Panel Discussion

Dr T P Sahoo, MD,DM(Medical Oncology)

Silverline Hospital, Bhopal

Dr Kumar Prabhash
Dr Tarachand Gupta
Dr M V Chandrakanth
Dr Nandini Menon

ARE ALL ICI THE SAME ??

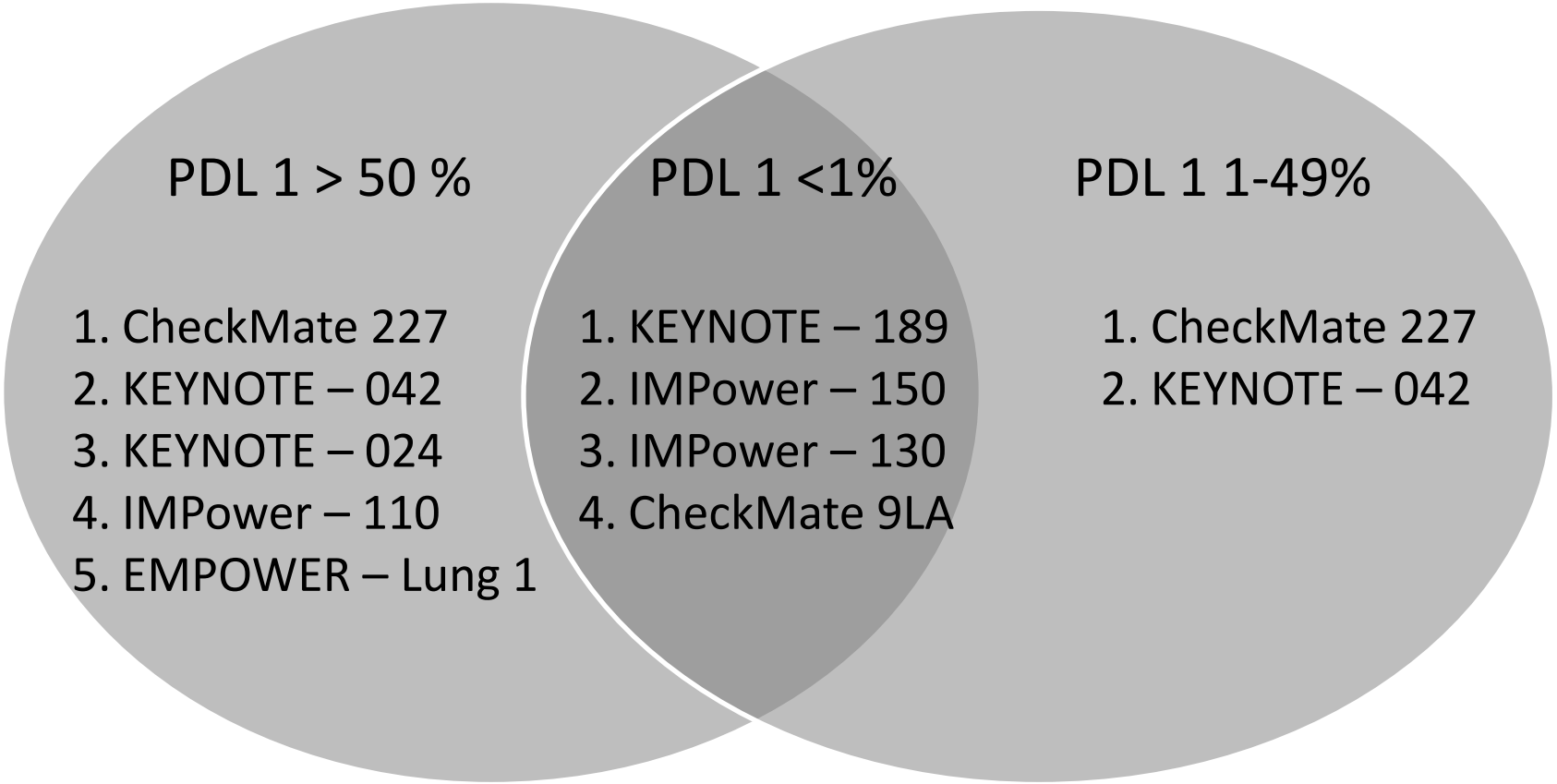
- 58 years old male, non smoker, presented with advanced NSCLC- non squamous
- No brain metastasis
- Liver – multiple metastasis with multiple lung and bone deposits
- PS – 1 bordering 2
- No targetable mutation
- PDL-1 – 55%

Options

- BSC alone
- ICI single agent
  - Which one ?
- Platinum doublet
- ICI and CT
- Any other choice ?

- What factors are to be considered for choosing ICI single agent vs combination ICI and chemotherapy ?
- Any choice of ICI ?
- IO vs IO+IO vs IO+CT vs CT alone

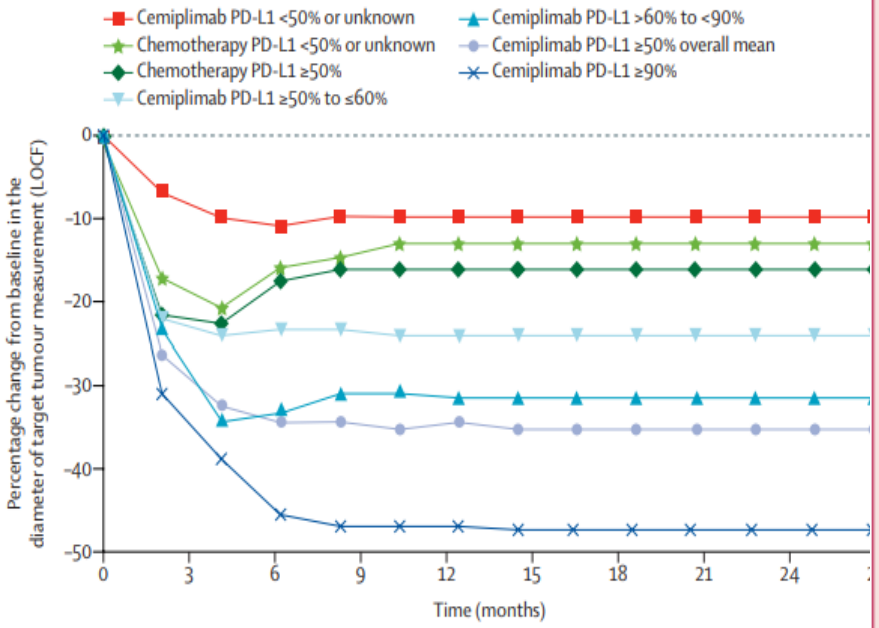
FIRST LINE TRIALS IN metNSCLC



Immunotherapy Options for Advanced NSCLC With High PD-L1 Expression Across Histologies

Parameter	KEYNOTE-024: Pembrolizumab (n = 154)[1]	IMpower110: Atezolizumab (n = 107)[2]	EMpower-Lung 1: Cemiplimab (n = 283)[3]	CheckMate 227: Nivo/Ipi (n = 205)[4]	CheckMate 9LA: Nivo/Ipi + CT (n = 76)[5]
PD-L1+ definition	TPS ≥50%*	TC3 or IC3†	TPS ≥50%*	TPS ≥50%‡	TPS ≥50%‡
ORR, %	46.1	40.2	39.0	45.4	38
Median DoR, mo	29.1	38.9	16.7	31.8	26.0
Median PFS, mo	7.7 (HR: 0.50)	8.2 (HR: 0.59)	8.2 (HR: 0.54)	6.7 (HR: 0.60)	7.5 (HR: 0.59)
Median OS, mo	26.3 (HR: 0.62)	20.2 (HR: 0.76)	NR (HR: 0.57)	21.2 (HR: 0.66)	18.9 (0.67)

*By PD-L1 22C3 IHC assay. †Staining of ≥50% tumor cells (TC3) or ≥10% tumor-infiltrating immune cells (IC3) by PD-L1 SP142 IHC assay. ‡PD-L1 28-8 IHC assay.
Caution needs to be taken when comparing data across trials.

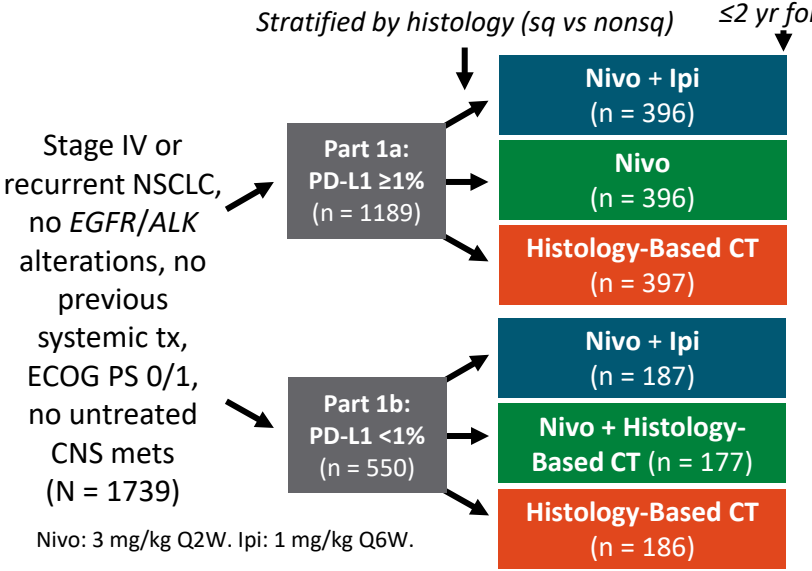


	PD-L1 ≥90%	PD-L1 >60 to <90%	PD-L1 ≥50 to ≤60%	PD-L1 <50% or unknown
Number of patients	98 *vs* 94	89 *vs* 90	96 *vs* 96	73 *vs* 74
Overall survival				
Median, months (95% CI)	NR (17·3–NE) *vs* 15·1 (11·1–NE)	22·1 (17·9–NE) *vs* 12·0 (9·6–19·2)	21·9 (13·2–NE) *vs* 14·0 (9·4–19·3)	16·5 (11·6–NE) *vs* 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.

