ADVANTAGES OF CHEMO-IMMUNOTHERAPY FOR NSCLC

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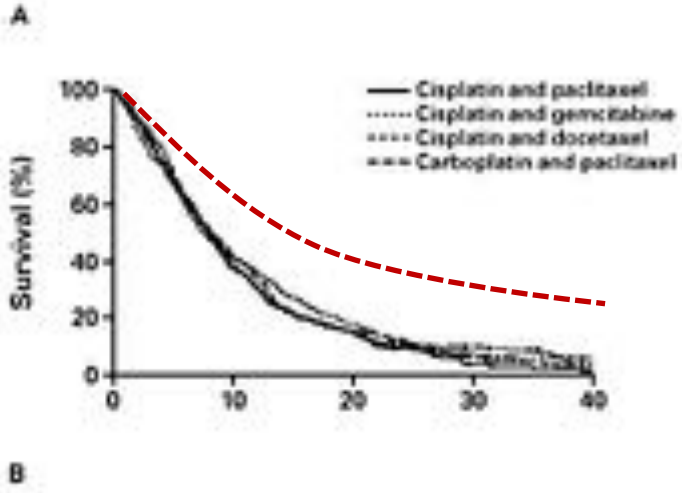
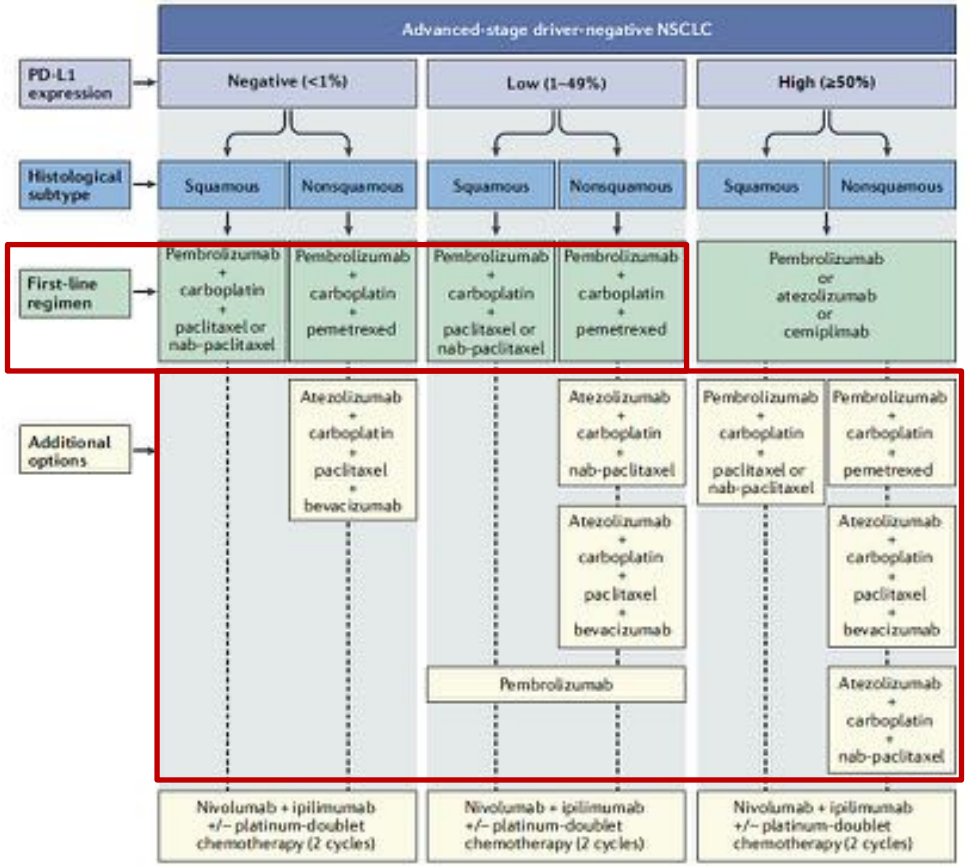
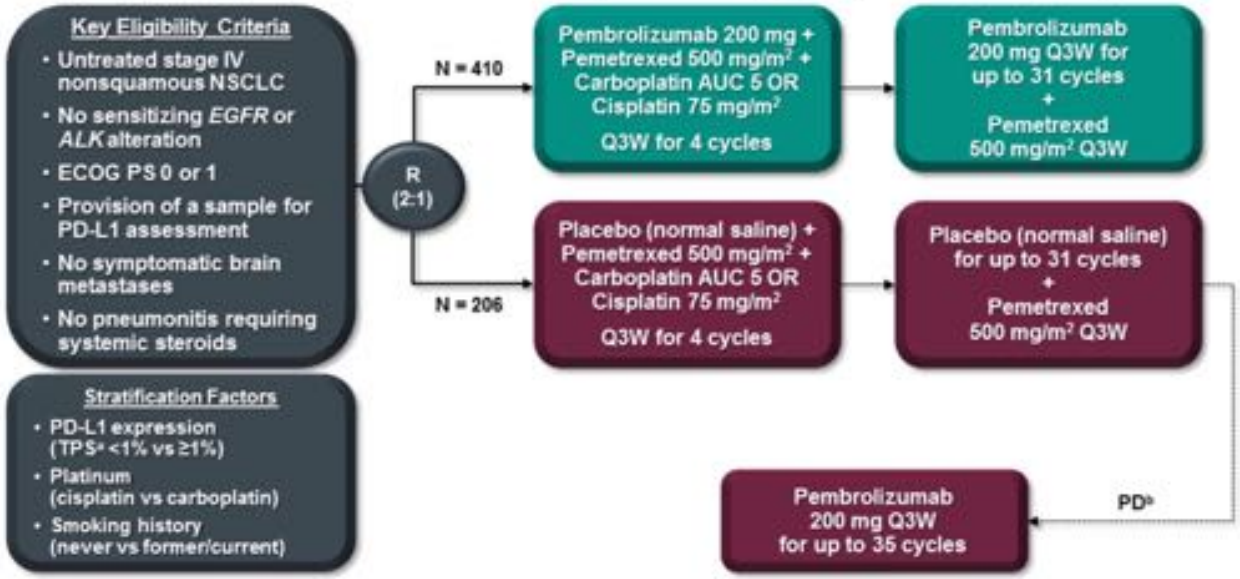


KN 189
KN 407
IMpower 150
Impower 131
Empower Lung 3

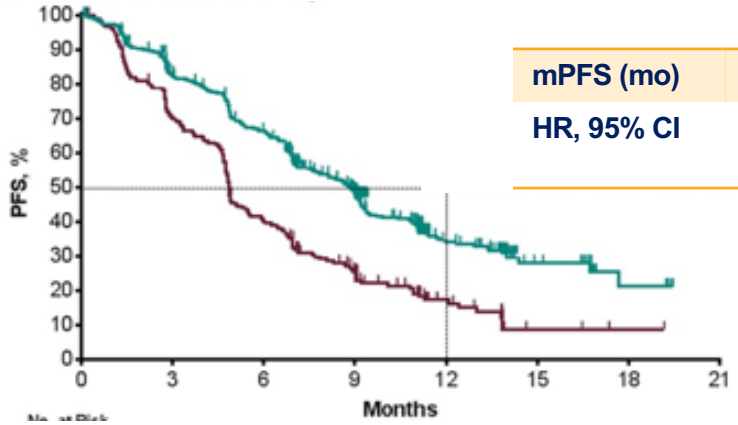


Grant et al, Nat Reviews 2021

KEYNOTE 189: Chemo+IO for 1L Non-Squamous NSCLC

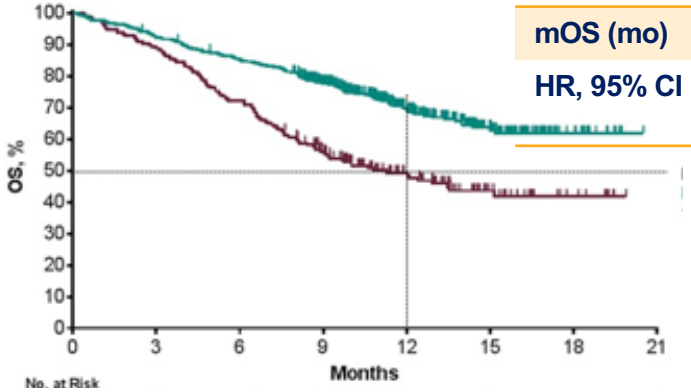


Progression Free Survival



	CPP	Control
mPFS (mo)	8.8 (7.6-9.2)	4.9 (4.7-5.5)
HR, 95% CI	0.52 (0.43-0.64) P = <0.00001	

Overall Survival



	CPP	Control
mOS (mo)	NR	11.3 (8.7-15.1)
HR, 95% CI	0.49 (0.38-0.64) P = <0.00001	

Frequency of PDL1 TPS	<1%	1-49%	≥50%	NE
Pembro/Chemo	31	31.2	32.2	5.6
Chemo	30.6	28.2	34	7.3

