Checkpoint Immunotherapy (CPI) for NSCLC in 2023: A Case-based Discussion

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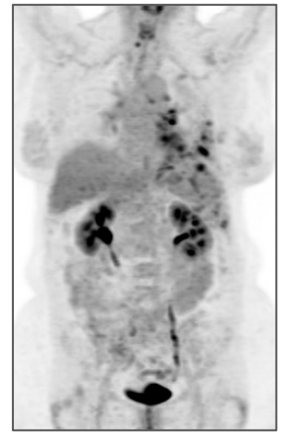
Controversies in 1st line CPI of Advanced Stage NSCLC

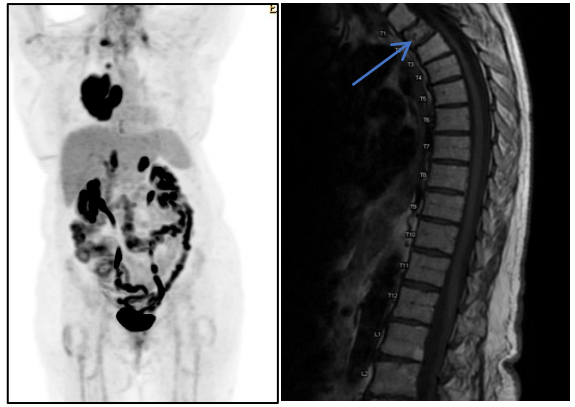
- Biomarker Selection for CPI
  - Rule out Oncogene Driver (CPI ~ineffective)
  - PD-L1 status
    - TPS vs CPS
    - ≥50% vs 1-49% vs <1%
  - Tumor Mutational Burden (TMB)
  - Immune Signatures (TIME) “Hot” + “Cold”-emerging
  - Genomic (KRAS, STK11, KEAP1)
- CPI Monotherapy vs CPI-Combinations –Stage IV (Therapeutic Decision-Making)
  - Clinical Features- “Aggressiveness”
  - PD-L1 score- <1%, 1-49%, 50% (50-60% vs 61-89% vs 90-100%)

Case Examples: Controversies in CPI therapy of Advanced Stage NSCLC

Case 1: 56 y/o woman, former smoker, with stage IV lung adenocarcinoma with lung & bone metastases. PS=1.
PD-L1 50%.



Case 2: 67 y/o woman with stage IV lung squamous carcinoma, large RUL mass, mediastinal LNs and multiple bone metastases, including T2 lesion on MRI. PS=1. PD-L1 <1%



Immunotherapy therapeutic landscape in advanced NSCLC: Phase III Trials in 1st Line Therapy

Study	Drug (vs CT)	PD-L1 selection	Control	Primary endpoint	HR primary endpoint	Result	Publication
KN-024	Pembro	≥50%	Platinum CT	PFS	0.50	Positive	Reck et al. *NEJM* 2016
CM026	Nivo	≥5%	Platinum CT	PFS	1.15	Negative	Carbone et al. *NEJM* 2017
KN-042	Pembro	≥1%	Platinum CT	OS	0.81 0.69 (50%)	Positive	Mok et al. *Lancet* 2019
IMpower110	Atezo	≥1%	Platinum CT	OS in TC3/IC3	0.59	Positive	Herbst et al. *NEJM* 2020
EMPOWER-Lung 1	Cemi	≥50%	Platinum CT	PFS, OS	0.54 (PFS) 0.57 (OS)	Positive	Sezer et al. *Lancet* 2021
MYSTIC	Durva or Durva/Tremi	≥25%	Platinum CT	PFS, OS	0.87 (PFS) durva 0.76 (OS) durva	Negative	Rizvi et al. *JAMA Oncol* 2020
CM227	Nivo or Nivo-Ipi	<1%/≥1% & TMB ≥10	Platinum CT	PFS, OS	0.58 (PFS) in TMB-H 0.62 (OS) in <1% 0.79 (OS) in ≥1%	Positive	Hellmann et al. *NEJM* 2018 Hellman et al. *NEJM* 2019
CM9LA	Nivo-Ipi-CT	≥1%	Platinum CT	OS	0.66	Positive	Paz Ares et al. *Lancet Oncol* 2021
KN-189 (NSQ)	Pembro-CT	≥1%	Platinum CT	PFS	0.52	Positive	Ghandi et al. *NEJM* 2018
KN-407 (SQ)	Pembro-CT	None	Platinum-Nab Pac	PFS, OS	0.56 (PFS) 0.64 (OS)	Positive	Paz Ares et al. *NEJM* 2018
IMpower150 (NSQ)	Atezo + Bev/Pac/Carbo	None	Bev/Pac/Carbo	PFS, OS	ACBP 0.71 (PFS) ACBP 0.78 (OS)	Positive	Socinski et al. *NEJM.* 2018
IMpower131 (SQ)	Atezo + nab Pac/Carbo	None	Pac/Carbo	PFS, OS	0.71 (PFS) 0.88 (OS)	Positive (PFS)	Jotte et al. *J Thorac Oncol* 2020
EMPOWER-Lung 3	Cemi-CT	None	Platinum CT	PFS, OS	0.56 (PFS) 0.71 (OS)	Positive	Gogishvili et al. Nat Med 2022
POSEIDON	Durva+Tremi-CT	None	Platinum CT	PFS, OS	0.77 (OS)	Positive	Johnson et al. JCO 2022

Parameters

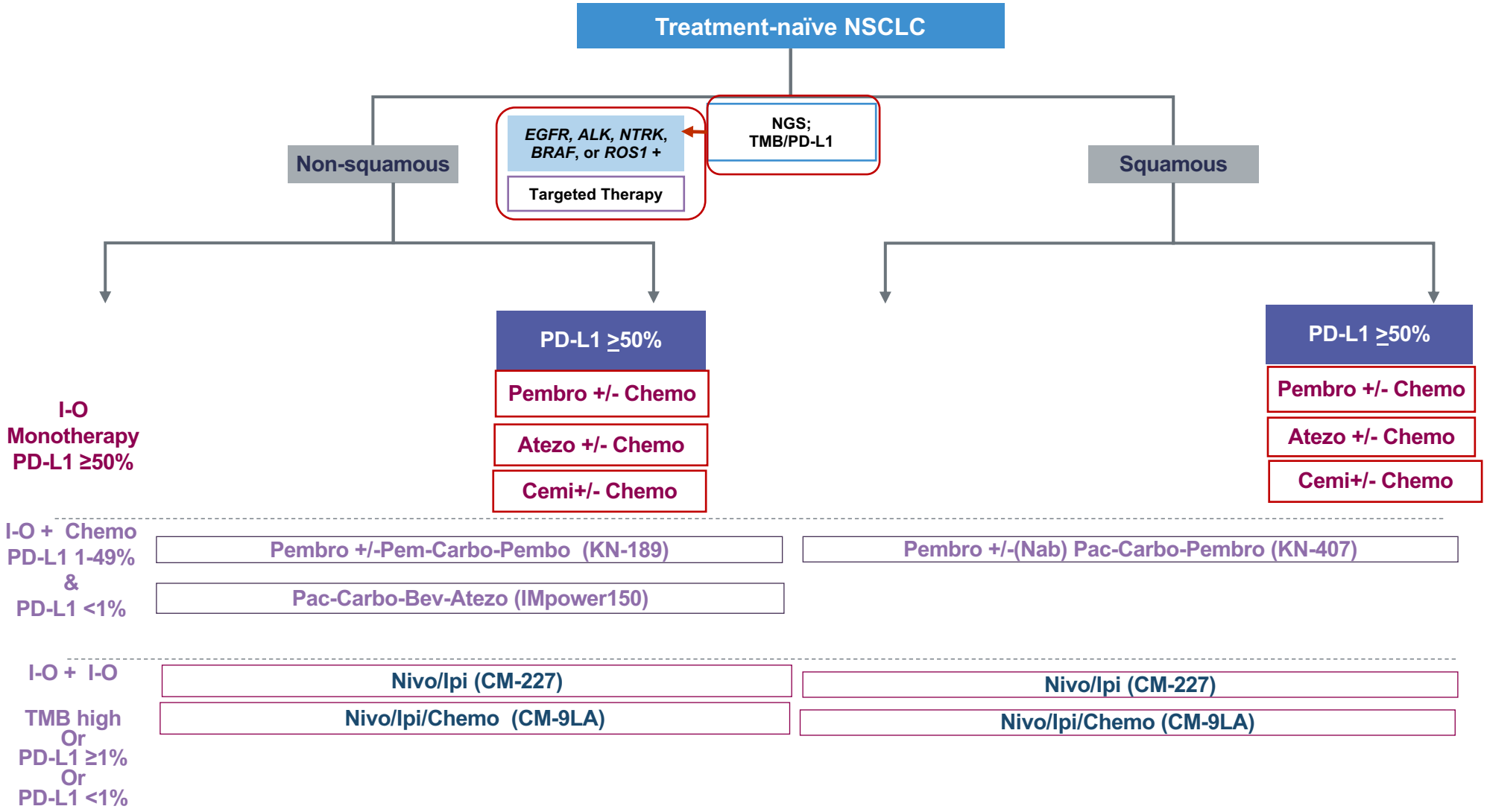
Test Regimen
ICI Monotherapy
ICI+CT
ICI+CT+Bev
ICI + CTLA-4

