NON-SMALL CELL LUNG CANCER (NSCLC) OPTIMAL SEQUENCE OF CHEMOTHERAPY AND IMMUNOTHERAPY

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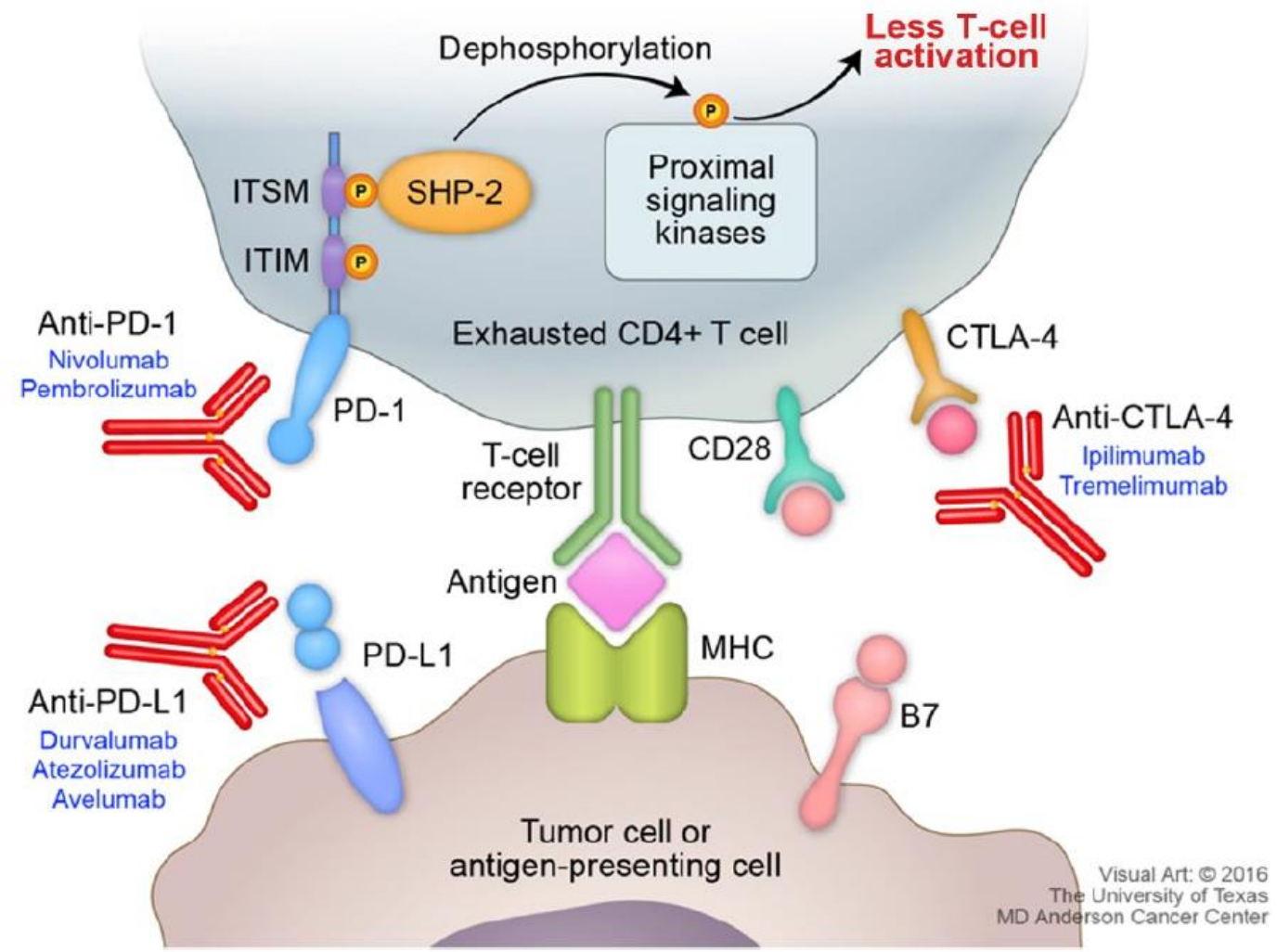
Disclosures

- Advisory Board Ad Hoc Consultant for Janssen, Lilly, BMS, Sanofi, and Merck.
- On the Speakers Bureau for AstraZeneca, Lilly, and Merck.

PD-1/PD-L1 Pathway and Immunotherapy Targets

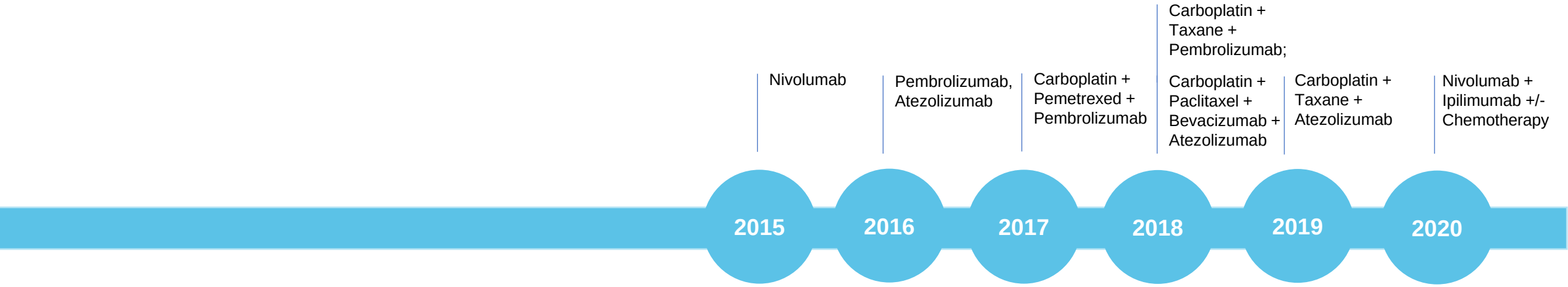


Schvartsman G, Ferrarotto R and Massarelli E. Ther Adv Med Oncol 2016

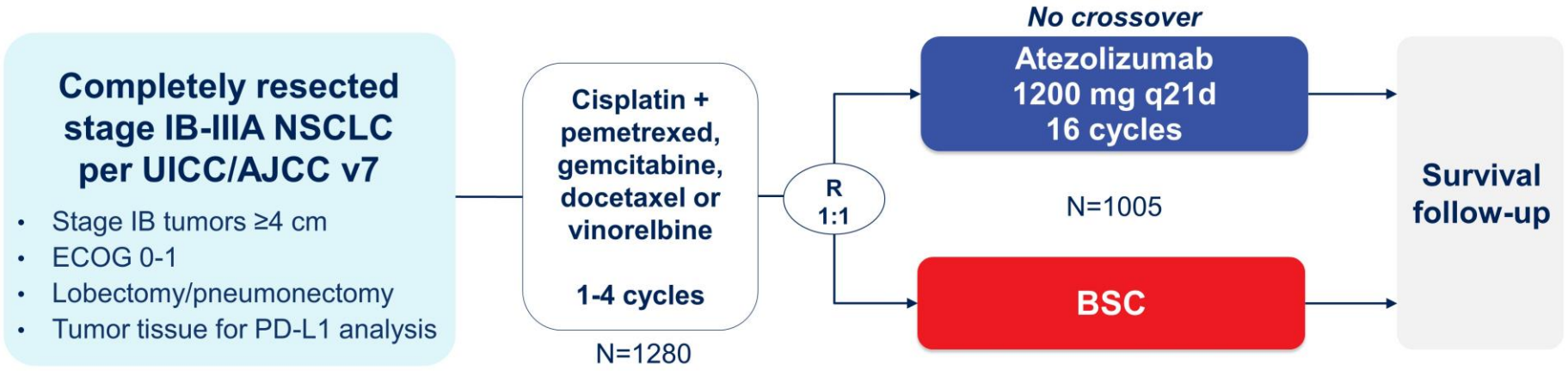
Treatment Approvals in Resectable Versus Metastatic NSCLC without Driver Mutations