Mo

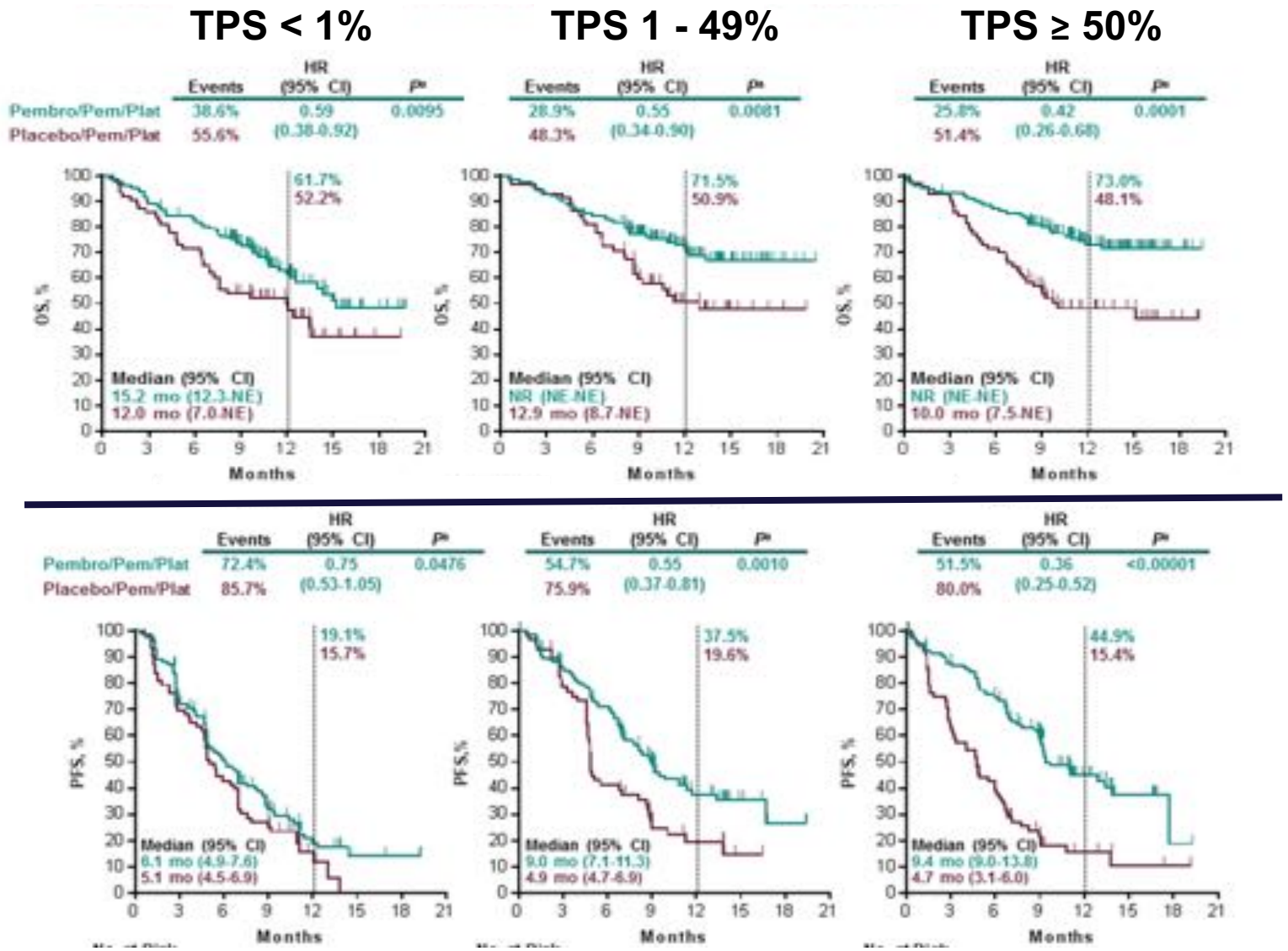
5-Yr Outcomes: PD-L1 ≥50%	Pembro + CT (n = 73)	Pbo + CT (n = 73)
ORR, %	62.1	25.7
mDoR, mo	15.3	7.1
5-yr OS, %	29.6	21.4

Gandhi, L. NEJM 2018.

KEYNOTE 189: OS & PFS varies by PD-L1 TPS

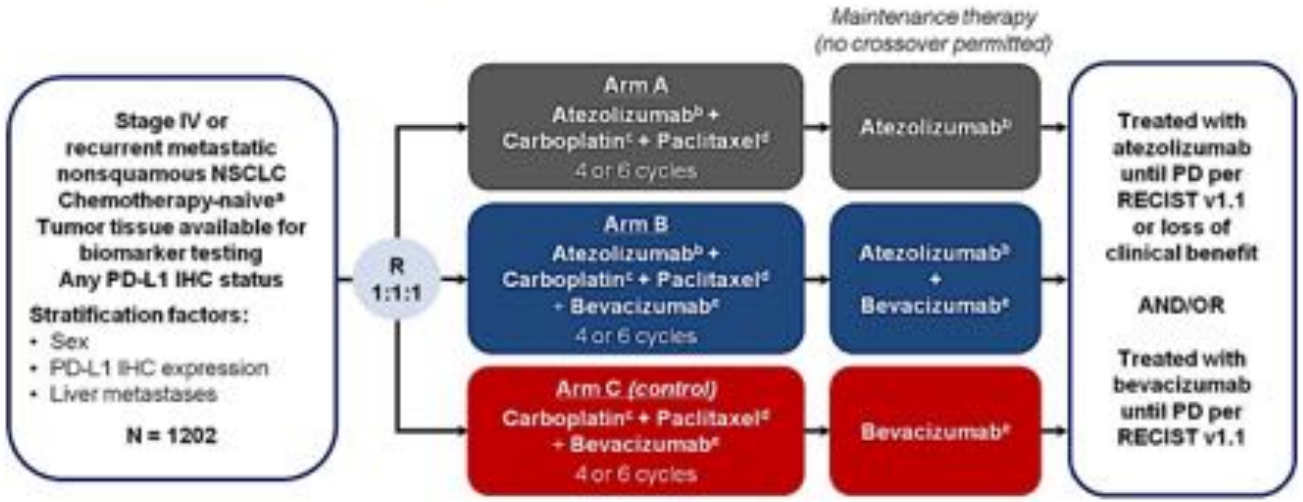
Overall Survival

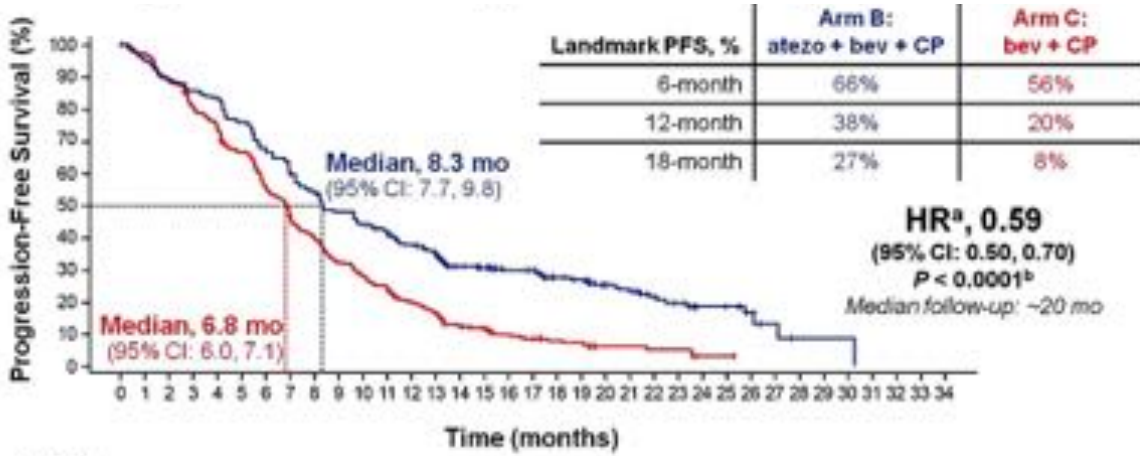
Progression Free Survival



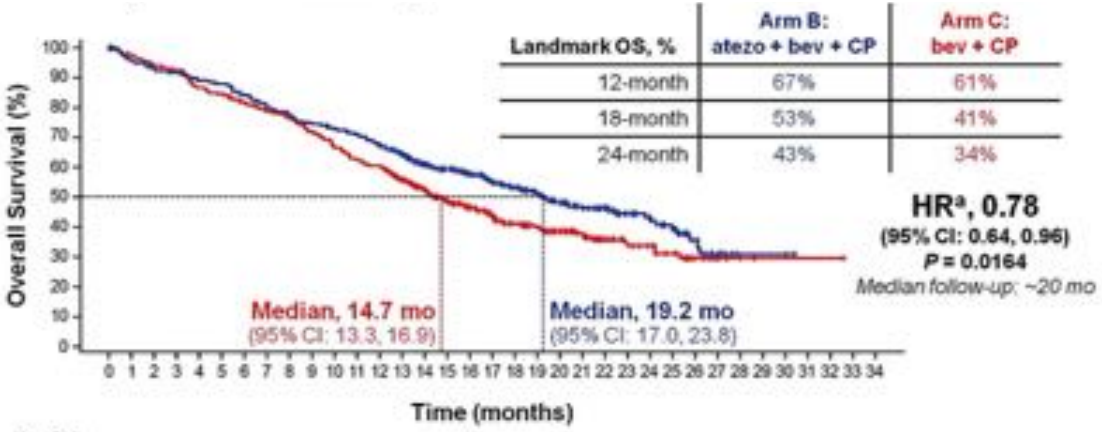
Gandhi, L. NEJM 2018.

