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Pasadena, California
16th Annual California Cancer Consortium Conference
RECENT ADVANCES AND NEW DIRECTIONS IN CANCER THERAPY
Presented by the CALIFORNIA CANCER CONSORTIUM CONFERENCE
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How I treat Stage IV Lung Adenocarcinoma without a Driver Mutation and Negative PD-L1 expression

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Disclosures

- Advisor: AbbVie, Amgen, AstraZeneca, EMD Serono, Genentech, Genmab, Lilly, Merck, Novartis, Regeneron, Targeted Oncology, Takeda
- Honoraria: Merck
- Research: AbbVie, Astellas, EMD Serono, Five Prime, Genentech, Lilly, Novartis, Regeneron,
- Royalty: UpToDate Author

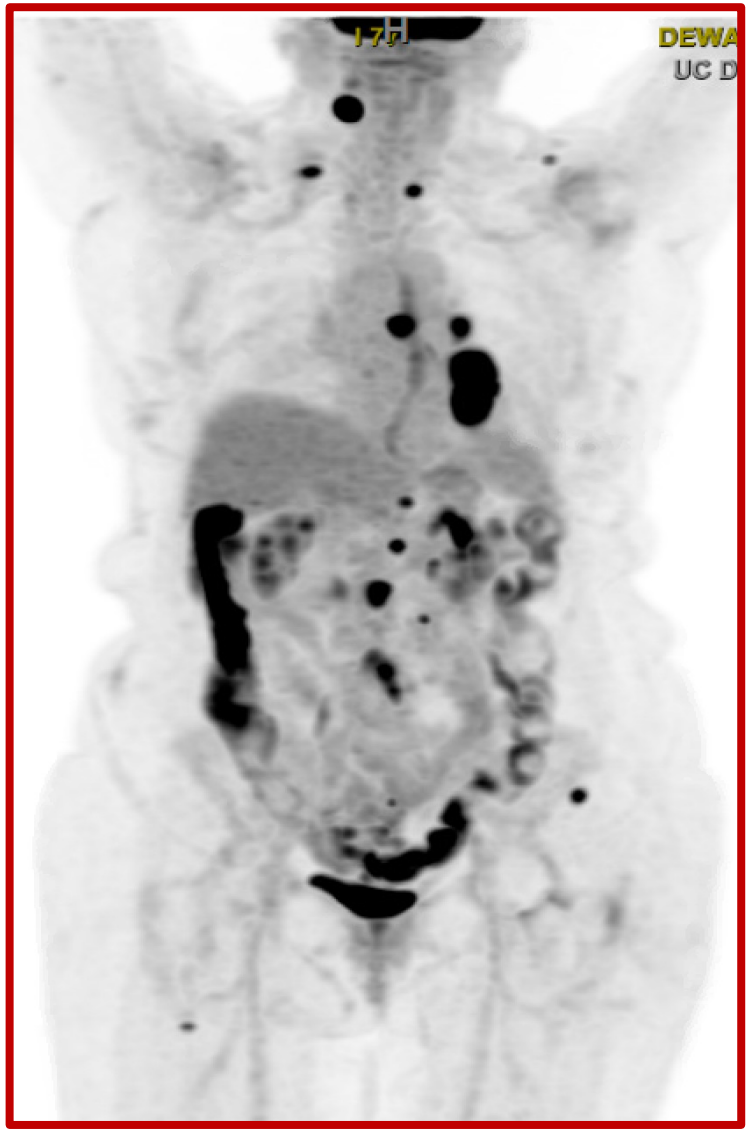
Case Presentation

72 yo WF who presented to her PCP with a persistent mild cough, DOE, fatigue and anorexia (PS-1).
Chest X-ray revealed a 4.1 cm mass in the LLL that was confirmed on CT. PET scan revealed additional mediastinal and retrocrural lymph nodes as well as bone metastases. Brain MRI was negative.
Transbronchial biopsy of the lung mass revealed moderately differentiated adenocarcinoma. PD-L1 0.
No actionable mutations. TMB 5.
Stage IV (T2aN2M1c)

PMH: GERD, HTN, osteoporosis

SH: 15 pack-years; quit 30 years ago

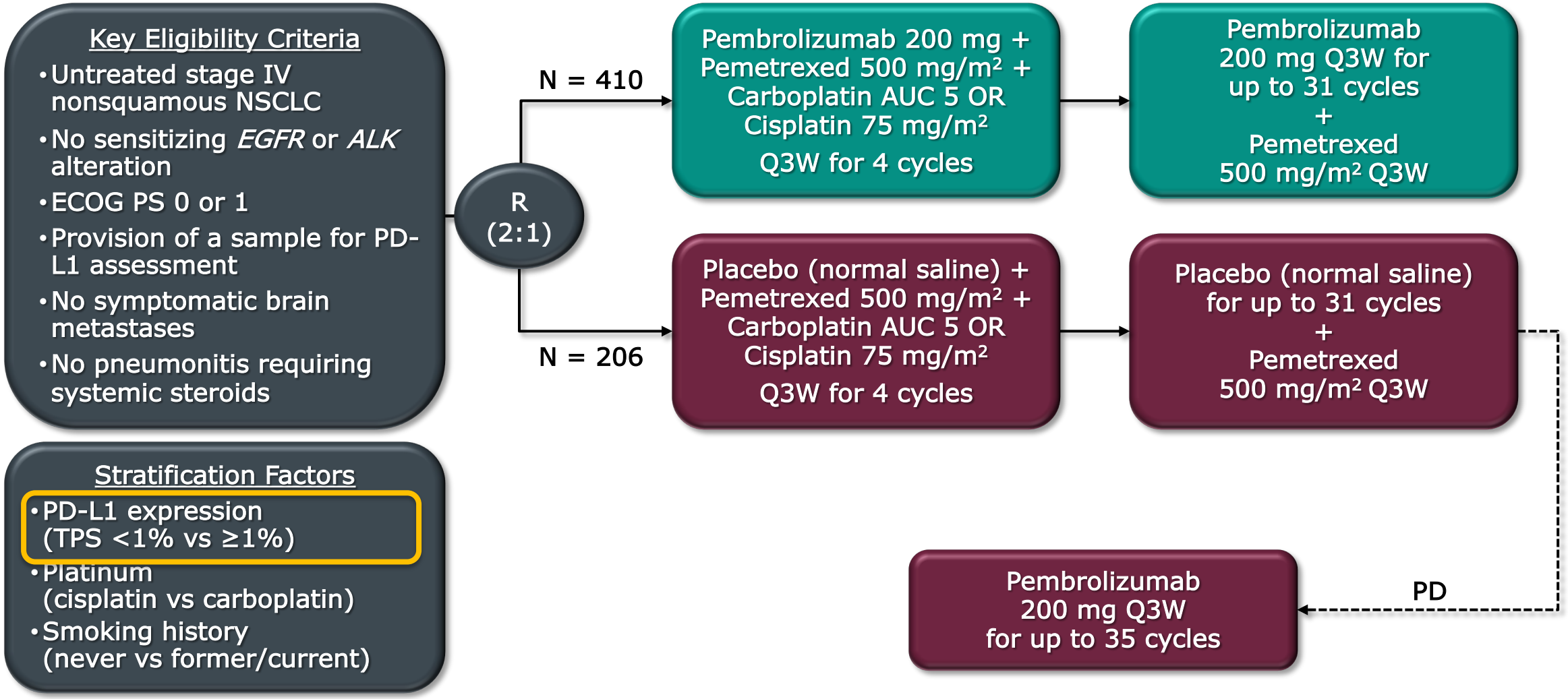
PE: Unremarkable; no palpable adenopathy



PD-L1 Negative Tumors

- Approximately one–third of patients do not express PD-L1 on the surface of their tumors.
- Patients are typically never smokers
- Patients with PD-L1 negative tumors have approximately a 10% ORR to immune checkpoint inhibitors (ICI) alone in the second line and beyond setting.
- A combination approach is needed for first line treatment.

Chemotherapy + ICI in PD-L1 Negative Expression NSCLC
Subset analysis of KEYNOTE-189