Resectable Disease

Metastatic Disease



IMpower010: Adjuvant Atezolizumab in Completely Resected Stage IB-IIIA NSCLC



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

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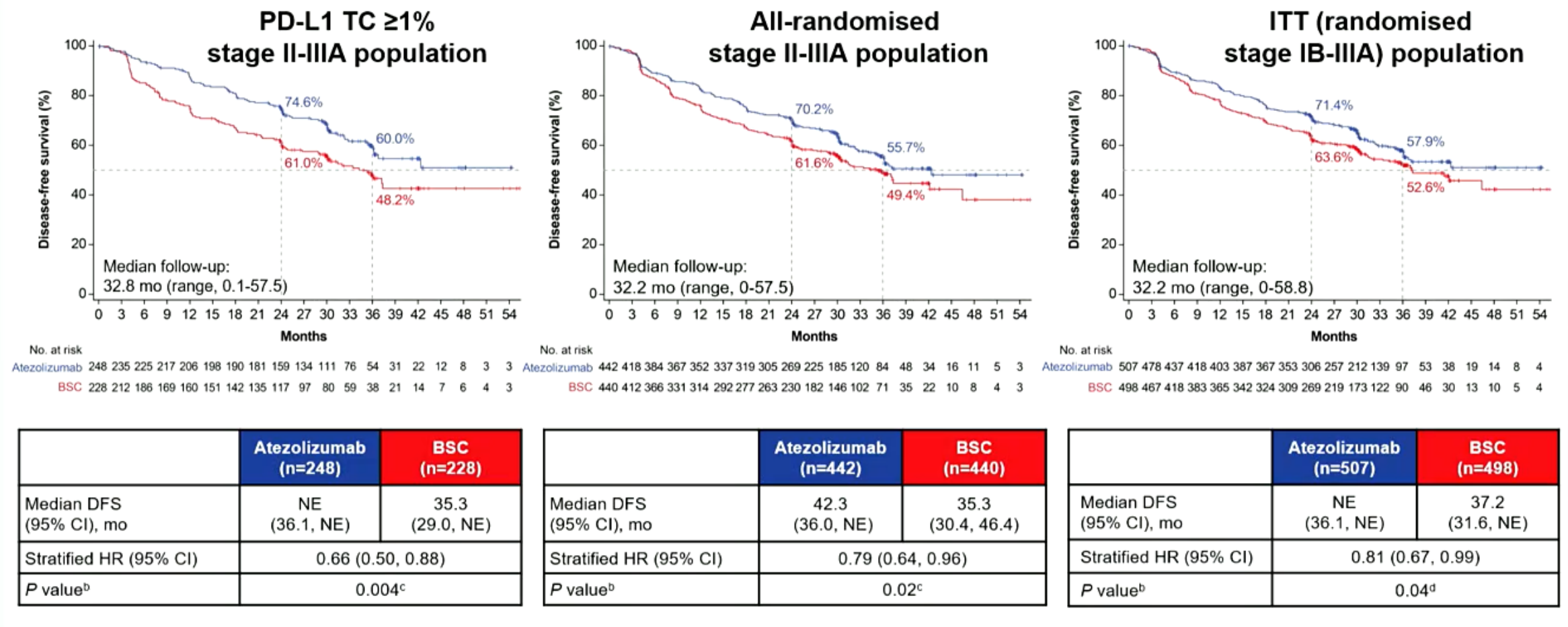
IMpower010: DFS Analyses



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

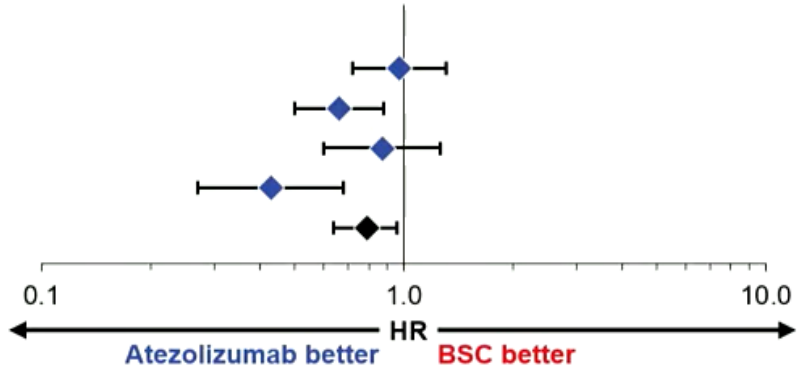
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

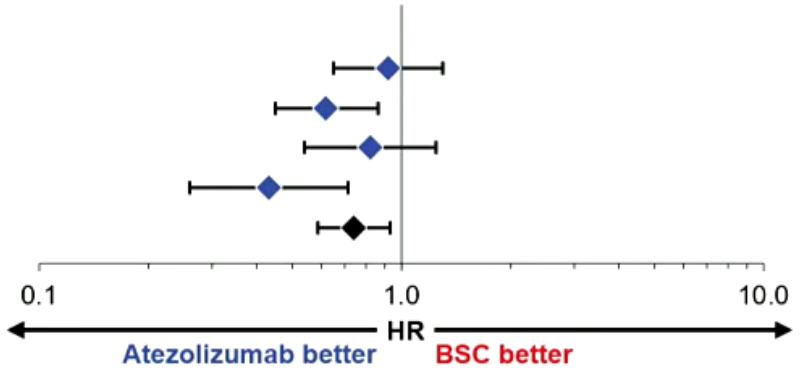
IMpower010: DFS by PD-L1 Status

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)

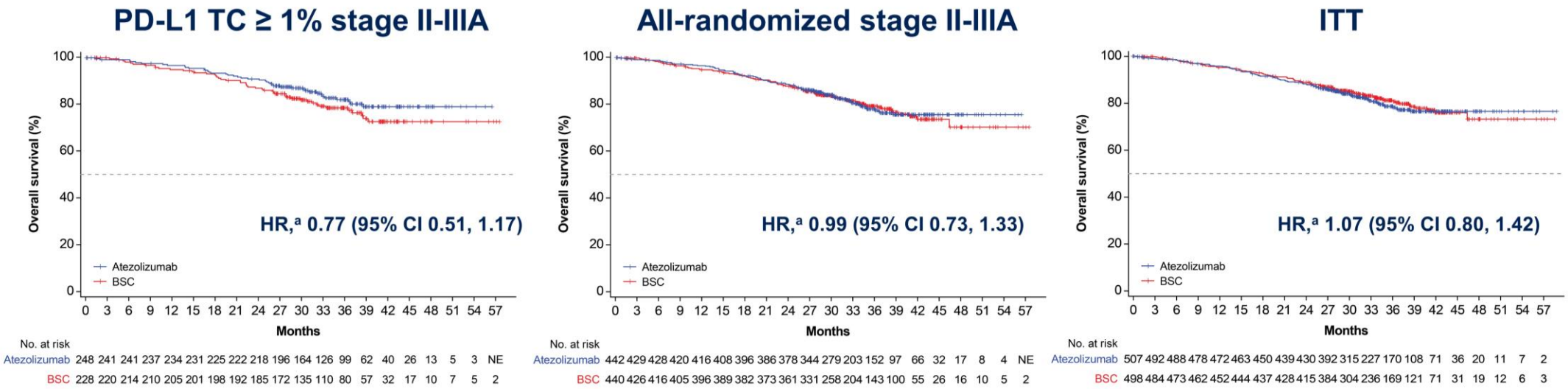


Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.

IMpower010: Overall Survival



- OS data were immature at this pre-planned DFS interim analysis
  - OS in the ITT population was not formally tested
  - A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Clinical cutoff: January 21, 2021. [a] Stratified.

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IMpower010: Safety Data

n (%)	Atezolizumab (n=495)	BSC (n=495)
Any-cause AE	459 (92.7)	350 (70.7)
Treatment-related AE	335 (67.7)	–
Grade 3-4 AE	108 (21.8)	57 (11.5)
Treatment-related grade 3-4 AE	53 (10.7)	–
Serious AE	87 (17.6)	42 (8.5)
Treatment-related serious AE	37 (7.5)	–
Grade 5 AE	8 (1.6)[b]	3 (0.6)[c]
Treatment-related grade 5 AE	4 (0.8)	–
AE leading to dose interruption of atezolizumab	142 (28.7)	–
AE leading to atezolizumab discontinuation	90 (18.2)	–
Immune-mediated AEs	256 (51.7)	47 (9.5)
Grade 3-4 immune-mediated AEs	39 (7.9)	3 (0.6)
Immune-mediated AEs requiring the use of systemic corticosteroids	60 (12.1)	4 (0.8)

- The safety profile was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy

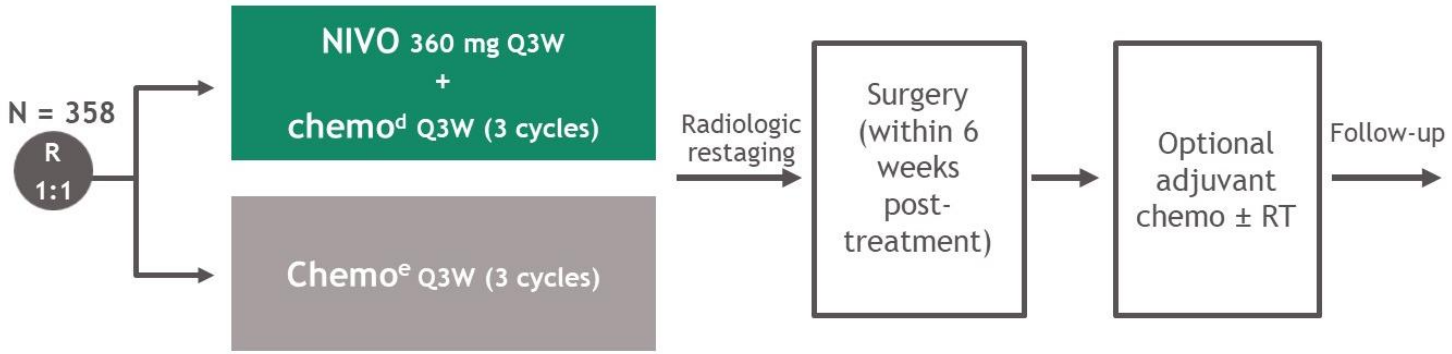
Adapted from Wakelee, H; ASCO 2021

CheckMate 816: Neoadjuvant Nivolumab + Platinum-Doublet Chemotherapy Versus Chemotherapy