Where Does Nivolumab/Ipilimumab Fit In?

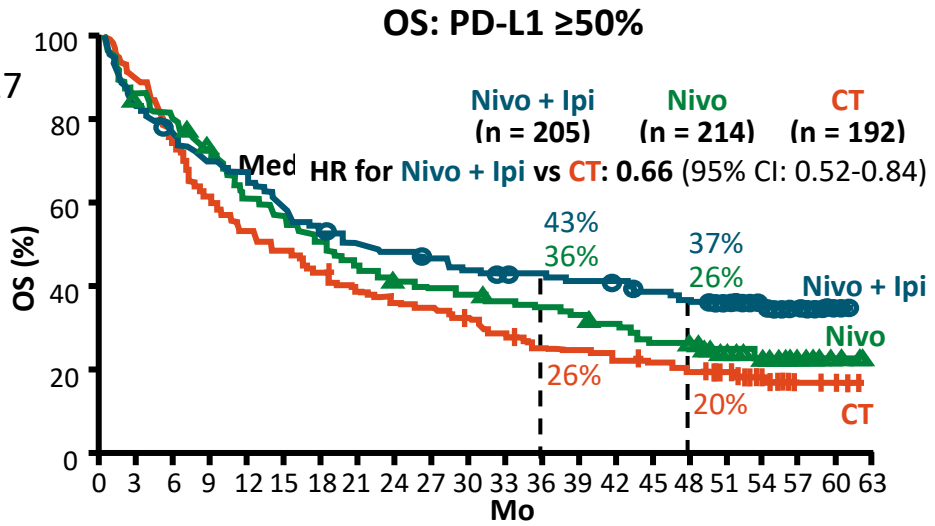
- Open-label, randomized phase III CheckMate 227



Nivo: 3 mg/kg Q2W. Ipi: 1 mg/kg Q6W.

- Primary endpoint: OS in PD-L1 ≥1% for Nivo/Ipi vs CT

- FDA approval for adv NSCLC with PD-L1 ≥1% granted i



Response Outcomes: PD-L1 ≥50%	Nivo/Ipi (n = 205)	Nivo (n = 214)	CT (n = 192)
ORR, % (n)	45.4 (93)	36.9 (79)	35.4 (68)
mDoR, mo (95% CI)	31.8 (20.7-51.		

Paz-Ares. ASCO 2021. Abstr 9016. Paz-Ares. J Thorac Oncol. 2022;17:289. Nivolumab PI.

Where Does Nivolumab/Ipilimumab + Chemo Fit in?

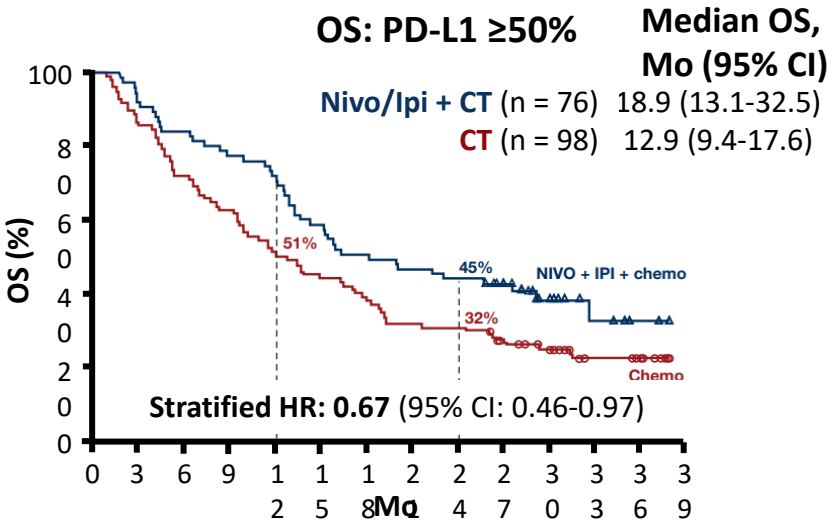
- Open-label, randomized phase III CheckMate 9LA trial

Stratified by PD-L1 expression (<1% vs ≥1%), sex, histology (squamous vs nonsquamous)

Patients with stage IV or recurrent NSCLC, no previous systemic tx, no sensitizing *EGFR/ALK* alterations, ECOG PS 0/1 (N = 719)

- **Nivo + Ipi*** + **Histology-based CT** Q3W x 2 cycles (n = 361)
- **Histology-based CT** Q3W x 4 cycles (n = 358)

*Nivo: 360 mg Q3W. Ipi: 1 mg/kg Q6W.



Response Outcomes: PD-L1 ≥50%	Nivo/Ipi + CT (n = 76)	CT (n = 98)
ORR, % (n)	38 (50)	31 (32)
mDoR, mo (95% CI)	26.0 (8.6-NR)	5.4 (3.9-10.9)

- Primary endpoint: OS
- FDA approval for advanced NSCLC regardless of PD-L1

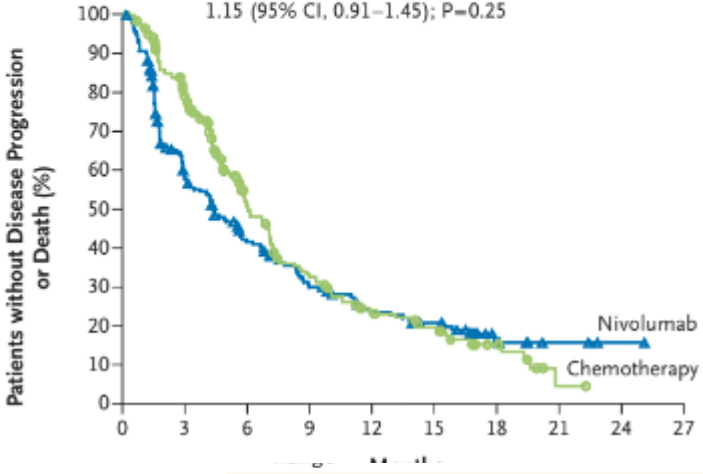
Reck. ESMO Open. 2021;6:100273. Nivolumab PI. 2021.

First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

A Progression-free Survival

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

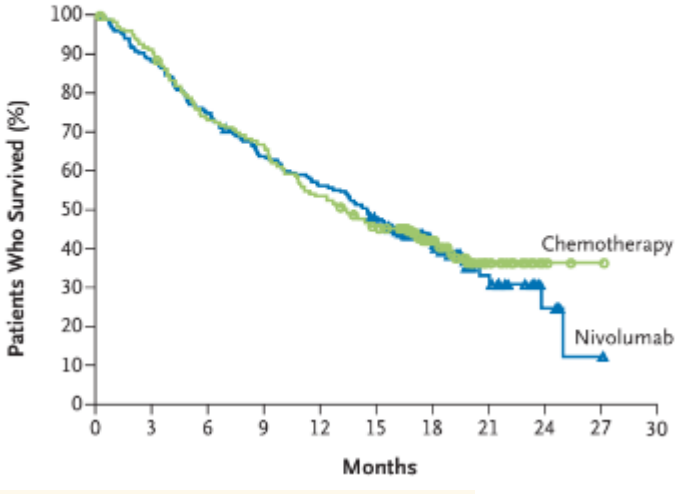
Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25



B Overall Survival

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

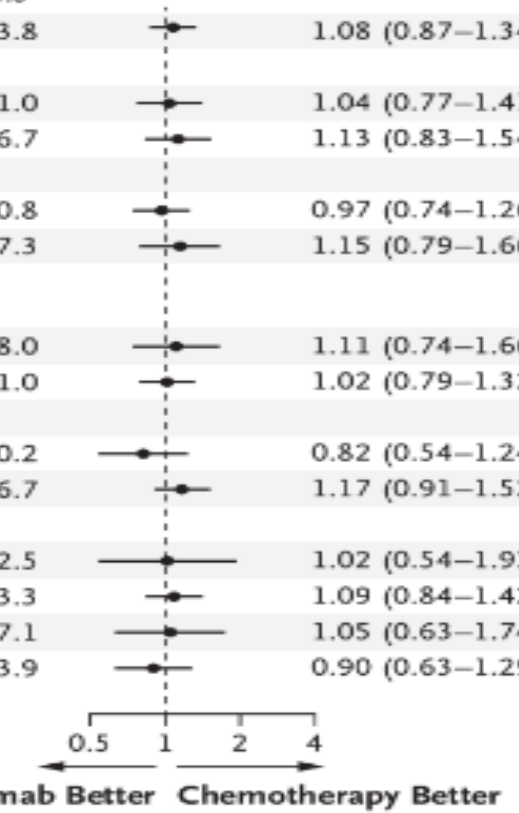
Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



PD-L1 expression level — no. (%)			
≥5%	208 (77)	210 (78)	418 (77)
≥50%	88 (32)	126 (47)	214 (40)

B Overall Survival

Subgroup	Nivolumab No. of Patients	Nivolumab Median Overall Survival *mo*	Chemotherapy No. of Patients	Chemotherapy Median Overall Survival *mo*	Unstratified Hazard Ratio (95% CI)
Overall	271	13.7	270	13.8	1.08 (0.87–1.34)
Age					
≥65 yr	123	13.3	137	11.0	1.04 (0.77–1.41)
<65 yr	148	14.1	133	16.7	1.13 (0.83–1.54)
Sex					
Male	184	13.1	148	10.8	0.97 (0.74–1.26)
Female	87	16.6	122	17.3	1.15 (0.79–1.66)
ECOG performance-status score					
0	85	16.6	93	18.0	1.11 (0.74–1.66)
≥1	185	12.7	177	11.0	1.02 (0.79–1.32)
Tumor histologic findings					
Squamous	65	10.5	64	10.2	0.82 (0.54–1.24)
Nonsquamous	206	14.5	206	16.7	1.17 (0.91–1.52)
Smoking status					
Never smoked	30	13.7	29	12.5	1.02 (0.54–1.93)
Former smoker	186	14.1	182	13.3	1.09 (0.84–1.42)
Current smoker	52	14.3	55	17.1	1.05 (0.63–1.74)
≥50% PD-L1 expression level	88	15.9	126	13.9	0.90 (0.63–1.29)



	KN 024	CM 026
Selection	22C3 and TPS – 50%	28-8 and TPS – 5%
Tissue blocks	New Metastatic site	Archival (upto 6 months old) ; KN-010
Never smoker	3%	11%
RT	No	37%
TAT allowed	**1 month (indolent?)**	

In practise how many are eligible for single agent IO?

