GOOD SCIENCE
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ESMO ADVANCED COURSE ON LUNG CANCER IN IMMUNOTHERAPY

Immunotherapy with Immune Checkpoint Inhibitors of Locally Advanced and Metastatic NSCLC in 1st and Later Lines

Maurice Pérol, Léon Bérard Cancer Centre, Lyon, France

Zürich, 3-4 July 2019

DISCLOSURES OF INTEREST

Advisory Boards : Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, AstraZeneca, Takeda

Institutional grants: Roche, AstraZeneca, Chugai, Takeda

Symposiums: Eli Lilly, Roche, AstraZeneca, Pfizer, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Takeda, MSD, Chugai

Immunotherapy with ICIs of Locally Advanced and Metastatic NSCLC in 1st and Later Lines

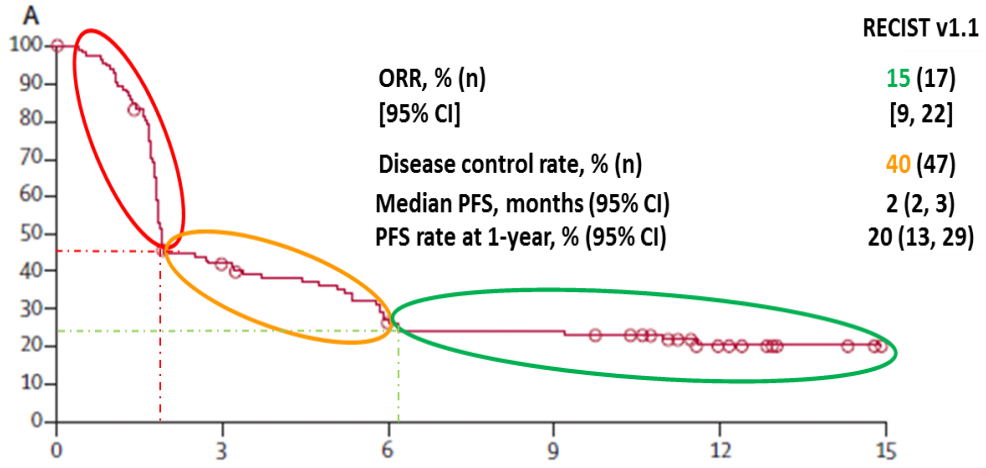
Outline

1. Immunotherapy in 2nd line treatment of NSCLC and the role of PD-L1
2. Development of immunotherapy in first line treatment of NSCLC
3. A new treatment algorithm
4. ICIs in locally advanced NSCLC: a new standard of care

Development of immunotherapy in 2nd line treatment of NSCLC

Nivolumab Early Trials
PFS and Long Term Survival in NSCLC

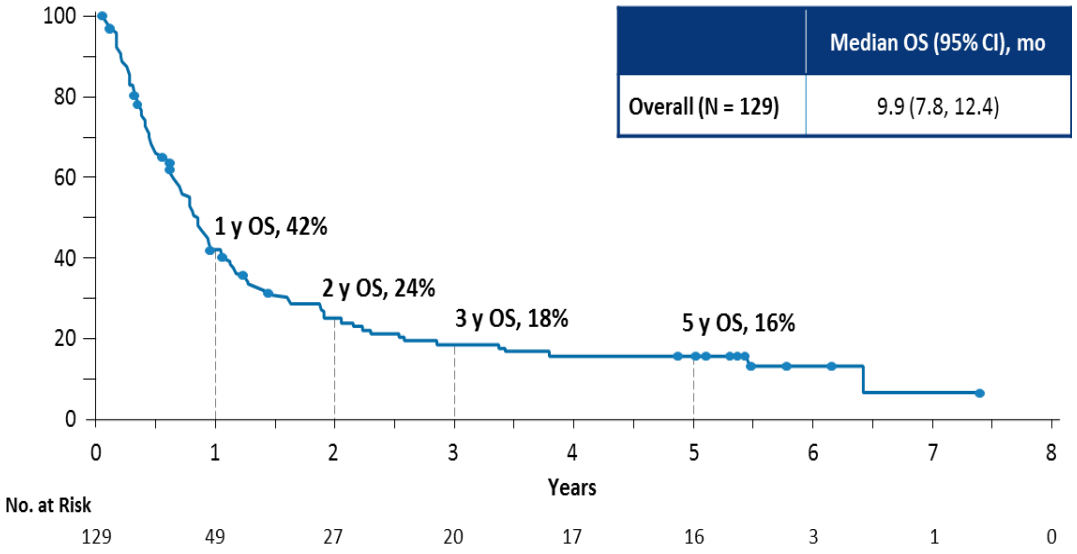
Progression-free survival (%)



Checkmate 063: Nivolumab as ≥ 3rd Line in Advanced Squamous Cell Carcinoma

Rizvi, Lancet Oncol 2015

OS (%)



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

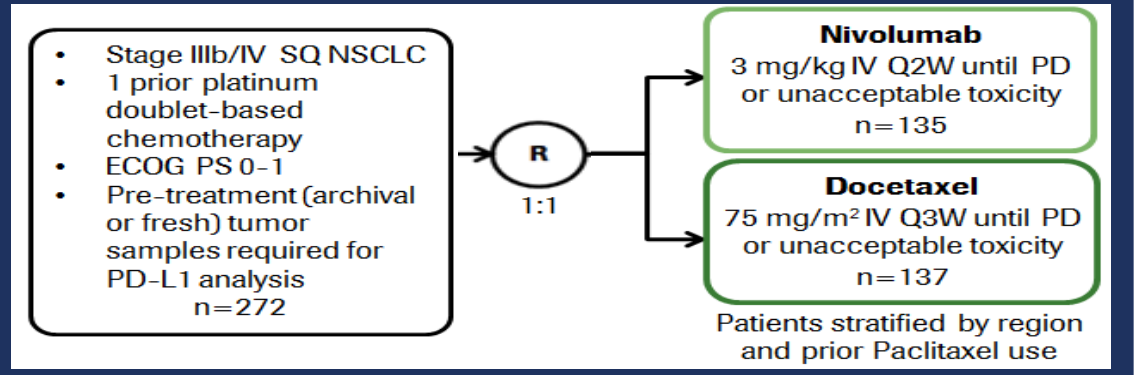
5-Year Estimates of OS CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

Brahmer, AACR 2017

Phase III Studies comparing anti-PD-1/PD-L1 with Docetaxel in 2nd – 3rd Line

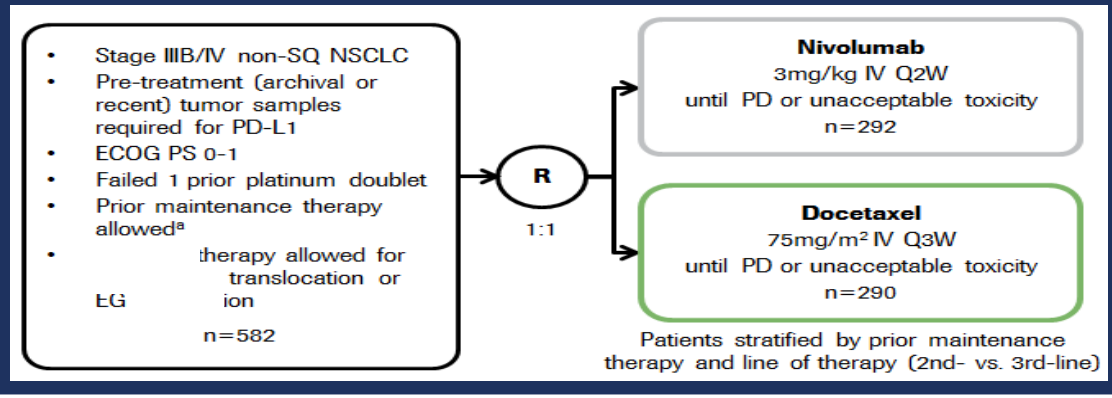
Nivolumab – CheckMate 017 (PIII)

2nd Line, squamous, PD-L1 All-Comer



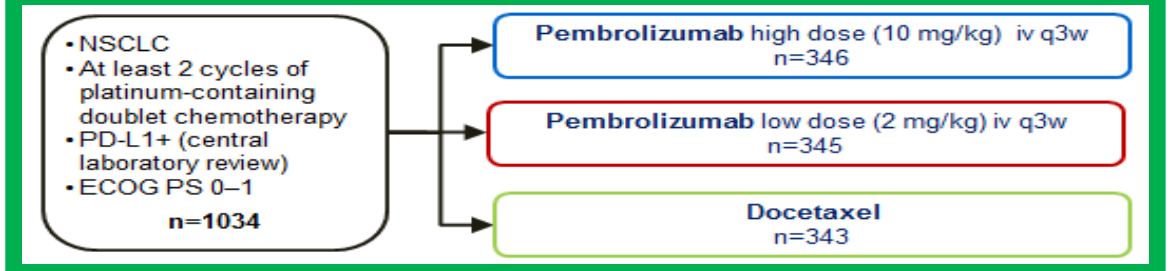
Nivolumab – CheckMate 057 (PIII)

2nd Line, non-squamous, PD-L1 All-Comer



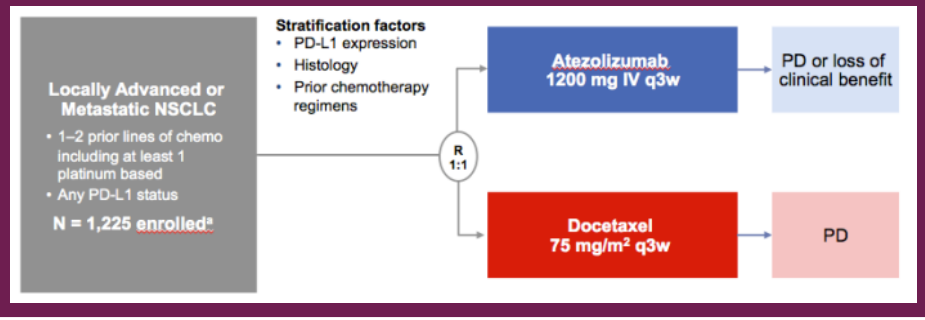
Pembrolizumab - Keynote 010 (PII/III)

2nd+ Line, PD-L1 TPS ≥1%



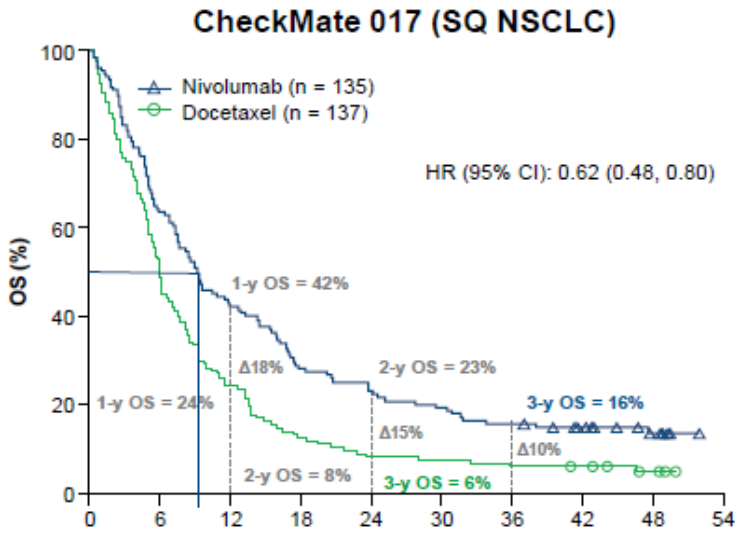
Atezolizumab – OAK (PIII)

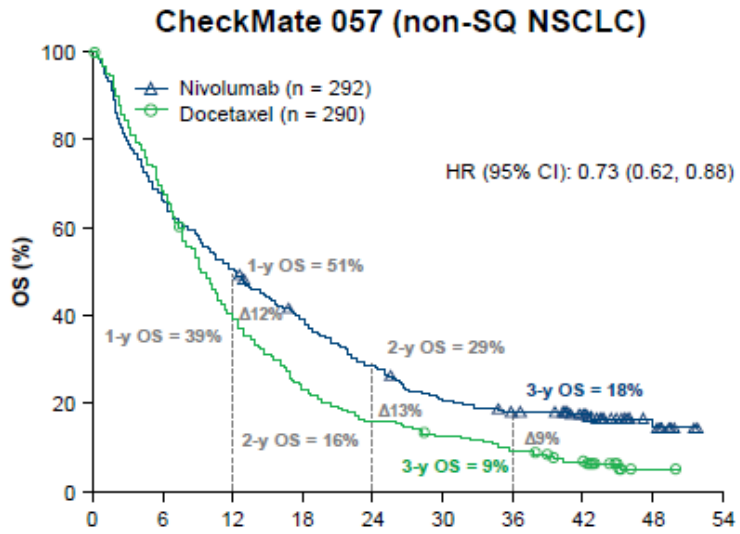
2nd+ Line, PD-L1 All-Comer

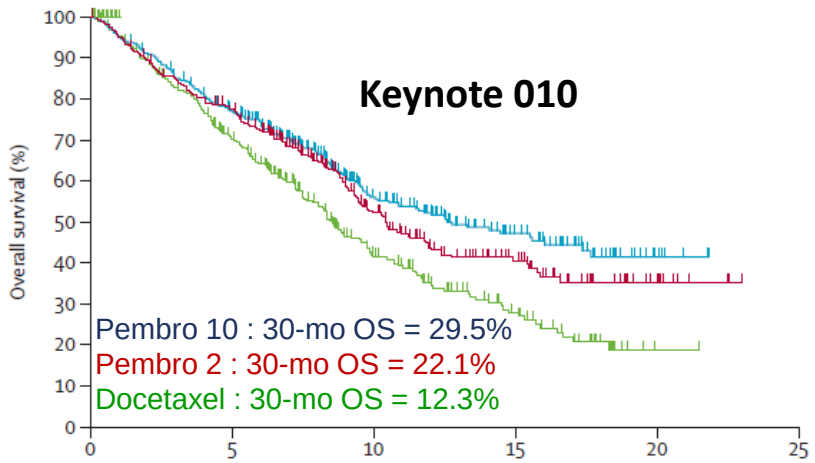


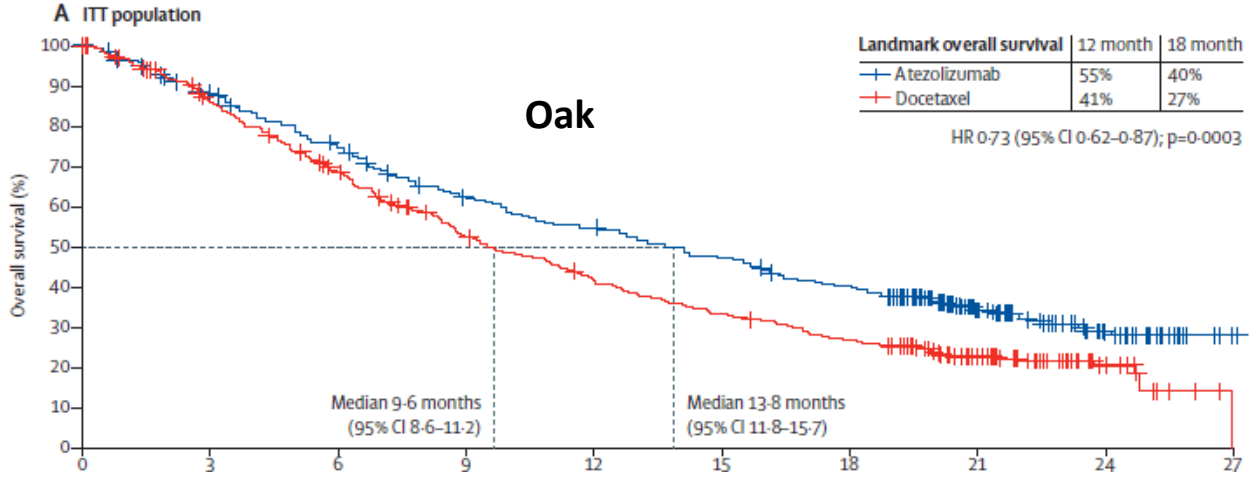
Borghaei NEJM 2015; Brahmer, NEJM 2015; Herbst, Lancet 2015; Rittmeyer, Lancet 2016; courtesy of M. Reck, WCLC 2017

Phase III Studies comparing anti-PD-1/PD-L with Docetaxel in 2nd – 3rd Line



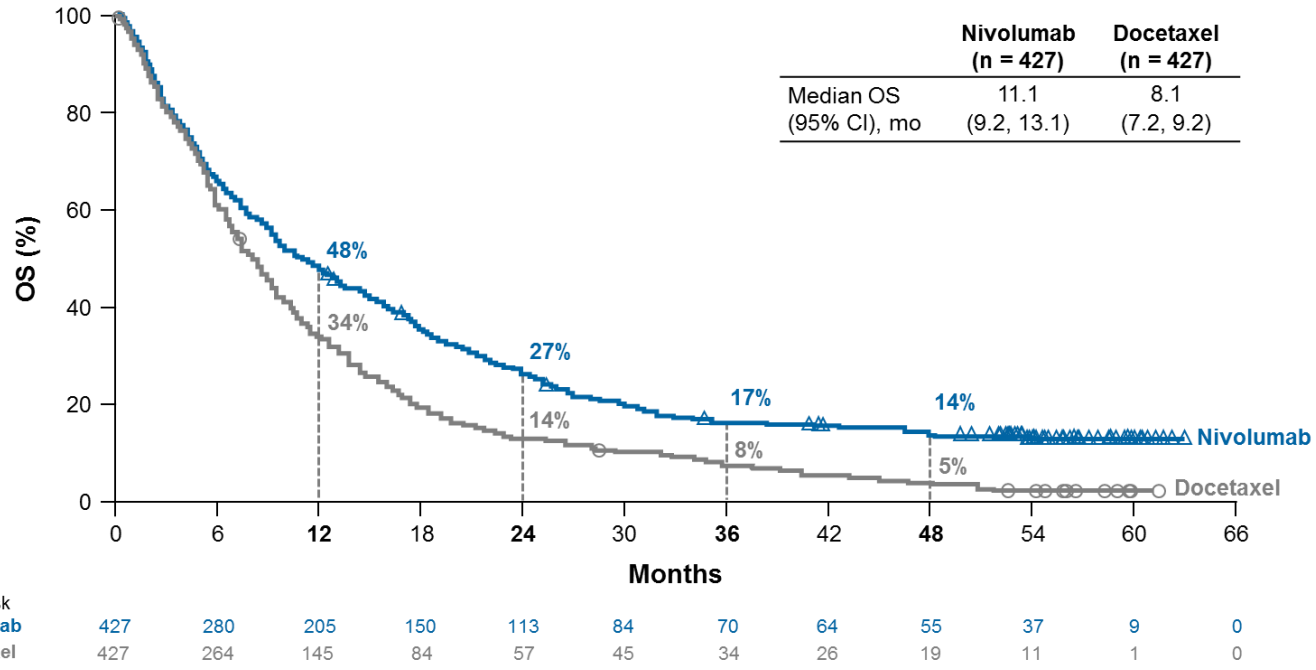






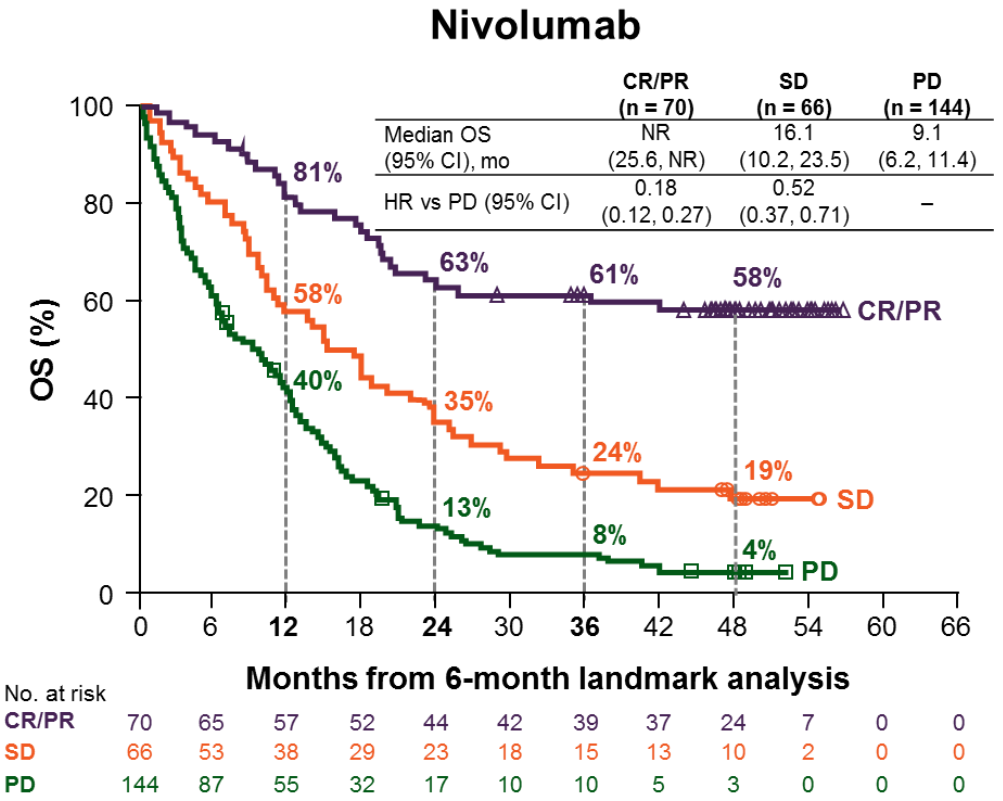
Borghaei NEJM 2015; Brahmer, NEJM 2015; Herbst, Lancet 2015; Rittmeyer, Lancet 2016

Long term survival in CheckMate 017 + 057 and landmark analysis of OS by response at 6 months



	Nivolumab (n = 427)	Docetaxel (n = 427)
Median OS (95% CI), mo	11.1 (9.2, 13.1)	8.1 (7.2, 9.2)

No. at risk												
Nivolumab	427	280	205	150	113	84	70	64	55	37	9	0
Docetaxel	427	264	145	84	57	45	34	26	19	11	1	0