IMpower150: ChemoIO + Bev for 1L Non-Squamous NSCLC (including EGFR and ALK)

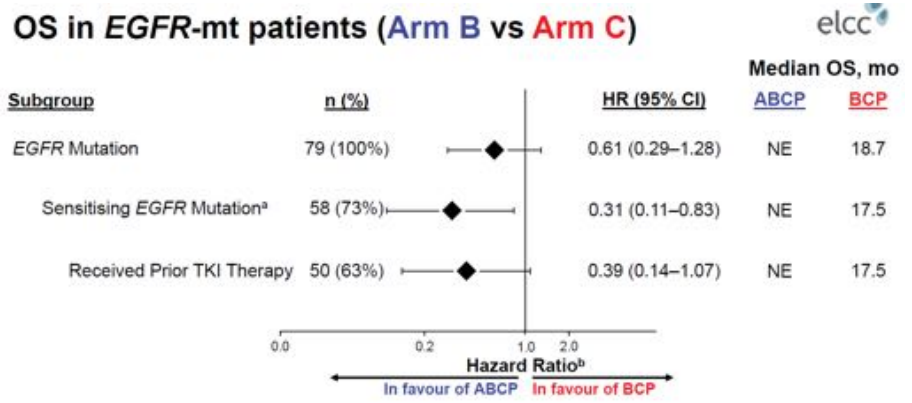




Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

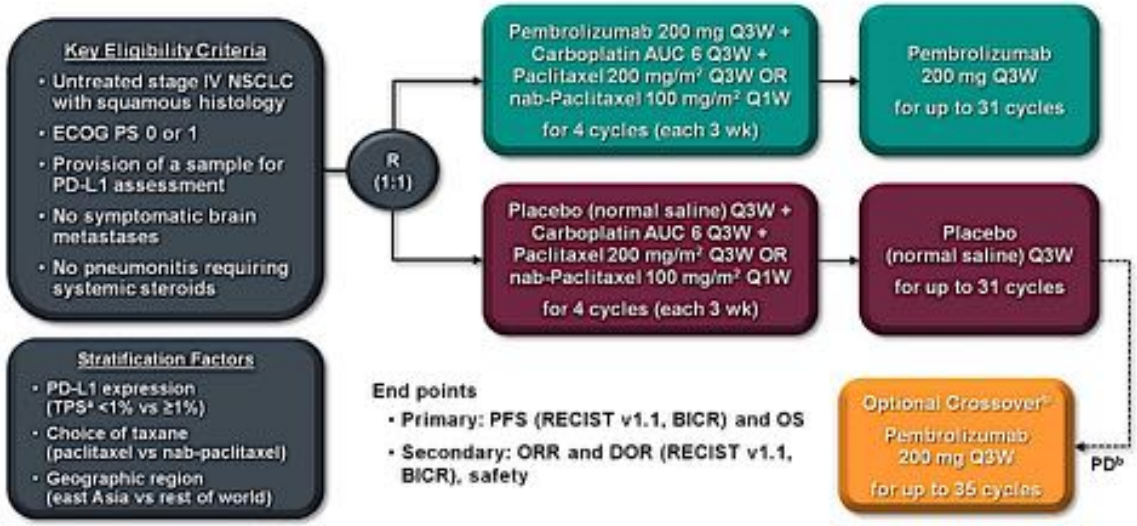


Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

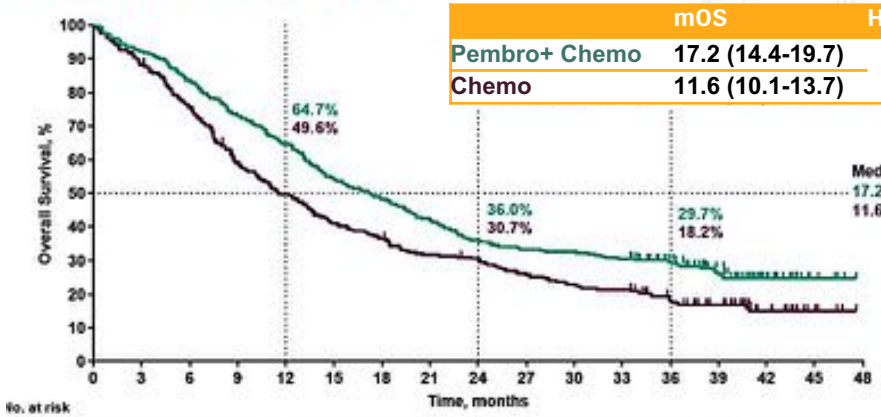


Kowanetz, Socinski AACR 2018, Socinski, et al. ASCO Annual Meeting 2018., Reck et al, ELCC 2019.

KEYNOTE 407: Chemo+IO for 1L Squamous NSCLC



Overall Survival[a]

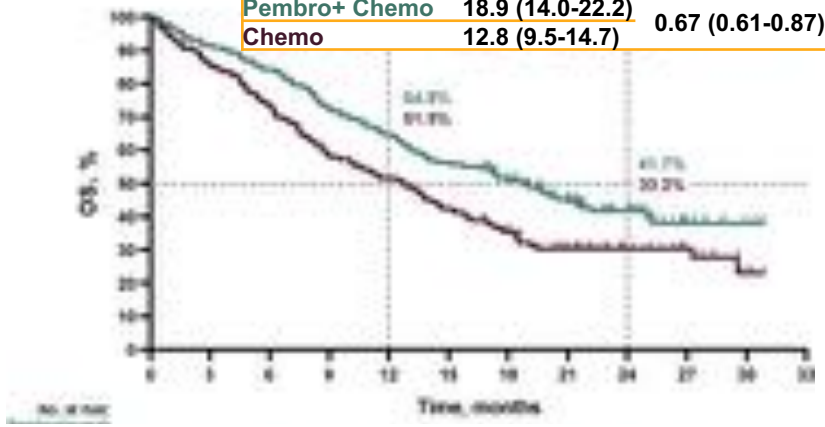


	mOS	HR
Pembro+ Chemo	17.2 (14.4-19.7)	0.71 (0.59-0.86)
Chemo	11.6 (10.1-13.7)	

5-Yr Outcomes: PD-L1 ≥50%	Pembro + CT (n = 73)	Pbo + CT (n = 73)
ORR, %	64.4	30.1
mDoR, mo	10.4	4.6
5-yr OS, %	23.3	8.3

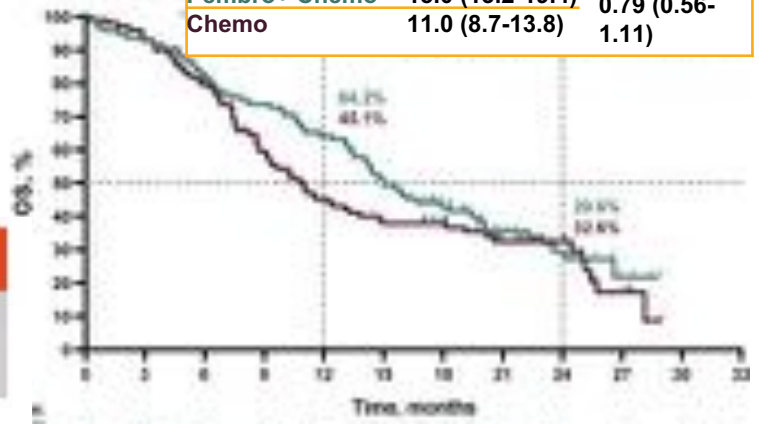
B Overall Survival: PD-L1 ≥ 1%

	mOS	HR
Pembro+ Chemo	18.9 (14.0-22.2)	0.67 (0.61-0.87)
Chemo	12.8 (9.5-14.7)	



C Overall Survival: PD-L1 < 1%

	mOS	HR
Pembro+ Chemo	15.0 (13.2-19.4)	0.79 (0.56-1.11)
Chemo	11.0 (8.7-13.8)	



Robinson et al, ELCC 202, Paz-Ares et al, JTO 2020

EMPower-Lung 03

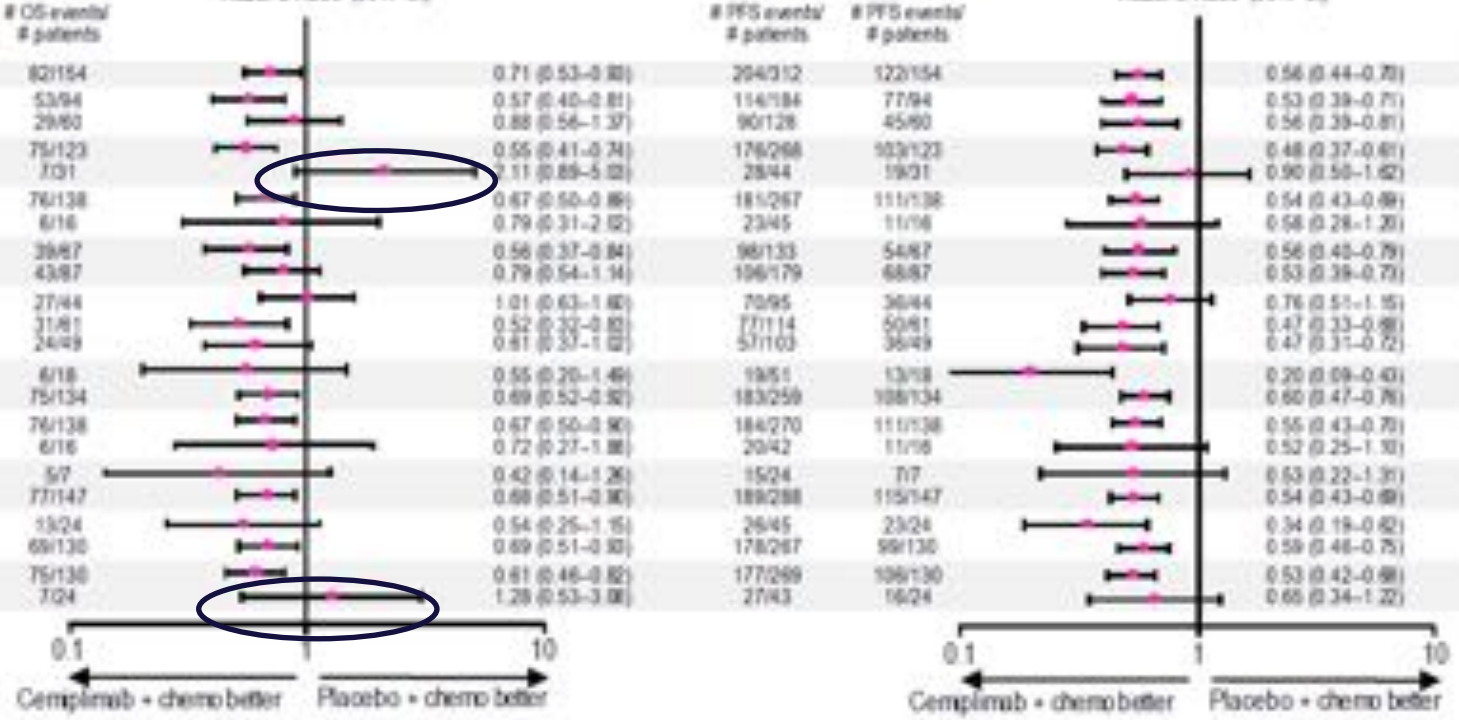
Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