Biomarker
None
PD-L1
TMB

Histology
All
SQ
NSQ

Primary Endpoint
PFS
OS
Both

Stage IV NSCLC: Biomarker-driven Therapeutic Landscape Algorithm



Gandara ELCC 2021. (Adapted from S Peters: ILCC 2020)

Immune Phenotype as potential Predictive Biomarkers for benefit from Checkpoint Immunotherapy

Tumor Neo-antigenicity

- Biomarkers indicative of hypermutation & neoantigens

Examples:

–TMB, MSI-high, Neoantigen load

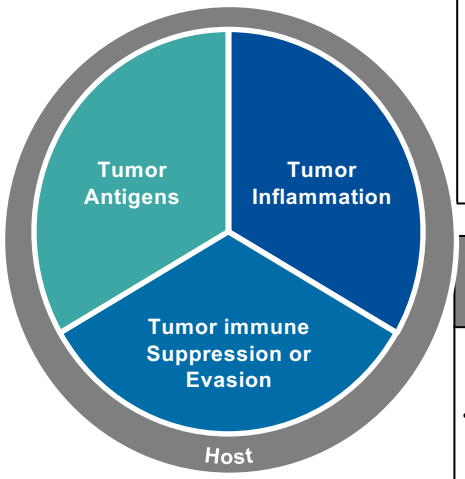
Tumor Microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an immuno-sensitive phenotype

Examples:

–PD-L1, Inflammatory signatures

–Determa IO (27 gene signature incorporating "hot" (inflammatory) & cold firbroblastic and EMT) components



Tumor Immune Suppression/Evasion

- Biomarkers that identify tumor immune system suppression or evasion beyond PD-1/CTLA-4

Examples:

–Tregs, MDSCs, IDO, LAG-3

–STK11 and KEAP1

–-ARID1A

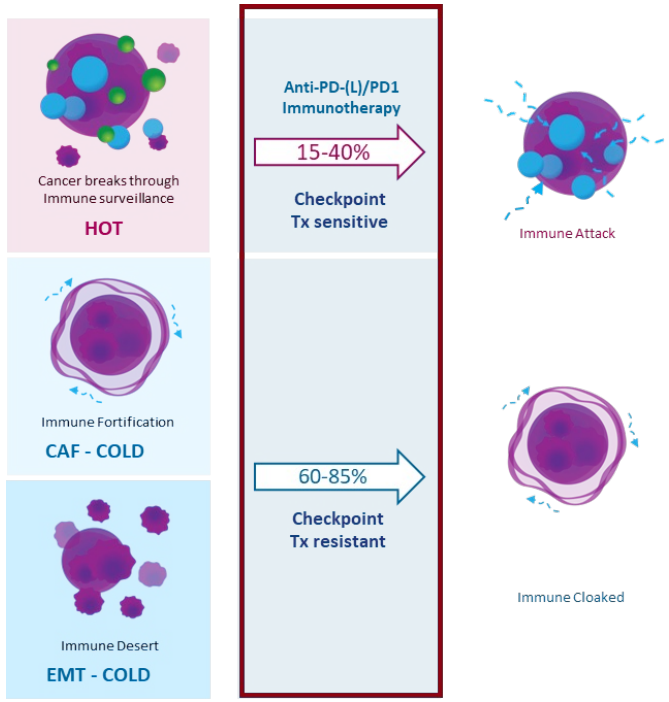
Host Environment (e.g. Microbiome)

- Biomarkers that characterize the host environment, beyond tumor microenvironment

Examples:

–Microbiome, germline genetics

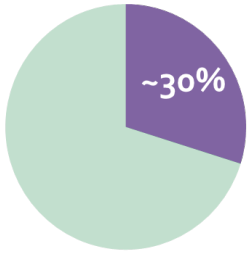
TIME-based Assays (Determa-IO)



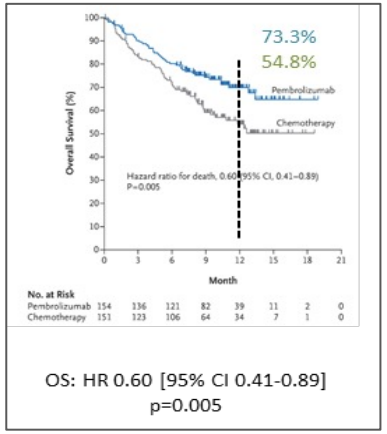
Saltman, Gandara et al. CLC 2022

Adapted from Blank CU, et al. *Science* 2016;352:658–660

PD-L1 ≥50% TPS distinguishes a Patient Subset with Substantial Benefit from CPI Monotherapy (KN024) as well as CPI + Chemotherapy (KN189)



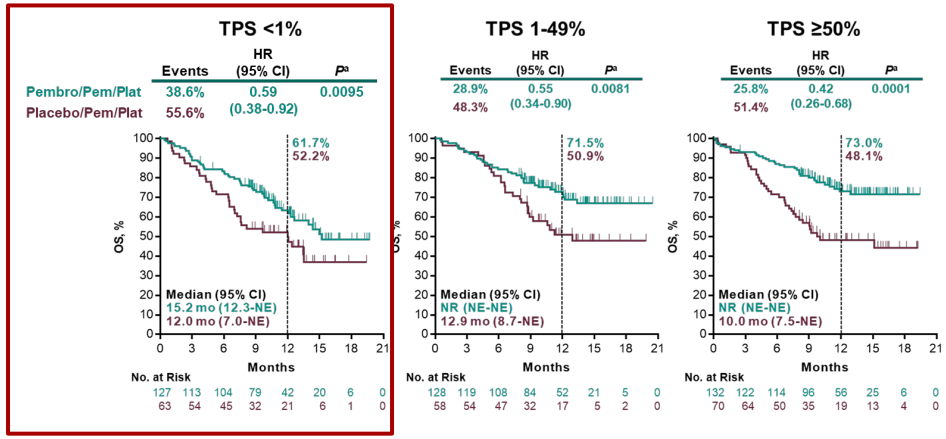
KeyNote 24: Pembro Monotherapy (OS by TPS ≥50%)



OS: HR 0.60 [95% CI 0.41-0.89]
p=0.005

Reck et al. NEJM 2016; 275:1823-1833

KeyNote 189: Pembro-Chemo (OS by PD-L1 TPS)

