THE EVOLVING ROLE OF DUAL CHECKPOINT INHIBITION

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Fox Chase Cancer Center

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Endorsed by

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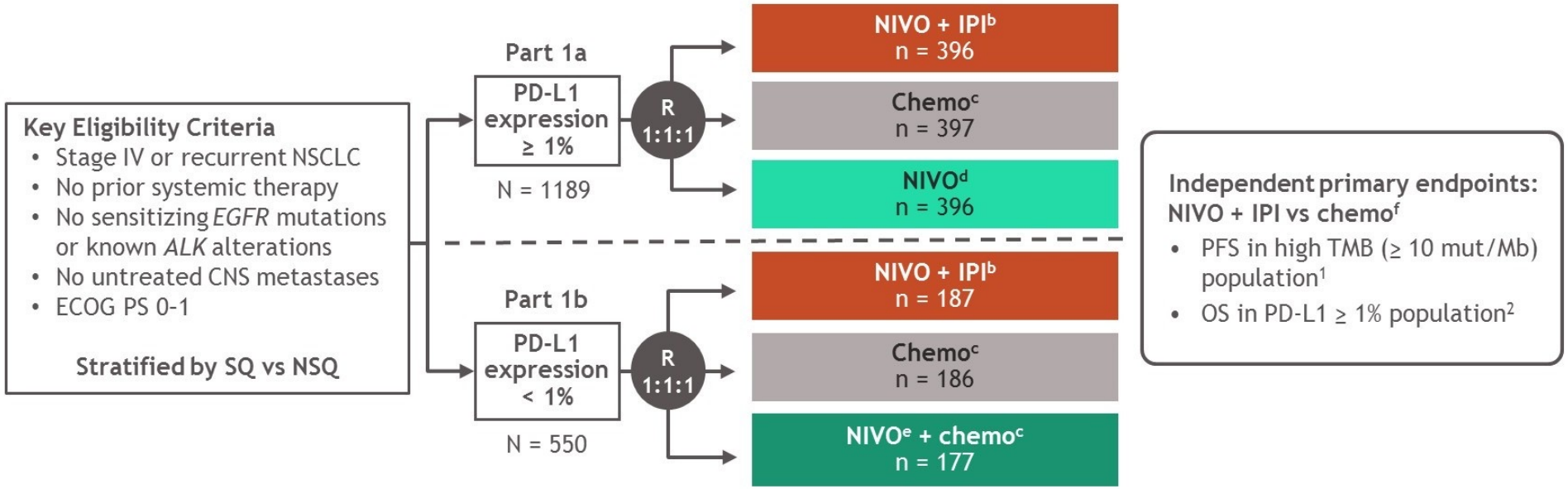
Rationale

- IO/IO combinations could avoid the toxicities of cytotoxic chemotherapy
- These combinations could lead to better long term efficacy by avoiding the potential impact of chemotherapy on immune cells
- A short course of chemotherapy with and IO/IO combination offers the short term benefits of chemotherapy but avoids the long term adverse events
- Allows for the use of platinum doublets at a later time
- Toxicities of these combinations depend on the specific pathways and drugs used

CheckMate-227



Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

CheckMate-227, Five year OS

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

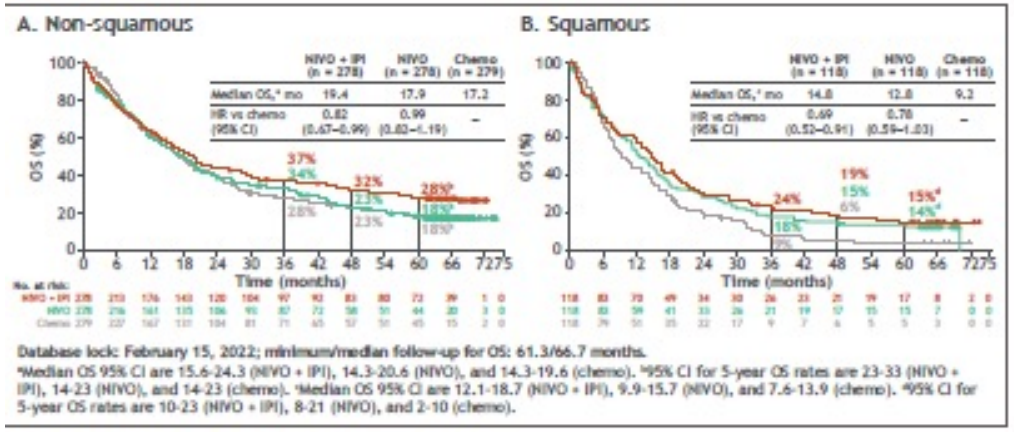


Figure 5. OS in patients with tumor PD-L1 < 1% by histology

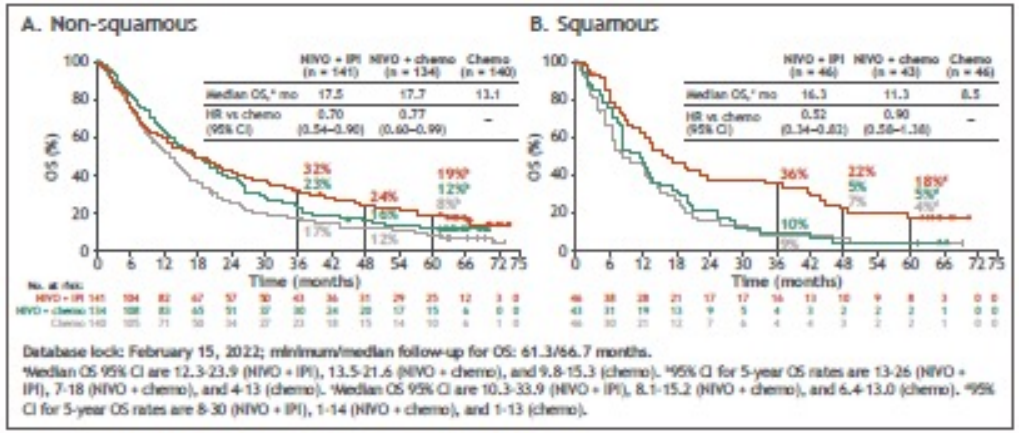
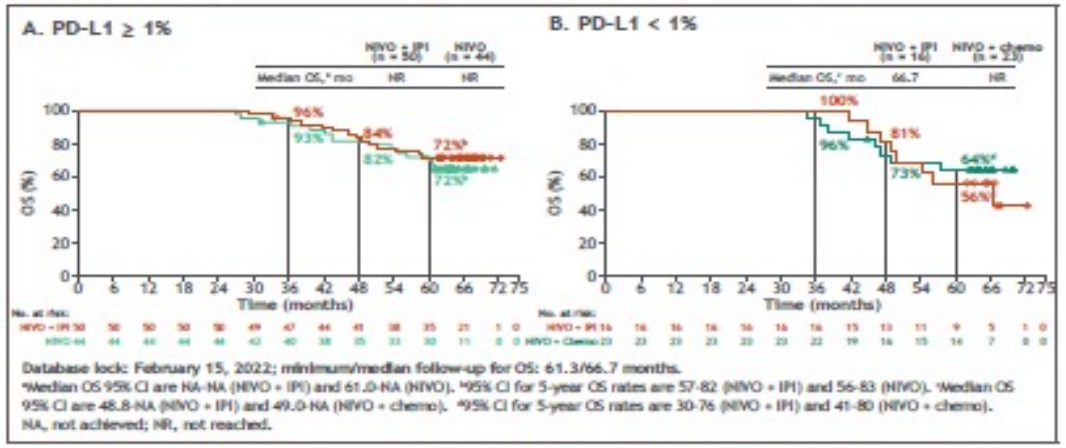


Figure 6. OS in patients who completed 2 years of immunotherapy

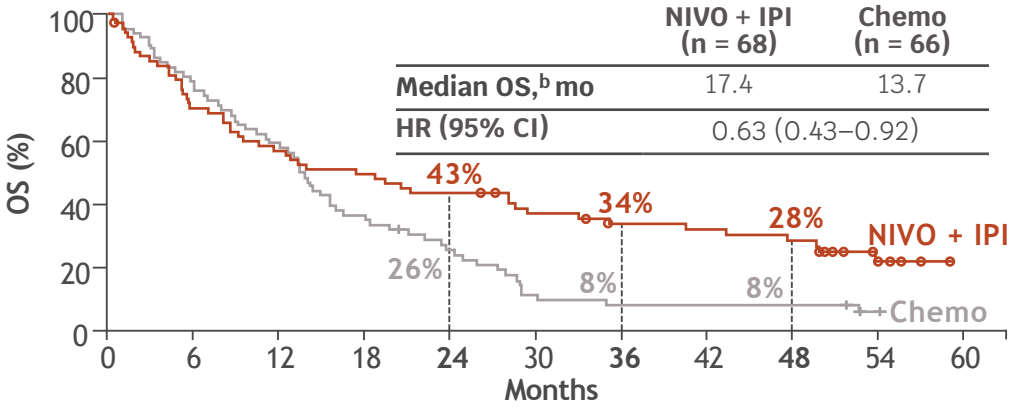


Borghaei, NACLC, Chicago, 2022, Brahmer, JCO, 2022

CheckMate-227, Subgroup Analysis

With baseline brain metastases[a]

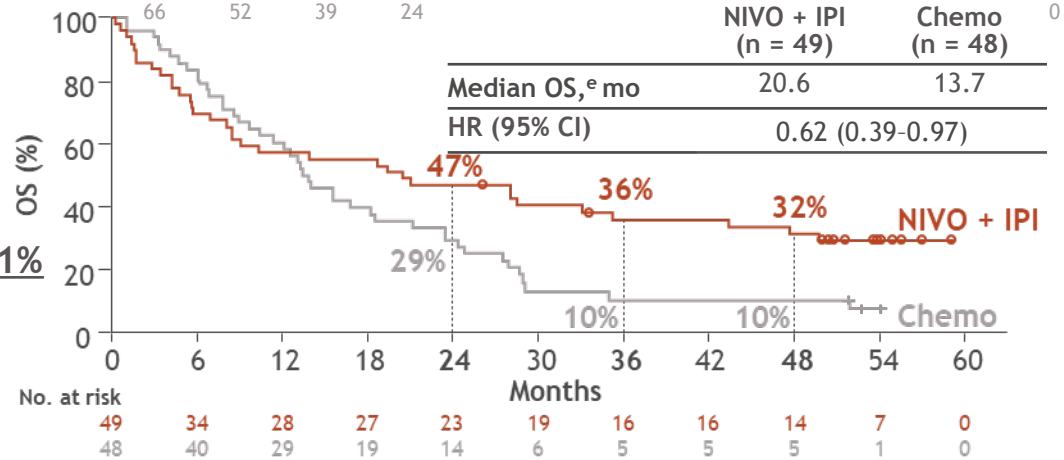
All randomized



	NIVO + IPI (n = 68)	Chemo (n = 66)
Median OS,[b] mo	17.4	13.7
HR (95% CI)	0.63 (0.43–0.92)	

