GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

SYSTEMIC TREATMENT IN NON-ONCOGEN ADDICTED NSCLC IMMUNOTHERAPY/CHEMO-IMMUNOTHERAPY

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DISCLOSURES

Personal financial interests

Consulation Honoraria: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, Lilly, MSD, Pfizer, Sanofi, Takeda, Pfizer

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Institutional financial interests

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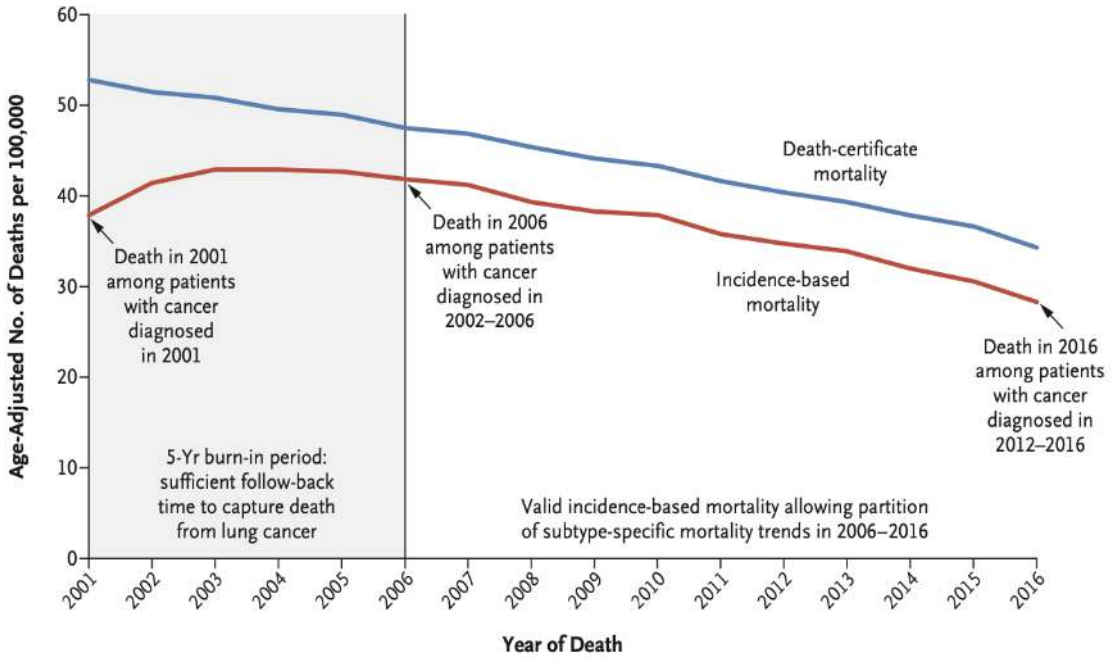
Research Grant: BMS, F. Merck, Pfizer

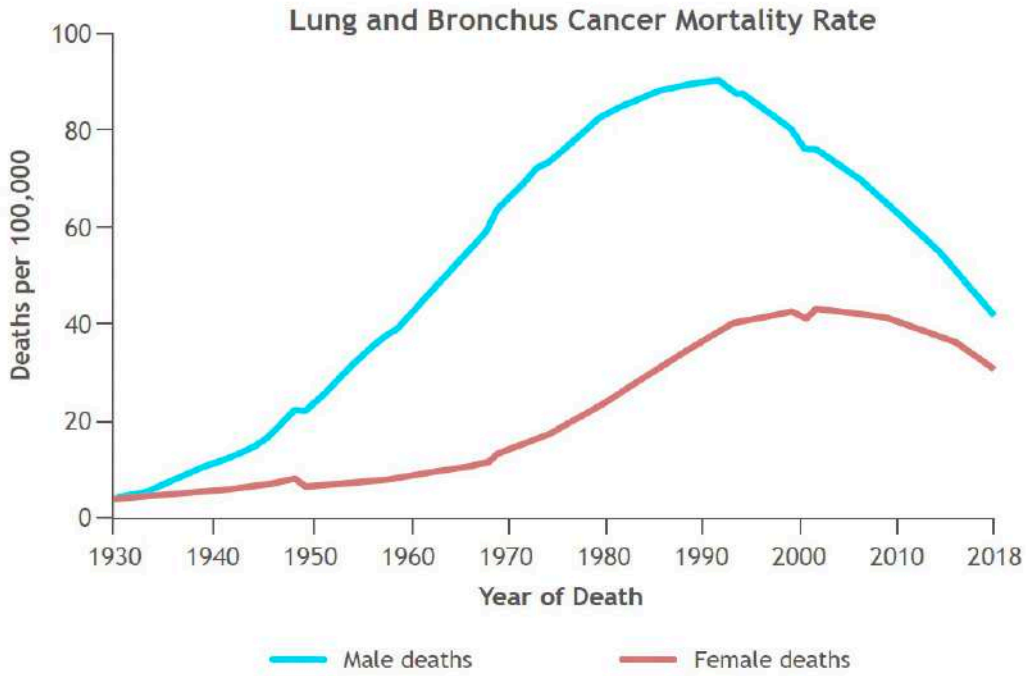
THE LONG WAY TO ACHIEVE IMPROVEMENTS IN SURVIVAL IN LUNG CANCER

The Effect of Advances in Lung-Cancer Treatment on Population Mortality

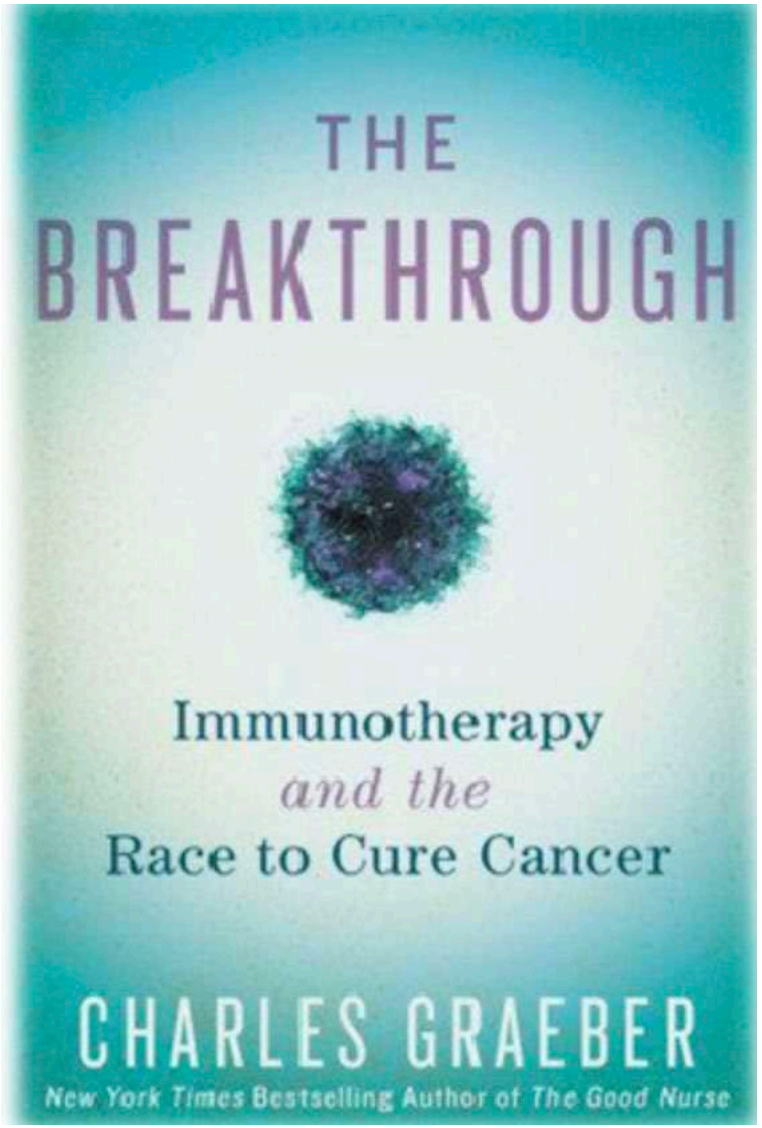
Nadia Howlader, Ph.D., Gonçalo Forjaz, D.V.M., Meghan J. Mooradian, M.D., Rafael Meza, Ph.D., Chung Yin Kong, Ph.D., Kathleen A. Cronin, Ph.D., Angela B. Mariotto, Ph.D., Douglas R. Lowy, M.D., and Eric J. Feuer, Ph.D.

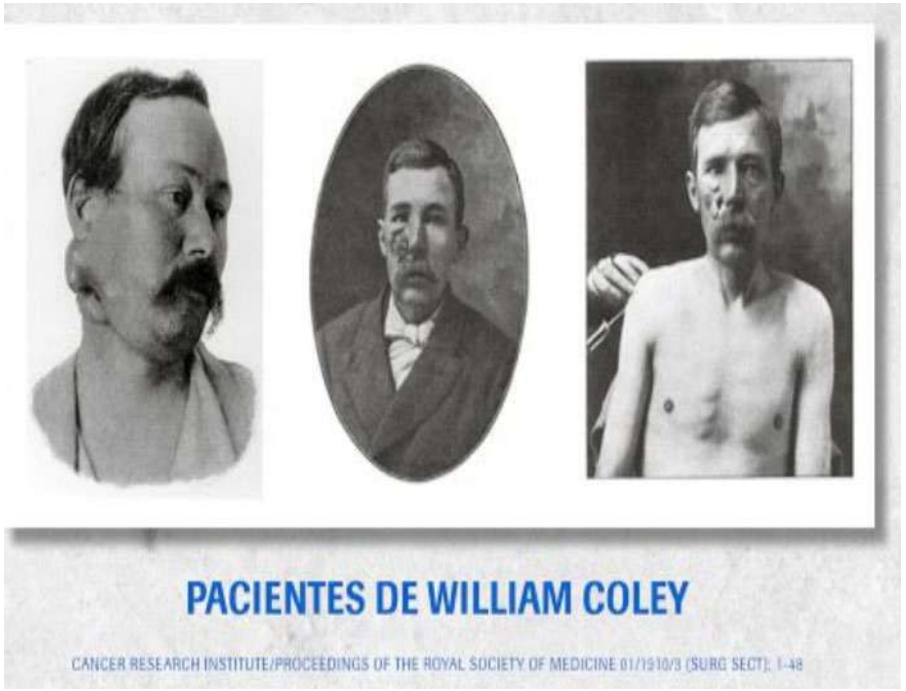


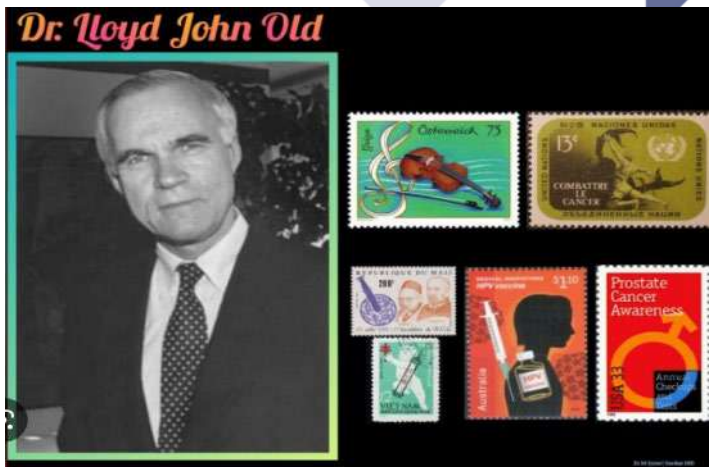
Howlader N,. N Engl J Med. August 13, 2020



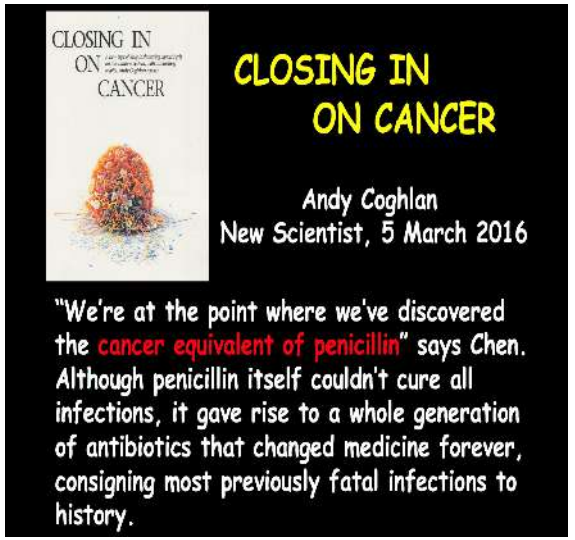
Siegel RL et al. CA Cancer J Clin. 2021

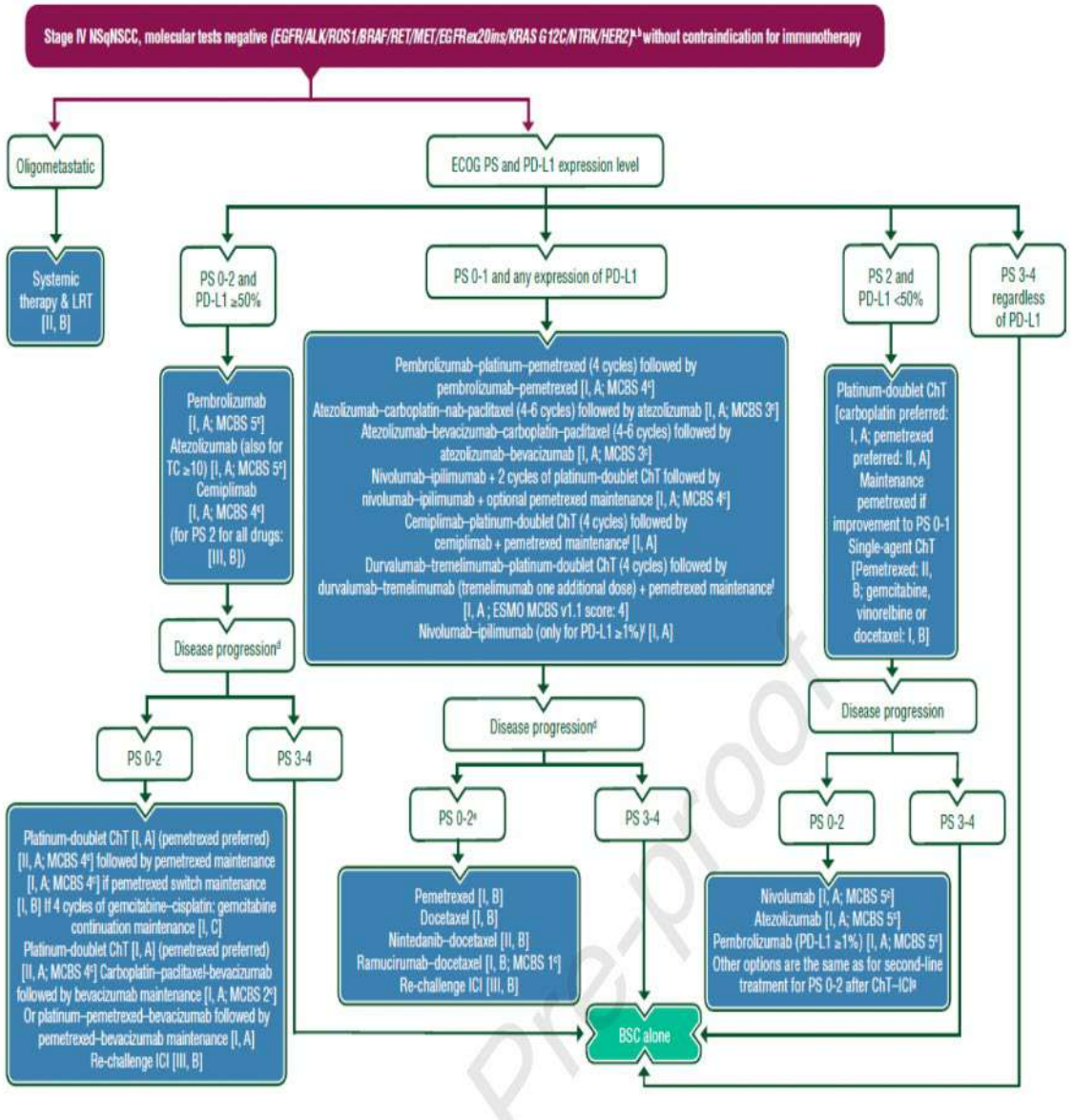


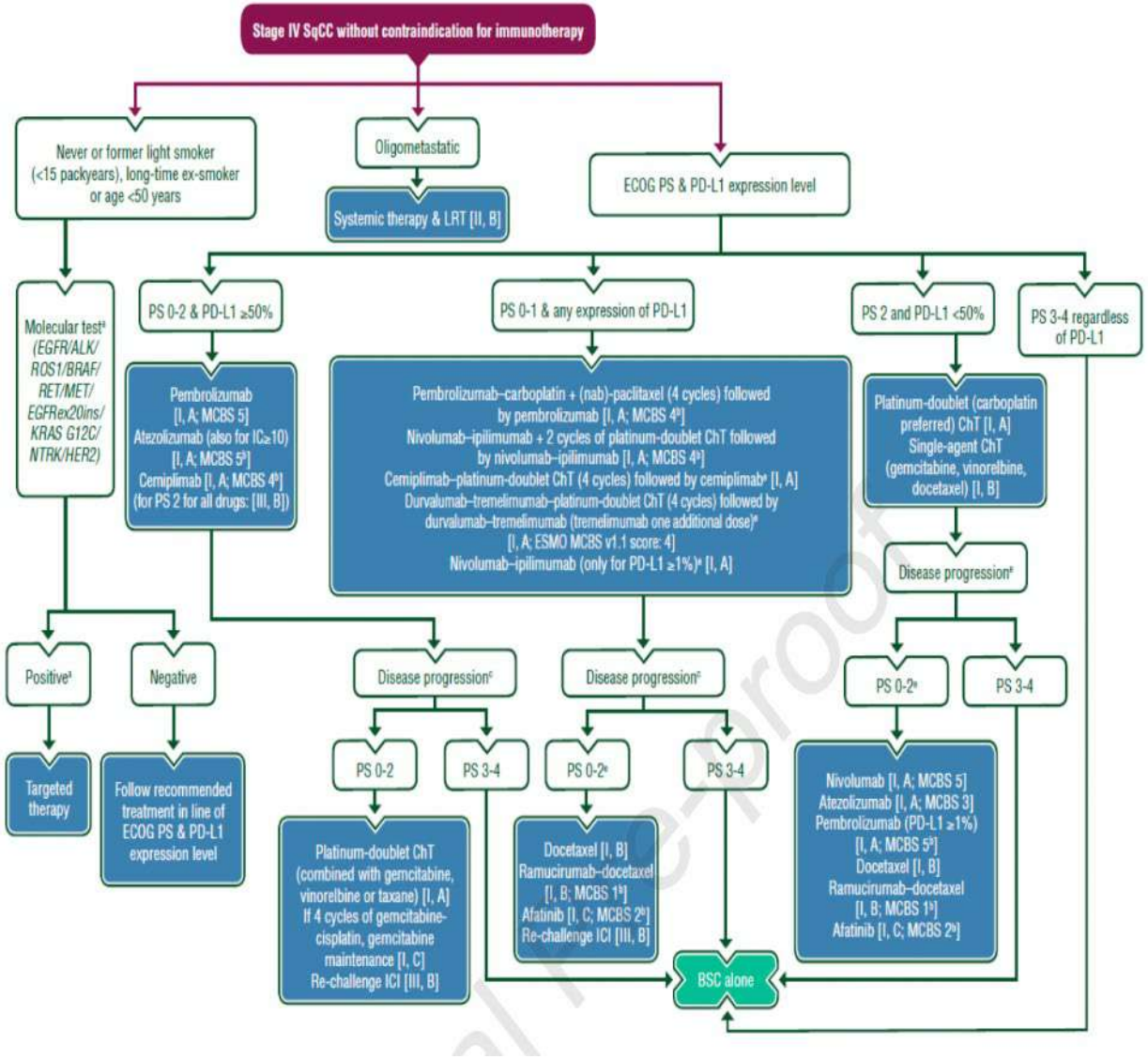




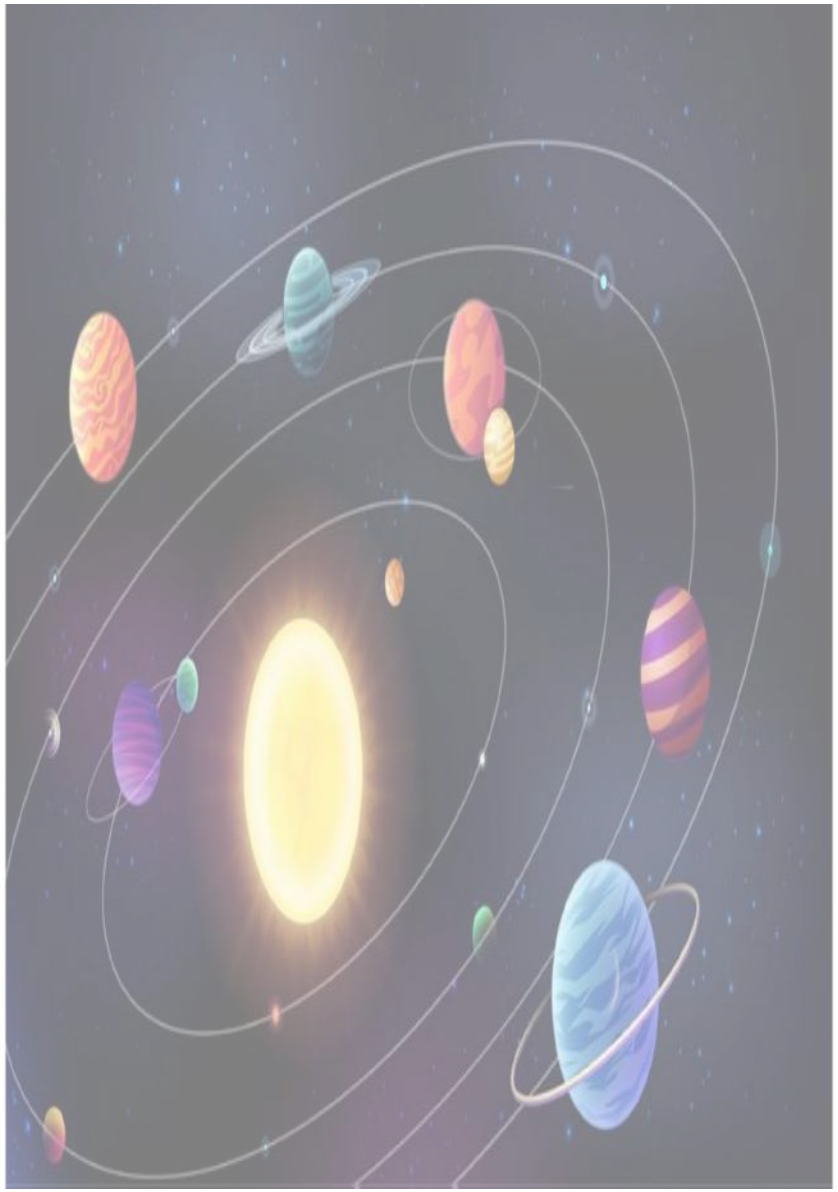

Tasuku Honjo y James P. Allison estudiaron dos proteínas presentes en las células T.. SAM YEH / AFP







