WHEN IS PD(L)-1 MONOTHERAPY ENOUGH?

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Detroit, Michigan

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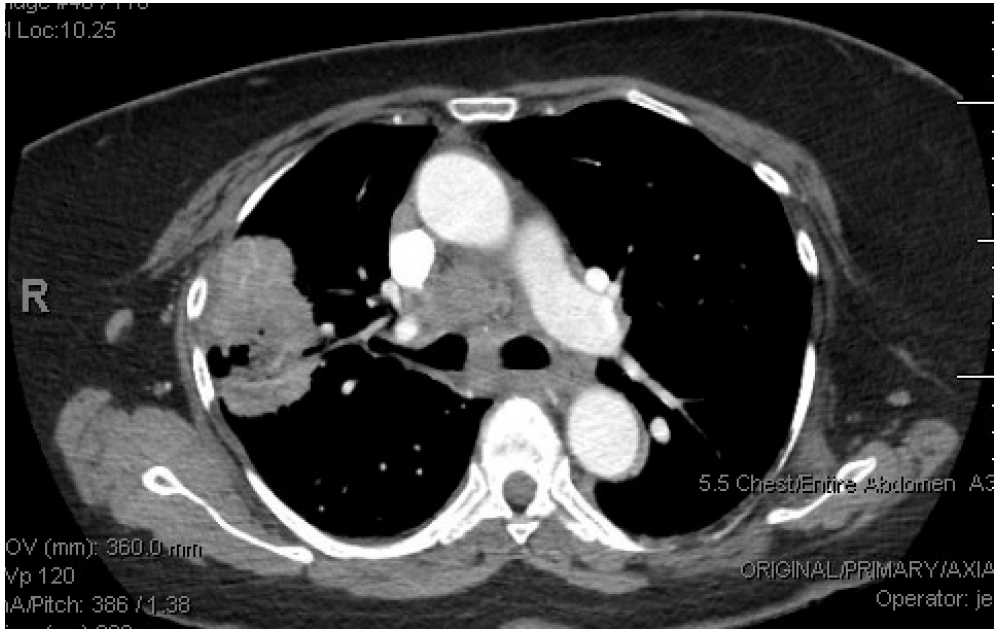
IDEOlogy Health
Creating Aha! Moments In Healthcare

Case- 66 year old female patient with CNS Metastasis

NGS- ARID1A, CDKN2A, TP53, NF1; PD-L1- 100%



August 2021

KEYNOTE 24- 5 year survival - 31.9%

Key End Points

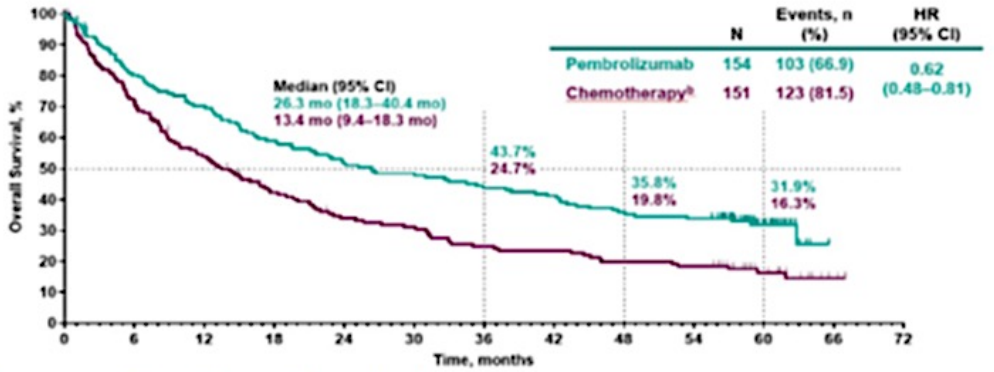
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

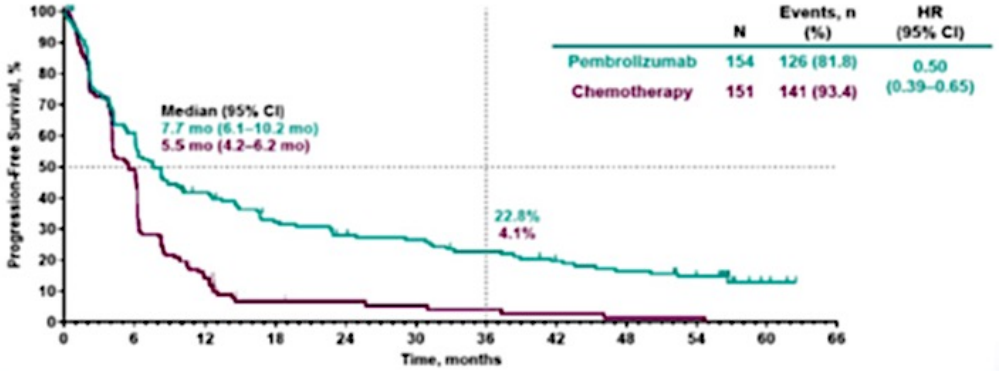
Exploratory: DOR

	Pembrolizumab N = 154	Chemotherapy N = 151
Objective response, n (%)	71 (46.1)	47 (31.1)
Best objective response, n (%)		
Complete response	7 (4.5)	0
Partial response	64 (41.6)	47 (31.1)
Stable disease	37 (24.0)	60 (39.7)
Progressive disease	35 (22.7)	25 (16.6)
Not evaluable	0	1 (0.7)
No assessment	11 (7.1)	18 (11.9)
Time to response, median (range), mo	2.1 (1.4–14.6)	2.1 (1.1–12.2)
DOR, median (range), mo	29.1 (2.2–60.8+)	6.3 (3.1–52.4)

Overall Survival



Progression Free Survival



Reck, et al , J Clin Oncol, 2021

PFS and OS with PD(L)-1 Monotherapy

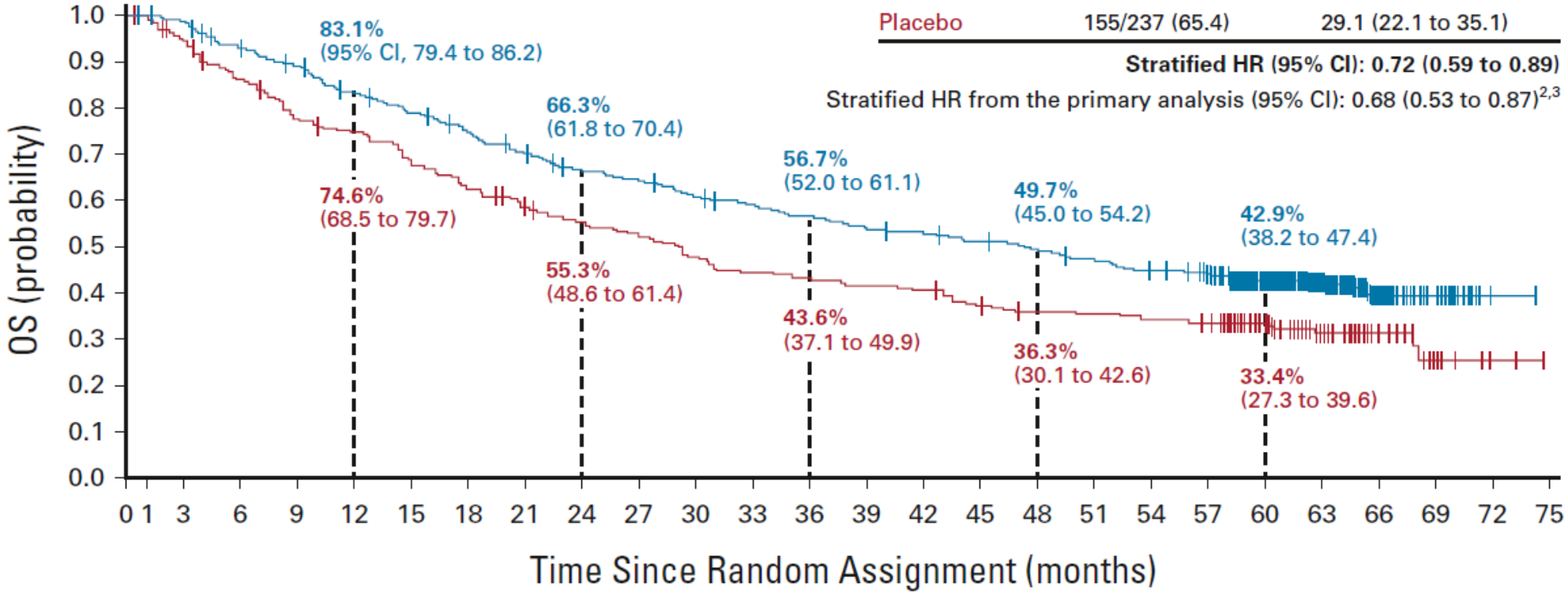
Trial	Treatment	PD-L1	ORR (%)	Median PFS	Median OS
KEYNOTE-024[a]	Pembrolizumab (n = 154)	≥ 50%	46.1	7.7 mo	26.3 mo
KEYNOTE-042	Pembrolizumab (n = 299)	≥ 50%	39	6.5 mo	20.0 mo
IMpower110[b]	Atezolizumab (n = 107)	TC3; IC3	38.3	8.2 mo	20.2 mo
EMPOWER-Lung 1[c]	Cemiplimab (n = 284)	≥ 50%	42.3	6.3 mo	23.4 mo