- 30% patients – PDL-1 ≥ 50%
  - 35% - NOT ELIGIBLE FOR SYSTEMIC THERAPY
  - 15-35% - EGFR/ALK +
  - 10% ON STEROIDS / IMMUNOSUPRESSIVES
  - **Effectively 10% are eligible for single agent IO**

So who would be eligible for single agent IO?

- PDL-1 - More than equal to more than 50% for sure
  - Higher the better
- Indolent / lesser tumor burden
- Probably frail (lesser toxicity)
- Would prefer in smokers than non smokers

Chemo-IO Options for Advanced Nonsquamous NSCLC With High PD-L1 Expression

Outcome	KEYNOTE-189: Pembrolizumab + Platinum CT (n = 132)[1-3]	IMpower150: Atezolizumab + Bevacizumab, Carboplatin/nab-Paclitaxel (n = 71)[4,5]	IMpower130 Atezolizumab + Platinum CT (n = 88)[6]
Median OS, mo	27.7	30.0	17.3
OS HR (95% CI)	0.59 (0.40-0.86)	0.70 (0.46-1.08)	0.84 (0.51-1.39)
ORR, %	62	69	NR

Caution needs to be taken when comparing data across trials.

1. Gandhi. 2018;378:2078. 2. Gadgeel. ASCO 2019. Abstract 9013. 3. Rodriguez-Abreu ASCO 2020. Abstract 9582.
4. Socinski. J Thorac Oncol. 2021;16:1909. 5. Socinski. ASCO 2018. Abstr 9002. 6. West. Lancet Oncol. 2019;20:924.

KEYNOTE-407: First-line Pembrolizumab + Chemo in Advanced Squamous NSCLC With High PD-L1

- Randomized, double-blind phase III trial

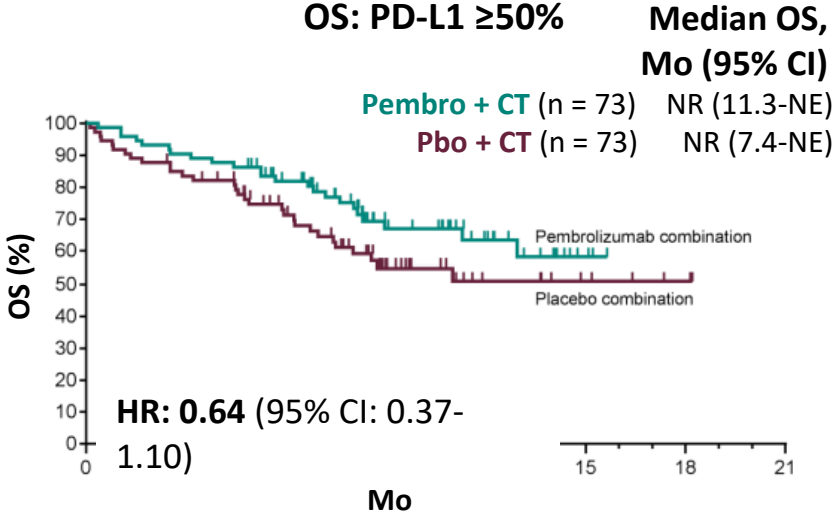
Previously untreated stage IV squamous NSCLC; any PD-L1 status, but biopsy for testing required; no brain mets; ECOG PS 0/1 (N = 563)

Pembro + Carbo/Pac or nab-Pac Q3W x 4 → **Pembro** ≤31 cycles

Pbo + Carbo/Pac or nab-Pac Q3W x 4 → **Pbo** ≤ 31 cycles

Crossover allowed on PD

OS: PD-L1 ≥50%



- Primary endpoint: PFS by RECIST v1.1 (BICR), OS
- Secondary endpoints: ORR and DoR by RECIST v1.1 (BICR), safety

Outcomes: PD-L1 ≥50%	Pembro + CT (n = 73)	Pbo + CT (n = 73)
ORR, % (n)	60.3 (44)	32.9 (24)
mPFS, mo (95% CI)	8.0 (6.1-10.3)	4.2 (2.8-4.6)

Paz-Ares. NEJM. 2018;37

Monotherapy Versus Combination in PD-L1 ≥ 50%

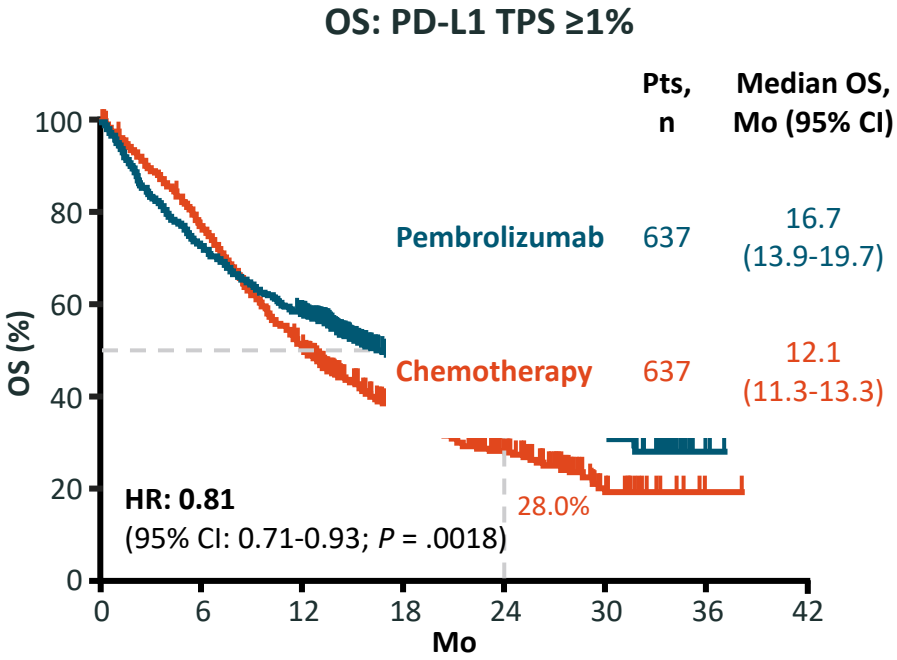
	KN 024/ 042	KN 189
3 years OS	31-44%	44%
Toxicity	31%	52%

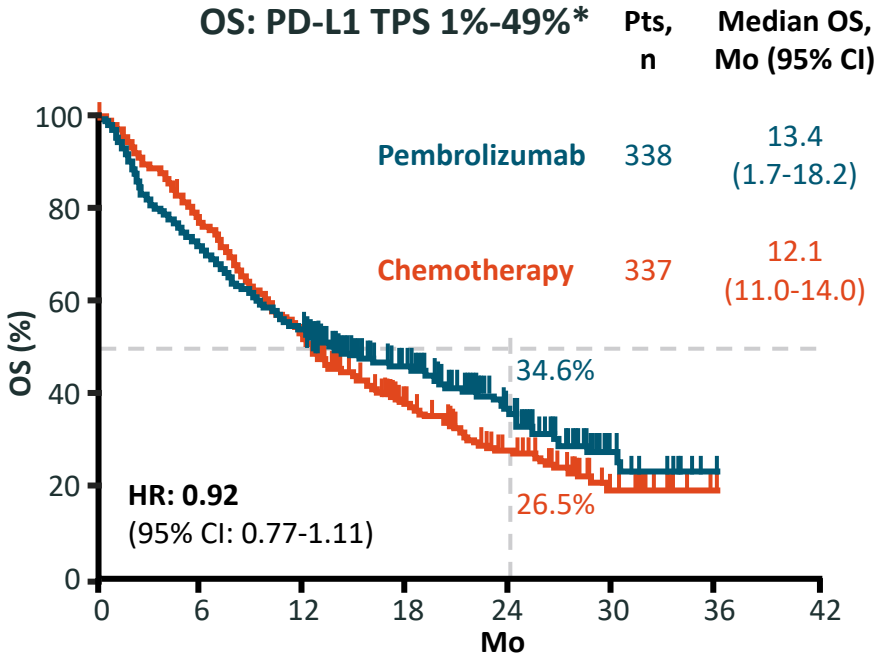
Smoking and bulk of disease – for now
PERSEE and INSIGNA will answer conclusively

Advanced NSCLC With PD-L1 TPS 1%-49%—Greatest Unmet Need

- IO
- IO plus chemotherapy
- IO plus IO
- IO plus IO plus chemotherapy

KEYNOTE-042: First-line Single-Agent Pembrolizumab in PD-L1–Positive Advanced NSCLC

