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Developing New Anti-CTLA4s for NSCLC: Is There Any Role?

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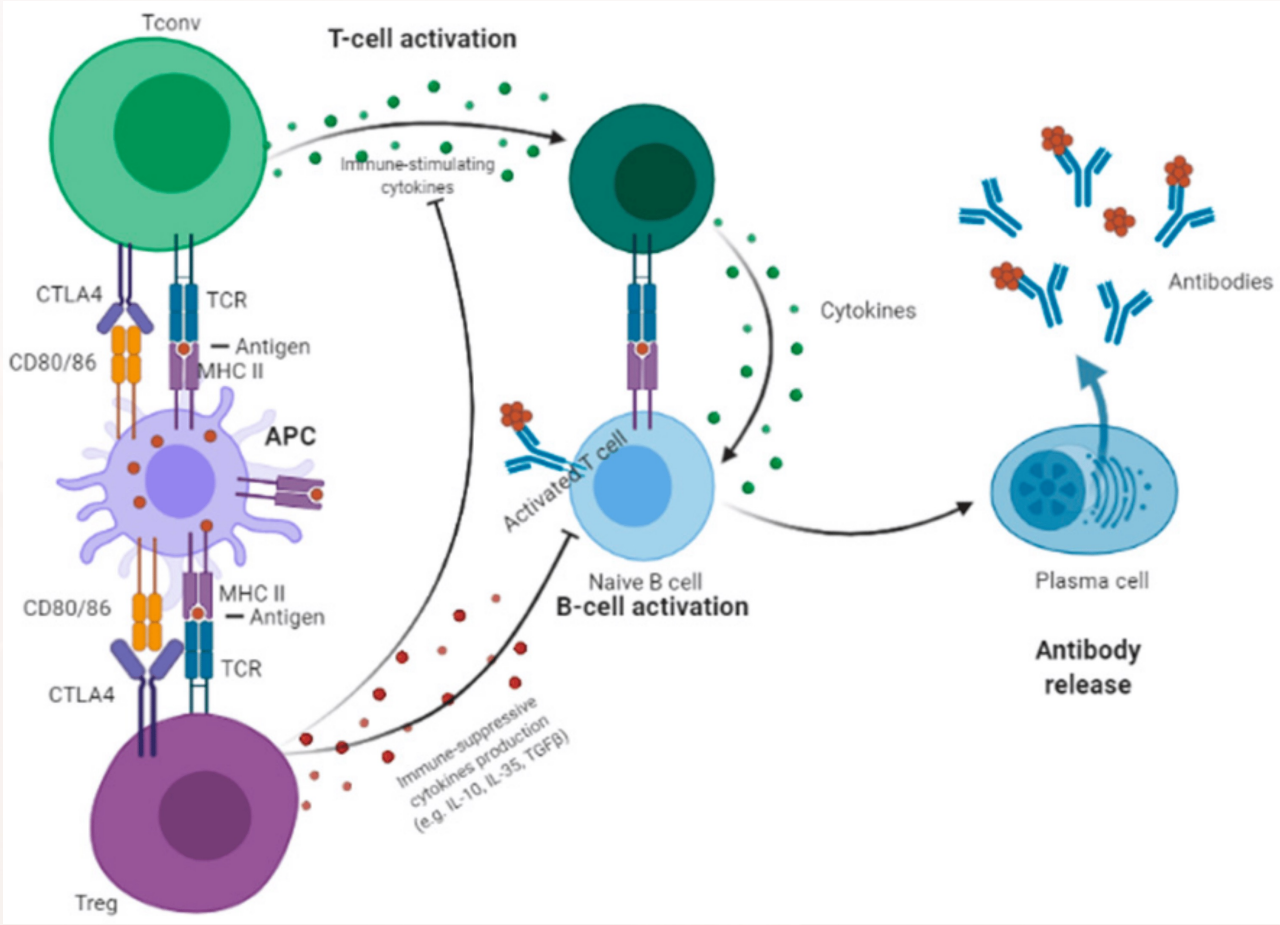
Rationale for Combining Anti-PD-1/PD-L1 and Anti-CTLA4 agents in NSCLC

- Act at different parts of cancer immunity cycle
  - Combining these agents is synergistic
  - May help overcome resistance to single agent IO
  - Preclinical data shows upregulation of tumor-infiltrating effector and T reg cells with combination



Sobhani N, et al. *Cancers (Basel).* 2021 Mar 22;13(6):1440

Use of CTLA-4 Inhibitors in NSCLC

- Monotherapy CTLA-4 inhibitors less effective with higher rates of serious irAEs compared to PD-1/PD-L1 inhibitors

- FDA approvals for:
    - Nivolumab/ipilimumab (Checkmate-227)- May 2020
    - Nivolumab/ipilimumab + 2 cycles of platinum-doublet chemotherapy (CheckMate-9LA)- May 2020
    - Tremelimumab/durvalumab + platinum-based chemotherapy (POSEIDON)- Nov 2022

Overview of Dual IO ± CT for the 1L Treatment of Metastatic NSCLC Without Driver Mutations