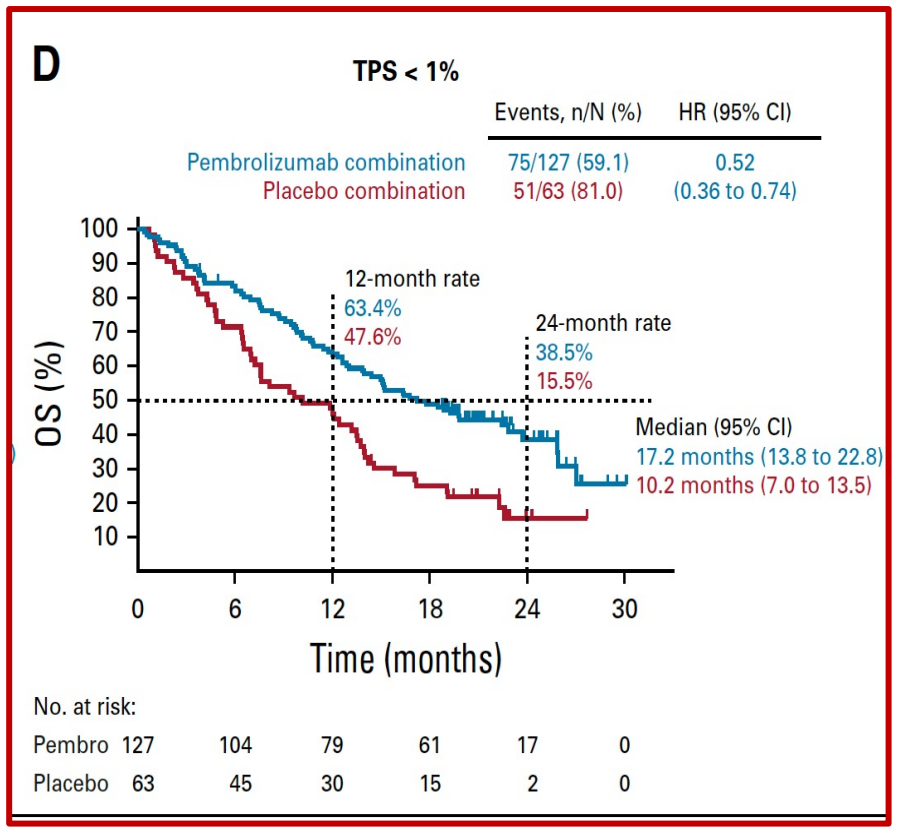


Gandhi et al, AACR and NEJM 2018

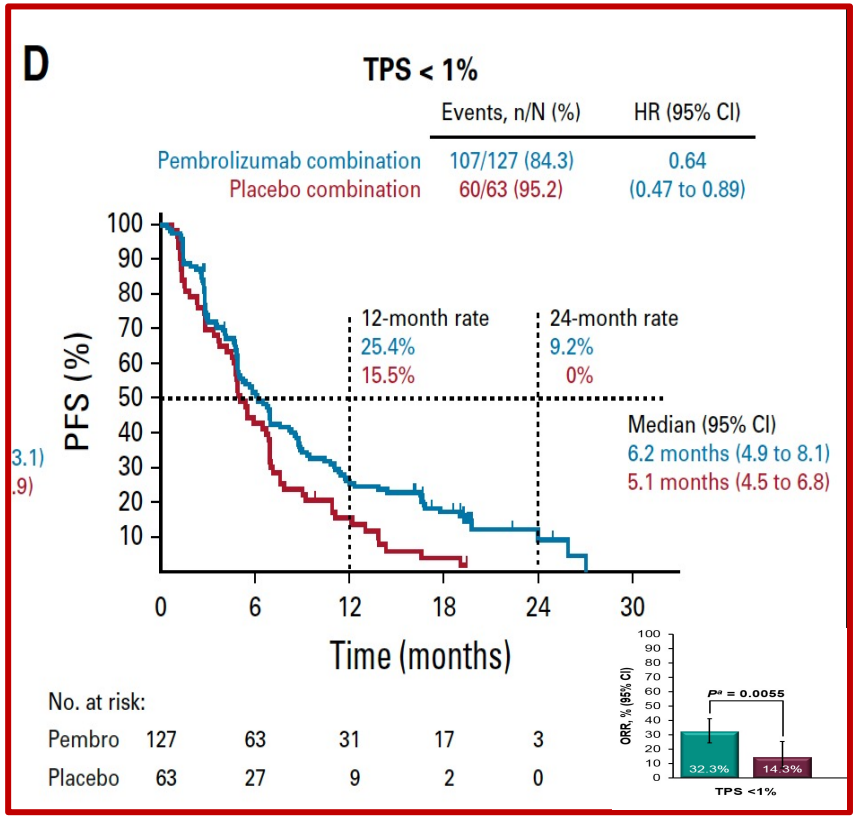
Keynote 189: Efficacy Results for PD-L1 negative NSCLC

Updated Analysis. N=190

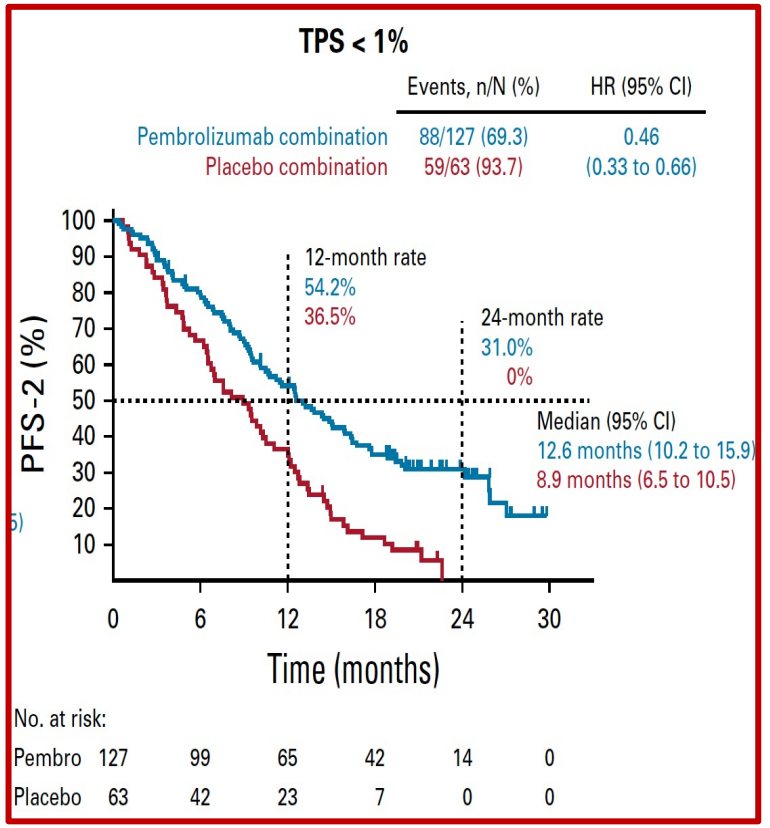
OS



PFS



PFS2



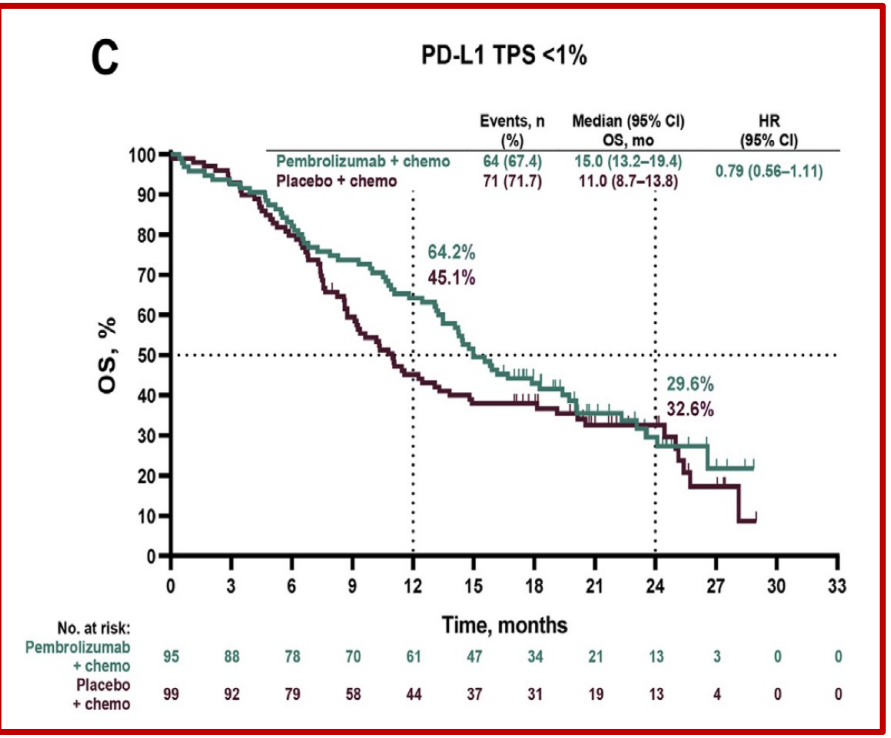
Combination chemotherapy + pembrolizumab improves overall survival

Gadgeel S, et al. JCO 2020

Keynote 407: Efficacy Results for PD-L1 negative NSCLC

Final Analysis N=185

OS



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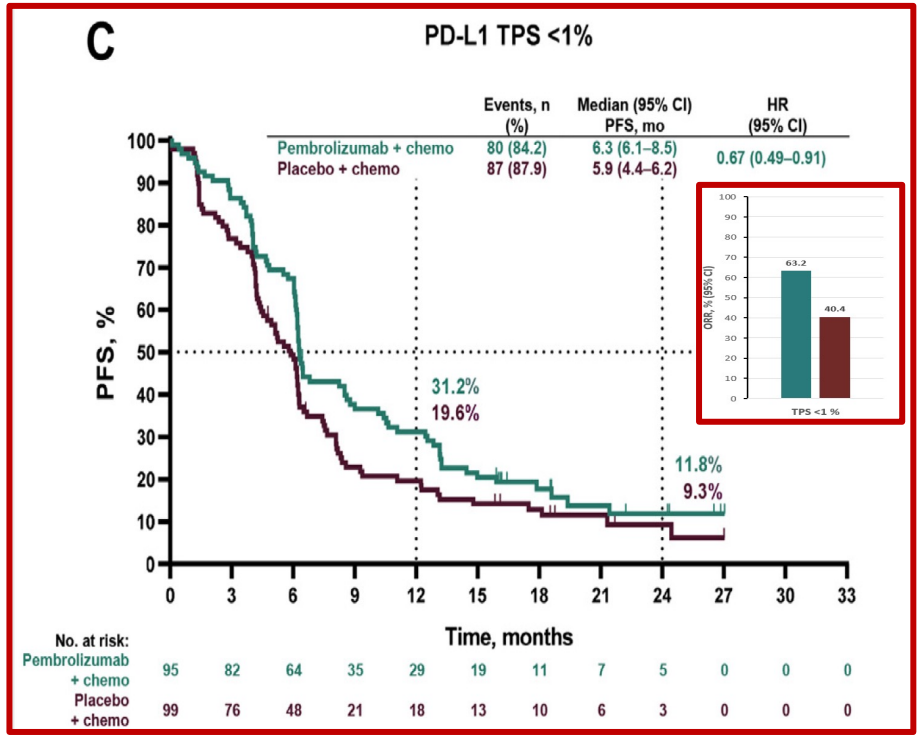