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

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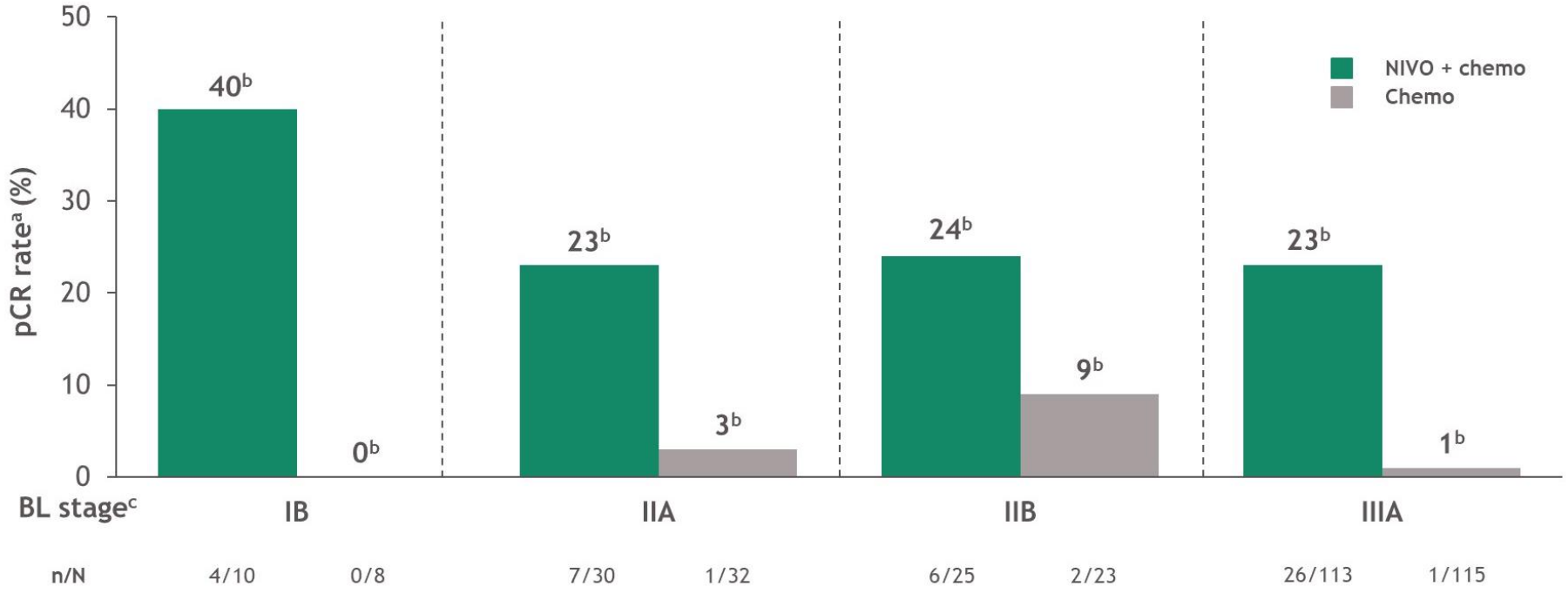
CheckMate 816: Response



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

[a]Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR; [b]95% CI: NIVO + chemo, chemo (stage): 12.2-73.8, 0.0-36.9 (IB); 9.9-42.3, 0.1-16.2 (IIA); 9.4-45.1, 1.1-28.0 (IIB); 15.6-31.9, 0.0-4.7 (IIIA); [c]Baseline stage of disease by CRF, TNM 7th edition used for classification; [d]pCR rate in patients with radiographic down-staging: 31% with NIVO + chemo vs 7% with chemo; pCR rate in patients without radiographic down-staging: 22% with NIVO + chemo vs 1% with chemo.

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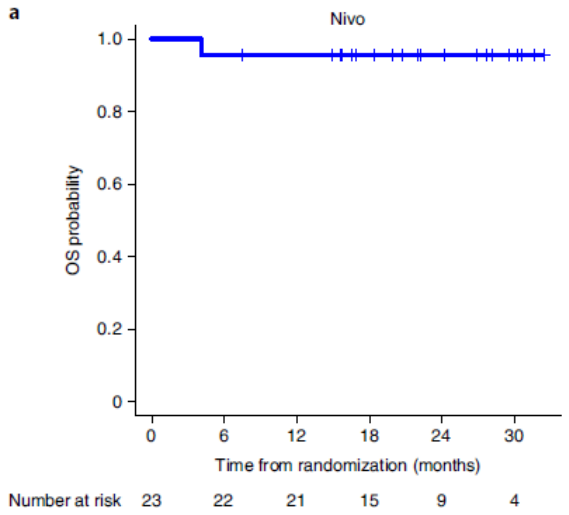
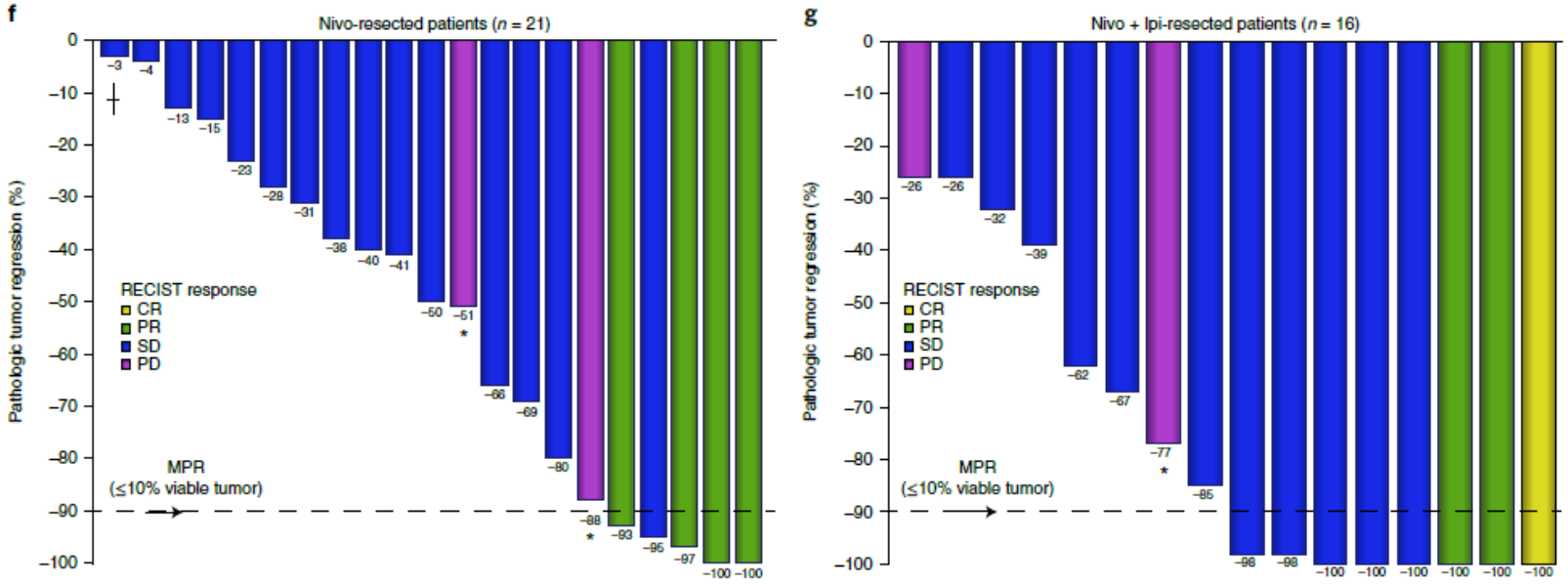
➢ Nivo + chemo significantly improved pCR rates and had greater depth of pathologic response

Adapted from Wakelee, H; ASCO 2021

NEOSTAR: Neoadjuvant Nivolumab versus Nivolumab + Ipilimumab in Locally Advanced NSCLC