PACIFIC- Survival

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Spigel DR J Clin Oncol 2022

IMpower010 Study of Adjuvant Atezolizumab After Chemotherapy for Completely Resected Stage IB-IIIA NSCLC

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

N = 1005

BSC

Survival follow-up

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS

Key exploratory endpoints

- OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

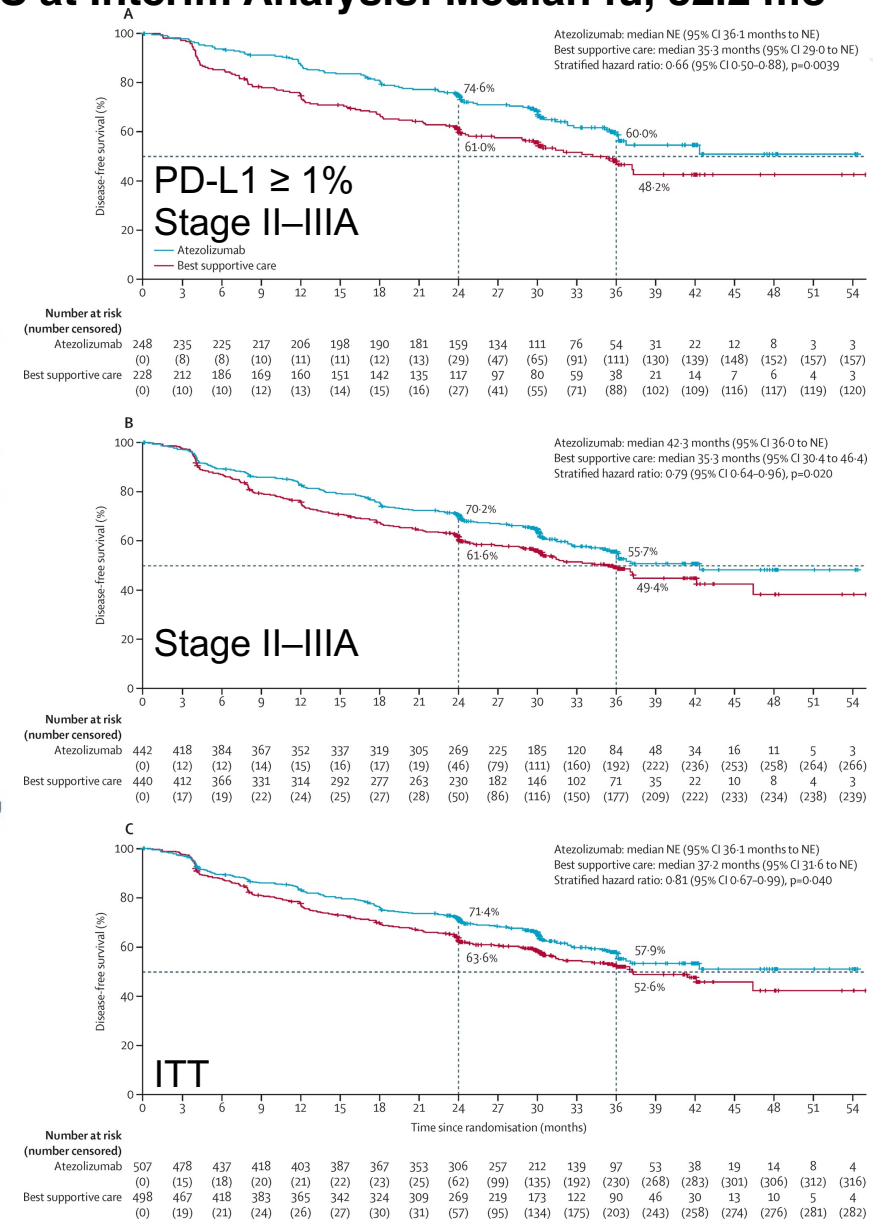
DFS in ITT population (stage IB-IIIA)[b]

If positive:

OS in ITT population[b]

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and follow up is ongoing
- Endpoint was not formally tested

DFS at Interim Analysis: Median fu, 32.2 mo[1]



WCLC 2022 - Update at median fu of 45.3 mo[2]:

- First prespecified IA of OS - immature
  - PD-L1 ≥ 1%, Stage II–IIIA: HR, 0.71 (95% CI, 0.49-1.03)
  - PD-L1 ≥ 50%: HR, 0.42 (95% CI, 0.23-0.78)
- Now new or unexpected safety signals
- Final DFS analysis not conducted (required number of DFS events not reached)

1. Felip E, et al. *Lancet.* 2021;398:1344-1357. 2. Felip E, et al. WCLC 2022.

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

- **Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)**
- **Placebo Q3W for ≤18 administrations (~1 yr)**

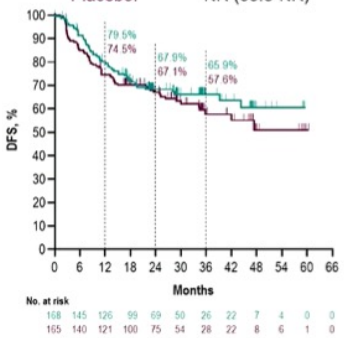
Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

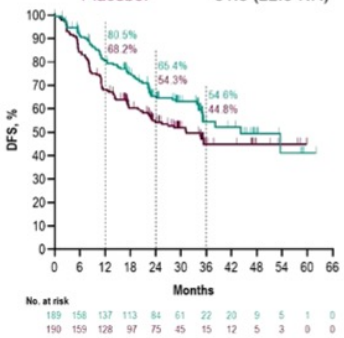
TPS ≥50%
HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

Median (95% CI), mo
Pembrolizumab: NR (44.3-NR)
Placebo: NR (35.8-NR)



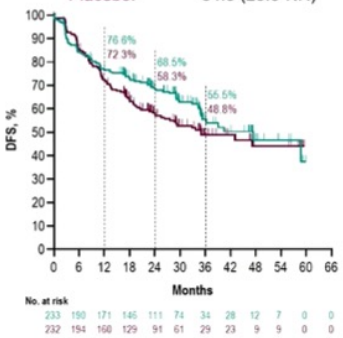
TPS 1-49%
HR 0.67 (95% CI, 0.48-0.92)

Median (95% CI), mo
Pembrolizumab: 44.2 (34.9-NR)
Placebo: 31.3 (22.5-NR)



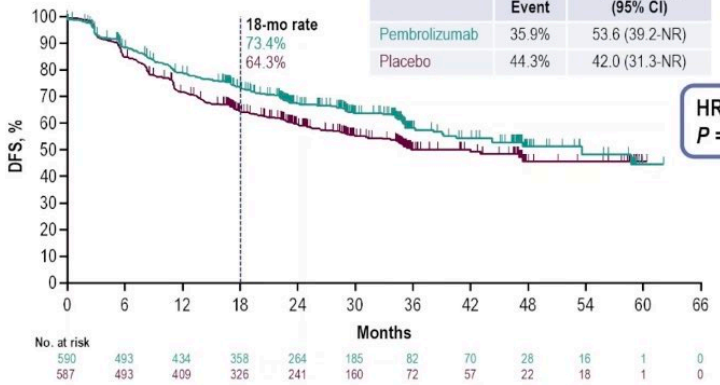
TPS <1%
HR 0.78 (95% CI, 0.58-1.03)

Median (95% CI), mo
Pembrolizumab: 47.4 (35.0-NR)
Placebo: 34.9 (25.5-NR)



DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

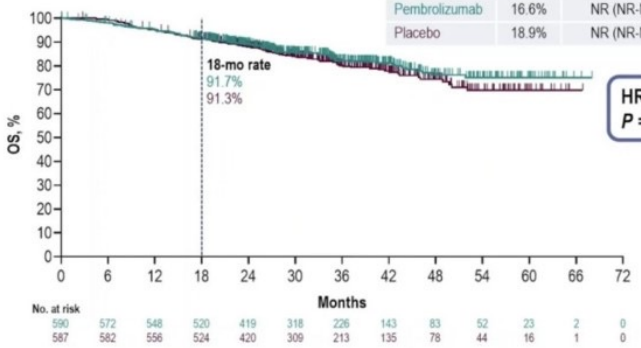
ESMO VIRTUAL PLENARY

16, 17 & 18 MARCH 2022

Luis Paz-Ares

OS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	16.6%	NR (NR-NR)
Placebo	18.9%	NR (NR-NR)



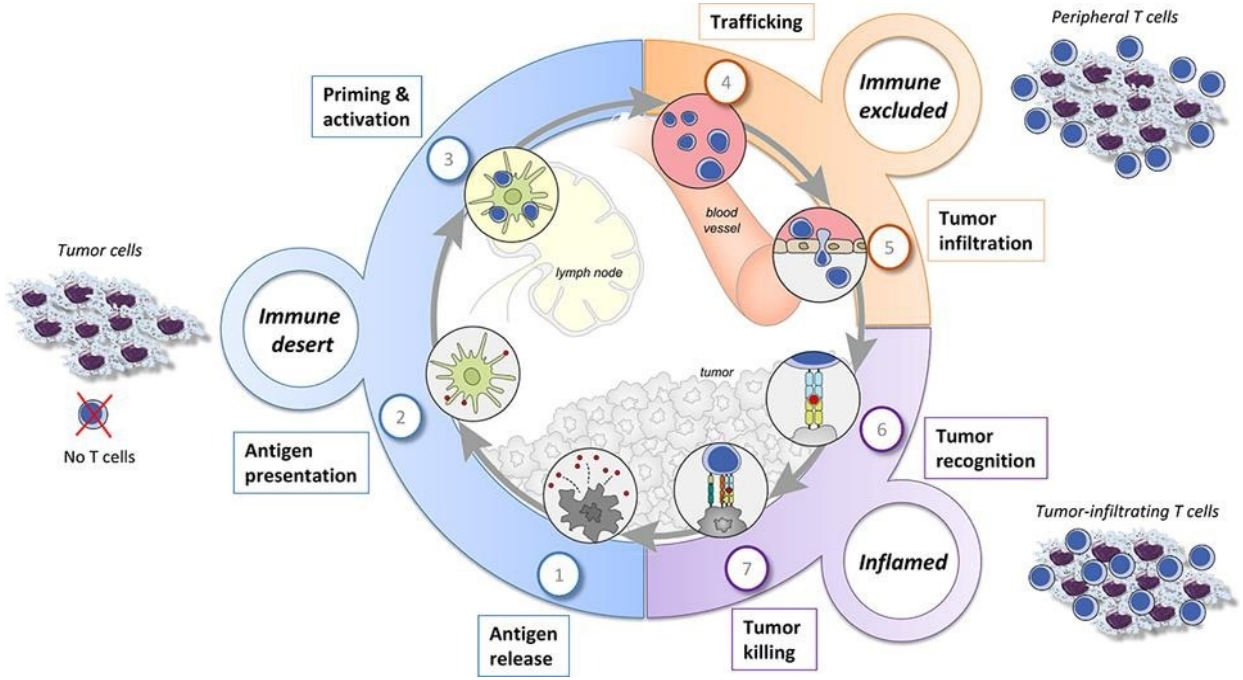
HR 0.87 (95% CI, 0.67-1.15)
***P* = 0.17**

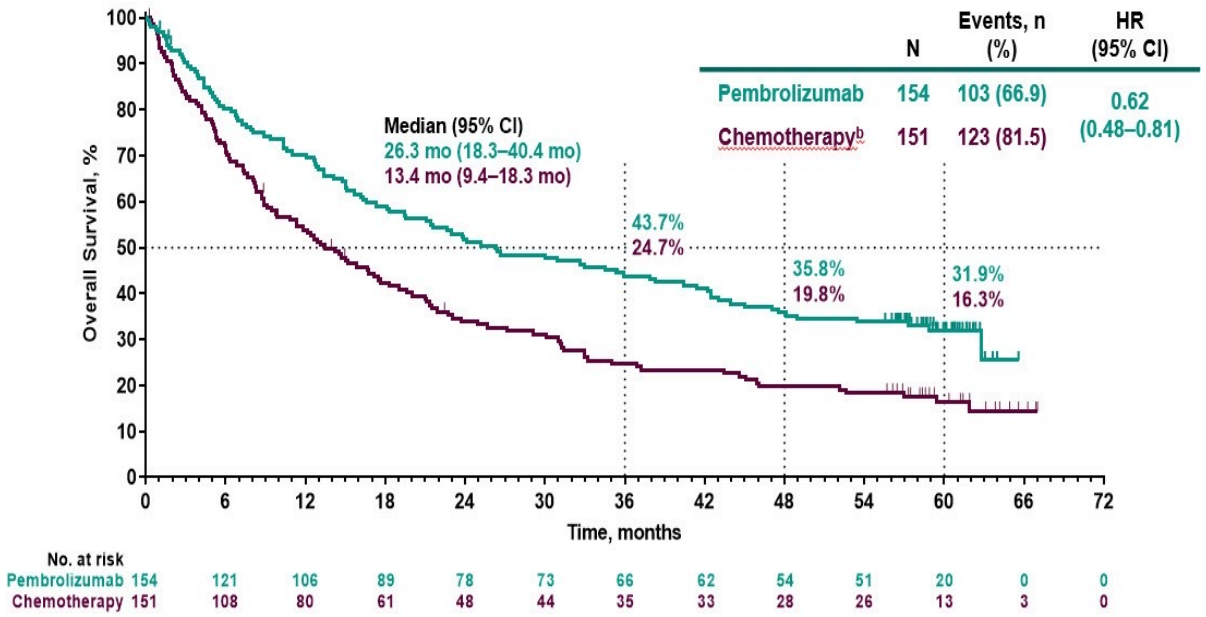
ESMO VIRTUAL PLENARY

Data cutoff date: September 20, 2021

Paz-Ares. ESMO Virtual Plenary March 2022.

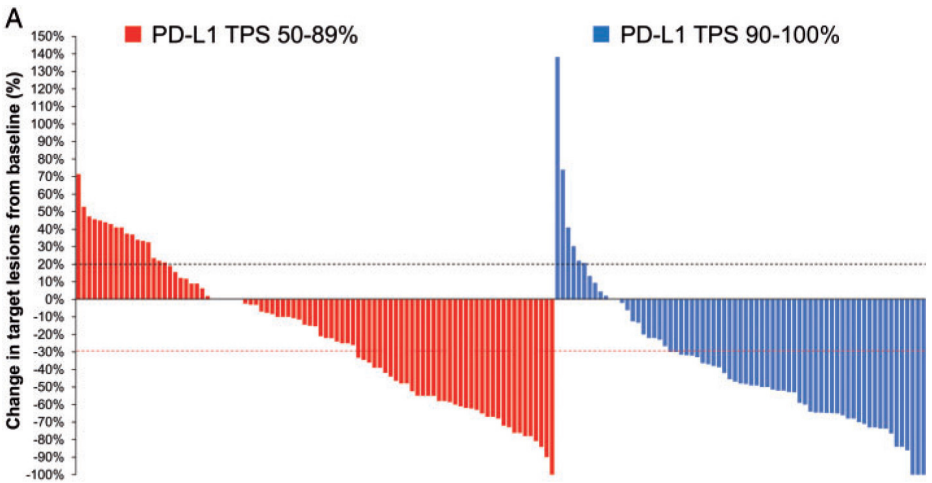
Tumor PD-L1 surrogate marker for Inflamed Tumor

