



# PD(L)1 MONOTHERAPY FOR NSCLC: DATA + HOW I USE IT

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Date April 19<sup>th</sup> 2024

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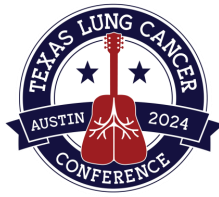
# Objectives

Data

Biomarkers

Building on Data

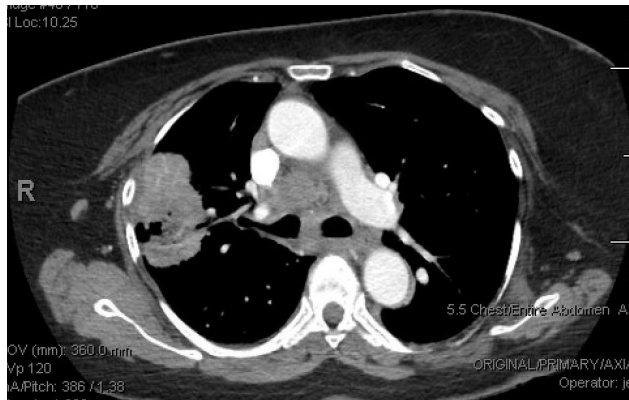
How I use it



# Cases-



66 year old with CNS Metastasis



August 2021

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

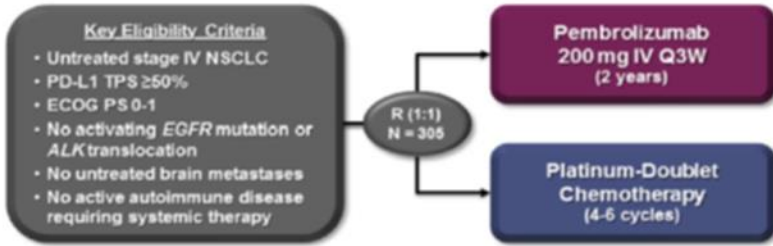
69 year old with multiple bone mets, 4 months post surgery for stage IB cancer



November 2023

NGS- Kras G13C, STK11, CDKN2A  
PD-L1- 70%

# KEYNOTE 24- 5 year survival - 31.9%



### Key End Points

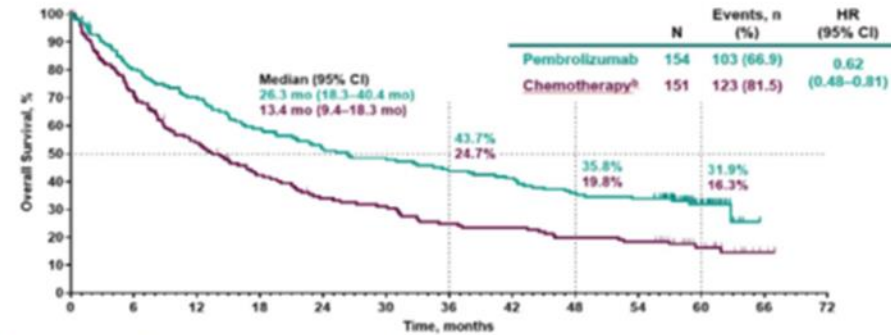
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

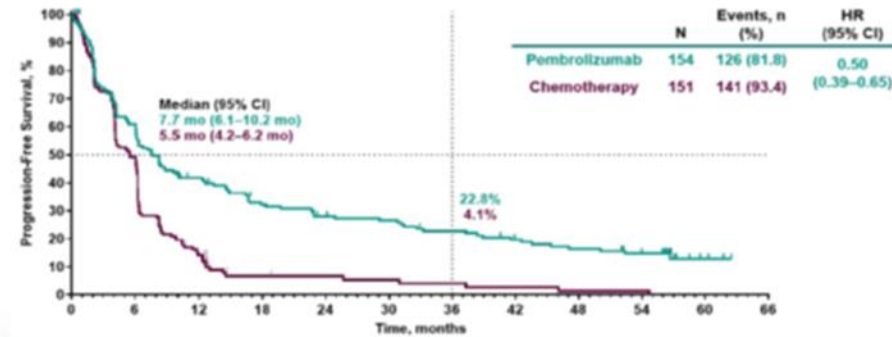
Exploratory: DOR

	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

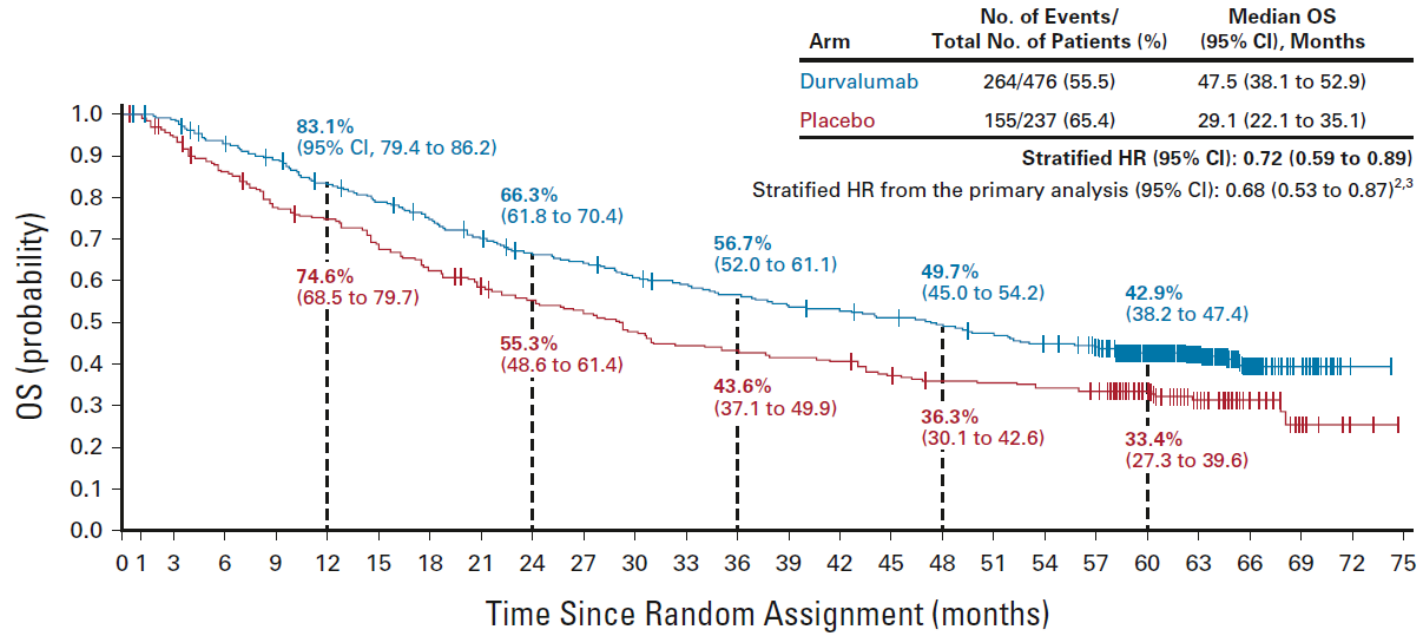
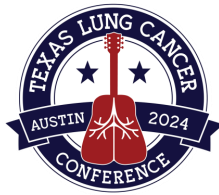


Trial	Treatment	PD-L1	ORR (%)	Median PFS	Median OS
KEYNOTE-024 <sup>[a]</sup>	Pembrolizumab (n = 154)	≥ 50%	46.1	7.7 mo	26.3 mo
KEYNOTE-042 <sup>[b]</sup>	Pembrolizumab (n = 299)	≥ 50%	39	6.5 mo	20.0 mo
IMpower110 <sup>[c]</sup>	Atezolizumab (n = 107)	TC3; IC3	40.2	8.2 mo	20.2 mo
EMPOWER-Lung 1 <sup>[d]</sup>	Cemiplimab (n = 284)	≥ 50%	42.3	8.1 mo	26.1 mo

References a. Reck JCO 2021; b. De Castro JCO 2002; c. Jassem JTO 2021; Ozguroglu Lancet Oncol 2023

