國立成功大學醫學院
College of Medicine, National Cheng Kung University

Advances in immunotherapy in lung cancer treatment

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- First line I/O or combination for no driver mutation NSCLC?
- What is the treatment strategy in special situation?
- New drug or new combination?
- Novel target?

NCCN Guidelines Version 2.2021
Non-Small Cell Lung Cancer

PD-L1 EXPRESSION POSITIVE (≥50%)[ll]

FIRST-LINE THERAPY[oo]

PD-L1 expression positive (≥50%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitors[hhh]

→ PS 0–2

Adenocarcinoma, large cell, NSCLC NOS →

- **Preferred**
  Pembrolizumab (category 1)
  or
  (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
  or
  Atezolizumab (category 1)
- **Other Recommended**
  Carboplatin + paclitaxel + bevacizumab[ss] + atezolizumab (category 1)
  or
  Carboplatin + albumin-bound paclitaxel + atezolizumab
  or
  Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)

Squamous cell carcinoma →

- **Preferred**
  Pembrolizumab (category 1)
  or
  Carboplatin + (paclitaxel or albumin-boun paclitaxel) + pembrolizumab (category 1)
  or
  Atezolizumab (category 1)
- **Other Recommended**
  Nivolumab + ipilimumab + paclitaxel + carboplatin
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)

See PD-L1 expression positive (≥1%–49%) NSCL-32

KN024: Pembro

KN189: Plat/PEM/Pembro

IMP110: Atezo

IMP150: CBDCA/PTX /Beva/Atezo

IMP130: CBDCA/nabPTX /Atezo

CM9LA: Plat/PEM/Nivo/Ipi

CM227: Nivo/Ipi

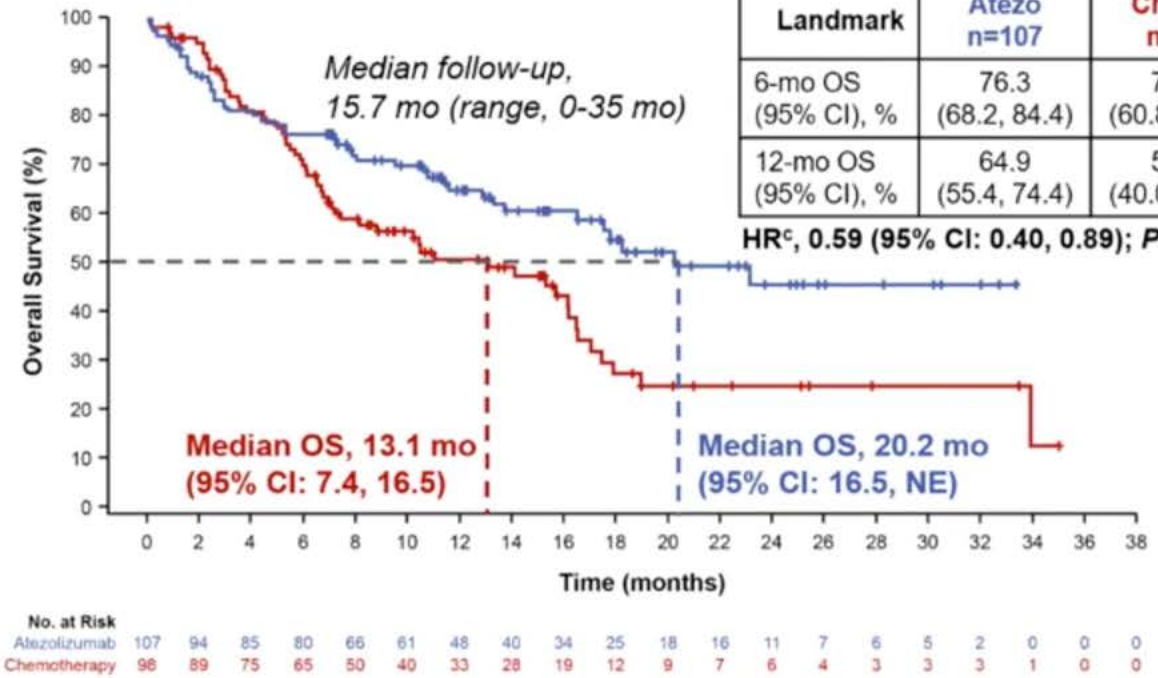
KN407: CBCZA/(nab)/PTX/Pembro

CM9LA: CBDCA/PTX /Nivo/Ipi

CM227: Nivo/Ipi

OS analysis in the high PD-L1 expression WT population IMpower 110

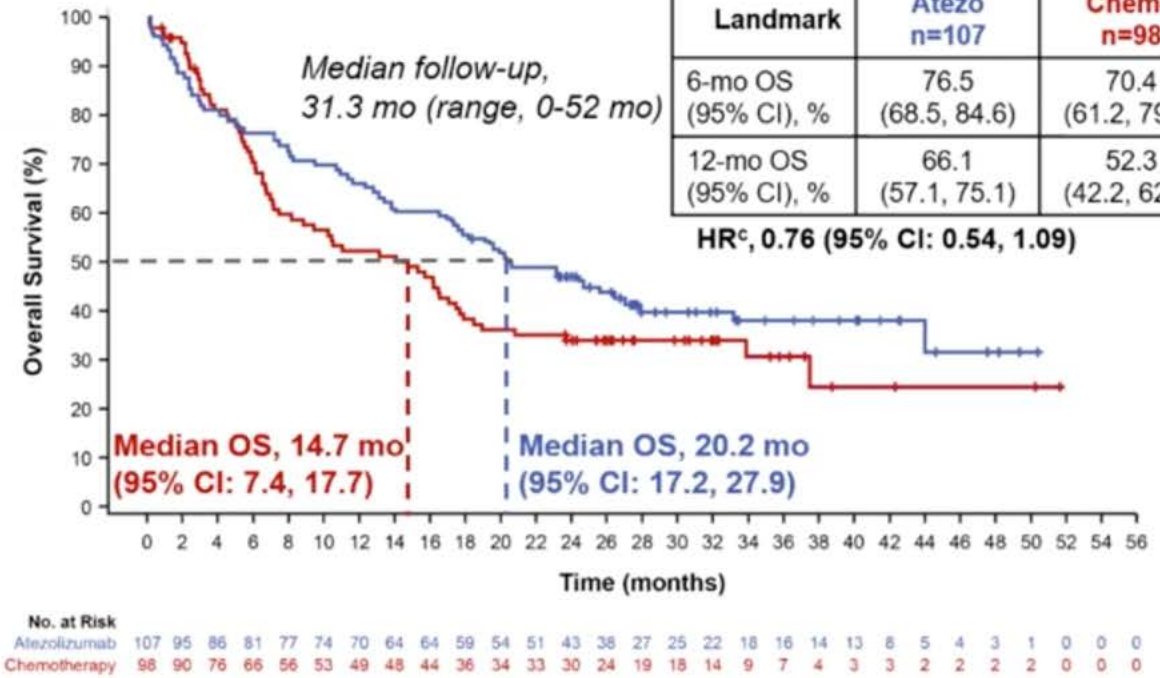
Primary analysis[1,a]



Landmark	Atezo n=107	Chemo n=98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)

HR[c], 0.59 (95% CI: 0.40, 0.89); *P*=0.0106[d]

Updated (exploratory) analysis[b]



Landmark	Atezo n=107	Chemo n=98
6-mo OS (95% CI), %	76.5 (68.5, 84.6)	70.4 (61.2, 79.6)
12-mo OS (95% CI), %	66.1 (57.1, 75.1)	52.3 (42.2, 62.4)

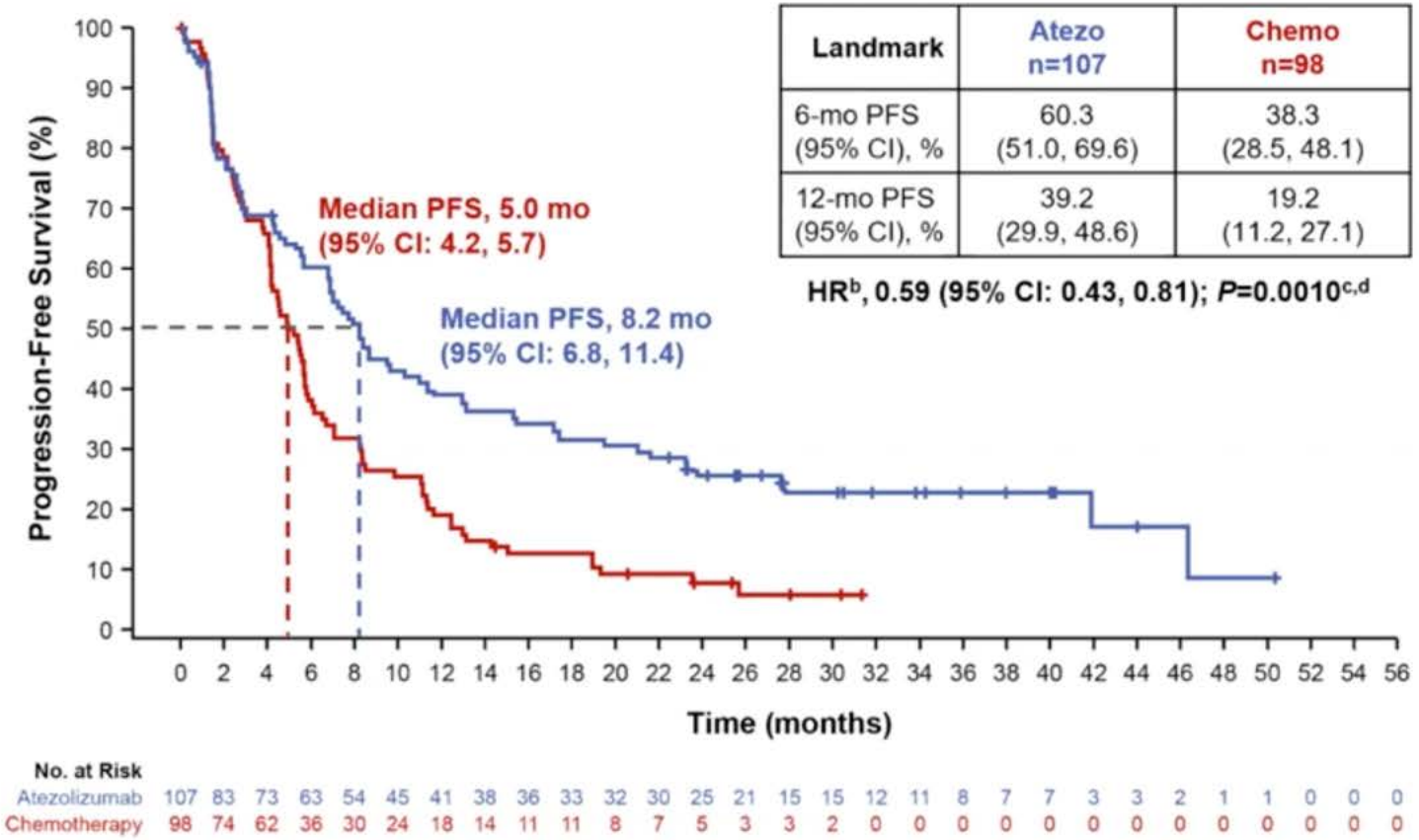
HR[c], 0.76 (95% CI: 0.54, 1.09)

- At the interim OS analysis of IMpower110, atezolizumab demonstrated significantly longer median OS (difference, 7.1 mo) in the high PD-L1 expression WT population vs chemotherapy, with an HR of 0.59[1]
  - Because the OS testing boundary was crossed at the interim OS analysis, this became the primary analysis for this population
- At this updated, exploratory OS analysis in the high PD-L1 expression WT population, continued OS improvement was observed in the atezolizumab vs chemotherapy arm
  - Median OS in the atezolizumab arm was the same as observed at the previous analysis (20.2 mo); in the chemotherapy arm, median OS increased (13.1 vs 14.7 mo)

[a] Data cutoff: 10 September 2018. [b] Data cutoff: 4 February 2020. [c] Stratified. [d] Stratified log-rank. 1. Herbst RS, et al. N Engl J Med 2020;383:1328-39.

Updated PFS[a], confirmed ORR and DOR in the high PD-L1 expression WT population

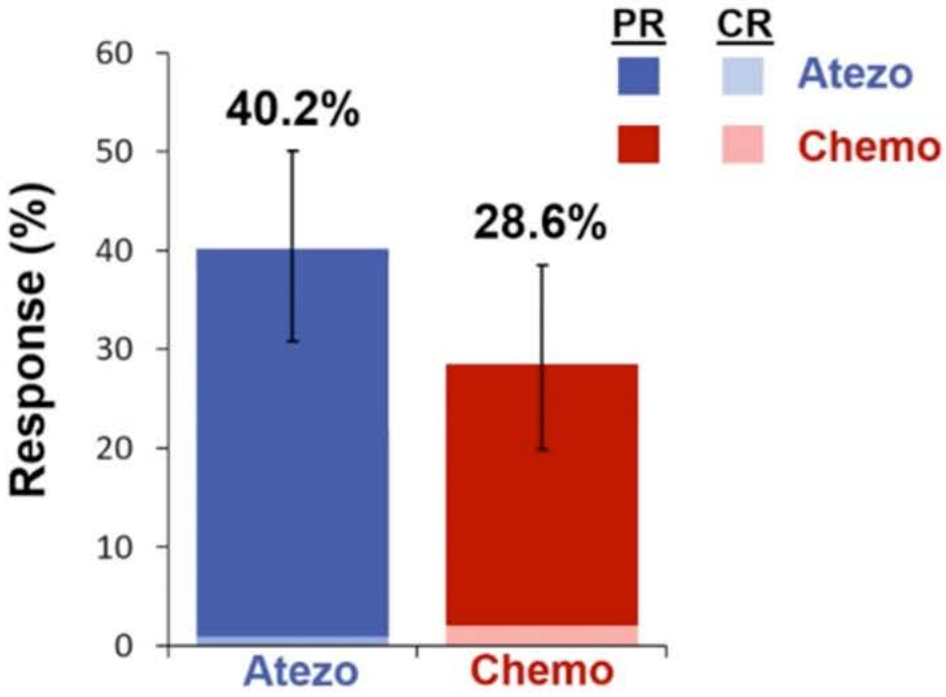
PFS



Landmark	Atezo n=107	Chemo n=98
6-mo PFS (95% CI), %	60.3 (51.0, 69.6)	38.3 (28.5, 48.1)
12-mo PFS (95% CI), %	39.2 (29.9, 48.6)	19.2 (11.2, 27.1)

HR[b], 0.59 (95% CI: 0.43, 0.81); *P*=0.0010[c,d]

Confirmed ORR and DOR



	Atezo	Chemo
mDOR (range), mo	38.9 (2.8-46.3+)	8.3 (2.6-30.0+)

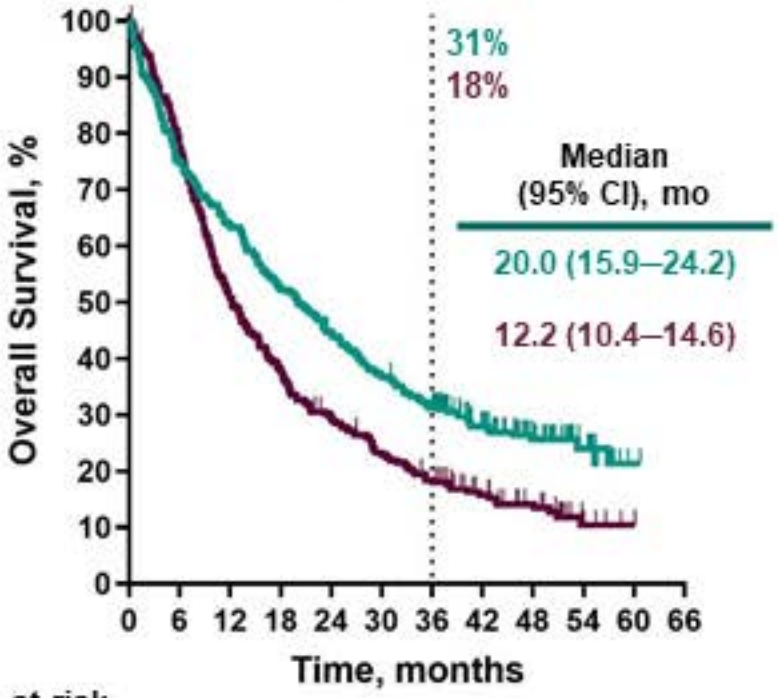
- Improved PFS, ORR, and DOR were seen in the atezolizumab vs chemotherapy arm in the high PD-L1 expression WT population

mDOR, median duration of response. [a] Investigator assessed per RECIST 1.1. [b] Stratified. [c] Stratified log-rank. [d] For descriptive purposes only. Data cutoff: 4 February 2020.

OS KN042

PD-L1 TPS ≥50%

	Events, n (%)	HR (95% CI)
Pembrolizumab	219 (73)	0.68 (0.57–0.82)
Chemotherapy	255 (85)	

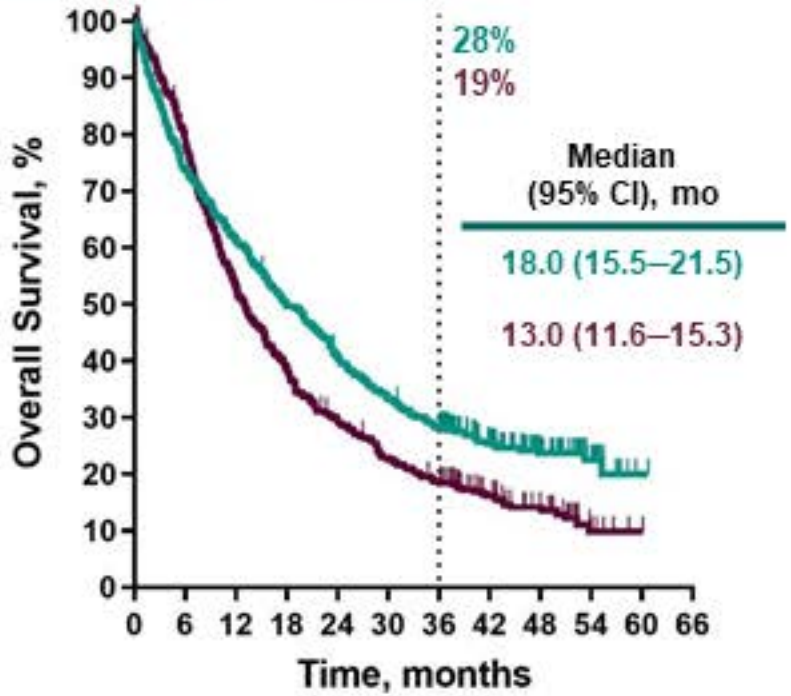


No. at risk

Pembro	299	190	132	89	35	1	0
Chemo	300	151	87	52	21	0	0

PD-L1 TPS ≥20%

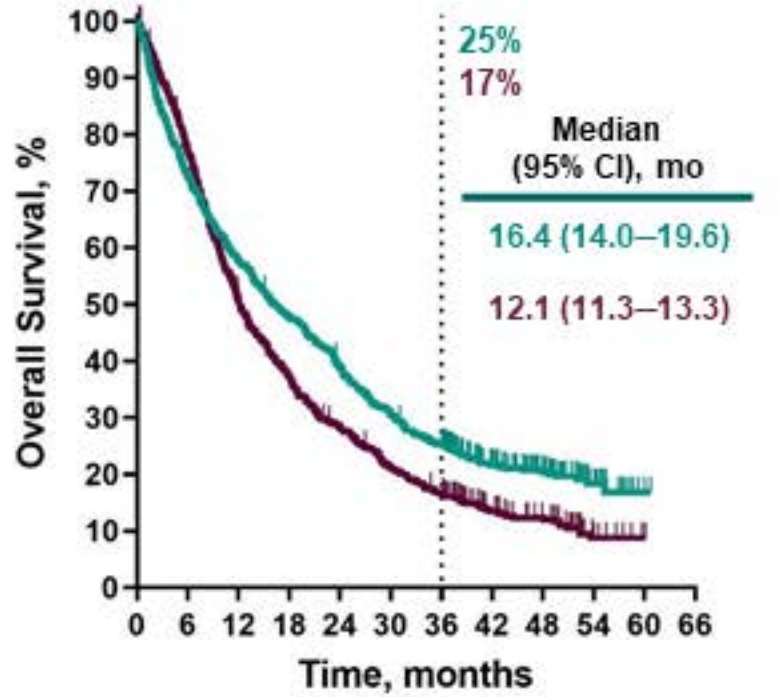
	Events, n (%)	HR (95% CI)
Pembrolizumab	311 (75)	0.75 (0.64–0.88)
Chemotherapy	341 (84)	



	413	253	166	112	45	1	0
	405	212	117	70	25	0	0

PD-L1 TPS ≥1%

	Events, n (%)	HR (95% CI)
Pembrolizumab	504 (79)	0.80 (0.71–0.90)
Chemotherapy	553 (87)	



	637	368	246	156	59	1	0
	637	319	177	100	40	0	0

HR, hazard ratio.
Data cutoff date: February 21, 2020.

Debate for I/O single or I/O+ chemo for NSCLC for high PDL1

I/O single

Better tolerated, similar OS

A response rate of 45% and median overall survival of 30 months.(KN024)

I/O+ chemo

Give Your Best Shot First

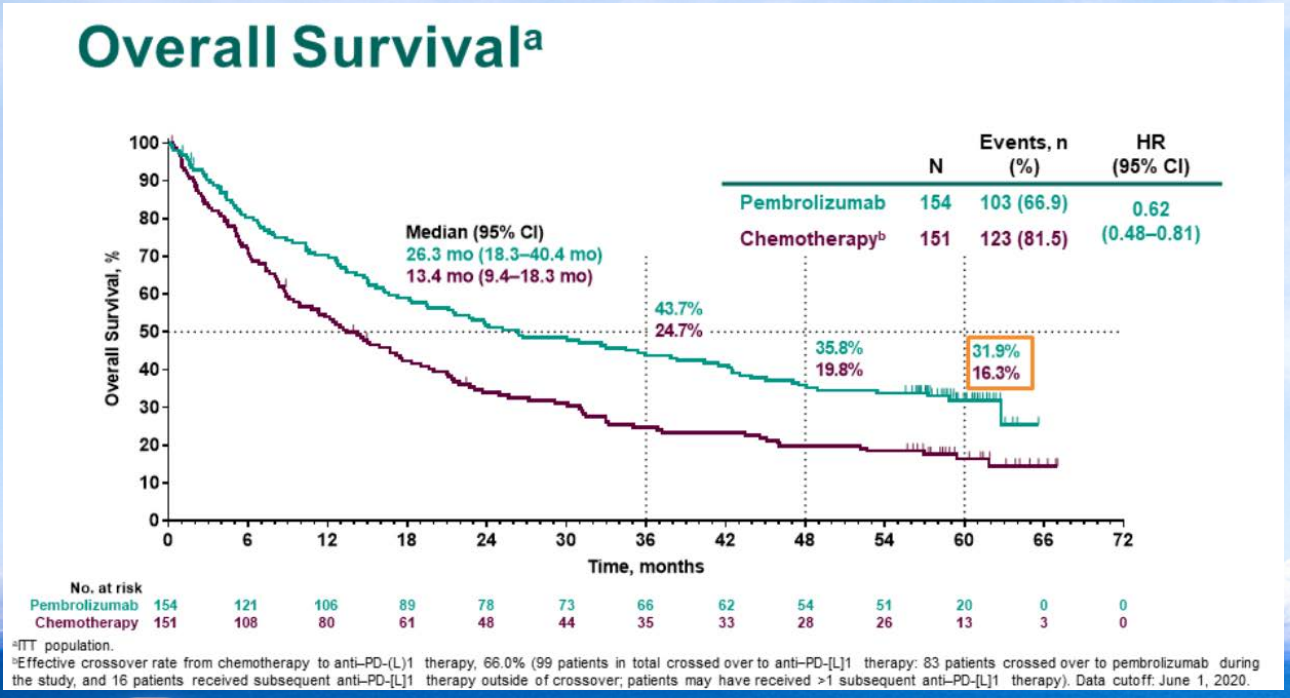
40% to 60% of patients with NSCLC never receive their intended second-line treatment

Debate for I/O single or I/O+ chemo for NSCLC for high PDL1

I/O single

Better tolerated, similar OS

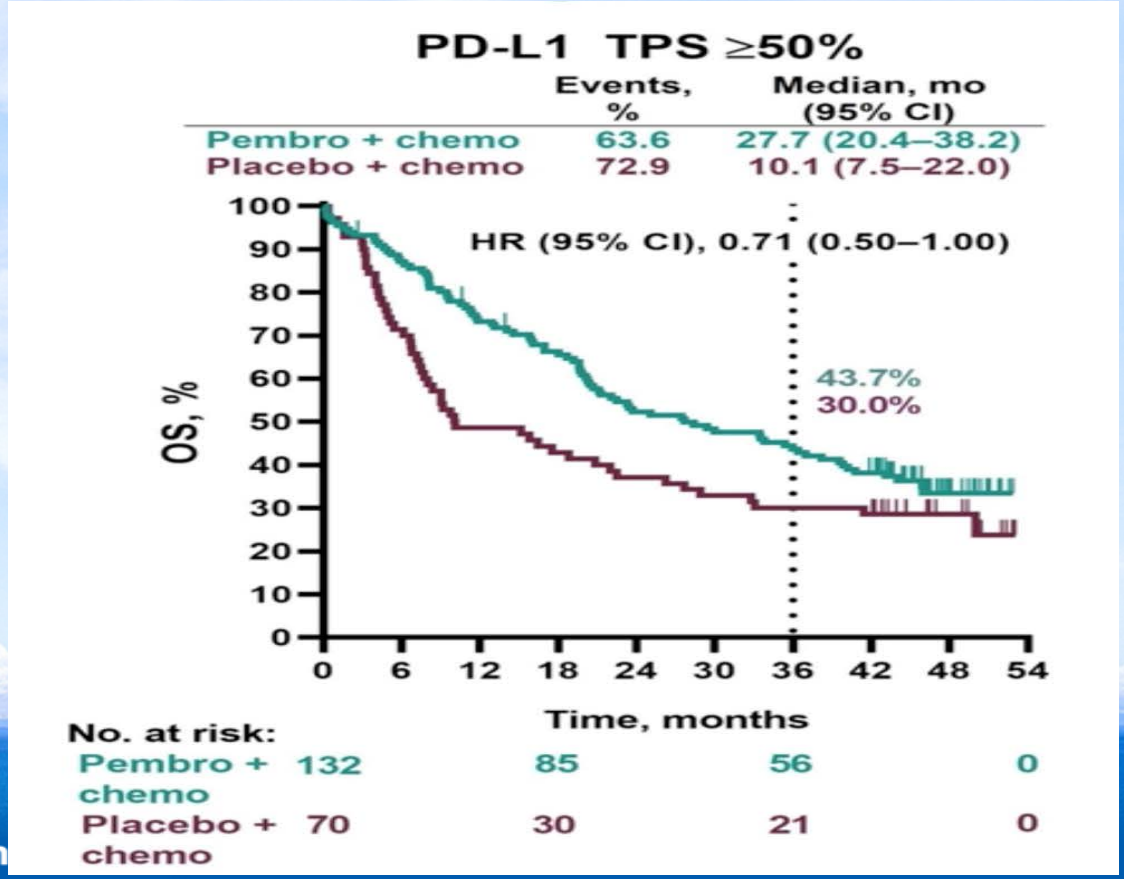
A response rate of 45% and median overall survival of 30 months.(KN024)



I/O+ chemo

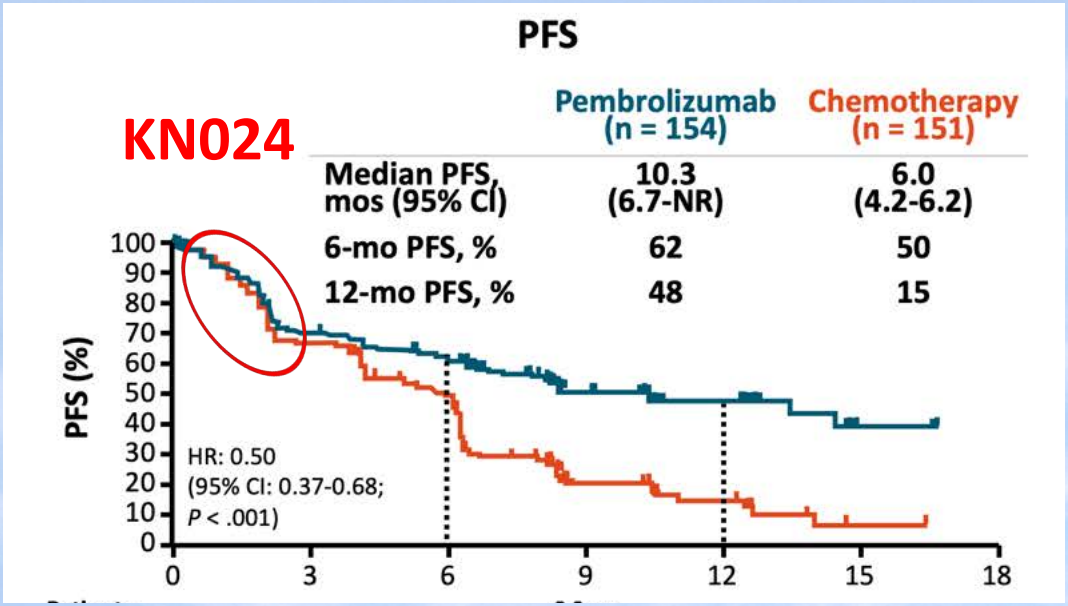
Give Your Best Shot First

40% to 60% of patients with NSCLC never receive their intended second-line treatment

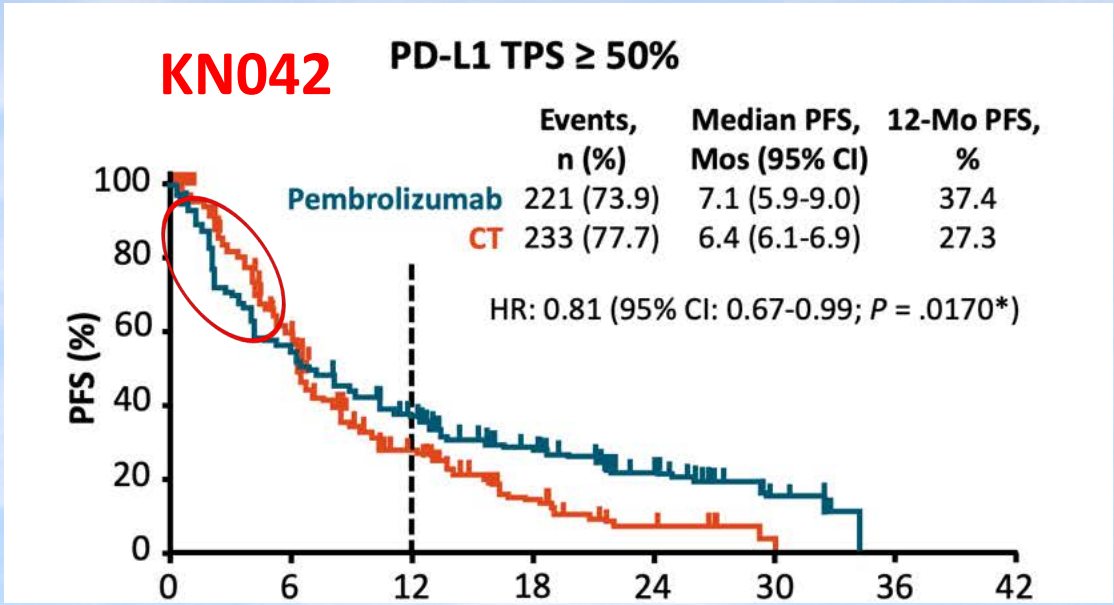


PD-L1 High Expresser (TPS≥50% or TC3/IC3)

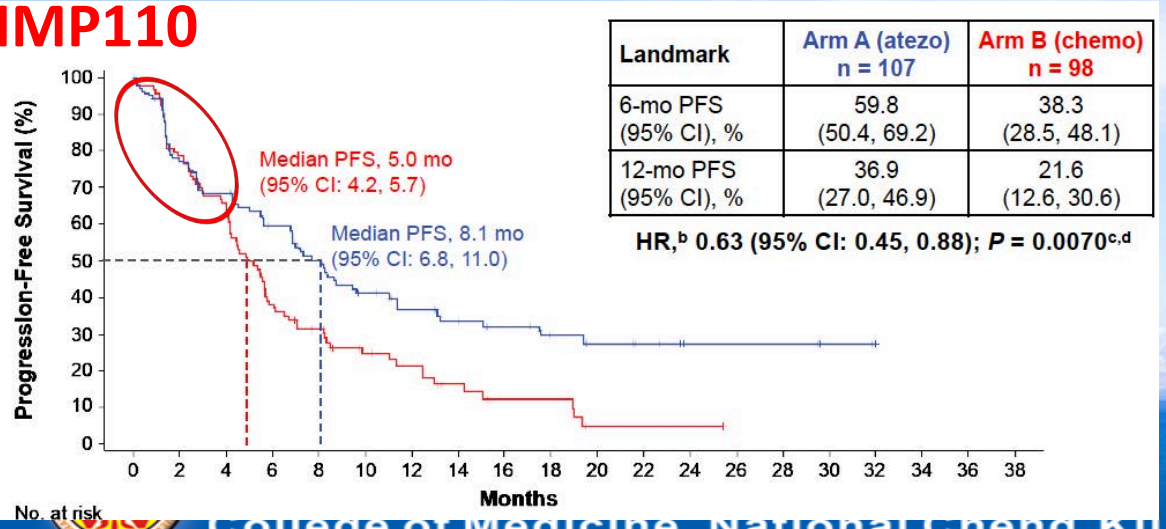
KN024

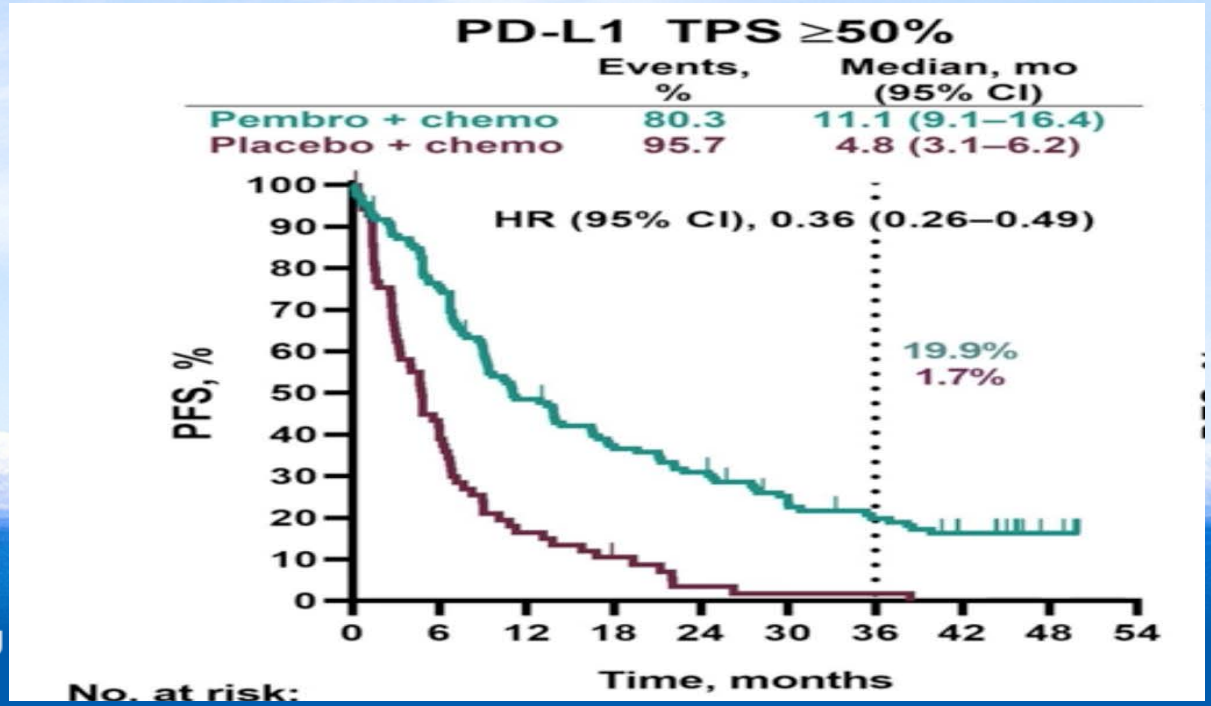


KN042



IMP110





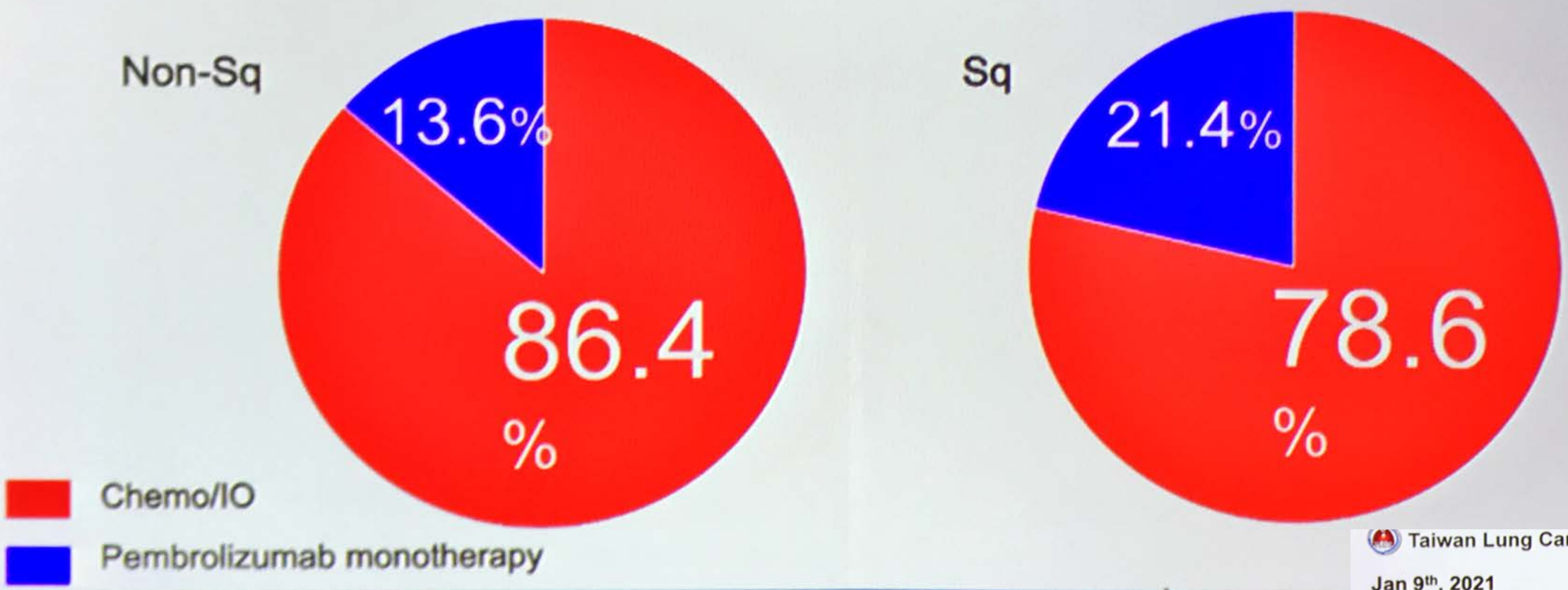
PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Study	KN042		KN024		IMp110		KN189	
NSQ/SQ(%)	61.8/38.5		82/18		70/30		100/0	
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	P+C	chemo
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	62.7	25.7
mDoR (mo)	22.0	10.8	29.1	6.3	38.9	8.3	15.1	7.1
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	11.1	4.8
	HR=0.83		HR=0.5		HR=0.59		HR=0.36	
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	27.7	10.1
	HR=0.68		HR=0.62		HR=0.59		HR=0.71	
2-yr OS(%)	45	30	51.7	34.2	45	25	45.7	27.3