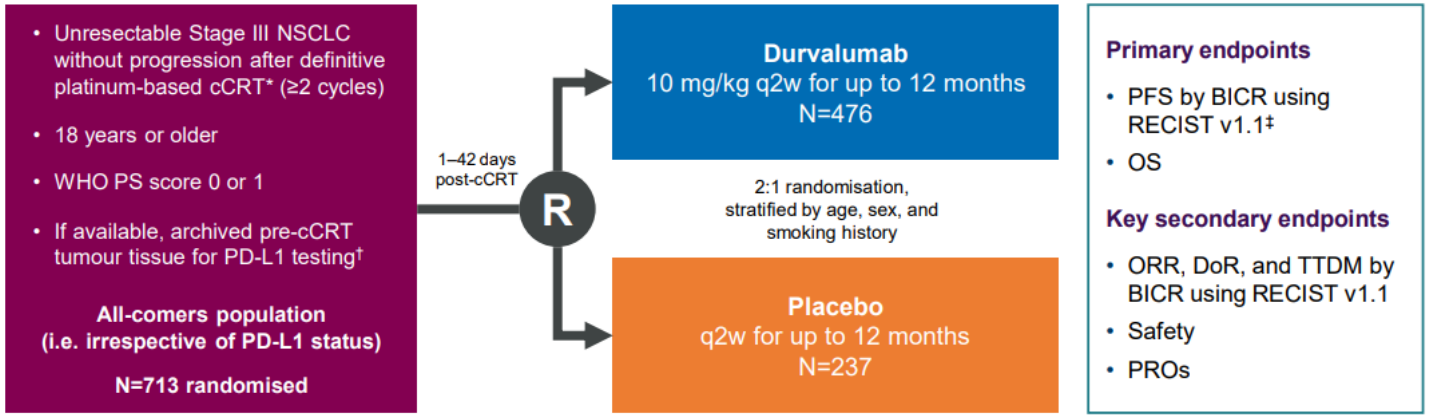


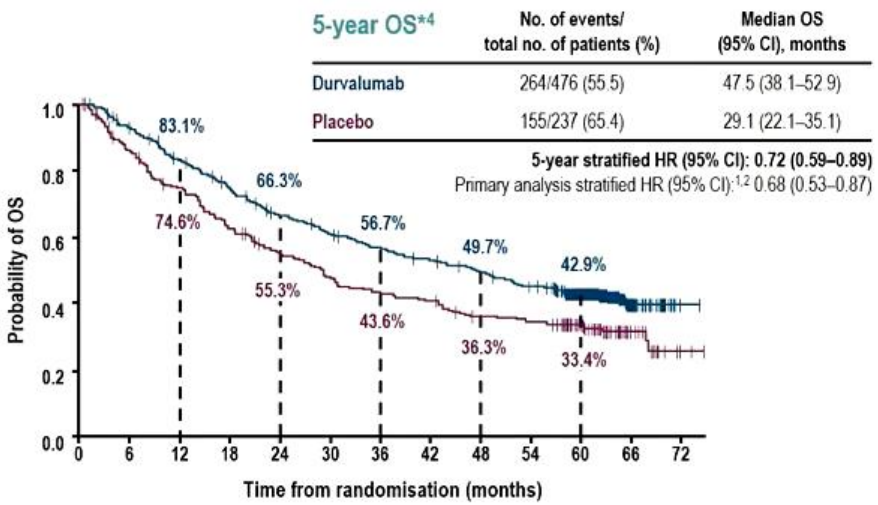


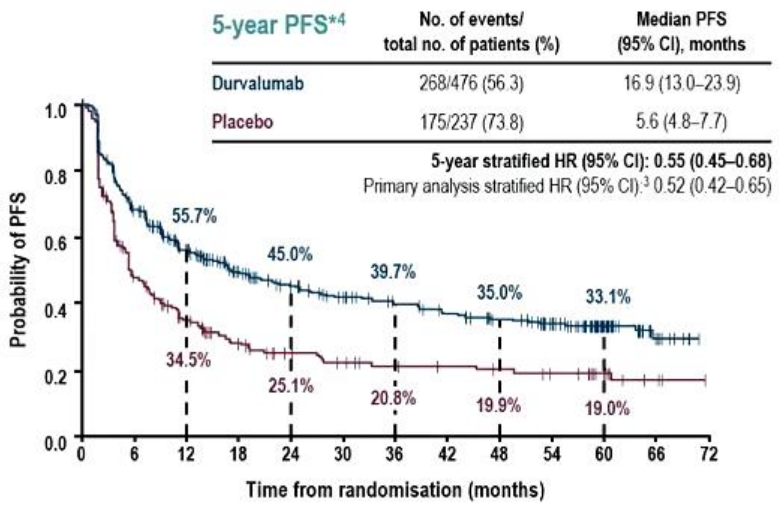
- Compared with nivolumab, nivolumab + ipilimumab resulted in higher pathologic complete response rates (10% versus 38%) and less viable tumor (median 50% versus 9%)
- Neoadjuvant nivolumab + ipilimumab-based therapy enhances pathologic responses, tumor immune infiltrates, and immunologic memory

Cascone, T; Nature Med 2021

PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC 5-Year Survival Update







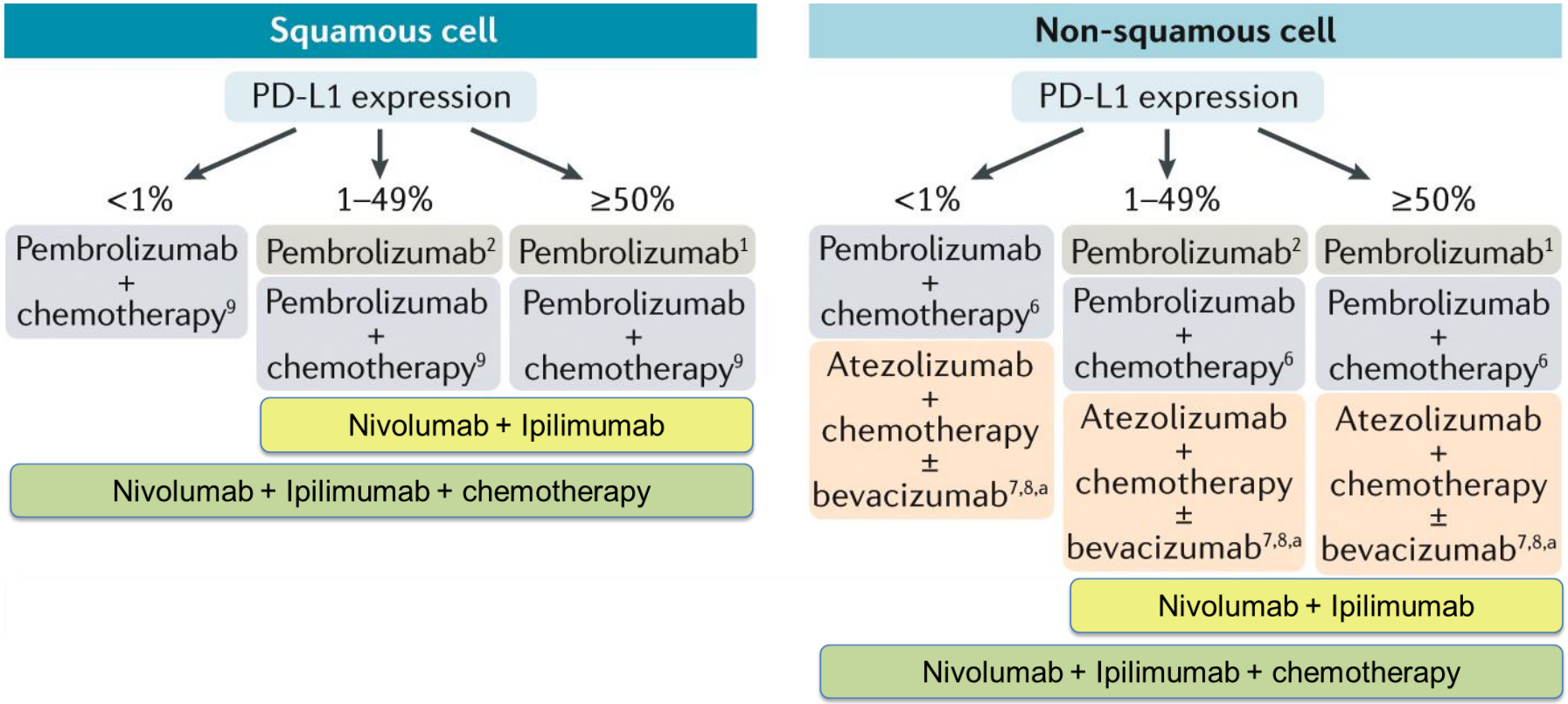
- In the PACIFIC trial, durvalumab after concurrent chemoradiation therapy significantly improved OS and PFS
- Updated 5-year results demonstrate sustained OS and PFS benefit
- The COAST trial is investigating durvalumab in combination with novel agents after concurrent chemoradiation in Stage III NSCLC

Immuno-Oncology Trials in Resectable NSCLC

Trial	NCT	Drug	Stage	Phase	Endpoint
IMpower 030	NCT03456063	CT + atezolizumab x 4 cycles → S → atezolizumab/placebo x 16 cycles	II-IIIB (cT3N2)	III	MPR, EFS
AEGEAN	NCT03800134	CT + durvalumab x 3 cycles → S → durvalumab/placebo x 12 cycles	IIA-IIIB	III	MPR
CheckMate 816	NCT02998528	CT + nivolumab x 3 cycles → S cs CT x 3 cycles → S	IB-IIIA	III	EFS, pCR
KEYNOTE 617	NCT03425643	CT + pembrolizumab x 4 cycles → S → pembrolizumab/placebo x 13 cycles	II-IIIB (cT3-4N2)	III	EFS, OS
SAKK 16/14	NCT02572843	CT x 3 → durvalumab x 2 cycles → S → durvalumab x 1 year	IIIA (N2)	II	EFS
PRICNEPS	NCT02994576	Atezolizumab x 1 cycles → S	IB-IIIA (no N2)	II	Toxicity
MK3475-223	NCT02938624	Pembrolizumab different dose/regimens → S	I-II	I	Toxicity, MPR
PEARLS	NCT02504372	S with or without CT → pembrolizumab/placebo	IB-IIIA	III	DFS
ANVIL	NCT02595944	S with or without CT → nivolumab vs observation	IB-IIIA	III	DFS, OS
KEYNOTE 671	NCT03425643	Pembrolizumab + platinum doublet chemotherapy → S	II-IIIB (T3-4N2)	III	EFS, OS