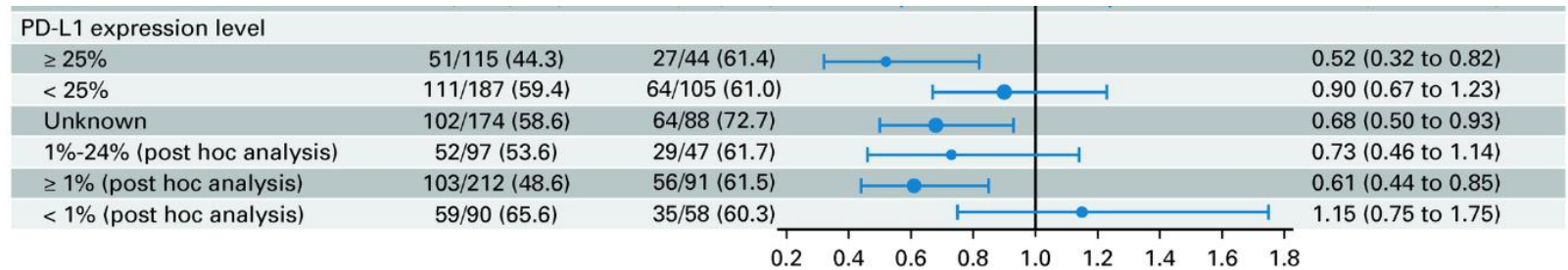


# PACIFIC- Survival



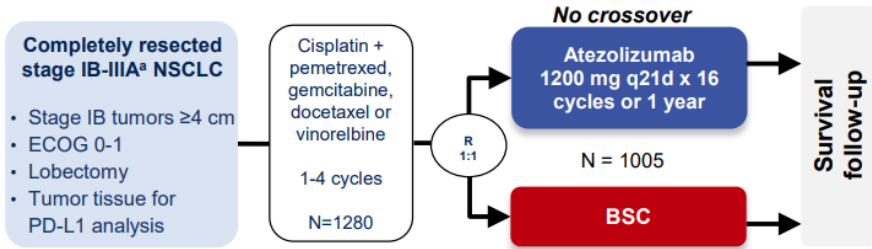
No. at risk:

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



## 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  $\geq 50\%$  | 3-yr and 5-year DFS

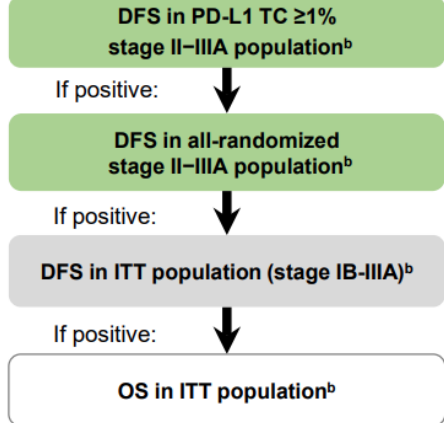
## Key exploratory endpoints

- 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.

<sup>a</sup> Per UICC/AJCC staging system, 7th edition. <sup>b</sup> Two-sided  $\alpha=0.05$ .

## Hierarchical statistical testing of endpoints



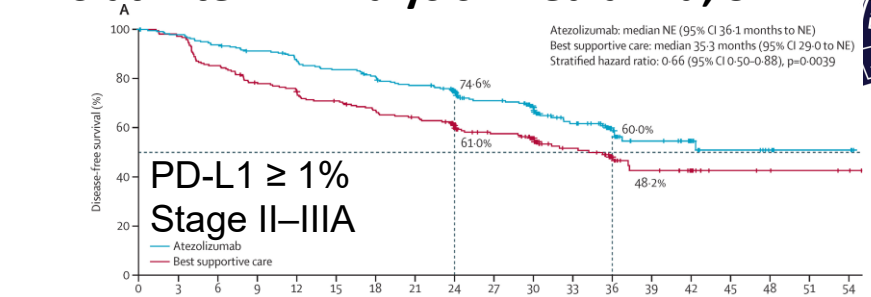
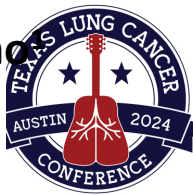
- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and follow up is ongoing
- Endpoint was not formally tested

## WCLC 2022 - Update at median fu of 45.3 mo<sup>2</sup>:

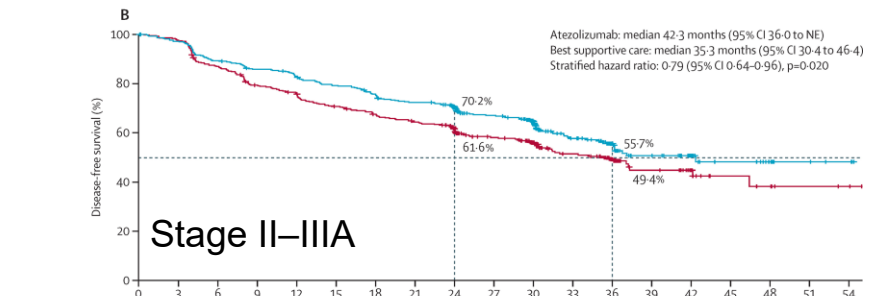
- First prespecified IA of OS - immature
  - PD-L1  $\geq 1\%$ , Stage II-IIIa: HR, 0.71 (95% CI, 0.49-1.03)
  - PD-L1  $\geq 50\%$ : HR, 0.42 (95% CI, 0.23-0.78)
- Now new or unexpected safety signals
- Final DFS analysis not conducted (required number of DFS events not reached)

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

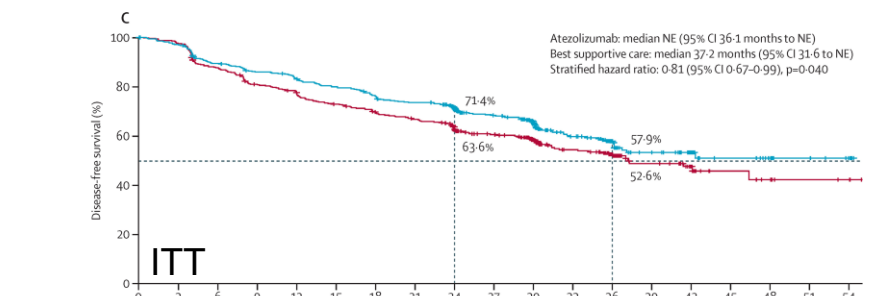
## DFS at Interim Analysis: Median fu, 32.2 mo



Number at risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
Best supportive care	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3
	(0)	(8)	(8)	(10)	(11)	(11)	(12)	(13)	(29)	(47)	(65)	(91)	(111)	(130)	(139)	(148)	(152)	(157)	(157)
	(0)	(10)	(10)	(12)	(13)	(14)	(15)	(16)	(27)	(41)	(55)	(71)	(88)	(102)	(109)	(116)	(117)	(119)	(120)

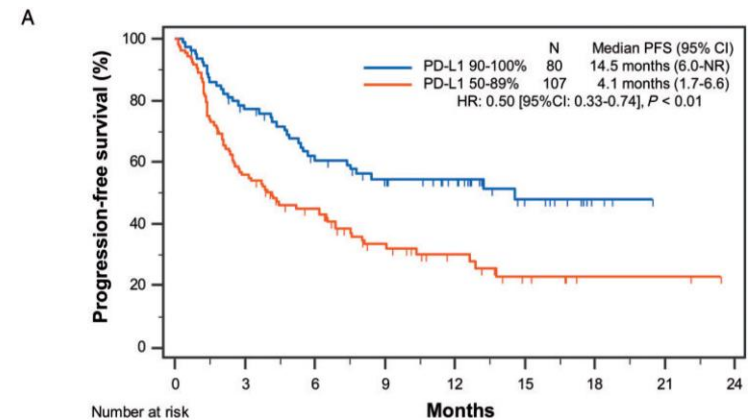
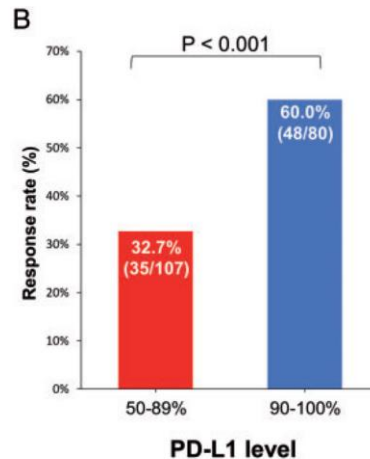
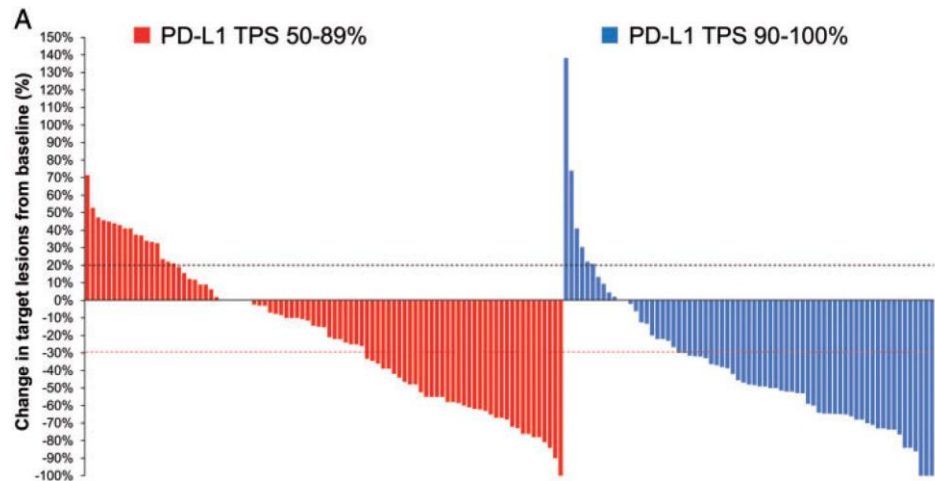