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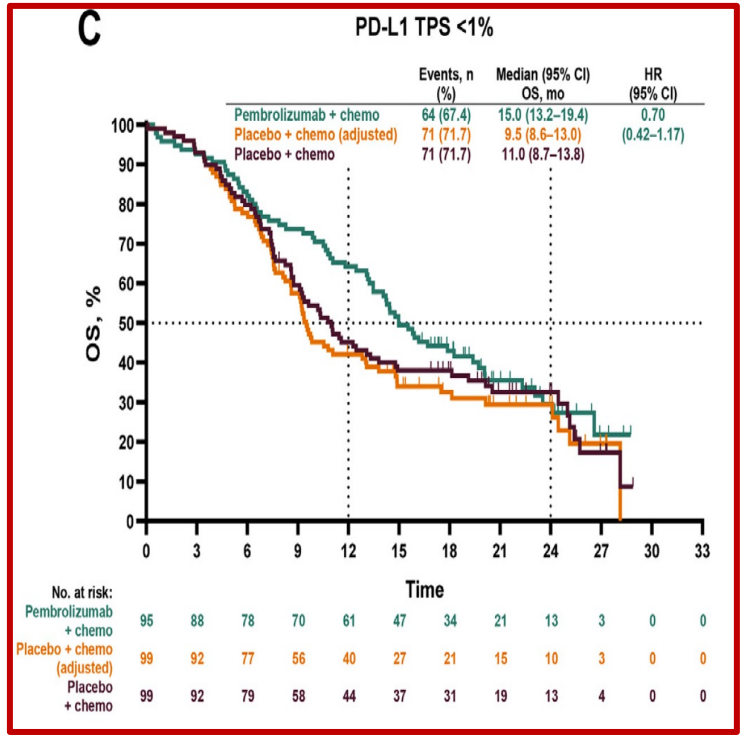
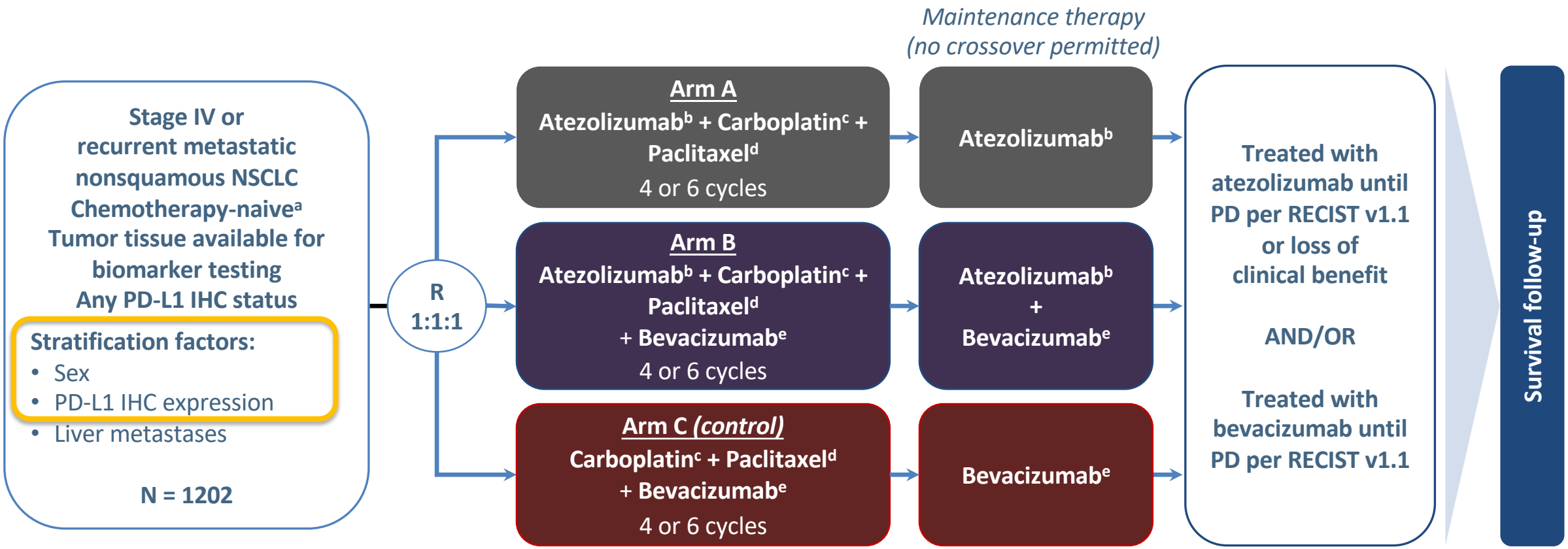


Combination chemotherapy + pembrolizumab DID NOT improve overall survival

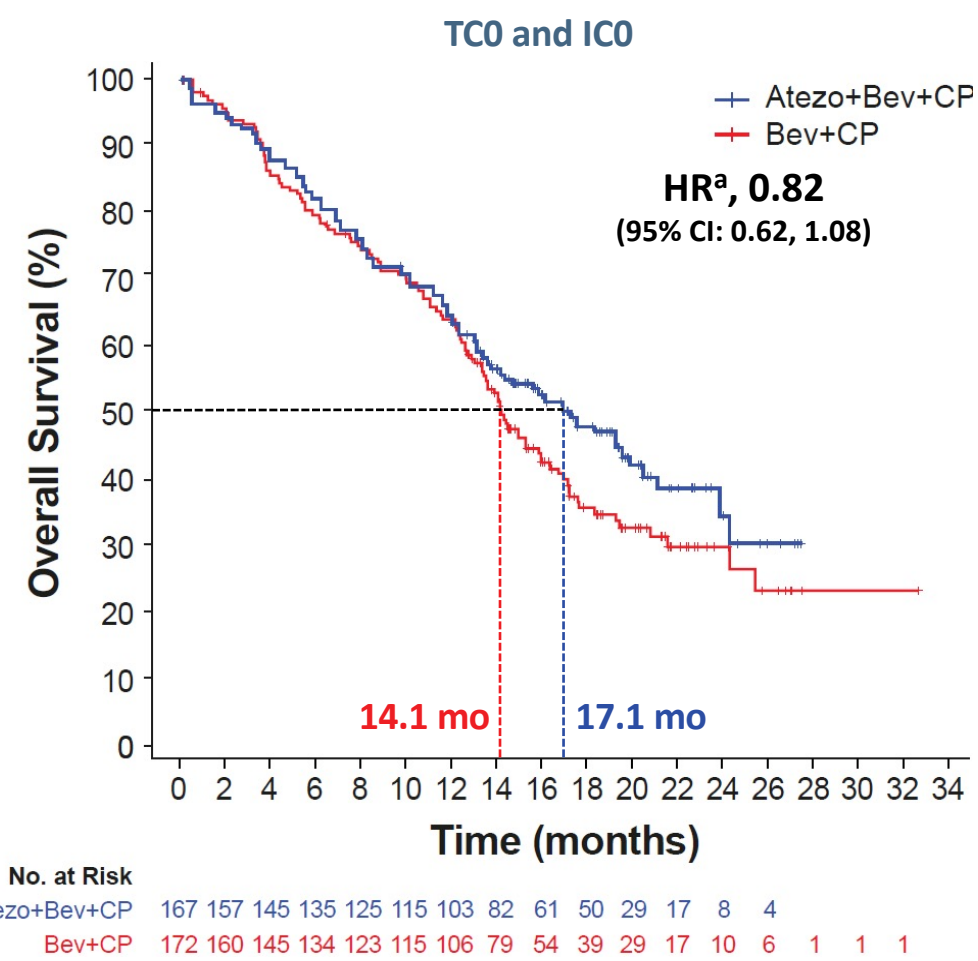
Paz-Ares L , et al. JTO 2020

Chemotherapy/Bevacizumab + ICI in PD-L1 Negative Nonsquamous NSCLC Subset Analysis of Impower 150

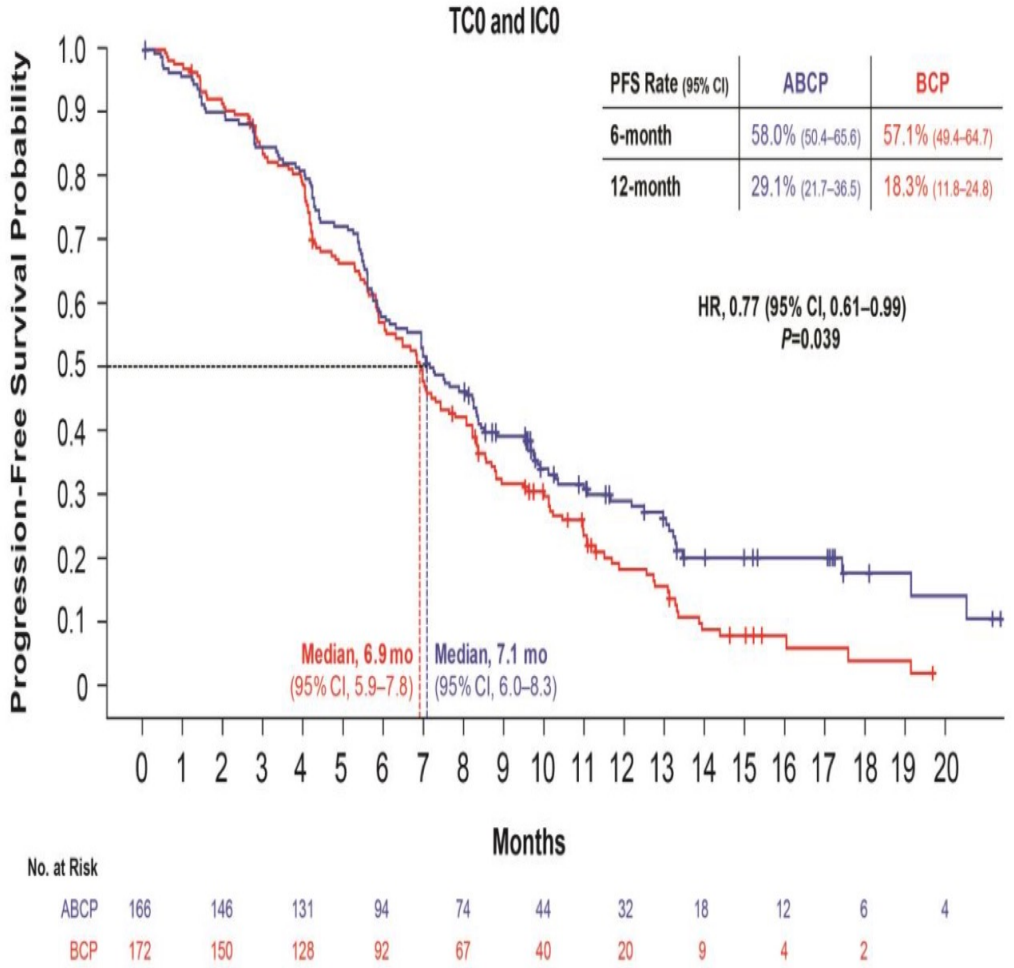


Socinski MA, et al. NEJM 2018.

