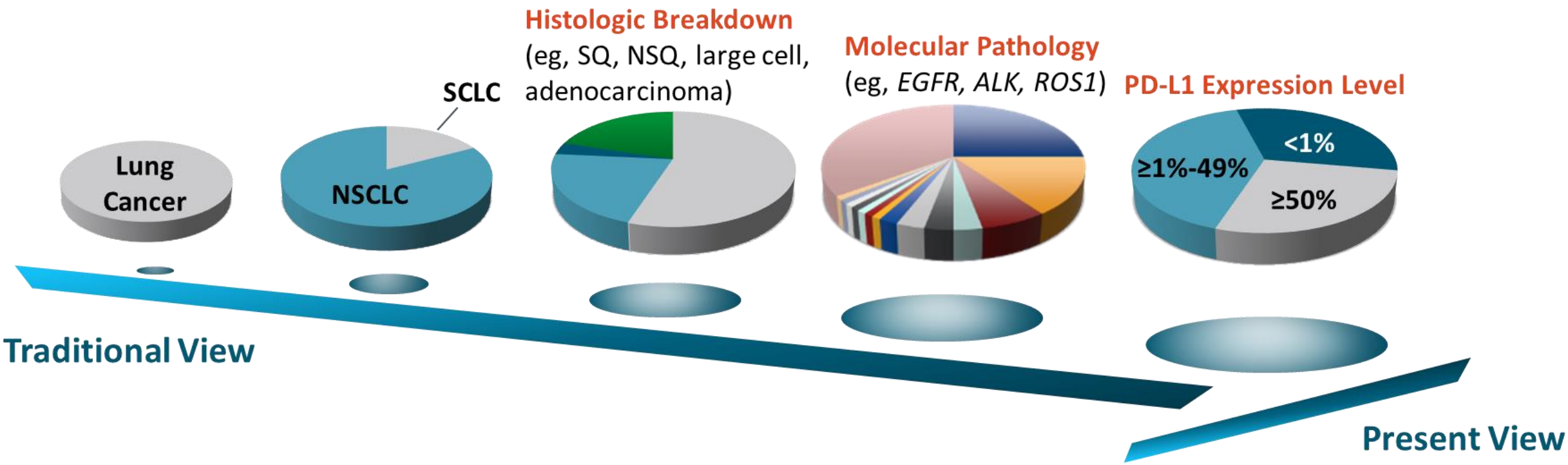
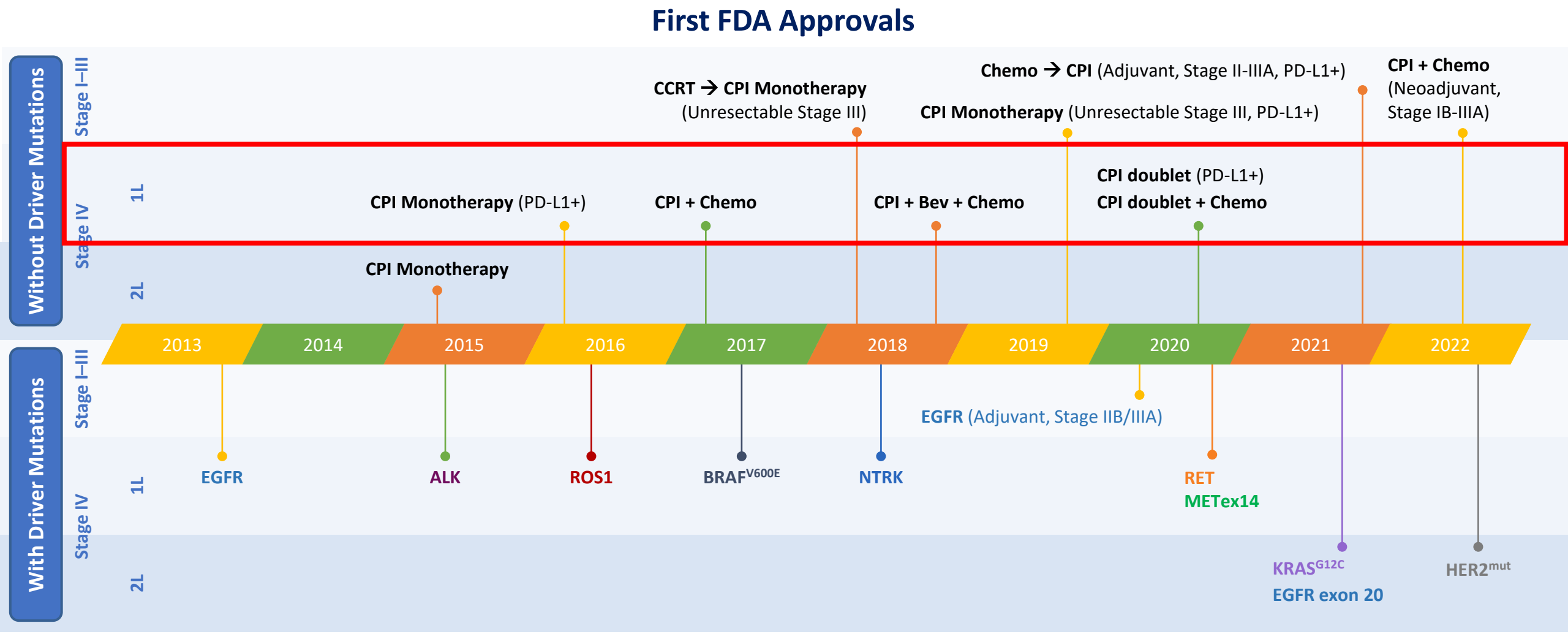
First line treatment decision of advanced NSCLC

대구가톨릭대학교병원
정치영

Evolution of therapy in lung cancer: Heterogenous disease



Numerous advances in treatment have been made for patients with NSCLC

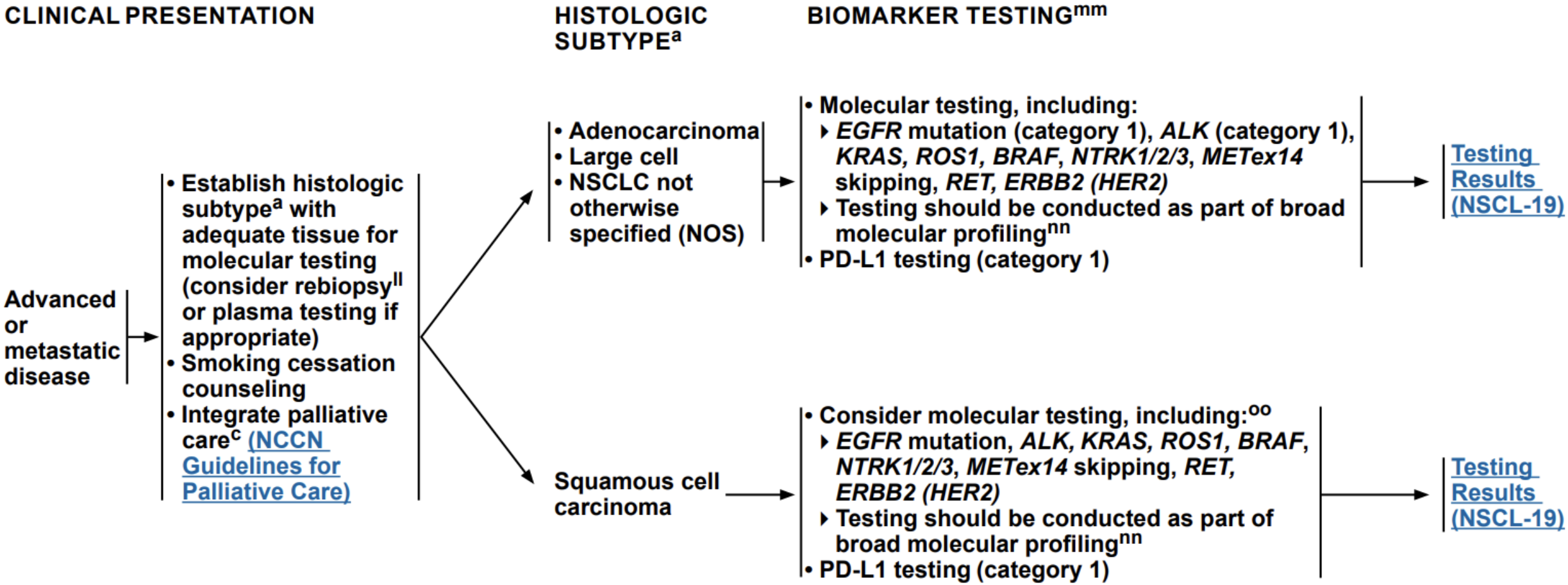


Thai. Lancet. 2021;398:535. Cheng. MedComm. 2021;2:692. Godoy. Biomark Res. 2023;11:7.

Contents

- **Guidelines: NCCN, ESMO, ASCO**
- **PD-L1 ≥ 50%: IO mono vs. IO + chemotherapy**
  PD-L1 ≥ 90% ?
- **PD-L1< 1%: IO + chemotherapy vs. Chemotherapy**

Guidelines: NCCN, ESMO, ASCO

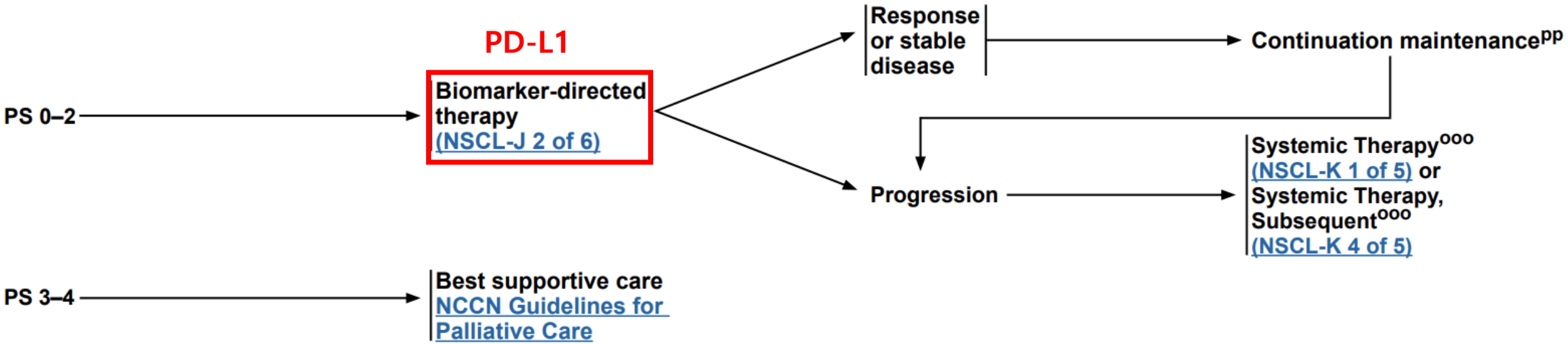

CLINICAL PRESENTATION
HISTOLOGIC SUBTYPE[a]
BIOMARKER TESTING[mm]
Advanced or metastatic disease
• Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[ll] or plasma testing if appropriate)
• Smoking cessation counseling
• Integrate palliative care[c] (NCCN Guidelines for Palliative Care)
• Adenocarcinoma
• Large cell
• NSCLC not otherwise specified (NOS)
• Molecular testing, including:
▸ EGFR mutation (category 1), ALK (category 1), KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET, ERBB2 (HER2)
▸ Testing should be conducted as part of broad molecular profiling[nn]
• PD-L1 testing (category 1)
Testing Results (NSCL-19)
Squamous cell carcinoma
• Consider molecular testing, including:[oo]
▸ EGFR mutation, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET, ERBB2 (HER2)
▸ Testing should be conducted as part of broad molecular profiling[nn]
• PD-L1 testing (category 1)
Testing Results (NSCL-19)

TESTING RESULTS[ll,mm]

EGFR **exon 19 deletion or exon 21 L858R mutation positive**	**NSCL-20**
EGFR **S768I, L861Q, and/or G719X mutation positive**	**NSCL-23**
EGFR **exon 20 insertion mutation positive**	**NSCL-24**
KRAS **G12C mutation positive**	**NSCL-25**
ALK **rearrangement positive**	**NSCL-26**
ROS1 **rearrangement positive**	**NSCL-29**
BRAF **V600E mutation positive**	**NSCL-31**
NTRK1/2/3 **gene fusion positive**	**NSCL-32**
METex14 **skipping mutation positive**	**NSCL-33**
RET **rearrangement positive**	**NSCL-34**
ERBB2 (HER2) **mutation positive**	**NSCL-35**
PD-L1 ≥1% and negative for actionable molecular biomarkers above	**NSCL-36**
PD-L1 <1% and negative for actionable molecular biomarkers above	**NSCL-37**

PD-L1 POSITIVE (≥1%)[mm] AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS[mmm]

FIRST-LINE THERAPY[pp,nnn]



PD-L1 ≥50% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

Preferred
- Pembrolizumab (category 1)[46,47]
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,d] + atezolizumab (category 1)[52]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[53]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[54]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

SQUAMOUS CELL CARCINOMA

Preferred
- Pembrolizumab (category 1)[46,47]
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[58]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[53]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

PD-L1 ≥1-49% First-line Therapy
Continuation Maintenance

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥1%–49% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

Preferred
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,d] + atezolizumab (category 1)[52]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[53]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[54]
- Nivolumab + ipilimumab (category 1)[57]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 1)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 1)[56]

Useful in Certain Circumstances
- Pembrolizumab (category 2B)[e,46,47]

SQUAMOUS CELL CARCINOMA

Preferred
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[58]

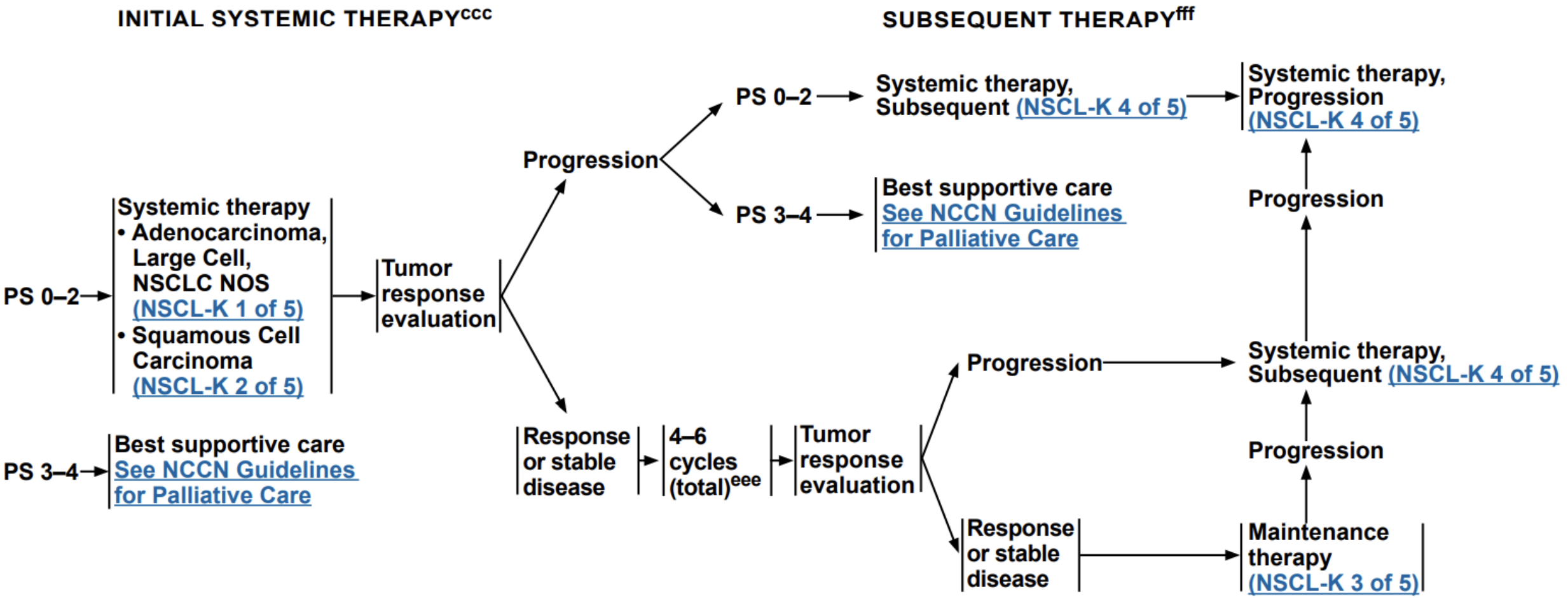
Other Recommended
- Nivolumab + ipilimuab + paclitaxel + carboplatin (category 1)[53]
- Nivolumab + ipilimumab (category 1)[57]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine[56]

Useful in Certain Circumstances
- Pembrolizumab (category 2B)[e,46,47]

PD-L1 ≥50% First-line Therapy

Continuation Maintenance

PD-L1 <1% AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS



SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

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

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

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

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e]
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e]

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

Useful in Certain Circumstances
- Bevacizumab[f]/carboplatin/paclitaxel (category 1)[9,g,h,i]
- Bevacizumab[f]/carboplatin/pemetrexed[9,10,g,h,i]
- Bevacizumab[f]/cisplatin/pemetrexed[11,g,h,i]
- Carboplatin/albumin-bound paclitaxel (category 1)[12]
- Carboplatin/docetaxel (category 1)[13]
- Carboplatin/etoposide (category 1)[14,15]
- Carboplatin/gemcitabine (category 1)[16]
- Carboplatin/paclitaxel (category 1)[17]
- Carboplatin/pemetrexed (category 1)[18]
- Cisplatin/docetaxel (category 1)[13]
- Cisplatin/etoposide (category 1)[19]
- Cisplatin/gemcitabine (category 1)[17,20]
- Cisplatin/paclitaxel (category 1)[21]
- Cisplatin/pemetrexed (category 1)[20]
- Gemcitabine/docetaxel (category 1)[22]
- Gemcitabine/vinorelbine (category 1)[23]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[18]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[25,26]
- Carboplatin/docetaxel[13]
- Carboplatin/etoposide[14,15]
- Carboplatin/gemcitabine[16]
- Carboplatin/paclitaxel[17]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[24]
- Docetaxel[27,28]
- Gemcitabine[29-31]
- Gemcitabine/docetaxel[22]
- Gemcitabine/vinorelbine[23]
- Paclitaxel[32-34]
- Pemetrexed[35]

Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5
References

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

SQUAMOUS CELL CARCINOMA (PS 0–1)

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

Preferred
- Pembrolizumab/carboplatin/paclitaxel (category 1)[36,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[36,e]

Other Recommended
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e]
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[8,e]

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

Useful in Certain Circumstances
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[13]
- Carboplatin/gemcitabine (category 1)[16]
- Carboplatin/paclitaxel (category 1)[17]
- Cisplatin/docetaxel (category 1)[13]
- Cisplatin/etoposide (category 1)[19]
- Cisplatin/gemcitabine (category 1)[19,20]
- Cisplatin/paclitaxel (category 1)[21]
- Gemcitabine/docetaxel (category 1)[22]
- Gemcitabine/vinorelbine (category 1)[23]

SQUAMOUS CELL CARCINOMA (PS 2)

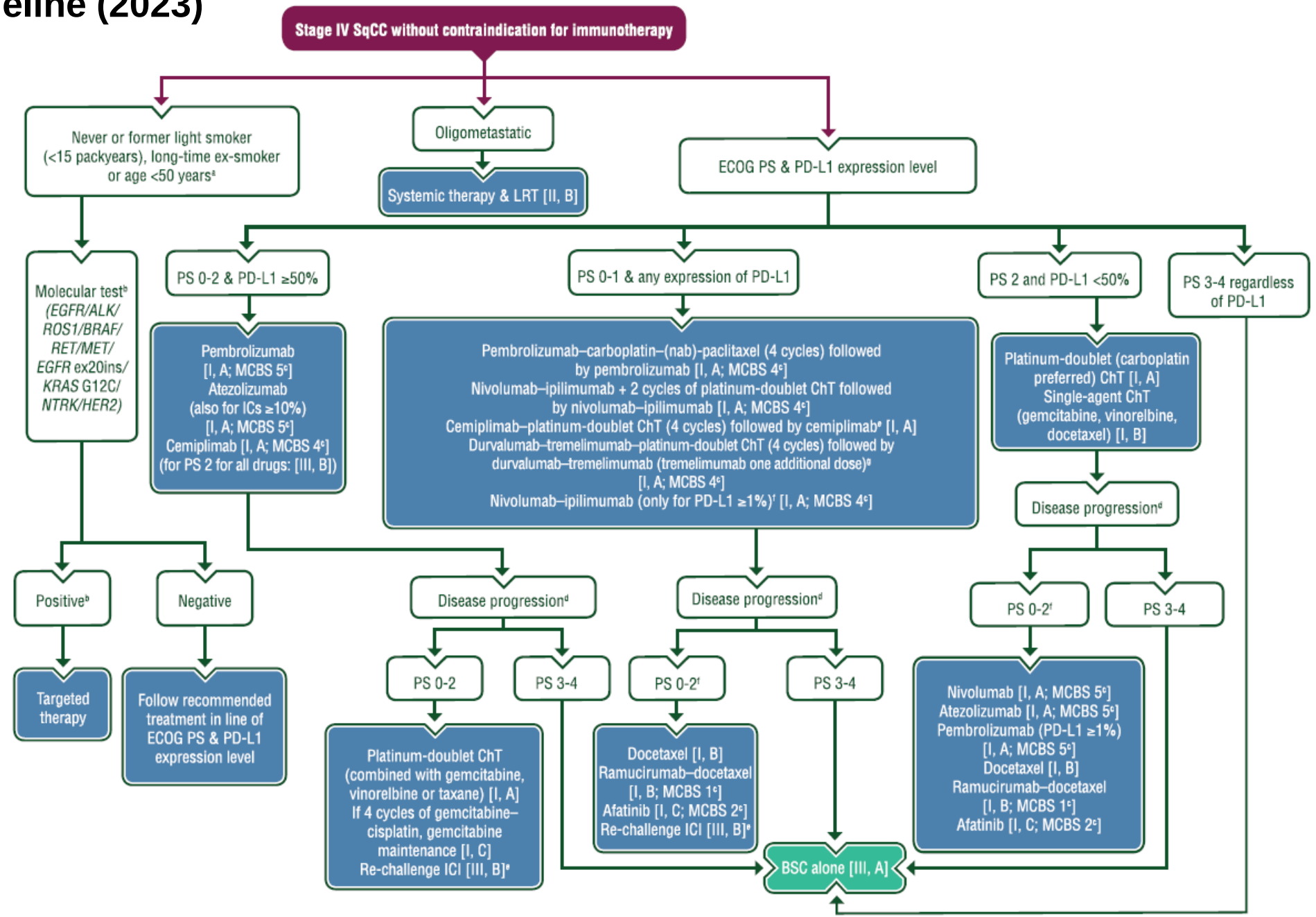
Preferred
- Carboplatin/albumin-bound paclitaxel[25,26]
- Carboplatin/gemcitabine[16]
- Carboplatin/paclitaxel[17]

Other Recommended
- Carboplatin/docetaxel[13]
- Carboplatin/etoposide[14,15]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[24]
- Docetaxel[27,28]
- Gemcitabine[29-31]
- Gemcitabine/docetaxel[22]
- Gemcitabine/vinorelbine[23]
- Paclitaxel[32-34]

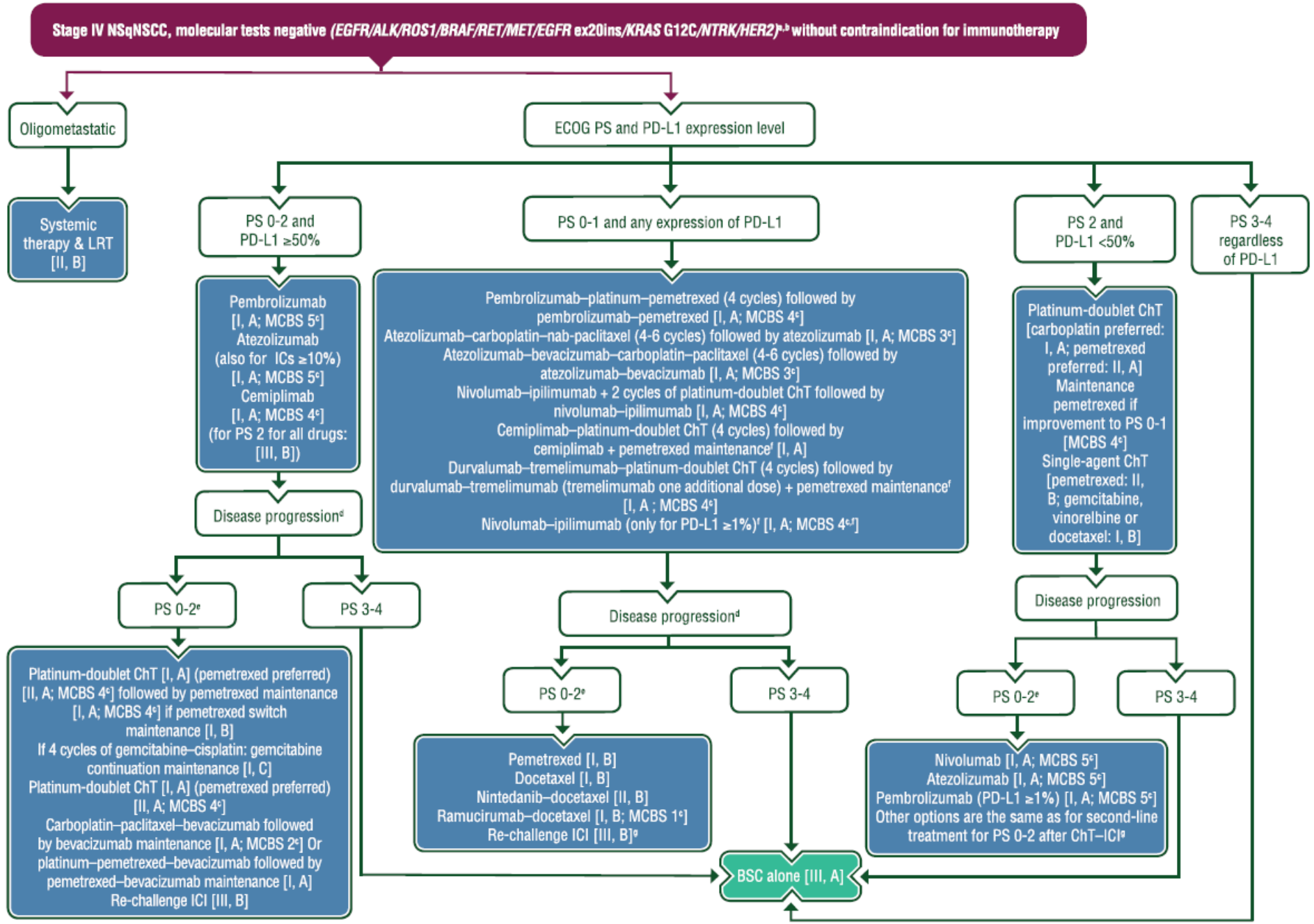
Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5

ESMO Guideline (2023)



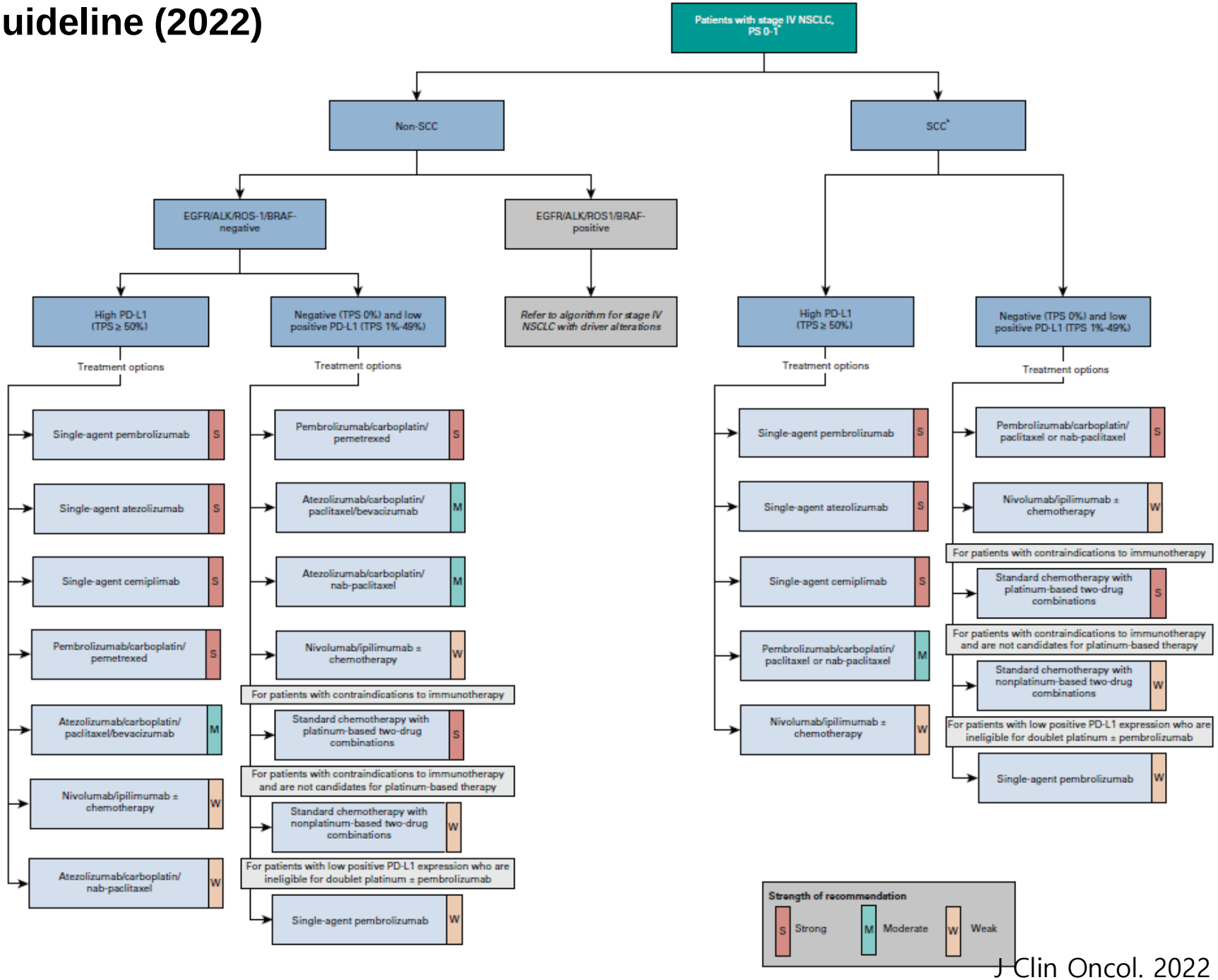
Ann Oncol. 2023 Apr;34(4):358-376.