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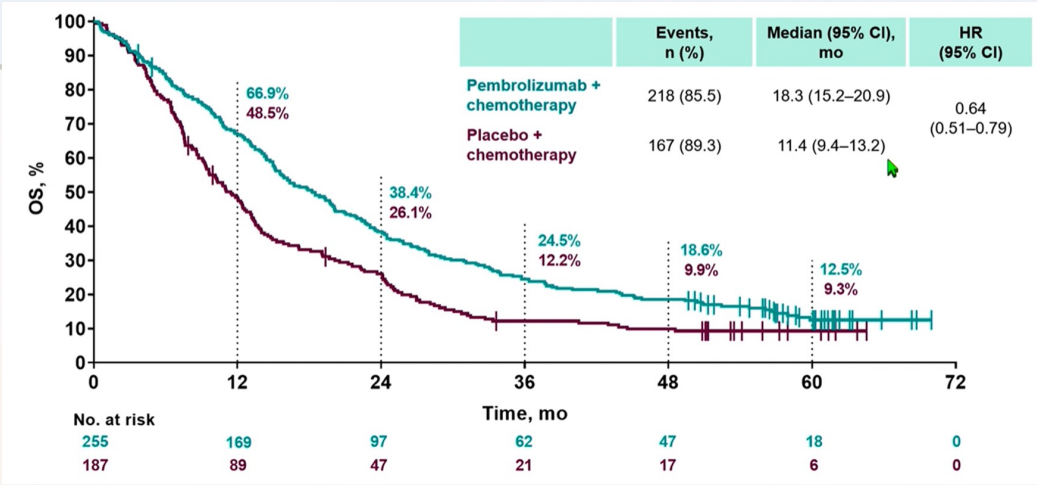
Study	CheckMate 227[1,2]	CheckMate 9LA[3]	POSEIDON[4]
Study arms			
Study population			
Patients, no.			
mOS in PD-L1 ≥50%, mo HR (95% CI)			
mOS in PD-L1 ≥1%, mo HR (95% CI)			
mOS in PD-L1 <1%, mo HR (95% CI)	▪ **Nivo + Ipi** 17.2 vs **Nivo + CT** 15.2 vs **CT** 12.2 ▪ **HR Nivo + Ipi:** 0.64 (0.51-0.81) ▪ **HR Nivo + CT:** 0.82 (0.65-1.02)	▪ **Nivo + Ipi + CT** 17.7 vs **CT** 9.8 ▪ 0.67 (0.51-0.88)	▪ **HR Durva + Treme + CT:** 0.77 (0.58-1.00) ▪ **HR Durva + CT:** 0.99 (0.76-1.30)
Grade ≥3 AEs, %			

No head-to-head studies have been conducted and direct comparisons cannot be made between these studies

1. Paz-Ares LG, et al. *J Thoracic Oncol*. 2021;17(2):289-308. **2.** Brahmer J, et al. ASCO 2022. Abstract LBA9025.
3. Reck M, et al. ASCO 2021. Abstract 9000. **4.** Johnson ML, et al. *J Clin Oncol.* 2023;41(6):1213-1227.