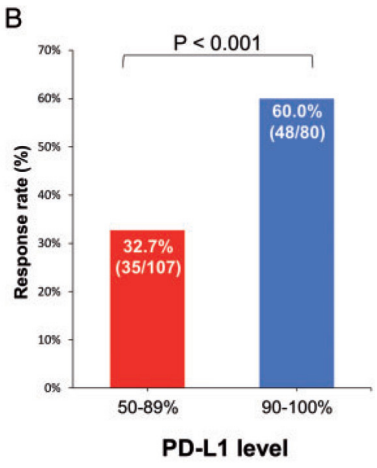


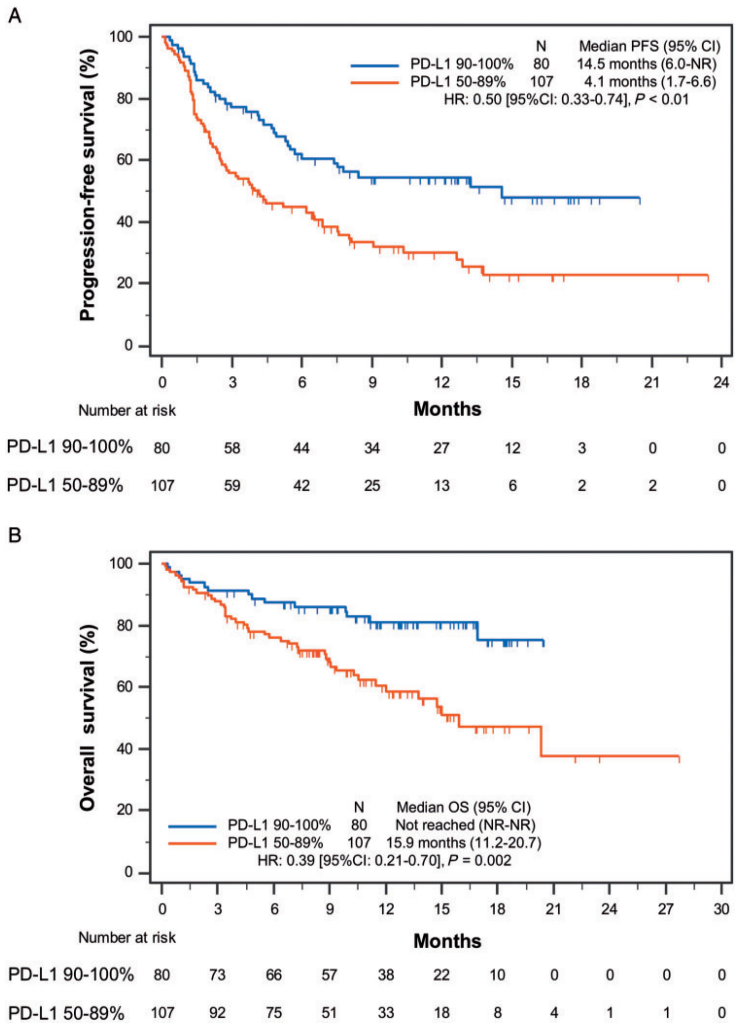


Chen, Mellman Immunity 2013; Gerard, et al, Cancer Treat Rev 2021

PD-L1 Expression a Continuous Variable

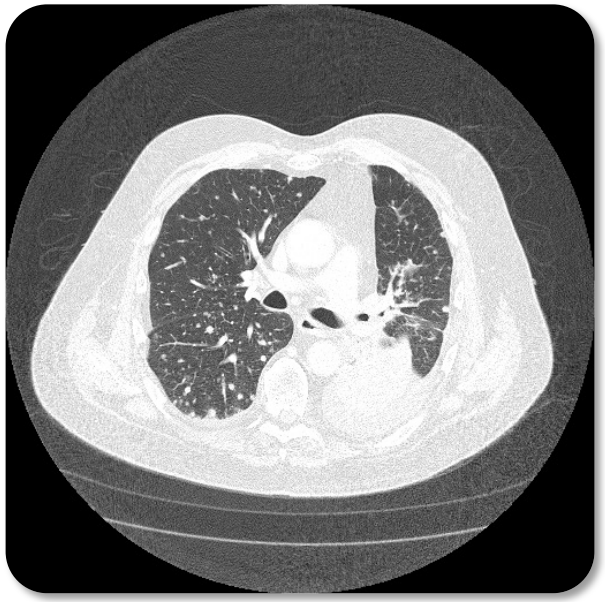




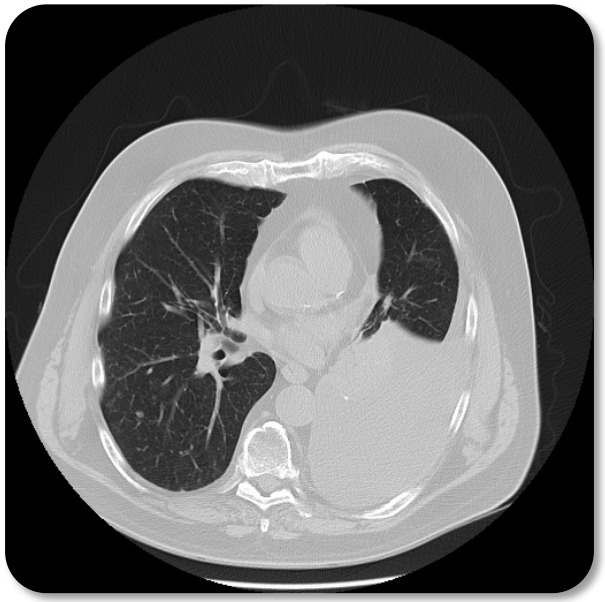


Aguilar EJ, Ann Oncol 2019

PD-L1 Biomarker with Limitations



6 Nov 2013



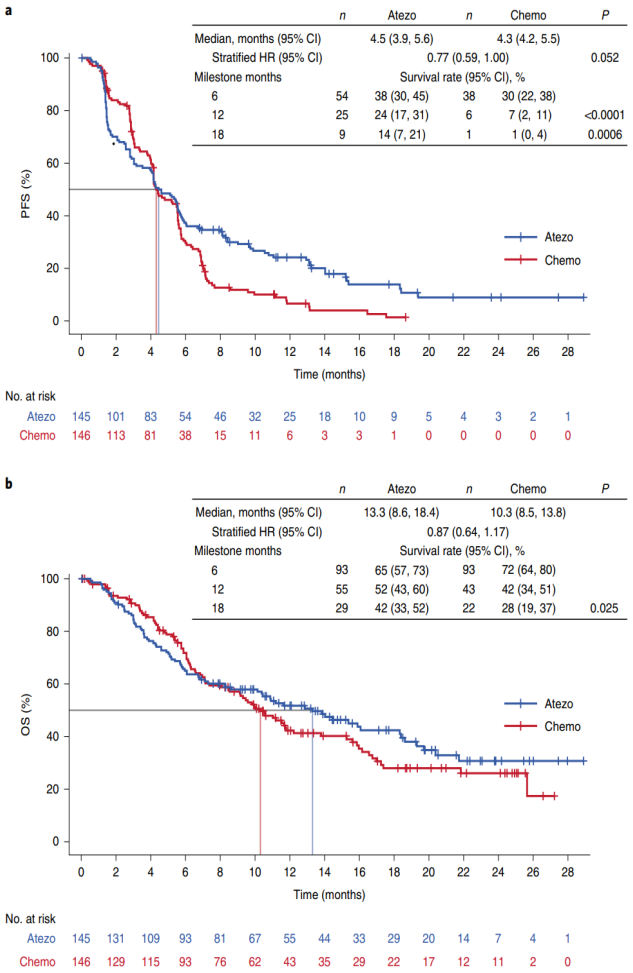
23 Jan 2023

	EGFR n=62	Kras n=65	pvalue
PD-L1 ≥ 50%	11%	17%	0.449
PD-L1 ≥ 5%	16%	31%	0.062
PD-L1 ≥ 50%+CD8TILs	2.1%	12%	0.066
PD-L1 ≥ 5%+CD8TILs	2.1%	20%	0.005