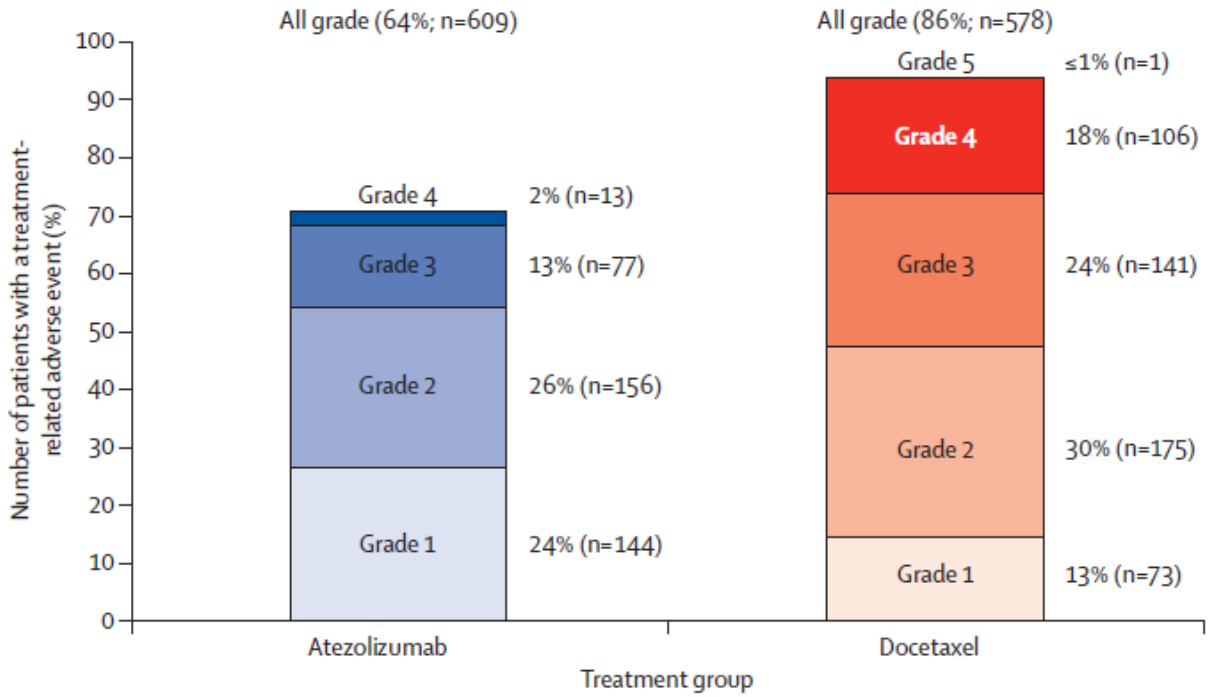


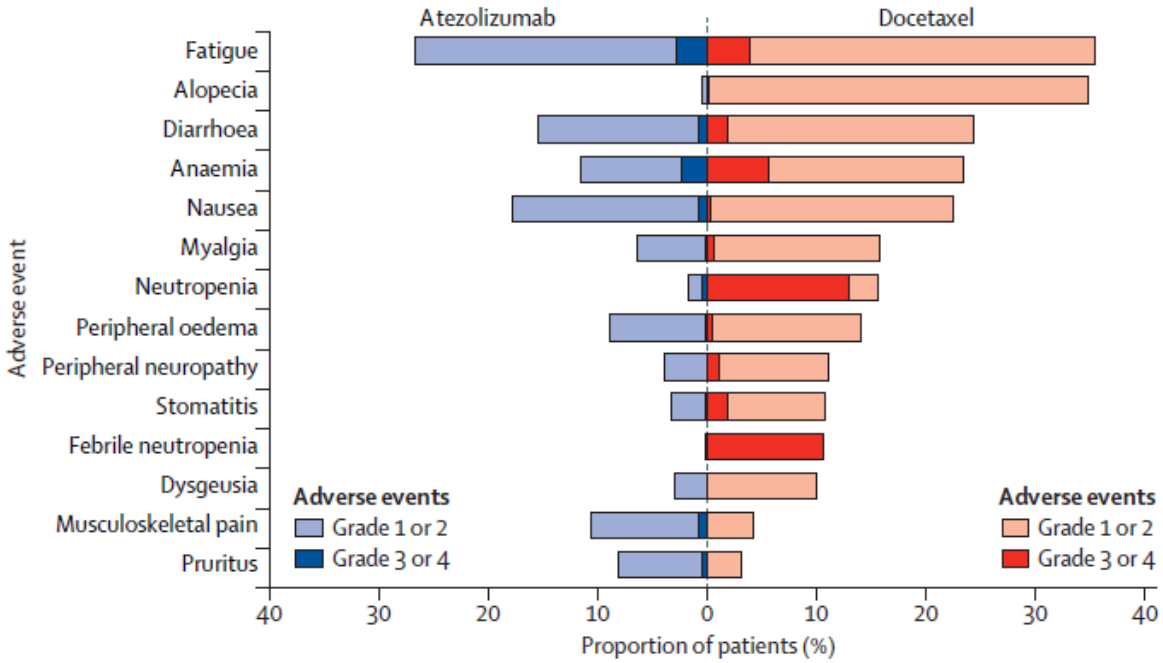
	CR/PR (n = 70)	SD (n = 66)	PD (n = 144)
Median OS (95% CI), mo	NR (25.6, NR)	16.1 (10.2, 23.5)	9.1 (6.2, 11.4)
HR vs PD (95% CI)	0.18 (0.12, 0.27)	0.52 (0.37, 0.71)	–

No. at risk												
CR/PR	70	65	57	52	44	42	39	37	24	7	0	0
SD	66	53	38	29	23	18	15	13	10	2	0	0
PD	144	87	55	32	17	10	10	5	3	0	0	0

Brahmer, AACR 2019

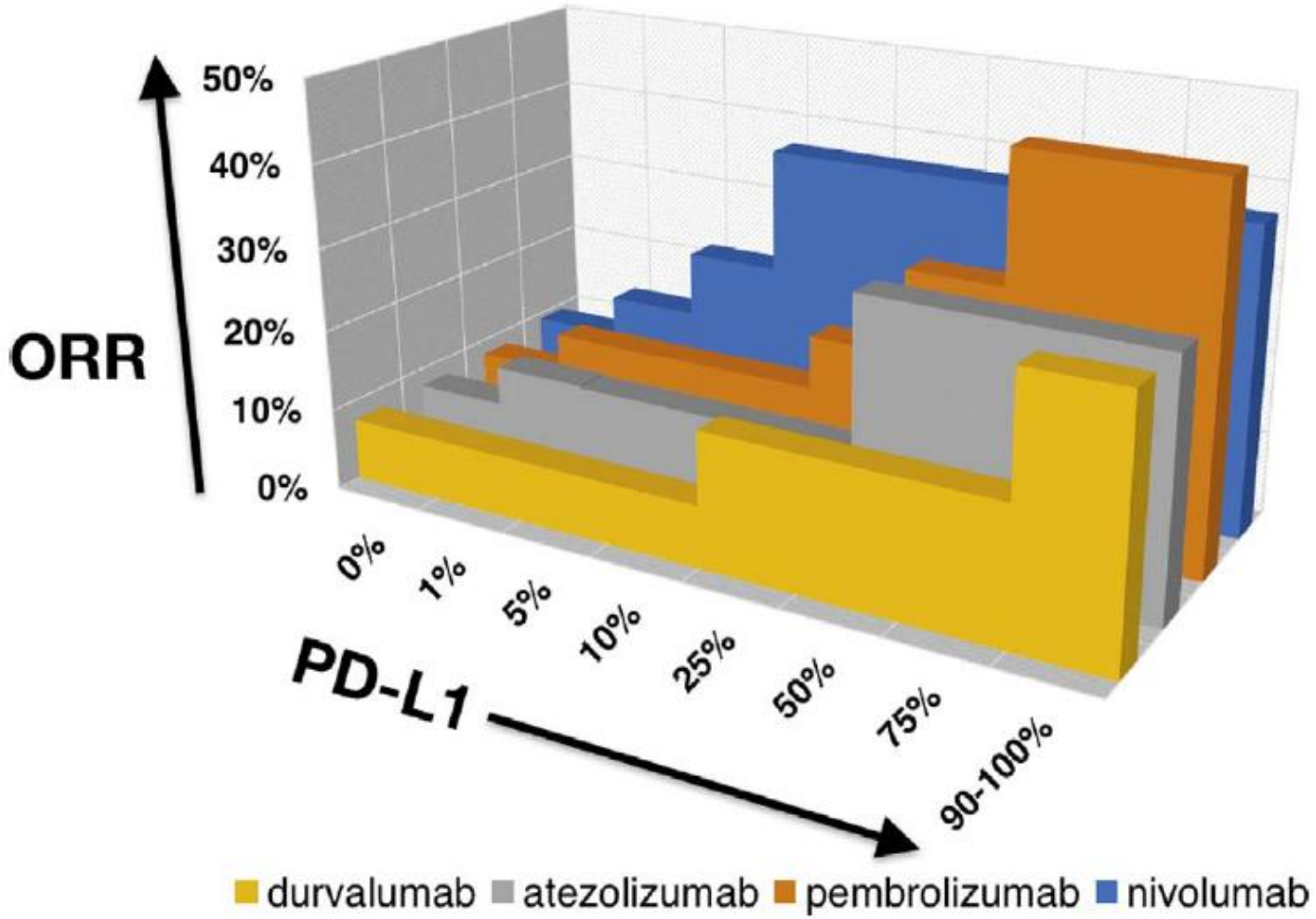
OAK: Tolerance Profile





Rittmeyer, Lancet 2016

PD-L1 Expression Level is Correlated to ORR

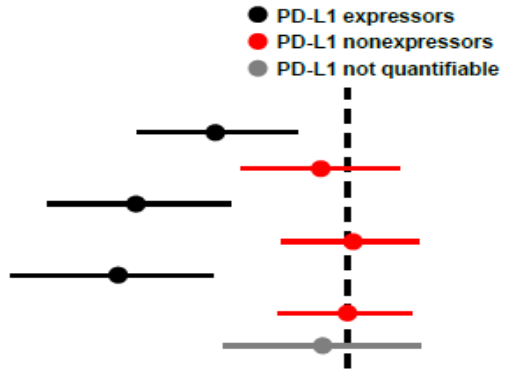


Vermaelen et al.; Sem Cancer Biol 2018

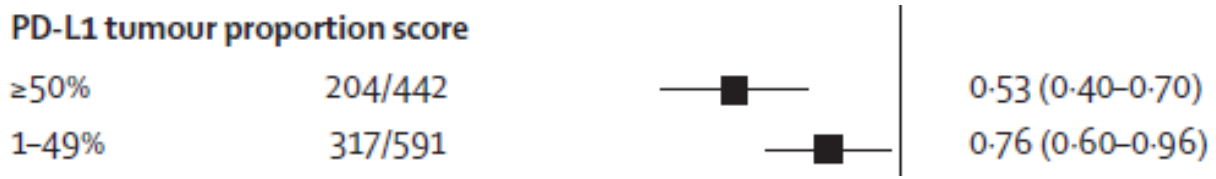
Impact of PD-L1 Expression Level on OS in Phase III Trials

Checkmate 057
Non-Squamous
Dako 28-8

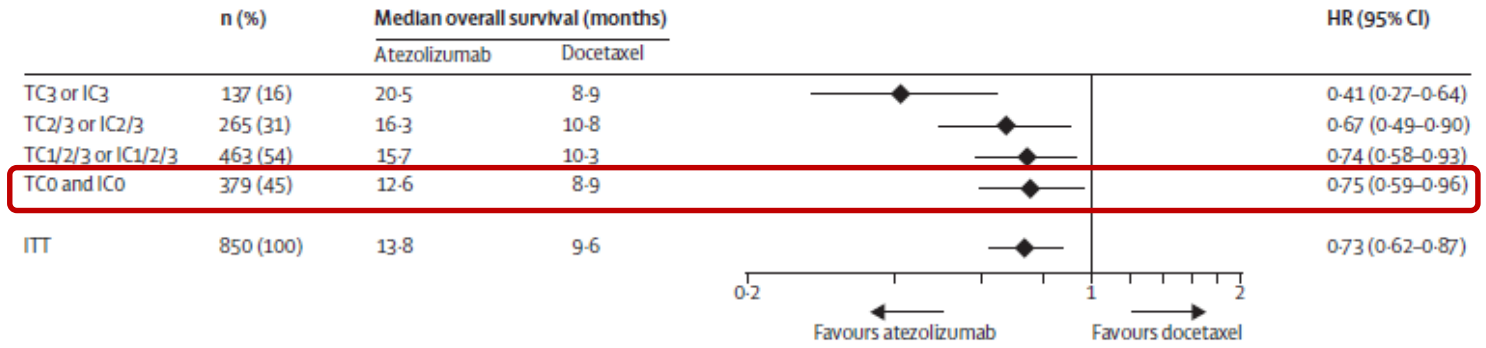
PD-L1 expression level	Nivo n	Doc n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable	61	66	0.91 (0.61, 1.35)	



Keynote-010
All histologies;
PD-L1 TPS ≥1%
Dako 22C3

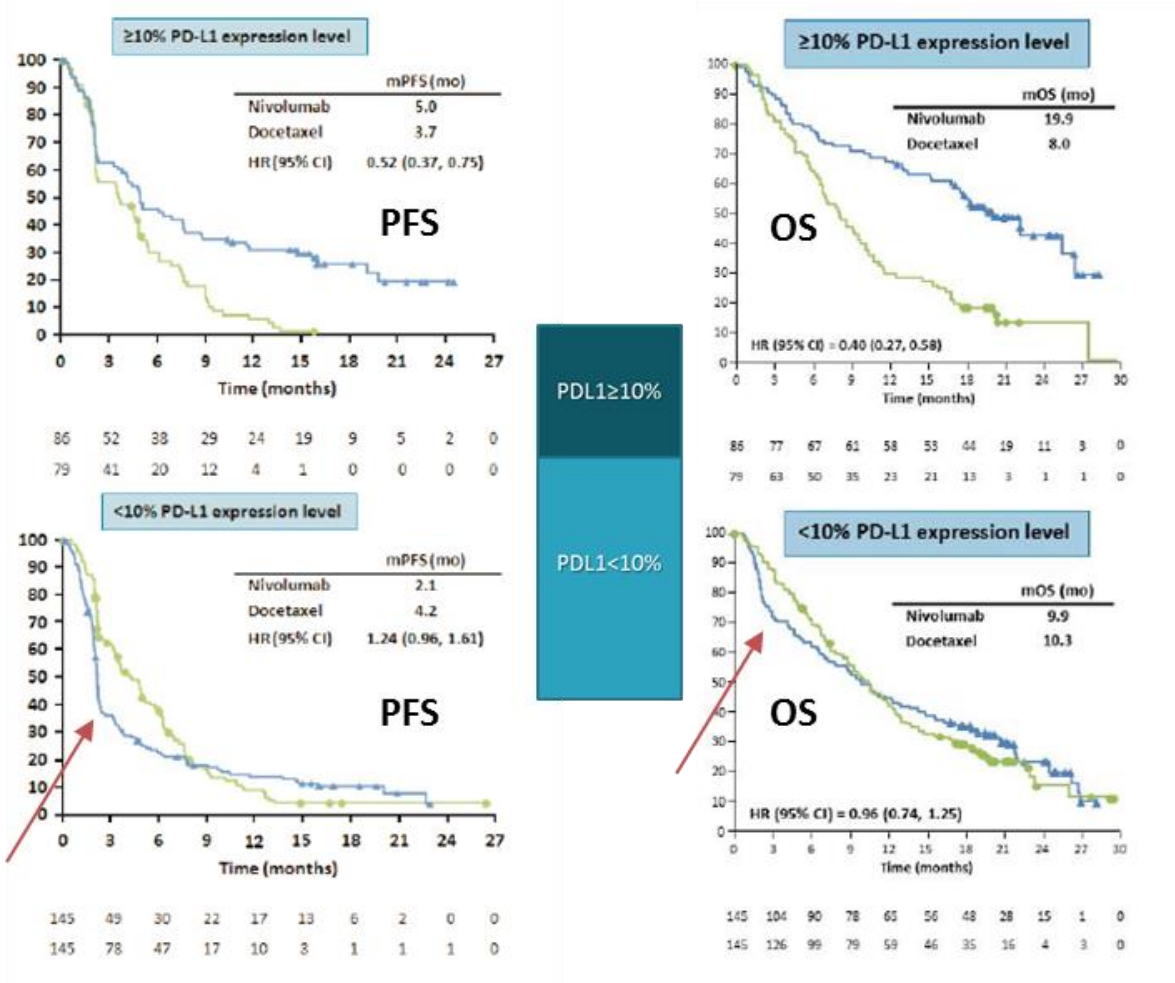


OAK
All comers
Ventana SP142



Can We Negatively Select Patients on PD-L1<1%?

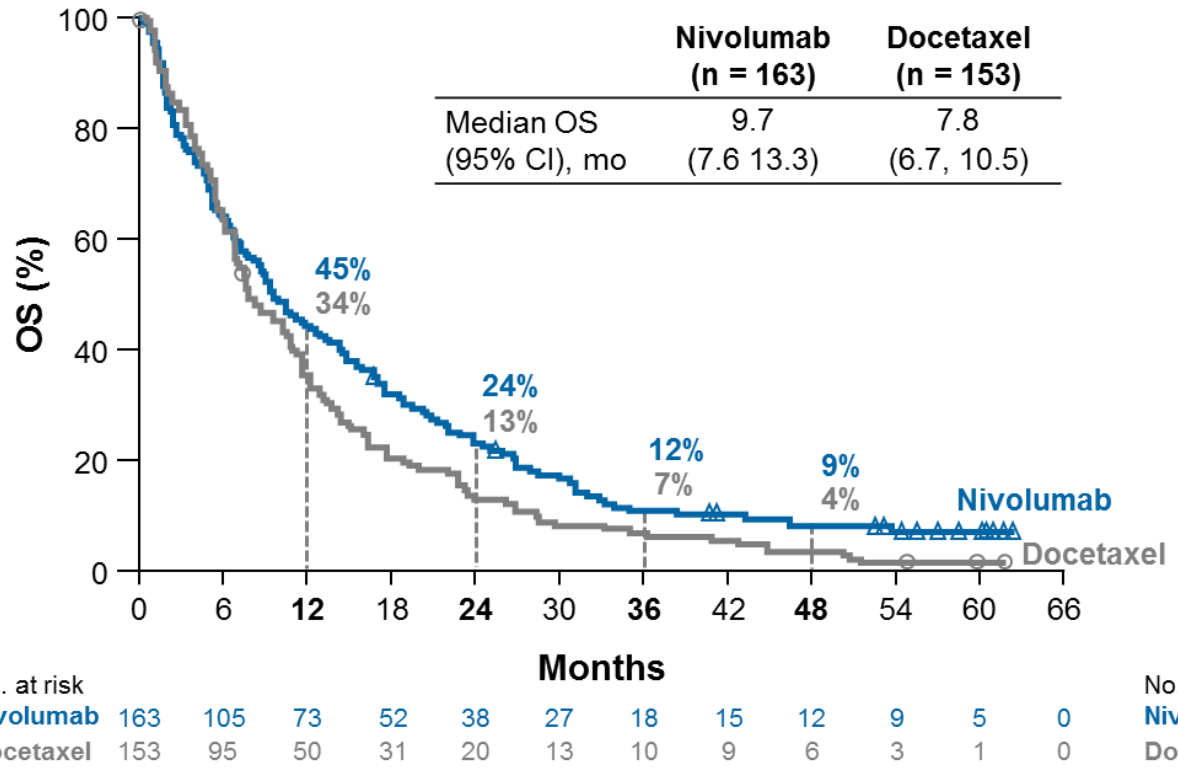
Drug	Histology	Testing	Cut-off PD-L1 -	% PD-L1-	ORR
Nivolumab (Checkmate 017)	Squamous	Dako 28.8	<1%	**40%**	**17%**
Nivolumab (Checkmate 057)	Non-squamous	Dako 28.8	<1%	**46%**	**9%**
Atezolizumab (Poplar)	All histologies	Ventana SP142	TC0 + IC0	**32%**	**7.8%**
Atezolizumab (Oak)	All histologies	Ventana SP142	TC0 + IC0	**45%**	**8%**
Durvalumab (phase I-II)	All histologies	Ventana SP263	<25%	**45%**	**6.1%**
Pembrolizumab (phase I)	All histologies	Dako 22C3	<1%	**39%**	**8.1%**
Avelumab (phase Ib)	All histologies	Dako 73.10	<1%	**14%**	**10%**



Brahmer, NEJM 2015; Borghaei, NEJM2015;373:1627-39; Fehrenbacher; Lancet 2016; Garon, NEJM 2015; Rebelatto, ASCO 2015; Herbst, Lancet 2015; Antonia, ESMO 2016; Gulley, ASCO 2015

Long term survival in CheckMate 017 + 057 by PD-L1 expression level

PD-L1 expression < 1%

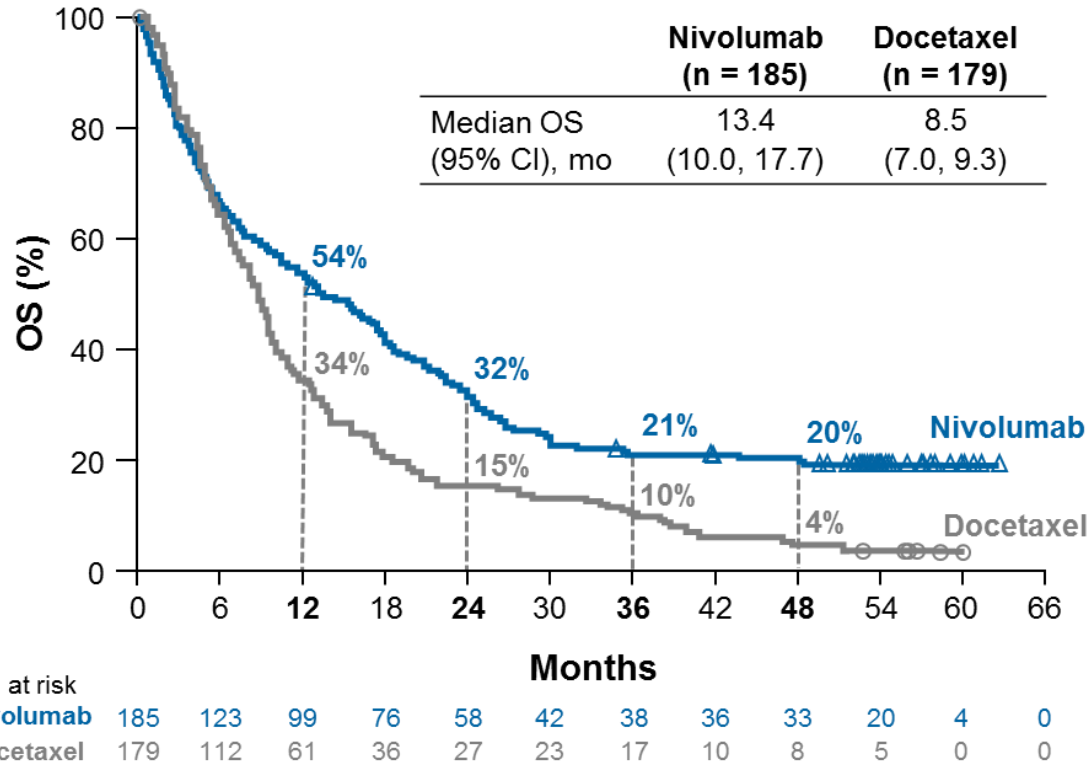


	Nivolumab (n = 163)	Docetaxel (n = 153)
Median OS (95% CI), mo	9.7 (7.6 13.3)	7.8 (6.7, 10.5)

No. at risk

Nivolumab	163	105	73	52	38	27	18	15	12	9	5	0
Docetaxel	153	95	50	31	20	13	10	9	6	3	1	0

PD-L1 expression ≥ 1%



	Nivolumab (n = 185)	Docetaxel (n = 179)
Median OS (95% CI), mo	13.4 (10.0, 17.7)	8.5 (7.0, 9.3)

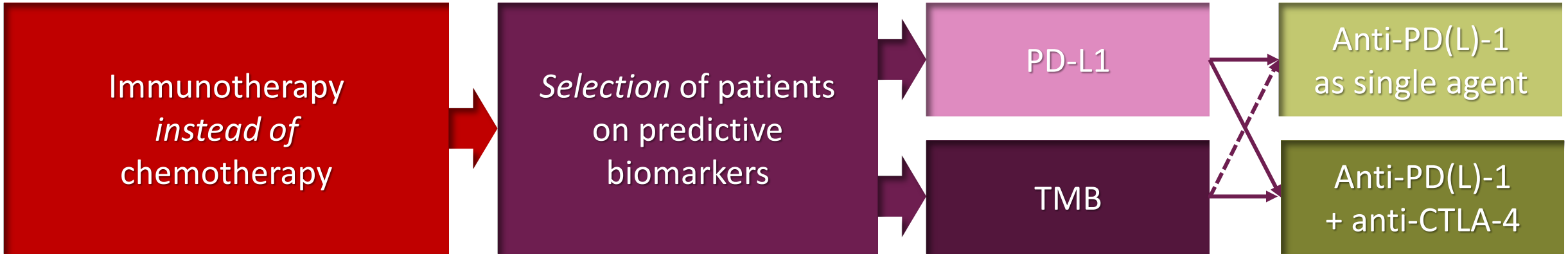
No. at risk

Nivolumab	185	123	99	76	58	42	38	36	33	20	4	0
Docetaxel	179	112	61	36	27	23	17	10	8	5	0	0