Number at risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
Best supportive care	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3
	(0)	(12)	(12)	(14)	(15)	(16)	(17)	(19)	(46)	(79)	(111)	(160)	(192)	(222)	(236)	(253)	(258)	(264)	(266)
	(0)	(17)	(19)	(22)	(24)	(25)	(27)	(28)	(50)	(86)	(116)	(150)	(177)	(209)	(222)	(233)	(234)	(238)	(239)



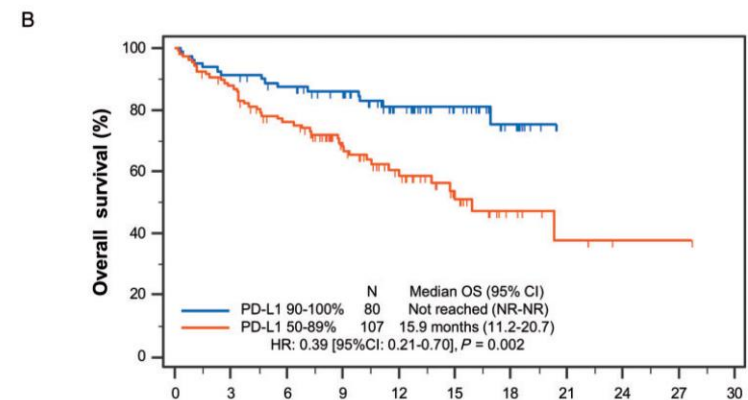
Number at risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
Best supportive care	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4
	(0)	(15)	(18)	(20)	(21)	(22)	(23)	(25)	(62)	(99)	(135)	(192)	(230)	(268)	(283)	(301)	(306)	(312)	(316)
	(0)	(19)	(21)	(24)	(26)	(27)	(30)	(31)	(57)	(95)	(134)	(175)	(203)	(243)	(258)	(274)	(276)	(281)	(282)

# PD-L1 Expression a Continuous Variable



Number at risk

	0	3	6	9	12	15	18	21	24
PD-L1 90-100%	80	58	44	34	27	12	3	0	0
PD-L1 50-89%	107	59	42	25	13	6	2	2	0



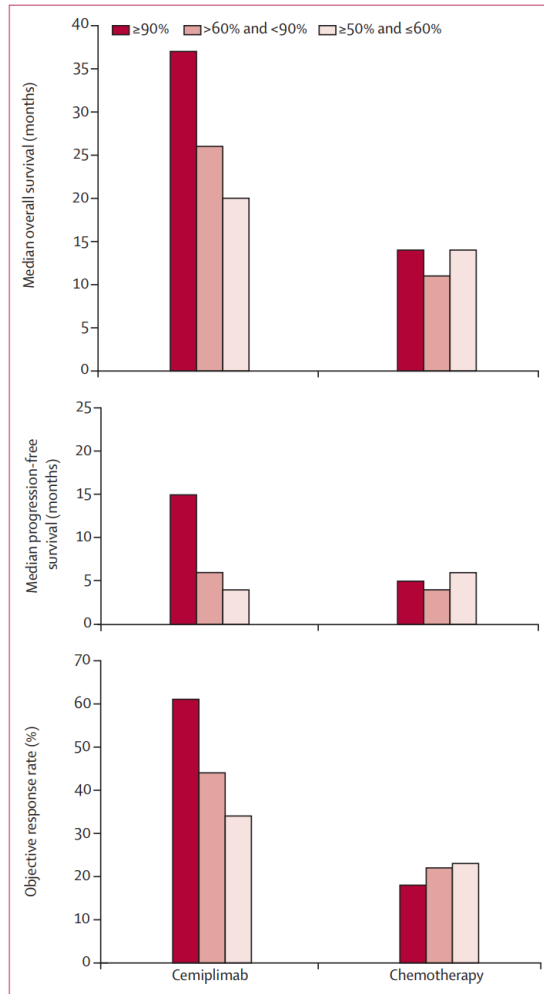
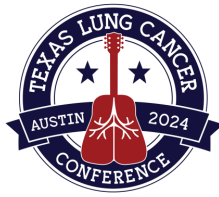
Number at risk

	0	3	6	9	12	15	18	21	24	27	30
PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

Aguilar EJ, Ann Oncol 2019



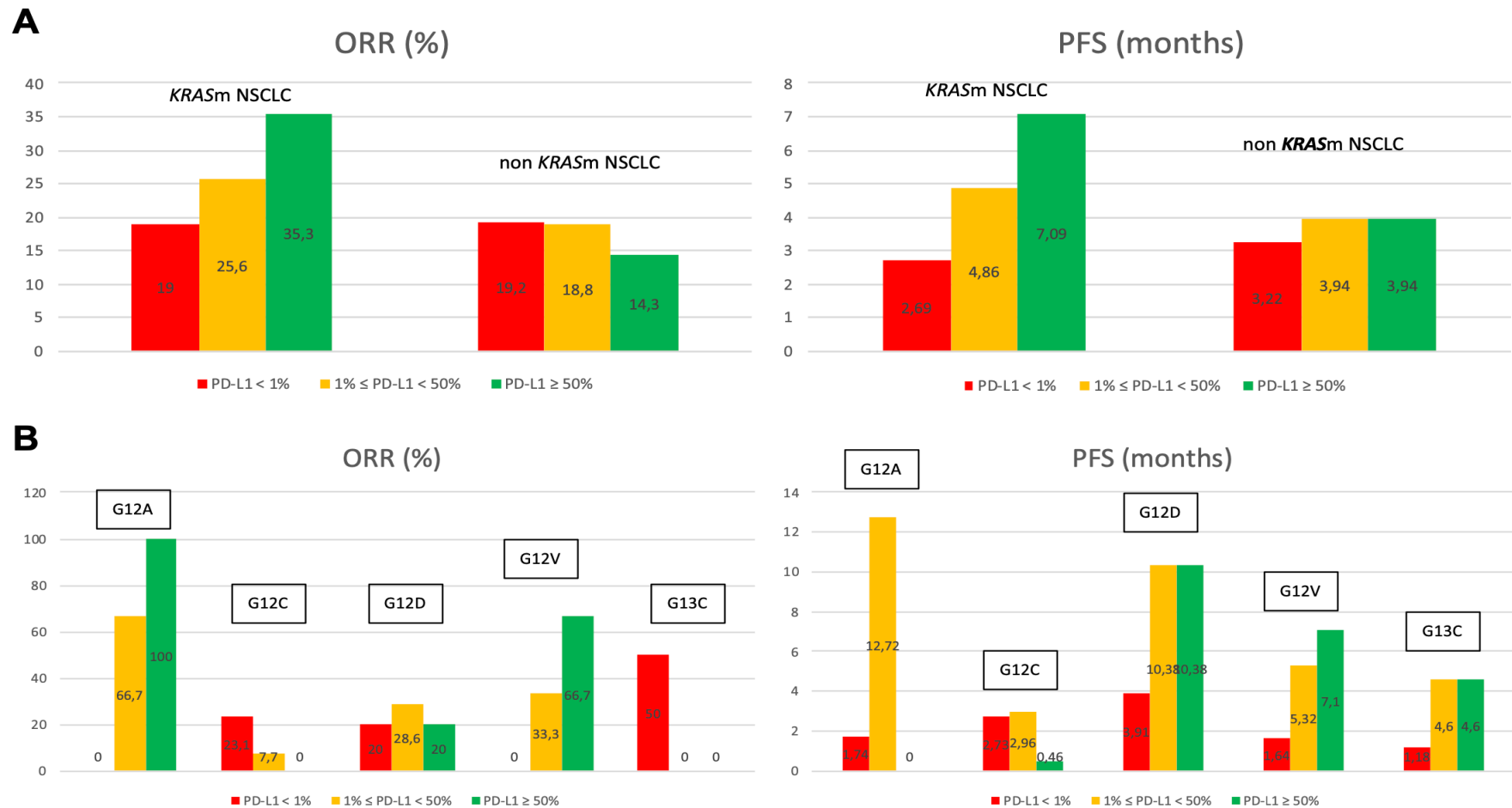
# EMPOWER-1: PD-L1 TPS Score and Efficacy



Overall survival, Progression free survival and Response rate was SUPERIOR with Cemiplimab in patients with TPS  $\geq 90\%$