Hendriks LE, et al. Ann Oncol. 2023



Yu et al Nat Rev Drug Discov 2019

Immune-strategy in first-line setting NSCLC

Non-SCC
Impower 150
TASUKI 52

SCC
KN 407
*Impower 131**
Orient 12
Rationale 307
Camel Sq

SCC and Non-SCC
Empower Lung 3
Choice 01
Gemstone 302

Non-SCC
KN 189
Orient 11
CameL
*Impower 132**
Impower 130
Rationale 304

CM 227
MYSTIC*
NEPTUNE*
BR34*
KN598*

CM 9LA
POSEIDON

KN 024
KN 042

*CM 026**
*JAVELIN LUNG 100**

Empower Lung 1

Impower 110
*BFAST**
IPSOS

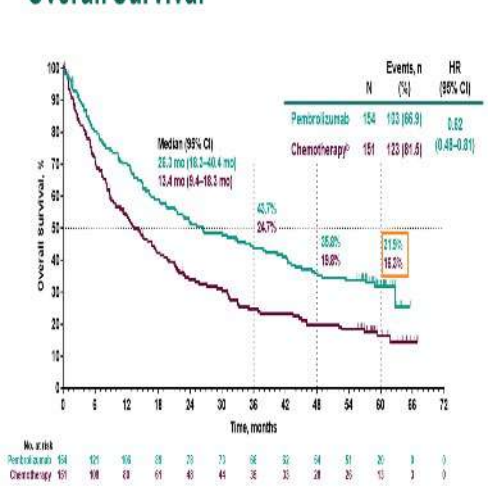
KN: Pembrolizumab
CheckMate: Nivo/ Ipi
Empower: Cemiplimab
Orient: sintilimab
Rationale: Tislelizumab
Camel: Camreluzimab
Tasuki: nivolumab
Choice: Toripalimab
Impower: Ateolizumab
Poseidon, Mystic, Neptune: Durva+/-Treme
Javelin: Avelumab
Gemstone: Sugemalimab

PD-1 inhibitor
PD-L1 inhibitor

*NS OS

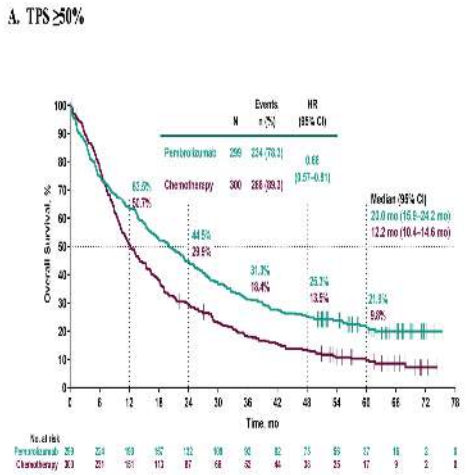
IO MONOTHERAPY IN UNPREVIOUSLY TREATED NSCLC, PD-L1 ≥50%

KEYNOTE 024, PD-L1 ≥50% (22C3)
Follow-up: 5-years



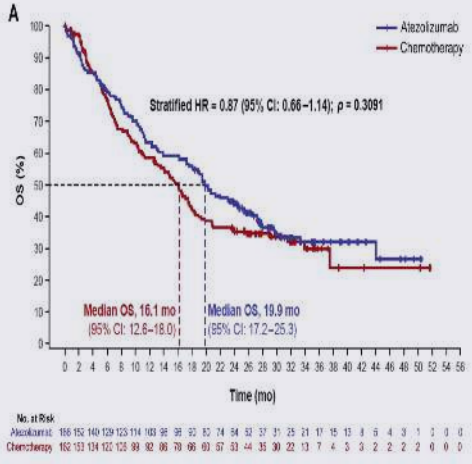
OS: **26.3** *vs.* **13.4** , HR 0.62

KEYNOTE 042, PD-L1 ≥50% (22C3)
Follow-up: 5 -years



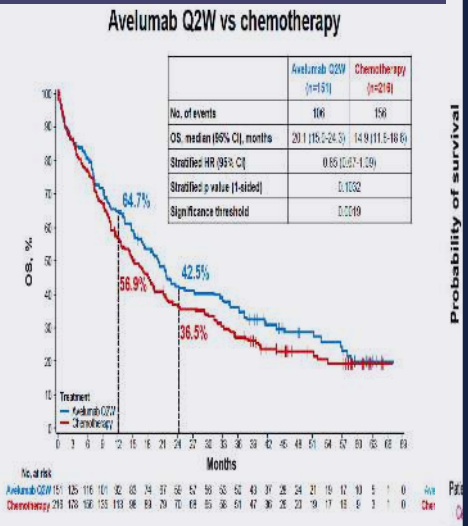
OS: **20.0** *vs.* **12.2** , HR 0.68

IMPOWER 110, PD-L1 TC3/IC3 (SP142)
Follow-up: 31 months



OS: **19.9** vs. **16.1** , HR 0.87

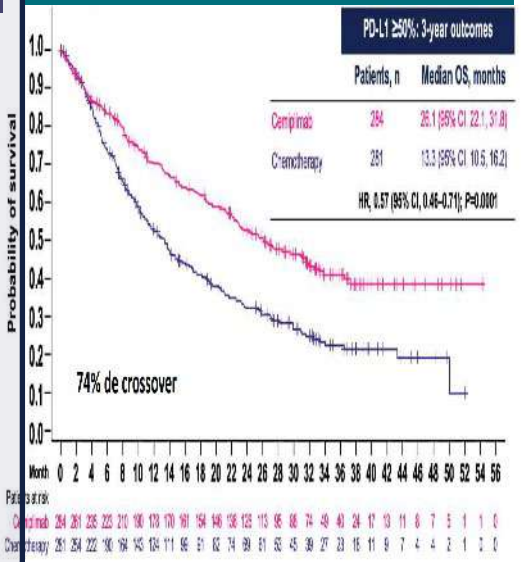
JAVELIN 100 (Dako IHC 73-19
Follow-up: 37.1 months



OS analyses favored avelumab vs chemotherapy but differences

OS: **20.1** vs. **14.9** , HR 0.85

EMPOWER LUNG 1 (22C3)
Follow-up: 37.1 months



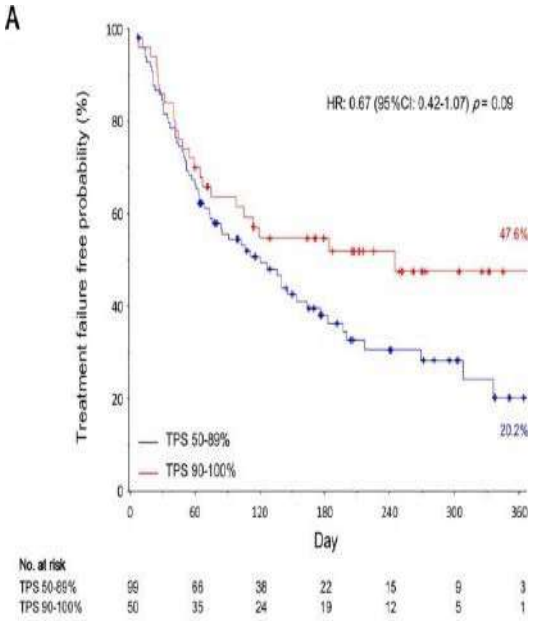
OS: **26.1** vs. **13.3** , HR 0.57

PD-1 inhibitor

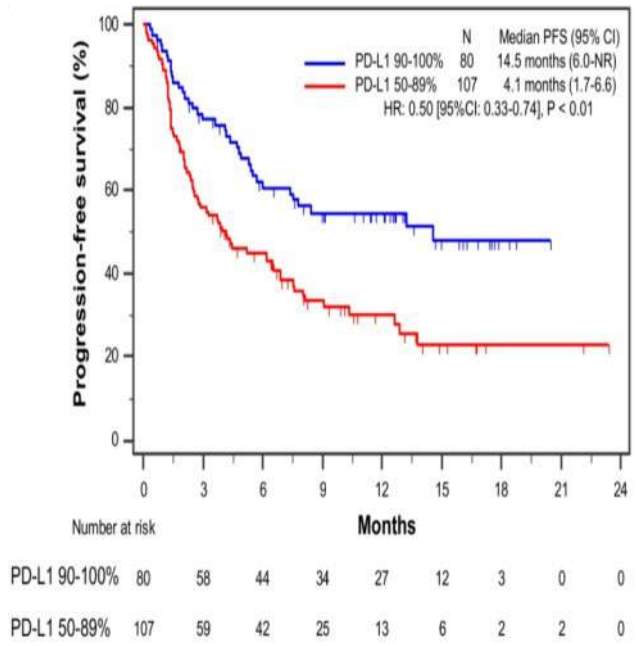
PD-L1 inhibitor

Reck M, et al. J Clin Oncol 2021; de Castro G, et al J Clin Oncol 2022; Jaseem et al. J Thorac Oncol 2021; Reck M, et al WCLC 2022; Ozguroglu M, et al. Ann Oncol 2022

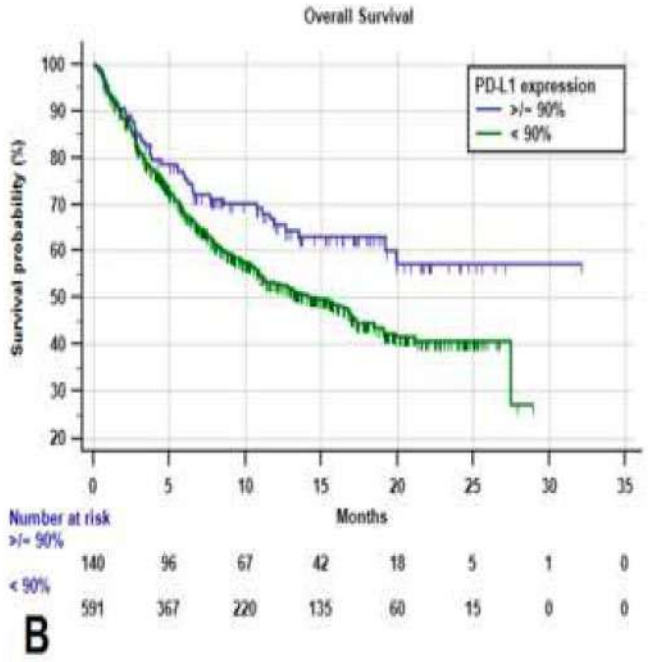
Is PD-L1 expression level relevant for decision?



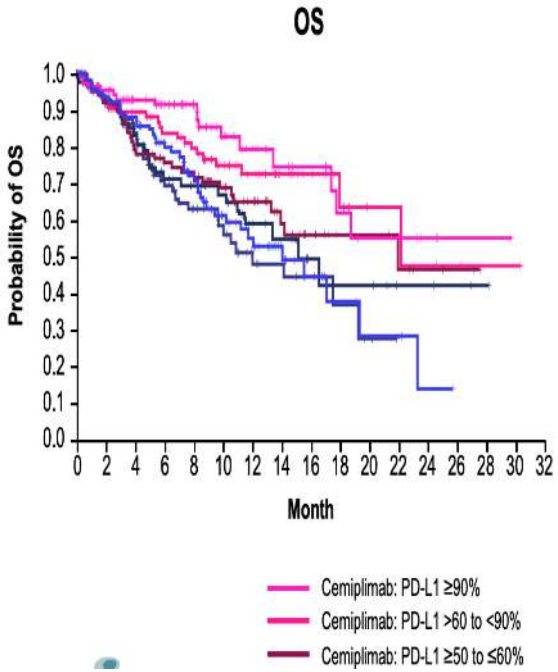
Edahiro et al , PLOS One 2019



Aguilar et al, Ann Oncol 2019

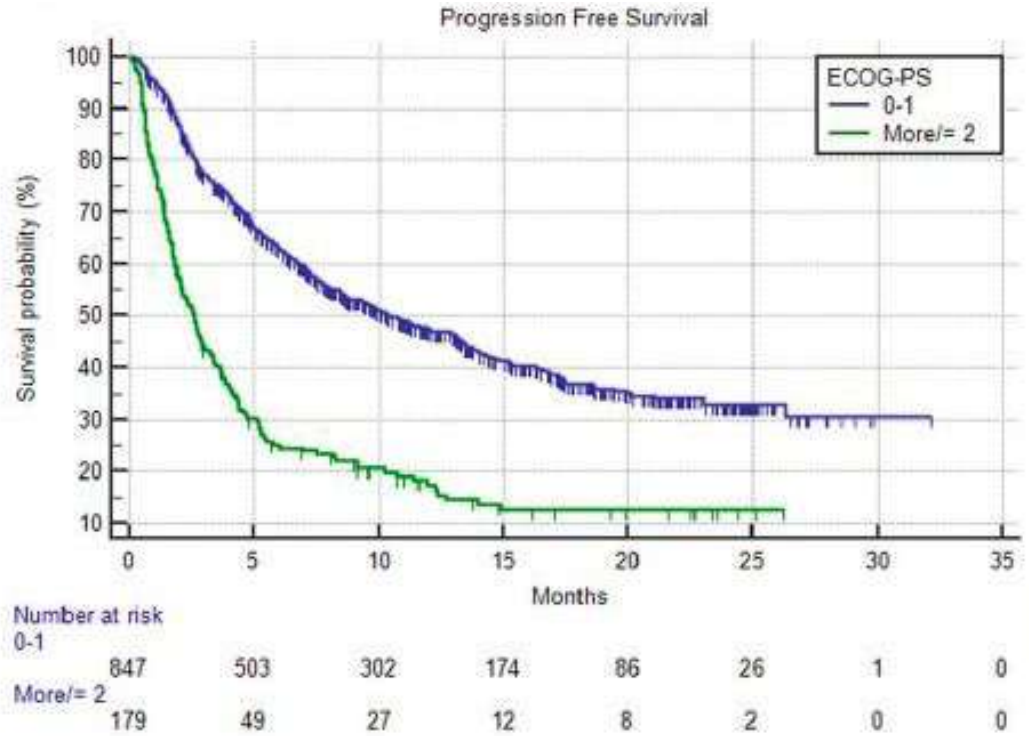


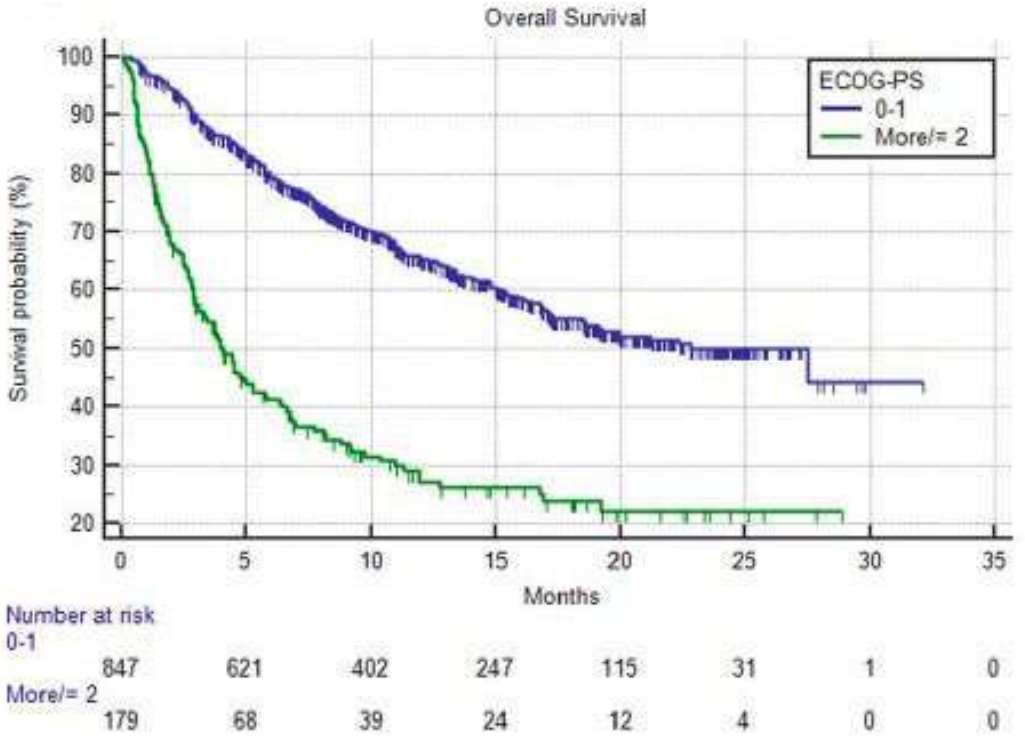
Cortellini et al. Cancer Immunol Immunother 2020



Sezer et al, ESMO 2020

Real-World Data: Pembrolizumab in PD-L1≥50% NSCLC Impact of PS





Cortellini et al; Cancer Immunotherapy 2020

IO COMBOS IN UNPREVIOUSLY TREATED NSCLC

	Trial	RR (%)	DOR (months)	PFS (HR)	OS (HR)
Non-Squamous	KEYNOTE 189	48	12.6	0.50	0.60
	IMpower 150 (ABCP arm)	64	9.0	0.57	0.80
	IMpower 132	47	6.2	0.60	0.86 (NS)
	IMpower 130	49	8.4	0.64	0.79
	TASUKI-52 (Nivolumab + BVZ)	62	11	0.56	0.85
	ORIENT 11	52	Not Reached	0.48	0.61
	RATIONALE 304	57	8.5	0.65	Immature
	CAMEL	61	17.6	0.60	0.73
	KEYNOTE 407	63	9.0	0.59	0.71
Squamous	IMpower 131	49	5.5	0.71	0.88 (NS)
	RATIONALE 307	73	8.2	0.52	Immature
	CAMEL-Sq	65	13.1	0.37	0.55
	ORIENT 12	45	6.1	0.54	0.57
	CheckMate 227 (PD-L1 ≥1%)	36	23.2	0.81	0.76
	CheckMate 9LA	38	13	0.67	0.72
	EMPOWER Lung03	43	15.6	0.56	0.71
Both histologies	MYSTIC (D+T arm, PD-L1 ≥ 25%)	34	Not Reached	1.05	0.85 (NS)
	POSEIDON (D + CT arm)	42	5.0	0.74	0.86 (NS)
	GEMSTONE-302	61	9.7	0.48	0.67
	CHOICE-01	63	8.3	0.58	0.81

PD-1 inhibitor

PD-L1 inhibitor

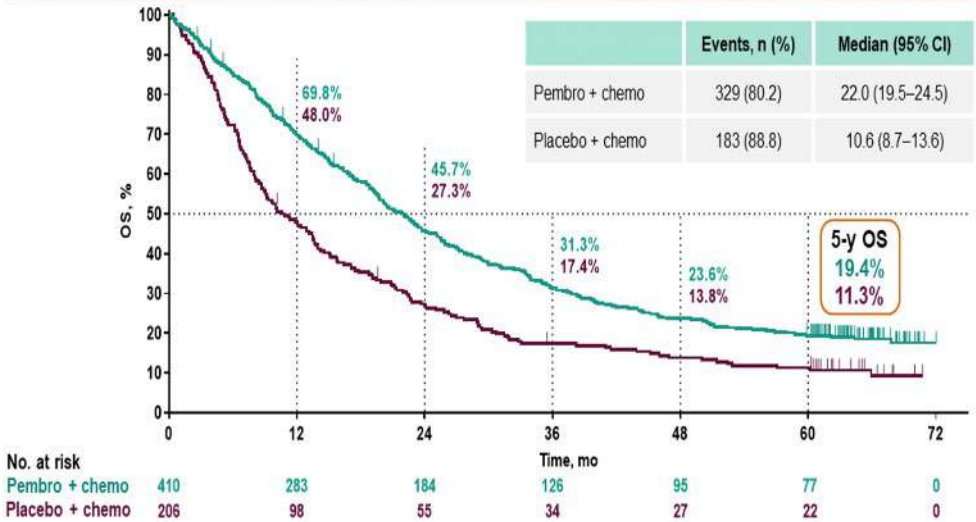
KN: Pembrolizumab
CheckMate: Nivo/ Ipi
Empower: Cemiplimab
Orient: sintilimab
Rationale: Tislelizumab
Camel: Camreluzimab
Tasuki: nivolumab
Choice: Toripalimab
Impower: Ateolizumab
Poseidon, Mystic, Neptune: Durva+/-Treme
Javelin: Avelumab
Gemstone: Sugemalimab

Gray – WCLC 2020 * Socinski – NEJM 2018 & JTO 2021 * Nishio – JTO 2020 * West – Lancet Oncol 2019 * Sugawara – Ann Oncol 2021 * Yang –JTO 2021 * Lu – JTO 2021 * Zhou – Lancet Resp Med 2020; Robinson – ELCC 2021 * Jotte – JTO 2020 * Wang – JAMA Oncol 2021 * Zhou – ELCC 2021 * Zhou - JTO 2021; Ramalingam – ASCO 2020 * Paz-Ares – ASCO 2021 * Reck – ASCO 2021 * Johnson –WCLC 2021 * Gogishvili –ESMO 2021 * Rizvi – JAMA Oncol 2020 * Zhou – ESMO Asia 2020 & WCLC 2021 * Wang – WCLC 2021 HR: Hazard Ratio. NS: Not significant.