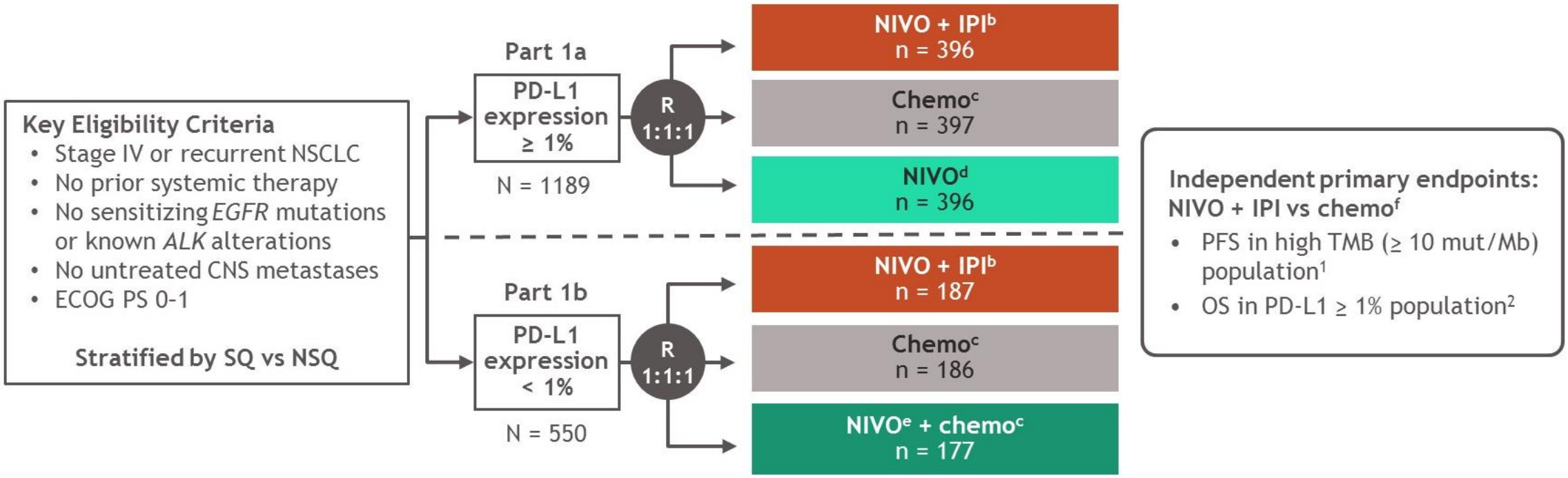
CT, adjuvant chemotherapy; DFS, disease-free survival; OS, overall survival; EFS, event free survival; MPR, major pathological response; pCR, pathological complete response; S, surgery.

Current First-Line Treatment in Metastatic NSCLC



Adapted from Chiang A& Herbst RS, Nature Reviews Clinical Oncology 2020

CheckMate 227 3 Year Update: Study Design

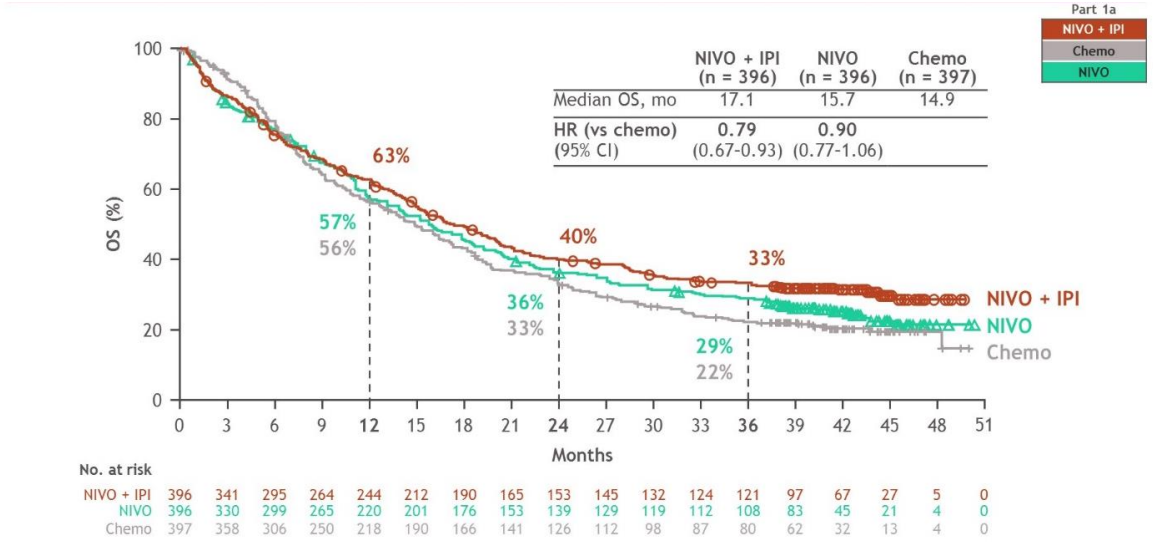


Minimum Follow-Up for OS: 37.7 months

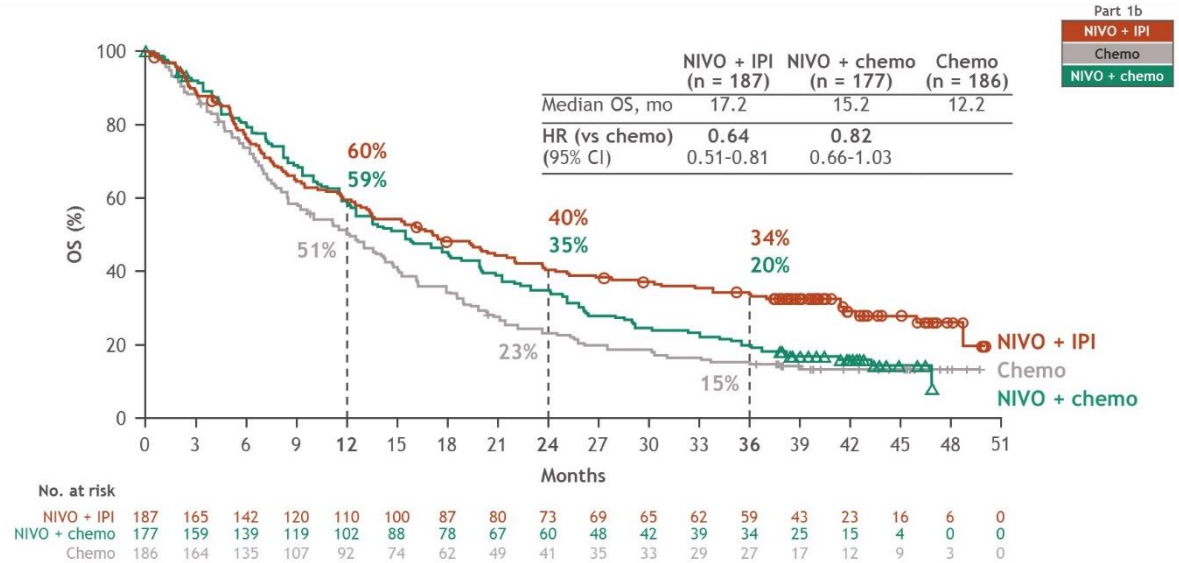
Presented by Ramalingam S. at ASCO 2020
Hellmann MD et al. N Engl J Med 2019