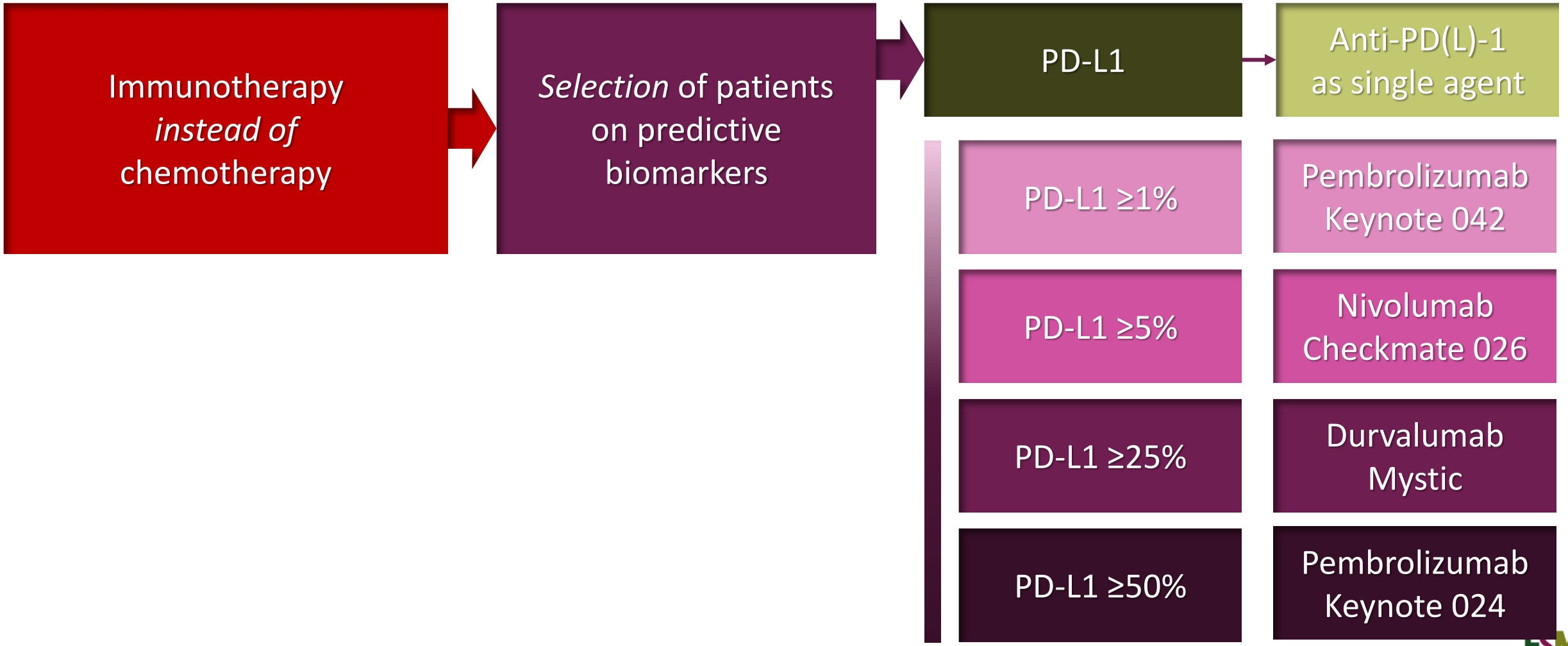
Brahmer, AACR 2019

Development of immunotherapy in first line treatment of NSCLC

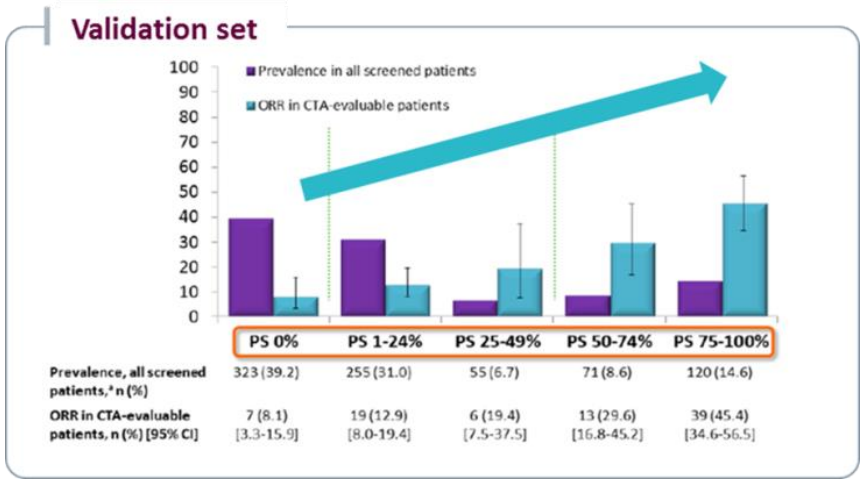
First strategy of ICIs development in 1st line treatment of advanced NSCLC



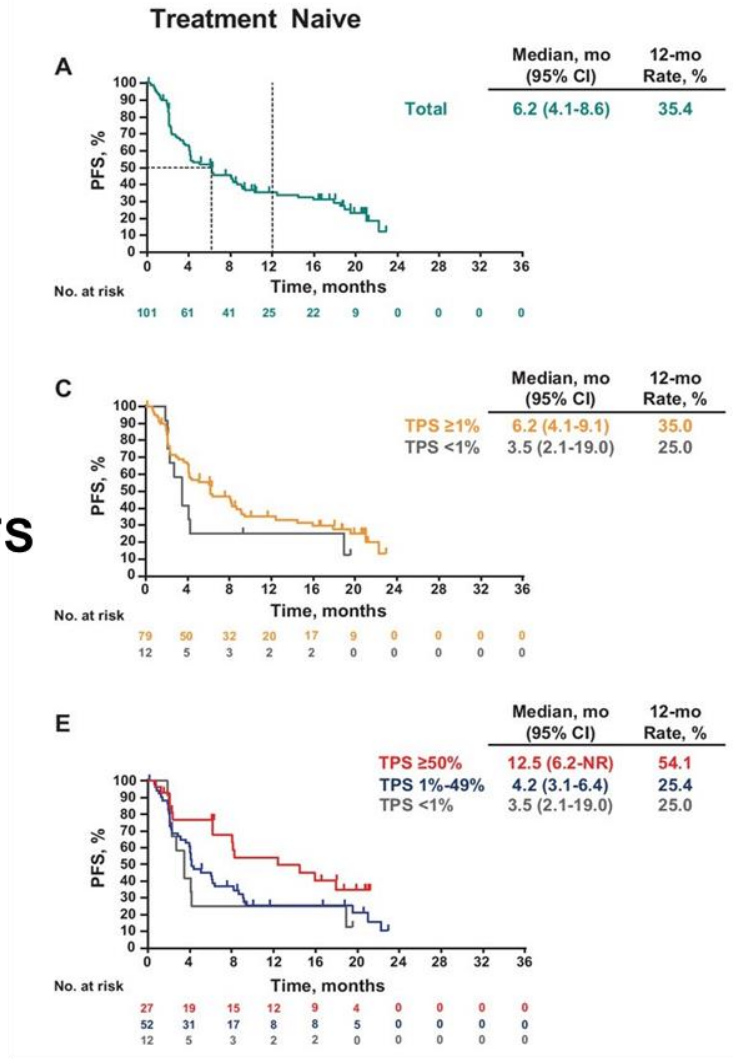
Strategy for using ICIs in 1st line
To replace cytotoxic chemotherapy



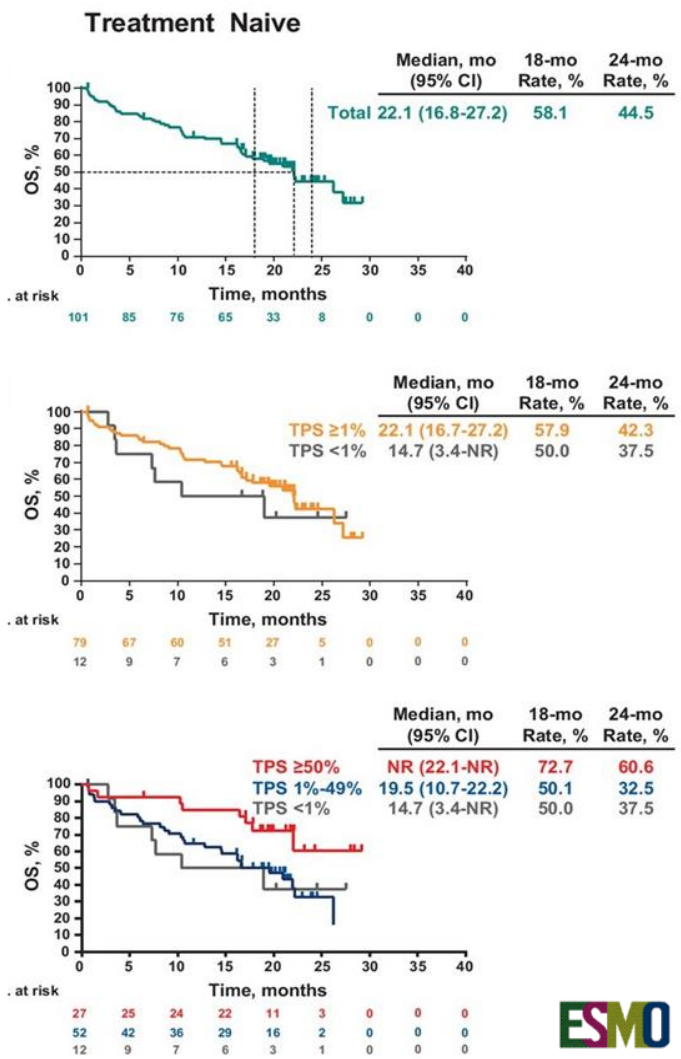
Keynote 001
Selection of a cutoff of PD-L1 expression for 1st line



PFS

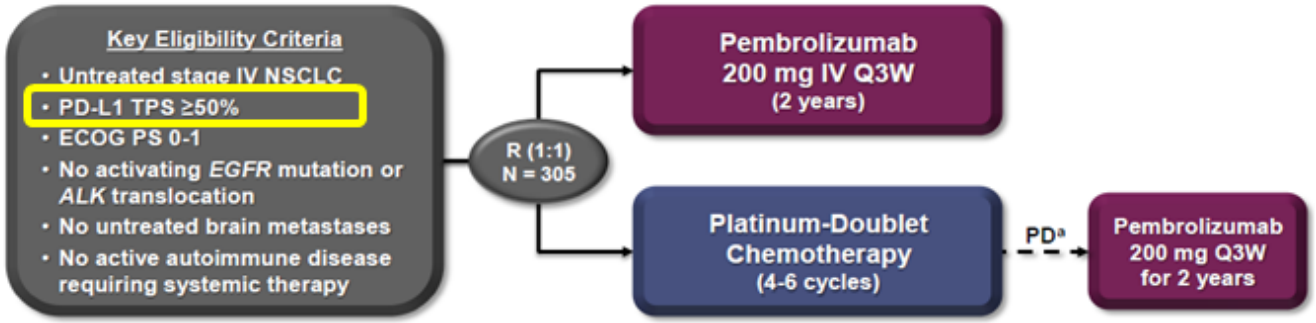


OS



Garon, NEJM 2015; Hui, ASCO 2016

Pembrolizumab in 1st line for PD-L1 ≥50% NSCLC Keynote 024



Key End Points

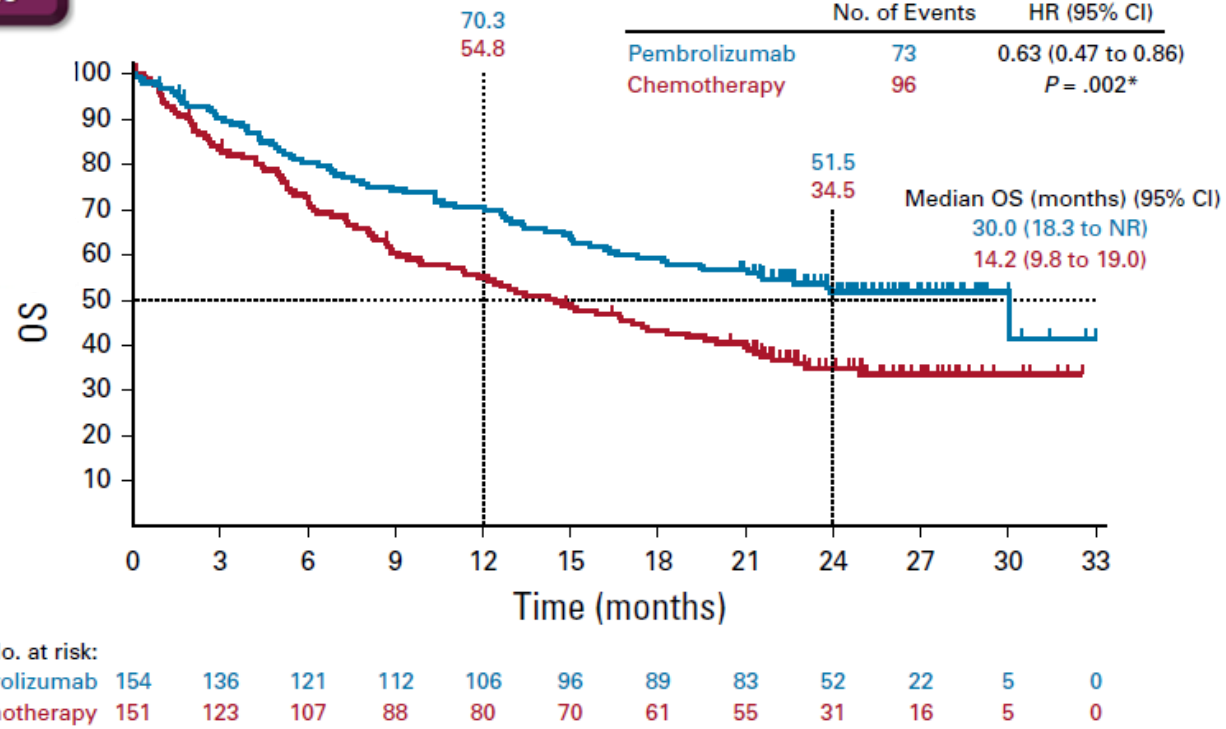
Primary: PFS (RECIST v1.1 per blinded, independent central review)

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.

Crossover rate: 64.2% (ITT)

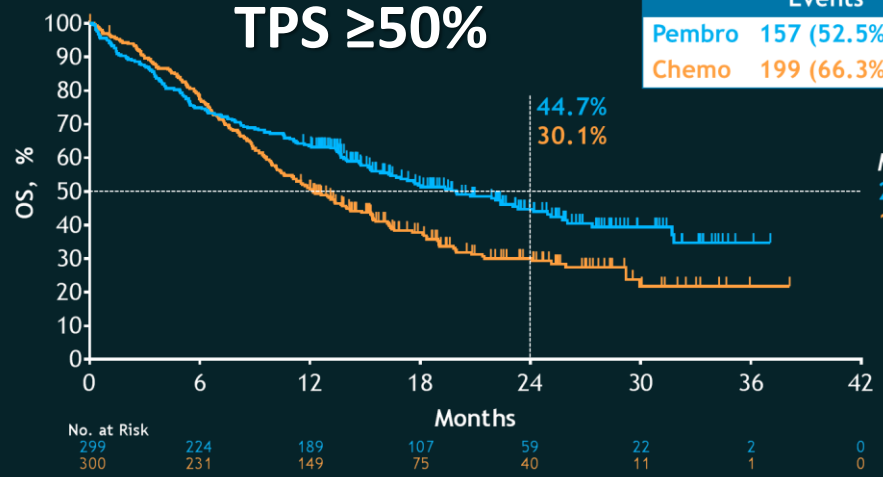


Reck, NEJM 2016; Reck, JCO 2019

Keynote 042: pembrolizumab *vs.* chemotherapy in PD-L1 ≥1% advanced NSCLC: overall survival

TPS ≥50%

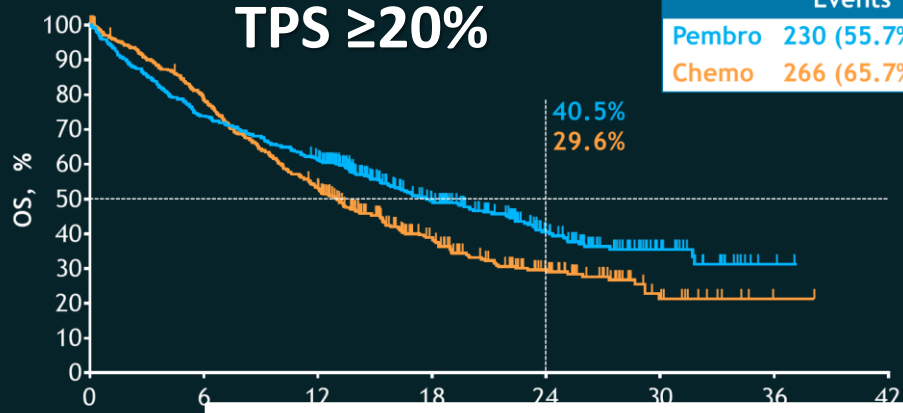
	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		



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

TPS ≥20%

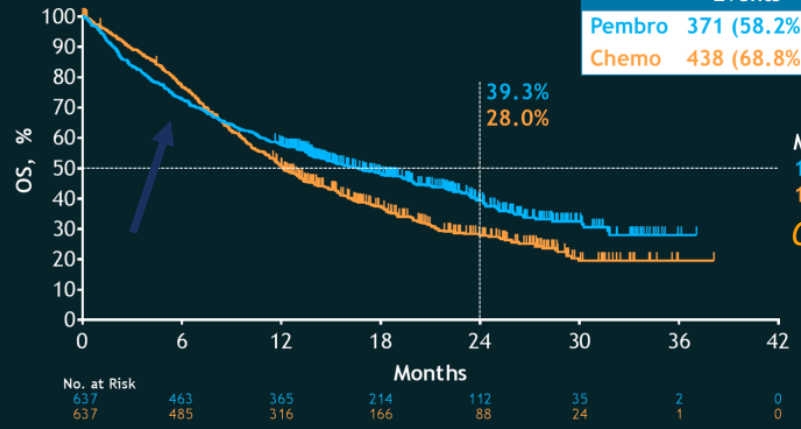
	Events	HR (95% CI)	P
Pembro	230 (55.7%)	0.77 (0.64-0.92)	0.0020
Chemo	266 (65.7%)		



Median (95% CI)
17.7 mo (15.3-22.1)
13.0 mo (11.6-15.3)

TPS ≥1%

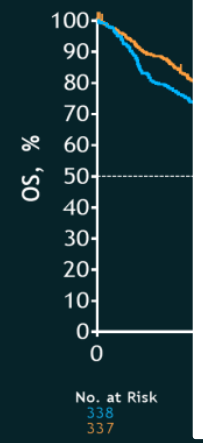
	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		



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

Crossover to immunotherap

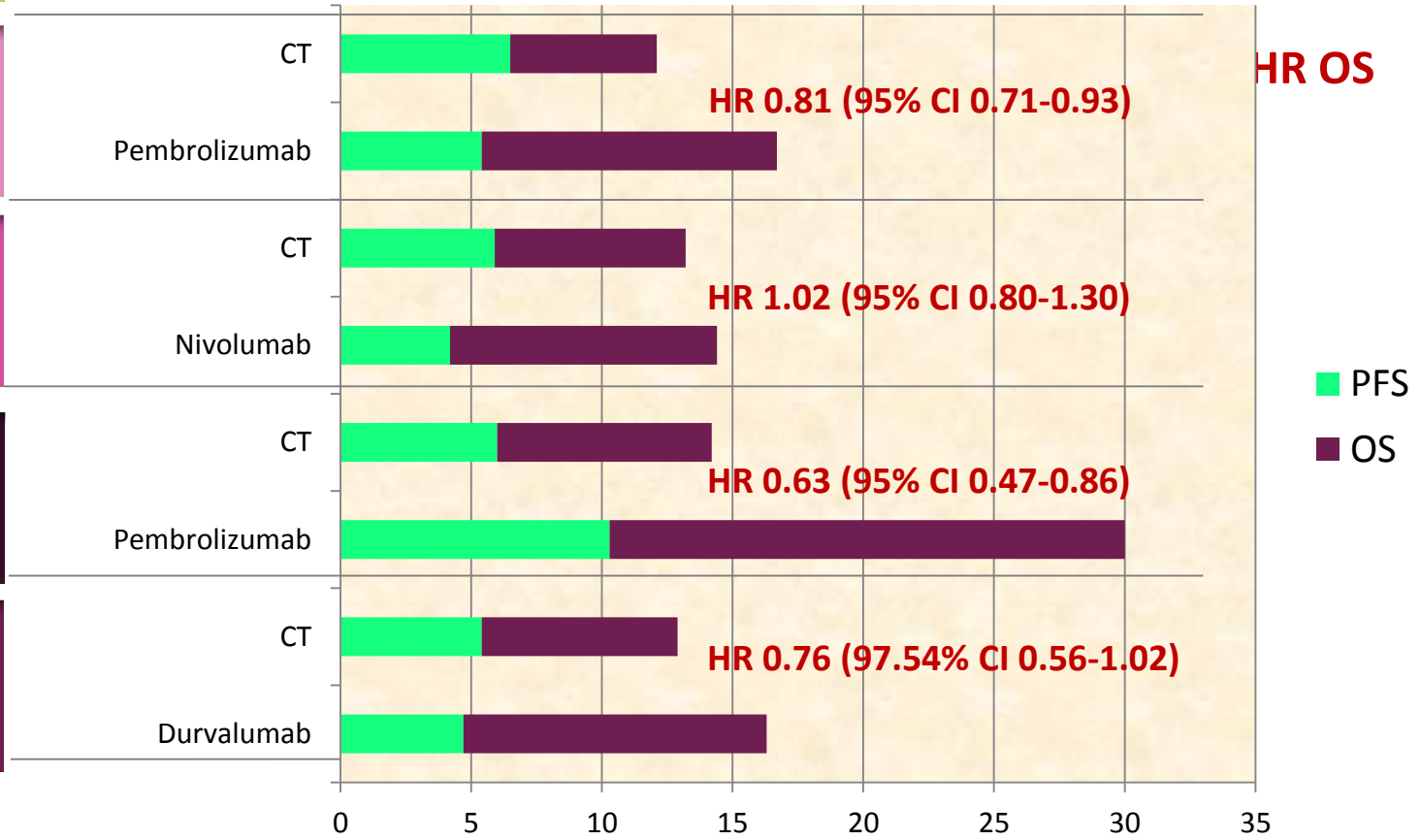
Overall



Lopes, ASCO 2018; Mok, Lancet 2019

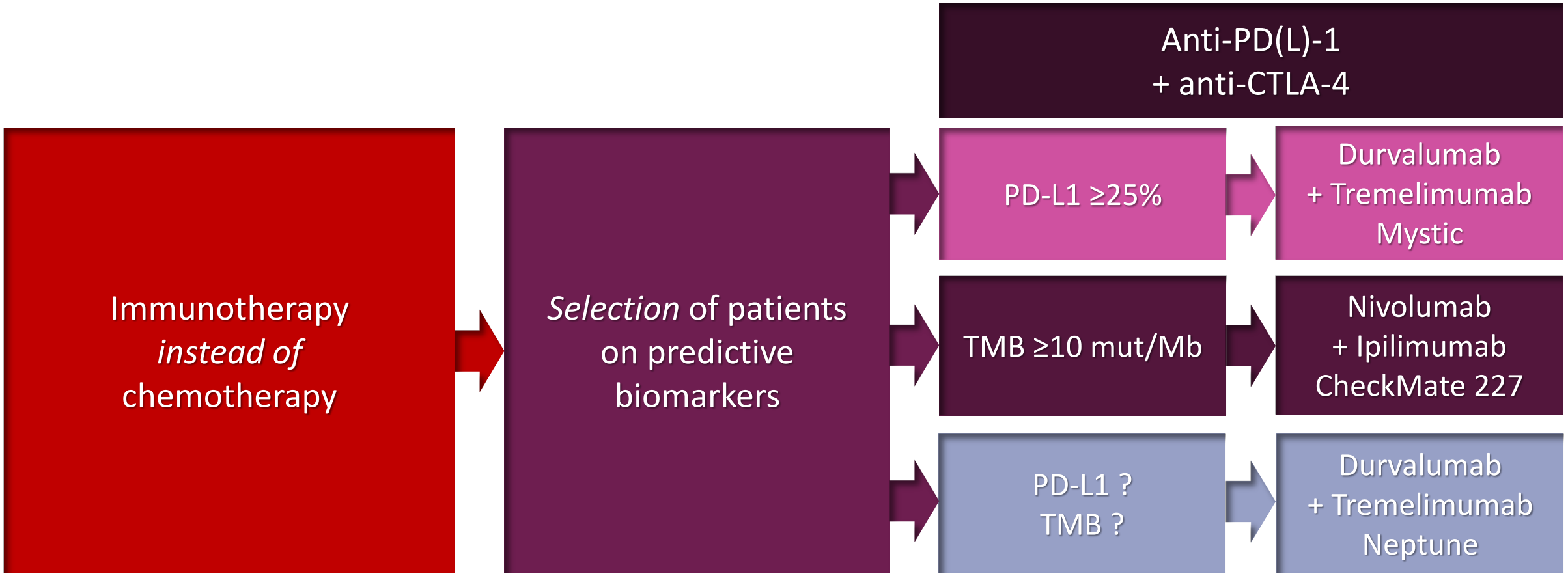
Anti-PD(L)-1 as single agent in 1st line PD-L1 level of expression does matter

PD-L1	Anti-PD(L)-1 monotherapy
PD-L1 ≥1%	Pembrolizumab Keynote 042
PD-L1 ≥5%	Nivolumab Checkmate 026
PD-L1 ≥50%	Pembrolizumab Keynote 024
PD-L1 ≥25%	Durvalumab Mystic