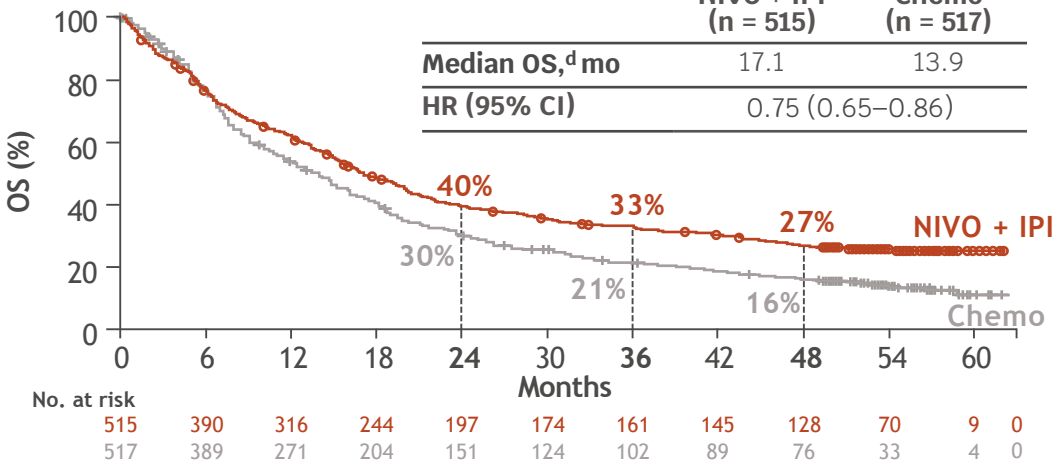
NIVO + IPI	68	47	38	33	29	23	19	18	16	7	0
Chemo	66	52	39	24							0

PD-L1 ≥ 1%

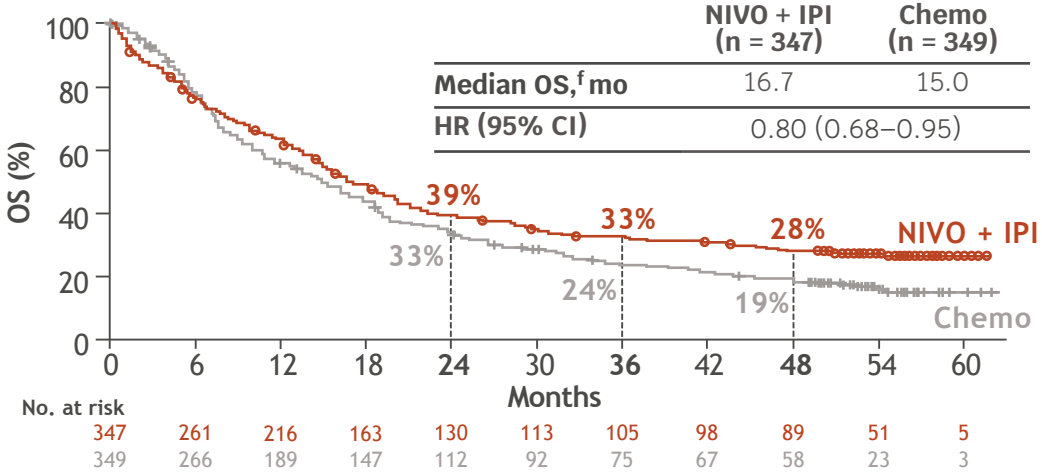


	NIVO + IPI (n = 49)	Chemo (n = 48)
Median OS,[e] mo	20.6	13.7
HR (95% CI)	0.62 (0.39-0.97)	

Without baseline brain metastases[c]



	NIVO + IPI (n = 515)	Chemo (n = 517)
Median OS,[d] mo	17.1	13.9
HR (95% CI)	0.75 (0.65–0.86)	

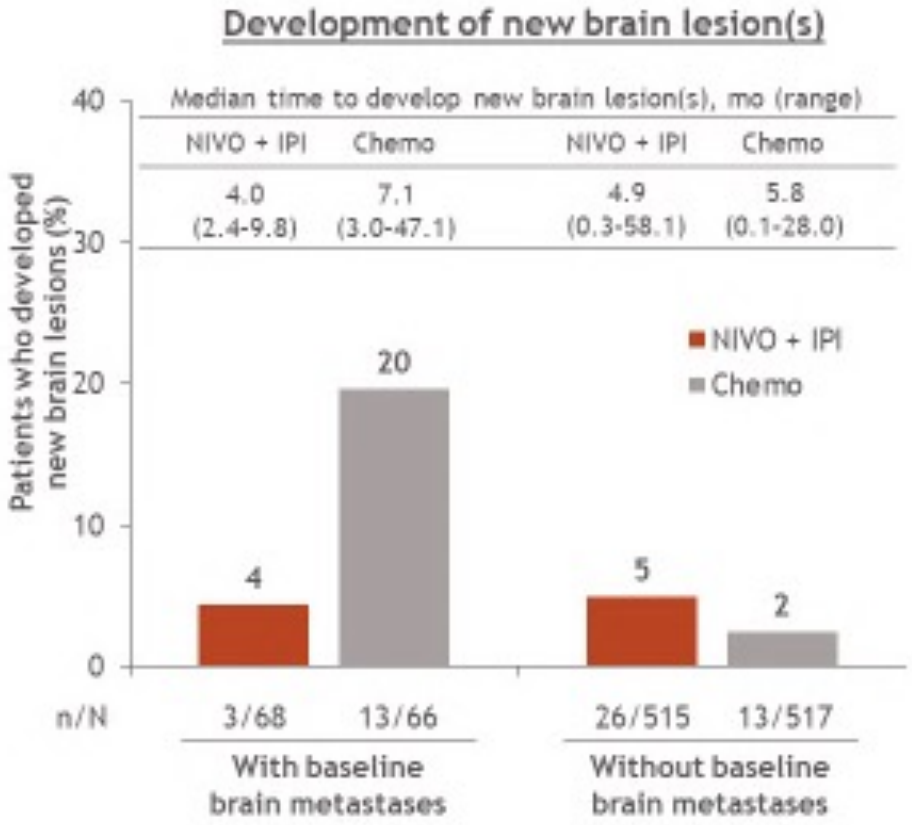


	NIVO + IPI (n = 347)	Chemo (n = 349)
Median OS,[f] mo	16.7	15.0
HR (95% CI)	0.80 (0.68–0.95)	

Dr. Martin Reck, ESMO-IO, 2021

Intracranial outcomes in all randomized patients, CM-227

Intracranial response[a]	With baseline brain metastases	
	NIVO + IPI (n = 68)	Chemo (n = 66)
ORR, n (%)	20 (29)	19 (29)
BOR,[c] n (%)		
CR	9 (13)	5 (8)
PR	11 (16)	14 (21)
SD	24 (35)	24 (36)
PD	3 (4)	4 (6)
DCR, n (%)	44 (65)	43 (65)
Median time to response, mo (range)	2.9 (1.2-11.8)	2.8 (1.2-20.7)
Median DOR, mo (95% CI)	45.5 (27.1-52.4)	32.0 (5.1-44.2)



[a]Per BICR; [b]By initial PD; [c]Unable to determine: 6% for NIVO + IPI (n = 4) and 4% for chemo (n = 3); unreported: 25% for NIVO + IPI (n = 17) and 24% for chemo (n = 16).

Safety summary in all treated patients, CM-227

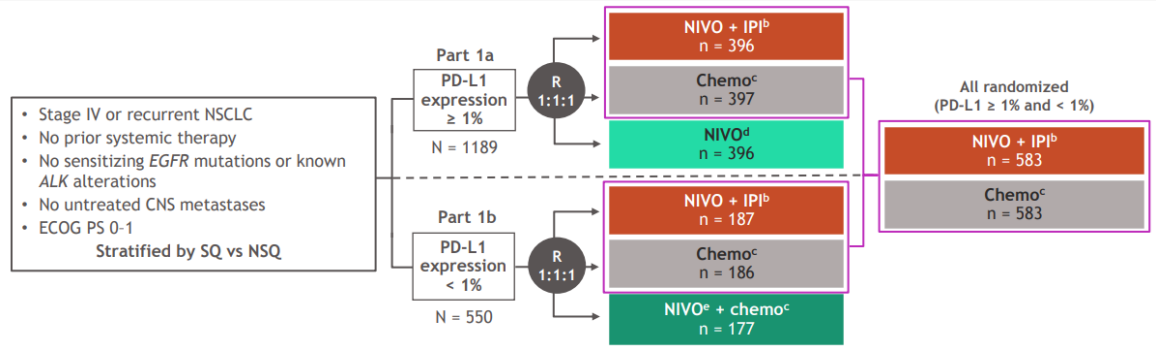
%	With baseline brain metastases				Without baseline brain metastases			
	NIVO + IPI (n = 64)		Chemo (n = 66)		NIVO + IPI (n = 512)		Chemo (n = 504)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs[a]	77	30	76	27	77	33	83	37
Treatment-related AEs leading to discontinuation of any component of the regimen	9	6	3	2	19	13	10	5
Treatment-related nervous system disorders (≥ 2%[b])								
Headache	5	0	2	0	2	0	1	0
Paraesthesia	3	0	2	0	1	0	2	0
Somnolence	3	0	0	0	0	0	< 1	0
Taste disorder	3	0	2	0	1	0	1	0
Dysgeusia	0	0	6	0	2	0	5	0
Treatment-related nervous system AEs leading to discontinuation of any component of the regimen	0	0	0	0	< 1	< 1	1	0
Treatment-related SAEs	19	14	9	4	25	19	14	12
Treatment-related deaths[c]	0		1		8		5	

- Median (range) treatment duration with NIVO + IPI versus chemo
  - 4.2 (0-24.4) versus 3.6 (0-49.4) months in patients with baseline brain metastases
  - 4.2 (0-25.5) versus 2.6 (0-49.1) months in patients without baseline brain metastases

Dr. Martin Reck, ESMO-IO, 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%

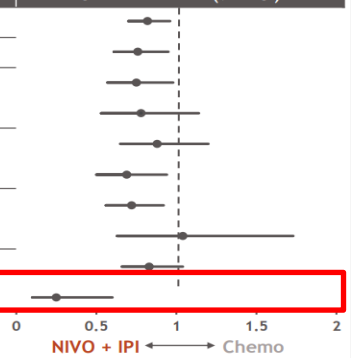
PD-L1 ≥50%: 37%

TMB≥10Mut/Mb : 40%

TMB<10Mut/Mb : 60%

B.

Subgroup, n[b]	4-y PFS rate, %		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

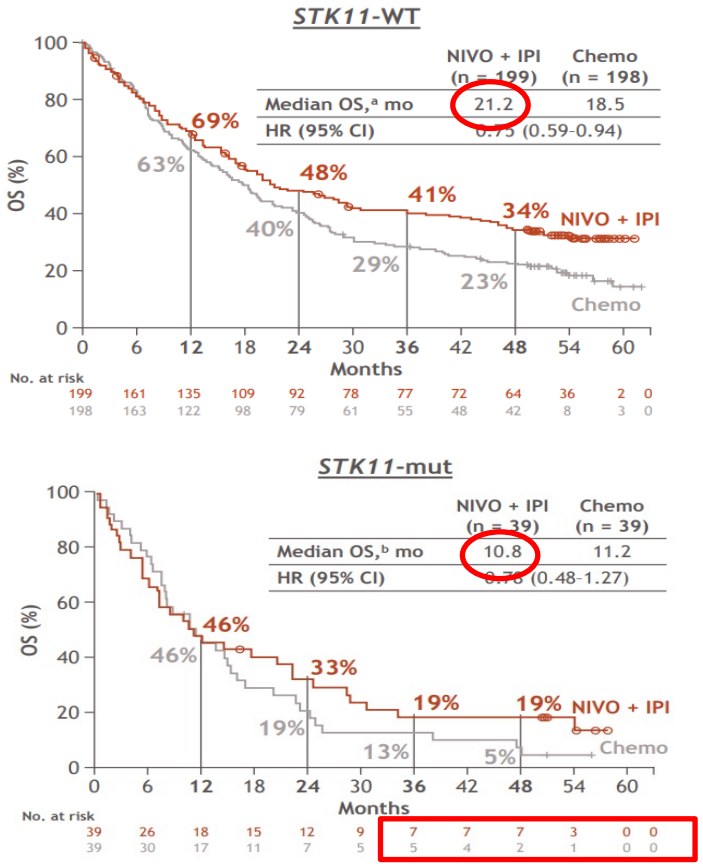


KEAP1^{MUT}(N=38)

Ipi/Nivo: mOS 24.4m

Chemo: mOS 8.9m

C.