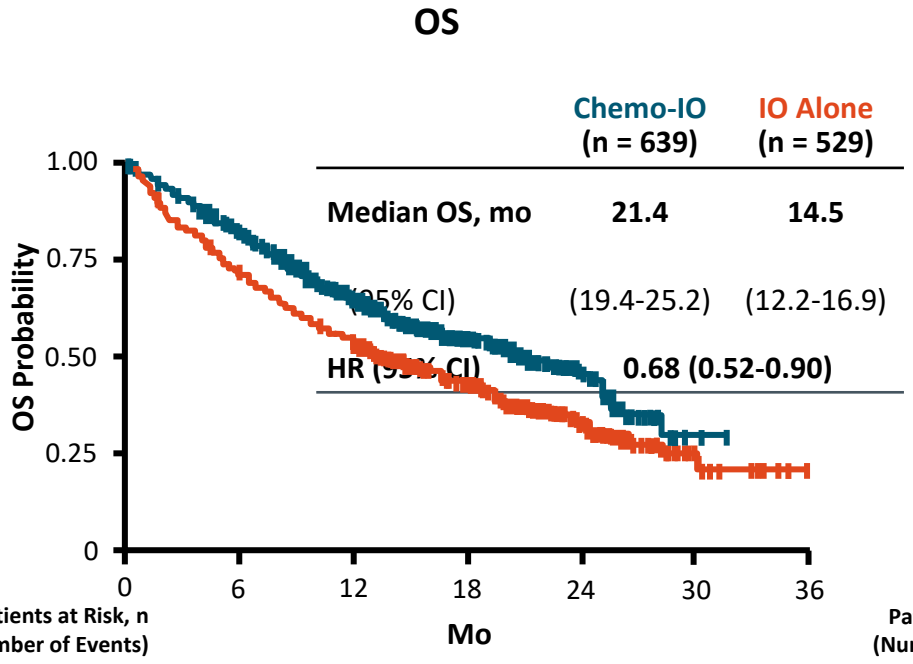


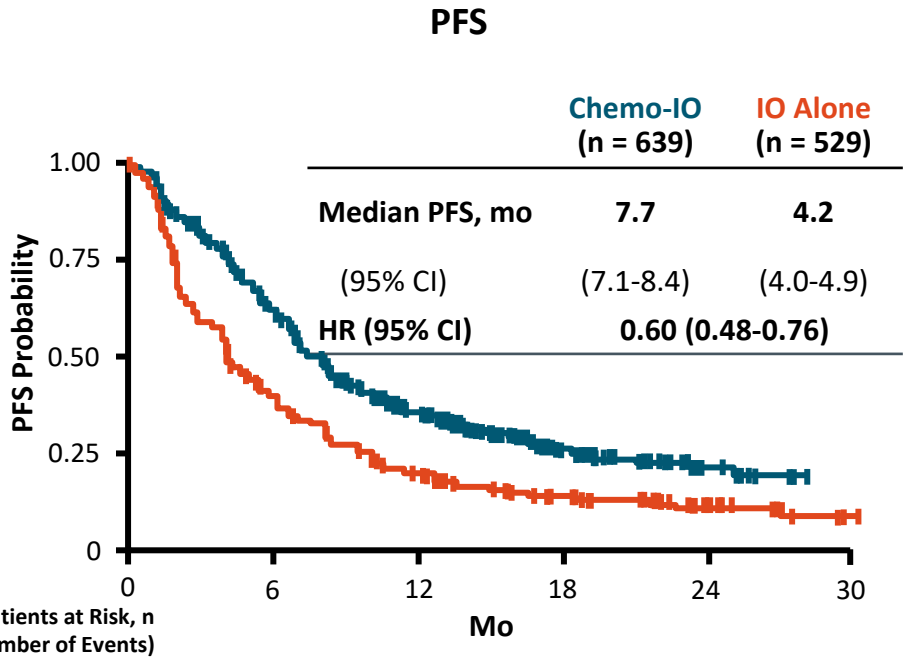


Mok. Lancet. 2019;393:1819.

*Exploratory analysis; no alpha allocated to this comparison.

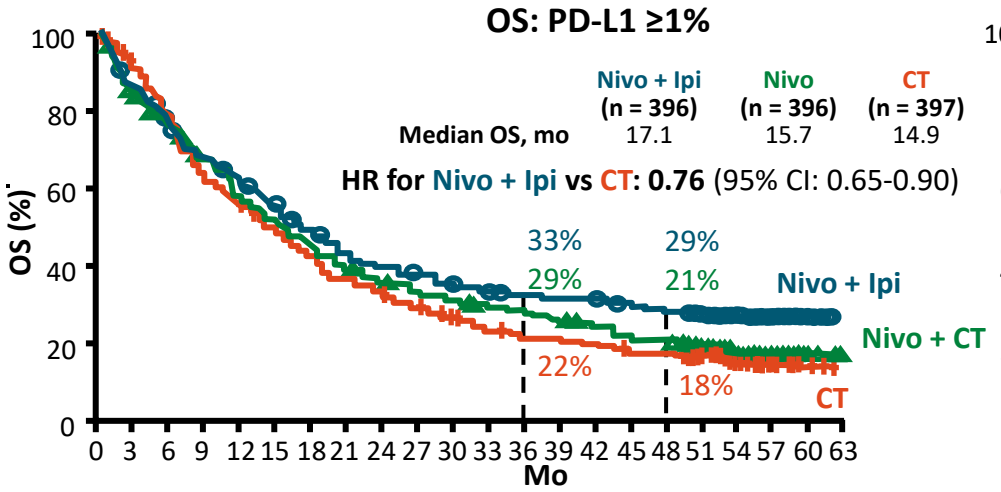
FDA Pooled Analysis: First-line Chemo-IO vs IO in Adv NSCLC With PD-L1 1% to 49%

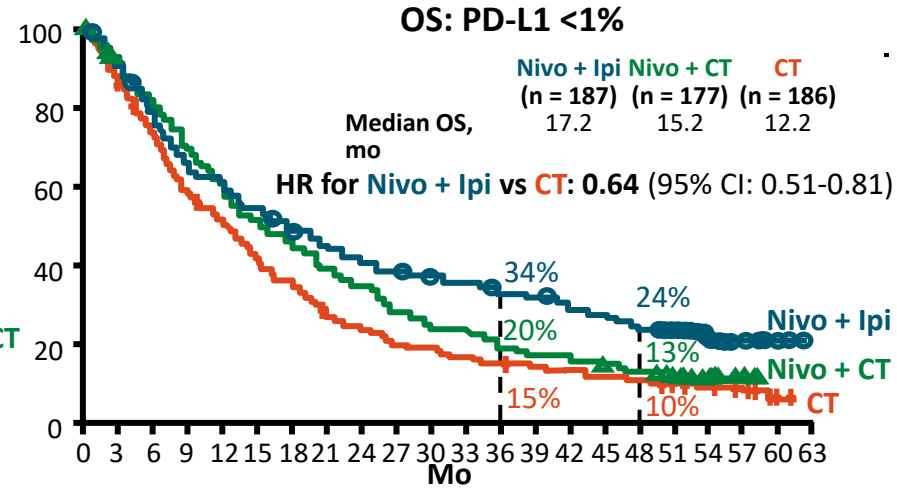




Akinboro. ASCO 2021. Abstr 9001.

1L Nivolumab + Ipilimumab for Advanced Nonsquamous NSCLC With PD-L1 Low and PD-L1 Negative (CM 227)

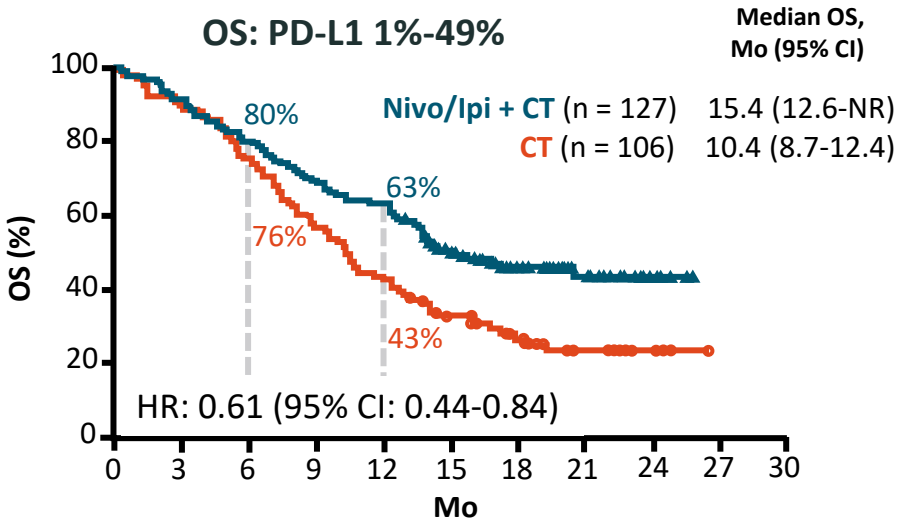


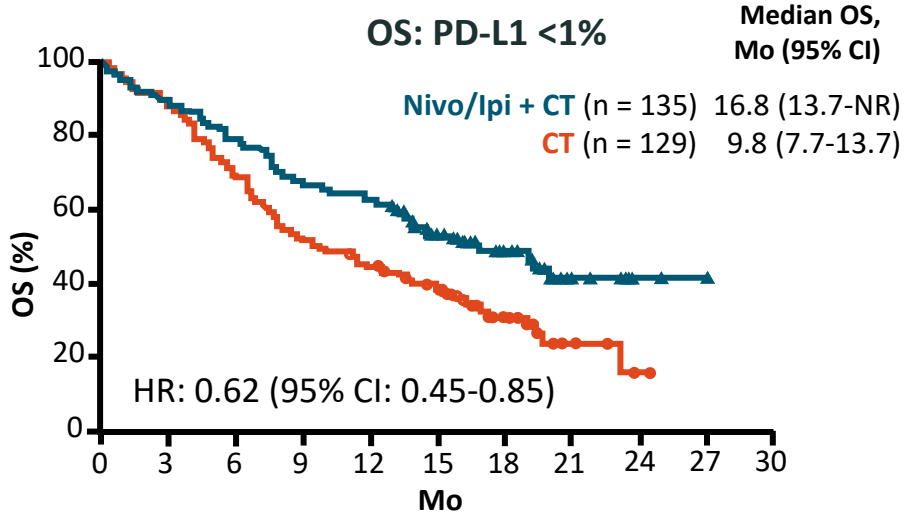


Response Outcomes: PD-L1 ≥1%	Nivo/Ipi (n = 396)	Nivo (n = 396)	CT (n = 397)
ORR, % (n)	36.4 (144)	27.5 (109)	30.0 (119)
mDoR, mo (95% CI)	23.2 (15.5-33.9)	15.5 (12.7-20.8)	6.7 (5.6-7.6)