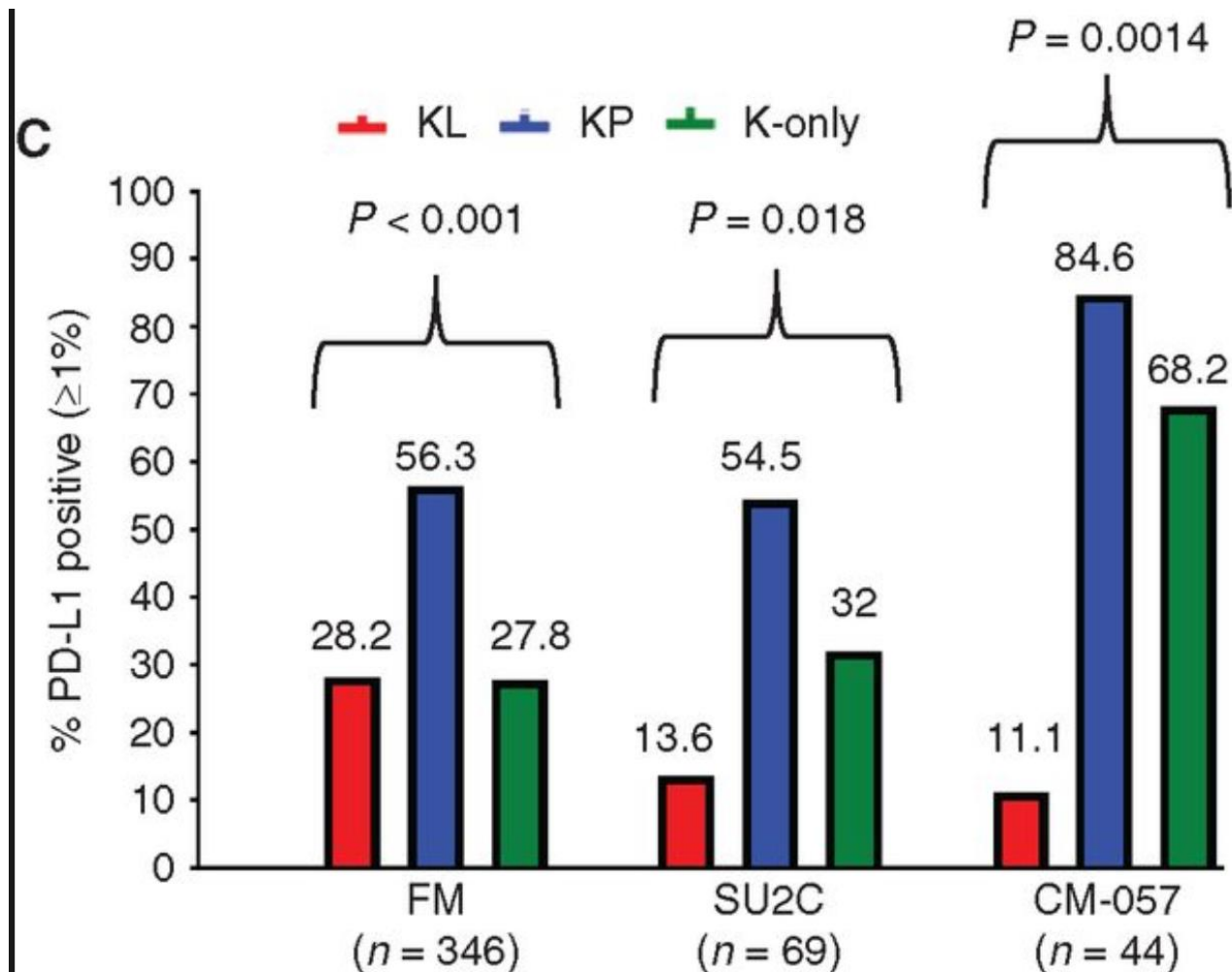
Ozgulgo M, et al Lancet Oncology 2023

# Impact of KRAS mutation on IO efficacy



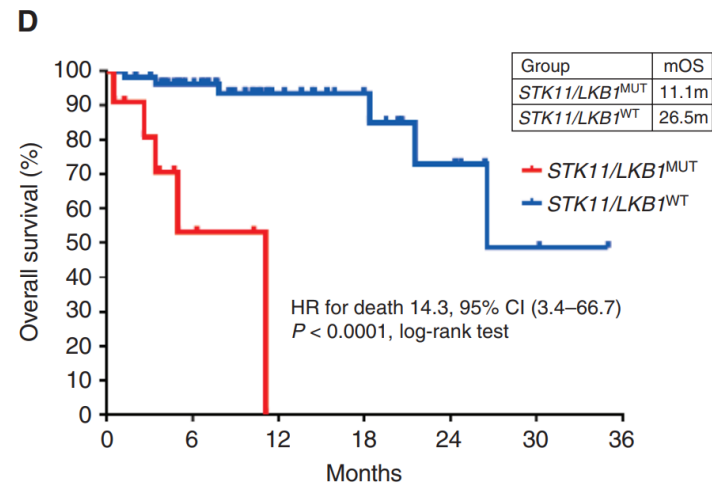
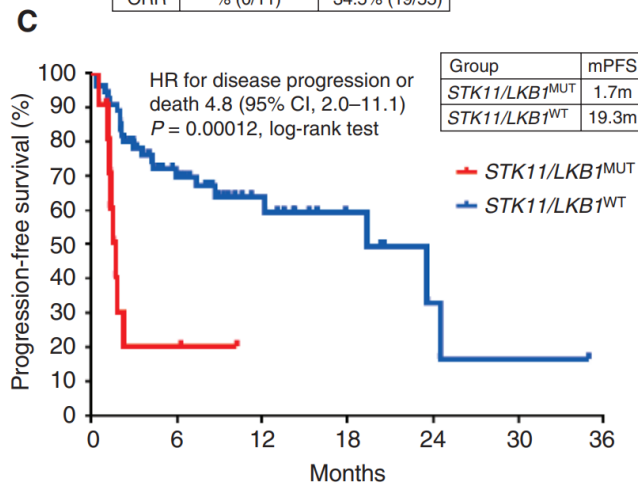
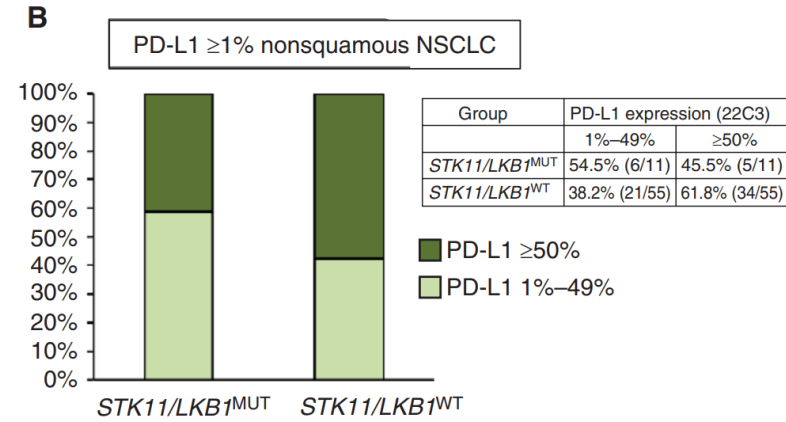
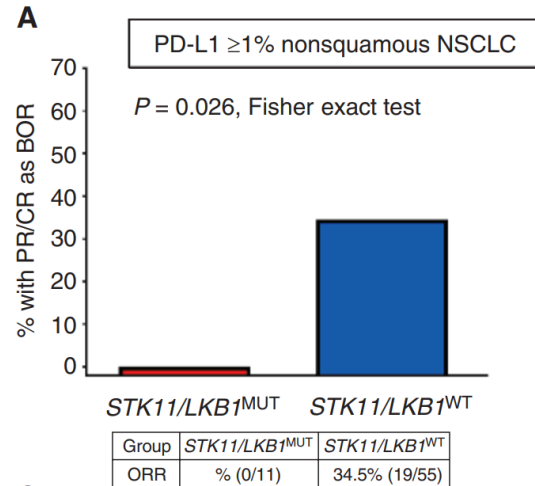
Jeanson A et al, J Thorac Oncol, 2019.

# Impact of STK11 mutation on IO efficacy



Skoulidis F et al, Cancer Discovery, 2019.