Enrolled on POPLAR trial
KRAS G12D, PD-L1- 1%

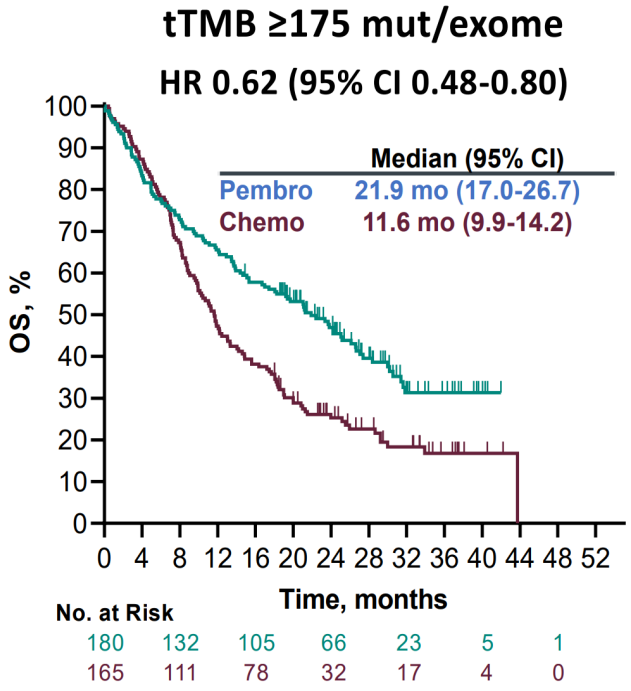
Gainor J, et al Clin Cancer Res 2016

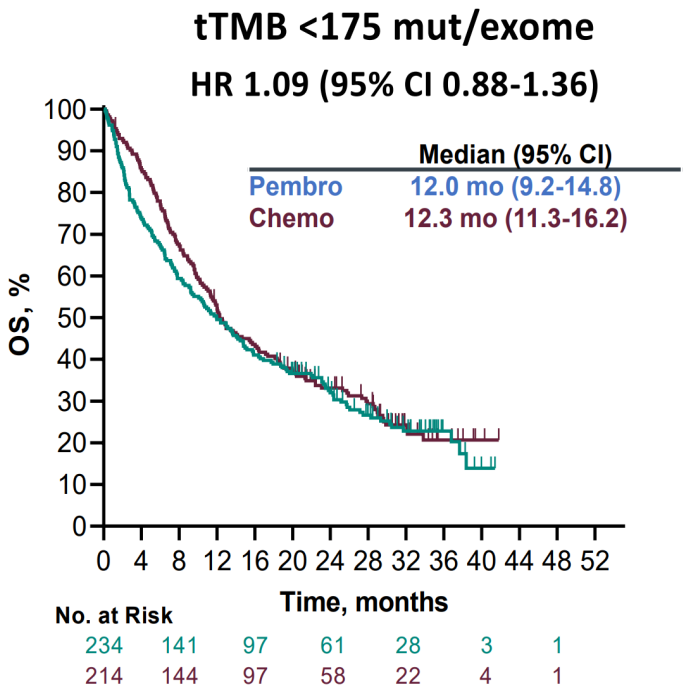
Role of Tumor Mutational Burden in PD-L1 positive NSCLC



Peters S, Nature Medicine 2022

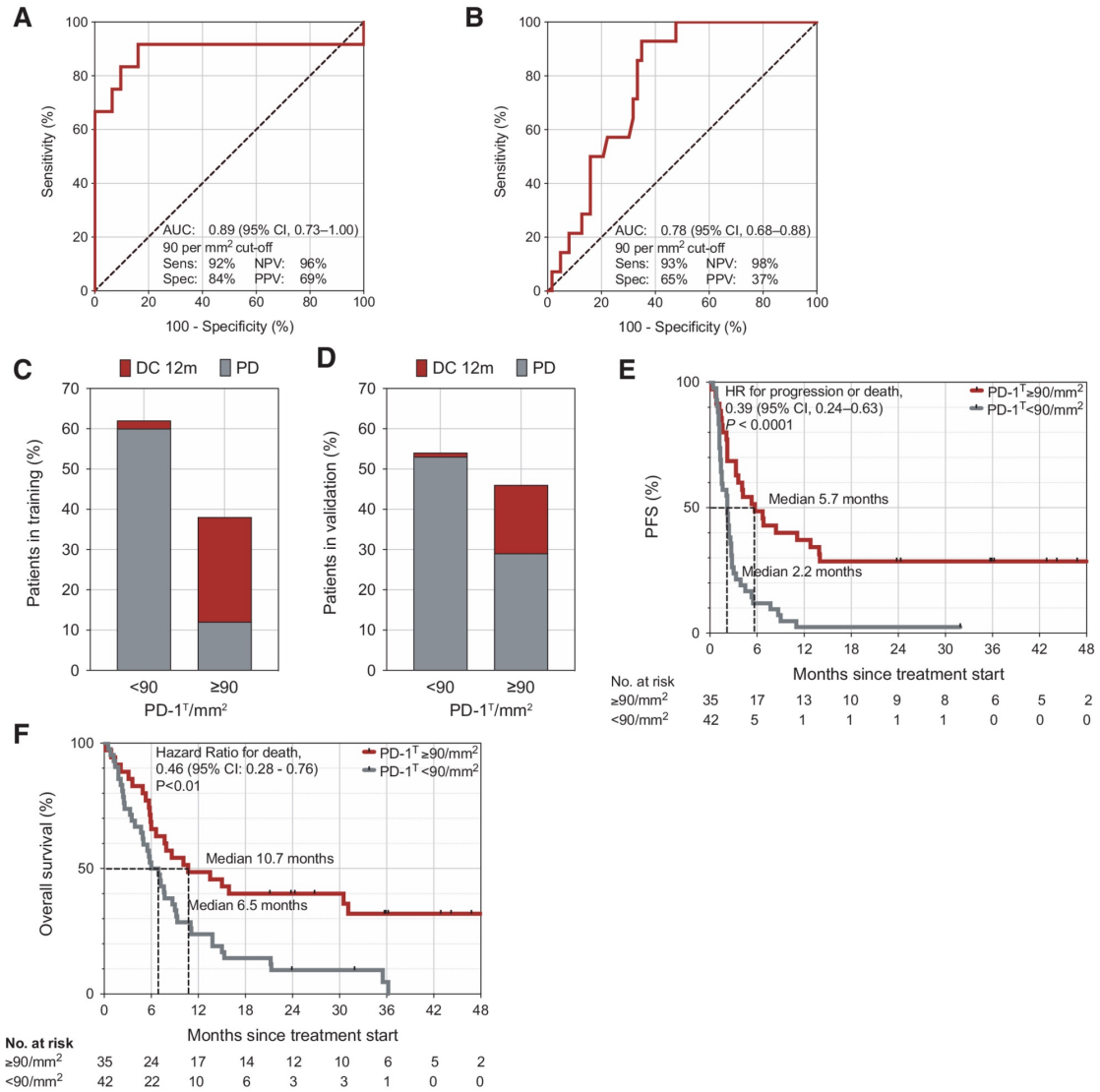
Clinical Utility for OS (KEYNOTE-042): tTMB Cutpoint of 175 mut/exome





Herbst R, ESMO 2019

PD-1^T TILs as a Predictive Biomarker for Benefit to PD-1 Blockade in Advanced NSCLC Patients