Response Outcomes: PD-L1 <1%	Nivo/Ipi (n = 187)	Nivo (n = 177)	CT (n = 186)
ORR, % (n)	27.3 (51)	37.9 (67)	23.1 (43)
mDoR, mo (95% CI)	18.0 (12.4-33.2)	8.3 (5.9-9.4)	4.8 (3.7-5.8)

First-line Nivolumab/Ipilimumab + 2 Cycles of CT for Adv NSCLC With PD-L1 1%-49% and PD-L1 <1% (CM 9LA)





Outcomes: PD-L1 1% to 49%	Nivo/Ipi + CT (n = 127)	CT (n = 106)
ORR, % (n)	39.4 (50)	24.5 (26)
mDoR, mo (95% CI)	10.0 (6.5-13.2)	5.6 (3.9-15.2)

Outcomes: PD-L1 <1%	Nivo/Ipi + CT (n = 135)	CT (n = 129)
ORR, % (n)	31.1 (42)	20.2 (26)
mDoR, mo (95% CI)	NR (6.0-NR)	4.3 (2.8-7.1)

IO/IO vs IO and CT

- Post progression – the use of doublet standard platinum CT is a option
- Otherwise – the most likely option will be docetaxel with VEGFi
- Chemofree regimens in patients with low marrow reserve or other organs compromised

KRAS MUTATIONS IN PATIENTS WITH NONSQUAMOUS NON–SMALL-CELL LUNG CANCER: PREVALENCE AND RELATIONSHIP WITH PD-L1 EXPRESSION, TUMOR MUTATION BURDEN AND SMOKING STATUS

Abstract 364 Table 1 *KRAS* Mutation Prevalence

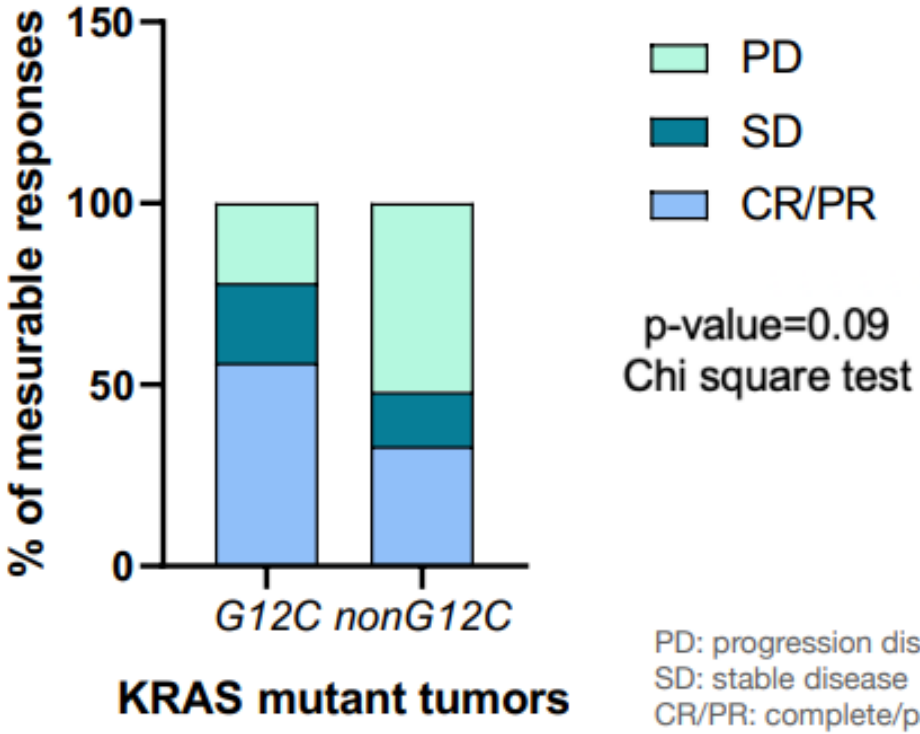
***KRAS* Mutation Prevalence, n (%)**	**N**	***KRAS* G12C**	***KRAS* G12D**	***KRAS* G12V**
Smoking status				
Current/former	480	64 (13.3)	22 (4.6)	29 (6.0)
Never	110	1 (0.9)	2 (1.8)	3 (2.7)
tTMB				
≥175 mutations/exome	253	44 (17.4)	7 (2.8)	16 (6.3)
<175 mut/exome	337	21 (6.2)	17 (5.0)	16 (4.7)
PD-L1 expression[a]				
TPS ≥50%	236	39 (16.5)	11 (4.7)	12 (5.1)
TPS 1%-49%	250	21 (8.4)	9 (3.6)	12 (4.8)
TPS <1%	99	5 (5.1)	4 (4.0)	8 (8.1)
tTMB and PD-L1 expression				
≥175 mut/exome and PD-L1 TPS ≥50%	109	31 (28.4)	3 (2.8)	7 (6.4)
≥175 mut/exome and PD-L1 TPS 1%-49%	94	11 (11.7)	4 (4.3)	5 (5.3)
≥175 mut/exome and PD-L1 TPS<1%	50	2 (4.0)	0	4 (8.0)
<175 mut/exome and PD-L1 TPS ≥50%	127	8 (6.3)	8 (6.3)	5 (3.9)
<175 mut/exome and TPS 1%-49%	156	10 (6.4)	5 (3.2)	7 (4.5)
<175 mut/exome and TPS <1%	49	3 (6.1)	4 (8.2)	4 (8.2)

[a]5 patients were unevaluable for PD-L1 TPS.

Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in KEYNOTE-042

	With Any KRAS Mutation		With KRAS G12C Mutation		Without Any KRAS Mutation	
	Pembro Mono-therapy (N = 30)	Chemo-therapy (N = 39)	Pembro Mono-therapy (N = 12)	Chemo-therapy (N = 17)	Pembro Mono-therapy (N = 127)	Chemo-therapy (N = 105)
ORR, % (95% CI)	56.7 (37.4-74.5)	18.0 (7.5-33.5)	66.7 (34.9-90.1)	23.5 (6.8-49.9)	29.1 (21.4-37.9)	21.0 (13.6-30.0)
PFS, median, mo (95% CI)	12 (8-NR)	6 (4-9)	15 (10-NR)	6 (4-8)	6 (4-7)	6 (6-8)
PFS, HR (95% CI)	0.51 (0.29-0.87)		0.27 (0.10-0.71)		1.00 (0.75-1.34)	
OS, median, mo (95% CI)	28 (23-NR)	11 (7-25)	NR (23-NR)	8 (5-NR)	15 (12-24)	12 (11-18)
OS, HR (95% CI)	0.42 (0.22-0.81)		0.28 (0.09-0.86)		0.86 (0.63-1.18)	

