Congresso Interregionale polmonare
Roma, 22 Settembre 2018

Immunoterapia tra I e II linea: quando il biomarcatore guida la scelta

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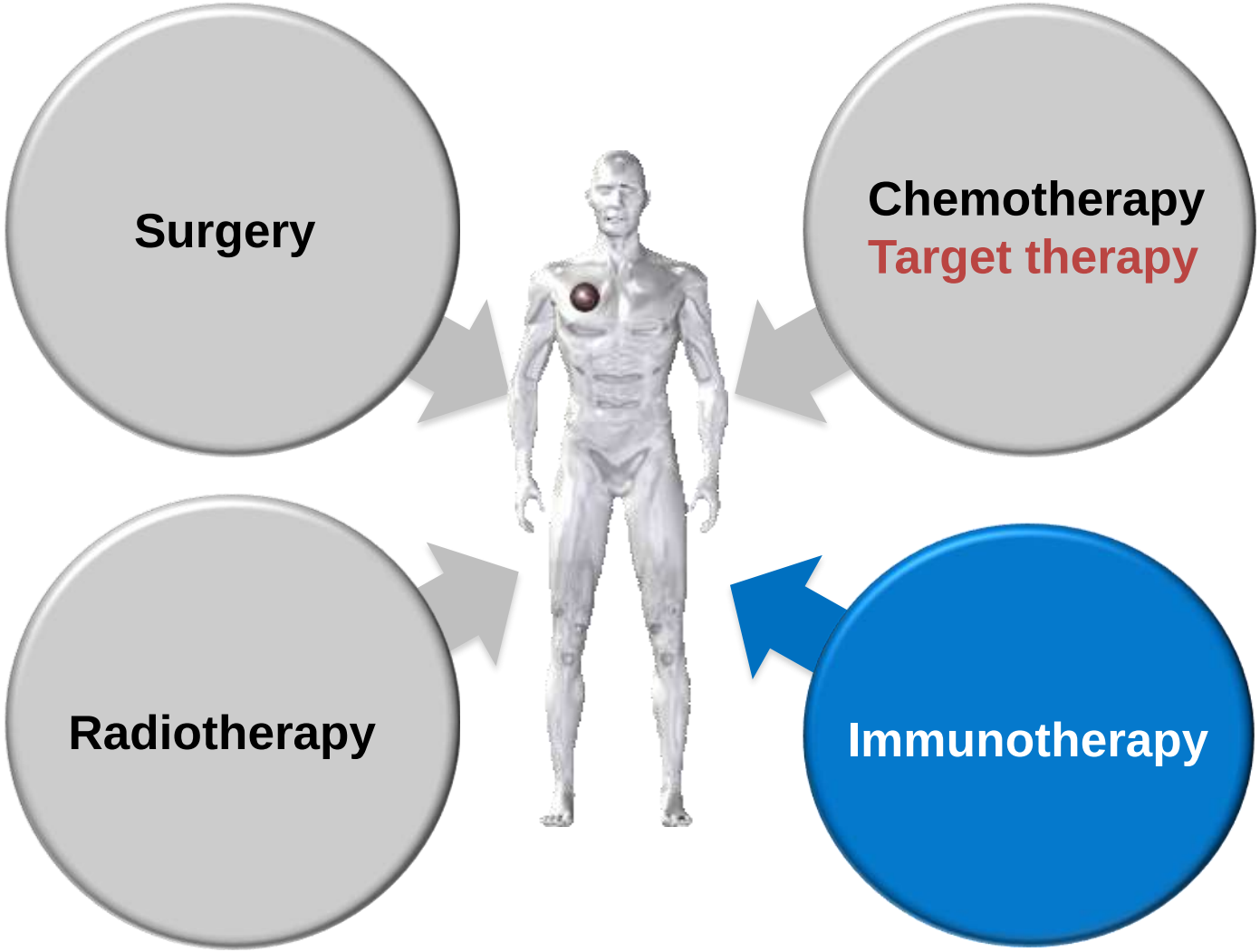
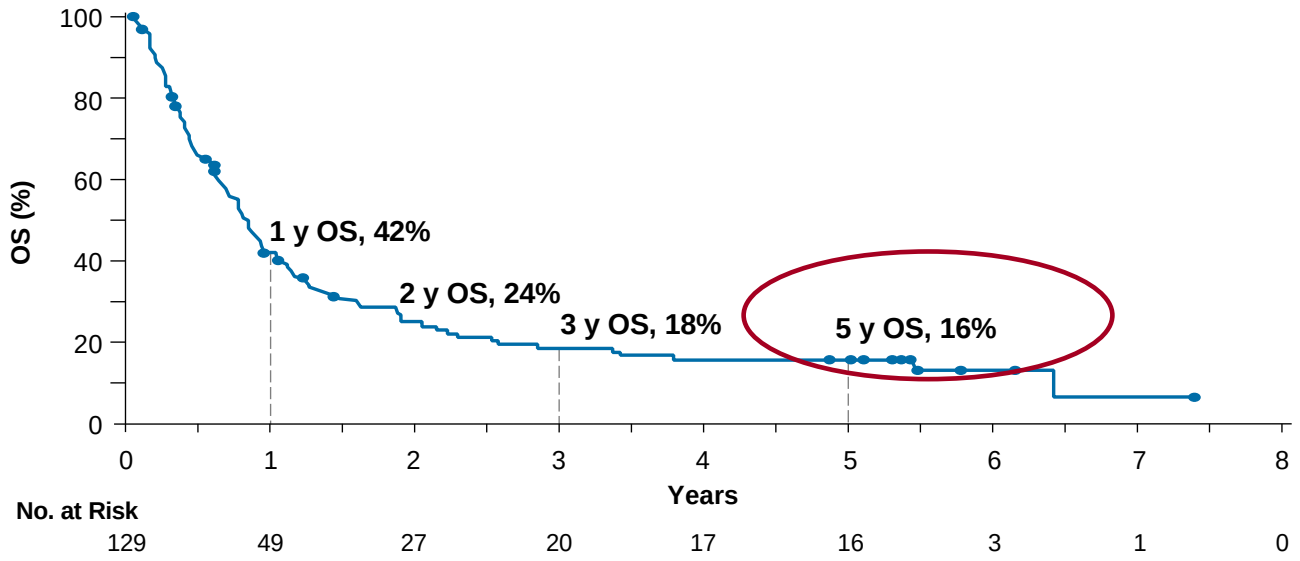
Evolving Therapeutic Options for Lung Cancer



5-Year Estimates of OS

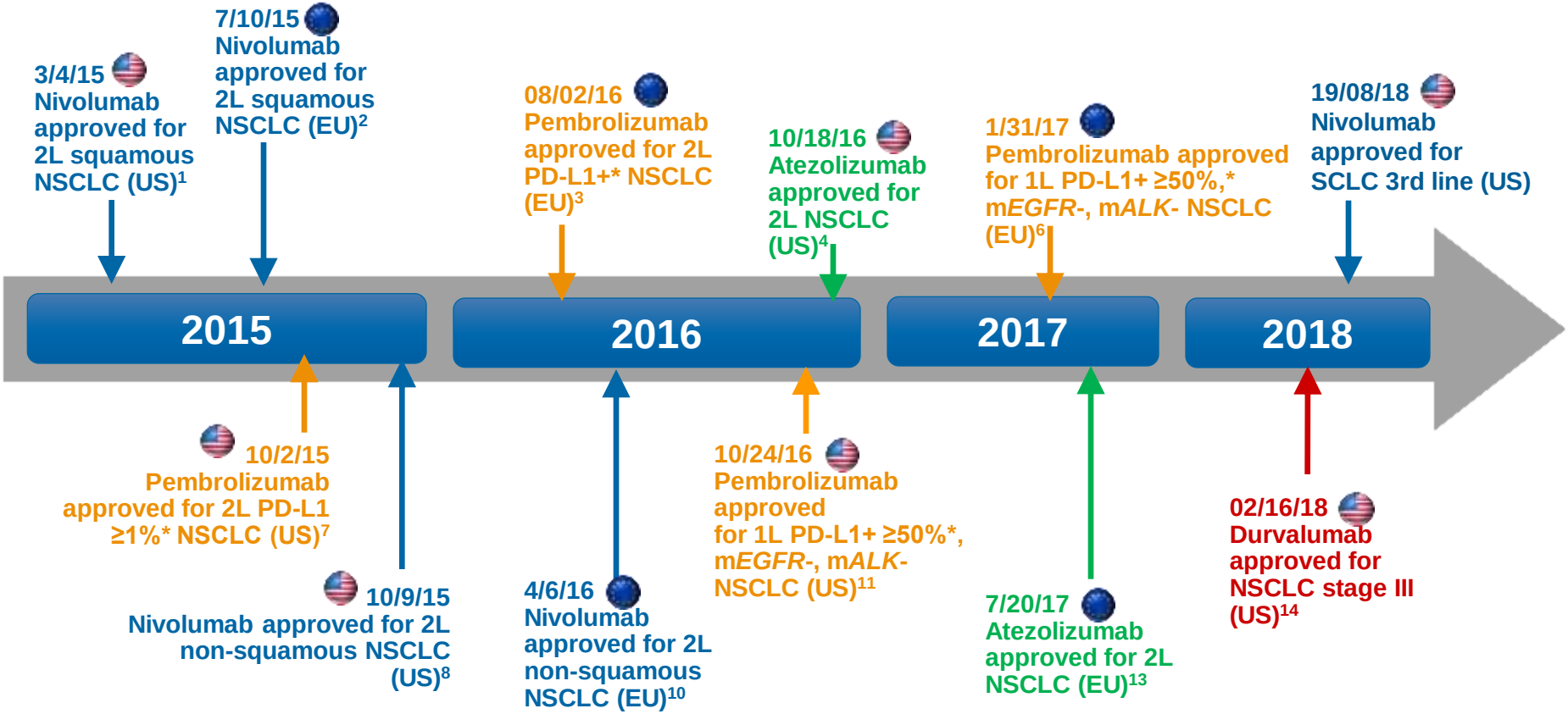
BMS CA209-003: phase 1 dose finding study in NSCLC

	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)



[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

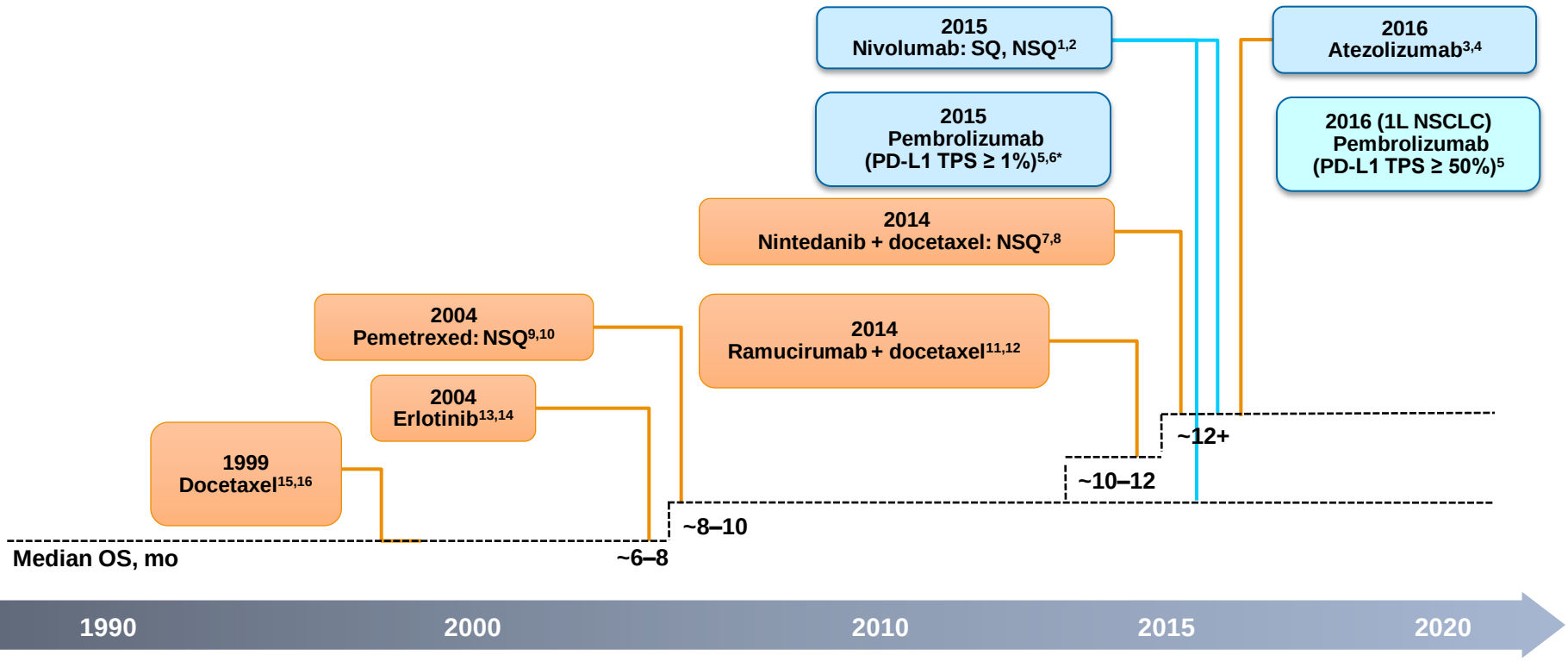
History of Checkpoint Inhibitors: Key Milestones in Lung cancer



*As determined using the Dako IHC 22C3 pharmDx assay.[12]

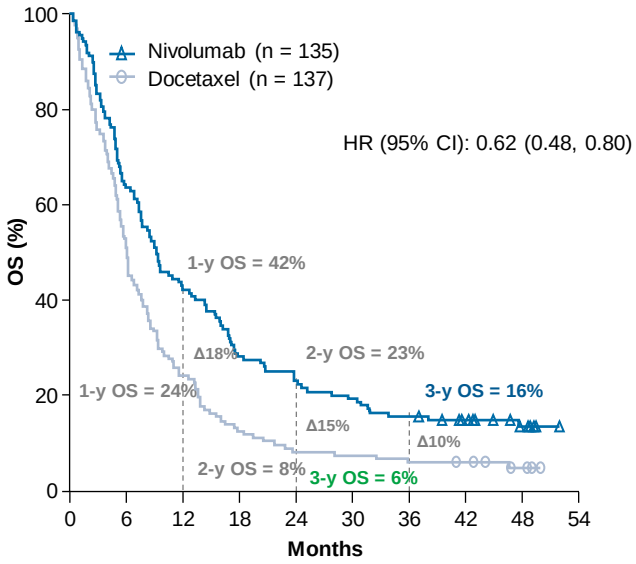
Abbreviations and references can be found in the speaker notes.

Evolution of Survival Outcomes in 2L+ Lung Cancer

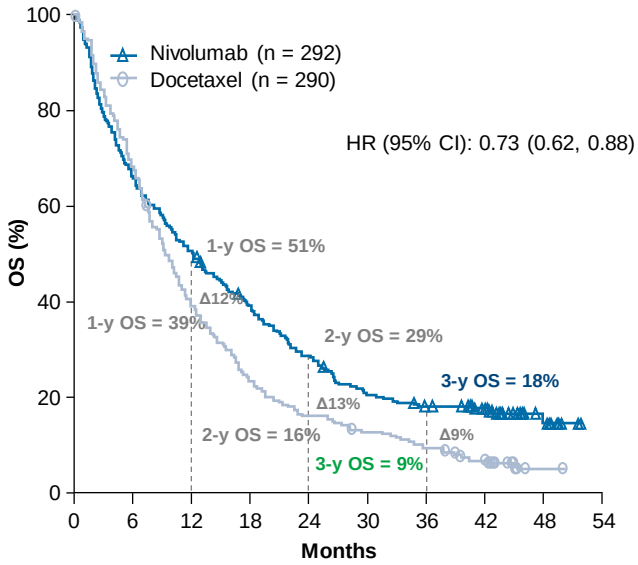


- **Anti-PD-1/PD-L1 mAb replaced docetaxel as the preferred second-line therapy based on improved OS, higher response rates, longer DOR, and fewer AEs and QoL compared with docetaxel**

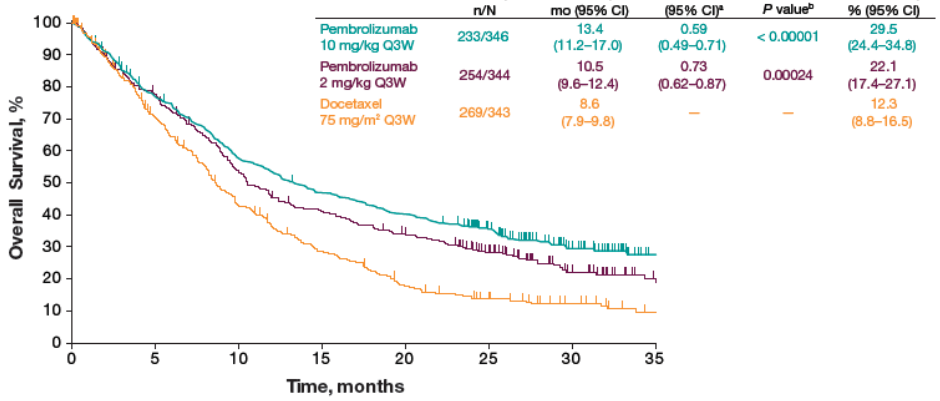
CheckMate 017



CheckMate 057



Keynote-010



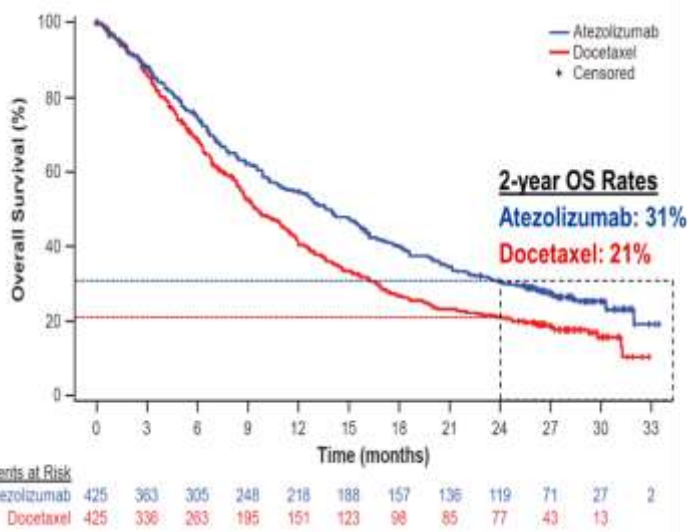
	Events, n/N	Median, mo (95% CI)	Hazard Ratio (95% CI)[a]	*P* value[b]	30-mo rate, % (95% CI)
Pembrolizumab 10 mg/kg Q3W	233/346	13.4 (11.2–17.0)	0.59 (0.49–0.71)	< 0.00001	29.5 (24.4–34.8)
Pembrolizumab 2 mg/kg Q3W	254/344	10.5 (9.6–12.4)	0.73 (0.62–0.87)	0.00024	22.1 (17.4–27.1)
Docetaxel 75 mg/m² Q3W	269/343	8.6 (7.9–9.8)	—	—	12.3 (8.8–16.5)

No. at risk

346	259	195	157	135	97	49	17
344	261	176	135	110	75	36	16
343	216	129	84	50	32	19	9

[a]Hazard ratio for comparison with docetaxel.
[b]*P* value for comparison with docetaxel. No formal statistical comparison of the difference between treatment arms was performed; therefore, *P* values are nominal only.

OAK



Why are biomarkers predictive of response needed in the I-O clinic?