ESMO Guideline (2023)



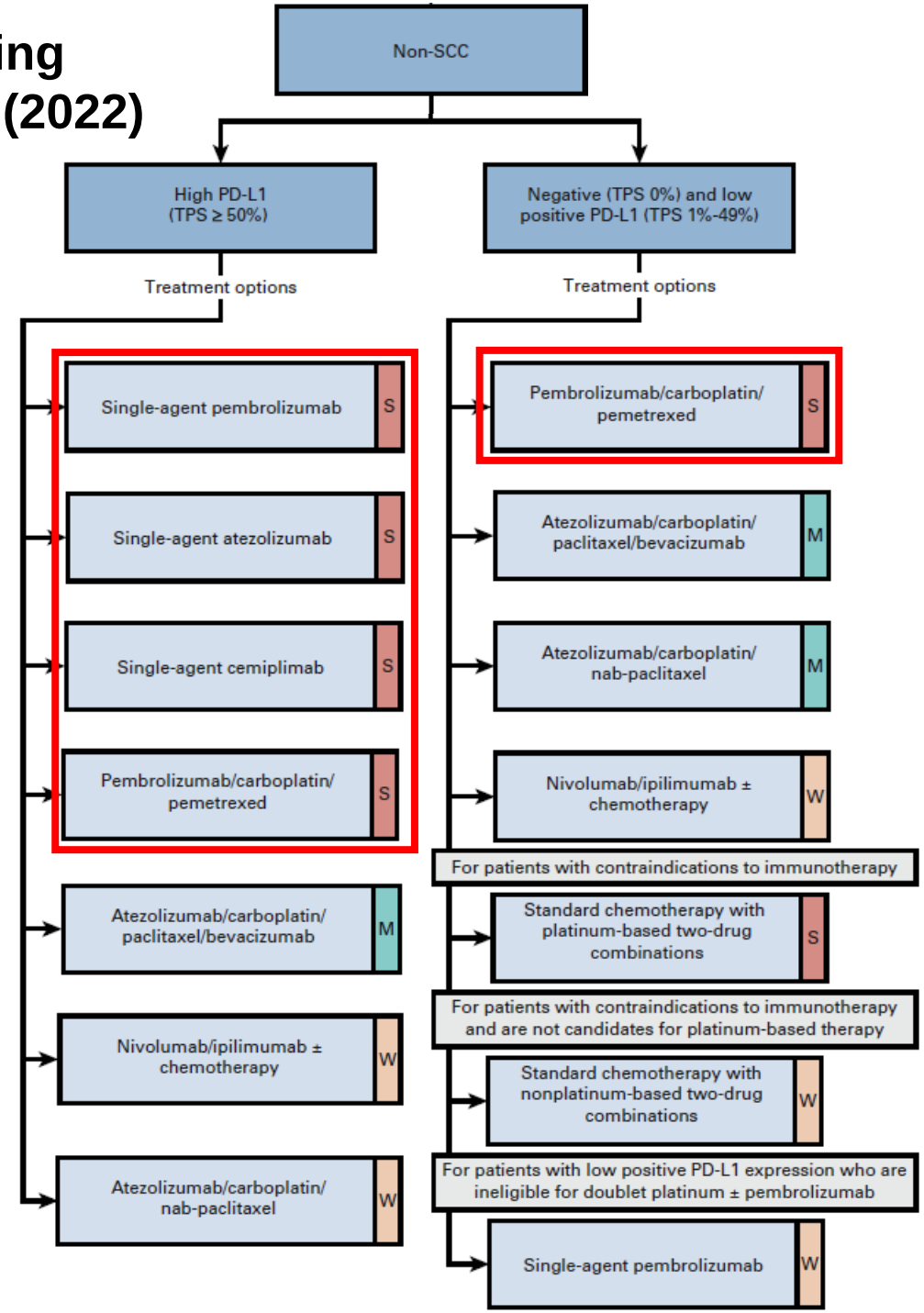
Ann Oncol. 2023 Apr;34(4):358-376.

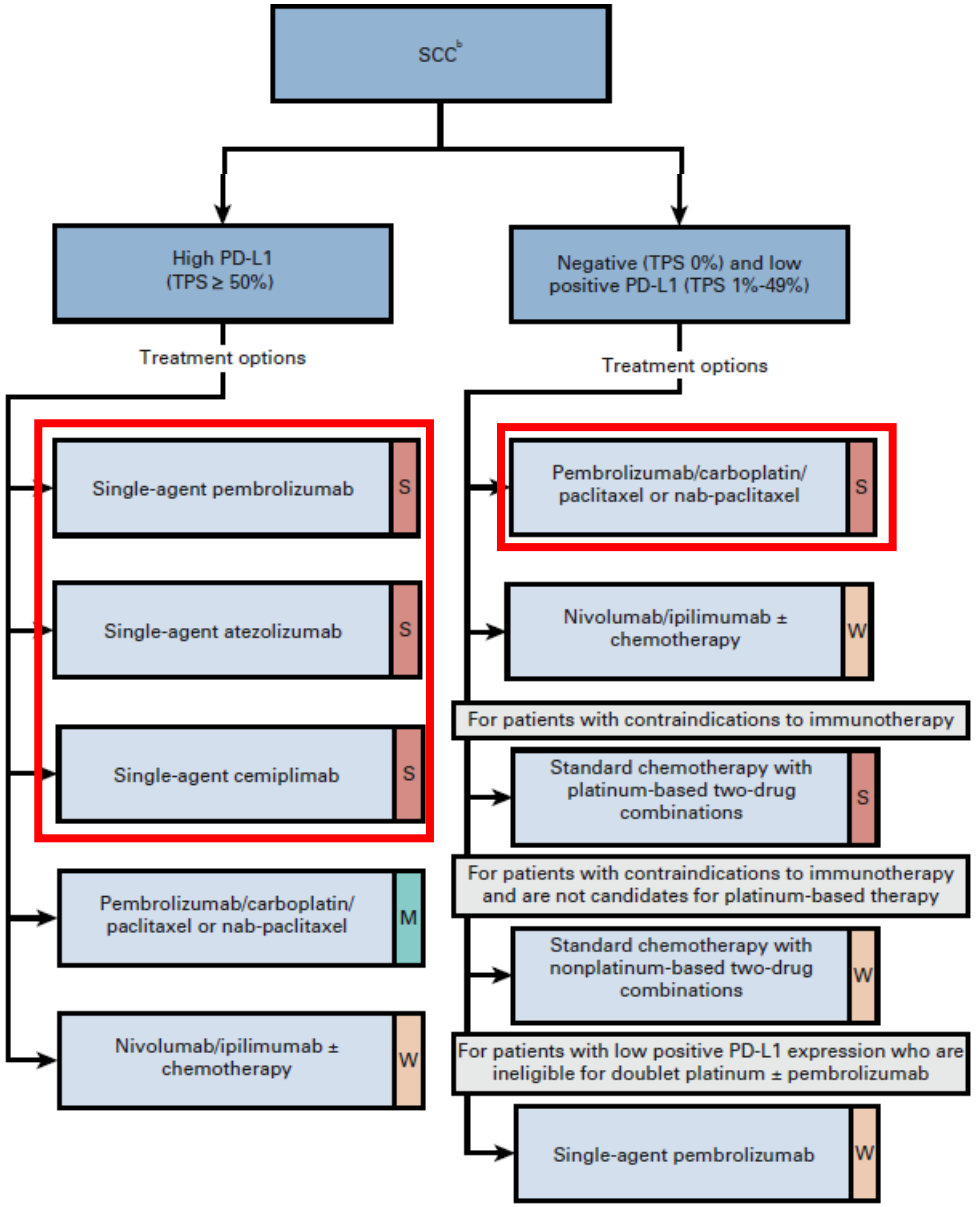
ASCO Living Guideline (2022)



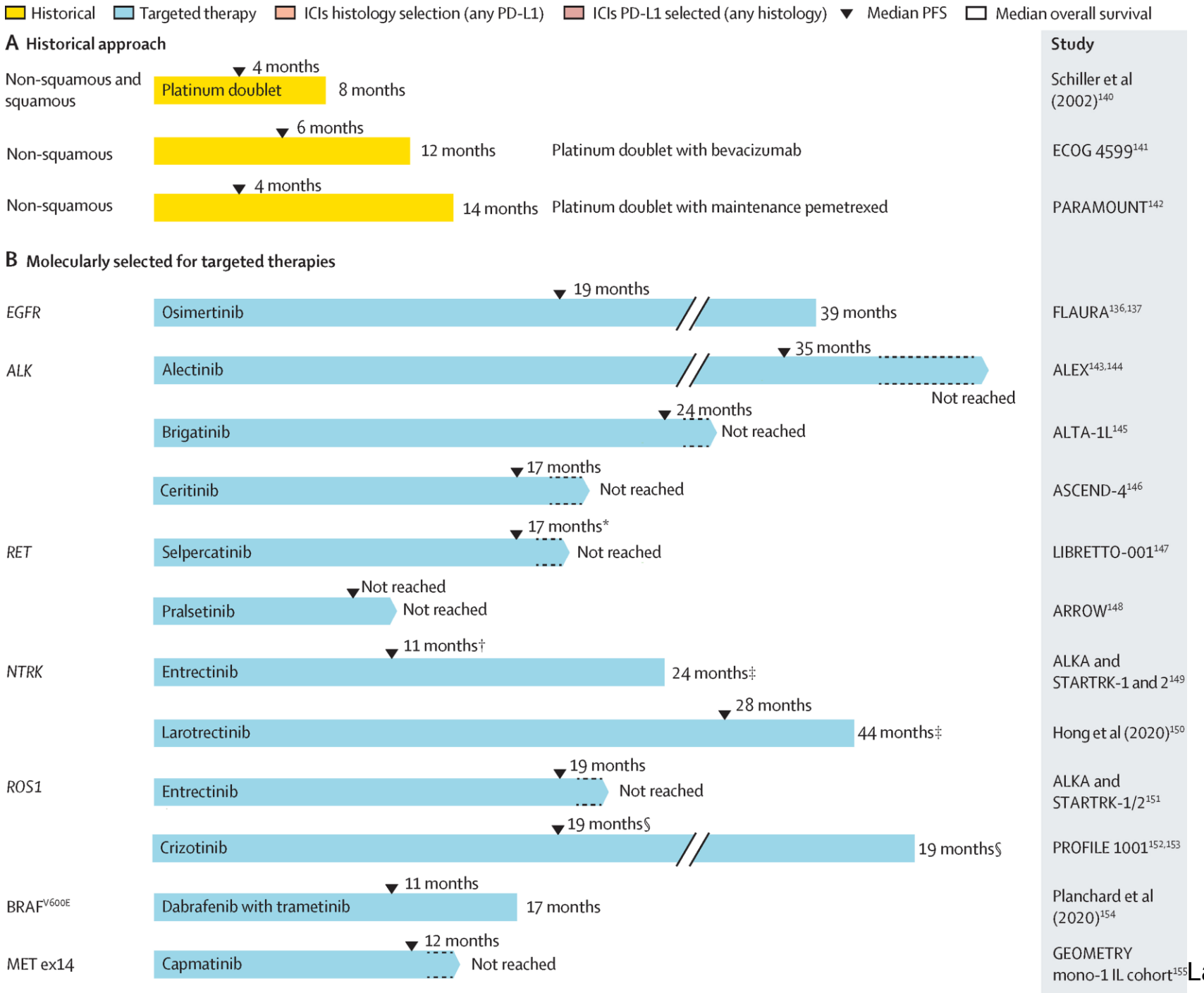
J Clin Oncol. 2022 Oct 1;40(28):3323-3343.

ASCO Living Guideline (2022)

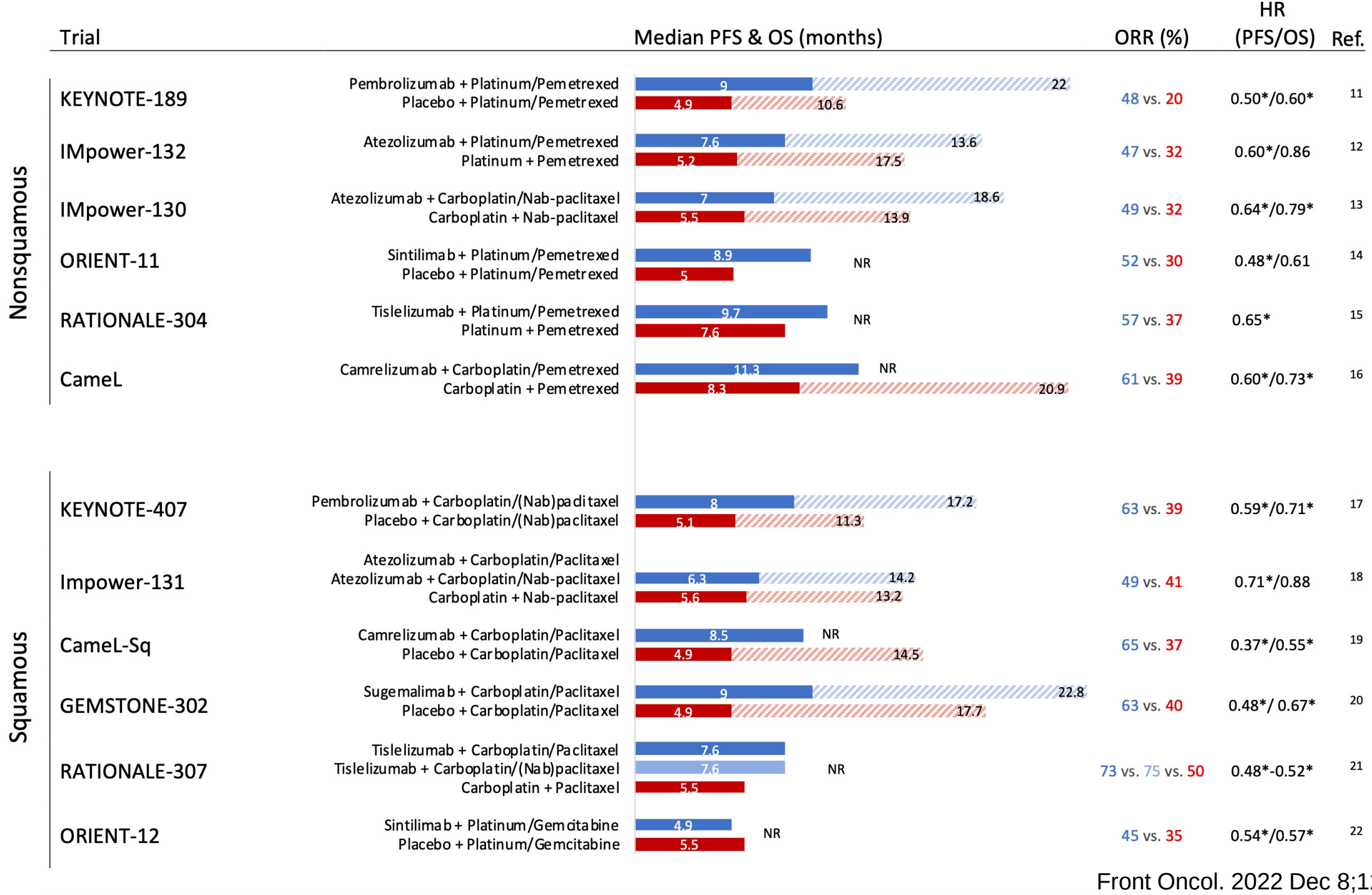




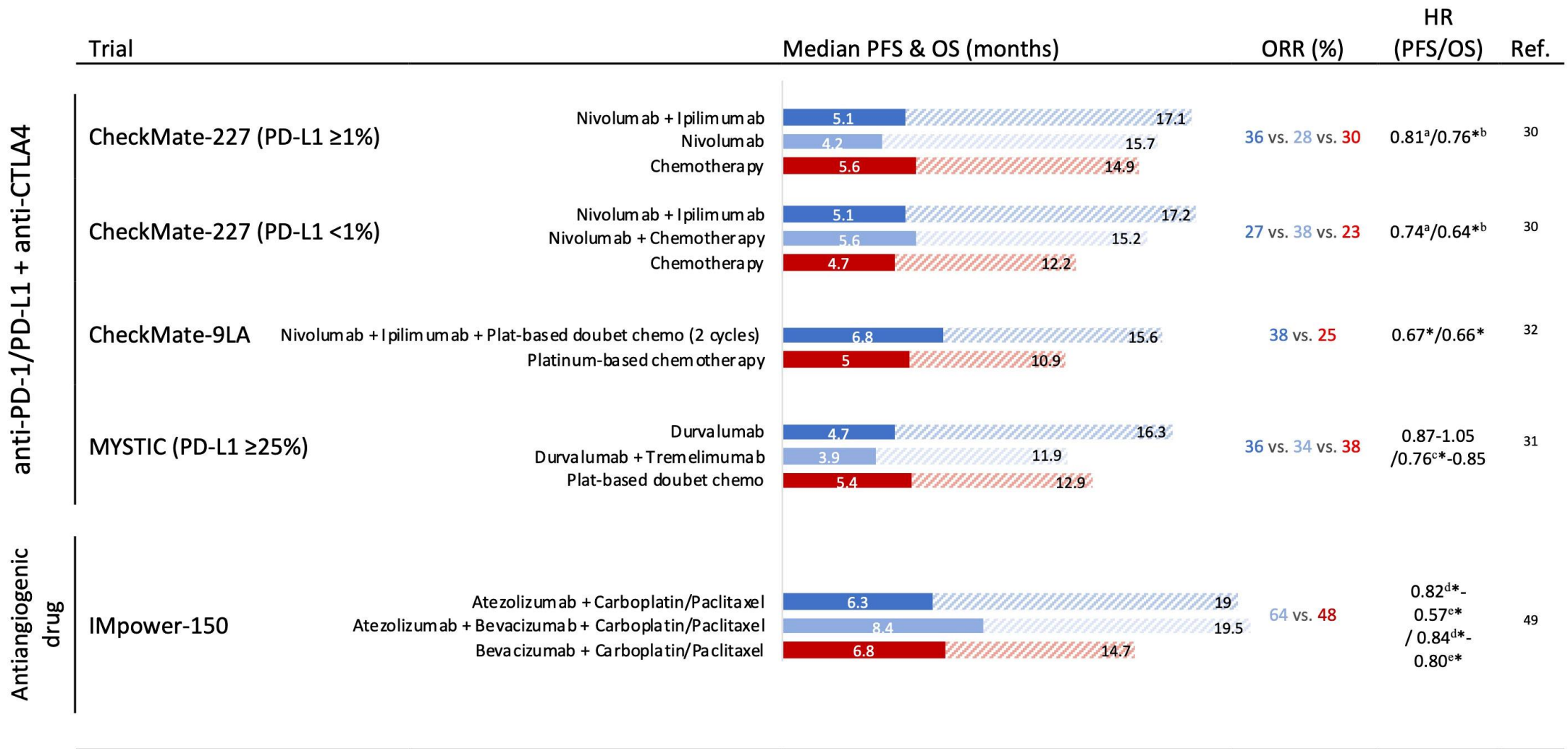
J Clin Oncol. 2022 Oct 1;40(28):3323-3343.



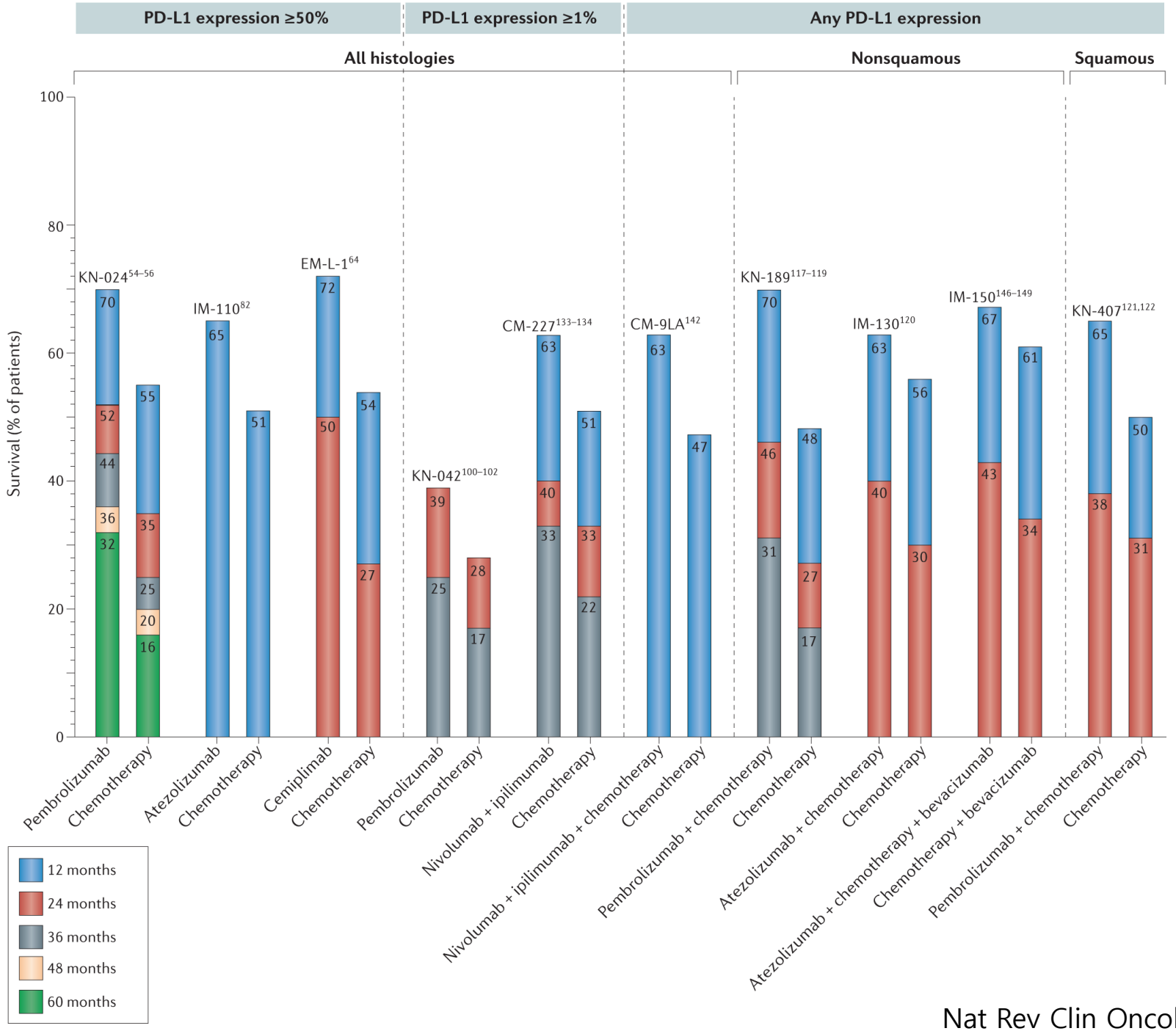
Lancet 2021;398:535–54



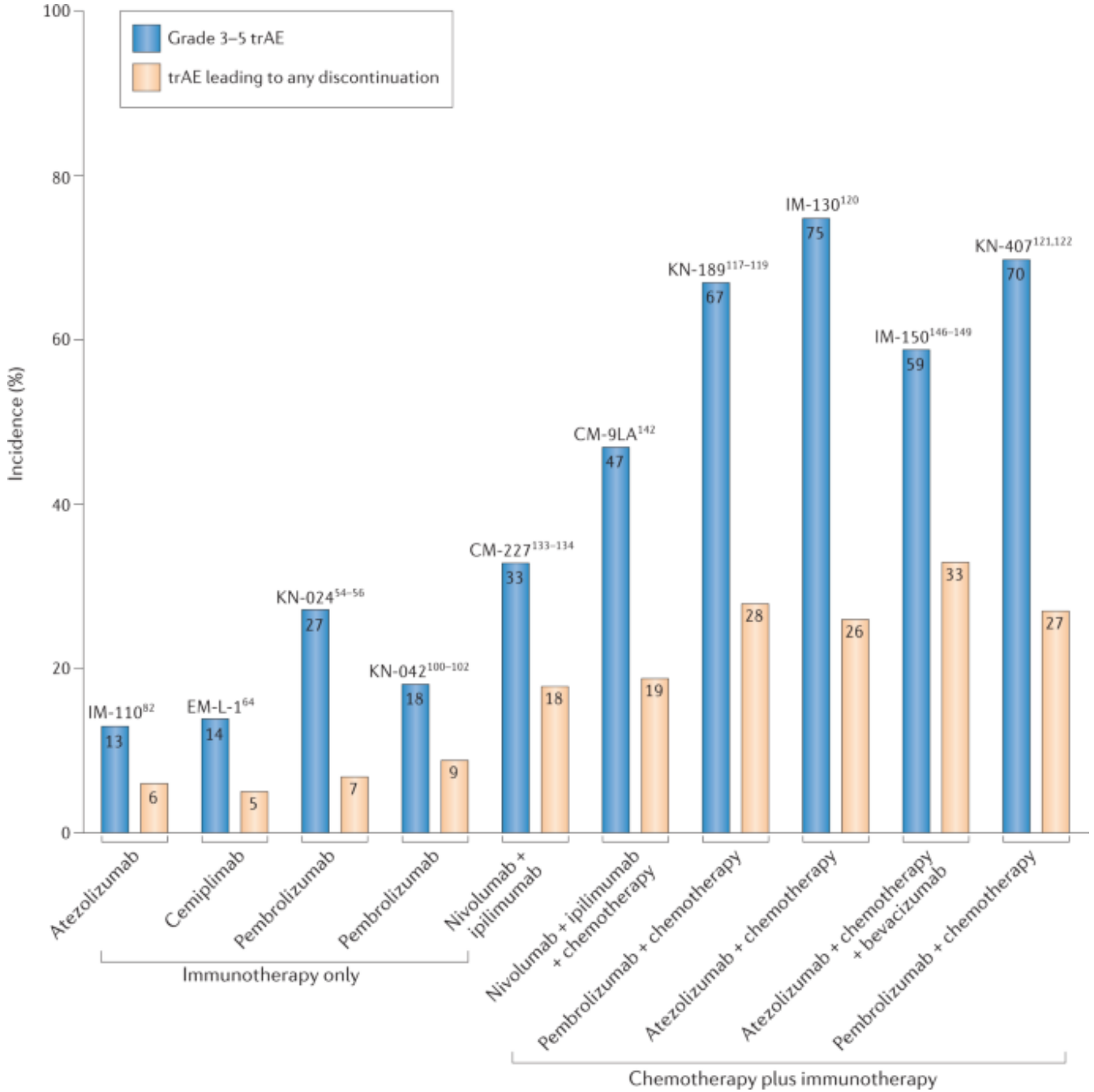
Front Oncol. 2022 Dec 8;12:962947



Front Oncol. 2022 Dec 8;12:962947



Nat Rev Clin Oncol. 2021 Oct;18(10):625-644.



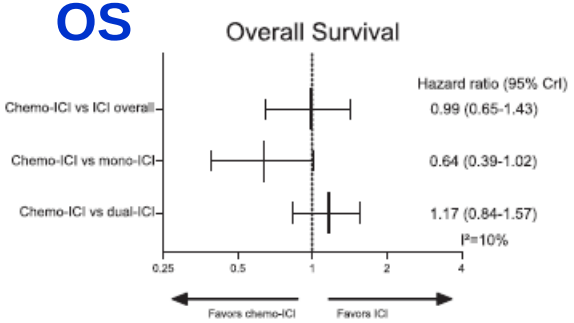
Nat Rev Clin Oncol. 2021 Oct;18(10):625-644.

PD-L1 ≥ 50%: IO mono vs. IO+Chemo

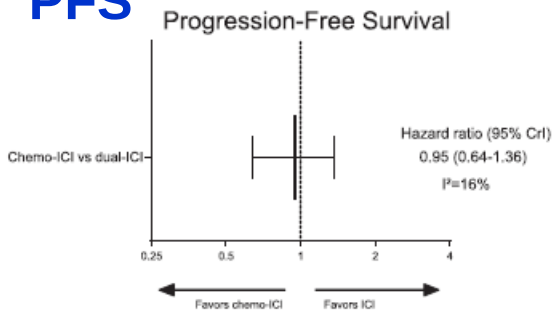
Meta-analysis: 1L treatment

PD-L1 Negative

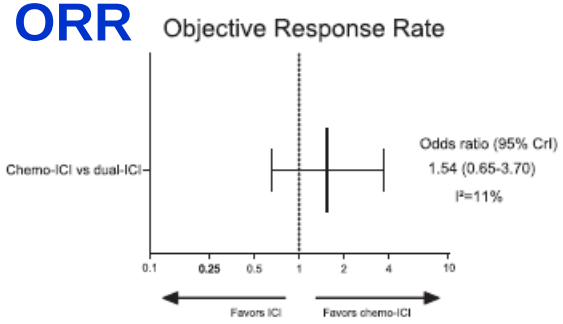
OS



PFS

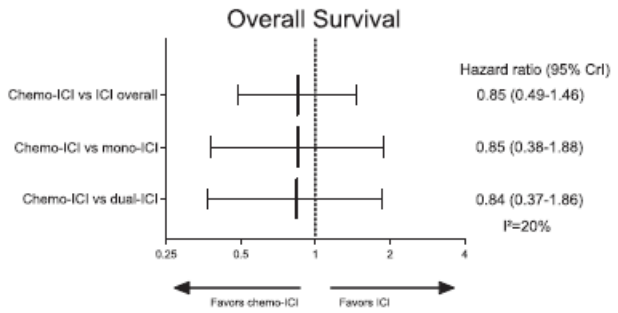


ORR

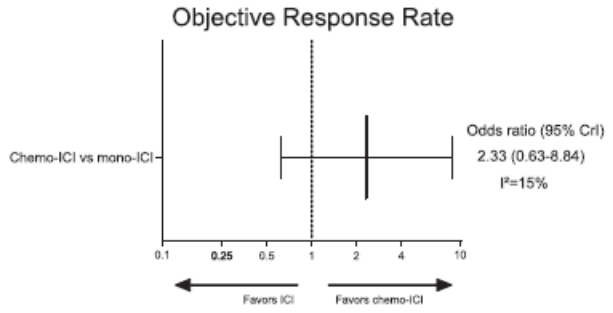


PD-L1 Low

OS

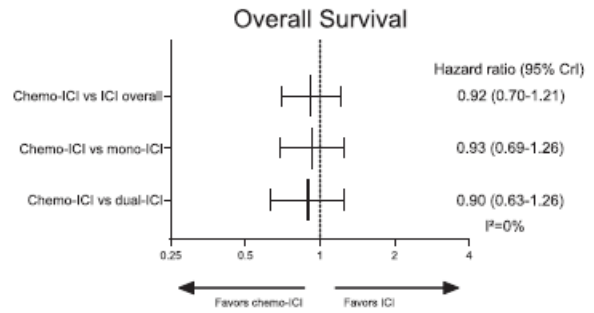


ORR

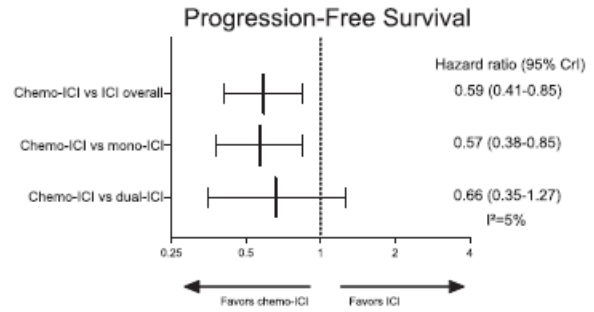


PD-L1 High

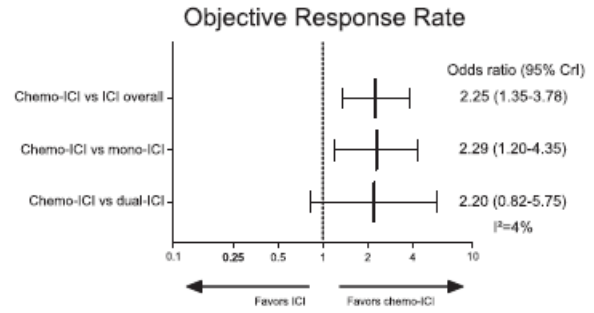
OS



PFS



ORR



Cancer. 2021 Mar 1;127(5):709-719.