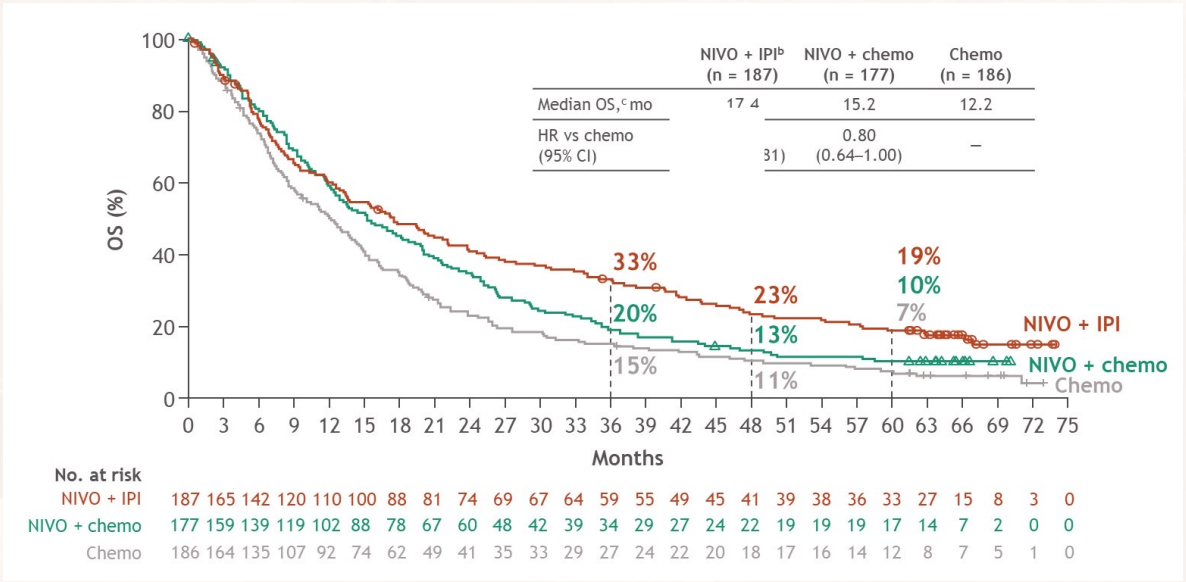
Slide credit: Curio Science

KEYNOTE-189/KEYNOTE-407
5-Year OS in Patients With PD-L1 <1%



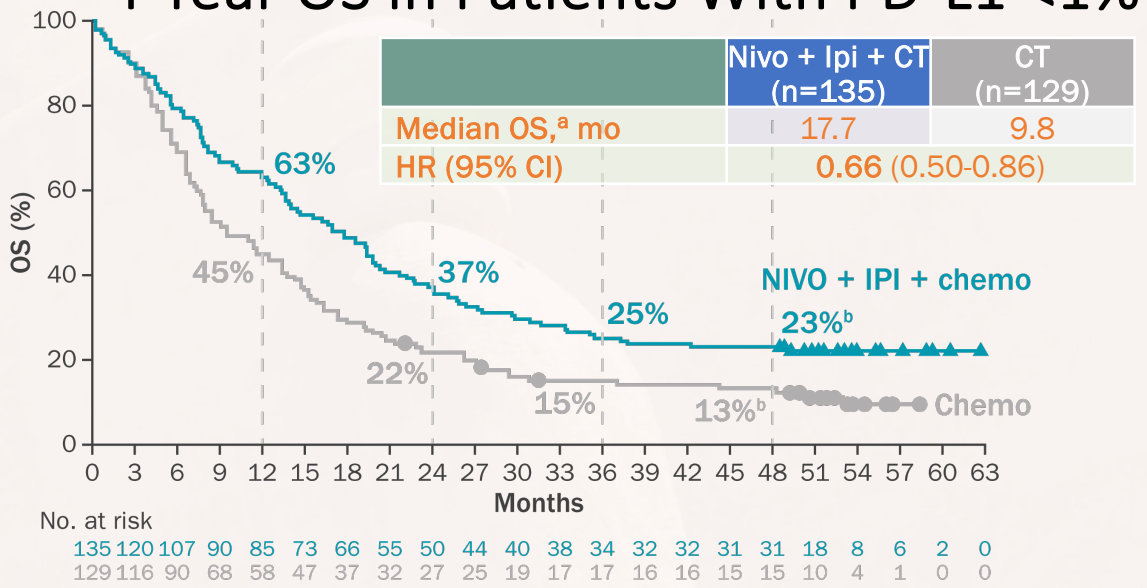
Gadgeel S, et al. WCLC 2023.Absract OA14.05.

CheckMate 227:
5-Year OS in Patients With PD-L1 <1%



Brahmer J, et al. *J Clin Oncol*. 2022;41(6):1200-1212.