*** This page was not intended to make direct comparison between trials or to show one's superiority*

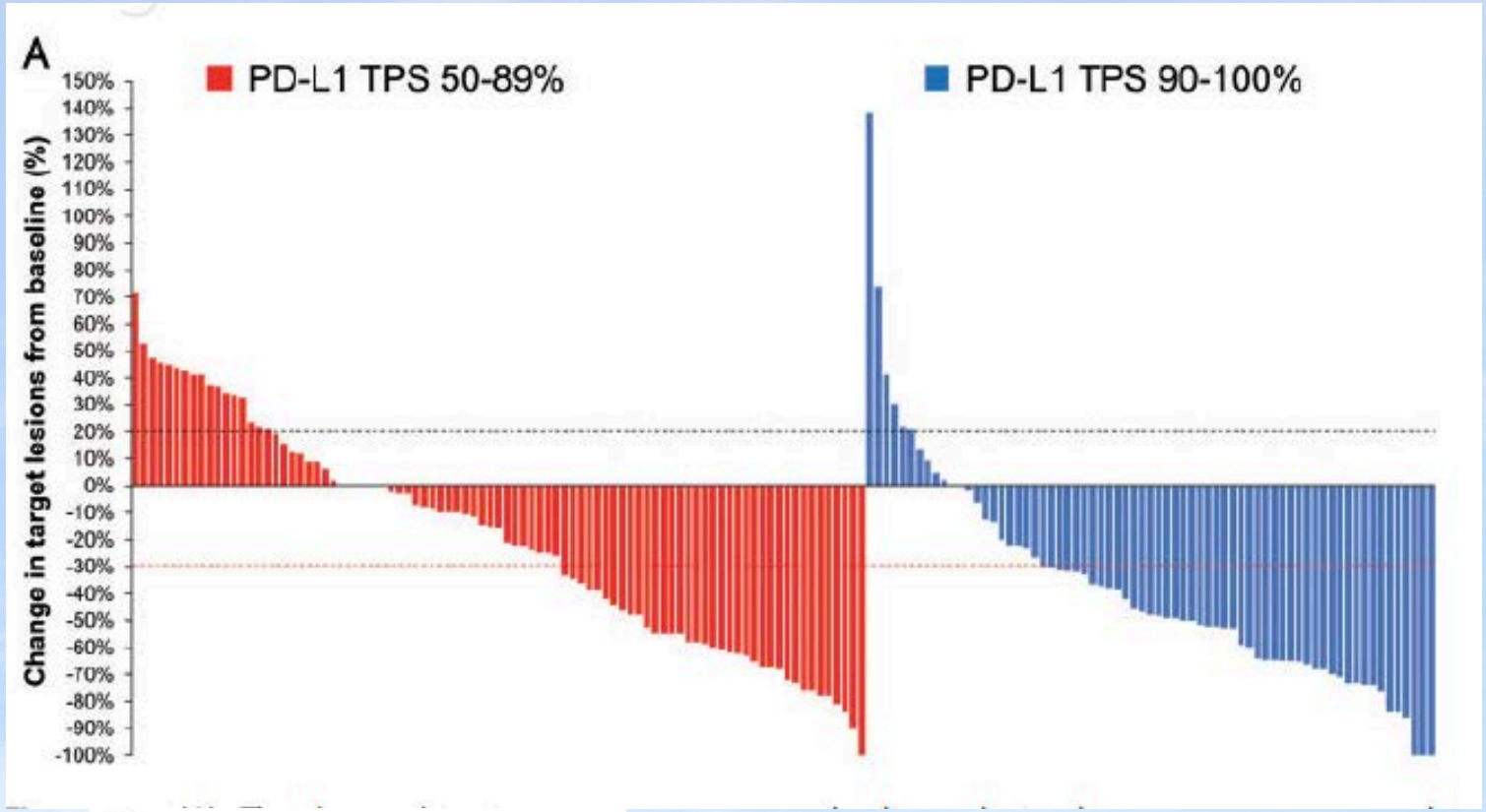
A questionnaire survey in JCOG investigators

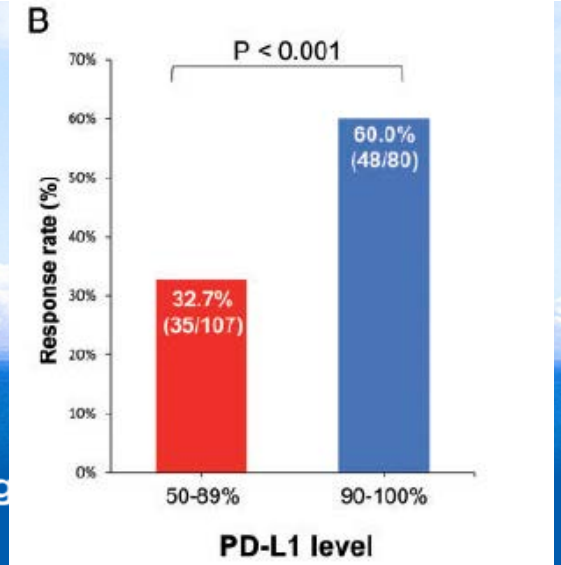
- We performed a questionnaire survey regarding to select the first-line therapy for advanced NSCLC patients with PD-L1 high expression in the JCOG study group.
- Most of Japanese investigators selected chemo/IO for this population.



Clinical characteristic	PD-L1 level 50%–89% N = 107 (%)	PD-L1 level 90%–100% N = 80 (%)	P value
Age, median (range)	68 (35–92)	68 (43–88)	0.70
Sex			
Male	57 (53.3)	38 (47.5)	0.46
Female	50 (46.7)	42 (52.5)	
Smoking status			
Current/former	97 (90.7)	78 (97.5)	0.07
Never	10 (9.3)	2 (2.5)	
Histology			
Adenocarcinoma	77 (72.0)	61 (76.3)	
Squamous cell carcinoma	20 (18.7)	8 (10.0)	0.20
NSCLC NOS	10 (9.3)	11 (13.8)	
KRAS mutation status			
Present	38 (41.3)	34 (48.6)	0.42
Absent	54 (58.7)	36 (51.4)	
Not assessed	15	10	
ECOG performance status			
0–1	86 (80.4)	67 (83.8)	0.57
≥2	21 (19.6)	13 (16.2)	

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.





Ann Oncol . 2019 Oct 1;30(10):1653-1659.

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Study	KN042		KN024		IMp110		Highest PDL1		KN189	
NSQ/SQ(%)	**61.5/38.5**		82/18		70/30				100/0	
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	Pembro ≧90 vs 50-89		P+C	chemo
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	60	32.7	62.7	25.7
mDoR (mo)	22.0	10.8	29.1	6.3	38.9	8.3			15.1	7.1
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	14.5	4.1	11.1	4.8
	HR=0.83		HR=0.5		HR=0.59		HR=0.5		HR=0.36	
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	15.9	27.7	10.1
	HR=0.68		HR=0.62		HR=0.59		HR=0.39		HR=0.71	
2-yr OS(%)	45	30	51.7	34.2	45	25				

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PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Study	KN042		KN024		IMp110		Highest PDL1		KN189	
NSQ/SQ(%)	**61.5/38.5**		82/18		70/30				100/0	
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	Pembro ≧90 vs 50-89		P+C	chemo
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	60	32.7	62.7	25.7
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2-yr OS(%)	45	30	51.7	34.2	45	25				

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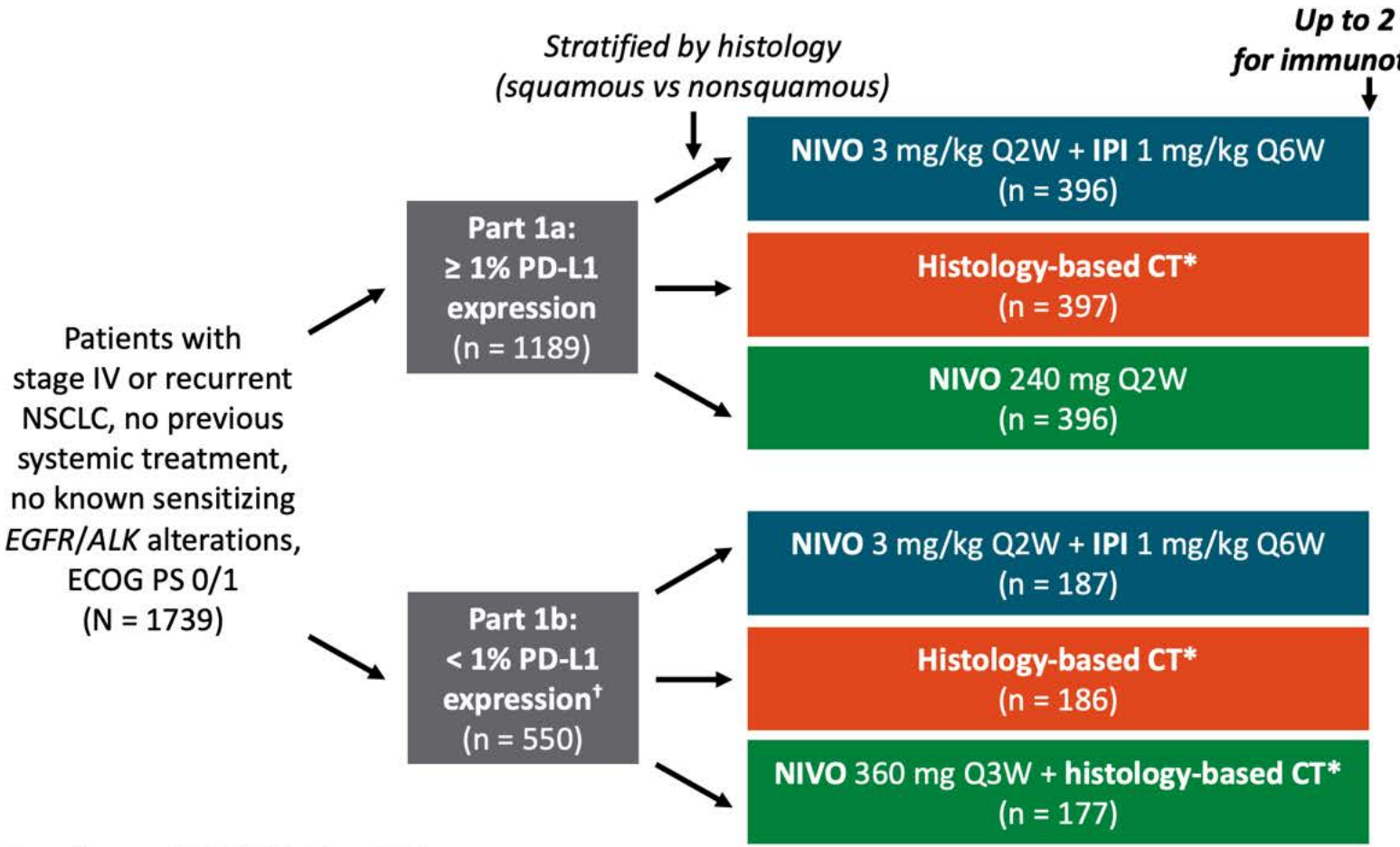
CheckMate 227 Part 1: Study Design

- Randomized, open-label, multipart phase III trial (Data cutoff: February 28, 2020)



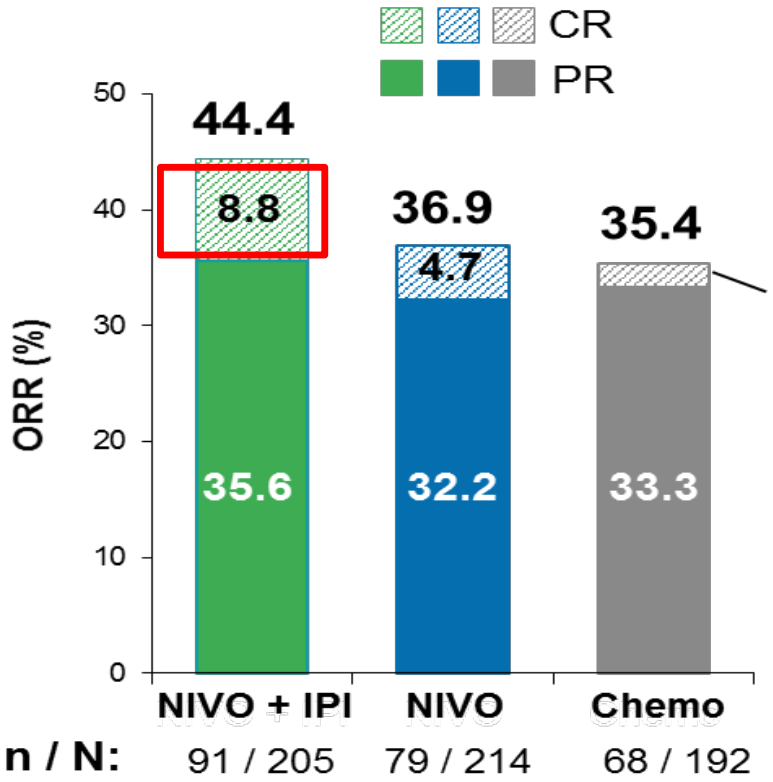
- **Dual primary endpoints for NIVO + IPI vs CT**
  - PFS in high TMB (≥ 10 mut/Mb) population
  - OS in PD-L1 ≥ 1% population

*_Nonsquamous_: pemetrexed + cisplatin or carboplatin Q3W for ≤ 4 cycles with optional maintenance (pemetrexed after chemo, or NIVO + pemetrexed after NIVO + pemetrexed)
Squamous: gemcitabine + cisplatin or carboplatin Q3W for ≤ 4 cycles.

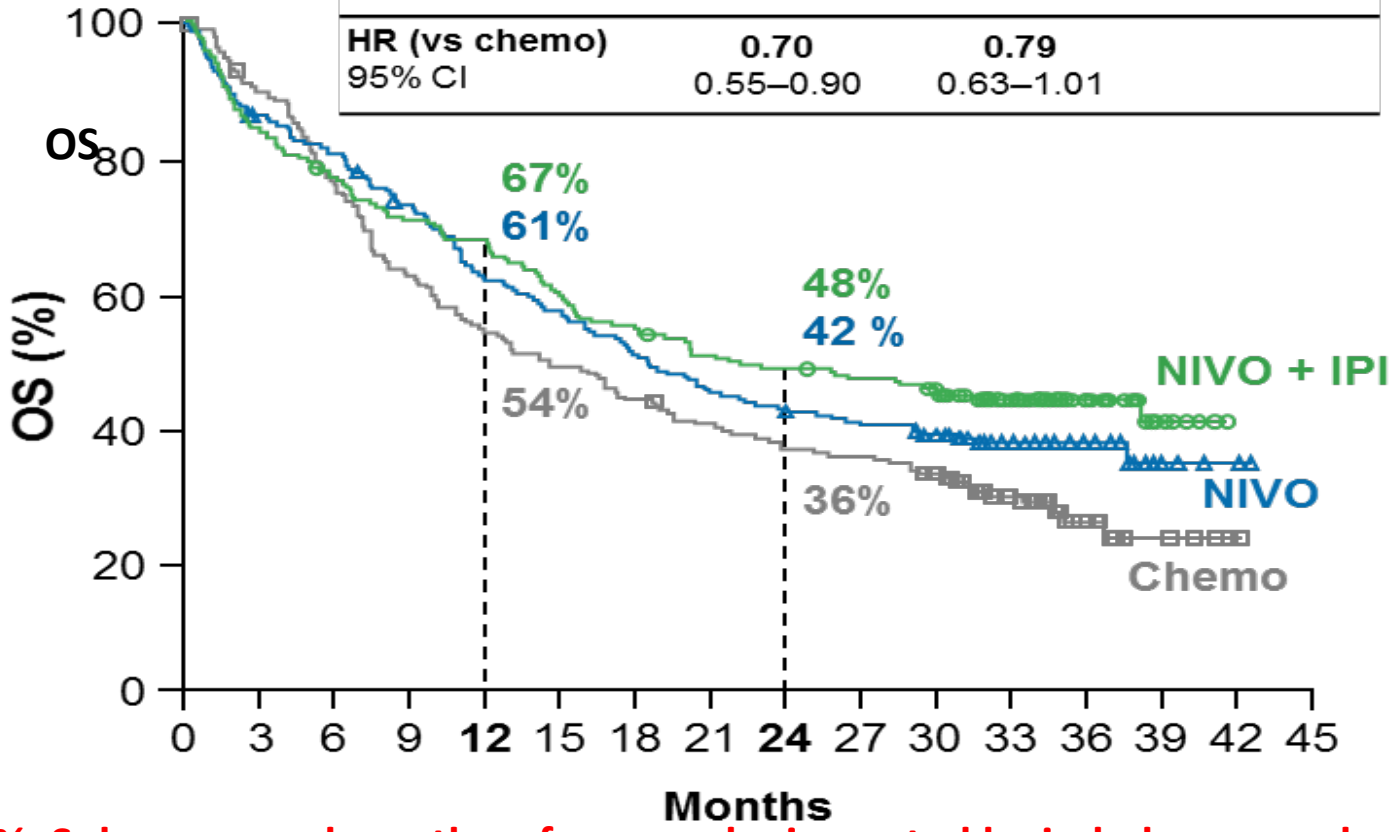
Ramalingam. ASCO 2020. Abstr 9500.

Slide credit: clinicaloptions.com

CHECKMATE-227: OS in PD-L1 ≥50%



	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	



Patients were not stratified by PD-L1 ≥ or <50%. Subgroup analyses therefore may be impacted by imbalances and should be interpreted with caution

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Study	KN042		KN024		IMp110		Highest PDL1		CM227	
NSQ/SQ(%)	61.8/38.5		82/18		70/30				72	28
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	Pembro ≧90 vs 50-89		N+I	C/T
ORR(%)	39.1	32.3	46.1	31.1	40.2	28.6	60	32.7	44.4	35.4
mDoR (mo)	27.3	10.8	29.1	6.3	38.9	8.3			31.8	5.8
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	14.5	4.1	6.7	5.8
	HR=0.85		HR=0.5		HR=0.59		HR=0.5		HR=0.62	
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	15.9	21.2	14.0
	HR=0.68		HR=0.62		HR=0.76		HR=0.39		HR=0.70	
2-yr OS(%)	45	30	51.7	34.2	45	35			48	36

*** This page was not intended to make direct comparison between trials or to show one's superiority*

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

	More SQ		Highly selective		≠PDL1>50		Only 11%		Subgroup analysis	
Study	**KN042**		**KN024**		**IMp110**		**Highest PDL1**		**CM227**	
NSQ/SQ(%)	61.5/38.5		82/18		70/30				72	28
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	Pembro ≧90 vs 50-89		N+I	C/T
ORR(%)	39.1	32.3	46.1	31.1	40.2	28.6	60	32.7	44.4	35.4
mDoR (mo)	27.3	10.8	29.1	6.3	38.9	8.3			31.8	5.8
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	14.5	4.1	6.7	5.8
	HR=0.85		HR=0.5		HR=0.59		HR=0.5		HR=0.62	
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	15.9	21.2	14.0
	HR=0.68		HR=0.62		HR=0.76		HR=0.39		HR=0.70	
2-yr OS(%)	45	30	51.7	34.2	45	35			48	36

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PD-L1 High Expresser (TPS≥50% or TC3/IC3)-C/T+I/O

Study	KN042		KN189		IMP130		IMP150		CM227		CM9LA		KN407	
NSQ/SQ(%)	61.5/38.5		100/0		100/0		100/0		72/28		69/31		0/100	
Regimen	Pemb	C/T	P+C	C/T	A+C	C/T	A+C +Bev	C+Bev	N+I	C/T	N+I +C	C/T	P+C	C/T
ORR(%)	39.1	32	62.1	25.7	49.2	31.9	69	49	44.4	35.4	50.0	30.6	64.4	30.1
mDoR (mo)	27.3	10.8	15.1	7.1	8.4	6.1	22.1	7.0	31.8	5.8	NR	5.4	9.2	4.6
mPFS (mo)	6.5	6.5	11.2	4.8	6.4	4.6	12.6	6.8	6.7	5.8	7.5	4.4	N/A	N/A
	HR=0.85		HR=0.35		HR=0.51		HR=0.39		HR=0.62		HR=0.61		HR=0.43	
mOS (mo)	20.0	12.0	27.7	10.1	17.3	16.9	25.2	15.0	21.2	14.0	18.0	12.6		
	HR=0.68		HR=0.59		HR=0.84		HR=0.70		HR=0.70		HR=0.66		HR=0.79	

*** This page was not intended to make direct comparison between trials or to show one's superiority*

PD-L1 High Expresser (TPS≥50% or TC3/IC3)-C/T+I/O

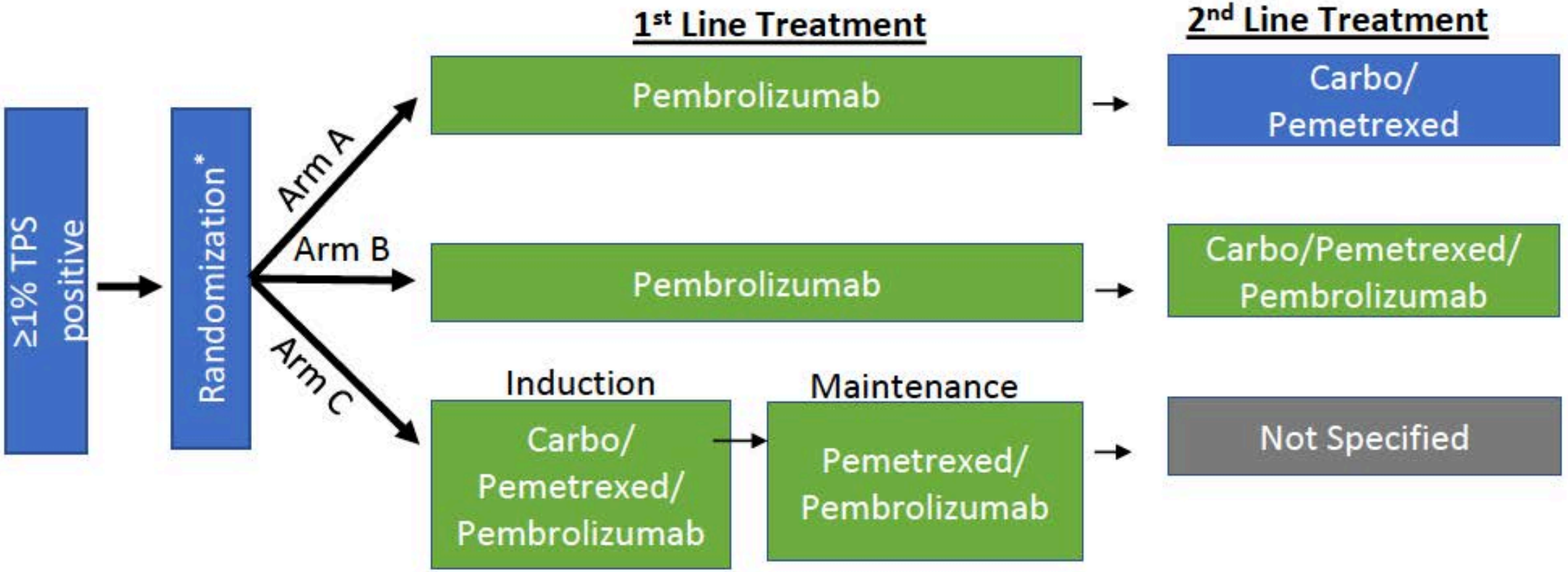
OS (not significant) Subgroup analyses

Study	KN042		KN189		IMP130		IMP150		CM227		CM9LA		KN407	
NSQ/SQ(%)	61.5/38.5		100/0		100/0		100/0		72/28		69/31		0/100	
Regimen	Pemb	C/T	P+C	C/T	A+C	C/T	A+C +Bev	C+Bev	N+I	C/T	N+I +C	C/T	P+C	C/T
ORR(%)	39.1	32	62.1	25.7	49.2	31.9	69	49	44.4	35.4	50.0	30.6	64.4	30.1
mDoR (mo)	27.3	10.8	15.1	7.1	8.4	6.1	22.1	7.0	31.8	5.8	NR	5.4	9.2	4.6
mPFS (mo)	6.5	6.5	11.2	4.8	6.4	4.6	12.6	6.8	6.7	5.8	7.5	4.4	N/A	N/A
	HR=0.85		HR=0.35		HR=0.51		HR=0.39		HR=0.62		HR=0.61		HR=0.43	
mOS (mo)	20.0	12.0	27.7	10.1	17.3	16.9	25.2	15.0	21.2	14.0	18.0	12.6		
	HR=0.68		HR=0.59		HR=0.84		HR=0.70		HR=0.70		HR=0.66		HR=0.79	

*** This page was not intended to make direct comparison between trials or to show one's superiority*

Combining Immunotherapy with Chemo

INSIGNA: A Randomized, Phase III Study of Firstline **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis

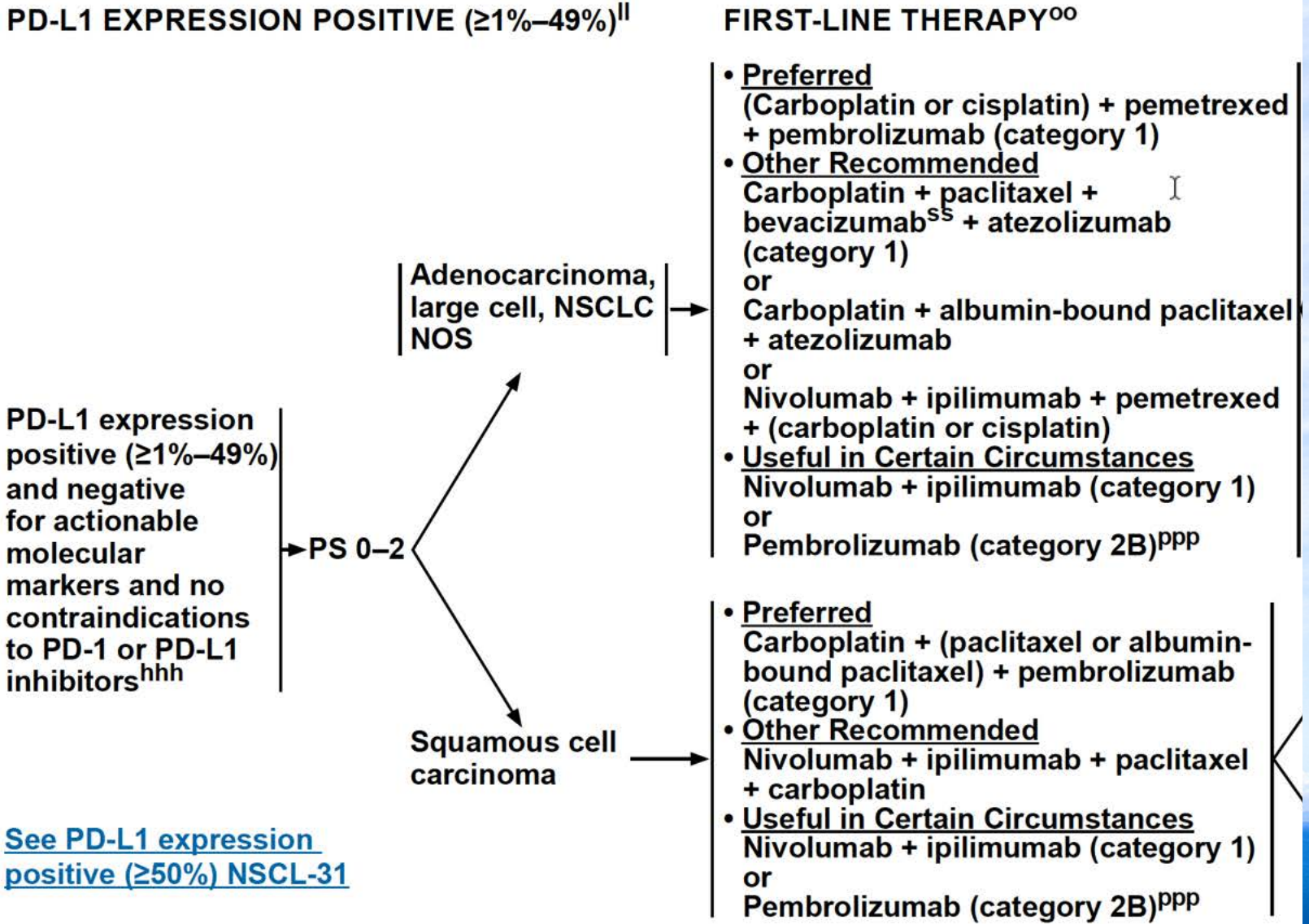


SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

Langer's Practical Strategy for PDL1 > 50% in advanced Non-squamous NSCLC

- **Pembro alone (SOC)**
  - Older, frailer patients
  - Lower metastatic burden
  - Significant co-morbidity
- **Combination Pembro and Pem/Carbo**
  - Younger, heartier patients
  - Higher metastatic burden
  - Greater symptomatology
  - More aggressive tumors
  - Limited co-morbidity

NCCN Guidelines Version 2.2021
Non-Small Cell Lung Cancer



KN189: Plat/PEM/Pembro

IMP150: CBDCA/PTX /Beva/Atezo

IMP130: CBDCA/nabPTX /Atezo

CM9LA: Plat/PEM/Nivo/Ipi

CM227: Nivo/Ipi

KN042: Pembro

KN407: CBCZA/(nab)/PTX/Pembro

CM9LA: CBDCA/PTX /Nivo/Ipi

CM227: Nivo/Ipi

KN042: Pembro

PD-L1 Low Expresser (TPS 1-49%)

OS (not significant)

Study	KN042		KN189		IMP130		IMP150		CM227		CM9LA		KN407	
NSQ/SQ (%)	61.5/38.5		100/0		100/0		100/0		72/18		69/31		0/100	
Regimen	Pemb	C/T	P+C	C/T	A+C	C/T	A+C+Bev	C+Bev	N+I	C/T	N+I+C	C/T	P+C	C/T
ORR(%)	16.6	21.7	50.0	20.7	49.2	31.9	58	41	26.7	24.9	39.4	24.5	55.3	42.3
mDoR (mo)	47.4	28.2	12.9	7.6	8.4	6.1	10.4	6.9			10.0	5.6	10.4	4.8
mPFS (mo)	-	-	9.4	4.9	8.3	6.0	8.3	6.6			6.9	5.3	-	-
	-		HR=0.53		HR=0.61		HR=0.56				HR=0.69		HR=0.52	
mOS (mo)	13.4	12.1	21.8	12.1	23.7	15.9	20.3	16.4	15.1	15.1	15.5	10.4	-	-
	HR=0.90		HR=0.66		HR=0.70		HR=0.80		HR=0.94		HR=0.69		HR=0.59	

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NCCN G
Ta

PD-L1 <1% AND NEGATIVE FC

INITIAL SYSTEMIC T

PS 0–2 → Systemic therapy
- Adenocarcinoma, Large Cell, NSCLC NOS (NSCL-K 1 of 5)
- Squamous Cell Carcinoma (NSCL-K 2 of 5)

PS 3–4 → Best supportive care See NCCN Guidelines for Palliative Care

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – INITIAL SYSTEMIC THERAPY OPTIONS[a,b]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]
- Nivolumab + ipilimumab[5,d]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)[6,d]

Contraindications to PD-1 or PD-L1 inhibitors[c]

Useful in Certain Circumstances
- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,f,g,h]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,f,g,h]
- Bevacizumab[e]/cisplatin/pemetrexed[9,f,g,h]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[16]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]
- Pemetrexed[33]

PD-L1 no Expresser (TPS <1%)

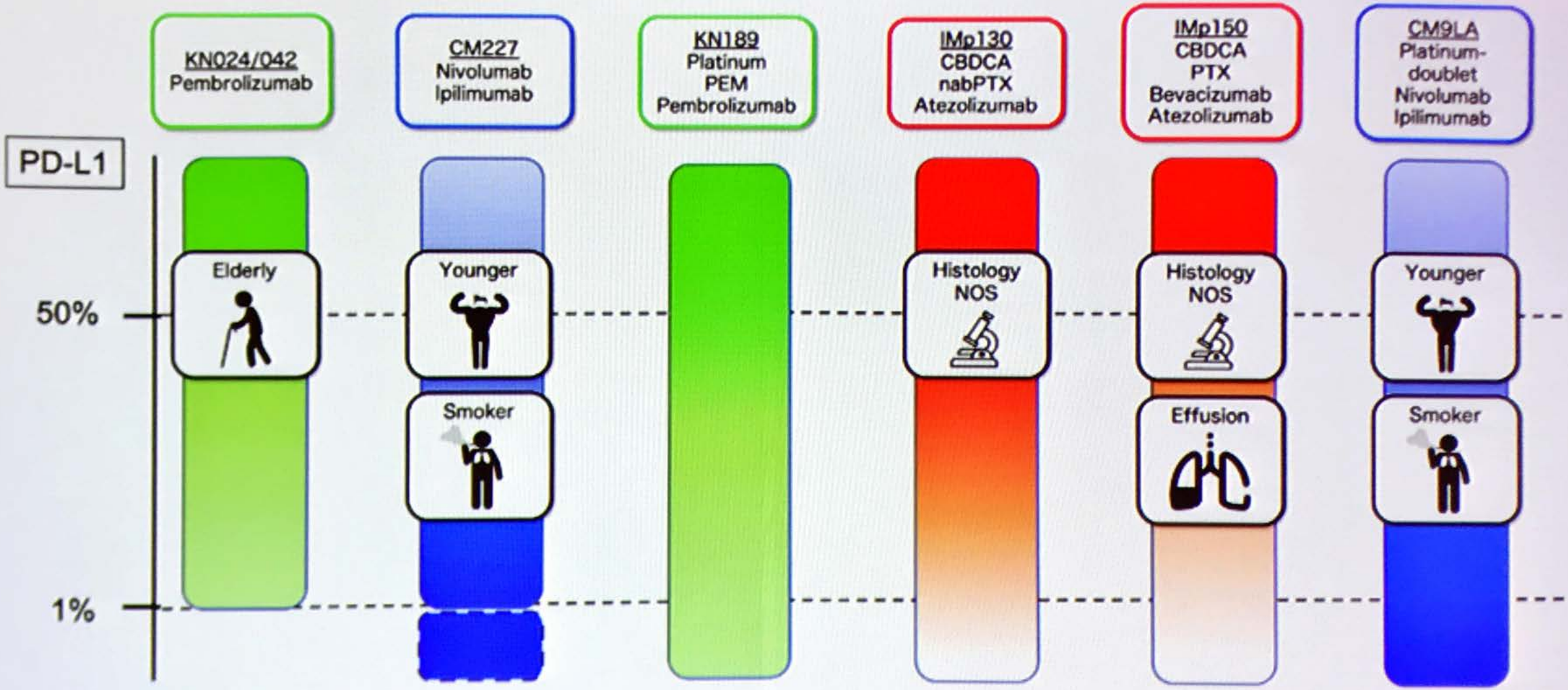
OS (not significant)

Study	KN189		IMP130		IMP150		CM227		CM9LA		KN407	
NSQ/SQ (%)	100/0		100/0		100/0		72/18		69/31		0/100	
Regimen	P+C	C/T	A+C	C/T	A+C+ Bev	C+Be v	N+I	C/T	N+I +C	C/T	P+C	C/T
ORR(%)	33.1	14.3	49.2	31.9	51	36	27.3	23.1	31.1	20.9	67.4	41.4
mDoR (mo)	10.8	7.8	8.4	6.1	8.2	5.5	18.0	4.8	NR	4.3	6.9	5.7
mPFS (mo)	6.2	5.1	6.2	4.7	7.1	6.9	5.8	4.6	5.82	4.86	6.3	5.9
	HR=0.67		HR=0.72		HR=0.77		HR=0.71		HR=0.77		HR=0.67	
mOS (mo)	17.2	10.2	15.2	12.0	17.1	14.1	17.2	12.2	16.8	9.8	15.0	11.0
	HR=0.51		HR=0.81		HR=0.82		HR=0.64		HR=0.62		HR=0.79	

*** This page was not intended to make direct comparison between trials or to show one's superiority*

Niigata Cancer Center Hospital
Satoru Miura

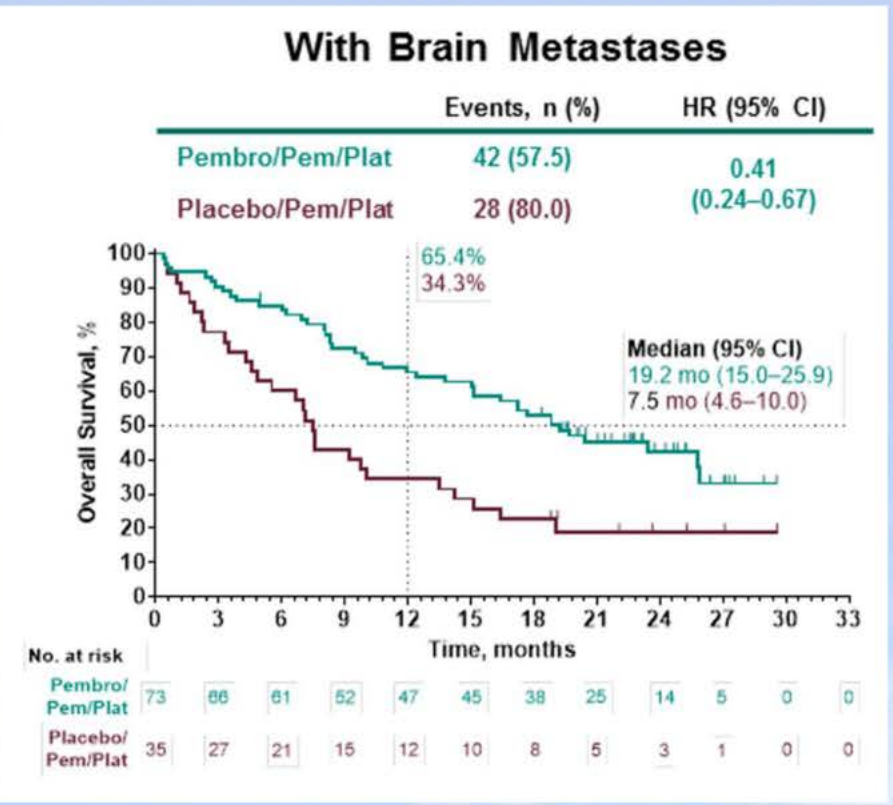
My Chemo/IO regimen selection ~Non-Sq~



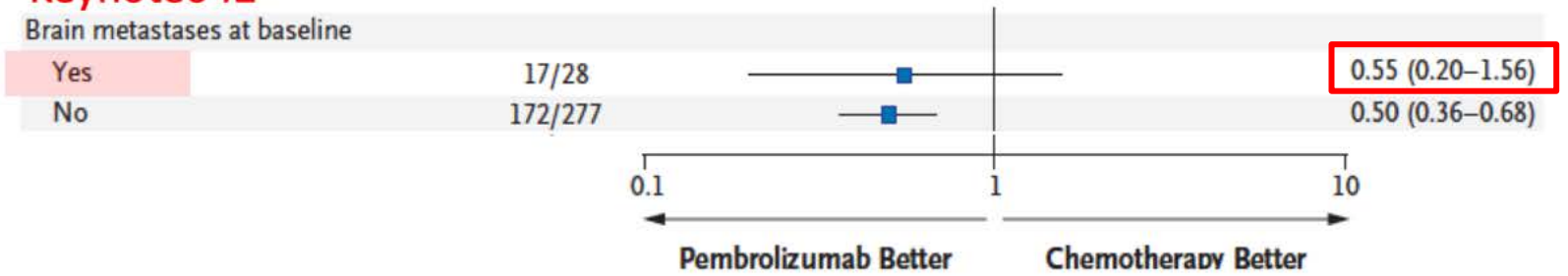
- First line I/O or combination for no driver mutation NSCLC
- What is the treatment strategy for special situation?
- New drug or new combination
- Novel target?