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

CheckMate 9LA study design

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)

N = 719

R 1:1

n = 361 → **NIVO** 360 mg Q3W + **IPI** 1 mg/kg Q6W + **Chemo[d]** Q3W (2 cycles)

n = 358 → **Chemo[d]** Q3W (4 cycles) with optional pemetrexed maintenance (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

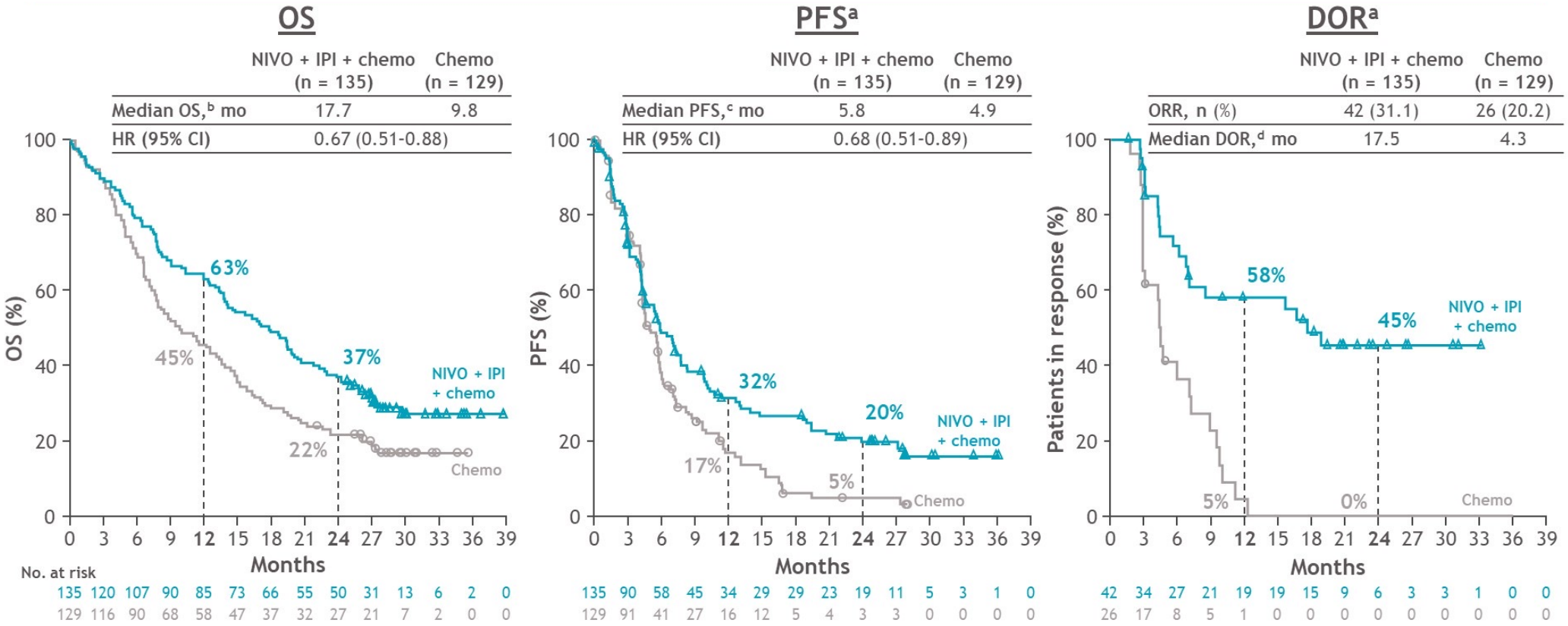
Exploratory endpoints
- Safety

DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[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.

Reck, M.; ASCO 2021

PD-L1 < 1%: efficacy outcomes

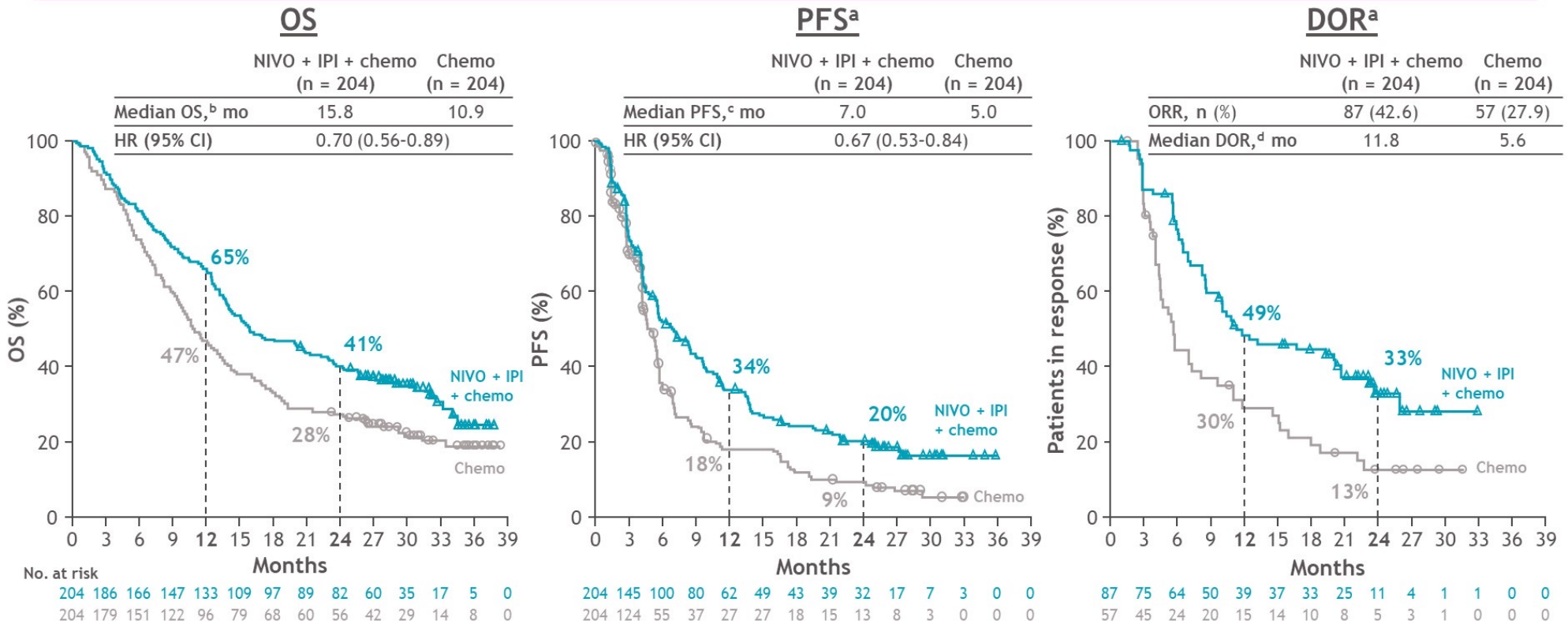


- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

[a]Per BICR; [b]95% CI = 13.7-20.3 (NIVO + IPI + chemo) and 7.7-13.5 (chemo); [c]95% CI = 4.4-7.6 (NIVO + IPI + chemo) and 4.2-5.7 (chemo); [d]95% CI = 6.7-NR (NIVO + IPI + chemo) and 2.8-7.1 (chemo); [e]95% CI = 0.54-1.04 (NSQ); [f]95% CI = 0.28-0.81 (SQ).

Reck, M.; ASCO 2021

PD-L1 ≥ 1%: efficacy outcomes

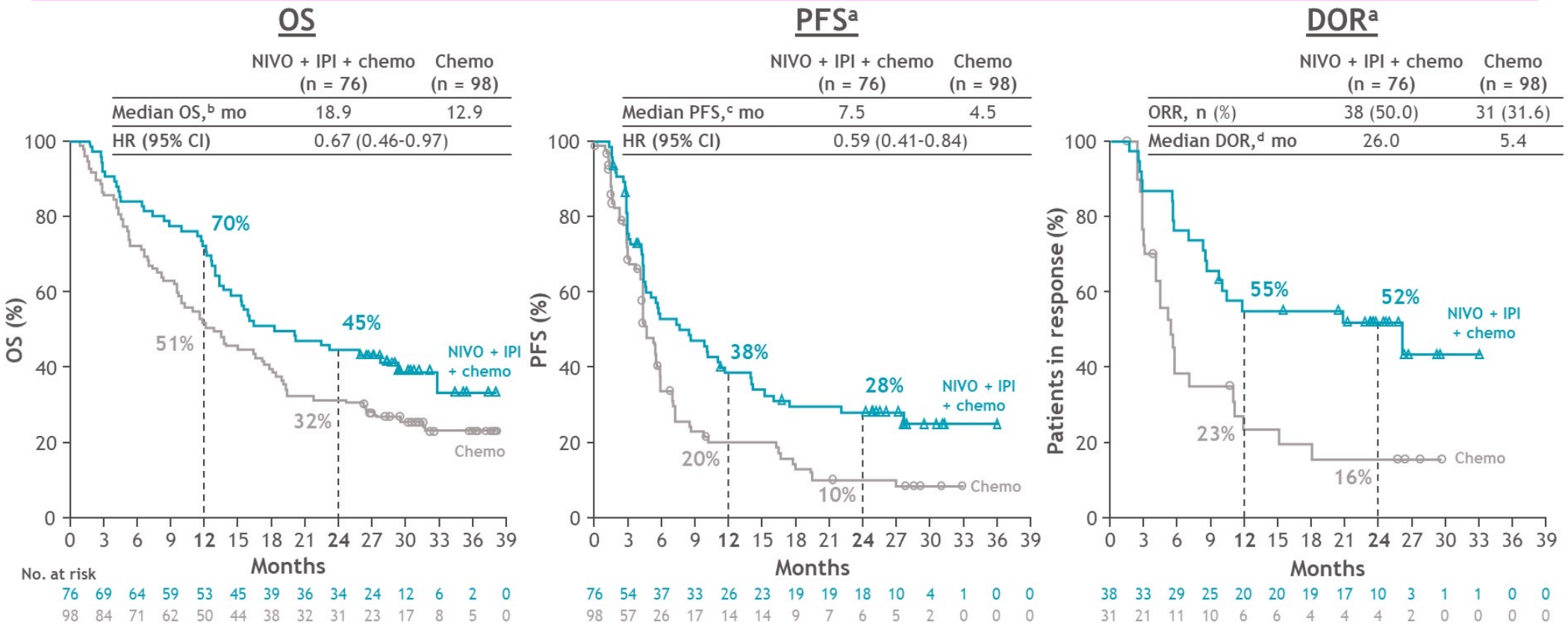


- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

[a]Per BICR; [b]95% CI = 13.8-22.2 (NIVO + IPI + chemo) and 9.5-13.2 (chemo); [c]95% CI = 5.6-8.9 (NIVO + IPI + chemo) and 4.2-5.6 (chemo); [d]95% CI = 8.5-20.7 (NIVO + IPI + chemo) and 4.3-9.6 (chemo); [e]95% CI = 0.53-0.95 (NSQ); [f]95% CI = 0.48-1.01 (SQ).