CheckMate 9LA :
4-Year OS in Patients With PD-L1 <1%



Carbone DP, et al. ASCO 2023. Abstract LBA9023.

POSEIDON: Updated 4-Year OS

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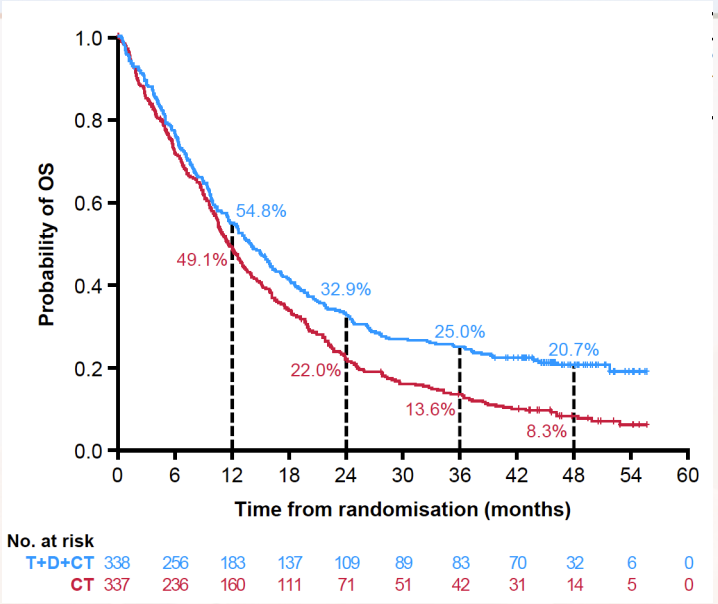
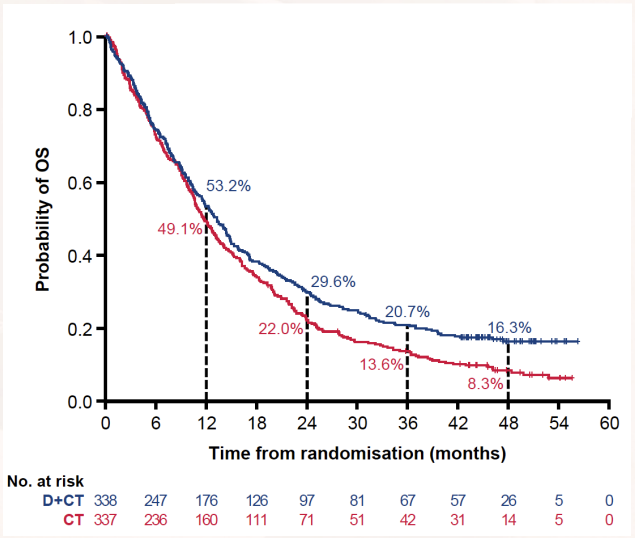
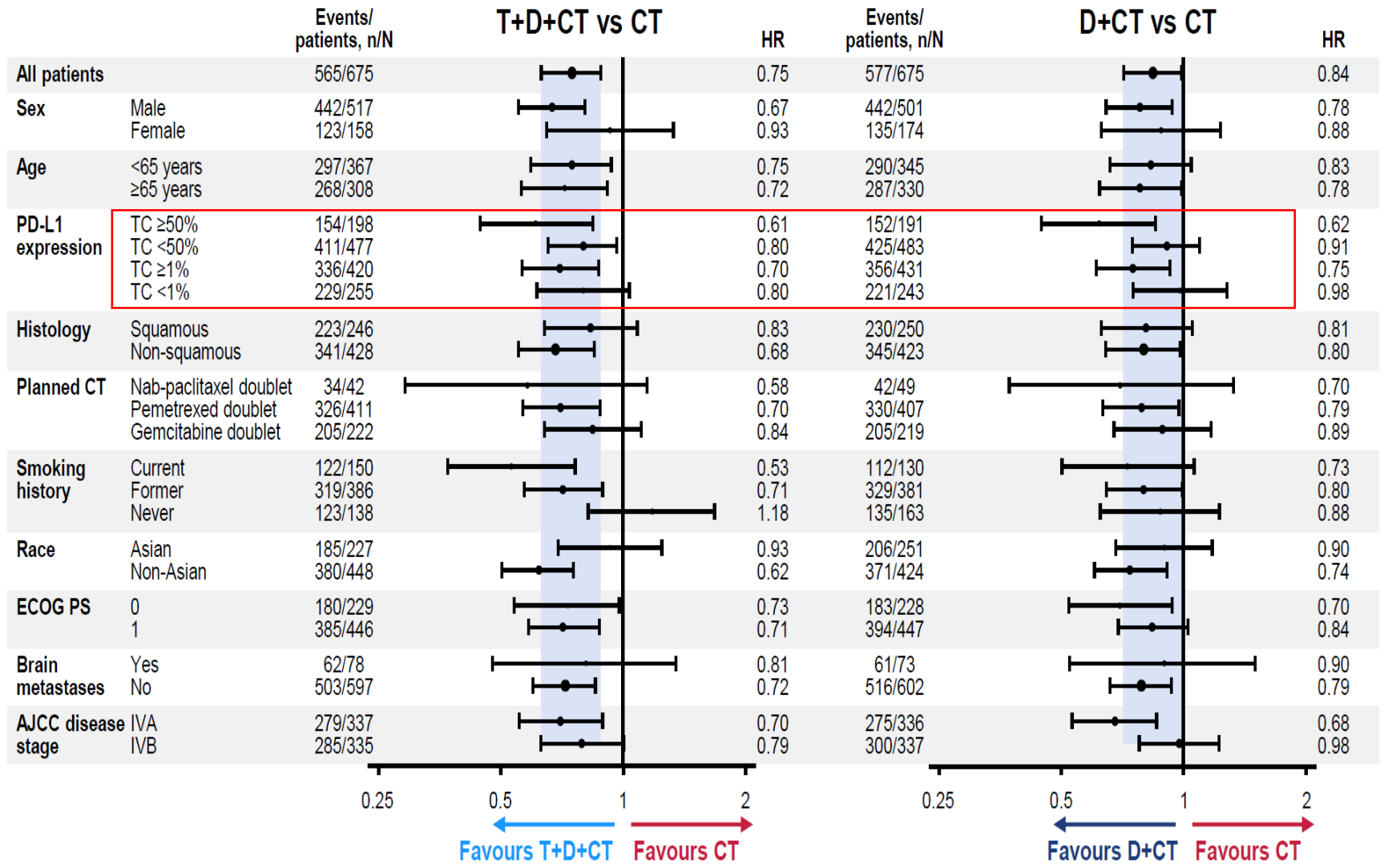
T+D+CT vs CT