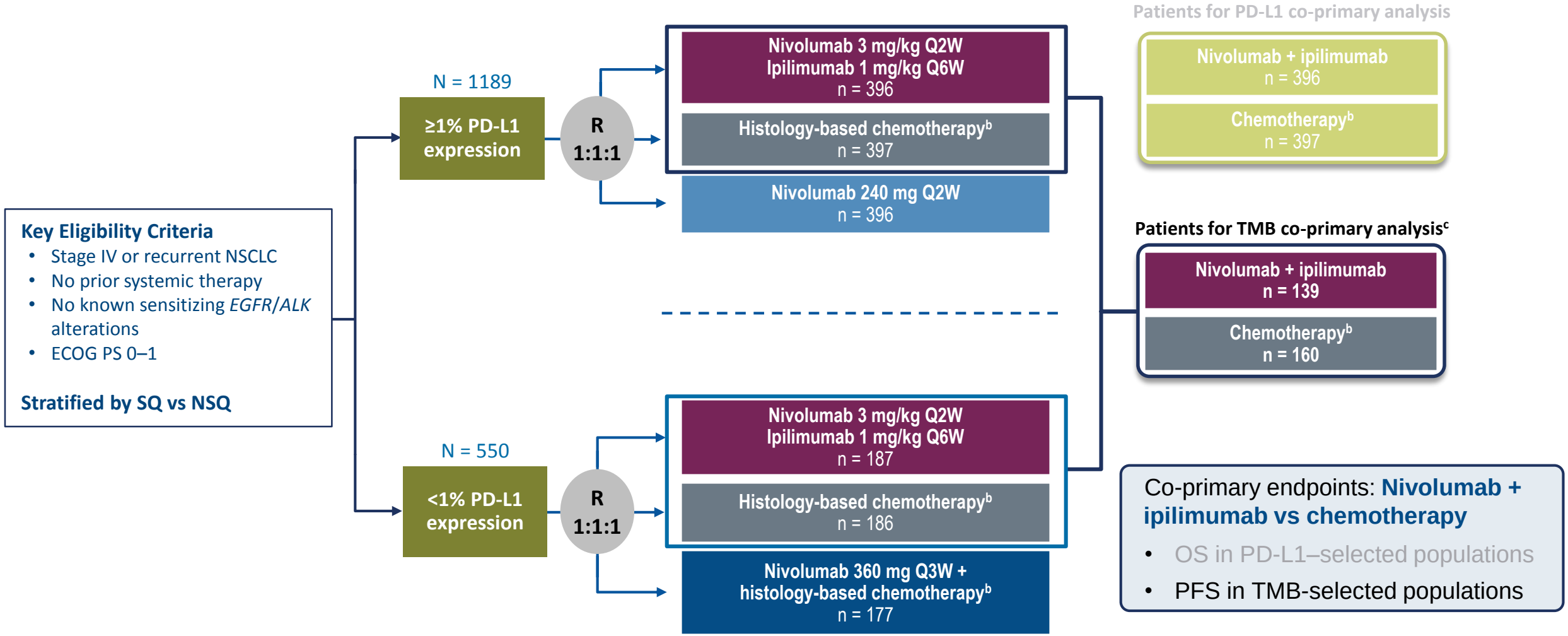


Lopes, ASCO 2018; Mok, Lancet 2019; Carbone, NEJM 2017; Reck, JCO 2019; Rizvi, ESMO-IO 2018

Strategy for using ICIs in 1st line
To replace cytotoxic chemotherapy

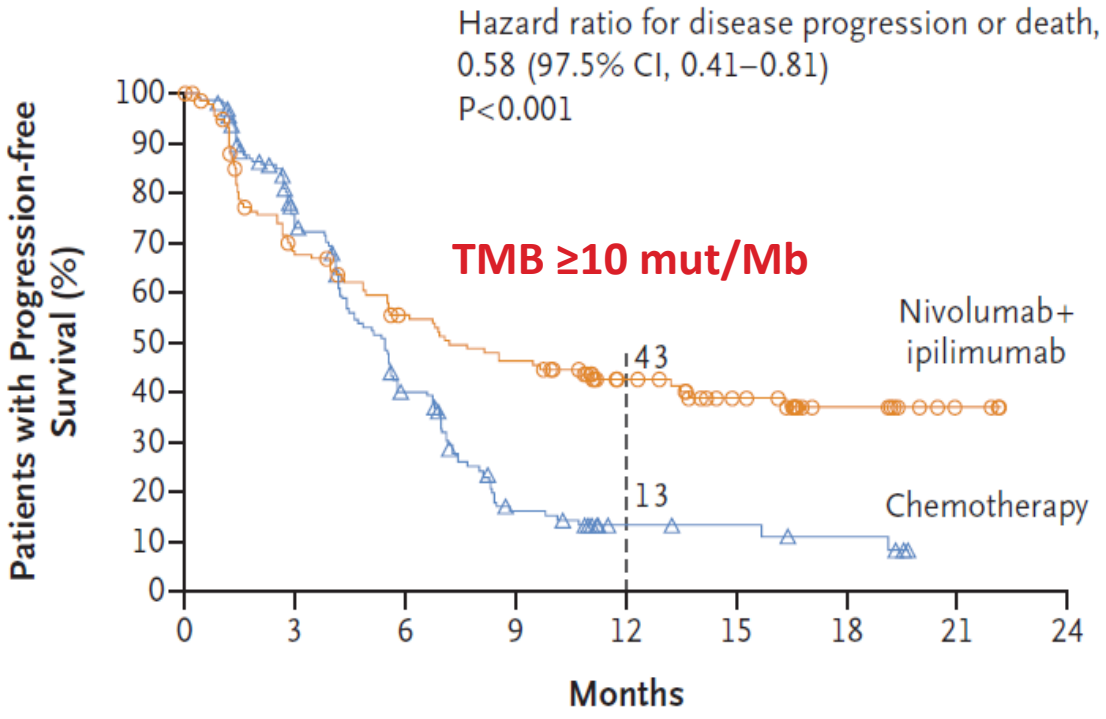


CheckMate 227 Part 1 Study Design

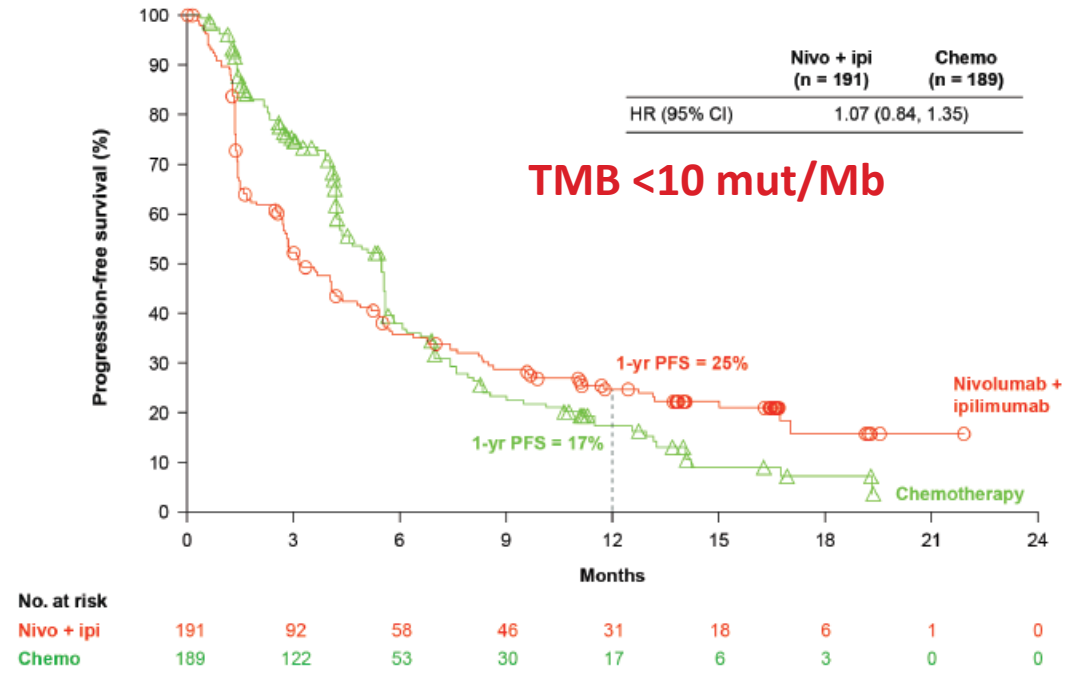


Hellmann, NEJM 2018

CheckMate 227 : nivolumab + ipilimumab *vs.* chemotherapy in 1st line: PFS according to TMB



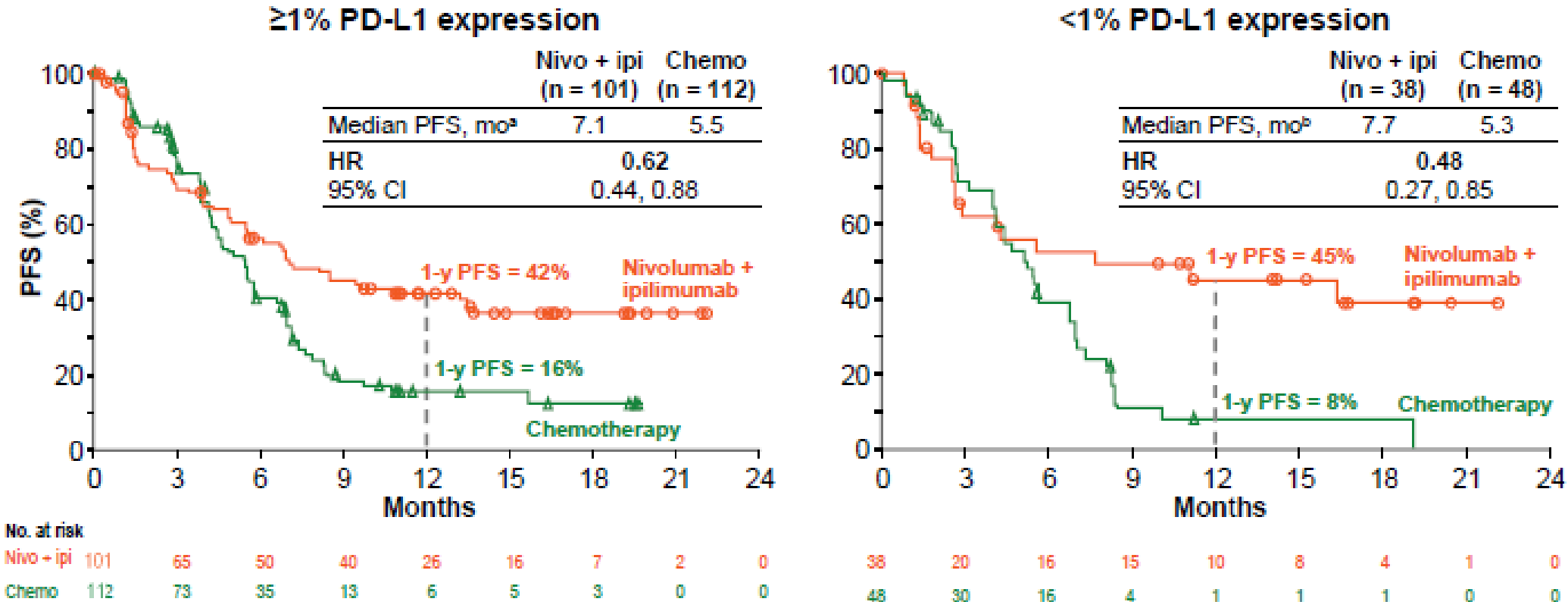
No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0



Hellmann, NEJM 2018

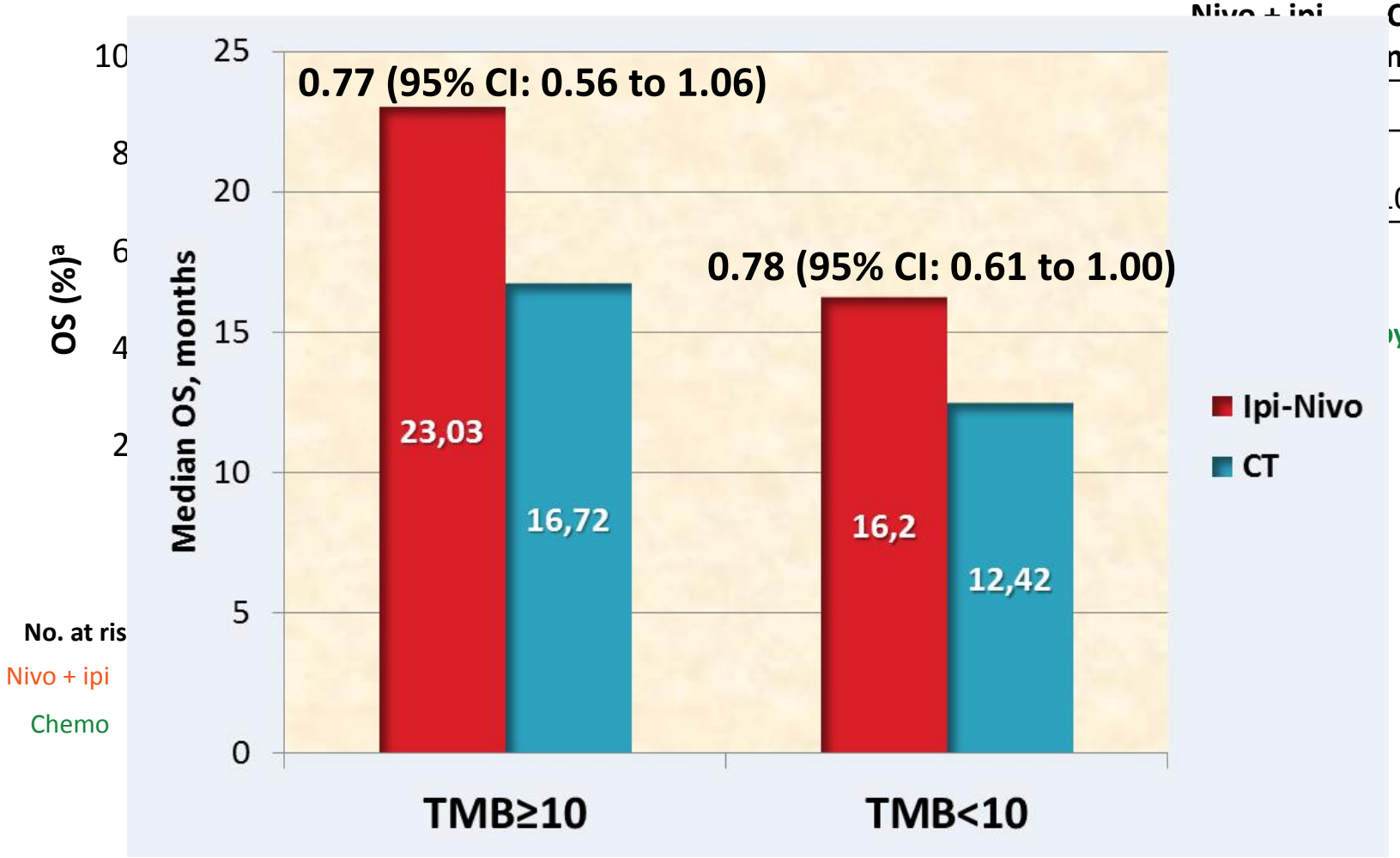
CheckMate 227 : nivolumab + ipilimumab *vs.* Chemotherapy in 1L with TMB ≥10 mut/Mb

PFS in patients with High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression



Hellmann, NEJM 2018

Preliminary Overall Survival with Nivolumab + Ipilimumab *vs*. Chemotherapy in Patients with High TMB (≥10 Mut/Mb)

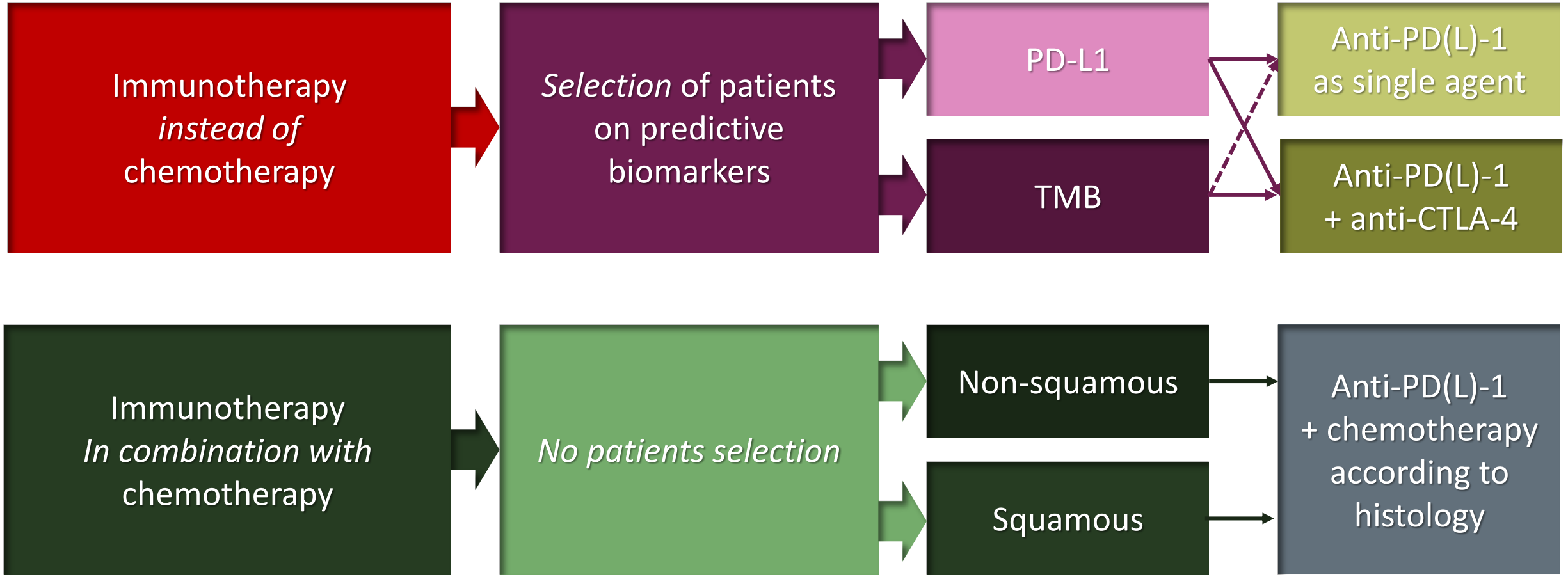


Chemo
n = 160)
16.4
.0

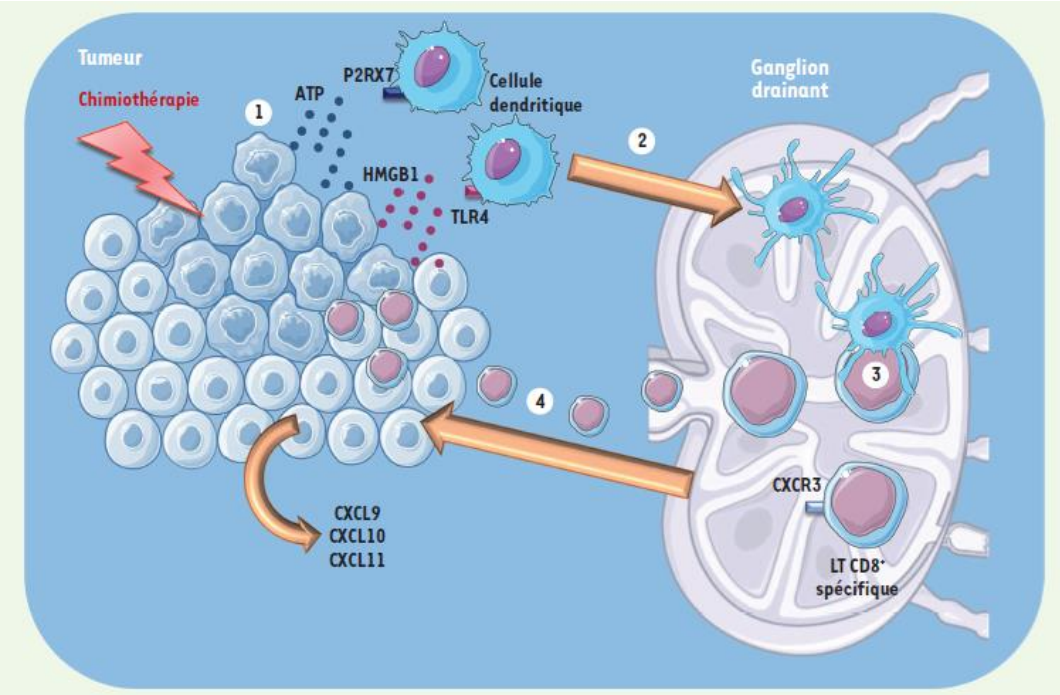
- Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored
- In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with disease progression[c])

Hellmann, NEJM 2018

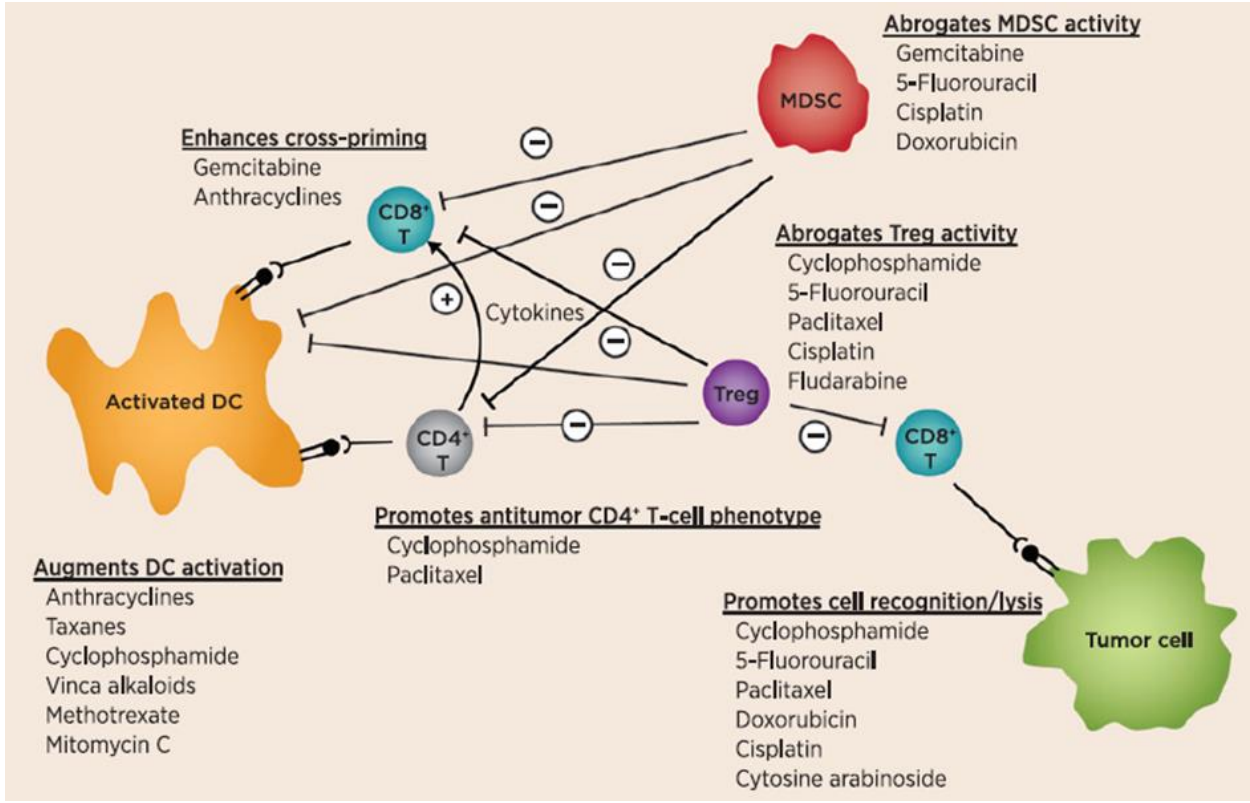
Strategies of ICIs development in 1st line treatment of advanced NSCLC