Reck, M.; ASCO 2021

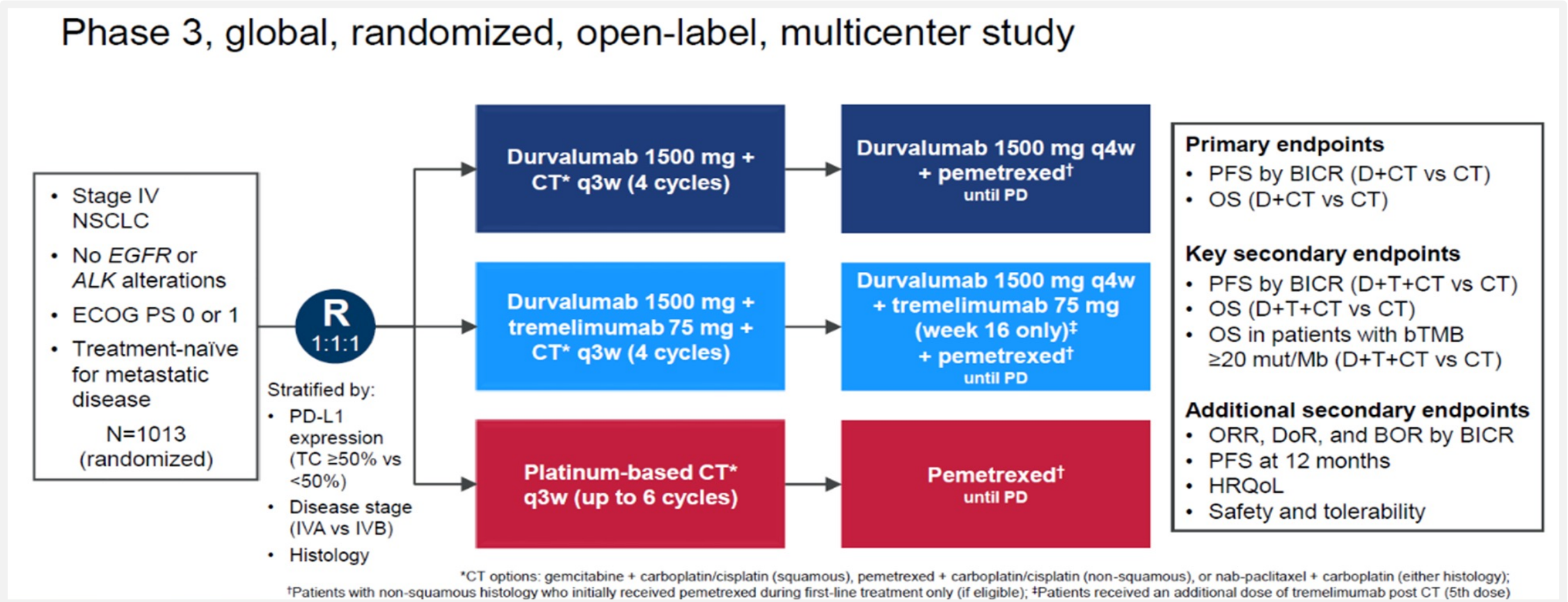
PD-L1 ≥ 50%: efficacy outcomes



[a]Per BICR; [b]95% CI = 13.1-32.5 (NIVO + IPI + chemo) and 9.4-17.6 for (chemo); [c]95% CI = 4.4-11.5 (NIVO + IPI + chemo) and 4.1-5.6 (chemo); [d]95% CI = 8.6-NR (NIVO + IPI + chemo) and 3.9-10.9 (chemo).

Reck, M.; ASCO 2021

POSEIDON Study Design



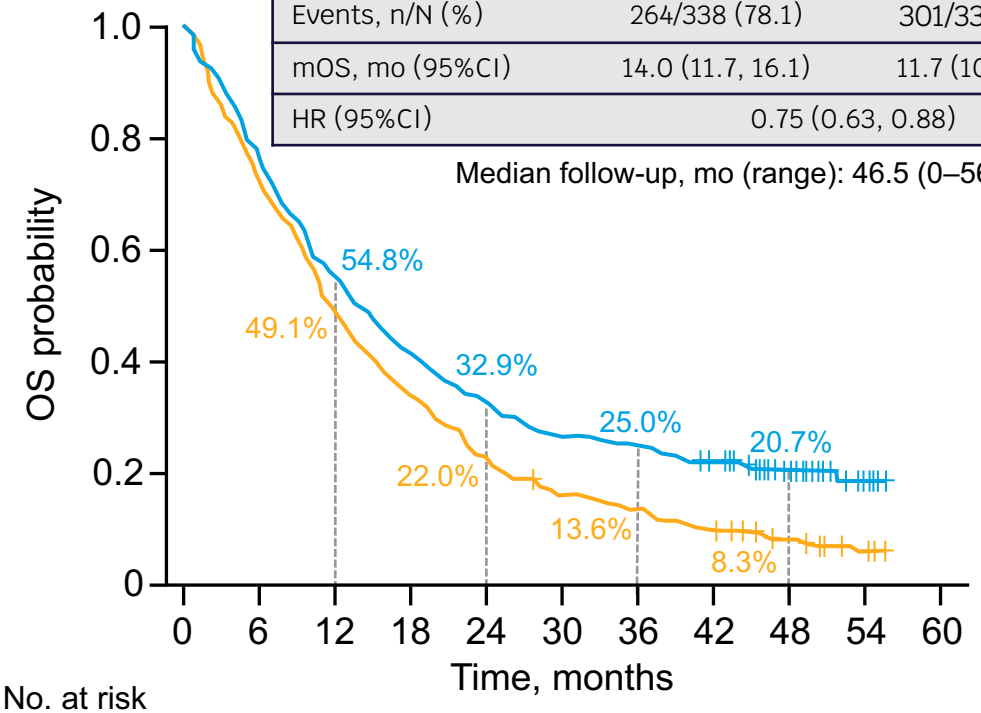
Dr. Melissa Johnson, 2021

LBA 59: Durvalumab (D) ± tremelimumab (T) + chemotherapy (CT) in 1L metastatic (m) NSCLC: overall survival (OS) update from POSEIDON after median follow-up (mFU) of approximately 4 years (y) – Johnson ML, et al

Overall survival

	D + T + CT	CT
Events, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, mo (95%CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
HR (95%CI)	0.75 (0.63, 0.88)	

Median follow-up, mo (range): 46.5 (0–56.6)

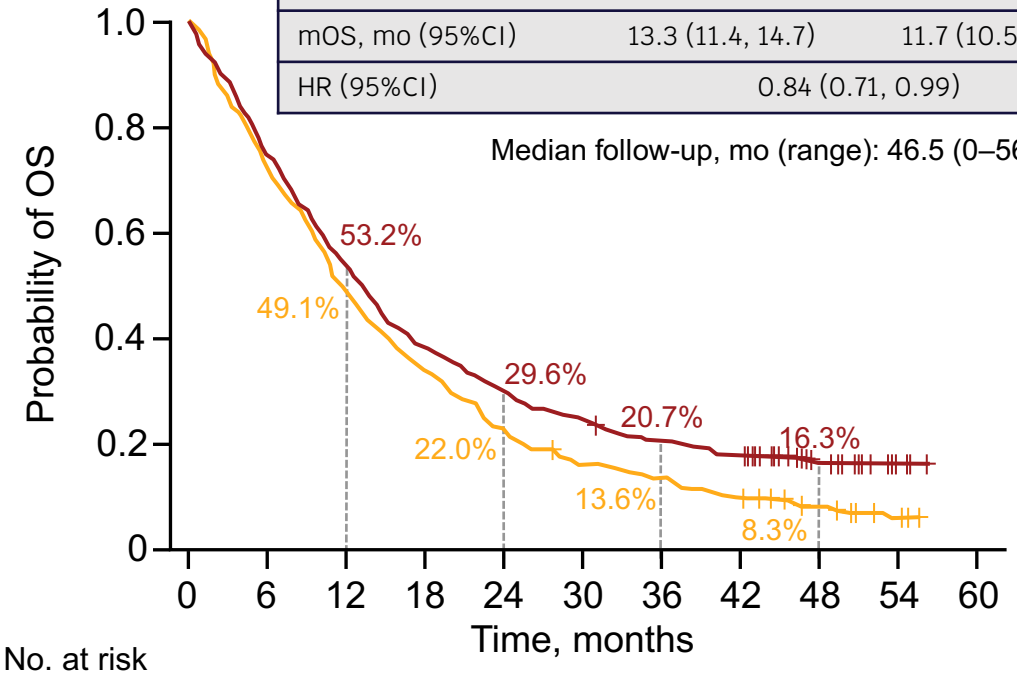


No. at risk

T + D + CT	338	256	183	137	109	89	83	70	32	6	0
CT	337	236	160	111	71	51	42	31	14	5	0

	D + CT	CT
Events, n/N (%)	276/338 (81.7)	301/337 (89.3)
mOS, mo (95%CI)	13.3 (11.4, 14.7)	11.7 (10.5, 13.1)
HR (95%CI)	0.84 (0.71, 0.99)	

Median follow-up, mo (range): 46.5 (0–56.6)