Identify those patients who would benefit more from a defined treatment, also avoiding treatment-related toxicities and saving resources on expensive therapies

The “perfect” biomarker

✓Easy and reliable to assess (molecularly defined)

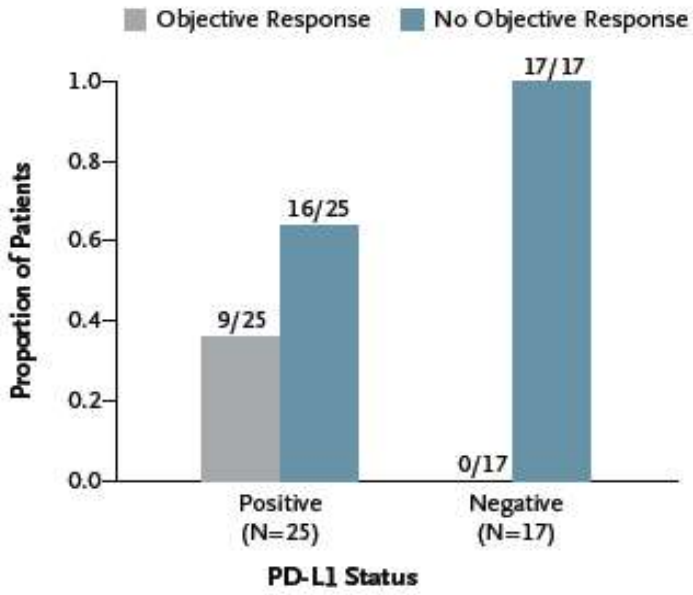
✓Limited/no need of tumor tissue (liquid biopsy)

✓Not influenced by tumor microenvironment (stable expression)

CONSOLIDATED IN THE CLINIC: **BRAF, ALK, ROS, EGFR, cKIT, …….**

PREDICTIVE MARKERS OF RESPONSE TO PD1/PD-L1 BLOCKADE

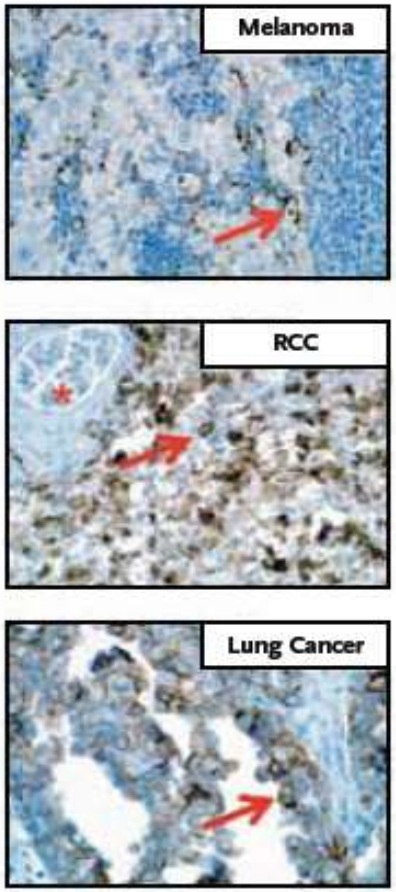
PD-L1 tumor expression



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

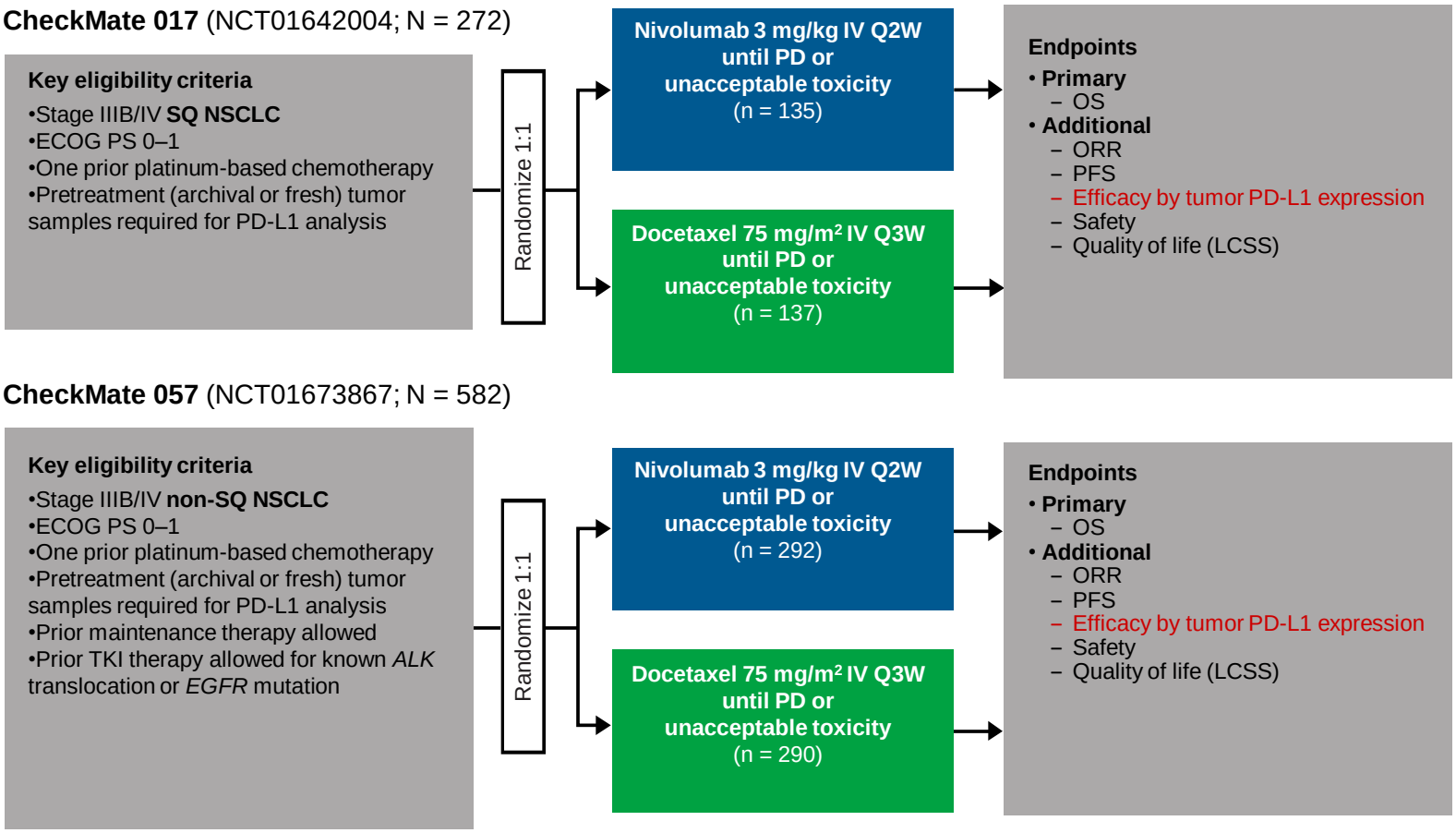
Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



Topalian S, et al., NEJM 2012

CheckMate 017 and CheckMate 057 Study Designs

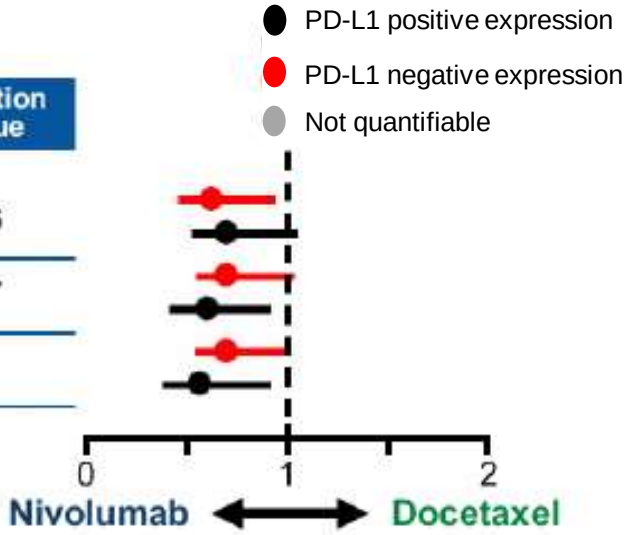


LCSS = Lung Cancer Symptom Scale; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; TKI = tyrosine kinase inhibitor

Survival benefit by PD-L1 expression

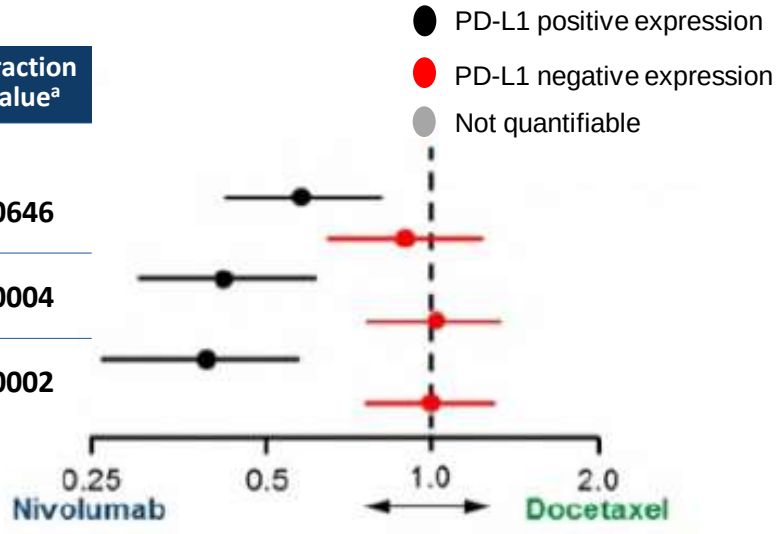
Checkmate 017 (Squamous)

PD-L1 Expression	Unstratified HR (95% CI)	Interaction *P*-value
OS		
<1%	0.58 (0.37, 0.92)	0.56
≥1%	0.69 (0.45, 1.05)	
<5%	0.70 (0.47, 1.02)	0.47
≥5%	0.53 (0.31, 0.89)	
<10%	0.70 (0.48, 1.01)	0.41
≥10%	0.50 (0.28, 0.89)	

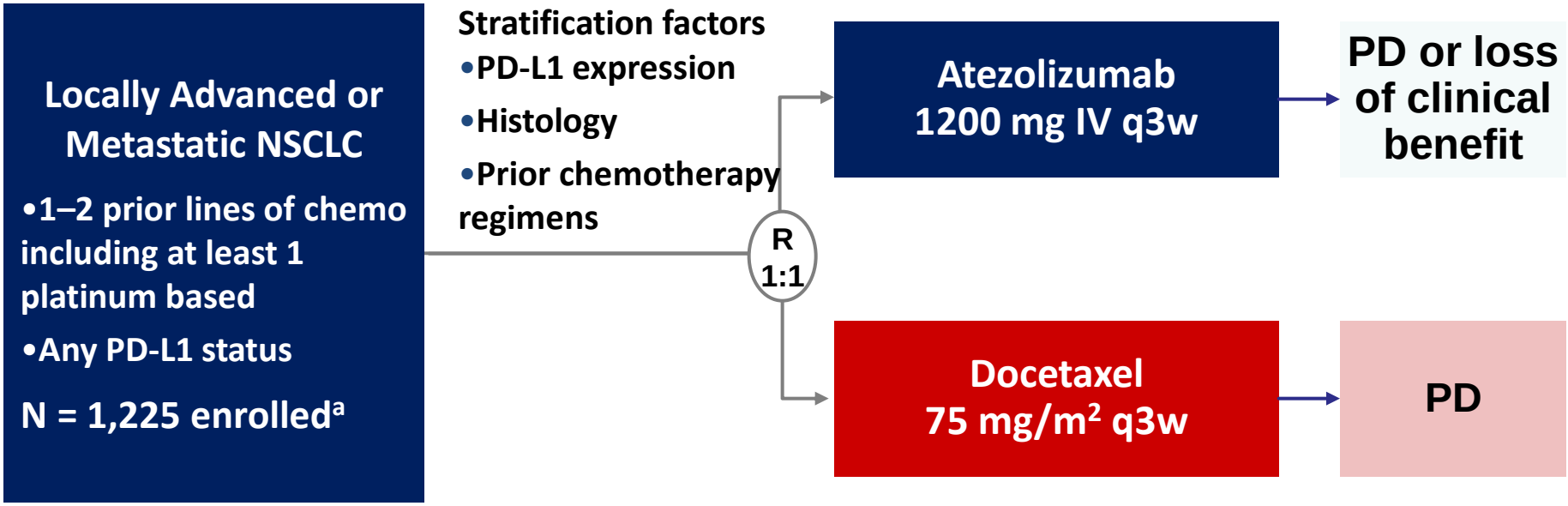


Checkmate 057 (Non-squamous)

PD-L1expression level	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS		
≥1%	**0.59 (0.43, 0.82)**	**0.0646**
<1%	**0.90 (0.66, 1.24)**	
≥5%	**0.43 (0.30, 0.63)**	**0.0004**
<5%	**1.01 (0.77, 1.34)**	
≥10%	**0.40 (0.26, 0.59)**	**0.0002**
<10%	**1.00 (0.76, 1.31)**	



OAK study design



Primary Endpoints (first 850 enrolled patients):

- **OS in the ITT population**
- **OS in patients with PD-L1 expression on ≥ 1% TC or IC**

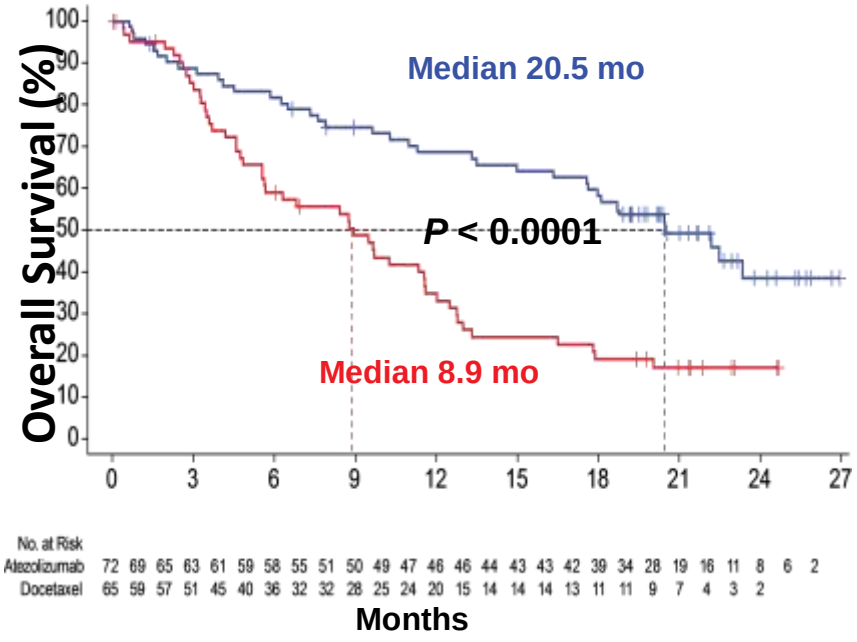
Secondary Endpoints: ORR, PFS, DoR, Safety

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression). TC, tumor cells; IC, tumor-infiltrating immune cells.

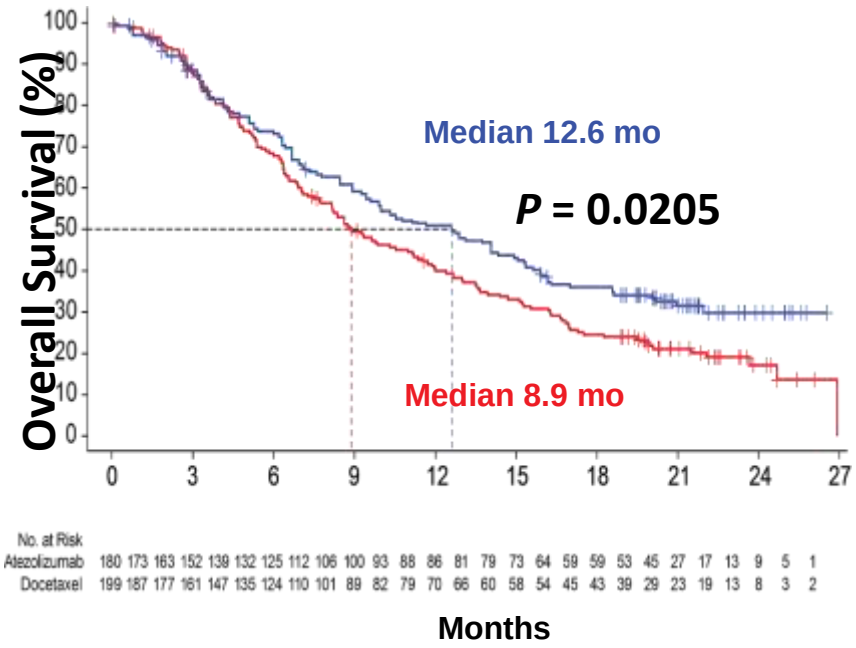
Barlesi et al. ESMO 2016

Overall survival based on PD-L1 and IC status

PD-L1 ≥ 50% TC or ≥ 10% IC
TC3 or IC3; 16% of patients



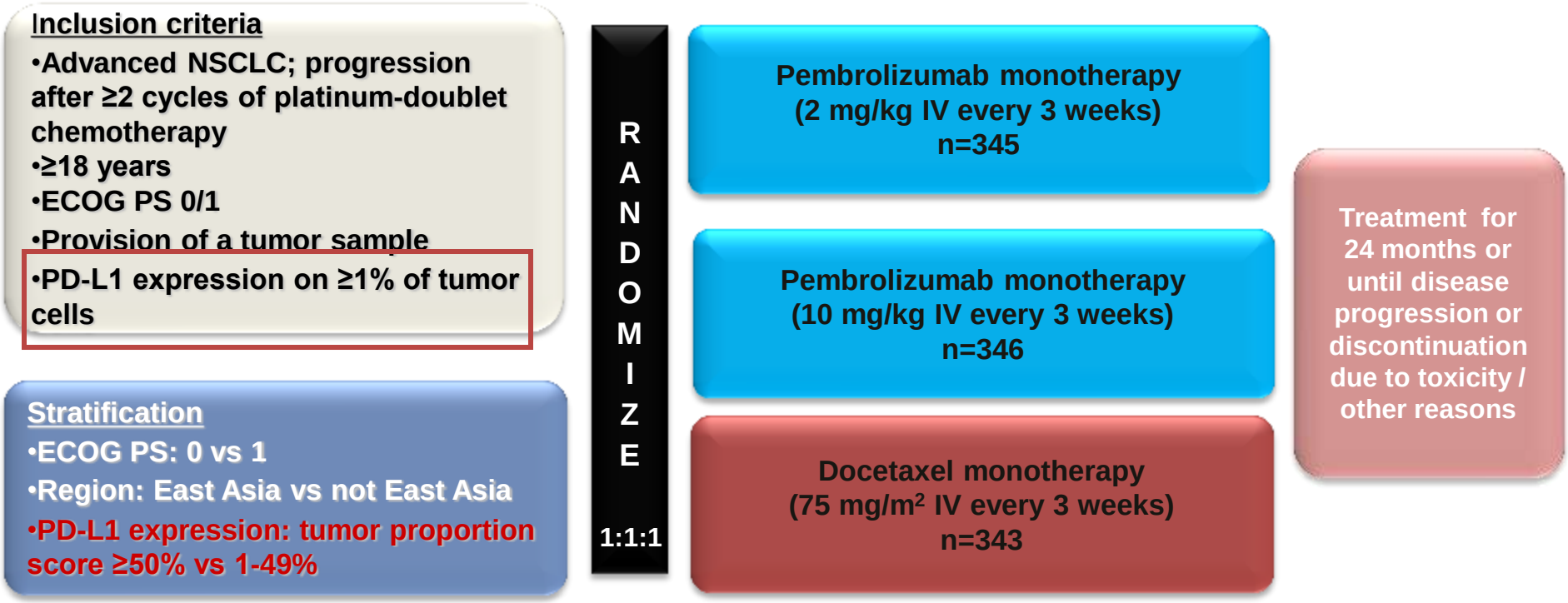
PD-L1 < 1% TC and IC
TC0 and IC0; 45% of patients



Atezolizumab
Docetaxel

Barlesi et al. ESMO 2016

Pembrolizumab in Pretreated, PD-L1-Positive NSCLC in the Phase 2/3 KEYNOTE-010 Trial

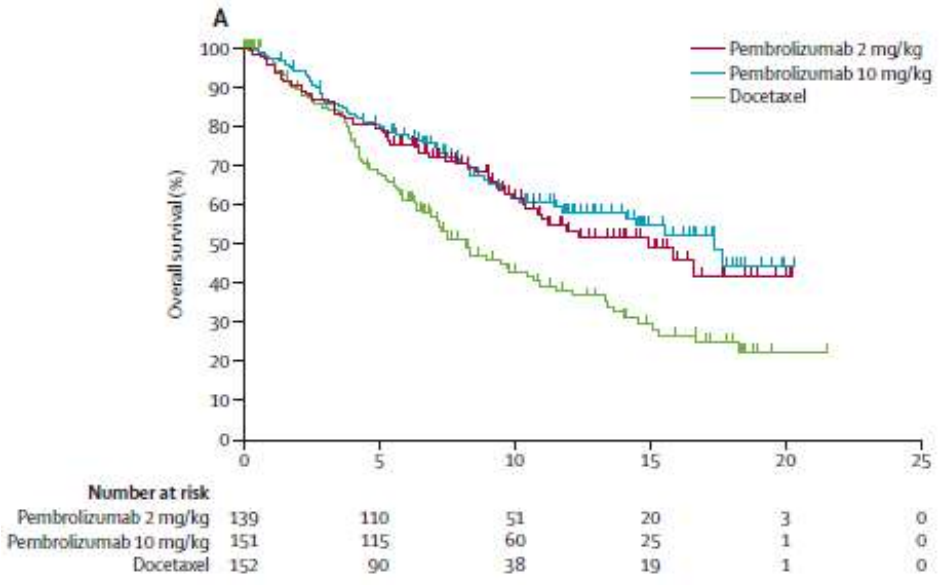


Primary endpoints	OS, PFS in total population and patients with tumor proportion score ≥50%
Secondary endpoints	Safety, response rate (as per RECIST version 1.1), duration of response