Slide Courtesy and adapted from J. Remón

KN 189

OS: ITT Population



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

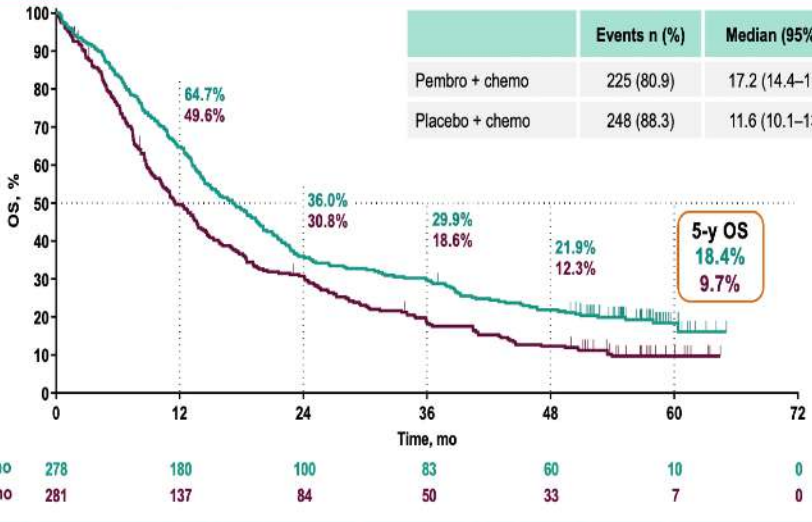
No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-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,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

OS: 22m vs. 10.6
HR 0.60 (0.50-0.72)
5y OS: 19.4% vs. 11.3%

KN 407

OS: ITT Population



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

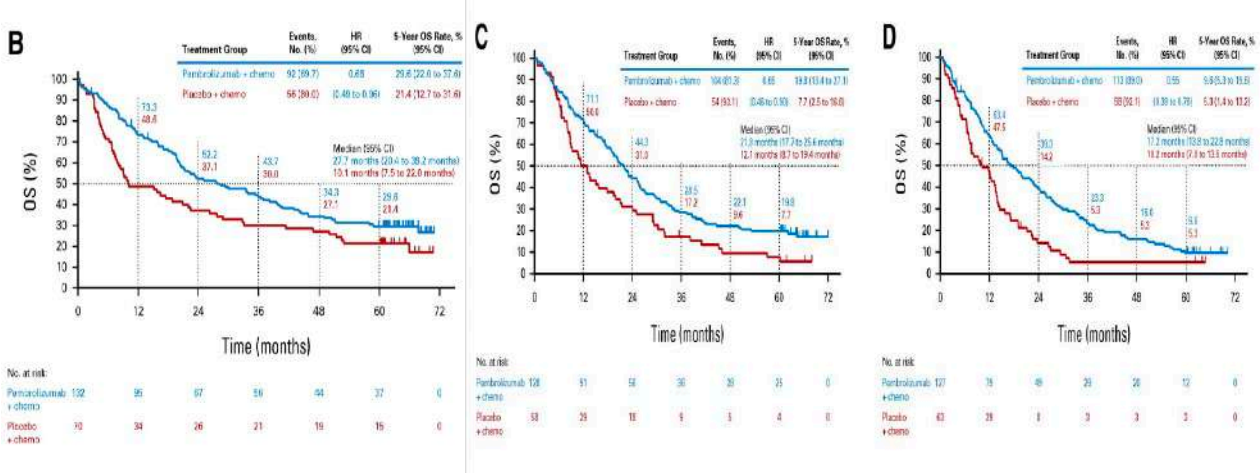
No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

OS: 17.2 vs. 11.6m
HR 0.71 (0.59-0.83)
5y OS: 18.4% vs. 9.7%

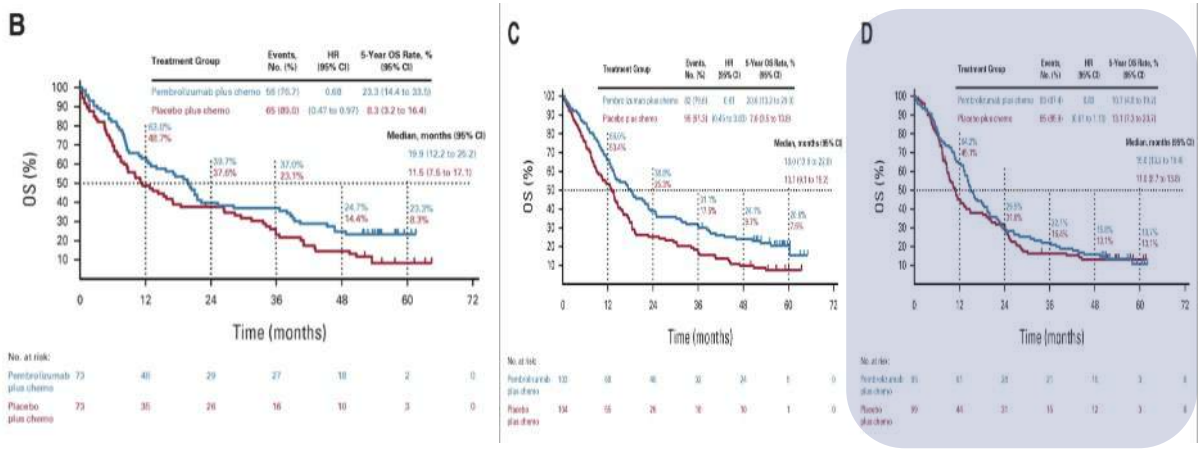
Garassino M, et al. ESMO 2022; Garassino et al, JCO 2023
Novello S, et al. ESMO 2022; Novello S, et al JCO 2023

KN 189



	PD-L1 TPS ≥50%		PD-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,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

KN 407



	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

ABSOLUTE BENEFIT IS MINIMAL IN THE PD-L1 NEGATIVE POPULATION

Garassino M, et al. ESMO 2022; Garassino et al, JCO 2023
Novello S, et al. ESMO 2022; Novello S, et al JCO 2023

PERLA Trial: phase II, randomised, double-blind study comparing dostarlimab (anti-PD-1) + CT vs pembrolizumab + CT in patients with 1L metastatic non-squamous NSCLC

Key eligibility criteria
- Histologically/cytologically confirmed metastatic non-squamous NSCLC (no mutations for which approved targeted therapy available)
- Documented PD-L1 status (22C3 pharmDx assay)
- ECOG PS 0–1, adequate organ function
- No prior systemic therapy for metastatic NSCLC

Stratification factors
- PD-L1 (TPS <1% vs 1–49% vs ≥50%)
- Smoking status (never vs former/current)

Disease assessments:
Clinic visits Q3W. Serial imaging at weeks 6 and 12, Q9W to week 48, then Q12W

N=243 Randomised 1:1

- **Dostarlimab** + CT* 500 mg Q3W via IV N=121
- **Pembrolizumab** + CT* 200 mg Q3W via IV N=122

Treatment until disease progression, unacceptable toxicity, or death (up to 35 cycles)

Endpoints
Primary: ORR (confirmed; RECIST v1.1) by BICR

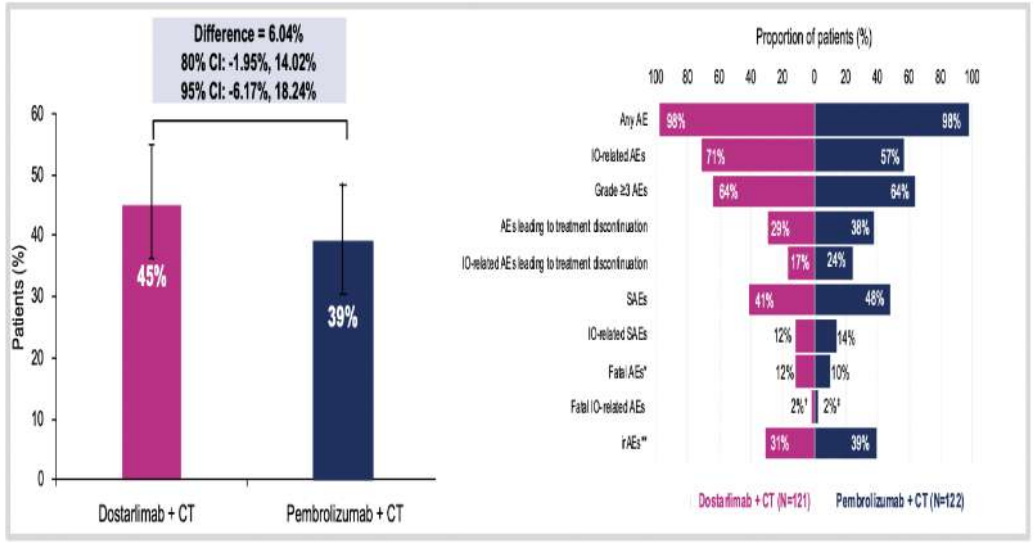
Secondary: incl. OS, PFS (RECIST v1.1) by INV, safety

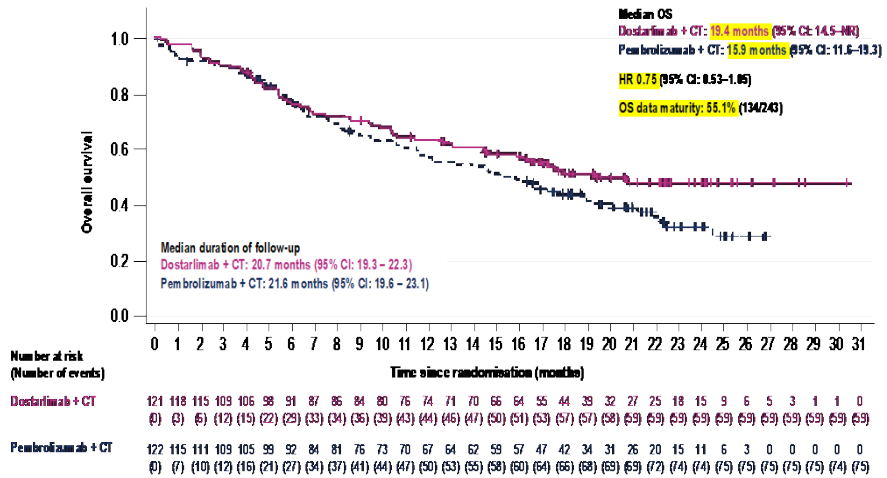
Exploratory: incl. DOR (RECIST v1.1) by BICR

Primary DCO: August 4, 2022
Pre-planned updated OS analyses DCO: July 7, 2023

Hypothesis: ORR of dostarlimab + CT is similar to ORR of pembrolizumab + CT in participants with 1L metastatic non-squamous NSCLC

With 240 patients (120 per treatment arm), the study has 85% power to detect a 15% difference in ORR between the two arms at the 10% one-sided type I error rate when the true ORR is 45% for both groups



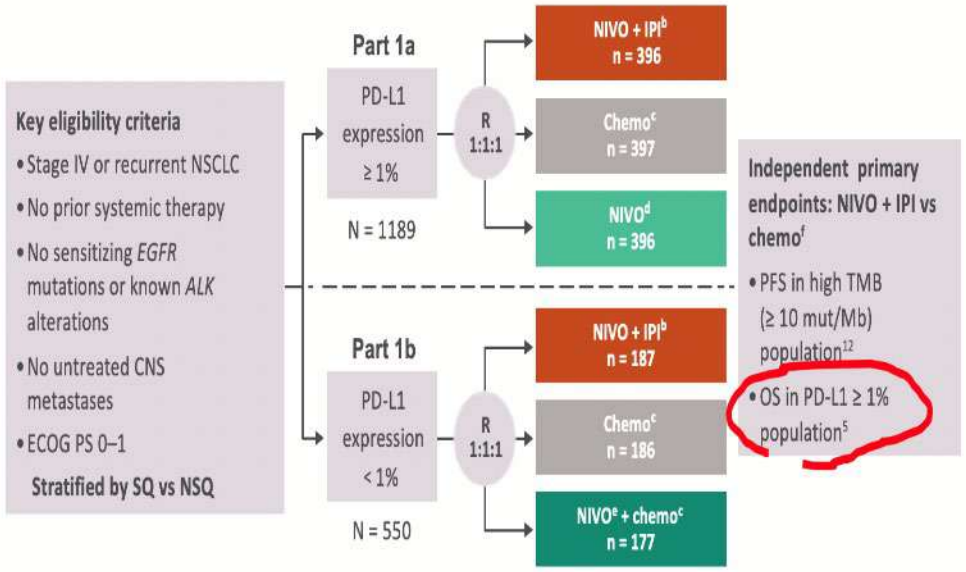


	Median OS (mo)
Pembro + Ch KN-189	22.0
Dostar + Ch PERLA	19.4
Pembro + Ch PERLA	15.9
Placebo + Ch KN-189	10.6

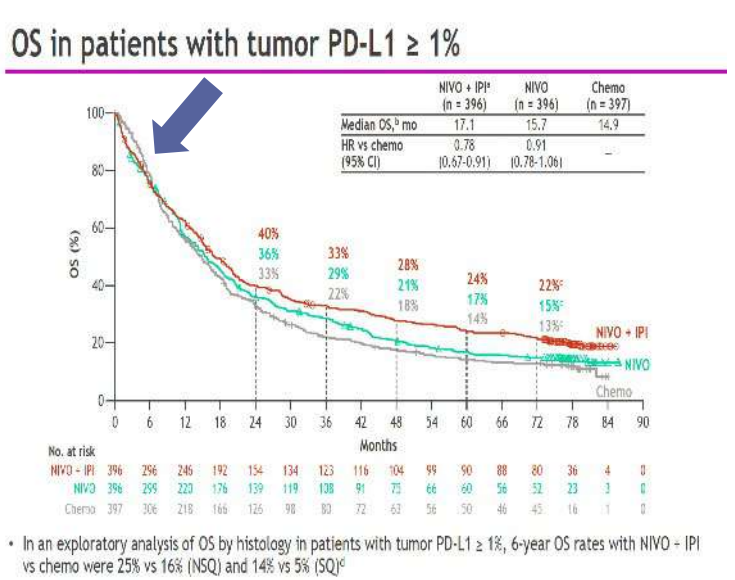
Peters S, ESMO 2023; Garassino M, JCO 2023

6

CheckMate 227

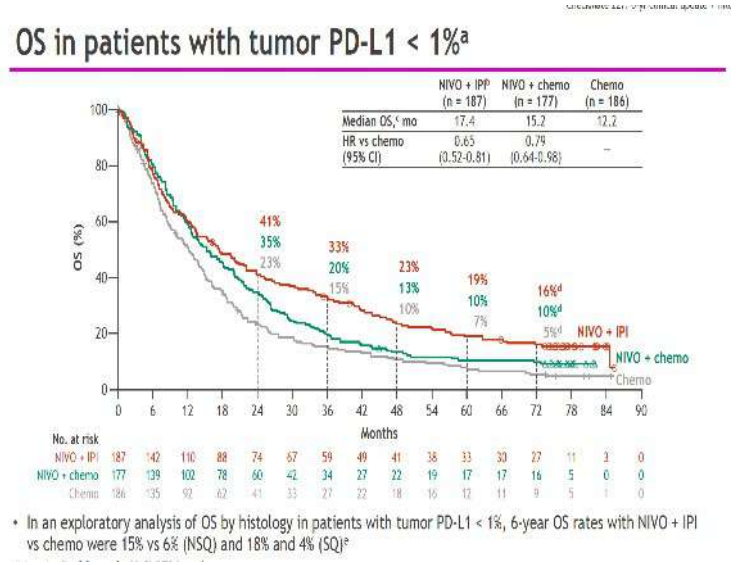


Efficacy in patients with tumor PD-L1 ≥ 1%



OS: 17.1m vs. 14.9m
HR 0.78 (0.66-0.91)
6y OS: 22% vs. 13%

Efficacy in patients with tumor PD-L1 < 1%



OS: 17.4m vs. 12.2m
HR 0.65 (0.52-0.8)
6y OS: 16% vs. 5%

Ramalingam et al. WCLC 2023

CheckMate 9LA

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)

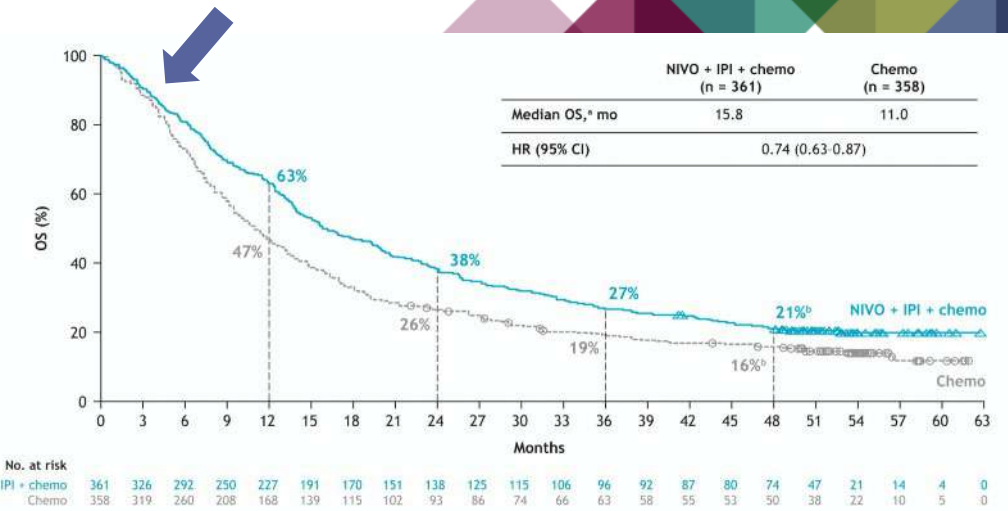
N = 719, R 1:1

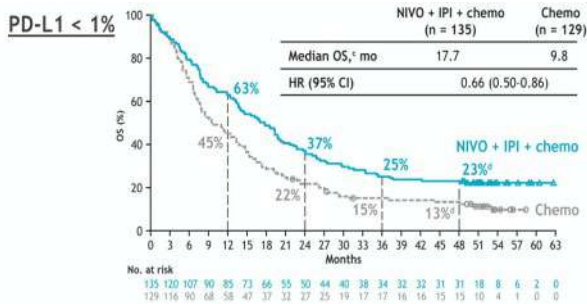
- n = 361: NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + Chemo[d] Q3W (2 cycles)
- n = 358: Chemo[d] Q3W (4 cycles) with optional pemetrexed maintenance (NSQ)

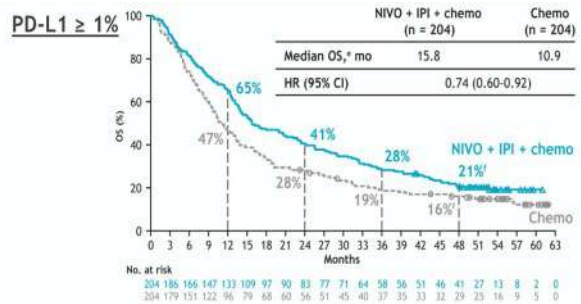
Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

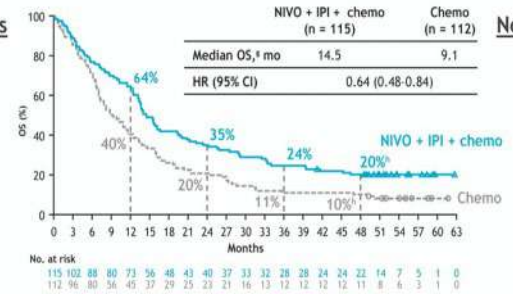
Primary endpoint
- OS

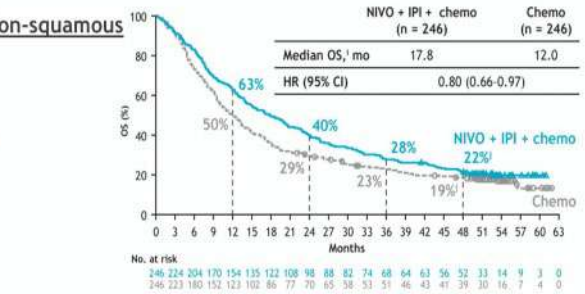
OS: 15.8 vs. 11.0
HR 0.74 (0.61-0.87)
4y OS: 21% vs. 16%







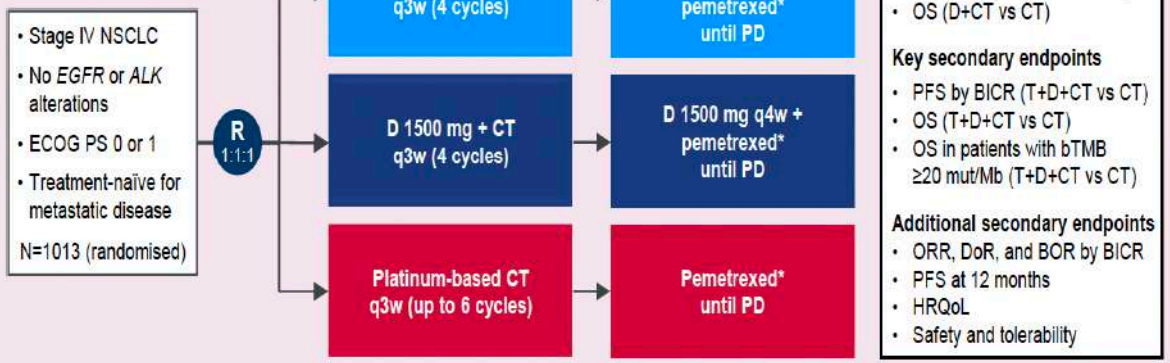




Carbone D, et al. ASCO 2023

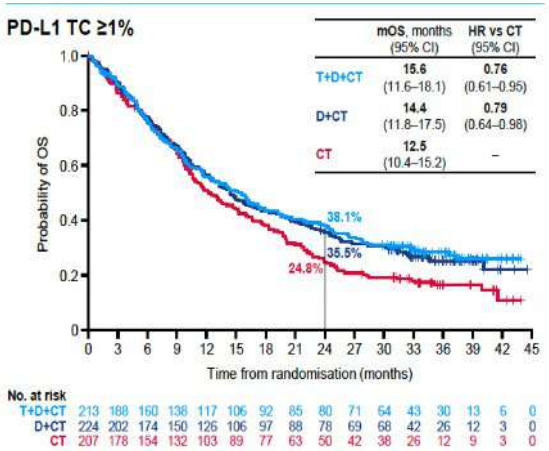
4 POSEIDON

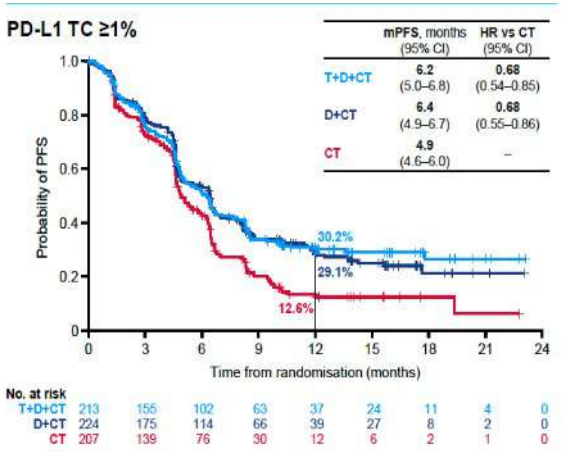
Figure 1. Study design



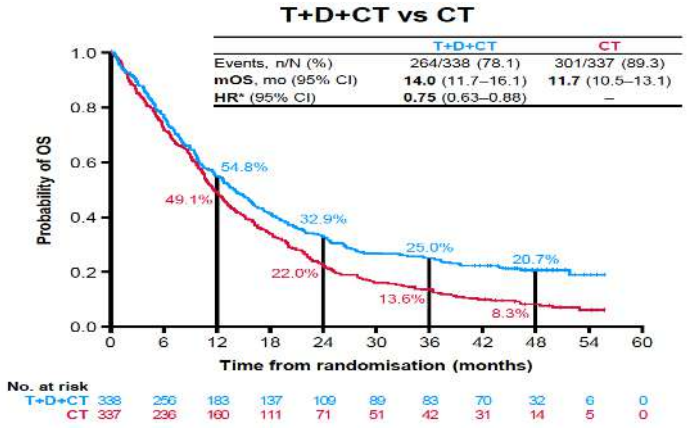
*Patients with non-squamous histology who initially received pemetrexed-platinum only (if eligible).