EMPOWER

OS and PFS by Subgroup

		Cemiplimab + chemo # OS events/ # patients	Placebo + chemo # OS events/ # patients	OS Hazard Ratio (95% CI)	Cemiplimab + chemo # PFS events/ # patients	Placebo + chemo # PFS events/ # patients	PFS Hazard Ratio (95% CI)
All patients		132/312	82/154	0.71 (0.53–0.93)	204/312	122/154	0.56 (0.44–0.70)
Age group	<65 years	72/184	53/94	0.57 (0.40–0.81)	114/184	77/94	0.53 (0.39–0.71)
	≥65 years	60/128	29/60	0.88 (0.56–1.37)	90/128	45/60	0.56 (0.39–0.81)
Gender	Male	113/268	75/123	0.55 (0.41–0.74)	176/268	103/123	0.48 (0.37–0.61)
	Female	19/44	7/31	2.11 (0.89–5.02)	28/44	19/31	0.90 (0.50–1.62)
Race	White	116/267	76/138	0.67 (0.50–0.89)	181/267	111/138	0.54 (0.43–0.69)
	Non-white	16/45	6/16	0.79 (0.31–2.02)	23/45	11/16	0.58 (0.28–1.20)
Histology	Squamous	57/133	39/87	0.56 (0.37–0.84)	98/133	54/87	0.56 (0.40–0.79)
	Non-squamous	75/179	43/87	0.79 (0.54–1.14)	106/179	68/87	0.53 (0.39–0.73)
PD-L1 level	<1%	54/95	27/44	1.01 (0.63–1.62)	70/95	36/44	0.76 (0.51–1.15)
	1–49%	40/114	31/81	0.52 (0.32–0.83)	77/114	60/81	0.47 (0.33–0.68)
	≥50%	38/103	24/49	0.61 (0.37–1.02)	57/103	36/49	0.47 (0.31–0.72)
ECOG PS	0	11/51	6/18	0.55 (0.20–1.49)	19/51	13/18	0.20 (0.09–0.43)
	1	119/259	75/134	0.69 (0.52–0.92)	183/259	108/134	0.60 (0.47–0.76)
Region	Europe	118/270	76/138	0.67 (0.50–0.90)	184/270	111/138	0.55 (0.43–0.70)
	Asia	14/42	6/16	0.72 (0.27–1.88)	20/42	11/16	0.52 (0.25–1.10)
Brain met	Yes	11/24	5/7	0.42 (0.14–1.26)	15/24	7/7	0.53 (0.22–1.31)
	No	121/288	77/147	0.68 (0.51–0.90)	189/288	115/147	0.54 (0.43–0.69)
Cancer stage	Locally advanced	16/45	13/24	0.54 (0.25–1.15)	26/45	23/24	0.34 (0.19–0.62)
	Metastatic	116/267	69/130	0.69 (0.51–0.93)	178/267	99/130	0.59 (0.46–0.75)
Smoking	Smokers	115/269	75/130	0.61 (0.46–0.82)	177/269	106/130	0.53 (0.42–0.68)
	Never smokers	17/43	7/24	1.28 (0.53–3.08)	27/43	16/24	0.65 (0.34–1.22)



#, number of; chemo, chemotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; met, metastasis; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Data cut-off date: 14 June 2021

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

FDA

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****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

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Oladimeji Akinboro, MD, MPH

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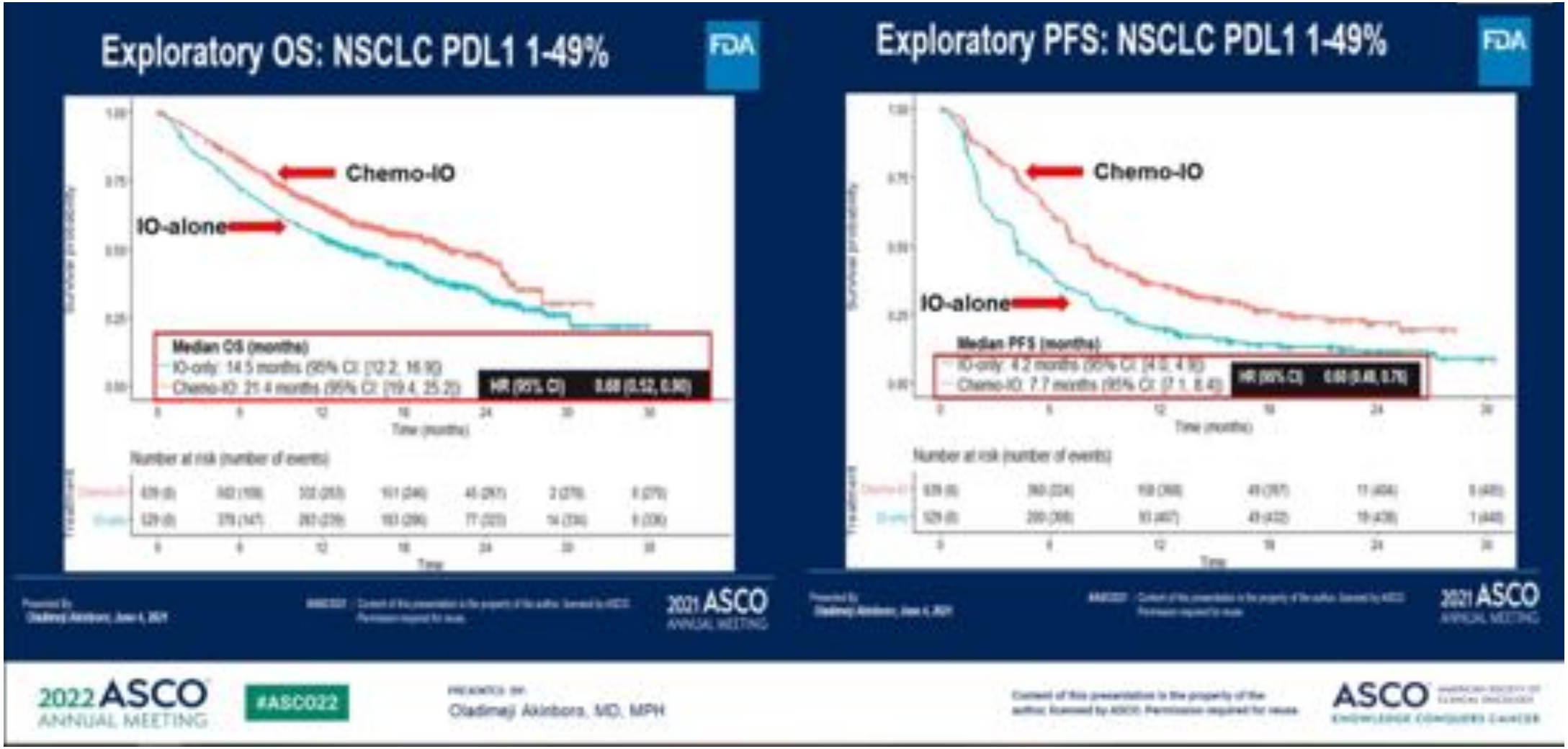
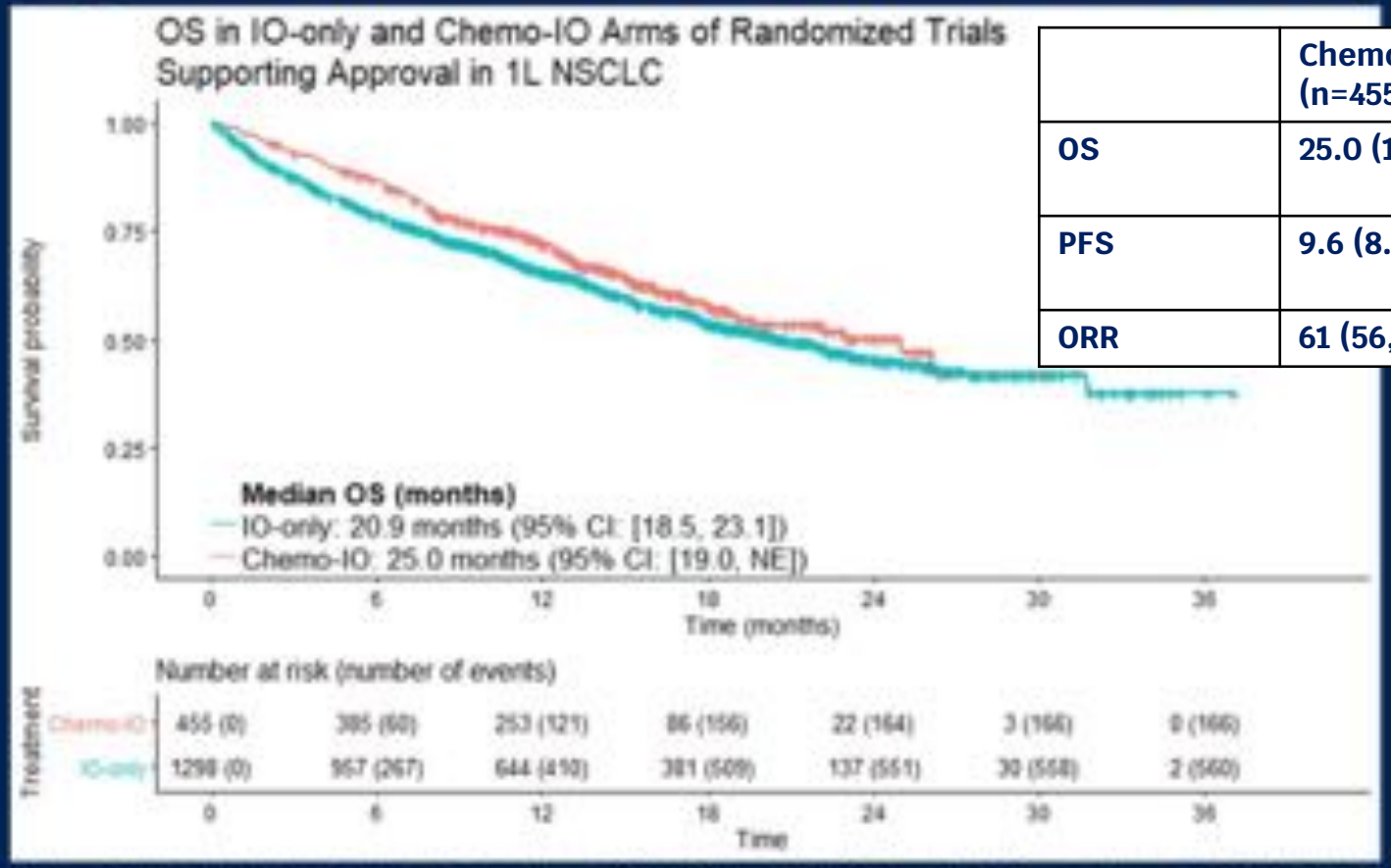
ASCO KNOWLEDGE CONQUERS CANCER