Herbst RS et al. *Lancet* 2016;387:1540-50

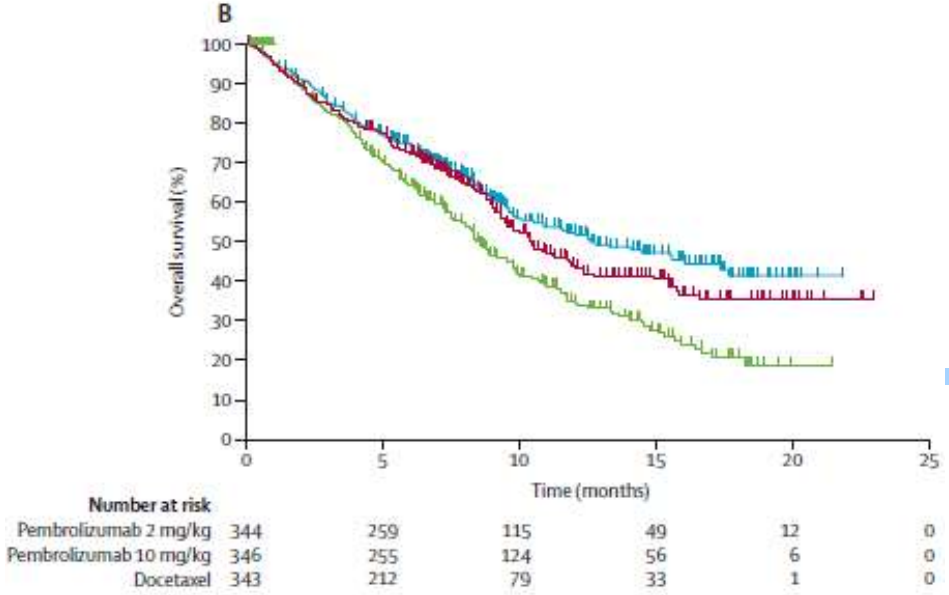
Keynote-010

PD-L1: ≥ 50%



MST
Pem 2 = 14.9 mos (HR 0.54)
Pem 10 = 17.3 mos (HR 0.50)
TXT = 8.2 mos

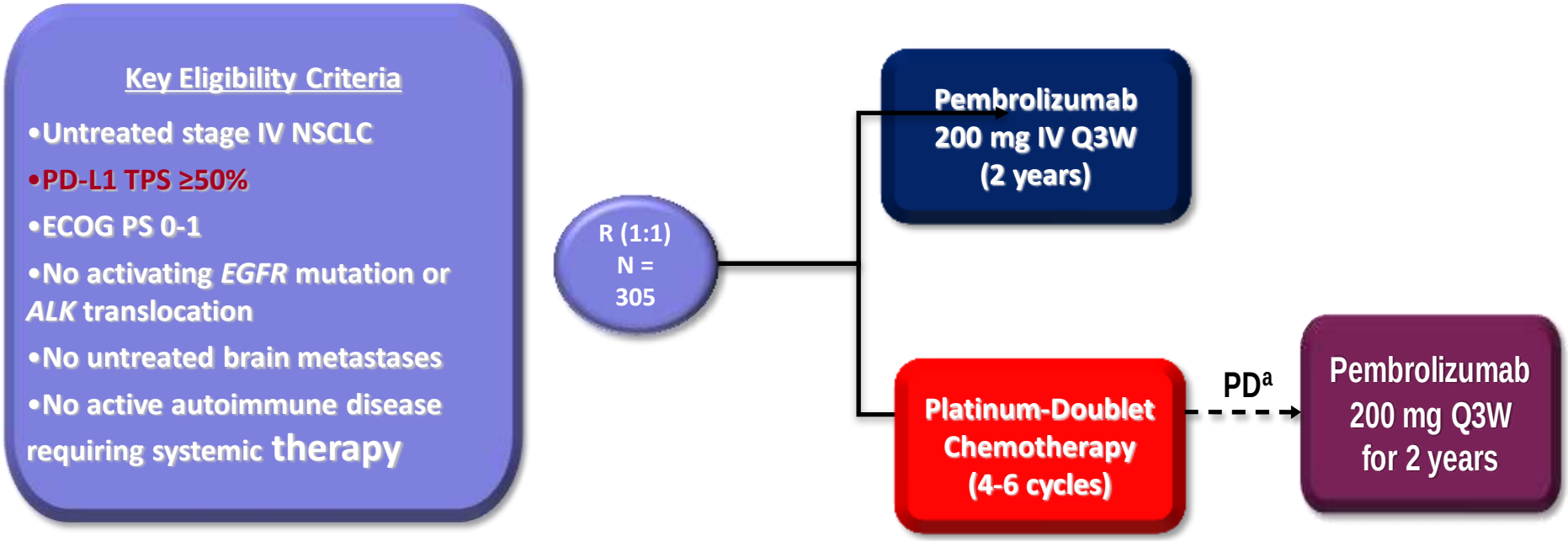
PD-L1: 1-49%



MST
Pem 2 = 10.4 mos (HR 0.71)
Pem 10 = 12.4 mos (HR 0.61)
TXT = 8.5 mos

Garon et al, NEJM 2015

KEYNOTE 024 study design



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

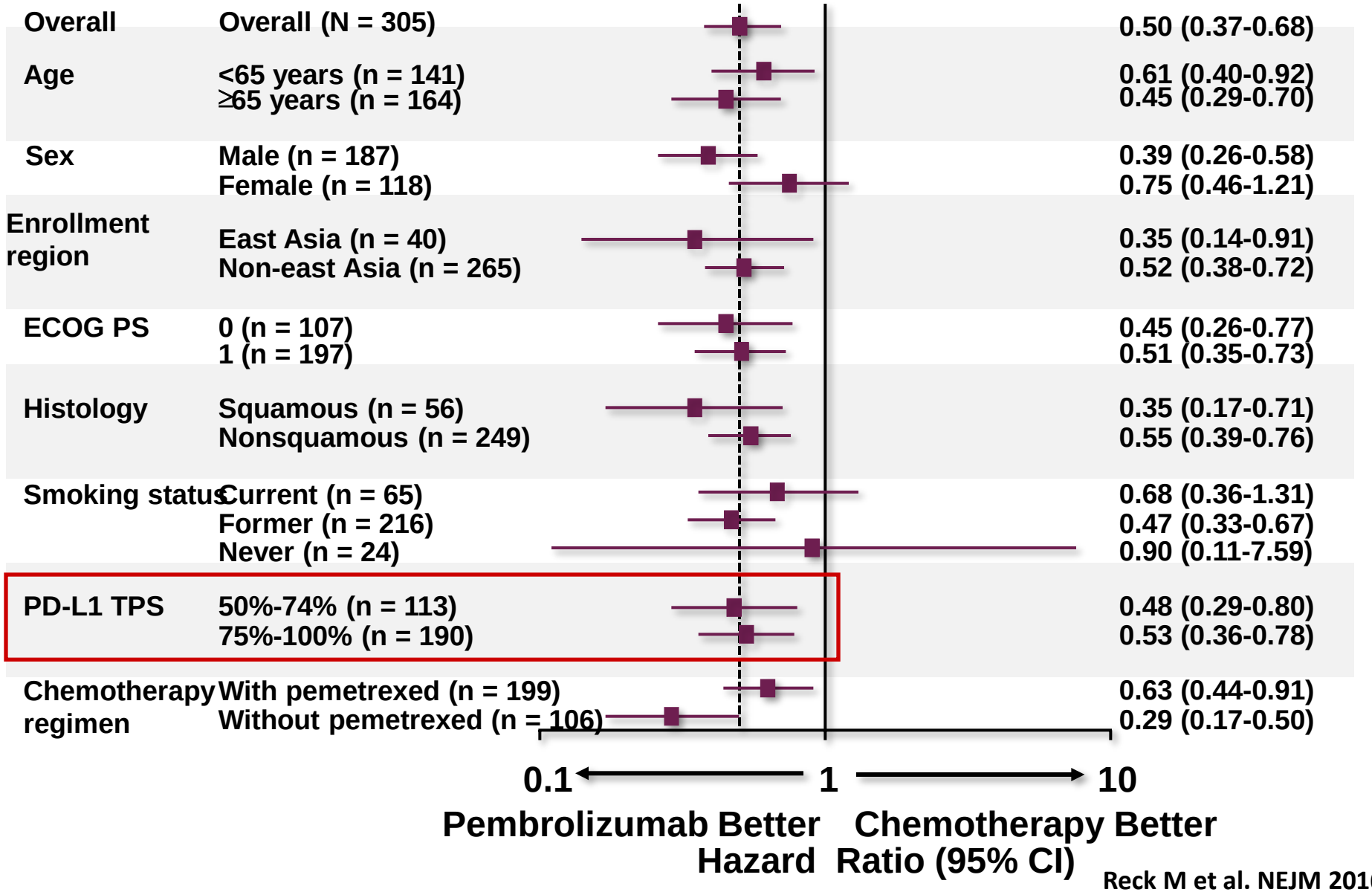
Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

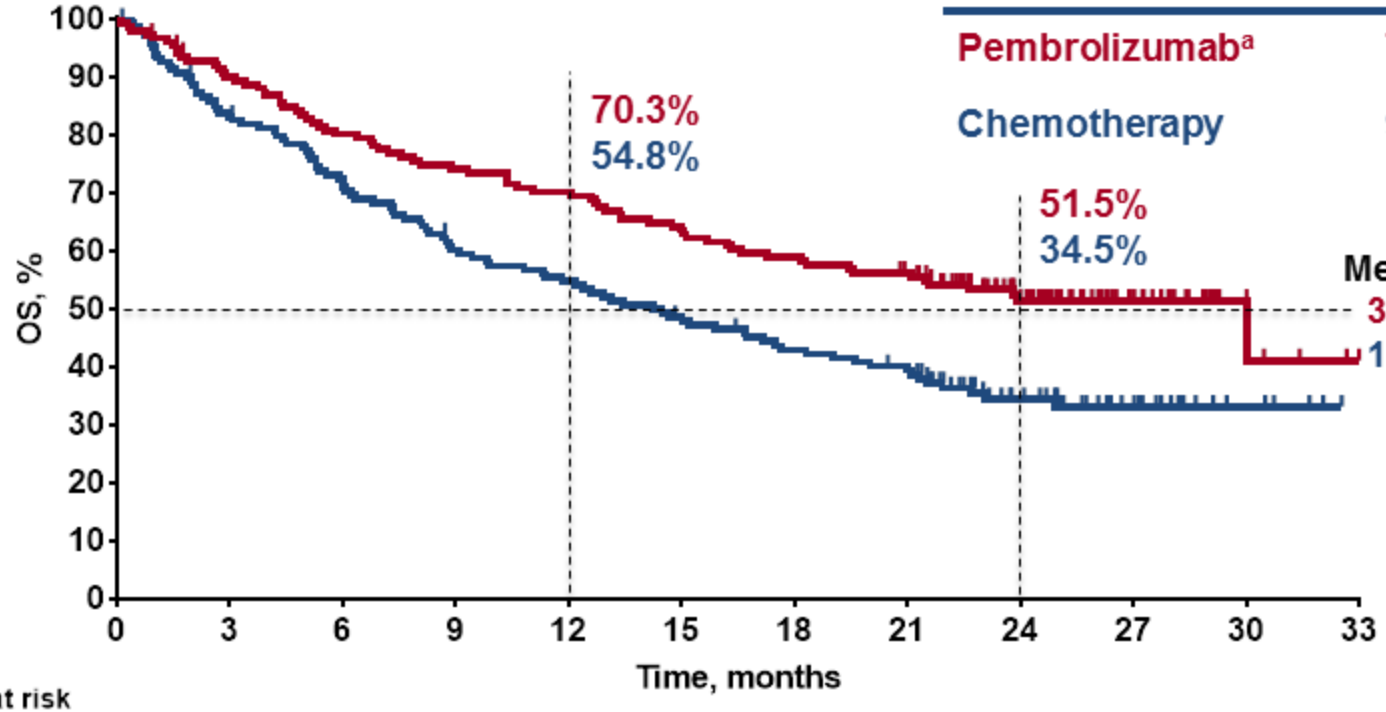
Reck M, et al. NEJM 2016

Progression-Free survival in subgroups



Reck M et al. NEJM 2016

Overall Survival: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86) *P* = 0.002[b]
Chemotherapy	96	

Median (95% CI)

30.0 mo (18.3 mo–NR)

14.2 mo (9.8 mo–19.0 mo)

No. at risk

Pembro	154	136	121	112	106	96	89	83	52	22	5	0
Chemo	151	123	107	88	80	70	61	55	31	16	5	0

Brahmer WCLC 2017

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Randomize 1:1

N = 637 → Pembrolizumab 200 mg Q3W for up to 35 cycles

N = 637 → Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m^2 Q3W[a] OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m^2 Q3W[a] for up to 6 cycles

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥50% vs 1-49%)

End points

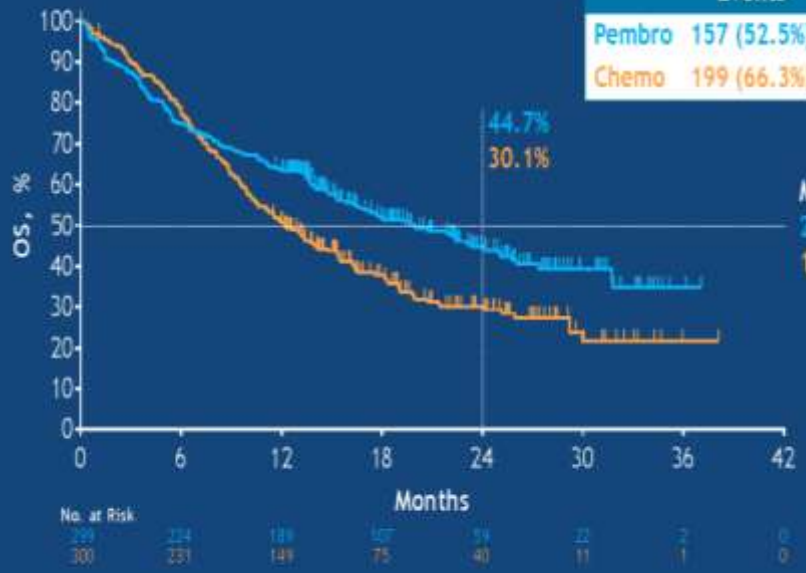
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Lopes KN042 ASCO 2018

Overall Survival: TPS ≥50%

	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		

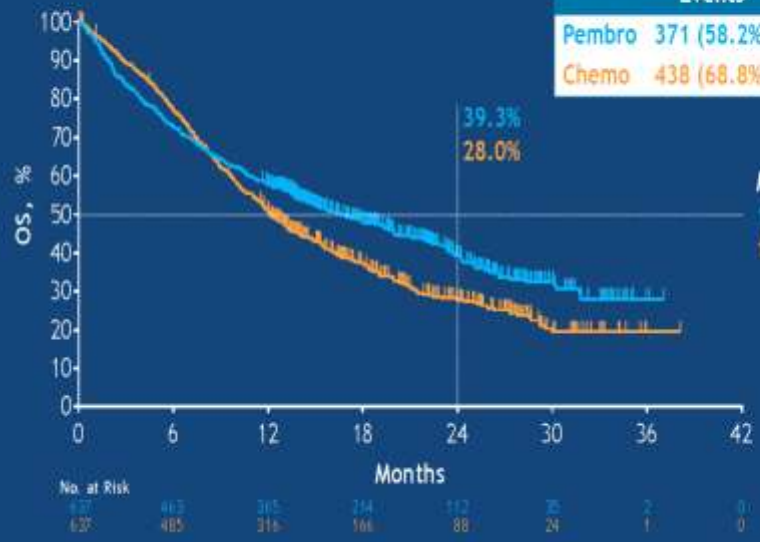


Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Lopes KN042 ASCO 201

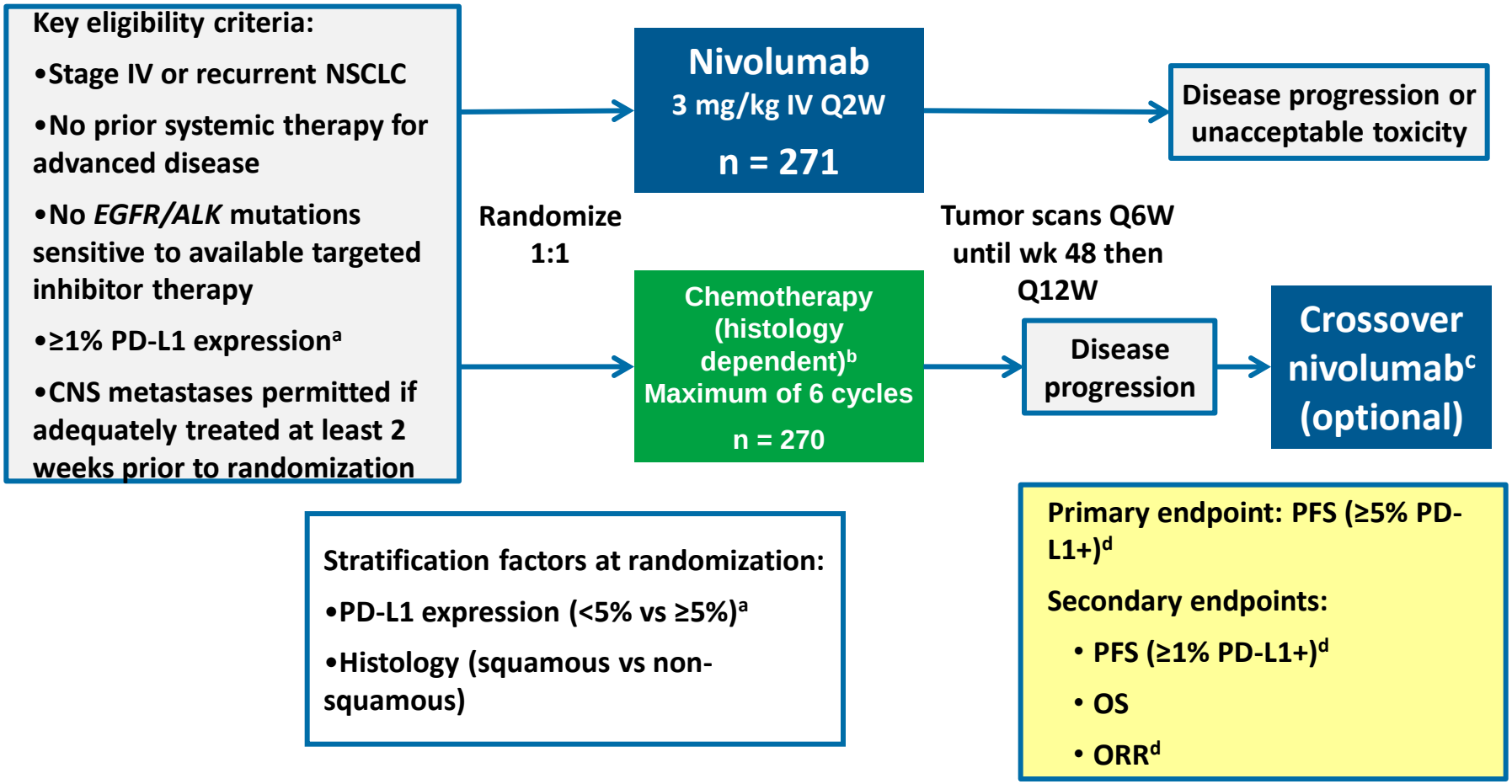
Overall Survival: TPS ≥1%

	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		



Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

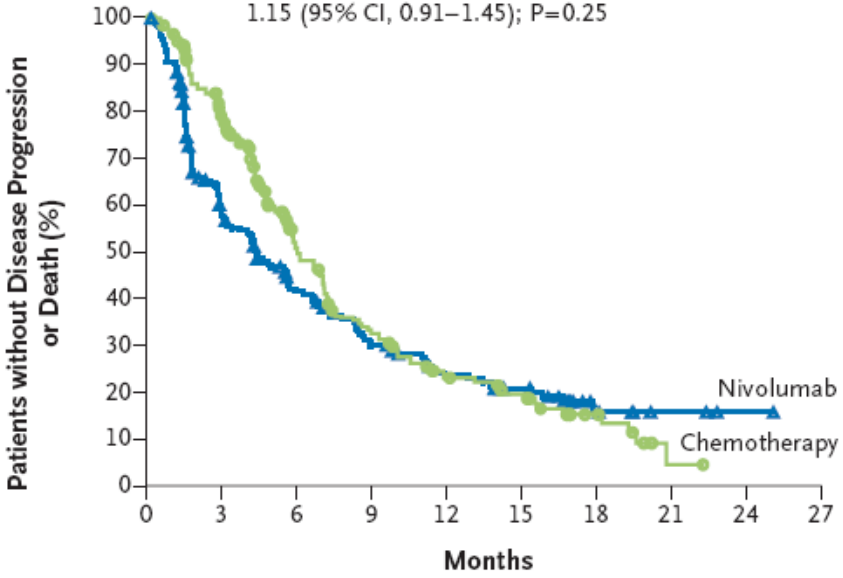
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



Socinski M et al. ESMO 2016

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

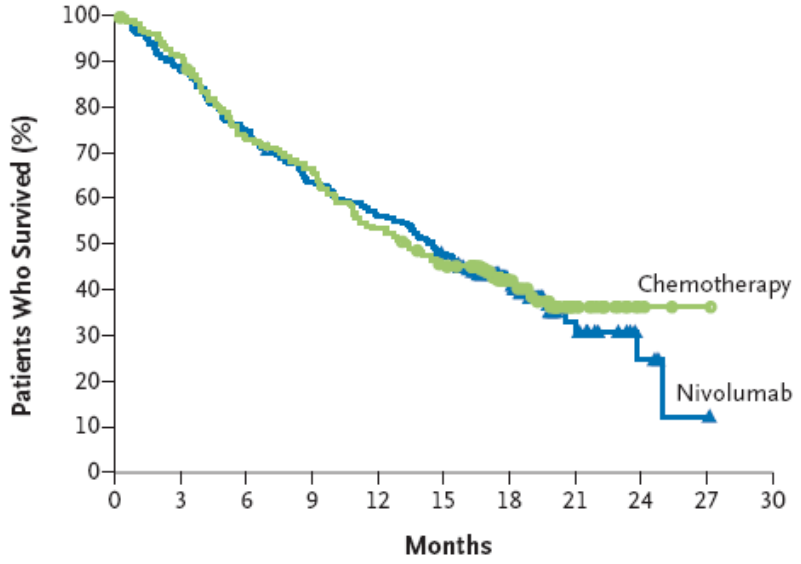
Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25



No. at Risk										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



No. at Risk											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Carbone DP et al: NEJM 2017; 376:2415