Efficacy in patients with tumor PD-L1 ≥ 1%

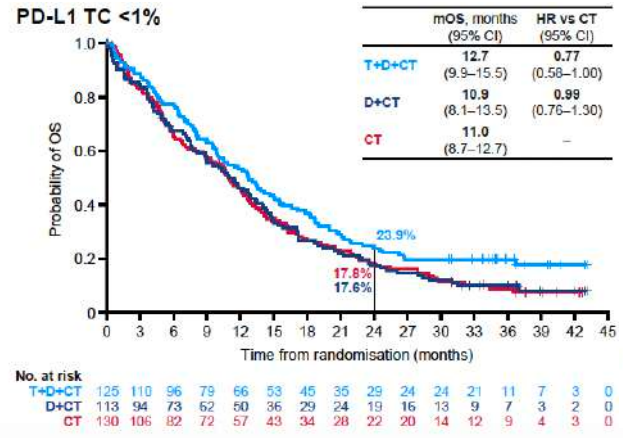


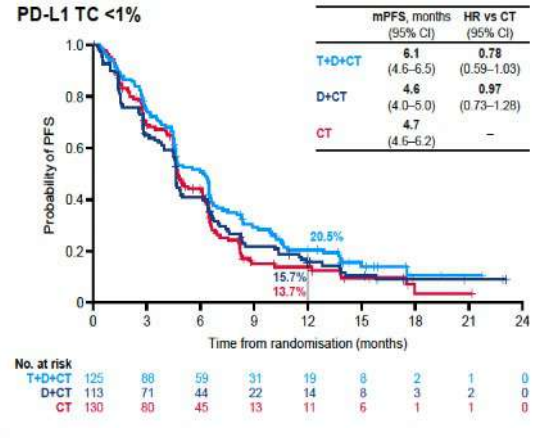


Efficacy in patients with tumor PD-L1 < 1%



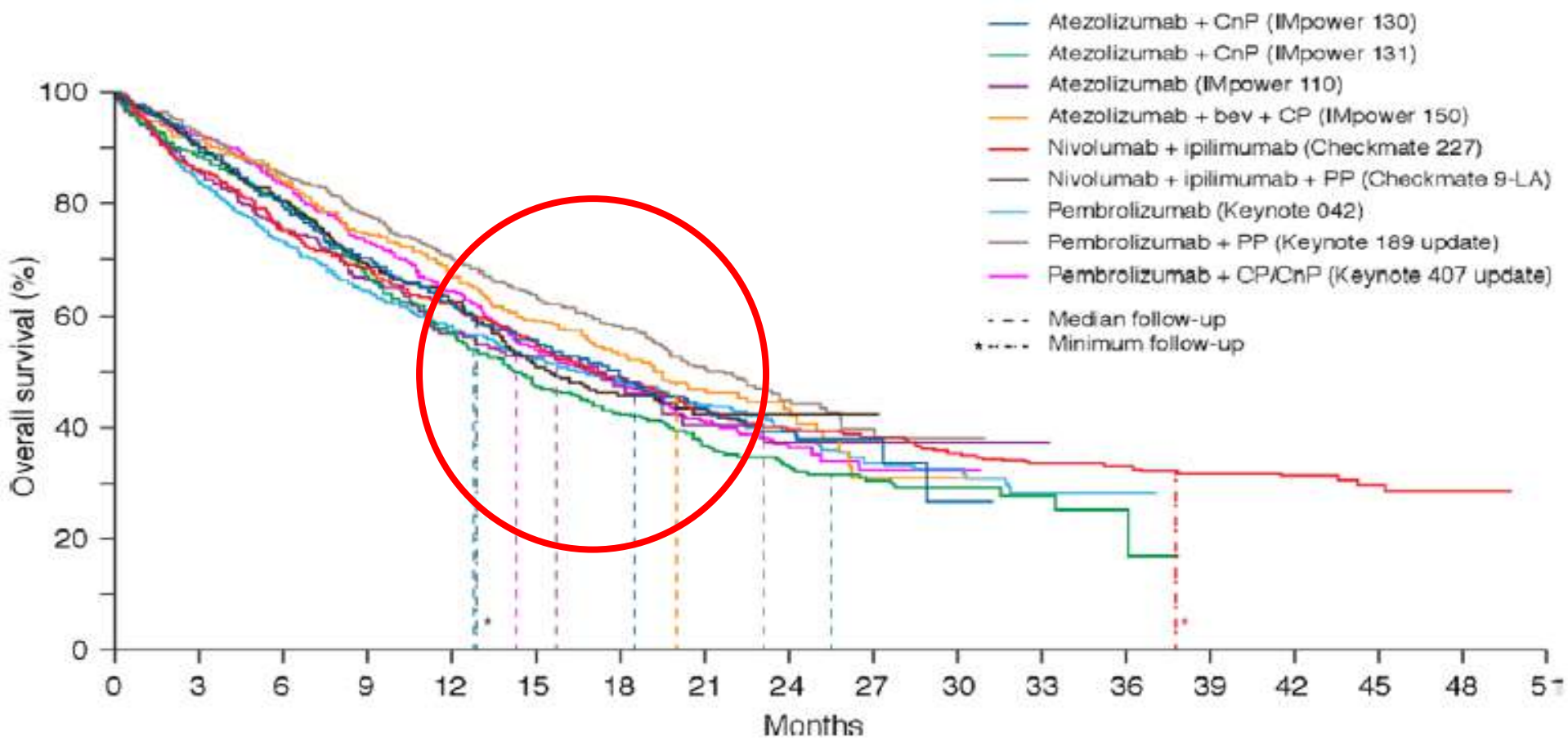
OS: 14m vs. 11.7m
HR 0.75 (0.63-0.88)
4y OS: 20.7% vs. 8.3%





Johnson M, et al. ESMO 2022
Garón E, et al. WCLC 2022

With so many options…difficult to choose



Friedlander et al. J Immunohter Cancer 2020

SINCE EFFICACY RESULTS LOOK PRETTY SIMILAR…

The data

- Efficacy Data
- Safety Data

The patient

- Age
- PS
- Gender
- Smoking habits
- Comorbilities
- Contraindications for IO
- Patient preference

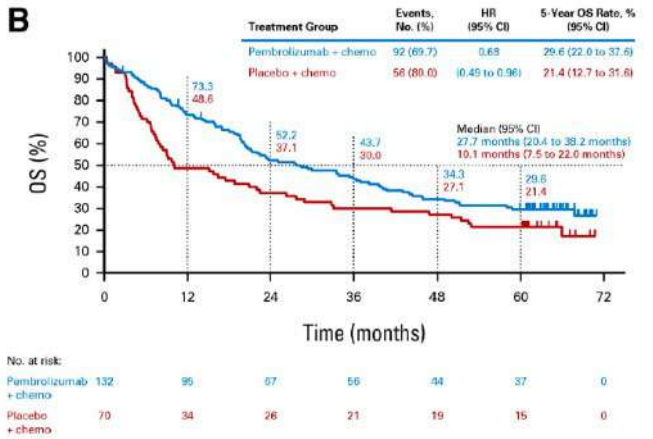
Disease

- Brain Metastasis
- Disease Burden

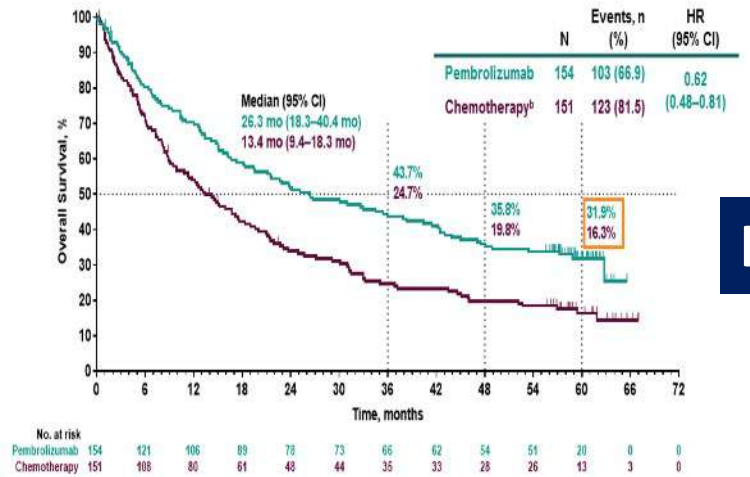
The tumor

- EGFR, ALK, ROS, BRAF, MET mutations
- PD-L1 expression
- TMB
- Other biomarkers (STK11, KRAS, p53, KEAP…)

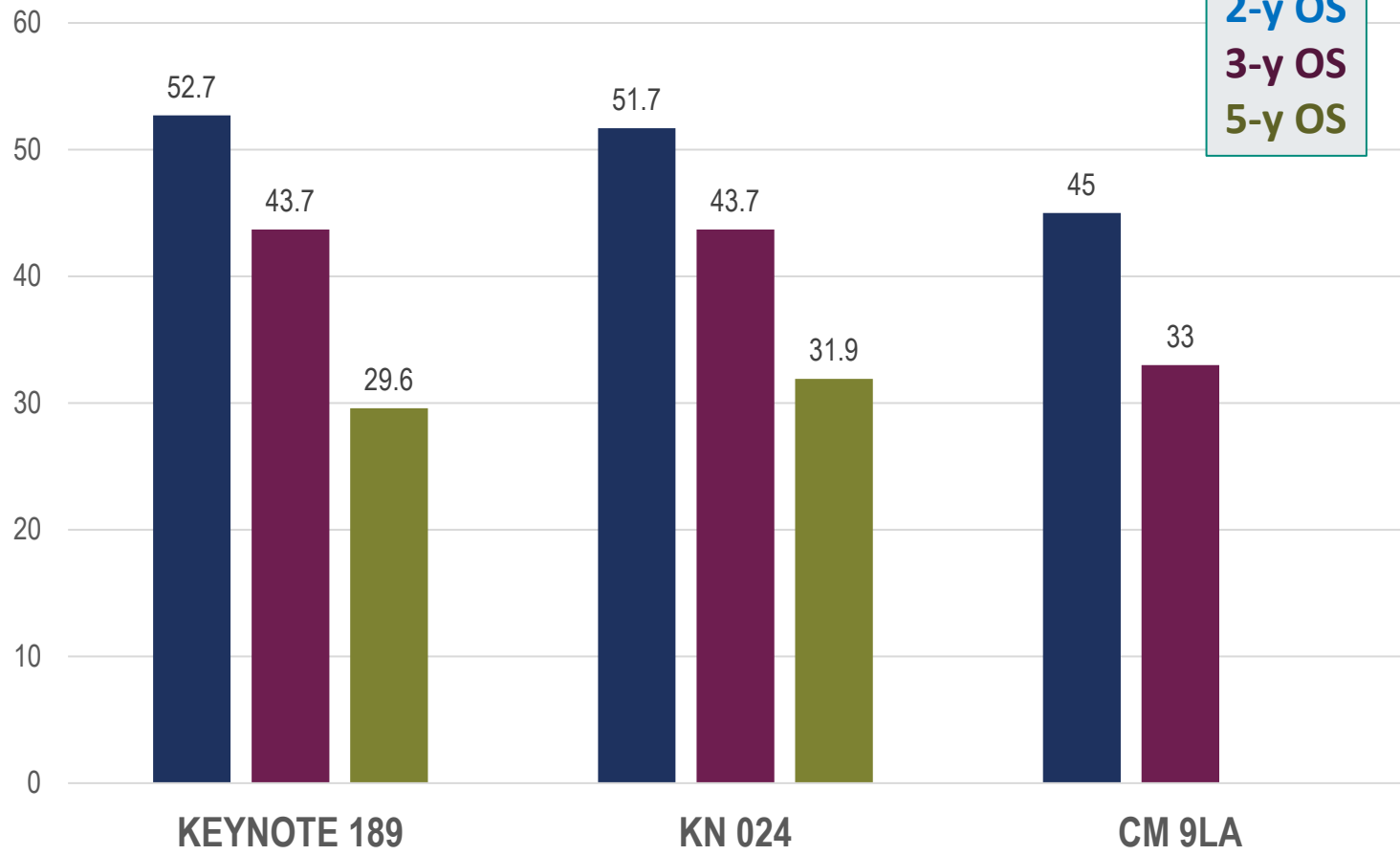
IO combos vs IO mono in PD-L1 ≥50%
Similar long term OS regardless of the strategy in PD-L1≥50%



KN 189

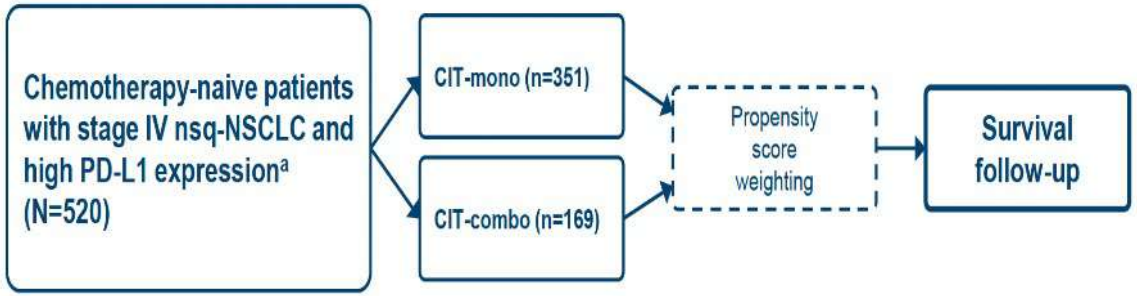


KN 024

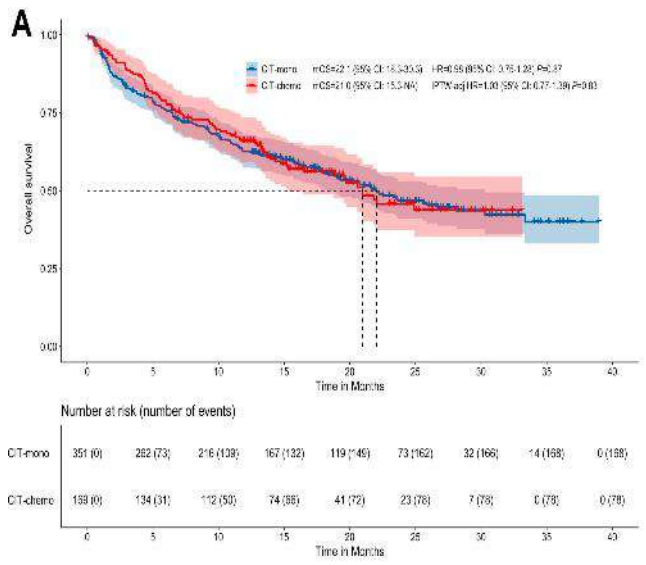


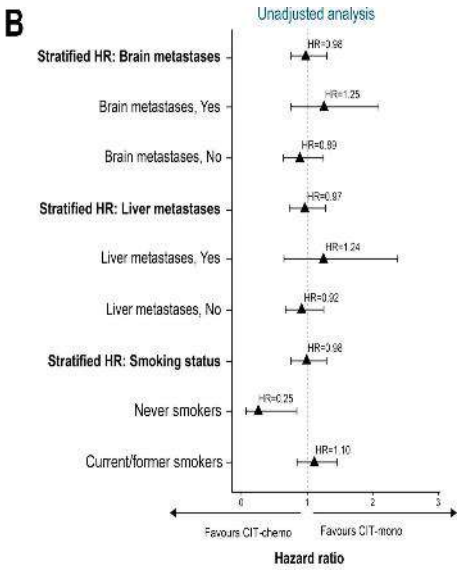
Rodriguez- Abreu Ann Oncol 2021; Reck et al. J Clin Oncol 2021
Reck et al. ESMO Open 2021, Garassino M, et al ESMO 2022; Paz-Ares L, et al ASCO 2022

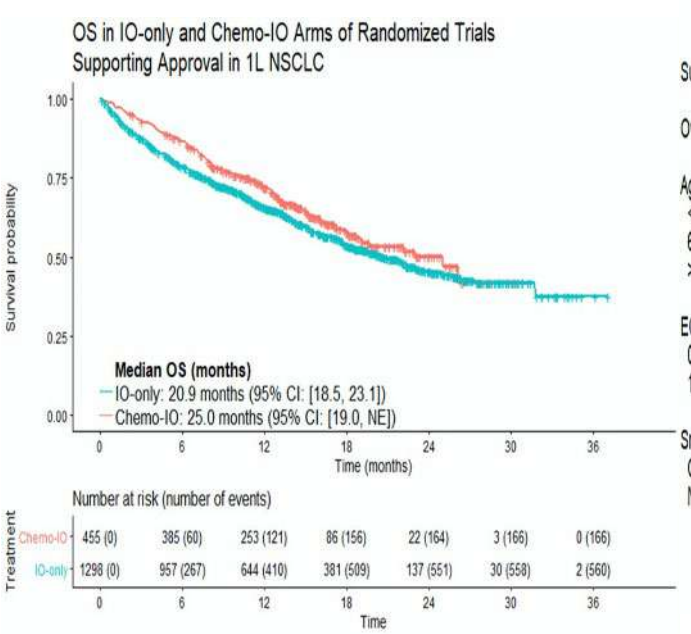
IO MONO VS. COMBOS IN PD-L1 ≥50% NSCLC SIMILAR OUTCOMES…

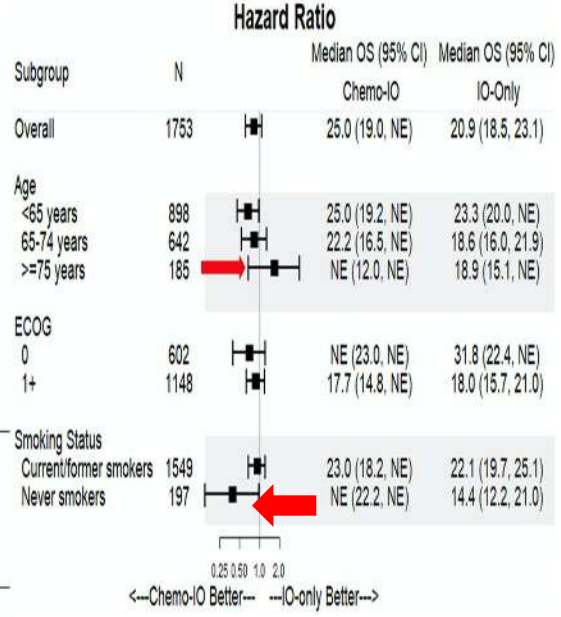


Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****





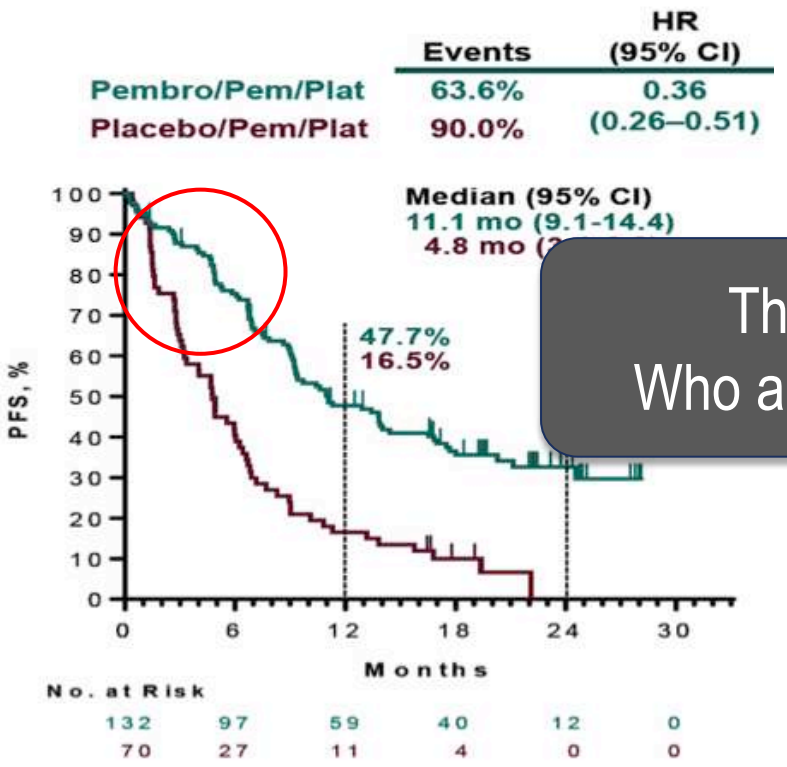




Perol M et al Ann Oncol 2022;
Akinboro et al. ASCO 2022

PFS in PD-L1 High NSCLC

KN-189 (TPS ≥50%)

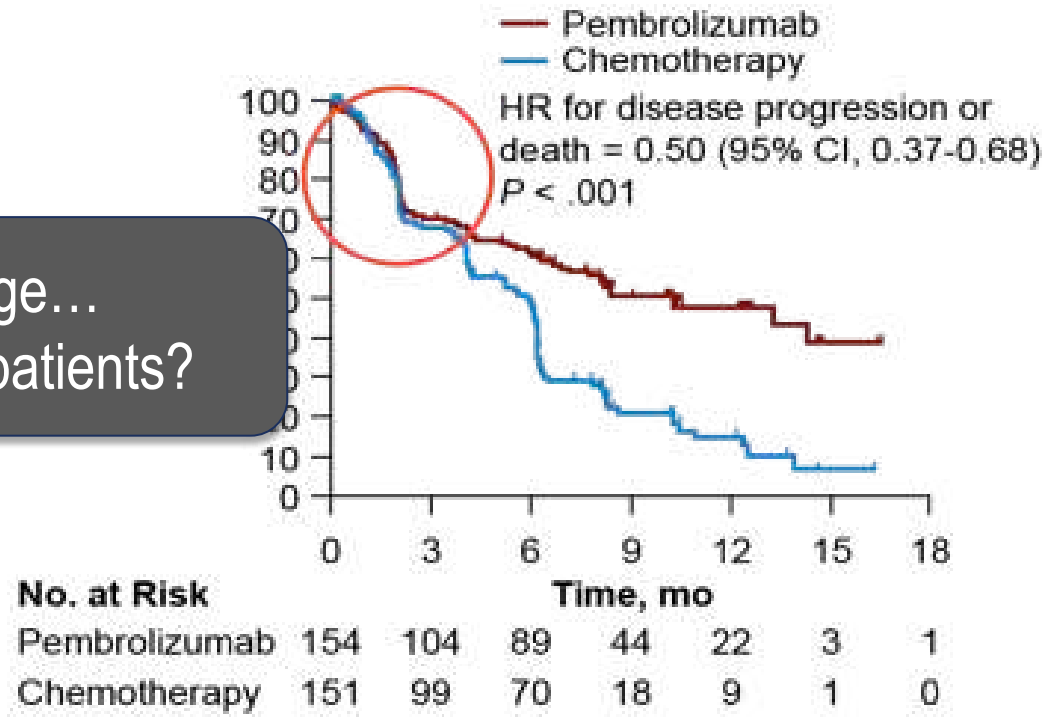


PFS: HR = 0.36
(95% CI, 0.26-0.51; *P* = .0001)

Median PFS: 11.1 vs 4.8 m
RR: 61.4% vs 22.9%

The challenge…
Who are these patients?