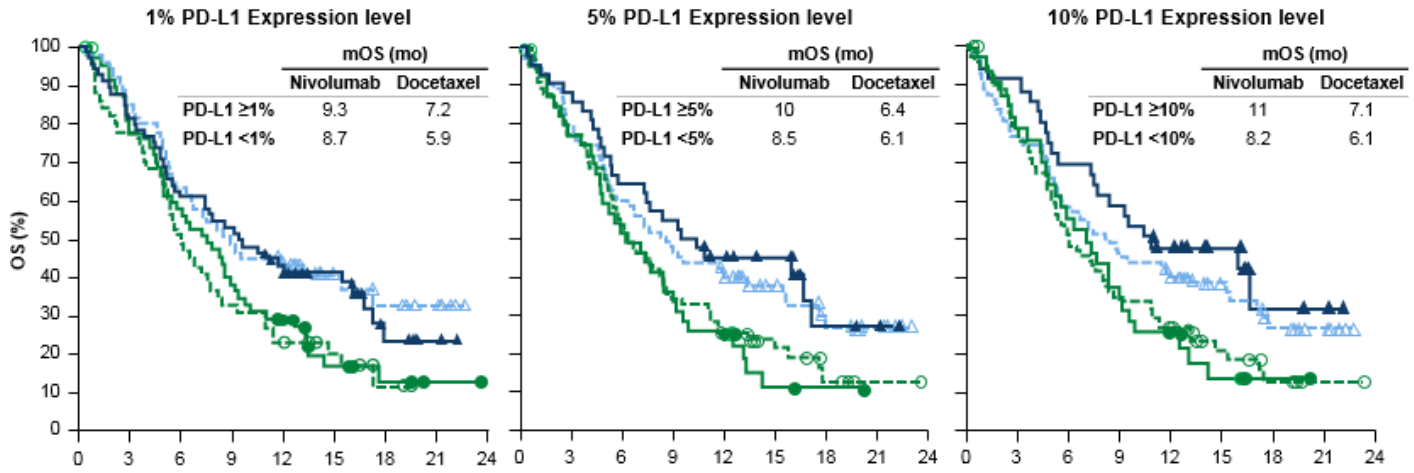


Gandhi et al. NEJM 2016

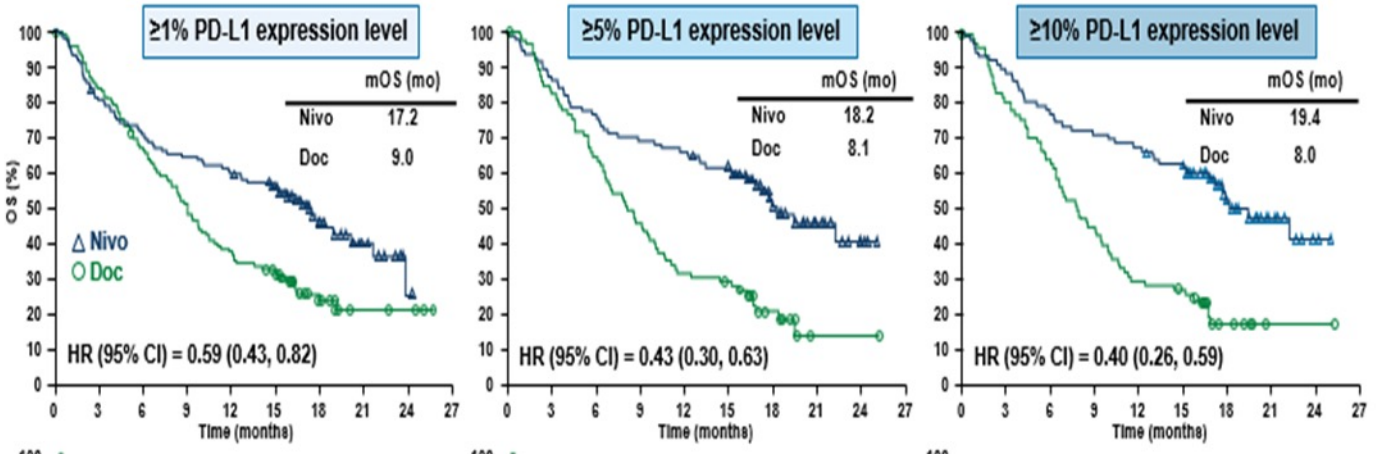
CheckMate 017 (Squamous) versus 057 (Non-Squamous): Nivolumab vs Docetaxel

OS by PD-L1 Expression

Squamous



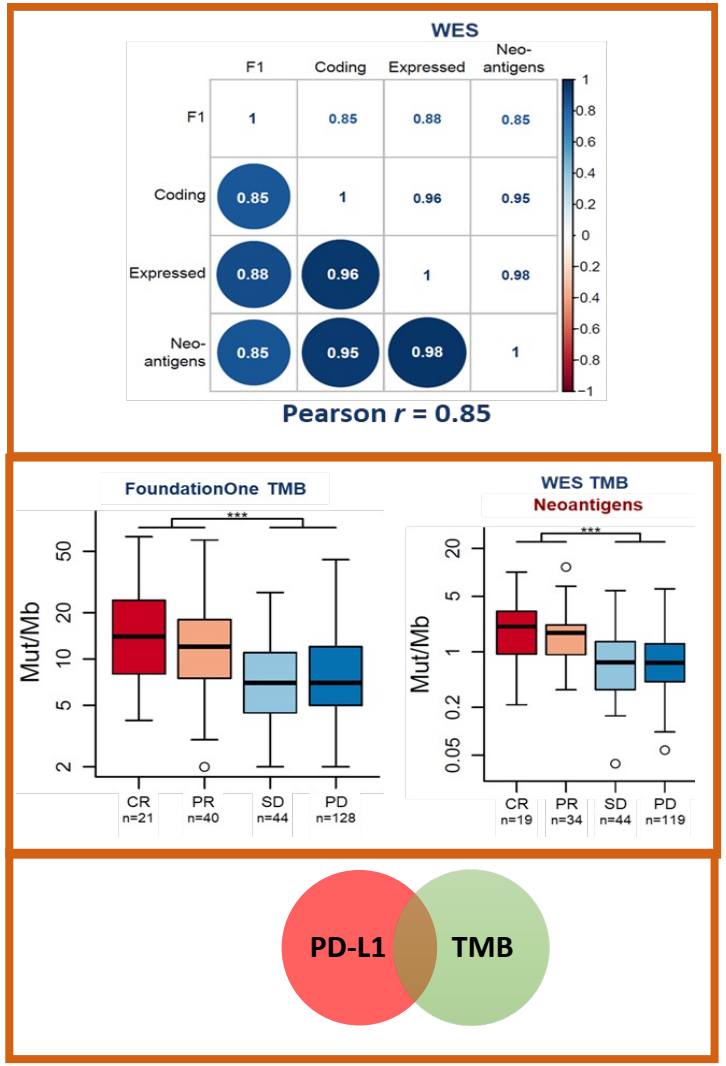
Non-Squamous



Survival benefit of nivolumab was independent of PDL1 expression levels in Squamous lung cancer but not Non-Squamous

Tumor Mutational Burden (TMB) as a Candidate Predictive Biomarker for Cancer Immunotherapy

- **TMB is an emerging predictive biomarker for cancer checkpoint immunotherapy (CIT)**
- **TMB can be estimated using whole-exome sequencing (WES) or comprehensive genomic profiling by NGS (e.g., FoundationOne & FACT in blood[bTMB]) . MSK-IMPACT. Guardant OMNI in blood[1-8]**
  - **Studies show that TMB either by WES or CGP correlate with each other & with efficacy of CPI therapy in multiple cancer types[1-3]**
- **Predicted neoantigen load (NAL), a component of TMB most closely linked to immune response, correlates with F1 TMB & OMNI[4,5,7,8]**
- **TMB identifies a distinct patient population not currently captured by PD-L1 IHC or other immune biomarkers[5,6]**



From Gandara, LeGrand et al: ASCO 2018

IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

1. Yarchoan M, et al. *N Engl J Med.* 2017; 2. Chalmers ZR, et al. *Genome Med.* 2017; 3. Goodman AM, et al. *Mol Cancer Ther.* 2017; 4. Efremova M, et al. *Front Immunol.* 2017; 5. Topalian SL, et al. *Nat Rev Cancer.* 2016; 6. Kowanetz M, et al. WCLC 2017. 7. Mariathansan, et al. Nature 2018. 8. Rizvi et al: ESMO IO 2018.

Pembrolizumab Approved for Patients with Tumor Mutational Burden-High (TMB-H) [≥10 Mutations/Megabase] Solid Tumors, as determined by an FDA-Approved Test, that Have Progressed Following Prior Treatment and who have no satisfactory alternative treatment options

KEYNOTE-158 (NCT02628067): Phase 2 Multicohort Study of Pembrolizumab for Select Previously Treated Advanced Solid Tumors

Patients

- Unresectable and/or metastatic cancer
- Progression on or intolerance to standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- Evaluable tumor sample for biomarker assessment

→ **Pembrolizumab 200 mg IV Q3W** for 2 years or until PD, intolerable toxicity, or withdrawal[a]

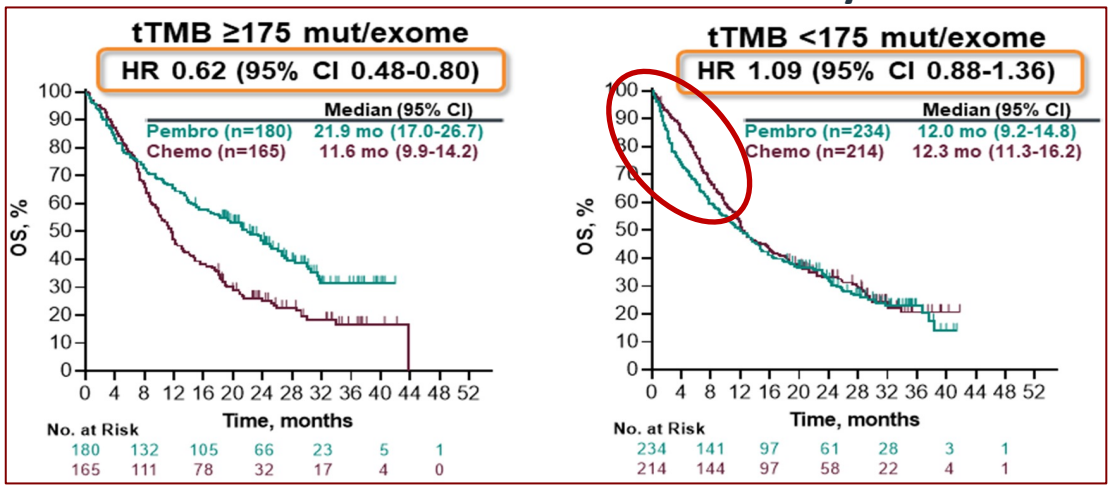
Included cancers

- Cohort A: anal squamous cell carcinoma
- Cohort B: biliary adenocarcinoma
- Cohort C: well or moderately differentiated neuroendocrine tumors
- Cohort D: endometrial carcinoma
- Cohort E: cervical squamous cell carcinoma
- Cohort F: vulvar squamous cell carcinoma
- Cohort G: small-cell lung cancer
- Cohort H: malignant pleural mesothelioma
- Cohort I: papillary or follicular thyroid carcinoma
- Cohort J: salivary gland carcinoma
- Cohort K: MSI-H solid tumors, excluding colorectal cancer (cohort excluded from this analysis)