Brain metastasis

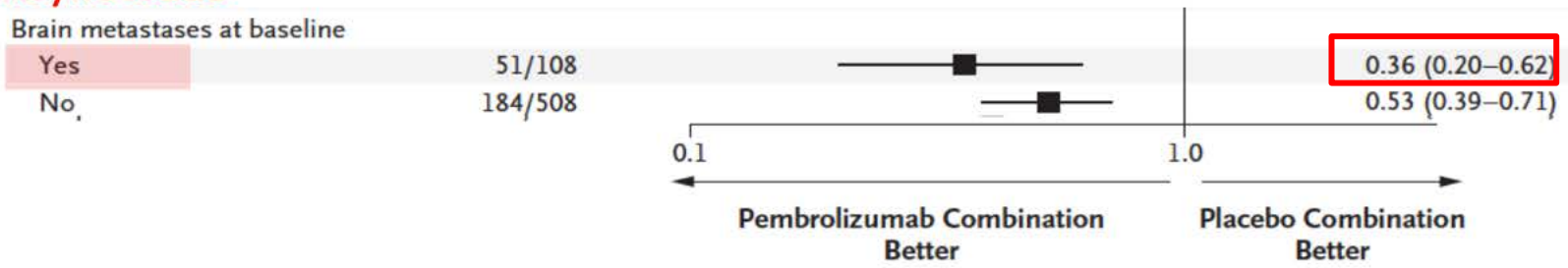
Checkmate 9LA	Untreated CNS metastases are excluded. Participants are eligible if CNS metastases are adequately treated and participants are neurologically returned to baseline
Checkmate 227	Subjects with untreated Central nervous system (CNS) metastases are excluded
Keynote 189	Subjects with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease-after amendment
IMpower150	Patients with active or untreated CNS metastasis were excluded



Keynote042



Keynote189



Untreated, asymptomatic brain metastases%

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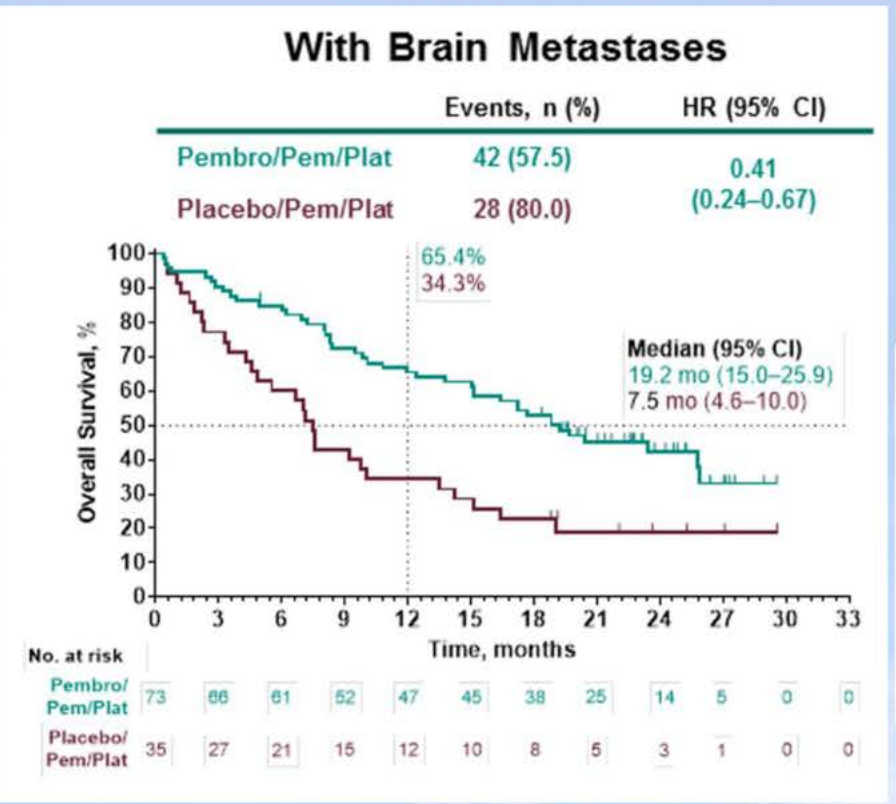
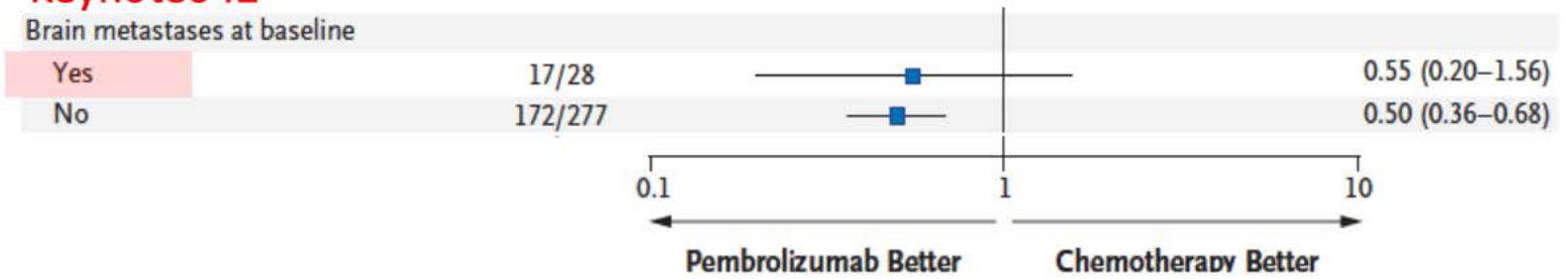
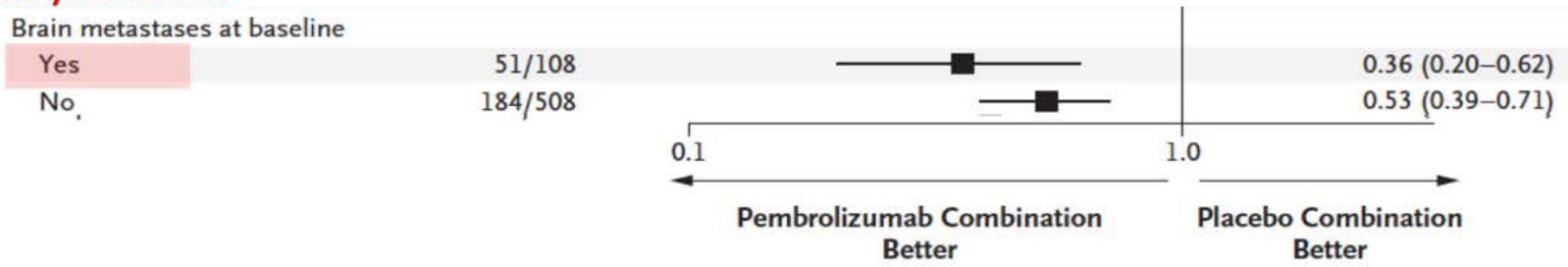


Untreated, asymptomatic brain metastases%

Keynote042

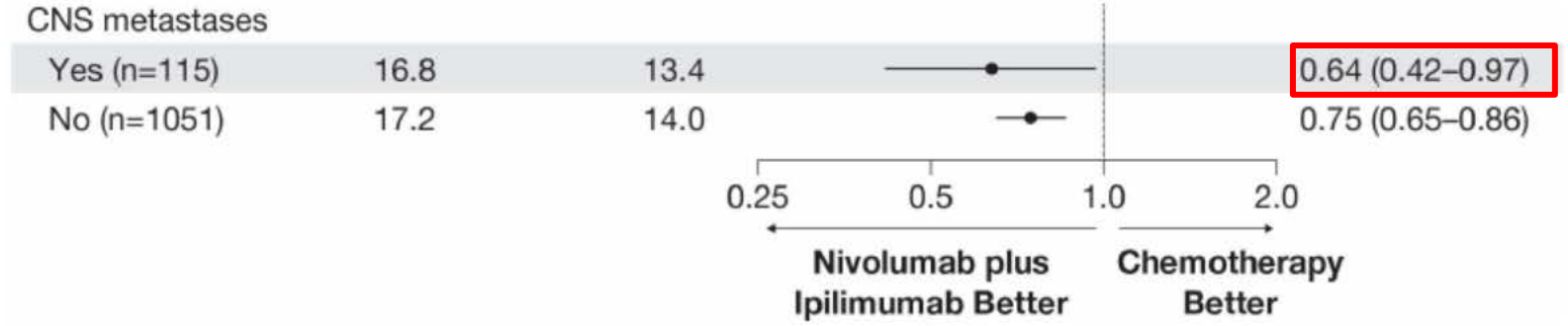


Keynote189



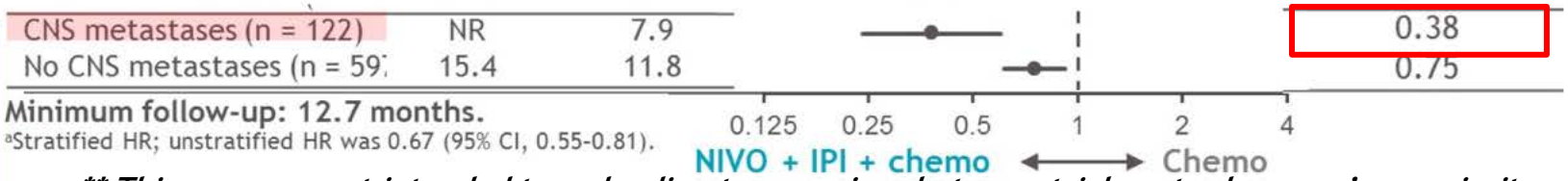
Checkmate 227

NIV+IPI C/T



Checkmate 9LA

NIV+IPI+C/T C/T



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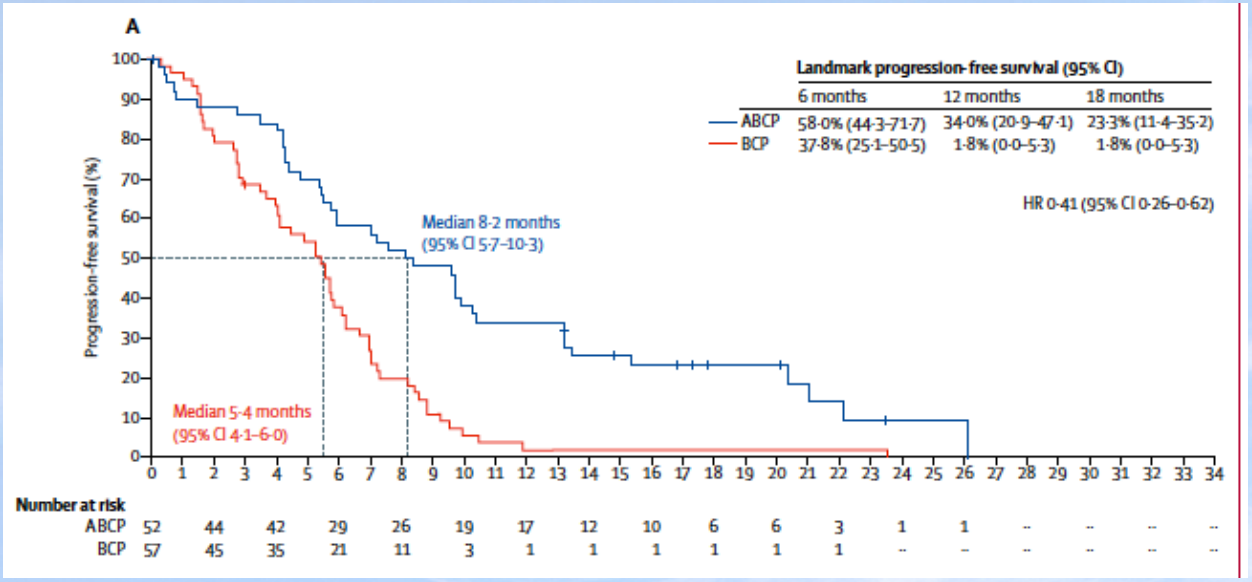
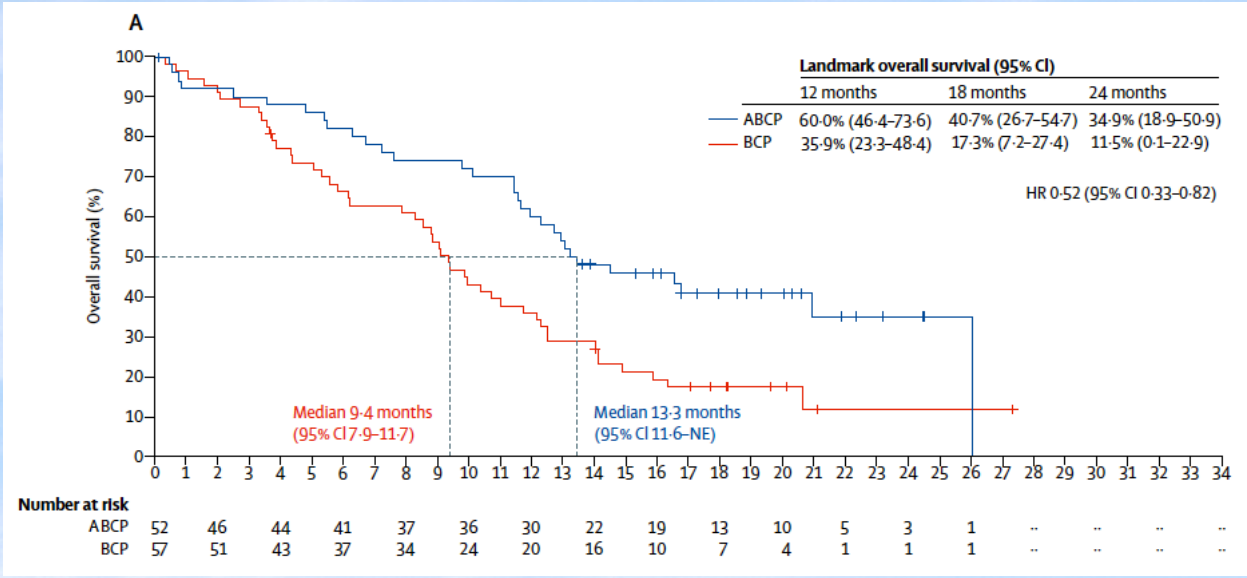
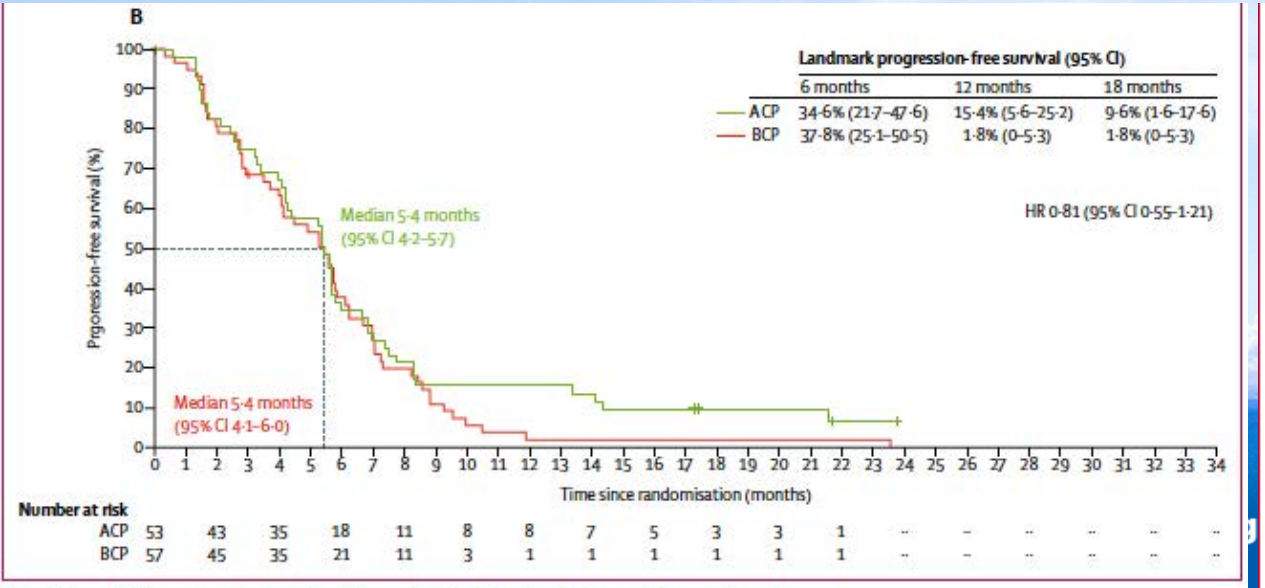
Liver metastasis

PFS



OS





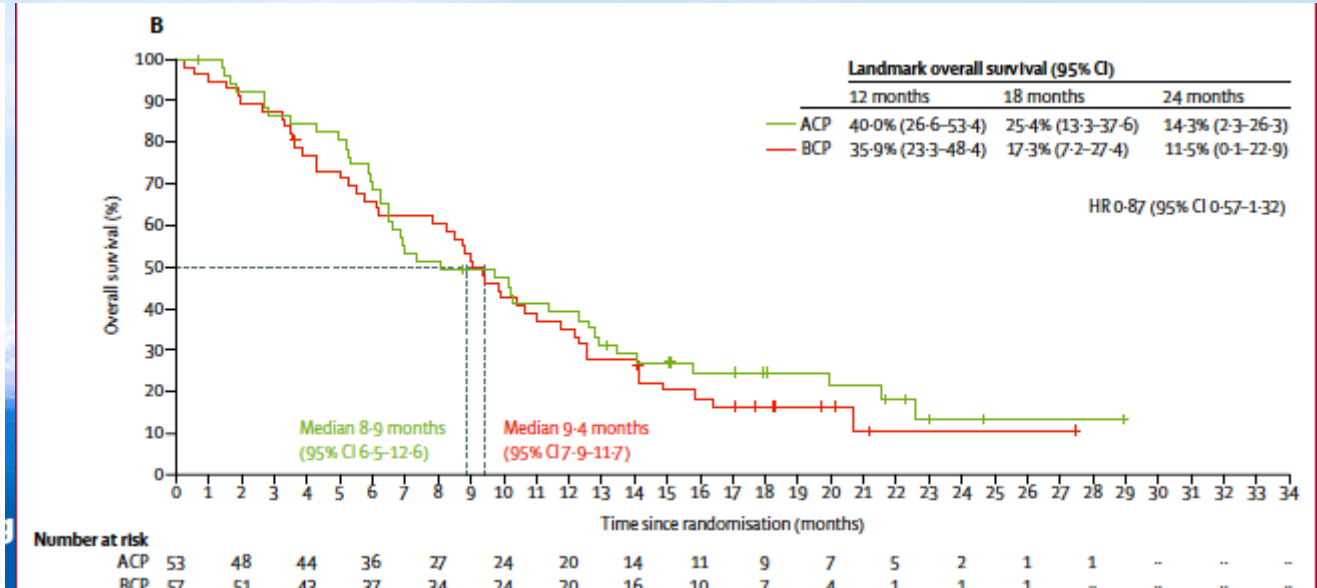
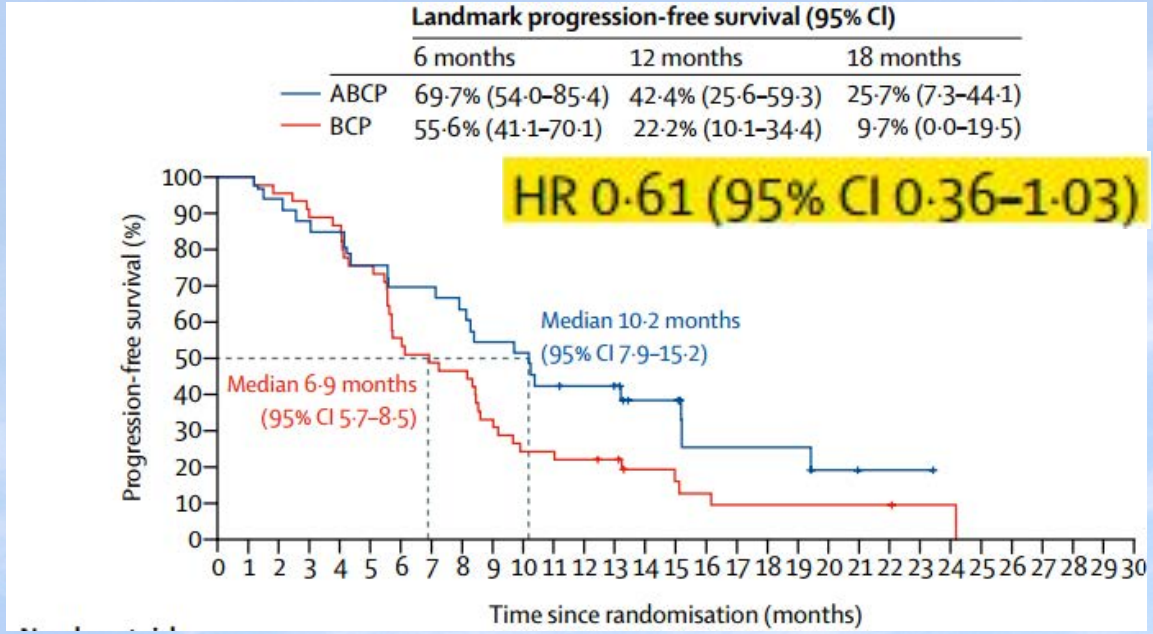
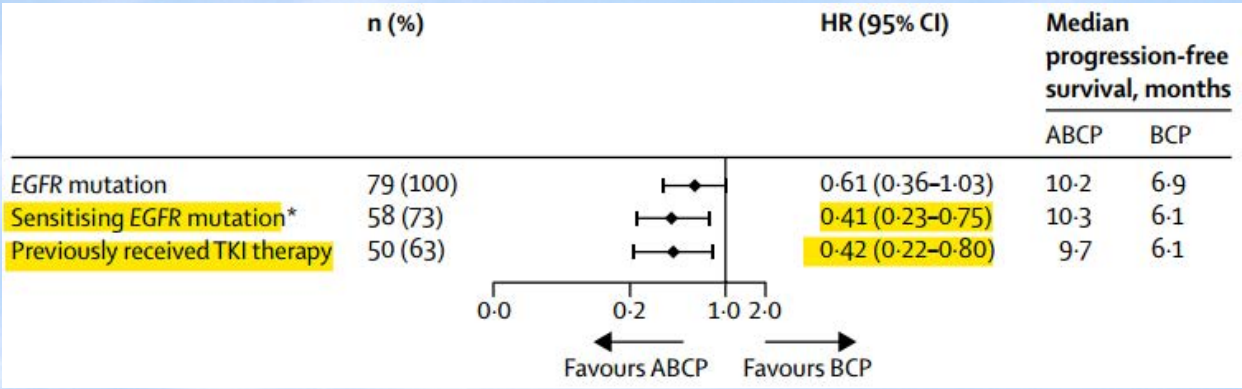


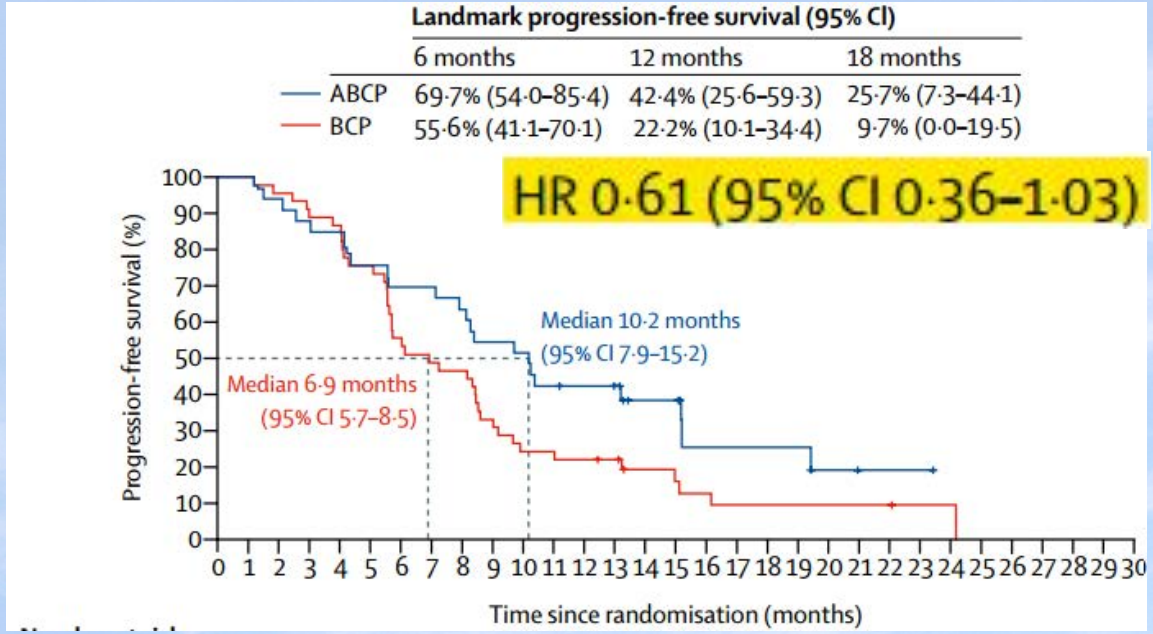
Figure 6: Investigator-assessed progression-free survival in patients with liver metastases at baseline

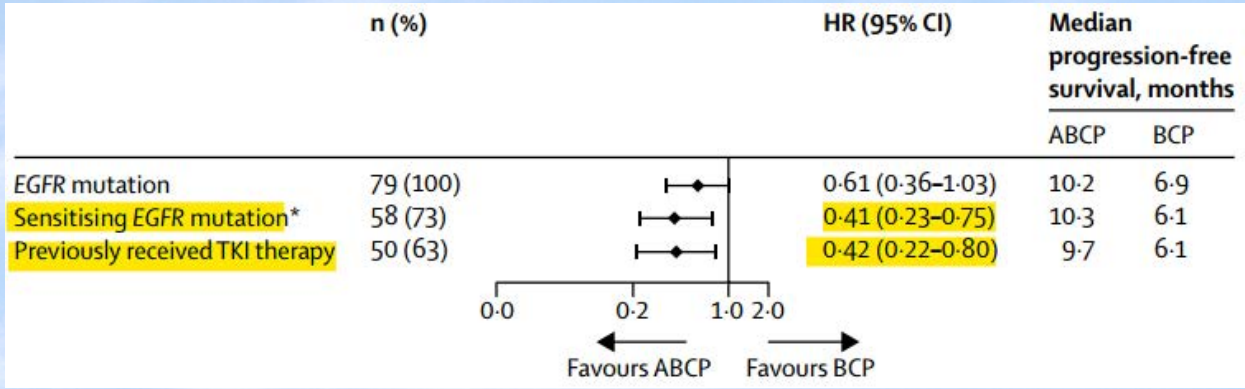
EGFR mutation

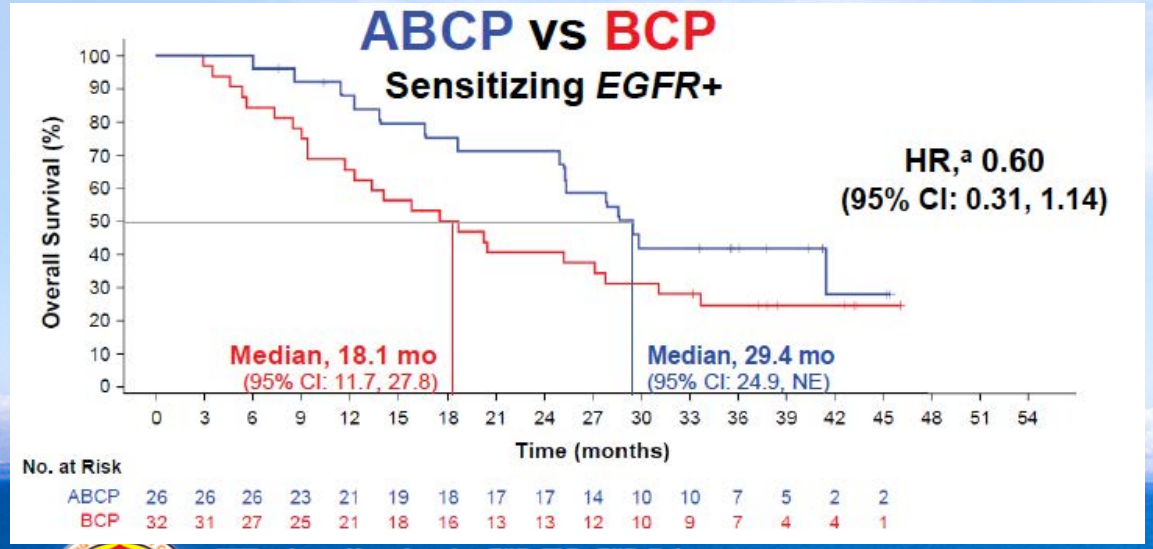


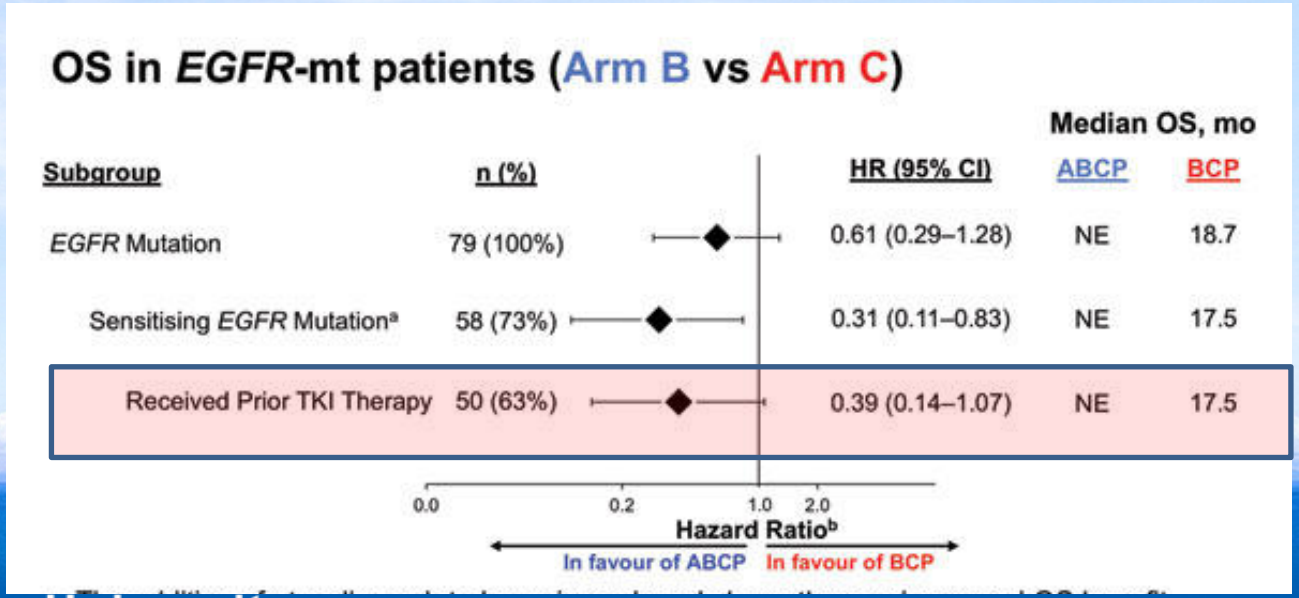


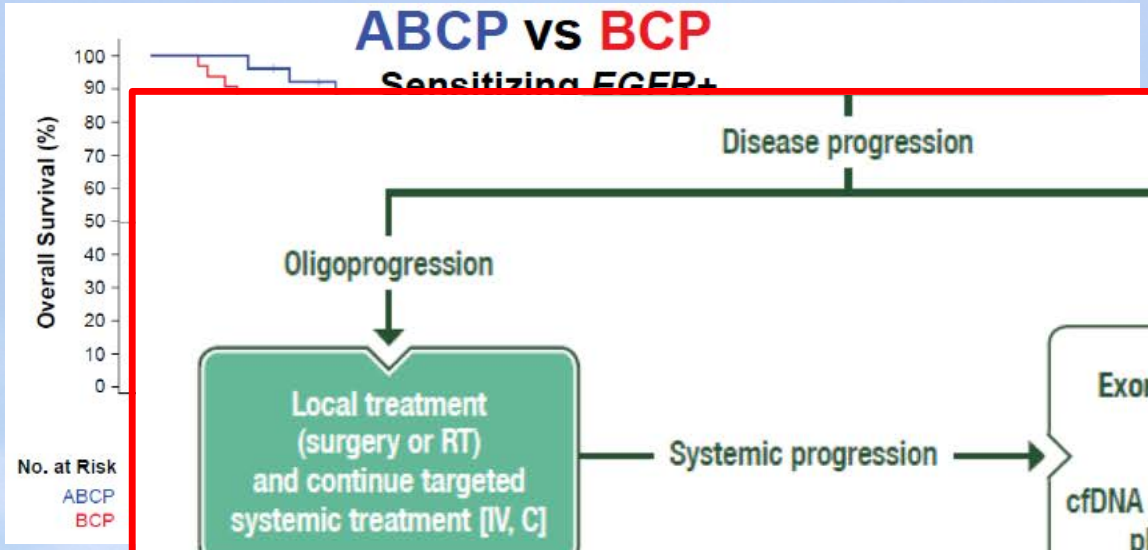
EGFR mutation

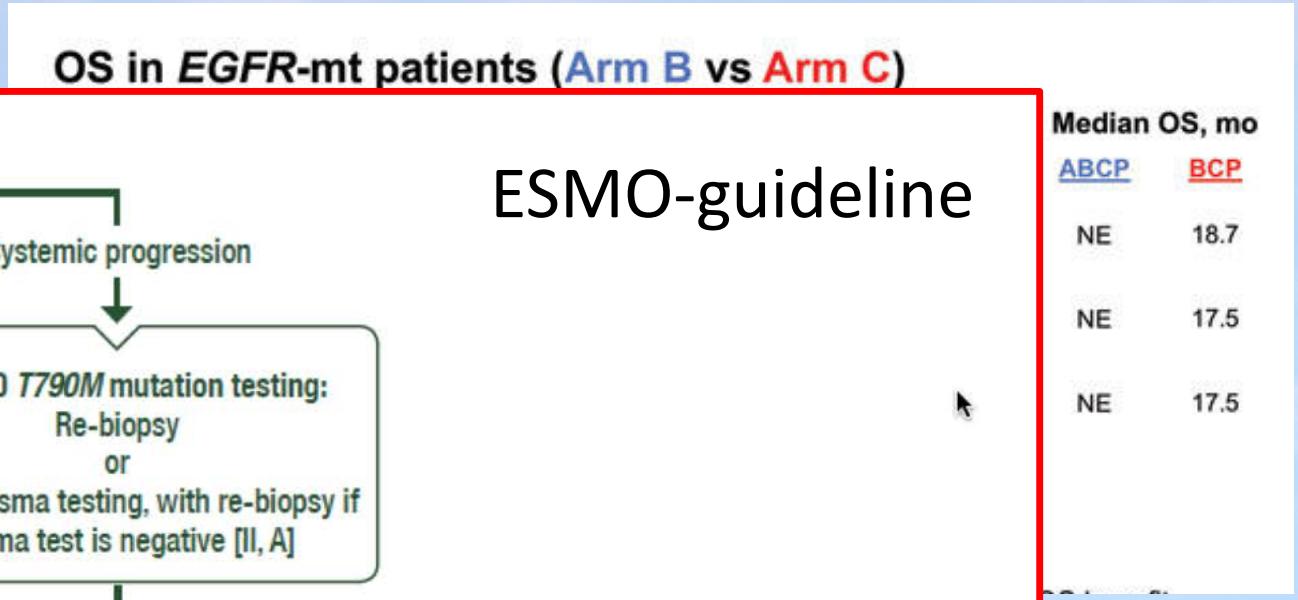












ESMO-guideline

Disease progression

Oligoprogression

Local treatment (surgery or RT) and continue targeted systemic treatment [IV, C]