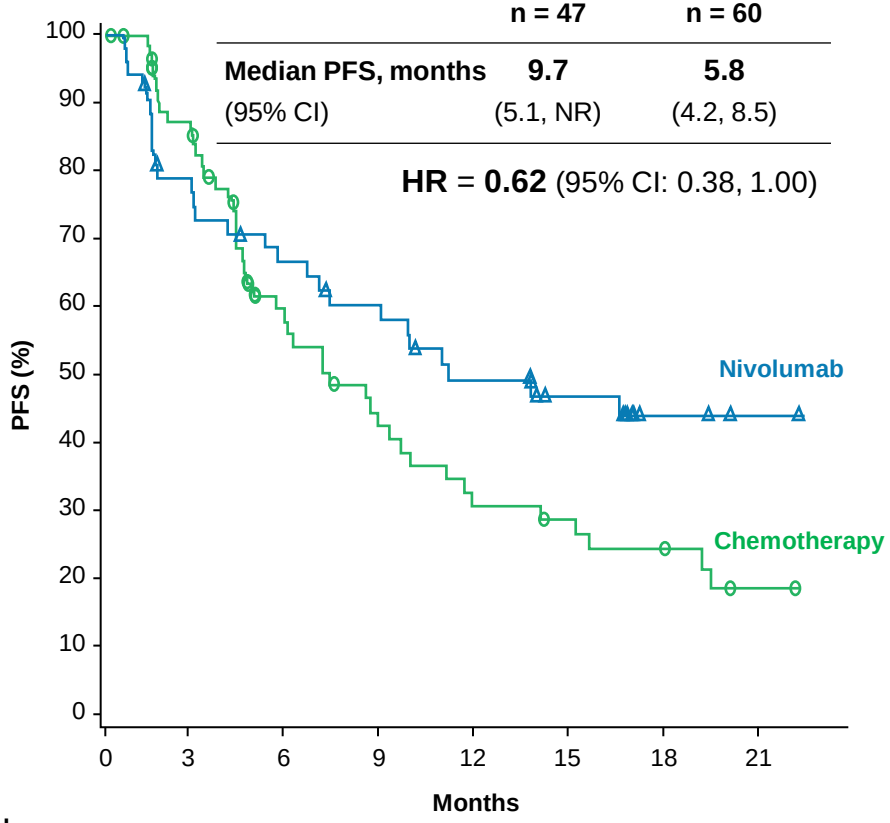
PFS by Tumor Mutation Burden Subgroup

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median PFS, months	**9.7**	**5.8**
(95% CI)	(5.1, NR)	(4.2, 8.5)

HR = 0.62 (95% CI: 0.38, 1.00)

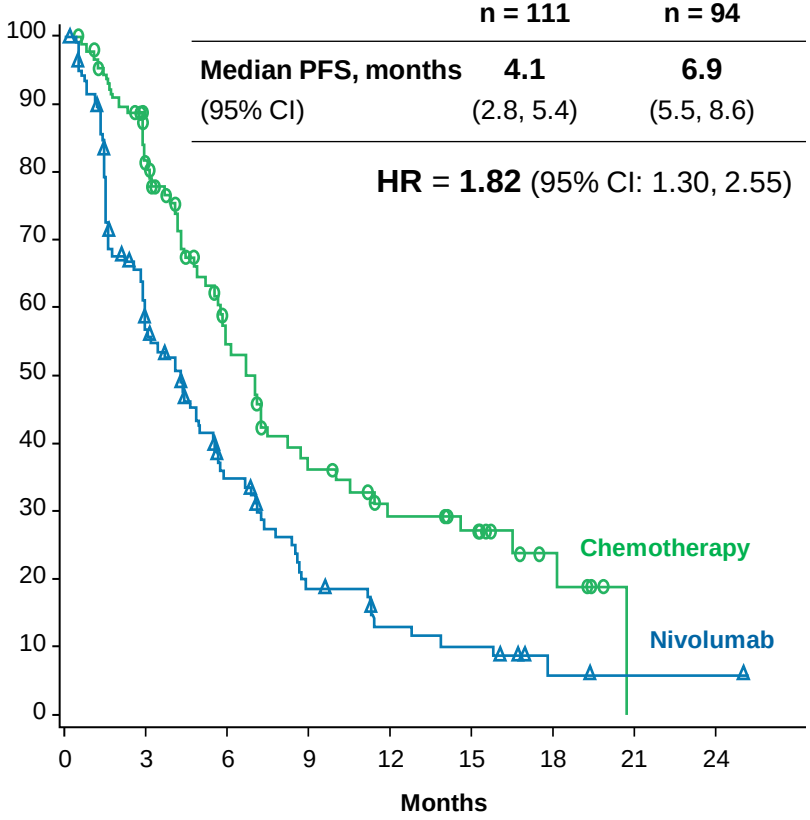


No. at Risk								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median PFS, months	**4.1**	**6.9**
(95% CI)	(2.8, 5.4)	(5.5, 8.6)

HR = 1.82 (95% CI: 1.30, 2.55)

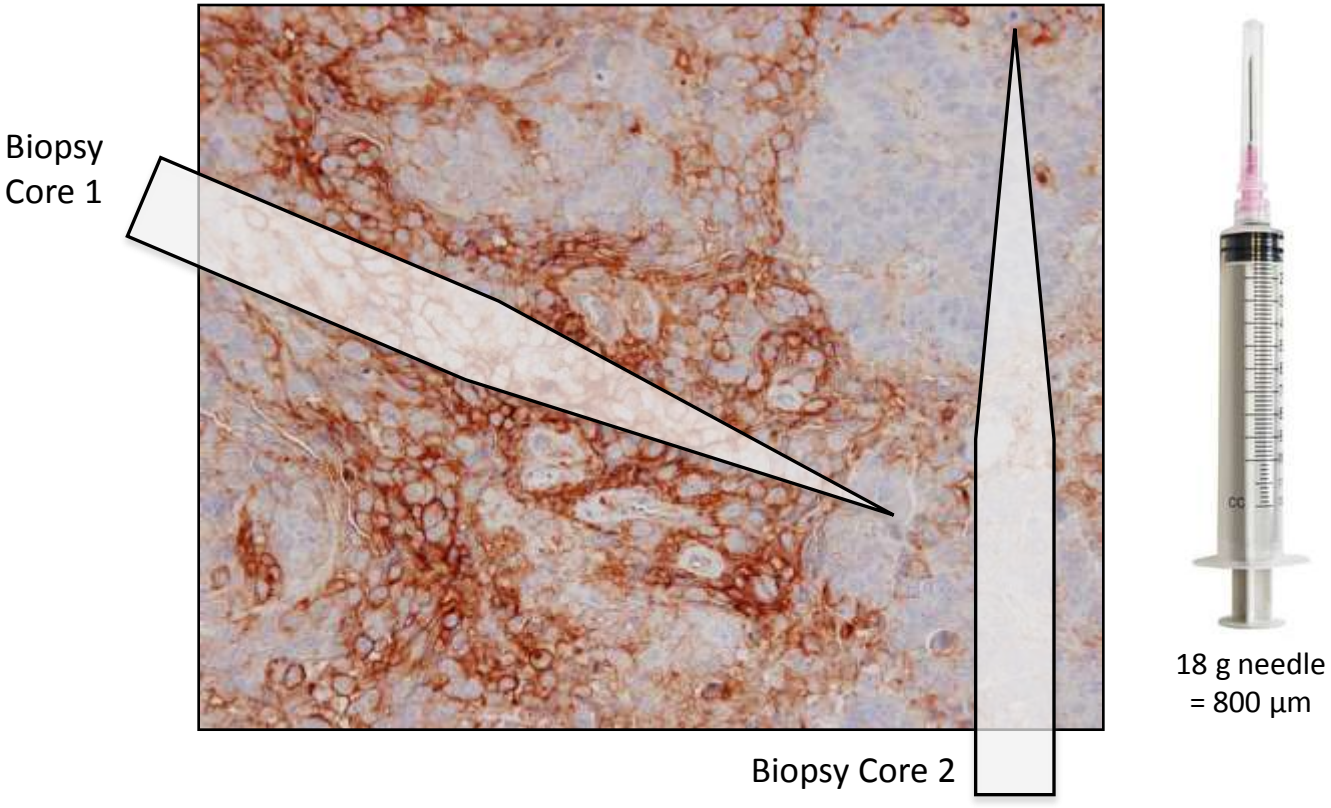


Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

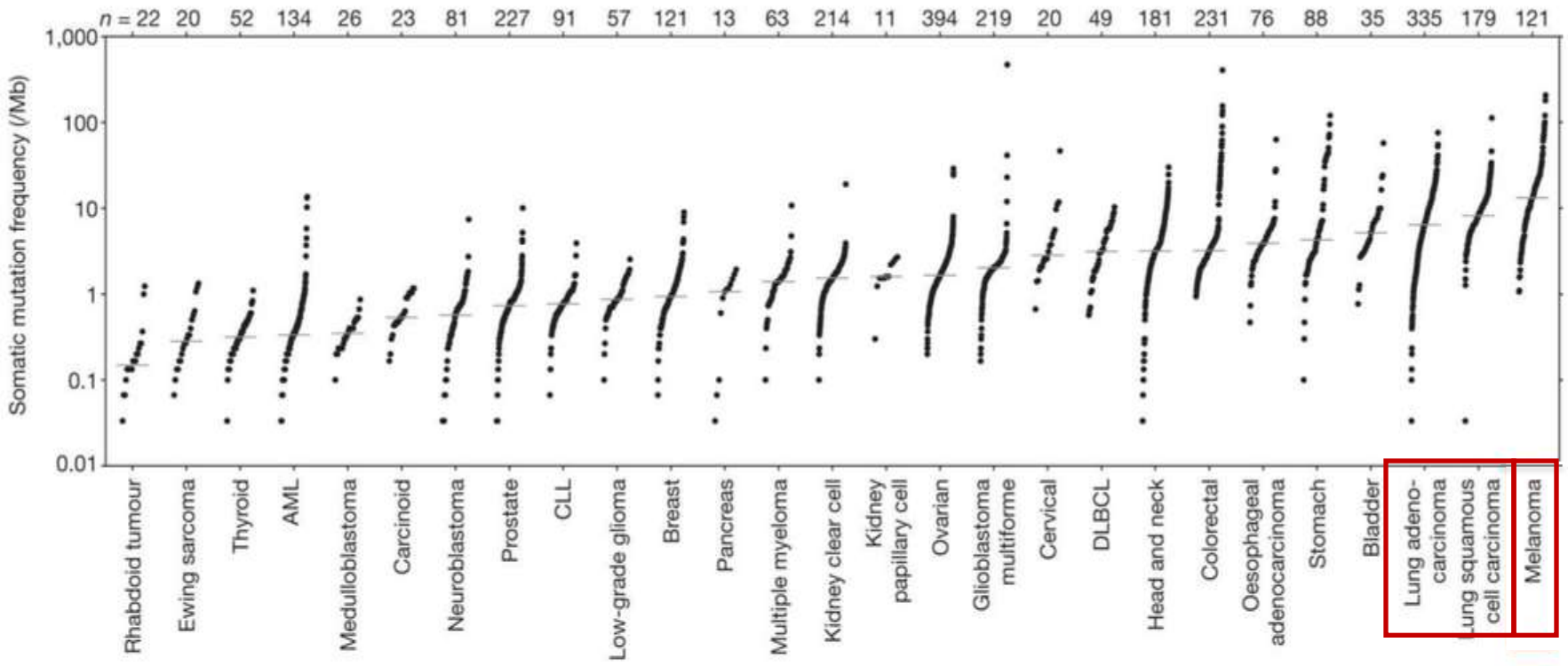
Predictive role of PDL-1 expression to PD-1/PDL-1 blockade: open questions

- ✓ There are different antibody (one mAb for each of the anti-PD-1/PD-L1 agents tested) and assay utilized
- ✓ Patients with PD-L1-negative tumors can respond to treatment
- ✓ PD-L1 is a highly dynamic and inducible marker (IFN-γ), and it should be tested as close as possible at the beginning of the PD-1/PD-L1 blockade treatment
- ✓ PD-L1 is heterogeneously expressed in tumor tissues→false negative cases

PD-L1 immunohistochemistry: Expression heterogeneity and potential for sampling error

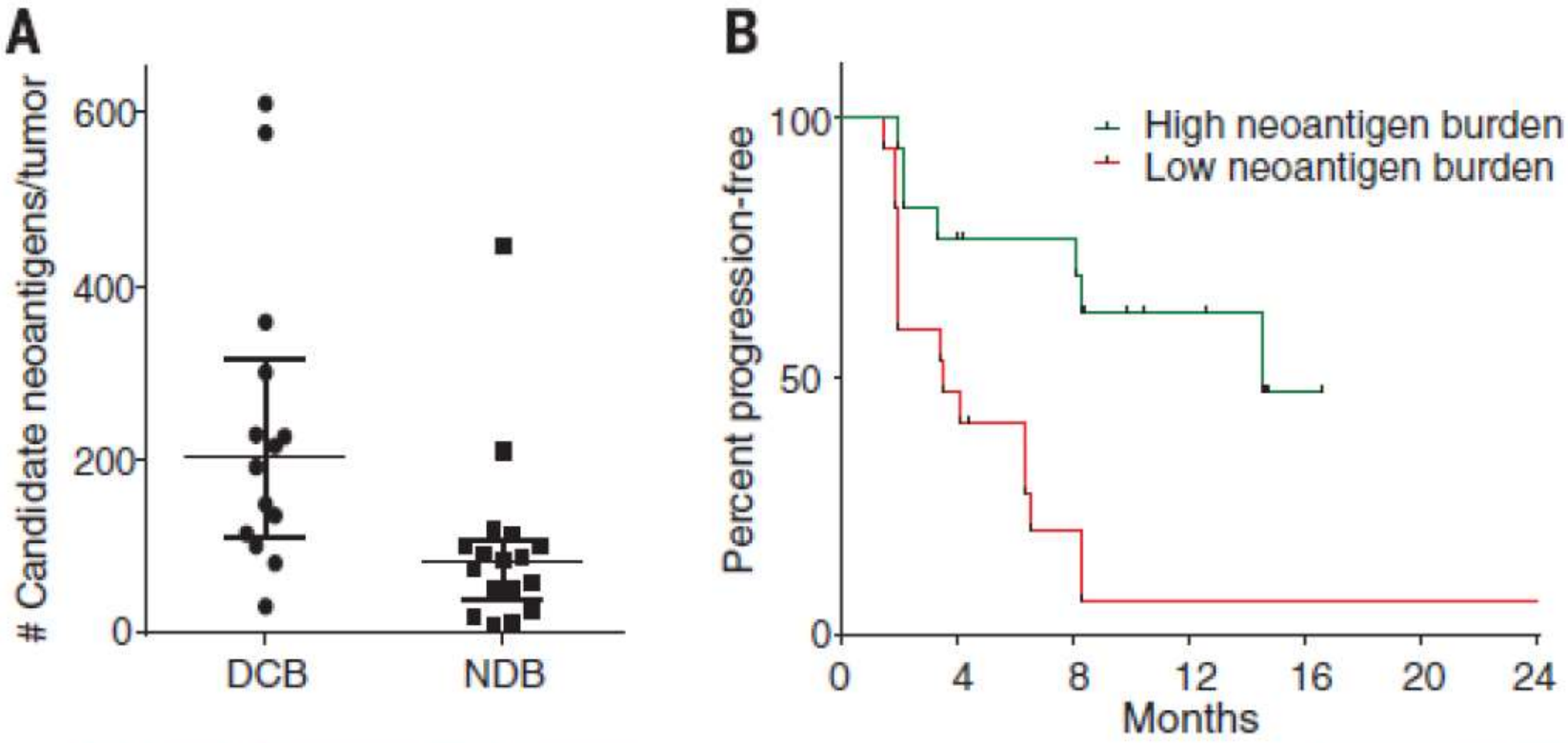


Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs



Lawrence et al, Nature 2013

Higher Neoantigen Burden is Associated with Response to Pembrolizumab in NSCLC



DCB: Durable clinical benefit (PR/SD >6months)
NDB: No durable benefit

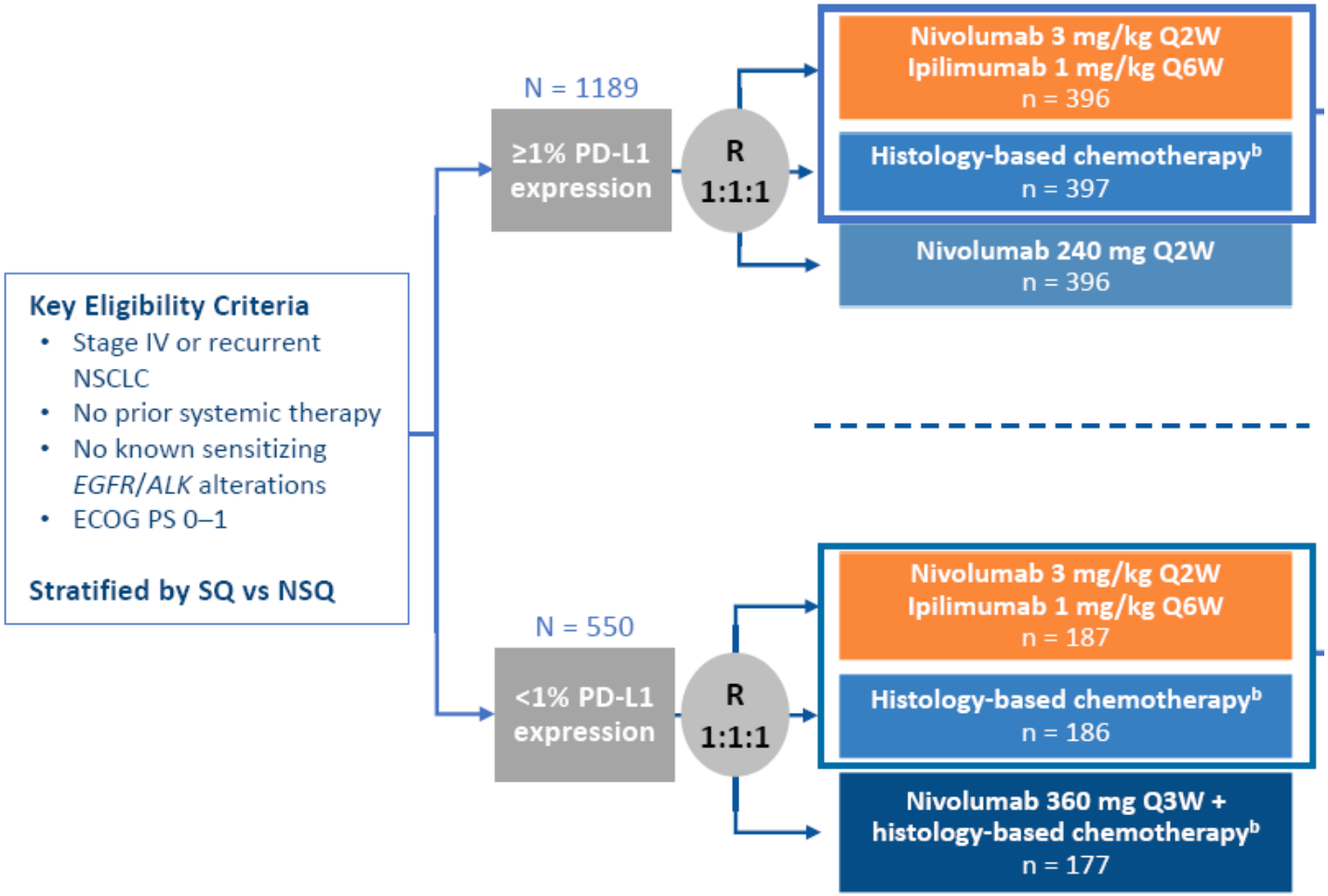
Rizvi et al *Science* 2015

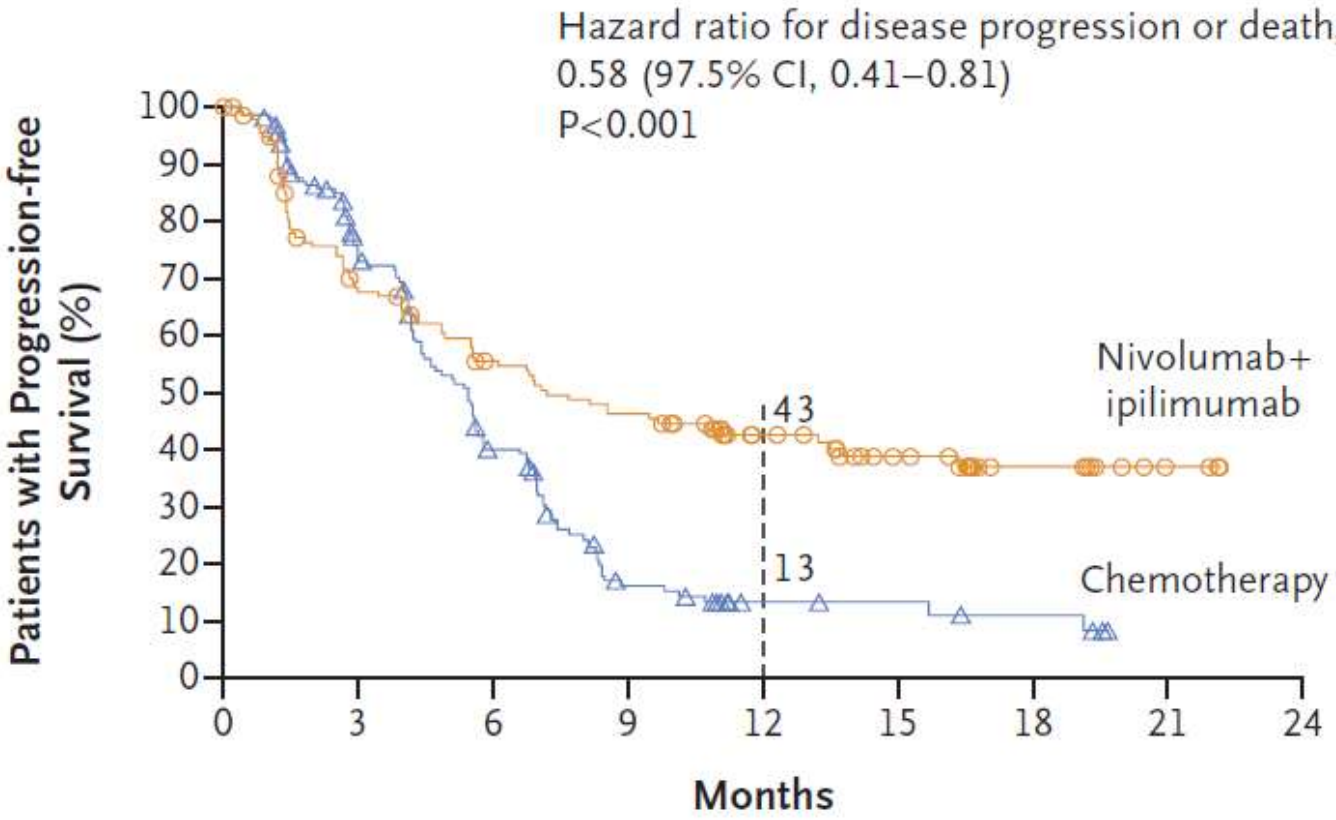
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