Impact of chemotherapy on immune response



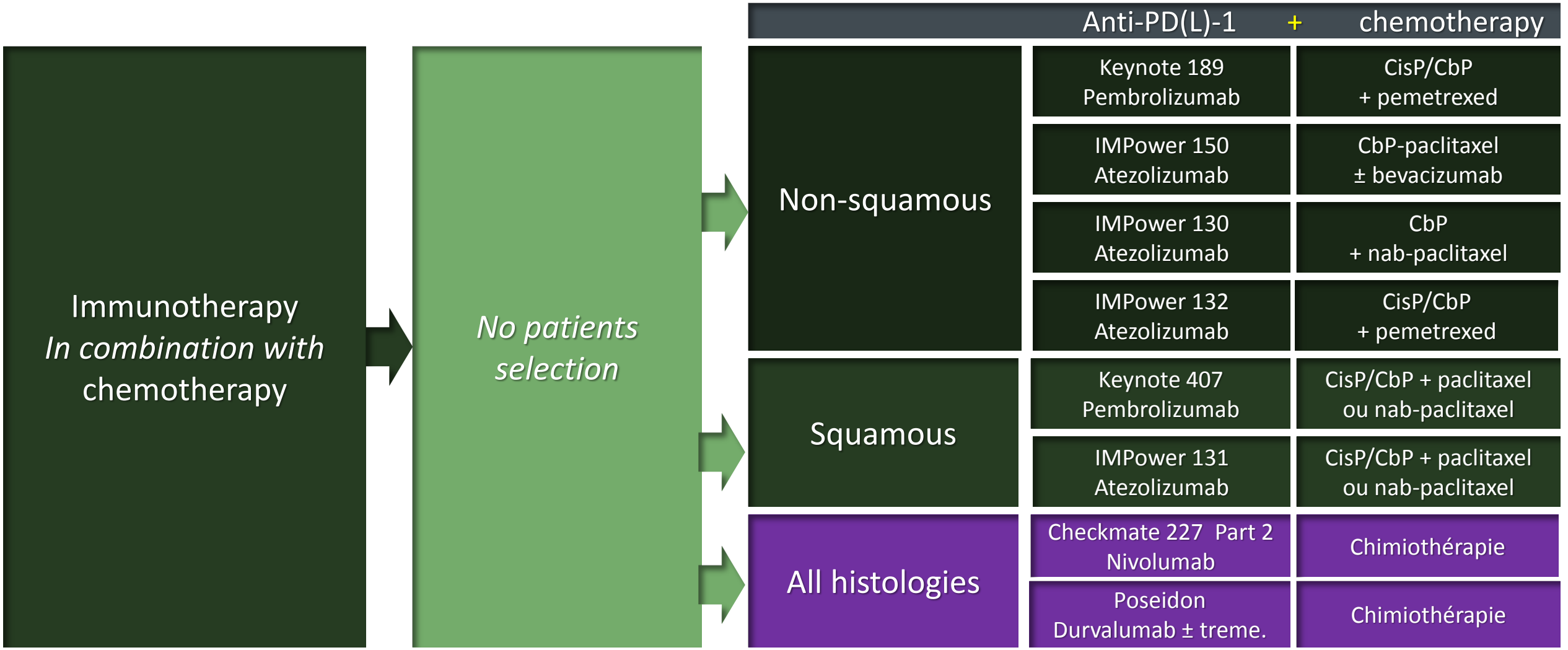
Immunogenic cell death



Impact on tumor microenvironment

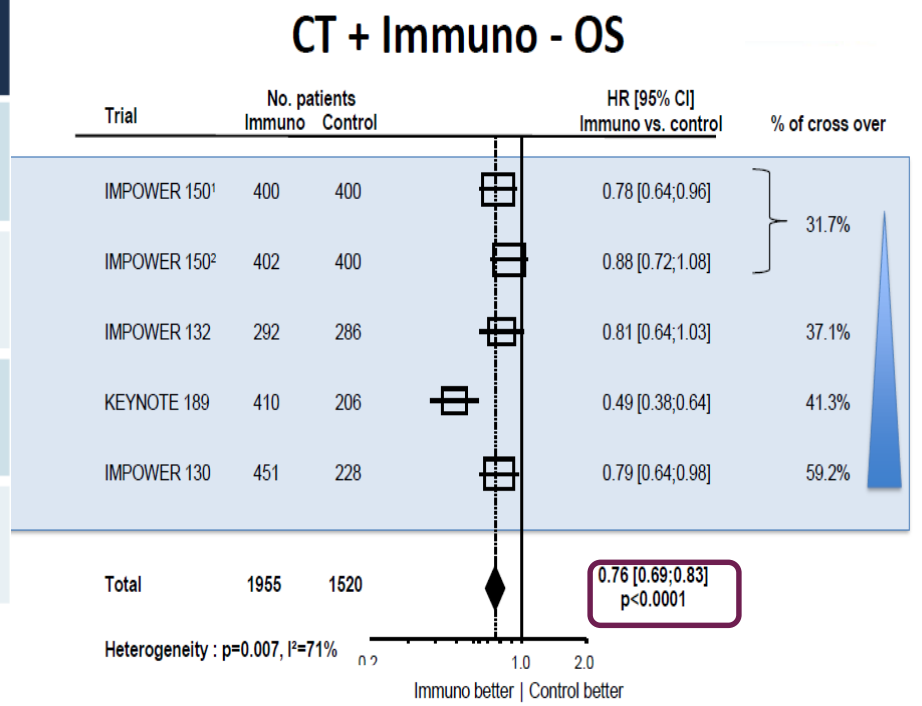
Hanoteau, Med Sci 2016; Emmens, CCR 2015

Strategy of ICIs development in 1st line treatment of advanced NSCLC: in combination with chemotherapy



Strategy of ICIs development in 1st line treatment of advanced NSCLC: in combination with chemotherapy

Anti-PD(L)-1 + chemotherapy			Patients	PFS (months)	OS (months)
Non-squamous	Keynote 189 Pembrolizumab	CisP/CbP + pemetrexed	616	5.6 *vs* 4.9 *HR 0.52*	NR *vs* 11.3 *HR 0.49*
	IMPower 150 Atezolizumab	CbP-paclitaxel ± bevacizumab	800	8.3 *vs* 6.8 *HR 0.59*	19.2 *vs* 14.7 *HR 0.78*
	IMPower 130 Atezolizumab	CbP + nab-paclitaxel	679	7.0 *vs* 5.5 *HR 0.64*	18.6 *vs* 13.9 *HR 0.79*
	IMPower 132 Atezolizumab	CisP/CbP + pemetrexed	578	7.6 *vs* 5.2 *HR 0.60*	18.1 *vs* 13.6 *HR 0.81*



Gandhi KN189, NEJM 2018; Socinski, NEJM 2018; Papadimitrakopoulou, WCLC 2018; Cappuzzo, ESMO 2018

Chemotherapy ± Pembrolizumab
Keynote 189 (non-squamous NSCLC): Updated Results

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors
- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

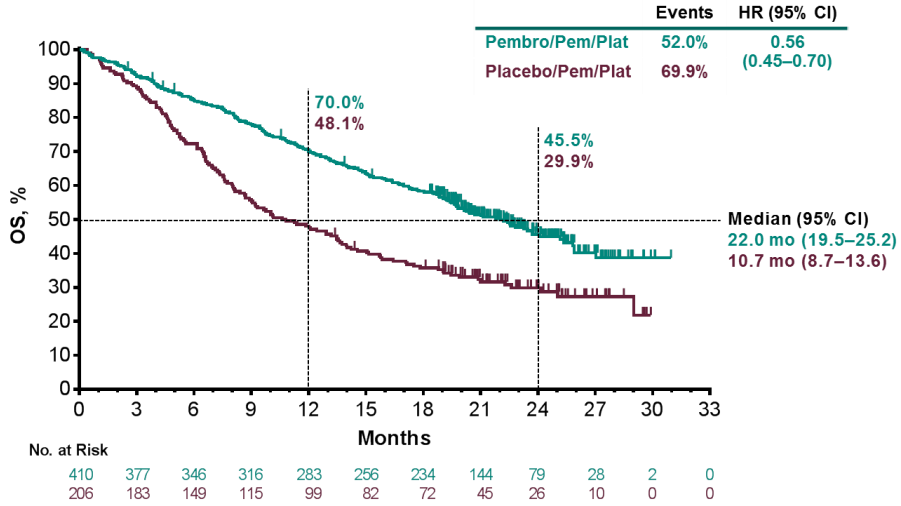
R (2:1)

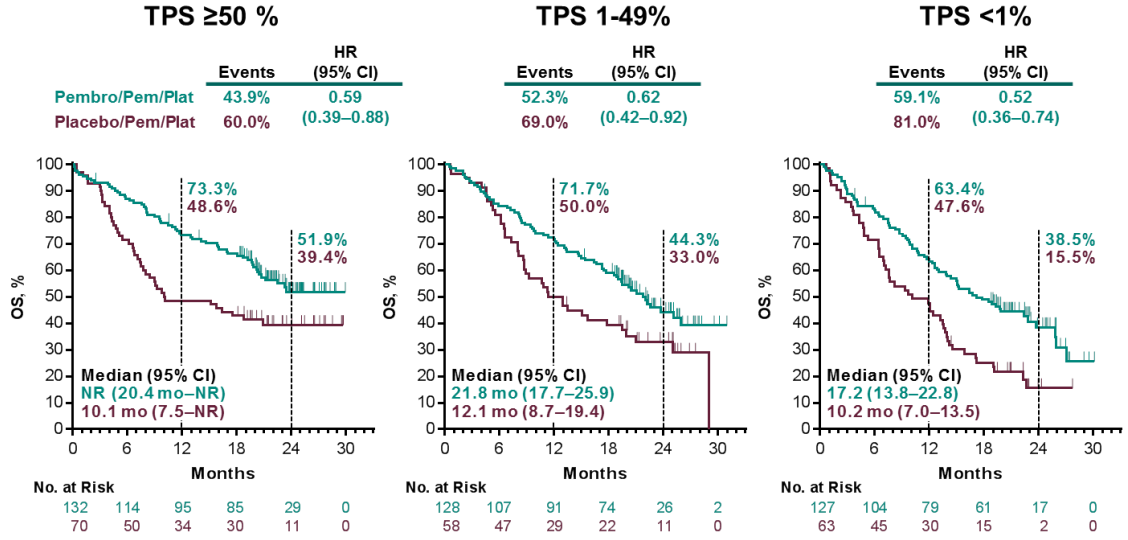
N = 410: Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles → Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

N = 206: Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles → Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

PD[b] → Pembrolizumab 200 mg Q3W for up to 35 cycles

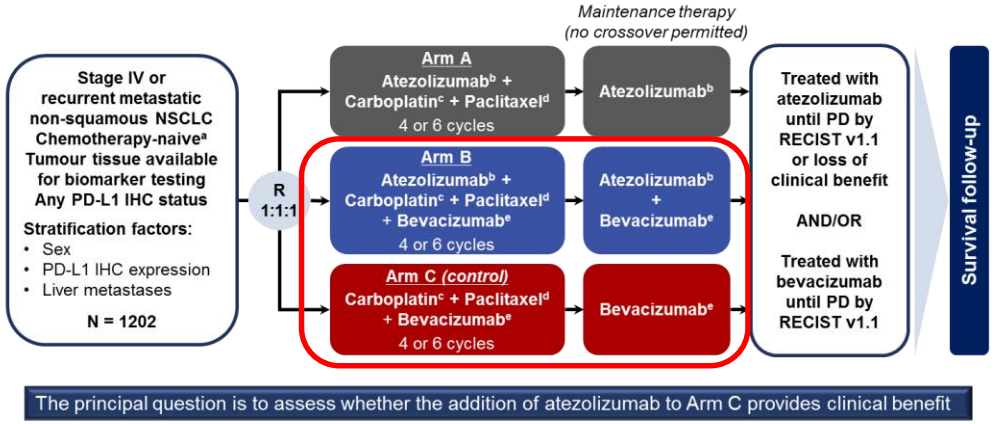
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.



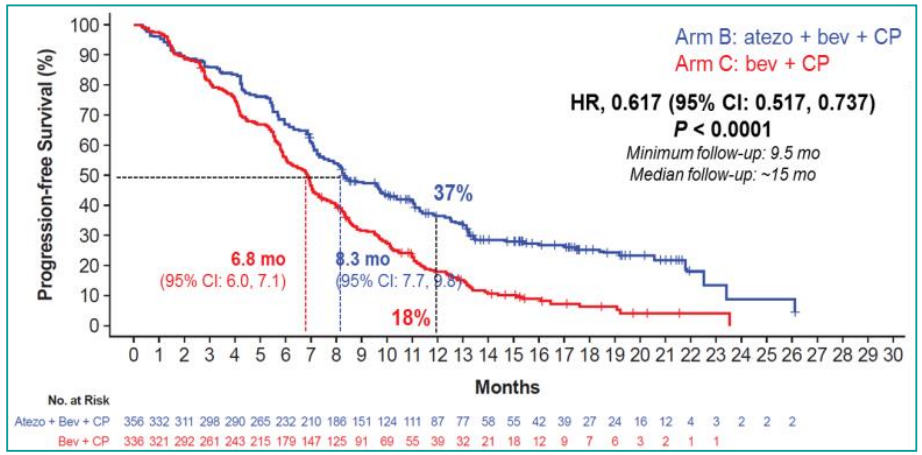


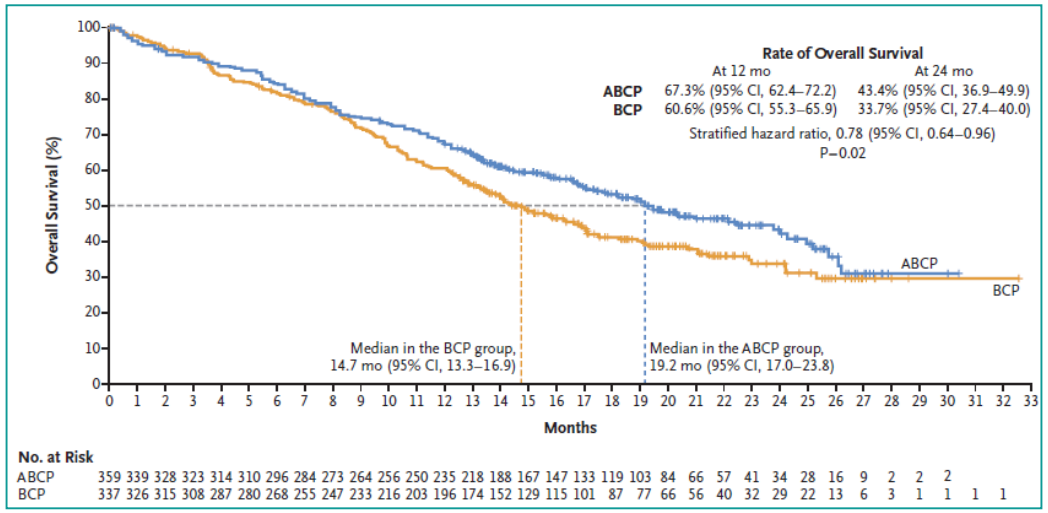
Gadgeel, ASCO 2019

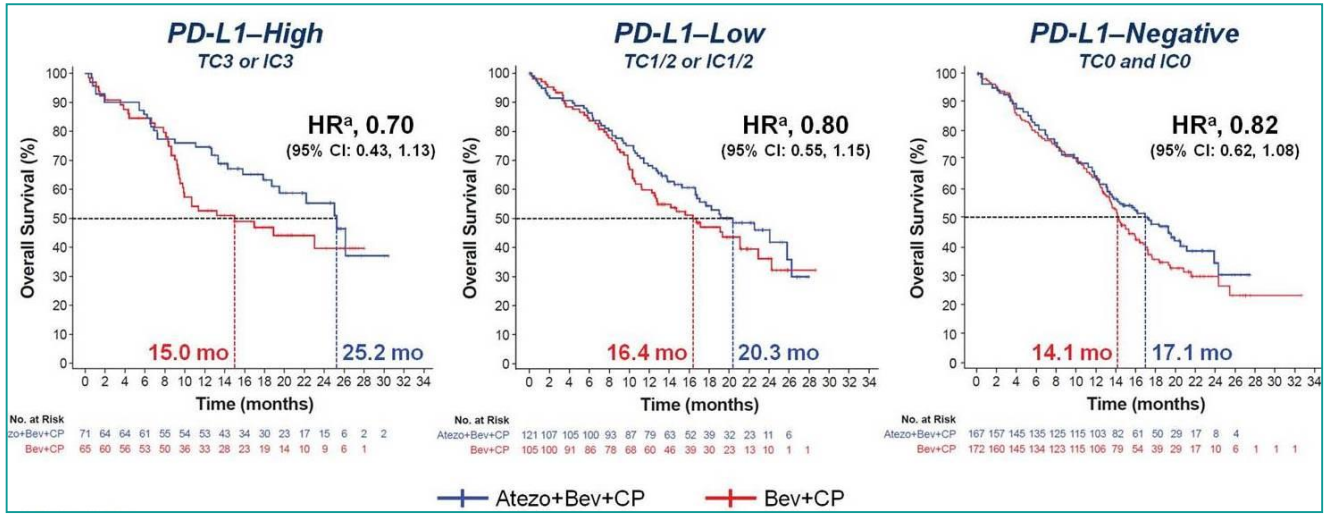
Chemotherapy + Bevacizumab ± Anti-PD-L1
IMPower 150 (non-squamous NSCLC)



[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m² IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.







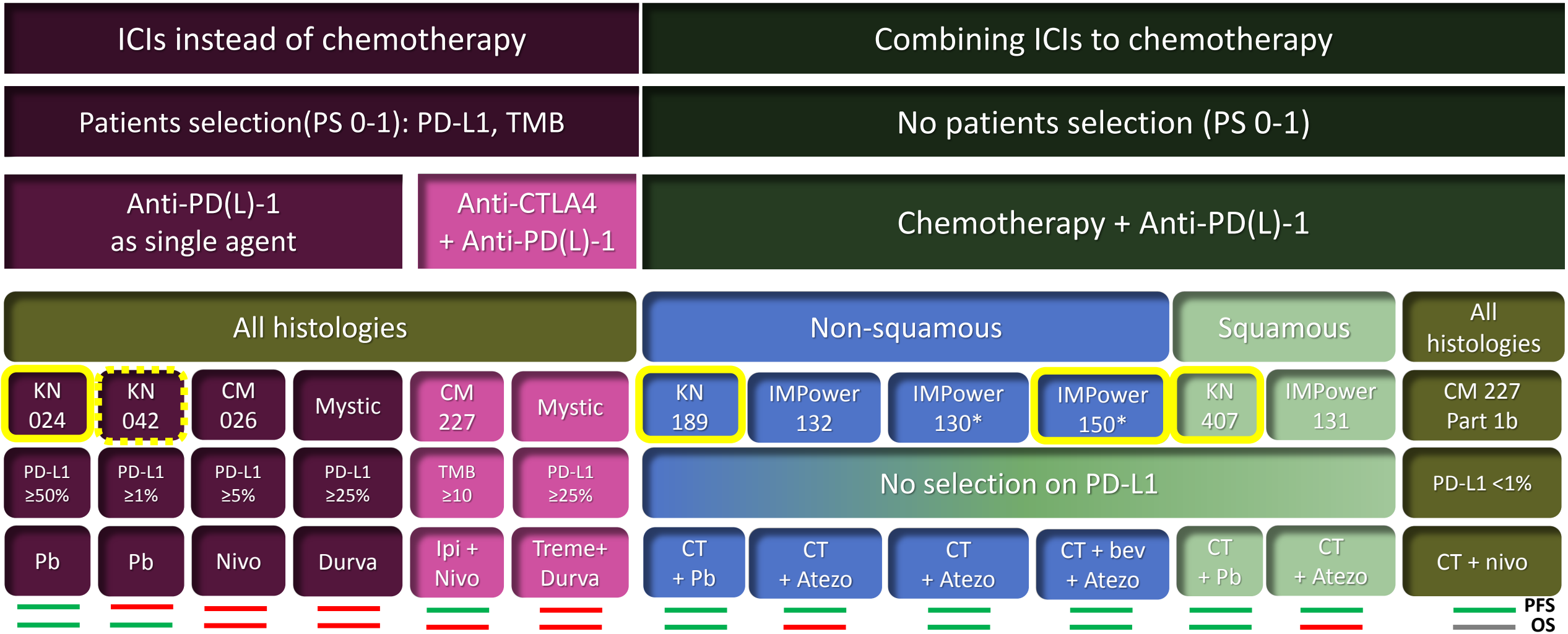
Socinski, ASCO 2018 and NEJM 2018

Strategy of ICIs development in 1st line treatment of advanced NSCLC: in combination with chemotherapy

	Anti-PD(L)-1 + chemotherapy		Patients	PFS (months)	OS (months)
Squamous	Keynote 407 Pembrolizumab	CisP/CbP + paclitaxel ou nab-paclitaxel	559	6.4 *vs* 4.8 *HR 0.56*	15.9 *vs* 11.3 *HR 0.64*
	IMPower 131 Atezolizumab	CisP/CbP + paclitaxel ou nab-paclitaxel	684	6.3 *vs* 5.6 *HR 0.71*	14.0 *vs* 13.9 HR 0.96

Paz-Ares, NEJM 2018; Jotte, ASCO 2018

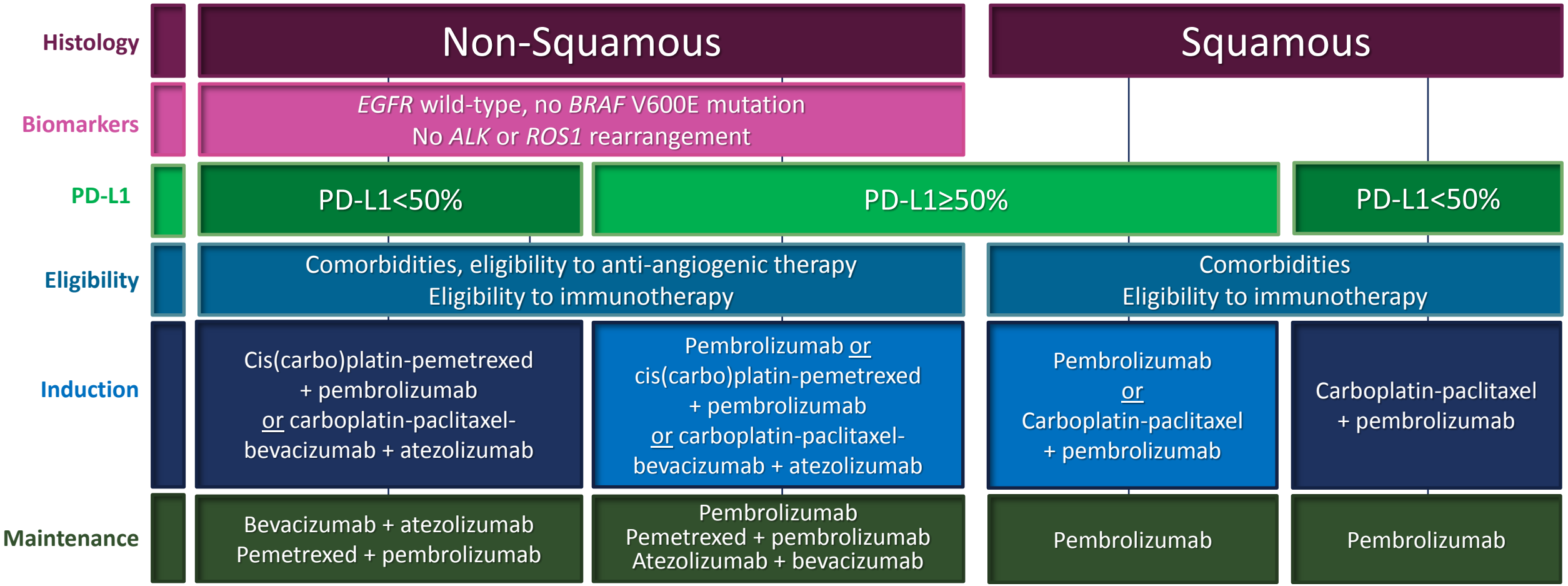
Summary of ICIs Development in 1st Line



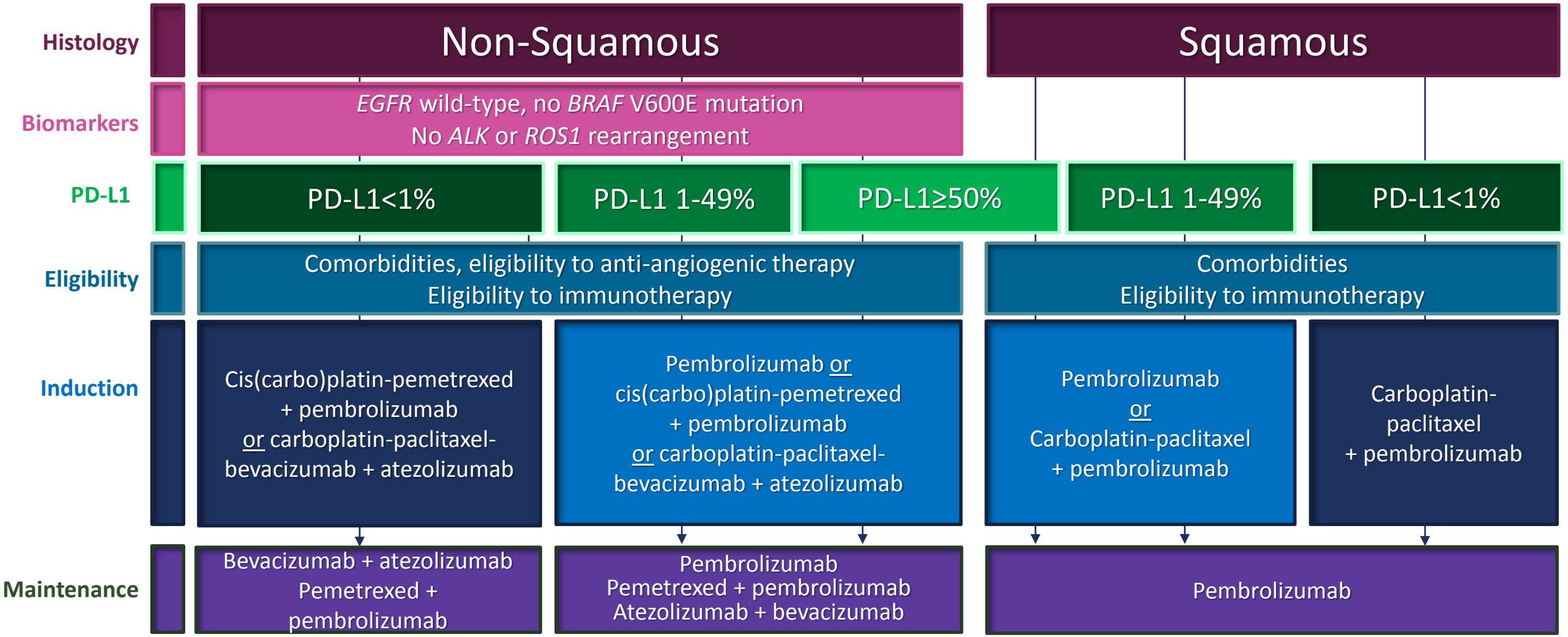
*: inclusion of patients with EGFR mutations and ALK rearrangement; Pb : pembrolizumab, Ipi : ipilimumab ; Nivo : nivolumab ; Durva : durvalumab; Treme : tremelimumab ; Atezo : atezolizumab ; bev : bevacizumab