CheckMate 227 3 Year Update: Overall Survival

PD-L1 ≥ 1%



PD-L1 < 1%

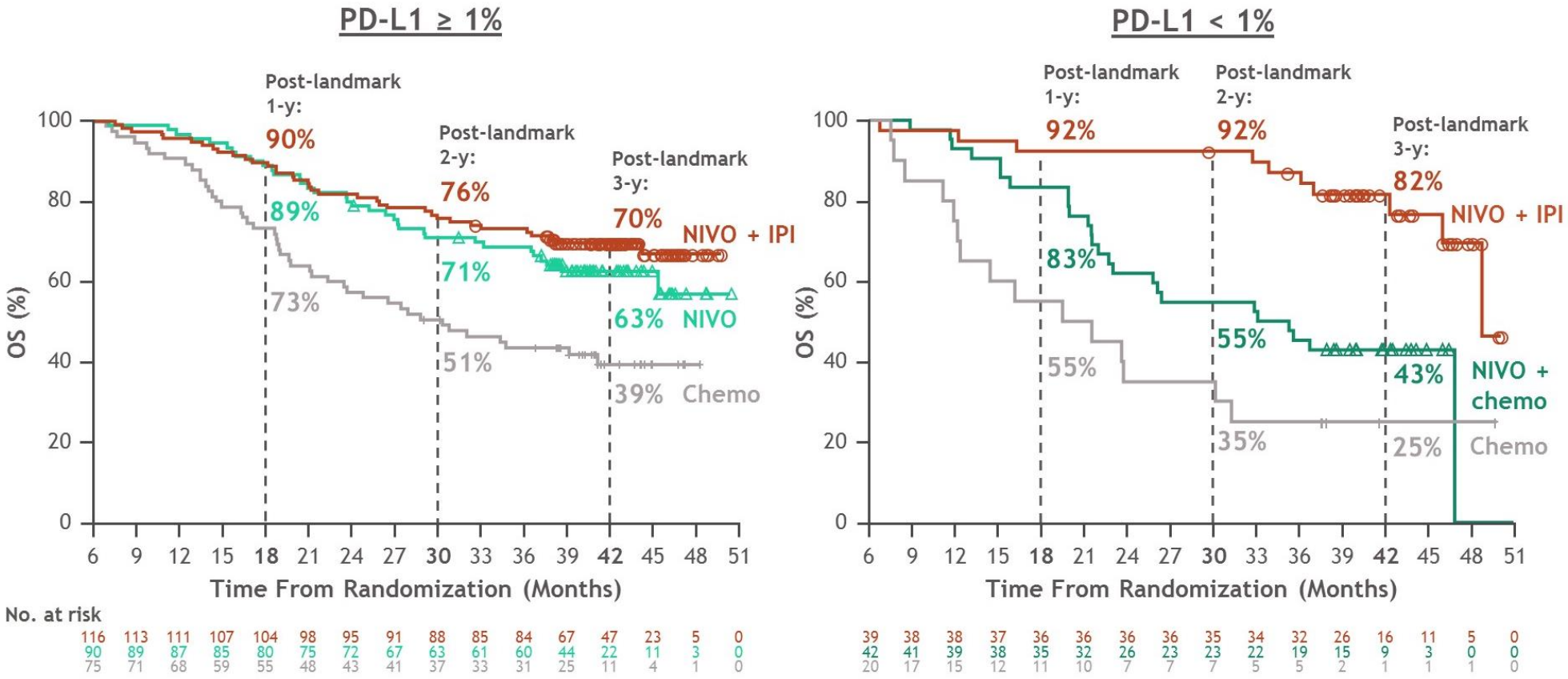


Minimum Follow-Up for OS: 37.7 months

City of Hope

Presented by Ramalingam S. at ASCO 2020
Hellmann MD et al. N Engl J Med 2019

CheckMate 227 3 Year Update: Post-Landmark Overall Survival Analysis in Responders at 6 Months



- Among patients with PD-L1≥1%, 70% of responders at 6 months in NIVO+IPI arm were alive 3 years later vs. 39% in chemo arm.
- Similar findings were found in patients with PD-L1<1%.

City of Hope.

Presented by Ramalingam S. at ASCO 2020
Hellmann MD et al. N Engl J Med 2019

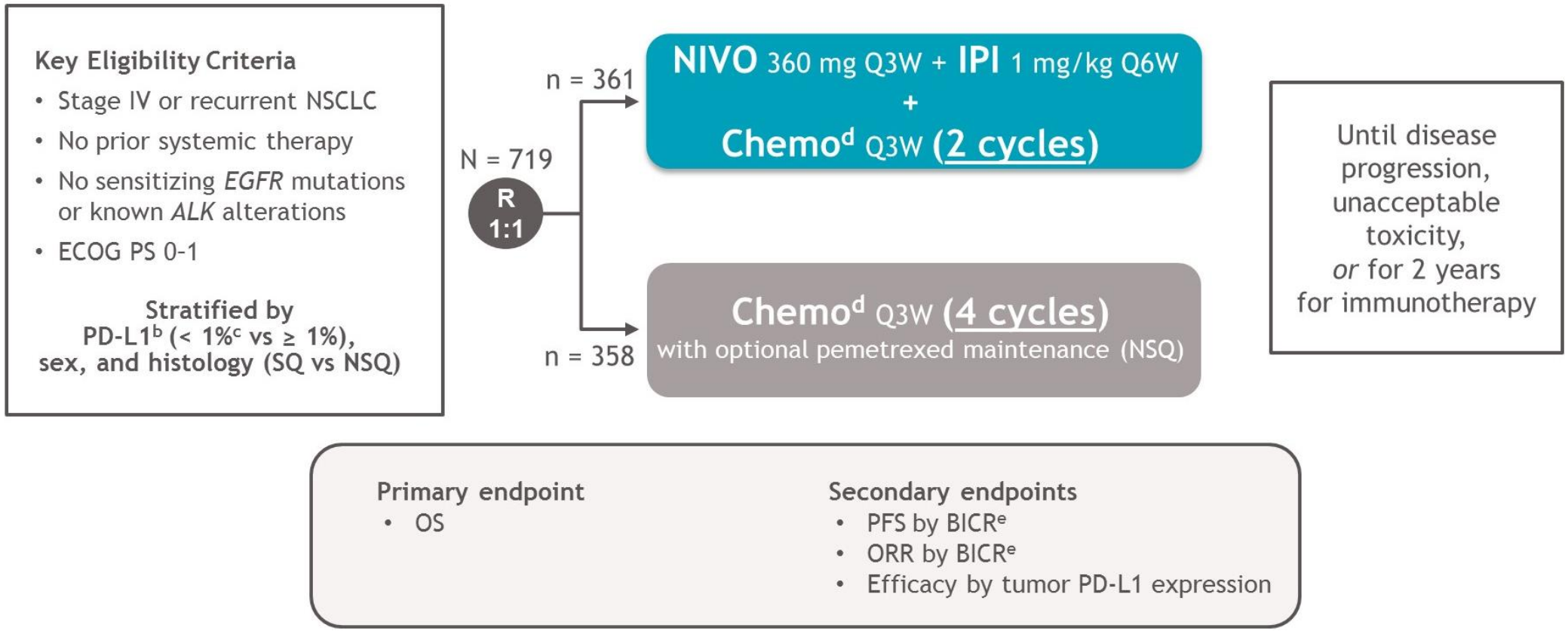
CheckMate 227 3 Year Update: Safety Summary

TRAE,[a] %	All randomized (PD-L1 ≥ 1% and PD-L1 < 1%)				PD-L1 ≥ 1%		PD-L1 < 1%	
	NIVO + IPI (n = 576)		Chemo (n = 570)		NIVO (n = 391)		NIVO + chemo (n = 172)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	77	33	82	36	66	20	92	56
TRAEs leading to discontinuation of any component of the regimen	18	12	9	5	12	7	14	8
Treatment-related deaths[b]	1		1		< 1		2	

Minimum Safety Follow-Up: 36.3 months

Presented by Ramalingam S. at ASCO 2020
Hellmann MD et al. N Engl J Med 2019

CheckMate 9LA: Study Design



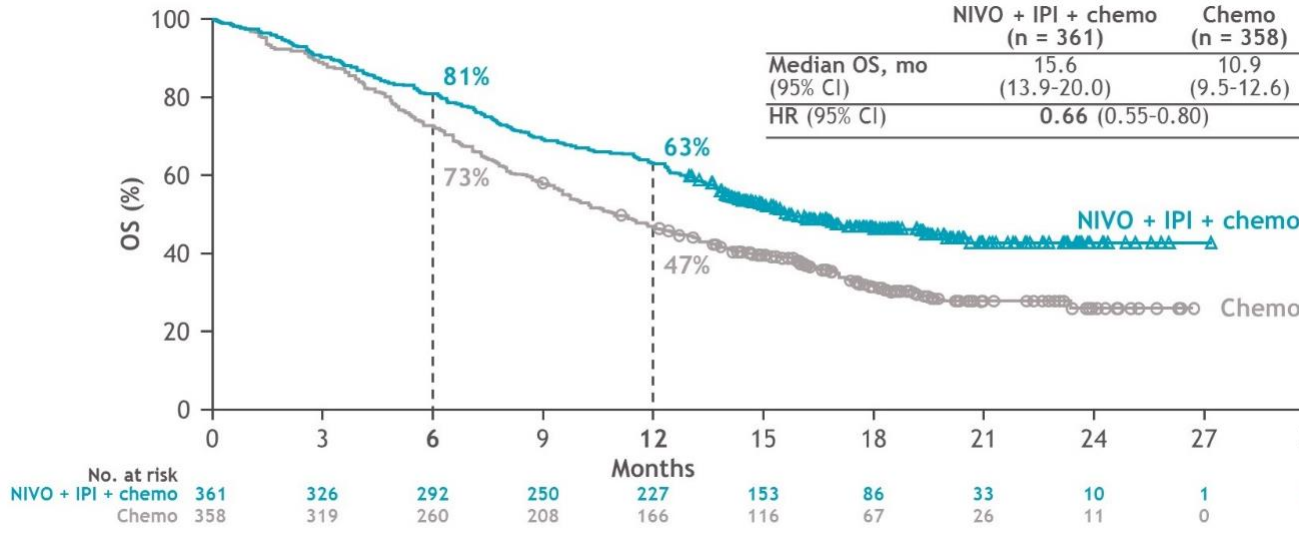
CheckMate 9LA: Patient Characteristics and Duration of Therapy

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Age, median (range), years	65 (35-81)	65 (26-86)
Female, %	30	30
ECOG PS,[a] %		
0	31	31
1	68	68
Smoking status, %		
Never smoker	13	14
Current / former smoker	87	86
Histology, %		
Squamous	31	31
Non-squamous	69	69
Metastases, %		
Bone	27	31
Liver	19	24
CNS	18	16
Tumor PD-L1 expression,[b] %		
< 1%[c]	40	39
≥ 1%[c]	60	61
1-49%[c]	38	32
≥ 50%[c]	22	29

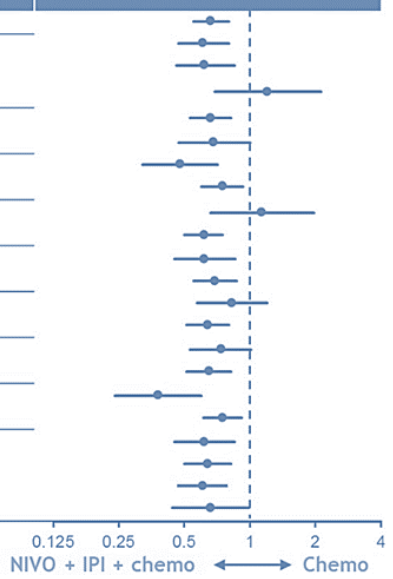
	NIVO + IPI + chemo (n = 358)	Chemo (n = 349)
Duration of therapy, median (range), mo	6.1 (0-23.5)	2.4 (0-24.0)
Number of doses, median (range)		
NIVO	9.0 (1-34)	Not applicable
IPI	4.0 (1-17)	
Treatment discontinuation, n (%)		
IPI	19[a] (5)	Not applicable
NIVO + IPI	265 (74)	
Cycles of chemotherapy received, n (%)		
1	25 (7)	23 (7)
2	333 (93)	49 (14)
3	Not applicable	17 (5)
4	Not applicable	260 (74)
Patients receiving pemetrexed maintenance therapy, n (%)	Not applicable	158[b] (45)
Patients still on treatment, n (%)	74 (21)	28 (8)

CheckMate 9LA: Primary Endpoint Overall Survival

- Minimum follow-up 12.7 months.
- PFS and ORR were also significantly improved with Nivo + Ipi + chemotherapy versus chemotherapy.