Systemic progression

Systemic progression

Exon 20 *T790M* mutation testing:
Re-biopsy
or
cfDNA plasma testing, with re-biopsy if plasma test is negative [II, A]

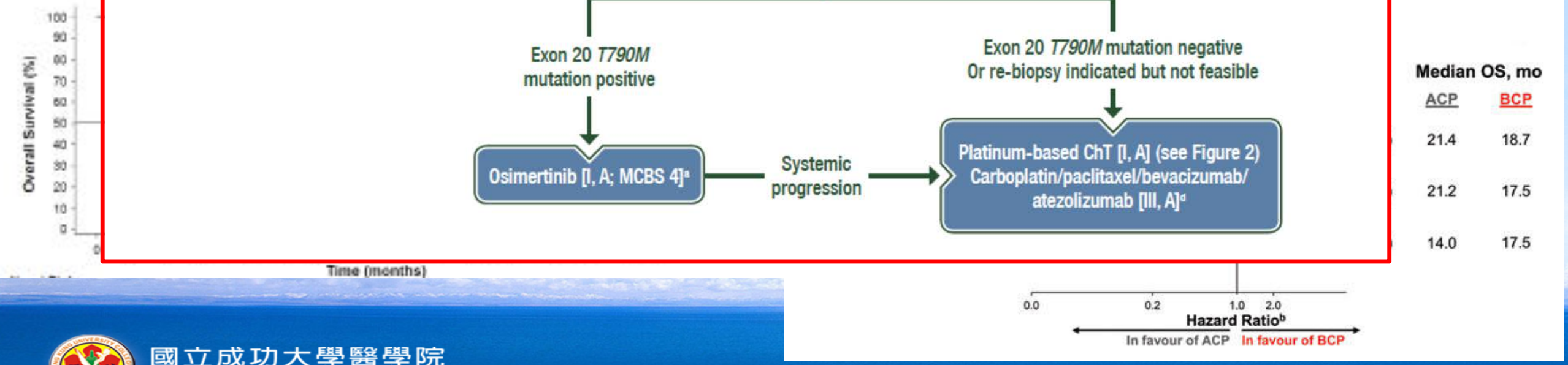
Exon 20 *T790M* mutation positive

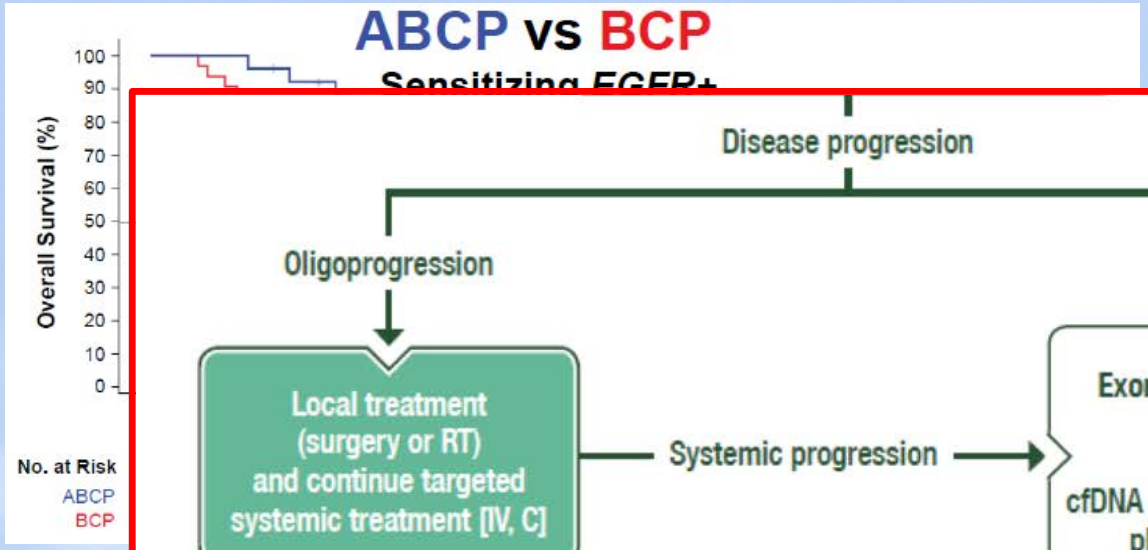
Osimertinib [I, A; MCBS 4][a]

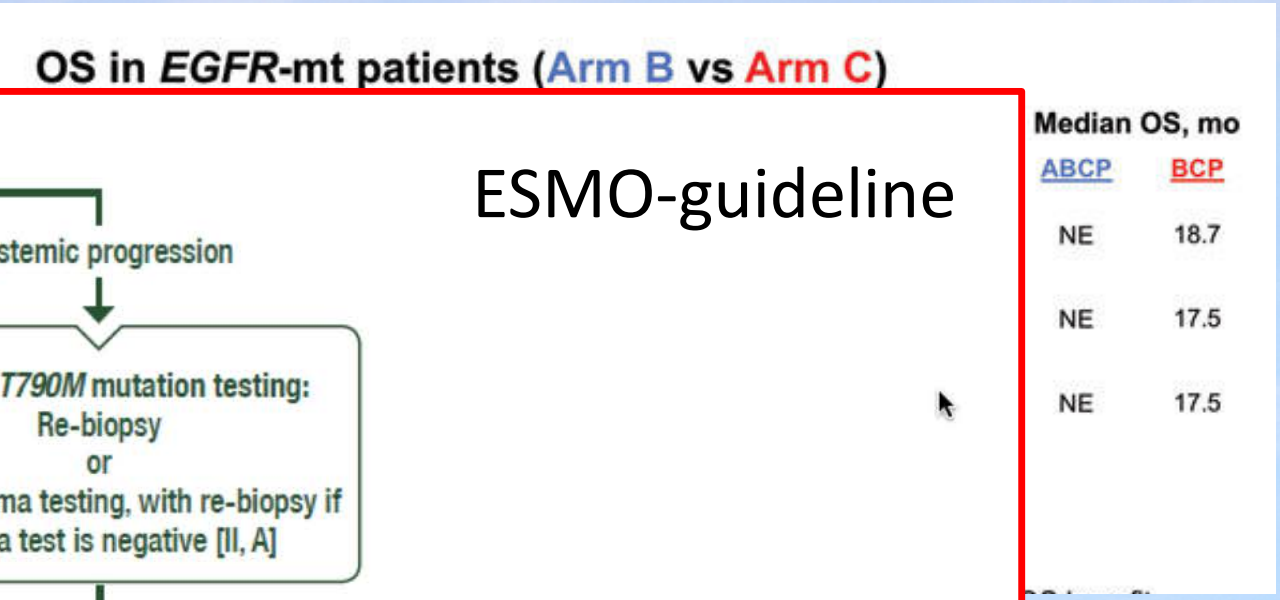
Systemic progression

Exon 20 *T790M* mutation negative
Or re-biopsy indicated but not feasible

Platinum-based ChT [I, A] (see Figure 2)
Carboplatin/paclitaxel/bevacizumab/
atezolizumab [III, A][d]







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Platinum-based ChT [I, A] (see Figure 2)
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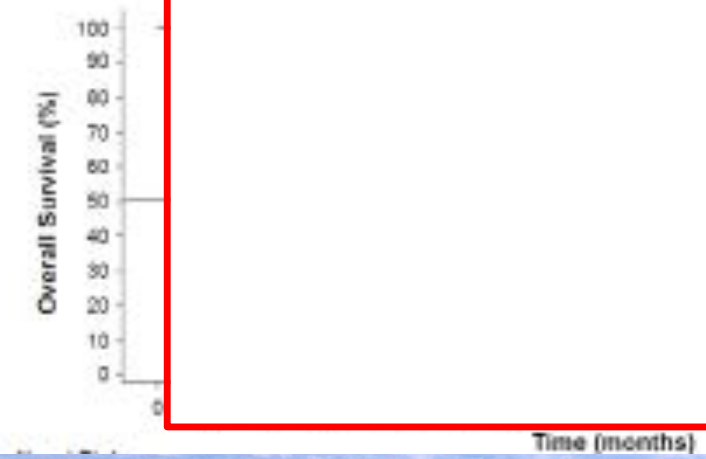
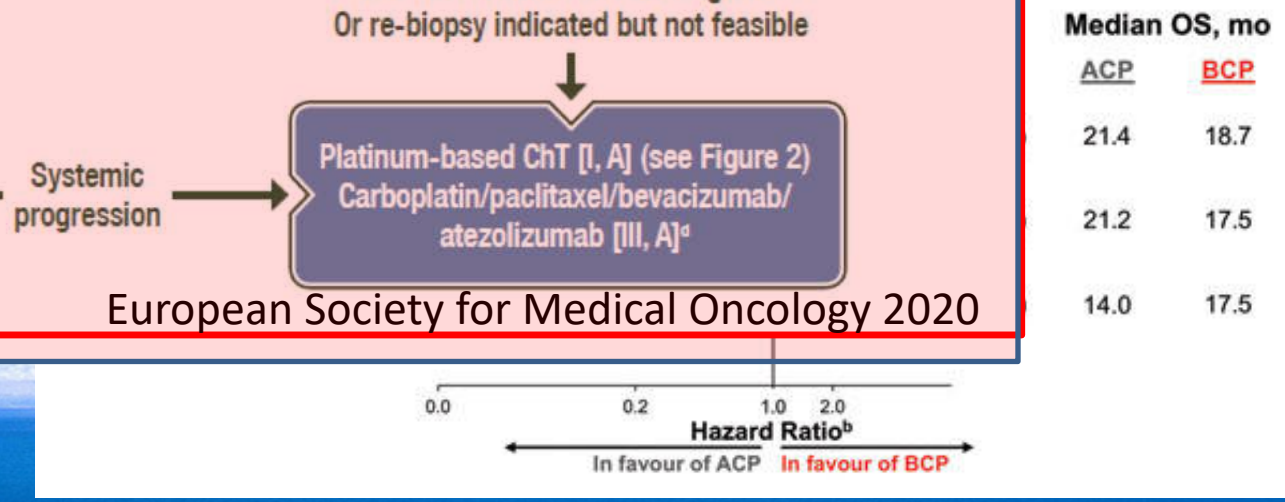
European Society for Medical Oncology 2020





VIRTUAL 2020 ESMO ASIA

HKU Med
LKS Faculty of Medicine
Department of Clinical Oncology
香港大學臨床腫瘤學系

Atezolizumab, Bevacizumab, Pemetrexed and Carboplatin Combination for Metastatic EGFR Mutated NSCLC after TKI Failure

A phase 2 single-arm clinical trial

Dr Lam, Tai Chung

Clinical Assistant Professor
Department of Clinical Oncology
LKS Faculty of Medicine, the University of Hong Kong

VIRTUAL 2020 ESMO ASIA

Methodology

- The study aimed to test the efficacy and safety of a **modified IMPower150 regimen**
- **Pemetrexed**-carboplatin was used instead of **taxane**-based regimen for better tolerance[1]
- A **lower dose of bevacizumab** (7.5mg/kg every 3 weeks) was used for higher cost-effectiveness[2] and possibly less toxicity[3]

Methodology

- The study aimed to test the efficacy and safety of a **modified IMPower150 regimen**
- **Pemetrexed**-carboplatin was used instead of **taxane**-based regimen for better tolerance[1]
- A **lower dose of bevacizumab** (7.5mg/kg every 3 weeks) was used for higher cost-effectiveness[2] and possibly less toxicity[3]

Study Population

1. Metastatic lung cancer with EGFR mutation, previously treated with TKI with radiological evidence of progression
2. For T790M mutation +ve, radiological progression on Osimertinib was required
3. Not treated by chemo / bevacizumab / immunotherapy before

→

4-6 Cycles Induction Treatment

Atezolizumab 1200 mg
Bevacizumab 7.5mg/kg
Pemetrexed 500 mg/m^2
Carboplatin AUC5

IV every 3 weeks

→

Maintenance Treatment till progression

Atezolizumab 1200 mg
Bevacizumab 7.5mg/kg
Pemetrexed 500 mg/m^2

IV every 3 weeks

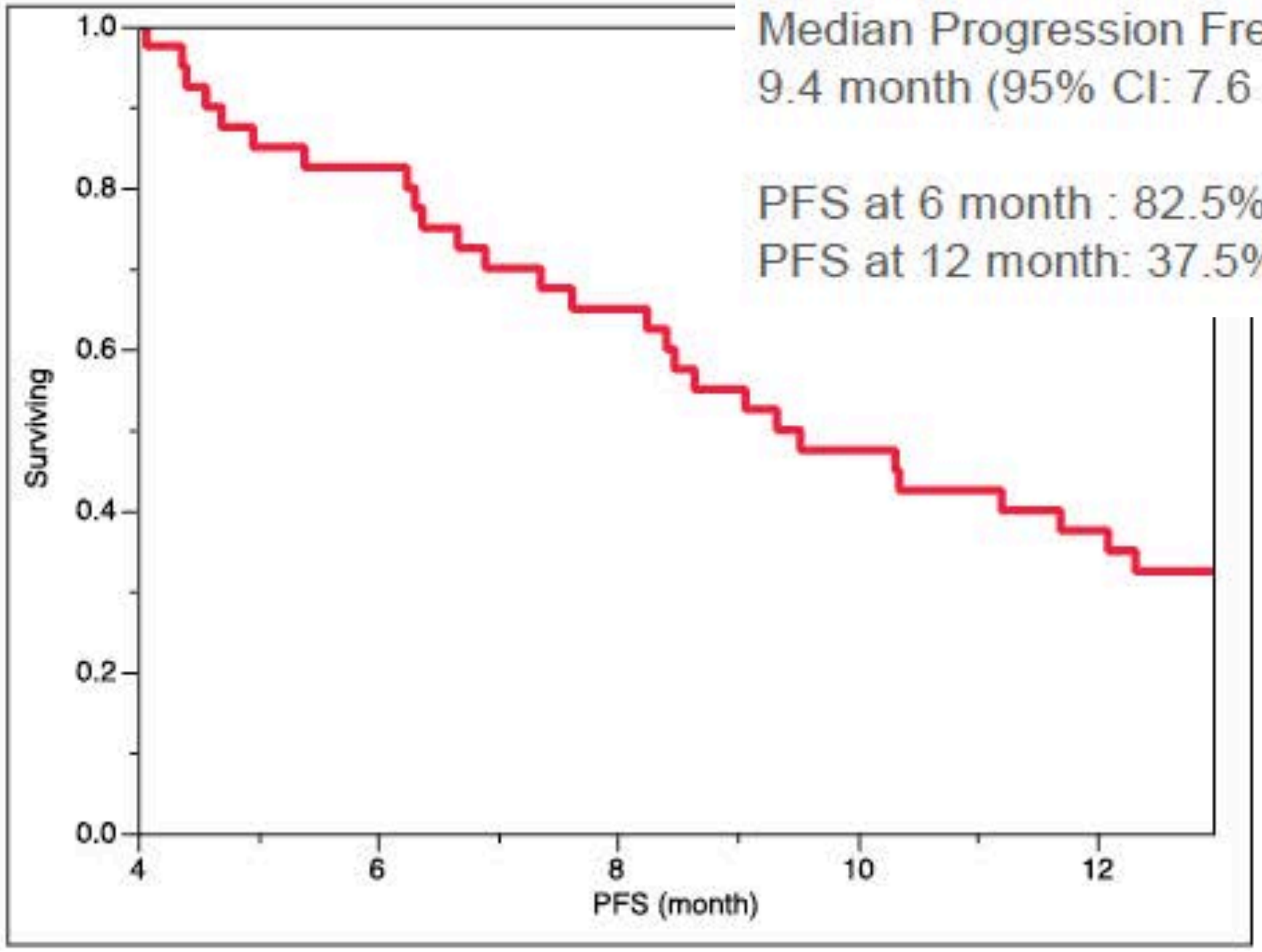
→

Primary end-point:
Overall response rate (ORR)

Secondary end-points:
1. Progression free survival
2. Overall survival
3. Quality of life (QoL)
4. Exploratory biomarkers in peripheral blood

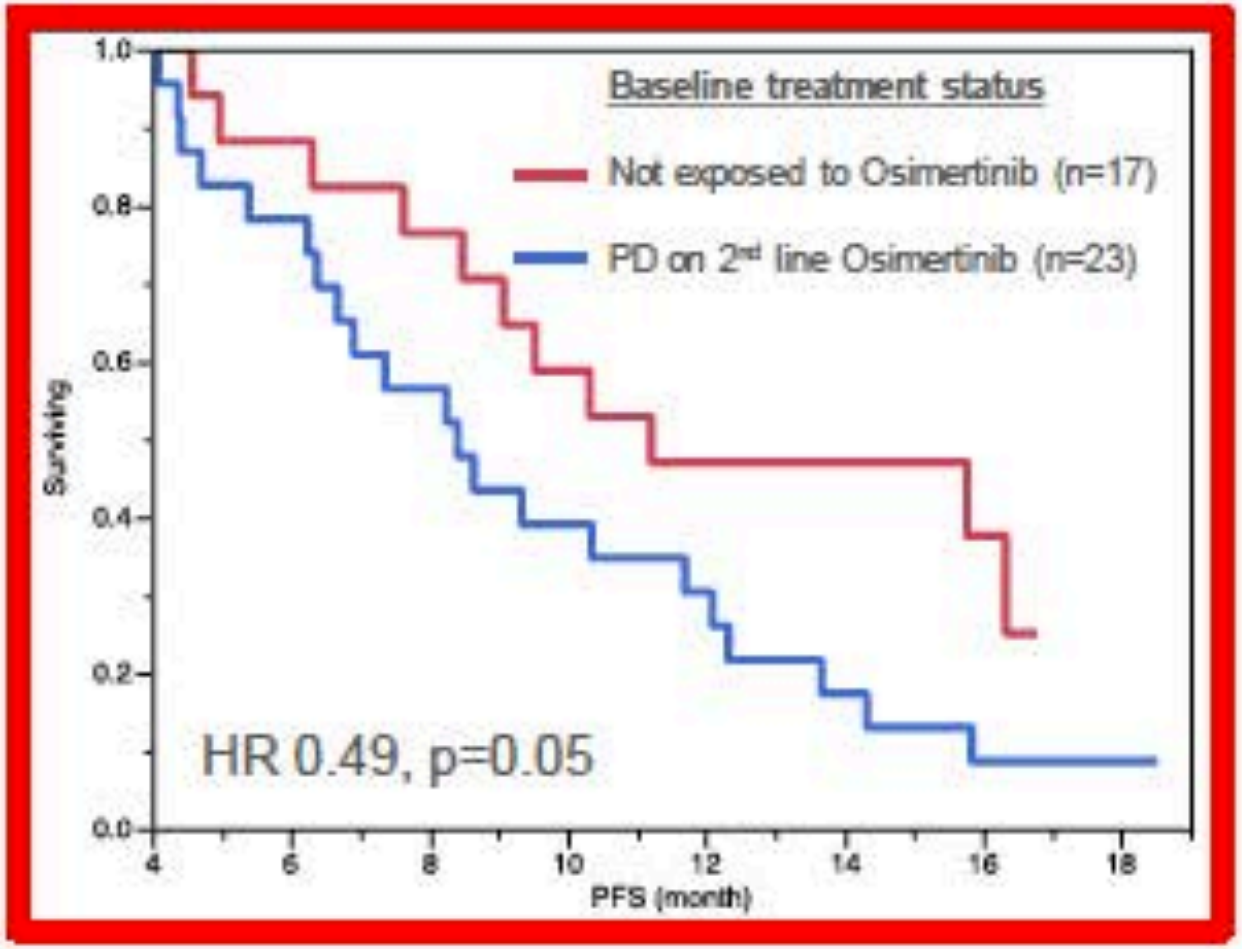
- A phase 2 single arm, single center study. Territory-wide recruitment in Hong Kong
- Recruitment was started in Oct 2018
- Enrollment of **40 subjects** was completed in May-2019
- Till 15-Aug-2020, median follow-up time was 15.0 months (IQR 11.0-17.1 months)

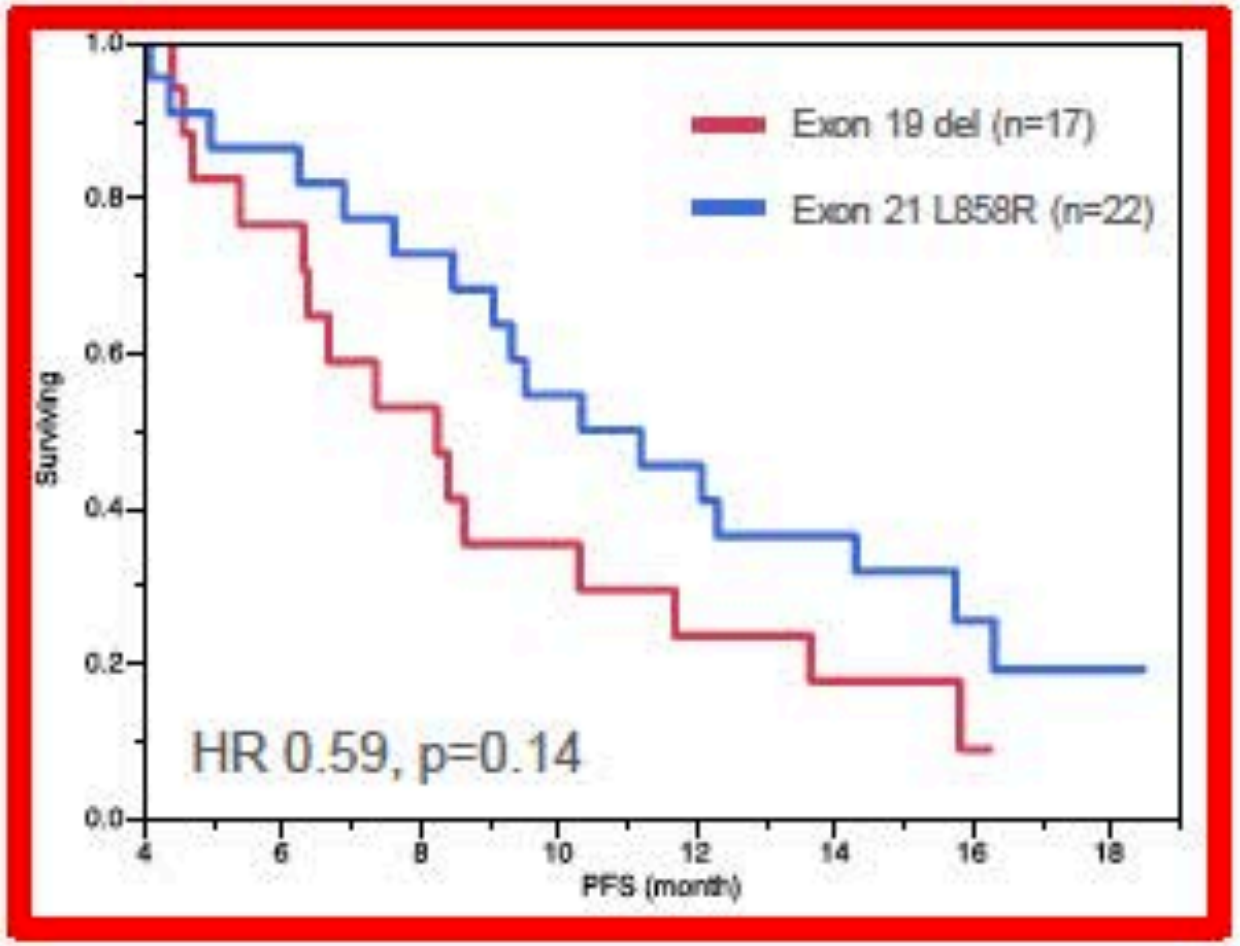
1. Lu S et al. Clinical Lung Cancer 2016; 17(5):e103-e112.
2. Ahn MJ et al. Asia Pac J Clin Oncol 2011; 7 Suppl 2:22-33.
3. Zhou M, et al. PLOS ONE 2013; 8(12):e81858.

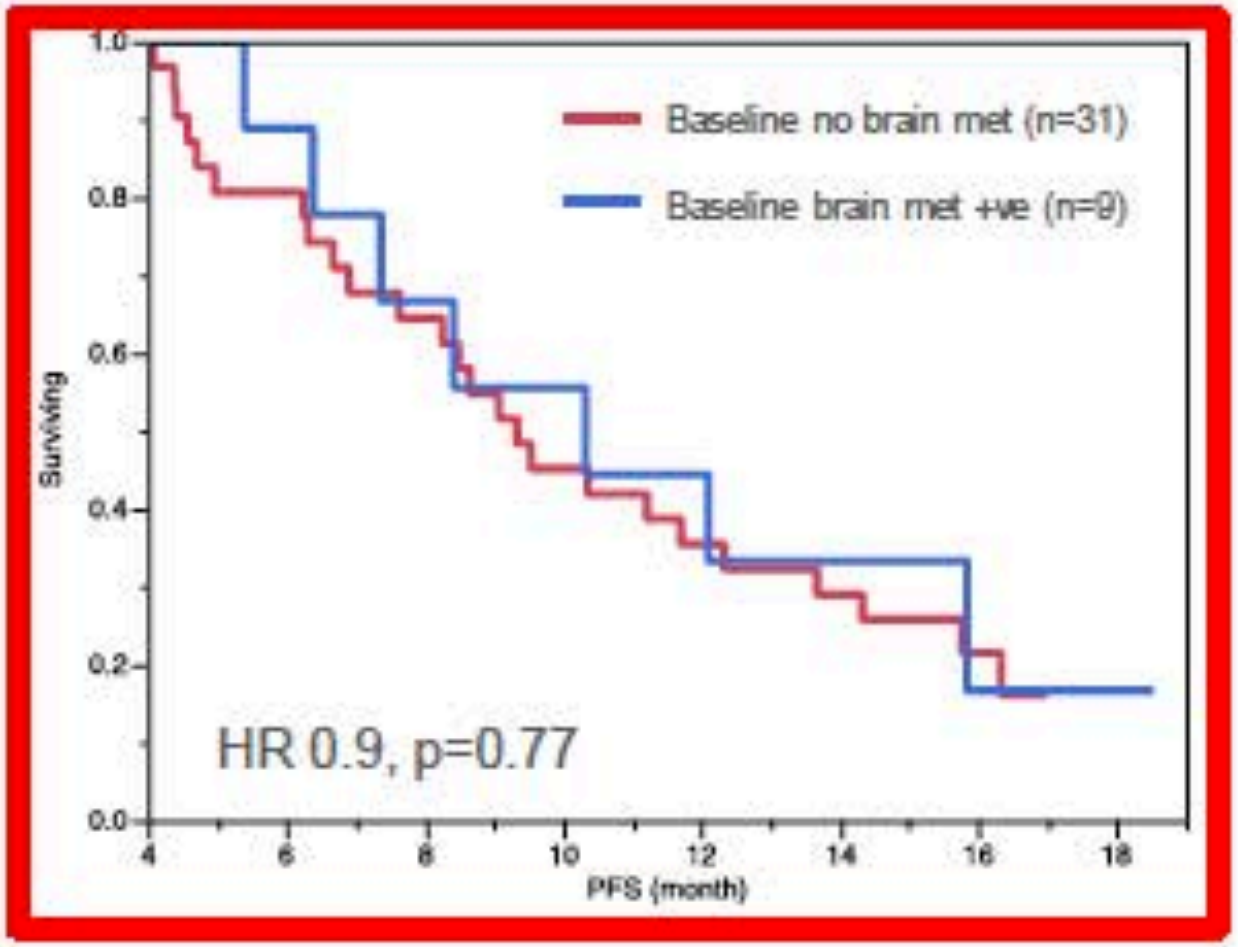


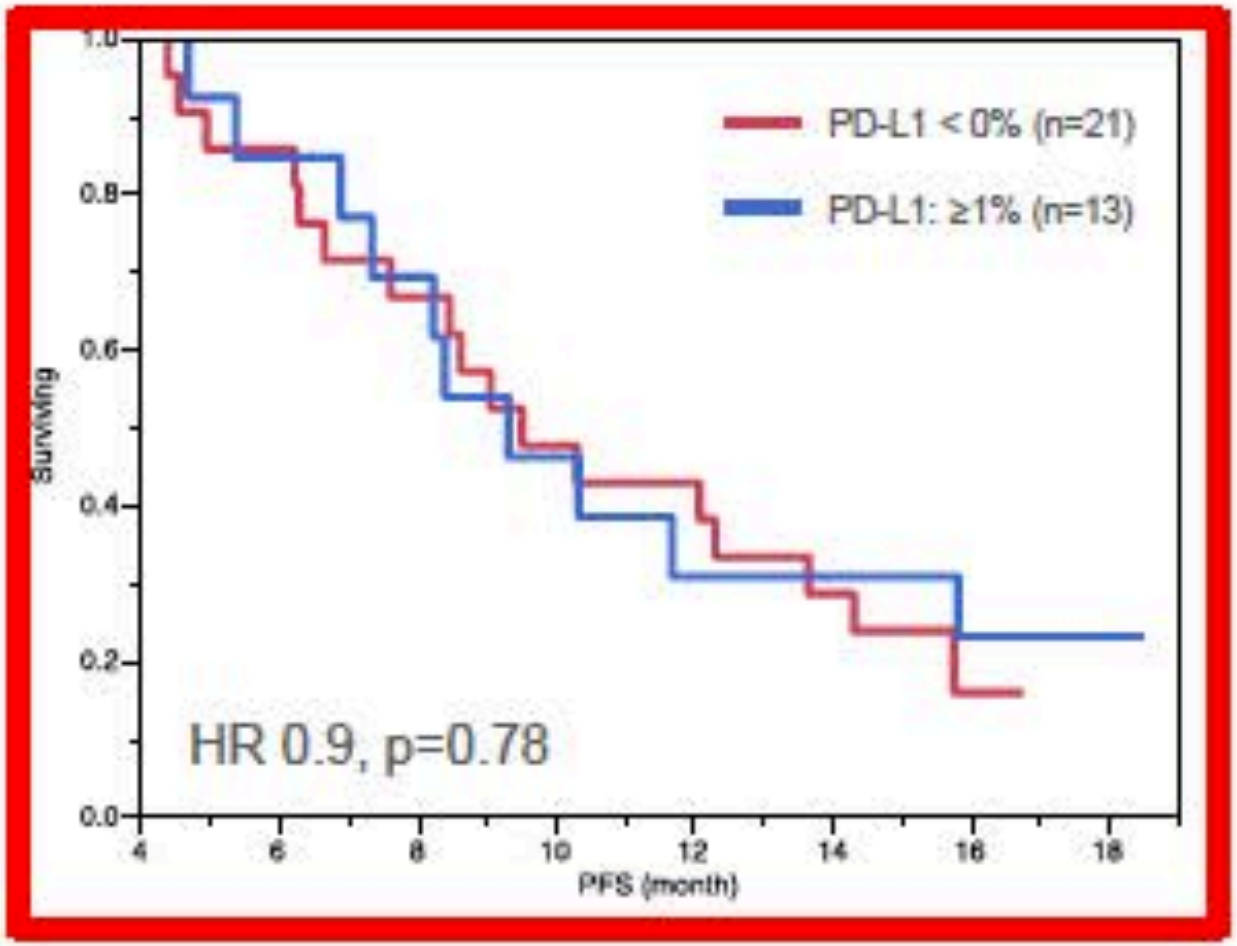
Median Progression Free Survival (PFS)
9.4 month (95% CI: 7.6 – 12.1 months)

PFS at 6 month : 82.5% (95% CI: 67-91%)
PFS at 12 month: 37.5% (95% CI: 23-52%)

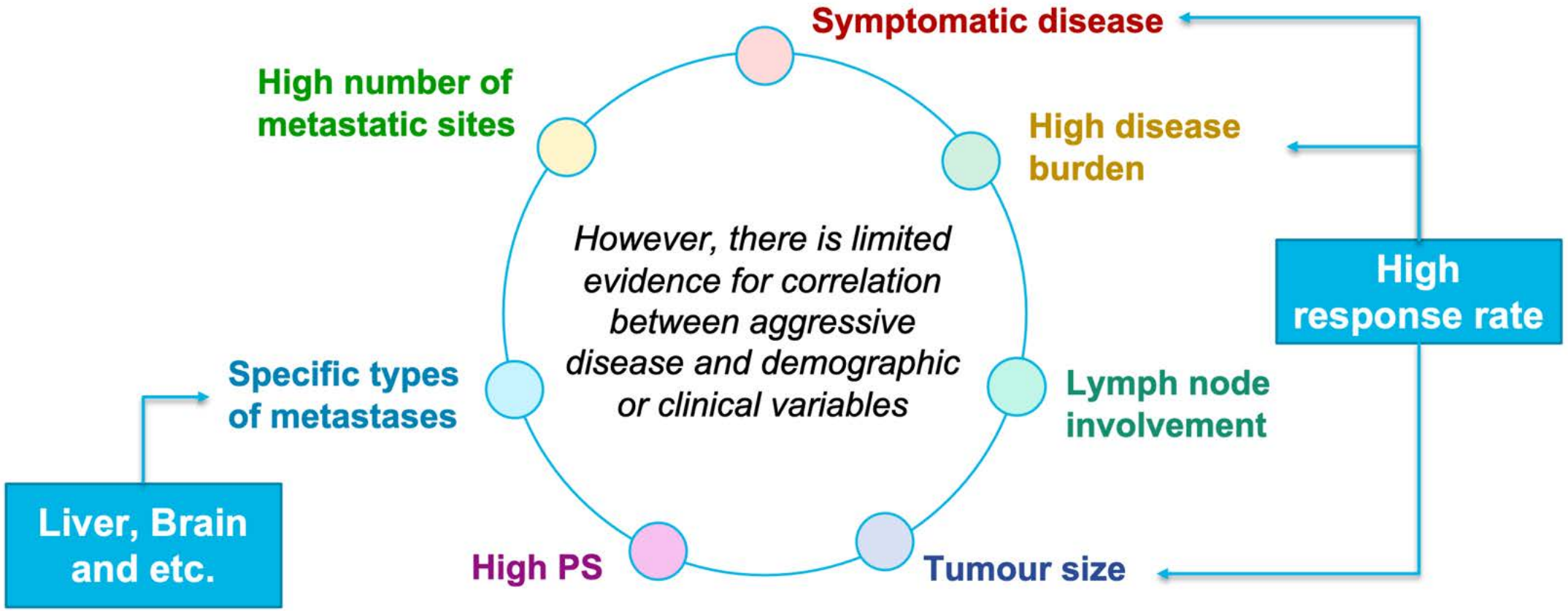

Baseline treatment status
Not exposed to Osimertinib (n=17)
PD on 2nd line Osimertinib (n=23)
HR 0.49, p=0.05
Surviving
PFS (month)