Clin Cancer Res. 2022;28(22):4893-4906.
doi:10.1158/1078-0432.CCR-22-0992

Dynamic CtDNA Assessment and outcomes with ICB

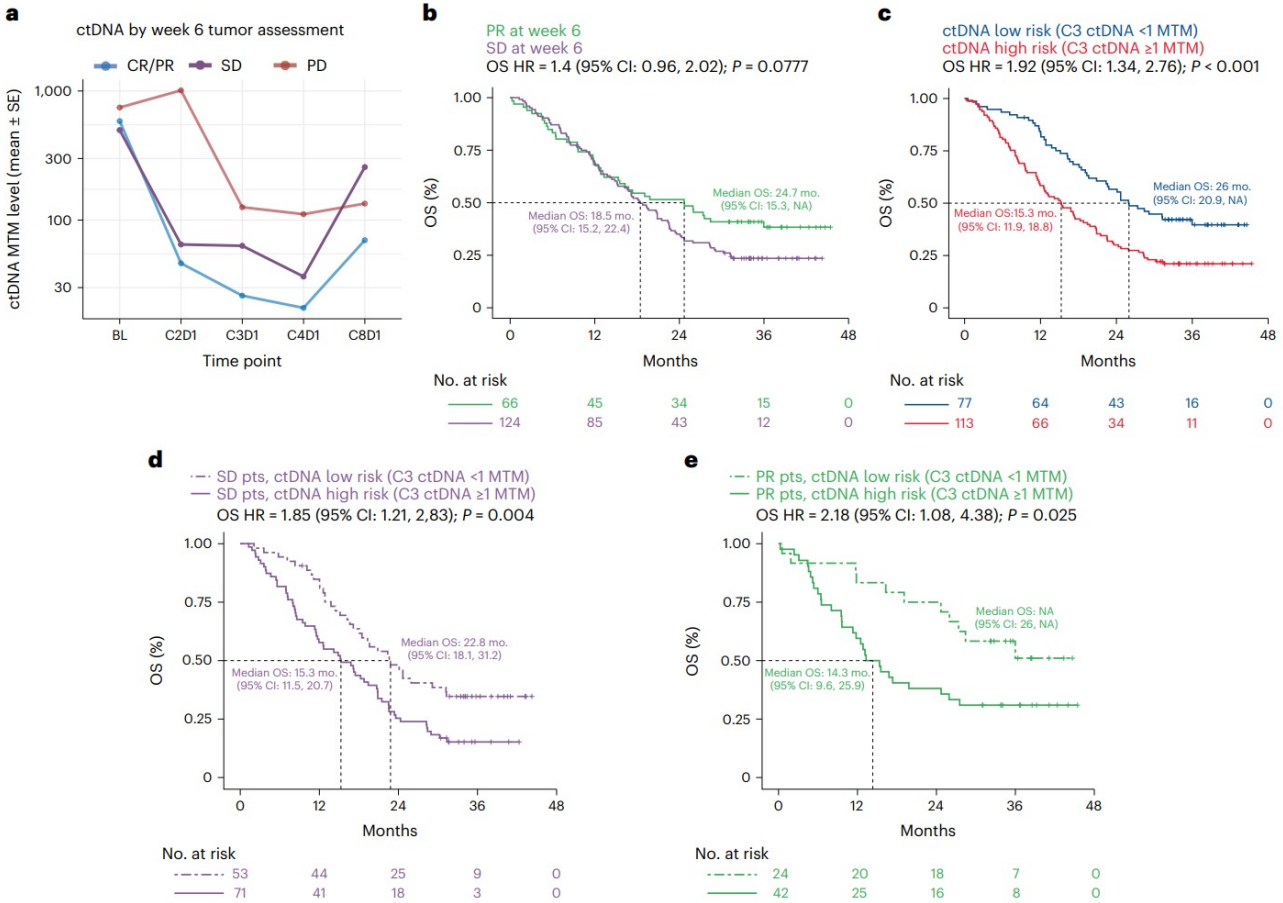


Fig. 2 | On treatment ctDNA dynamics associate with clinical outcomes in the training dataset. a, On-treatment ctDNA levels as measured by MTM (per milliliter plasma) across longitudinal time points for patients with week 6 radiographic assessments of treatment response of PD (red), SD (purple) and CR/PR (blue). **b**, KM curves showing OS for patients with SD (purple) versus PR (green) as determined at the week 6 radiographic assessment of treatment response. A univariable Cox proportional-hazards model was used to estimate HR and log-rank test to report *P* value. **c**, KM curves showing OS for patients with C3D1 ctDNA levels below the LOD of the assay (<1 MTM, ctDNA low risk, blue) versus near or above the LOD (≥1 MTM, ctDNA high risk, red). A univariable Cox proportional-hazards model was used to estimate HR and log-rank test to report *P* value. The exact *P* value for '*P* < 0.001' is 0.00029871. **d**,**e**, KM curves showing OS for patients with SD (**d**) and PR (**e**) at week 6 who are further risk stratified by ctDNA levels at C3D1. A univariable Cox proportional-hazards model was used to estimate HR and log-rank test to report *P* value. MTM, mean tumor molecules.

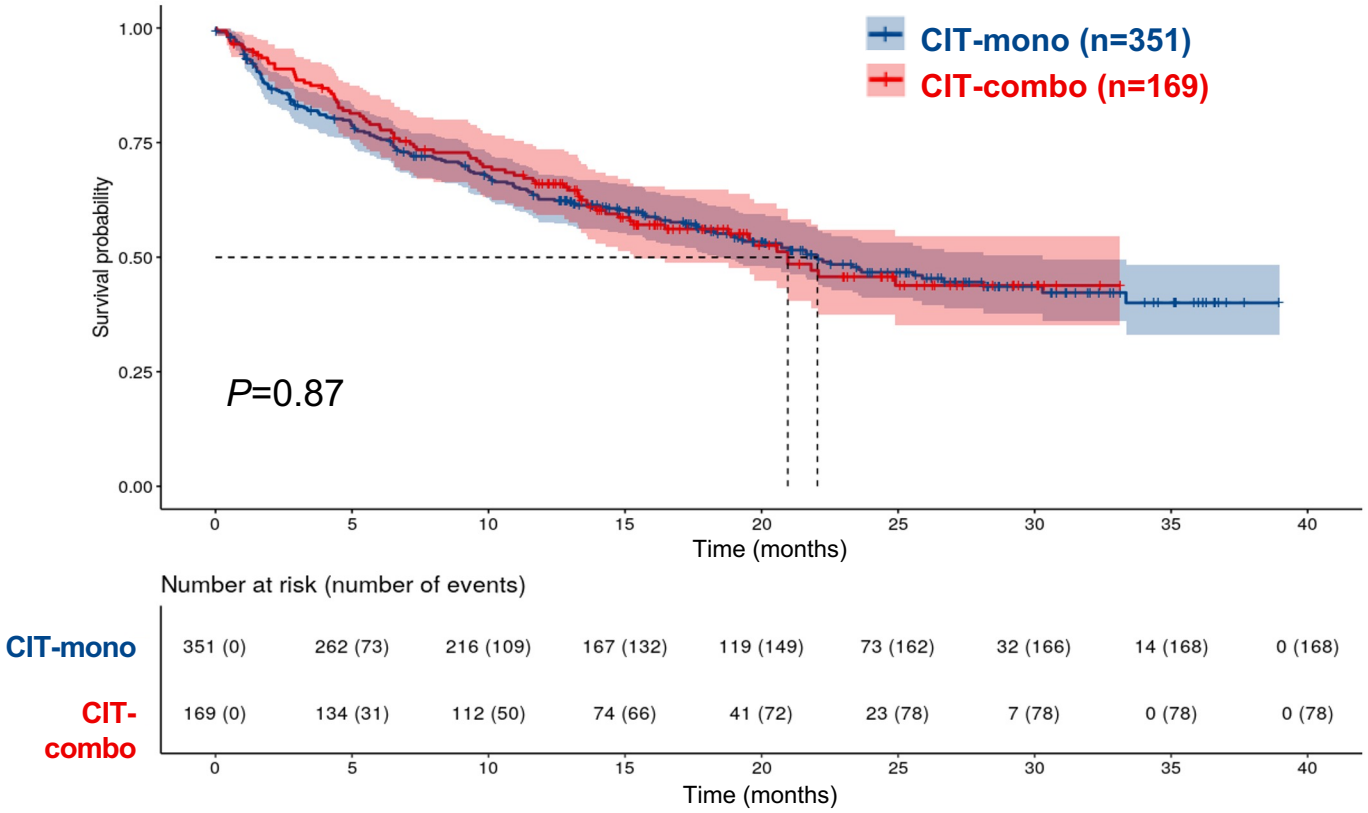
Assaf Z, Nature Medicine 2023

Primary outcome: Overall survival

Unadjusted analysis

	CIT-mono (n=351)	CIT-combo (n=169)
Events, n (%)	168 (49)	78 (46)
OS, mo Median (95% CI)	22.05 (18.33, 30.29)	20.96 (15.31, NA)
Follow-up, mo Median (IQR)	23.46 (15.74, 28.71)	19.92 (14.92, 26.25)

CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	0.98 (0.75, 1.28)	0.868
Adjusted analysis	1.03 (0.77, 1.39)	0.833



