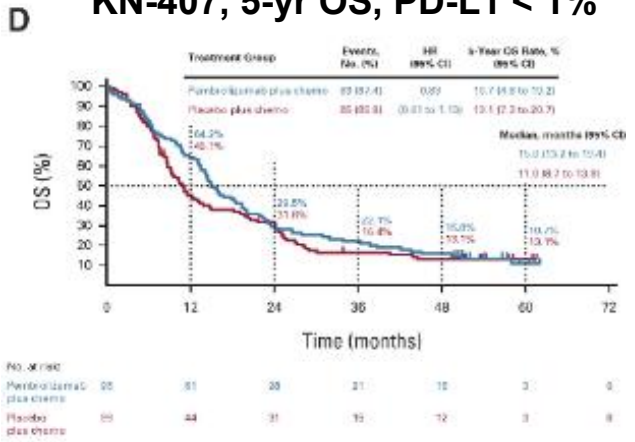
How do I use this Information?

- For KEAP1 and STK-11 mutation positive tumors, I prefer a PD(L)-1/CTLA4 combination.
- I use at least two cycles of chemotherapy with the dual IO combination.
- In the absence of randomized prospective trials the available retrospective data should be interpreted with caution. However, there are now multiple datasets of retrospective data pointing to the same conclusion.
- The TRITON Study is attempting to answer this question:



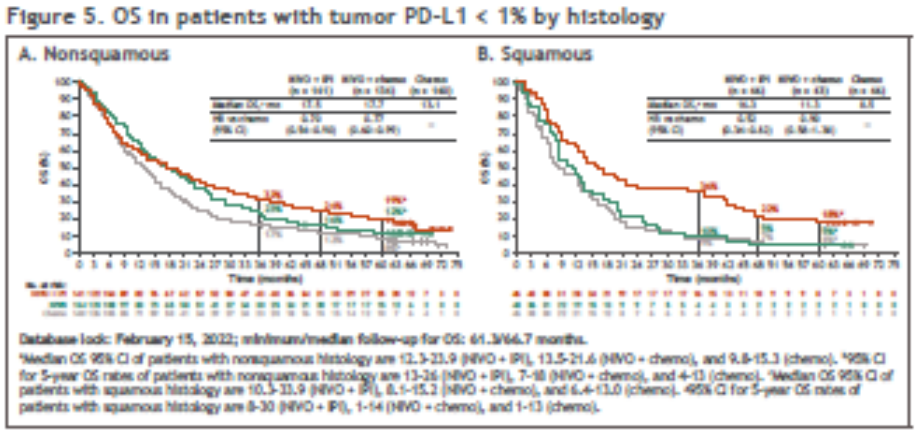
Possible role in PD-L1 <1% sub group

KN-407, 5-yr OS, PD-L1 < 1%



5 yr OS: 10.7 vs 13.1

CM-227, 5-yr OS, PD-L1 <1%

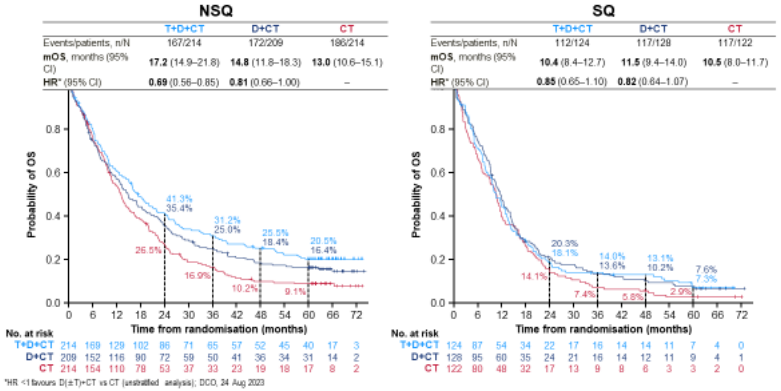


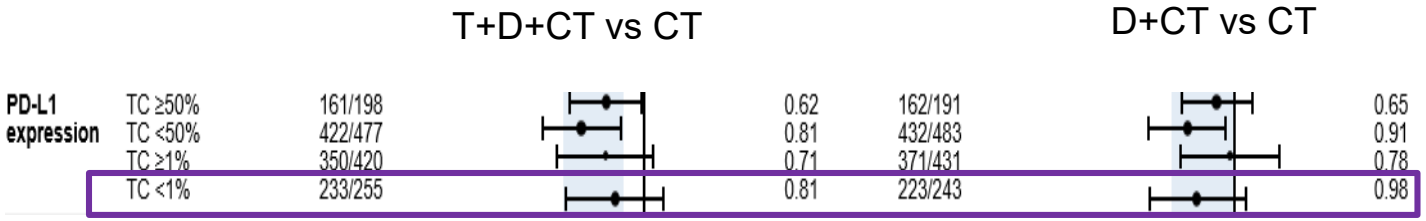
5 yr OS: 24% vs 14% (PD-L1≥1%); 19% vs 7% (PD-L1 <1%)

ESMO IMMUNO-ONCOLOGY

POSEIDON: Updated OS by Histology

Long-term OS benefit with T+D+CT vs CT more pronounced in NSQ with HR 0.69 and 5-yr OS rates 20.5% vs 9.1%





References: Novello, JCO, Feb 3, 2022; Borghaei, NACLC, 2022; Peters, ESMO-IO, 2023

Is there a role in PD-L1 negative tumors?

- Again, no prospective, randomized trials to answer this question
- The “tail of the curve” seems to favour a dual IO approach
- Patient preferences, toxicity and other factors could influence the use of a dual IO approach with or without chemotherapy vs chemo-IO