ASCO 2022: FDA pooled analysis of Outcomes of anti-PD1 +/- chemo in 1L NSCLC



Exploratory OS: Chemo-IO vs IO in NSCLC PD-L1 ≥50%

FDA



	Chemo-IO (n=455)	IO alone (n=1298)	HR (95% CI)
OS	25.0 (19.0, NE)	20.9 (18.5-23.1)	0.82 (0.62-1.08)
PFS	9.6 (8.4-11.1)	7.1 (6.3, 8.3)	0.69 (0.55, 0.87)
ORR	61 (56, 66)	43 (41, 46)	OR 1.2 (1.1, 1.3)

Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR=hazard ratio; IO=immunotherapy; NE=not estimable; NSCLC=non-small-cell lung cancer; OS=overall survival; PD-L1=programmed death ligand-1.

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Summary: Advanced/Metastatic NSCLC PD-L1 ≥ 50%

FDA

- Our pooled analysis does not suggest a difference in OS for Chemo-IO vs IO-alone though there appears to be a slight numerical advantage favoring Chemo-IO
- Observed differences in PFS and ORR between Chemo-IO and IO-alone to be interpreted in the context of the OS findings and the exploratory nature of this analysis
- Older adults aged ≥75 years may have better OS and PFS outcomes with IO-only regimens
- These support shared decision-making in selecting a therapeutic approach

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IO=immunotherapy; NSCLC=non-small-cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1

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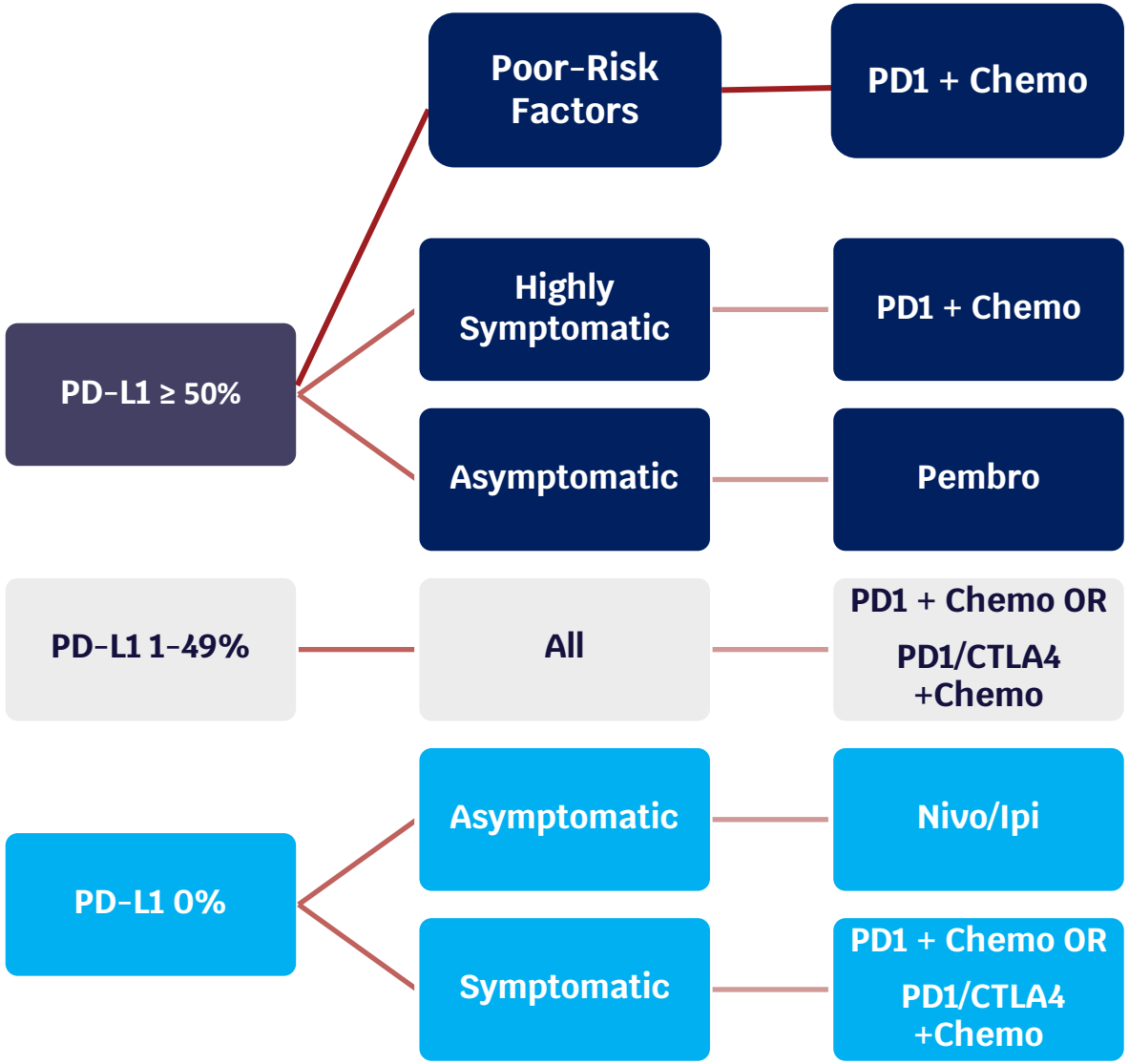
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

What do I do?


PD-L1 ≥ 50%
Poor-Risk Factors
PD1 + Chemo
Highly Symptomatic
PD1 + Chemo
Asymptomatic
Pembro
PD-L1 1-49%
All
PD1 + Chemo OR PD1/CTLA4 +Chemo
PD-L1 0%
Asymptomatic
Nivo/Ipi
Symptomatic
PD1 + Chemo OR PD1/CTLA4 +Chemo

KN 042: Not Everyone who is PDL1≥ 50% Benefits From Pembro Monotherapy

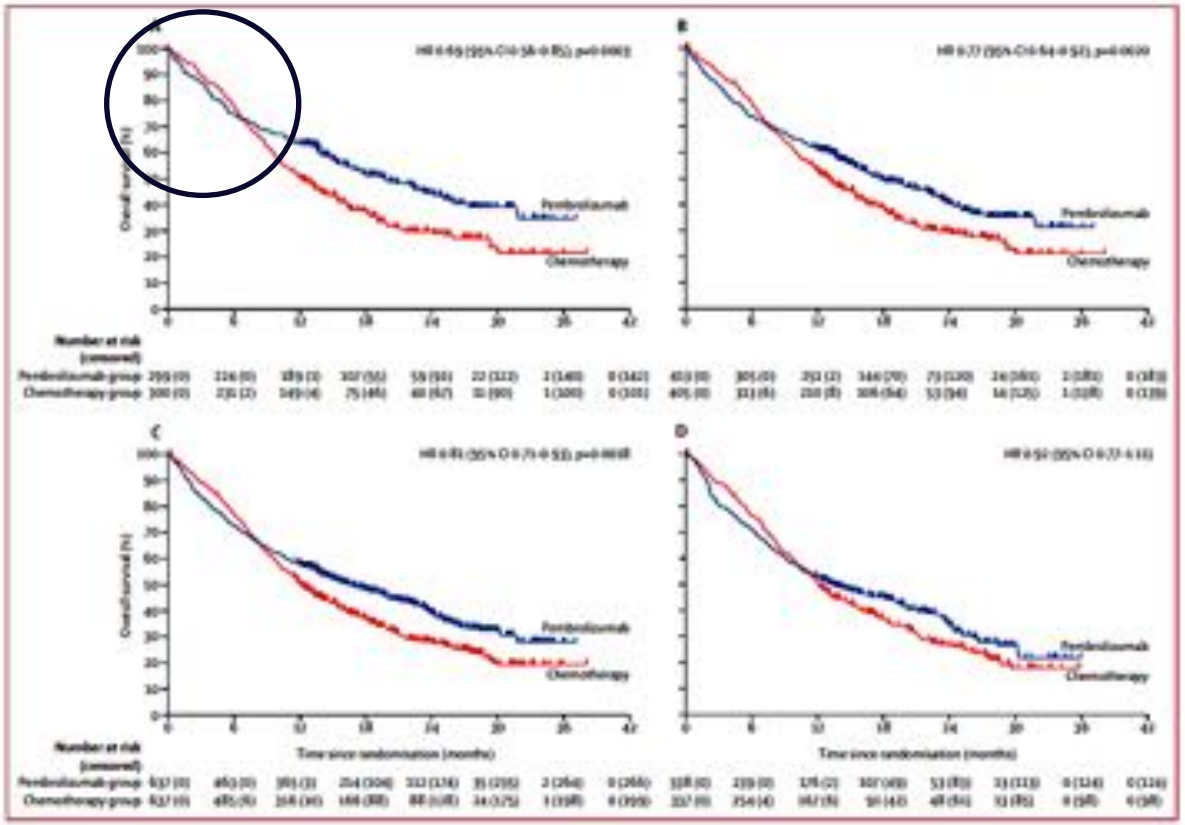
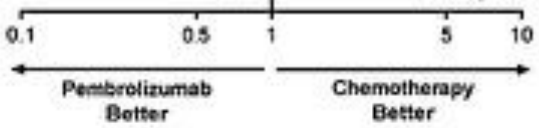