Similar results from FDA Analysis

Ongoing Phase III PERSEE Trial

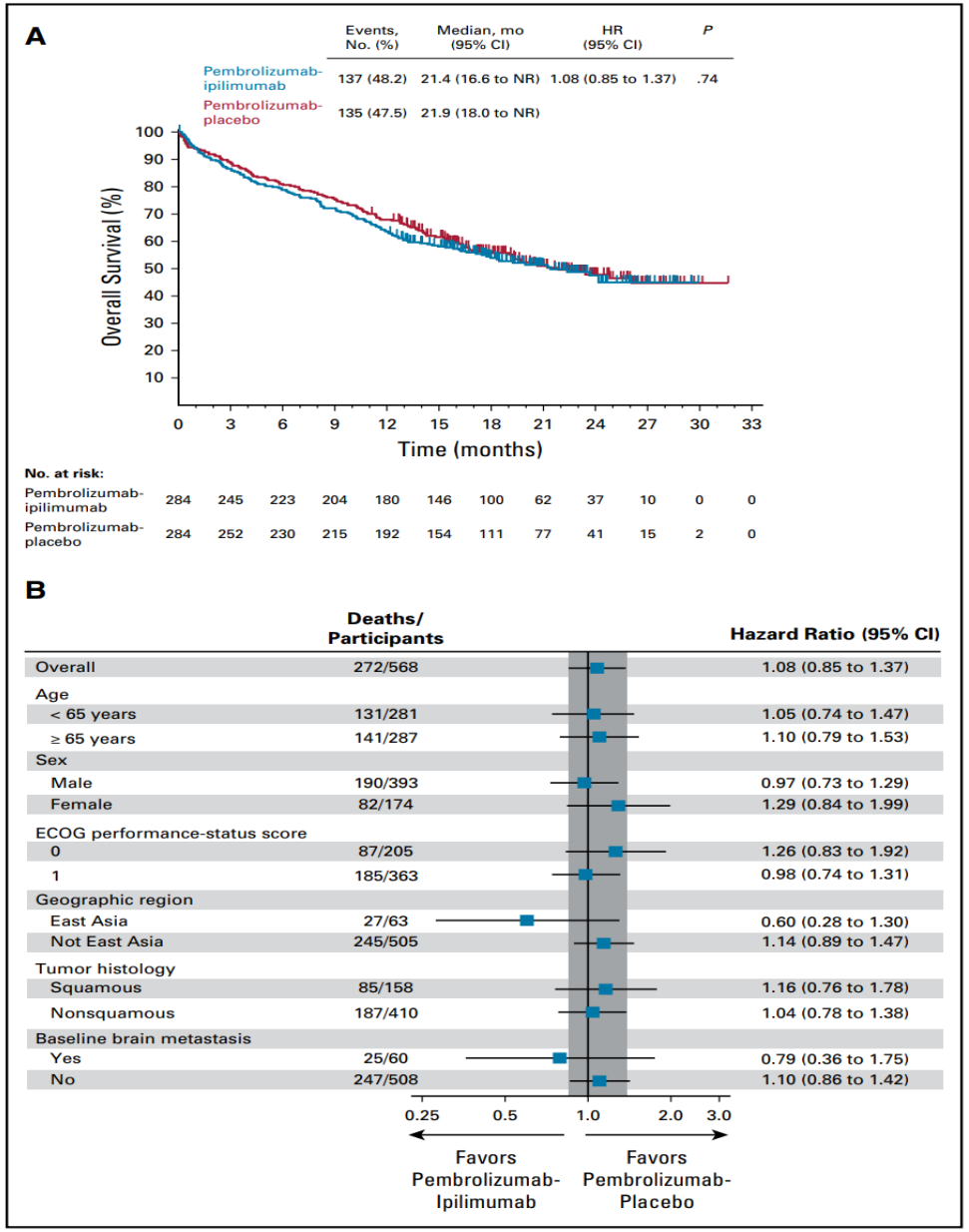
NCT04547504

Akinboro O, ASCO 2022

Peters, S, ESMO 2021

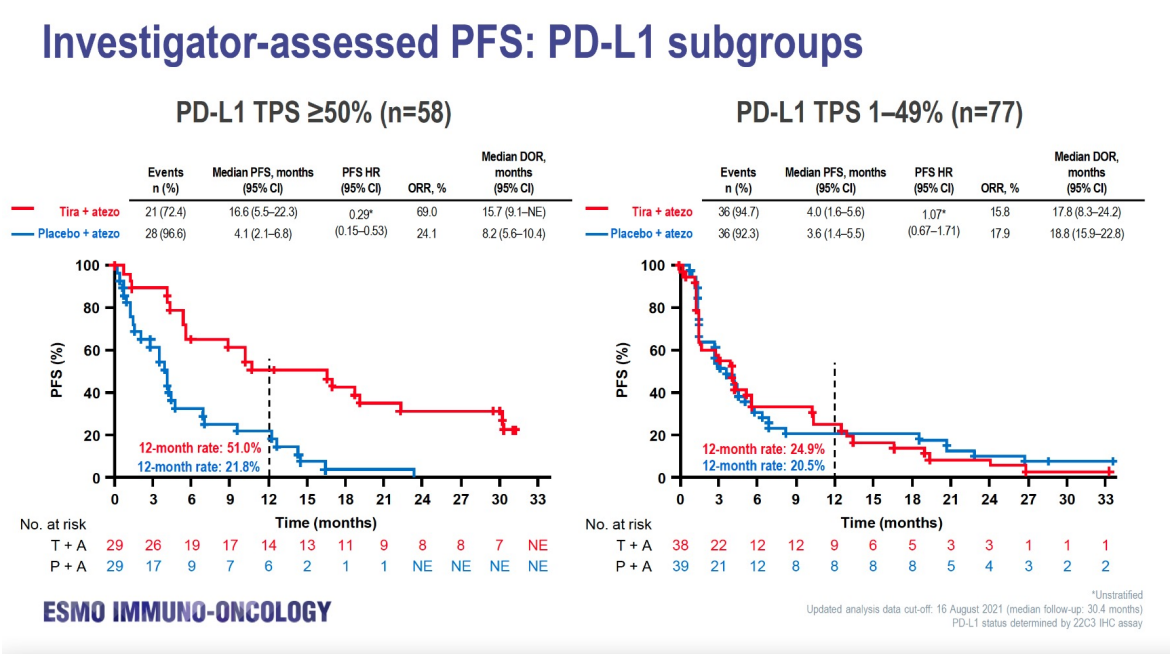
KEYNOTE 598

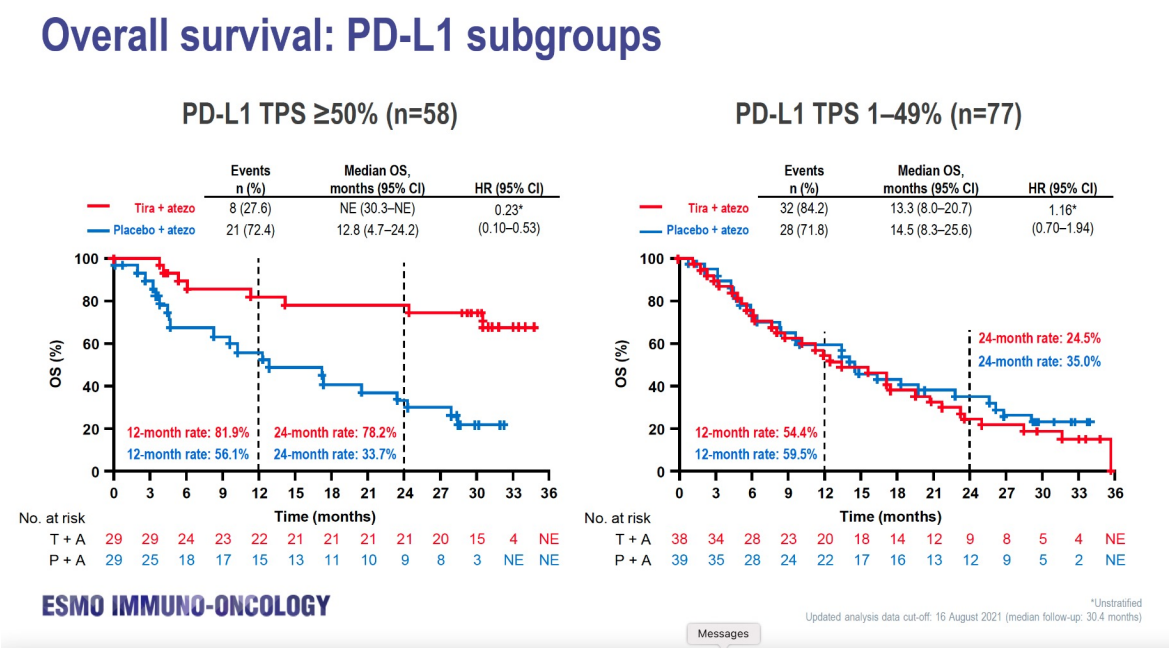
KEYNOTE 598
PDL1 ≥ 50%
Pembrolizumab+Ipilimumab
Vs.
Pembrolizumab



Boyer M, J Clin Oncol 2021

CITYSCAPE- Tiragolumab +Atezolizumab





≥ 50%- 16.1mo vs. 4.1mo, HR- 0.29
1-49%- 4.0mo vs. 3.6mo, HR- 1.07

≥ 50%- NE vs. 12.8mo, HR- 0.23
1-49%- 13.3mo vs. 14.5mo, HR- 1.16

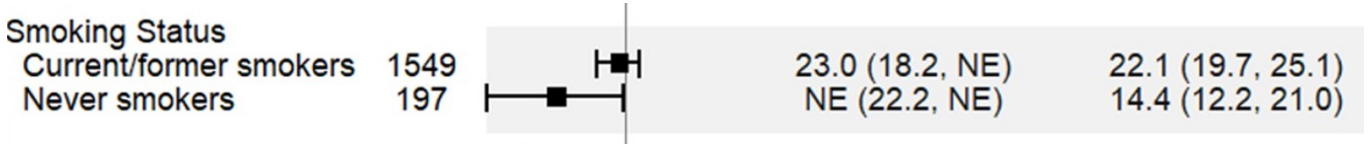
SKYSCRAPER 1- Tiragulomab plus atezolizumab did not demonstrate improved PFS (co-primary endpoint) compared to atezolizumab in PDL1 high NSCLC patients, at first interim analysis
May 11th 2022, Press Release