D+CT vs CT





Johnson ML, et al. *J Clin Oncol.* 2023;41(6):1213-1227.

Johnson M, et al. ESMO 2022. Abstract LBA59.

Reduced PFS/OS Benefit in Patients With *STK11* or *KEAP1* Mutations Treated With Anti-PD-(L)1: An Unmet Need

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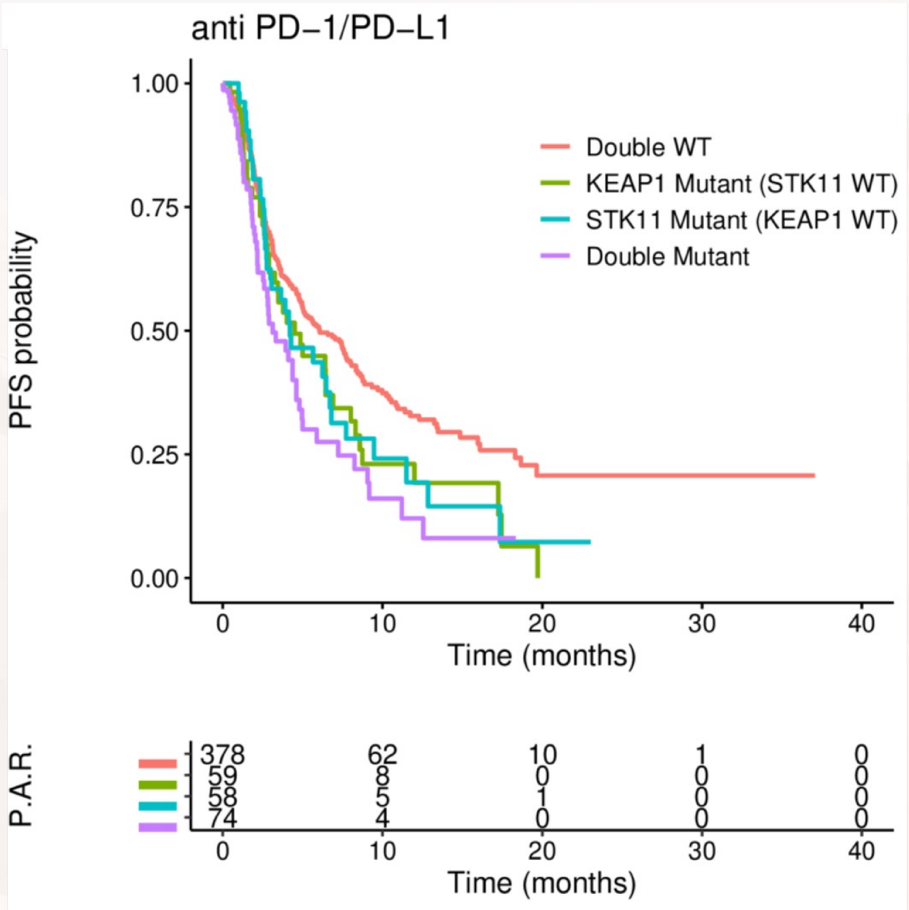
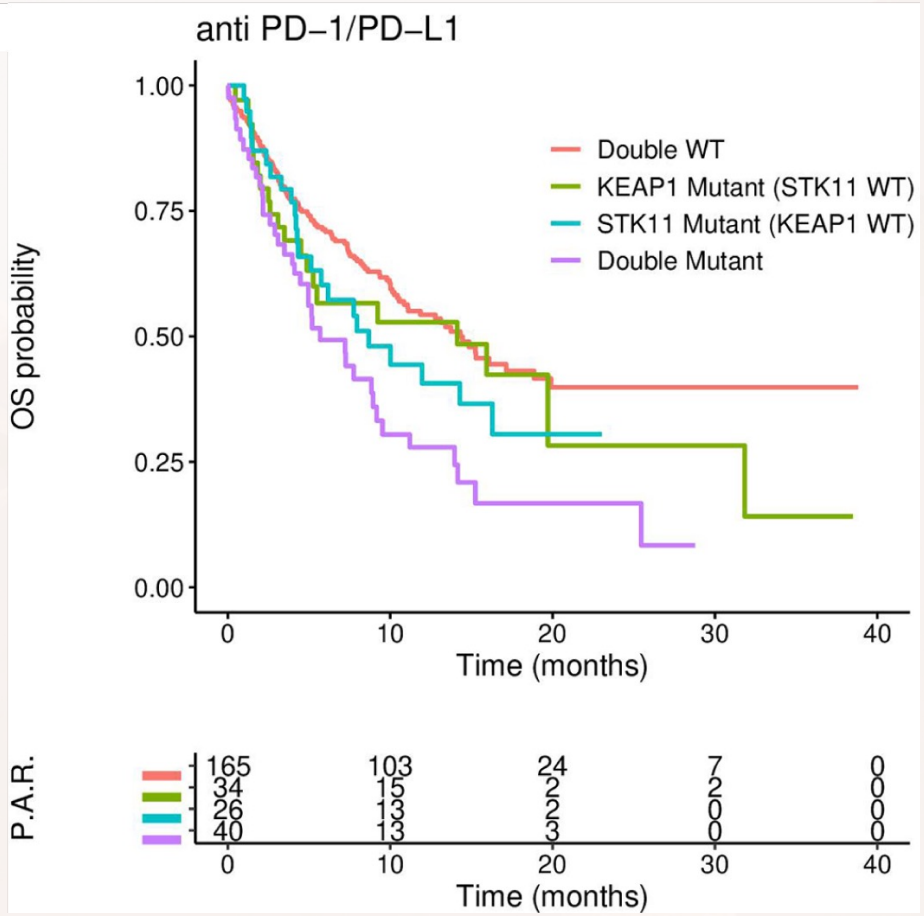
PFS and OS of Patients Treated With Anti–PD-(L)1 by *KEAP1* and *STK11* Mutations





Papillon-Cavanagh S, et al. *ESMO Open.* 2020:5(2):e000706.

KEYNOTE-189: Reduced OS Benefit From the Addition of Pembrolizumab to Platinum Doublet Chemotherapy in Patients With *STK11*^{MUT} and *KEAP1*^{MUT} NSCLC

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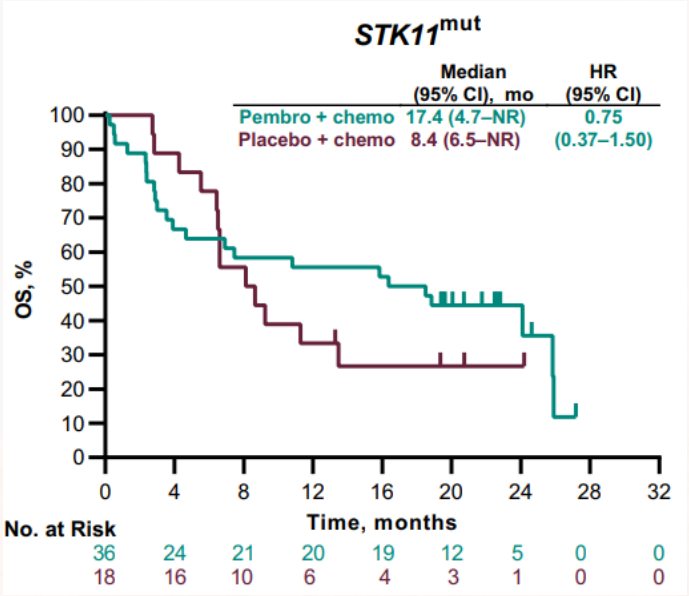