Network meta-analysis: 1L treatment

OS

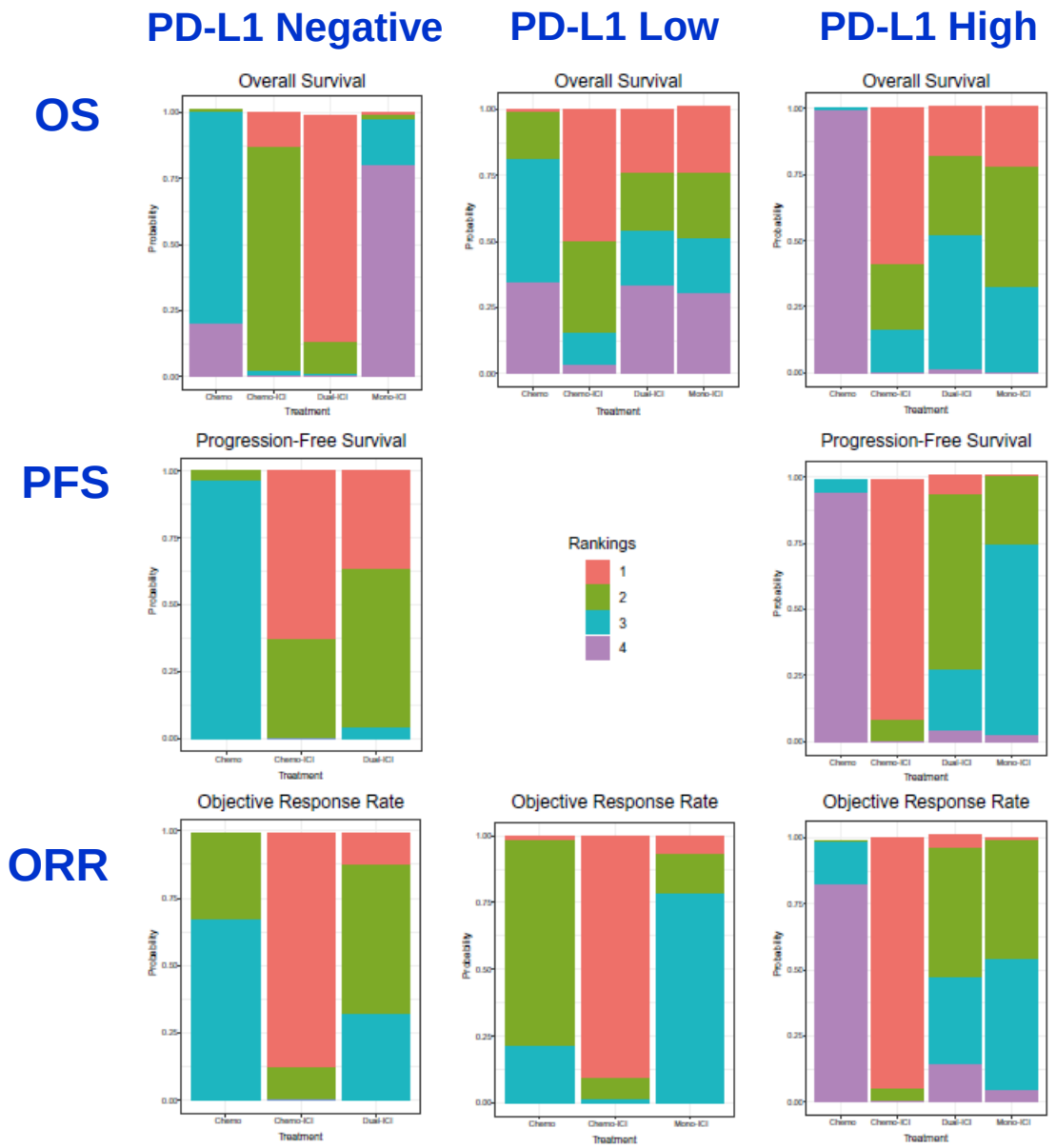
PD-L1 negative	Chemo-ICI	1.17 (0.84-1.57)	0.64 (0.39-1.02)	**0.76 (0.62-0.90)**[a]
		Dual-ICI	**0.55 (0.32-0.94)**[a]	**0.64 (0.49-0.85)**[a]
			Single-agent ICI	1.17 (0.76-1.86)
				Chemotherapy
PD-L1 low	Chemo-ICI	0.84 (0.37-1.86)	0.85 (0.38-1.88)	0.79 (0.55-1.12)
		Dual-ICI	1.02 (0.36-2.89)	0.94 (0.45-1.97)
			Single-agent ICI	0.92 (0.45-1.90)
				Chemotherapy
PD-L1 high	Chemo-ICI	0.90 (0.63-1.26)	0.93 (0.69-1.26)	**0.65 (0.51-0.84)**[a]
		Dual-ICI	1.04 (0.76-1.39)	**0.73 (0.57-0.93)**[a]
			Single-agent ICI	**0.70 (0.60-0.83)**[a]
				Chemotherapy

PFS

PD-L1 negative	Chemo-ICI	0.95 (0.64-1.36)	NA	**0.70 (0.58-0.82)**[a]
		Dual-ICI	NA	0.73 (0.50-1.07)
			Single-agent ICI	—
				Chemotherapy
PD-L1 low	Chemo-ICI	NA	NA	**0.63 (0.52-0.75)**[a]
		Dual-ICI	NA	NA
			Single-agent ICI	NA
				Chemotherapy
PD-L1 high	Chemo-ICI	0.66 (0.35-1.27)	0.57 (0.38-0.85)	**0.41 (0.31-0.55)**[a]
		Dual-ICI	0.85 (0.44-1.63)	0.62 (0.35-1.09)
			Single-agent ICI	0.73 (0.54-0.98)
				Chemotherapy

Cancer. 2021 Mar 1;127(5):709-719.

Bayesian ranking profiles: 1L treatment



Chemo Chemo-ICI Dual-ICI Mono-ICI

Cancer. 2021 Mar 1;127(5):709-719.

FDA pooled analysis: 1L IO±Chemo vs. IO mono, PD-L1 ≥ 50%

12 clinical trials

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****

ASCO 2022 abstract 9000

FDA pooled analysis: 1L IO+Chemo vs. IO mono, PD-L1 ≥ 50%

OS, PFS & ORR

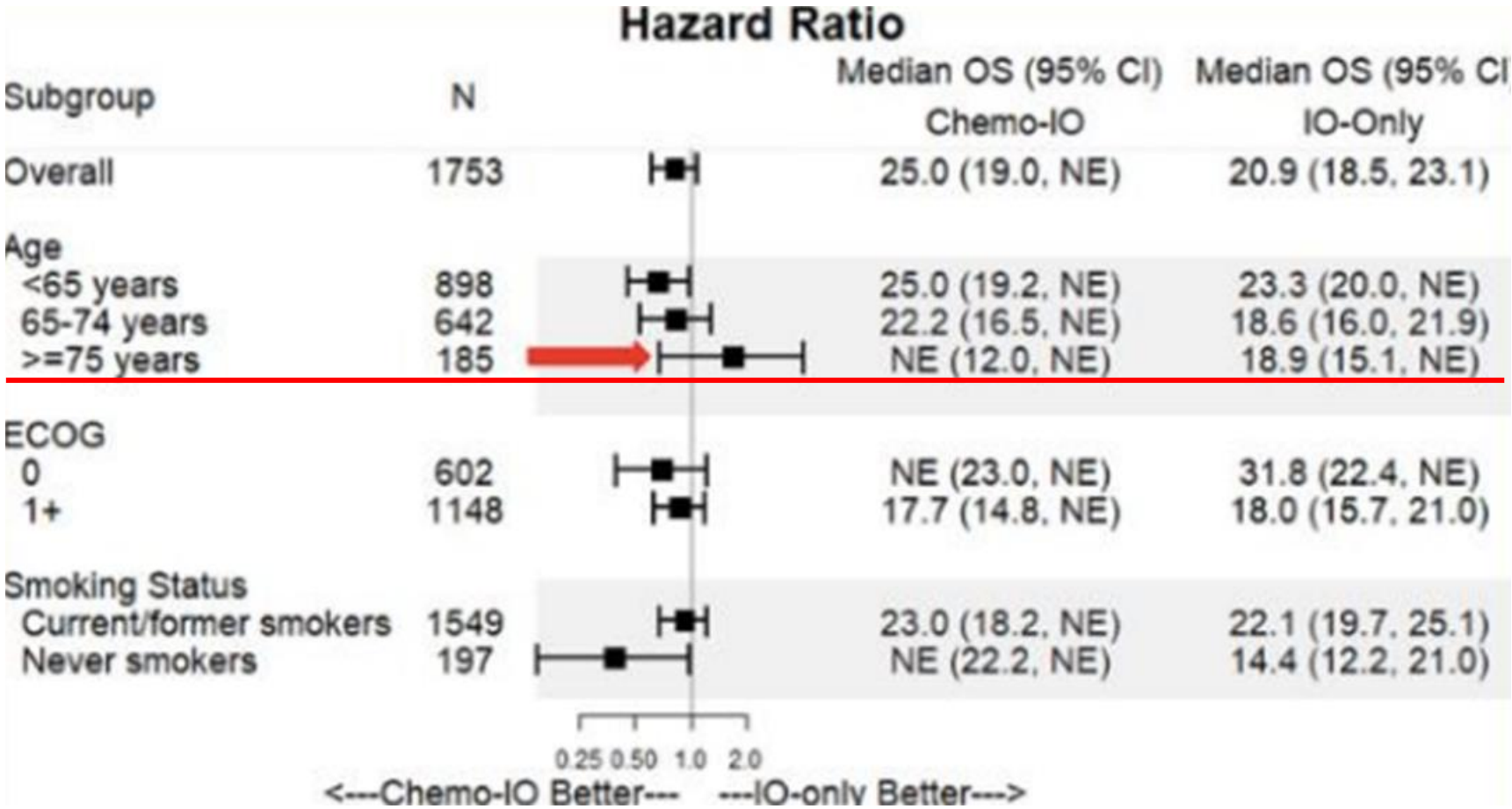
	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

ASCO 2022 abstract 9000

FDA pooled analysis: 1L IO+Chemo vs. IO mono, PD-L1 ≥ 50%

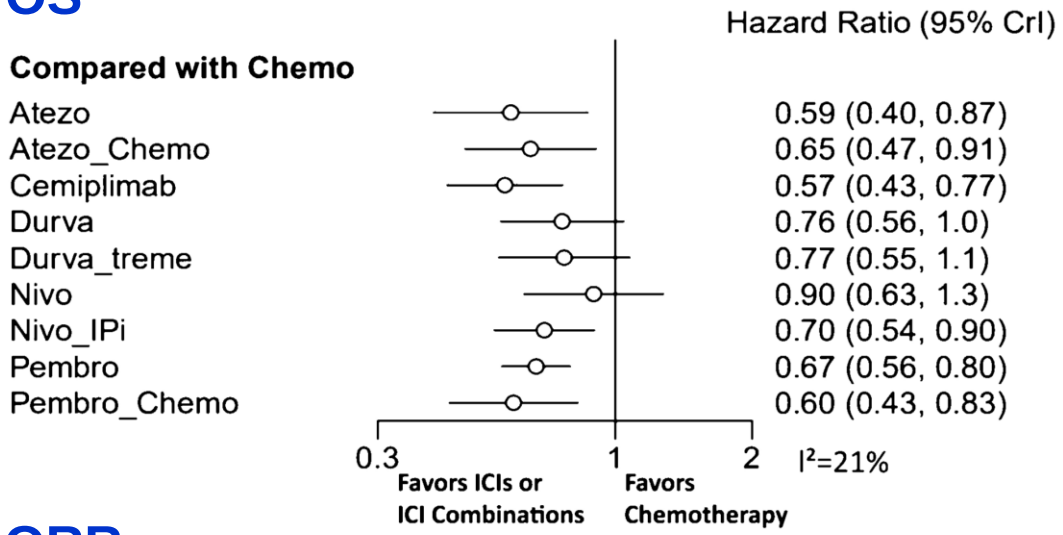
OS (subgroup analysis)



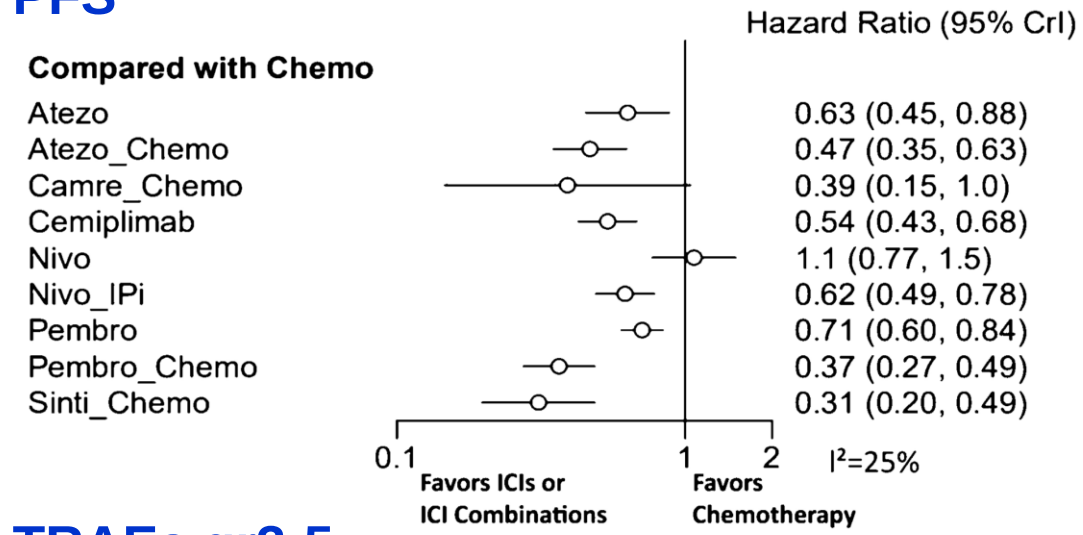
ASCO 2022 abstract 9000

Meta-analysis: 1L treatment, PD-L1 ≥ 50%

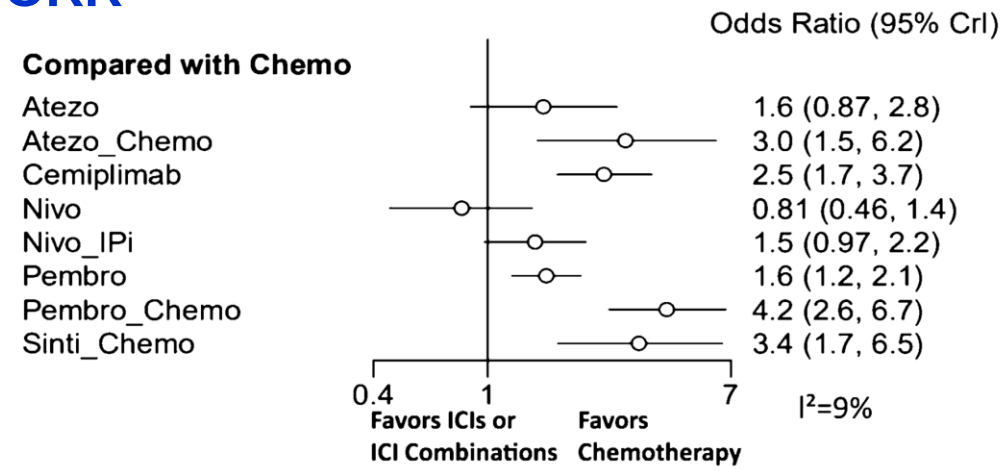
OS



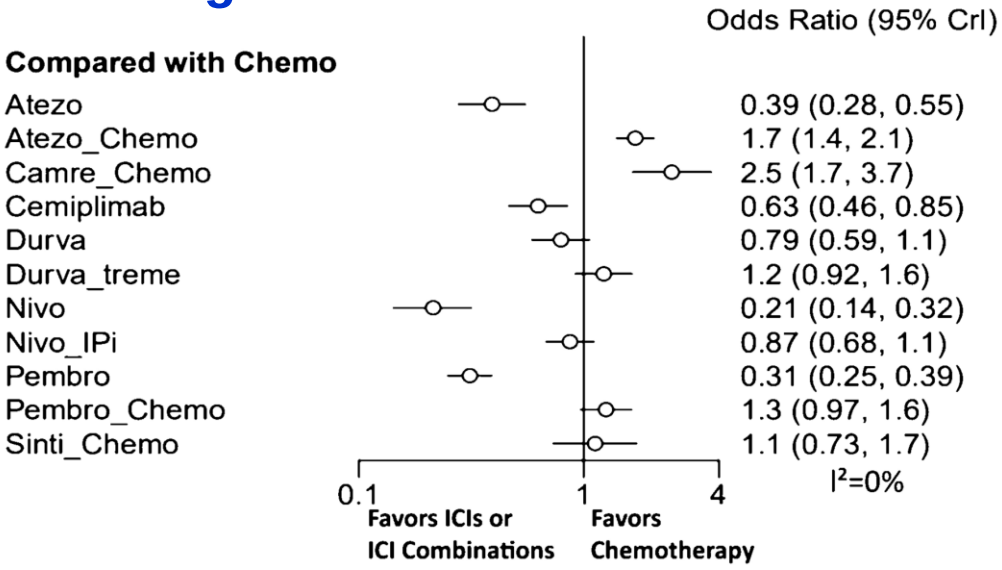
PFS



ORR



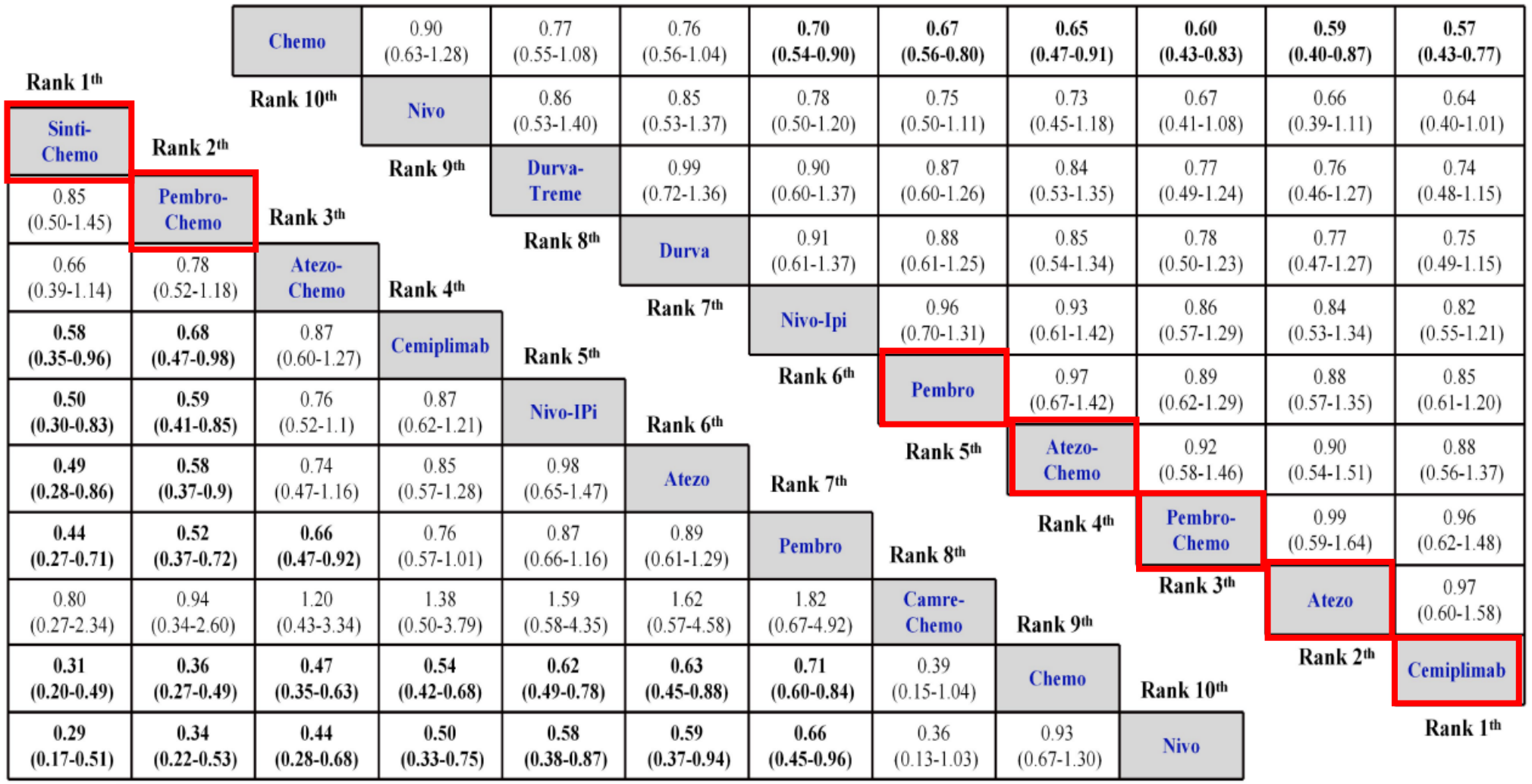
TRAEs gr3-5



Cancer Immunol Immunother. 2022 Jun;71(6):1345-1355.

Network meta-analysis: 1L treatment, PD-L1 ≥ 50%

OS



PFS \ OS	Chemo	Nivo	Durva-Treme	Durva	Nivo-Ipi	Pembro	Atezo-Chemo	Pembro-Chemo	Atezo	Cemiplimab
Sinti-Chemo (Rank 1th)	0.90 (0.63-1.28)	0.77 (0.55-1.08)	0.76 (0.56-1.04)	**0.70 (0.54-0.90)**	**0.67 (0.56-0.80)**	**0.65 (0.47-0.91)**	**0.60 (0.43-0.83)**	**0.59 (0.40-0.87)**	**0.57 (0.43-0.77)**
Pembro-Chemo (Rank 2th)	0.85 (0.50-1.45)	0.86 (0.53-1.40)	0.85 (0.53-1.37)	0.78 (0.50-1.20)	0.75 (0.50-1.11)	0.73 (0.45-1.18)	0.67 (0.41-1.08)	0.66 (0.39-1.11)	0.64 (0.40-1.01)
Atezo-Chemo (Rank 3th)	0.66 (0.39-1.14)	0.78 (0.52-1.18)	0.99 (0.72-1.36)	0.90 (0.60-1.37)	0.87 (0.60-1.26)	0.84 (0.53-1.35)	0.77 (0.49-1.24)	0.76 (0.46-1.27)	0.74 (0.48-1.15)
Cemiplimab (Rank 4th)	**0.58 (0.35-0.96)**	**0.68 (0.47-0.98)**	0.87 (0.60-1.27)	0.91 (0.61-1.37)	0.88 (0.61-1.25)	0.85 (0.54-1.34)	0.78 (0.50-1.23)	0.77 (0.47-1.27)	0.75 (0.49-1.15)
Nivo-IPi (Rank 5th)	**0.50 (0.30-0.83)**	**0.59 (0.41-0.85)**	0.76 (0.52-1.1)	0.87 (0.62-1.21)	0.96 (0.70-1.31)	0.93 (0.61-1.42)	0.86 (0.57-1.29)	0.84 (0.53-1.34)	0.82 (0.55-1.21)
Atezo (Rank 6th)	**0.49 (0.28-0.86)**	**0.58 (0.37-0.9)**	0.74 (0.47-1.16)	0.85 (0.57-1.28)	0.98 (0.65-1.47)	0.97 (0.67-1.42)	0.89 (0.62-1.29)	0.88 (0.57-1.35)	0.85 (0.61-1.20)
Pembro (Rank 7th)	**0.44 (0.27-0.71)**	**0.52 (0.37-0.72)**	**0.66 (0.47-0.92)**	0.76 (0.57-1.01)	0.87 (0.66-1.16)	0.89 (0.61-1.29)	0.92 (0.58-1.46)	0.90 (0.54-1.51)	0.88 (0.56-1.37)
Camre-Chemo (Rank 8th)	0.80 (0.27-2.34)	0.94 (0.34-2.60)	1.20 (0.43-3.34)	1.38 (0.50-3.79)	1.59 (0.58-4.35)	1.62 (0.57-4.58)	1.82 (0.67-4.92)	0.99 (0.59-1.64)	0.96 (0.62-1.48)
Chemo (Rank 9th)	**0.31 (0.20-0.49)**	**0.36 (0.27-0.49)**	**0.47 (0.35-0.63)**	**0.54 (0.42-0.68)**	**0.62 (0.49-0.78)**	**0.63 (0.45-0.88)**	**0.71 (0.60-0.84)**	0.39 (0.15-1.04)	0.97 (0.60-1.58)
Nivo (Rank 10th)	**0.29 (0.17-0.51)**	**0.34 (0.22-0.53)**	**0.44 (0.28-0.68)**	**0.50 (0.33-0.75)**	**0.58 (0.38-0.87)**	**0.59 (0.37-0.94)**	**0.66 (0.45-0.96)**	0.36 (0.13-1.03)	0.93 (0.67-1.30)	Cemiplimab (Rank 1th)

Cancer Immunol Immunother. 2022 Jun;71(6):1345-1355.

Network meta-analysis: 1L treatment, PD-L1 ≥ 50%

ORR

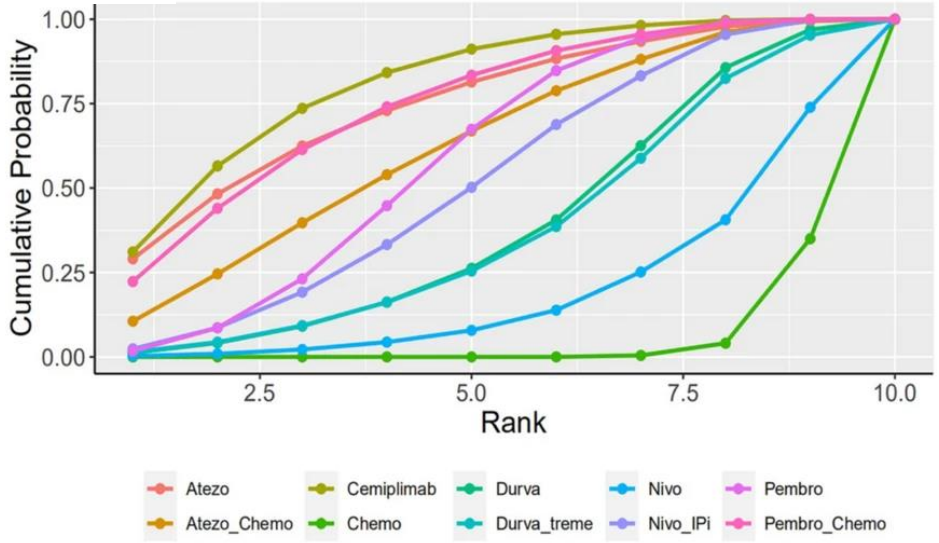
Rank 1th Camre-Chemo	Rank 2th 1.45 (0.93-2.27)	Rank 3th **1.96 (1.22-3.17)**	Rank 4th **2.01 (1.22-3.31)**	Rank 5th **2.19 (1.22-3.94)**	Rank 6th **2.46 (1.66-3.7)**	Rank 7th **2.84 (1.77-4.55)**	Rank 8th **3.11 (1.89-5.14)**	Rank 9th **3.94 (2.39-6.51)**	**6.29 (3.71-10.7)**	**7.91 (5.00-12.6)**	**11.55 (6.59-20.5)**
	Atezo-Chemo 1.35 (0.98-1.86)	Pembro-Chemo 1.38 (0.97-1.96)	Durva-treme 1.51 (0.94-2.41)	Sinti-Chemo 1.70 (1.40-2.06)	Chemo 1.95 (1.43-2.67)	Nivo-IPi 2.14 (1.51-3.05)	Durva 2.71 (1.89-3.88)	Cemiplimab 3.21 (2.09-4.96)	Atezo 4.34 (2.92-6.46)	Pembro 5.45 (4.06-7.36)	Nivo 7.96 (5.14-12.5)
		1.02 (0.69-1.51)	1.09 (0.65-1.84)	1.12 (0.68-1.84)	1.26 (0.97-1.63)	1.45 (1.01-2.07)	1.59 (1.07-2.34)	2.01 (1.35-2.98)	3.21 (2.09-4.96)	4.03 (2.86-5.71)	5.88 (3.68-9.54)
			Durva-treme 1.23 (0.92-1.65)	1.13 (0.73-1.73)	1.15 (0.9-1.47)	1.30 (0.79-2.13)	1.42 (0.84-2.39)	1.80 (1.06-3.04)	2.88 (1.66-5.00)	3.61 (2.23-5.88)	5.28 (2.95-9.49)
				Sinti-Chemo 1.41 (0.96-2.07)	1.26 (0.94-1.69)	1.39 (0.94-2.05)	1.55 (1.16-2.07)	1.96 (1.29-2.99)	3.14 (2.00-4.95)	3.94 (2.72-5.72)	5.75 (3.53-9.47)
					Chemo 1.56 (0.87-2.82)	1.60 (1.21-2.11)	1.74 (1.00-3.03)	2.06 (0.92-4.74)	2.30 (1.07-5.02)	2.87 (1.55-5.35)	
						Nivo-Ipi 1.07 (0.52-2.19)	1.10 (0.67-1.78)	1.63 (0.81-3.26)	1.93 (0.77-4.92)	2.15 (0.89-5.26)	2.69 (1.27-5.72)
							Atezo 1.02 (0.53-1.96)	1.59 (1.00-2.54)	1.88 (0.88-4.09)	2.10 (1.03-4.32)	2.62 (1.53-4.55)
								Pembro 1.19 (0.53-2.69)	1.32 (0.62-2.85)	1.65 (0.91-3.03)	
									Cemiplimab 1.11 (0.42-2.96)	1.39 (0.58-3.26)	
										Atezo-Chemo 1.25 (0.56-2.80)	
											Sinti-Chemo Pembro-Chemo

TRAEs gr3-5

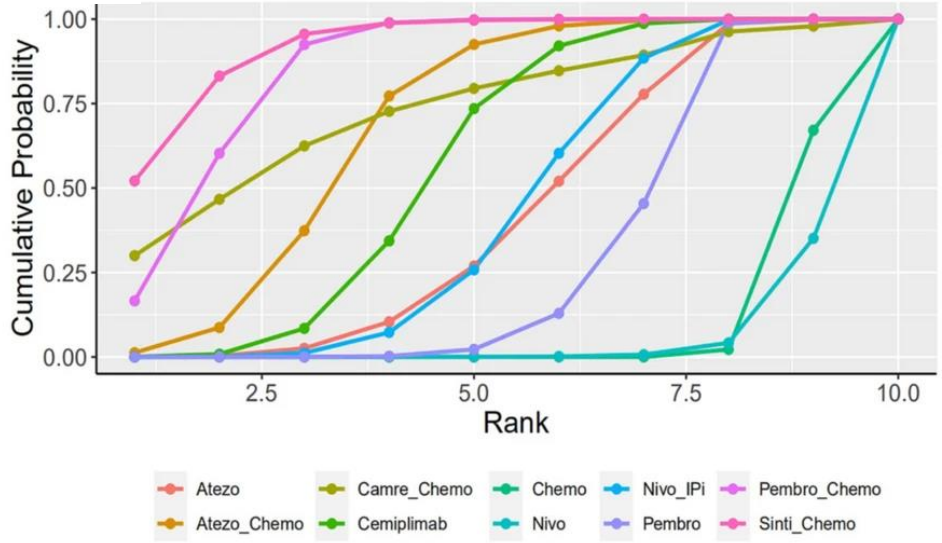
Cancer Immunol Immunother. 2022 Jun;71(6):1345-1355.