Tumor Mutational Burden (TMB) in CPI Monotherapy vs CPI + Chemo Trials: TMB predictive in CPI Monotherapy but not with CPI-Chemotherapy

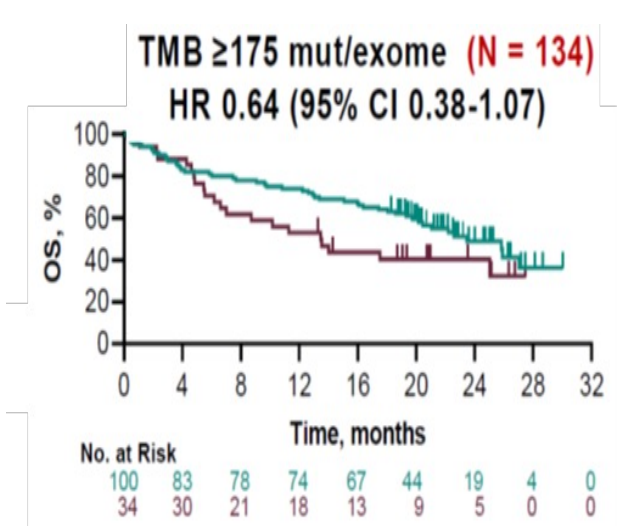
Phase III Trials	Mono- or Combination	TMB	PFS	OS
KN-010	Pembro Mono	WES-tissue	√	√
KN-042	Pembro Mono	WES-tissue	√	√
KN-189	Pembro + Chemo	WES-tissue	No	No
KN-407	Pembro + Chemo	WES-tissue	No	No

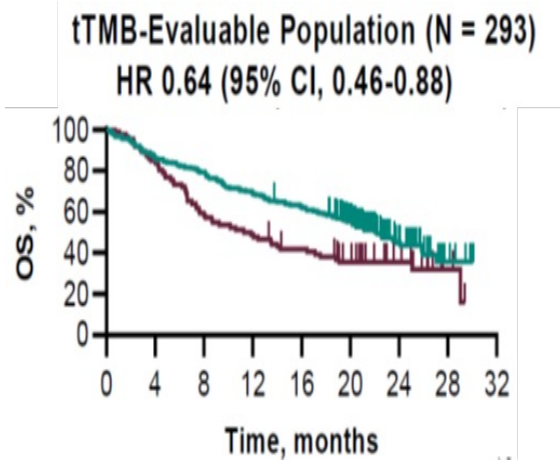
KN-042: Pembro vs Chemo: tTMB by WES



Herbst: ESMO 2019

KN-189: Pembro+Chemo vs Chemo (Non-Squamous): tTMB by WES

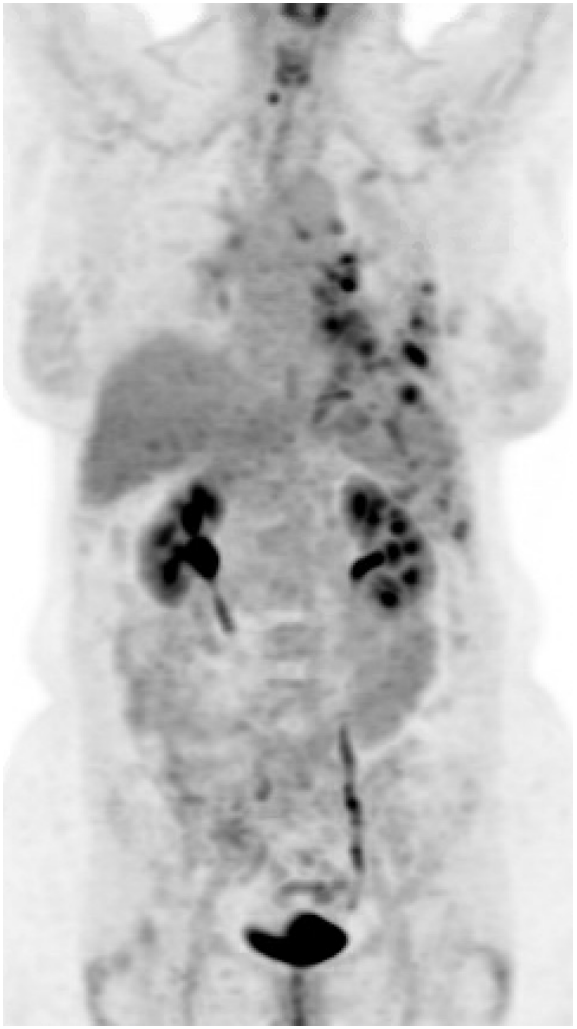




Garissino: ESMO 2019

Checkpoint Immunotherapy for NSCLC: Case 1*

- 56-year-old woman, former remote smoker (15 pack-years), presents with cough
- PS=1
- PET/CT: FDG avid LLL primary. Mediastinal and hilar adenopathy + bilateral lung nodules, bone metastases & pleural implants
- Brain MRI: negative for metastatic disease
- Biopsy of pleural implant positive for lung adenocarcinoma (TTF1+)
- PD-L1 (22C3) is 50%



*Cases may have been modified for educational purposes

Checkpoint Immunotherapy for NSCLC: Case 1*

Question 1: What would be your approach in this patient with LUAD, PD-L1 50%?

1. **Begin therapy with single agent pembrolizumab or atezolizumab or cemiplimab**
2. **Begin therapy with pemetrexed-carboplatin + pembrolizumab (KN189)**
3. **Delay therapy while performing plasma ctDNA by next generation sequencing (NGS); ~TRT about 7 days**
4. **Delay therapy while performing tumor tissue testing by next generation sequencing (NGS); ~TRT about 14 days on available specimen**
5. **Delay therapy while performing both tumor tissue testing + plasma ctDNA by NGS; ~TRT about 14 days on available specimen**
6. **Begin platinum-based chemotherapy while awaiting results of plasma ctDNA NGS**

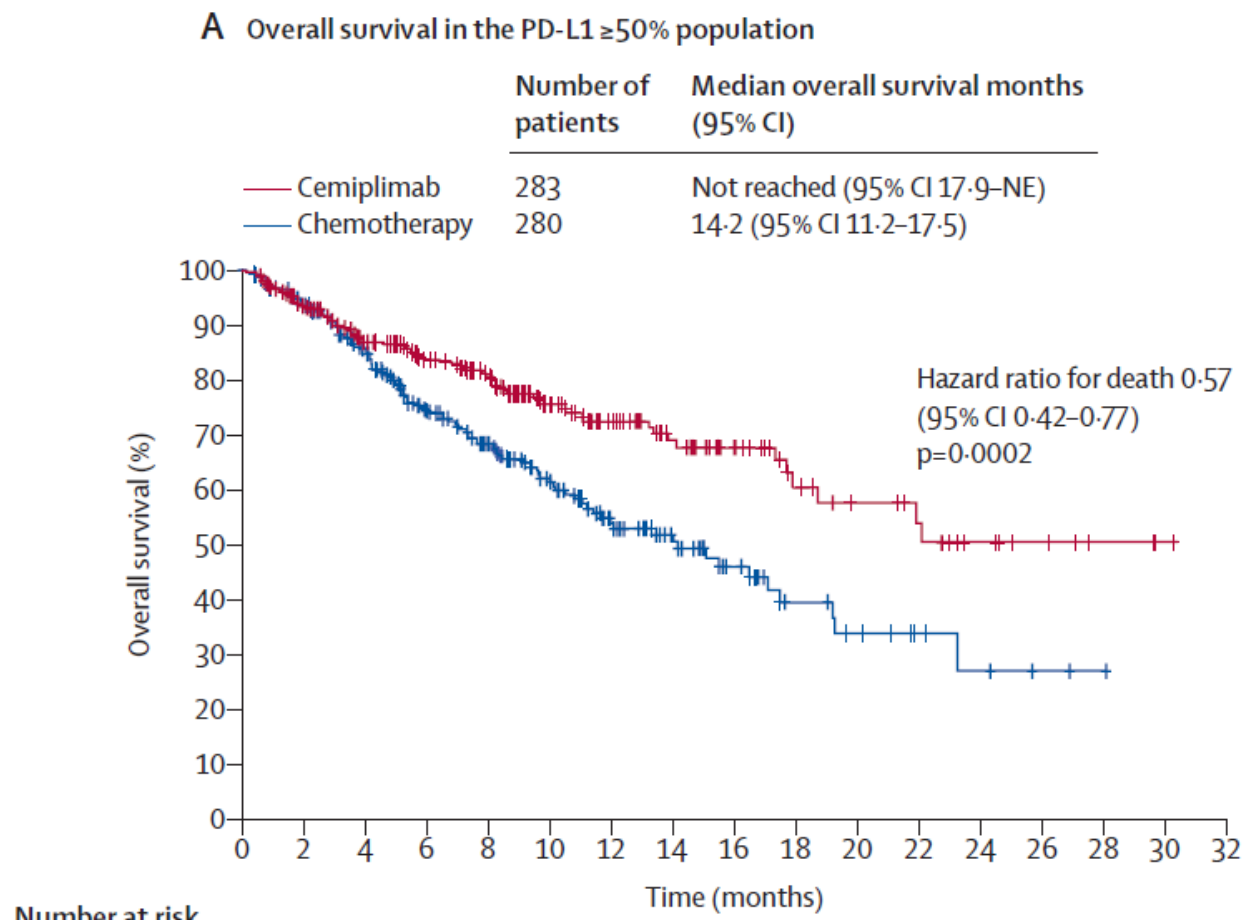
Checkpoint Immunotherapy for NSCLC: Case 1*

Plasma ctDNA returns in 7 days: *KRAS* G12C & STK11 mutations (PD-L1 TPS 50%).
You cancel the tissue tumor molecular analysis.