Cho B, Lancet 2022

Other Factors

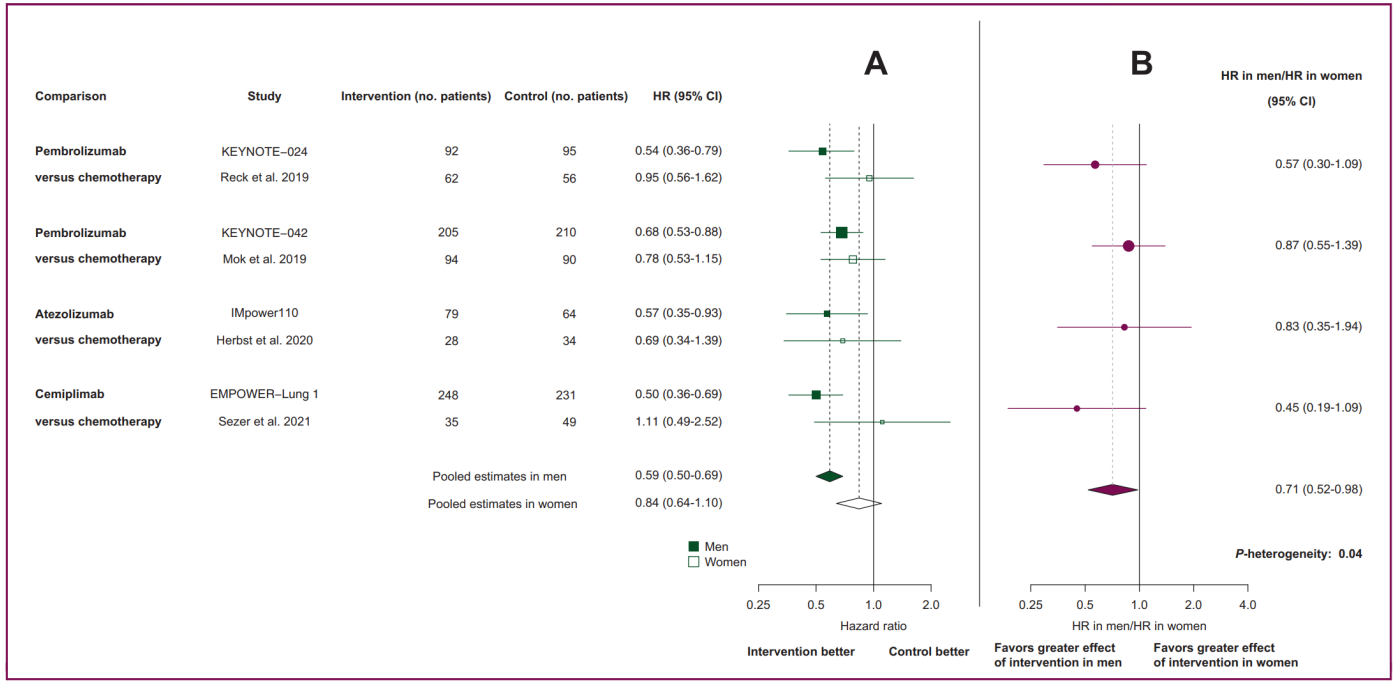
1. Smoking Status[1]

No survival advantage in never smokers



2. Sex-Based Difference[2]

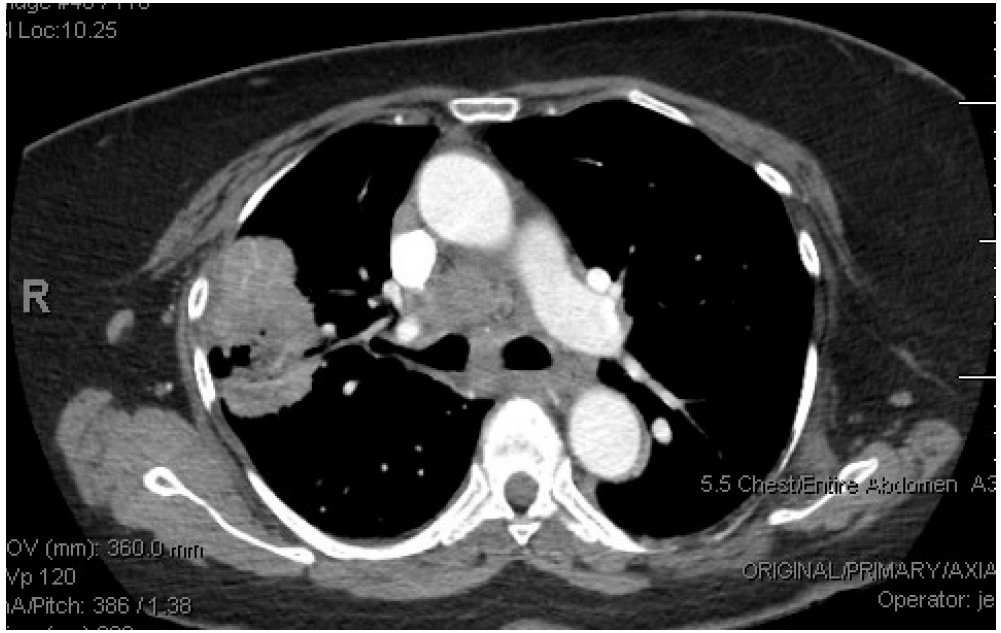
Female patients have worse outcome than Men



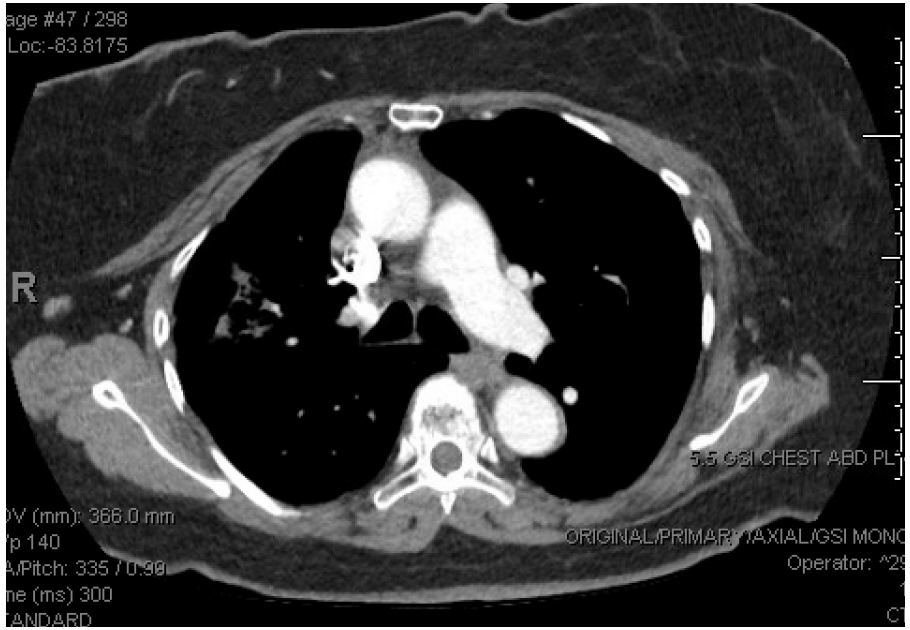
1. Akinboro O, ASCO 2022; 2. Conforti F, et al ESMO Open 2021

Case- 66 year old female patient with CNS Metastasis

NGS- ARID1A, CDKN2A, TP53, NF1; PD-L1- 100%



August 2021



January 2022

When is PD(L)-1 Enough?

In March 2023

1. Definite- Advanced NSCLC patients with high tumor PD-L1 and not very high tumor burden
2. Definite- Unresectable stage III NSCLC patients following chemotherapy and radiation
3. Definite- Early-stage NSCLC patients with tumor PD-L1 ≥ 50% following surgery and adjuvant chemotherapy
4. Maybe- Advanced NSCLC patients with tumor PD-L1 ≥ 1% and high TMB
5. Maybe- Early-stage NSCLC patients with tumor PD-L1 ≤ 50% following surgery and adjuvant chemotherapy.

Cho B, Lancet 2022