Impower 150: Efficacy Results for PD-L1 negative NSCLC



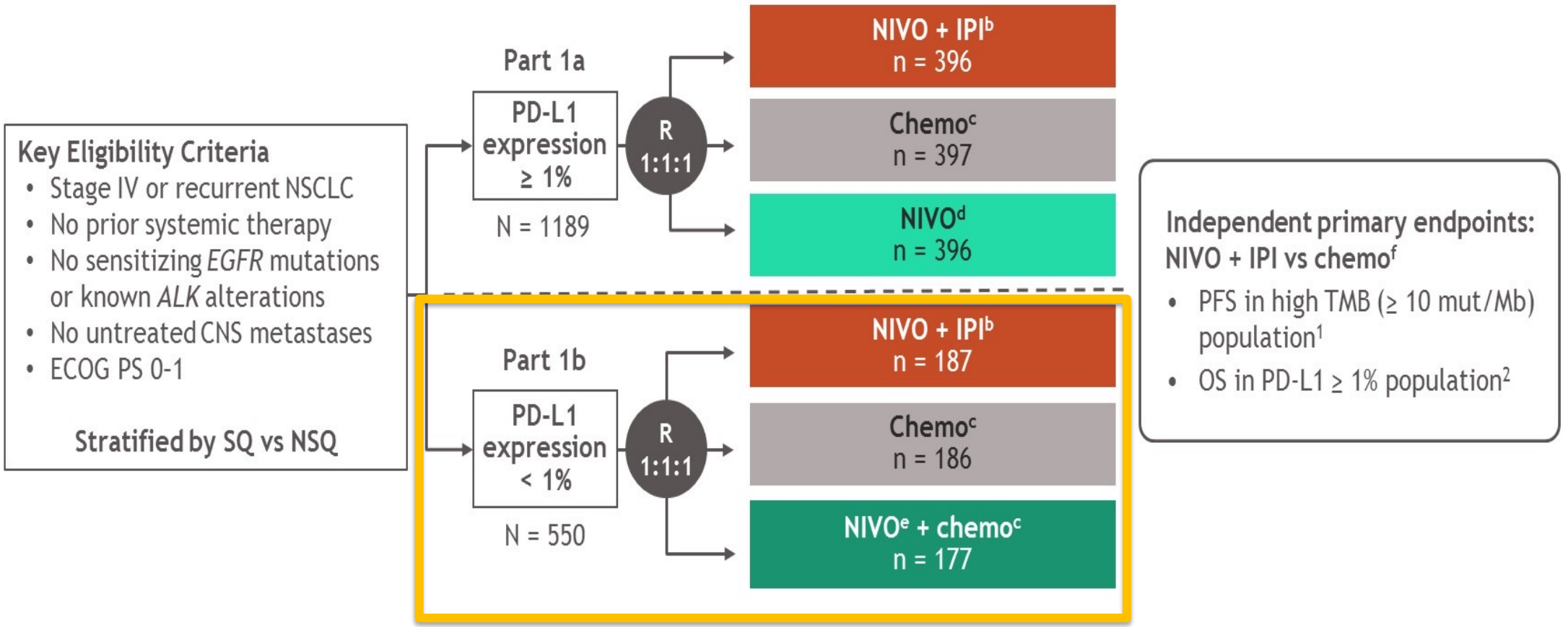
AACR 2020 update HR 0.90; median OS 16.9 mos



Combination chemotherapy + bevacizumab + atezolizumab DID NOT improve overall survival

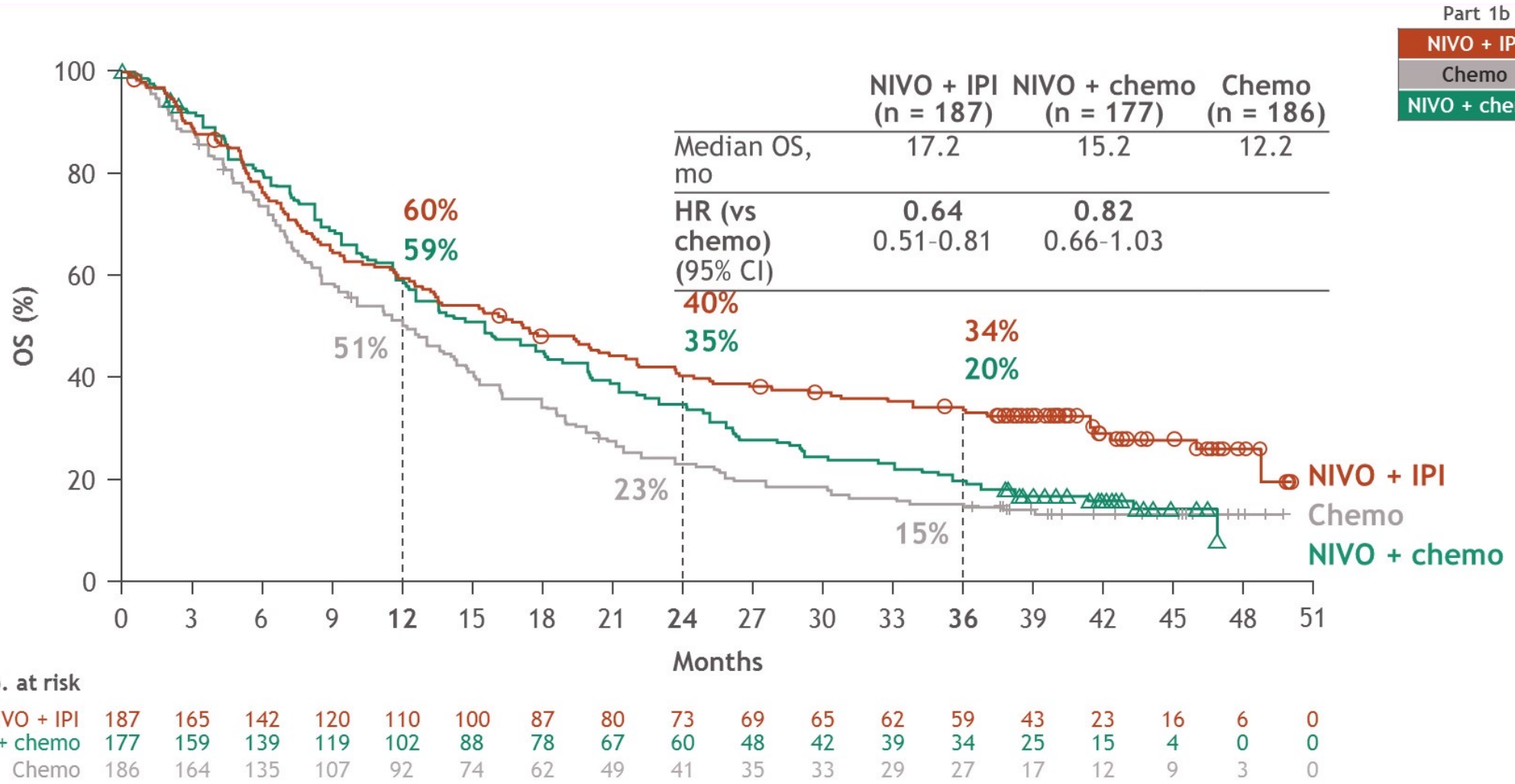
Socinski MA, et al. NEJM 2018

ICI Combination in PD-L1 Negative Expression NSCLC CheckMate 227



Ramaligan S et al. ASCO 2020

CheckMate 227 3-Year Update
OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1) < 1%)