Question 2: What do you recommend for first-line systemic therapy?

1. **Sotorasib or Adagrasib**
2. **Single agent pembrolizumab or atezolizumab or cemiplimab**
3. **Carboplatin/pemetrexed/pembrolizumab (KN 189)**
4. **Nivolumab + ipilimumab (CM 227)**
5. **Carboplatin/paclitaxel/bevacizumab/atezolizumab (IM 150)**
6. **Platinum-based chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA)**

EMPOWER-Lung 1: Cemiplimab vs Chemo
Outcomes improve with increasing PD-L1 Levels



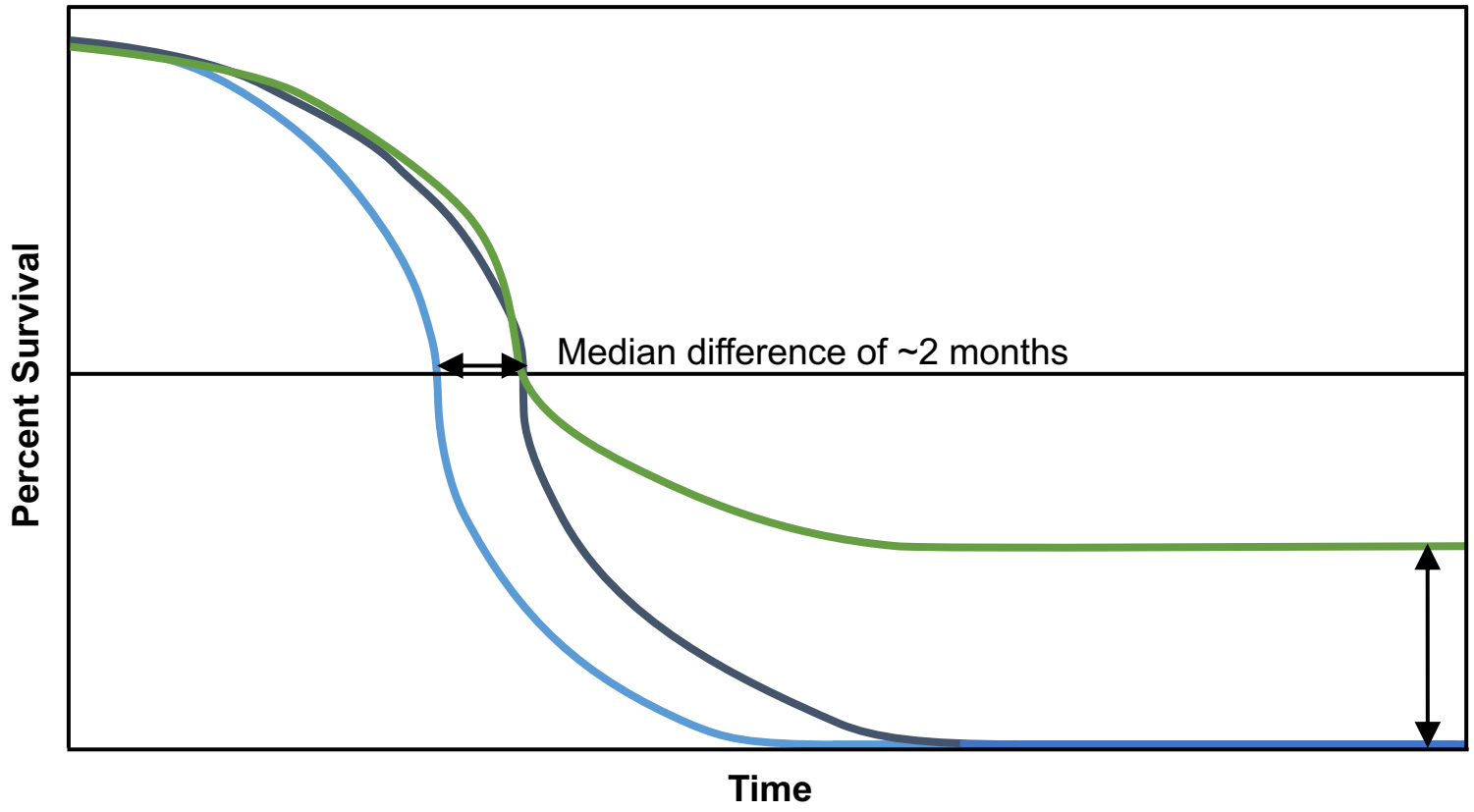
	PD-L1 ≥90%	PD-L1 >60 to <90%	PD-L1 ≥50 to ≤60%	PD-L1 <50% or unknown
Number of patients	98 *vs* 94	89 *vs* 90	96 *vs* 96	73 *vs* 74
Overall survival				
Median, months (95% CI)	NR (17·3–NE) *vs* 15·1 (11·1–NE)	22·1 (17·9–NE) *vs* 12·0 (9·6–19·2)	21·9 (13·2–NE) *vs* 14·0 (9·4–19·3)	16·5 (11·6–NE) *vs* 15·2 (10·2–NE)
Hazard ratio (95% CI)	0·46 (0·25–0·85)	0·47 (0·27–0·80)	0·77 (0·49–1·23)	1·082 (0·68–1·72)
Progression-free survival				
Median, months (95% CI)	15·3 (10·4–18·7) *vs* 5·9 (4·3–6·2)	6·2 (4·2–8·4) *vs* 4·2 (4·1–5·7)	4·3 (2·8–6·3) *vs* 6·2 (5·0–6·2)	4·1 (2·6–6·1) *vs* 5·0 (4·2–6·2)
Hazard ratio (95% CI)	0·28 (0·17–0·46)	0·55 (0·38–0·80)	0·79 (0·56–1·12)	0·82 (0·56–1·18)
Tumour response				
Objective response rate, % (95% CI)	46 (36–56) *vs* 18 (11–27)	39 (29–50) *vs* 20 (12–30)	32 (23–43) *vs* 23 (15–33)	26 (17–38) *vs* 22 (13–33)

Data are median (95% CI), hazard ratio (95% CI), and objective response rate % (95% CI). NE=not evaluable. NR=not reached. PD-L1=programmed cell death ligand 1.

Table 3: Correlation of survival and objective response with baseline PD-L1 proportion scores for cemiplimab versus chemotherapy

Sezer et al, Lancet 2021; 397:592-604.

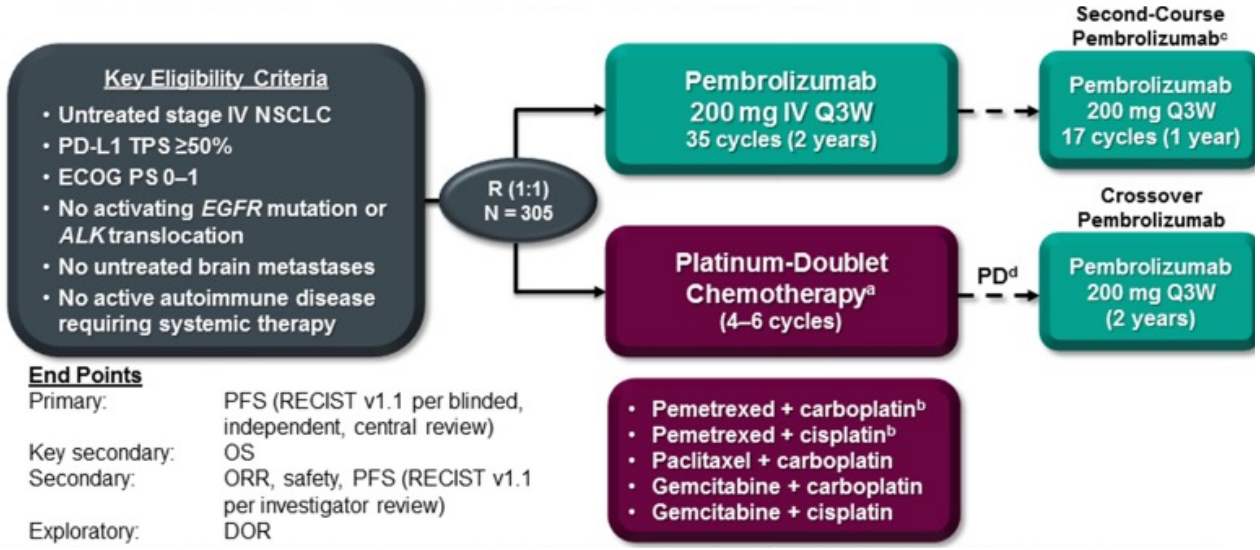
Extending the Tail of the Kaplan-Meier Curve: Potential for "Cure"