Checkmate-227-part 1



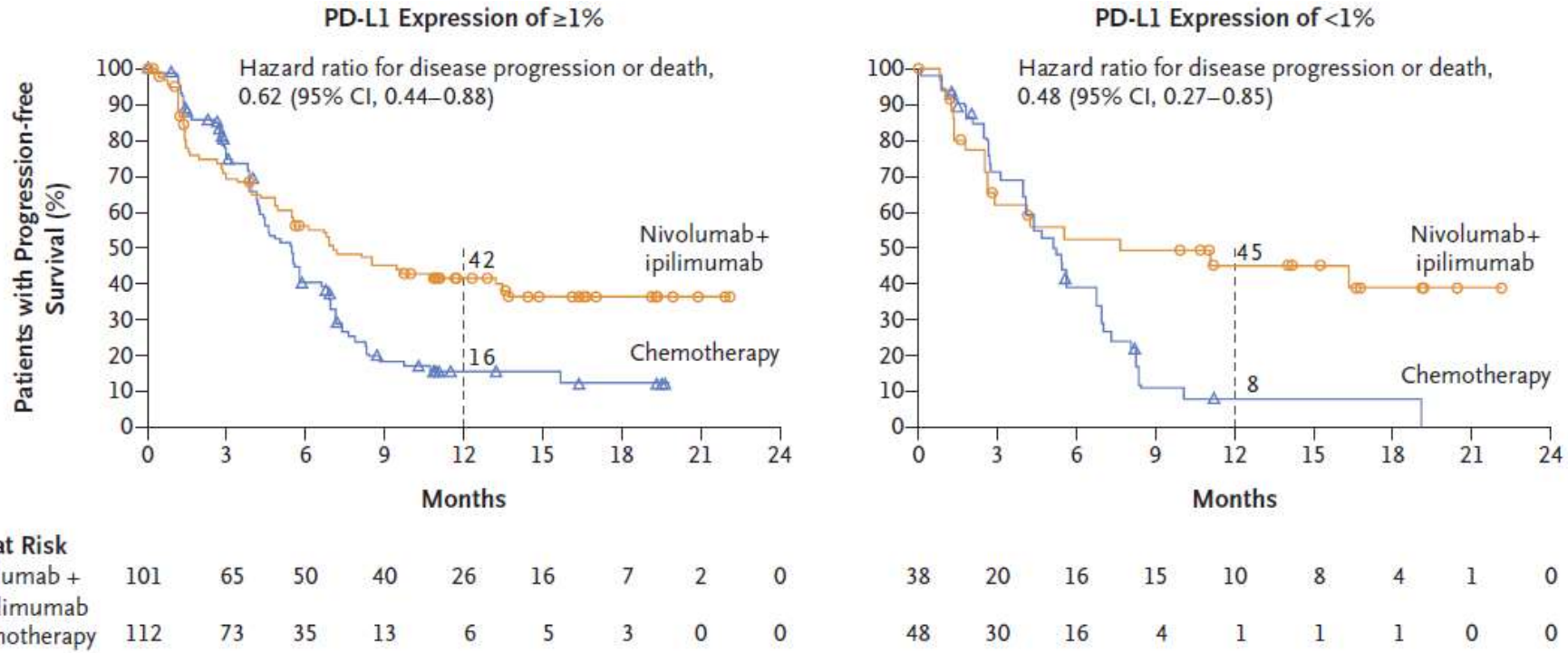


No. at Risk

Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

Hellmann MD et al, NEJM 2018

Ipilimumab/nivolumab is better than platinum-CT in TMB≥10Mb irrespective of PD-L1 (Checkmate 227)



No. at Risk									
Nivolumab + ipilimumab	101	65	50	40	26	16	7	2	0
Chemotherapy	112	73	35	13	6	5	3	0	0

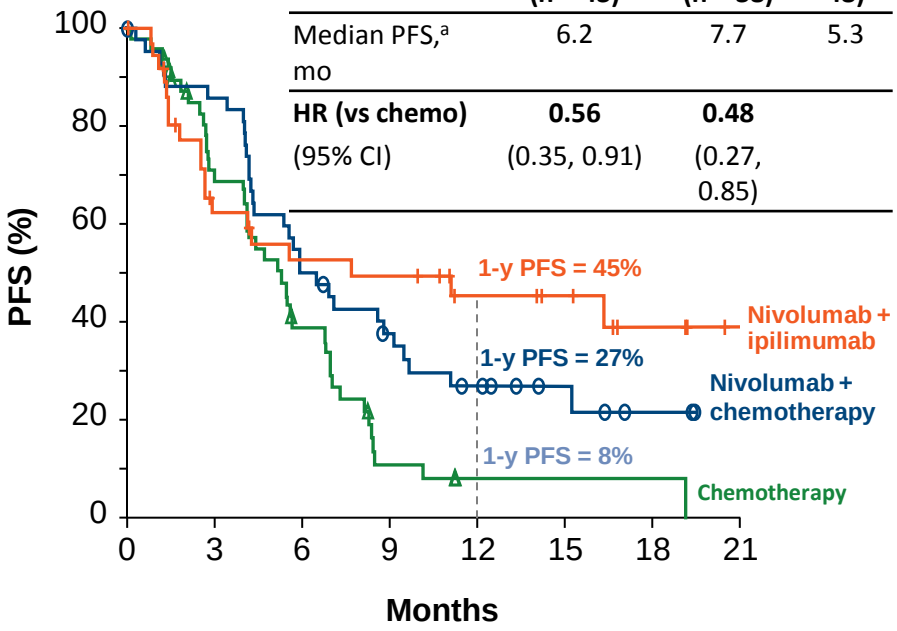
No. at Risk									
Nivolumab + ipilimumab	38	20	16	15	10	8	4	1	0
Chemotherapy	48	30	16	4	1	1	1	0	0

Hellmann MD et al, NEJM 2018

Checkmate- 227: PFS in Nivolumab + Chemotherapy and Nivolumab + Ipilimumab by TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

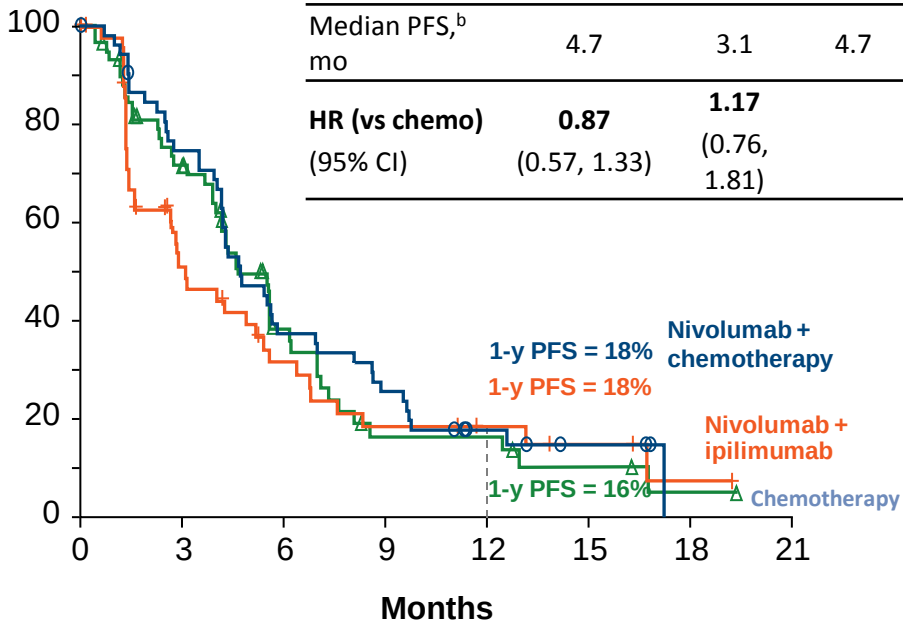
	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo)	**0.56**	**0.48**	
(95% CI)	(0.35, 0.91)	(0.27, 0.85)	



No. at risk								
Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 54)	Nivo + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo)	**0.87**	**1.17**	
(95% CI)	(0.57, 1.33)	(0.76, 1.81)	



No. at risk								
Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

Exploratory analysis

[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

Predictive role of TMB: open questions

- TMB is a dynamic marker

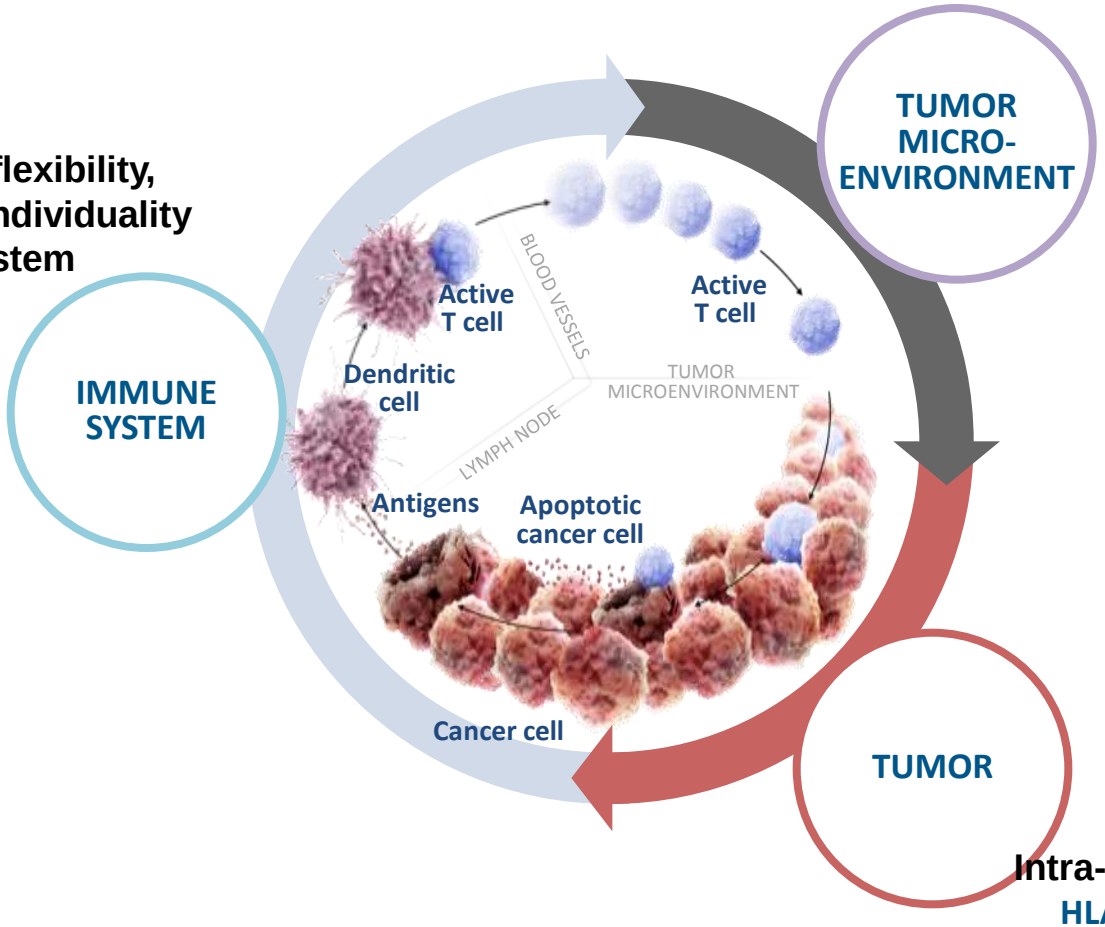
- Different cutoff utilized in early phase studies

- Immune chekpoint blockade could be effective also in tumors with a low TMB (kidney)

- Assay not easy (time, expensive....)

The complexity (*hurdles*) of biomarkers in I-O

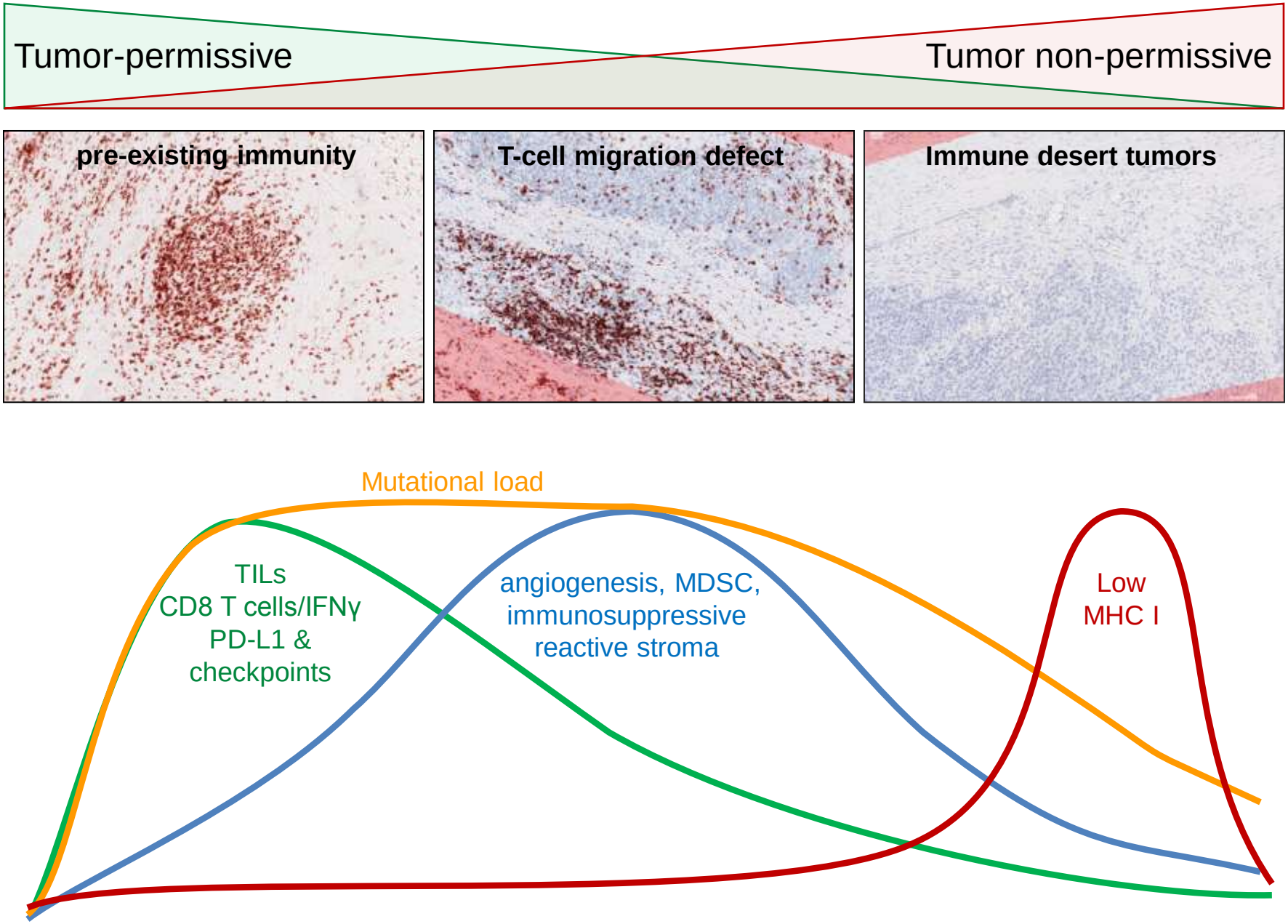
High complexity, flexibility, adaptability and individuality of the immune system



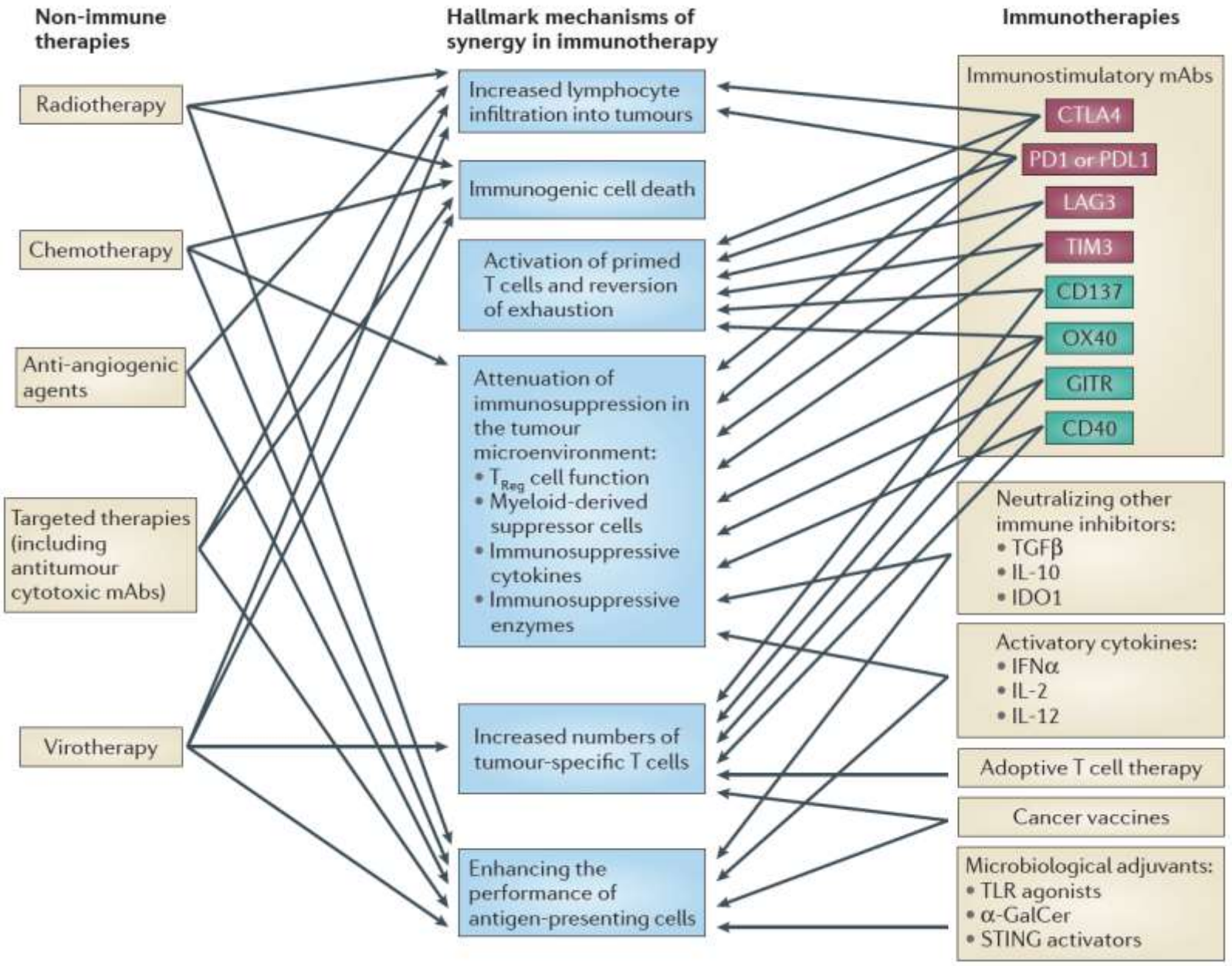
Heterogeneity of tumor microenvironment

Intra-/inter-tumor heterogeneity

- **HLA I/II**
- **Tumor Associated Antigens**
- **Antigen Processing Machinery**
- **Co-stimulatory Molecules**

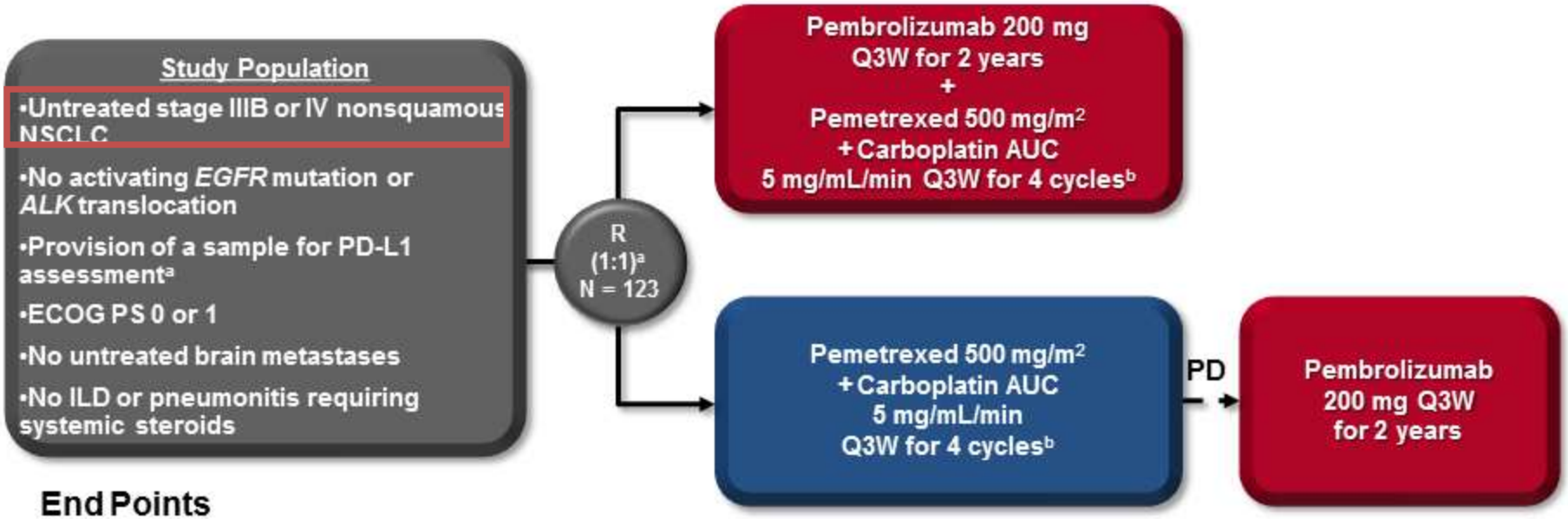


Adapted from Hedge PS, et al. Clin Cancer Res 2016; 22(8) 1865-1874.