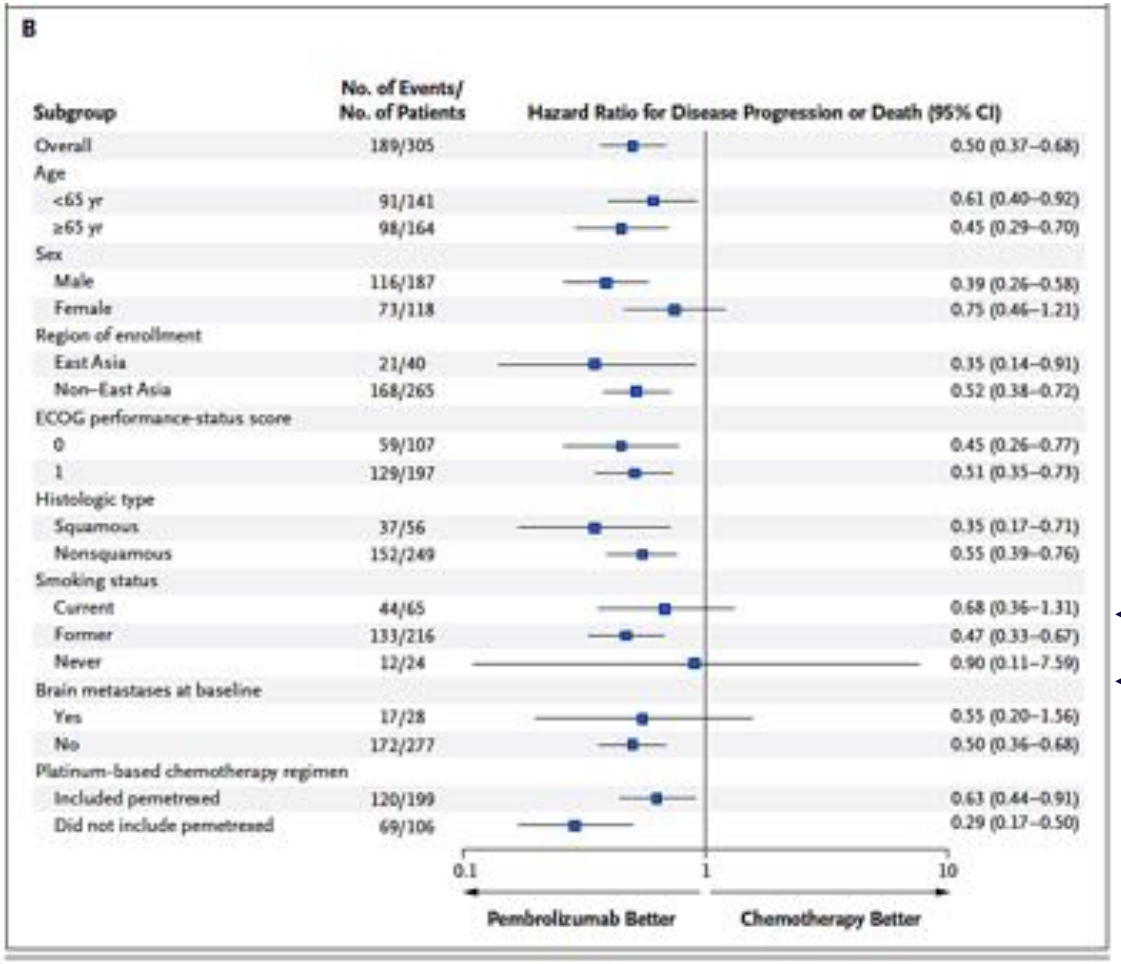
Figure S2: Analysis of Overall Survival in Key Subgroups. (A) PD-L1 TPS ≥50% population. (B) PD-L1 TPS ≥20% population. (C) PD-L1 TPS ≥1% population. CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; PD-L1=programmed death ligand 1; TPS=tumour proportion score.

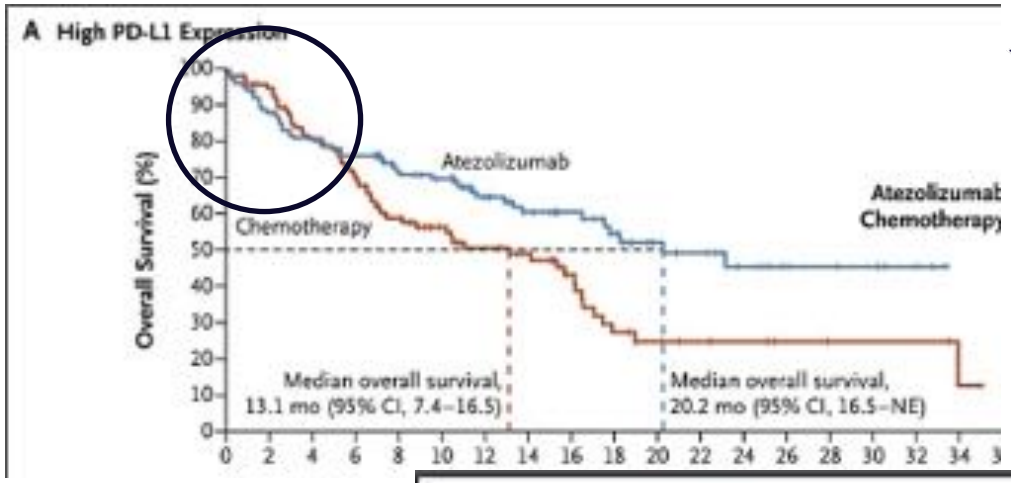
A. Tumour Propertion Score ≥50%

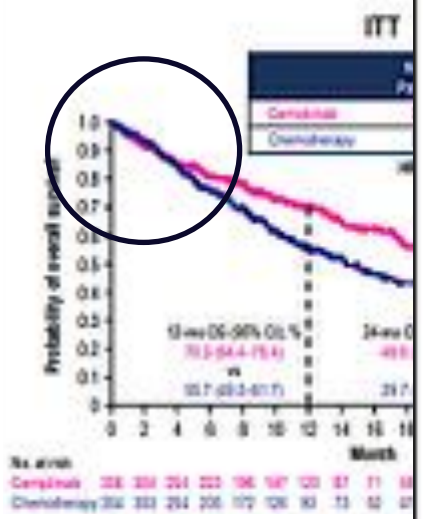
Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	356/599	0·69 (0·56-0·85)
Age		
<65 yr	189/328	0·81 (0·60-1·08)
≥65 yr	167/271	0·58 (0·42-0·80)
Sex		
Male	248/415	0·68 (0·53-0·88)
Female	108/184	0·78 (0·53-1·15)
ECOG performance status		
0	94/187	0·57 (0·37-0·86)
1	262/412	0·74 (0·58-0·95)
Geographic region		
East Asia	97/186	0·83 (0·55-1·23)
Rest of world	259/413	0·65 (0·50-0·83)
Histologic features		
Squamous	144/221	0·53 (0·38-0·75)
Nonsquamous	212/378	0·82 (0·63-1·07)
Smoking status		
Never	73/131	1·10 (0·69-1·75)
Former	208/352	0·60 (0·46-0·80)
Current	75/116	0·71 (0·43-1·16)
Chemotherapy regimen		
Pemetrexed and carboplatin	179/319	0·76 (0·56-1·02)
Paclitaxel and carboplatin	177/280	0·60 (0·44-0·82)
Disease status		
Locally advanced	34/62	0·28 (0·12-0·67)
Metastatic	322/537	0·75 (0·60-0·94)