Response to IT by KRAS mut among 59 pt that received IT



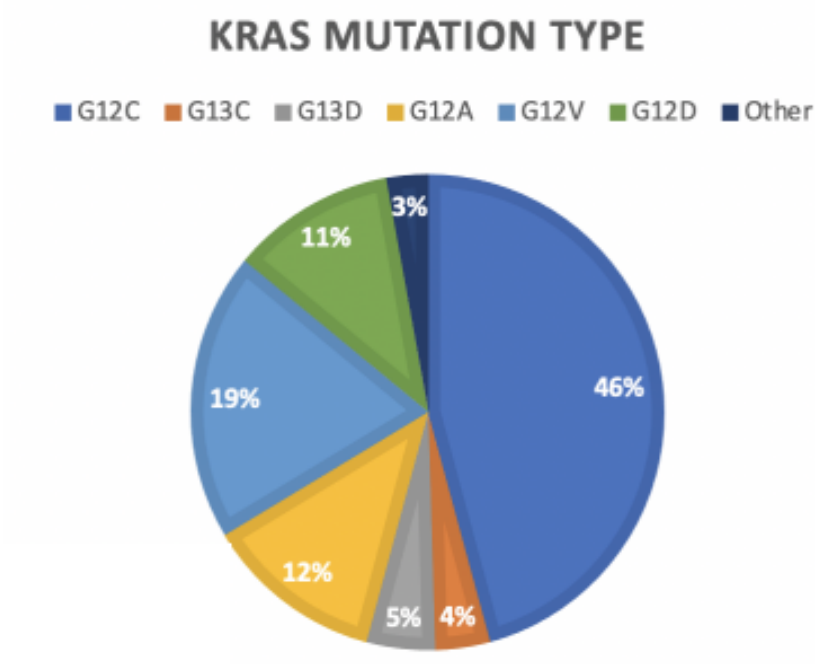
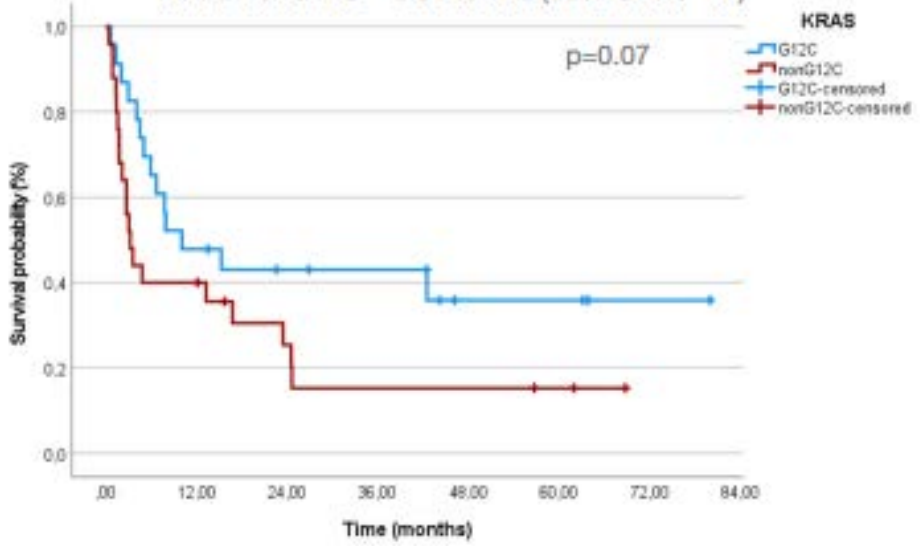


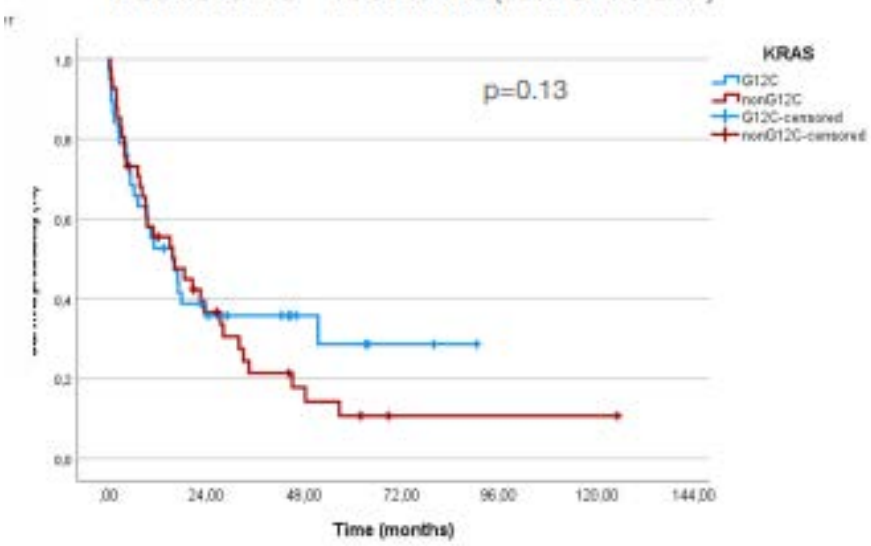
Figure 1. KRAS mut type (107 pt)

PD: progression disease
SD: stable disease
CR/PR: complete/partial response

mPFS G12C = 10.1 months (95% CI 0-21)
mPFS nonG12C = 3.3 months (95% CI 1.8-4.7)



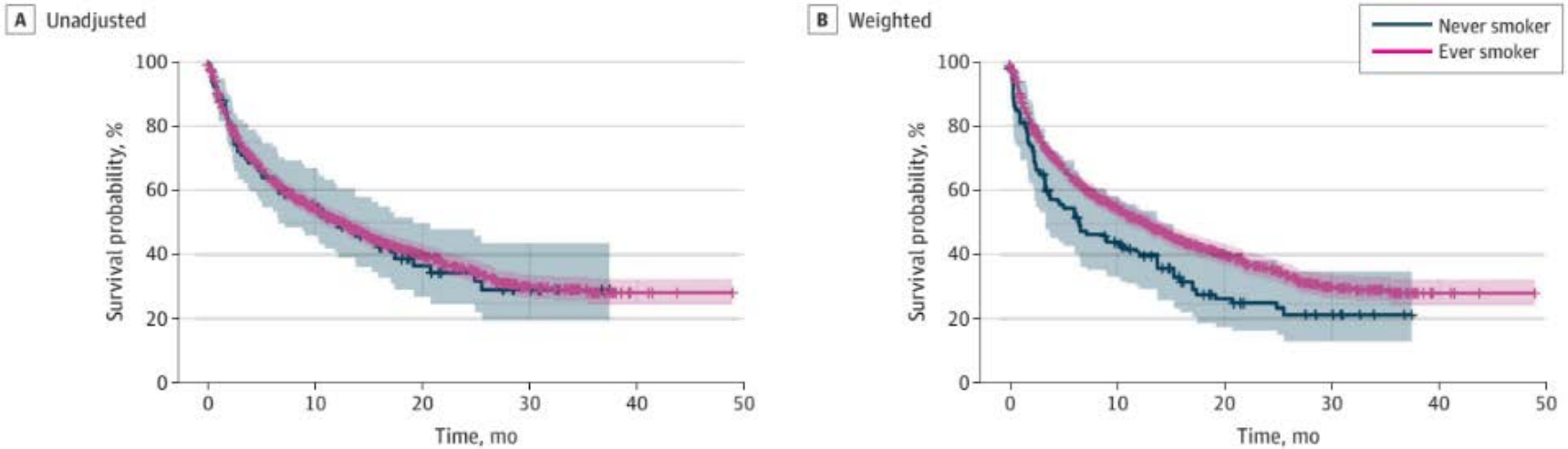
mOS G12C = 17.9 months ((95% CI 0-51.7)
mOS nonG12C = 18.6 months (95% CI 4.8-32.2)



- What about frontline KRAS inhibitor and ICI ?
  - Krystal -7 /1 trials
  - 57%RR with DCR of 100%

Does smoking make a difference in your decision for ICI ?

Figure. Kaplan-Meier Curves for Never-Smokers vs Ever-Smokers Who Initiated First-line Pembrolizumab Monotherapy Showing Unadjusted and Inverse Probability Treatment Weighting–Adjusted Comparisons



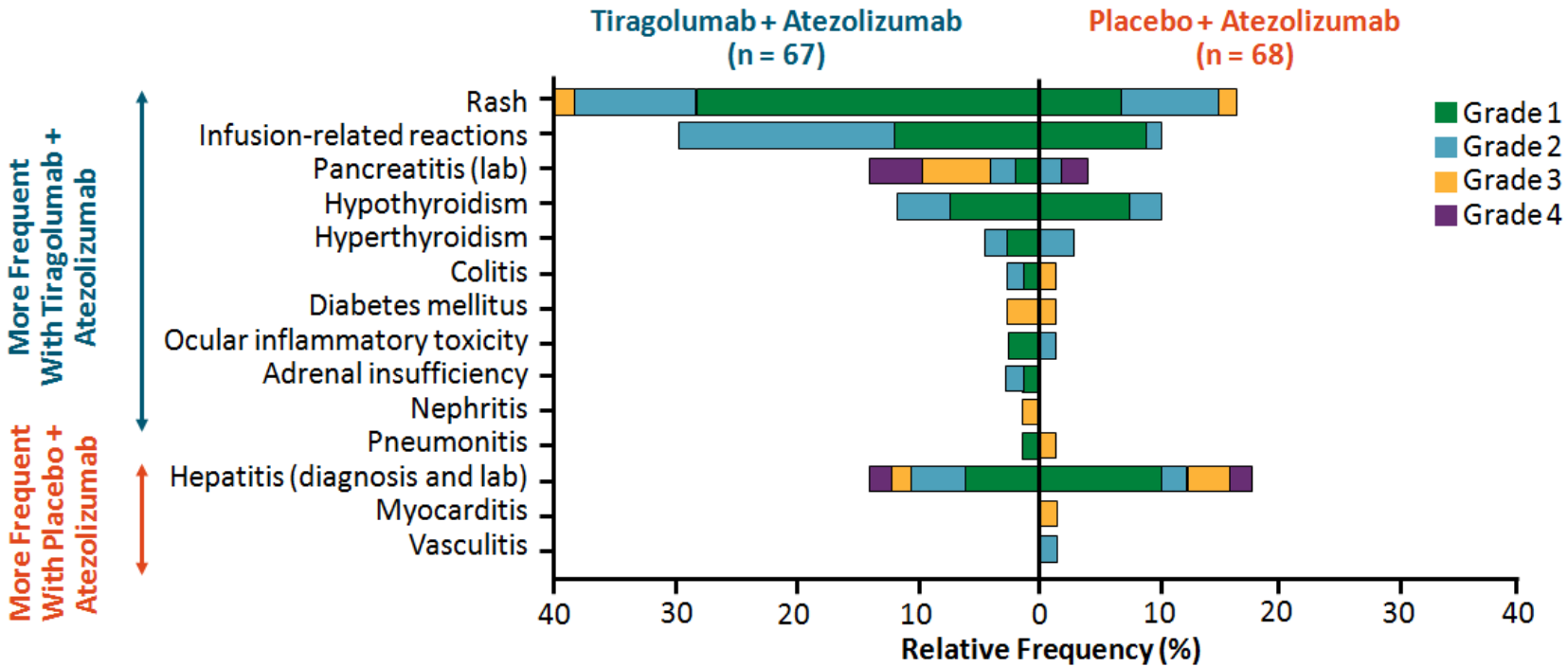
- Another target being actively evaluated in multiple trials is T-cell immunoreceptor with Ig and ITIM domains (TIGIT)