# STK11 and PD-L1 TPS $\geq 1\%$

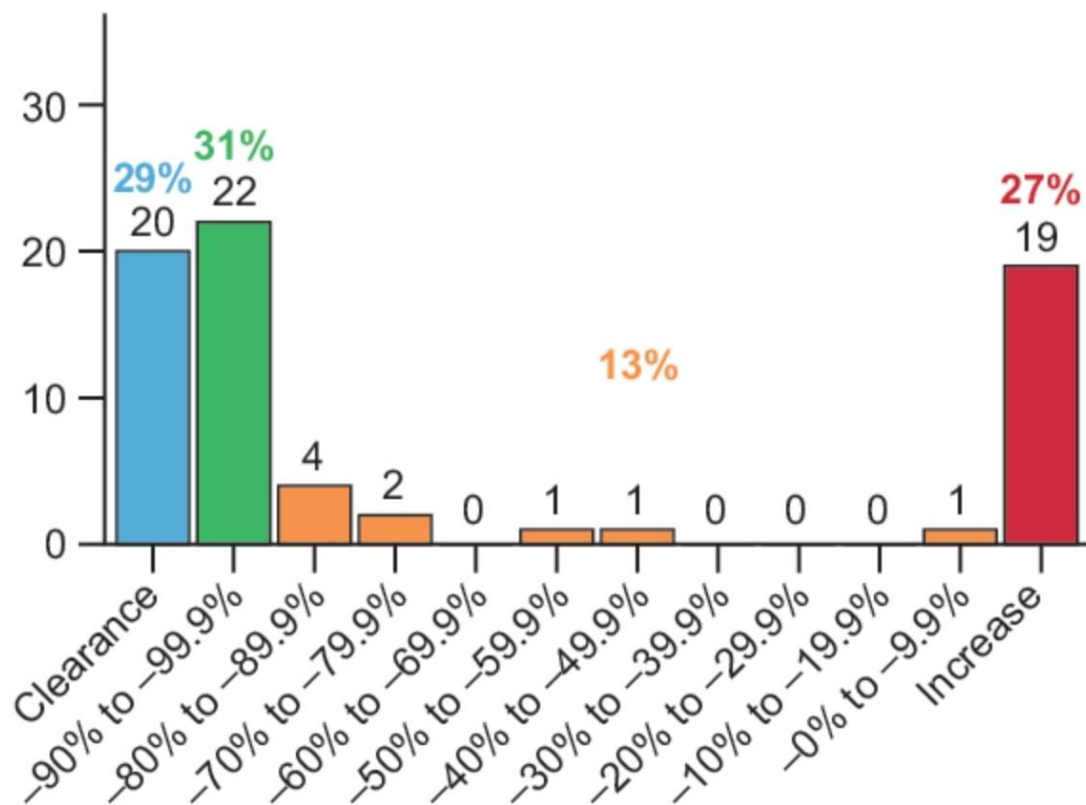


Skoulidis, Cancer Discovery 2018

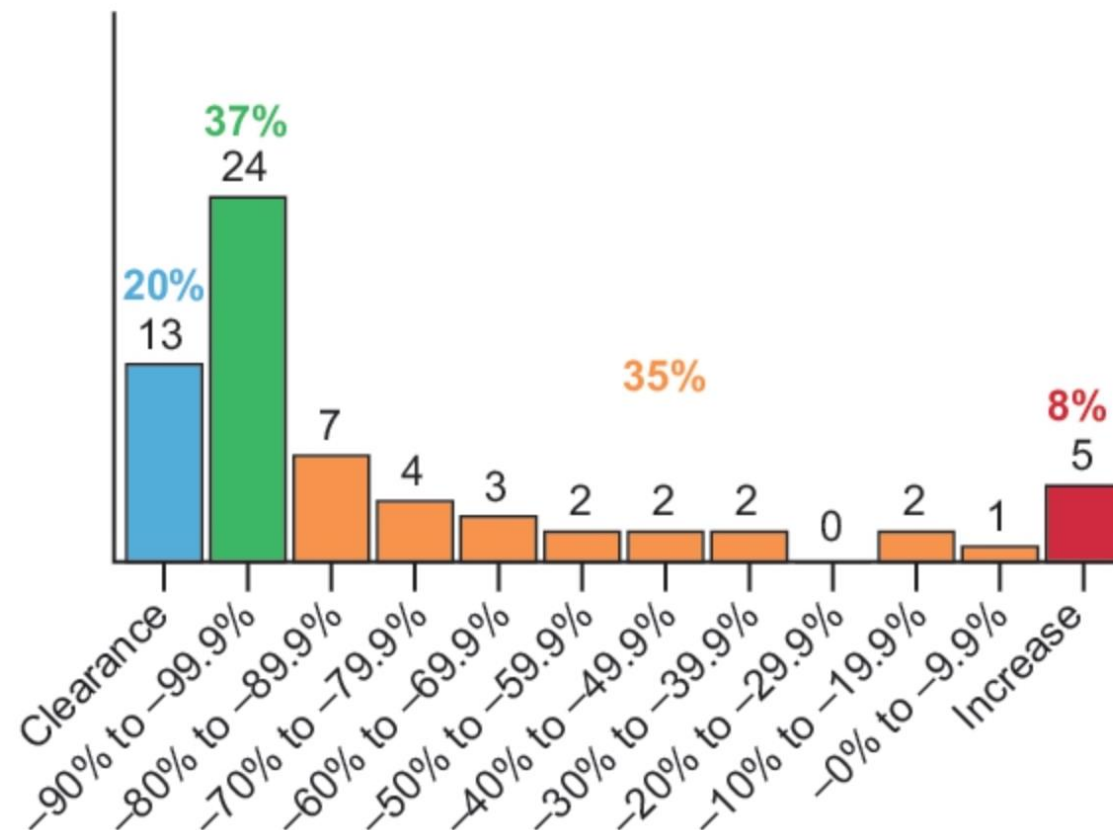
# CT-DNA clearance data in Empower-01 study



**Cemiplimab n=67  
Week 9**



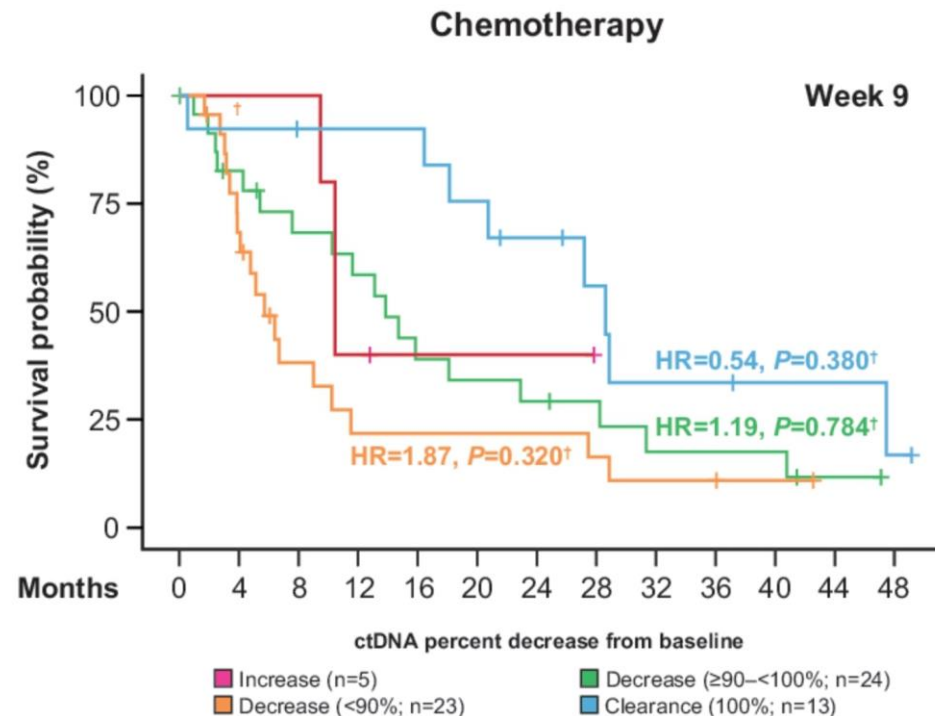
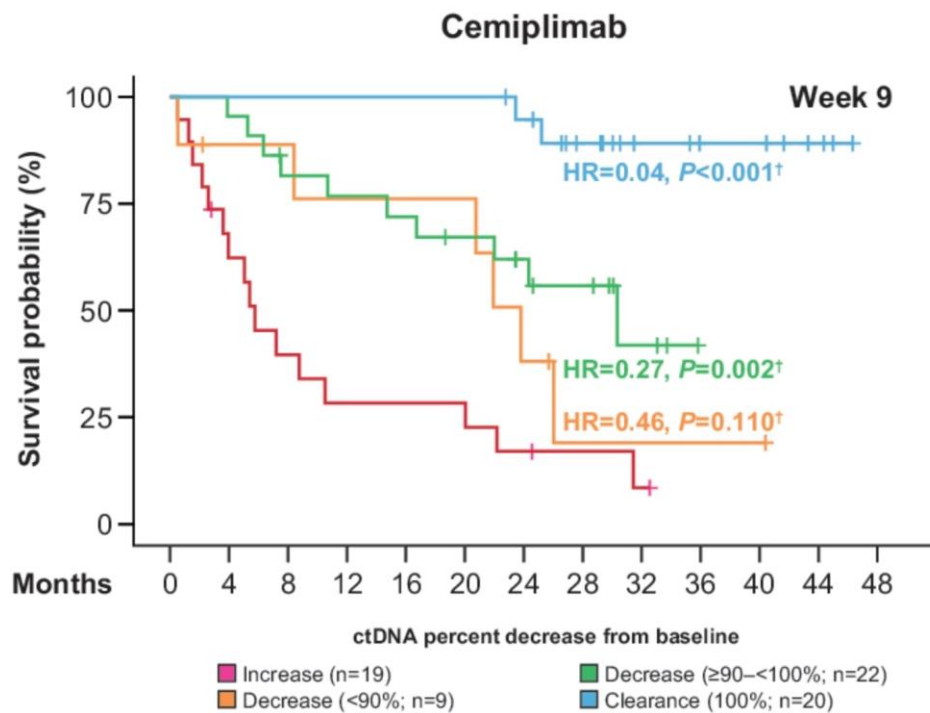
**Chemotherapy n=65  
Week 9**



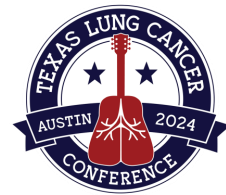
Vokes N et al, ASCO 2023.