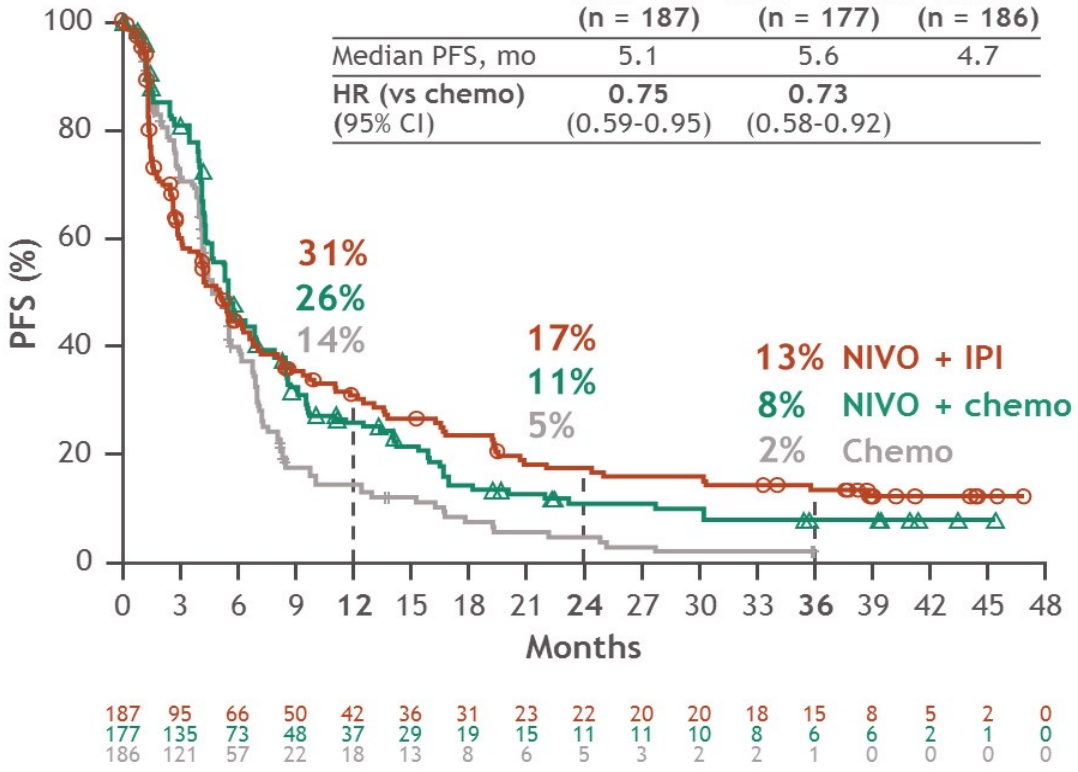


Ipilimumab + Nivolumab improves overall survival

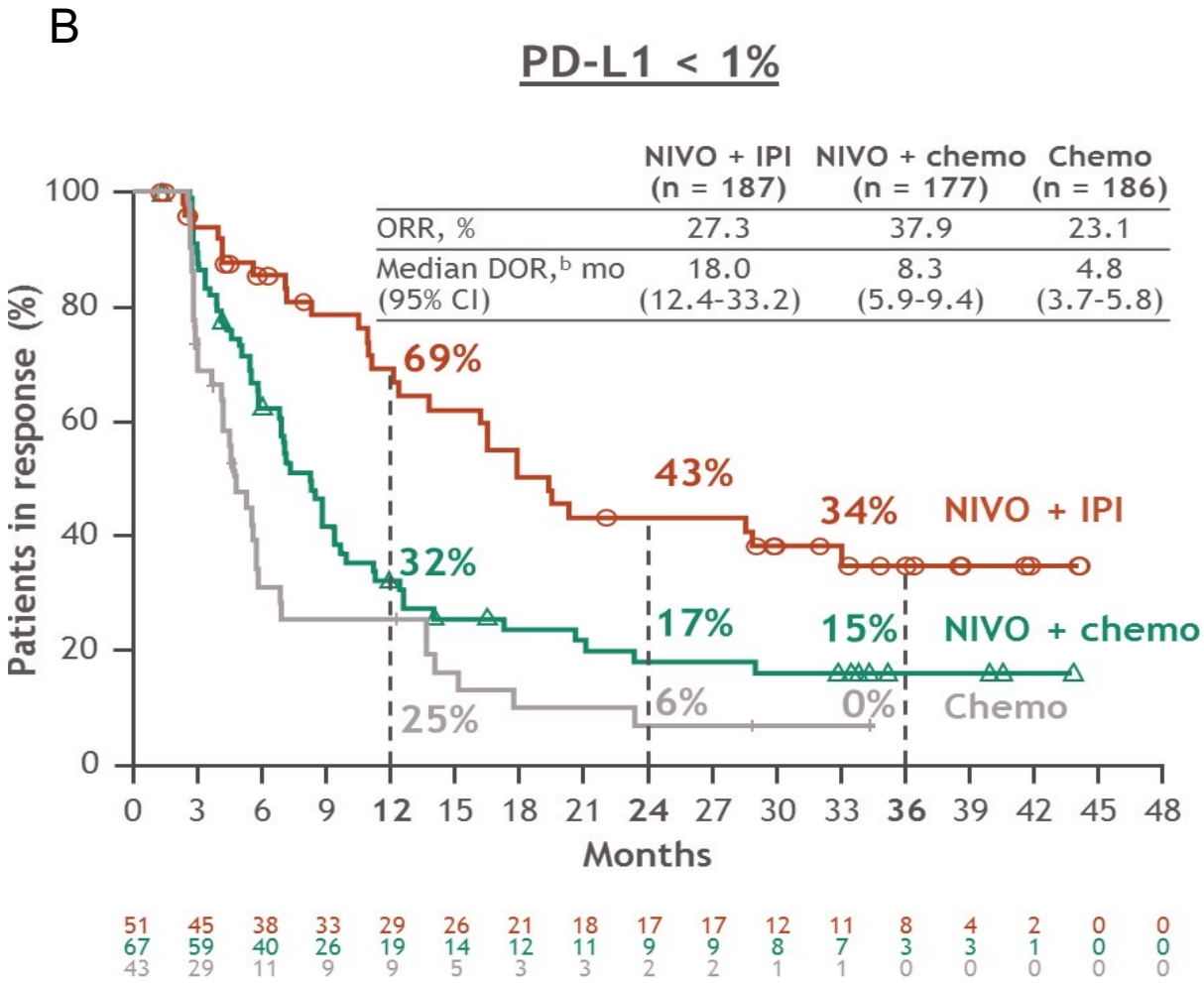
Ramaligan S et al. ASCO 2020

3-year update: PFS and DOR among patients with PD-L1 < 1%

A



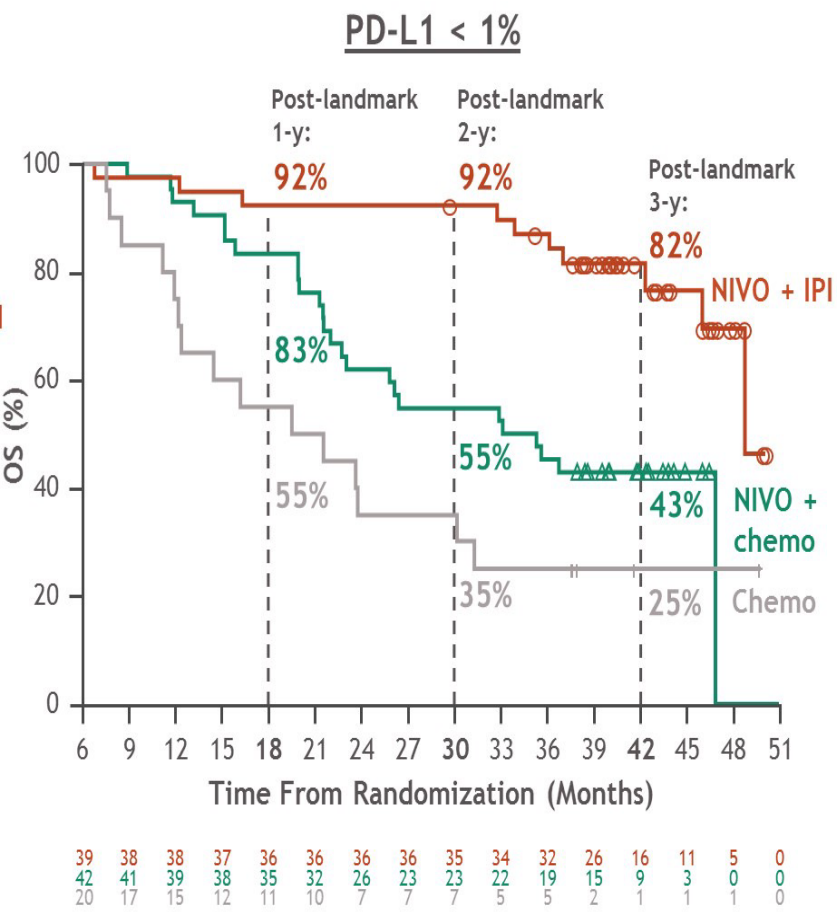
B



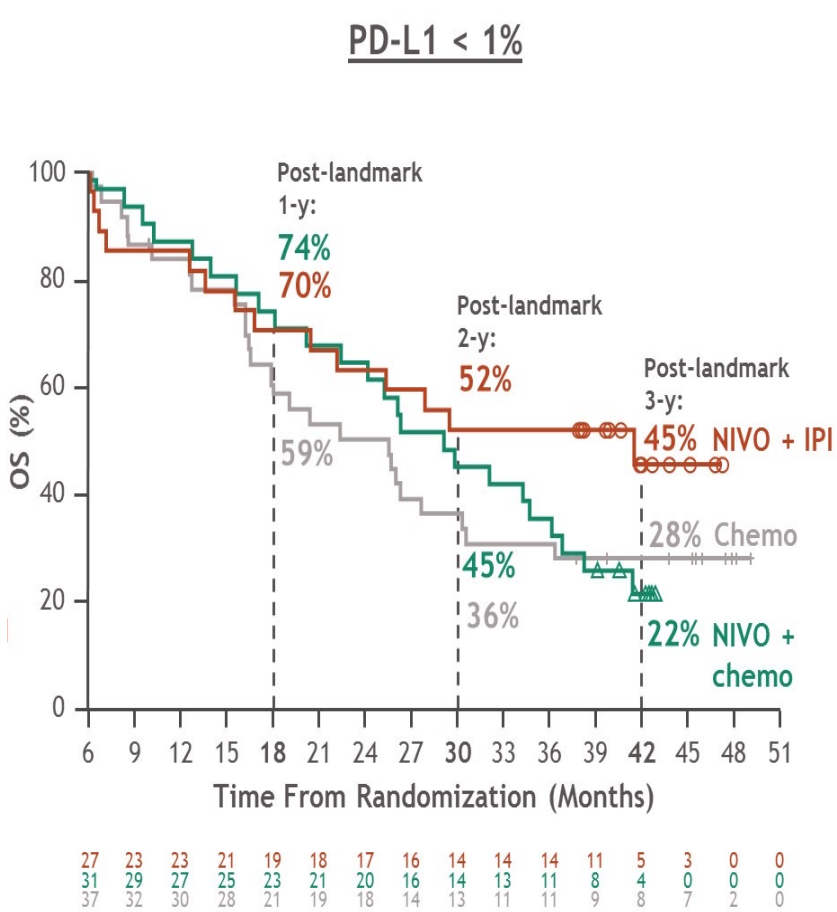
Ramaligan S et al. ASCO 2020

Exploratory Landmark Analysis

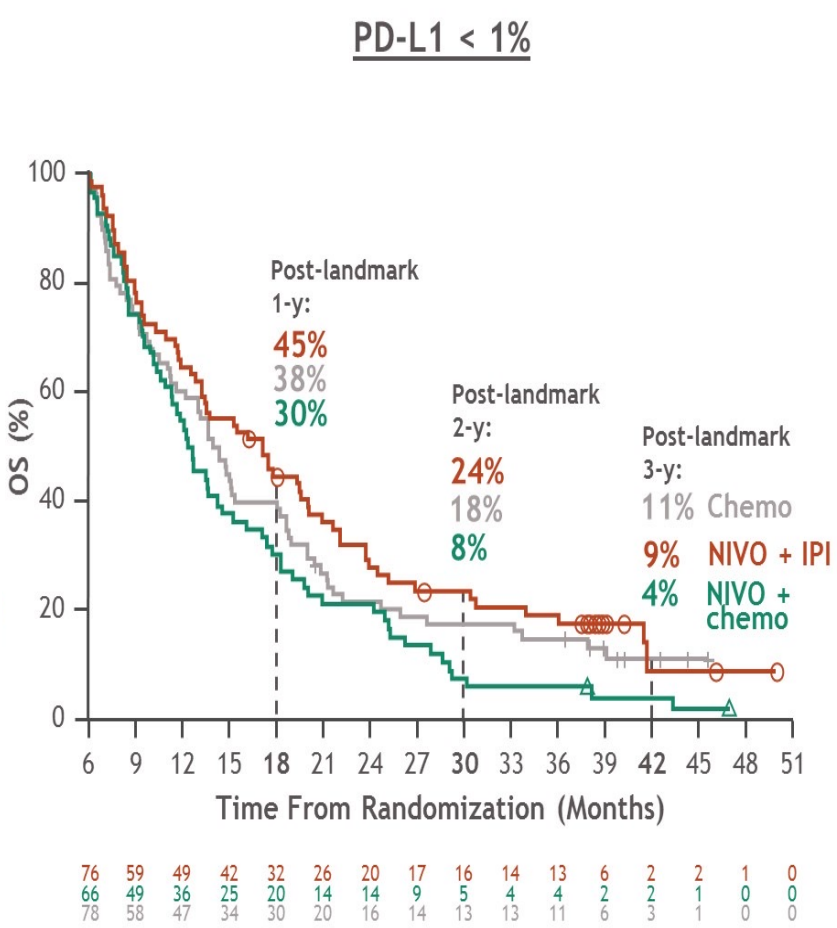
Responders at 6 months



Stable Disease at 6 months



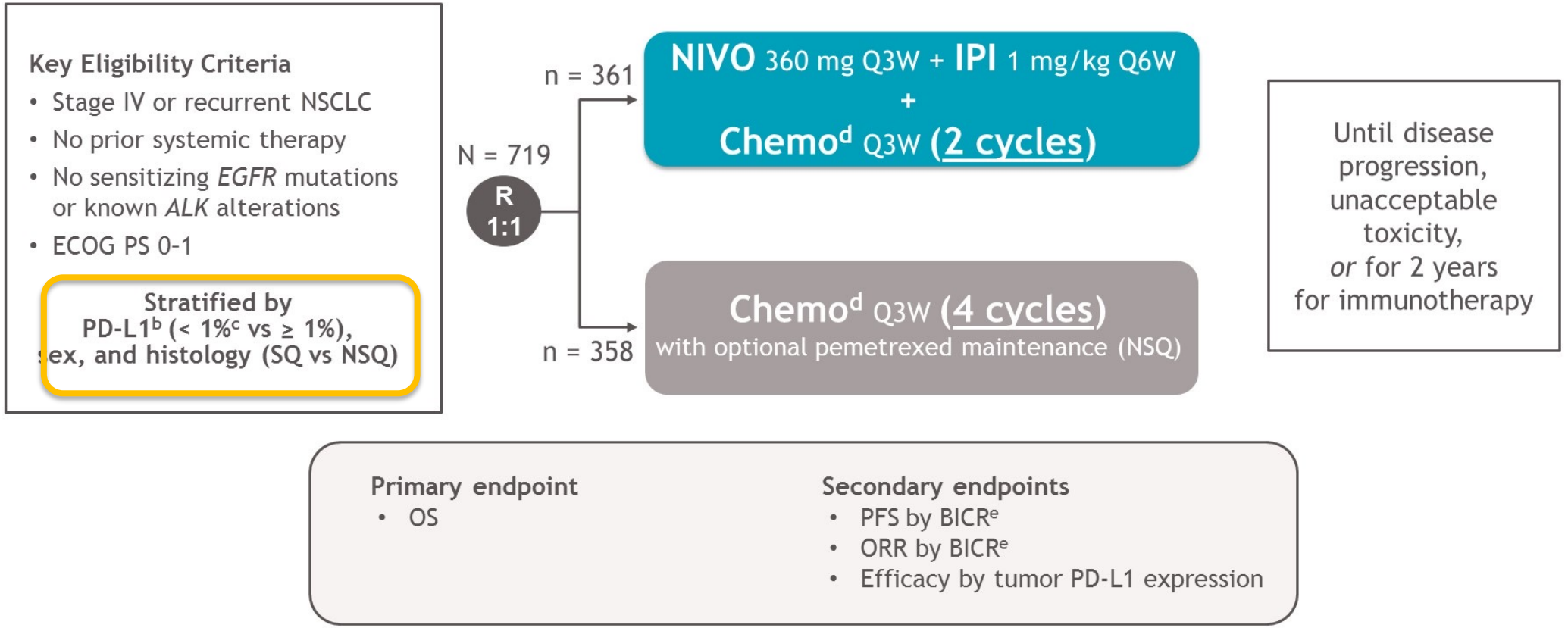
Progressive Disease at 6 months



Ramaligan S et al. ASCO 2020