KN-024



PFS: HR = 0.50
(95% CI, 0.37-0.68; *P* < .001)

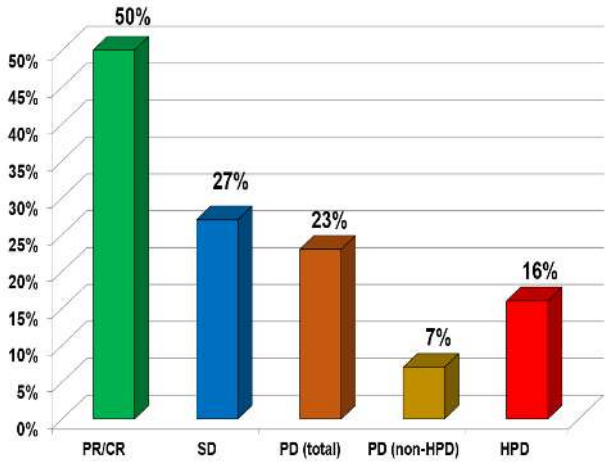
Median PFS: 10.3 vs 6.0 m
RR: 44.8% vs 27.8%

Gadgeel ASCO 2019; Gandhi, NEJM 2018; Reck, NEJM 2016

Hyperprogressive disease…

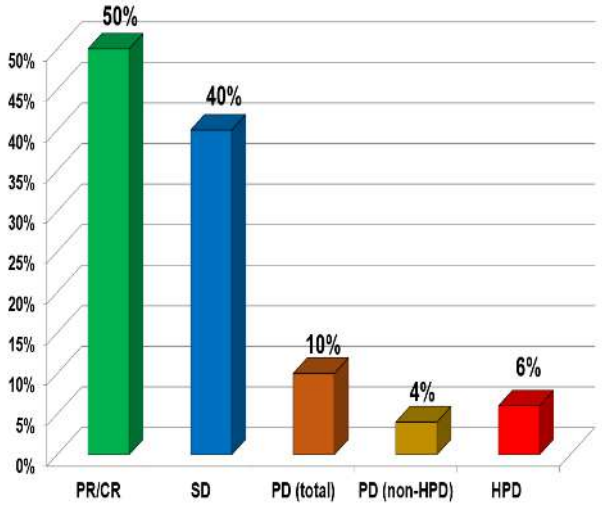
Tumor burden…

Single agent ICI
PD-L1 ≥ 50%

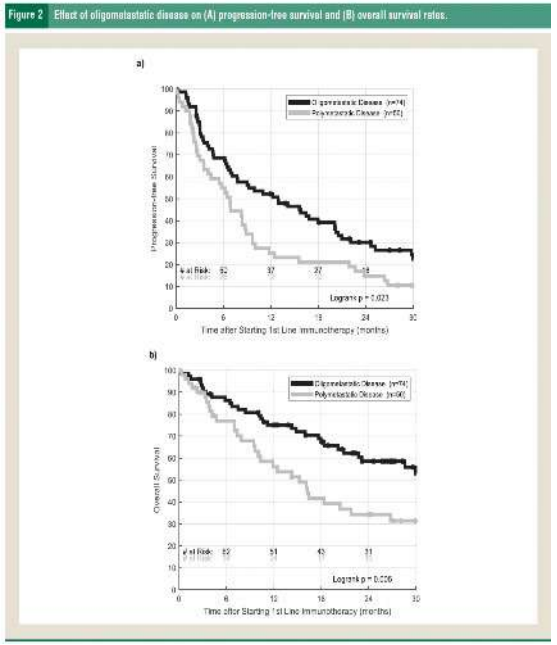


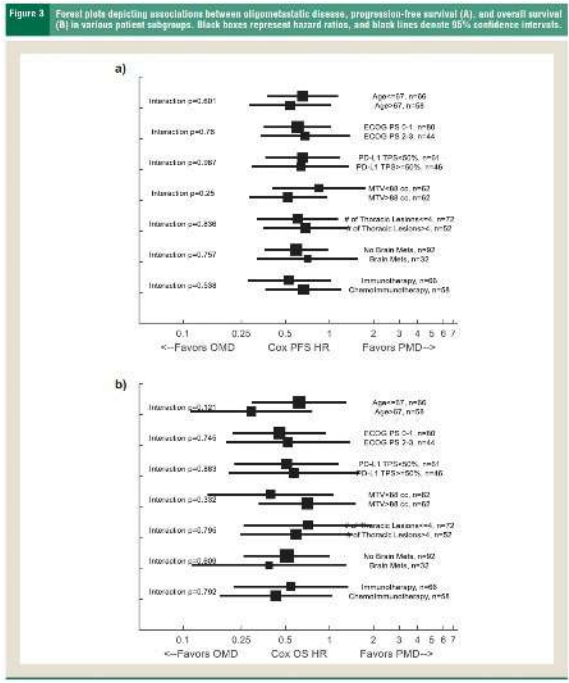
N=44

Chemo + ICI
All comers



N=50





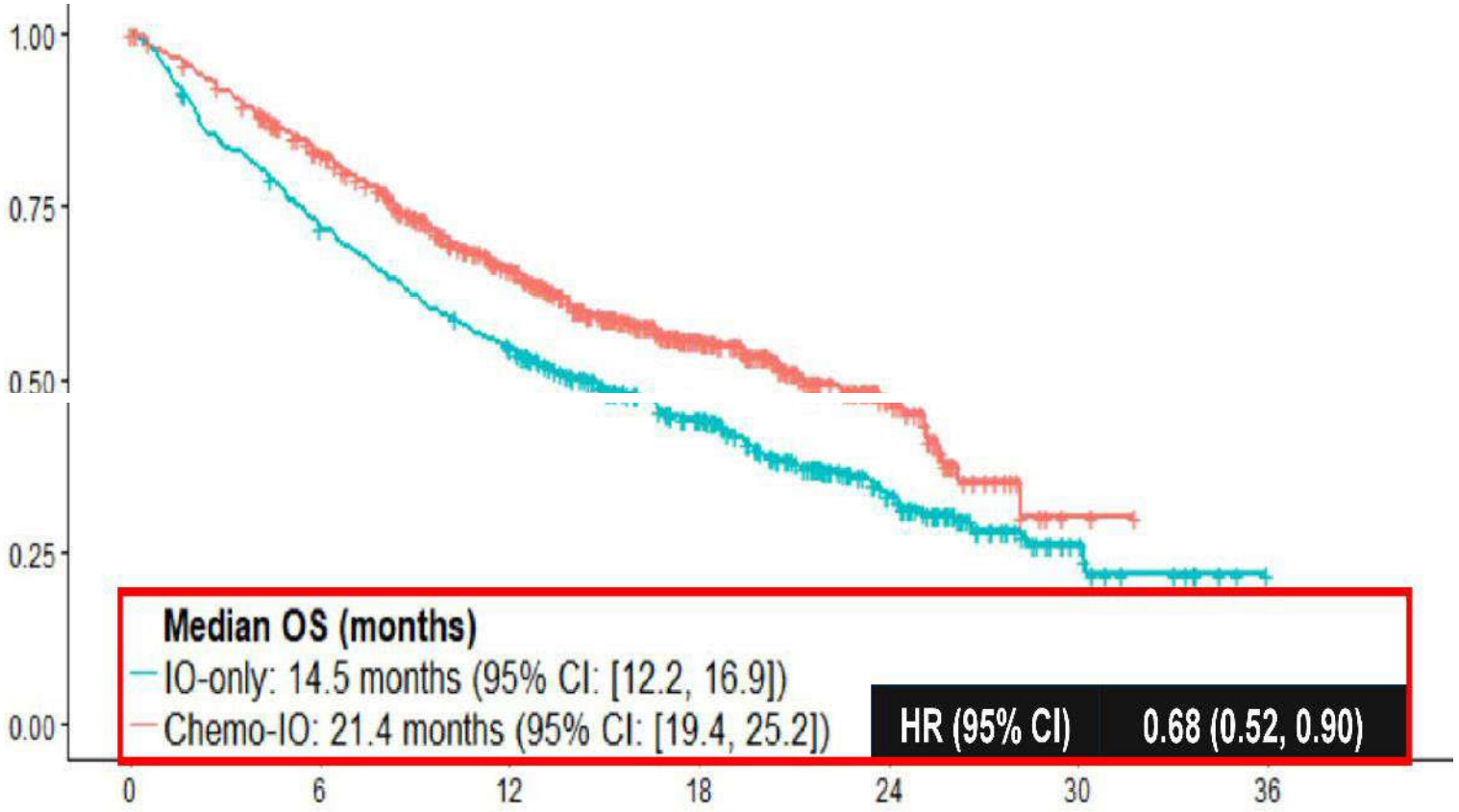
HPD occurs in up to 16% of PD_L1 TPS ≥50% pts upon first-line single agent ICI and is associated with por baseline PS, dNLR>3 and poor survival after adjustement fo potential prognostic variables

For advanced NSCLC patients receiving first-line IMT, the **presence of extrathoracic OMD and low volumetric disease burden on PET are favorable prognostic factors**

Ferrara R, et al. ESMO 2020
Andraos et al. Clin Lung Cancer 2022

IO MONO VS COMBOS IN PD-L1 1-49% NSCLC… COMBOS BETTER

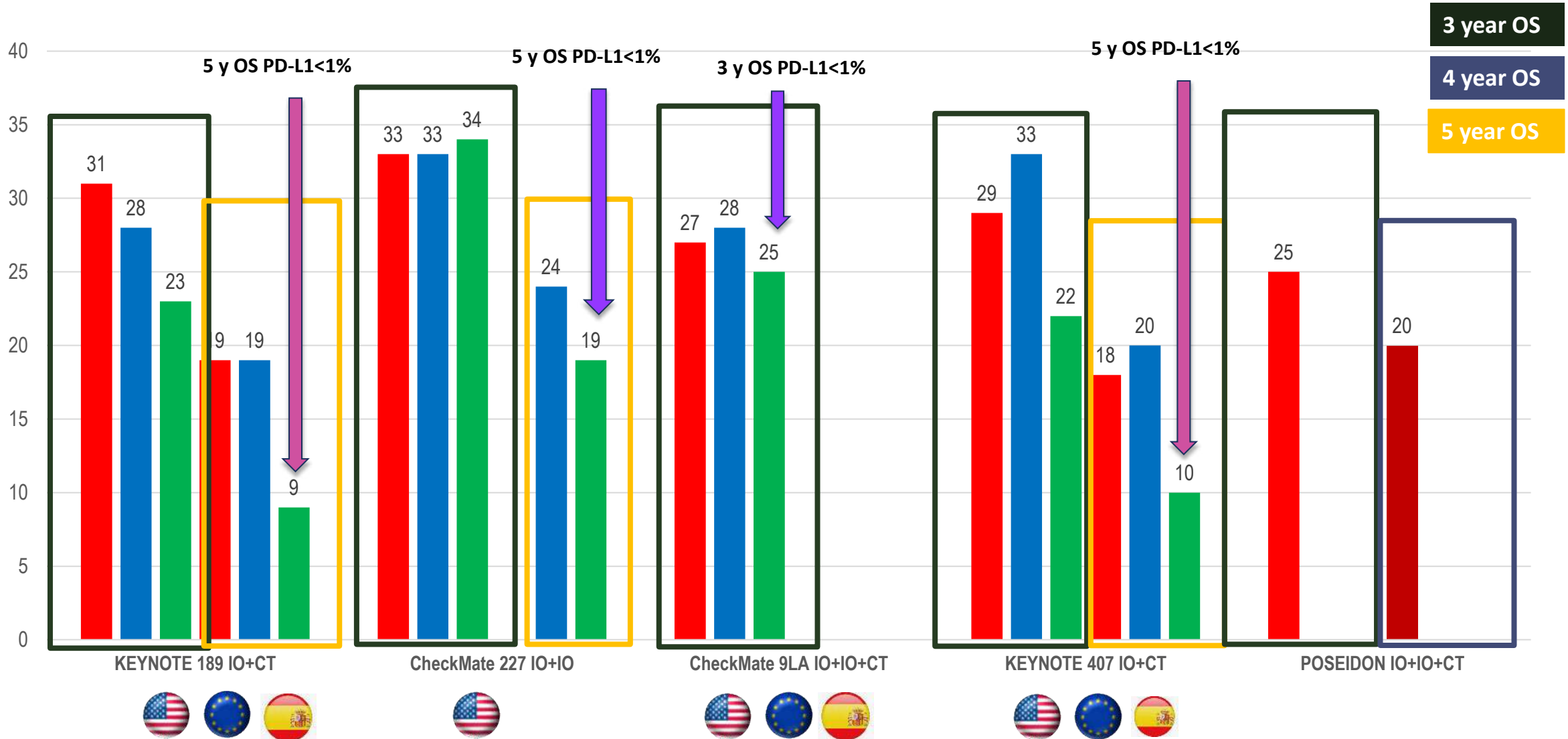
Trial*
Immunotherapy-only (PD-L1 ≥1%)
KEYNOTE-042
CHECKMATE-227
Chemo-immunotherapy
KEYNOTE-189
KEYNOTE-407
KEYNOTE-021 (cohort G)
IMPOWER-150**
IMPOWER-130
CA2099LA



Akinboro et al. ASCO 2021

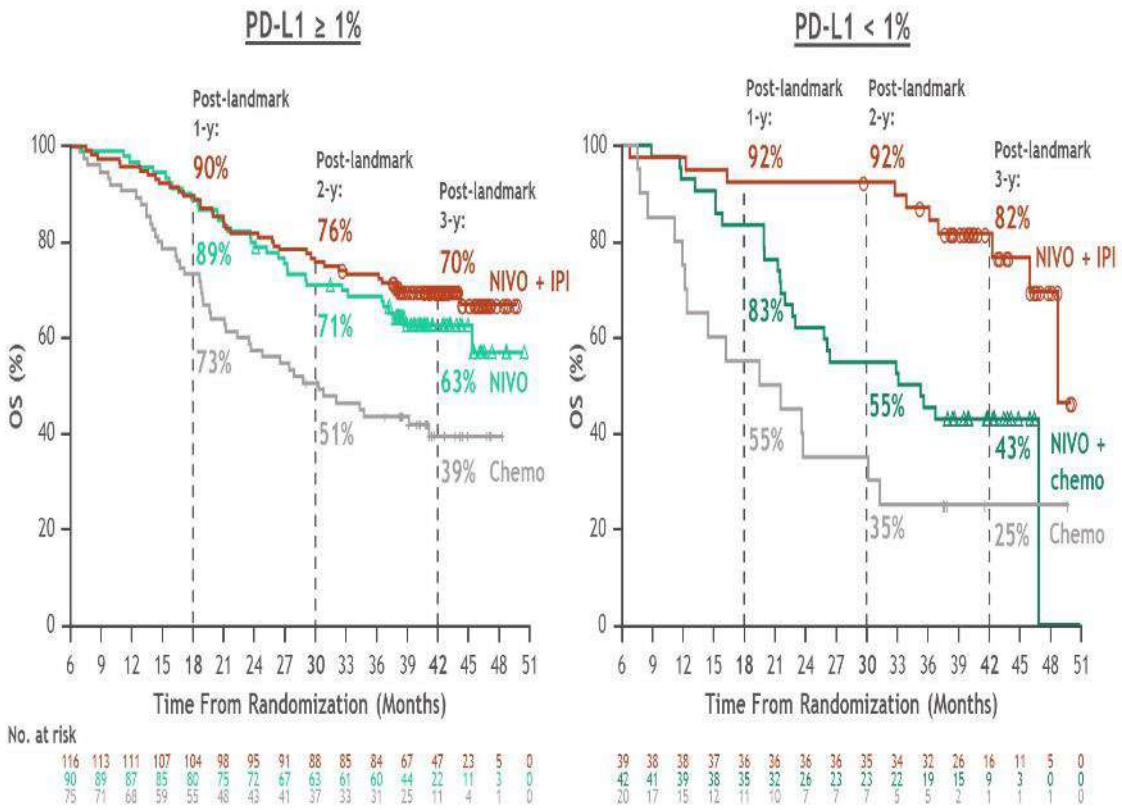
THE TALE OF THE CURVE…
ACCORDING TO PD-L1 EXPRESSION

3-y OS in the whole population
3-y OS in the PD-L1 ≥1-49%/ > 1%
3-y OS in the PD-L1 <1%
5-y OS in the whole population
5.Y OS in the PD-L1 >1%/ 1-49%
5-y OS in the PD-L1<1%

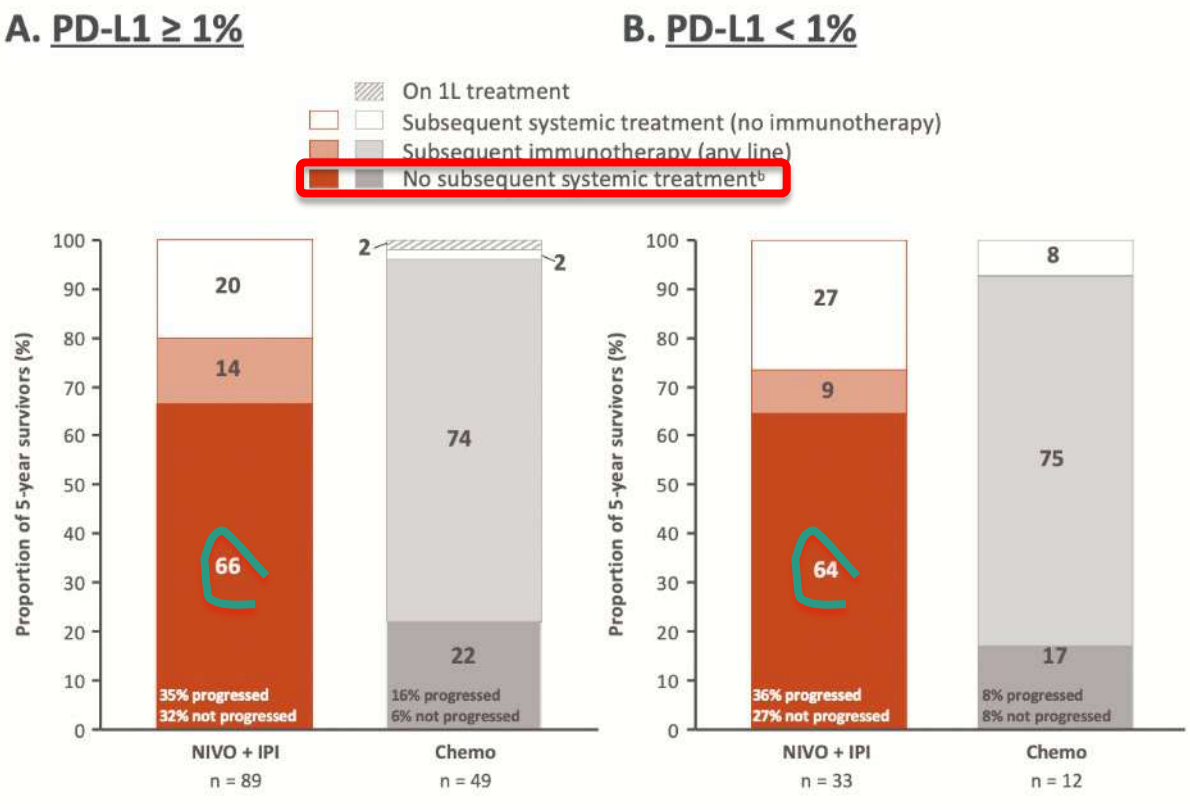


Reponse and long term activity

CM227: Post-landmark OS in CR/PR PD-L1≥ 1% and PD-L1< 1%



CM 227: Treatment status in 5-year survivors

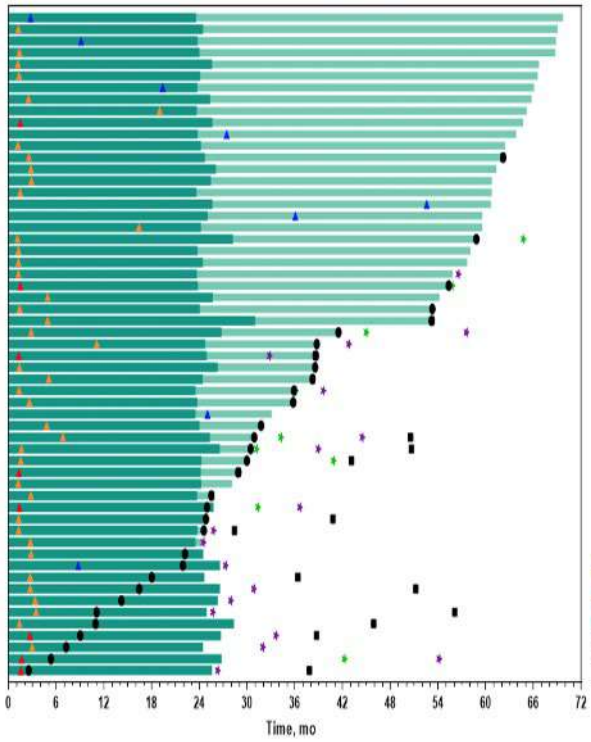


Ramalingam et al ASCO 2020; Brahmer J, et al. ASCO 2022

Patients who completed treatment, better outcome

KEYNOTE 189

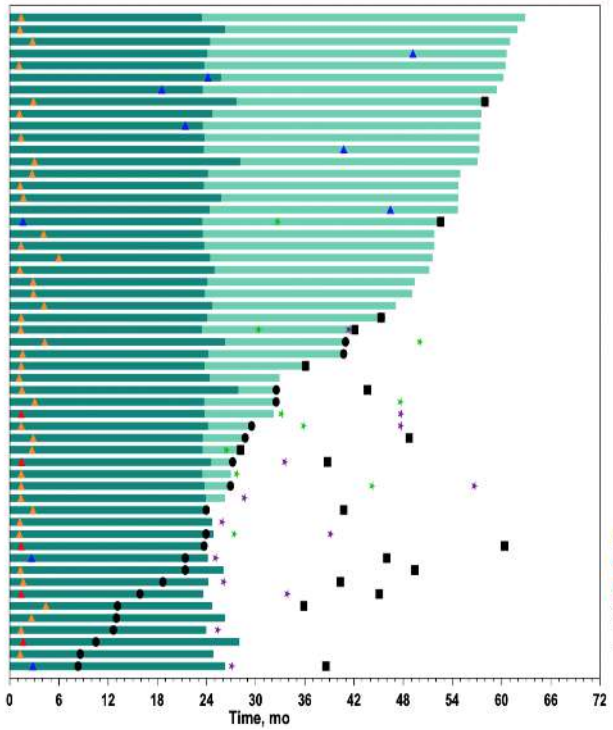
Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