# Empower 01: correlation between ct-DNA clearance and overall survival



Vokes N et al, ASCO 2023.

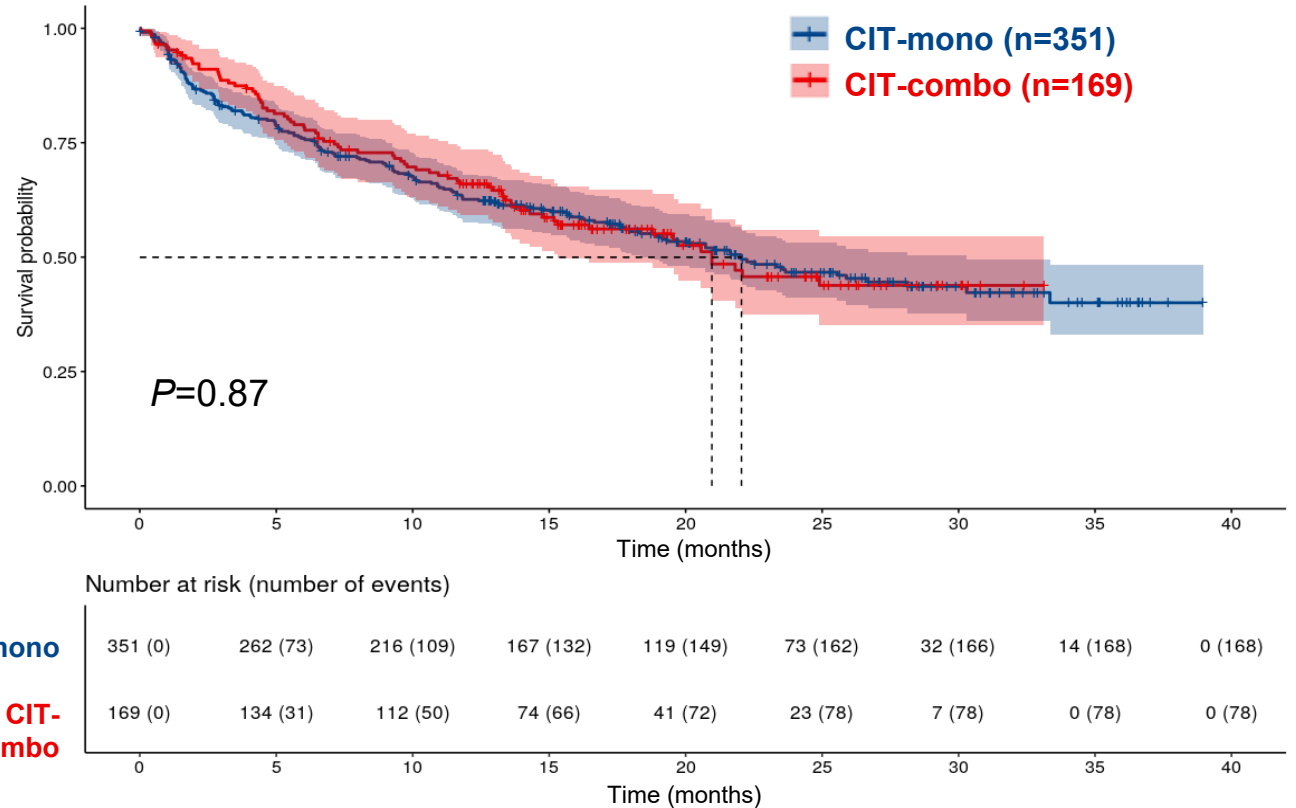


# FLATIRON Data: Overall survival in PDL1≥50%

## Unadjusted analysis

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

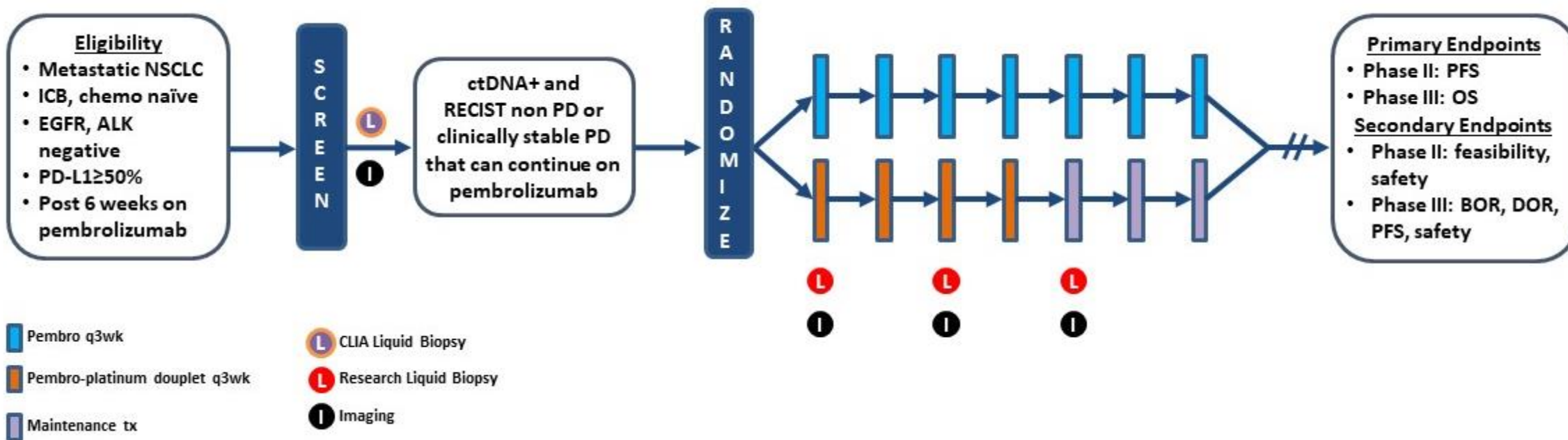
Akinboro O, ASCO 2022

## Ongoing Phase III PERSEE Trial

NCT04547504

Peters, S, ESMO 2021

# BR.36 stage 2-A Biomarker-Directed, Open Label, Multi-Center Phase II/III Study of Molecular Response Adaptive Immuno-Chemotherapy in Patients with NSCLC



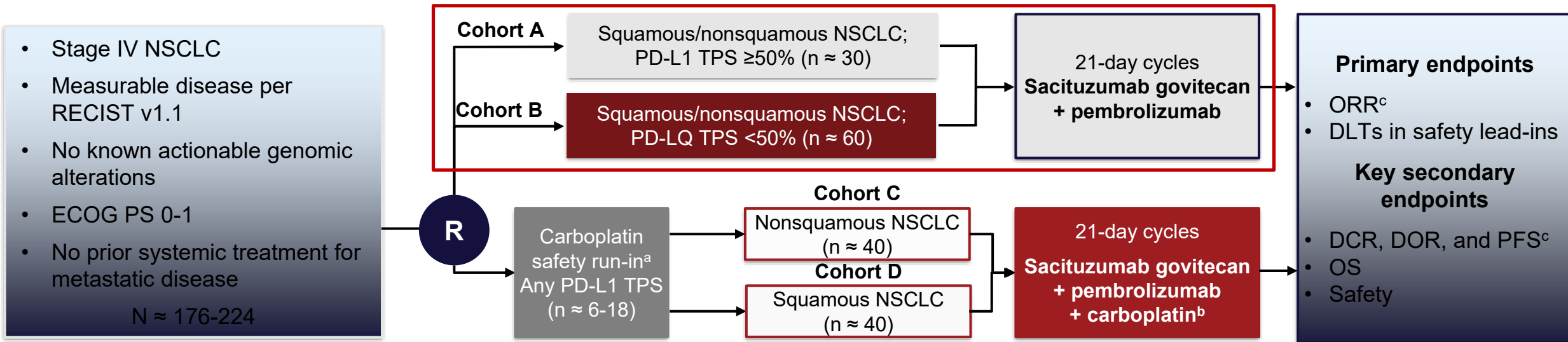
Slide courtesy from Dr. Valsamo Anagnostou