A new treatment algorithm in 1st line of stage IV NSCLC

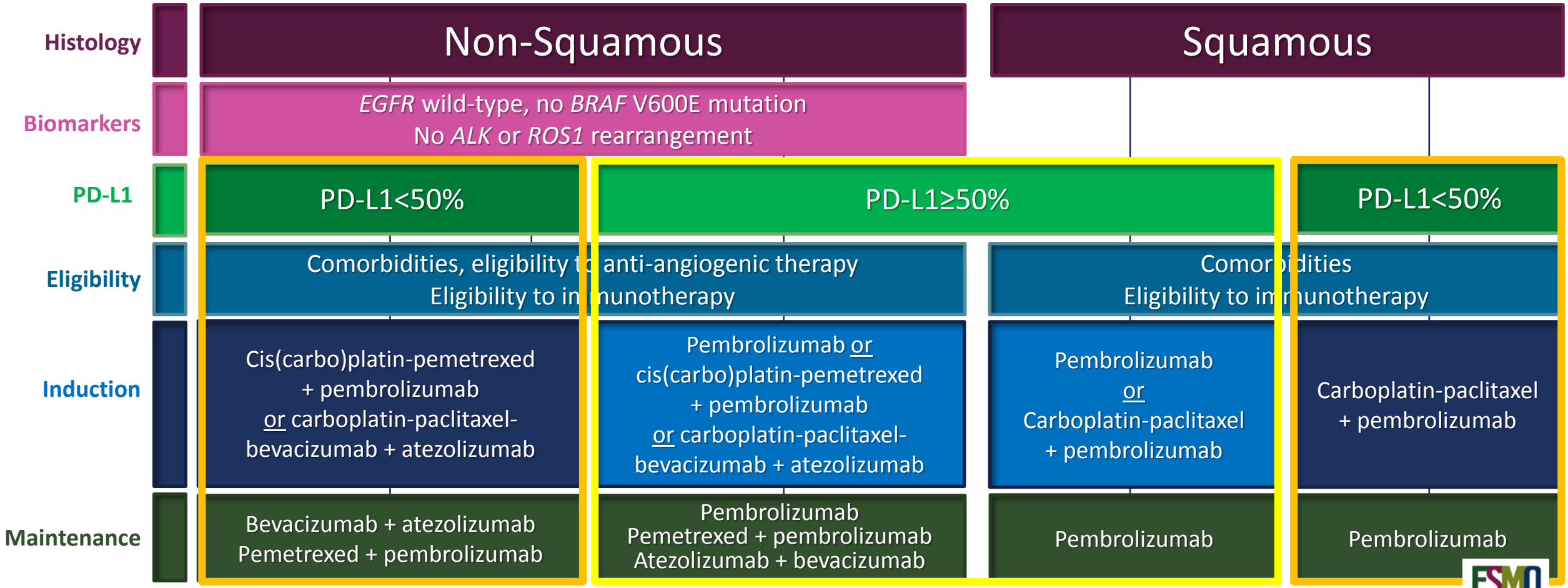
Advanced NSCLC without targetable oncogenic addiction
First line treatment algorithm



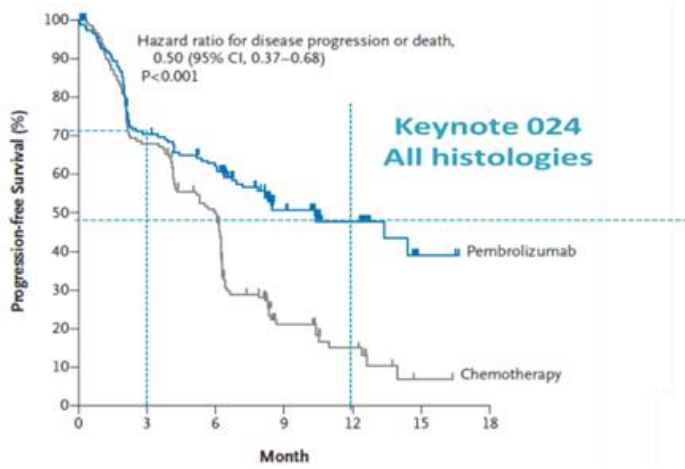
Advanced NSCLC without targetable oncogenic addiction
First line treatment algorithm

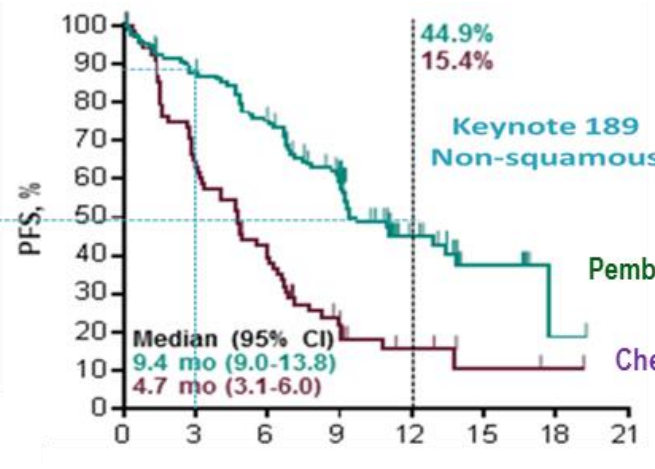


Advanced NSCLC without targetable oncogenic addiction
First line treatment algorithm



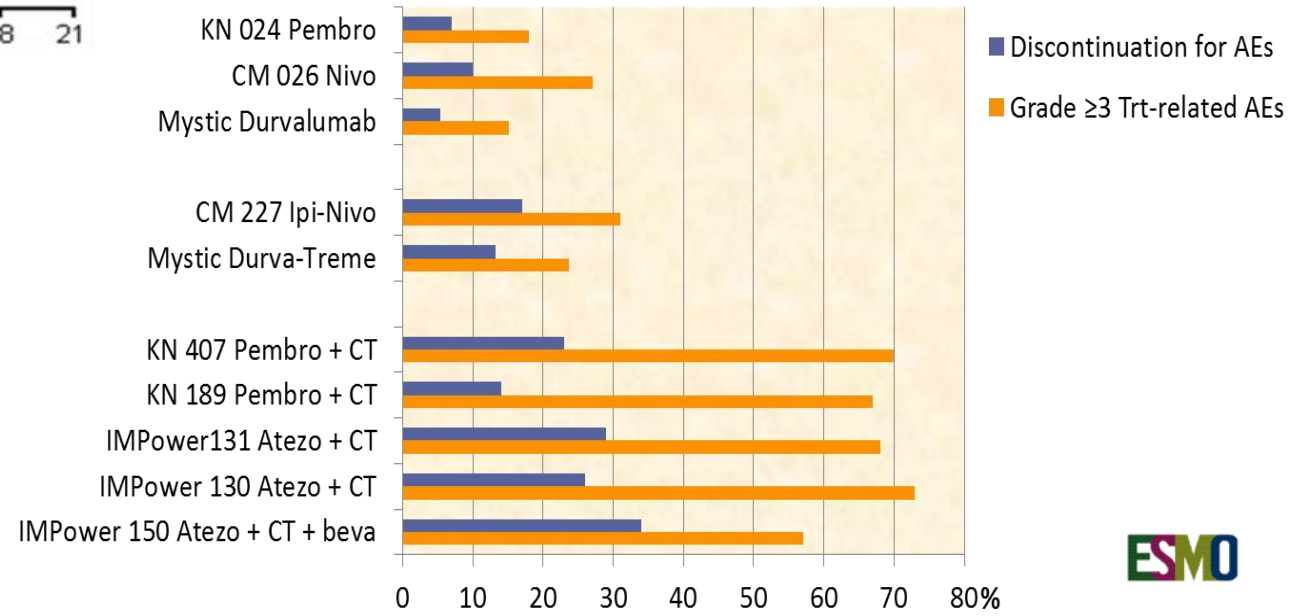
PD-L1 ≥50%: pembrolizumab as a single agent or in combination with chemotherapy?





PFS

Tolerance



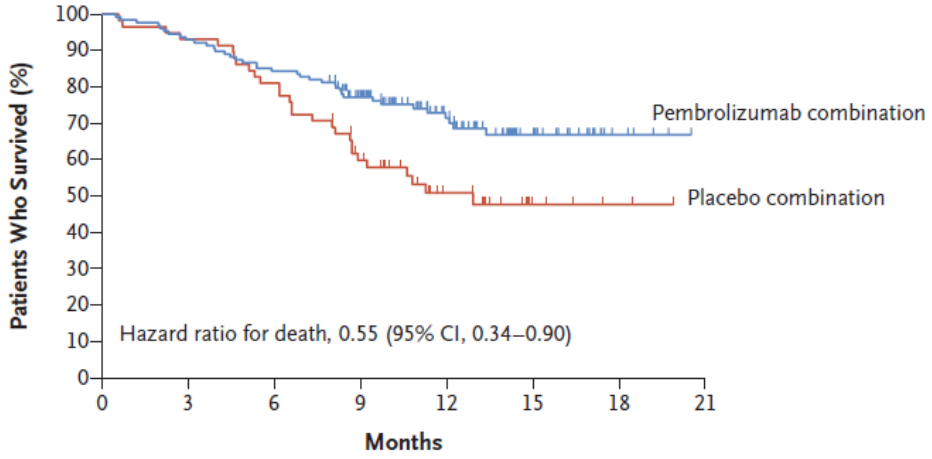
Reck, NEJM 2016; Carbone, NEJM 2017; Hellmann, NEJM 2018; Gandhi L, NEJM 2018; Socinski, NEJM 2018; Rizvi, ESMO-IO 2018

Should every patient be treated with 1st line ICI?

PD-L1 1 – 49%

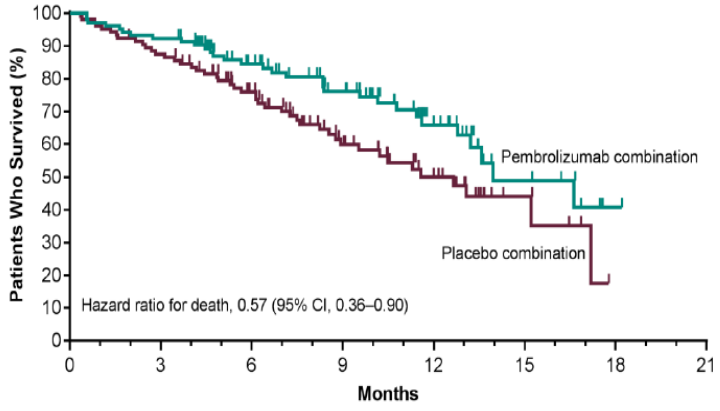
Chemotherapy + Pembrolizumab

Keynote 189
Non squamous



No. at Risk								
Pembrolizumab combination	128	119	108	84	52	21	5	0
Placebo combination	58	54	47	32	17	5	2	0

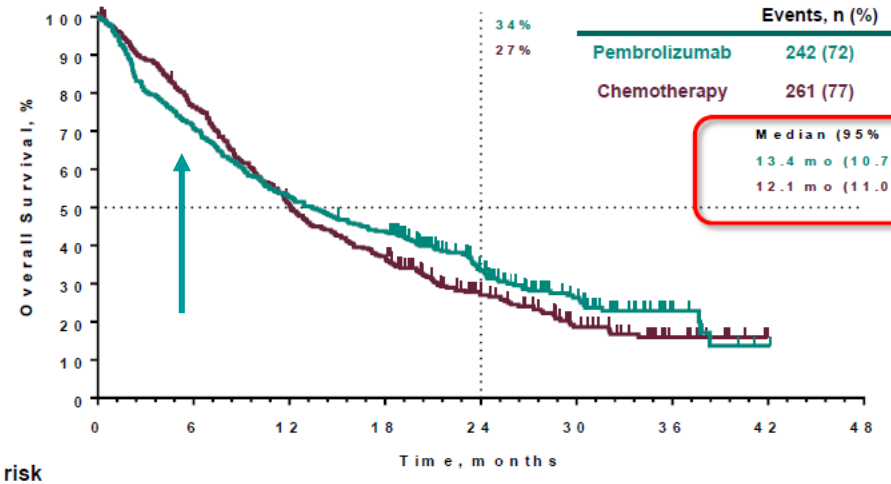
Keynote 407
Squamous



No. at Risk								
Pembrolizumab combination	103	95	68	50	25	9	1	0
Placebo combination	104	90	66	37	21	6	0	0

Pembrolizumab single agent

Keynote 042
All histologies



	Events, n (%)	HR (95% CI)
Pembrolizumab	242 (72)	0.91 (0.77–1.09)
Chemotherapy	261 (77)	

Median (95% CI)
13.4 mo (10.7–16.9)
12.1 mo (11.0–14.0)

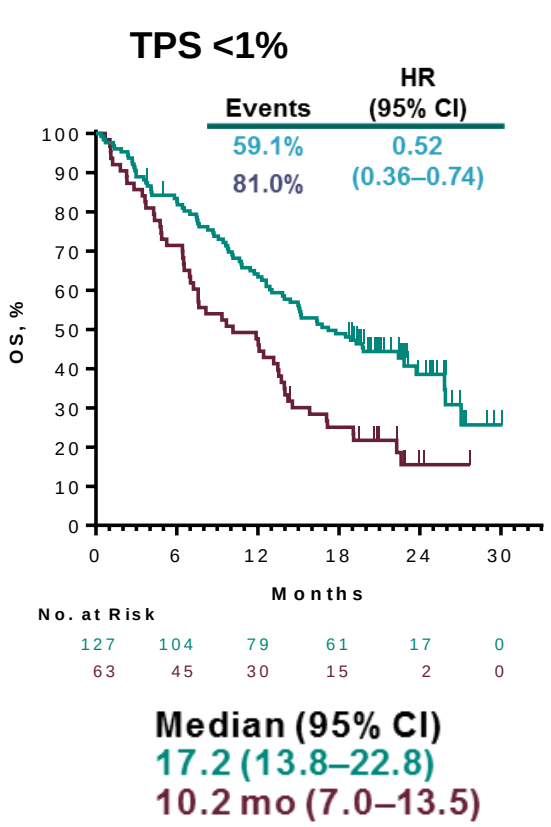
No. at risk									
Pembro/ Pem/Plat	338	239	178	147	84	41	9	0	0
Placebo/ Pem/Plat	337	254	168	123	67	34	12	0	0

ESMO

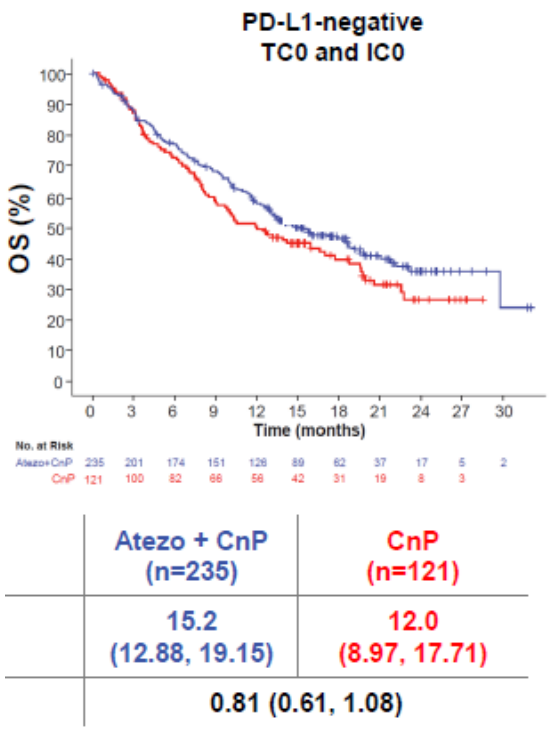
Gandhi L, NEJM 2018; Paz-Ares, NEJM 2018; Mok, ELCC 2019

Should every patient be treated with 1st line ICI?

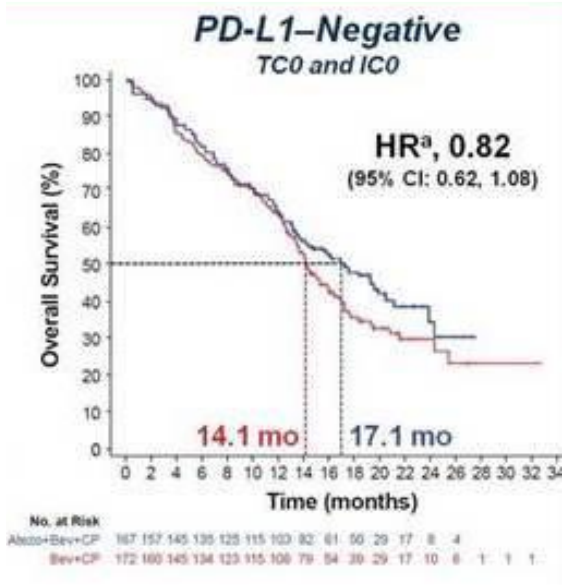
PD-L1 <1%



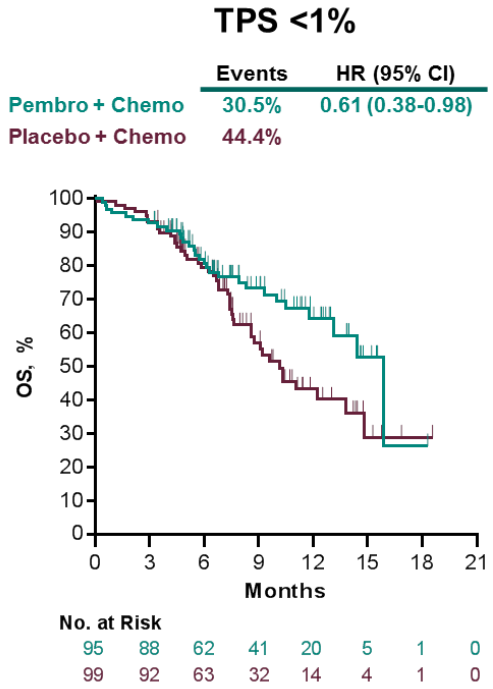
Keynote 189
Non-squamous



ImPower 130
Non-squamous



ImPower 150
Non-squamous



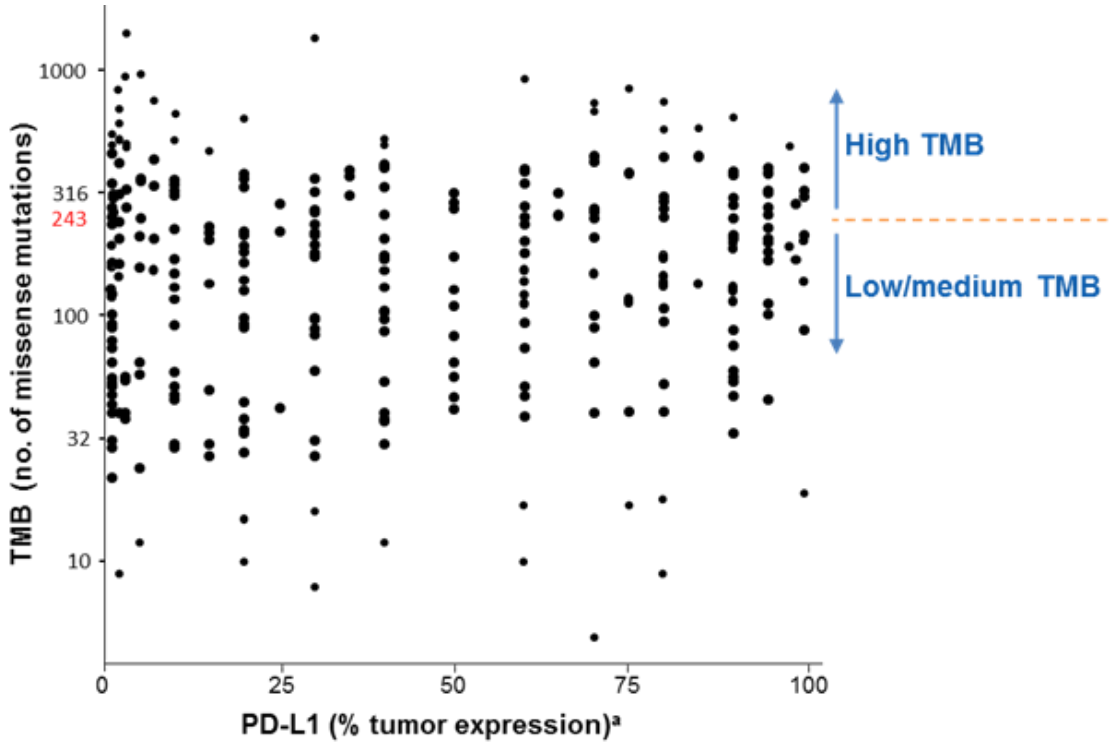
Keynote 407
Squamous

Gandhi L, NEJM 2018; Socinski, NEJM 2018; Cappuzzo, ESMO 2018; Paz-Ares, ASCO 2018; Gadgeel, ASCO 2019

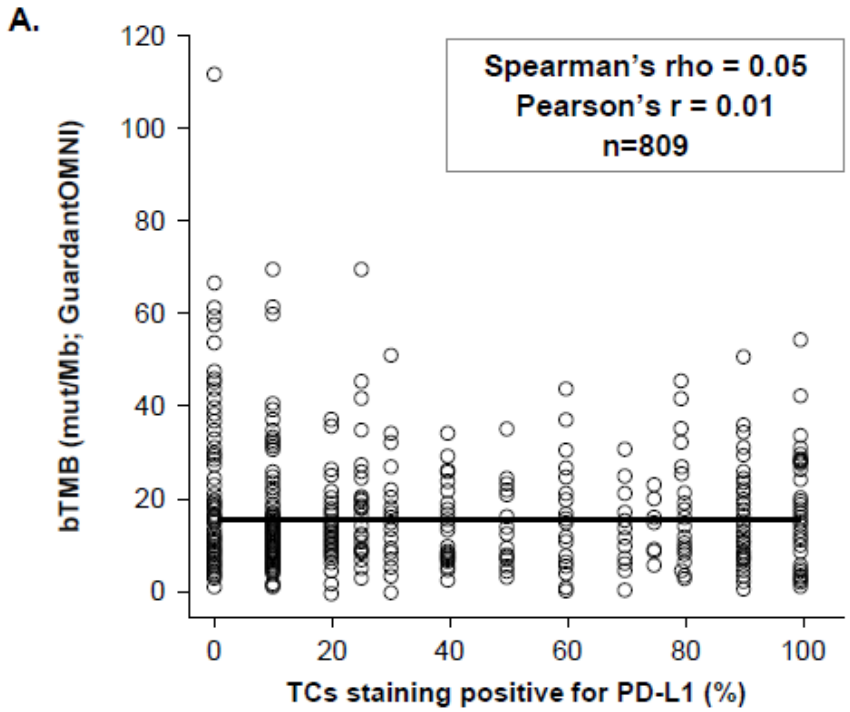
Is there a room for TMB as a predictive biomarker?