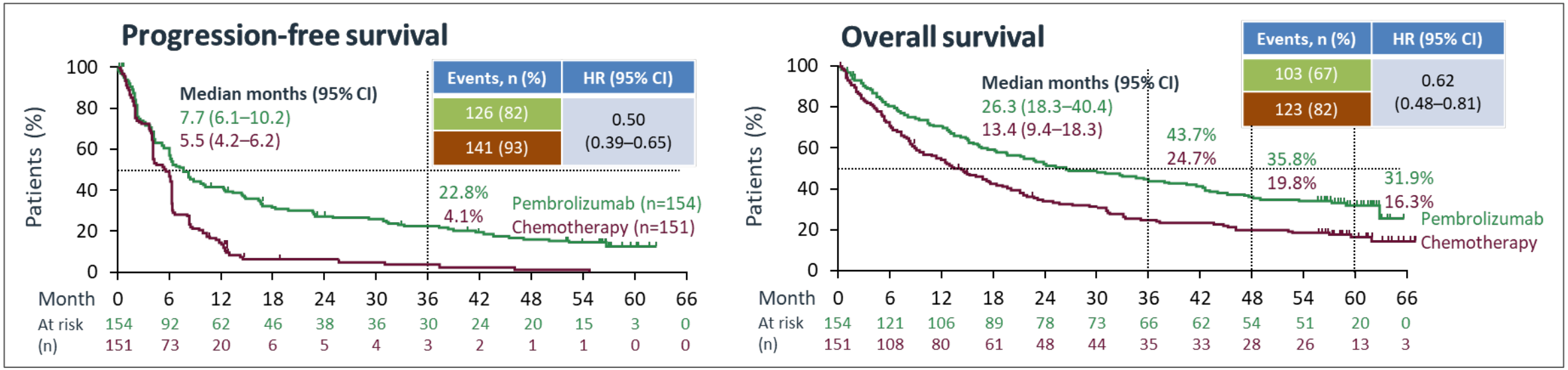


The "ail: of the OS curve for long term survival is the most important aspect of PD-1/PD-L1 therapy

Gandara D, et al. UCDCC 2015

KEYNOTE-024: 5-year progression-free and overall survival among patients with metastatic NSCLC and PD-L1 ≥50% receiving pembrolizumab





Brahmer JR, et al. ESMO 2020. Abstract LBA51.

KEYNOTE-189 5-year update: pembrolizumab + pemetrexed/platinum for nonsquamous NSCLC

Key criteria
- Metastatic non-squamous NSCLC
- Measurable disease
- ECOG PS 0–1
- EGFR wild-type
- EM:4/ALK fusion negative
- No active CNS metastases

Stratification factors
- PD-L1 score (≥1% vs <1%
- Smoking status
- Cisplatin vs carboplatin

R 2:1

Pembrolizumab 200 mg Q3W Carboplatin/cisplatin Pemetrexed x4 cycles → **Pembrolizumab** Pemetrexed → PD → FU

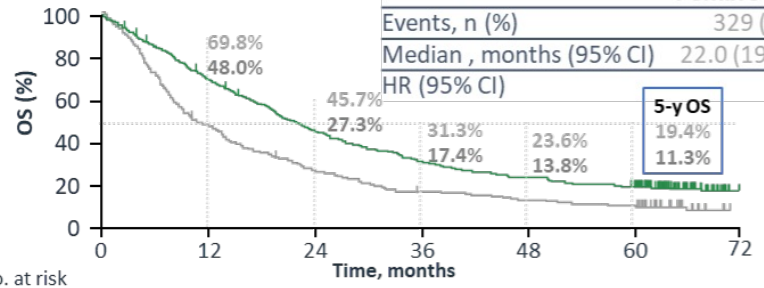
Carboplatin/cisplatin Pemetrexed + saline x4 cycles → **Premetrexed + saline** → PD → Cross over to **pembrolizumab**

Primary endpoint:
- PFS (target HR 0.7)

Secondary endpoints:
- OS
- ORR
- AE

Exploratory: QL

OS (ITT population)

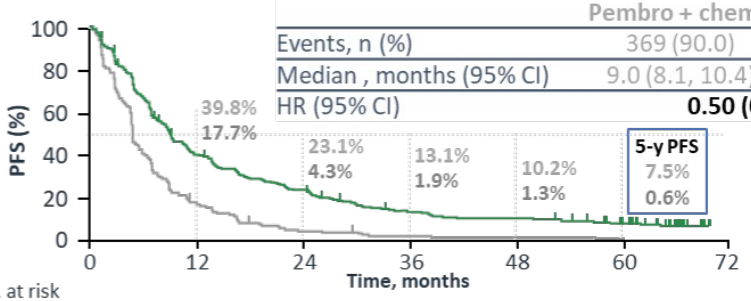


	Pembro + chemo	Placebo + chemo
Events, n (%)	329 (80.2)	183 (88.8)
Median , months (95% CI)	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)
HR (95% CI)	0.60 (0.50, 0.72)	

No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	96	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1PD-L1 TPS 1– 49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Placebo + chemo (n=70)	Pembro + chemo (n=128)	Placebo + chemo (n=58)	Pembro + chemo (n=127)	Placebo + chemo (n=63)
OS HR (95% CI)	0.68 (0.49, 0.96)		0.65 (0.46, 0.90)		0.55 (0.39, 0.76)	
5-y OS rate[b], %	29.6	21.4	19.8	7.7	9.6	5.3

PFS (ITT population)



	Pembro + chemo	Placebo + chemo
Events, n (%)	369 (90.0)	201 (97.6)
Median , months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
HR (95% CI)	0.50 (0.42, 0.60)	

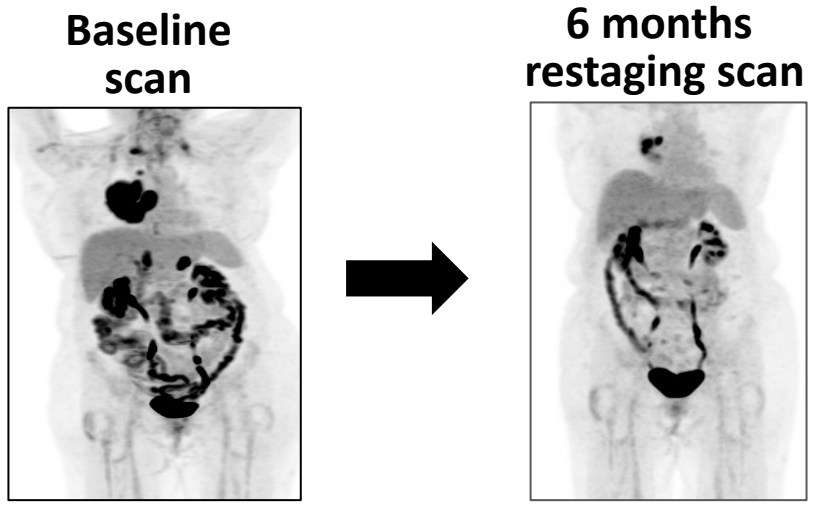
No. at risk							
Pembro + chemo	410	158	91	49	37	21	0
Placebo + chemo	208	35	8	3	2	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1PD-L1 TPS 1– 49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Placebo + chemo (n=70)	Pembro + chemo (n=128)	Placebo + chemo (n=58)	Pembro + chemo (n=127)	Placebo + chemo (n=63)
PFS HR (95% CI)	0.35 (0.25, 0.49)		0.57 (0.41, 0.80)		0.67 (0.49, 0.92)	
5-y PFS rate[b], %	12.8	0	6.5	1.9	2.4	0

1. Gandhi L, et al. N Engl J Med. 2018;387(22):2078-2092. 2. Rodríguez-Abreu D, et al. Ann Oncol. 2021;32(7):881-895 Garassino MC, et al. ESMO 2022. Abstract 973MO