Cumulative ranking probability: 1L treatment, PD-L1 ≥ 50%

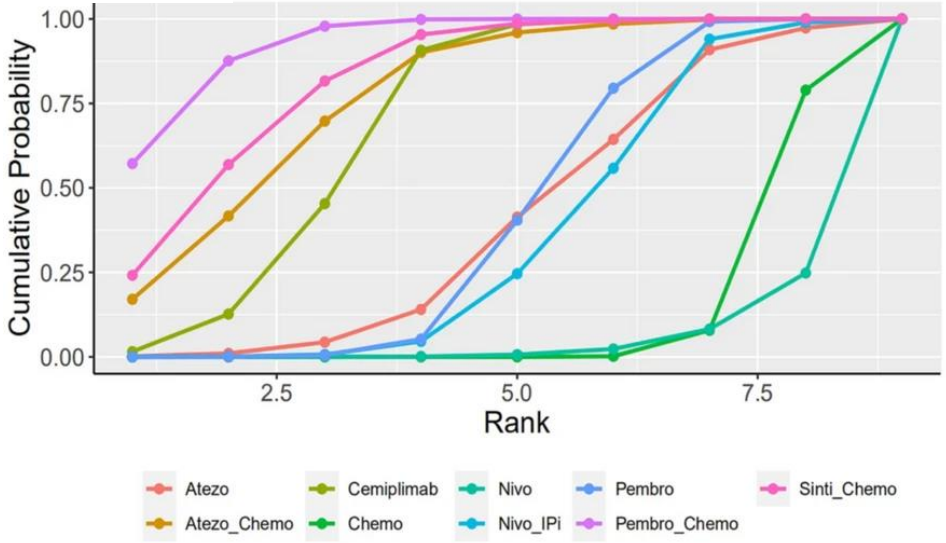
OS



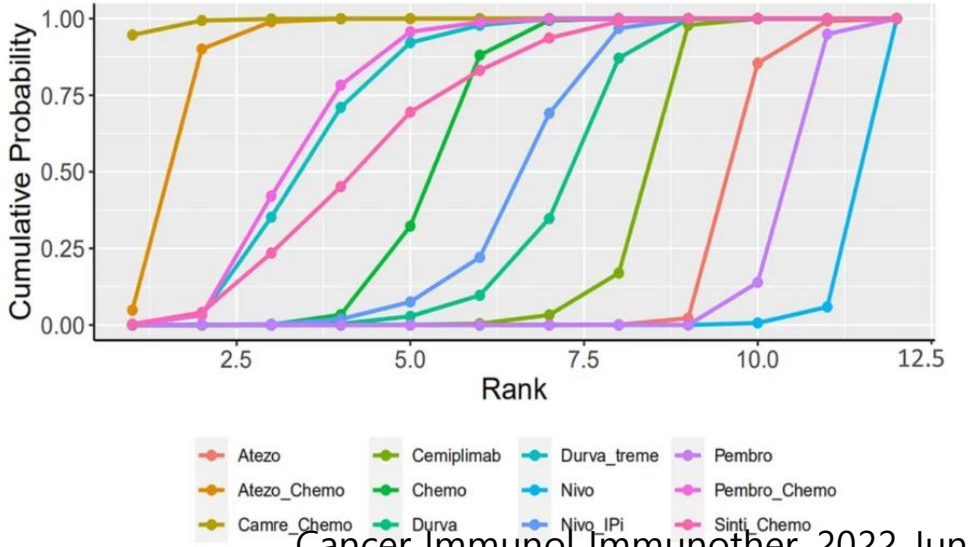
PFS



ORR



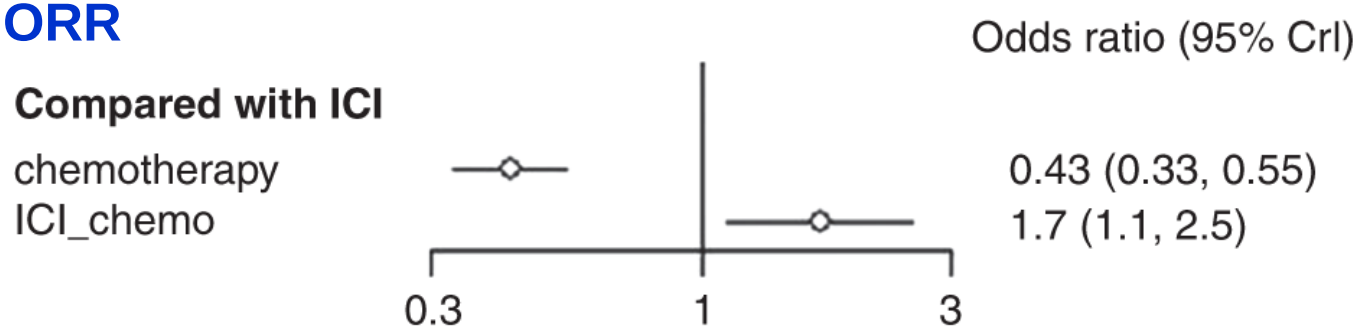
TRAEs gr3-5



Cancer Immunol Immunother. 2022 Jun;71(6):1345-1355.

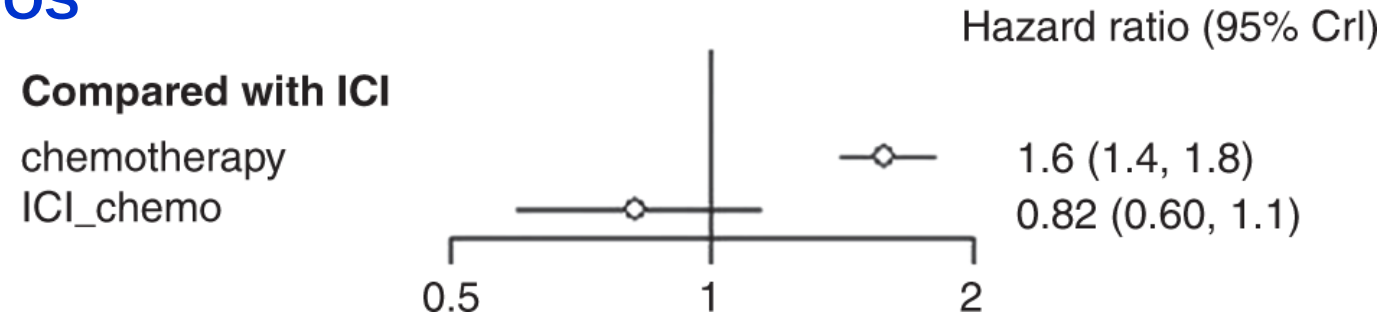
Network meta-analysis: 1L treatment, PD-L1 ≥ 50%

ORR



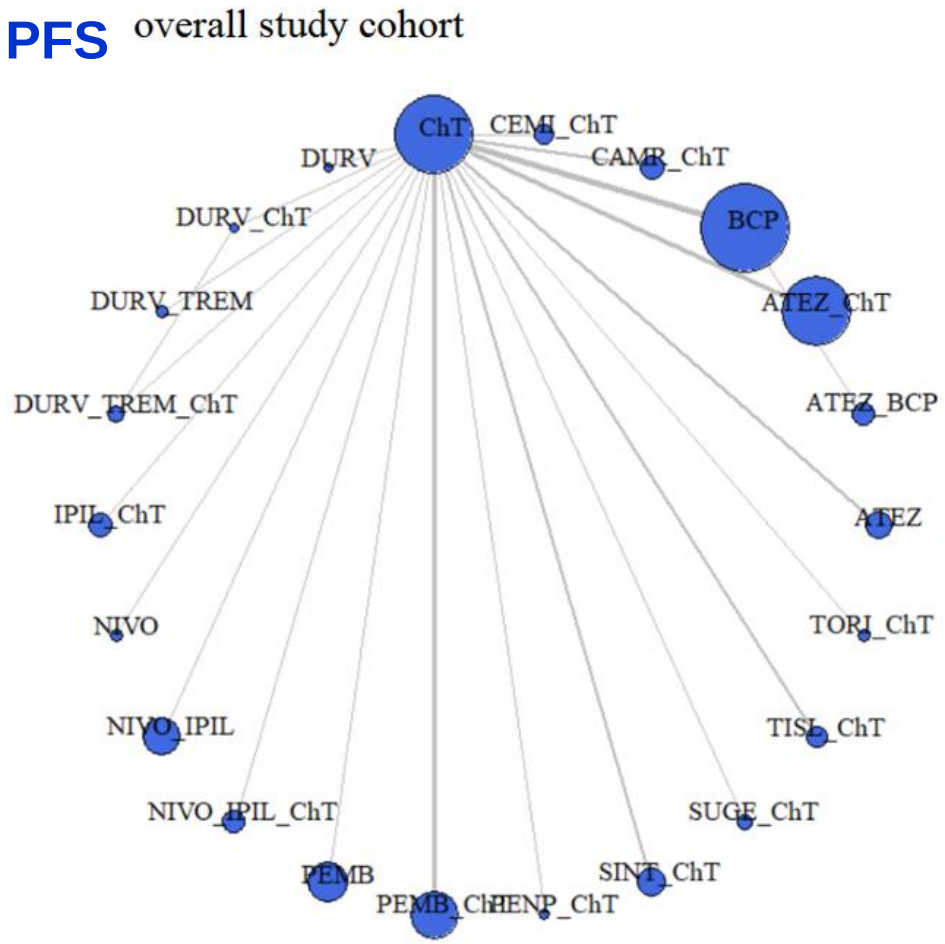
PFS

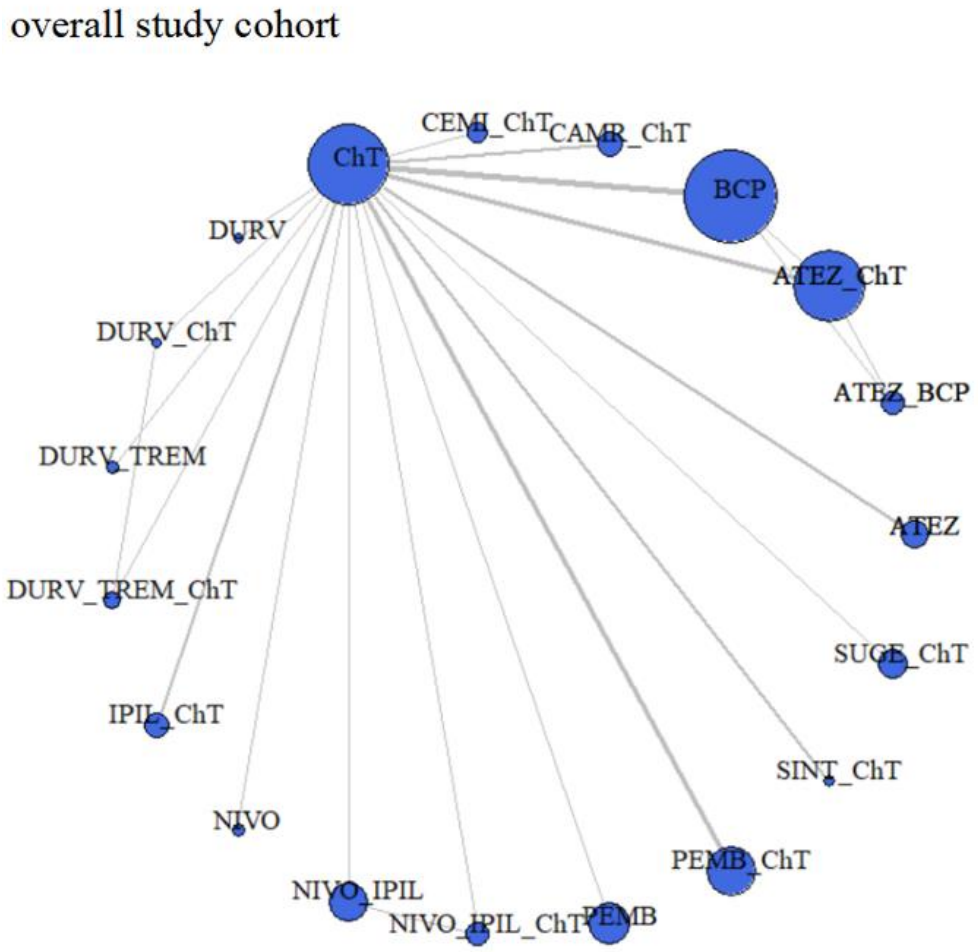
OS



Br J Cancer. 2022 Sep;127(5):948-956.

Network meta-analysis (NMA) of comparisons for PFS (A) and OS (B)





PLoS One. 2023 Apr 18;18(4):e0283719.

Study	Years	Study design	Sample size	Median ages (years)	Male/ female	Histology	Disease stage	PD-L1 expression	Therapeutic regimen	ChT therapy Drug	Follow-up (month)
Keynote-189 [4, 24, 25]	2018, 2020	double blind, phase III	410/206	65/64	363/ 253	non-squ	IV	All	PEMB + ChT vs. ChT	CAB (AUC = 6)/3w or CIS (75mg/ m^2/3w) +PEM (500mg/m^2/3w)	23.1
Keynote-024 [5, 6, 26]	2016, 2019	open-label, phase III	154/151	64.5/63	187/ 118	squ/non-squ	IIIB-IV	≥50%	PEMB vs. ChT	CIS (75mg/ m^2/3w) or CAB (AUC = 5–6)/3w +PEM (500mg/m^2/3w) or PTX (200 mg/m^2 Q3W) or GEM (1250 mg/m2 d1,8 of Q3W)	25.2
Keynote-042 [27]	2019	open-label, phase III	637/637	63/64	902/ 372	squ/non-squ	IV	≥1%	PEMB vs. ChT	1) CAB (AUC = 5–6)/ 3w+ PEM (500mg/m^2) /3w or PTX (200 mg/ m^2 Q3W)	12.8
Keynote-598 [28]	2020	double blind, phase III	284/284	64/65	393/ 175	squ/non-squ	IV	≥50%	PEMB+IPIL vs. PEMB+placebo		20.6
Keynote-407 [29, 30]	2018, 2020	double blind, phase III	278/281	65/65	455/ 104	squ	IV	All	PEMB+ ChT vs. ChT	CAB (AUC = 6, d1)/ 3w+PTX (200mg/m^2/3w d1) or nab- PTX (100mg/m^2/ 3w d1, 8, 15), 4 circle	14.3
IMpower110 [8, 31]	2020, 2021	open-label, phase III	277/277	NG/NG	NG/ NG	squ/non-squ	IV	≥1%	ATEZ vs. ChT	CIS (75mg/ m^2/3w) or CAB (AUC = 6)/3w +PEM (500mg/m^2/3w) or GEM (1000 mg/m2 d1,8 of Q3W)	15.7
IMpower130 [32]	2019	open-label, phase III	483/240	64/65	415/ 309	non-squ	IV	All	ATEZ + ChT vs. ChT	CAB (AUC = 6)/3w +nab-PTX (100mg/ m^2/w), 4 or 6C	19.2
IMpower131 [33]	2020	open-label, phase III	343/340	65/65	557/ 126	squ	IV	All	ATEZ+ ChT vs. ChT	CAB (AUC = 6)/3w+ +PTX (200mg/m^2/3w d1) or nab-PTX (100mg/m^2/w), 4 or 6C	18.1
IMpower132 [34]	2020	open-	292/286	64/63	384/	non-squ	IV	All	ATEZ + ChT vs.	CAB (AUC = 6)/3w or	14.8

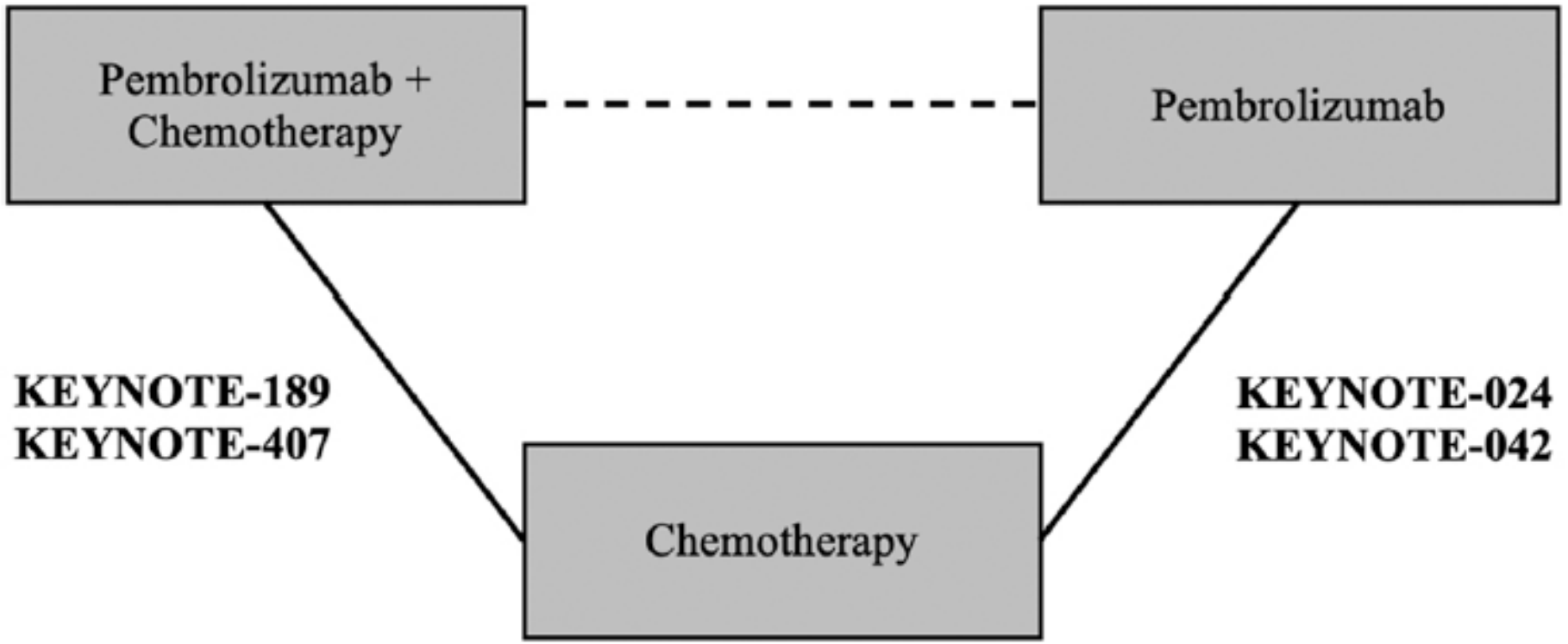
The optimal treatment regimens for NSCLC according to PD-L1 expression level and different pathological types

	OS		PFS	
	Best regimen	**Rank probability (%)**	**Best regimen**	**Rank probability (%)**
PD-L1 TPS expression				
< 1%	NIVO+IPIL+ChT	80.6	PEMB+ChT	84.2
1–49%	CEMI+ChT	86.9	CAMR+ChT	89.5
>50%	CEMI	79.2	CAMR+ChT	90.4
Squamous	CEMI+ChT	74.6	SUGE+ChT	91.2
Non-squamous	PEMB+ChT	94.6	ATEZ+BCP	92.3
Overall	PEMB+ChT	89.5	PENP+ChT	95.7

Abbreviation: ATEZ, atelizumab; BEV, bevacizumab; CAMR, camrelizumab; CEMI, cemiplimab; ChT, chemotherapy; IPIL, ipilimumab; NIVO, nivolumab; PEMB, pembrolizumab; PENP, Penpulimab; SUGE, sugemalimab.

https://doi.org/10.1371/journal.pone.0283719.t002

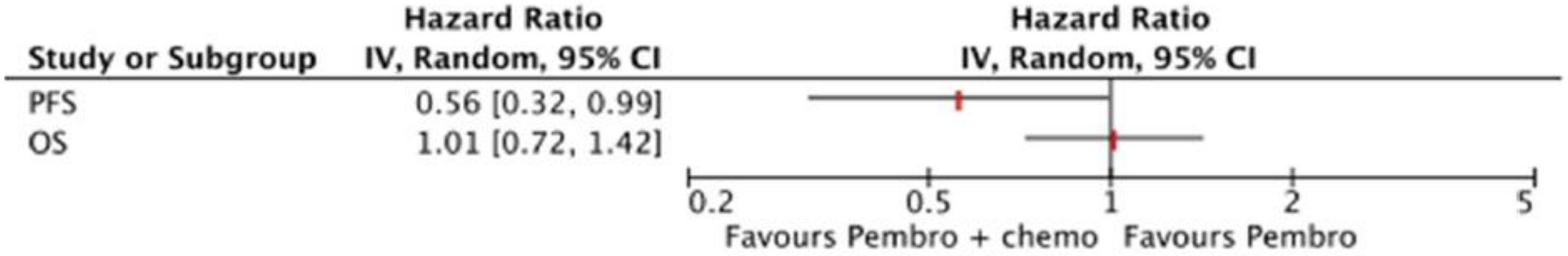
Meta-analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 ≥ 50%



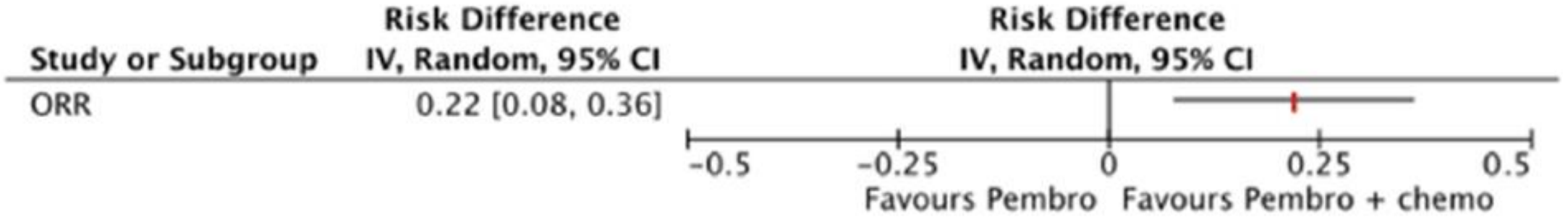
Crit Rev Oncol Hematol. 2022 May;173:103660.

Network meta-analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 ≥ 50%

PFS & OS



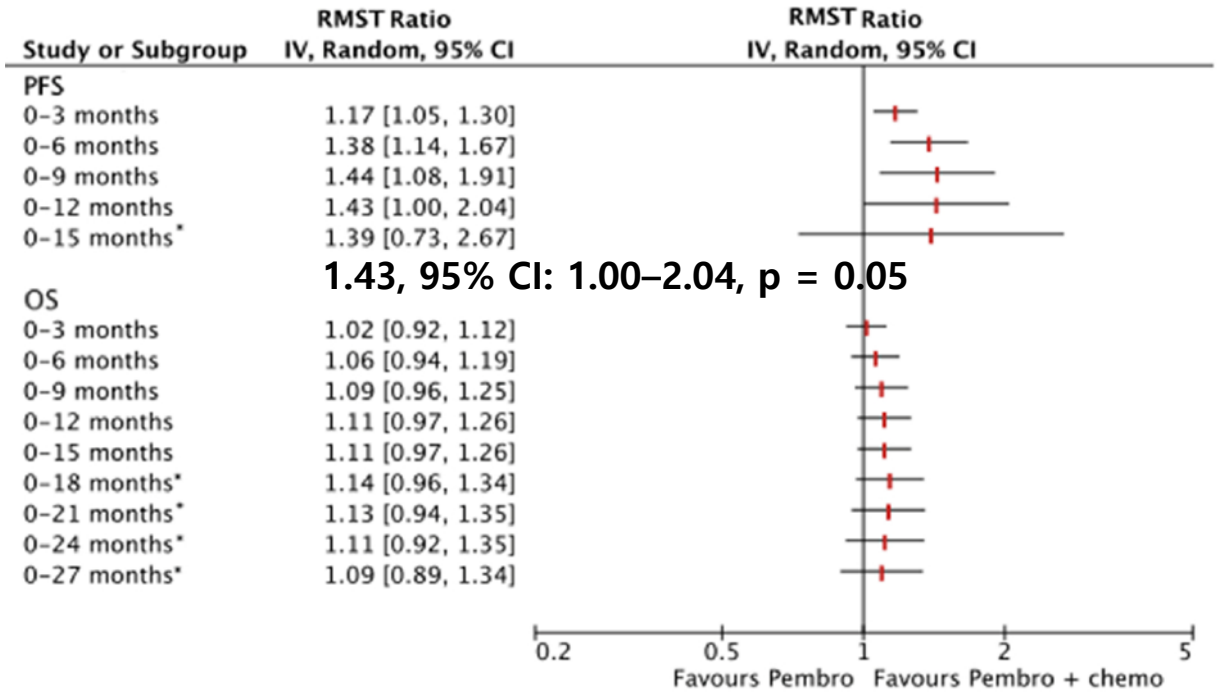
ORR

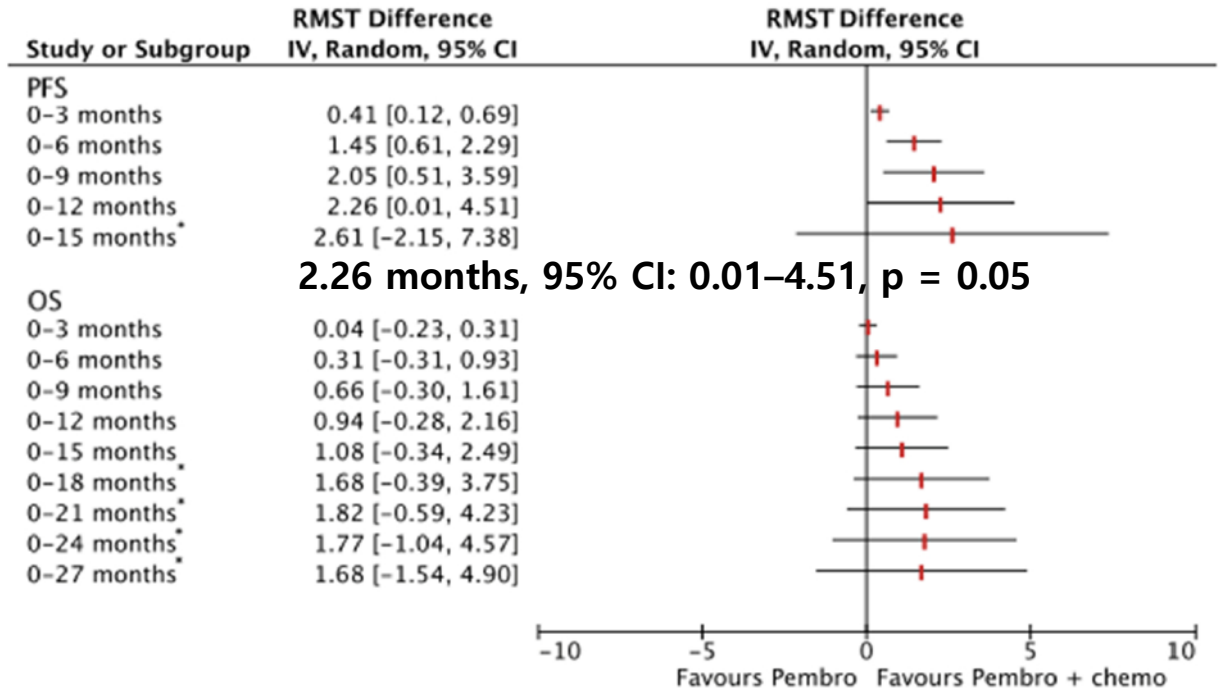


Crit Rev Oncol Hematol. 2022 May;173:103660.

Network meta-analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 ≥ 50%

PFS & OS



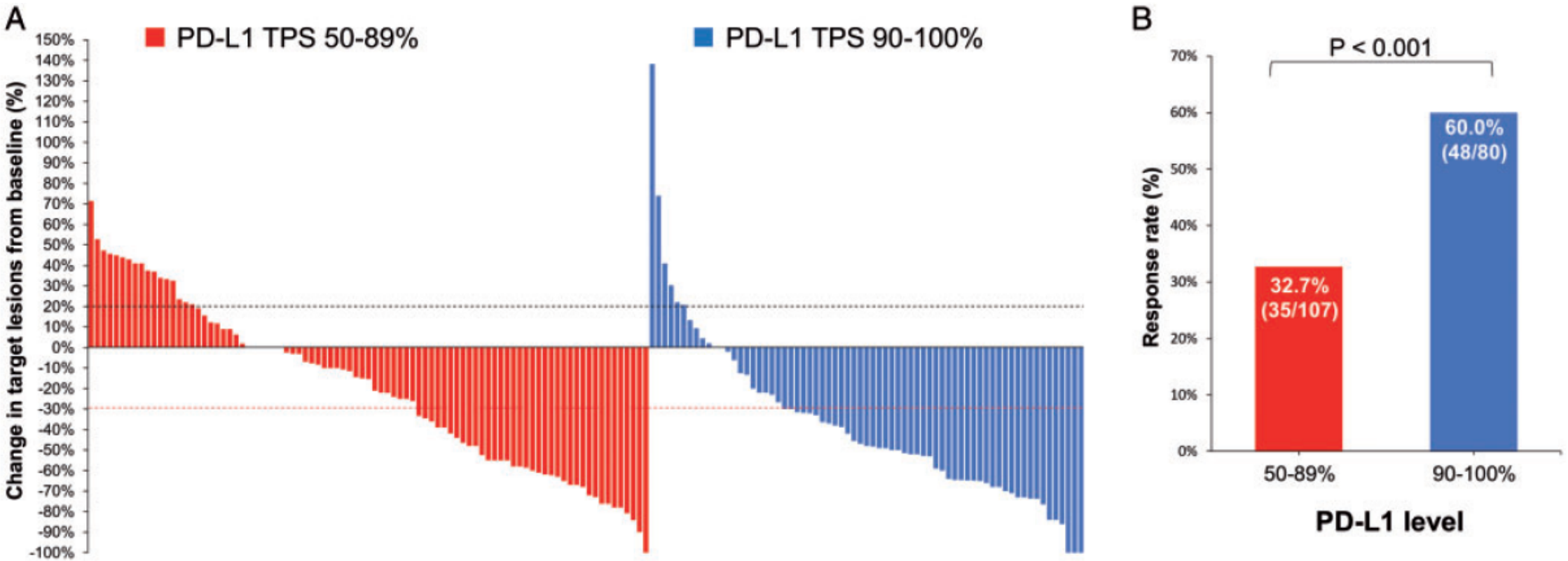


*Restricted mean survival time (RMST)

Crit Rev Oncol Hematol. 2022 May;173:103660.

Retrospective analysis: 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

ORR

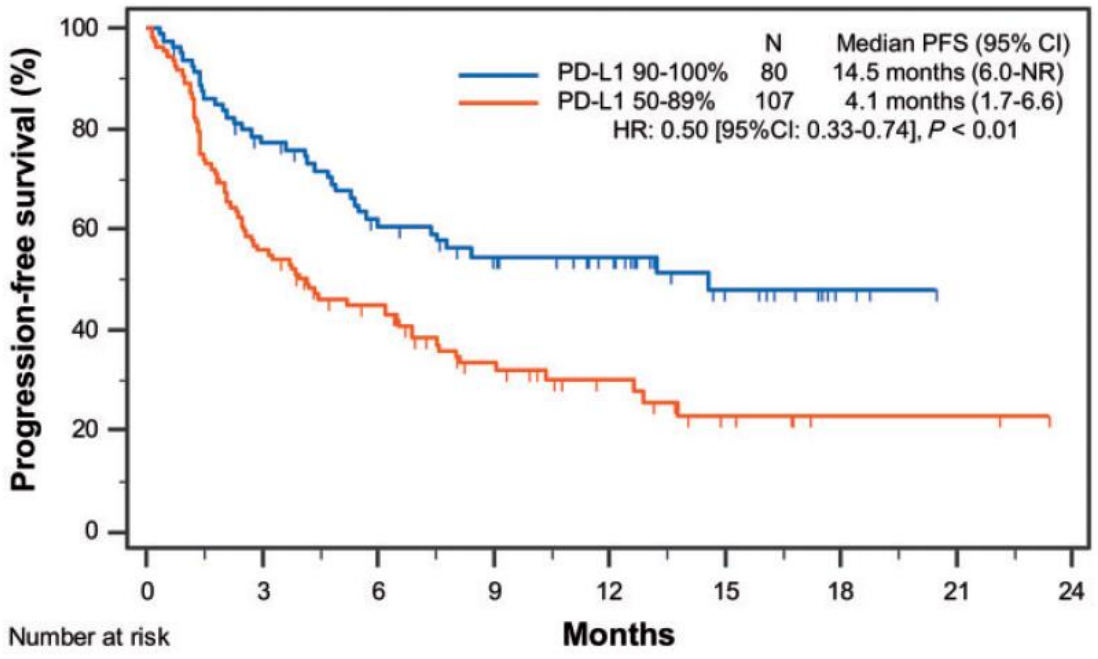


Ann Oncol. 2019 Oct 1;30(10):1653-1659.