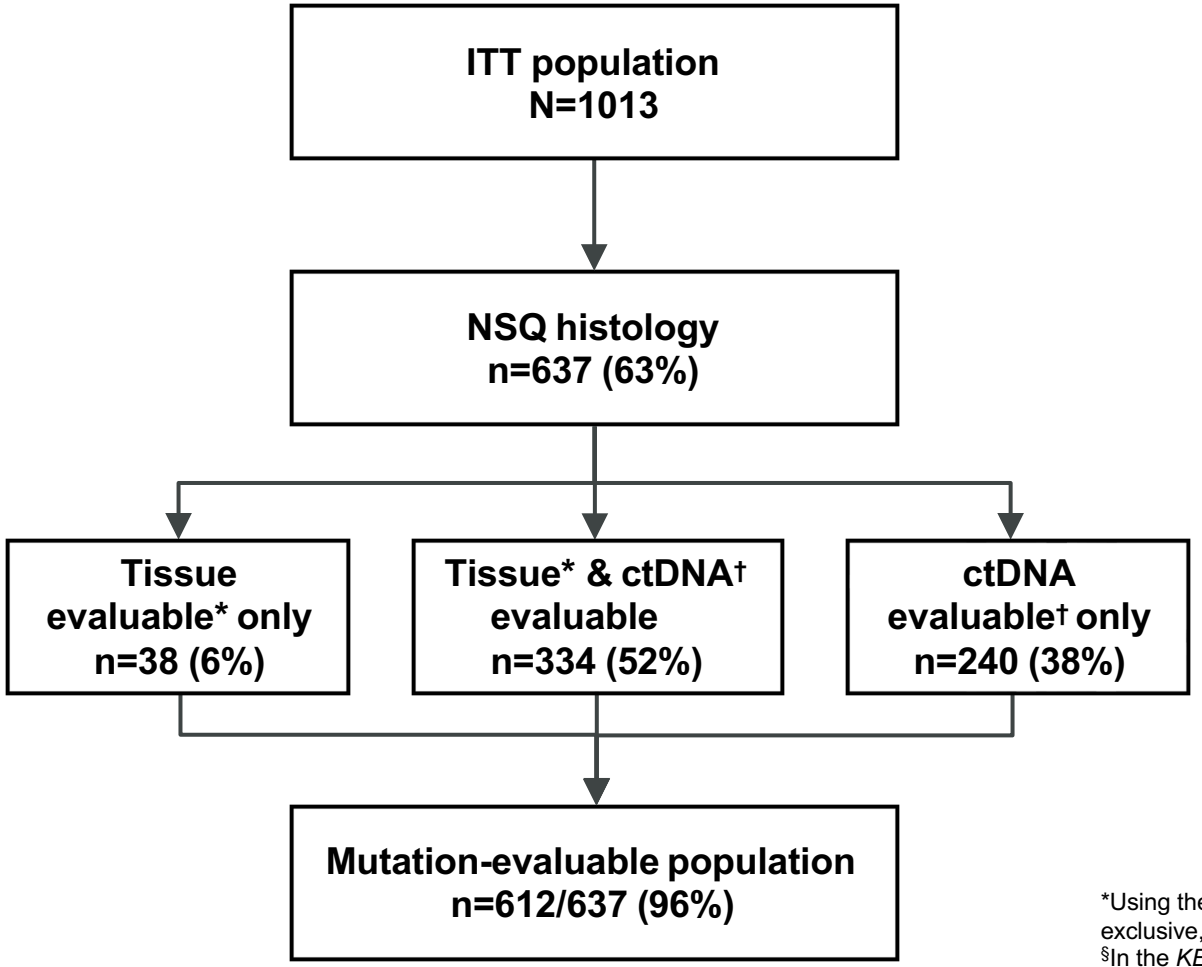


No. at risk

D + CT	338	247	176	126	97	81	67	57	26	5	0
CT	337	236	160	111	71	51	42	31	14	5	0

Johnson ML, et al. Ann Oncol 2022;33(suppl):Abstr LBA59

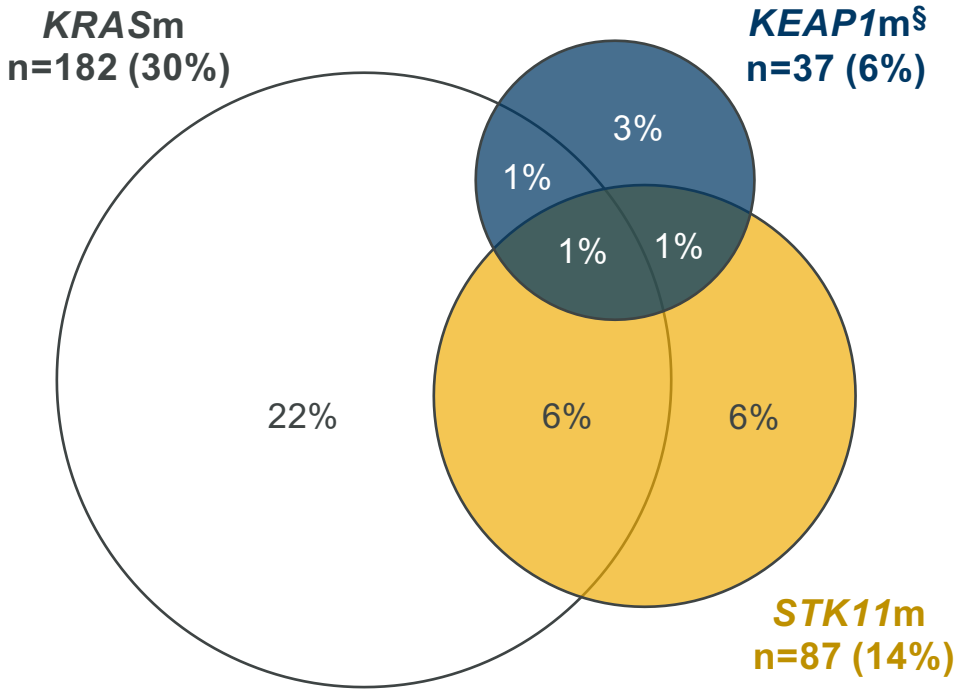
Prevalence of *STK11*, *KEAP1* and *KRAS* Mutations in Patients from POSEIDON with NSQ Histology



Dr. Solange Peters, WCLC, 2022

Mutation-evaluable population‡

(n=612; **96%** of randomised patients with NSQ histology)



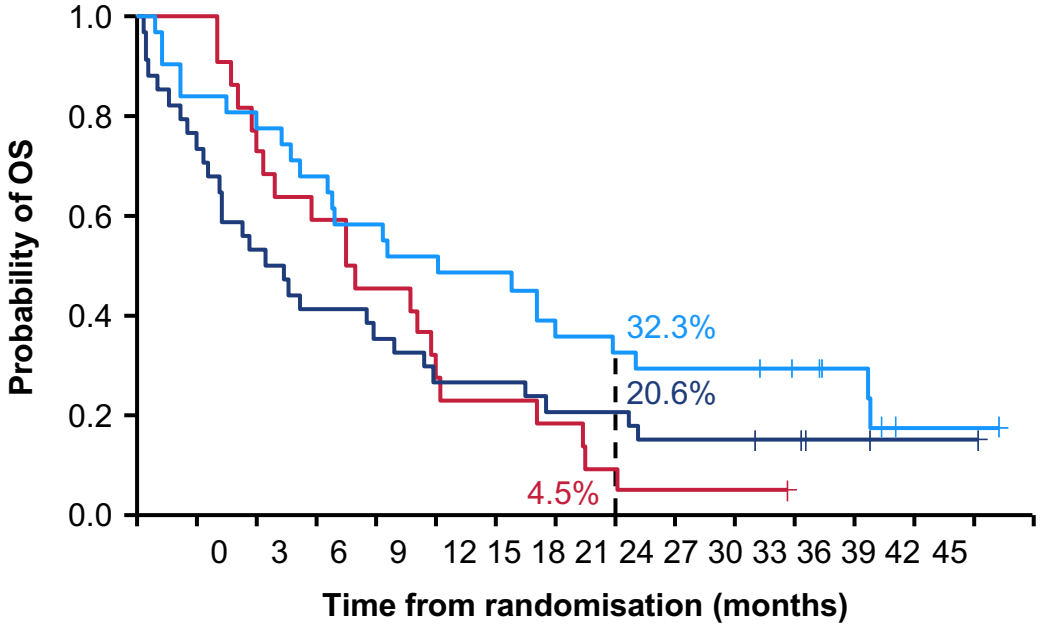
*Using the FoundationOne CDx panel; †Using the Guardant360 CDx panel; ‡Mutation categories are not mutually exclusive, with some patients having co-mutations;
§In the *KEAP1*m subgroup, outcomes were assessed among mutation-evaluable patients irrespective of tumour histology (n=51), due to small sample size

OS by *STK11* Mutation Status

OS benefit observed for T+D+CT vs CT in STK11m with HR 0.56 and estimated 32.3% alive at 2 yrs vs 4.5%

*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)	–

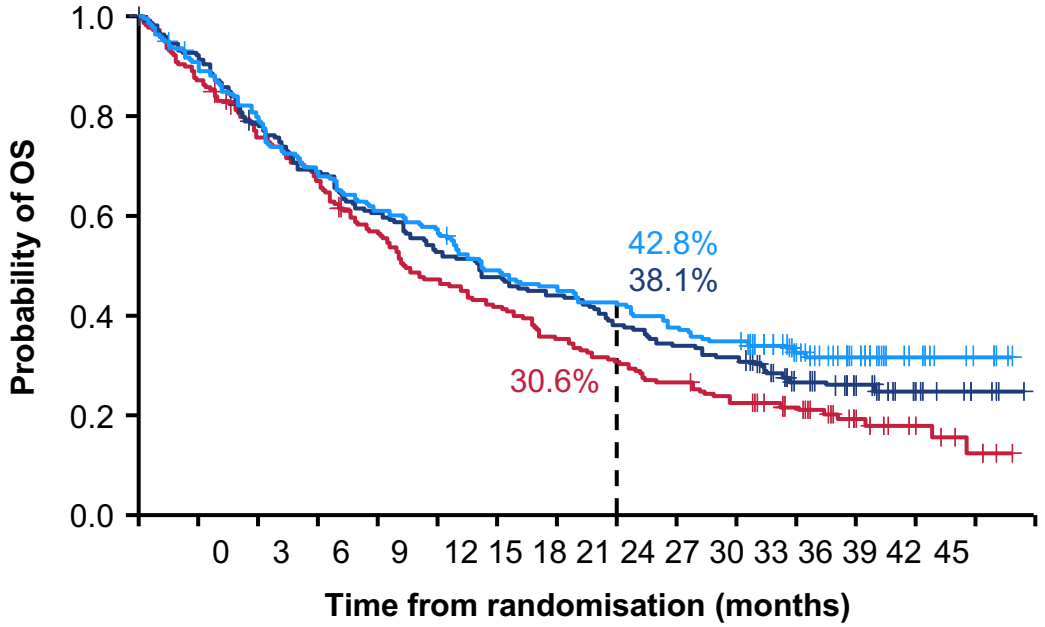


No. at risk

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

Dr. Solange Peters, WCLC, 2022

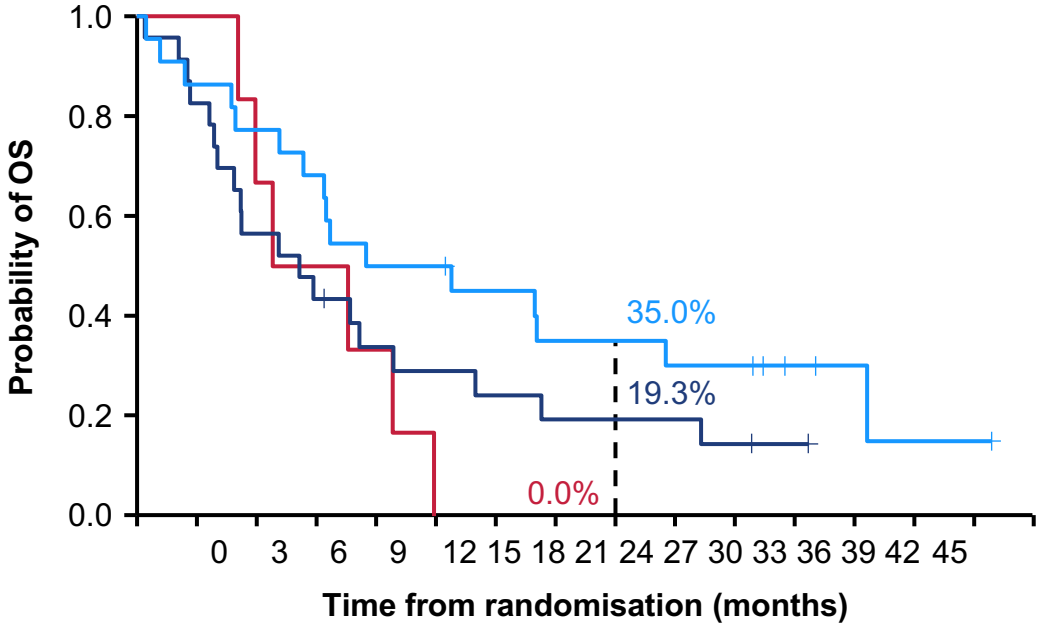
DCO, data cut-off; mo, months; mOS, median OS