Melero I, Nar Rev Cancer 2015

KEYNOTE-021 Cohort G



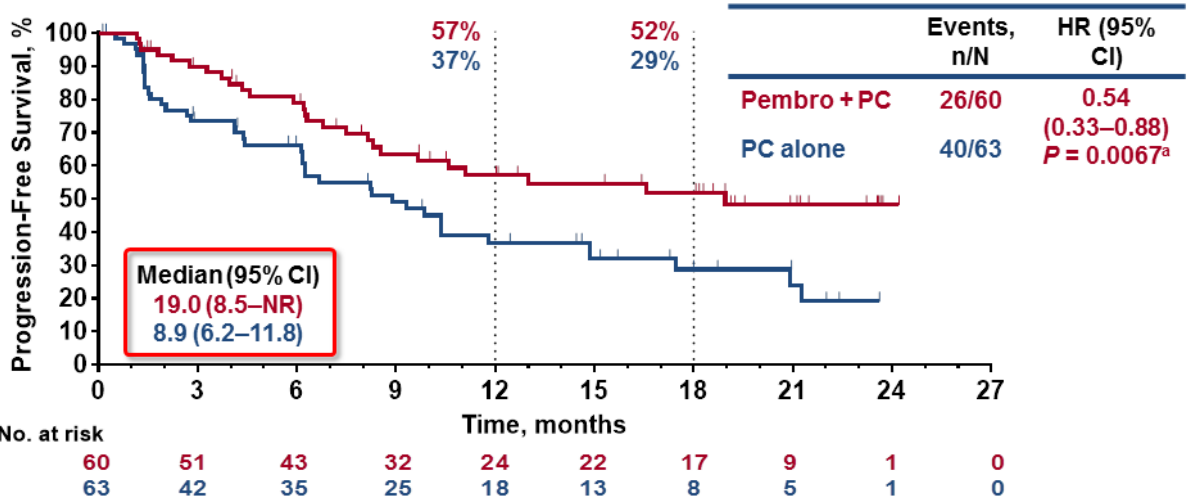
End Points

- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all *P* values are nominal (one-sided $P < 0.025$)

Borghaei WCLC 2017

Borghaei WCLC 2017

Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)

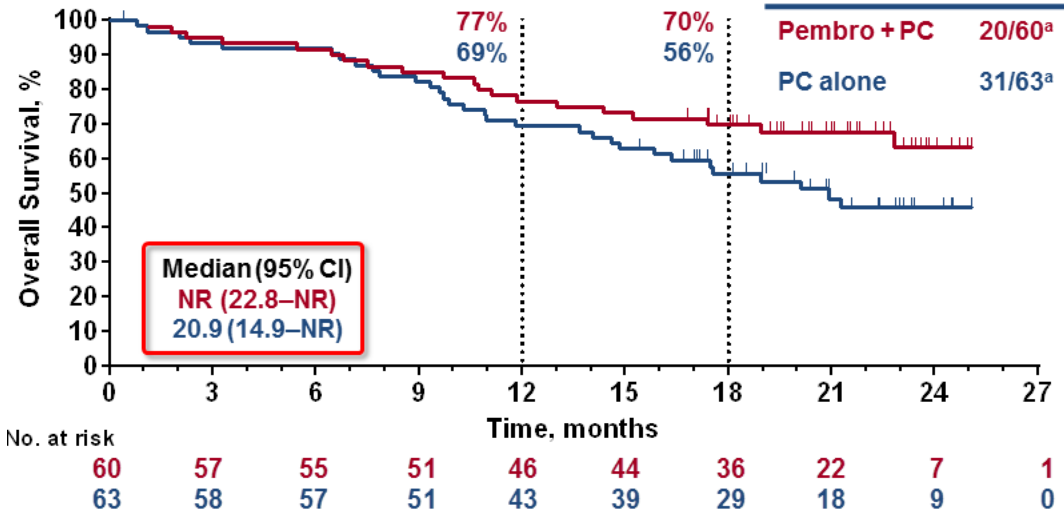


	Events, n/N	HR (95% CI)
Pembro + PC	26/60	0.54 (0.33–0.88)
PC alone	40/63	*P* = 0.0067[a]

Borghaei WCLC 2017

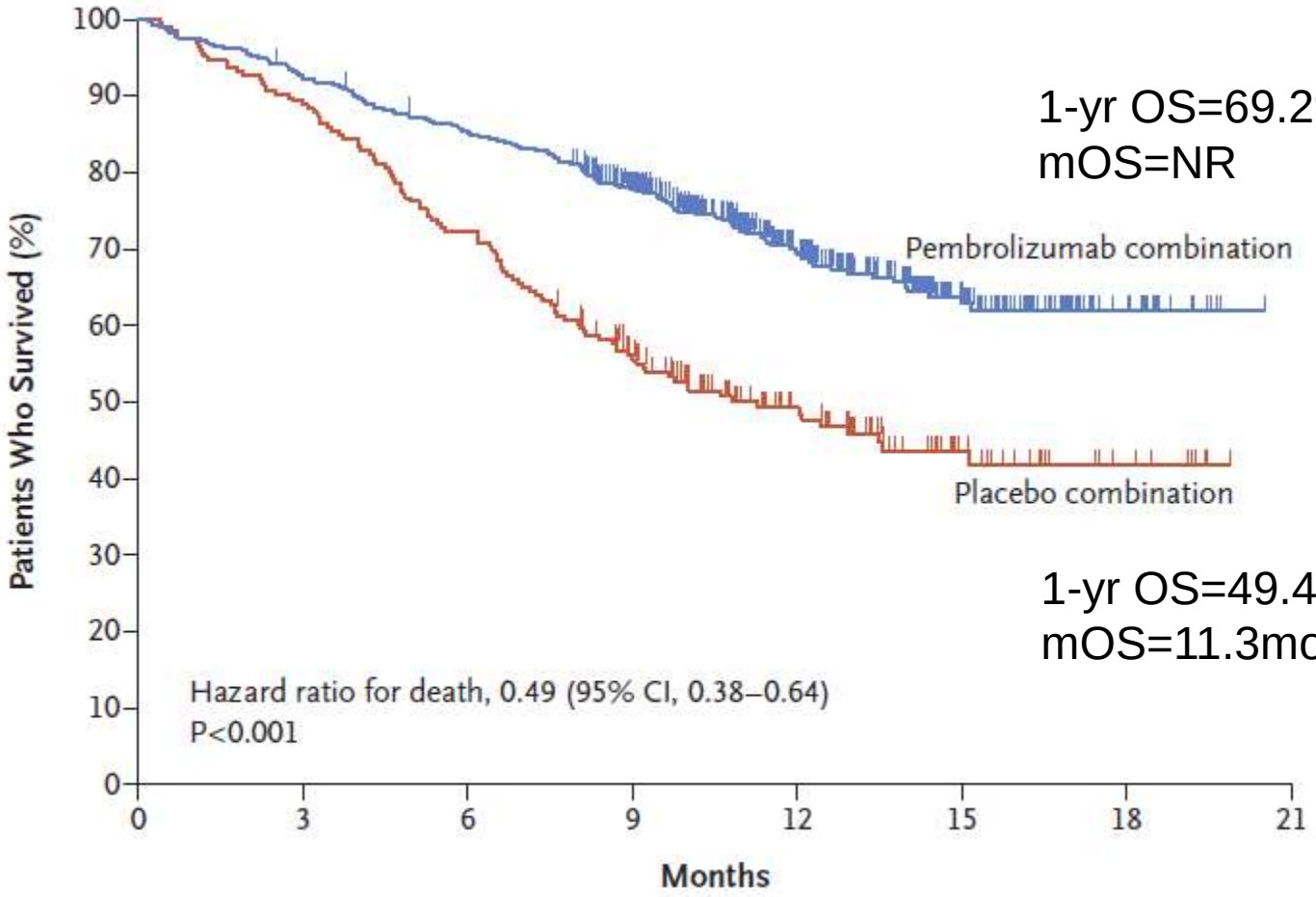
Overall Survival
Data Cut-Off: May 31, 2017

Median Follow-Up: 18.7 mo



	Events, n/N	HR (95% CI)
Pembro + PC	20/60[a]	0.59 (0.34–1.05)
PC alone	31/63[a]	*P* = 0.03[b]

KEYNOTE-189 - Overall Survival



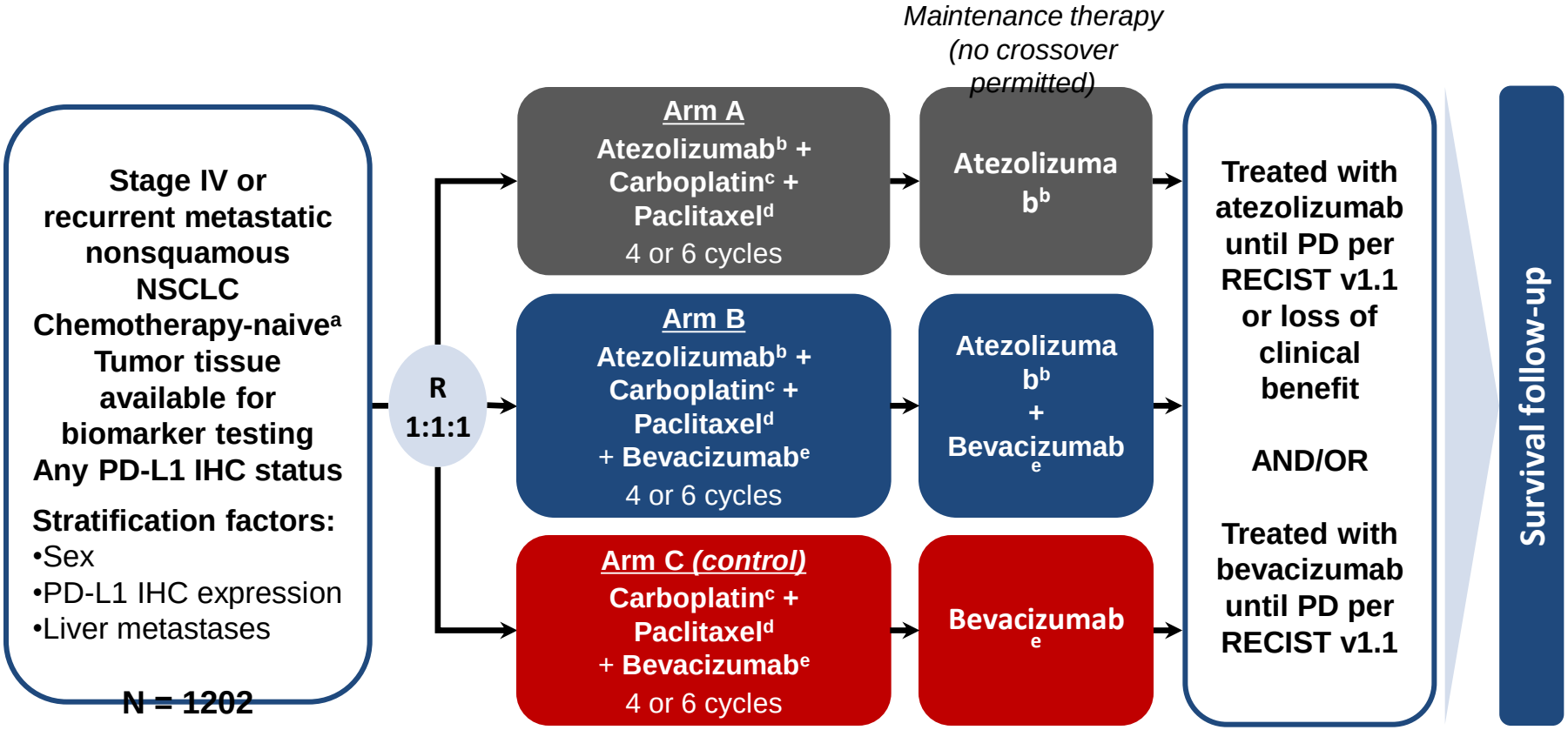
1-yr OS=69.2%
mOS=NR

1-yr OS=49.4%
mOS=11.3mo

No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

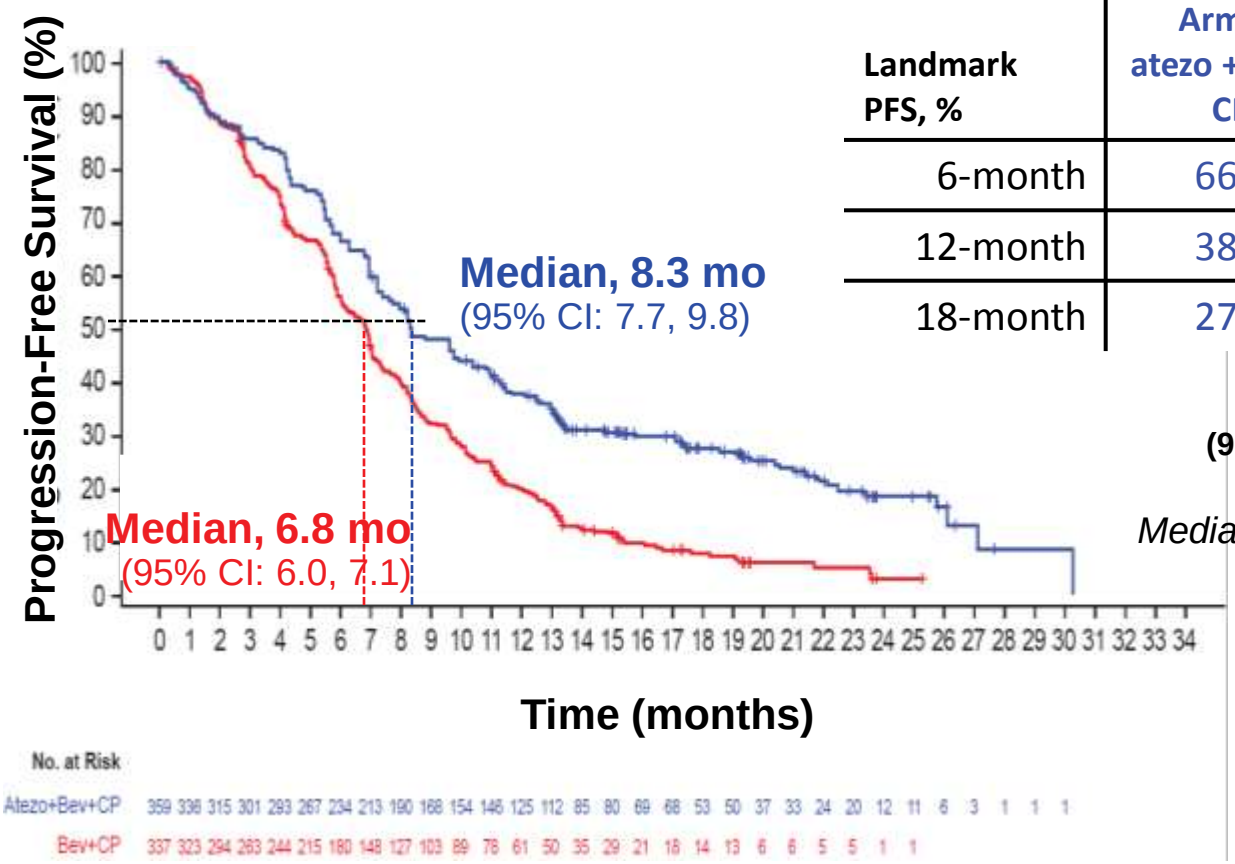
Gandhi L et al, NEJM 2018

IMpower150 Study Design



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

Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)

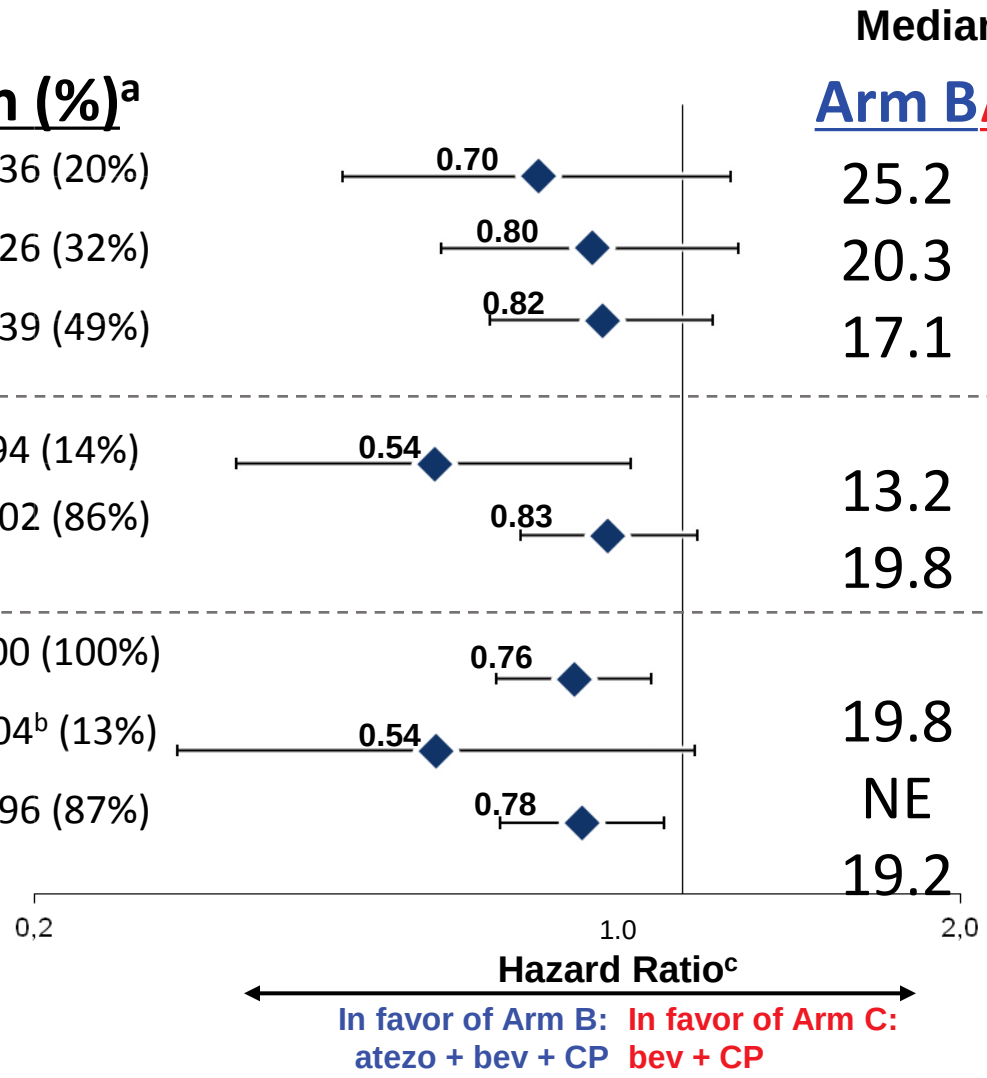


Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.59
(95% CI: 0.50, 0.70)
***P* < 0.0001[b]**
Median follow-up: ~20 mo

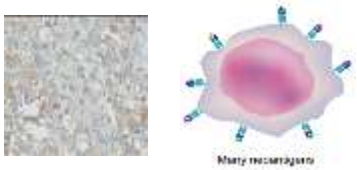
- Statistically significant and clinically meaningful PFS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was previously observed[1] and continued to improve with additional follow-up

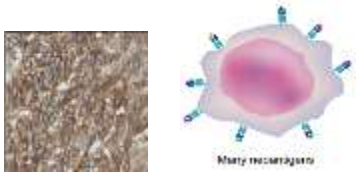
OS in Key Subgroups (Arm B vs Arm C)



Future theoretical treatment scenarios

Non squamous / squamous NSCLC





Low PD-L1 (< 50%)	Low PD-L1 (< 50%)	High PD-L1 (> 50%)	High PD-L1 (> 50%)
Low TMB (< 10/MB)	High TMB (≥ 10/MB)	Low TMB (< 10/MB)	High TMB (≥ 10/MB)
	Nivolumab+Ipilimumab	Pembrolizumab	Pembrolizumab
			Nivolumab+Ipilimumab (high tumor burden or rapid growth kinetics)

or high tumor burden

Pembrolizumab+CT

Atezolizumab+CT +/- Bevacizumab

Pembrolizumab (PS=2 or low tumor burden)

Best option: enrollment in a clinical trial!