NCT04093167, Anagnostou et al., Nat Med, 2023

# EVOKE-02: Study Design



## An Open-Label, Multicohort, Phase 2 Study

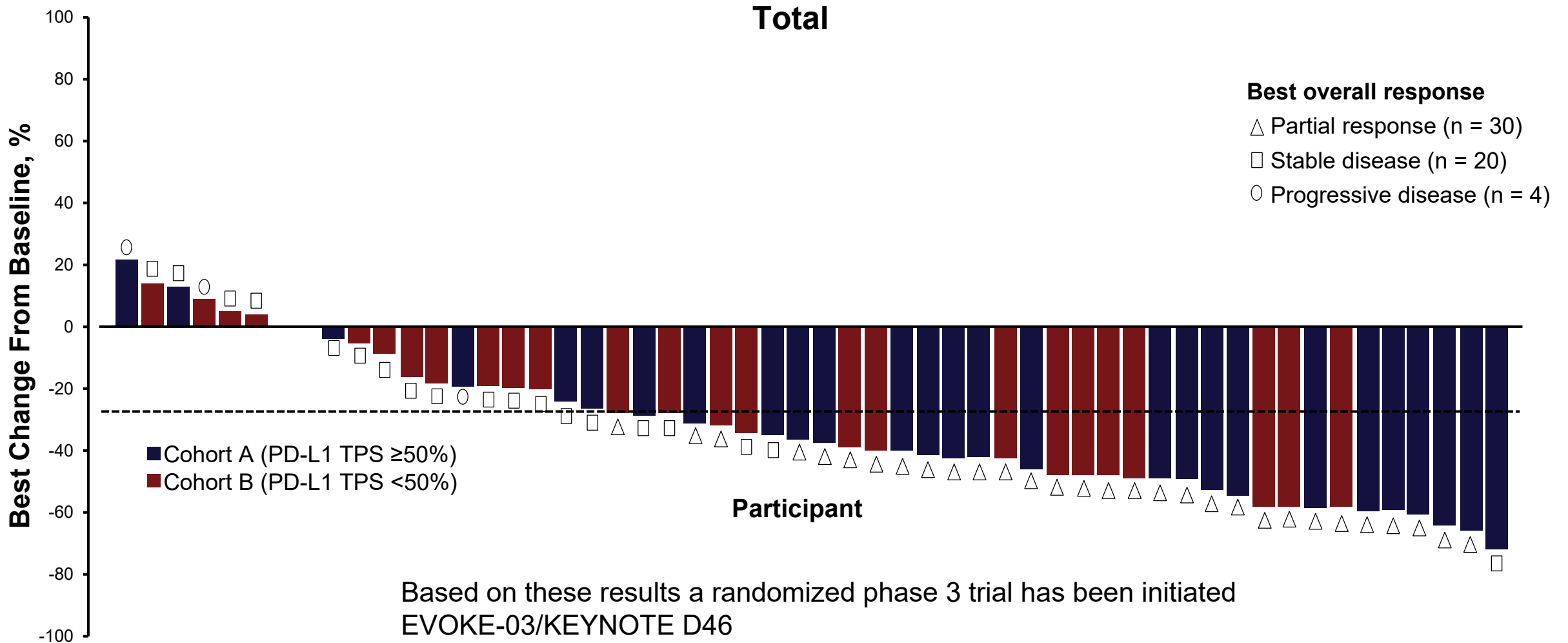


- **At data cutoff (June 16, 2023), median (range) follow-up for cohorts A and B was 5.0 mo (95% CI, 1.7-12.0) and 5.8 mo (95% CI, 1.0-12.2), respectively**
- **The preliminary efficacy data reported in this presentation are results by investigator assessment**

<sup>a</sup> Dose de-escalation safety run-in period to determine the RP2D of SG for cohorts C and D. <sup>b</sup> Carboplatin dosed as area under the concentration versus time curve 5. <sup>c</sup> Per RECIST v1.1.

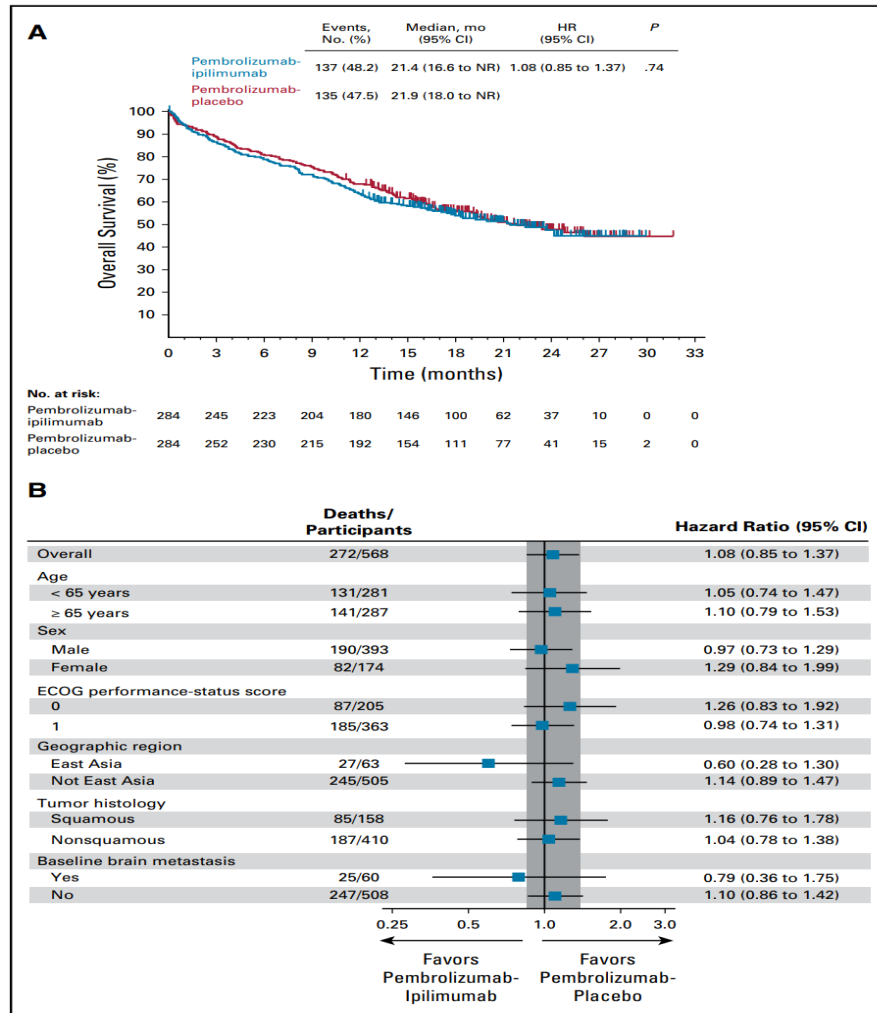
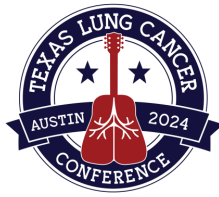
1. Cho BC et al. WCLC 2023. Abstract OA05.04.

# EVOKE-02: Change in Target Lesions





# KEYNOTE 598



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

Boyer M, J Clin Oncol 2021

# CITYSCAPE- Tiragolumab+Atezolizumab



## Investigator-assessed PFS: PD-L1 subgroups

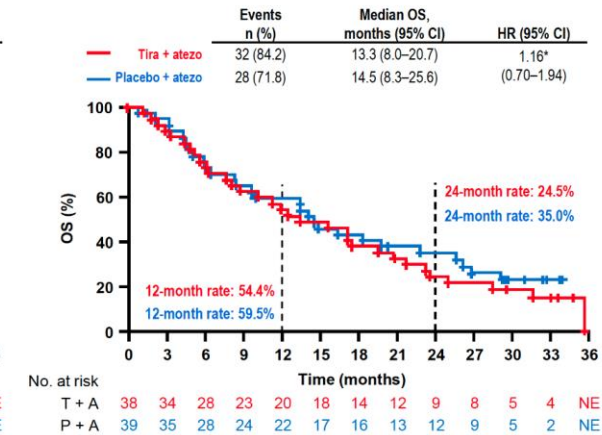
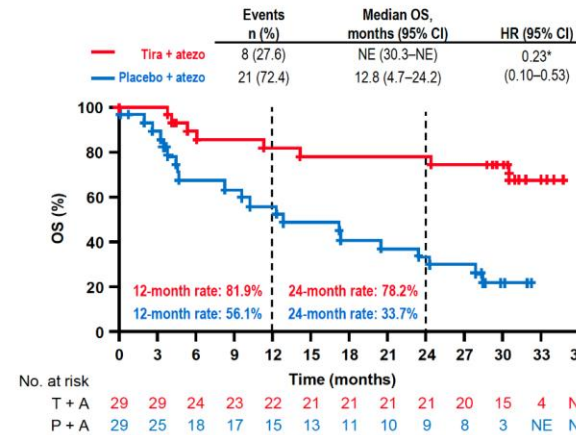
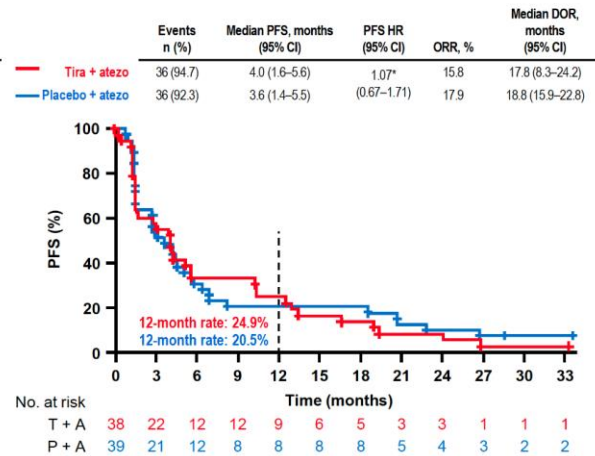
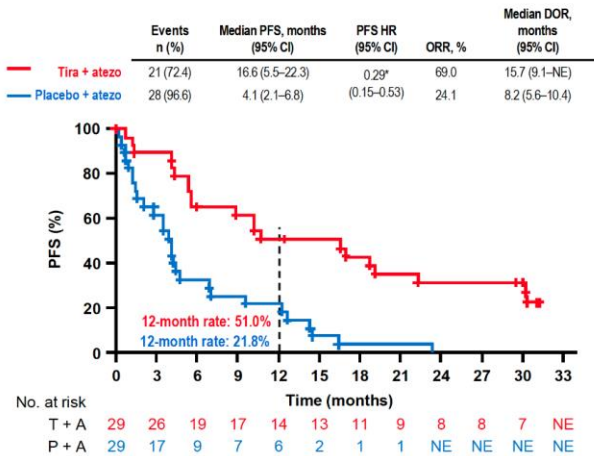
## Overall survival: PD-L1 subgroups