TMB is independant of PD-L1 level of expression

CheckMate 026, WES

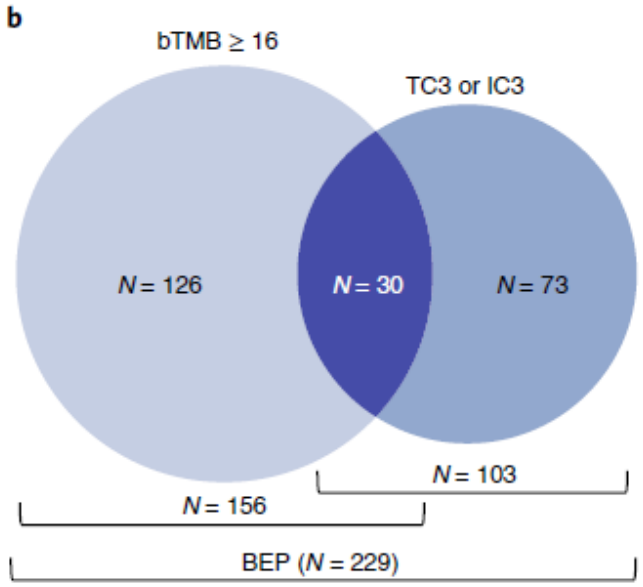


Mystic, blood TMB

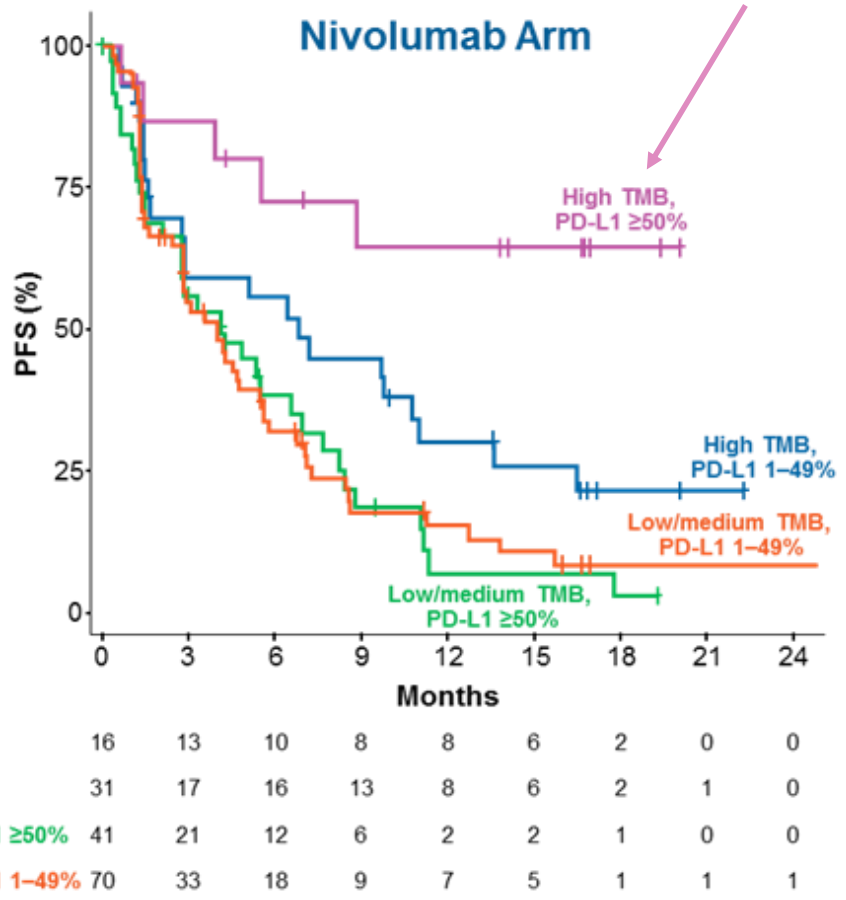


Peters, AACR 2017; Rizvi, ASCO 2019

Using TMB and PD-L1 as Two Independent Biomarkers



	N	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥ 16	156	0.64 (0.46-0.91)	0.64 (0.44-0.93)
TC3 or IC3	103	0.62 (0.41-0.93)	0.44 (0.27-0.71)
bTMB ≥ 16 and TC3 or IC3	30	0.38 (0.17-0.85)	0.23 (0.09-0.58)

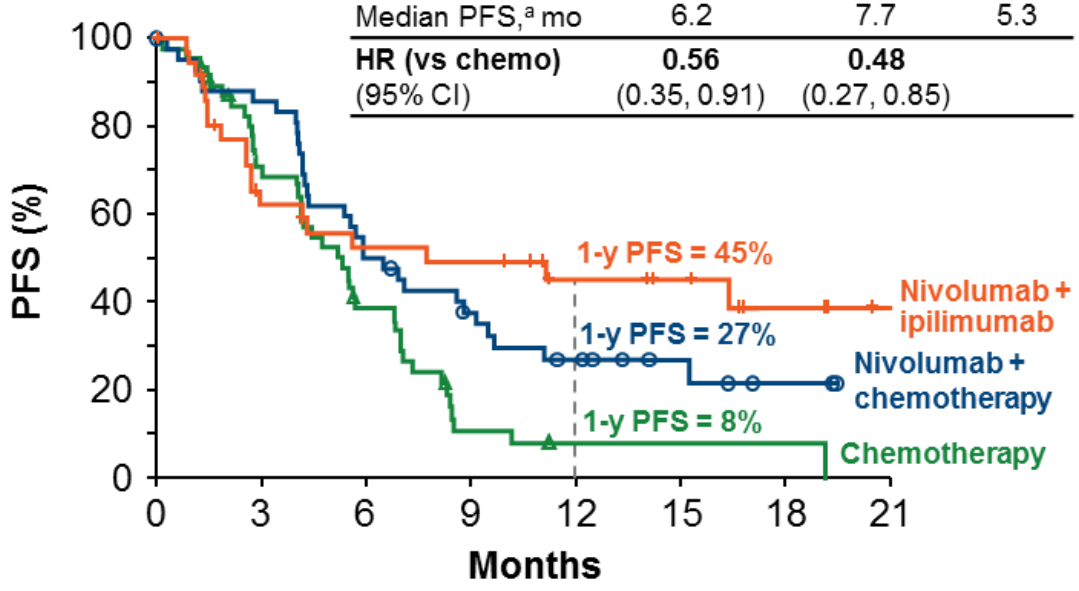


Gandara, Nat Med 2018; Peters S et al., AACR 2017

Checkmate 227 Part 1b (PD-L1<1%): PFS
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) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	

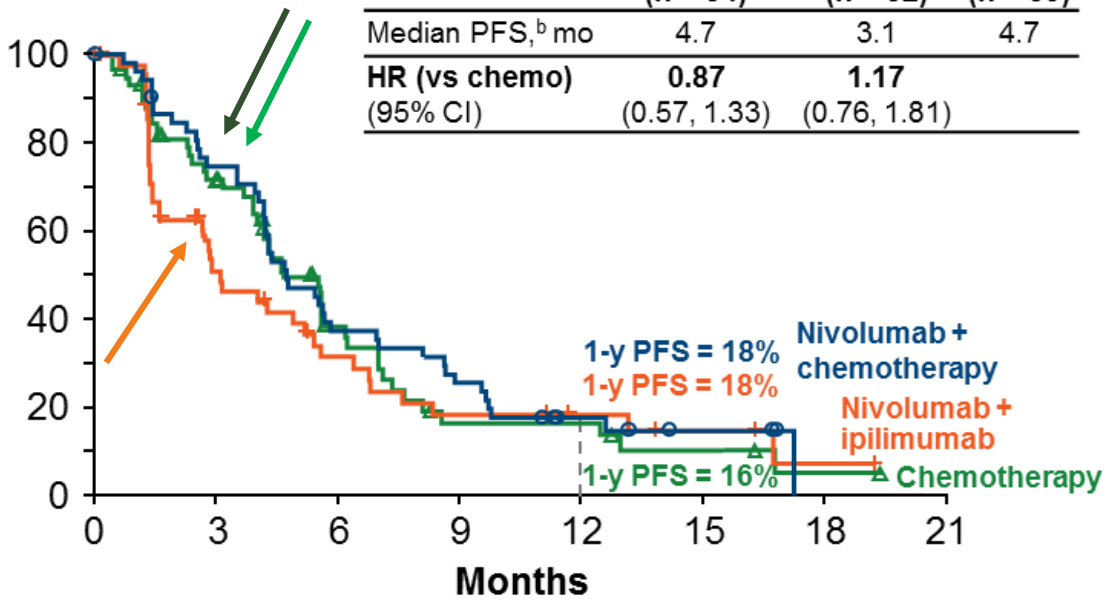


No. at risk

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) (95% CI)	**0.87** (0.57, 1.33)	**1.17** (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

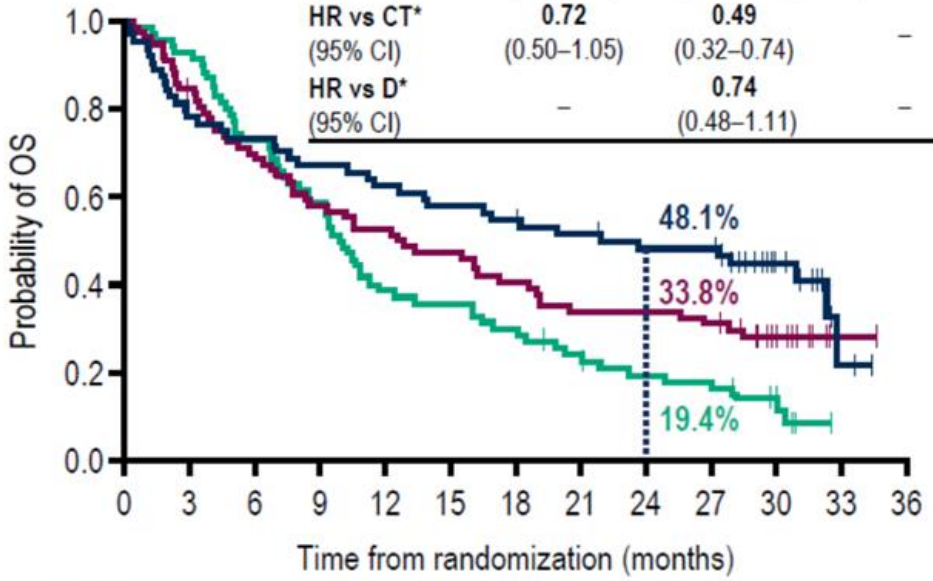
[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

Borghaei H, ASCO 2018

TMB can be predictive of OS benefit from anti-PD(L)-1 ± anti-CTLA-4 therapy

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	12.6 (7.8–18.6)	21.9 (11.4–32.8)	10.0 (8.1–11.7)
HR vs CT* (95% CI)	0.72 (0.50–1.05)	0.49 (0.32–0.74)	–
HR vs D* (95% CI)	–	0.74 (0.48–1.11)	–

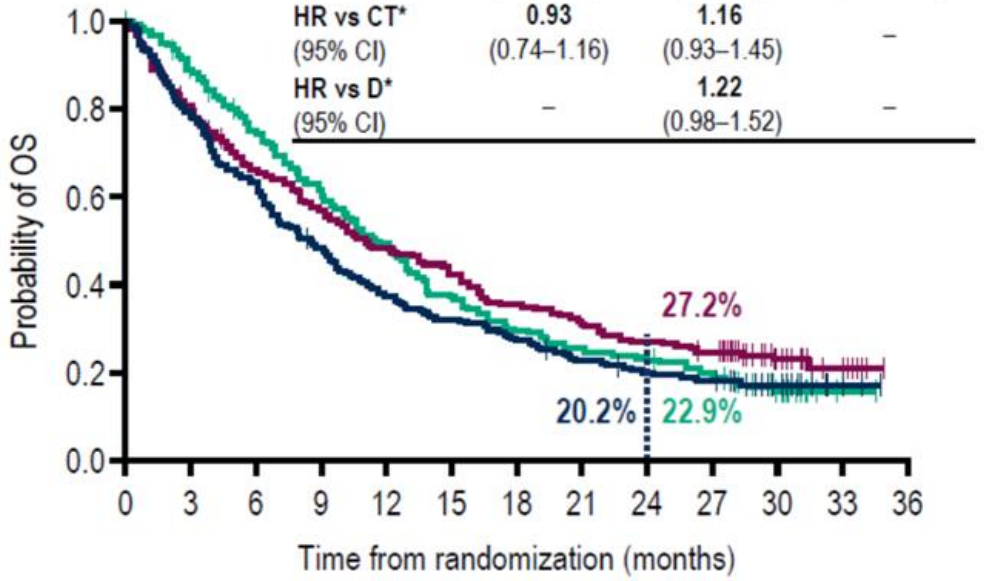


No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

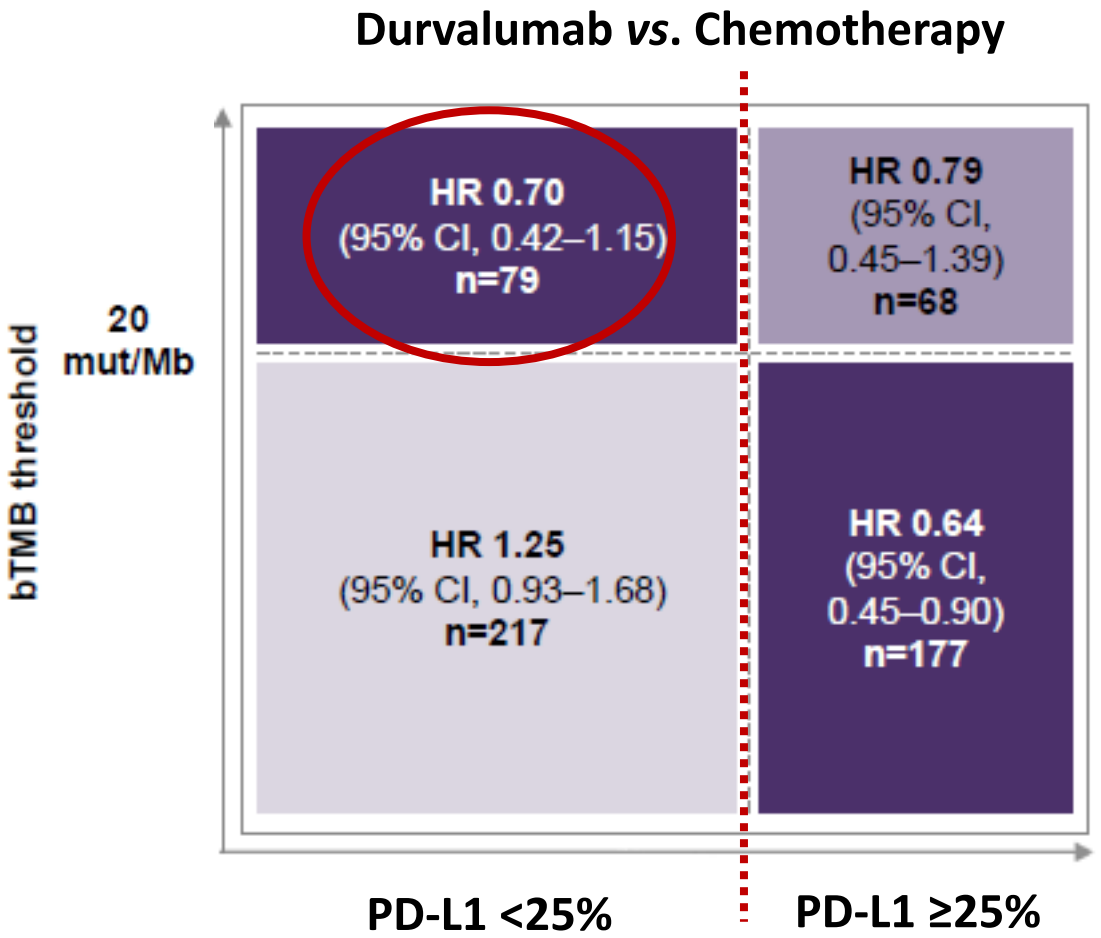
	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	11.0 (8.9–14.9)	8.5 (6.7–9.8)	11.6 (9.6–13.1)
HR vs CT* (95% CI)	0.93 (0.74–1.16)	1.16 (0.93–1.45)	–
HR vs D* (95% CI)	–	1.22 (0.98–1.52)	–

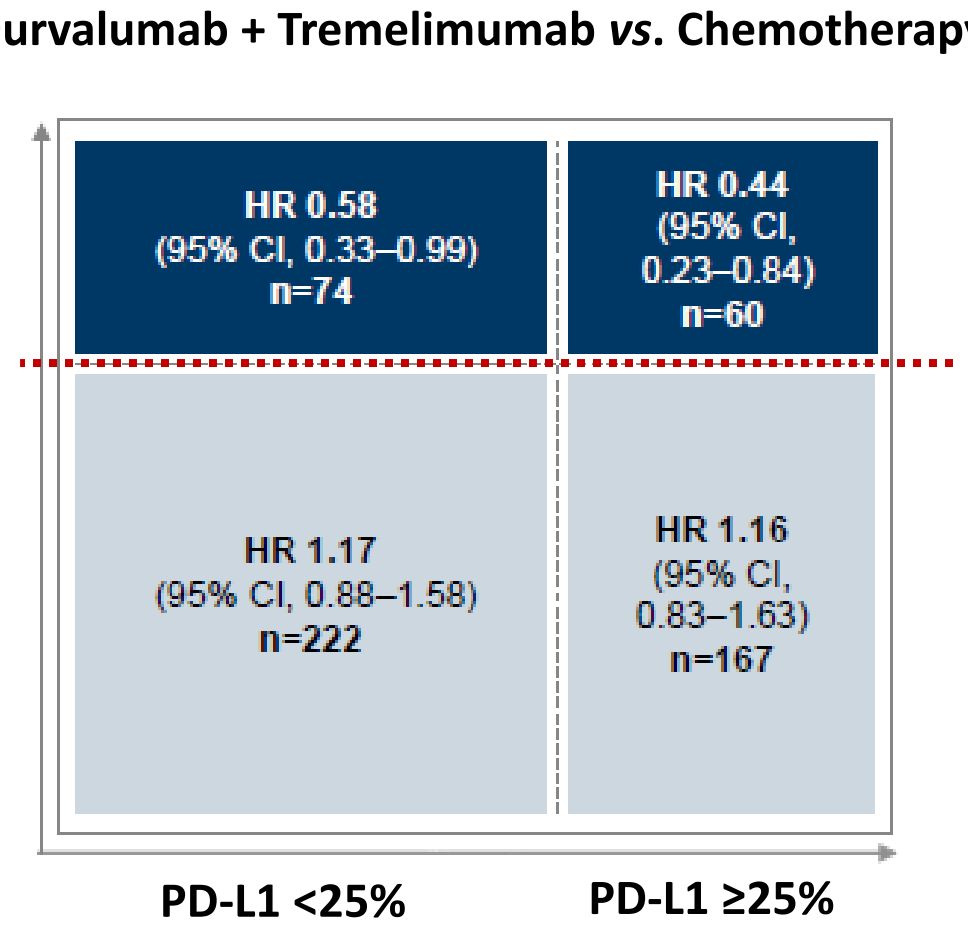


D	209	167	134	114	98	86	72	63	55	49	21	8	0
D+T	204	161	129	98	75	65	55	45	39	35	18	4	0
CT	185	162	135	110	89	68	53	45	41	34	17	1	0

Peters S et al;, AACR 2019

Mystic: Tremelimumab + Durvalumab or Durvalumab *vs*. Chemotherapy According to bTMB and PD-L1 Expression

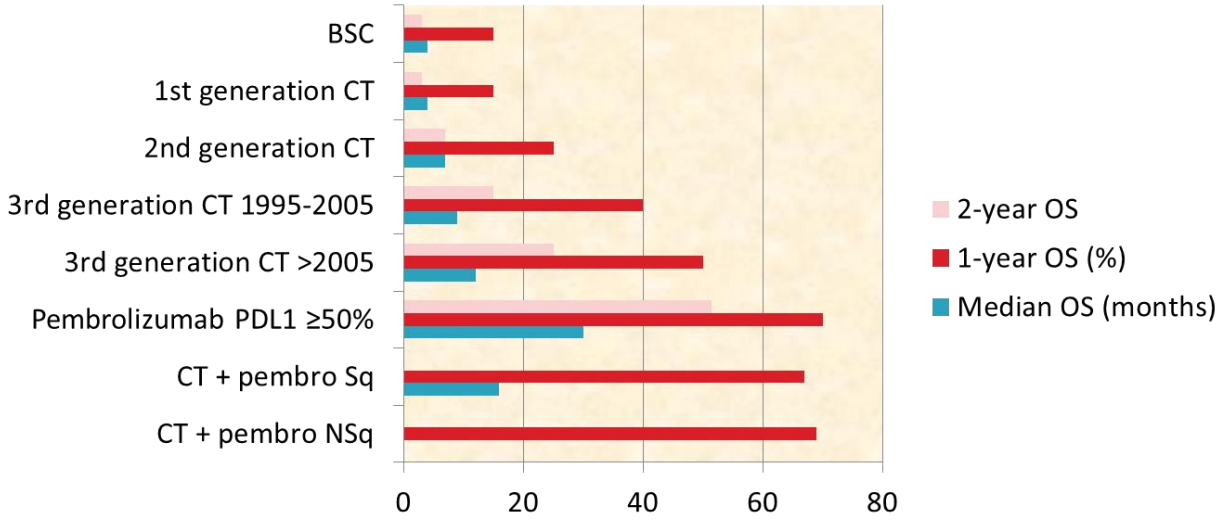


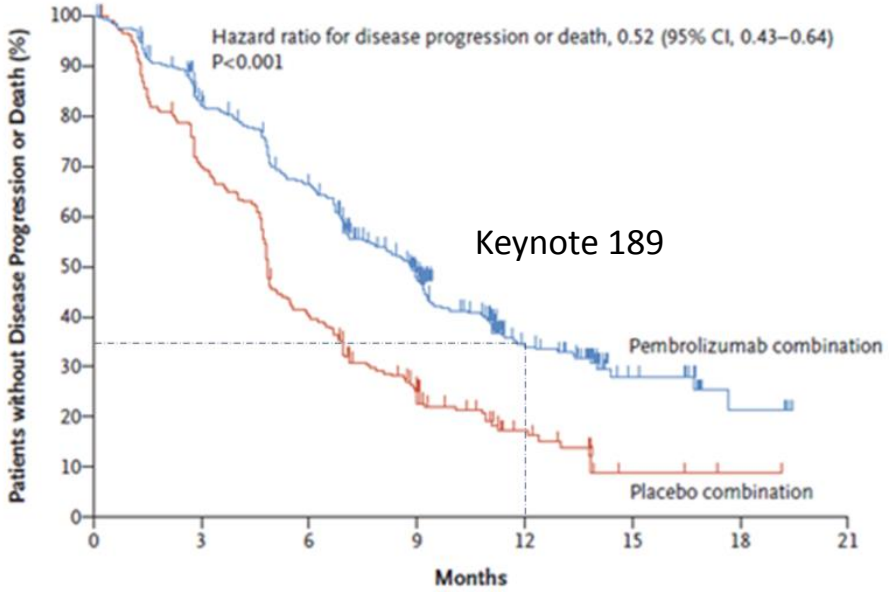


Rizvi N, ASCO 2019

All patients eligible for ICIs will receive anti-PD(L)-1 in 1st line treatment

- **Anti-PD(L)-1 are becoming the cornerstone of the 1st line treatment of advanced NSCLC, either as single agent for pembrolizumab or in combination with chemotherapy**
  - ICIs have increased of ≈20% the proportion of patients alive at 1 year
  - > 60% patients will experience disease progression during the 1st year of treatment despite CT+ anti-PD(L)-1