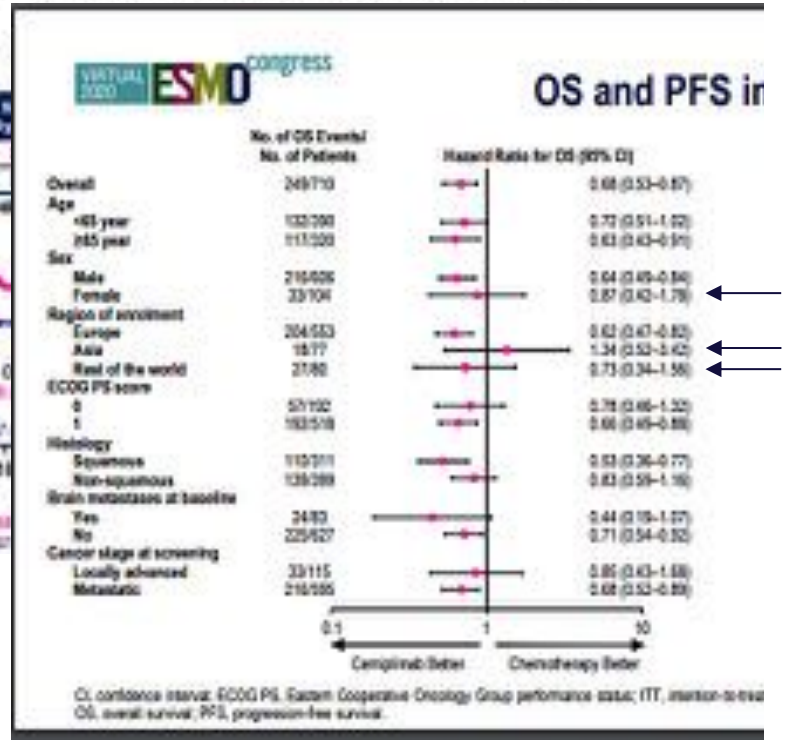


Even in KN24, also IMP110 + EMP-Lung 01

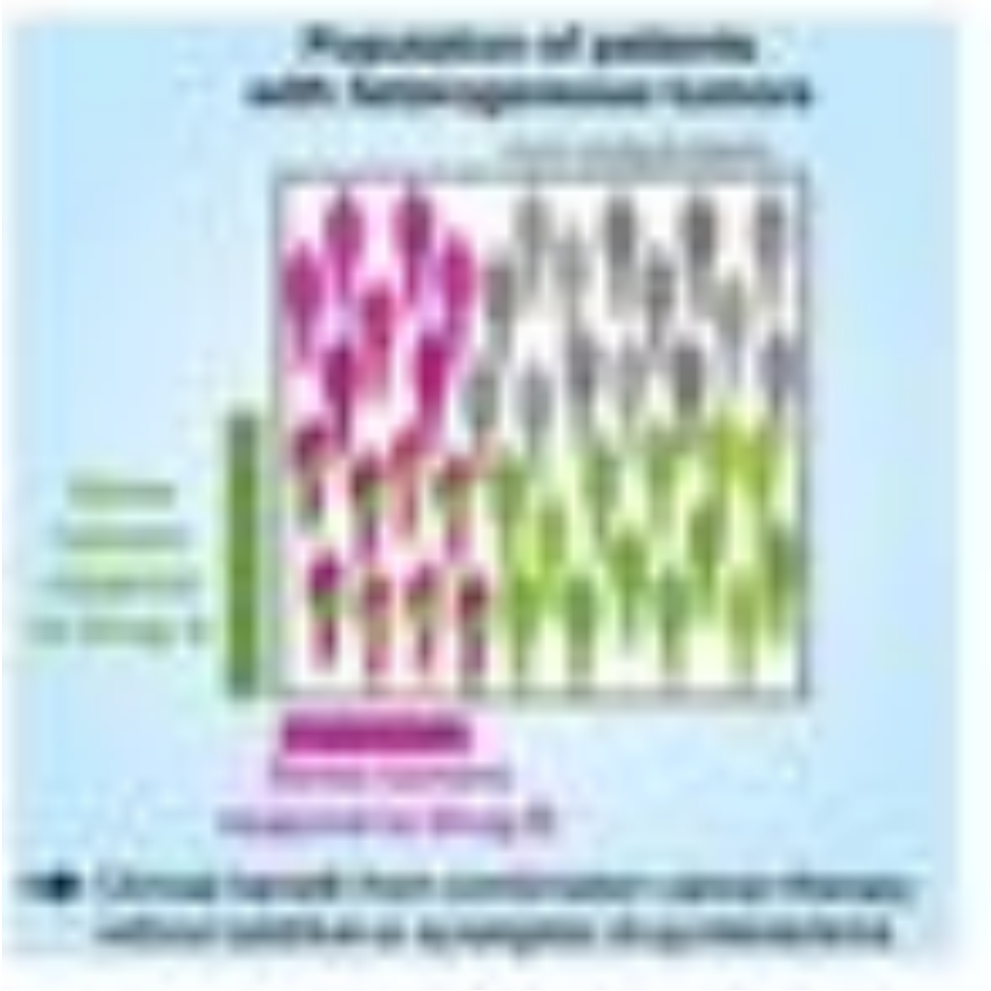


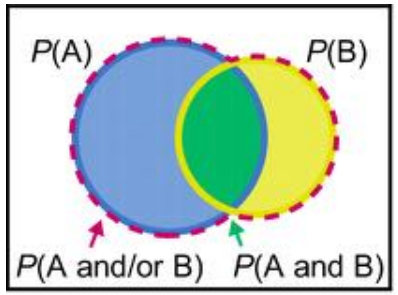






The Elephant In the Middle of the Room: Patient Heterogeneity

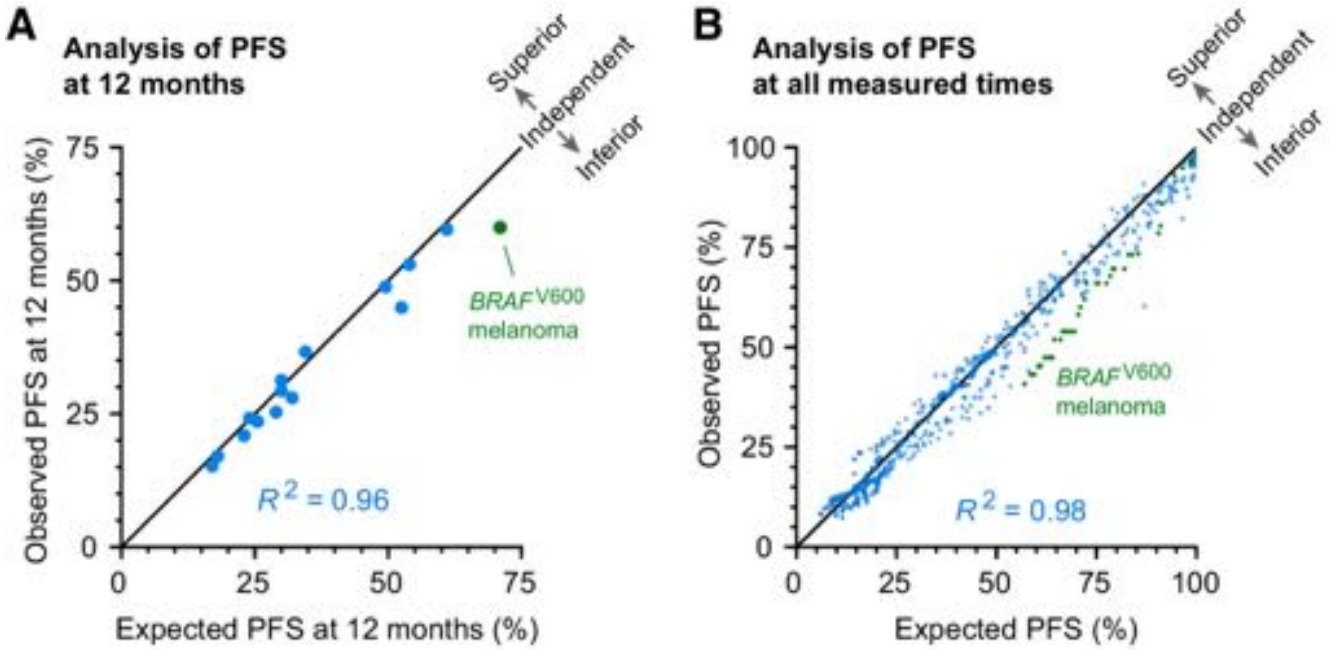




If $P(B) > P(A \text{ and } B)$

$\Rightarrow P(A \text{ and/or } B) > P(A)$

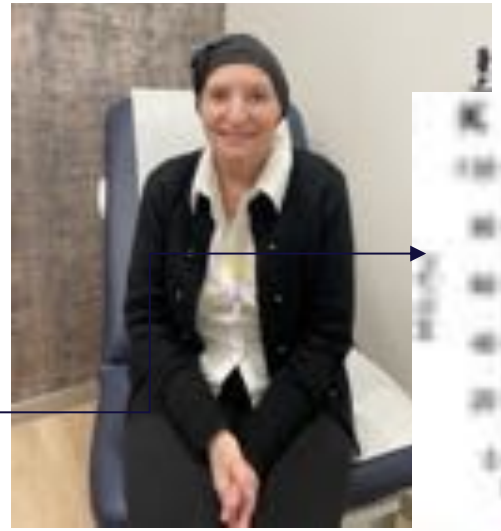
$\Rightarrow$ Combination therapy can be superior to monotherapy via independent drug action [where combining A and B does not increase $P(A)$, $P(B)$]