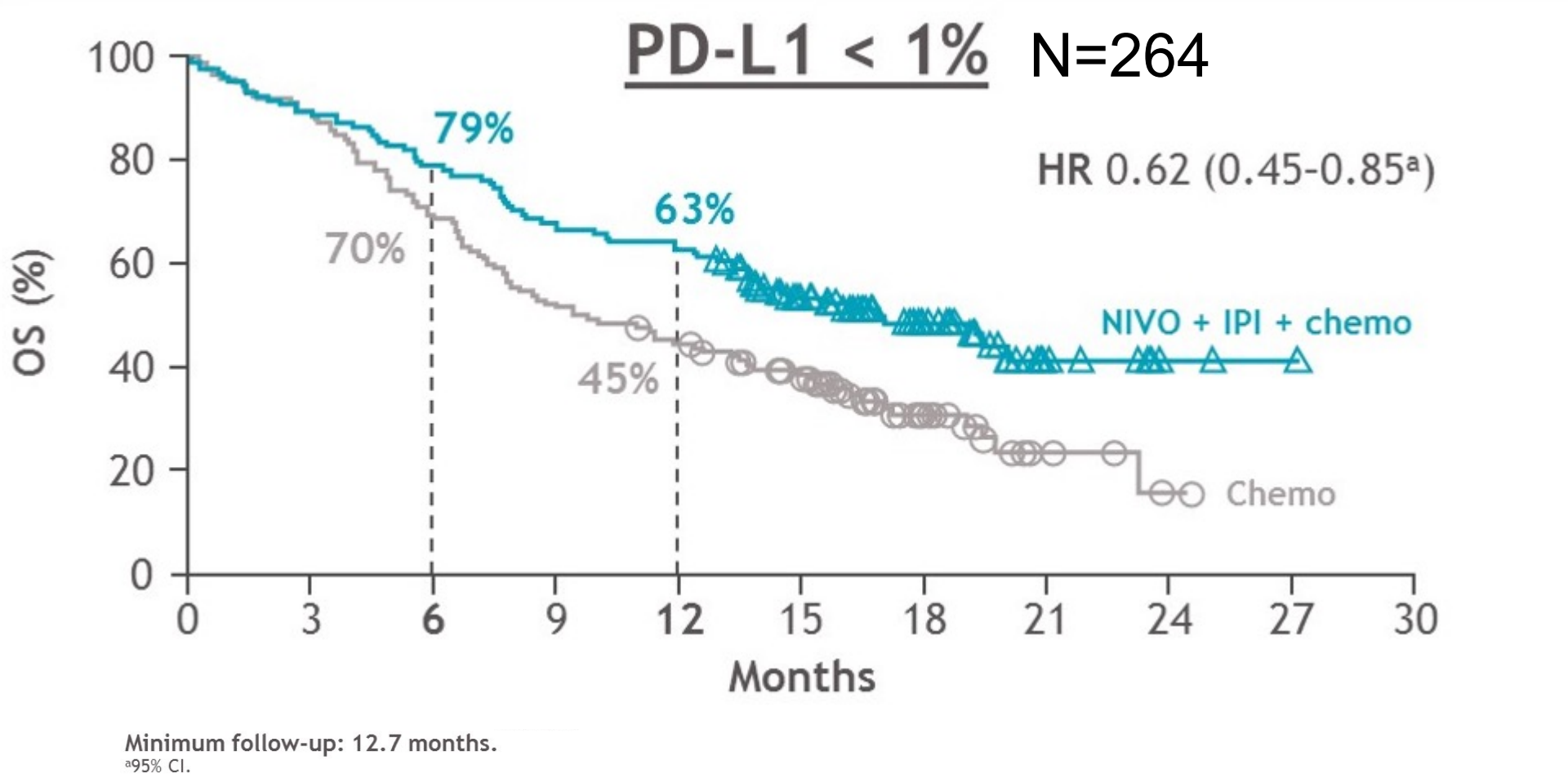
ICI Combination + Chemotherapy in PD-L1 Negative Expression NSCLC

CheckMate 9LA study design



Reck M, et al. ASCO 2020

Overall survival by PD-L1 expression level



Minimum follow-up: 12.7 months.
[a]95% CI.

Reck M, et al. ASCO 2020

Summary Table

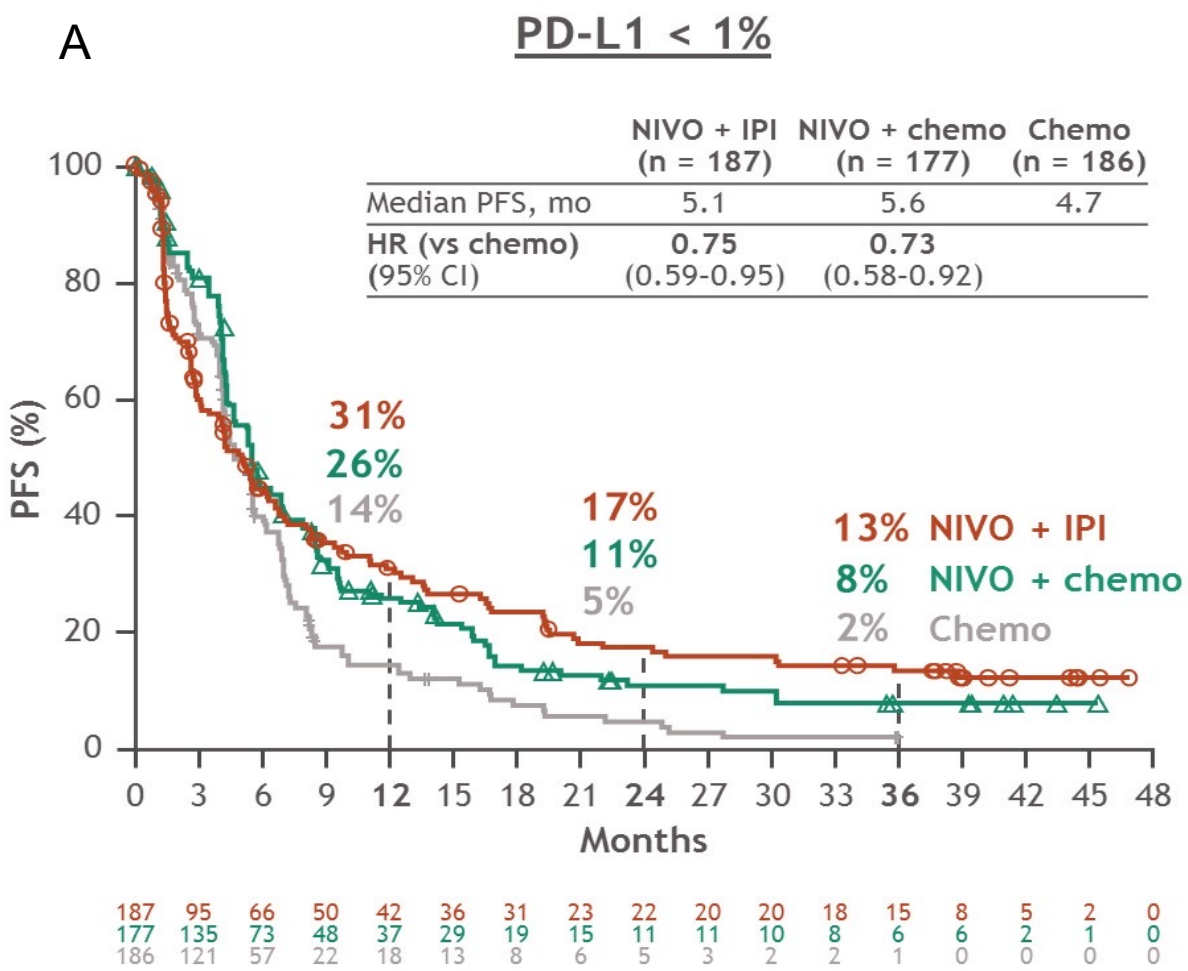
Trial	N	Med OS	HR	2 yr OS	DOR	≥ GR 3 IRAE *
KNT 189 (adeno)	190	17.0 mos	0.52	38.5%	10.8 mos	10.9%
KNT 407 (SCCA)	194	15.9 mos	0.79	29.5%	6.9 mos	13.3%
IMpower 150	339	17.1 mos	0.82	NR	NR	13.4%
CHMT 227	373	17.2 mos	0.62	40.4%	18.0 mos	33%
CHMT 9LA	264	16.8 mos	0.62	NR	NR	22%