Gandhi, NEJM 2018

PD-L1 still remains the only decision-making biomarker

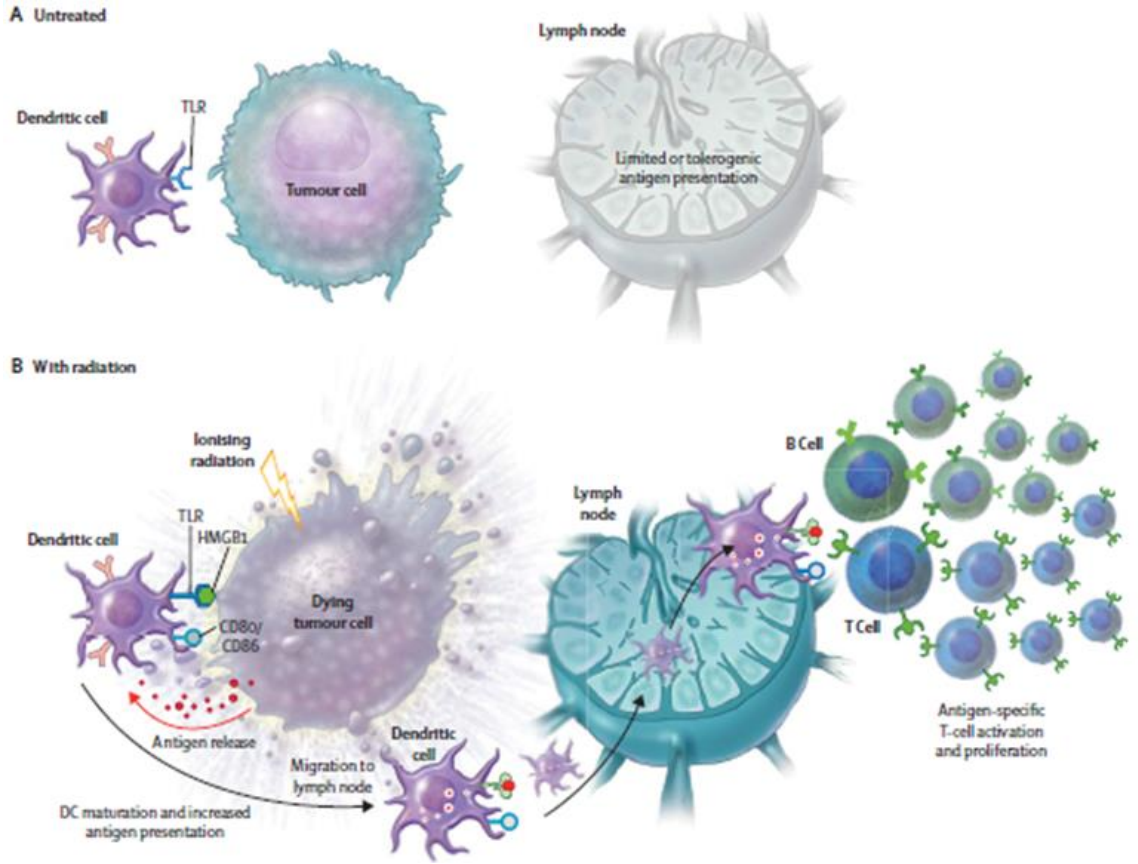
- **PD-L1 ≥50%**
  - Pembrolizumab as monotherapy = SoC
  - Addition of chemotherapy prevents early disease progression without obvious evidence of synergy at the cost of increased toxicity
- **PD-L1 <50%**
  - Combination of anti-PD(L)-1 + chemotherapy = standard of care
  - Some patients may not need addition of ICIs to chemotherapy: low TMB + PD-L1 <1% but still to be prospectively validated
- **Need for additional biomarkers**
  - TMB might be the next step but not ready for the prime time yet: feasibility, standardization, turn around time, cost, questionable impact on OS
  - Biomarkers for chemo-ICIs combinations

ICIs in locally advanced NSCLC

A new standard of care

Rationale for CPIs in Stage III NSCLC

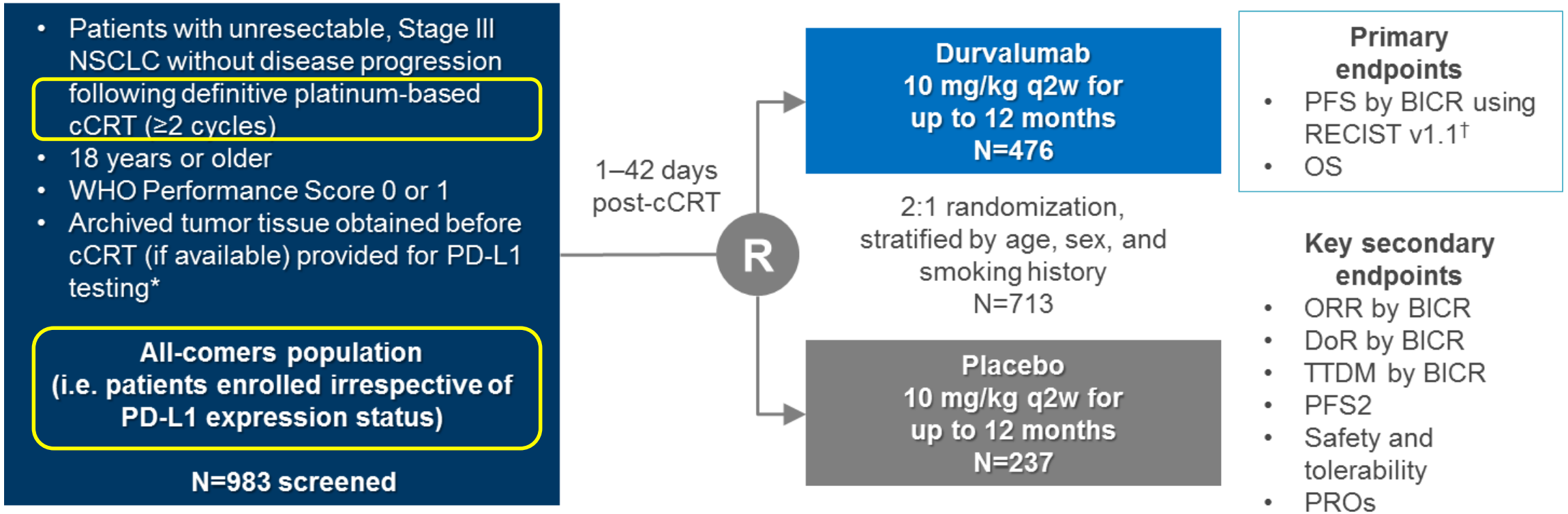
- Potential synergy
  - Upregulation of TILs and PD-L1
  - Release of TAAs
  - Immunogenic cell death
- Immunotherapy is better tolerated than chemotherapy
- Immunotherapy may be more active in earlier stages (%MPR in operable disease)



Sharabi. Lancet Oncol 2015;

Pacific Study Design

Phase 3. randomized. double-blind. placebo-controlled. multicenter. international study

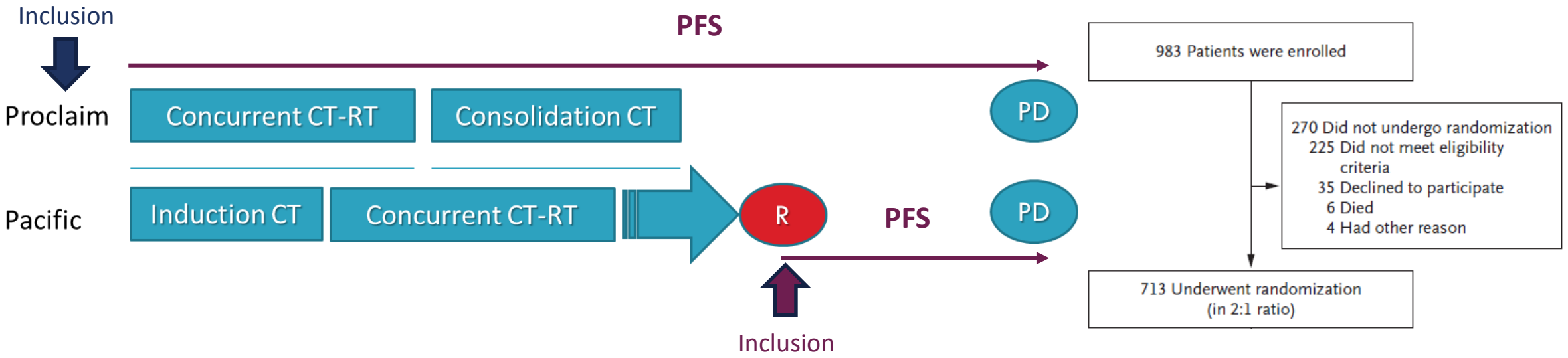


*Using the Ventana SP263 immunohistochemistry assay.
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression.
BICR. blinded independent central review; cCRT. concurrent CRT; DoR. duration of response; OS. overall survival; ORR. objective response rate; PD-L1. programmed cell death ligand-1; PFS. progression-free survival; PFS2. time to progression; PROs. patient-reported outcomes; RECIST. Response Evaluation Criteria in Solid Tumors; TTDM. time to death or distant metastasis.
ClinicalTrials.gov number: NCT02125461.

Antonia SJ. et al. N Engl J Med 2017; 377: 1919–1929.

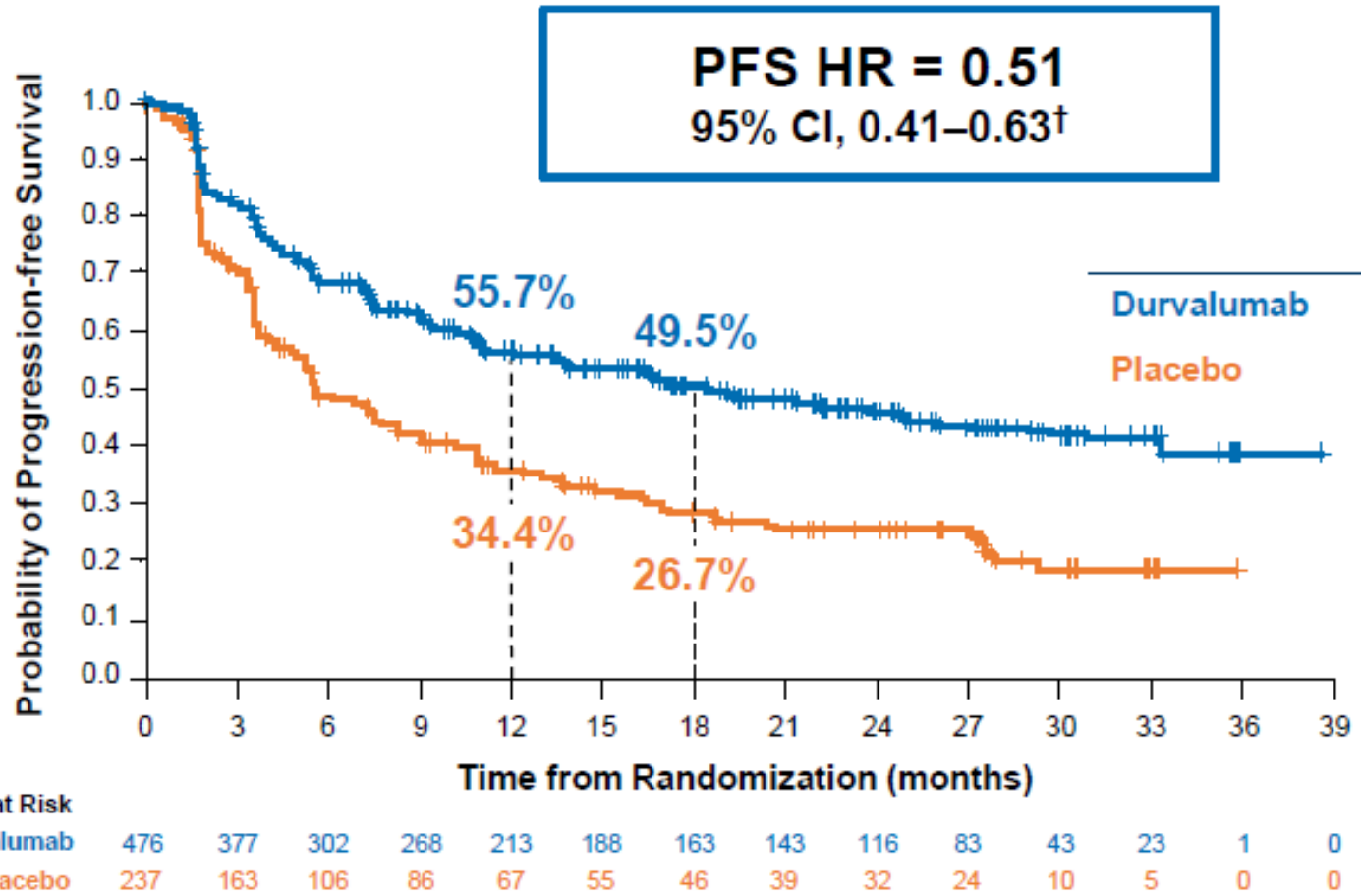
Patients Characteristics

- Selection of patients eligible to a randomized trial after definitive chemo-radiation therapy
  - Patients with disease progression (local and/or distant) were non-eligible (≈ 5% in Proclaim)
  - Patients with severe side effects from chemo-radiation therapy were likely not eligible
  - Then, inclusion of the patients with the best prognosis (ORR ≈ 47% *vs*. 34% in Proclaim)



Antonia et al., NEJM 2018

Co-Primary Endpoint: PFS by BICR*



	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

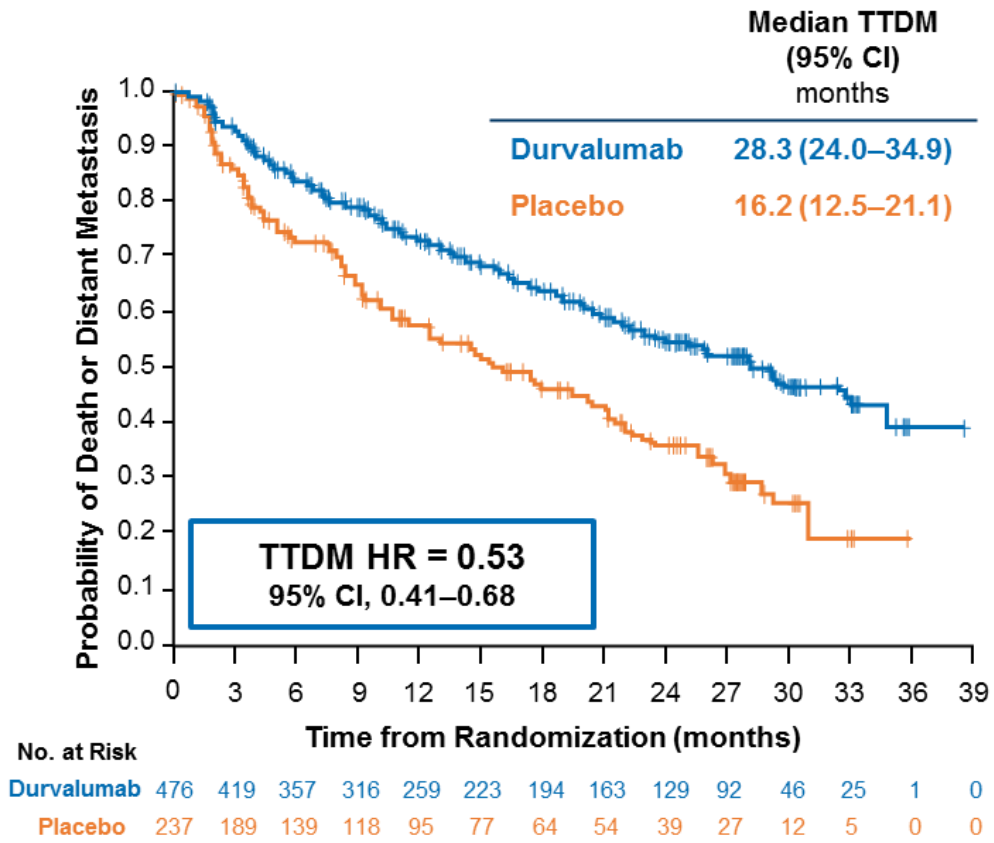
Median follow-up
25.2 months

*Blinded Independent Committee Review

Antonia et al.. WCLC 2018

Pacific: Reduction of the Risk of Metastatic Relapse

Updated Time to Death or Distant Metastasis (TTDM) by BICR* (ITT)



Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

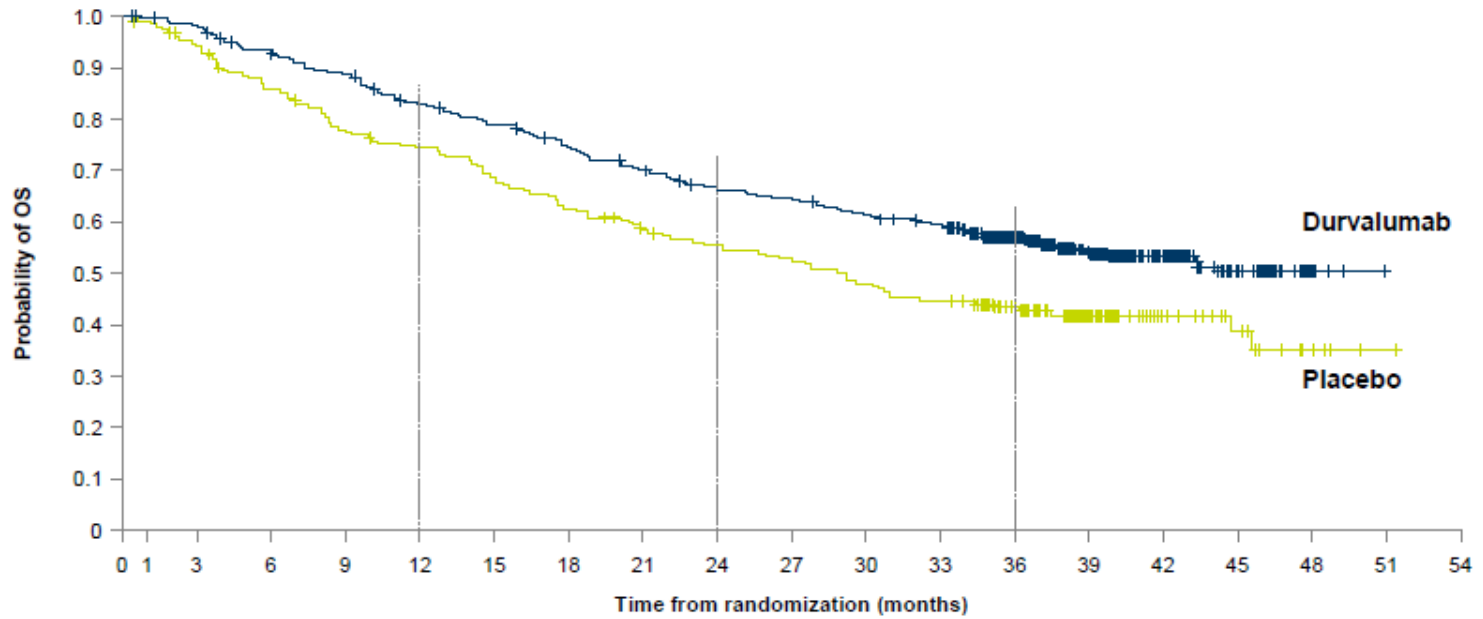
Antonia SJ. et al.. WCLC and N Engl J Med 2018

Pacific: Updated Overall Survival

Over 50% of patients who received durvalumab are alive at 36 months

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



No. at risk																		
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

NR, not reached

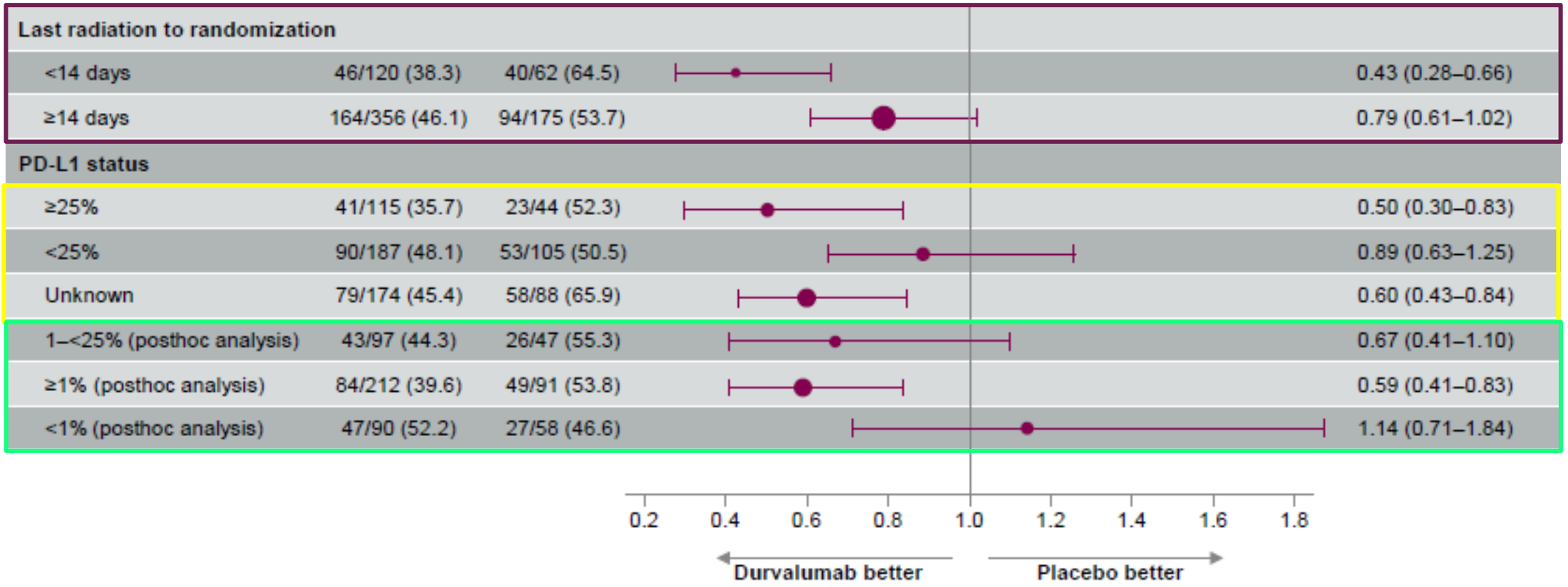
Gray J. et al.. ASCO 2019

Indirect Comparison of PFS & OS between Pacific and Chemoradiation Trials for Stage III NSCLC

	No. of Pts	Median PFS	Median OS and 2-yr OS
PACIFIC CRT⇒Durvalumab	476	17.2 m (from randomization)	Not reached **2-yr: 66.3%**
PACIFIC (Control arm) CRT	237	5.6 m (from randomization)	29.1 months 2-yr: 55.3%
RTOG 0617 CBDCA/Paclitaxel + TRT 60 Gy	217	11.8 m	28.7 months 2-yr: 57.6%
PROCLAIM CDDP/Pemetrexed +TRT	301	11.4 m	26.8 months 2-yr: 52%

Gray J. et al.. ASCO 2019; Senan. JCO 2015; Bradley. Lancet Oncol 2015

Subgroup analysis according to time from radiation to randomization and PD-L1 expression



Gray J. et al.. ASCO 2019

"Pneumonitis"

Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*	Durvalumab (N=475)	Placebo (N=234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

	Overall Study				Concurrent Phase			
	Arm A (n = 283)		Arm B (n = 272)		Arm A (n = 283)		Arm B (n = 272)	
CTCAE Term	Any Gr*	Gr 3–4	Any Gr*	Gr 3–4	Any Gr†	Gr 3–4	Any Gr†	Gr 3–4
Pneumonitis	**48 (17.0)**	5 (1.8)	29 (10.7)	7 (2.6)	4 (1.4)	0 (0.0)	4 (1.5)	2 (0.7)

Antonia et al., NEJM 2017; Senan, JCO 2015

Locally Advanced NSCLC
Building on a New Standard of Care

- Locally advanced NSCLC is treated with a curative intent
- The Pacific trial with consolidation durvalumab has established a new SoC: ≈ +14% patients alive at 3 years and likely ≈ +10% patients cured
- Next steps
  - Addition of CPIs to concurrent chemoradiation is feasible and assessed in clinical trials
  - Replacement of chemotherapy with immunotherapy in selected patients might maintain efficacy and decrease toxicity