Retrospective analysis: 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

PFS

A

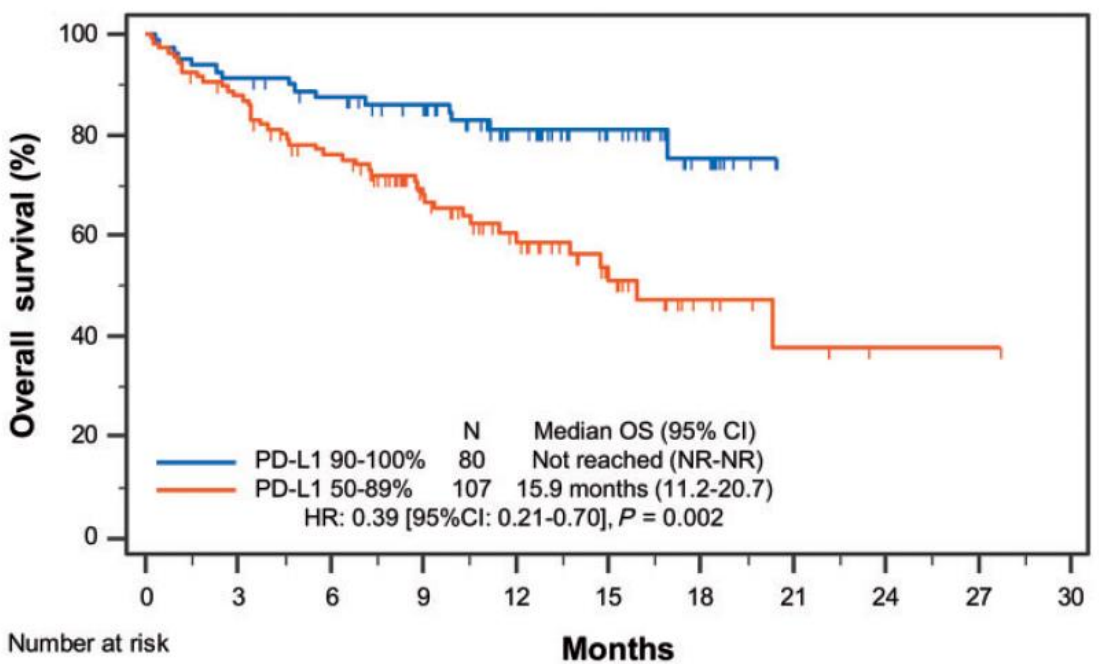


Number at risk

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

OS

B



Number at risk

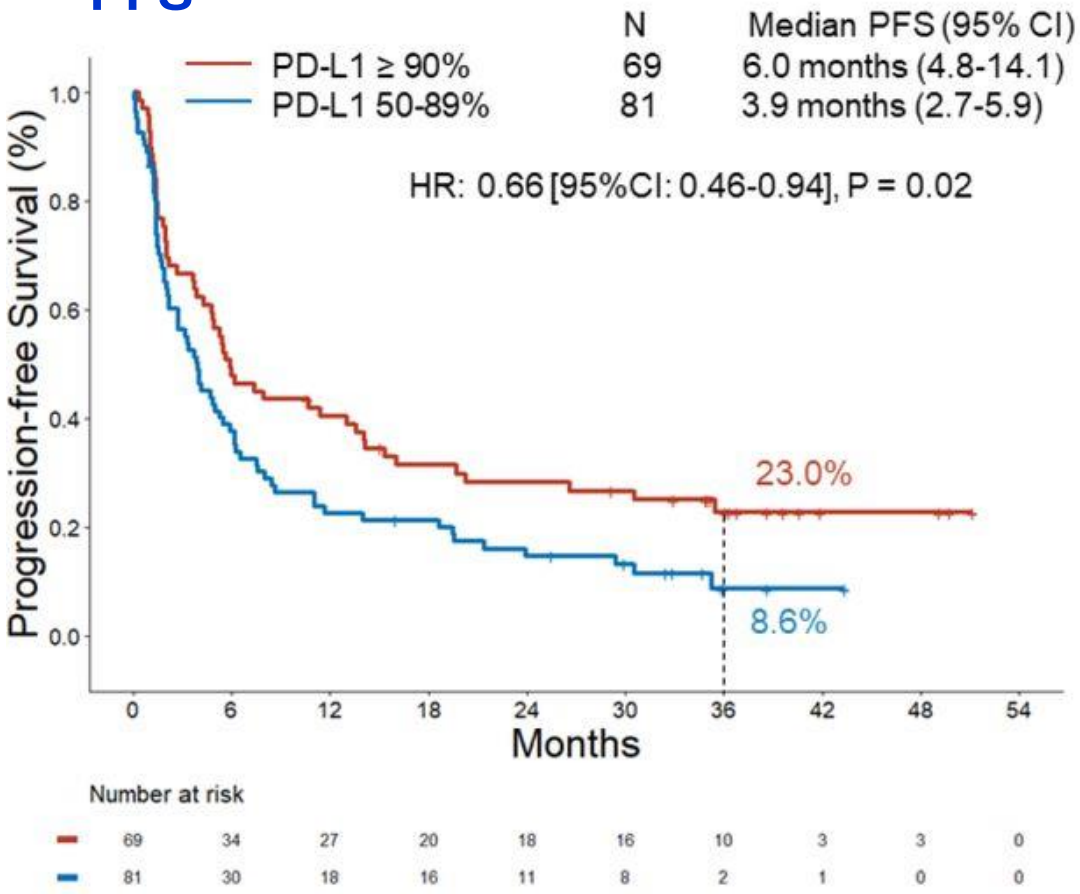
PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

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

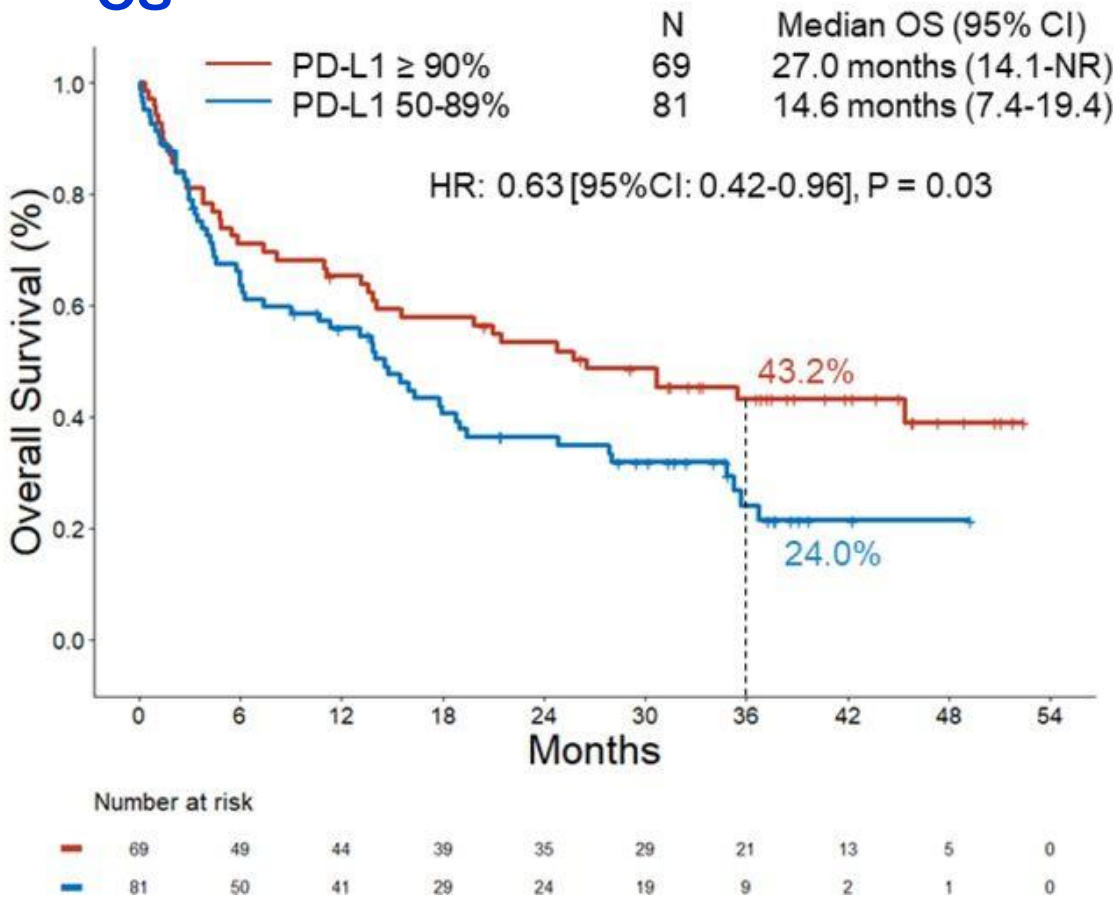
Retrospective analysis: 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

3-year outcomes

PFS



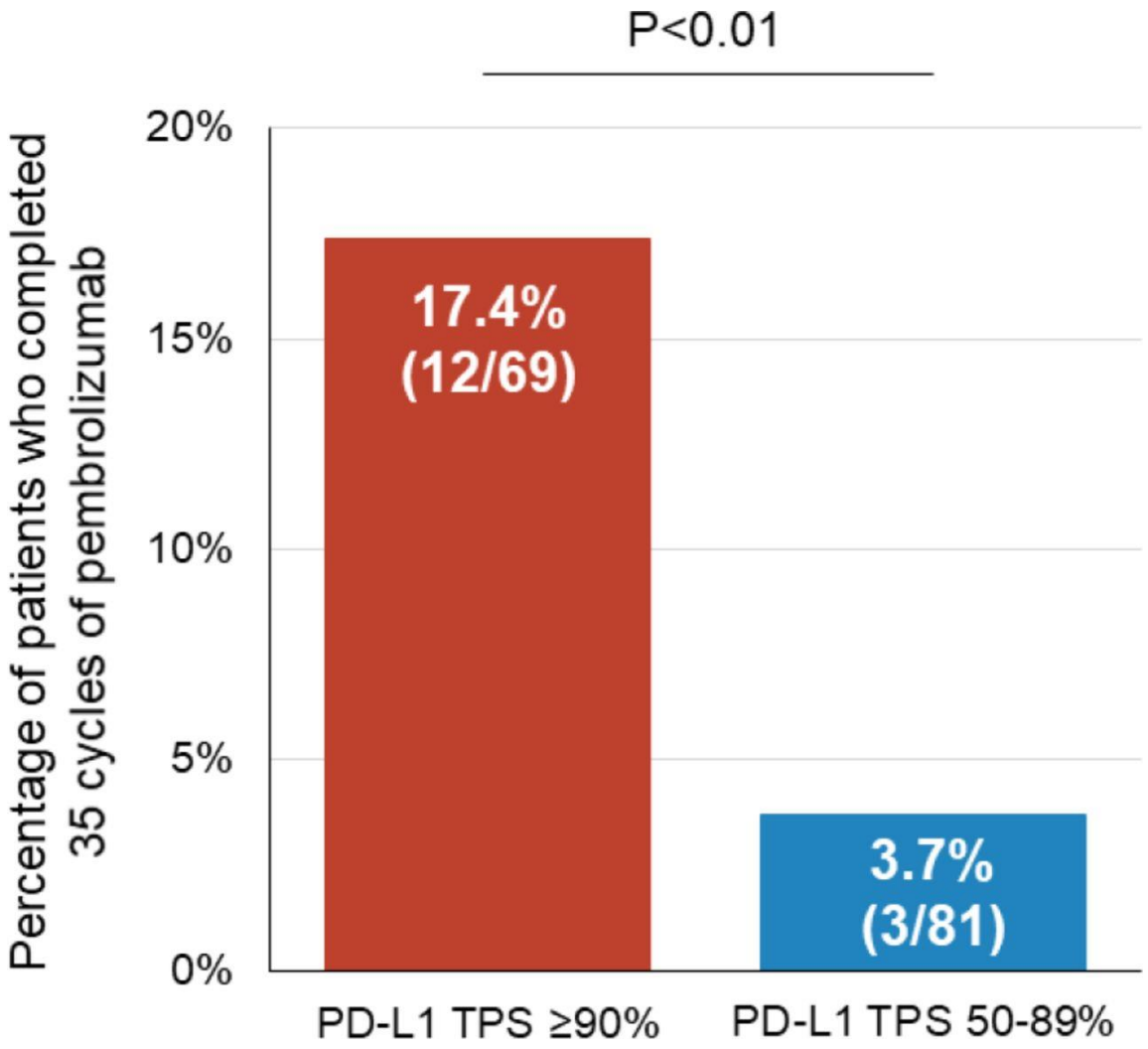
OS



J Immunother Cancer. 2021;9(Suppl2):A312

Retrospective analysis: 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

3-year outcomes

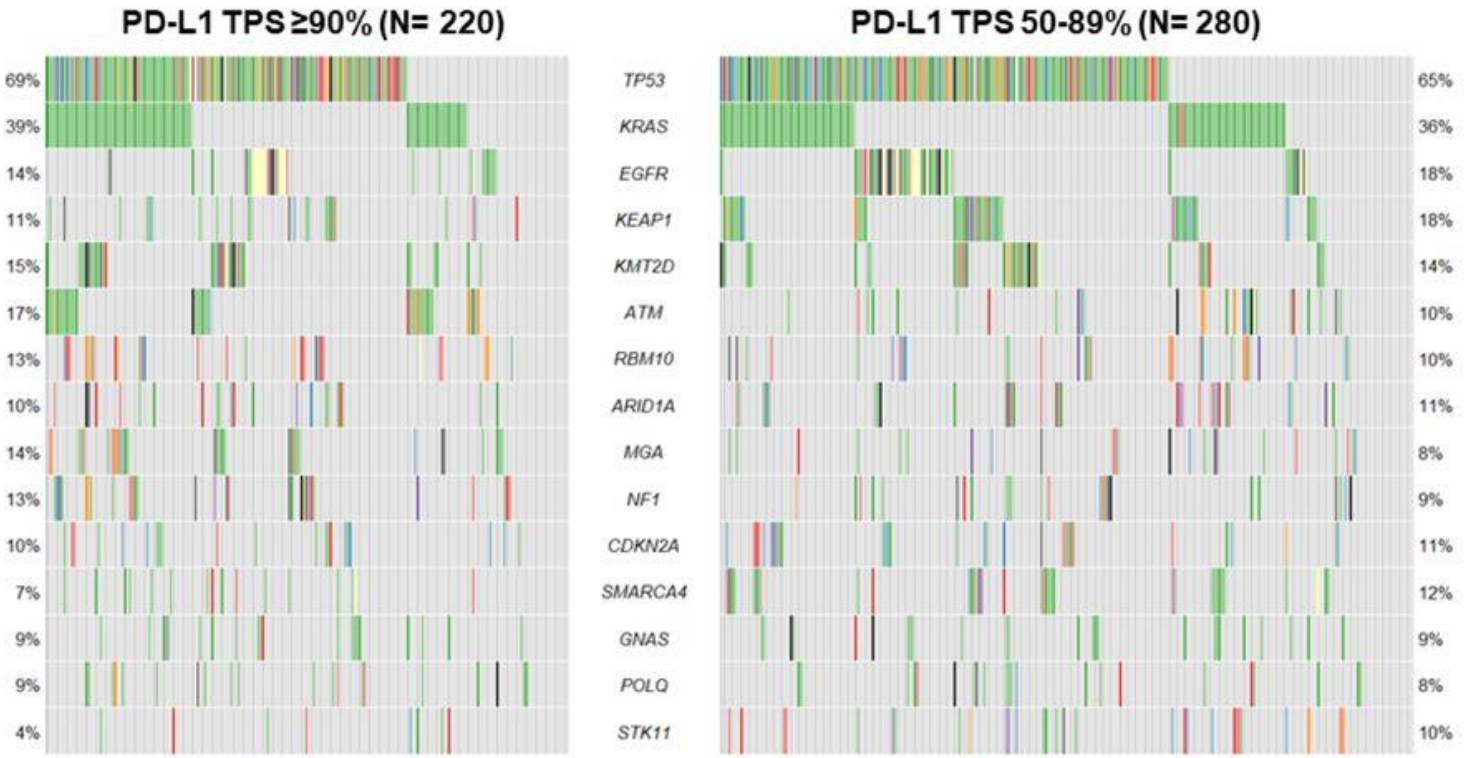


J Immunother Cancer. 2021;9(Suppl2):A312

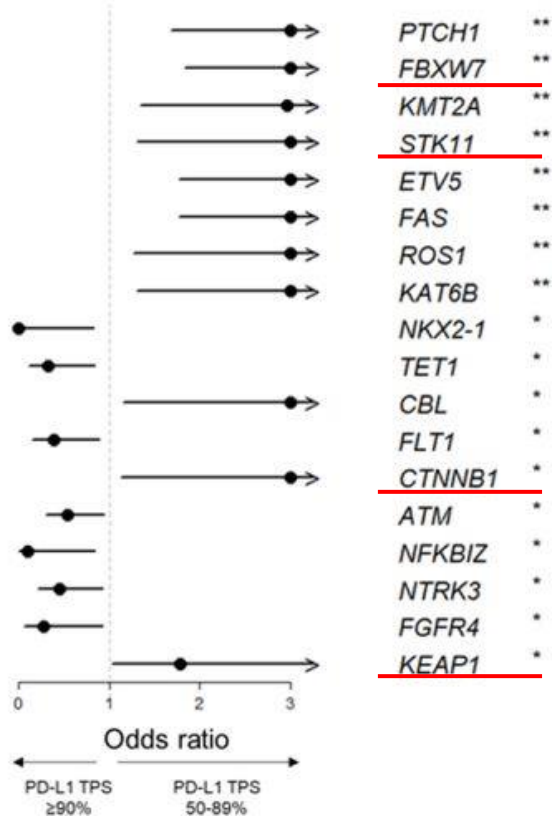
Retrospective analysis: 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

3-year outcomes

A



Gene mutation enrichment analysis



J Immunother Cancer. 2021;9(Suppl2):A312

Retrospective analysis (Japan): 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

ORR

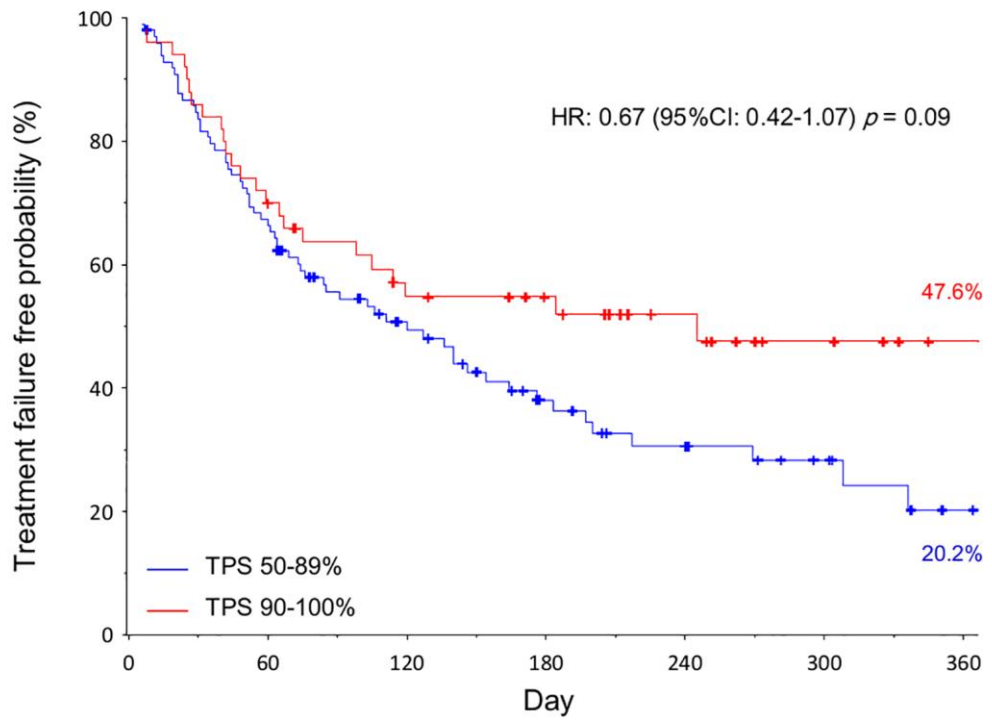
Response		TPS 90–100% cohort (N = 50)	TPS 50–89% cohort (N = 99)	Total (N = 149)	*p* value
Best response—no. (%)					
	Complete response	1 (2.0)	1 (1.0)	2 (1.3)	0.49
	Partial response	28 (56.0)	45 (45.5)	73 (49.0)	
	Stable disease	9 (18.0)	24 (24.2)	33 (22.2)	
	Progression disease	12 (24.0)	25 (25.3)	37 (24.8)	
	Not evaluated	0 (0.0)	4 (4.0)	4 (2.7)	
Objective response rate—no. (%)		29 (58.0)	46 (46.5)	75 (50.3)	0.23
Disease control rate—no. (%)		38 (76.0)	70 (70.7)	108 (72.5)	0.56

PLoS One. 2019 Jul 31;14(7):e0220570.

Retrospective analysis (Japan): 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

TTF

A

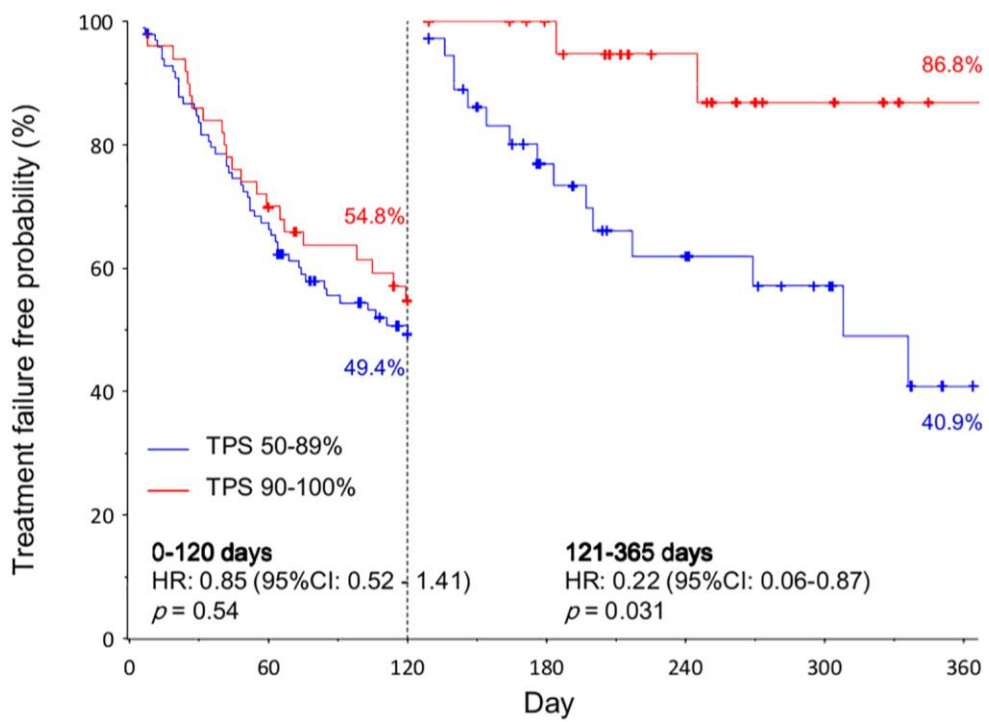


No. at risk

TPS 50-89%	99	66	38	22	15	9	3
TPS 90-100%	50	35	24	19	12	5	1

TTF (≤120 vs. >120 days)

B



No. at risk

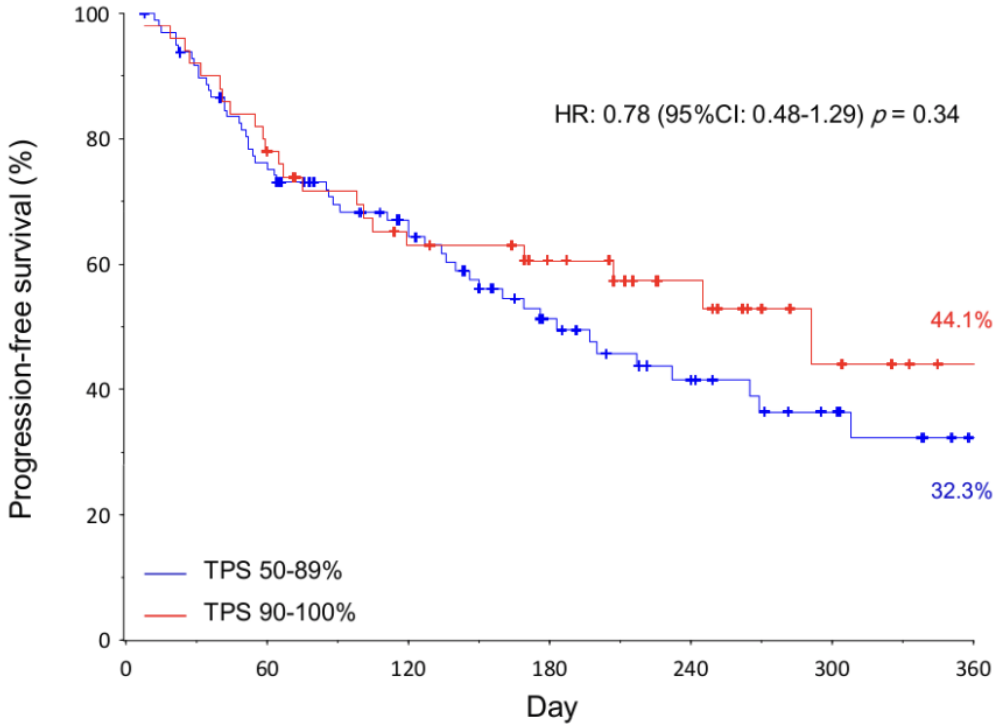
TPS 50-89%	99	66	38	22	15	9	3
TPS 90-100%	50	35	24	19	12	5	1

PLoS One. 2019 Jul 31;14(7):e0220570.

Retrospective analysis (Japan): 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

PFS

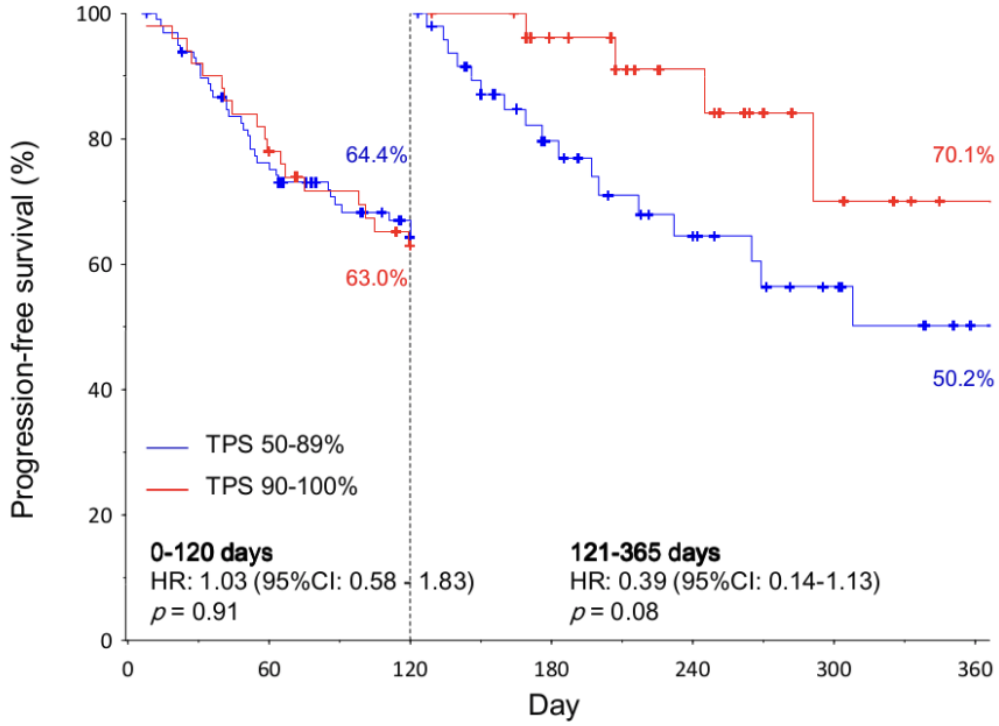
A



No. at risk							
TPS 50-89%	99	73	51	29	19	11	4
TPS 90-100%	50	39	28	21	13	5	1

PFS (≤120 vs. >120 days)

B



No. at risk							
TPS 50-89%	99	73	51	29	19	11	4
TPS 90-100%	50	39	28	21	13	5	1

PLoS One. 2019 Jul 31;14(7):e0220570.

Retrospective analysis (Japan): 1L Pembro, PD-L1 50-89% vs. PD-L1 90-100%

Immune-related AEs

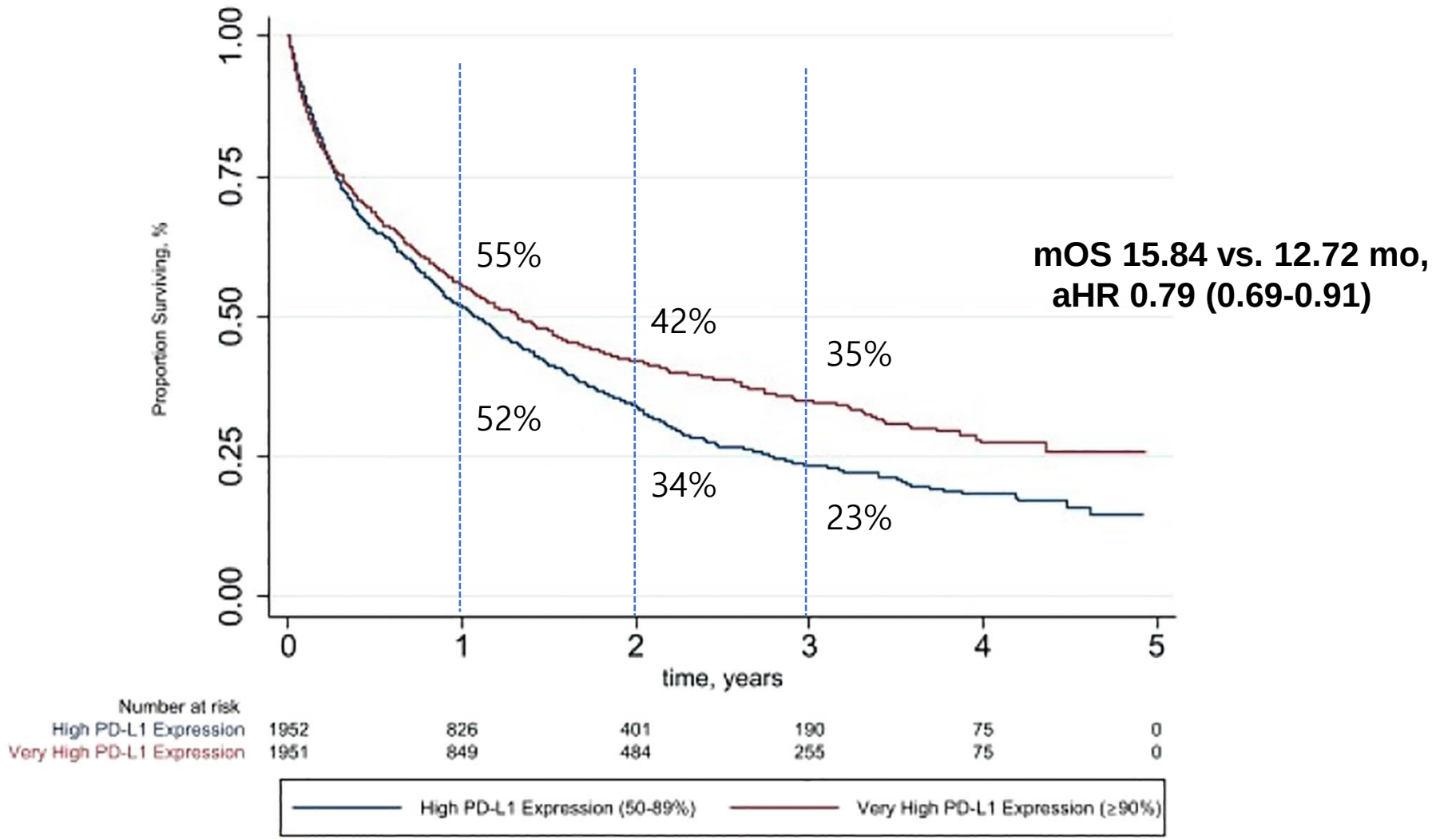
	TPS 90–100% cohort	TPS 50–89% cohort	
Adverse event	**(N = 50)**	**(N = 99)**	***p* value**
Early irAE—no. (%)	18 (36.0)	29 (29.3)	0.46
irAE grade 3 or 4—no. (%)	8 (16.0)	19 (19.2)	0.82
irAE leading to withdrawal from treatment- no. (%)	4 (8.0)	19 (19.2)	0.09

PLoS One. 2019 Jul 31;14(7):e0220570.