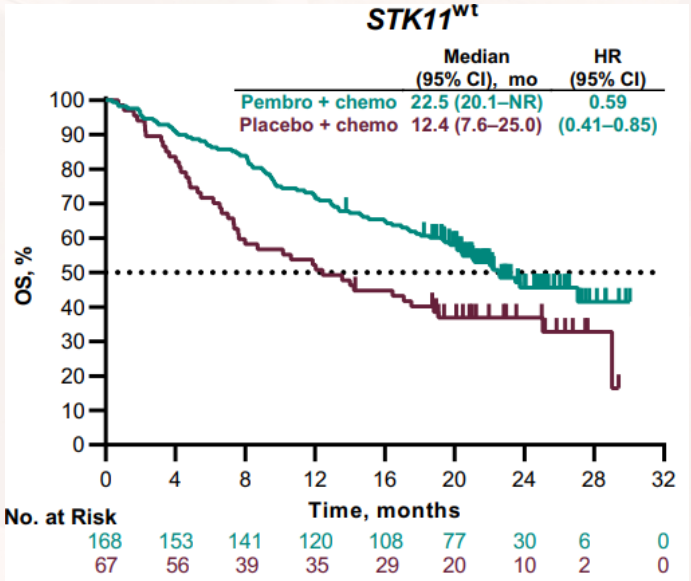

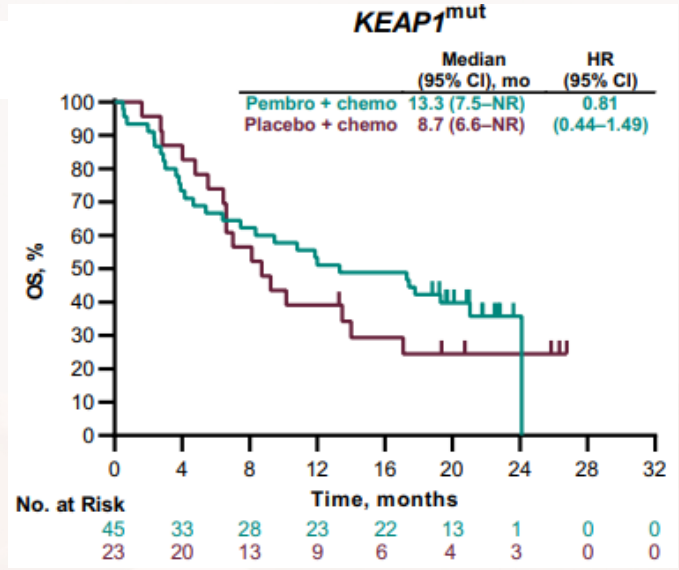

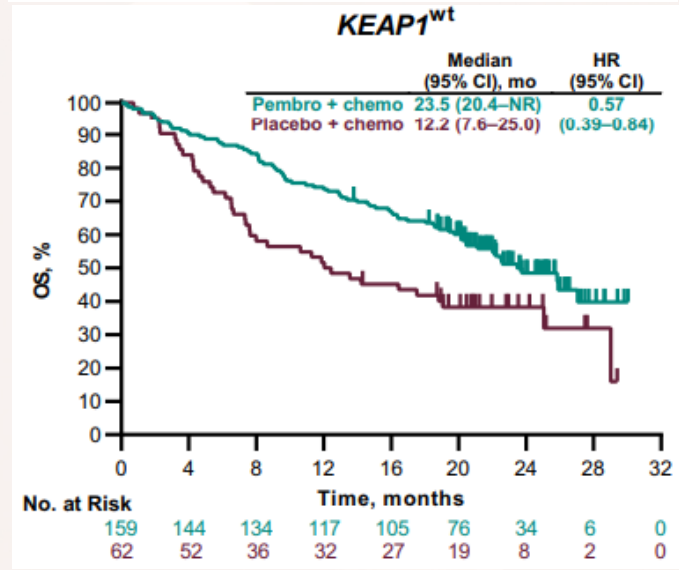

Garassino MC, et al. *JTO Clin Res Rep.* 2022;4(1):100431.

POSEIDON: Updated 4-yr OS by *STK11* and *KEAP1* Mutation Status

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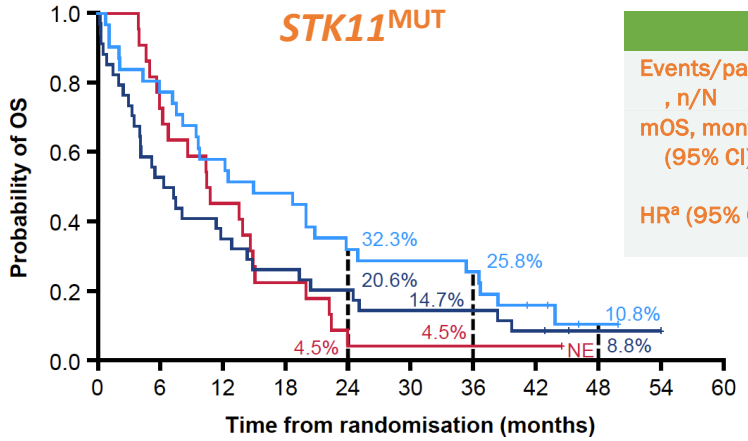
STK11^{MUT}

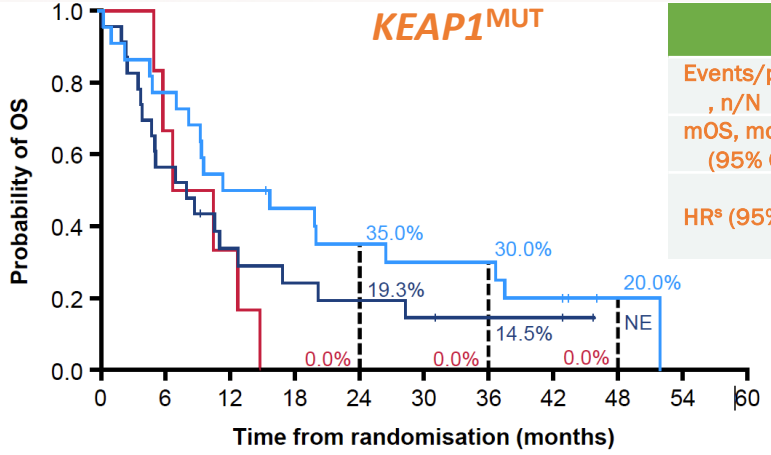


	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	31/34	21/22
mOS, months (95% CI)	15.0 (8.2-23.8)	6.9 (3.6-12.9)	10.7 (6.0-14.9)
HR[a] (95% CI)	0.62 (0.34-1.12)	1.06 (0.61-1.89)	–