KEYNOTE 407

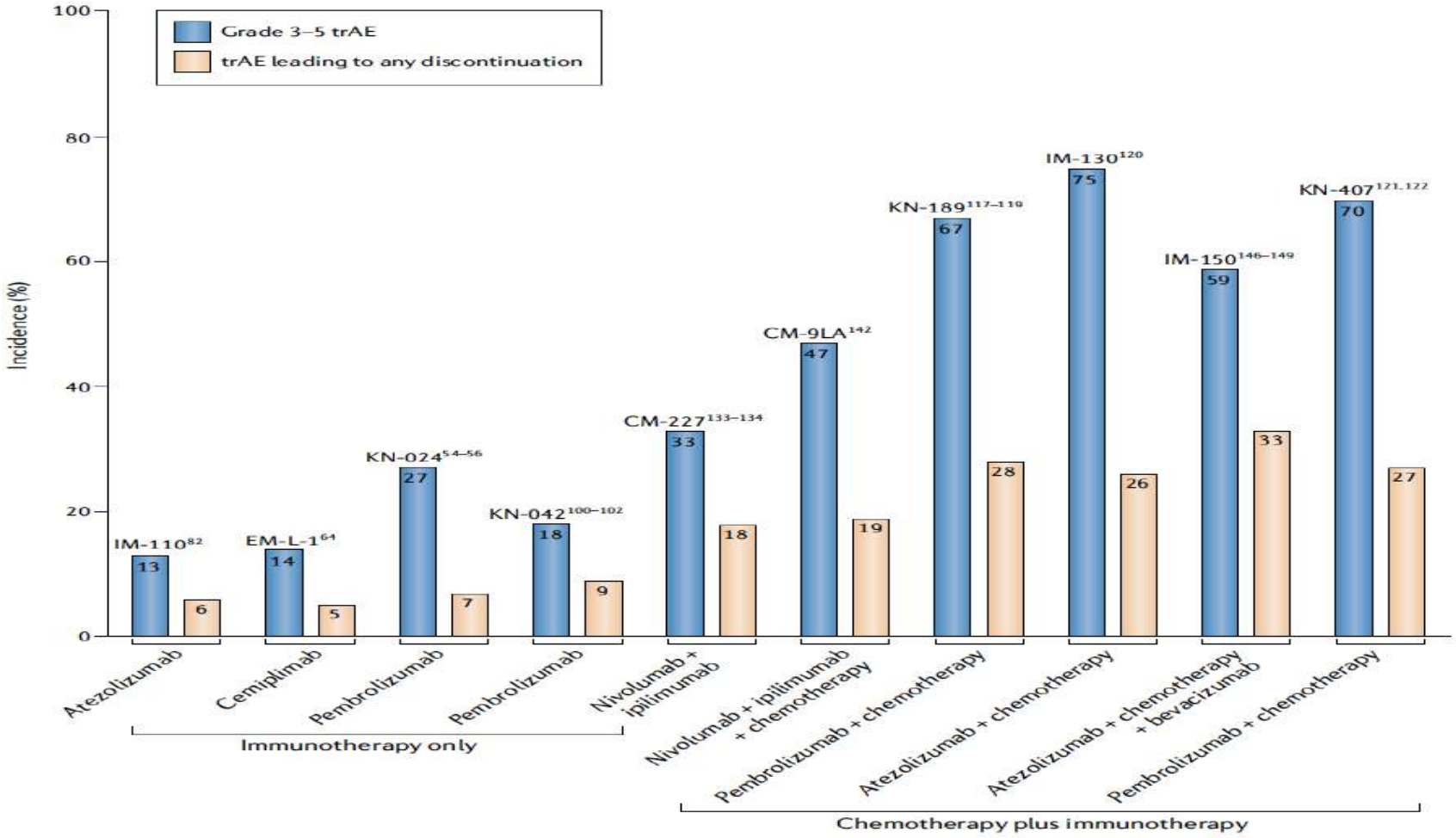
Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



	n = 55
ORR (95% CI),[a] %	90.9 (80.0–97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] mo	NR (7.1 to 61.5+)
3-y OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

Garassino M, et al ESMO 2022; Novello S, et al. ESMO 2022

SHOULD TOXICITY BE AN ELEMENT FOR DECISSION?



Grant M, et al. Nat Rev Clin Oncol 2021

Expanding the population eligible for IO treatment

eNerGy
What about PS STATUS AND AGE?

eNerGy : a study dedicated to elderly and PS2 patients

eNerG

Key Eligibility Criteria
- Stage IV or recurrent
- Squamous or Non-Squamous
- No prior systemic therapy for advanced disease
- No known EGFR mutations or ALK or ROS1 alteration
- Age ≥ 70 ECOG PS 0-1 or PS 2

Stratified by :
· Age ≥ versus < 70 years
· PS 0/1 versus 2
· Histology : squamous/non-squamous

R 1:1

n = 109 → **NIVO** 240 mg Q2W + **IPI** 1 mg/kg Q6W

2.9% PD-L1>50%

n = 107 → **Chemo** Q3W (**4 cycles**) Platinum doublet with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

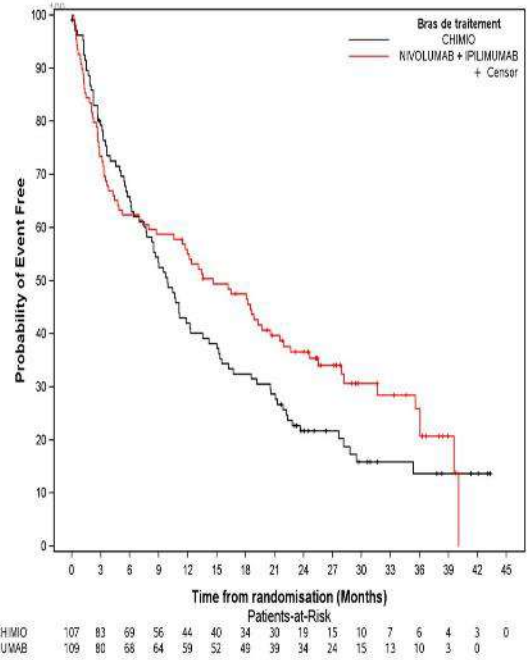
Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Efficacy by tumor PD-L1 expression
- QOL, geriatric mini dataset

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: H Lena MD

Primary endpoint : Overall survival in ITT population

Overall survival whole population



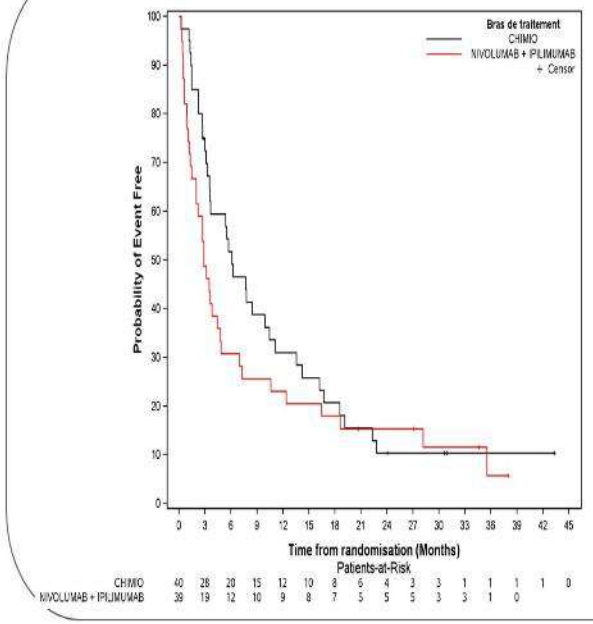
	NIVO IPI n = 109	Chemo n =107
Median OS, mo (95% CI)	14.7 (8-19.7)	9.9 (7.7-12.3)
HR (95% CI)	0.85 (0.62–1.16) *P* = 0.2978	
Survival 1 year	55% 45.2%-63.8%	42% 32.5%-51.2%
Survival 2 years	36.6% 27.5%-45.7%	21% 14.3%-30.0%

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: H Lena MD

Lena H, et al. ASCO 2022

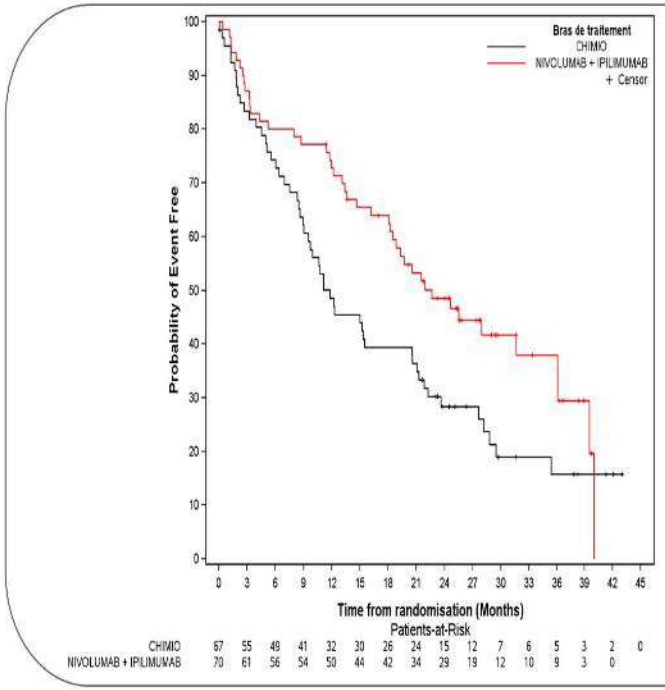
Overall survival PS 2 patients

Overall survival (ITT population) – PS 2



	NIVO IPI n = 40	Chemo n = 39
Median OS (95% CI)	2.9 (1.4-4.8)	6.1 (3.5-10.4)

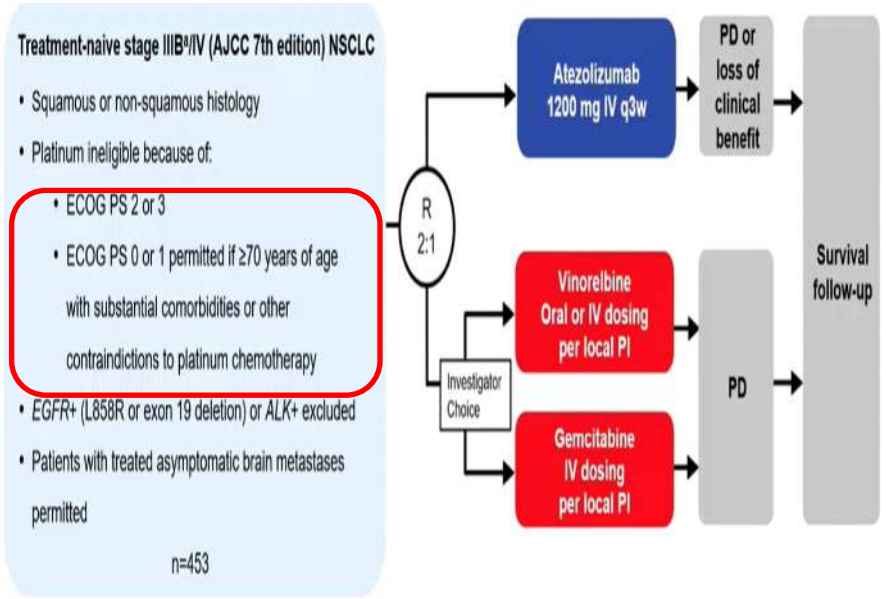
Overall Survival elderly patients PS 0-1



	NIVO IPI n = 70	Chemo n = 67
Median OS, mo (95% CI)	22.6 (18.1-36)	11.8 (8.9-20.5)
HR (95% CI)	**0.63** (0.42–0.95)	

Lena H, et al. ASCO 2022

IPSOS: PHASE III COMPARING ATEZOLIZUMAB VS SINGLE-AGENT CHEMOTHERAPY IN PATIENTS NOT ELIGIBLE FOR A PLATINUM-BASED REGIMEN



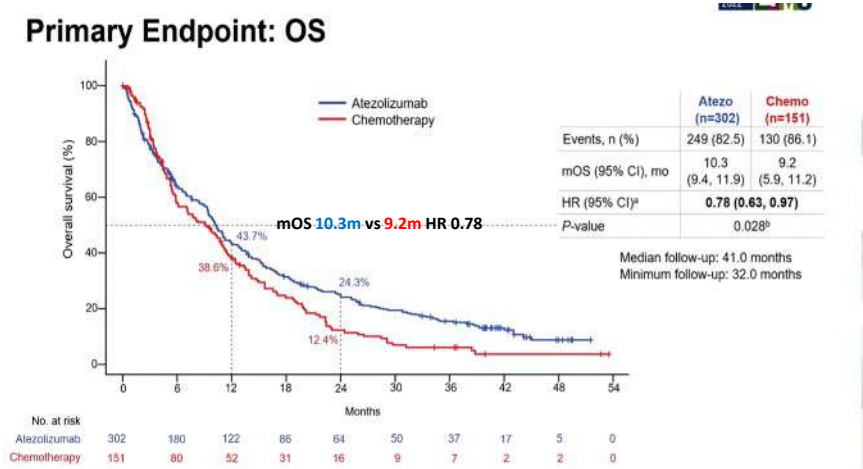
Stratification factors:
- Histology (squamous or non-squamous)
- PD-L1 expression level by SP142 IHC assay (TC3 or IC3 vs TC0/1/2 or IC0/1/2[b] vs unknown)
- Brain metastases (yes/no)

Primary endpoint:
- OS

Secondary endpoints:
- OS rates at 6, 12, 18 and 24 months
- PFS
- Objective response rate
- Duration of response
- OS and PFS in PD-L1 positive subgroup[c]

Other endpoints:
- PROs
- Safety
- Exploratory biomarker analyses

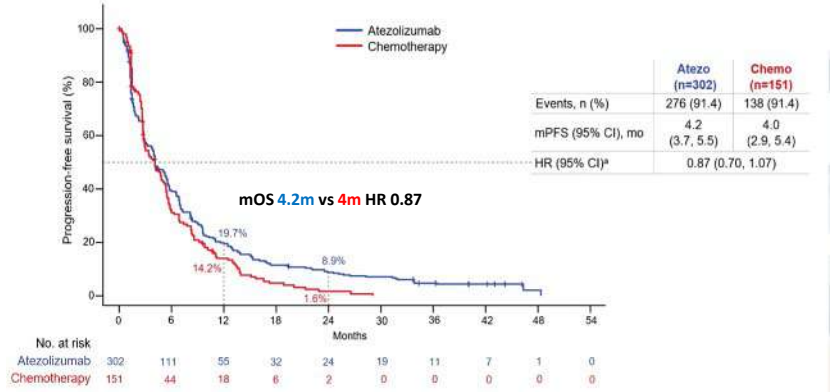
Primary Endpoint: OS



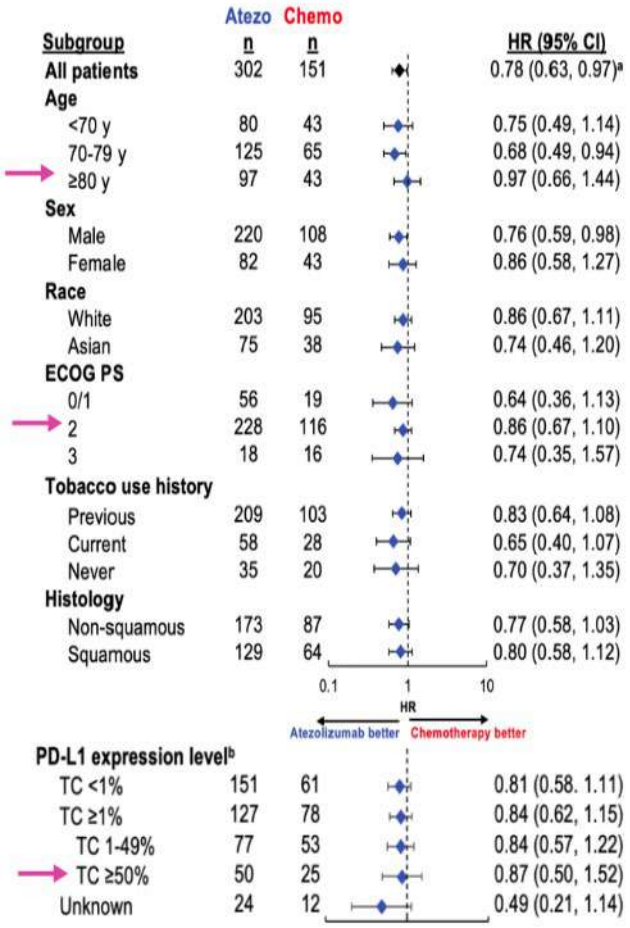
	Atezo (n=302)	Chemo (n=151)
Events, n (%)	249 (82.5)	130 (86.1)
mOS (95% CI), mo	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
HR (95% CI)[a]	0.78 (0.63, 0.97)	
P-value	0.028[b]	

Median follow-up: 41.0 months
Minimum follow-up: 32.0 months

Secondary Endpoints: PFS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	276 (91.4)	138 (91.4)
mPFS (95% CI), mo	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
HR (95% CI)[a]	0.87 (0.70, 1.07)	



Lee et al. ESMO 2022; Lee et al, Lancet 2023

Beyond clinical characteristics

Do patients with *KRASm* NSCLC respond differently to 1L ICI ± chemo than those with *KRASwt* NSCLC?

Patients with advanced NSCLC from 12 randomized trials submitted to FDA for marketing approval

Some trials included *EGFR* & *ALK* mutated NSCLC

- ICI+chemo
- ICI alone
- Chemo alone

Differences in ORR, OS?

Subgroups:
KRAS: wildtype, mutant, G12C

PD-L1 TPS: high(≥50%), low(1-49%), negative(<1%)

Statistical Methods

- ORR 95% CIs estimated using Clopper-Pearson exact method
- OS medians and 95% CI estimated with Kaplan-Meier method
- OS hazard ratios estimated with Cox proportional hazards model stratified by trial with treatment arm, KRAS status, and treatment by KRAS interaction as covariates

12 Randomized 1L Trials of ICI+Chemo, ICI Alone, or Chemo Alone Arms Submitted for Marketing Approval

N = 8888

KRAS mutation status reported
N = 1430 (16%)

	KRASwt N = 875 (61%)	*KRASm* N = 555 (39%)	*KRAS G12C* N = 157 (11%)
PD-L1 TPS, %			
Negative (<1%)	40	36	37
Low (1-49%)	32	32	32
High (≥50%)	27	31	31
Treatment Arm, %			
ICI+Chemo	35	39	37
ICI alone	27	24	29
Chemo alone	36	36	34

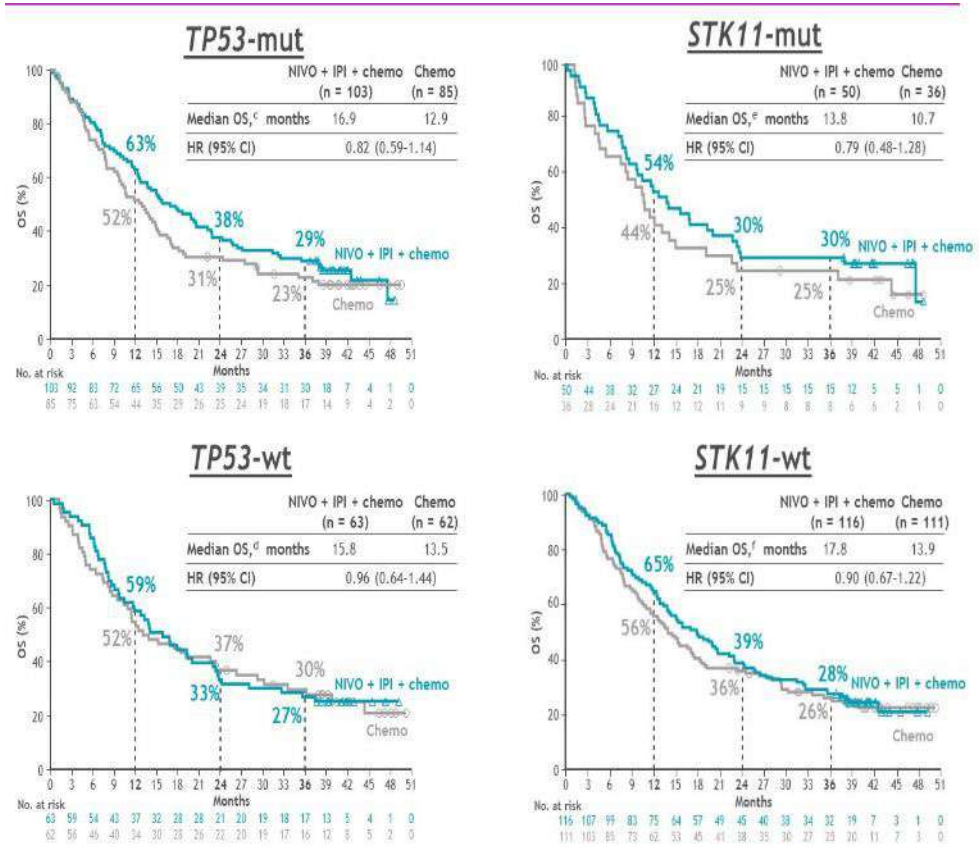
Results: Median OS according to *KRAS* status

Patients with *KRASm* NSCLC have similar OS to those with *KRASwt* NSCLC

Study Therapy	Median OS, mos (95% CI)		
	KRASwt	*KRASm*	*KRAS G12C*
ICI+chemo	**18.7** (16.0, 25.2) N=313	**22.4** (18.2, NE) N=219	**20.8** (11.3, NE) N=58
	HR 1.12 (95% CI: 0.86, 1.46)		
ICI alone	**16.4** (13.4, 19.7) N=240	**16.2** (11.1, NE) N=135	**11.8** (8.2, NE) N=45
	HR 1.01 (95% CI: 0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR 1.02 (95% CI: 0.81, 1.29)		

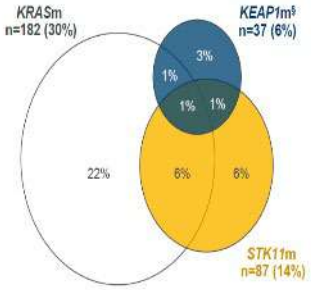
Nakajama E, et al. ASCO 2022

CHECKMATE 9LA
OS by oncogenic mutation status



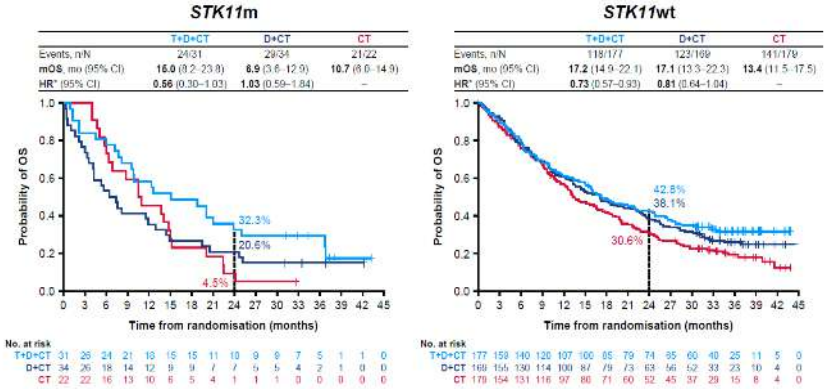
POSEIDON:
OS by oncogenic mutation status

Mutation-evaluable population‡
(n=612; **96%** of randomised patients with NSQ histology)



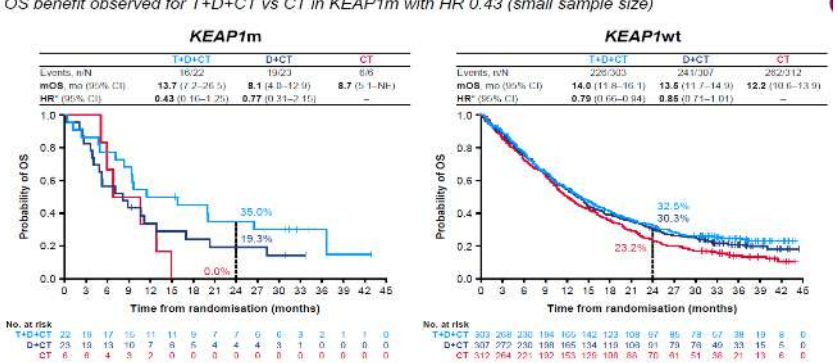
OS by *STK11* Mutation Status

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%



OS by *KEAP1* Mutation Status

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



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

Paz Ares L, et al. ASCO 2022
Peters S, et al. WCLC 2022

CAN WE DO BETTER?