Retrospective cohort: 1L Pembro, PD-L1 50-89% vs. PD-L1 ≥ 90%

OS

***Nationwide U.S. (n=1,952)**



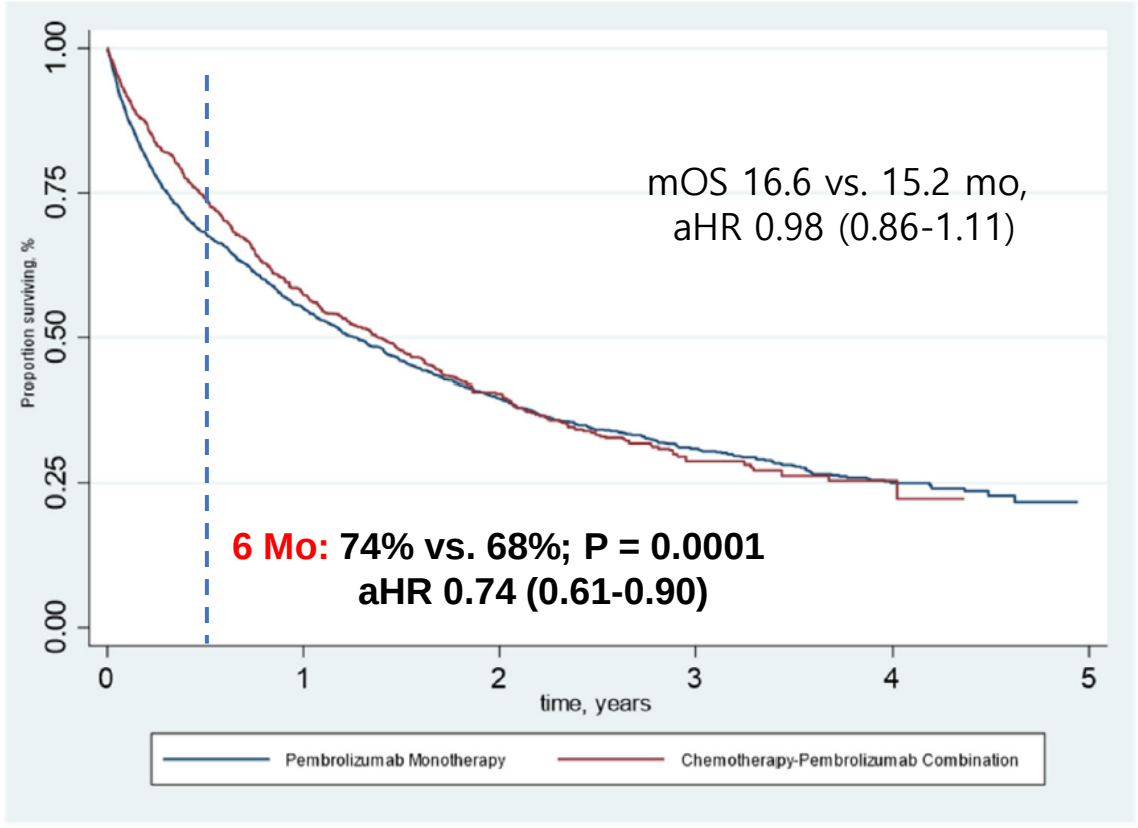
mOS 15.84 vs. 12.72 mo,
aHR 0.79 (0.69-0.91)

Clin Lung Cancer. 2022 Dec;23(8):731-736.

Retrospective cohort: 1L Pembro+Chemo vs. Pembro, PD-L1 ≥ 50% or ≥ 90%

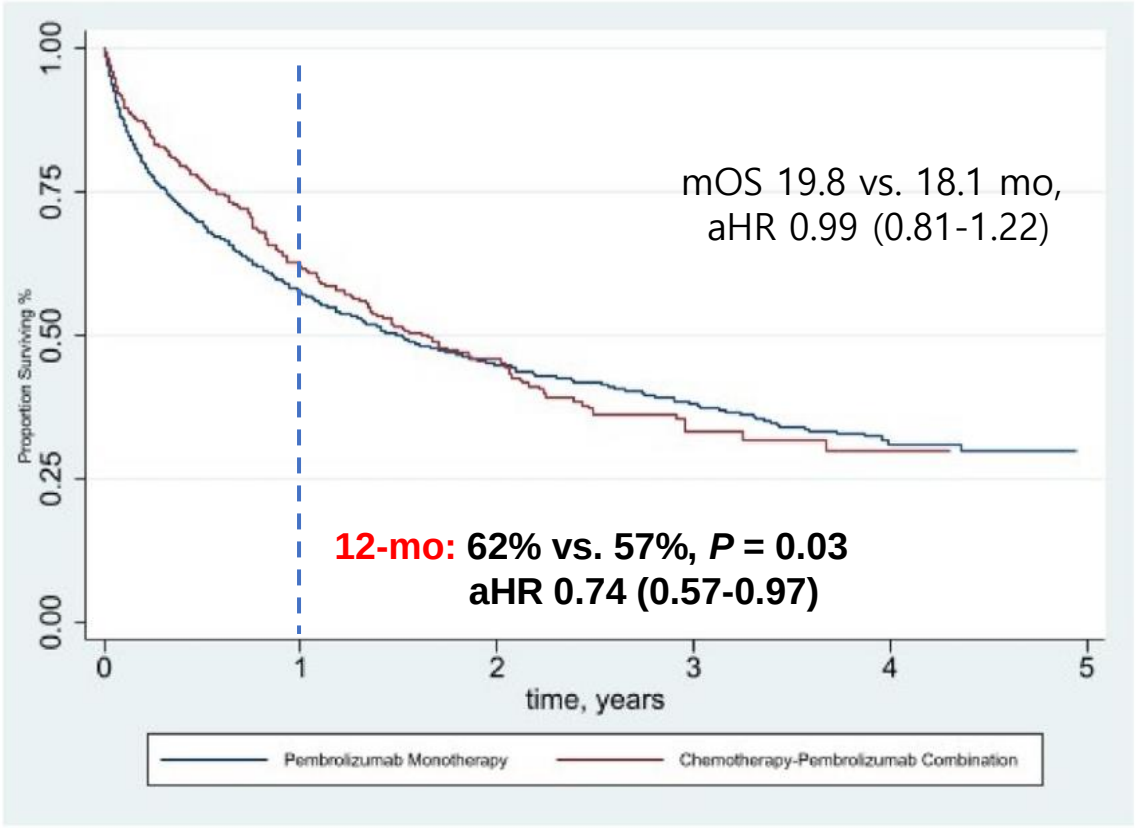
*Nationwide U.S. (n=3,086)

OS: PD-L1 ≥ 50%



	Time, years	0	1	2	3	4	5
Chemoimmunotherapy IPTW adjusted[a]		3090	1252	551	172	32	0
Immunotherapy alone IPTW adjusted[a]		3055	1359	728	375	130	0

OS: PD-L1 ≥ 90%



	Time, years	0	1	2	3	4	5
Chemoimmunotherapy IPTW adjusted[a]		1382	593	273	82	16	0
Immunotherapy alone IPTW adjusted[a]		1376	624	368	198	59	0

Clin Lung Cancer. 2023 May;24(3):235-243.

PD-L1 ≥ 50%: IO mono vs. IO+Chemo

- IO mono (single agent anti-PD-1/PD-L1)
  : remain mainstay of treatment, esp. PD-L1 ≥ 90%

- ORR, PFS: IO+Chemo > IO mono
- OS : IO+Chemo ~ IO mono

- IO+Chemo: rapidly progressive disease, high tumor burden

- IO mono: poor PS, elderly…

PD-L1 ≥ 50%: IO mono vs. IO+Chemo

- **IO+Chemo**

  : immunotherapy enhancing the anti-tumor effect of chemotherapy

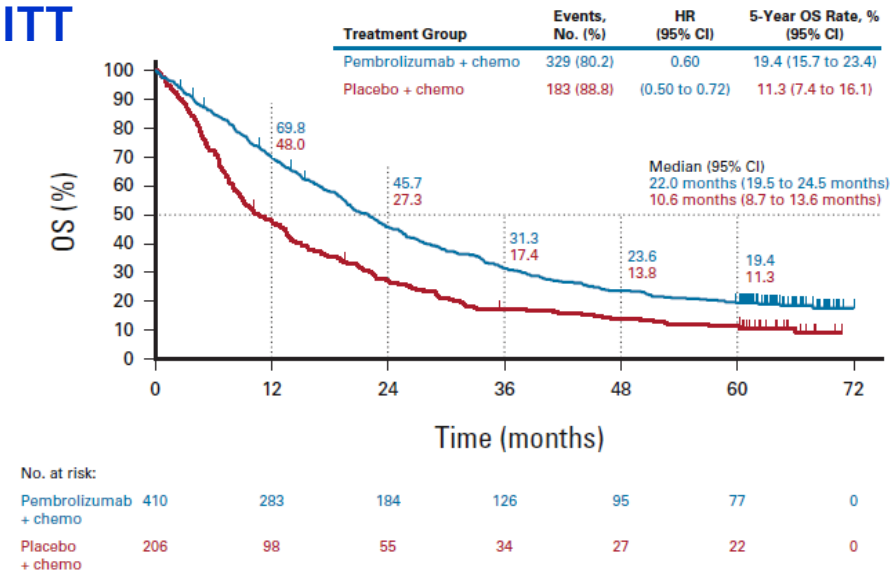
  protection against hyperprogression or primary immunotherapy resistance

- **Future researches should also explore the optimal cutoff value of PD-L1**

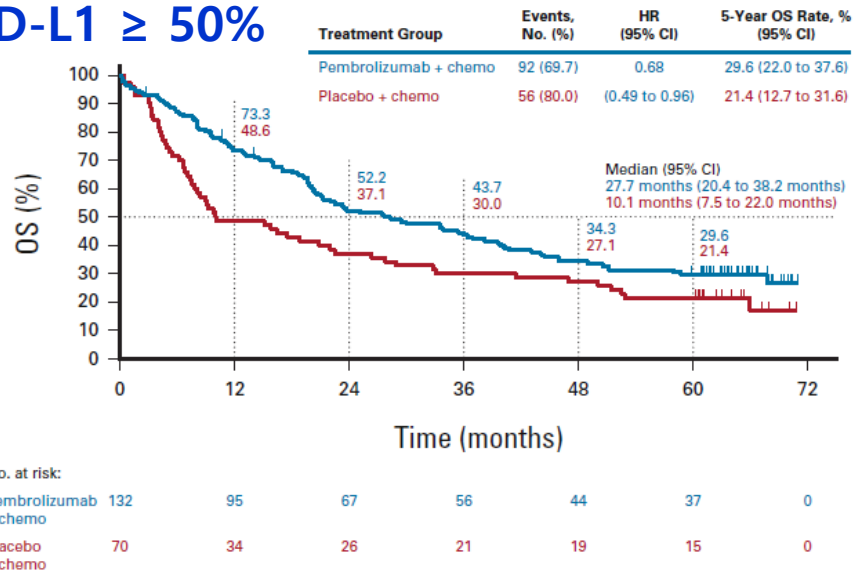
PD-L1 < 1%: IO+Chemo vs. Chemo

KEYNOTE-189: 1L Pembro+Chemo vs. Pembro, NonSQ

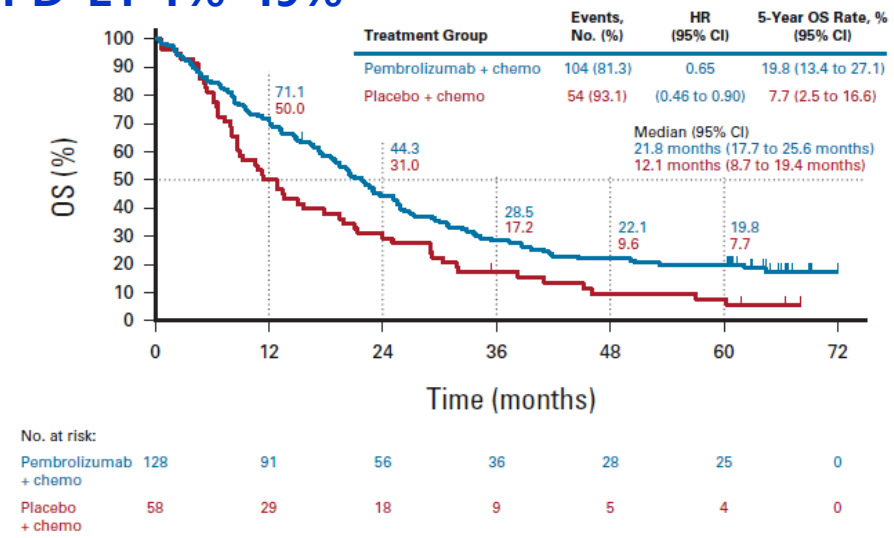
5-year OS ITT



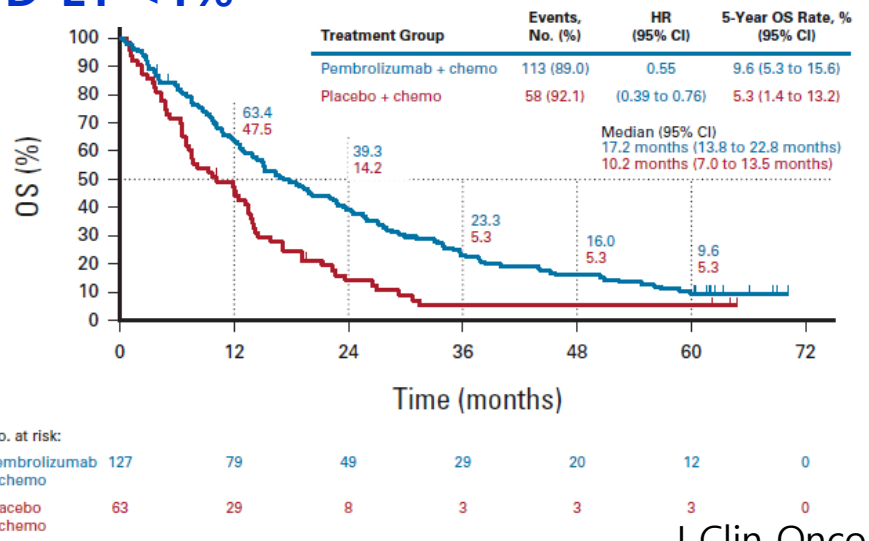
PD-L1 ≥ 50%



PD-L1 1%-49%



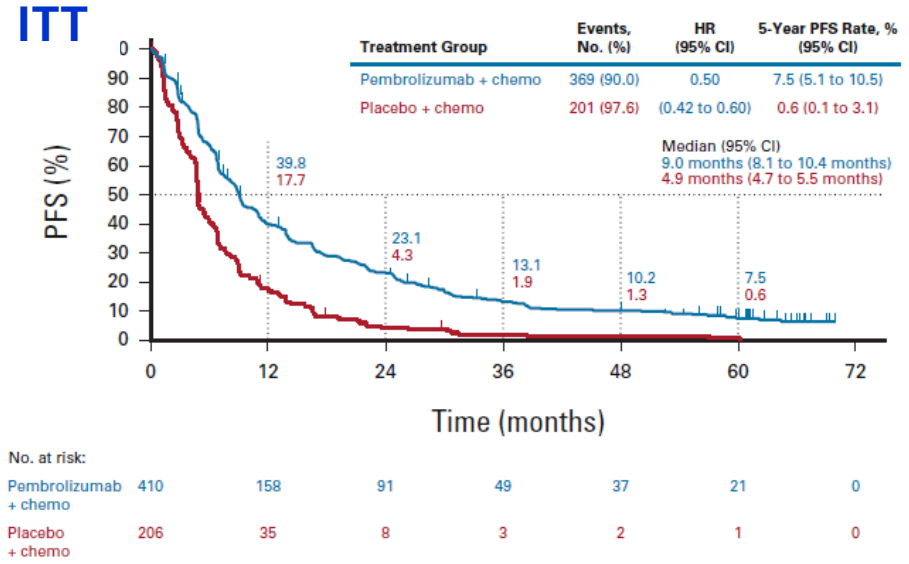
PD-L1 <1%



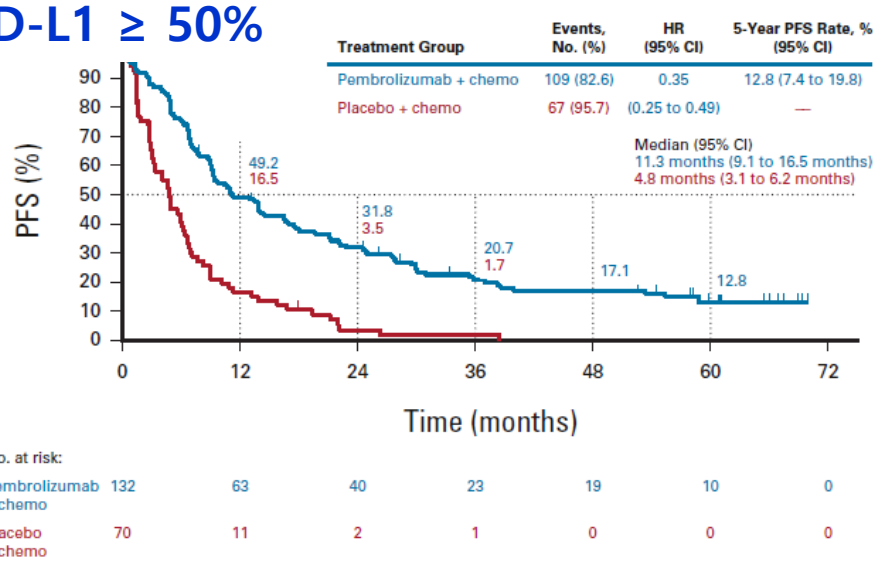
J Clin Oncol 2023;41:1992-1998

KEYNOTE-189: 1L Pembro+Chemo vs. Pembro, NonSQ

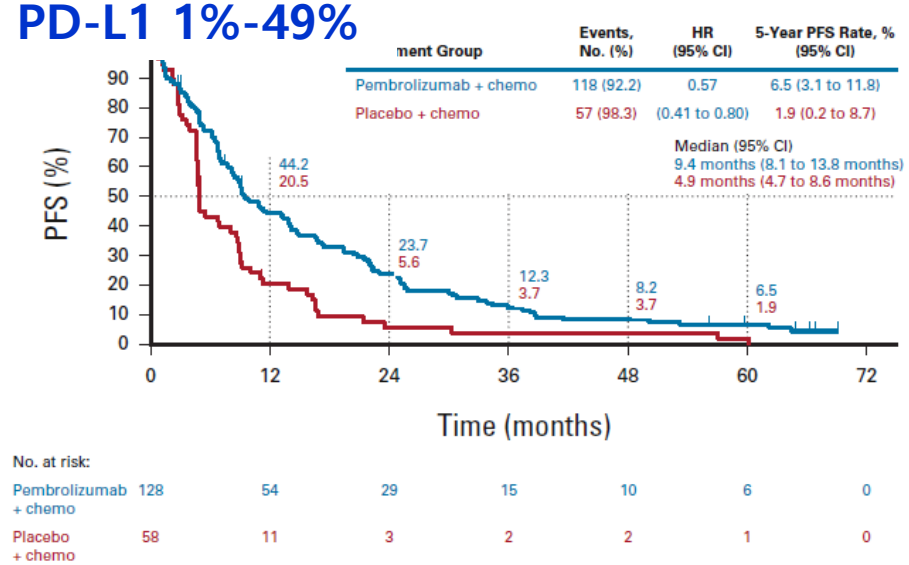
5-year PFS ITT



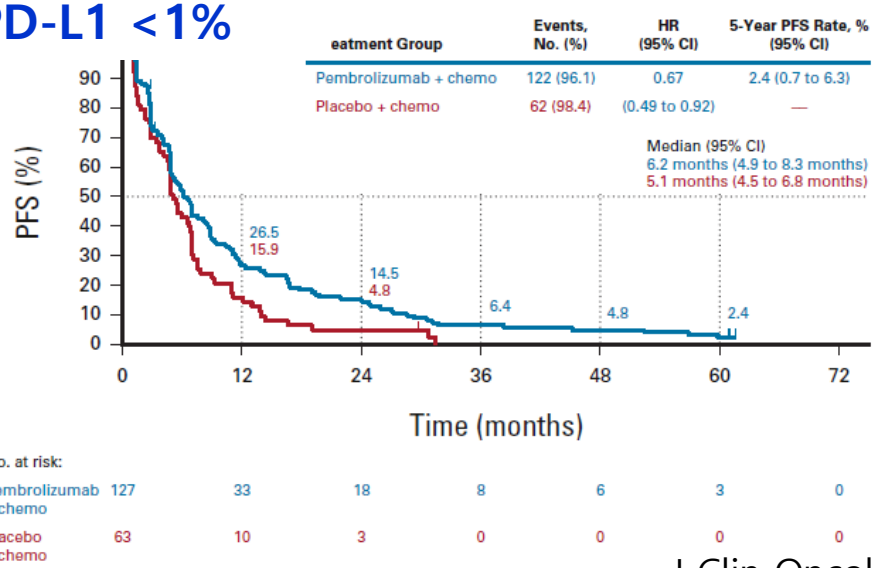
PD-L1 ≥ 50%



PD-L1 1%-49%



PD-L1 <1%

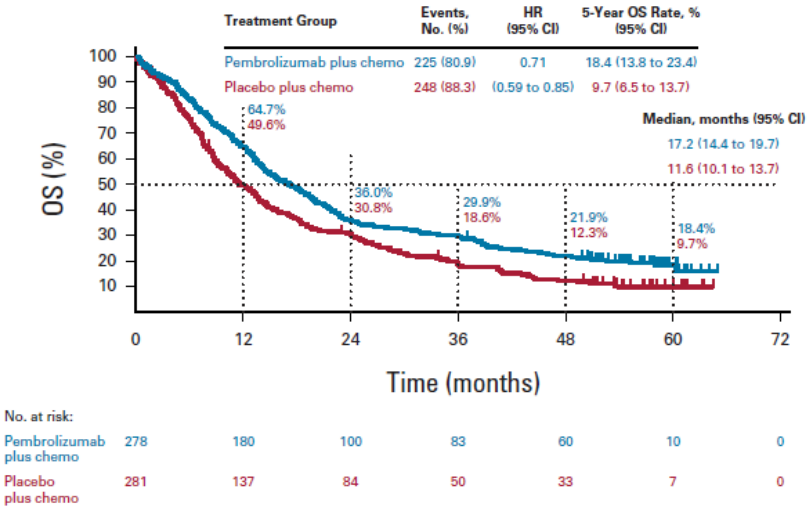


J Clin Oncol 2023;41:1992-1998

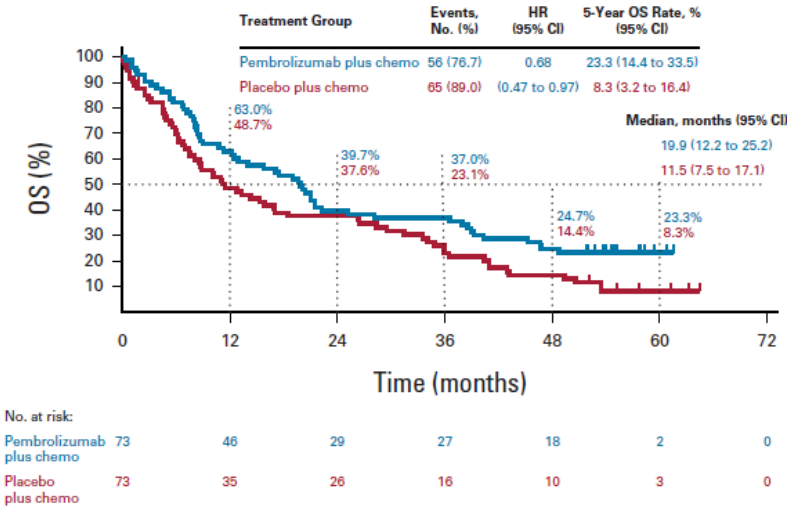
KEYNOTE-407: 1L Pembro+Chemo vs. Pembro, SQ

5-year OS

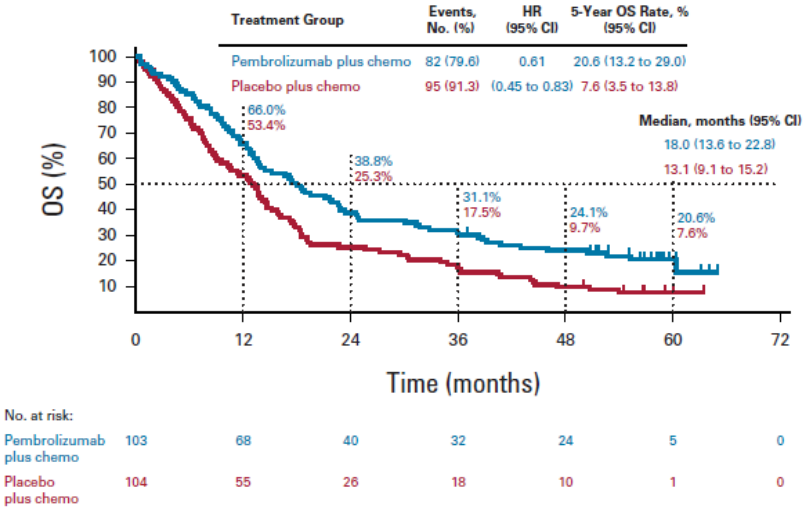
ITT



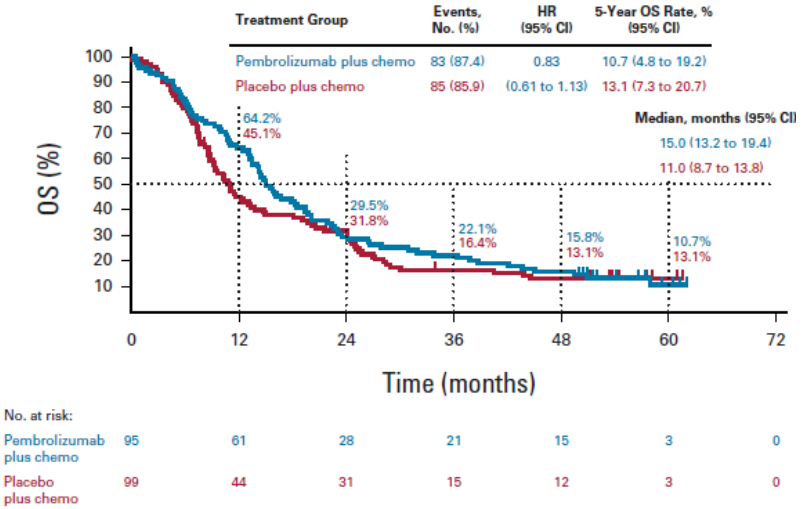
PD-L1 ≥ 50%



PD-L1 1%-49%



PD-L1 <1%

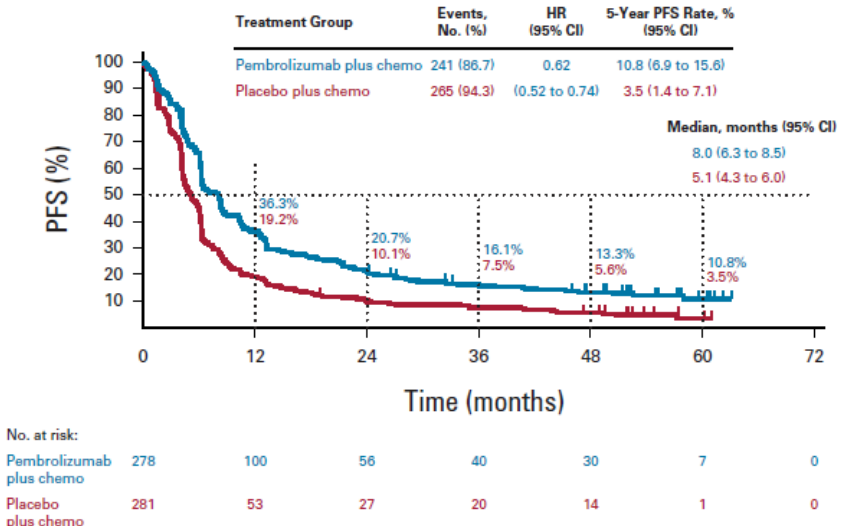


HR 0.83 (0.61-1.13)

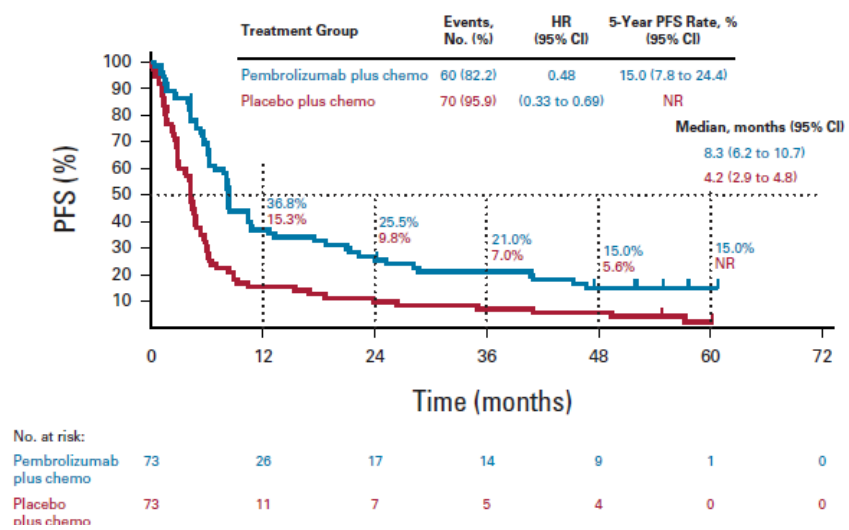
J Clin Oncol 41:1999-2006.