No. at risk

T+D+CT	31	24	18	15	10	9	8	4	1	0	0
D+CT	34	18	12	9	7	5	5	3	1	0	0
CT	22	16	10	5	1	1	1	1	0	0	0

KEAP1^{MUT}

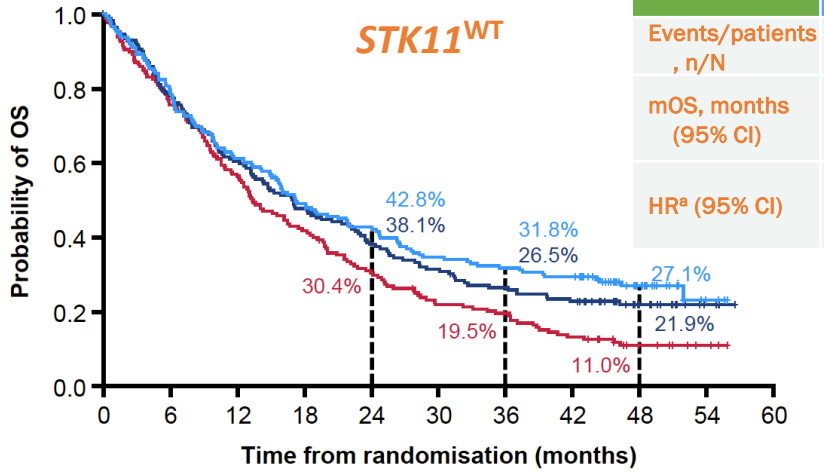


	T+D+CT	D+CT	CT
Events/patients, n/N	18/22	19/23	6/6
mOS, months (95% CI)	13.7 (7.2-26.5)	8.1 (4.0-12.9)	8.7 (5.1-NE)
HR[a] (95% CI)	0.43 (0.16-1.25)	0.77 (0.31-2.15)	–

No. at risk

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

STK11^{WT}

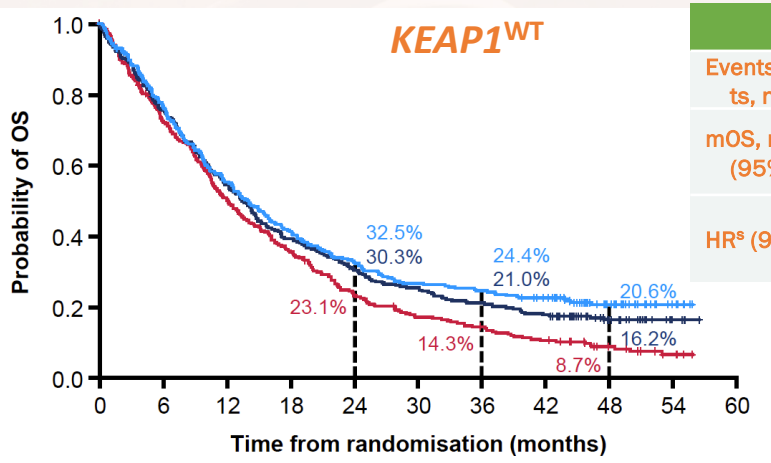


	T+D+CT	D+CT	CT
Events/patients, n/N	127/177	129/169	151/179
mOS, months (95% CI)	17.2 (14.9-22.1)	17.1 (13.3-22.3)	13.4 (11.5-17.5)
HR[a] (95% CI)	0.70 (0.55-0.89)	0.77 (0.61-0.89)	–

No. at risk

T+D+CT	177	140	107	85	74	60	55	51	23	3	0
D+CT	169	130	100	79	63	52	43	37	19	4	0
CT	179	131	97	71	51	36	31	21	9	4	0

KEAP1^{WT}



	T+D+CT	D+CT	CT
Events/patients, n/N	236/303	253/307	278/312
mOS, months (95% CI)	14.0 (11.8-16.1)	13.5 (11.7-14.9)	12.2 (10.6-13.9)
HR[a] (95% CI)	0.75 (0.63-0.89)	0.81 (0.69-0.97)	–

No. at risk

T+D+CT	303	230	165	123	97	79	73	63	30	6	0
D+CT	307	230	165	119	91	76	63	53	26	5	0
CT	312	221	153	108	69	50	41	30	14	5	0

Johnson M, et al. ESMO 2022. Abstract LBA59.

Negative Ph III Trials with PD-(L)1 + CTLA-4

Study	S1400I[1]	MYSTIC[2]	NEPTUNE[3]	ARTIC[4]	KEYNOTE-589[5]
Study arms	Nivo + Ipi vs Nivo	Durva + Treme vs Durva vs chemo	Durva + Treme vs chemo	Durva + Treme vs. SOC	Pembro + Ipi vs. Pembro + placebo
Study populations	Chemo naïve Stage IV SCC	Chemo naïve Stage IV NSCLC, PD-L1 ≥25%	Chemo naïve Stage IV NSCLC, ≥20 mut/Mb	≥2 prior lines NSCLC, PD-L1 TC <25%	First line PD-L1 ≥50% NSCLC
No of pts	252	488	129	469	568
mOS (mos)	10 vs. 11	11.9 (p=0.20) vs. 16.3 vs. 12.9 (p=0.04)	11.7 vs. 9.1 (p=0.081)	11.5 vs. 8.7 (p=0.109)	21.4 vs. 21.9

1. Gettinger S, et al. *JAMA Oncol.* 2021;7(9):1368-1377. Peters S, et al. *Cancer Res*. 2019;79(Suppl 13):CT074 3. Mok T, et al. *J Thorac Oncol.* 2016;11(4) 4. Kowalski DM, et al. Annals of Oncology. 2018;29(supp_8) 5.