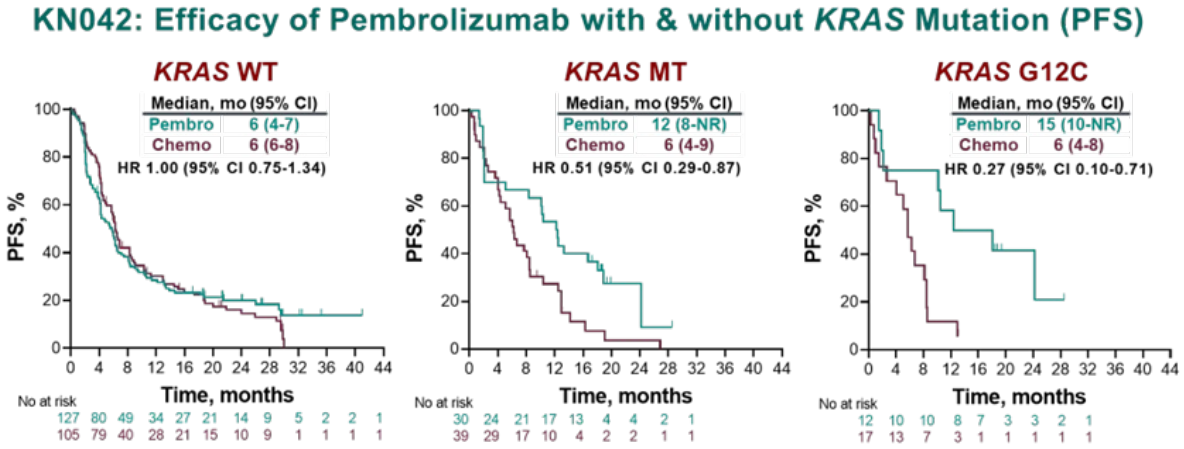
Checkpoint Immunotherapy for NSCLC: Case 1

- **This patient with lung adenocarcinoma (PD-L1 50%, KRAS G12C/STK11-mutated), receives pembrolizumab single agent**
- **Restaging scans show a near complete response.**



Impact of $KRAS^{G12C}$, STK11 & KEAP1 mutations on CPI Efficacy in NSCLC

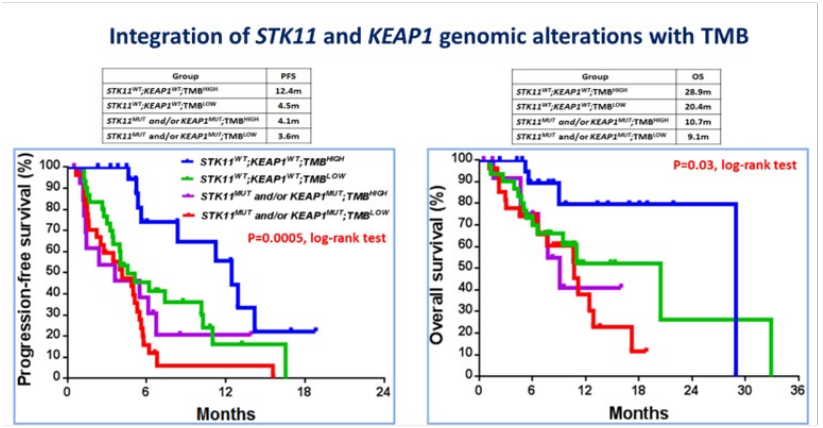
- G12C is the most frequent KRAS mutation in NSCLC
- G12C is highly associated with tobacco carcinogenesis & is high neo-antigenic (making G12C-mutated NSCLC a good candidate for immunotherapy)



Lopes et al. ESMO IO 2019

- Mutations such as STK11 & KEAP1 may alter biology & decrease CPI efficacy

Impact of STK11 & KEAP1 mutations on CPI: Predictive or Prognostic of poor Outcomes?

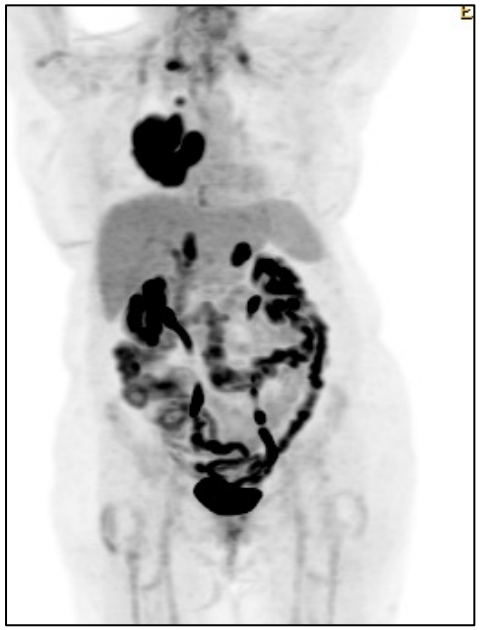


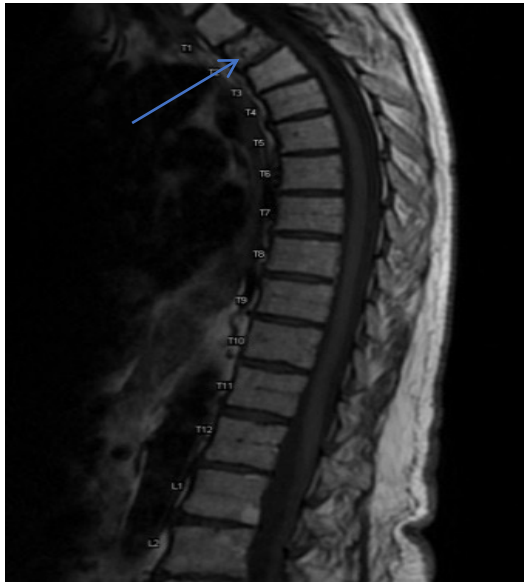
Skoulidis et al. CCR 2020

Checkpoint Immunotherapy for NSCLC: Case 2*

- 67-year-old woman with 30 pack per year smoking history presents with cough, fatigue and upper back pain (PS=1)

- CXR and subsequent CT scan show a large RUL peri-hilar mass with mediastinal LNs and multiple bone metastases, including T2 lesion on MRI.
- CT biopsy shows squamous cell carcinoma. p40+, TTF1-
- PD-L1 <1%





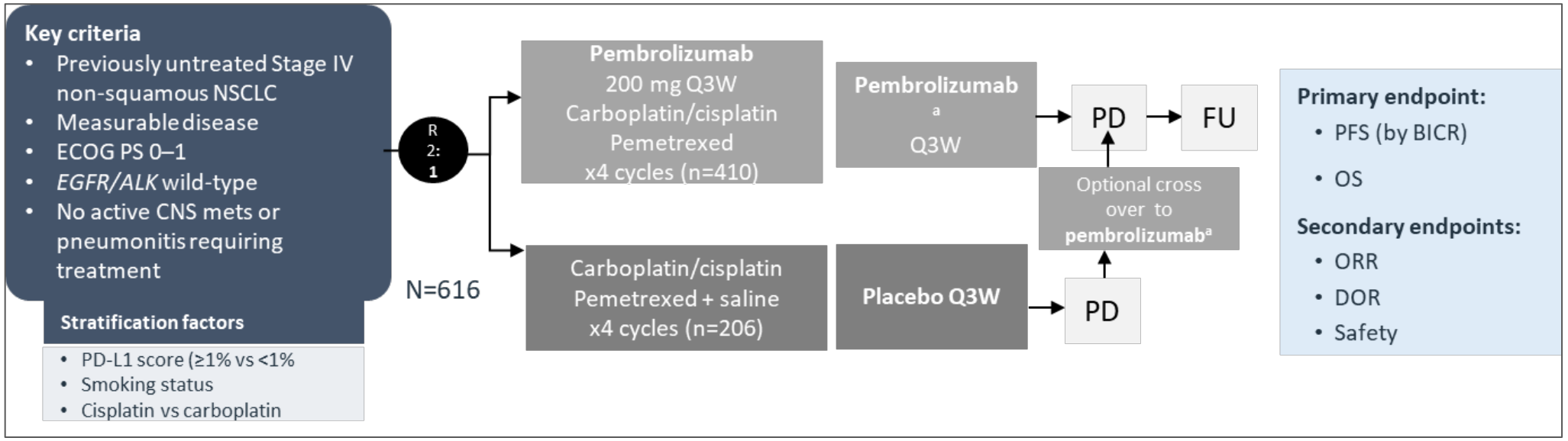
*Cases may have been modified for educational purposes

Checkpoint Immunotherapy for NSCLC: Case 2*

Question 2: What treatment would you recommend for this patient with stage IV squamous lung cancer, PD-L1 <1%, PS=1 and highly motivated for therapy?