Exon 19 del (n=17)
Exon 21 L858R (n=22)
HR 0.59, p=0.14
Surviving
PFS (month)


Baseline no brain met (n=31)
Baseline brain met +ve (n=9)
HR 0.9, p=0.77
Surviving
PFS (month)


PD-L1 < 0% (n=21)
PD-L1: ≥1% (n=13)
HR 0.9, p=0.78
Surviving
PFS (month)

Efficacy in patients with bulky disease and multiple metastasis



- Reck et al. Future Oncol 2019; Zietemann et al. Lung Cancer 2011

IMpower150: efficacy outcomes of high and low disease burden subgroups defined by SLD

Total -OS: 19.5 versus 14.7, HR:0.8
ORR: 64% vs 48%

Atezolizumab + bevacizumab + chemotherapy showed improved OS, PFS and ORR vs bevacizumab + chemotherapy regardless of disease burden

	High burden (SLD ≥3rd quartile)		Low burden (SLD <3rd quartile)	
	Arm B Atezo + bev + CP (n=91)	Arm C Bev + CP (n=85)	Arm B Atezo + bev + CP (n=266)	Arm C Bev + CP (n=252)
Median OS, months	15.5	10.7	20.3	17.1
OS HR (95% CI)	0.70 (0.5–0.97)		0.83 (0.68–1.02)	
Median PFS, months	7.3	5.8	9.6	7.1
PFS HR (95% CI)	0.52 (0.37–0.72)		0.59 (0.49–0.71)	
ORR, %*	62	41	53	40
Time to response, months	1.5	1.6	1.8	1.5

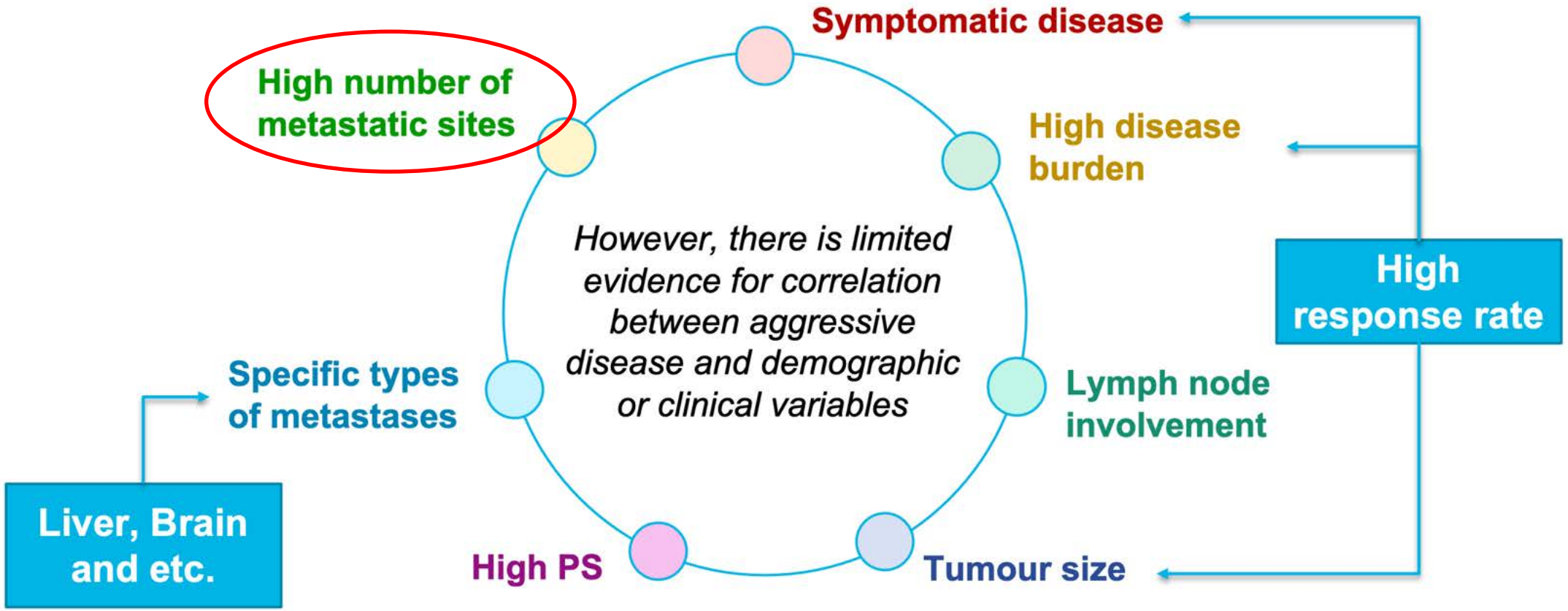
- Benefit seen with Arm B was even more pronounced in patients with high versus low disease burden
- ORR benefit when atezolizumab was added to bevacizumab + CP was more pronounced in patients with high versus low disease burden. Time to response was not impacted by disease burden in either arm

Data cut-off: 13 September, 2019.

*Pts with baseline measurable disease. **SLD, sum of the longest diameter.3rd quartile was 108mm, with 'high' defined as SLD ≥108mm and 'low' defined as <108mm.**

Jotte et al. ASCO 2020 (e21637)

Efficacy in patients with bulky disease and multiple metastasis



- Reck et al. Future Oncol 2019; Zietemann et al. Lung Cancer 2011

IMpower150: efficacy outcomes of high and low disease burden subgroups defined by number of metastatic sites

Atezolizumab + bevacizumab + chemotherapy showed improved OS, PFS and ORR vs bevacizumab + chemotherapy regardless of disease burden

	High burden (no of met sites ≥median)		Low burden (no of met sites <median)	
	Arm B Atezo + bev + CP (n=210)	Arm C Bev + CP (n=190)	Arm B Atezo + bev + CP (n=149)	Arm C Bev + CP (n=148)
Median OS, months	17.6	12.5	22.5	21.5
OS HR (95% CI)	0.72 (0.58–0.90)		0.89 (0.67–1.17)	
Median PFS, months	7.7	6.0	11.0	7.9
PFS HR (95% CI)	0.56 (0.45–0.69)		0.56 (0.43–0.72)	
ORR, %*	57	40	53	40
Time to response, months	1.6	1.5	1.7	1.5

- Benefit seen with Arm B was even more pronounced in patients with high versus low disease burden
- ORR benefit when atezolizumab was added to bevacizumab + CP was more pronounced in patients with high versus low disease burden. Time to response was not impacted by disease burden in either arm

Data cut-off: 13 September, 2019.

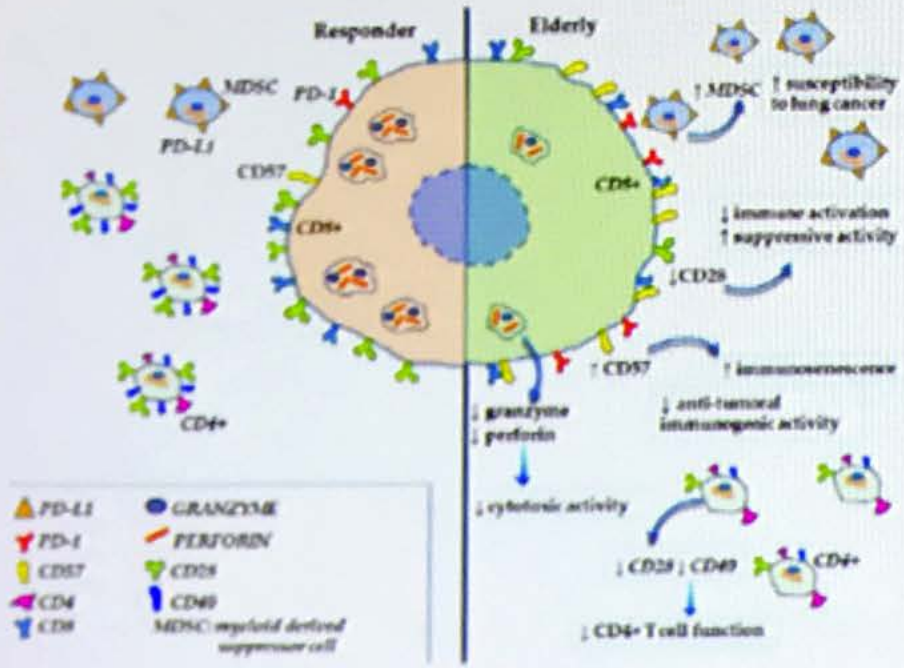
*Pts with baseline measurable disease.

Median number of metastatic sites at baseline: the median number of sites was 2, with 'high' defined as ≥2 metastatic sites and 'low' defined as <2 metastatic sites.

Jotte et al. ASCO 2020 (e21637)

Clinical question of Chemo/IO combo: Elderly patients ?

- Aging is associated with decline and impairment in immune response.
- KN189 regimen did not achieve a significant survival benefit in elderly patients (≥ 75 years).
- However, the corresponding data were post-hoc and comprised of small group analysis including bias



KN189 EMA assessment report

	Age Category	N Pembro	N Control	HR(95% CI)
OS	<65	197	115	0.43(0.31-0.61)
	65-74	178	69	0.51(0.32-0.81)
	75-84	35	22	2.09(0.84-5.23)
PFS	<65	197	15	0.43(0.32-0.56)
	65-74	178	69	0.64(0.45-0.91)
	75-84	35	22	1.73(0.77-3.90)
ORR	<65	197	15	Δ+27.1
	65-74	178	69	Δ+32.2
	75-84	35	22	Δ+14.4

KN-189 EMA Assessment report, July 2018

Perrotta et al. Int J Mol Sci, 2019

*** This page was not intended to make direct comparison between two trials or to show one's superiority*

Impact of Age on Efficacy of IO-chemo combinations: Subgroup Analyses in KN-189 and KN-407 - OS

KN-189[1]

	Subgroup	Number of Deaths/ Number of Patients	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Overall	Overall	235/616		0.49 (0.38–0.64)
Age	<65 years	133/312		0.43 (0.31–0.61)
	≥65 years	102/304		0.64 (0.43–0.95)

KN-407[2]

	Subgroup	Number of Deaths/ Number of Patients	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Overall	Overall	205/559		0.64 (0.49–0.85)
Age	<65 years	88/254		0.52 (0.34–0.80)
	≥65 years	117/305		0.74 (0.51–1.07)

Data cutoff dates: KEYNOTE-189, November 8, 2017; KEYNOTE-407, April 3, 2018

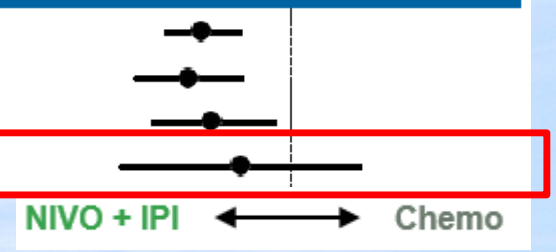
1. Gandhi L et al. *N Engl J Med* 2018;378(22):2078-2092. 2. Paz-Ares L et al. *N Engl J Med* 2018;379(21):2040-2051.

*** This page was not intended to make direct comparison between two trials or to show one's superiority*

Impact of Age on Efficacy of IO/IO + chemo combinations: Subgroup Analyses in CM-227 and CM-9LA - OS

CM-227 part 1[1]

Subgroup	Median OS, months NIVO + IPI n = 583	Chemo n = 583	Unstratified HR	Unstratified HR (95% CI)
All randomized (N = 1166)	17.1	13.9	0.73[a]	
< 65 years (n = 611)	16.6	14.2	0.70	
65 to < 75 years (n = 442)	18.7	13.0	0.76	
≥ 75 years (n = 113)	15.1	12.4	0.84	



CM-9LA[2]

Subgroup	Median OS, mo NIVO + IPI + chemo n = 361	Chemo n = 358	Unstratified HR	Unstratified HR (95% CI)
All randomized (N = 719)	15.6	10.9	0.66[a]	
< 65 years (n = 354)	15.6	10.7	0.61	
65 to < 75 years (n = 295)	19.4	11.9	0.62	
≥ 75 years (n = 70)	8.5	11.5	1.21	

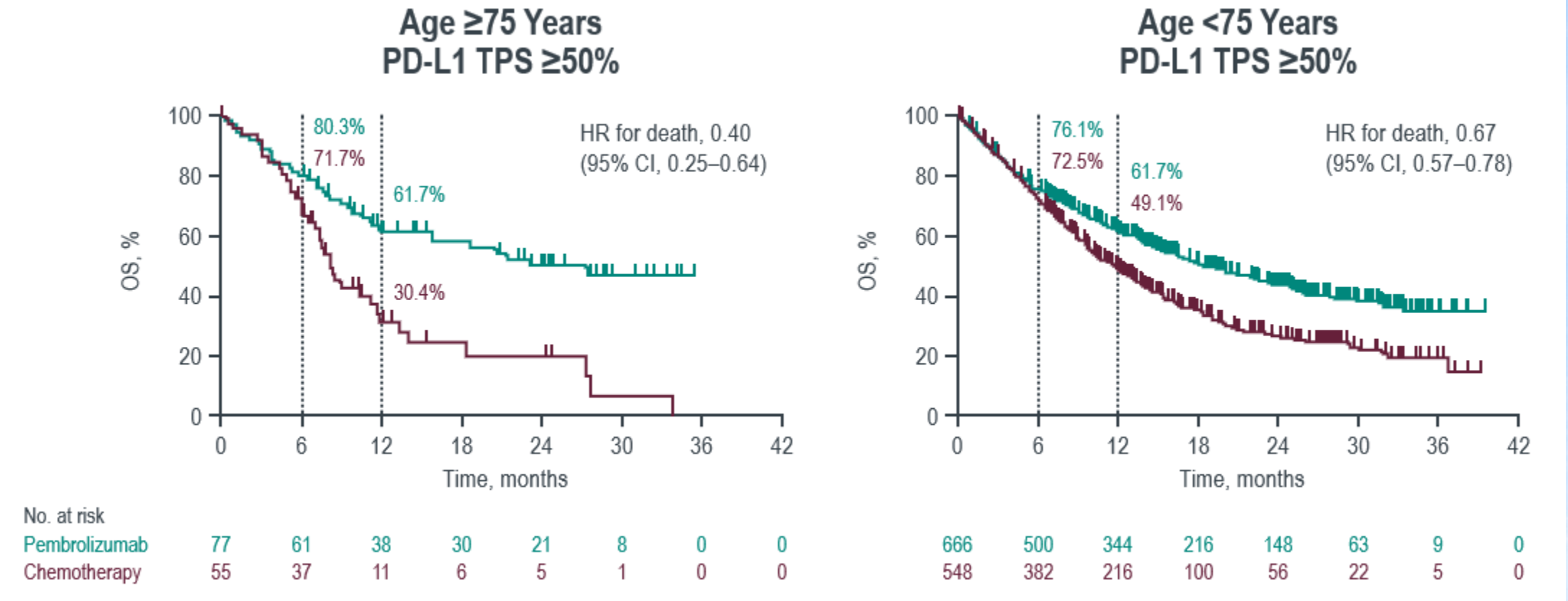
1. Peters S et al. ESMO 2019 2. Reck M et al. ASCO 2020

Impact of Age on Efficacy Outcomes of IO monotherapy: OS from Pooled Analysis of KN-010, KN-024, and KN-042 (PD-L1 TPS >1%)

Figures reprinted with permission from *Elsevier*: Nosaki K et al. *Lung Cancer*. 2019;135:188–195.

Data cutoff dates: KEYNOTE-010, March 24, 2017; KEYNOTE-024, May 9, 2016; KEYNOTE-042, February 26, 2018.
Nosaki K et al. *Lung Cancer*. 2019;135:188–195.

Impact of Age on Efficacy Outcomes of IO monotherapy: OS from Pooled Analysis of KN-010, KN-024, and KN-042 (PD-L1 TPS >1%)



Data cutoff dates: KEYNOTE-010, March 24, 2017; KEYNOTE-024, May 9, 2016; KEYNOTE-042, February 26, 2018.
Nosaki K et al. *Lung Cancer*. 2019;135:188–195.

- First line I/O or combination for no driver mutation NSCLC
- What is the treatment strategy for special situation?
- New drug or new combination
- Novel target?

VIRTUAL 2020 ESMO congress

EMPOWER

EMPOWER-Lung 1: Phase 3 First-line (1L) Cemiplimab Monotherapy vs Platinum-Doublet Chemotherapy (Chemo) in Advanced Non-Small Cell Lung Cancer (NSCLC) with Programmed Cell Death-Ligand 1 (PD-L1) ≥50%

Ahmet Sezer,[1] Saadettin Kilickap,[2] Mahmut Gümüş,[3] Igor Bondarenko,[4] Mustafa Özgüroğlu,[5] Miranda Gogishvili,[6] Haci M Turk,[7] Irfan Cicin,[8] Dmitry Bentsion,[9] Oleg Gladkov,[10] Philip Clingan,[11] Virote Sriuranpong,[12] Naiyer Rizvi,[13] Bo Gao,[14] Siyu Li,[14] Sue Lee,[14] Chieh-I Chen,[14] Tamta Makharadze,[15] Semra Paydas,[16] Marina Nechaeva,[17] Frank Seebach,[18] David M Weinreich,[18] George D Yancopoulos,[18] Giuseppe Gullo,[18] Israel Lowy,[18] Petra Rietschel[18]

[1]Department of Medical Oncology, Başkent University, Adana, Turkey; [2]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey; [3]Department of Medical Oncology, School of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; [4]Department of Oncology and Medical Radiology, Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [5]Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey; [6]High Technology Medical Centre, University Clinic Ltd, Tbilisi, Georgia; [7]Department of Medical Oncology, Bezmialem Vakif University, Medical Faculty, Istanbul, Turkey; [8]Department of Medical Oncology, Trakya University, Edirne, Turkey; [9]Sverdlovsk Regional Oncology Centre, Sverdlovsk, Russia; [10]LLC, "EVIMED", Chelyabinsk, Russia; [11]Southern Medical Day Care Centre and Illawarra Health and Medical Research Institute, University of Wollongong/Illawarra Cancer Centre, Wollongong Hospital, Wollongong, New South Wales, Australia; [12]Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [13]Division of Hematology/Oncology, Columbia University Medical Center, New York, New York, USA; [14]Regeneron Pharmaceuticals, Inc., Basking Ridge, New Jersey, USA; [15]LTD High Technology Hospital Medicenter, Batumi, Georgia; [16]Department of Medical Oncology, Faculty of Medicine, Cukurova University, Adana, Turkey; [17]Arkhangelsk Clinical Oncology Center, Arkhangelsk, Russia; [18]Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA

VIRTUAL ESMO congress 2020

EMPOWER

EMPOWER-Lung 1 Study Design (NCT03088540)

Treatment beyond progression?

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → Optional continuation of cemiplimab + 4 cycles of chemotherapy

Arm B
4–6 cycles of investigator's choice chemotherapy

PD → Optional crossover to cemiplimab monotherapy

Follow-up

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

N=710

Five interim analyses were prespecified per protocol

Second interim analysis (1 March 2020) presented here

ALK, anaplastic lymphoma kinase; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomised; ROS1, c-ros oncogene 1; ROW, rest of the world.

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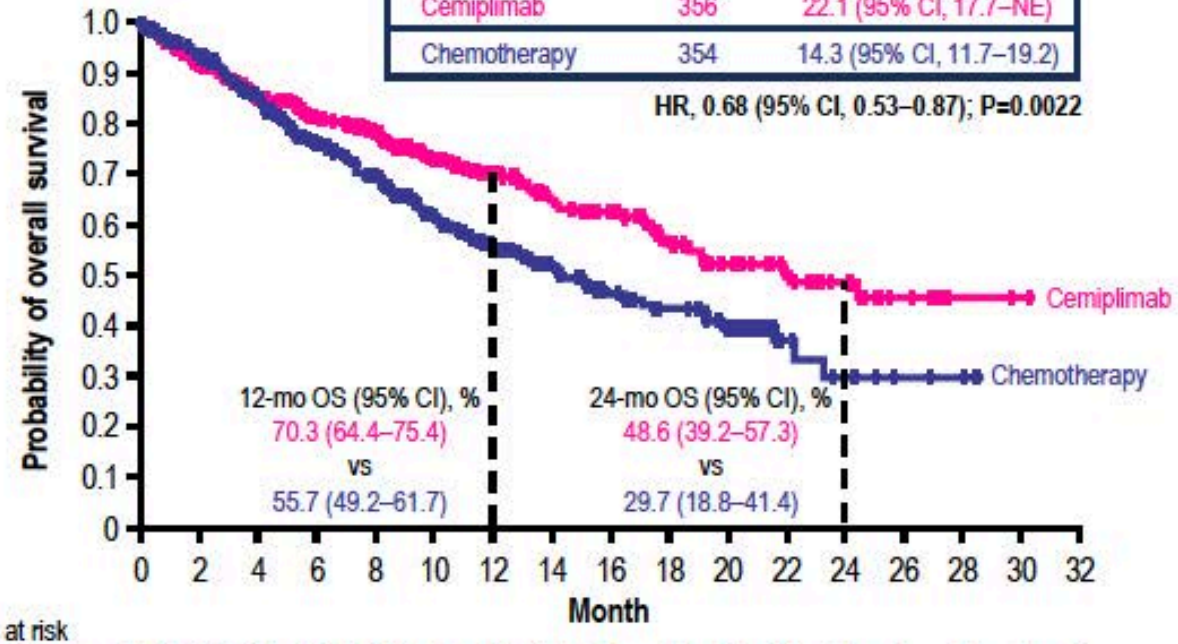
EMPOWER

Overall Survival

ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	356	22.1 (95% CI, 17.7–NE)
Chemotherapy	354	14.3 (95% CI, 11.7–19.2)

HR, 0.68 (95% CI, 0.53–0.87); P=0.0022



No. at risk

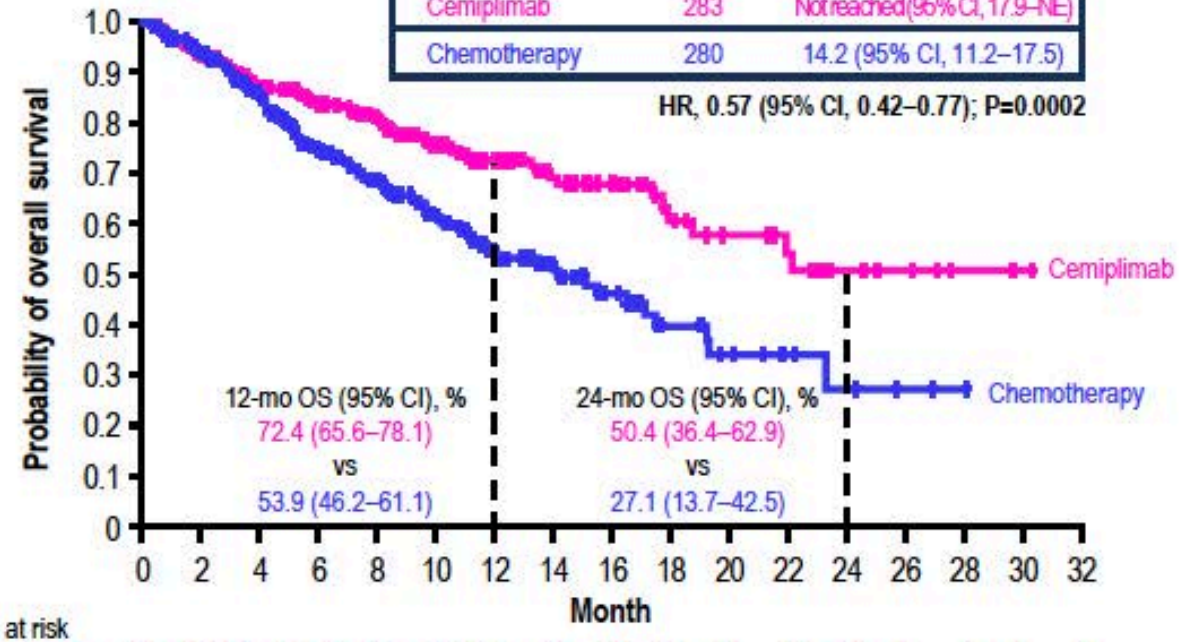
Cemiplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
Chemotherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

Median duration of follow-up:
Cemiplimab → 13.1 months (range: 0.1–31.9)
Chemotherapy → 13.1 months (range: 0.2–32.4)

PD-L1 ≥50% ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	283	Not reached (95% CI, 17.9–NE)
Chemotherapy	280	14.2 (95% CI, 11.2–17.5)

HR, 0.57 (95% CI, 0.42–0.77); P=0.0002



No. at risk

Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
Chemotherapy	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

Median duration of follow-up:
Cemiplimab → 10.8 months (range: 0.1–31.9)
Chemotherapy → 10.2 months (range: 0.2–29.5)

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mo, month; NE, not evaluable; OS, overall survival; PD-L1, programmed cell death-ligand 1.

Data cut-off date: 1 March 2020 (interim analysis #2)

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Different design

Study	KN042		KN024		IMp110		EMpower	
NSQ/SQ(%)	61.8/38.5		82/18		70/30		56.8/43.2	
Regimen	Pemb	C/T	Pemb	C/T	Atezo	C/T	Cemi	C/T
ORR(%)	39.1	32.3	46.1	31.1	40.2	28.6	39.2	20.4
mDoR (mo)	27.3	10.8	29.1	6.3	38.9	8.3	16.7	6.0
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	8.2	5.7
	HR=0.85		HR=0.5		HR=0.59		0.54	
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	12.4
	HR=0.68		HR=0.62		HR=0.76		0.57	
2-yr OS(%)	45	30	51.7	34.2	45	35		

*** This page was not intended to make direct comparison between trials or to show one's superiority*

LBA55

WJOG @Be Study: A Phase II Study of Atezolizumab with Bevacizumab for Non-Squamous Non-Small-Cell Lung Cancer with High PD-L1 Expression

JapicCTI-184038

Takashi Seto, Kaname Nosaki, Mototsugu Shimokawa, Ryo Toyozawa, Shunichi Sugawara, Hidetoshi Hayashi, Haruyasu Murakami, Terufumi Kato, Seiji Niho, Hideo Saka, Masahide Oki, Hiroshige Yoshioka, Isamu Okamoto, Haruko Daga, Koichi Azuma, Hiroshi Tanaka, Kazumi Nishino, Miyako Satouchi, Nobuyuki Yamamoto, Kazuhiko Nakagawa
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Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, Department of Biostatistics, Yamaguchi University Graduate School of Medicine, Ube, Japan, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Japan, Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, 7Department of Respiratory Medicine, Kanagawa Cancer Center, Yokohama, Japan, Department of Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata, Japan, Research Institute for Diseases of the Chest, Kyushu University, Fukuoka, Japan, Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University, Kurume, Japan, Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan, Department of Thoracic Oncology, Hyogo Cancer Center, Akashi, Japan, Internal Medicine III, Wakayama Medical University, Wakayama, Japan

Study Design

WJOG10718L; A single arm, open label, multi-institutional study

Advanced Non-Sq NSCLC

- PD-L1 TPS ≥ 50% (Dako 22C3)
- w/o EGFR/ALK/ROS1 alterations
- ECOG PS=0-1
- No prior therapy
- Fit to anti-angiogenesis therapy

→ **Atezolizumab 1200mg + Bevacizumab 15mg/kg**

Every 3 weeks
Up to 2years

→ **Until PD or intolerable toxicity**

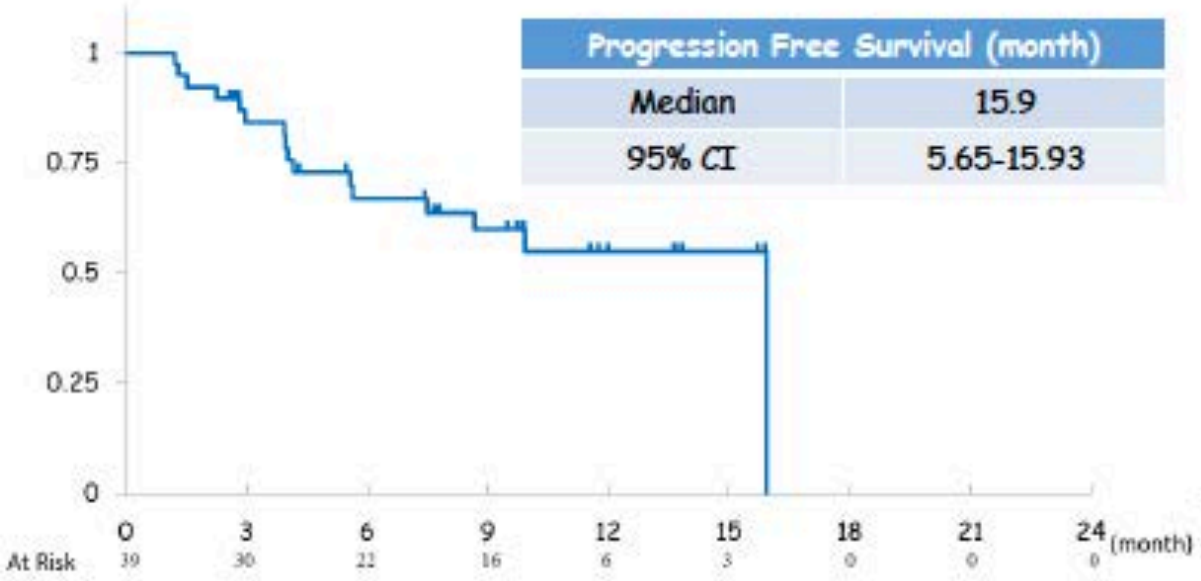
JapicCTI-184038

Sample size: 38
Threshold-Expected ORR: 40-62%.
One side α = 0.05 1-β = 0.8

Primary endpoint: ORR (IRC)
Secondary endpoints: PFS (IRC), DoR (IRC), OS, Safety

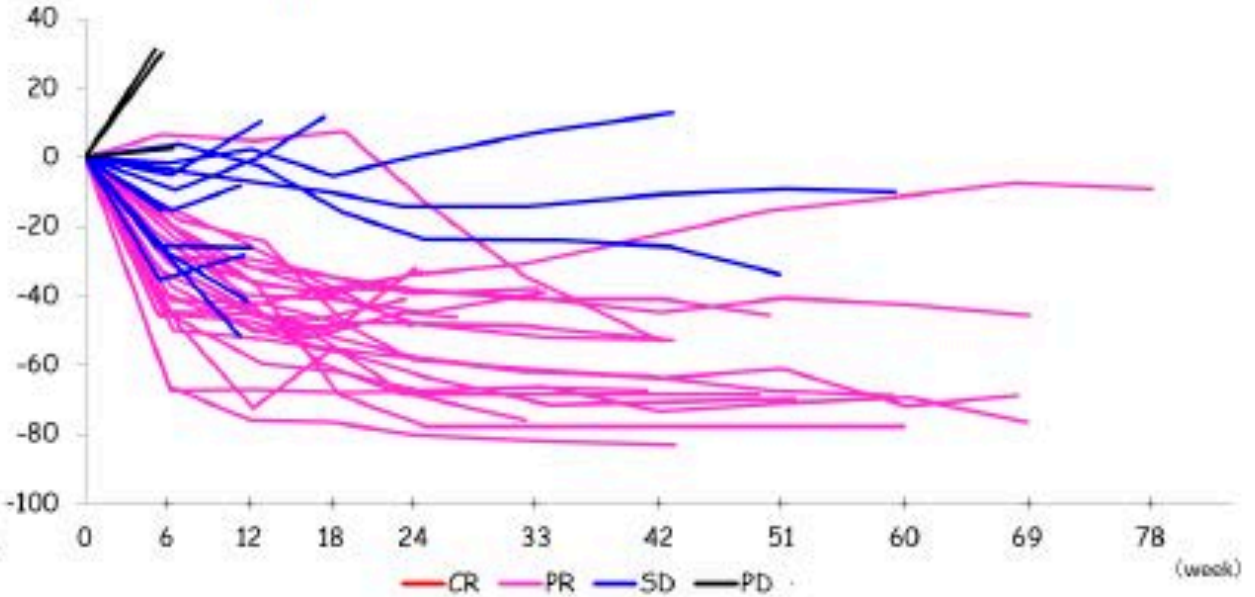
Progression Free Survival & Spider Plots Curve (IRC)

Progression Free Survival



Progression Free Survival (month)	
Median	15.9
95% CI	5.65-15.93

Spider plots
Tumor response ratio from the start of treatment



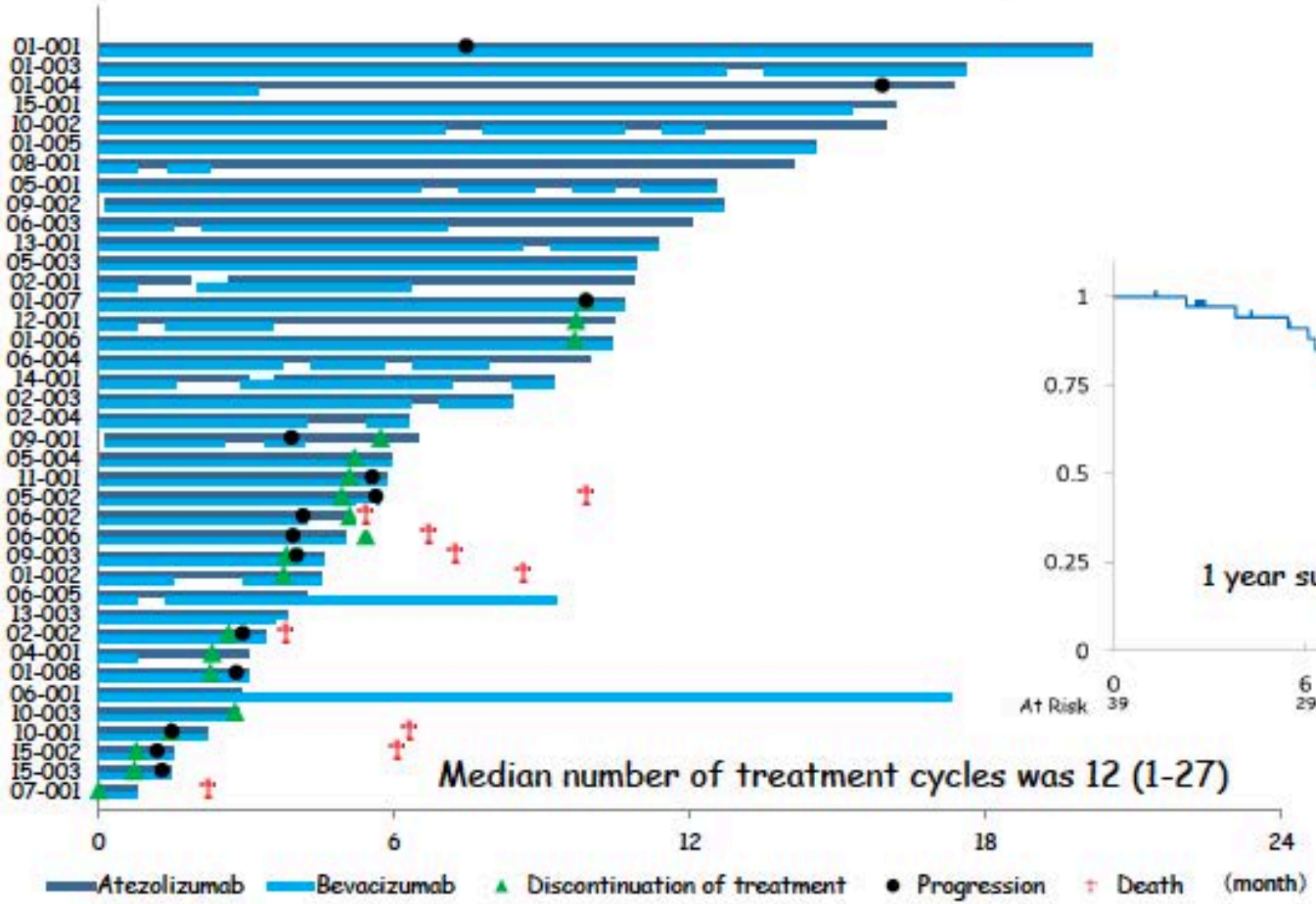
Progression free rate n=39		
month	6	12
%	66.8	54.9
95% CI	48.90 - 79.70	35.65 - 70.60