Future theoretical treatment scenarios

Non squamous / squamous cell lung cancer

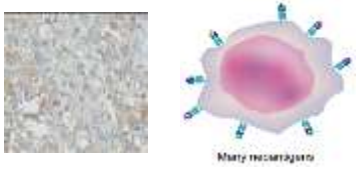

Low PD-L1 (< 50%)

Low TMB (< 10/MB)

Pembrolizumab+CT

Atezolizumab+CT +/- Bevacizumab

Pembrolizumab (PS=2 or low tumor burden)



Low PD-L1 (< 50%)

High TMB (≥ 10/MB)

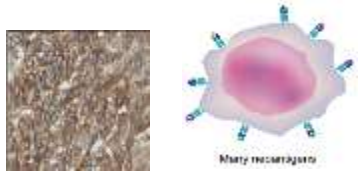
Nivolumab+Ipilimumab

High PD-L1 (> 50%)

Low TMB (< 10/MB)

Pembrolizumab

or high tumor burden



High PD-L1 (> 50%)

High TMB (≥ 10/MB)

Pembrolizumab

Nivolumab+Ipilimumab (high tumor burden or rapid growth kinetics)

Presence of targetable alteration (EGFR, ALK, ROS-1, BRAF)

Medical Oncology and Immunotherapy
Center for Immuno-Oncology
University Hospital of Siena - Italy

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Bristol-Myers Squibb

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AIRC

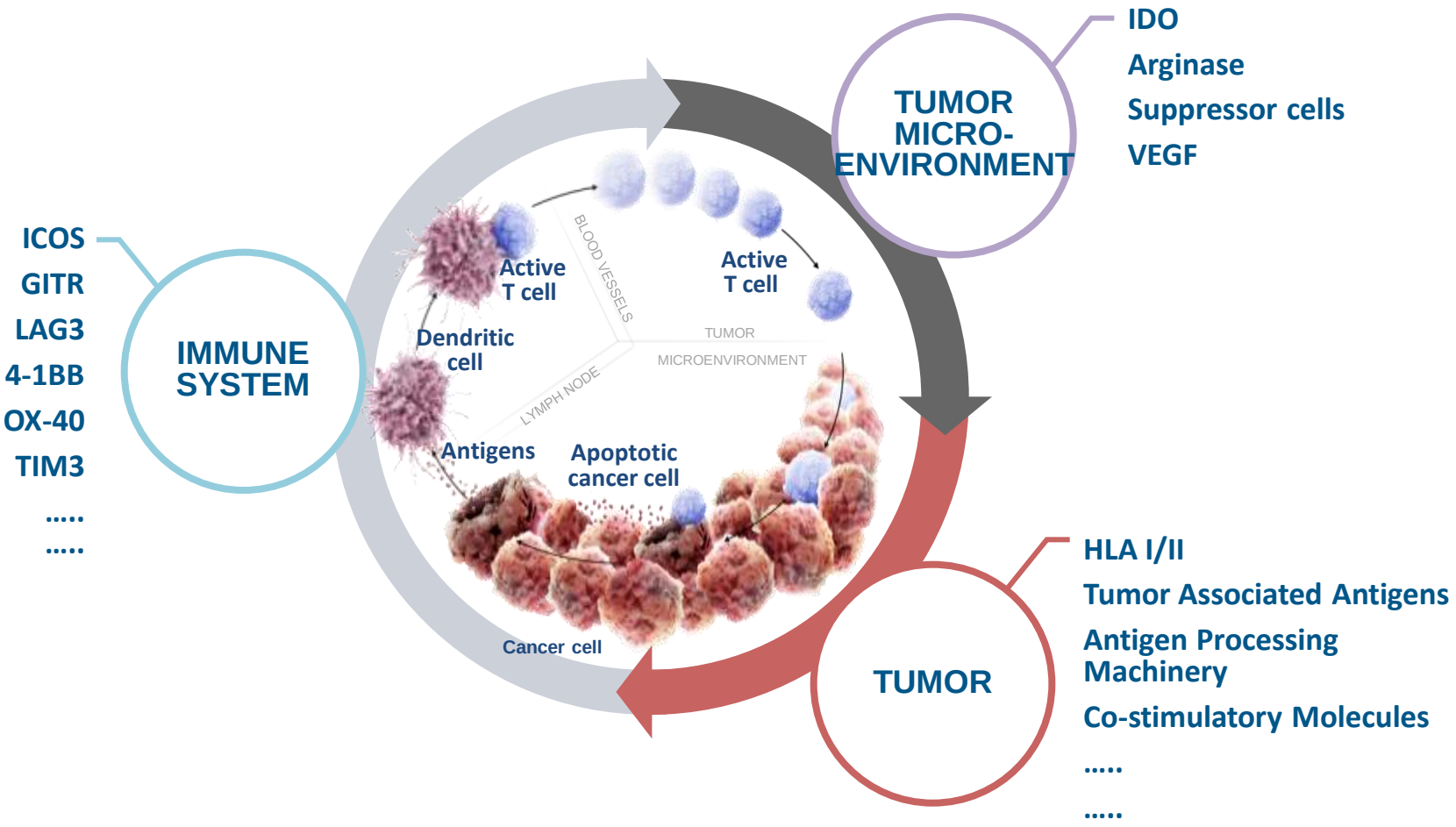
Ministero della Salute

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

Pfizer

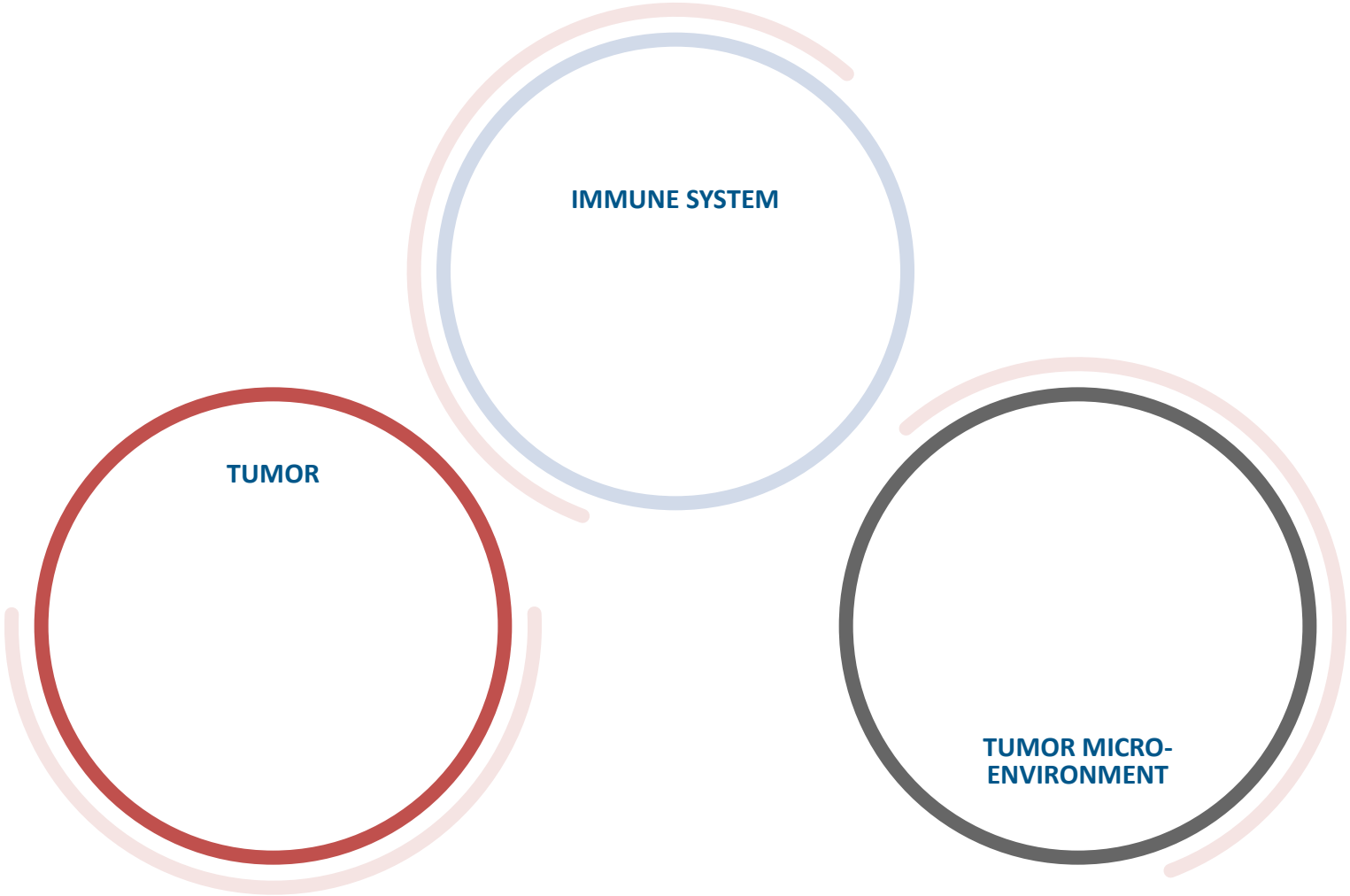
astex pharmaceuticals

Targeting and modulating multiple compartments



The future of Cancer Immunotherapy

Targeting tailored combinations to multiple key components



Implications of this particular biomarker

- Assessment of immune cells
  - Relevance of immune cells present?
  - Cytology samples lack architecture
- Rule in / Rule out
  - Biomarker to predict patient **will** benefit (and to what degree)
  - Biomarker to predict patient will **not** benefit
  - 10% is easier than 5% is easier than 1%
- A complex assessment!

Biomarker not predictive in Squamous (017) but predictive in Non-Squamous (057)

- Same drug, same biomarker
- Current/Former smokers
  - **017** - 92% **057** - 79.5%, EGFR/ALK in 17.5%
- **Greater mutational load in 017 squamous cell cancers?**

- Immune system and squamous versus glandular epithelia?
- Does the immune status or immune microenvironment differ between these patients?
- Immune infiltrates in and around tumours differ.
- Does the mutation burden make a difference? Are immunomodulatory mechanisms different?
- Are the cut offs correct? Are 1, 5 & 10% too low?

PD-L1 immunohistochemistry as a biomarker

- Is it the correct marker?
- Does the oncology community trust immunohistochemistry?
- Are our expectations of a biomarker in this setting reasonable?
- **Four drugs, four different 'biomarker tests', all for 'PD-L1'**

PD-L1 immunohistochemistry as a biomarker

- Is it the correct marker?
- Does the oncology community trust immunohistochemistry?
- Are our expectations of a biomarker in this setting reasonable?
- **Four drugs, four different 'biomarker tests', all for 'PD-L1'**

Recently presented results with anti-PD-1 and anti-PD-L1 mAb for NSCLC

Compound	n	Study population	Treatment	ORR (RECIST)	OS	Treatment-related grade 3/4 AEs
Anti-PD-1 antibodies						
Nivolumab CMSTO (2014)	129	Pretreated advanced solid tumors, NSCLC subanalysis	Nivolumab 1, 3 or 10 mg/kg iv. q2w	17% (all doses) 15% in PD-L1+ 14% in PD-L1-	Median: 9.9 months 1 year: 42% 2 year: 24%	14% (mostly fatigue), three treatment-related deaths (pneumonia)
Nivolumab CMSTO (2014)	20	First-line advanced NSCLC	Nivolumab 3 mg/kg iv. q2w	30% 50% in PD-L1+ 0% in PD-L1-	Median: NR 1 year: 75%	20% (liver tests, hyperglycemia, rash)
Pembrolizumab ESMO (2014)	217	Pretreated advanced NSCLC	Pembrolizumab 2 mg/kg q3w or 10 mg/kg q3w or 10 mg/kg q2w	20% (all doses) 37% in strong PD-L1+, 17% in weak PD-L1+, 10% in PD-L1-	Median: 8.2 months 6 month: 59%	9% (mostly pneumonitis)
Pembrolizumab ESMO (2014)	38	First-line advanced NSCLC	Pembrolizumab 2 mg/kg q3w or 10 mg/kg q3w or 10 mg/kg q2w	26% (all doses)	Median: NR 6 month: 86%	One grade 3 pericardial effusion
Anti-PD-L1-antibodies						
MPDL3280A ESMO (2014)	53	Pretreated advanced NSCLC	MPDL3280A 1–20 mg/kg iv. q3w	50% in PD-L1+ 15% in PD-L1-	–	12%
MEDI4736 ASCO (2014)	13	Advanced NSCLC (mostly pretreated)	MEDI4736 0.1–10 mg/kg iv. q2w or 15 mg/kg iv. q3w	23% (all doses) 26% in PD-L1+ 10% in PD-L1-	–	0% (all AEs were grade 1–2)

AE: Adverse event; ASCO: American Society of Clinical Oncology meeting; CMSTO: Chicago Multidisciplinary Symposium on Thoracic Oncology; ESMO: European Society of Medical Oncology meeting; iv.: Intravenous; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; Q2w: Every 2 weeks; q3w: Every 3 weeks.

Vansteenkiste J, et al, Future Oncology 2015

PD-L1 expression as biomarker

	Atezolizumab (Roche)	Nivolumab (Bristol-Myers Squibb)	Pembrolizumab (MERCK)	Durvalumab (AstraZeneca / MedImmune)
Detection antibody[1]	**SP142**	**28-8**	**22C3**	**SP263**
IHC platform[1]	Ventana	Dako	Dako	Ventana
Tested cells	NSCLC (IC and TC) UBC (IC)	Lung (TC)	NSCLC (TC) UBC (TC and stroma)	NSCLC (TC)
Estimated PD-L1 prevalence in NSCLC	16%*[2] TC3 IC3 37%*[2] TC2/3 IC2/3 68%*[2] TC1/2/3 IC1/2/3	*PD-L1⁺ as ≥5% of TCs* ~46%[1]	*PD-L1⁺ as ≥50% of TCs* ~25%[1]	*PD-L1⁺ as ≥25% of TCs* ~41%[1]

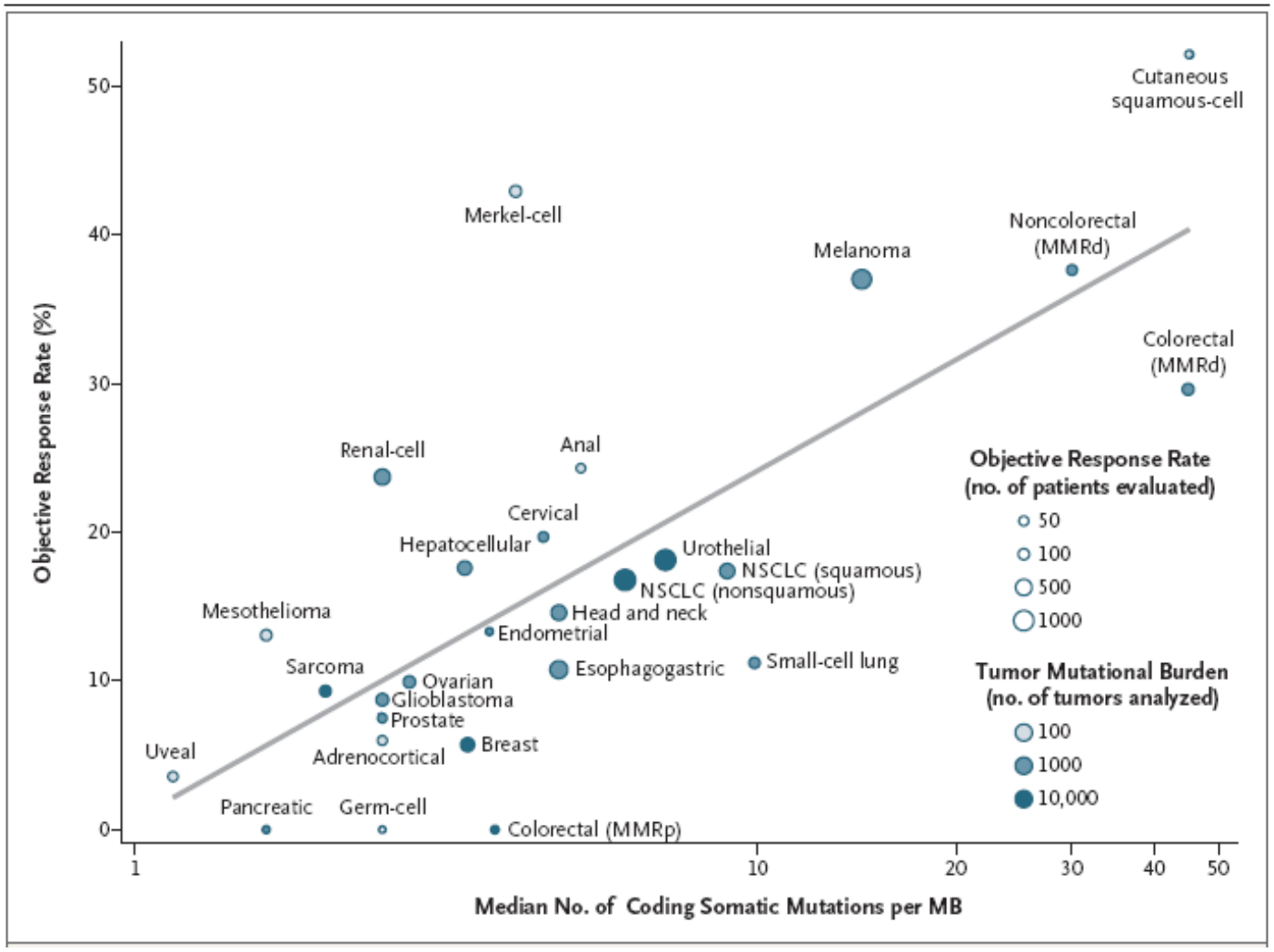
IC, immune cells; TC, tumour cell; UBC, urothelial bladder cancer

1. Kerr KM, et al. *J Thorac Oncol* 2015;10(7):985–9;
2. Spira AI, et al. *J Clin Oncol* 2015;33(15_Suppl.):Abstract 8010

PD-L1 immunohistochemistry as a biomarker

- Is it the correct marker?
- Does the oncology community trust immunohistochemistry?
- Are our expectations of a biomarker in this setting reasonable?
- **Four drugs, four different 'biomarker tests', all for 'PD-L1'**

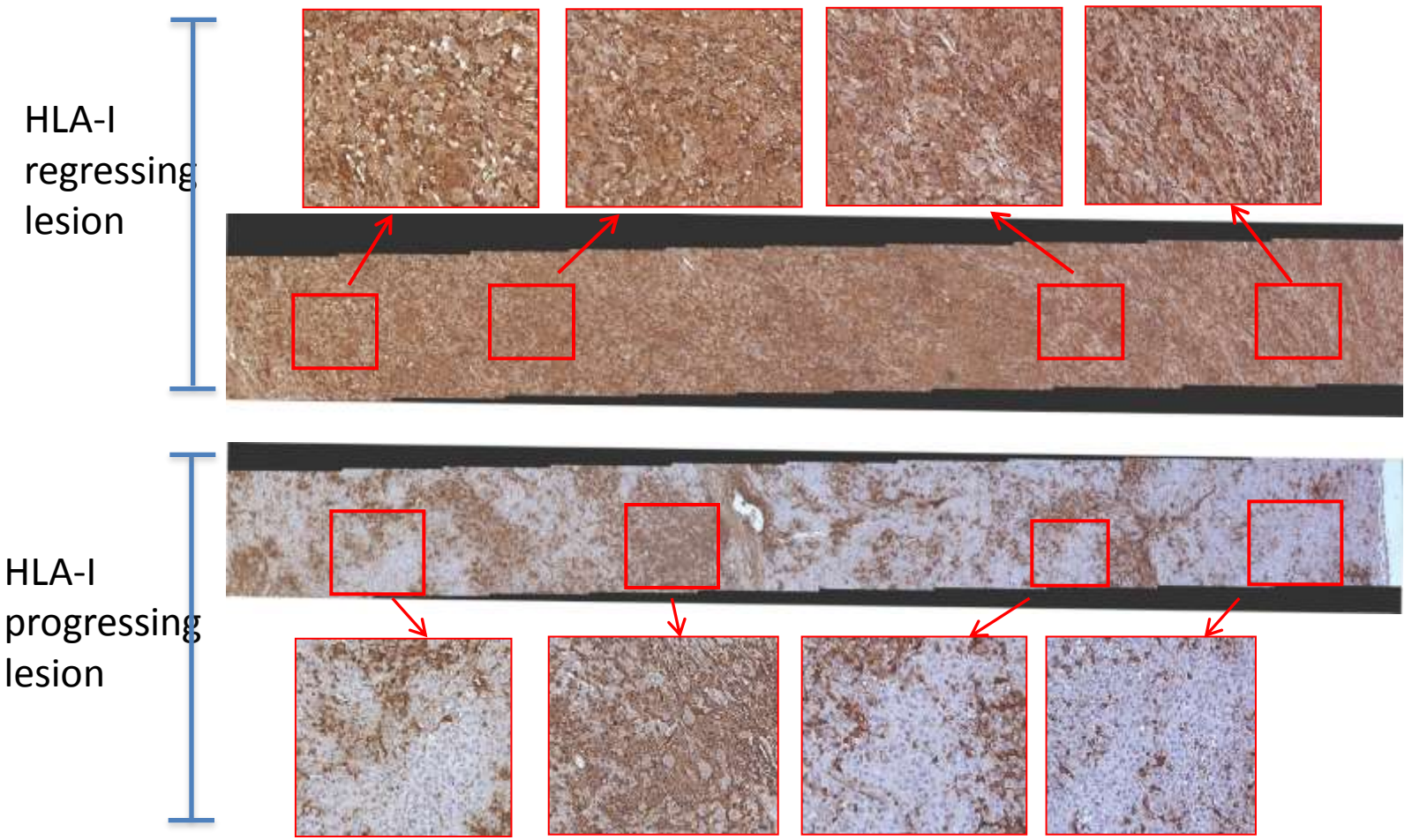
Correlation between TMB and ORR with anti-PD1 and PDL1 therapy in 27 tumor types



Yarchoan M, NEJM 2017

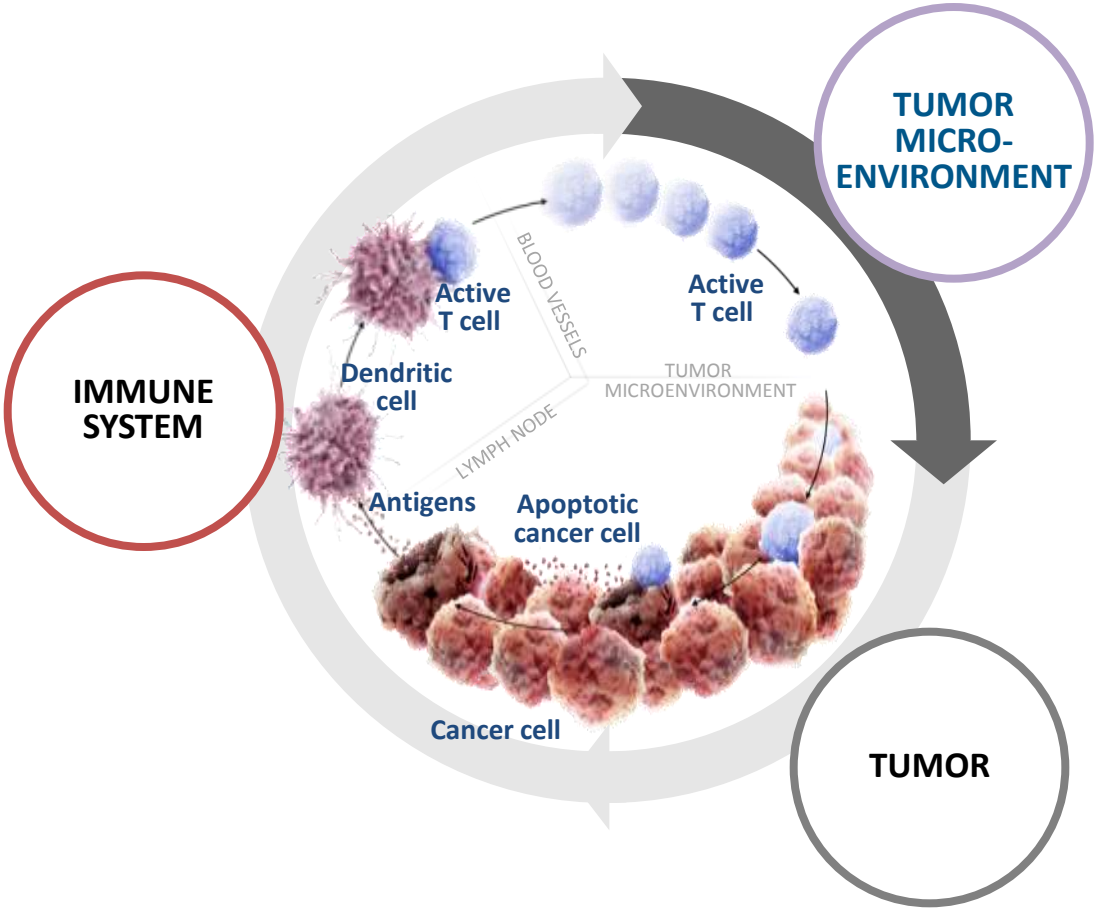
Why some patients do not respond to immunotherapy?