KEYNOTE-407: 1L Pembro+Chemo vs. Pembro, SQ

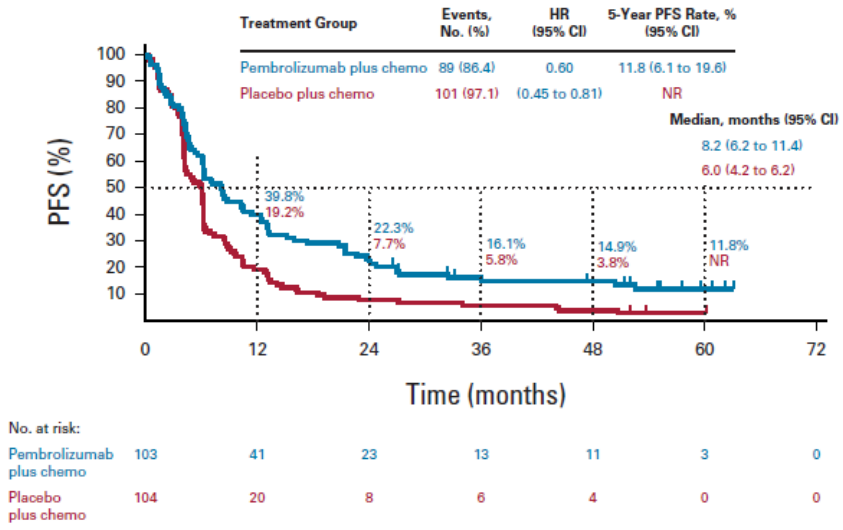
5-year PFS ITT



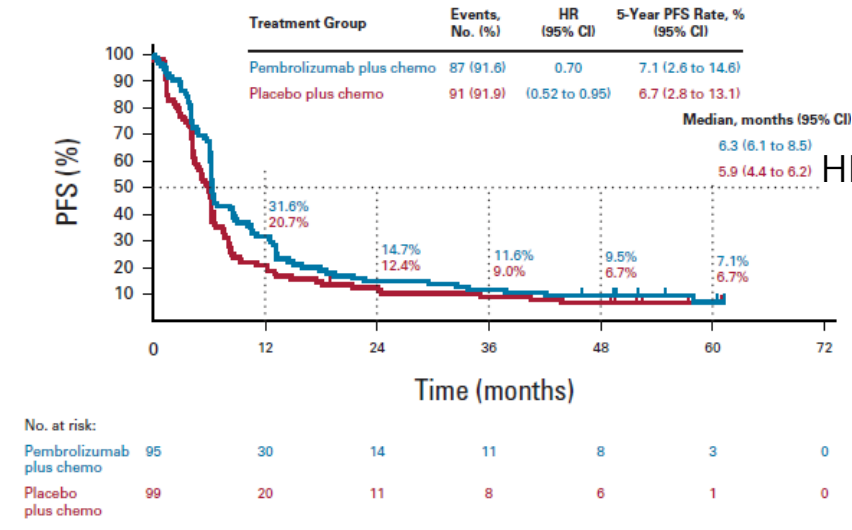
PD-L1 ≥ 50%



PD-L1 1%-49%



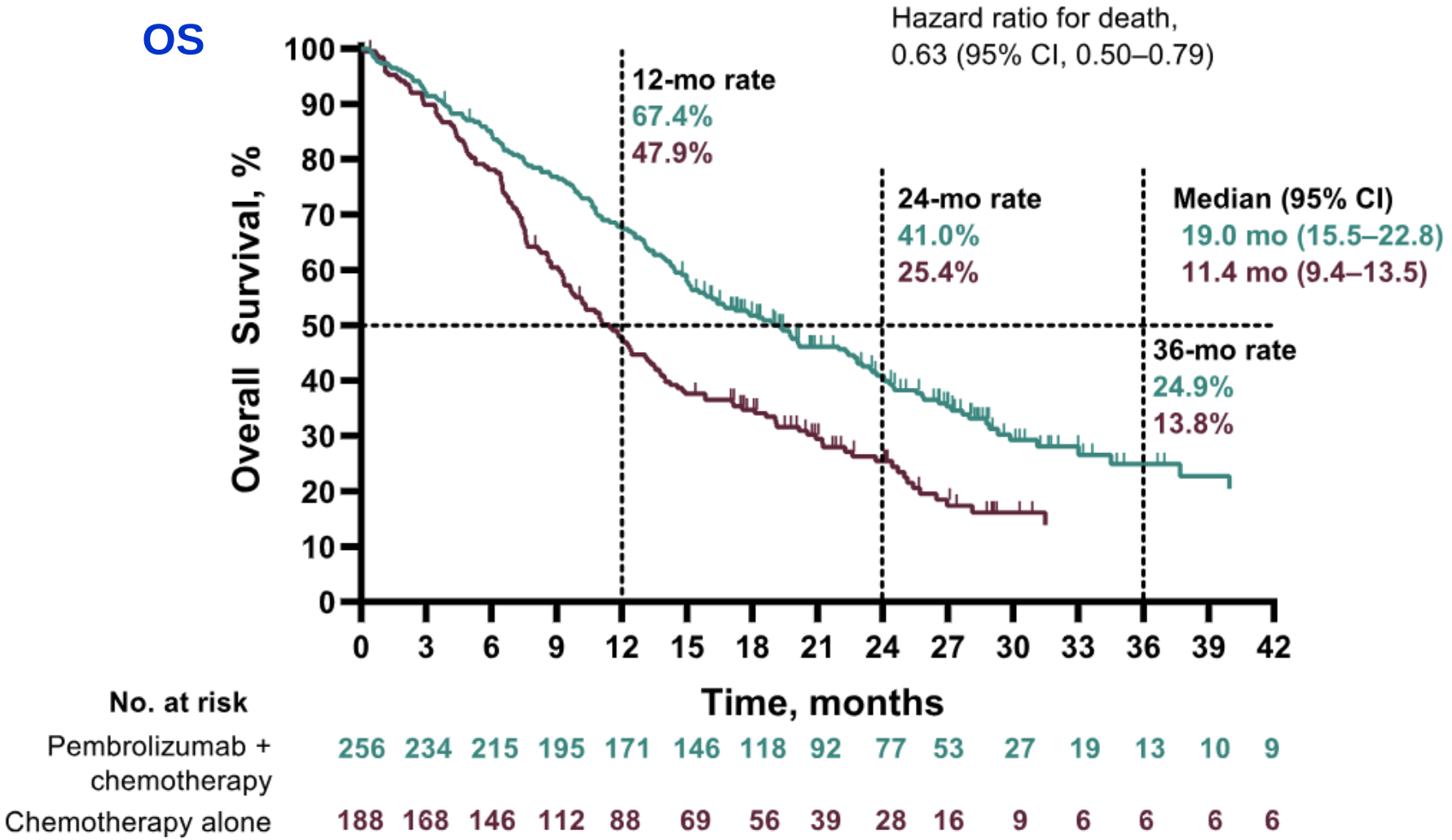
PD-L1 <1%



HR 0.70 (0.52-0.95)

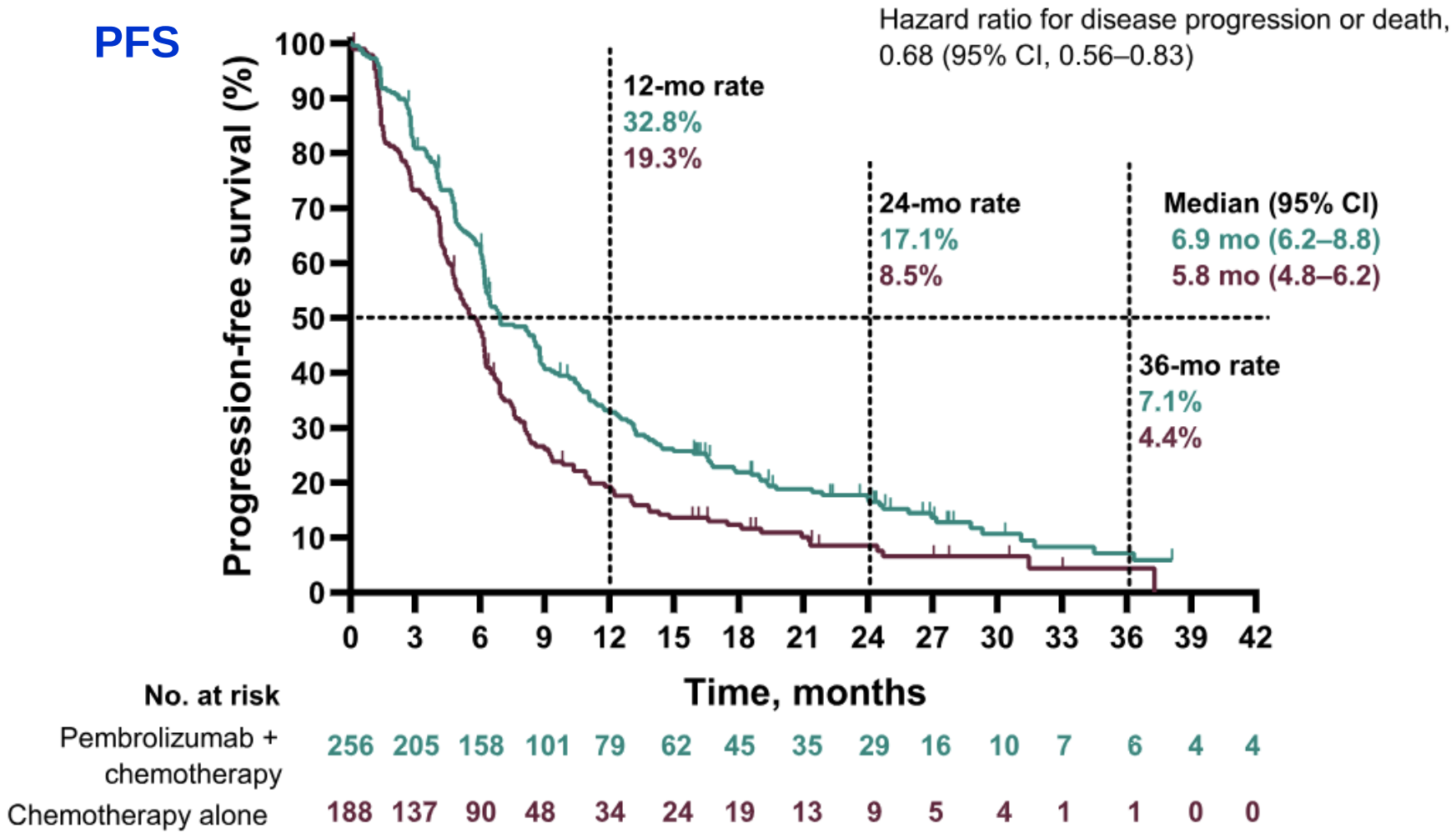
J Clin Oncol 41:1999-2006.

Pooled analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 < 1% (KEYNOTE-021 G, -189, -407)



Cancer. 2020 Nov 15;126(22):4867-4877.

Pooled analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 < 1% (KEYNOTE-021 G, -189, -407)



Cancer. 2020 Nov 15;126(22):4867-4877.

Pooled analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 < 1% (KEYNOTE-021 G, -189, -407)

ORR

	Pembrolizumab + Chemotherapy (n = 256)	Chemotherapy Alone (n = 188)
ORR[a]		
No. of patients	128	56
% (95% CI)	50.0 (43.7-56.3)	29.8 (23.4-36.9)
Best overall response, No. (%)		
Complete response	2 (0.8)	5 (2.7)
Partial response	126 (49.2)	51 (27.1)
Stable disease	90 (35.2)	79 (42.0)
Progressive disease	20 (7.8)	32 (17.0)
Not evaluable[b]	11 (4.3)	12 (6.4)
No assessment[c]	7 (2.7)	9 (4.8)
Time to response, median (range), mo	1.6 (1.2-26.3)	1.4 (1.2-26.9)
DOR, median (range), mo[d]	8.5 (1.1+ to 46.0)	6.9 (1.4+ to 30.1+)
Ongoing response, No. (%)[e]	20 (15.6)	9 (16.1)

Cancer. 2020 Nov 15;126(22):4867-4877.

Pooled analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 < 1% (KEYNOTE-021 G, -189, -407)

All cause AEs

	Pembrolizumab + Chemotherapy (n = 255), No. (%)		Chemotherapy Alone (n = 186), No. (%)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any event	253 (99.2)	182 (71.4)	184 (98.9)	134 (72.0)
Event leading to discontinuation of study drug	93 (36.5)	64 (25.1)	31 (16.7)	24 (12.9)
Event leading to death	27 (10.6)	27 (10.6)	12 (6.5)	12 (6.5)
Event leading to treatment-related death	13 (5.1)	13 (5.1)	3 (1.6)	3 (1.6)
Event occurring in ≥20% of patients in either group				
Anemia	132 (51.8)	41 (16.1)	105 (56.5)	41 (22.0)
Nausea	131 (51.4)	5 (2.0)	88 (47.3)	5 (2.7)
Fatigue	98 (38.4)	15 (5.9)	56 (30.1)	6 (3.2)
Diarrhea	88 (34.5)	9 (3.5)	48 (25.8)	6 (3.2)
Constipation	82 (32.2)	1 (0.4)	59 (31.7)	3 (1.6)
Decreased appetite	86 (33.7)	2 (0.8)	57 (30.6)	0
Neutropenia	72 (28.2)	38 (14.9)	52 (28.0)	37 (19.9)
Cough	59 (23.1)	1 (0.4)	48 (25.8)	0
Thrombocytopenia	65 (25.5)	22 (8.6)	46 (24.7)	15 (8.1)
Vomiting	61 (23.9)	6 (2.4)	31 (16.7)	4 (2.2)
Alopecia	55 (21.6)	1 (0.4)	43 (23.1)	1 (0.5)
Asthenia	53 (20.8)	11 (4.3)	36 (19.4)	9 (4.8)
Rash	53 (20.8)	1 (0.4)	23 (12.4)	2 (1.1)
Dyspnea	40 (15.7)	3 (1.2)	38 (20.4)	1 (0.5)

Cancer. 2020 Nov 15;126(22):4867-4877.

Pooled analysis: 1L Pembro+Chemo vs. Pembro, PD-L1 < 1% (KEYNOTE-021 G, -189, -407)

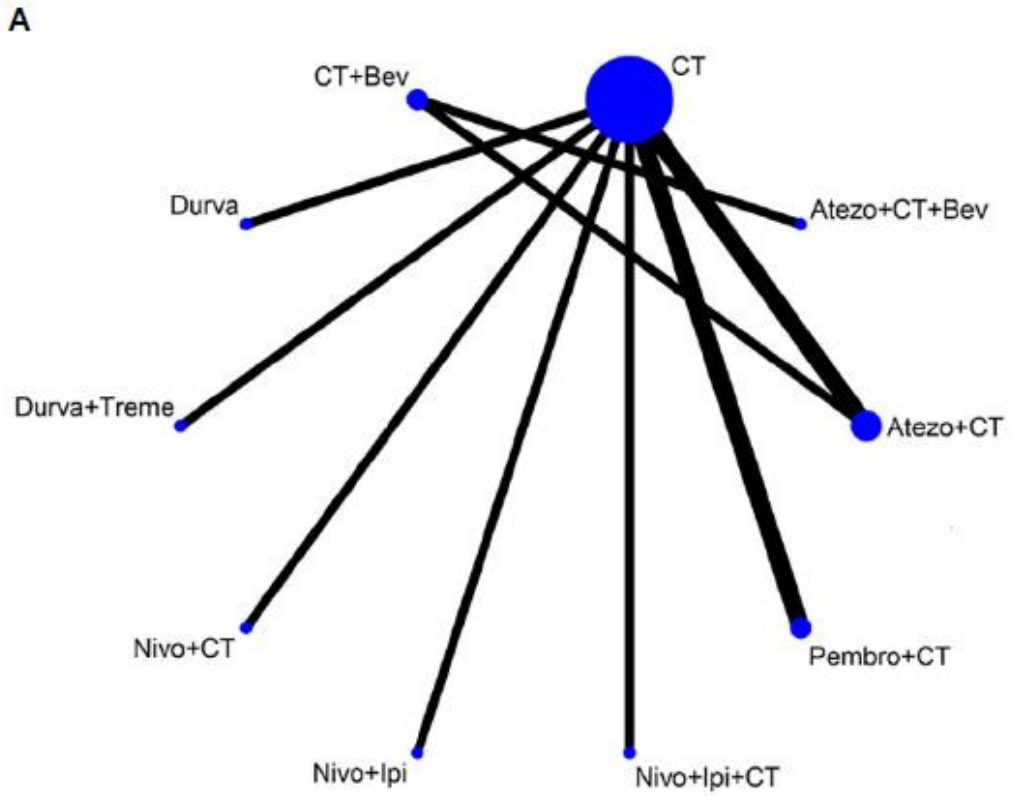
Immune-mediated AEs

	Pembrolizumab + Chemotherapy (n = 255), No. (%)		Chemotherapy Alone (n = 186), No. (%)	
	Any Grade	Grade 3-5[a]	Any Grade	Grade 3-5[a]
Any event	74 (29.0)	31 (12.2)	23 (12.4)	6 (3.2)
Hypothyroidism	19 (7.5)	1 (0.4)	6 (3.2)	0
Pneumonitis	18 (7.1)	11 (4.3)	4 (2.2)	2 (1.1)
Hyperthyroidism	14 (5.5)	0	5 (2.7)	0
Infusion reactions	12 (4.7)	3 (1.2)	4 (2.2)	0
Colitis	5 (2.0)	3 (1.2)	1 (0.5)	1 (0.5)
Nephritis	5 (2.0)	4 (1.6)	1 (0.5)	1 (0.5)
Hepatitis	5 (2.0)	4 (1.6)	0	0
Severe skin reactions	4 (1.6)	2 (0.8)	3 (1.6)	3 (1.6)
Hypophysitis	3 (1.2)	1 (0.4)	0	0
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	2 (0.8)	0	0	0
Encephalitis	1 (0.4)	1 (0.4)	0	0
Guillain-Barre syndrome	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	0	0
Myositis	1 (0.4)	0	0	0

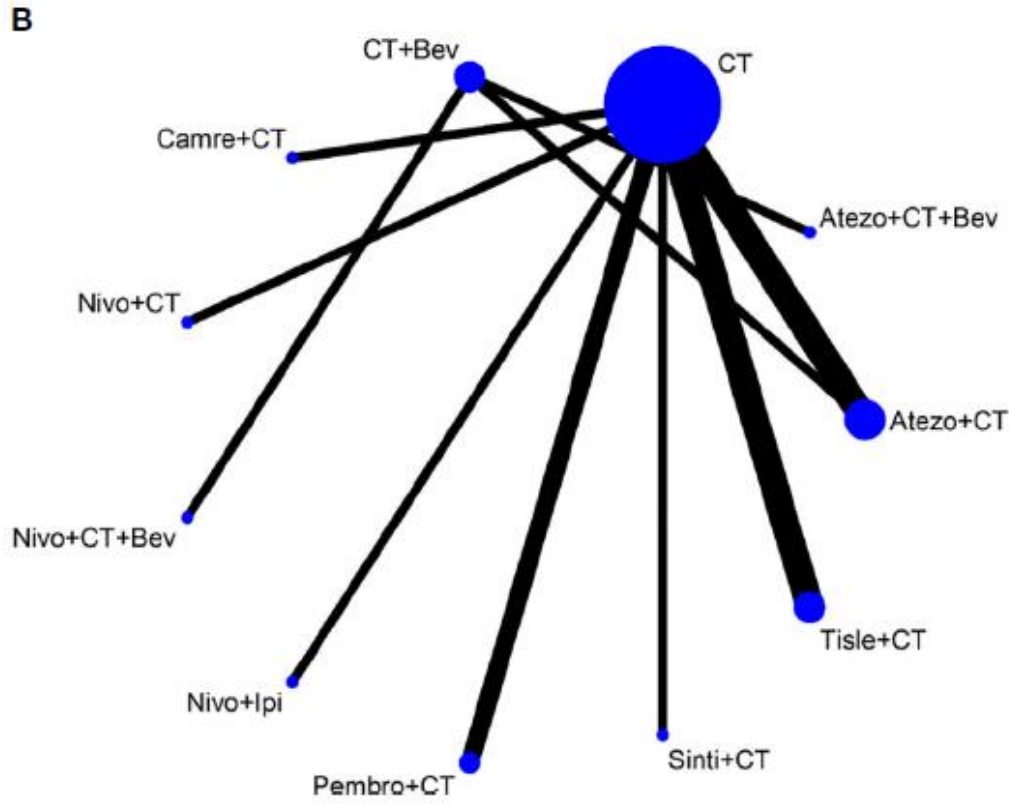
Cancer. 2020 Nov 15;126(22):4867-4877.

Network meta-analysis: 1L treatment, PD-L1 negative

OS



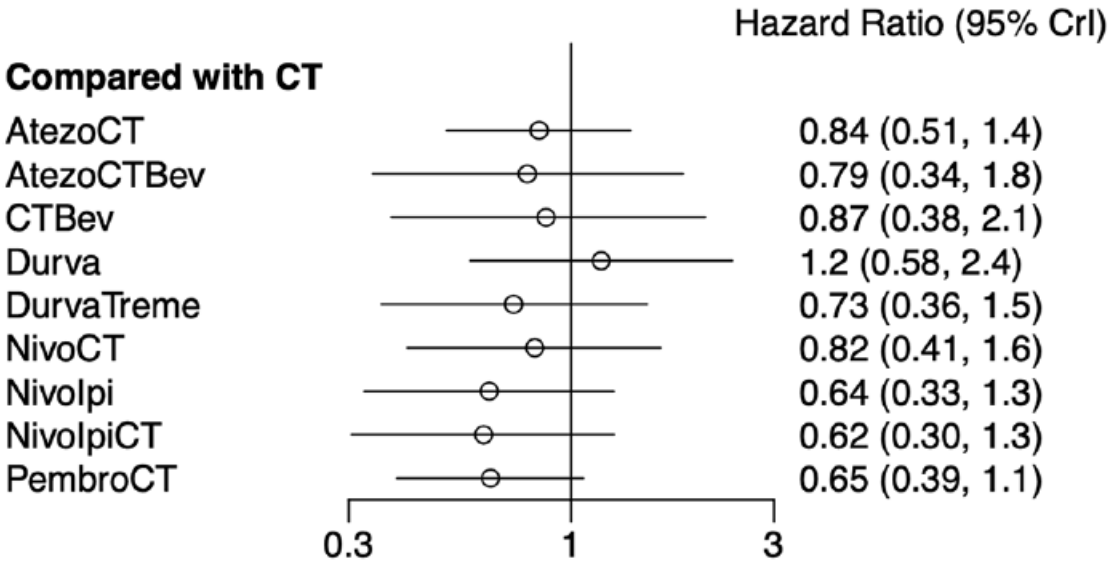
PFS



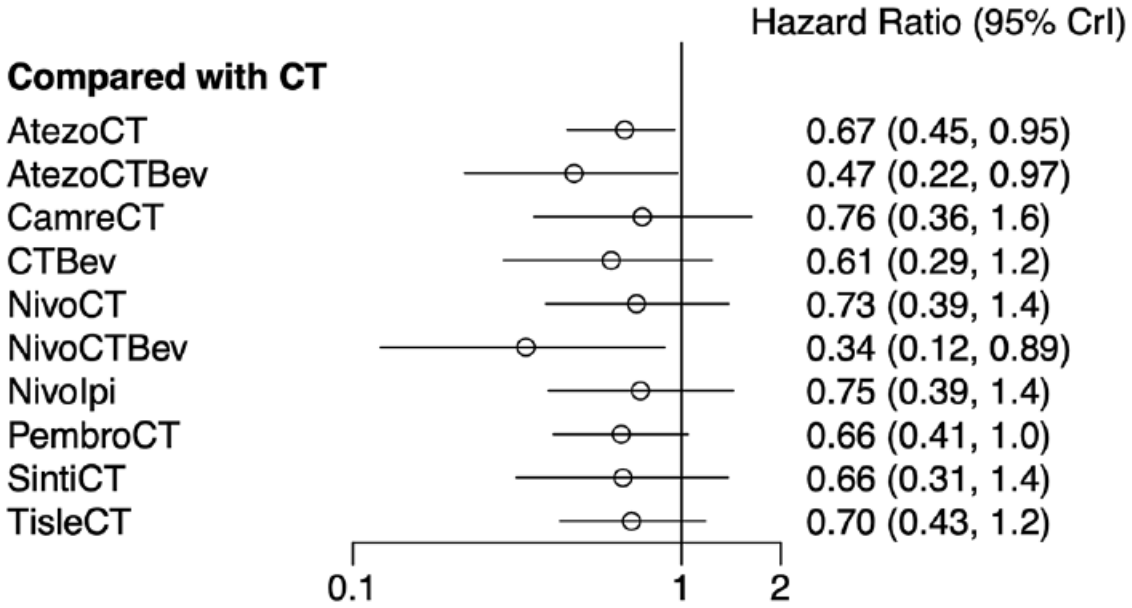
Front Oncol. 2021 Jun 23;11:657545.

Network meta-analysis: 1L treatment, PD-L1 negative

OS



PFS



Front Oncol. 2021 Jun 23;11:657545.

Network meta-analysis: 1L treatment, PD-L1 negative

OS

Atezo+CT	0.94 (0.47, 1.88)	1.19 (0.72, 1.96)	1.04 (0.53, 2.08)	1.40 (0.58, 3.35)	0.87 (0.37, 2.12)	0.98 (0.42, 2.26)	0.76 (0.33, 1.75)	0.74 (0.32, 1.76)	0.77 (0.38, 1.55)
1.06 (0.53, 2.13)	**Atezo+CT+Bev**	1.27 (0.55, 2.93)	1.11 (0.55, 2.22)	1.50 (0.49, 4.57)	0.93 (0.30, 2.84)	1.04 (0.35, 3.09)	0.81 (0.27, 2.44)	0.79 (0.26, 2.39)	0.82 (0.31, 2.19)
0.84 (0.51, 1.38)	0.79 (0.34, 1.83)	**CT**	0.87 (0.38, 2.07)	1.18 (0.58, 2.39)	0.73 (0.36, 1.51)	0.82 (0.41, 1.63)	0.64 (0.33, 1.26)	0.62 (0.30, 1.26)	0.65 (0.39, 1.07)
0.96 (0.48, 1.89)	0.90 (0.45, 1.82)	1.15 (0.48, 2.65)	**CT+Bev**	1.35 (0.44, 4.13)	0.84 (0.27, 2.53)	0.94 (0.31, 2.76)	0.73 (0.25, 2.19)	0.71 (0.24, 2.18)	0.74 (0.27, 1.95)
0.71 (0.30, 1.71)	0.67 (0.22, 2.03)	0.85 (0.42, 1.73)	0.74 (0.24, 2.25)	**Durva**	0.62 (0.29, 1.32)	0.70 (0.26, 1.92)	0.54 (0.20, 1.46)	0.53 (0.19, 1.46)	0.55 (0.23, 1.30)
1.15 (0.47, 2.73)	1.08 (0.35, 3.30)	1.37 (0.66, 2.80)	1.20 (0.40, 3.66)	1.61 (0.76, 3.44)	**Durva+Treme**	1.12 (0.42, 3.05)	0.87 (0.32, 2.34)	0.85 (0.31, 2.36)	0.88 (0.36, 2.11)
1.02 (0.44, 2.38)	0.96 (0.32, 2.89)	1.22 (0.62, 2.43)	1.07 (0.36, 3.18)	1.44 (0.52, 3.87)	0.89 (0.33, 2.39)	**Nivo+CT**	0.78 (0.40, 1.57)	0.76 (0.29, 2.03)	0.79 (0.33, 1.83)
1.31 (0.57, 3.03)	1.23 (0.41, 3.71)	1.56 (0.79, 3.07)	1.37 (0.46, 4.03)	1.84 (0.68, 4.98)	1.14 (0.43, 3.09)	1.28 (0.64, 2.53)	**Nivo+Ipi**	0.97 (0.36, 2.56)	1.01 (0.43, 2.32)
1.35 (0.57, 3.17)	1.27 (0.42, 3.83)	1.61 (0.79, 3.29)	1.40 (0.46, 4.24)	1.89 (0.68, 5.21)	1.18 (0.42, 3.27)	1.32 (0.49, 3.49)	1.03 (0.39, 2.75)	**Nivo+Ipi+CT**	1.04 (0.43, 2.47)
1.30 (0.64, 2.65)	1.22 (0.46, 3.28)	1.55 (0.94, 2.57)	1.35 (0.51, 3.66)	1.83 (0.77, 4.35)	1.13 (0.47, 2.78)	1.27 (0.55, 2.99)	0.99 (0.43, 2.32)	0.96 (0.41, 2.30)	**Pembro+CT**

PFS

Atezo+CT	0.70 (0.37, 1.35)	1.13 (0.50, 2.71)	**1.49 (1.05, 2.23)**	0.91 (0.48, 1.71)	1.09 (0.53, 2.34)	0.50 (0.20, 1.28)	1.11 (0.54, 2.45)	0.97 (0.55, 1.84)	0.99 (0.44, 2.28)	1.05 (0.57, 2.06)
1.43 (0.74, 2.70)	**Atezo+CT+Bev**	1.61 (0.57, 4.79)	**2.12 (1.03, 4.58)**	1.30 (0.68, 2.45)	1.55 (0.59, 4.32)	0.71 (0.28, 1.82)	1.59 (0.61, 4.41)	1.39 (0.58, 3.47)	1.41 (0.50, 4.01)	1.50 (0.62, 3.86)
0.88 (0.37, 2.00)	0.62 (0.21, 1.74)	**Camre+CT**	1.32 (0.61, 2.81)	0.81 (0.27, 2.23)	0.96 (0.36, 2.58)	0.44 (0.12, 1.51)	0.99 (0.37, 2.67)	0.86 (0.35, 2.10)	0.87 (0.30, 2.52)	0.93 (0.37, 2.37)
0.67 (0.45, 0.95)	**0.47 (0.22, 0.97)**	0.76 (0.36, 1.63)	**CT**	0.61 (0.29, 1.24)	0.73 (0.39, 1.39)	**0.34 (0.12, 0.89)**	0.75 (0.39, 1.44)	0.66 (0.41, 1.04)	0.66 (0.31, 1.38)	0.70 (0.43, 1.18)
1.10 (0.58, 2.09)	0.77 (0.41, 1.47)	1.24 (0.45, 3.70)	1.64 (0.81, 3.49)	**CT+Bev**	1.20 (0.46, 3.22)	0.55 (0.28, 1.10)	1.23 (0.47, 3.38)	1.07 (0.46, 2.65)	1.09 (0.39, 3.10)	1.15 (0.49, 2.92)
0.92 (0.43, 1.87)	0.65 (0.23, 1.70)	1.04 (0.39, 2.81)	1.37 (0.72, 2.59)	0.84 (0.31, 2.16)	**Nivo+CT**	0.46 (0.14, 1.48)	1.03 (0.54, 1.96)	0.9 (0.40, 1.97)	0.91 (0.34, 2.39)	0.97 (0.42, 2.20)
2.00 (0.78, 5.08)	1.40 (0.55, 3.57)	2.27 (0.66, 8.10)	**2.97 (1.13, 8.26)**	1.82 (0.91, 3.57)	2.18 (0.68, 7.31)	**Nivo+CT+Bev**	2.23 (0.70, 7.42)	1.95 (0.66, 6.02)	1.98 (0.57, 6.86)	2.10 (0.71, 6.67)
0.90 (0.41, 1.84)	0.63 (0.23, 1.65)	1.01 (0.37, 2.71)	1.33 (0.70, 2.54)	0.81 (0.30, 2.11)	0.97 (0.51, 1.86)	0.45 (0.13, 1.43)	**Nivo+Ipi**	0.87 (0.39, 1.93)	0.88 (0.33, 2.35)	0.94 (0.42, 2.15)
1.03 (0.54, 1.83)	0.72 (0.29, 1.71)	1.16 (0.48, 2.82)	1.53 (0.96, 2.45)	0.93 (0.38, 2.18)	1.12 (0.51, 2.48)	0.51 (0.17, 1.51)	1.14 (0.52, 2.55)	**Pembro+CT**	1.01 (0.42, 2.39)	1.07 (0.54, 2.17)
1.01 (0.44, 2.27)	0.71 (0.25, 2.00)	1.15 (0.40, 3.36)	1.51 (0.72, 3.19)	0.92 (0.32, 2.56)	1.10 (0.42, 2.91)	0.50 (0.15, 1.74)	1.13 (0.43, 3.06)	0.99 (0.42, 2.38)	**Sinti+CT**	1.06 (0.43, 2.68)
0.95 (0.49, 1.76)	0.67 (0.26, 1.62)	1.08 (0.42, 2.72)	1.42 (0.85, 2.34)	0.87 (0.34, 2.05)	1.04 (0.46, 2.36)	0.48 (0.15, 1.41)	1.07 (0.47, 2.41)	0.93 (0.46, 1.85)	0.94 (0.37, 2.32)	**Tisle+CT**

Front Oncol. 2021 Jun 23;11:657545.