Questions and Controversies

- No direct comparison of chemo-IO vs. PD-(L)1/CTLA-4
- Role of PD-L1 versus TMB as predictive biomarkers
- Role of anti-CTLA-4 after PD-1 inhibition unclear
- Identify which patients are most likely to benefit from dual inhibition
  - Need prospective trials
  - Avoid added clinical and financial toxicity in pts who don’t need both drugs
- Other novel drug combinations
  - LAG3, IDO, CD137, OX40, TIGIT

Other Ongoing Phase III trials

- <u>EMPOWER-Lung 2: Stage IV NSCLC PD-L1 ≥50%</u>
  - Cemiplimab + Ipilimumab + Platinum doublet

    vs.
  - Cemiplimab + Ipilimumab

    vs.
  - Pembrolizumab
- <u>PRESERVE-003 phase III trial</u>
  - ONC-392: novel target-preserving anti-CTLA-4 antibody, selectively depletes T reg cells in tumor microenvironment
  - Preclinical studies found ONC-032 to be more effective and less toxic compared to other immunotherapies
  - PRESERVE 011: Of 22 evaluable patients who progressed on prior IO, 6 patients with PR (ORR=27%), 12 patients with SD (DCR=82%)

eVOLVE-Lung02 Study Design

Bispecific antibody
targeting PD-1 and CTLA-4

Stage IV NSCLC
N=900 (N=600 in PD-L1<1%)
- NSQ and SQ histologies
- *EGFR, ALK,* and *ROS1* driver negative (NSQ)
- No prior chemotherapy for Stage IV NSCLC
- ECOG PS 0 or 1
- PD-L1 TC <50%

R 1:1

Volrustomig 750 mg* + Chemotherapy q3w x 4 → **Volrustomig 750 mg* + (for NSQ) pemetrexed q3w**

Pembrolizumab 200mg + Chemotherapy q3w x 4 → **Pembrolizumab + (for NSQ) pemetrexed q3w x up to 31 additional cycles** → **(For NSQ) pemetrexed q3w**

Primary Endpoints in PD-L1 TC <1% (dual)
- PFS (By BICR)
- OS

Key Secondary Endpoints in ITT (PD-L1 TC <50%)
- PFS (by BICR)
- OS

Stratification factors
- Histology (NSQ versus SQ)
- PD-L1 TC (<1% versus 1-49%)
- Smoking history (current/former versus never)
- Region (Asia vs Non-Asia)

Chemotherapy regimens:
For non-squamous histology, pemetrexed (500 mg/m^2) + carboplatin (AUC 5). Pemetrexed maintenance therapy allowed.
For squamous histology, paclitaxel (200 mg/m^2) + carboplatin (AUC 6).

Design Features
- Global trial, ~230 sites in ~30 countries
- N=900 (600 pts PD-L1 TC <1%; 300 pts PD-L1 TC 1-49%)
- NSQ:SQ ratio as 65:35
- AGA testing should be done locally at site (centrally available **only** if no site capability)

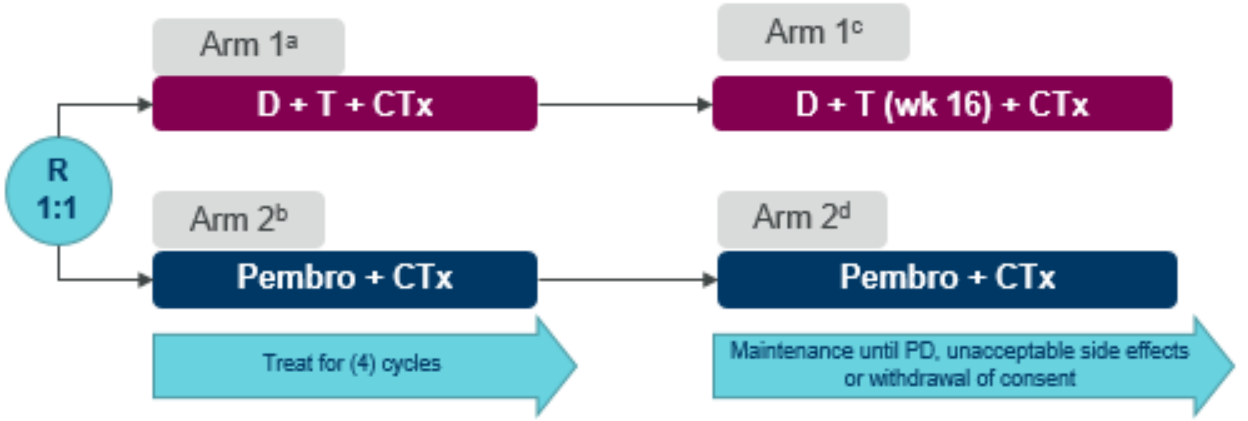
TRITON study design

Phase IIIb randomized, open-label, multicenter study

Study Population

STK11 +/- KEAP1 +/-KRASm

- **N = 280**
- Metastatic non-squamous NSCLC
- No prior systemic treatment for metastatic disease
- No EGFR or ALK alterations
- **Local testing**
- ECOG PS 0 or 1
- Tissue Sample requirement (TBC)



Stratification: STK11, KEAP1, KRAS → PD-L1 >1%, PD-L1 <1%

Primary endpoints

- OS in ITT
- OS in STK11/KEAP1

Key secondary endpoints

- PFS
- ORR, DoR
- Safety/Tolerability
- PRO/QoL

Exploratory Analysis

- Outcomes by PD-L1 expression
- Outcomes by different commutations