Treatment beyond PD/ Escalation/ De-escalation

Treatment duration

ctDNA

New agents and new combinations

Treatment beyond PD/ escalating treatment????

ORIGINAL ARTICLE

IASLC

Atezolizumab Treatment Beyond Progression in Advanced NSCLC: Results From the Randomized, Phase III OAK Study

David R. Gandara, MD,[a,*] Joachim von Pawel, MD,[b] Julien Mazieres, MD, PhD,[c]

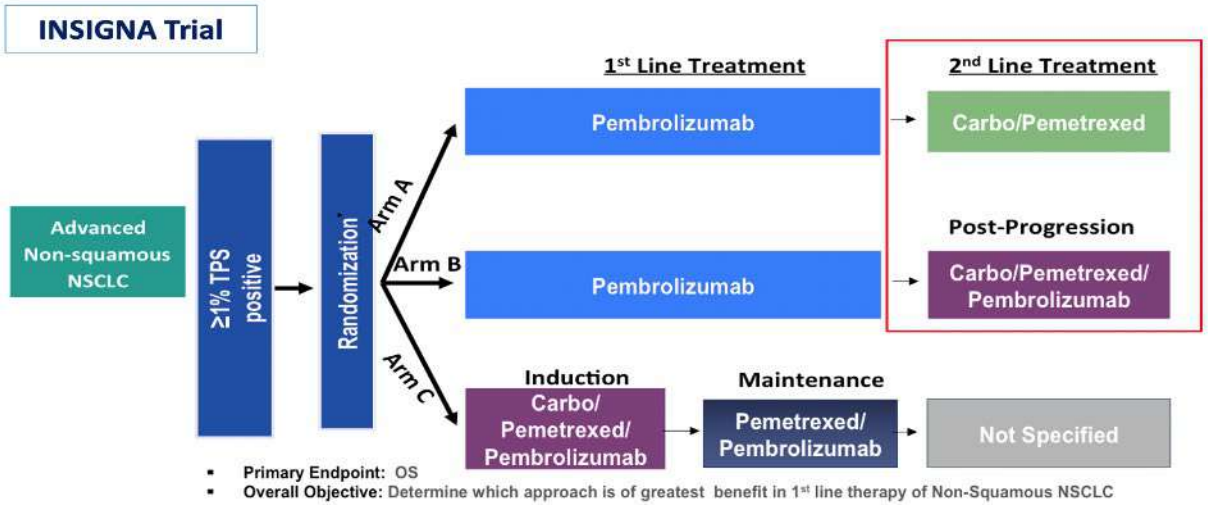
Exciting EMPOWER-Lung 1 Cohort A results

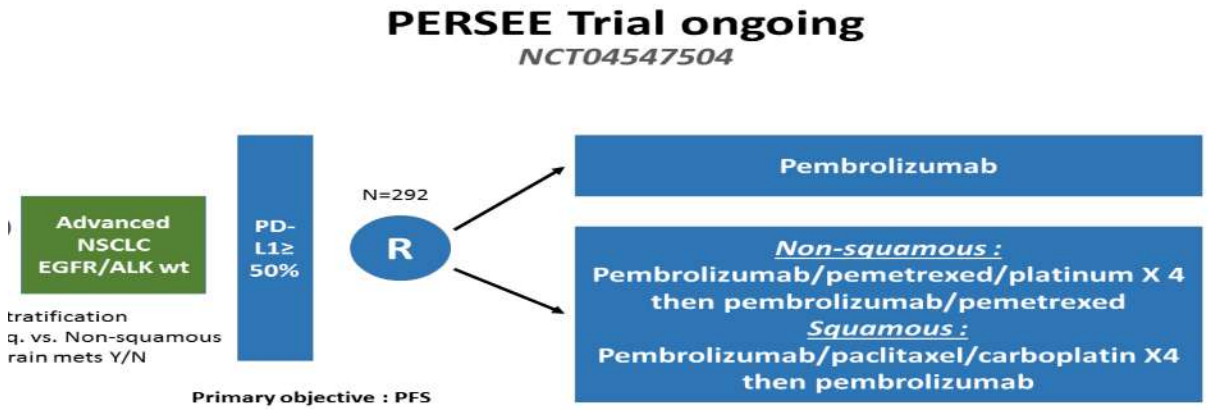
Prolonged Survival in the 2nd Line Setting

nued Cemiplimab Beyond Progression with Addition of Chemoth

	Cemiplimab Beyond Progression N=64	
OS	Period 1+2 Randomization to Death	Period 2 Day 1 of Continued Treatment to Death
Median (95% CI, months)	27.4 (23.0, 31.8)*	15.1 (11.3, 18.7)
Estimated Survival Probability, % (95% CI)		
6 months	100 (NE, NE)	91.9 (81.6, 96.5)

Continued cemiplimab with addition of chemotherapy beyond progression appears superior to historical data for chemotherapy in the 2nd line setting where median OS is 8.4 months (range: 5.6 - 11.2) (Bersanelli et al., Lung Cancer, 2020)





Gandara D, et al. J Thorac Oncol 2018; Ozguroglu M, et al. ESMO 2022

Treatment duration

DICIPLE

Multicenter, non-inferiority, randomized phase III trial

Histogically-proven stage IV NSCLC:
- Measurable disease
- PS 0-1
- 18 – 75 years
- Any PDL1
- w/o EGFR/ALK alterations
- chemo & i.o naive

n = 1360

Nivolumab 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

At 6 months patients with disease control Randomized 1:1

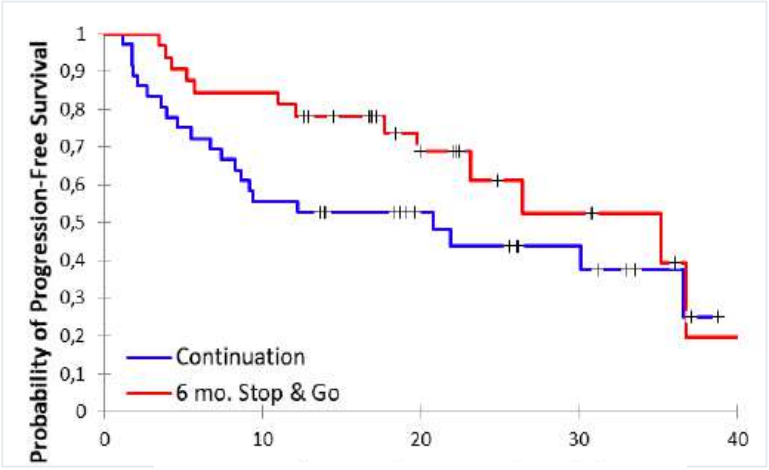
n = 868

Stratification factors:
- SCC/non-SCC
- PD-L1 (<1%, 1-49%, ≥50%)
- Ever smokers/never-smokers
- response: PR/SD
- PS = 0 *vs.* PS=1

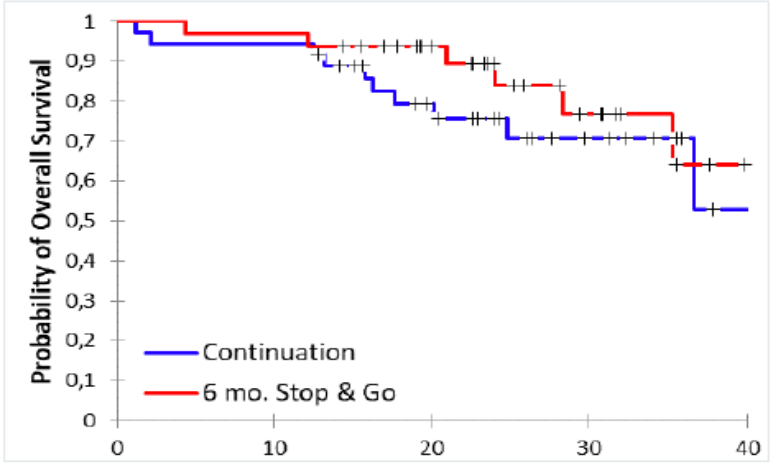
Arm A: **Nivolumab** 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w → *Prog* → **Platinum-based doublet recommended**

Arm B: **Observation** → *Prog* → **Nivolumab** 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

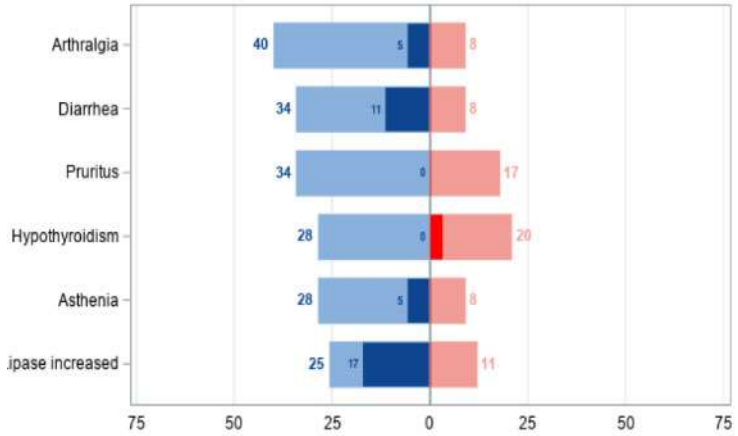
- Primary endpoint : **PFS from randomization**
- Secondary endpoints : safety and tolerance, overall survival, quality of life, PD-L1 tumour expression prognostic and predictive value
- CT-scan f.u q8 weeks for 1 year, then q12 weeks in both arms



mPFS: 35.2 *vs.* 20.8 mo., p=0.12



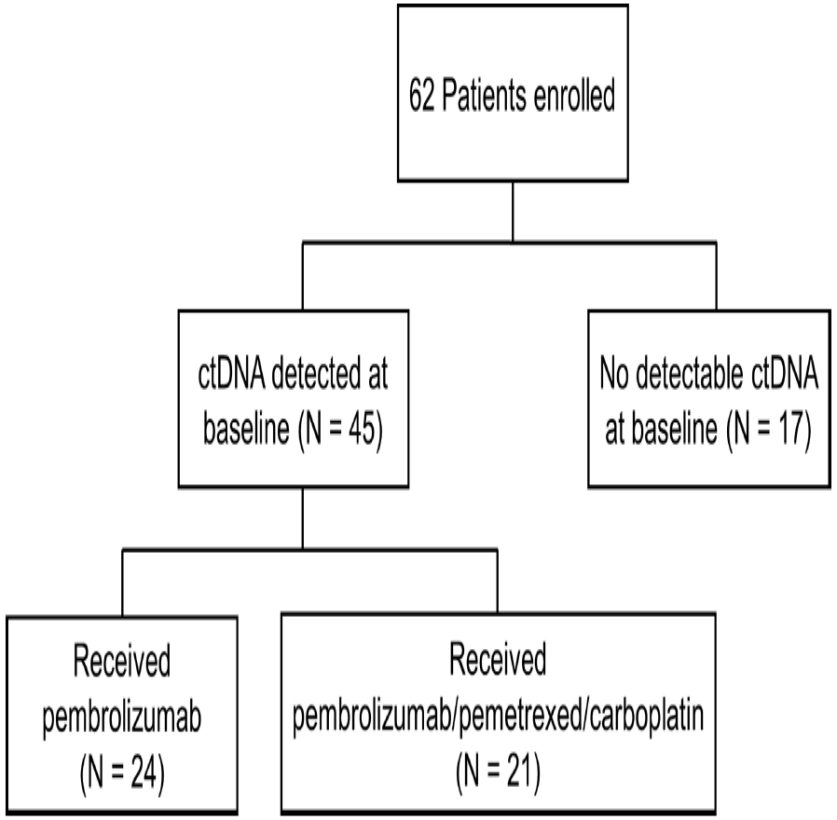
mOS: NR *vs.* NR mo., p=0.33

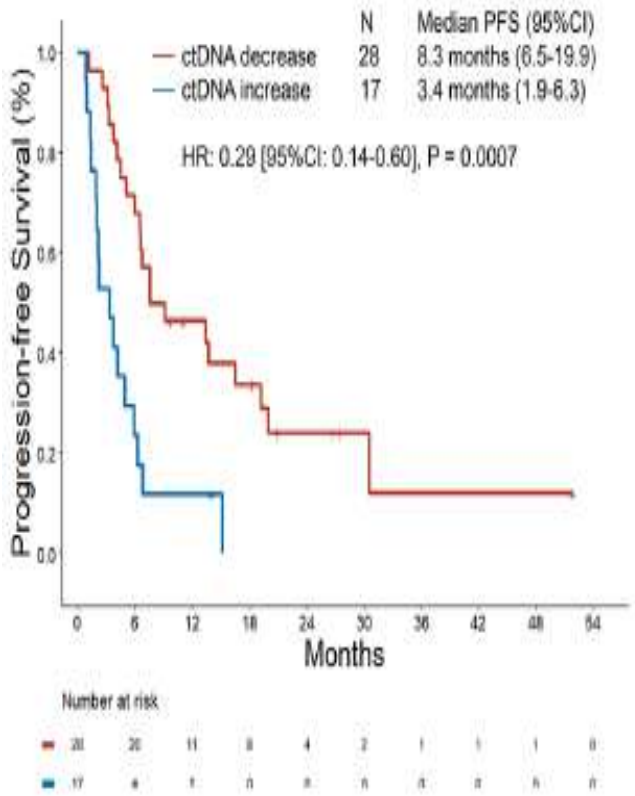


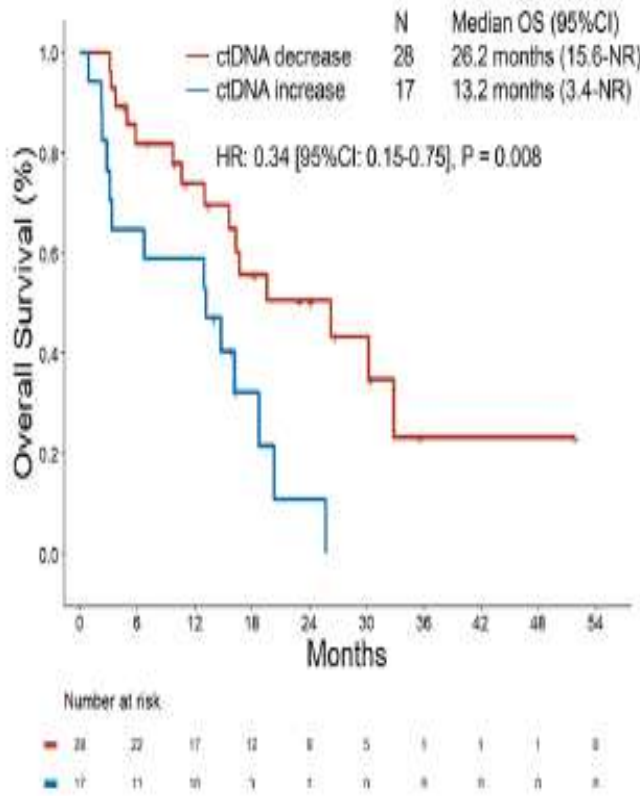
Lower G ≥3 ir-AEs with stop *vs.* continue

Zalcman e al. ESMO 2022

ctDNA: could be an early marker of efficacy?







Ricciuti et al. JITC 2021

It is difficult to improve on immunotherapy outcomes in first line

Despite promising phase I or II* data, phase III trials negative

Trial	Phase	Drugs	N	PFS, HR	OS, HR
KEYNOTE 598 PD-L1≥50%	III	**Pembrolizumab ± Ipilimumab**	568	1.06 (0.86-1.30)	1.08 (0.85-1.37)
SKYSCRAPER-01 PD-L1 ≥50%	III	**Atezolizumab ± Tiragolumab (aTIGIT)**	135	Press release: NEG for co-primary endpoint PFS OS still immature	
INTREPID-Lung 037 PD-L1 ≥80% (73-10)	III	**Pembrolizumab *vs.* M7824 (bifunct fusion protein targeting TGF-beta & PD-L1)**	304	1.23 (0.89-1.71)	1.20 (0.89-1.81)
LEAP007 PD-L1 ≥1%	III	**Pembrolizumab ± Lenvatinib (multikinase inhibitor)**	623	0.78 (0.64-0.95)	1.10 (0.87-1.39)

Primary** (~PD, SD < 6mo) or secundary resistance** (~CR, PR, SD ≥6mo) frequently develops

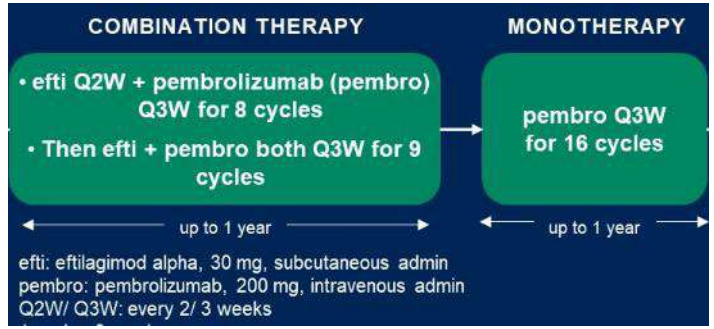
Slide courtesy J Remon, adapted

Boyer JCO 2021 – Cho JTO 2023 - Csoszi ESMO IO 2021 - Kluger JITC 2019 - Kluger JITC 2023 – Rizvi JITC 2023 ** definitions slightly different for IO mono – IO combo and chemo-IO

aLAG3

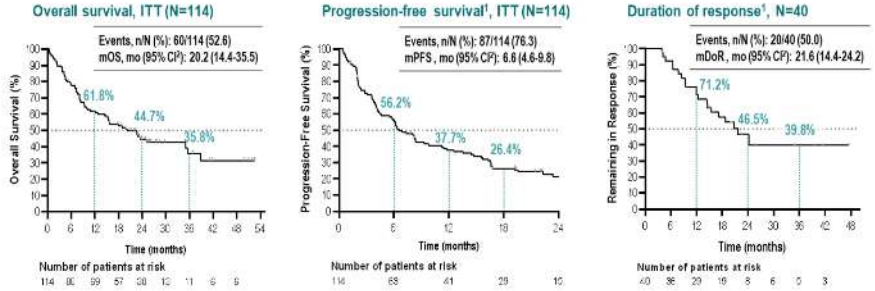
TACTI-002 1st line efti (sLAG3-Ig) + pembro

PART A ONLY
- Advanced/metastatic (stage IIIb /IV) NSCLC (SQ & NSQ)
- Not amenable to ALK/EGFR based therapies or therapy with curative intent
- Treatment naive for advanced or metastatic disease

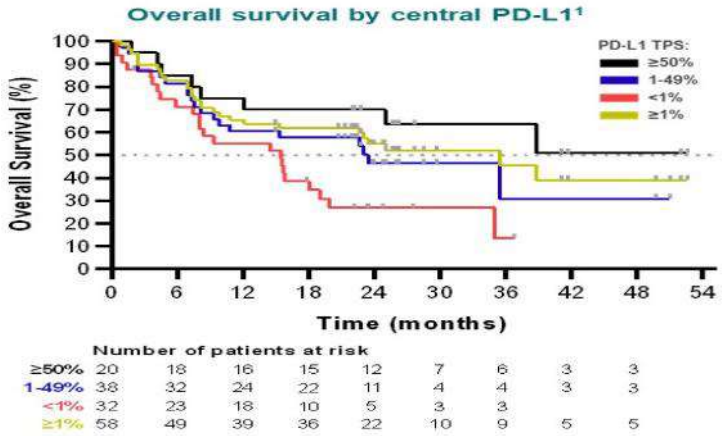


Efficacy - ITT

- Median OS of 20.2 mo in ITT where ~75% of patients had PD-L1 TPS score <50%, including ~35% with PD-L1 TPS of <1%.
- 45/114 (39.5%) received 2nd line therapy → mostly chemotherapy-based (42/45; 93.3%).
- Median DoR of 21.6 mo in the ITT.