PD-L1 TPS ≥50% (n=58)

PD-L1 TPS 1-49% (n=77)

PD-L1 TPS ≥50% (n=58)

PD-L1 TPS 1-49% (n=77)



ESMO IMMUNO-ONCOLOGY

ESMO IMMUNO-ONCOLOGY

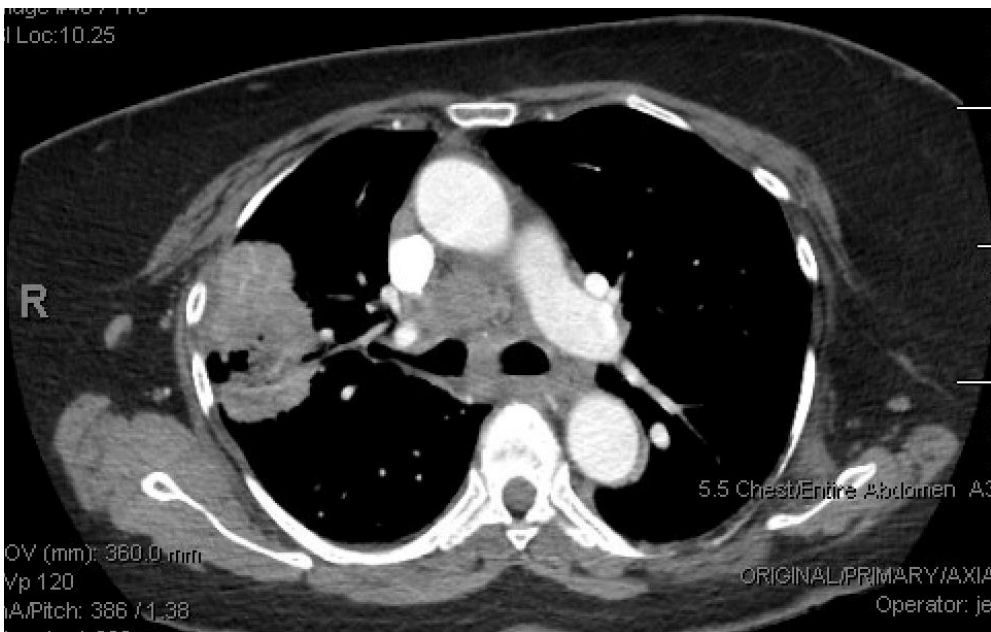
≥ 50%- 16.1mo vs. 4.1mo, HR- 0.29  
1-49%- 4.0mo vs. 3.6mo, HR- 1.07

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

SKYSCRAPER 1- Tiragulomab plus atezolizumab demonstrated numerically superior overall survival 22.9 versus 16.7 months, (HR-0.81) in PDL1 high NSCLC patients, at second interim analysis. Data not mature August 23<sup>rd</sup> 2023, Press Release  
Cho B, Lancet 2022

# Case- 66 year old female patient with CNS Metastasis

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



August 2021

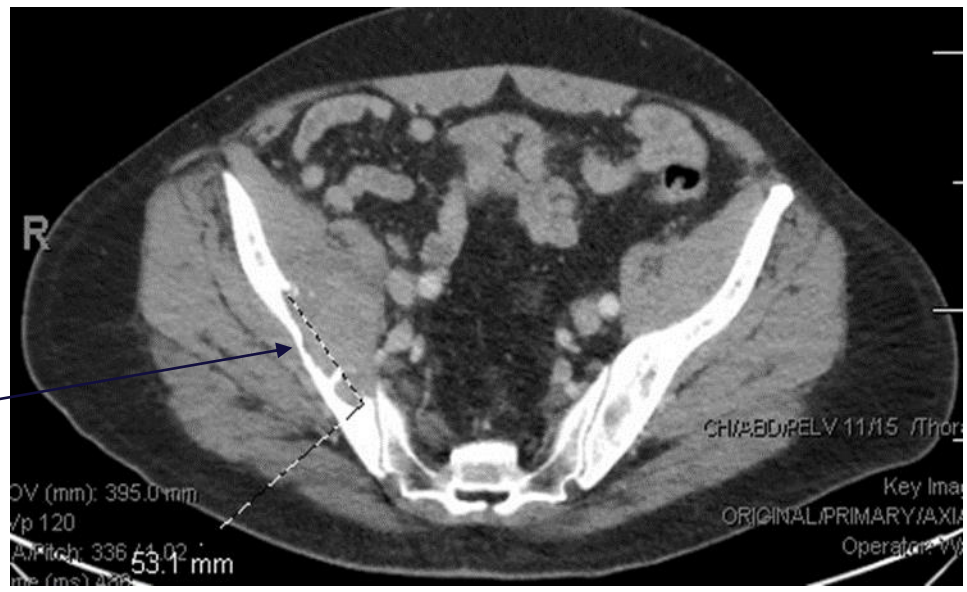


February 2024

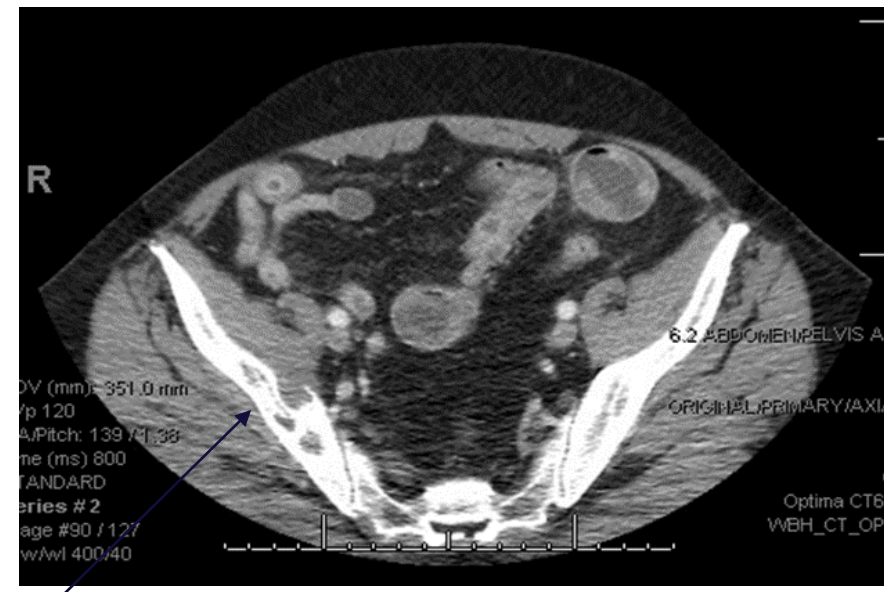
Single agent Pembrolizumab for 2 years

# Case- 69 year old with multiple bone mets 4 months post surgery

NGS- Kras G13C, STK11, CDKN2A, PDL1- 70%



November 2023

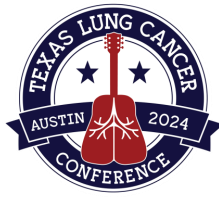


March 2024

Treated with Checkmate 9LA

Patient has immune mediated hepatitis. Currently on steroid taper

# Future Directions



- **5-year survival ranges from 25-30% in PD-L1 high NSCLC patients treated with anti-PD(L)-1 therapy**
- **Biomarkers that identify long-term survivors remain to be defined**
- **Combination treatments-IO, ADC and chemotherapy, in clinical trials**