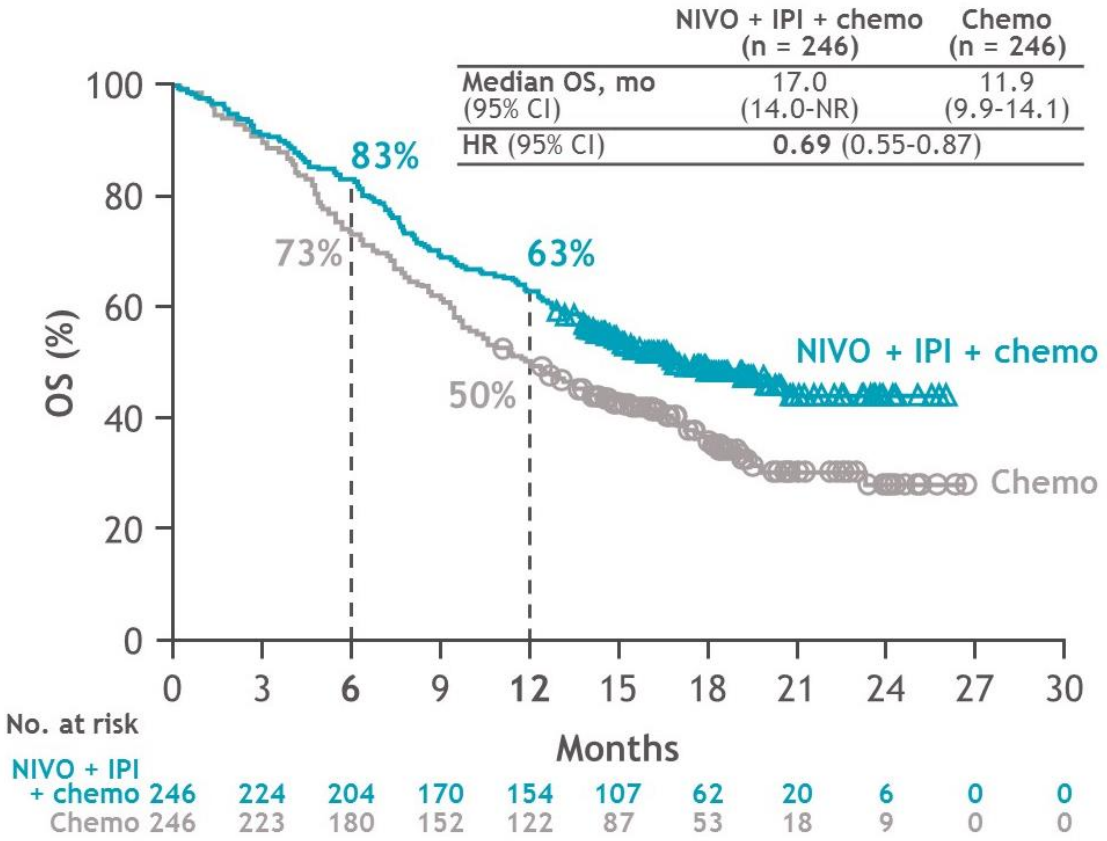
Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



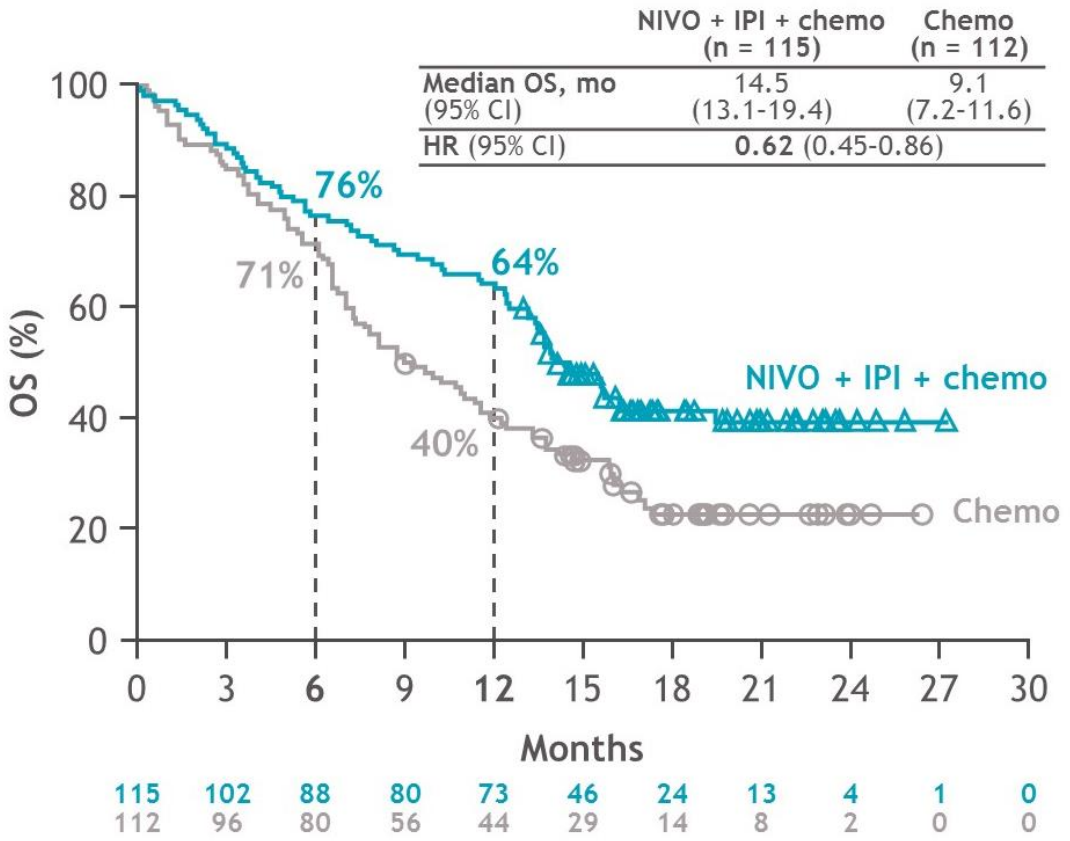
Minimum follow-up: 12.7 months.
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