OS by *KEAP1* Mutation Status

OS benefit observed for T+D+CT vs CT in KEAP1m with HR 0.43 (small sample size)

*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)	–

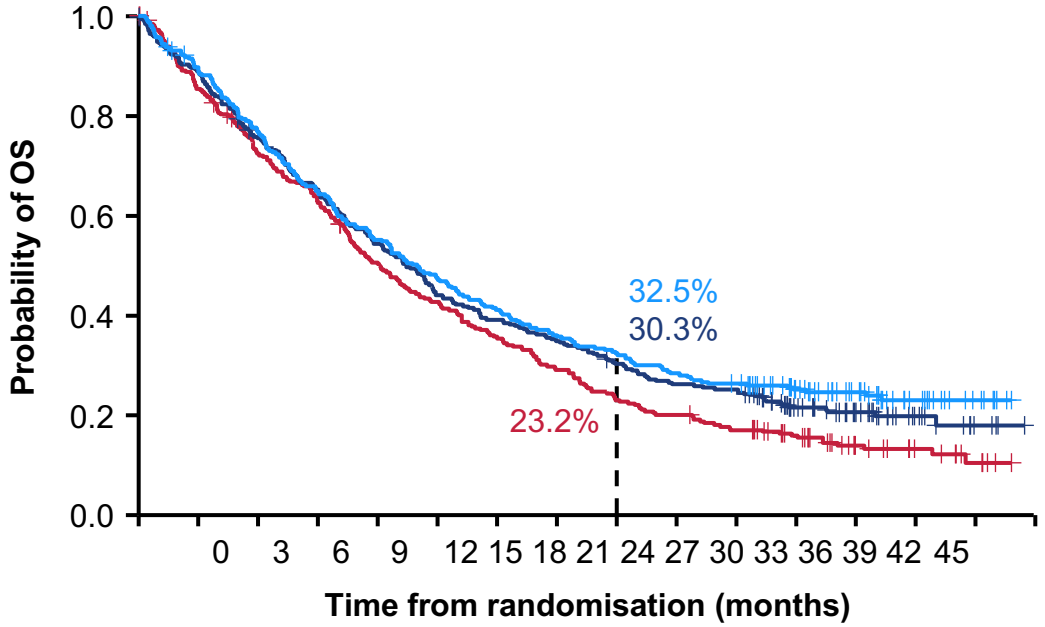


No. at risk

T+D+CT	22	19	17	15	11	11	9	7	7	6	6	3	2	1	1	0
D+CT	23	19	13	10	7	6	5	4	4	4	3	1	0	0	0	0
CT	6	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events, n/N	226/303	241/307	262/312
mOS, mo (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.79** (0.66–0.94)	**0.85** (0.71–1.01)	–



No. at risk

T+D+CT	303	268	230	194	165	142	123	108	97	85	78	57	38	19	8	0
D+CT	307	272	230	198	165	134	119	106	91	79	76	49	33	15	5	0
CT	312	264	221	192	153	129	108	88	70	61	51	38	21	13	6	0

Dr. Solange Peters, WCLC, 2022

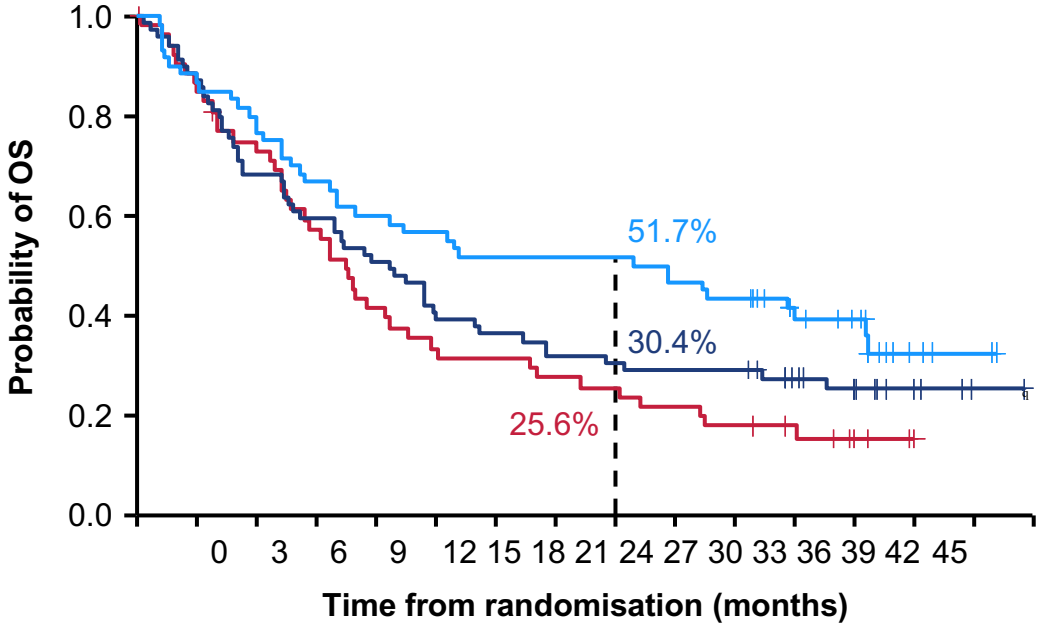
HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

OS by *KRAS* Mutation Status

OS benefit observed for T+D+CT vs CT in KRASm with HR 0.56 and estimated 51.7% alive at 2 yrs vs 25.6%

*KRAS*m

	T+D+CT	D+CT	CT
Events, n/N	38/60	51/69	43/53
mOS, mo (95% CI)	**25.7** (9.9–36.5)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.56** (0.36–0.88)	**0.80** (0.53–1.21)	–

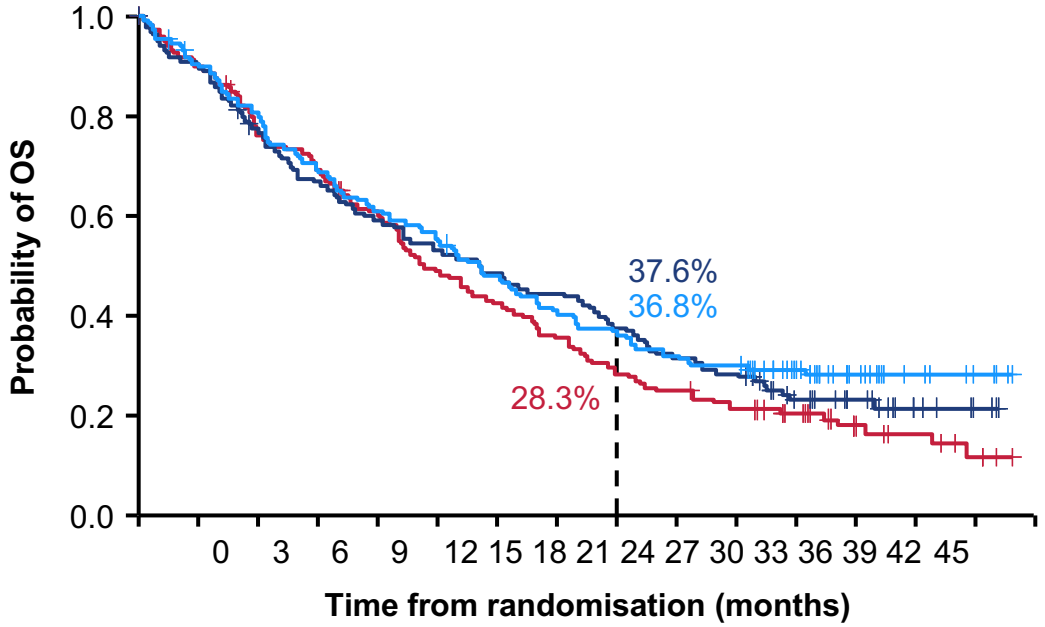


No. at risk

T+D+CT	60	53	46	40	36	34	31	31	31	28	26	17	14	4	2	0
D+CT	69	61	47	41	35	27	25	22	21	20	20	14	9	4	1	0
CT	53	44	37	29	21	17	16	14	13	11	9	7	3	0	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events, n/N	104/148	101/134	119/148
mOS, mo (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.80** (0.62–1.04)	**0.86** (0.66–1.12)	–



No. at risk

T+D+CT	148	132	118	101	89	81	69	59	53	46	43	30	16	8	4	0
D+CT	134	120	101	87	77	69	63	58	49	41	37	23	16	7	3	0
CT	148	132	110	100	86	69	60	50	40	35	29	22	12	8	4	0

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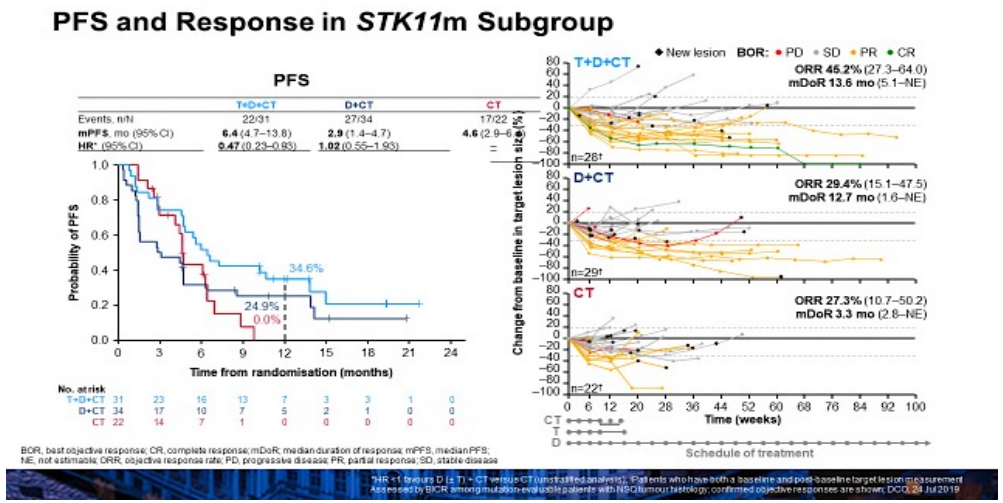
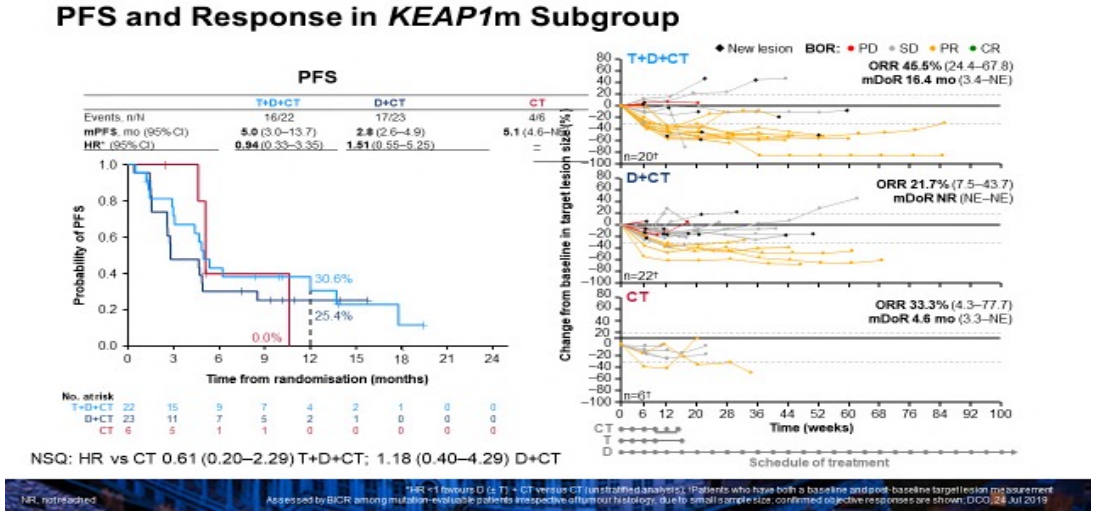
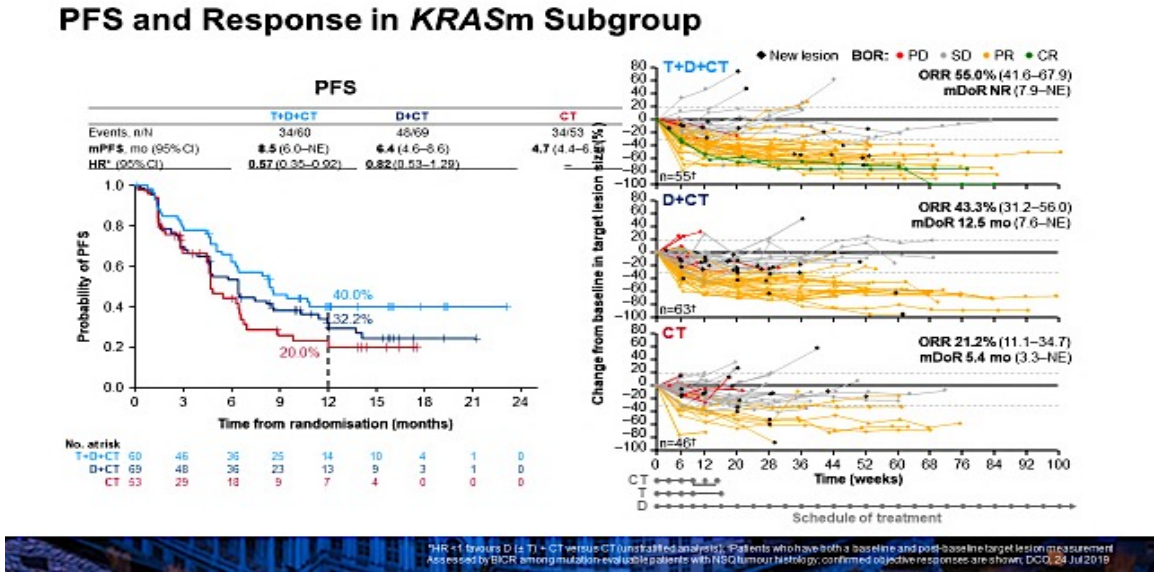
POSIEDON Sub-group Analysis