The gene expression profile of the tumor microenvironment as an approach to the identification of mechanisms of resistance to immune checkpoint blockade

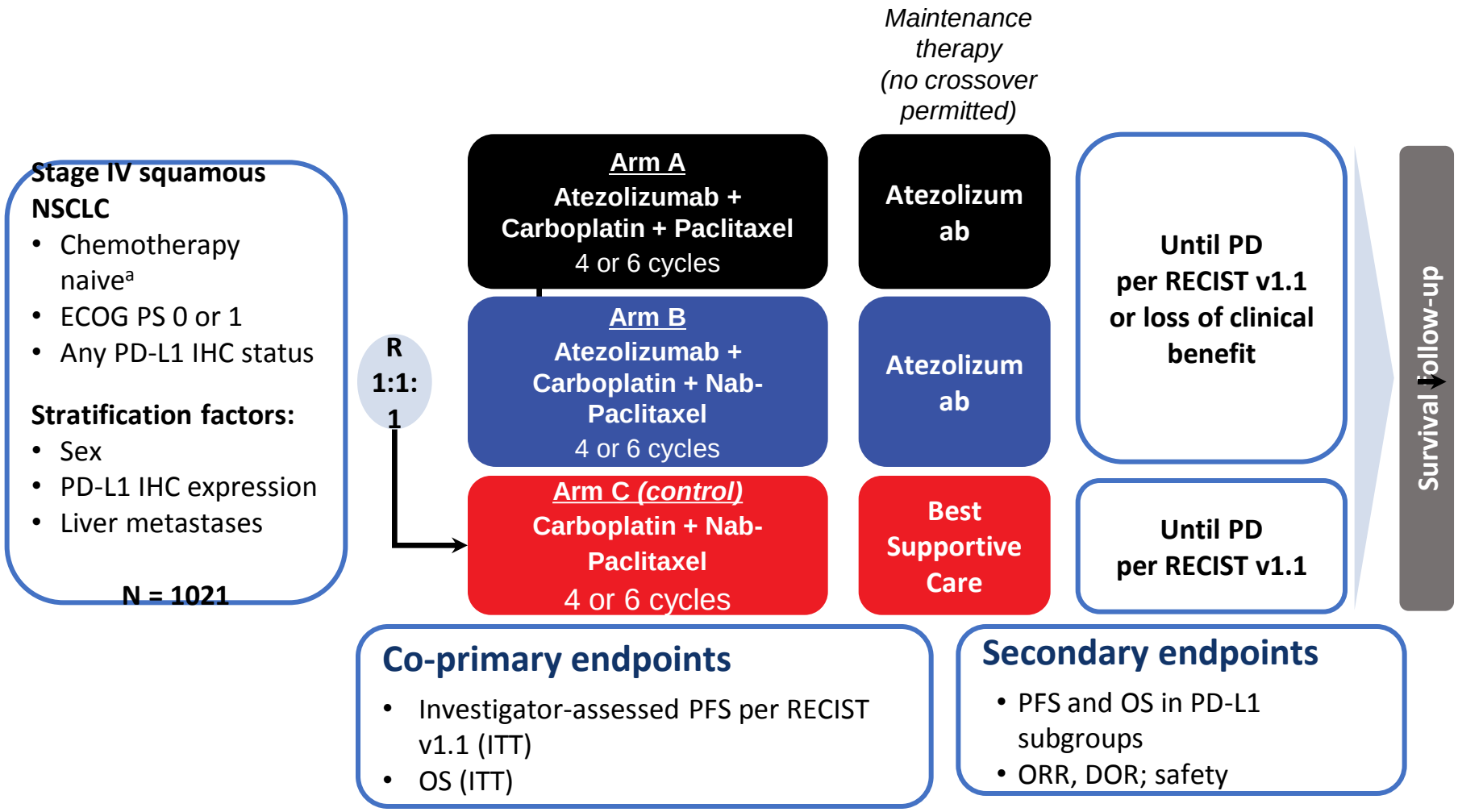


Courtesy of Andrea Anichini, INT Milano

Targeting and modulating multiple compartments



IMpower131: Study Design

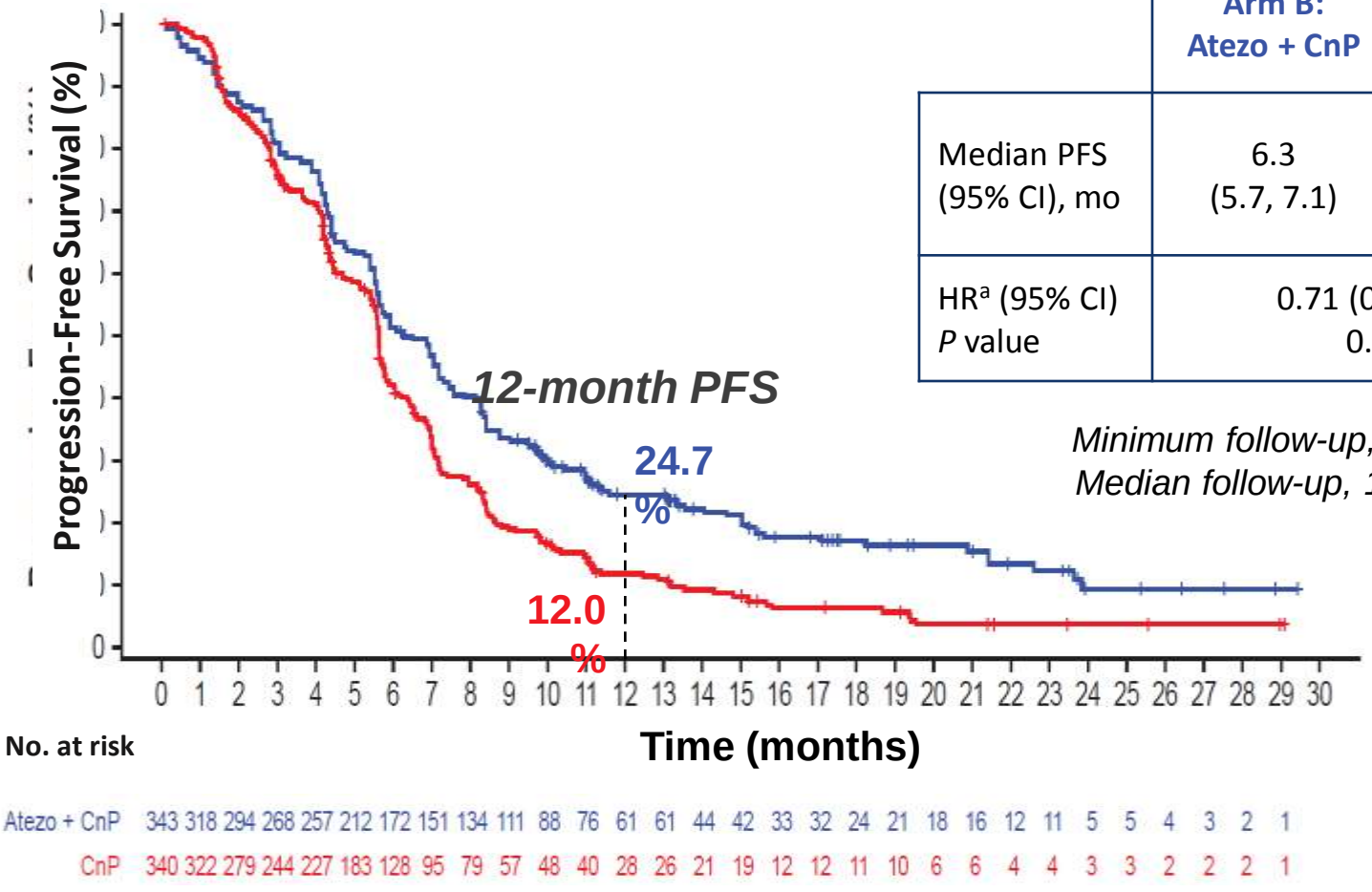


Jotte R, et al. IMpower131 PFS Analysis.

https://bit.ly/2snPEzb

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)

	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	



Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

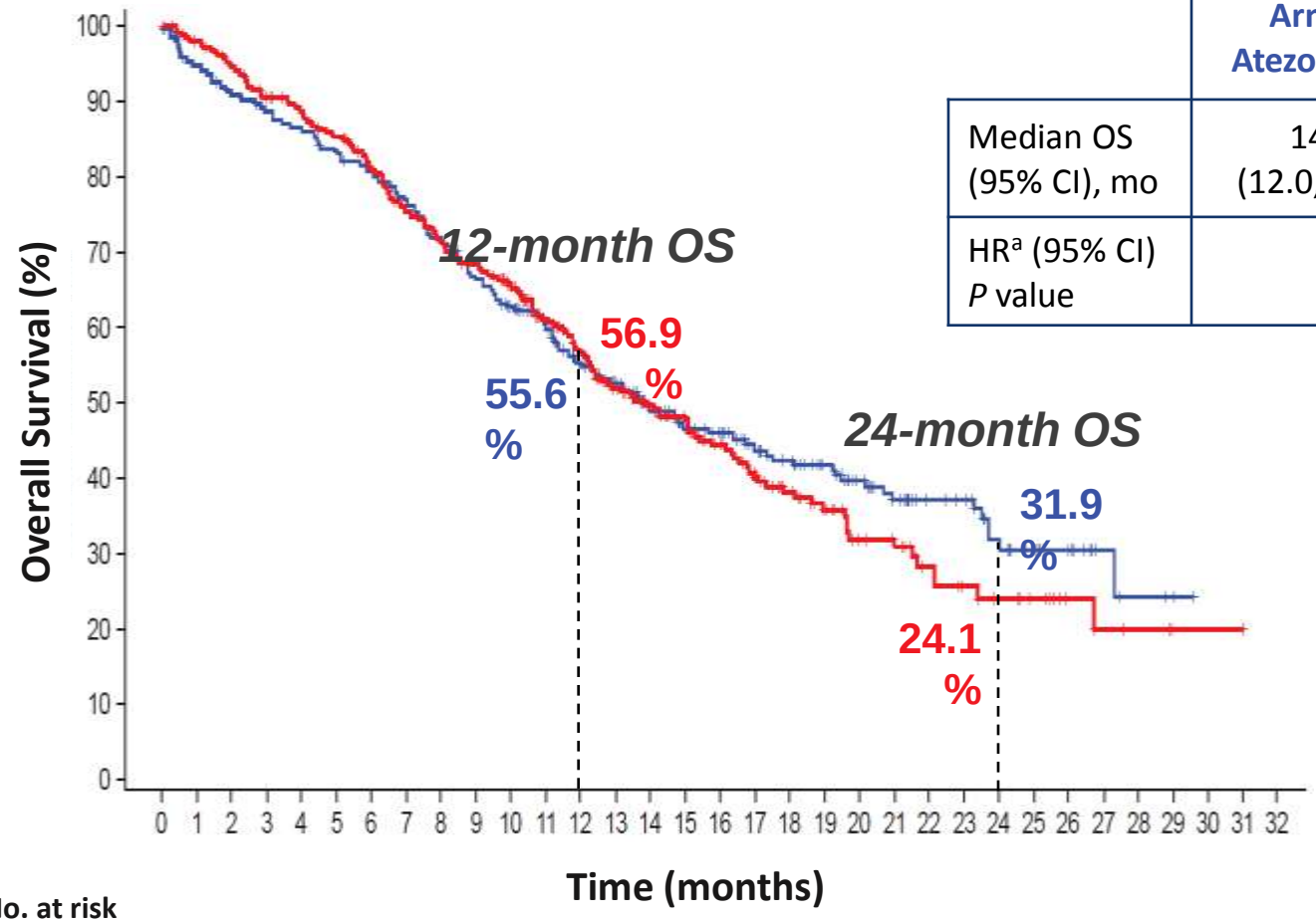
Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

Jotte R, et al. IMpower131 PFS Analysis.

https://bit.ly/2snPEzb

First Interim OS in the ITT Population (Arm B vs Arm C)

	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	



No. at risk

Atezo + CnP	343	319	306	298	290	279	269	256	239	220	203	177	150	137	118	103	95	81	73	63	51	42	34	32	23	16	12	5	3	2
CnP	340	324	311	295	285	271	255	238	224	213	196	167	142	120	103	94	76	66	53	43	32	30	21	17	14	11	6	4	3	2	1	1

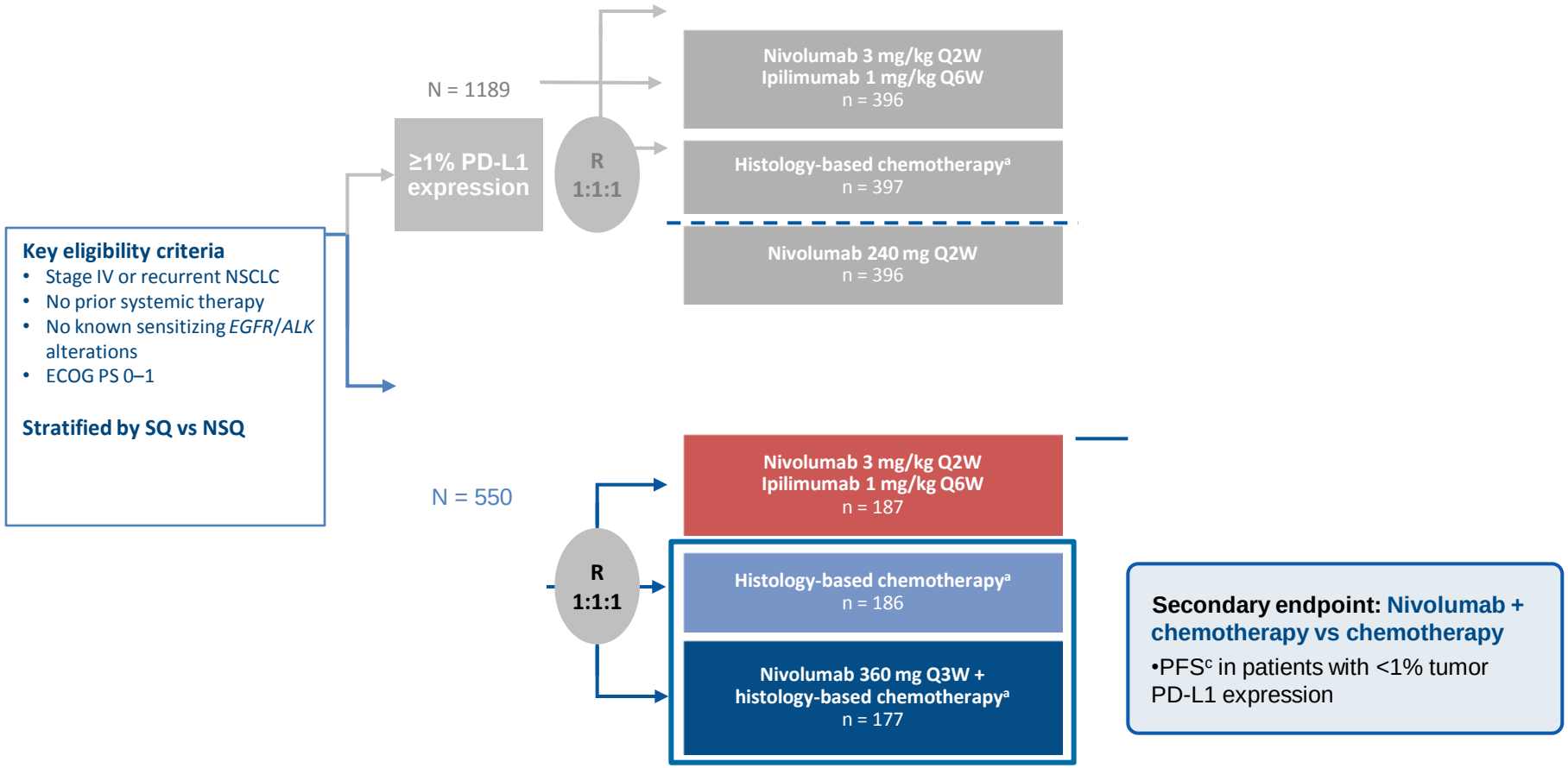
Data cutoff: January 22, 2018.

[a] Stratified HR.

Jotte R, et al. IMpower131 PFS Analysis.

https://bit.ly/2snPEzb

CheckMate 227 Part 1 Study Design



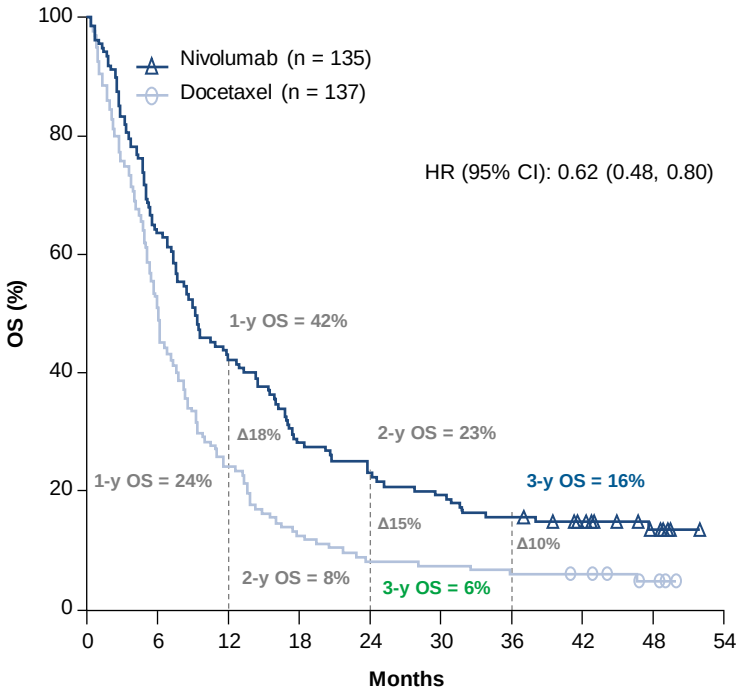
- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

OS (3 years' minimum follow-up)

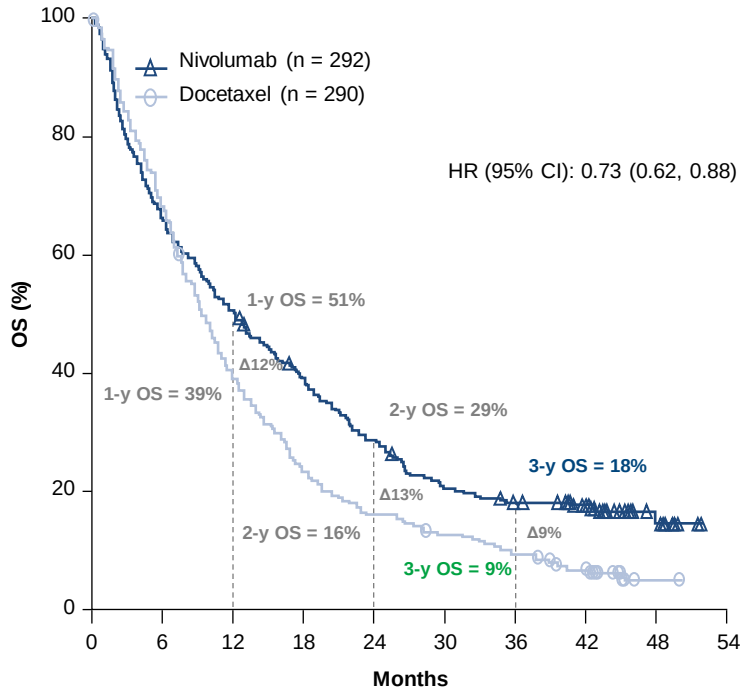
CheckMate 017 (SQ NSCLC)



No. of patients at risk

Nivolumab	135	86	57	38	31	26	21	16	8	0
Docetaxel	137	69	33	17	11	10	8	7	3	0

CheckMate 057 (non-SQ NSCLC)



No. of patients at risk

Nivolumab	292	192	148	114	82	58	49	39	7	0
Docetaxel	290	192	118	67	46	35	26	16	1	0

CI = confidence interval; HR = hazard ratio