PFS events: 16/39 (41.0%)

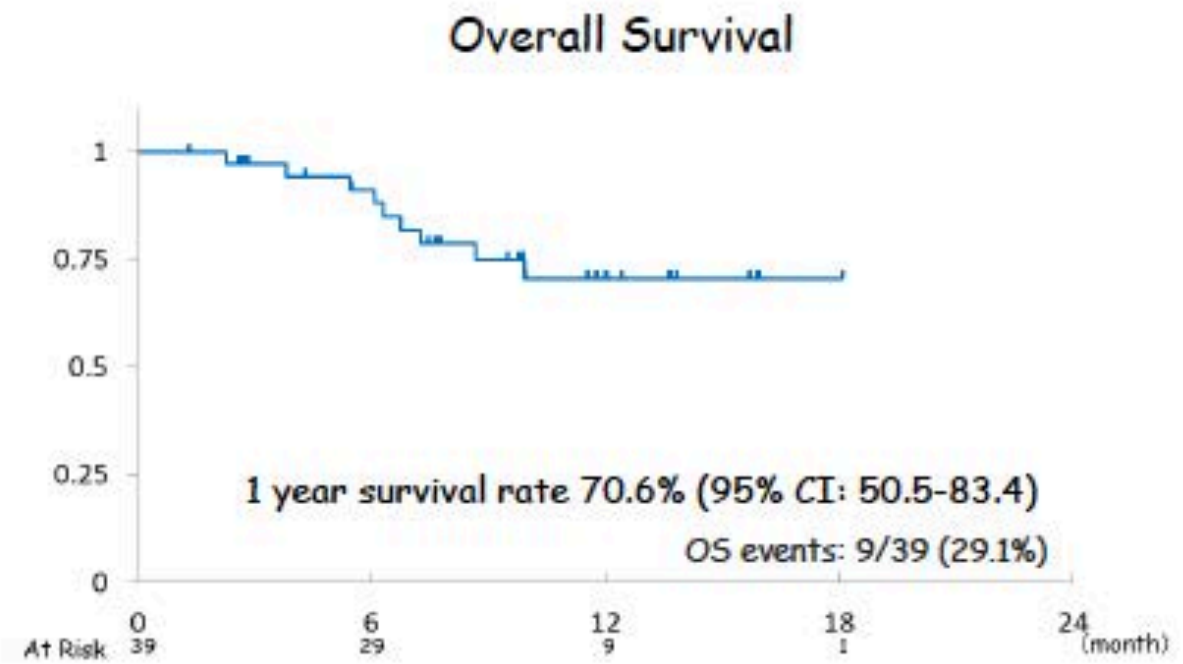
Duration response rate n=25		
month	6	12
%	72.2	48.2
95% CI	48.03 - 86.58	16.24 - 74.56

Median duration of response 10.4 months (95% CI: 4.63-NR)

Swimmer's Plots (IRC) & Overall Survival



Median number of treatment cycles was 12 (1-27)



Different design

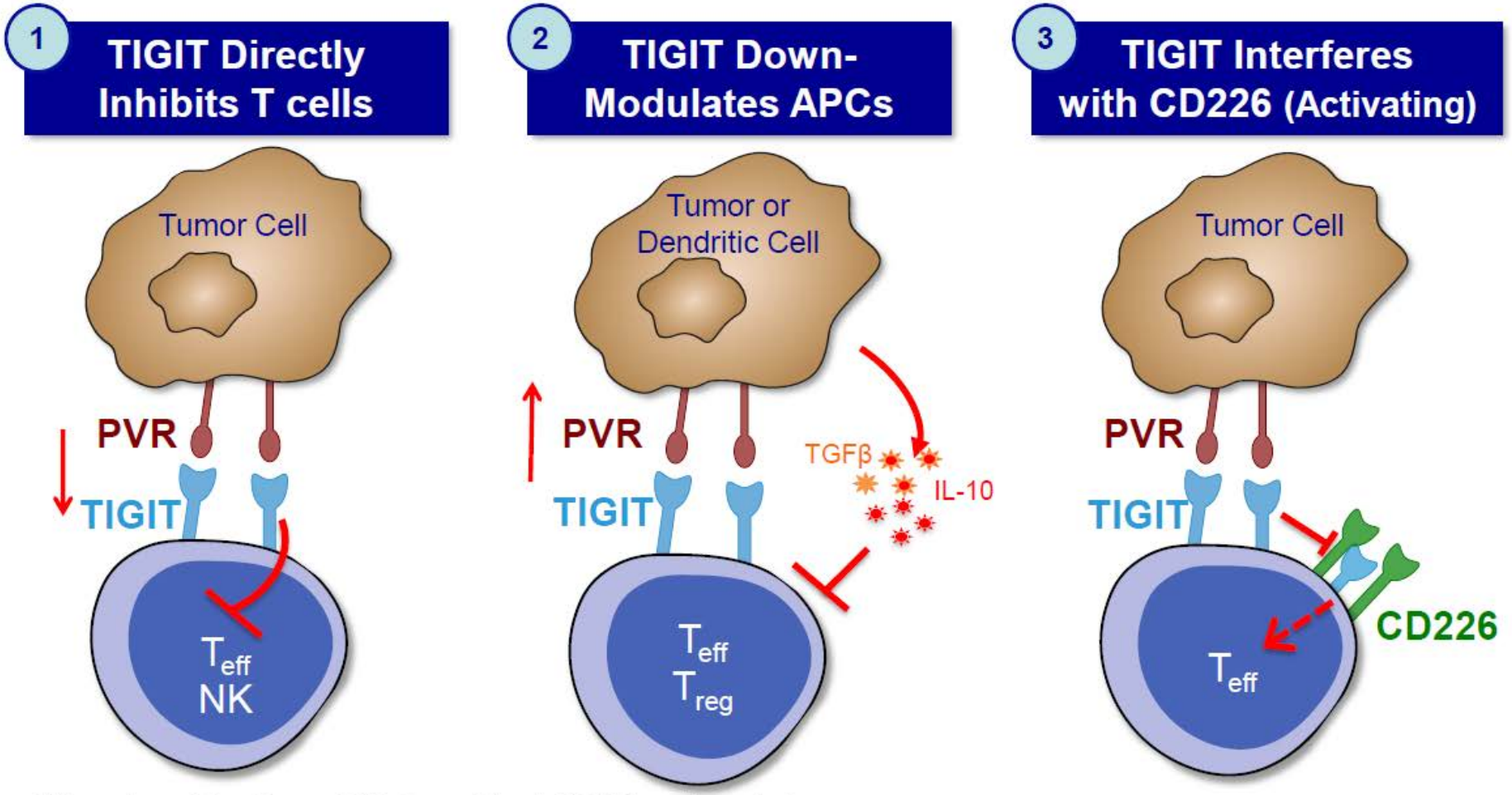
Single arm

Study	KN042		KN024		IMp110		EMpower		@B
NSQ/SQ(%)	61.8/38.5		82/18		70/30		56.8/43.2		94.5/5.1
Regimen	Pemb	C/T	Pemb	C/T	Atez	C/T	Cemi	C/T	A+Bev
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	39.2	20.4	64.1
mDoR (mo)	22.0	10.8	29.1	6.3	38.9	8.3	16.7	6.0	10.4
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	8.2	5.7	15.9
	HR=0.83		HR=0.5		HR=0.59		0.54		
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	12.4	
	HR=0.68		HR=0.62		HR=0.59		0.57		
2-yr OS(%)	45	30	51.7	34.2	45	25			

*** This page was not intended to make direct comparison between trials or to show one's superiority*

How does TIGIT Inhibit T-Cell Function?

CD8+ T cells	CD4+ T cells	NK cells
Inhibitory	Inhibitory	Inhibitory



Slide courtesy of Jane Grogan, PhD, Research Lead, TIGIT Team, Genentech

CITYSCAPE: Study Design

- Randomized, double-blind, placebo-controlled, phase II trial

Stratified by PD-L1 TPS (1% to 49% vs ≥ 50%), histology (nonsquamous vs squamous), tobacco use (yes vs no)

Stage IV NSCLC; no prior systemic therapy for advanced disease; *EGFR/ALK* wild-type; PD-L1 TPS ≥ 1%* (N = 135)

*By 22C3, local, or central PD-L1 IHC assay.

Tiragolumab 600 mg IV Q3W + **Atezolizumab** 1200 mg IV Q3W (n = 67)

Placebo 600 mg IV Q3W + **Atezolizumab** 1200 mg IV Q3W (n = 68)

Until PD or loss of benefit

No crossover allowed

- Co-primary endpoints: ORR, PFS

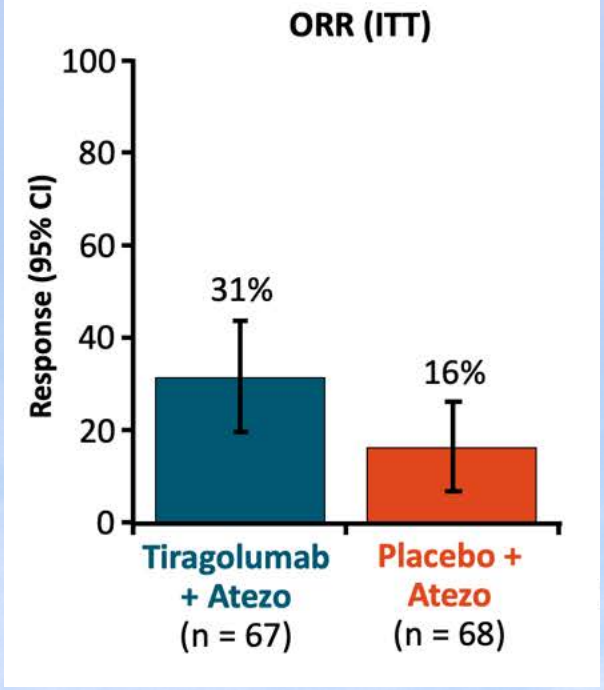
22C3 IHC pharmDx Dako assay

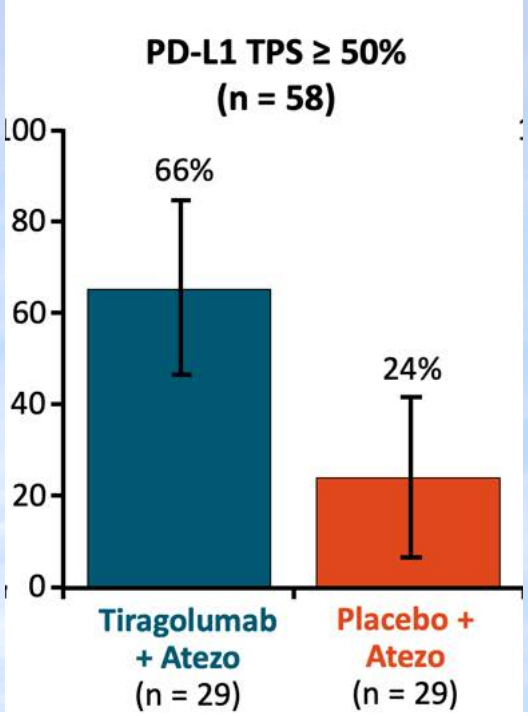
~~SP142 IHC assay~~

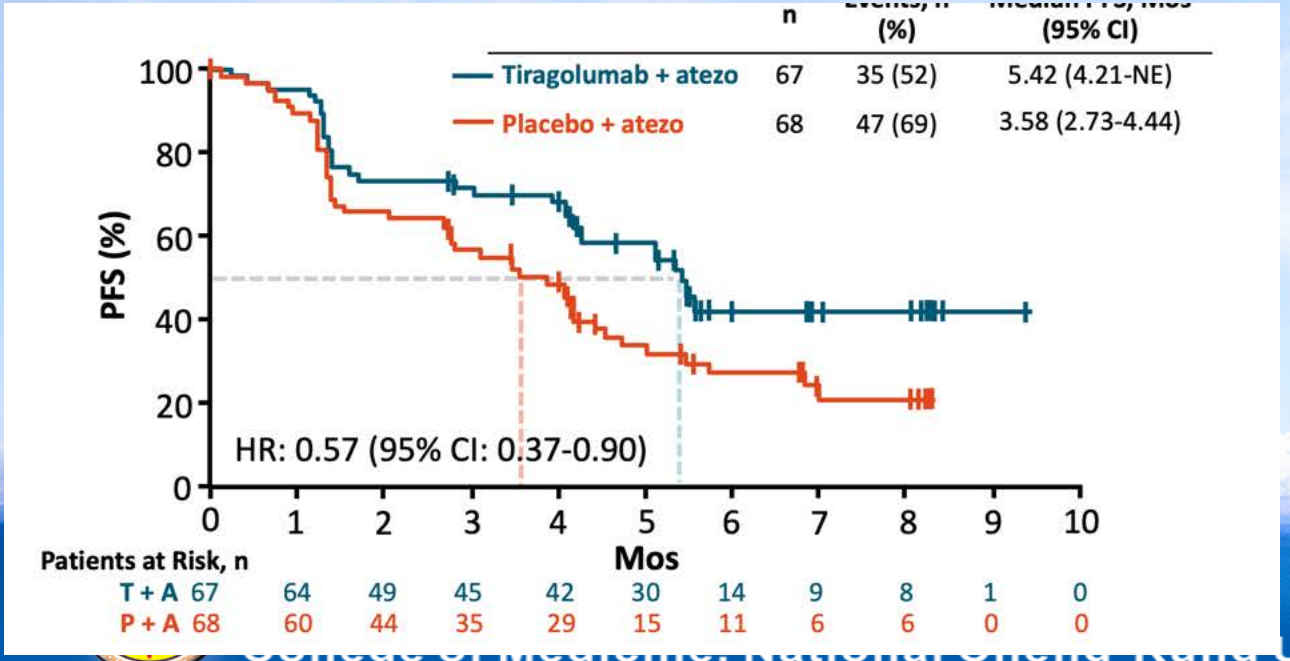
- Secondary endpoints: DoR, OS, safety, PROs
- Exploratory endpoint: efficacy by PD-L1 status

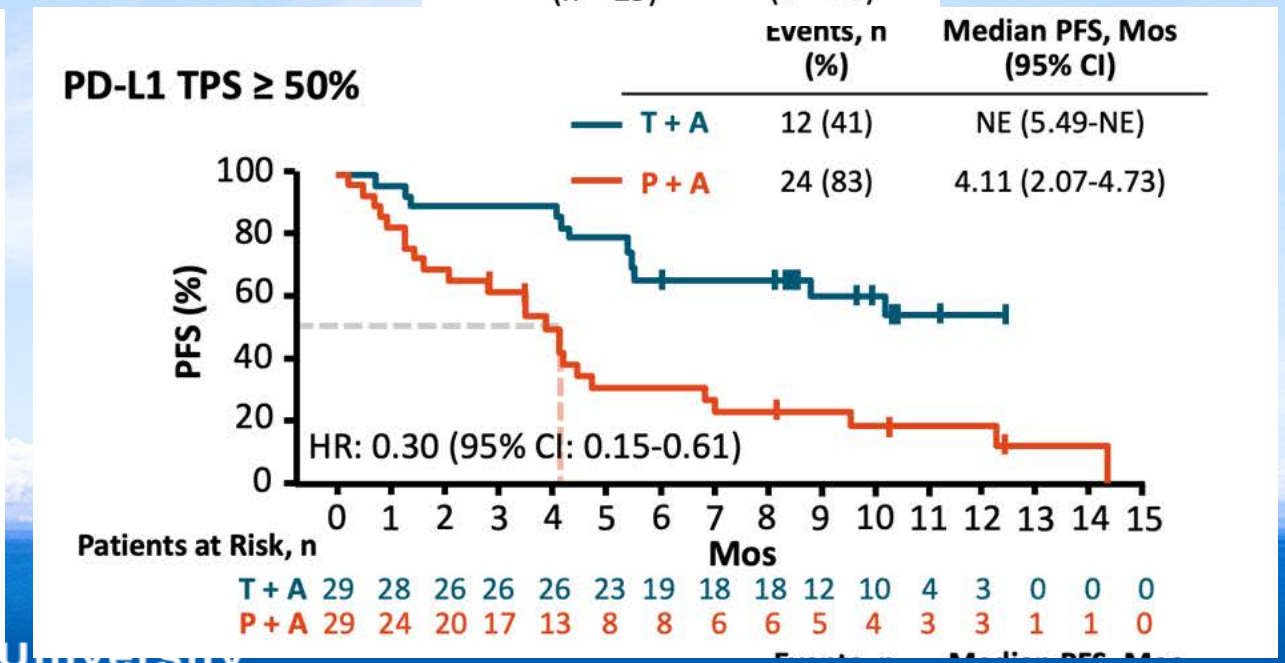
Rodriguez-Abreu. ASCO 2020. Abstr 9503.

Slide credit: clinicaloptions.com


ORR (ITT)
Response (95% CI)
100
80
60
40
20
0
31%
16%
Tiragolumab + Atezo (n = 67)
Placebo + Atezo (n = 68)


PD-L1 TPS ≥ 50% (n = 58)
100
80
60
40
20
0
66%
24%
Tiragolumab + Atezo (n = 29)
Placebo + Atezo (n = 29)


n
(%)
(95% CI)
Tiragolumab + atezo 67 35 (52) 5.42 (4.21-NE)
Placebo + atezo 68 47 (69) 3.58 (2.73-4.44)
PFS (%)
100
80
60
40
20
0
HR: 0.57 (95% CI: 0.37-0.90)
0 1 2 3 4 5 6 7 8 9 10
Mos
Patients at Risk, n
T + A 67 64 49 45 42 30 14 9 8 1 0
P + A 68 60 44 35 29 15 11 6 6 0 0


PD-L1 TPS ≥ 50%
Events, n (%)
Median PFS, Mos (95% CI)
T + A 12 (41) NE (5.49-NE)
P + A 24 (83) 4.11 (2.07-4.73)
PFS (%)
100
80
60
40
20
0
HR: 0.30 (95% CI: 0.15-0.61)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Mos
Patients at Risk, n
T + A 29 28 26 26 26 23 19 18 18 12 10 4 3 0 0 0
P + A 29 24 20 17 13 8 8 6 6 5 4 3 3 1 1 0

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

Different design | Single arm | Phase II only

Study	KN042		KN024		IMp110		EMpower		@B	Cityscape	
NSQ/SQ(%)	**61.5/38.5**		82/18		70/30		56.8/43.2		94.5/5.1	60/40	
Regimen	Pemb	C/T	Pemb	C/T	Atez	C/T	Cemi	C/T	A+Bev	Tirag+ Atezo	Atezo
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	39.2	20.4	64.1	66	24
mDoR (mo)	22.0	10.8	29.1	6.3	38.9	8.3	16.7	6.0	10.4		
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	8.2	5.7	15.9	NE	4.1
	HR=0.83		HR=0.5		HR=0.59		0.54				
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	12.4			
	HR=0.68		HR=0.62		HR=0.59		0.57				
2-yr OS(%)	45	30	51.7	34.2	45	25					

*** This page was not intended to make direct comparison between trials or to show one's superiority*

PD-L1 High Expresser (TPS≥50% or TC3/IC3)

SP142 IHC assay

22C3 IHC
PDL1>50

Study	KN042		KN024		IMp110		EMpower		@B	Cityscape	
NSQ/SQ(%)	**61.5/38.5**		82/18		70/30		56.8/43.2		94.5/5.1	60/40	
Regimen	Pemb	C/T	Pemb	C/T	Atez	C/T	Cemi	C/T	A+Bev	Tirag+ Atezo	Atezo
ORR(%)	39.1	32	46.1	31.1	40.2	28.6	39.2	20.4	64.1	66	24
mDoR (mo)	22.0	10.8	29.1	6.3	38.9	8.3	16.7	6.0	10.4		
mPFS (mo)	6.5	6.5	7.7	5.5	8.2	5.0	8.2	5.7	15.9	NE	4.1
	HR=0.83		HR=0.5		HR=0.59		0.54				
mOS (mo)	20.0	12.0	26.3	13.4	20.2	14.7	NR	12.4			
	HR=0.68		HR=0.62		HR=0.59		0.57				
2-yr OS(%)	45	30	51.7	34.2	45	25					

*** This page was not intended to make direct comparison between trials or to show one's superiority*

TASUKI
NIVOLUMAB CLINICAL TRIALS

VIRTUAL 2020 ESMO congress

ONO-4538-52 / TASUKI-52

Randomized phase III trial of nivolumab in combination with carboplatin, paclitaxel, and bevacizumab as first-line treatment for patients with advanced or recurrent non-squamous NSCLC

Jong-Seok Lee (presenting author), Shunichi Sugawara, Jin-Hyoung Kang, Hye Ryun Kim, Naoki Inui, Toyoaki Hida, Ki Hyeong Lee, Tatsuya Yoshida, Hiroshi Tanaka, Cheng-Ta Yang, Makoto Nishio, Yuichiro Ohe, Tomohide Tamura, Nobuyuki Yamamoto, Chong-Jen Yu, Hiroaki Akamatsu, Yoshinobu Namba, Naoki Sumiyoshi, and Kazuhiko Nakagawa

Study Design

Key Eligibility Criteria

- Treatment-naïve stage IIIB / IV non-squamous NSCLC patients
- No sensitizing *EGFR* or *ALK* alterations
- PD-L1 all comer
- ECOG PS 0–1

N = 550

R 1:1

Nivolumab / Carboplatin / Paclitaxel / Bevacizumab[a)]
NIVO : 360 mg IV q3w

SD, PR, CR

Nivolumab / Bevacizumab

Treatment was continued until PD, unacceptable toxicity

Placebo / Carboplatin / Paclitaxel / Bevacizumab[a)]

SD, PR, CR

Placebo / Bevacizumab

- **Primary Endpoint:**
  - PFS assessed by IRRC[b)]
- **Secondary Endpoint:**
  - OS, ORR, Safety

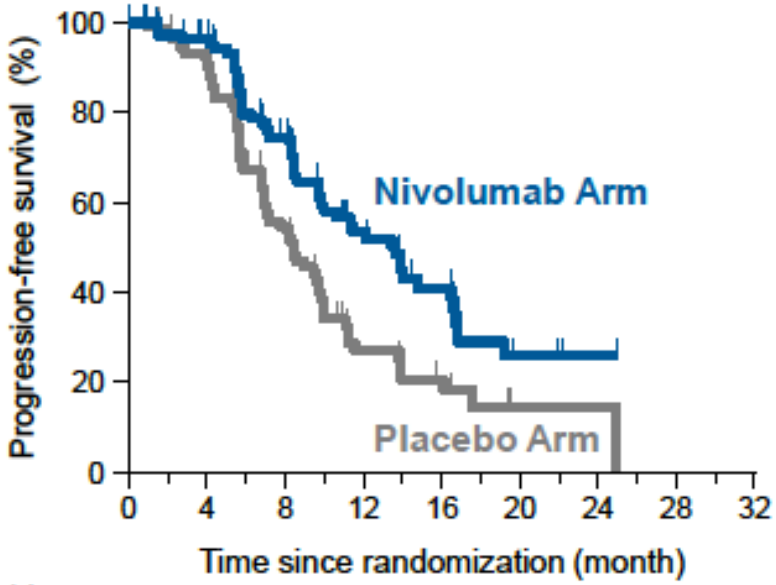
Stratification Factors

- **PD-L1 (IHC 28-8) : ≥ 50%, 1%–49%, < 1% or indeterminate**
- **ECOG PS : 0, 1**
- **Sex : Male, Female**

a) Carboplatin (AUC 6), paclitaxel (200 mg/m^2), and bevacizumab (15 mg/kg) every 3 weeks for up to 6 cycles; b) Independent Radiographic Review Committee

PFS by PD-L1 Expression Level

PD-L1 < 1% or indeterminate

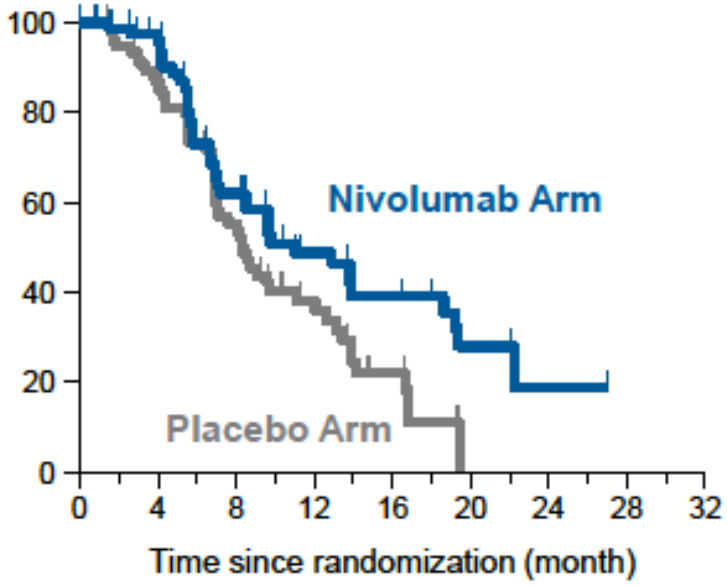


No. at risk

Nivolumab Arm	120	98	65	34	18	5	1	0	0
Placebo Arm	120	100	46	14	8	1	1	0	0

	Nivolumab Arm N = 120	Placebo Arm N = 120
Median PFS, mo (95% CI)	13.6 (9.8–16.6)	8.4 (7.0–9.8)
HR (95% CI)	0.55 (0.38–0.78)	

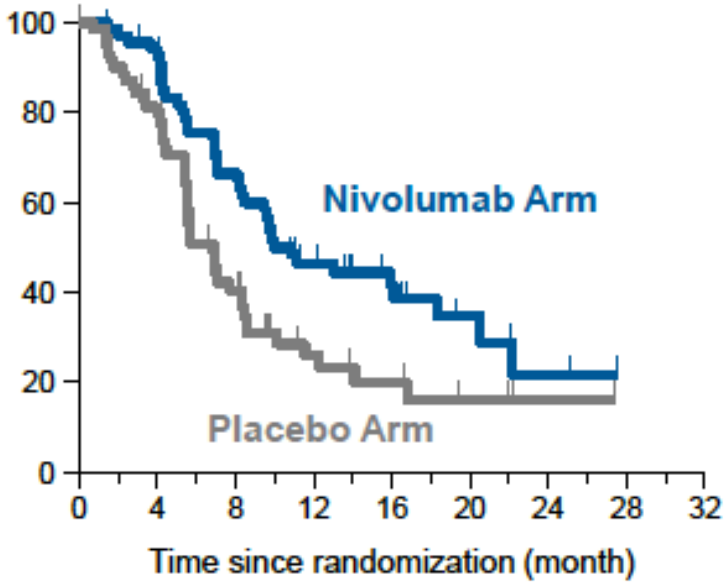
PD-L1 1%–49%



Nivolumab Arm	82	67	39	21	13	4	1	0	0
Placebo Arm	81	62	35	17	7	0	0	0	0

	Nivolumab Arm N = 82	Placebo Arm N = 81
Median PFS, mo (95% CI)	11.0 (7.2–18.6)	8.4 (7.0–11.1)
HR (95% CI)	0.63 (0.42–0.96)	

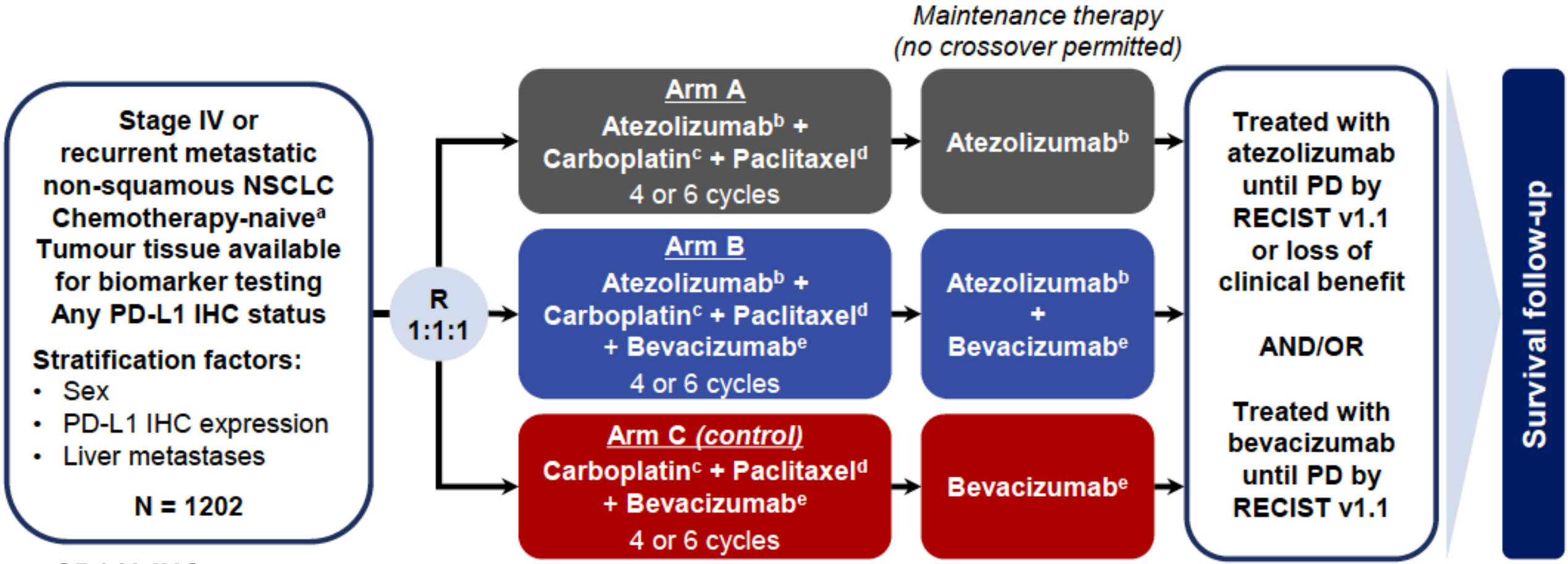
PD-L1 ≥ 50%



Nivolumab Arm	73	61	41	24	14	6	2	0	0
Placebo Arm	74	53	23	10	6	3	1	0	0

	Nivolumab Arm N = 73	Placebo Arm N = 74
Median PFS, mo (95% CI)	9.9 (8.3–18.3)	6.9 (5.6–8.3)
HR (95% CI)	0.55 (0.36–0.83)	

IMpower150 study design

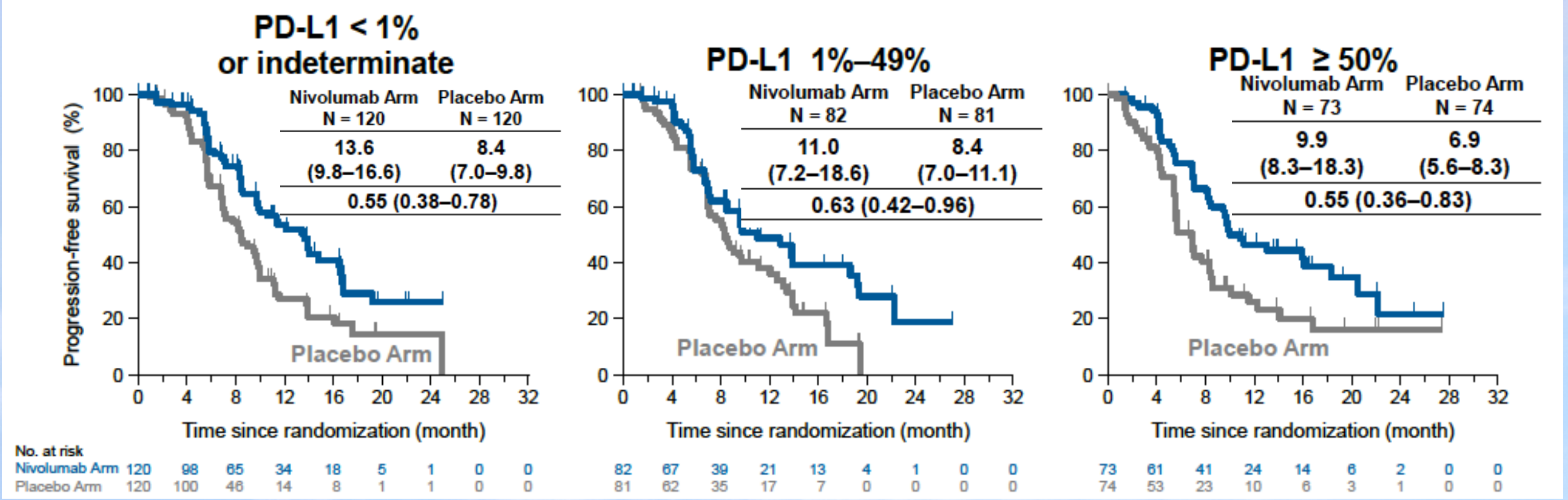


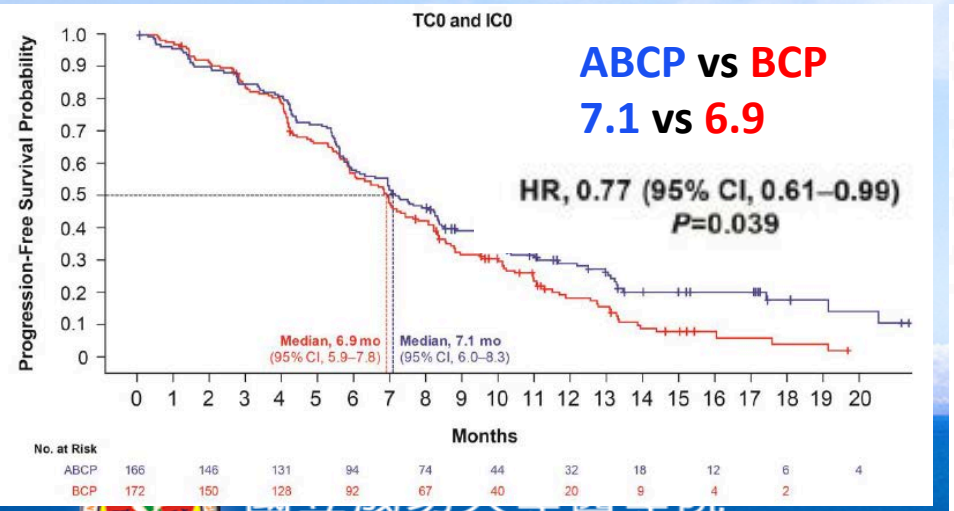
SP142 IHC assay

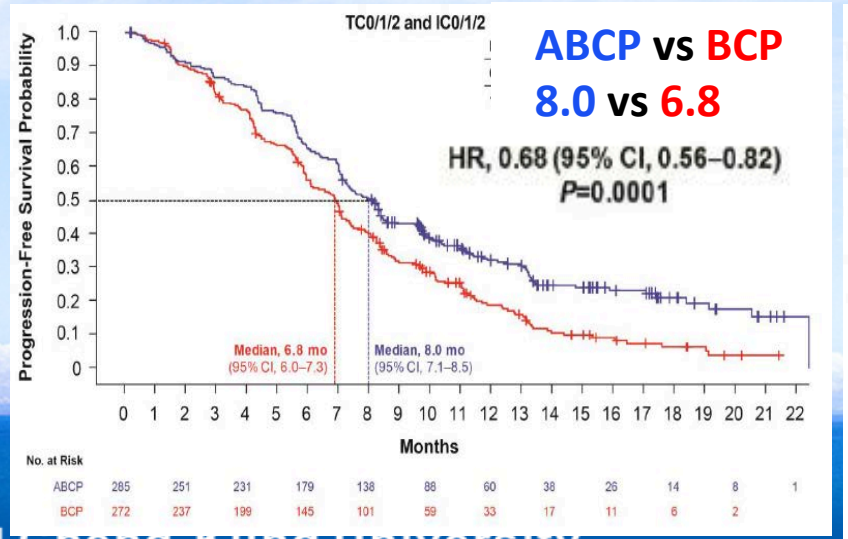
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

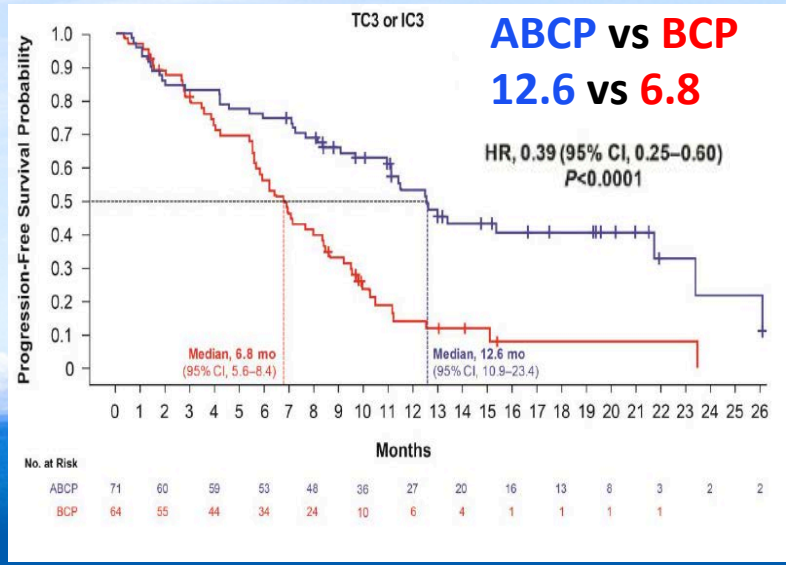
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.