Dr. Solange Peters, WCLC, 2022

Other IO/IO Combinations

9003: A phase II study (TACTI-002) in first-line metastatic non–small cell lung carcinoma investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: Updated results from a PD-L1 unselected population – Felip E, et al

- **Study objective**
  - To evaluate the updated efficacy of 1L eftilagimod alpha + pembrolizumab in patients with NSCLC in Part A of the TACTI-002 trial

Key patient inclusion criteria
- Metastatic NSCLC
- No prior therapy
- No amenable to ALK/EGFR based therapies or therapy with curative intent
- Any PD-L1 status
- ECOG PS 0–1

(n=114)

→ Eftilagimod alpha 30 mg SC q2w + pembrolizumab 200 mg IV q3w (8 cycles) then eftilagimod 30 mg SC + pembrolizumab 200 mg IV q3w for (9 cycles)

→ Pembrolizumab q3w (16 cycles)

Primary endpoint
- ORR

Secondary endpoints
- DoR, PFS, OS, biomarkers, safety

9003: A phase II study (TACTI-002) in first-line metastatic non–small cell lung carcinoma investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: Updated results from a PD-L1 unselected population – Felip E, et al

- **Key results**

Response	iRECIST (n=114)	RECIST 1.1 (n=114)
BOR, n (%)		
CR	2 (1.8)	2 (1.8)
PR	42 (36.8)	41 (36.0)
SD	40 (35.1)	39 (34.2)
PD	19 (16.7)	21 (18.4)
NE	11 (9.6)	11 (9.6)
ORR, % (95%CI)	44 (38.6) [29.6, 48.2]	43 (37.7) [28.8, 48.3]
DCR, % (95%CI)	84 (73.7) [64.6, 81.5]	82 (71.9) [62.7, 80.0]

Tumor response by central PD-L1 status					
Response, n (%) [95%CI]	PD-L1 <1% (n=32)	PD-L1 <1–49% (n=36)	PD-L1 ≥50% (n=19)	PD-L1 ≥1% (n=56)	PD-L1 <50% (n=68)
ORR	9 (28.1) [13.8, 46.8]	15 (41.7) [25.5, 59.2]	10 (52.6) [28.9, 75.6]	25 (45.5) [32.0, 59.5]	24 (35.3) [24.1, 47.8]
DCR	22 (68.8) [50.0, 83.9]	28 (77.8) [60.9, 89.9]	15 (79.0) [54.4, 94.0]	43 (78.2) [65.0, 88.2]	50 (73.5) [61.4, 83.5]

Tumor response by central and local PD-L1 status					
Response, n (%) [95%CI]	PD-L1 <1% (n=37)	PD-L1 <1–49% (n=40)	PD-L1 ≥50% (n=31)	PD-L1 ≥1% (n=71)	PD-L1 <50% (n=77)
ORR	9 (24.3) [11.8, 41.2]	16 (40.0) [24.9, 56.7]	16 (51.6) [33.1, 69.9]	32 (45.1) [33.2, 57.3]	25 (32.5) [22.2, 44.1]
DCR	26 (70.3) [53.2, 84.1]	30 (75.0) [58.8, 87.3]	24 (77.4) [58.9, 90.4]	54 (76.1) [64.5, 85.4]	56 (72.7) [61.4, 82.3]

Felip, ASCO 2022

Other IO/IO Combinations

9003: A phase II study (TACTI-002) in first-line metastatic non–small cell lung carcinoma investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: Updated results from a PD-L1 unselected population – Felip E, et al

- **Study objective**
  - To evaluate the updated efficacy of of the TACTI-002 trial

Key patient inclusion criteria
- Metastatic NSCLC
- No prior therapy
- No amenable to ALK/EGFR based therapies or therapy with curative intent
- Any PD-L1 status
- ECOG PS 0–1

(n=114)

Primary endpoint
- ORR

- **Key results (cont.)**

	n	Events, n (%)	mPFS, mo (95%CI)
Overall	114	69 (60.5)	6.9 (4.4, 8.4)
PD-L1 status			
≥50%	31	16 (51.6)	11.8 (5.5, 16.8)
1–49%	40	23 (57.5)	9.3 (4.1, 14.9)
>1%	37	27 (73.0)	4.2 (3.6, 6.1)
≥1%	71	39 (54.9)	8.4 (6.1, 14.0)

TEAEs, n (%)	
Any	113 (99.1)
Serious	45 (39.5)
Grade ≥3	59 (51.8)
Grade 4	5 (4.4)
Grade 5	12 (10.5)
Led to discontinuation	23 (20.2)

TRAEs, n (%)	
Serious	10 (8.8)
Grade ≥3	12 (10.5)
Grade 5	3 (2.6)
Led to discontinuation	11 (9.6)

- **Conclusions**
  - In patients with metastatic NSCLC, 1L eftilagimod alpha + pembrolizumab showed promising antitumor activity regardless of PD-L1 status and was generally well-tolerated

Felip E, et al. J Clin Oncol 2022;40(suppl):Abstr 9003 50

9003: A phase II study (TACTI-0 carcinoma investigating eftilagi pembrolizumab: Updated result

static non–small cell lung LAG-3 protein) and lected population – Felip E, et al

Tumor response by central PD-L1 status			
PD-L1 <1–49% (n=36)	PD-L1 ≥50% (n=19)	PD-L1 ≥1% (n=56)	PD-L1 <50% (n=68)
15 (41.7) [25.5, 59.2]	10 (52.6) [28.9, 75.6]	25 (45.5) [32.0, 59.5]	24 (35.3) [24.1, 47.8]
28 (77.8) [60.9, 89.9]	15 (79.0) [54.4, 94.0]	43 (78.2) [65.0, 88.2]	50 (73.5) [61.4, 83.5]

Tumor response by central and local PD-L1 status			
PD-L1 <1–49% (n=40)	PD-L1 ≥50% (n=31)	PD-L1 ≥1% (n=71)	PD-L1 <50% (n=77)
16 (40.0) [24.9, 56.7]	16 (51.6) [33.1, 69.9]	32 (45.1) [33.2, 57.3]	25 (32.5) [22.2, 44.1]
30 (75.0) [58.8, 87.3]	24 (77.4) [58.9, 90.4]	54 (76.1) [64.5, 85.4]	56 (72.7) [61.4, 82.3]

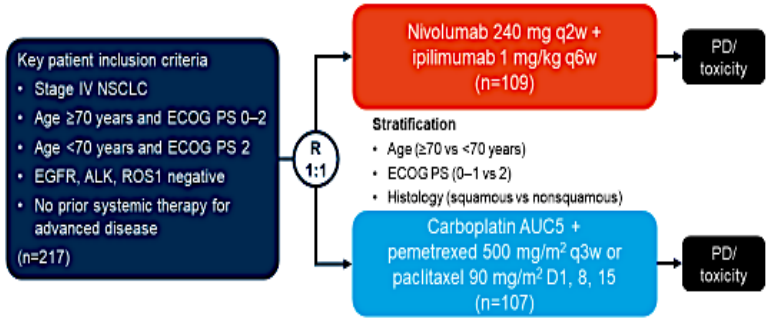
Felip E, et al. J Clin Oncol 2022;40(suppl):Abstr 9003 49

Felip, ASCO 2022

Special Populations

9011: Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study) – Lena H, et al

- **Study objective**
  - To evaluate the efficacy and safety of 1L nivolumab + ipilimumab in patients with ECOG PS 2 or elderly (≥70 years) patients with advanced NSCLC in the eNErgy trial*



Primary endpoint
- OS

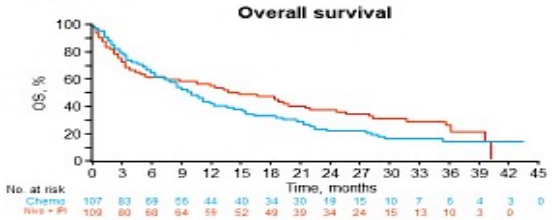
Secondary endpoints
- PFS, ORR, QoL, safety

*Randomization stopped early after an interim analysis showed risk of futility

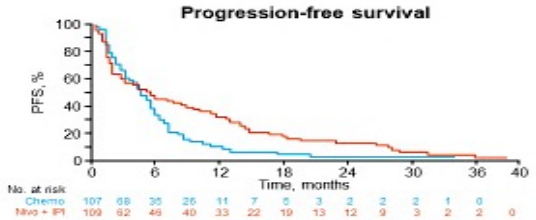
Lena H, et al. J Clin Oncol 2022;40(suppl):Abstr 9011 51