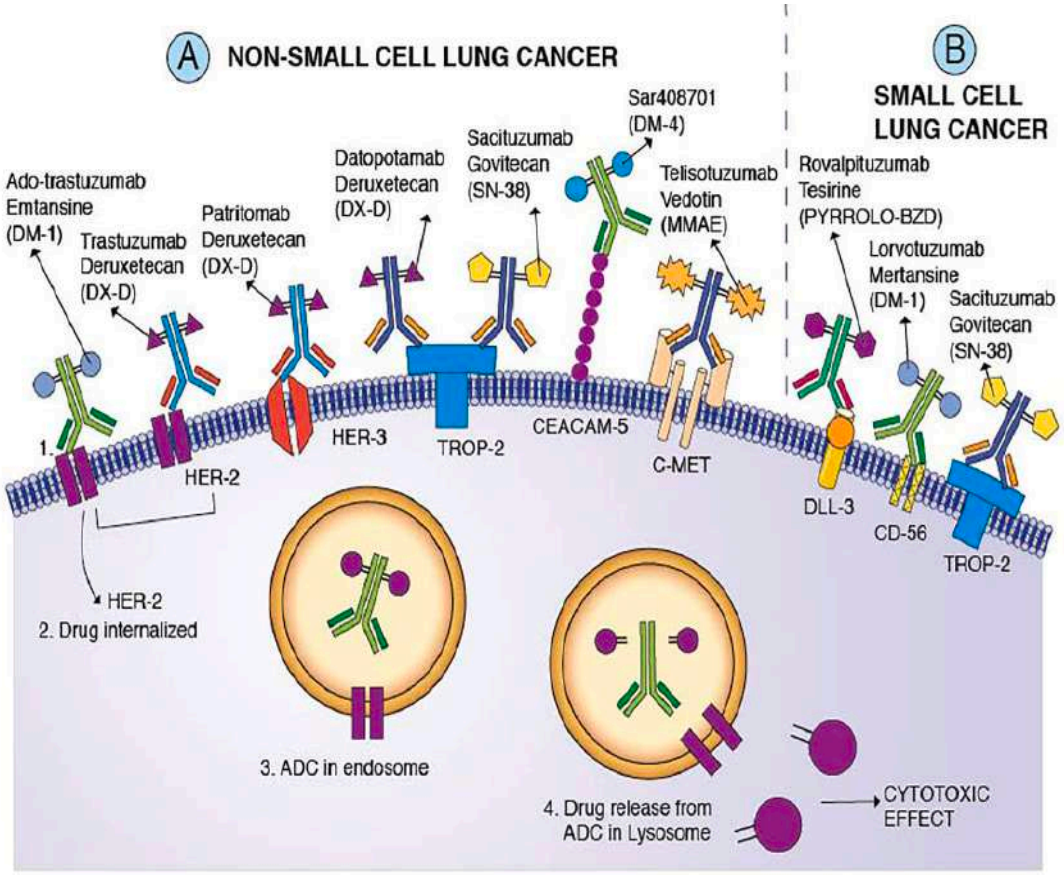


Efficacy parameter	<1%[1], n (%), N=32	1-49%[1], n (%), N=38	≥50%[1], n (%), N=20	≥1%[1], n (%), N=58
ORR[2,3], % (95% CI)[4]	31.3 (16.1-50.0)	44.7 (28.6-61.7)	55.0 (31.5-76.9)	48.3 (35.0-61.8)
mPFS[2], mo (% events)	4.2 (90.6)	9.3 (71.1)	16.5 (70.0)	11.2 (70.7)
mDoR[2], mo (% events)	20.7 (57.1)	NR (35.7)	18.7 (63.6)	24.2 (48.0)
mOS, mo (% events)	15.5 (71.9)	23.4 (52.6)	NR (40.0)	35.5 (48.3)

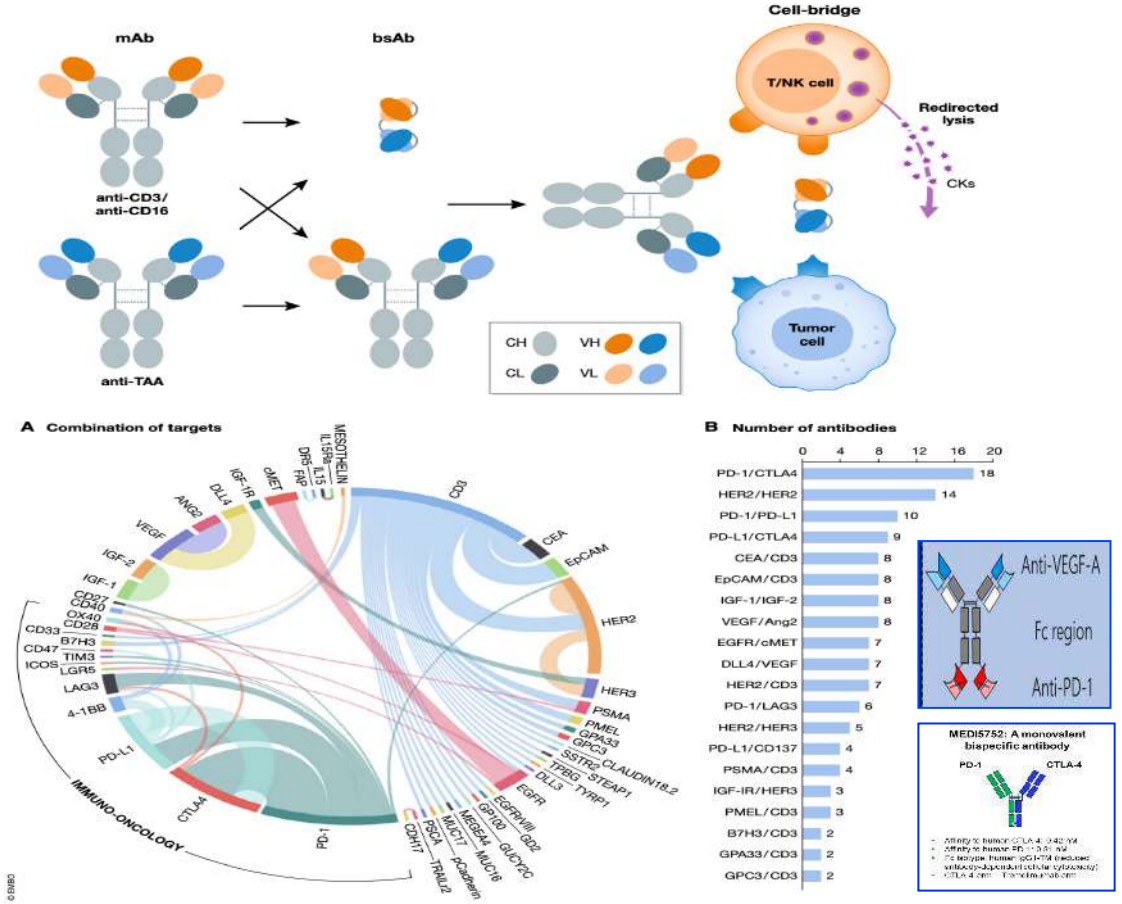


Most promising agents

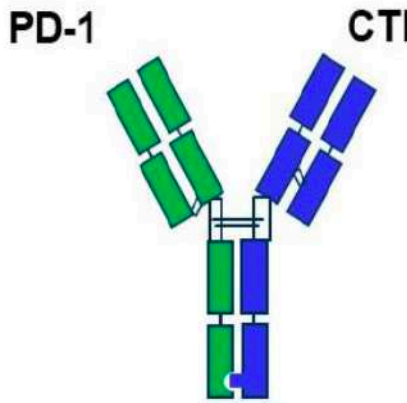
ANTIBODY DRUG CONJUGATED



BISPECIFIC ANTIBODIES



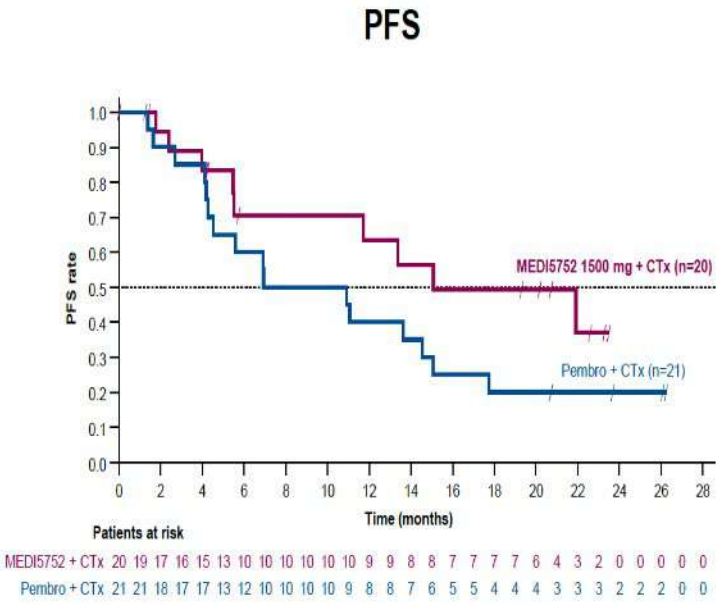
MEDI5752: A monovalent bispecific antibody



- Affinity to human CTLA-4: 0.42 nM
- Affinity to human PD-1: 0.81 nM
- Fc isotype: human IgG1-TM (reduced antibody-dependent cellular cytotoxicity)
- CTLA-4 arm = Tremelimumab arm

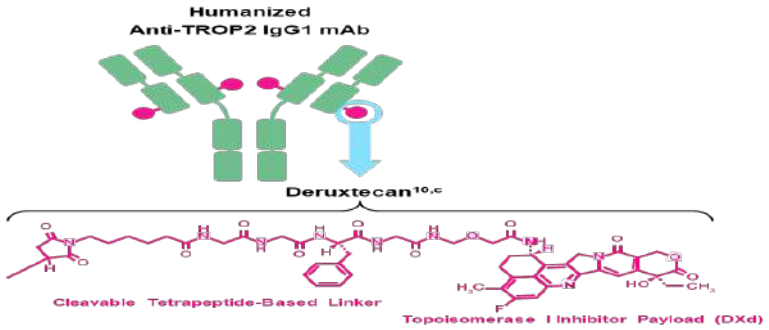
MEDI5752 1500 mg + CTx improved DOR, PFS and OS over pembrolizumab + CTx in first-line non-squamous NSCLC

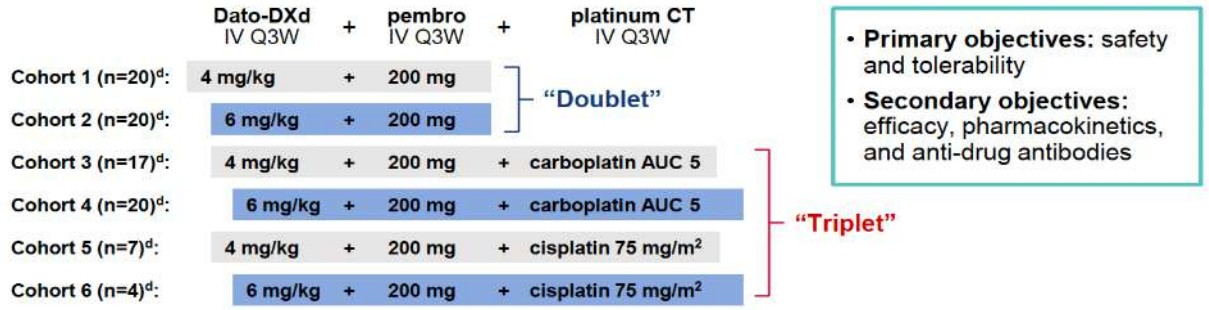
1L Non-squamous NSCLC	Randomised cohort (N=41)	
	MEDI5752 1500 mg + CTx (n=20)	Pembrolizumab + CTx (n=21)
Median follow-up, months (range)	22.8 (0.8–26.9)	14.5 (1.6–27.9)
ORR, n (%)	10 (50.0)	10 (47.6)
Disease control rate, n (%)	17 (85.0)	20 (95.2)
Median DOR, months (95% CI)	20.5 (4.1–NE)	9.9 (2.8–NE)
Median PFS, months	15.1	8.9
Median OS, months	NR	16.5
ORR, PD-L1 <1%, n/N (%) (95% CI)	5/9 (55.6) (21.2–86.3)	3/10 (30.0) (6.7–65.2)
Median PFS, PD-L1 <1%, months	13.4	9



Ahn et al. ESMO 2022

TROPION-LUNG02: DATOPOTAMAB DERUXTECAN PLUS PEMBROLIZUMAB AND PLATINUM CHEMOTHERAPY IN ADVANCED NSCLC





Antitumor Activity

In the overall population:

ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

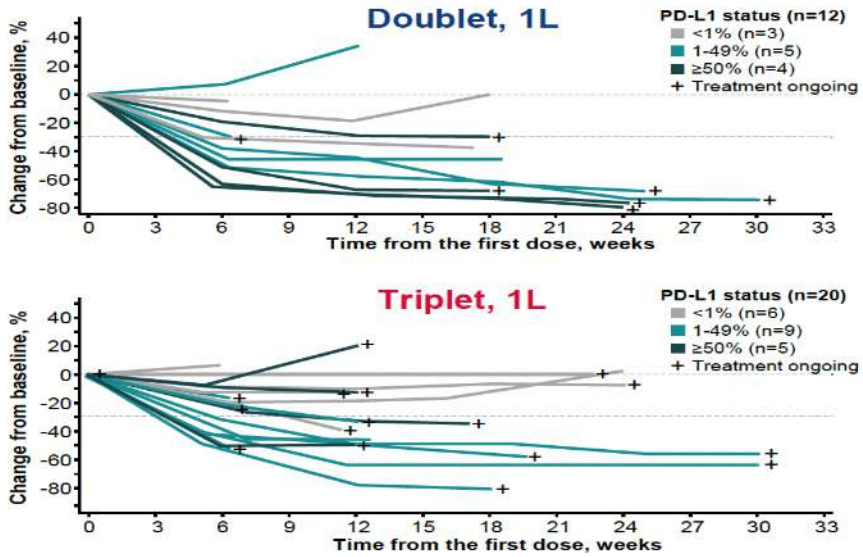
BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%

Data cutoff: May 2, 2022

Percent Change in Sum of Diameters[a]

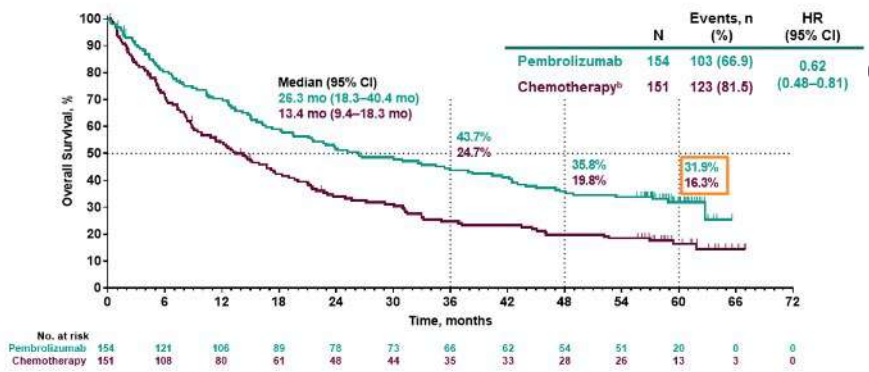


HAVE WE REACHED A PLATEAU?

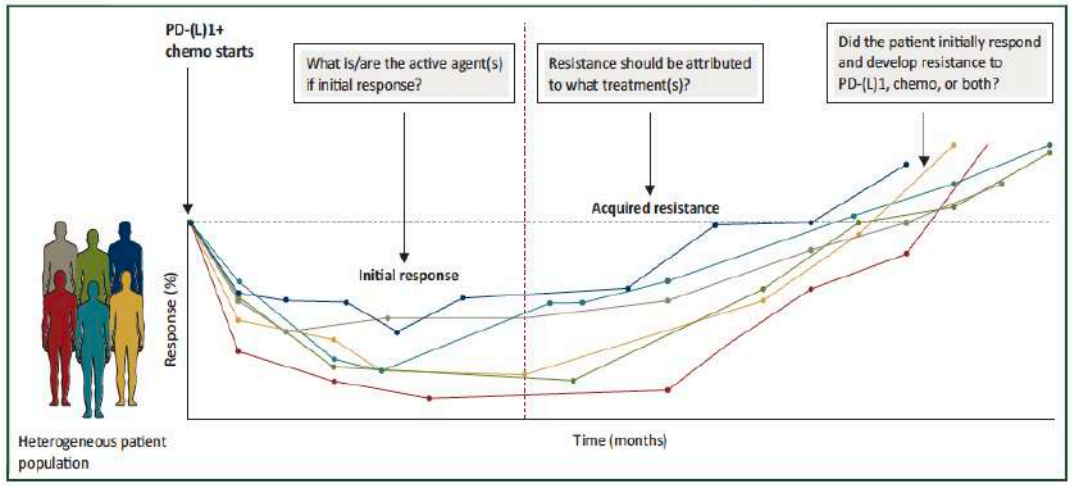
Understanding Resistance…
Monotherapy/ ICI combinations…

KEYNOTE 024

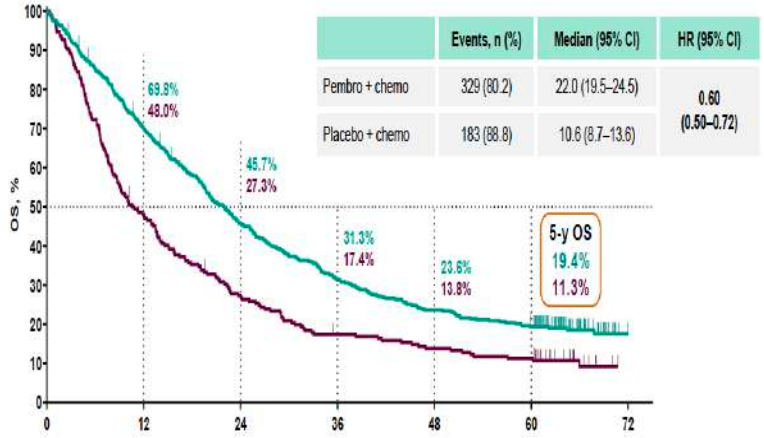
Overall Survival[a]



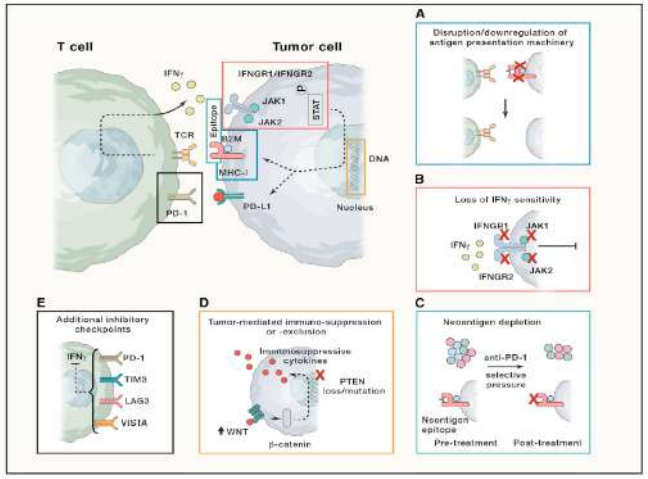
5-y OS: 32%

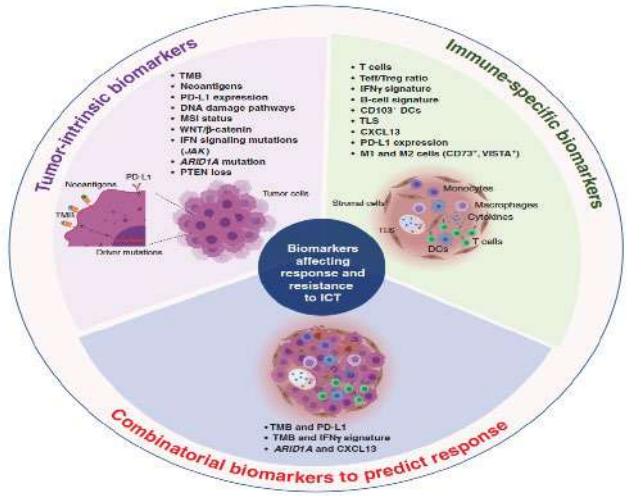


KEYNOTE 189



5-y OS: 19.4%



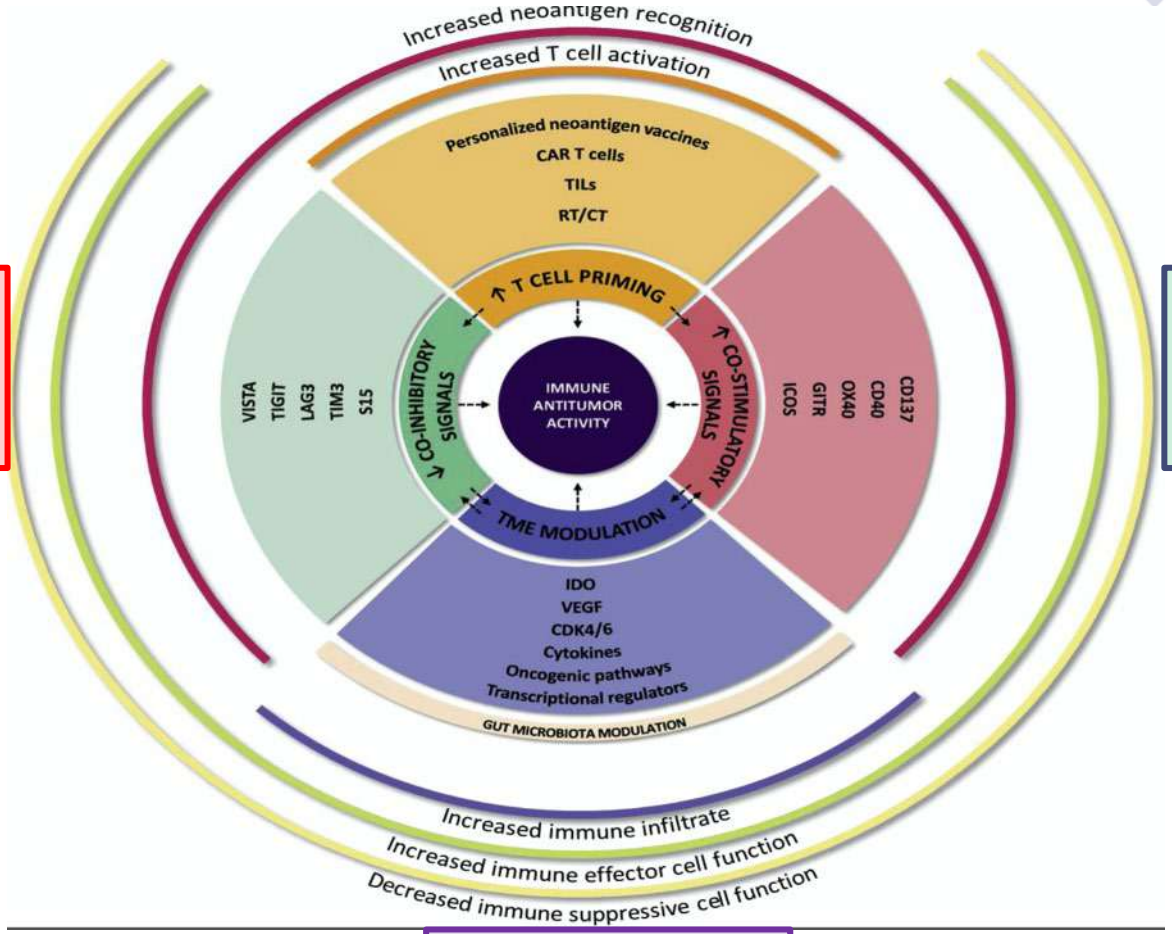


Reck M, et al. J Clin Oncol 2021; Gadgeel S, et al. J Clin Oncol 2020; Garassino ESMO 2022; Schoenfeld et al. Ann Oncol 2021; Schoenfeld et al. Cancer Cell 2020; Sharma et al. Cancer Disc 2021

Increase tumor Specific T-lymphocytes "STEER THE CAR"

Tamper with inhibitory receptors

"RELEASE THE BREAKS"



Act agonistically on Activator receptors "STEP ACCELERATOR"

Remodeling the TME and reveling immunosuppression "PAVE THE ROAD"

Attilli et al. Lung Cancer 2021

SOME THOUGHTS

- **IO mono, IO COMBOS WORK**
- **Different and efficient treatment alternatives should be considered according to tumor characteristics and patient health and expectations**
- **So far…many subgroups analyses, many hypothesis, enough to stablish "high level of recommendation"???**
- **IO+CT in PD-L1>50%**
  - Never smokers
  - STK11
  - High risk/ high tumor burden
  - Women
- **Many new options, different approaches, different combinations…but still we need to understand much better the who, what, when and how to use the "stunning amount" of the data we have so far**

The message…

Good things come from good science