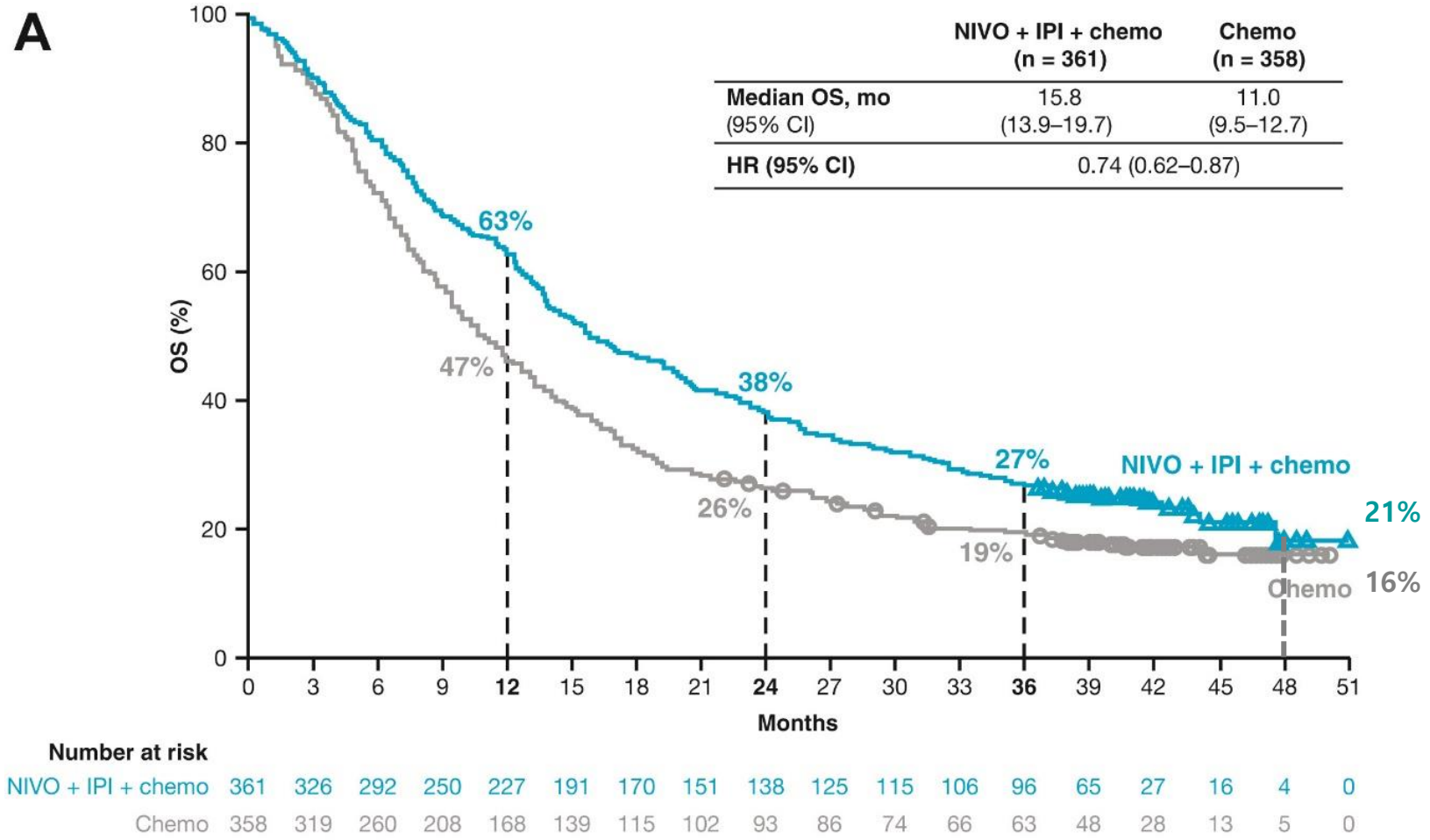
Network meta-analysis: 1L treatment, PD-L1 negative

	Ranking probability for the best (OS, %)	Ranking probability for the best (PFS, %)
Atezo + CT	0.71	0.20
Atezo + CT + Bev	8.46	11.93
Camre + CT	NR	2.71
CT	0.00	0.00
CT + Bev	3.46	0.46
Durva	0.48	NR
Durva + Treme	12.61	NR
Nivo + CT	2.97	1.77
Nivo + CT + Bev	NR	**72.92**
Nivo + Ipi	22.39	1.44
Nivo + Ipi + CT	**30.09**	NR
Pembro+CT	18.81	1.86
Sinti + CT	NR	5.26
Tisle + CT	NR	1.45

Front Oncol. 2021 Jun 23;11:657545.

CheckMate 9LA: 4-year update, 1L NIVO+IPI+Chemo vs. Chemo

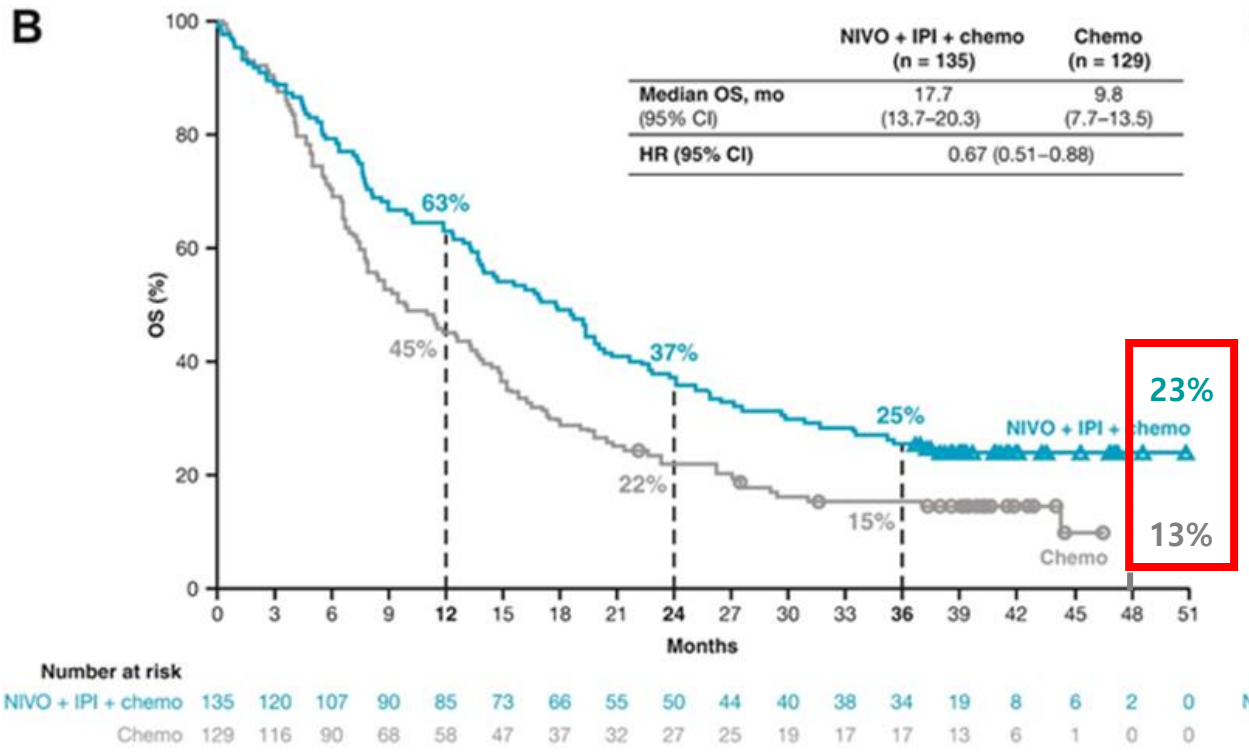
OS: All randomized patients



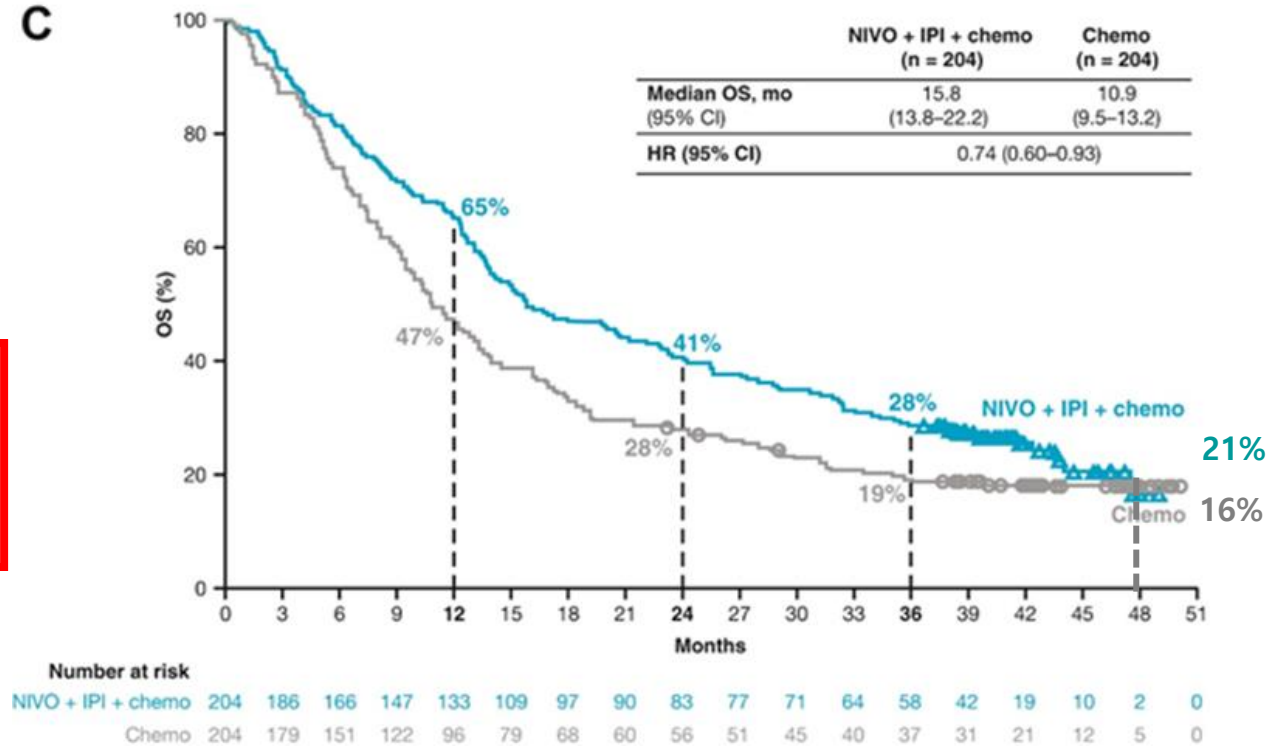
J Thorac Oncol 2023;18:204-22. ASCO 2023.

CheckMate 9LA: 4-year update, 1L NIVO+IPI+Chemo vs. Chemo

OS: PD-L1 < 1%



OS: PD-L1 ≥ 1%

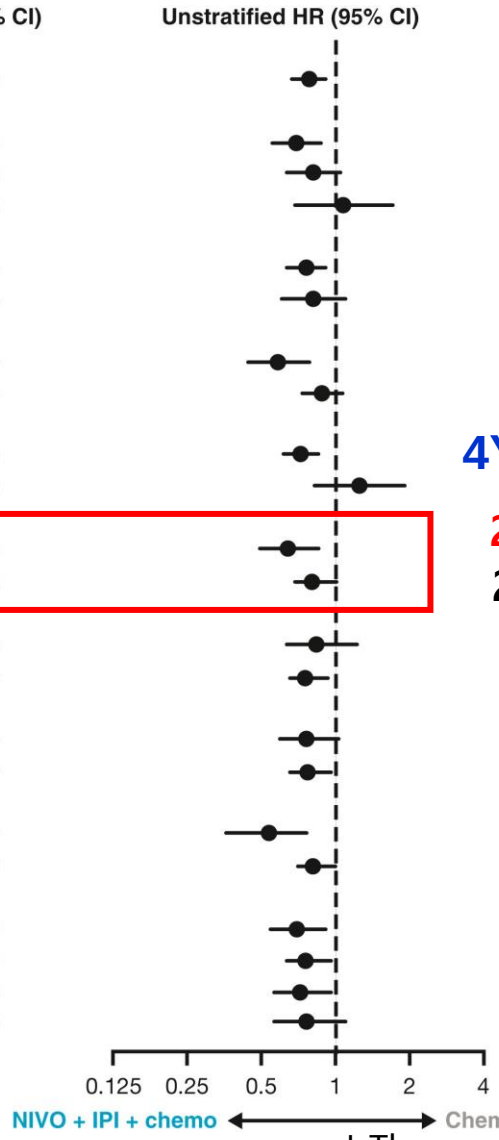


J Thorac Oncol 2023;18:204-22.

CheckMate 9LA: 4-year update, 1L NIVO+IPI+Chemo vs. Chemo

OS by prespecified subgroups

Subgroup	NIVO + IPI + chemo n = 361	Chemo n = 358	Unstratified HR (95% CI)
All randomized (N = 719)	15.8 (13.9–19.7)	11.0 (9.5–12.7)	0.75 (0.63–0.88)
<65 years (n = 354)	15.9 (13.4–21.7)	10.7 (9.1–13.1)	0.66 (0.52–0.84)
≥65 to <75 years (n = 295)	19.0 (15.6–24.1)	11.9 (9.0–14.1)	0.78 (0.60–1.02)
≥75 years (n = 70)	8.51 (5.6–13.5)	11.5 (5.8–15.2)	1.05 (0.65–1.71)
Male (n = 504)	14.2 (12.9–16.9)	9.8 (8.2–11.5)	0.73 (0.60–0.88)
Female (n = 215)	22.2 (15.8–27.4)	15.9 (11.0–18.4)	0.78 (0.57–1.07)
ECOG PS 0 (n = 227)	27.3 (20.3–33.4)	13.9 (12.1–17.0)	0.55 (0.41–0.75)
ECOG PS ≥1 (n = 490)	13.5 (11.9–15.3)	9.7 (8.2–11.4)	0.85 (0.70–1.04)
Smoker (n = 621)	16.2 (14.0–20.0)	10.4 (9.0–12.2)	0.69 (0.58–0.82)
Never smoker (n = 98)	14.1 (8.0–22.8)	14.4 (10.2–23.3)	1.23 (0.79–1.92)
Squamous (n = 227)	14.5 (13.1–19.3)	9.1 (7.2–11.6)	0.64 (0.48–0.86)
Non-squamous (n = 492)	17.8 (14.1–20.7)	12.0 (9.9–13.9)	0.80 (0.65–0.98)
Liver metastases (n = 153)	10.2 (7.4–12.4)	8.2 (6.6–10.0)	0.84 (0.60–1.18)
No liver metastases (n = 566)	19.3 (15.5–22.7)	12.4 (10.4–14.4)	0.74 (0.62–0.90)
Bone metastases (n = 209)	11.9 (8.6–15.0)	8.3 (6.7–9.8)	0.75 (0.56–1.00)
No bone metastases (n = 510)	19.7 (15.6–23.3)	12.4 (10.7–14.8)	0.76 (0.62–0.93)
CNS metastases (n = 123)	19.9 (12.4–25.6)	7.9 (5.0–10.7)	0.49 (0.33–0.73)
No CNS metastases (n = 596)	15.6 (13.8–19.3)	11.8 (10.0–13.7)	0.81 (0.67–0.97)
PD-L1 <1% (n = 264)	17.7 (13.7–20.3)	9.8 (7.7–13.5)	0.67 (0.51–0.88)
PD-L1 ≥1% (n = 408)	15.8 (13.8–22.2)	10.9 (9.5–13.2)	0.74 (0.60–0.93)
PD-L1 1–49% (n = 234)	15.2 (12.6–21.2)	10.4 (8.7–12.4)	0.70 (0.53–0.93)
PD-L1 ≥50% (n = 174)	18.9 (13.1–29.1)	12.9 (9.4–17.6)	0.75 (0.53–1.07)



4YR survival

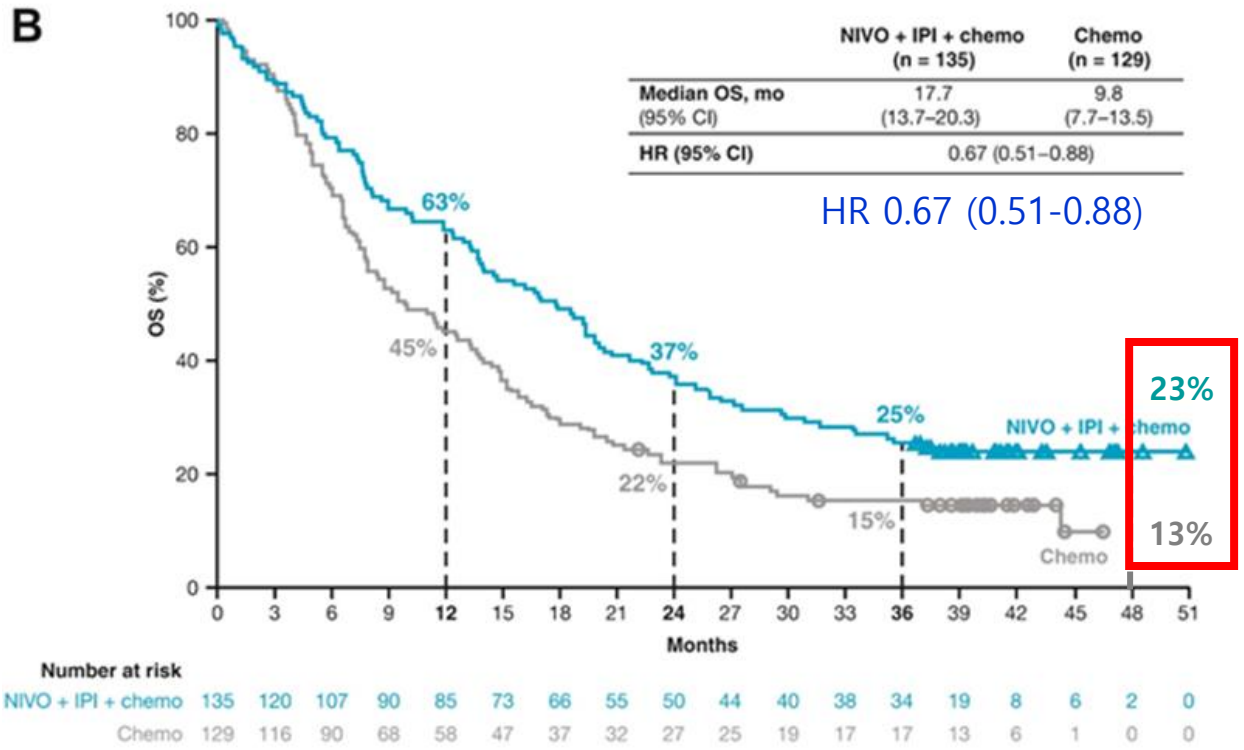
20% vs. 10%

22% vs. 19%

J Thorac Oncol 2023;18:204-22.

OS: CheckMate 9LA vs. KEYNOTE-189/KEYNOTE-407

CheckMate 9LA (4-year)



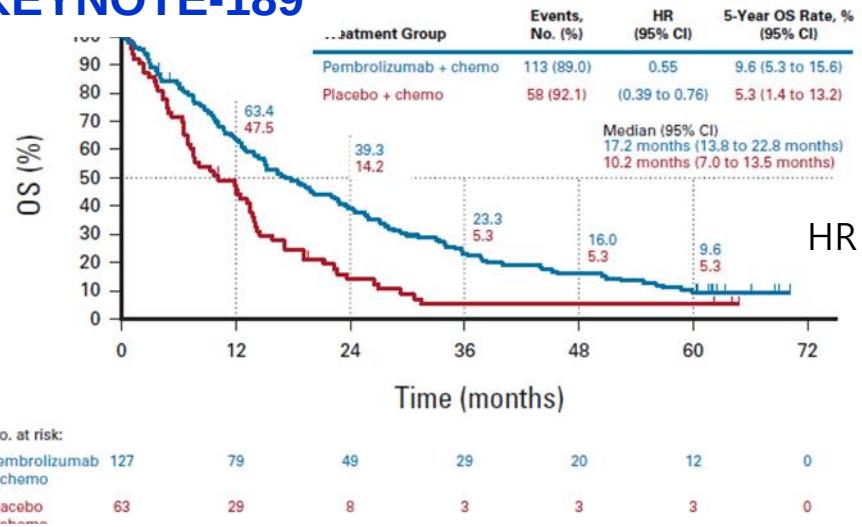
	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS, mo (95% CI)	17.7 (13.7–20.3)	9.8 (7.7–13.5)
HR (95% CI)	0.67 (0.51–0.88)	

HR 0.67 (0.51-0.88)

SQ 20% vs. 10%

NonSQ 22% vs. 19%

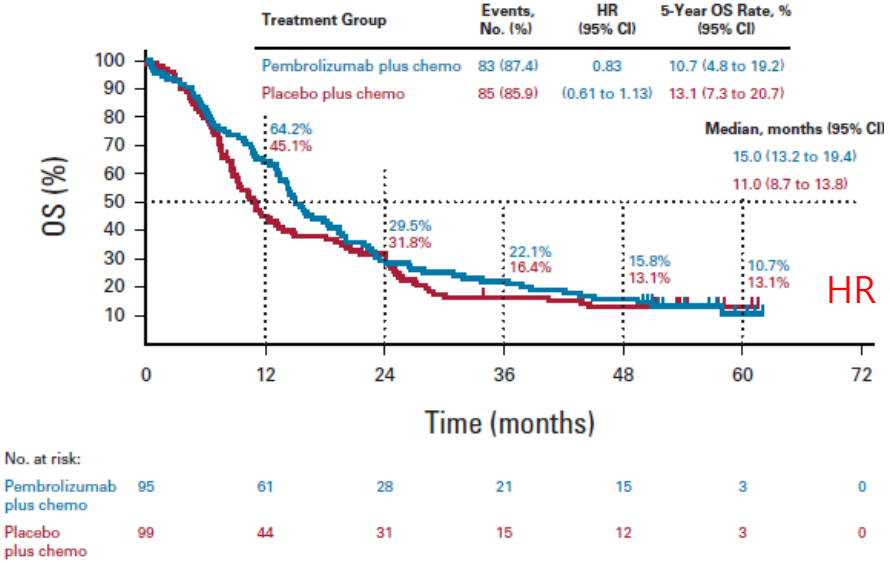
KEYNOTE-189



Treatment Group	Events, No. (%)	HR (95% CI)	5-Year OS Rate, % (95% CI)
Pembrolizumab + chemo	113 (89.0)	0.55	9.6 (5.3 to 15.6)
Placebo + chemo	58 (92.1)	(0.39 to 0.76)	5.3 (1.4 to 13.2)

HR 0.55 (0.39-0.76)

KEYNOTE-407



Treatment Group	Events, No. (%)	HR (95% CI)	5-Year OS Rate, % (95% CI)
Pembrolizumab plus chemo	83 (87.4)	0.83	10.7 (4.8 to 19.2)
Placebo plus chemo	85 (85.9)	(0.61 to 1.13)	13.1 (7.3 to 20.7)

HR 0.83 (0.61-1.13)

PD-L1 < 1%: IO+Chemo vs. Chemo

- **ORR, PFS, OS: IO+Chemo > Chemo**
- **IO+Chemo ~ IO/IO+Chemo ~ IO/IO**

5 European countries*: Real-world evidence survey

Characteristics of patients with EGFR/ALK-WT mNSCLC by 1L treatment group

	Total population	1L Treatment group						*p* value
		IO monotherapy	IO + chemotherapy	Chemotherapy only	Chemotherapy combination	Targeted therapy	Other	
Age, years								
n	1086	333	271	430	30	15	7	< 0.0001
Mean (SD)	66.2 (8.9)	67.5 (8.6)	62.9 (8.3)	67.1 (8.7)	65.1 (7.9)	62.9 (13.2)	82.4 (6.5)	
Current ECOG PS score, n (%)								
n	1083	332	270	429	30	15	7	< 0.0001
0	240 (22.2)	91 (27.4)	79 (29.3)	65 (15.2)	2 (6.7)	3 (20.0)	0 (0.0)	
1	644 (59.5)	205 (61.7)	166 (61.5)	240 (55.9)	21 (70.0)	11 (73.3)	1 (14.3)	
2	150 (13.9)	30 (9.0)	17 (6.3)	99 (23.1)	3 (10.0)	0 (0.0)	1 (14.3)	
3	27 (2.5)	4 (1.2)	3 (1.1)	15 (3.5)	1 (3.3)	1 (6.7)	3 (42.9)	
4	22 (2.0)	2 (0.6)	5 (1.9)	10 (2.3)	3 (10.0)	0 (0.0)	2 (28.6)	
breathing complications								
Weight loss	305 (28.1)	75 (22.5)	73 (26.9)	141 (32.8)	9 (30.0)	5 (33.3)	2 (28.6)	0.0684

*France, Germany, Italy, Spain and UK

BMC Cancer. 2023 Jun 30;23(1):603.

1L Treatment of patients with EGFR/ALK-WT mNSCLC by PD-L1 expression & histology

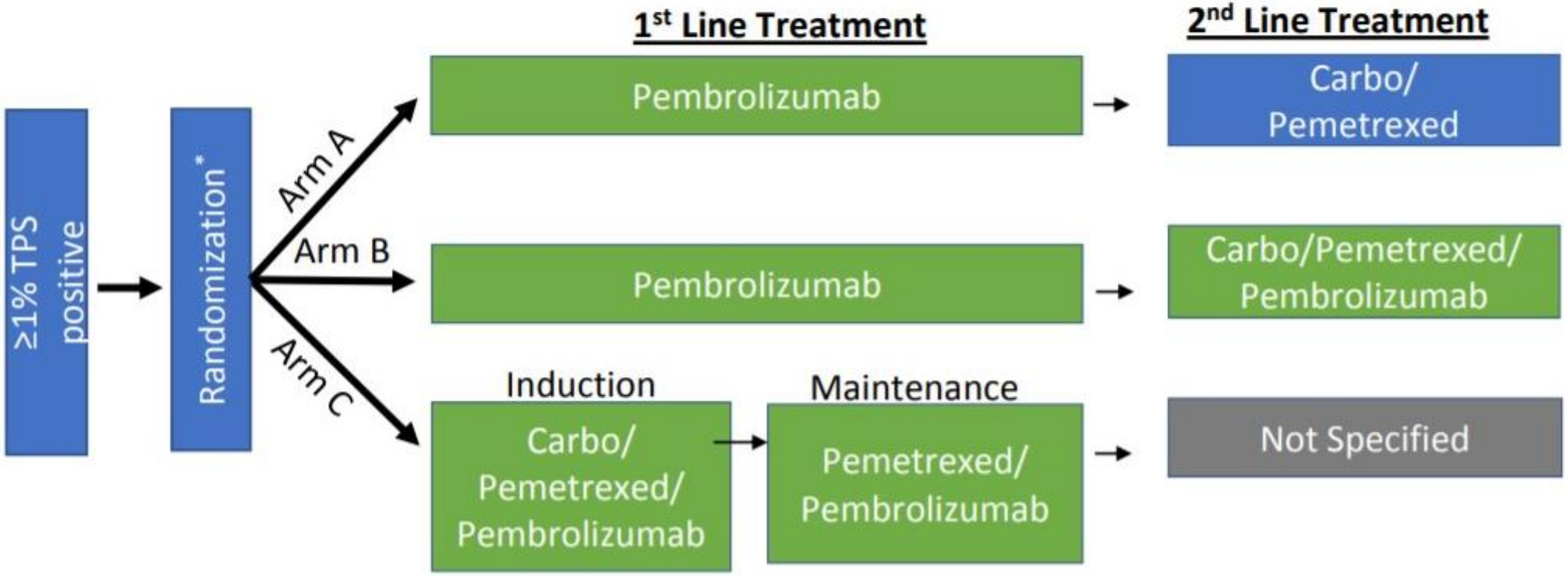
	Total population	PD-L1% expression			*p* value
		< 1	1 – 49	≥ 50	
1L mNSCLC[a] Treatment group					
1L treatment group, n (%)					
n	1021	234	420	367	
IO monotherapy	330 (32.3)	6 (2.6)	27 (6.4)	297 (80.9)	< 0.0001
IO + chemotherapy	268 (26.2)	62 (26.5)	155 (36.9)	51 (13.9)	
IO + non-chemotherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Chemotherapy only	385 (37.7)	146 (62.4)	222 (52.9)	17 (4.6)	
Chemotherapy combination	25 (2.4)	16 (6.8)	8 (1.9)	1 (0.3)	
Targeted	11 (1.1)	3 (1.3)	7 (1.7)	1 (0.3)	
Other	2 (0.2)	1 (0.4)	1 (0.2)	0 (0.0)	

	Total population	Histology				*p* value
		Squamous cell carcinoma	Adenocarcinoma	Large-cell carcinoma	Other	
1L mNSCLC[a] Treatment group, n (%)						
n	1086	361	689	24	12	
IO monotherapy	333 (30.7)	121 (33.5)	200 (29.0)	7 (29.2)	5 (41.7)	< 0.0001
IO + chemotherapy	271 (25.0)	50 (13.9)	215 (31.2)	4 (16.7)	2 (16.7)	
IO + non-chemotherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Chemotherapy only	430 (39.6)	177 (49.0)	239 (34.7)	9 (37.5)	5 (41.7)	
Chemotherapy combination	30 (2.8)	5 (1.4)	22 (3.2)	3 (12.5)	0 (0.0)	
Targeted	15 (1.4)	3 (0.8)	11 (1.6)	1 (4.2)	0 (0.0)	
Other	7 (0.6)	5 (1.4)	2 (0.3)	0 (0.0)	0 (0.0)	

BMC Cancer. 2023 Jun 30;23(1):603.

INSIGNA trial

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



1L immunotherapy±chemo in PS2 patients

Panel questions	Expert conclusions
PS 2 assessment	
Q1. Is ECOG PS scale still adequate for clinical condition assessment in the immunotherapy era?	At all panelists, ECOG PS scale is considered not adequate and needs subclassifications according to the determinants of PS impairment (tumor-related versus comorbidities).
Q2. In A-NSCLC patients with PS 2 does the determinant of poor PS (tumor-related or comorbidity) affect your treatment choice?	Yes, with particular concern regarding chemotherapy agents rather than immunotherapy *per se*.
Single-agent immunotherapy	
Q3. In A-NSCLC patients with PS 2 and PD-L1 ≥50% is single-agent immunotherapy feasible and safe?	Yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q4. In A-NSCLC patients with PS 2 and PD-L1 ≥50% is single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients. However, PS 2 is a strong negative prognostic factor and results are, as with any treatment, inferior compared to PS 0-1 patients.
Combined chemotherapy and immunotherapy	
Q5. In A-NSCLC patients with squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to platinum-based doublet tolerability.
Q6. In A-NSCLC patients with squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q7. In A-NSCLC patients with non-squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to platinum-based doublet tolerability. However, pemetrexed-based doublets are generally better tolerated as compared to chemotherapy regimens used in squamous histology.
Q8. In A-NSCLC patients with non-squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q9. In A-NSCLC patients with PS 2 is combined chemotherapy plus double immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to additional toxicity from anti-CTLA-4.
Q10. In A-NSCLC patients with PS 2 is combined chemotherapy plus double immunotherapy effective?	Probably yes, to date in the absence of prospective phase III trials including PS 2 patients.
Preferred treatments	
Q11. In A-NSCLC patients with PS 2 and PD-L1 ≥50%, does the PD-L1 value affect your choice between single-agent immunotherapy and combined chemo–immunotherapy?	No

International Experts Panel Meeting by the Italian Association of Thoracic Oncology (AIOT) ESMO Open. 2022 Feb;7(1):100355.

1L immunotherapy±chemo in elderly patients

Elderly age subset[a] / ICI-based treatment	Single-agent anti-PD-1/PD-L1 (≥50 %)	Chemotherapy plus single-agent anti-PD-1/PD-L1	Chemotherapy plus dual-agent ICIs
≥ 70 years	✓	• Caution on prolonged pemetrexed maintenance • Consider chemo-free regimens or alternative backbone chemo if available	No major safety concerns considering a two-cycle chemo-therapy only
≥ 80 years	✓	CAUTION Only in selected cases, but in squamous histology consider combo with: • nab-paclitaxel • gemcitabine • weekly taxanes	No major safety concerns in fit patients considering a two-cycle chemotherapy only

International Experts Panel Meeting by the Italian Association of Thoracic Oncology (AIOT)

ESMO Open. 2023 Apr;8(2):101192.

Algorithm of treatment on NSCLC (negative mutation)