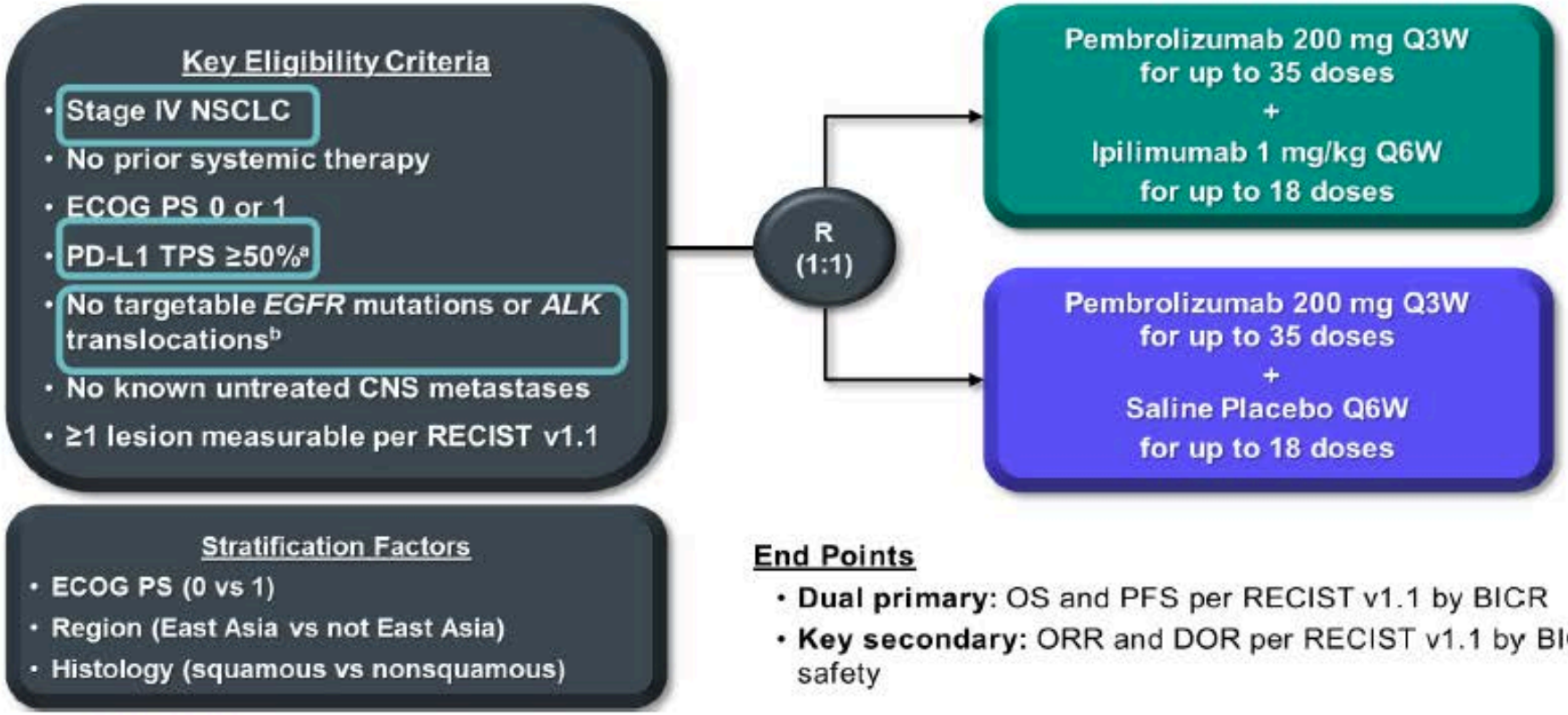




*** This page was not intended to make direct comparison between trials or to show one's superiority*

KEYNOTE-598 Study Design

Phase 3, global, randomised, open-label, multicentre study



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

[a]Assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent).
[b]Patients with *ROS1* rearrangement were also excluded if *ROS1* testing and treatment were locally approved and accessible.
KEYNOTE-598 ClinicalTrials.gov identifier, NCT03302234. BICR, blinded independent central review.

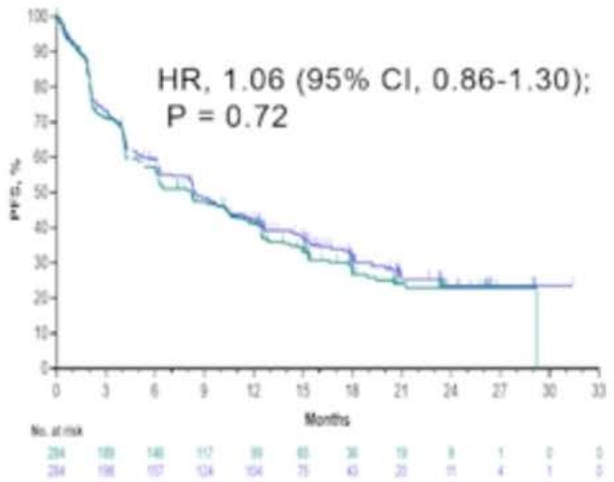
Efficacy of Pembro-Ipi vs Pembro in PD-L1 expression ≥ 50% NSCLC patients

Summary of Response

	Pembro-Ipi N = 284	Pembro-Pbo N = 284
ORR, % (95% CI)	45.4% (39.5-51.4)	45.4% (39.5-51.4)
	Best response, n (%)	
CR	13 (4.6%)	8 (2.8%)
PR	116 (40.8%)	121 (42.6%)
SD	70 (24.6%)	73 (25.7%)
PD	51 (18.0%)	44 (15.5%)

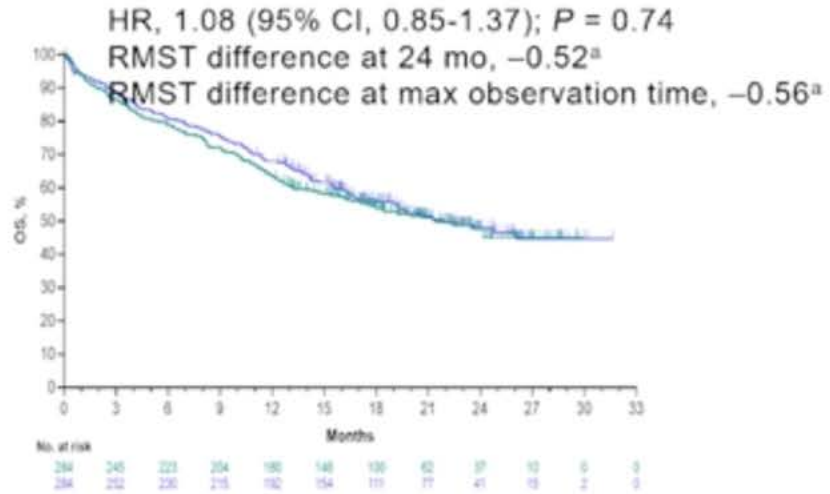
PFS by BICR

	Median (95% CI)
Pembro-Ipi	8.2 mo (6.0-10.5)
Pembro-Pbo	8.4 mo (6.3-10.5)

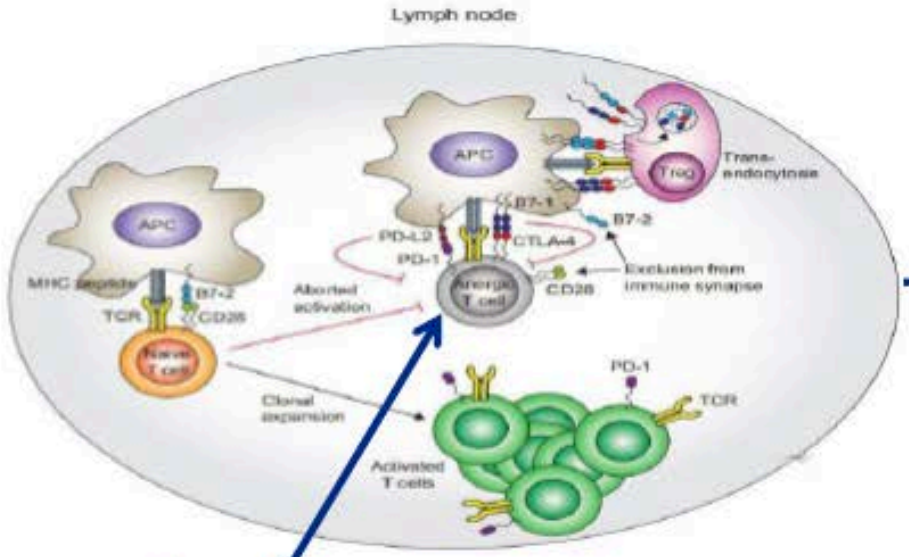


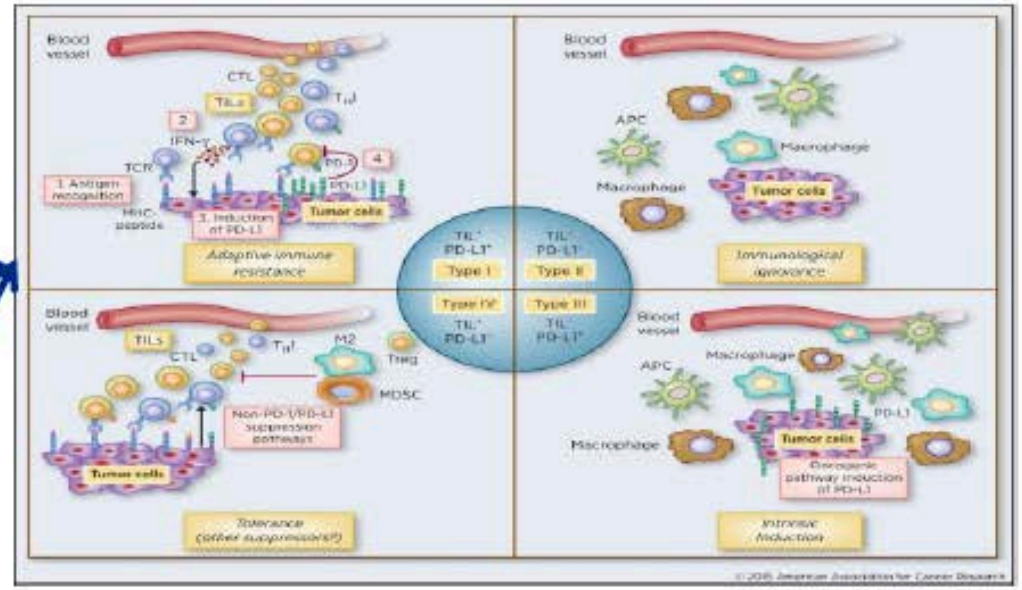
OS by BICR

	Median (95% CI)	RMST at 24 mo	RMST at Max Time
Pembro-Ipi	21.4 mo (16.6-NR)	16.09 mo	18.76 mo
Pembro-Pbo	21.9 mo (18.0-NR)	16.61 mo	19.32 mo



Potential rationale for the non-beneficial treatment of double blockade in PD-L1≥50% NSCLC population





CTLA-4 blockade allows for activation and proliferation of extra T-cell clones

PD-L1≥50% population presents with high level of pre-actived CD8+T cells already, hence additional CTLA-4 blockade may not bring clinical benefits as expected

1, Teng MW. Cancer Res. 2015 Jun 1;75(11):2139-45.
2, Andrew M Intlekofer. J Leukoc Biol . 2013 Jul;94(1):25-39.

National Cancer Centre Singapore
SingHealth

Randomised phase 2 study of Nivolumab (N) versus Nivolumab and Ipilimumab (NI) combination in *EGFR* mutant NSCLC

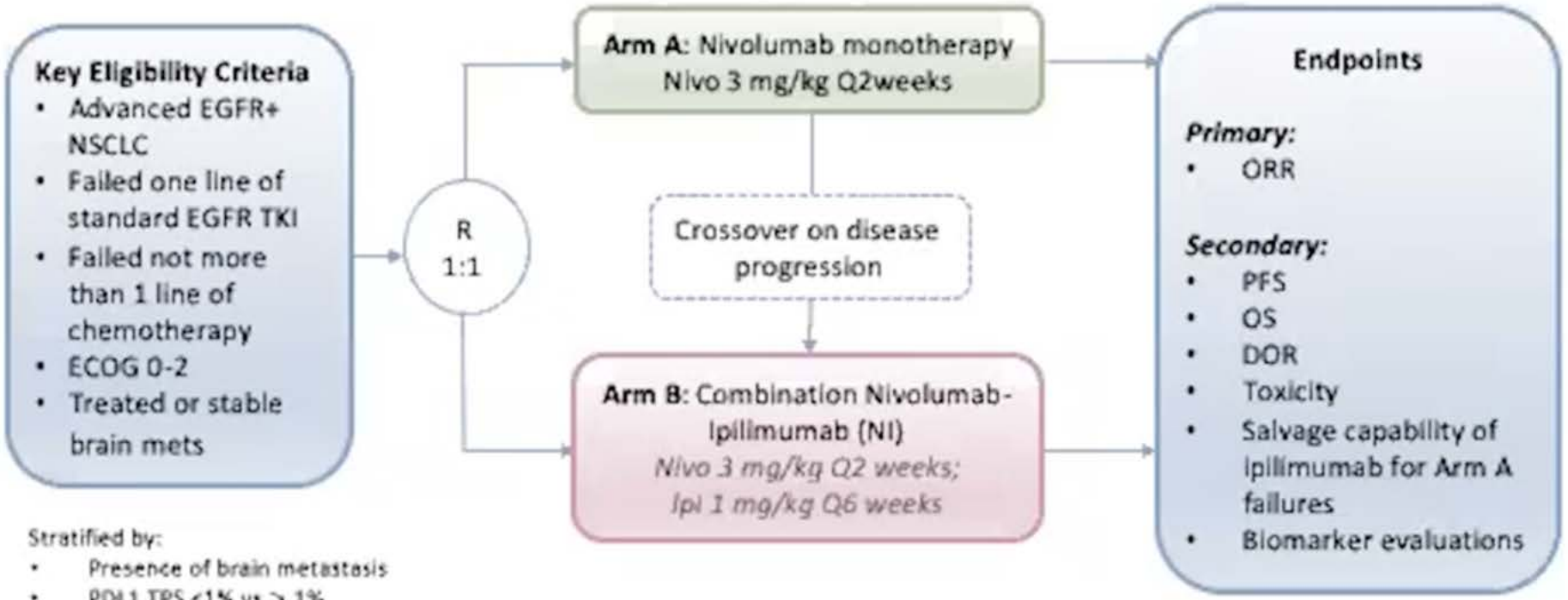
Gillianne G.Y. Lai[1], Jacob J.S. Alvarez[2], Jia Chi Yeo[2], Ngak Leng Sim[2], Aaron C. Tan[1], Siqin Zhou[1], Lisda Suteja[1], Tze Wei Lim[1], Neha Rohatgi[2], Joe P.S. Yeong[3], Angela Takano[3], Kiat Hon Lim[3], Apoorva Gogna[3], Chow Wei Too[3], Kun Da Zhuang[3], Amit Jain[1], Wan Ling Tan[1], Ravindran Kanesvaran[1], Quan Sing Ng[1], Mei Kim Ang[1], Tanujaa Rajasekaran[1], Lanying Wang[1], Chee Keong Toh[1], Wan-Teck Lim[1], Wai Leong Tam[2], Florent Ginhoux[4], Sze Huey Tan[1], Anders M.J. Skanderup[2], Daniel S.W. Tan[1], Eng-Huat Tan[1]

[1]National Cancer Centre Singapore, [2]Genome Institute of Singapore,
[3]Singapore General Hospital, [4]Singapore Immunology Network

IASLC 2020 World Conference on Lung Cancer Singapore
JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

Randomised Phase II Study of Nivolumab(N) versus Nivolumab and Ipilimumab(NI) combination in EGFR Mutant NSCLC

Study Design



Stratified by:
- Presence of brain metastasis
- PDL1 TPS <1% vs ≥ 1%

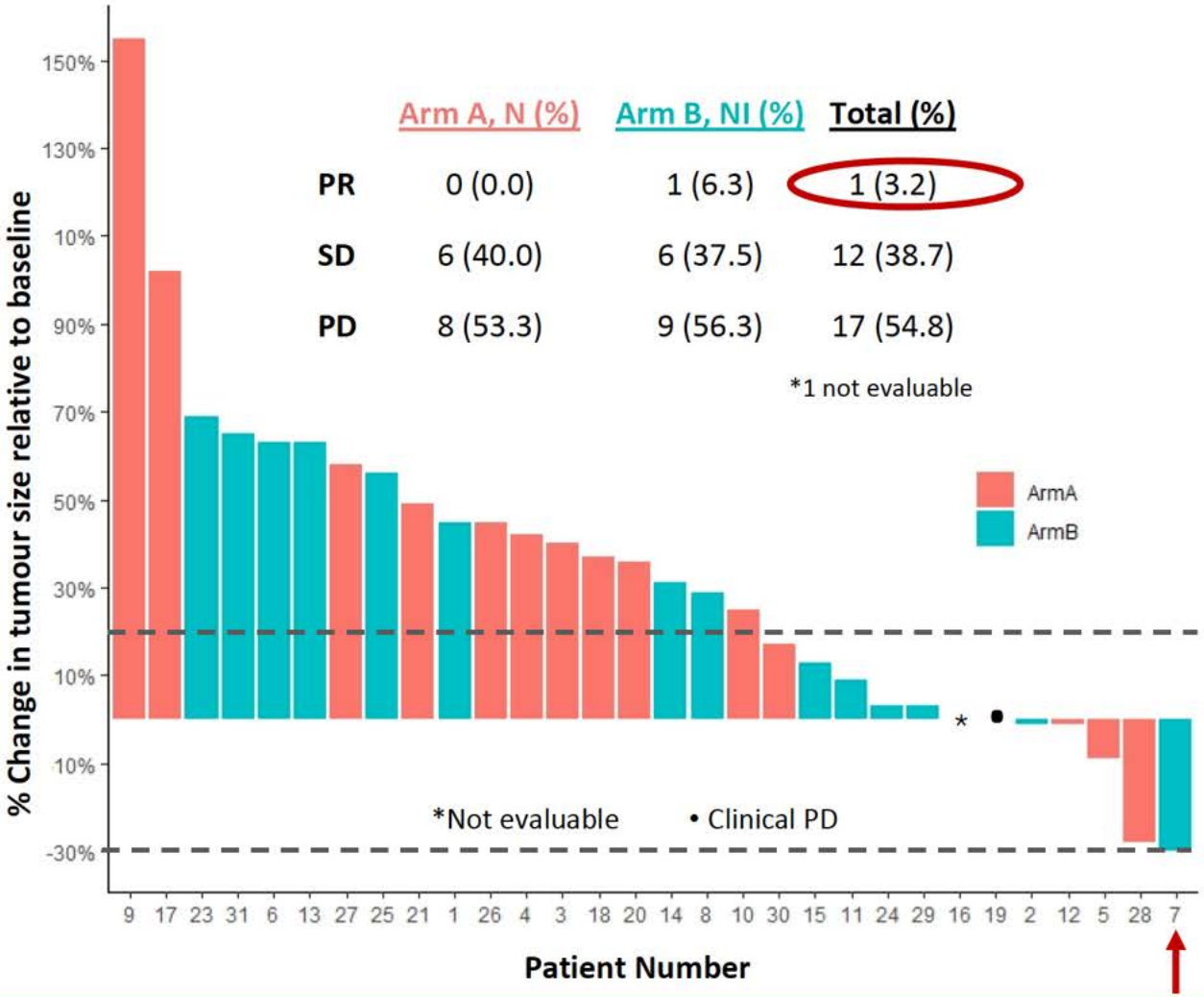
Assuming 10% ORR in A and 30% ORR in B, with a two-sided significance level of 5% and power of 90%,
target of 92 randomized patients per arm

Gillianne Lai
MBBS, MRCP, MMed

Best Overall Response

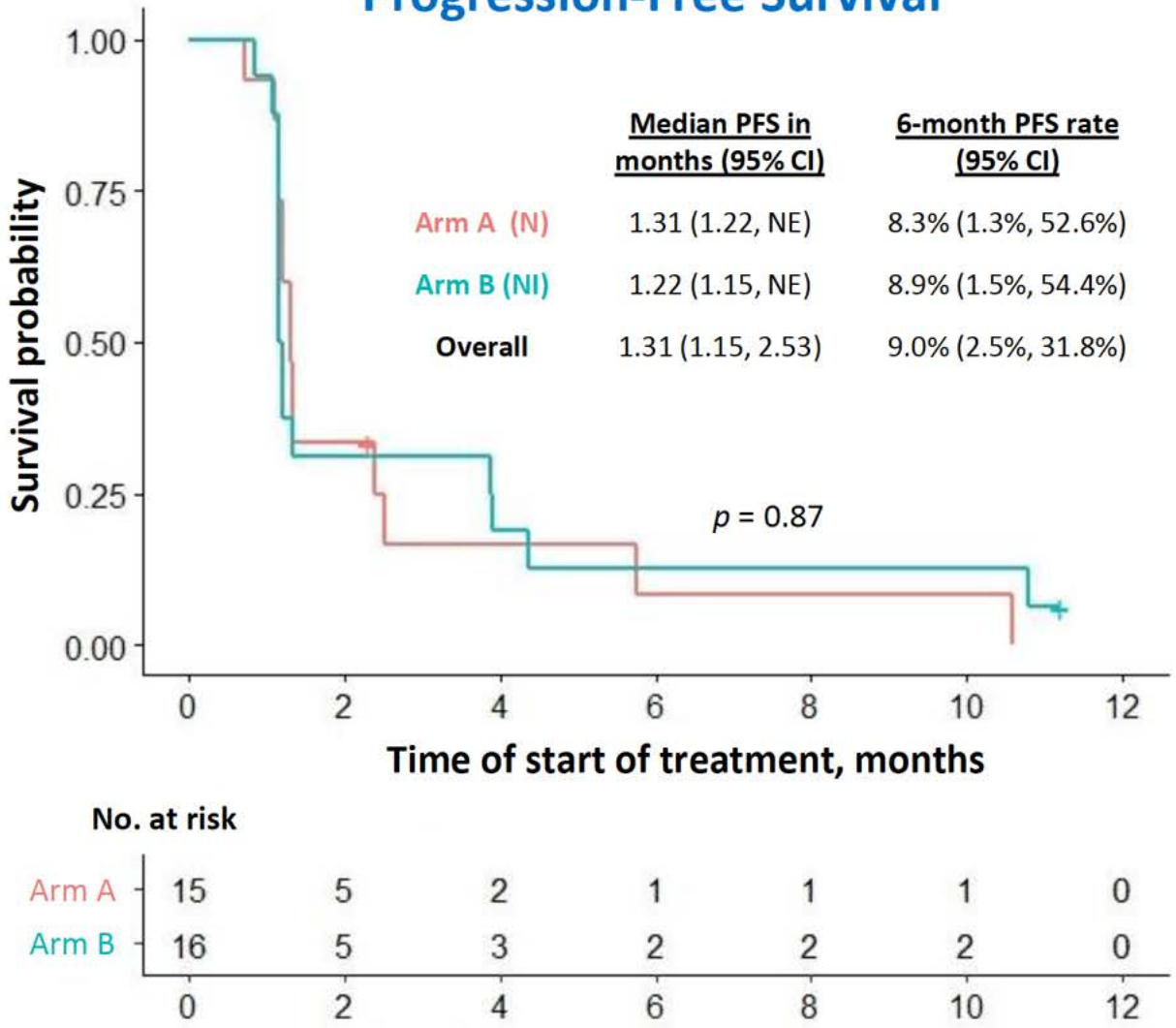
	Arm A, N (%)	Arm B, NI (%)	Total (%)
PR	0 (0.0)	1 (6.3)	1 (3.2)
SD	6 (40.0)	6 (37.5)	12 (38.7)
PD	8 (53.3)	9 (56.3)	17 (54.8)

*1 not evaluable



Progression-Free Survival

	Median PFS in months (95% CI)	6-month PFS rate (95% CI)
Arm A (N)	1.31 (1.22, NE)	8.3% (1.3%, 52.6%)
Arm B (NI)	1.22 (1.15, NE)	8.9% (1.5%, 54.4%)
Overall	1.31 (1.15, 2.53)	9.0% (2.5%, 31.8%)



National Cancer Centre Singapore
SingHealth

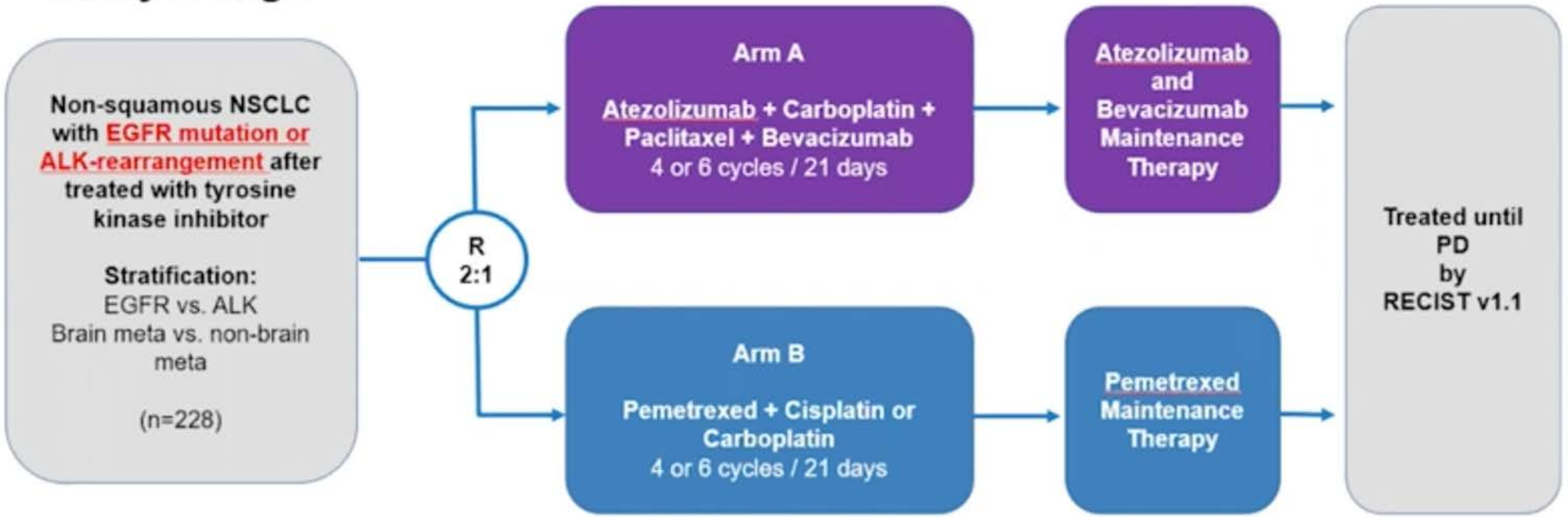
Conclusion

- **Immune checkpoint inhibition did not result in clinical benefit in EGFR TKI-resistant NSCLC**
- **GEP and TMB did not predict for response to checkpoint inhibition in oncogene-addicted NSCLC**
- **The use of immunotherapy post-EGFR TKI did not result in increased safety concerns**
- **Intracranial failure is an important consideration when choosing immunotherapy for *EGFR* mutant NSCLC patients**
  - Combinatorial approaches may be a potential solution

ATLAS:

Randomized phase III trial comparing atezolizumab/bevacizumab/carbo/taxol vs pemetrexed/platinum in EGFR TKI failed NSCLC (Korea multicenter trial)

Study Design



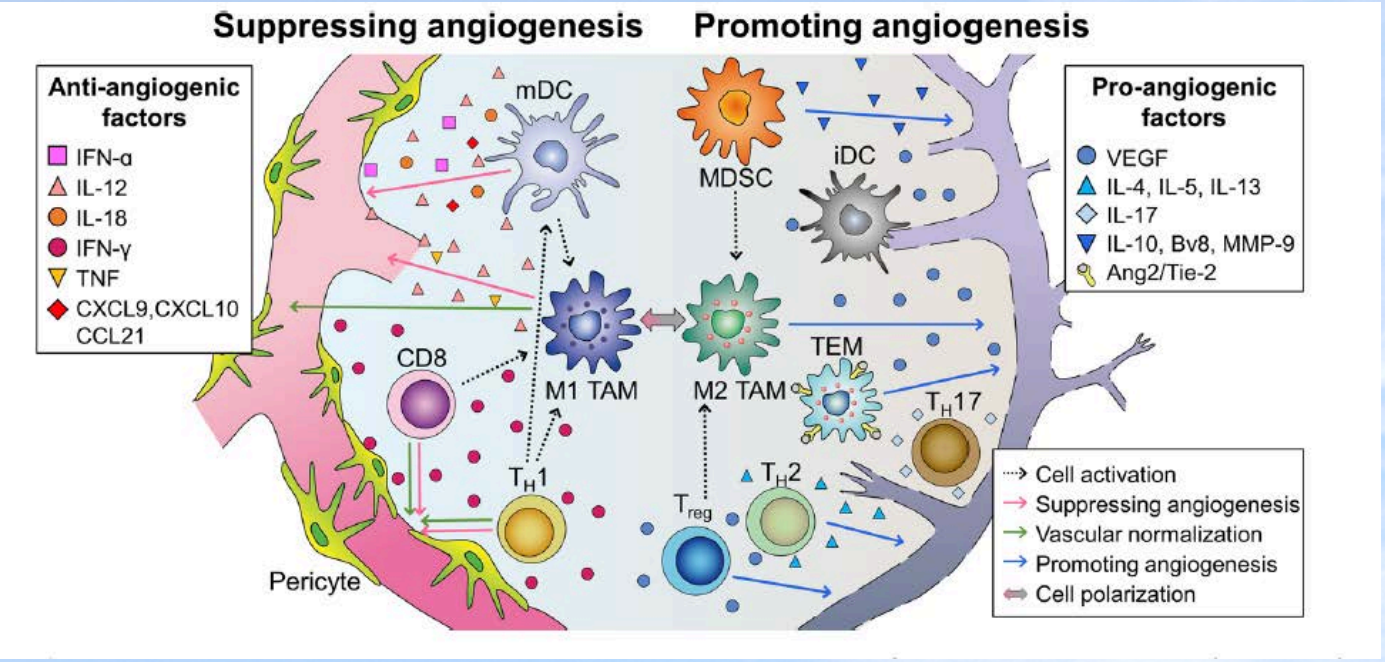
Co-primary endpoint:
Progression-free survival according to RECIST v1.1
Secondary endpoint:
Overall survival, objective response rate, duration of response according to RECIST v1.1, quality of life
OS rate at 1 and 2 years, PFS rate at 1 and 2 years

Exploratory biomarker analysis: PD-L1 expression profile, gene expression profile, TMB, blood based biomarker

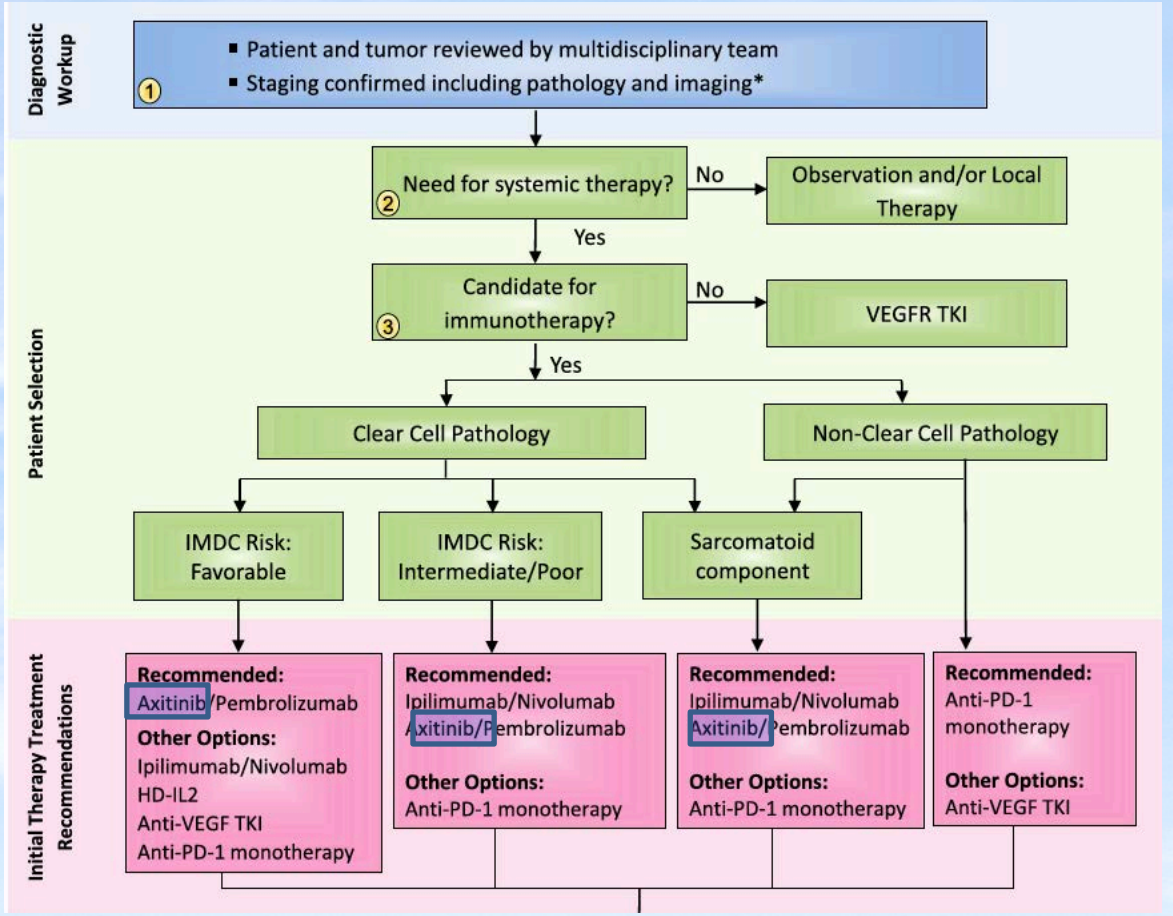
P.I Myung-Ju Ahn

- First line I/O or combination for no driver mutation NSCLC
- What is the treatment strategy for special situation?
- New drug or new combination
- Novel target?