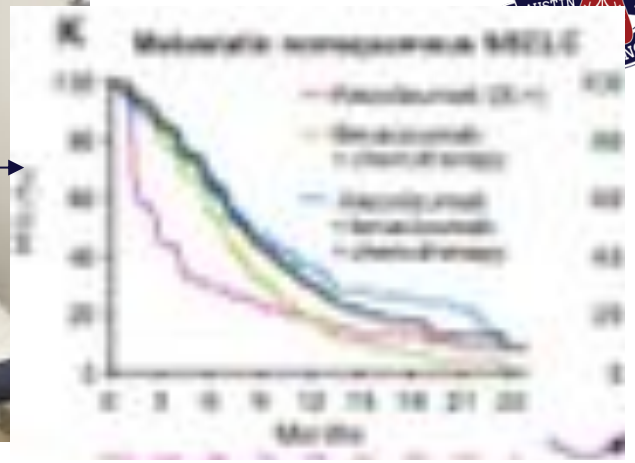


Clin Cancer Res. 2022;28(2):368-377. doi:10.1158/1078-0432.CCR-21-2275

PDL1=90%;
ctDNA= PIK3CA R108H; STK11
P/w chest pain and brain metastasis

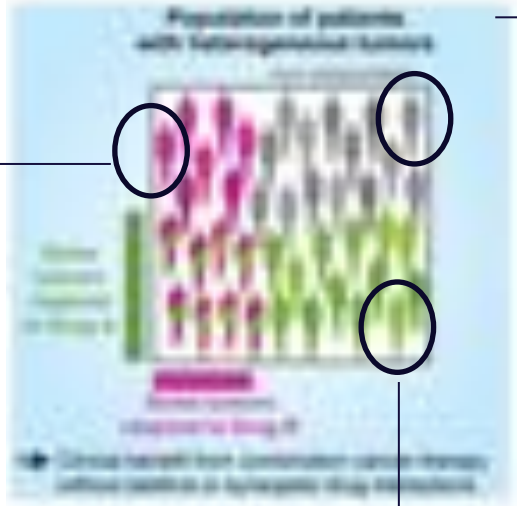
CPP s/p 6 months

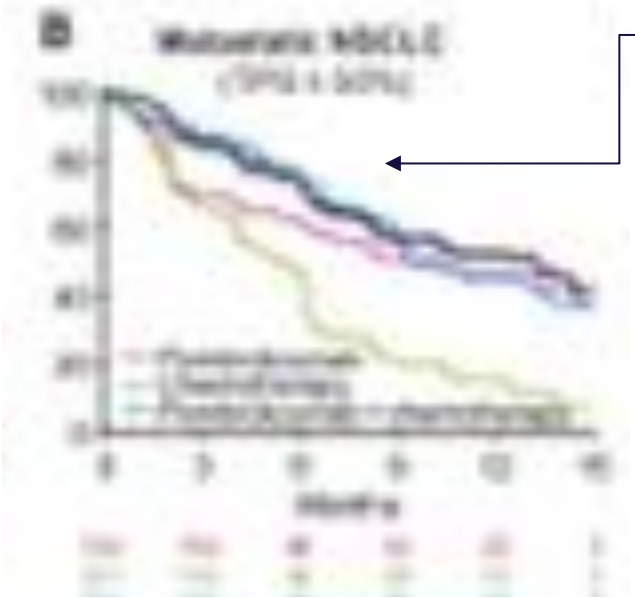


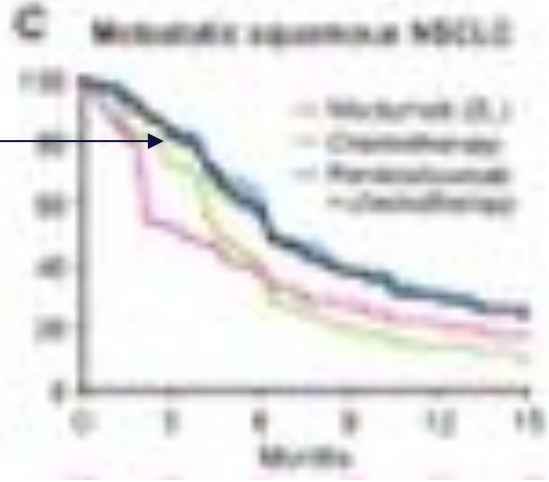


PDL1=10%
ctDNA=KRAS G12S, TP53, ATM

CPP s/p 7 months; P alone 1 yr

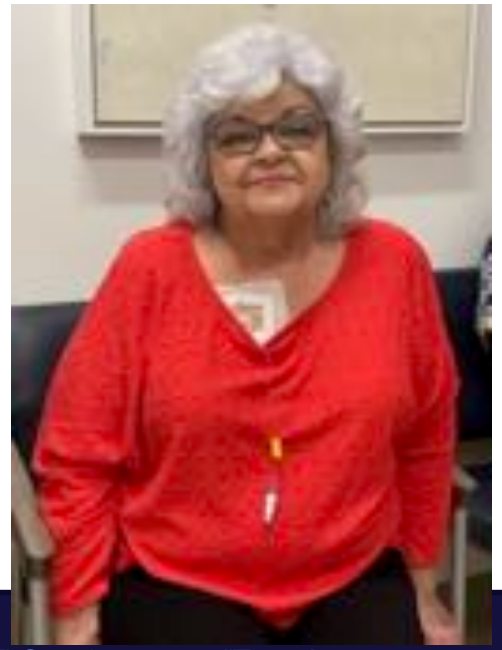






PDL1=100%; TMB 8
Tempus=TP53, KDM61, NFE2L2, LRP1B;

CAP s/p 6 months cb pneumonitis



Clin Cancer Res. 2022;28(2):368-377. doi:10.1158/1078-0432.CCR-21-2275

Ongoing Trials

INSIGNA

H. Borghaei/A. Chiang

Primary Endpoint: OS

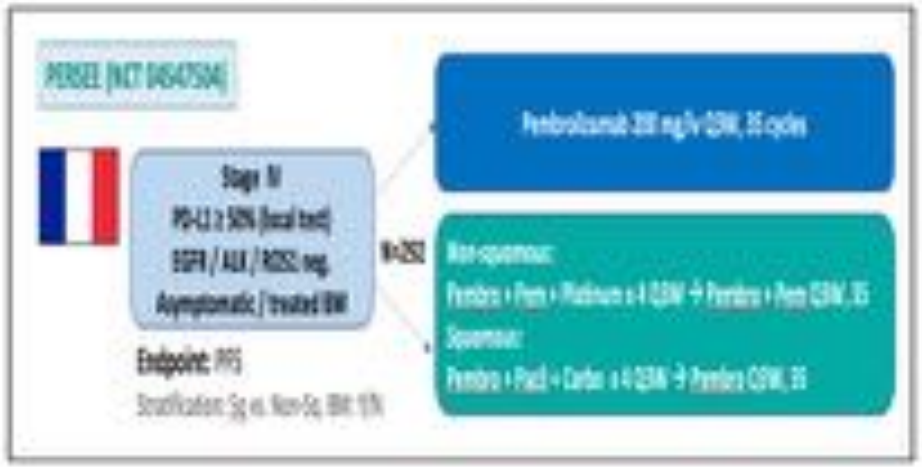
Integrated Biomarker Objective:

- To establish a **predictive signature** for clinical benefit (OS), to treatment with chemo combined with pembrolizumab versus pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50%).
- To establish a **prognostic signature** associated with better outcome (OS) to 1st line treatment with pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50% TPS).

Persee

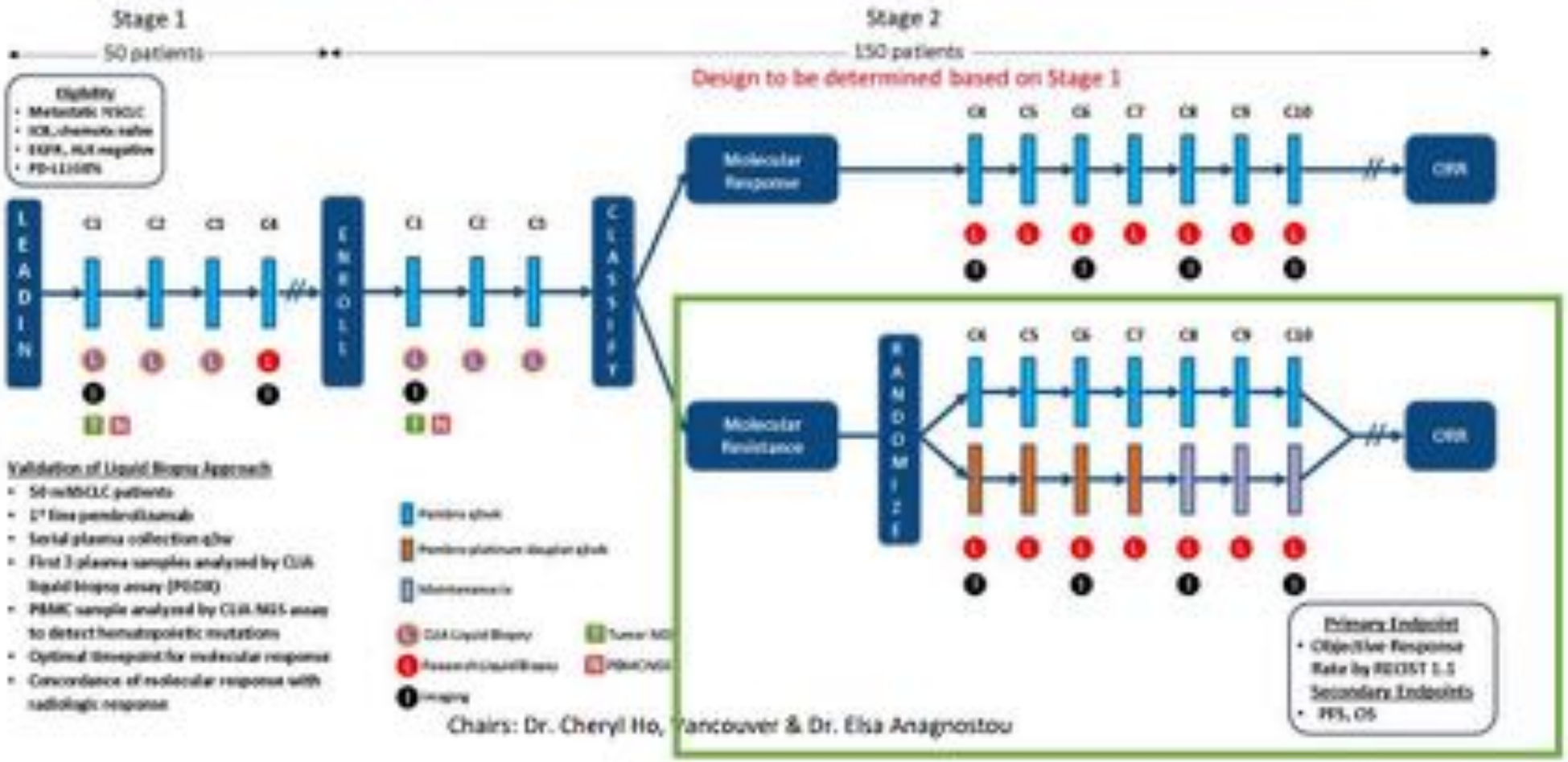
GFPC 01-2020

R. Descourt / C. Decroisette



Slide courtesy of Natasha Leighl

A Biomarker-Directed, Open Label, Multi-Center Phase II Study of Molecular Response Adaptive Immuno-Chemotherapy in Patients with NSCLC



Slide courtesy of Natasha Leighl

In Collaboration with the Canadian Clinical Trials Group, the Cancer Research Institute and the Mark Foundation, NCT04093167

Conclusions

- **Not all patients benefit from chemo, IO or chemo-IO like the long-term IO responders and so "Bet-Hedging" becomes our default strategy in order to leave no patient behind**
- **However, we should be careful not to assume synergism or even additivity are happening for our 1L NSCLC patients with this approach**
- **Biomarkers are critical to further define WHO should receive WHAT front-line strategies**