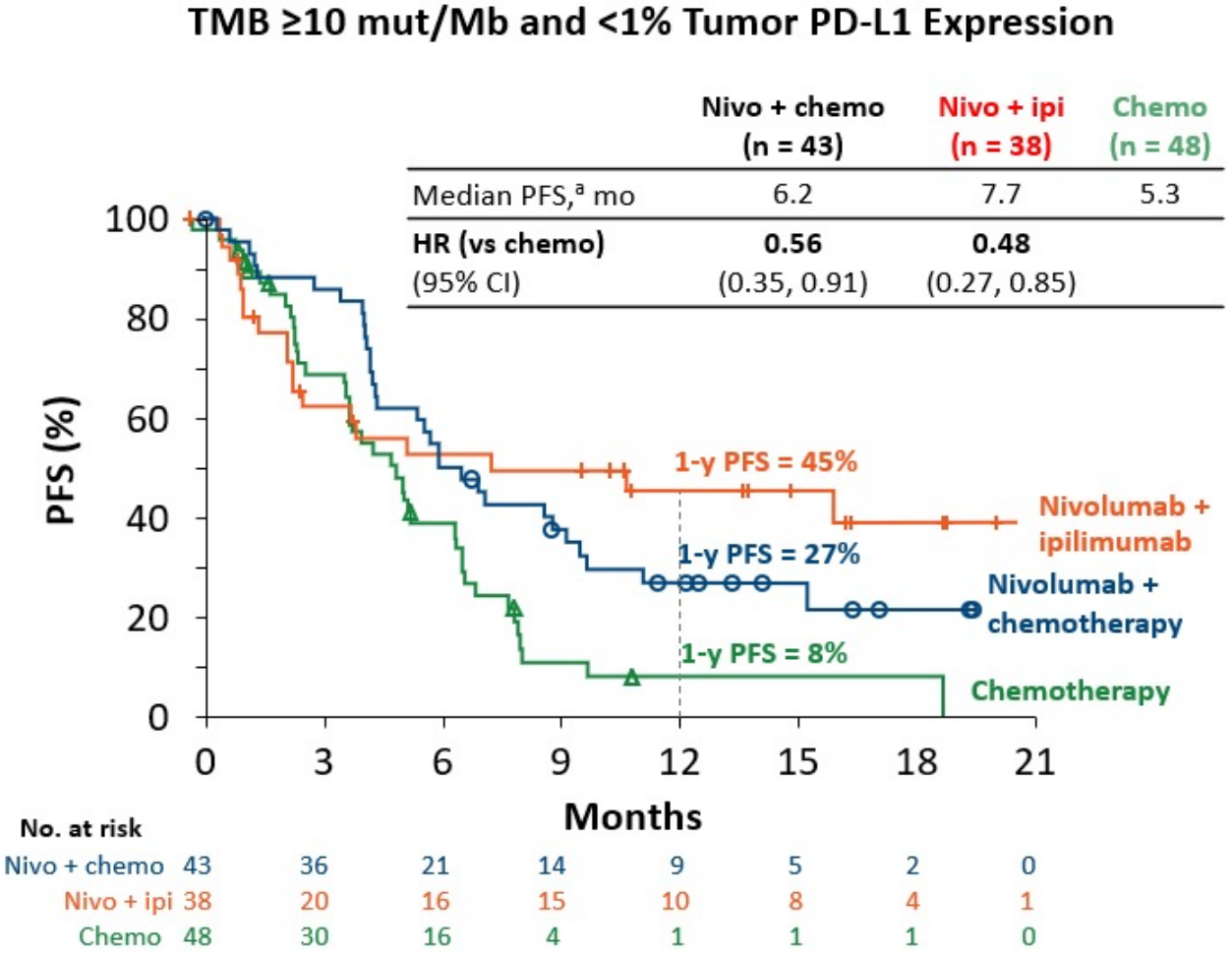
* All patients

How do we identify the PD-L1 negative patients that are most likely to respond to immunotherapy?

CheckMate 227

A





20% of PD-L1- tumors were TMB high; 51 patients overall had an ORR

Hellmann MD et al. Oral presentation at AACR 2018. CT077

How do we identify the PD-L1 negative patients that are most likely to respond to immunotherapy?

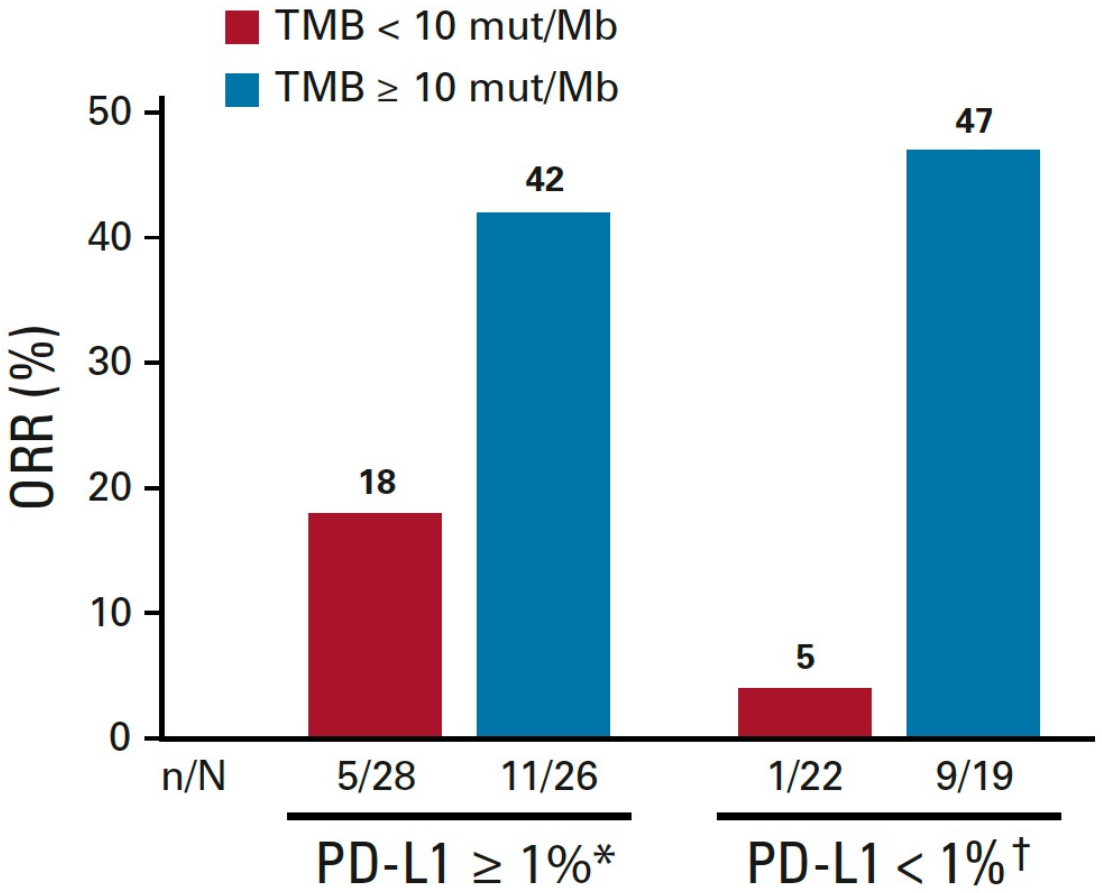
CheckMate 568

Key eligibility criteria
- Stage IV or recurrent stage IIIb NSCLC
- No prior systemic therapy
- No known sensitizing *EGFR/ALK* alterations
- ECOG PS 0–1

→ Nivolumab 3 mg/kg every 2 weeks
Ipilimumab 1 mg/kg every 6 weeks
(N = 288)
→ Until disease progression or unacceptable toxicity or maximum of 2 years

Primary end points:
- ORR* in PD-L1 ≥ 1% and < 1% populations†

Select secondary end points:
- PFS and OS
- ORR, PFS, and OS by TMB



16.6% of PD-L1 negative patients were TMB high

Ready N, et al. JCO 2019

Beyond PD-L1 Negative Expression and Primary IO Resistance

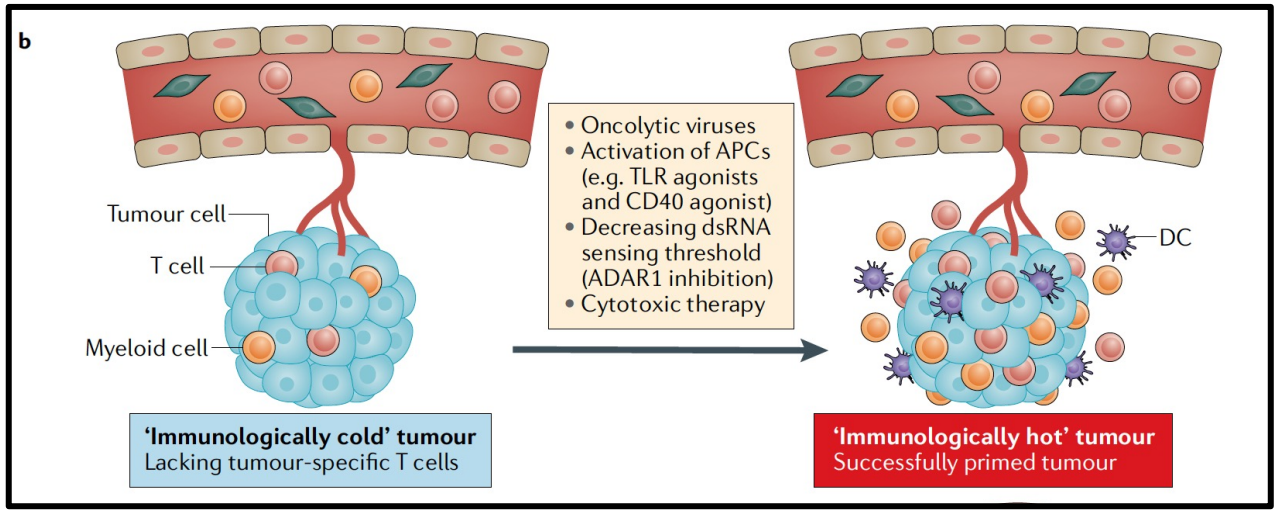
Tumor Intrinsic Factors
Insufficient tumor antigenicity
Disruption of interferon-γ signaling
Loss of MHC
Oncogenic signaling WNT-β-catenin, CDK-4/6 & MAPK signaling Loss of PTEN
Tumor dedifferentiation/stemness