1. Anti-angiogenesis:



RCC



Journal for ImmunoTherapy of Cancer volume 7, Article number: 354 (2019

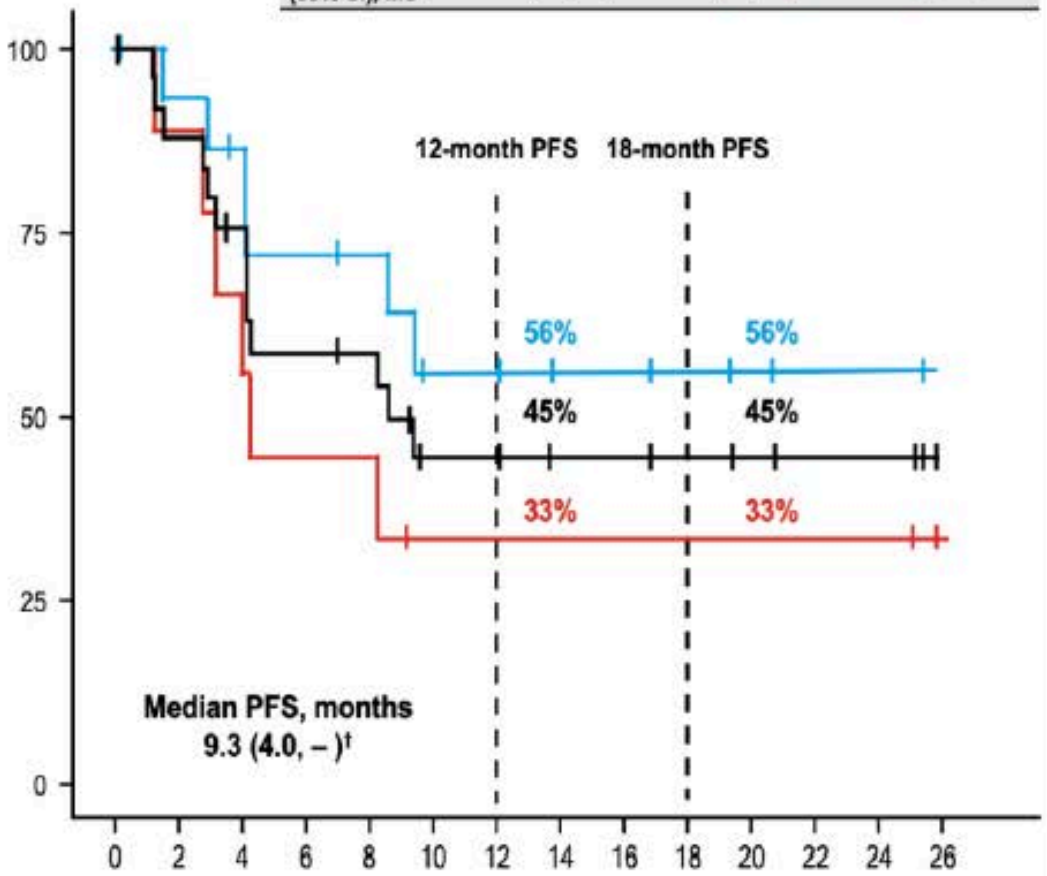
Ramucirumab: mAb targeting VEGFR2

Phase 1 study of ramucirumab/pembrolizumab in advanced treatment-naive NSCLC

Herbst JTO 2020

Response	PD-L1 TPS 1%-49% (n = 9)	PD-L1 TPS ≥ 50% (n = 16)	Total (N = 26)[a]
BOR, n (%; 95% CI)			
CR	0 (0; 0-33.6)	1 (6.3; 0.2-30.2)	1 (3.8; 0.1-19.6)
PR	2 (22.2; 2.8-60)	8 (50.0; 24.7-75.3)	10 (38.5; 20.2-59.4)
SD	6 (66.7; 29.9-92.5)	5 (31.3; 11-58.7)	11 (42.3; 23.4-63.1)
PD	1 (11.1; 0.3-48.2)	1 (6.3; 0.2-30.2)	3 (11.5; 2.4-30.2)
NA	0	1 (6.3)	1 (3.8)
ORR, % (95% CI)	2 (22.2; 2.8-60)	9 (56.3; 29.9-80.2)	11 (42.3; 23.4-63.1)
DCR,[b] % (95% CI)	8 (88.9; 51.8-99.7)	14 (87.5; 61.7-98.4)	22 (84.6; 65.1-95.6)

PFS	All Patients (n = 26)	PD-L1 TPS 1%-49% (n = 9)	PD-L1 TPS ≥50% (n = 16)
# Events (%)	11 (42.3)	5 (55.6)	5 (31.3)
Median PFS (95% CI), mo	9.3 (4.0, –)[†]	4.2 (1.2, –)	– (4.0, –)



Phase III LEAP-006 safety run-in (Part 1): 1L pembrolizumab+CT with lenvatinib for metastatic NSCLC *Nishio ESMO 2020*

Figure 1. LEAP-006 Study Design

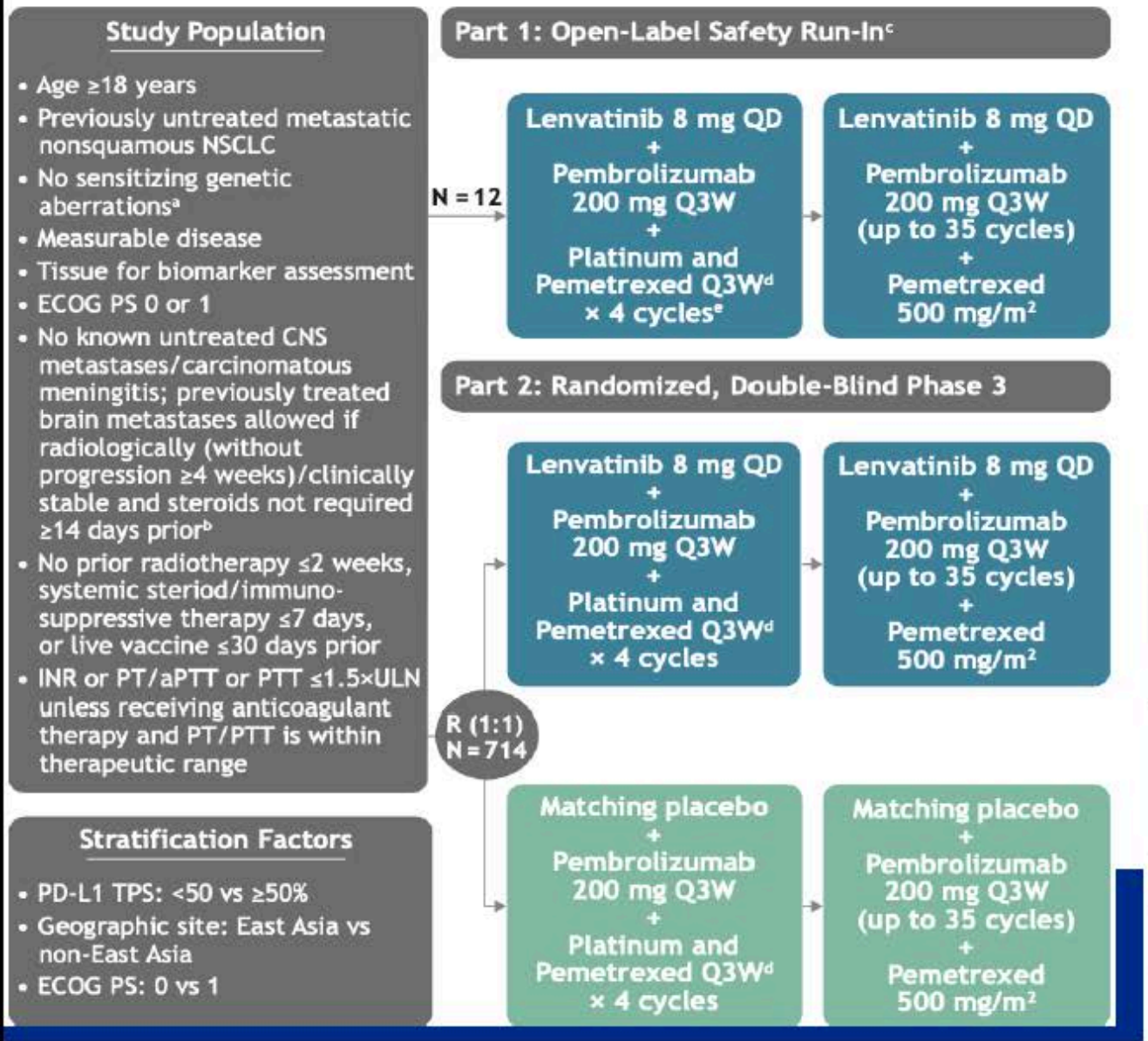


Table 3. Summary of Safety and Tolerability

	N = 13[a]
Treatment-related AEs	12 (92.3)
Leading to death[b]	0
Leading to discontinuation of any study treatment	1 (7.7)
Leading to discontinuation of all study treatment	0
Grade 3–5 AEs occurring in ≥2 patients[c]	7 (53.8)
Hypertension	4 (30.8)
Hyponatremia	2 (15.4)
Pneumonia	2 (15.4)

Table 4. Best Overall Response (BICR Assessment Per RECIST Version 1.1)

	N = 13	
	n (%)	95% CI[a]
Overall response (CR + PR)	9 (69.2)	38.6–90.9
CR	0	0–24.7
PR	9 (69.2)	38.6–90.9
SD	3 (23.1)	5.0–53.8
Disease control (CR + PR + SD)	12 (92.3)	64.0–99.8
Progressive disease	0	0.0–24.7
Not evaluable[a]	1 (7.7)	0.2–36.0

Cabozantinib: multitargeted TKI of VEGFR, MET, RET, ROS and TAM family

Cabozantinib/atezolizumab in previously-ICI-treated NSCLC: Cohort 7 COSMIC-021

NSCLC Cohort 7

- Radiographic progression on or after one prior ICI treatment
- ≤2 lines of prior systemic anticancer therapy for metastatic NSCLC
- ECOG PS 0–1
- Patients with known *EGFR* mutations, *ALK* or *ROS1* rearrangement, or *BRAF V600E* mutation were excluded

→ Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30) → Extended enrollment* (N=50)

Confirmation of initial results

Table 2. Tumor Response per Investigator by RECIST v1.1

	NSCLC Cohort 7 (N=30)
Objective response rate (80% CI), %	27 (16–40)
Best overall response, n (%)	
Partial response	8 (27)
Stable disease	17 (57)
Progressive disease	4 (13)
Not evaluable	1 (3.3)
Disease control rate, n (%)	25 (83)
Duration of objective response, median (range), months	5.7 (2.6–6.9)
Time to objective response, median (range), months	1.4 (1–4)

Disease control rate = complete response + partial response + stable disease. ORR was similar between patients with 1 vs 2 prior lines of therapy (PR/SD/PD/unknown 4/8/3/0 for 15 patients with 1 prior line and 4/9/1/1 for 15 patients with 2 prior lines).

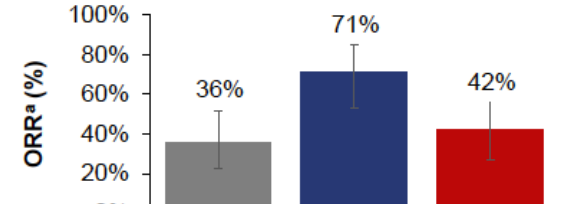
Table 4. Immune-Related Adverse Events

	NSCLC Cohort 7 (N=30)	
	Any Grade	Grade 3
Any AE, n (%)	6 (20)	0
Hyperthyroidism	1 (3.3)	0
Hypothyroidism	1 (3.3)	0
Lipase increased	1 (3.3)	0
Myocarditis*	1 (3.3)	0
Pain	1 (3.3)	0
Pneumonitis*	1 (3.3)	0
Rash	1 (3.3)	0

Neal ASCO 2020

1. Anti-angiogenesis:

ORR and DOR in *EGFR*-mt patients



	Atezo + CP	Atezo + bev + CP	Bev + CP
Median DOR (range), mo	5.6 (2.6–15.2)	11.1 (2.8–18.0)	4.7 (2.6–13.5)

- The addition of bevacizumab to atezolizumab and chemotherapy almost doubled the overall response rate and duration of response in *EGFR*-mt patients

	VEGFR			PDGFR		FGFR				Others
	1	2	3	α	β	1	2	3	4	
Sorafenib	-	+	+	-	+	-	-	-	-	c-KIT(+), FLT3(+)
Sunitinib	+	+	+	+	+	-	-	-	-	FLT3(+), c-KIT(+), RET(+)
Axitinib	+	+	+	-	+	-	-	-	-	c-KIT(+)
Vatalanib	+	+	+	-	+	-	-	-	-	c-KIT(+)
Nintedanib	+	+	+	+	+	+	+	+	-	FLT3(+), Src(+)
Pazopanib	+	+	+	+	+	+	-	+	-	c-KIT(+)
Vandetanib	+	+	+	-	+	+	-	-	-	EGFR(+), RET(+)
Apatinib	+	+	+	-	+	+	-	-	-	FLT3(+)
Fuquintinib	+	+	+	-	-	+	-	-	-	RET(+)
Anlotinib	+	+	+	+	+	+	+	+	+	c-KIT(+)

- **Biomarker for anti-angiogenesis combination?**
- **In RCC, but not in NSCLC**
- **Multiple kinase inhibitor + I/O, higher toxicity**

1. Anti-angiogenesis:

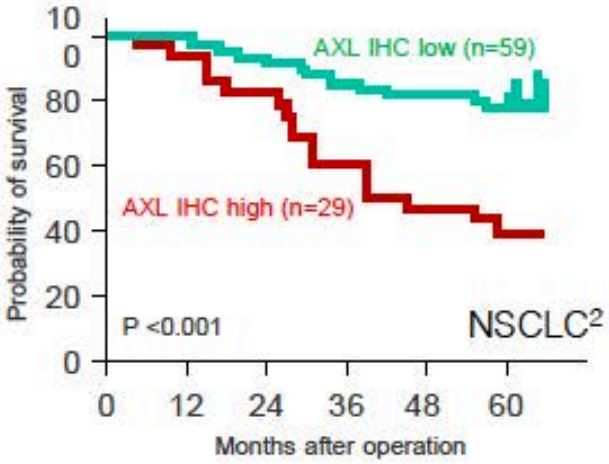
2. Selective AXL inhibitor

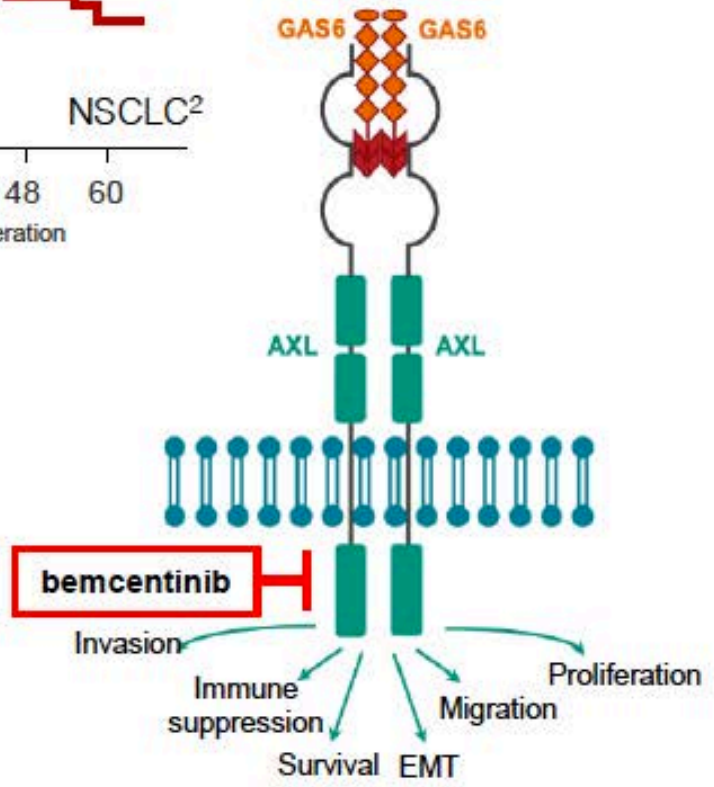
A phase II study of the oral selective AXL inhibitor bemcentinib with pembrolizumab in refractory patients with advanced NSCLC (Abstract #3647)

Dr. Matthew Krebs, MB ChB, FRCP, PhD
The University of Manchester and The Christie NHS Foundation Trust
UK

Study Rationale

- AXL drives tumor **EMT and resistance to CTL-mediated tumor cell killing**[1]
- AXL receptor tyrosine kinase is **negatively prognostic** in many cancers including NSCLC[2]
- AXL expression is associated with **anti-PD-1 therapy failure** in melanoma patients[3]
- AXL is expressed by immuno-suppressive **tumor-associated M2 macrophages and dendritic cells**[4]
- Bemcentinib is a first-in-class highly **selective, potent, oral small molecule AXL kinase inhibitor**
- Bemcentinib **reverses EMT, repolarizes TAMs and potentiates immunotherapy** in mouse models[4]





[1]Terry, 2019; [2]Ishikawa, 2012, [3]Hugo, 2016; Davidsen,2017; [4]Ludwig, 2018, Davidsen, submitted

Study Design

Cohort A • Previously treated with a platinum-containing chemotherapy • CPI-naïve • Demonstrable PD	**Interim Analysis** **Cohort A** **Stage 1** **N=22 patients** (each patient has the potential for at least 24 weeks follow-up)	**Final Analysis** **Cohort A** **Stage 2** **N=48 patients** (each patient has the potential for at least 24 weeks follow-up)
Cohort B • Previously treated with PD-L1 or PD-1 inhibitor mono- therapy • ≥12 weeks clinical benefit followed by PD	**Interim Analysis** **Cohorts B** **Stage 1** **N=16 patients** (each patient has the potential for at least 24 weeks follow-up)	**Final Analysis** **Cohorts B** **Stage 2** **N=29 patients** (each patient has the potential for at least 24 weeks follow-up)
Cohort C • Previous 1st line combination checkpoint inhibitor + platinum doublet • ≥12 weeks clinical benefit on 1st line therapy followed by PD	**Interim Analysis** **Cohorts C** **Stage 1** **N=13 patients** (each patient has the potential for at least 24 weeks follow-up)	**Final Analysis** **Cohorts C** **Stage 2** **N=29 patients** (each patient has the potential for at least 24 weeks follow-up)

Cohort B

Patient summary / disposition	
Median treatment duration, weeks	8.9
Ongoing, n (%)	2 (9)
Discontinued, n (%)**	20 (91)
Radiologically evaluable patients*, n (%)**	19 (86)
cAXL positive	7 (37)
cAXL negative	7 (37)
cAXL not evaluable or awaiting data	5 (26)

Patient / disease characteristics	n=22
Male, n (%)	17 (77.3)
Age, median (range), years	63.5 (40-86)
Smoking history	
Never smoked	0 (0)
Race, n (%)	
White	20 (90.9)
Black	2 (9.1)
ECOG PS, n (%)	
0	8 (36.4)
1	14 (63.6)
Prior lines of treatment, median (range)	2 (1-3)
Prior platinum-based chemotherapy	
Yes	12 (54.5)
No	10 (45.5)
Mutations, n (%)	
KRAS	4 (18.2)
BRAF	2 (9.1)

Cohort B

Patient summary / disposition	
Median treatment duration, weeks	8.9
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Discontinued**, n (%)	20 (91)
Radiologically evaluable patients***, n (%)	19 (86)
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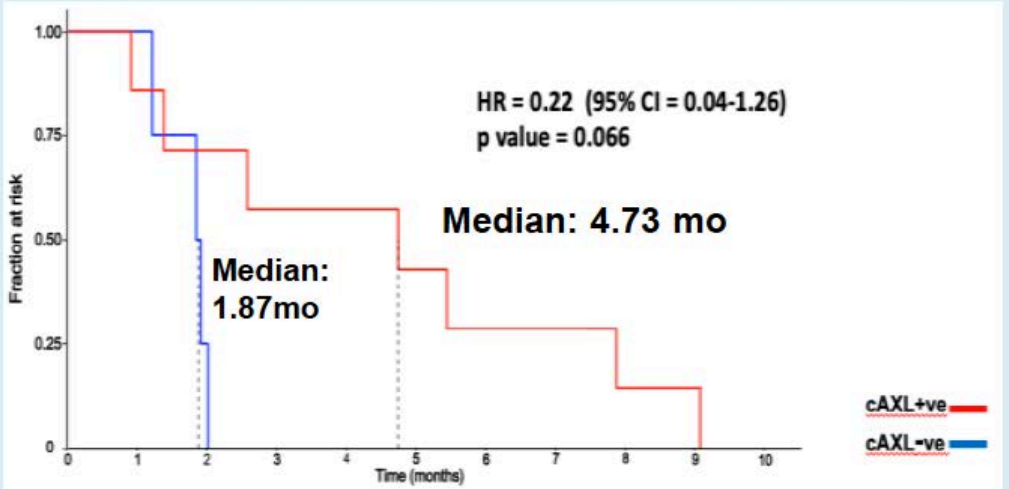
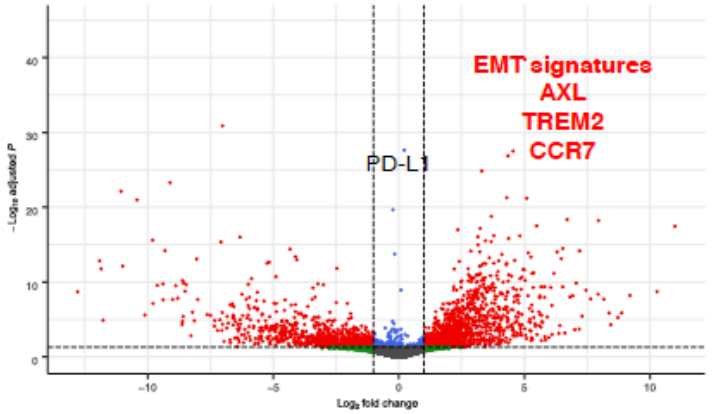
Yes	12 (54.5)
No	10 (45.5)
Mutations, n (%)	
KRAS	4 (18.2)
BRAF	2 (9.1)

Previously reported PFS, Cohort B1 (Gabra, *et al.* Next Gen IO Congress, 2020.):



Clinical translational findings

Whole tumor gene expression of Cohort B1 patients benefiting from bemcentinib-pembrolizumab



Volcano Plot: Differential gene expression analysis of patients showing benefit (n=5) vs patients with PD (n=3)

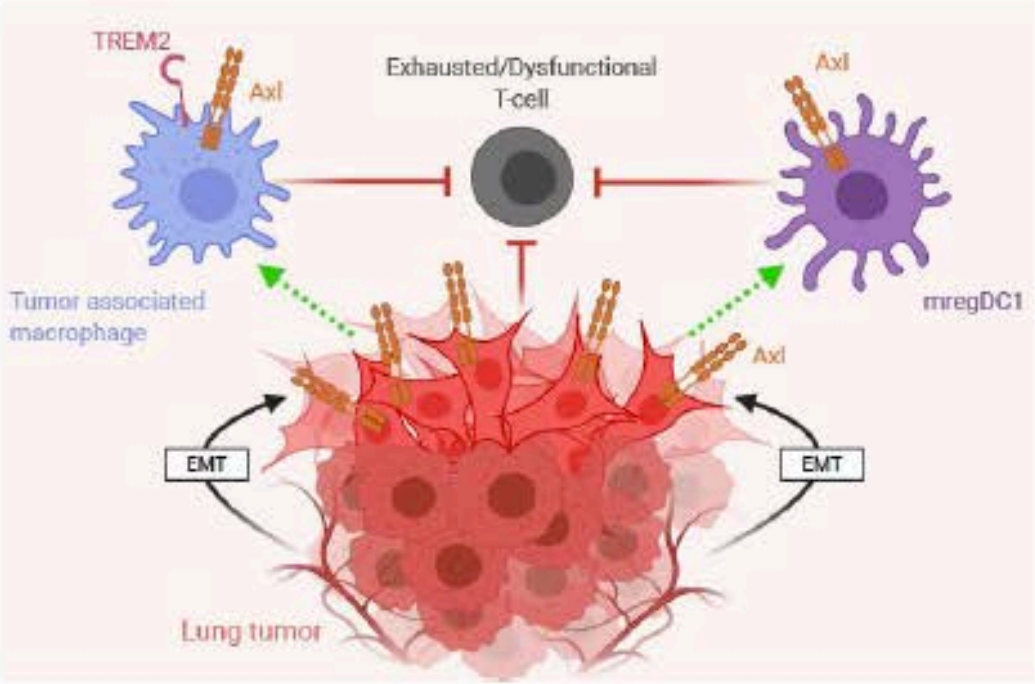
RNAseq analysis identifies gene signatures from benefiting patients:

- Increased AXL expression
- Genes associated with tumor cell EMT[1]
- Presence of TREM2+ TAMs[#,2]
- Presence of CCR7+ mregDC1[##,3]

Common gene signatures observed in Cohort A and B suggest a common mechanism of immune suppression in intrinsic (Cohort A) and acquired (Cohort B) resistance to CPIs

Summary Of Key Points

- Bemcentinib-pembrolizumab combination well tolerated and clinically active in CPI-naïve and CPI-refractory cAXL+ NSCLC
- Bemcentinib may reverse acquired resistance to checkpoint inhibition by targeting AXL+ TREM2 macrophages and regulatory DCs
- Recruitment ongoing in CPI-refractory and chemo-CPI-refractory patient populations
- Findings support further development of AXL inhibition with bemcentinib to extend efficacy of immunotherapy in biomarker-selected refractory NSCLC

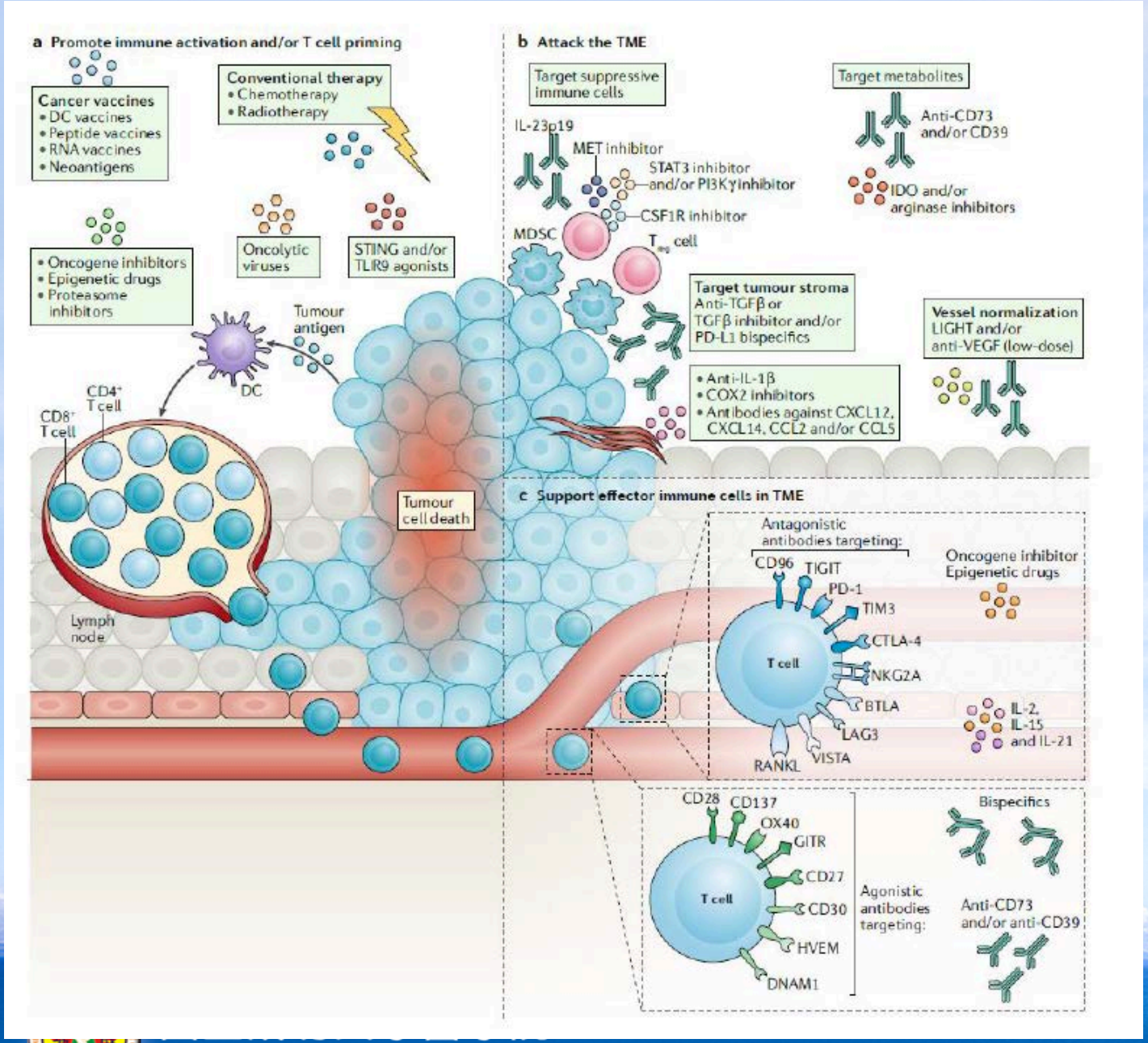


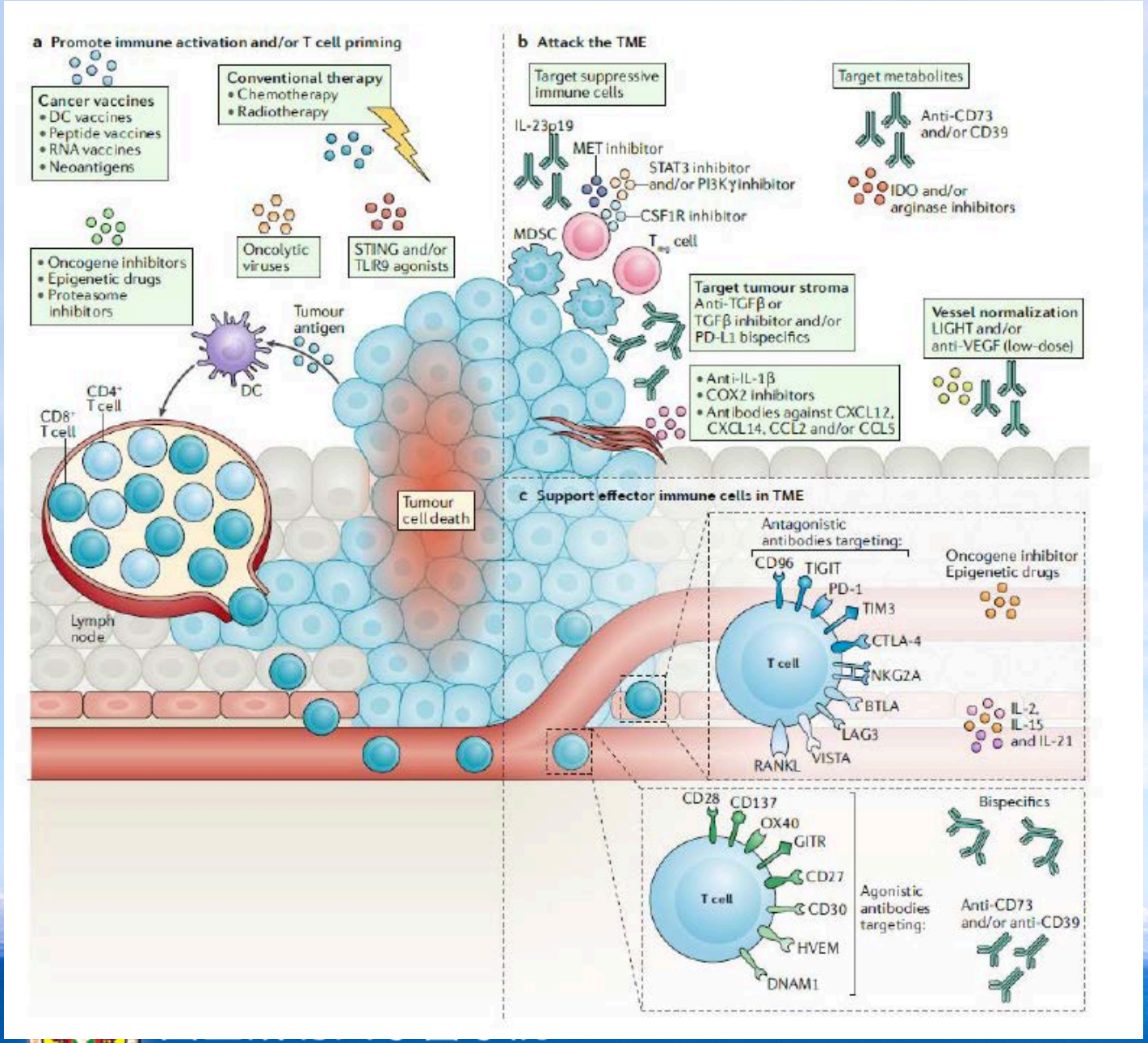
Proposed mechanism (Spicer, *et al.* SITC, 2020): AXL+ suppressive myeloid cells drive T cell dysfunction/exhaustion; bemcentinib inhibition of AXL reverses this state of immune suppression in the microenvironment, and promotes checkpoint inhibitor re-engagement

Promote immune activation

Cancer Vaccines

Tumor Infiltrating Lymphocytes TIL





Promote immune activation

Cancer Vaccines

Tumor Infiltrating Lymphocytes TIL

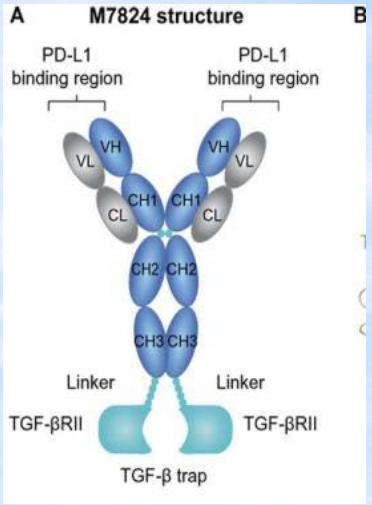
Attack the TME

TGFβ

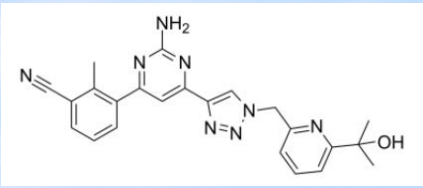
VEGFR

IL 1β

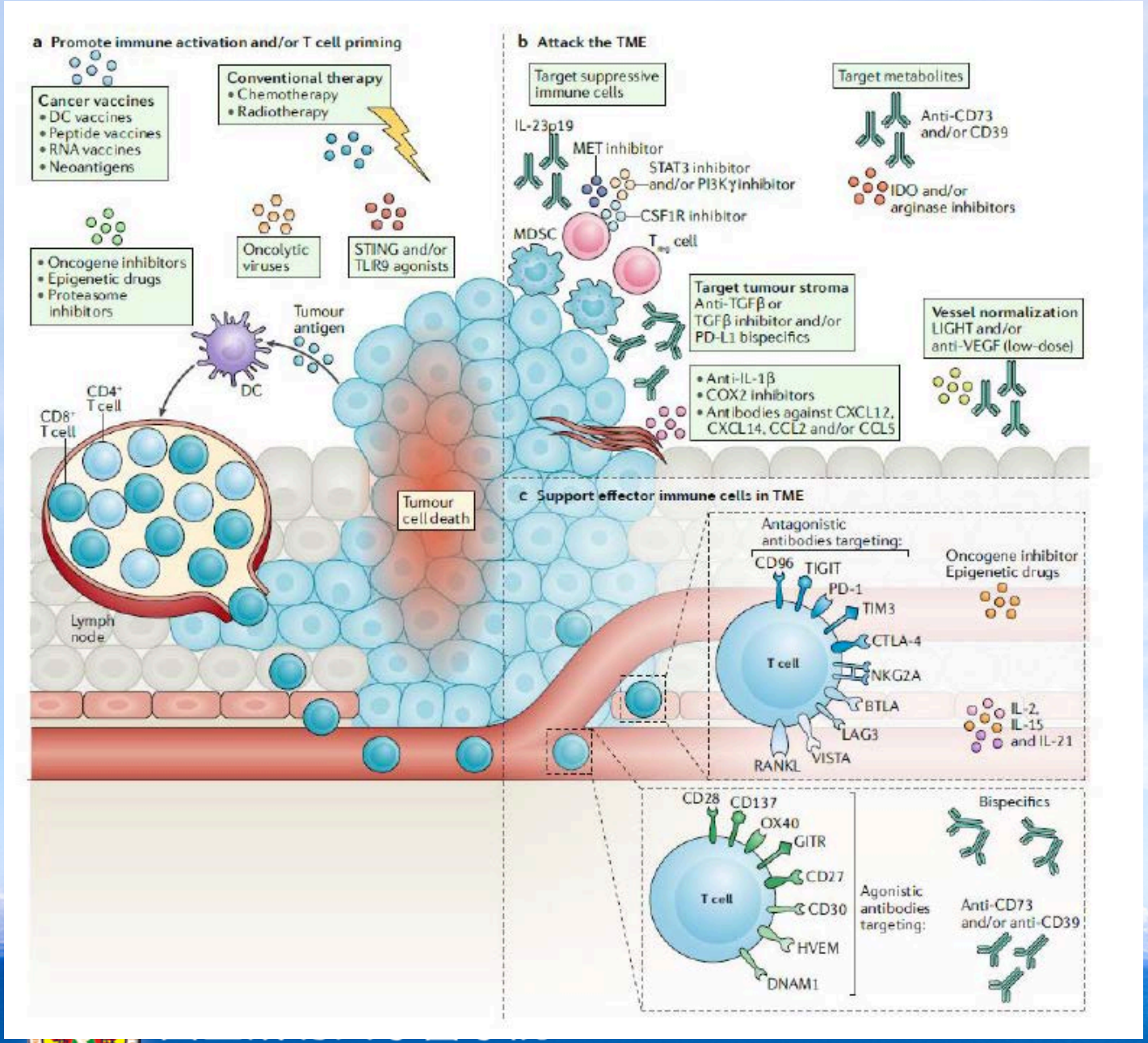
A2aR



Etrumadenant(AB928): Dual Antagonist of A2aR and A2bR



IL-1β canakinumab (CANOPY study



Promote immune activation

Cancer Vaccines

Tumor Infiltrating Lymphocytes TIL

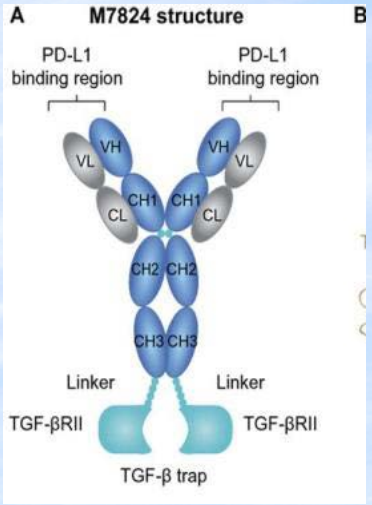
Attack the TME

TGFβ

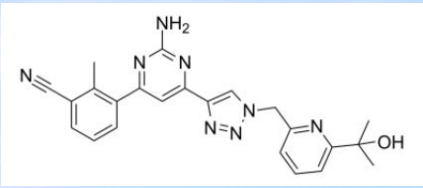
VEGFR

IL 1β

A2aR



Etrumadenant(AB928): Dual Antagonist of A2aR and A2bR



IL-1β canakinumab (CANOPY study

Support effector immune cells in TME

PD -(L)1, TIGIT, TIM3, LAG3

Take home message:

1.Chemo+I/O provided better ORR and PFS

- The choice of first line I/O depends on OS, DOR, and other specific situation (BM, liver metastasis, Post-TKI, bulky disease ,and elderly patients)

2.What is the key issue in developing new I/O strategy?

- I/O with other I/O or anti-angiogenesis as first line, KN598, N/I or N after TKI
- I/O with other I/O or anti-angiogenesis after failure of I/O-Biomarker?

Thanks

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