9011: Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study) – Lena H, et al

- **Key results**



	NIVO + IPI (n=109)	Chemo (n=107)
mOS, mo (95%CI)	14.7 (8, 19.7)	9.9 (7.7, 12.3)
HR (95%CI); p-value	0.85 (0.62, 1.16); 0.2978	
1-yr OS rate, % (95%CI)	55 (45.2, 63.8)	42 (32.5, 51.2)
2-yr OS rate, % (95%CI)	36.6 (27.5, 45.7)	21 (14.3, 30.0)



	NIVO + IPI (n=109)	Chemo (n=107)
mPFS, mo (95%CI)	5.5 (2.8, 8.7)	4.5 (3.5, 5.6)
HR (95%CI)	0.75 (0.56, 1.01)	
1-yr PFS rate, (95%CI)	31.9 (23.3, 40)	10.9 (5.8, 17)

Lena H, et al. J Clin Oncol 2022;40(suppl):Abstr 9011 52

9011: Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study) – Lena H, et al

- **Key results (cont.)**

OS	Nivo + IPI	Chemo
PS 2, n	40	39
mOS, mo (95%CI)	2.9 (1.4, 4.8)	6.1 (3.5, 10.4)
Elderly PS 0–1, n	70	67
mOS, mo (95%CI)	22.6 (18.1, 36.0)	11.8 (8.9, 20.5)
HR (95%CI)	0.63 (0.42, 0.95)	

TRAEs, %	Nivo + IPI	Chemo
Any	74.3	89.3
Grade ≥3	31.4	49.5
Led to discontinuation	54.3	34.0
Serious	39.0	25.2
Led to death	3.8	1.9

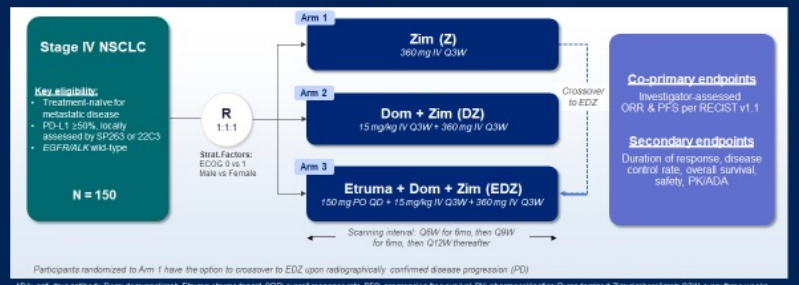
- **Conclusions**
  - In elderly patients with PS 0-1, but not in patients with PS 2, with advanced NSCLC, nivolumab + ipilimumab demonstrated numerical, but not significant, survival benefit over chemotherapy alone and no new safety signals were reported

Lena H, et al. J Clin Oncol 2022;40(suppl):Abstr 9011 53

Lena. ASCO 2022

TIGIT Continues….

ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



ADA, anti-drug antibody; Dom: domvanalimab; Etruma: etrumadenant; ORR: overall response rate; PFS: progression-free survival; PK: pharmacokinetics; R: randomized; Zim: zimberelimab; Q3W: every three weeks

- As of the clinical cut-off date (31 August 2022), a total of 150 patients were randomized with a median follow-up of 11.8 months (range: 0.03 – 23.5)

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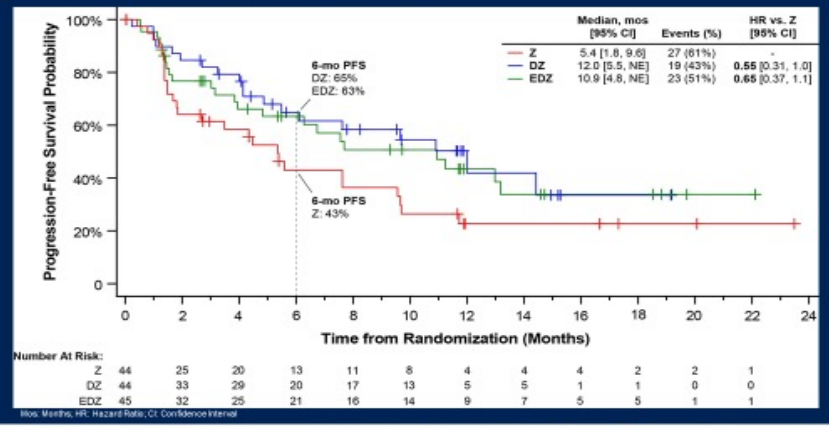
Progression-Free Survival – ITT-13



Mos: Months, HR: Hazard Ratio; CI: Confidence Interval

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Immune-related TEAEs (≥ 10% Overall)

Safety evaluable population, n (%)	Arm 1 (Z) (n=50)	Arm 2 (DZ) (n=49)	Arm 3 (EDZ) (n=50)
Any Immune-related TEAE*	24 (48)	23 (47)	30 (60)
Pneumonitis	7 (14)	4 (8)	5 (10)
Grade ≥3	3 (6)	1 (2)	2 (4)
Pruritus	8 (16)	3 (6)	5 (10)
Rash	6 (12)	5 (10)	9 (18)

*Designation of immune-related TEAEs based on basket of Preferred Terms.

- Majority of pneumonitis events reported were primarily Grade 1 – 2. No clear increase in rates of pneumonitis in Dom-containing arms compared to Zim alone
- Rash was reported with greater frequency in Arm 3 and were all Grade 1 – 2
  - Majority of subjects received treatment with topical corticosteroids and reported resolution of symptoms. No cases of rash led to study treatment discontinuation

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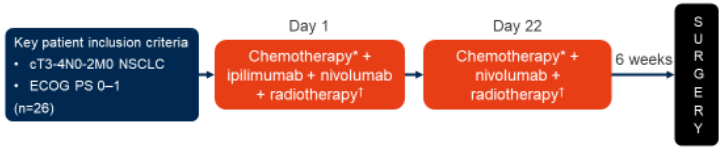
Dr. Melissa Johnson, ASCO Plenary, December 2022

Early Stage Disease and IO/IO

950O: Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: the INCREASE trial – Bahce I, et al

- **Study objective**
  - To evaluate the efficacy and safety of neoadjuvant nivolumab + ipilimumab + chemoradiotherapy prior to surgery in patients with locally advanced NSCLC in the INCREASE study



Primary endpoints
- pCR/MPR,‡ safety

Secondary endpoints
- EFS, OS

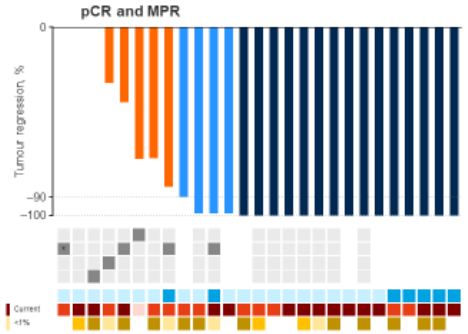
*Platinum-doublet chemotherapy; †once daily dose of 2 Gy; ‡defined as a residual viable tumour cells percentage of ≤10%

Bahce I, et al. Ann Oncol 2022;33(suppl):Abstr 950O 23

950O: Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: the INCREASE trial – Bahce I, et al

- **Key results**

	pCR, n (%)	MPR, n (%)
Operated patients (n=24)	15 (63) (p<0.001)*	19 (79)
Received induction‡ (n=27)	15 (55) (p=0.003)*	19 (70)



*Binomial probability using 30% pCR as historical reference; ‡excluding patients on treatment.
*This patient developed pleural metastases during induction therapy and did not receive surgery

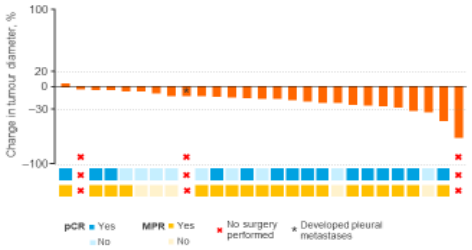
Bahce I, et al. Ann Oncol 2022;33(suppl):Abstr 950O 25

950O: Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: the INCREASE trial – Bahce I, et al

- **Key results (cont.)**

BOR, n (%)	iTP* (n=27)	Resected (n=24)
CR	0	0
PR	4 (15)	3 (12.5)
SD	22 (81)	21 (87.5)
PD	1 (4)	0

n (%)	pCR (n=15)	MPR (n=19)
PR	2 (13)	2 (11)
SD	13 (87)	17 (89)



*Excluding patients on treatment

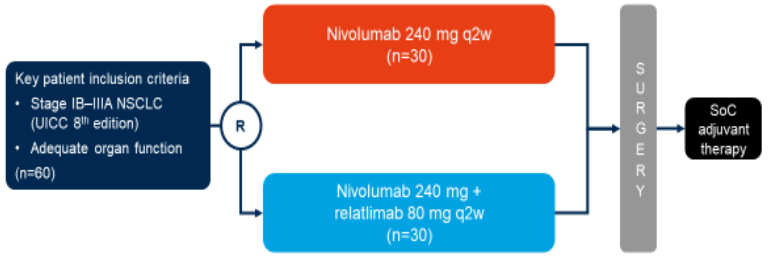
Bahce I, et al. Ann Oncol 2022;33(suppl):Abstr 950O 26

Bache I, et al, ESMO, 2022

Neoadjuvant IO/IO

LBA37: A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer (NEOpredict-Lung) – Schuler MH, et al

- **Study objective**
  - To evaluate the efficacy of nivolumab or nivolumab + relatlimab (a LAG-3 targeting mAb) prior to surgery in patients with NSCLC in the phase 2 NEOpredict-Lung study



Primary endpoint
- Feasibility (surgery ≤D43)

Secondary endpoints
- Histopathological response, radiological response, DFS, OS, safety

Schuler MH, et al. Ann Oncol 2022;33(suppl):Abstr LBA37 15

LBA37: A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer (NEOpredict-Lung) – Schuler MH, et al

- **Key results**

	Nivolumab (n=30)	Nivolumab + relatlimab (n=30)
Feasibility (surgery ≤D43), %	100	100
ORR (RECIST v1.1), %	10	27
ORR (PERCIST v1.0), %	38	38
Complete/major pathological response*, %	27	30
12-mo DFS rate, % (95%CI)	92 (70, 98)	91 (66, 98)
12-mo OS rate, % (95%CI)	92 (70, 98)	100
R0 resection rate, %	100	97

*2 patients excluded at surgery

Schuler MH, et al. Ann Oncol 2022;33(suppl):Abstr LBA37 16

LBA37: A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer (NEOpredict-Lung) – Schuler MH, et al

- **Key results (cont.)**

Grade ≥3 TRAEs, n (%)	Nivolumab (n=30)	Nivolumab + relatlimab (n=30)
Atrial fibrillation	1 (3)	-
Hyperthyroidism	1 (3)	-
Hepatic	1 (3)	1 (3)

- **Conclusions**
  - In patients with resectable NSCLC, preoperative treatment with nivolumab + relatlimab is safe and feasible and demonstrated a preliminary efficacy signal

Schuler MH, et al. Ann Oncol 2022;33(suppl):Abstr LBA37 17

Schuler. Annals Onc. 2022.

Conclusions

- **IO/IO combinations, with or without chemotherapy, are attractive options for some patients:**
  - Refusing chemotherapy
  - Not eligible for chemotherapy
- **Specific Sub groups might benefit more from an IO/IO approach**
  - Perhaps KEAP1 or STK11 mutations
- **Novel combinations with TIGIT or LAG-3 have the potential of improving clinical outcomes in specific populations**
- **Neoadjuvant or adjuvant treatment options with IO/IO combinations are under investigation**
- **Toxicity management and degree of clinical efficacy would be key to success**