Tumor Microenvironment
Heterogeneity of TME
Lack of a preexisting immune response

Patient-Intrinsic Factors
Host immune system
HLA genotype
Gut microbiota
Neutrophil/Lymphocyte Ratio
BMI

Kalbasi A and Ribas AI Nature Review 2020

Therapeutic Strategies to Enhance IO Responsive in PD-L1 Negative NSCLC



ALLIANCE TRIAL

Stage 4 NSCLC
PS-0-2
PD-L1 (-)

→ R → I/O(+/-chemo)

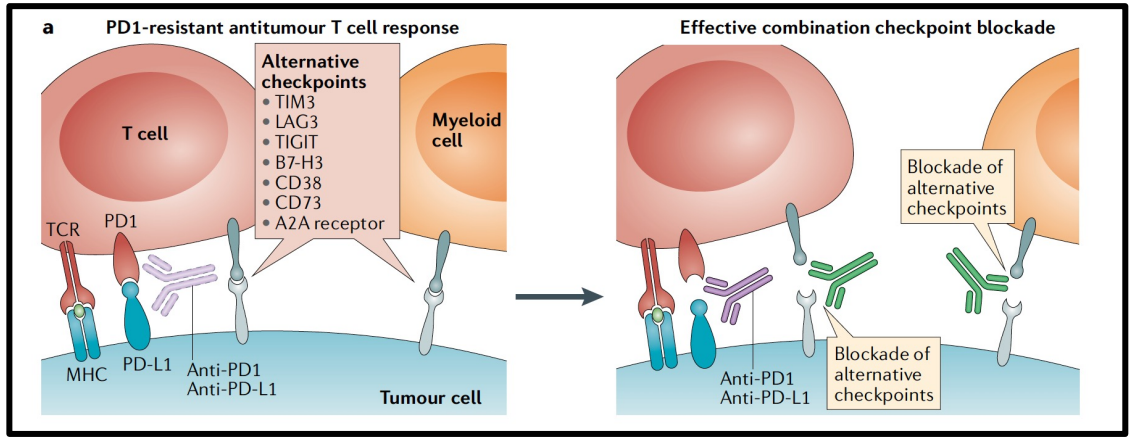
→ R → SBRT +I/O(+/-chemo)

SBRT to one site (8Gy x 3 fractions, administered every other day) within 30 days of registration but not on days where systemic therapy is administered

phase II portion, 100 patients; primary endpoint PFS
phase III portion 427 patients; primary endpoint OS

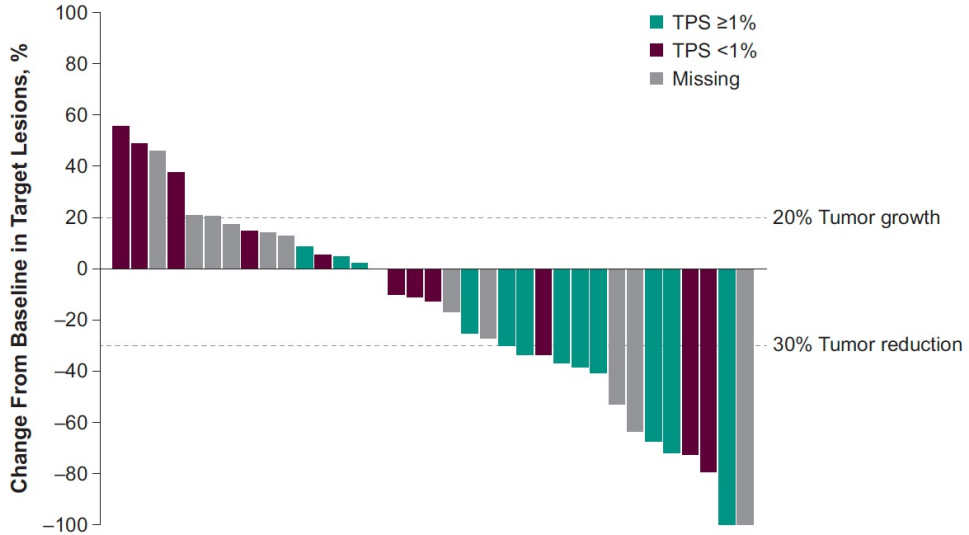
Kalbasi A and Ribas Al Nature Review 2020

Therapeutic Strategies to Enhance IO Responsiveness in PD-L1 Negative NSCLC



Vibostolimab (anti-TIGIT antibody) + Pembrolizumab

Figure 1. Best Change From Baseline in Target Lesions Based on Investigator Assessment per RECIST v1.1 in Patients With Anti-PD-1/PD-L1-Naive NSCLC[a]



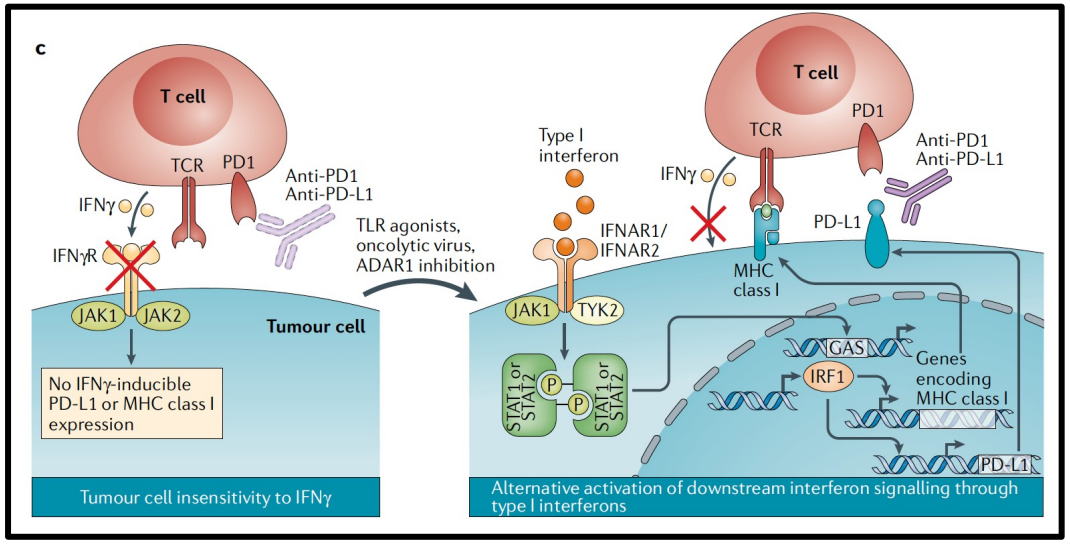
Patients With Available PD-L1 Data	Without Confirmation	With Confirmation[a]
TPS ≥1%: responders, n	6	4
TPS ≥1%: ORR, % (95% CI)	46 (19-75)	31 (9-61)
TPS <1%: responders, n	3	3
TPS <1%: ORR, % (95% CI)	25 (6-57)	25 (6-57)

Table 3. PFS by TPS Status in Patients With Anti-PD-1/PD-L1-Naive NSCLC[a]

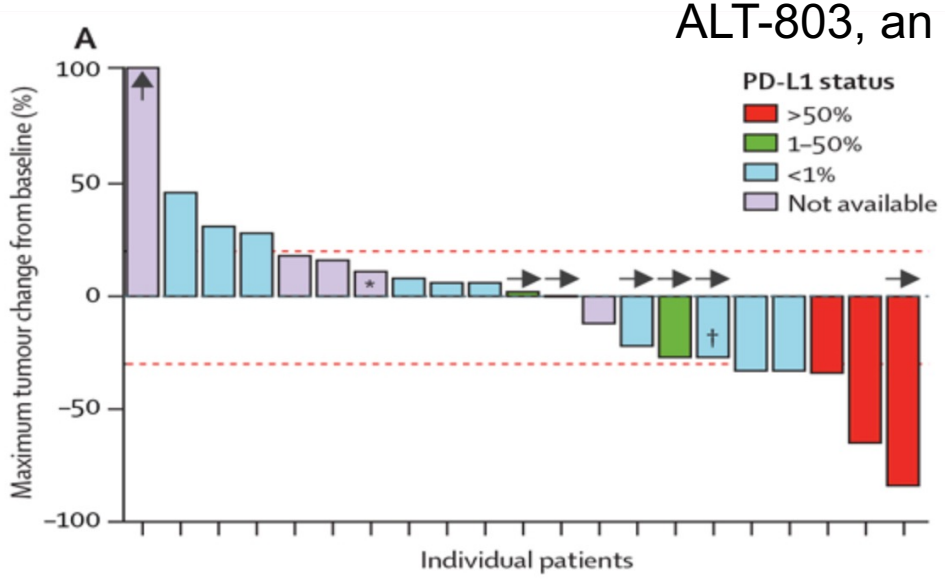
	TPS ≥1% n = 13	TPS <1% n = 12
Median (95% CI), months	8.4 (3.9-10.2)	4.1 (1.9-NR)

Kalbasi A and Ribas AI Nature Review 2020;Niu J, et al. ESMO 2020 #1401P

Therapeutic Strategies to Enhance IO responsiveness in PD-L1 negative NSCLC



ALT-803, an IL-15 superagonist + nivolumab



	Objective responses (n, %, 95% CI)	Disease control (n, %, 95% CI)
All patients	6 (29%, 11–52)	16 (76%, 53–92)
PD-1 relapsed and refractory	3 (27%, 6–61)	10 (91%, 59–99)
PD-LI negative (<1%)	3 (30%, 7–65)	7 (70%, 35–93)
PD-L1 positive (>50%)	3 (75%, 19–99)	4 (100%, 40–100)

SWOG 1800D

Kalbasi A and Ribas AI Nature Review 2020; Wrange J, et al. Lancet Oncol 2018

PD-L1 negative tumors

- One third of patients with NSCLC have PD-L1 negative tumors.
- Combination therapies (chemotherapy + ICI or dual ICIs) are the treatment of choice with small subset of patients enjoying durable responses.
- PD-L1 negative tumors are heterogenous. High TMB may identify PD-L1 negative tumors more likely to respond to ICIs.
- Future immuno-therapeutic advances will require a better understanding of the interplay between the tumor, TME and host.
- Trials specific for PD-L1 negative tumors should be considered.