- TIGIT is a coinhibitory receptor that regulates T-cell and natural killer-cell activation and proliferation, with expression patterns similar to PD-1 and dual blockade leading to synergistic antitumor effects in preclinical models

CITYSCAPE: Background

- TIGIT: inhibitory immune checkpoint receptor expressed on multiple immune cells, including T-cells and NK cells
  - Inhibits T-cell and NK cell activity by binding to PVR ligand on tumor cells and APCs
  - Expression strongly correlated with PD-1 expression, particularly in T-cells in NSCLC
- Tiragolumab: fully human TIGIT antibody that prevents TIGIT binding to PVR
- Combined TIGIT and PD-L1 inhibition may lead to enhanced antitumor activity
  - Preclinical evidence for synergistic antitumor activity with antibody combination[1]
  - Phase I study of tiragolumab + atezolizumab showed preliminary evidence of antitumor activity and acceptable tolerability in patients with solid tumors[2]
- Current phase II study compared efficacy, safety of first-line tiragolumab + atezolizumab vs placebo + atezolizumab in patients with metastatic NSCLC[3]

CITYSCAPE: Updated Immune-Mediated AEs



PFS (%)

Pa

T+A 67 64 49 48 45 38 31 30 30 22 20 10 9 1 1 0
P+A 68 61 45 38 32 22 20 15 15 10 9 7 7 1 1 0

0 HR: 0.89 (95% CI: 0.53-1.49)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Mos

Patients at Risk, n
T+A 38 36 23 22 19 15 12 12 12 10 10 6 6 1 1 0
P+A 39 37 25 21 19 14 12 9 9 5 5 4 4 0 0 0

OS, efficacy analysis by PD-L1

Updated analysis data cutoff: December 2, 2019. Median f/u: 10.9 mos.

Case

- 85 years old male , smoker, advanced NSCLC-Non squamous
- PDL-1 unknown
- PS-2
- No targetable mutations
- What are your options ?

- BSC alone
- ICI single agent
- Single agent CT
- Platinum doublet
- ICI and CT
- Enrol for a clinical trial

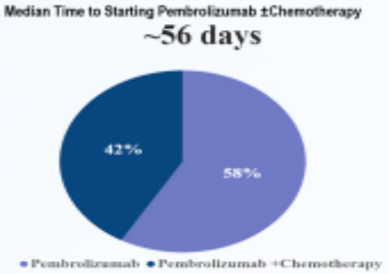
#45P Pembrolizumab versus Best Supportive Care Survival Outcomes in ECOG Performance Status 2 NSCLC Patients

A. Elegbede[1], A. Pabani, [1,2] A. Gibson, [1] W.Y Cheung, [1,2]

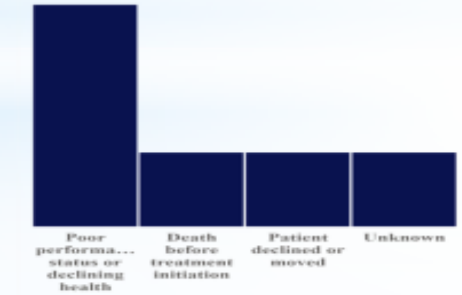
[1]University of Calgary, Calgary, Canada, [2]Medical Oncology, Tom Baker Cancer Center, Calgary AB, Canada

ECOG Performance Status 2 NSCLC Patients N = 54

A. Systemic Treatment Regimen



B. Reasons For No Systemic Treatment



C.

Table 1: ECOG 2 NSCLC Patients Receiving First-Line Pembrolizumab ± Chemotherapy (Pembro) Versus Best Supportive Care (BSC)

Survival Outcomes in months	Pembro, n=36	BSC, n=18	P value**
Median Overall Survival (mOS)	21	2	**<0.01**
mOS in KRAS mutant	27	2	**<0.01**
mOS in PD-L1 ≥50%	22	2	**<0.01**
mOS in PD-L1 1-49%	9	2	**<0.01**
mOS in PD-L1 <1%	9	3	**0.04**
Clinical characteristics, n (%)			
Median Body mass index (range), kg/m^2	26 (15-38)	23 (16-42)	
Age >70 years	13 (36)	11 (61)	0.09
Male Sex	21 (58)	10 (56)	1.0
Had at least 1 co-morbidity	22 (61)	14 (78)	0.36
>1 comorbidity	5 (23)	6 (43)	0.27
Brain metastasis at any time during disease course	12 (33)	5 (28)	0.76
Squamous histology	1 (3)	3 (17)	0.1
PD-L1 positive (>1%)	28 (78)	12 (67)	0.08
PD-L1 ≥50%	21 (58)	5 (28)	0.08
KRAS mutant	20 (56)	13 (72)	0.13

** LogRank for Kaplan Meier Survival and Fisher Exact For Descriptive Statistics

Figures and Table: Type of first-line systemic regimen received (A), Reasons for no systemic treatment (B) and comparison of clinical characteristics and survival outcomes in treated (Pembro) versus non-treated (BSC) groups among ECOG 2 NSCLC Patients

Baseline Characteristics

	Atezolizumab (n=302)	Chemotherapy (n=151)
Age		
Median (range), y	75.0 (33, 94)	75.0 (37, 89)
<70 y, n (%)	80 (26.5)	43 (28.5)
70-79 y, n (%)	125 (41.4)	65 (43.0)
≥80 y, n (%)	97 (32.1)	43 (28.5)
ECOG PS, n (%)		
0/1	56 (18.5)	19 (12.6)
2	228 (75.5)	116 (76.8)
3	18 (6.0)	16 (10.6)
Sex, male, n (%)	220 (72.8)	108 (71.5)
Race, n (%)[a]		
White	203 (67.2)	95 (62.9)
Asian	75 (24.8)	38 (25.2)
Histology, n (%)[b]		
Non-squamous	173 (57.3)	87 (57.6)
Squamous	129 (42.7)	64 (42.4)

	Atezolizumab (n=302)	Chemotherapy (n=151)
Brain metastases, n (%)[b]		
Yes	27 (8.9)	13 (8.6)
No	273 (90.4)	137 (90.7)
Missing	2 (0.7)	1 (0.7)
Smoking status, n (%)		
Previous	209 (69.2)	103 (68.2)
Current	58 (19.2)	28 (18.5)
Never	35 (11.6)	20 (13.2)
PD-L1 expression level, n (%)[c]		
TC <1%	151 (50.0)	61 (40.4)
TC ≥1%	127 (42.1)	78 (51.7)
TC 1-49	77 (25.5)	53 (35.1)
TC ≥50%	50 (16.6)	25 (16.6)
Unknown	24 (7.9)	12 (7.9)

	Atezolizumab (n=302)	Chemotherapy (n=151)
Number of patients with any subsequent anti-cancer therapy, n (%)	**61 (20.2)**	**45 (29.8)**
Chemotherapy, n (%)	48 (15.9)	16 (10.6)
Cancer Immunotherapy, n (%)	4 (1.3)	28 (18.5)
TKI, n (%)	10 (3.3)	5 (3.3)
Other, n (%)		1 (0.7)

Duration of response – 14 vs 7 months

	e	Vinorelbine (n=84)
Median treatment duration, m		1.8 (0-21)
Median number of cycles initi		3.0 (1-31)

	Atezolizumab (n=300)	Chemotherapy (n=147)
All-grade AE, n (%)	275 (91.7)	143 (97.3)
Treatment-related AE	171 (57.0)	118 (80.3)
Grade 3-4 AE, n (%)	136 (45.3)	71 (48.3)
Treatment-related Grade 3-4 AE	49 (16.3)	49 (33.3)
Serious AE, n (%)	146 (48.7)	53 (36.1)
Treatment-related SAE	35 (11.7)	23 (15.6)
Grade 5 AE, n (%)	35 (11.7)	13 (8.8)
Treatment-related Grade 5 AE	3 (1.0)	4 (2.7)
AE leading to discontinuation of study drug, n (%)	39 (13.0)	20 (13.6)
AE leading to modification/interruption of study drug, n (%)	96 (32.0)	71 (48.3)

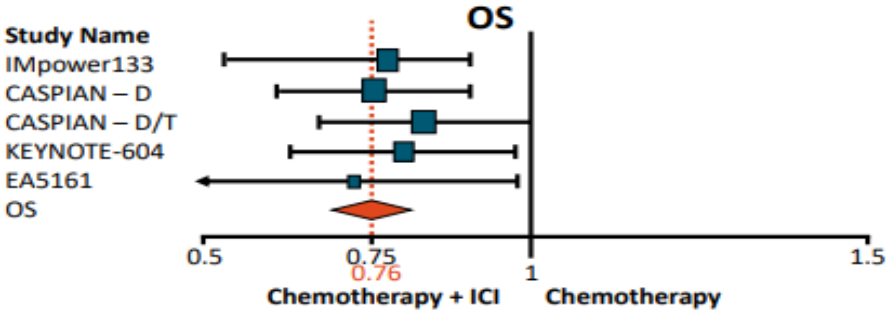
- 45 years old smoker , extensive stage SCLC , no brain metastasis, PS- 1, treatment options
  - CT doublet (CDDP vs Carboplatin)
  - CT doublet and ICI
    - Which ICI?
  - CT doublet followed by ICI maintenance
  - any other protocol