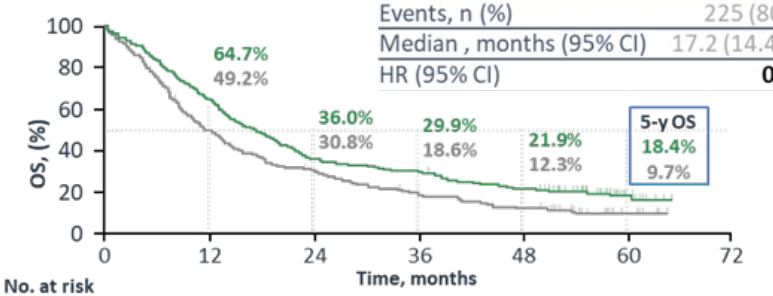
1. **Platinum + gemcitabine or paclitaxel/Nab-paclitaxel**
2. **Taxane/Carboplatin/Pembrolizumab (KN407)**
3. **Platinum/Gemcitabine/Cemiplimab (EMPOWER-Lung 3)**
4. **Nivo-ipilimumab (CM227)**
5. **Platinum-based chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA)**
6. **Other**

KEYNOTE-407 (5-year update): Pembrolizumab + chemotherapy in squamous NSCLC



OS (ITT population)

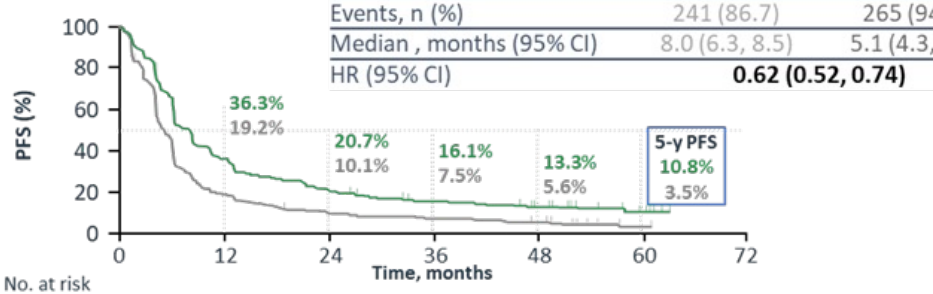
	Pembro + chemo	Placebo + chemo
Events, n (%)	225 (80.9)	265 (94.3)
Median , months (95% CI)	17.2 (14.4, 19.7)	11.6 (10.1, 13.7)
HR (95% CI)	**0.71 (0.59, 0.85)**	



No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

PFS (ITT population)

	Pembro + chemo	Placebo + chemo
Events, n (%)	241 (86.7)	265 (94.3)
Median , months (95% CI)	8.0 (6.3, 8.5)	5.1 (4.3, 6.0)
HR (95% CI)	**0.62 (0.52, 0.74)**	

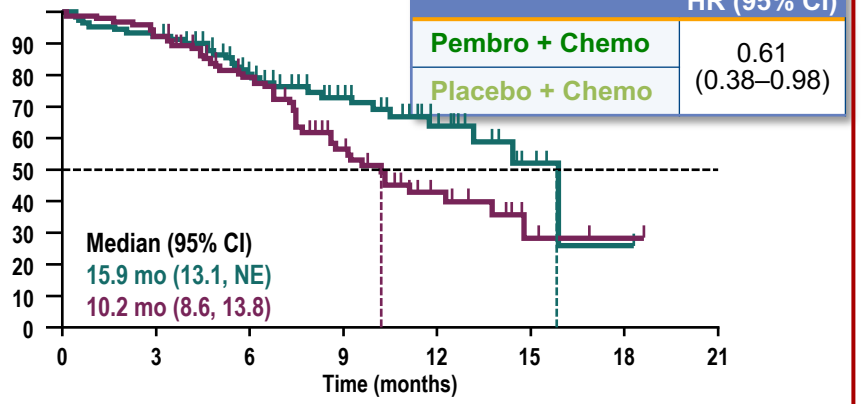


No. at risk							
Pembro + chemo	278	100	56	40	30	7	0
Placebo + chemo	281	53	27	20	14	1	0

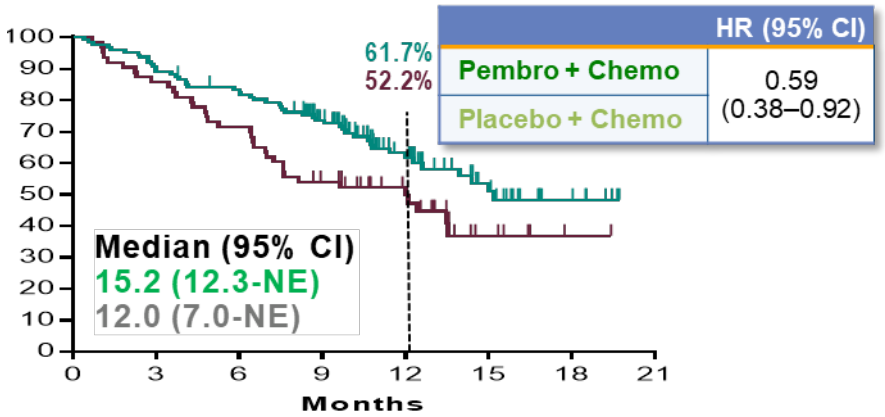
Paz-Ares, et al. N Engl J Med 2018;379:2040–51. 2. Paz-Ares, et al. J Thorac Oncol 2020;15:1657–69. Novello S, et al. ESMO 2022. Abstract 974MO

Efficacy of CPI-Chemotherapy or CPI/CPI Combinations in 1st line NSCLC PD-L1 negative (PD-L1 <1%)

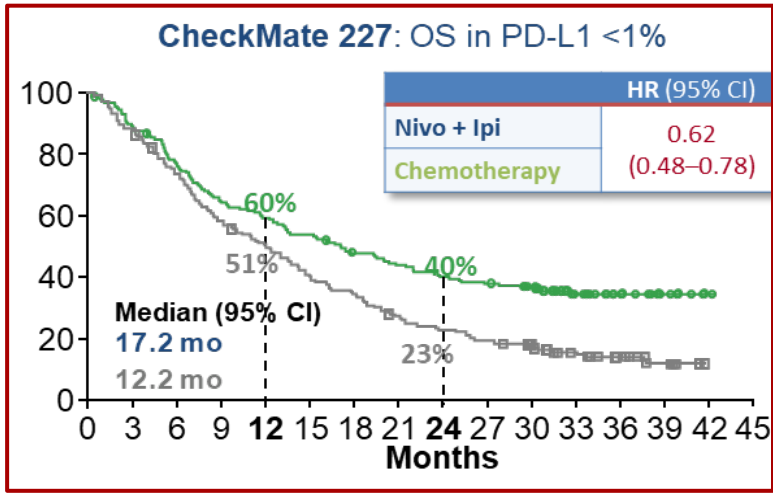
KEYNOTE-407: OS in PD-L1 <1%, SQ



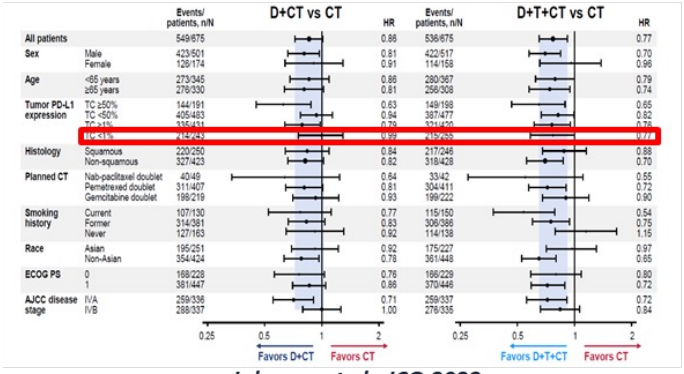
KEYNOTE-189: OS in PD-L1 <1%, NSQ



CheckMate 227: OS in PD-L1 <1%

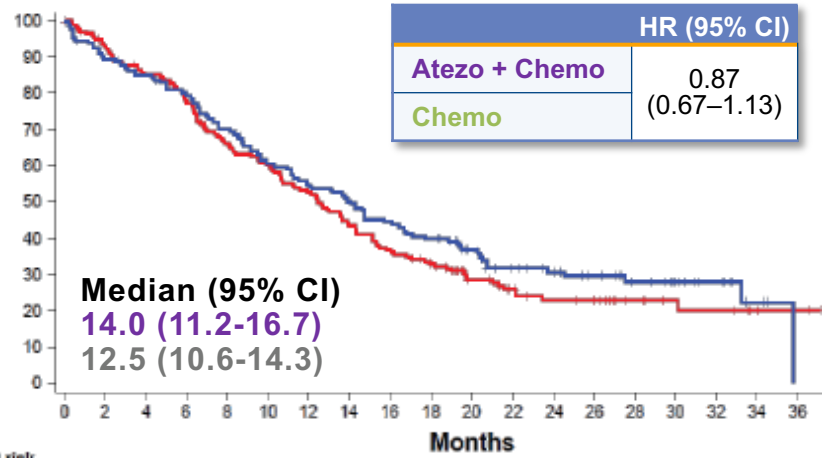


POSEIDON: Durva-Treme-Chemo in PD-L1 <1%



Johnson et al. JCO 2022

IMpower 131: OS in PD-L1 TC0/IC0, SQ



PD-L1 is an "incomplete" biomarker for CPI: it does not tell the whole story