CheckMate 9LA: Primary Endpoint Overall Survival by Histology

Non-squamous NSCLC

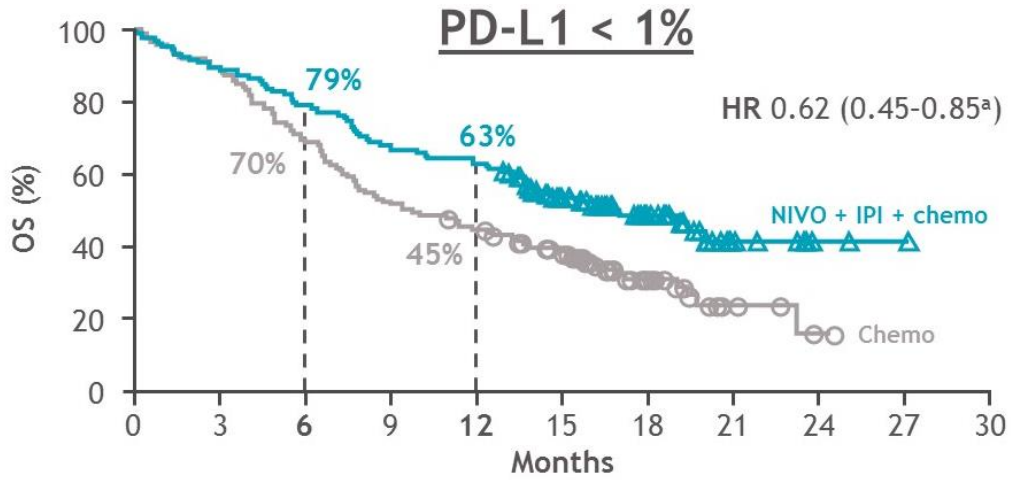


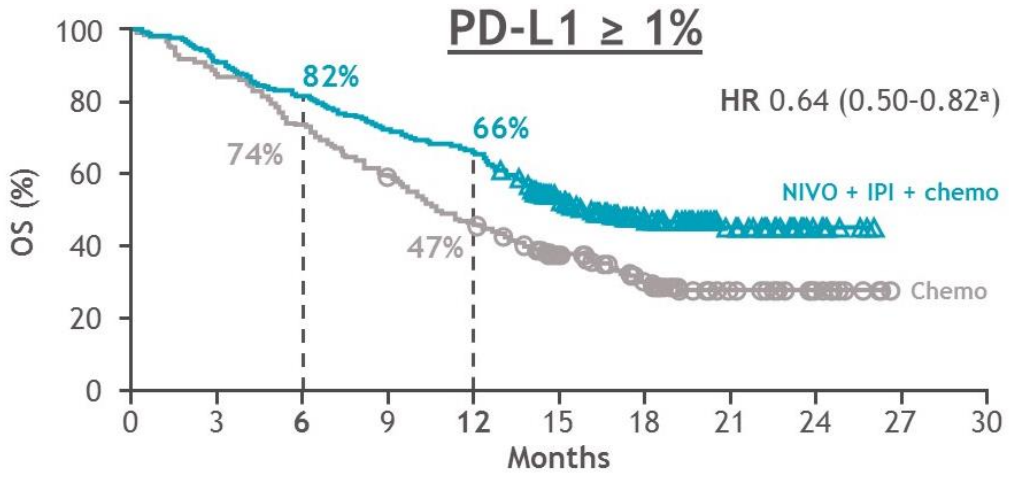
Squamous NSCLC

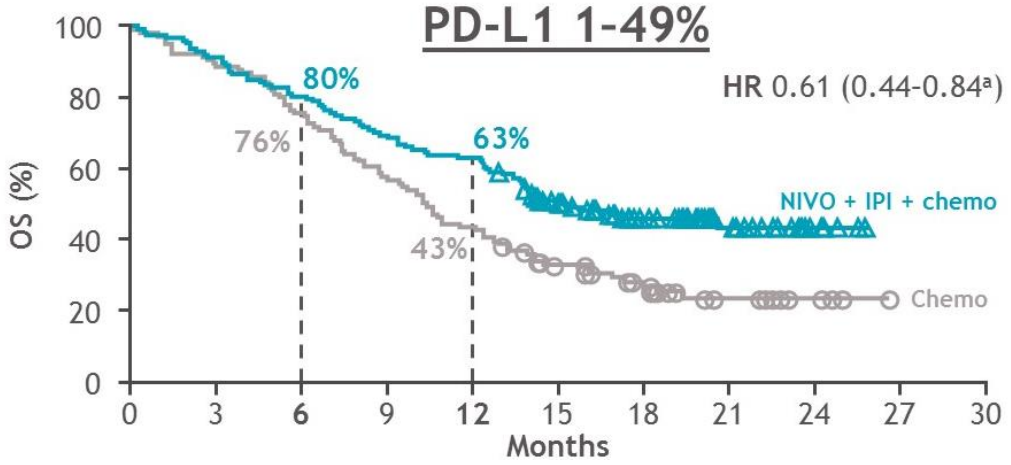


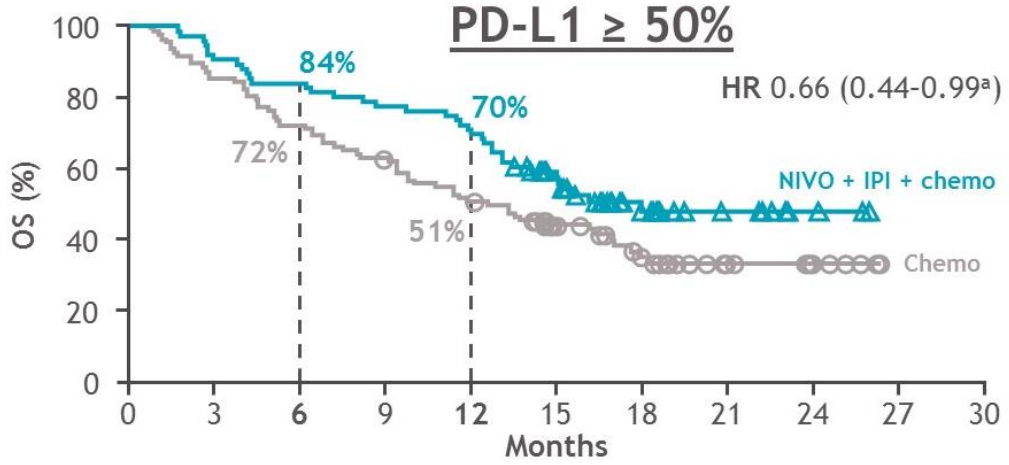
Minimum Follow-Up 12.7 months

CheckMate 9LA: Primary Endpoint Overall Survival by PD-L1 Status









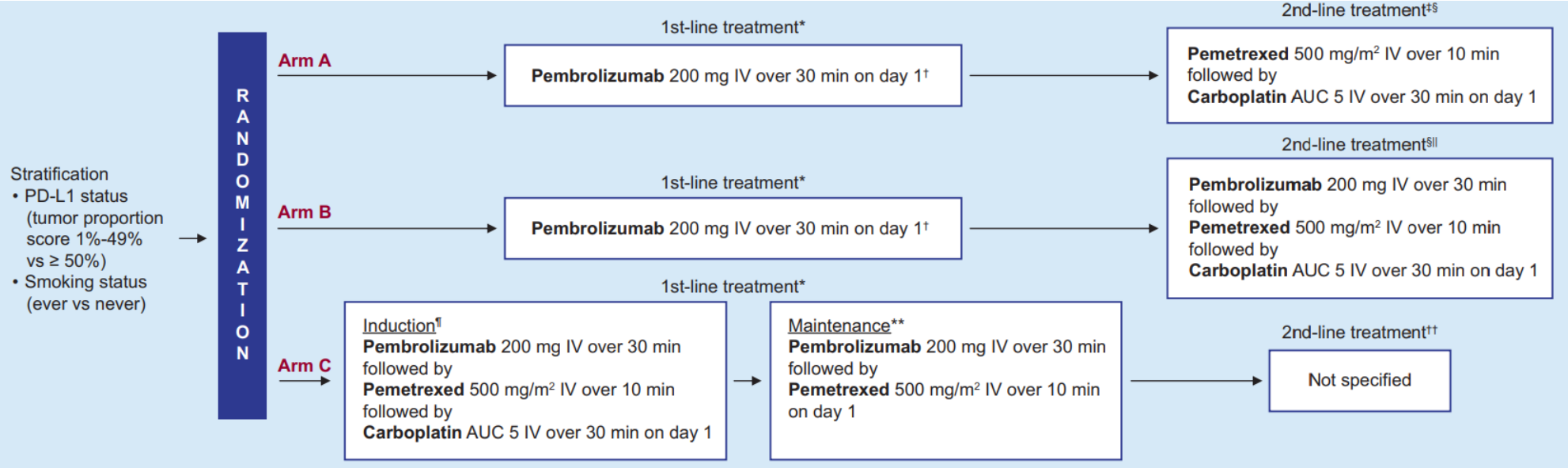
Minimum Follow-Up 12.7 months

Immuno-Oncology Clinical Trials in First-Line Metastatic NSCLC

Study	Selection	Design	PFS	OS
KN024[1]	ADENO AND SCC PD-L1 > 50%	Pembro vs Chemo	10.3 vs 6.1 HR = 0.62	30 vs 14.2 HR = 0.63
KN042[2]	ADENO AND SCC PD-L1 > 1%	Pembro vs Chemo	7.1 vs 6.4 HR: 1.07	20 vs. 12 HR: 0.81
CHKMTE 227[3]	ADENO AND SCC PD-L1 > 1% PD-L1 < 1%	Ipilimumab + Nivo vs chemo	>1% HR 0.82 <1% HR 0.75	>1% 17.1 vs 14.9 HR: 0.79 <1% 17.2 vs 12.2 HR: 0.62
KN189[4]	ADENO PD-L1 0%-100%	Chemo/pembro vs chemo	8.8 vs 4.9 HR = 0.52	22 vs 11.3 HR = 0.49
IMpower150[5]	ADENO[Bev elig] PD-L1 0%-100%	Chemo/bev/atezo vs chemo/bev	8.3 vs 6.8 HR = 0.62	19.2 vs 14.7 HR = 0.78
KN407[6]	SCC PD-L1 0%-100%	Chemo/pembro vs chemo	6.4 vs 4.8 HR = 0.56	15.9 vs 11.3 HR = 0.64
IMpower130[7]	ADENO PD-L1 0%-100%	Nab-pacli/atezo vs chemo	7.0 vs 5.5 HR = 0.64	18.6 vs 13.9 HR = 0.79
Impower 110[8]	ADENO AND SCC PD-L1 > 50% (or IC >10%)	Atezolizumab v Chemo	8.1 vs 5.0 HR: 0.63	20.2 vs 13.1 HR 0.59

Conclusions

- Molecular predictors for response to immunotherapy are currently under validation in larger cohorts of metastatic NSCLC patients
- Immunotherapy + chemotherapy combinations appear to be superior to monotherapy
- The ongoing phase III INSIGNA trial (NCT03793179) is investigating the approach to first-line immunotherapy + chemotherapy treatment and how to optimize treatment sequencing



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