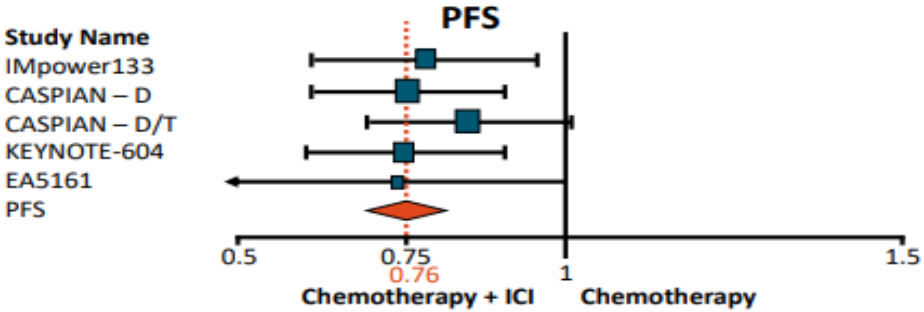
Table 3. Summary of clinical trials about anti-CTLA-4 in ES-SCLC

Trial	Phase	No. of Patients	Treatment	FDA Approval	OS	PFS	ORR (%)	AEs (%)
CheckMate 451	III	834	Nivolumab plus Ipilimumab vs. Nivolumab vs. placebo	No	9.2 months vs. 9.6 months (HR, 0.92; 95% CI: 0.75-1.12; P=0.37)	1.7 months (1.5-2.6) vs. 1.9 months (1.6-2.6) vs. 1.4 months (1.4-1.5)	9.1 vs. 11.5 vs. 4.2	Grade 3/4 AEs 52.2 vs. 11.5 vs. 8.4
CASPIAN trial	III	537	Durvalumab + Tremelimumab + chemotherapy vs. chemotherapy	Yes	10.4 months vs. 10.5 months (HR, 0.81; 95% CI, 0.67-0.97; P=0.02)	16.9% (95% CI: 12.6-21.7) vs. 5.3% (95% CI: 2.9-8.8)	58 vs. 58	Serious AEs 47.4 vs. 36.5
CA184-156	III	1132	Ipilimumab + chemotherapy vs. chemotherapy	No	11 months vs. 10.9 months (HR 0.94; 95% CI: 0.81-1.09; P=0.3775)	4.6 months vs. 4.4 months (HR 0.85; 95% CI: 0.75-0.97; P=0.0161)	62 vs. 62	Grade 3/4 AEs 48 vs. 45
CheckMate-032	I/II	243	Nivolumab vs. Nivolumab + Ipilimumab	No	5.7 months (3.8-7.6) vs. 4.7 months (3.1-8.3)	1.4 months (1.3-1.4) vs. 1.5 months (1.4-2.2)	11.6 vs. 21.9	Grade 3/4 AEs 12.9 vs. 37.5

(95% CI: 3.0-4.2)

Frontline Chemoimmunotherapy in SCLC: Summary of Efficacy





	IMpower133	CASPIAN		KEYNOTE-604	EA5161 (Phase 2)
		Durvalumab	Durvalumab/Trem		
Median PFS, mos ▪ HR (95% CI)	5.2 0.77 (0.62-0.96)	5.1 0.78 (0.65-0.94)	4.9 0.84 (0.70-1.01)	4.5 0.75 (0.61-0.91)	5.5 0.68 (0.48-1.0)
Median OS, mos ▪ HR (95% CI)	12.3 0.76 (0.54-0.91)	12.9 0.75(0.59-0.91)	10.4 0.82 (0.68-1.00)	10.8 0.80 (0.64-0.98)	11.3 0.67 (0.46-0.98)
12-mos OS, %	51.7	52.8	43.8	45.1	~ 48
24-mos OS, %	~ 22	22.2	23.4	22.5	NR

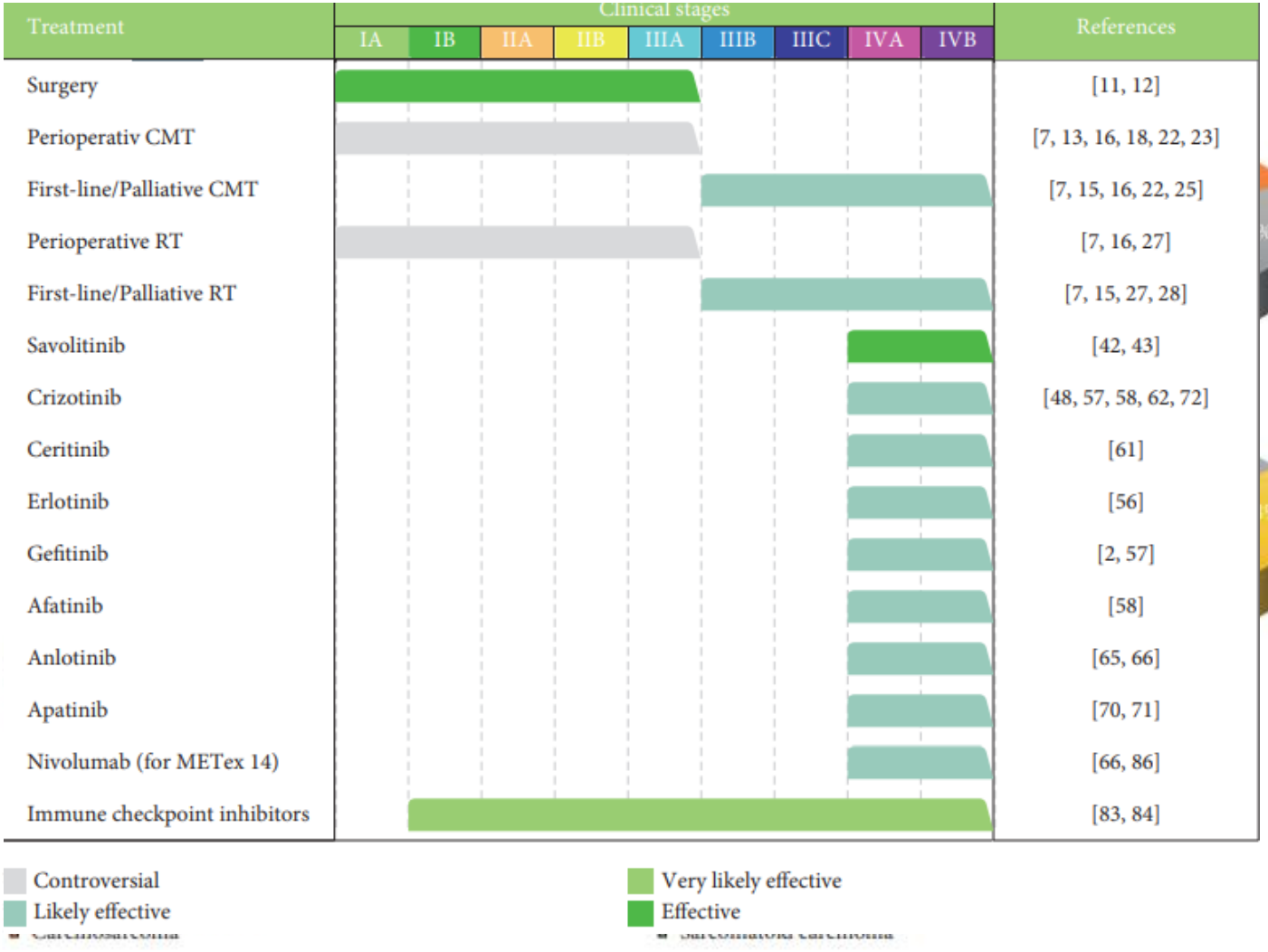
Leal. ASCO 2020. Abstr 9000.

Study Design differentiators – CASPIAN vs IMP133 vs KN604

	IMP133	CASPIAN
All comers (no biomarker selection)	✓	✓
Untreated brain metastasis excluded	✓	
PCI allowed in control arm	✓ (~10%)	✓
PCI allowed in experimental arm	✓ (~10%)	
Up to 6 cycles of chemo in control arm		✓
Cisplatin		✓
Carboplatin	✓	✓

CASPIAN study inclusion criteria is reflective of real-world clinical practice

- Allowed treatment with either cis- or carboplatin
- Included patients with either asymptomatic/untreated or treated brain metastases
- Compared against up to 6 cycles of chemotherapy* with optional PCI


Treatment
Clinical stages
IA
IB
IIA
IIB
IIIA
IIIB
IIIC
IVA
IVB
References
Surgery
[11, 12]
Perioperativ CMT
[7, 13, 16, 18, 22, 23]
First-line/Palliative CMT
[7, 15, 16, 22, 25]
Perioperative RT
[7, 16, 27]
First-line/Palliative RT
[7, 15, 27, 28]
Savolitinib
[42, 43]
Crizotinib
[48, 57, 58, 62, 72]
Ceritinib
[61]
Erlotinib
[56]
Gefitinib
[2, 57]
Afatinib
[58]
Anlotinib
[65, 66]
Apatinib
[70, 71]
Nivolumab (for METex 14)
[66, 86]
Immune checkpoint inhibitors
[83, 84]
Controversial
Likely effective
Very likely effective
Effective

	RR	DCR	DoR
Camrelizumab +Apatinib (1-49%)	66.7%	66.7%	2.53 mo
Camrelizumab alone (≥ 50%)	54.5%	90.1%	3.19 mo

- Exciting times in the treatment landscape of lung cancer (specially NSCLC)
- Options are expanding and survivals are improving with lesser toxicity