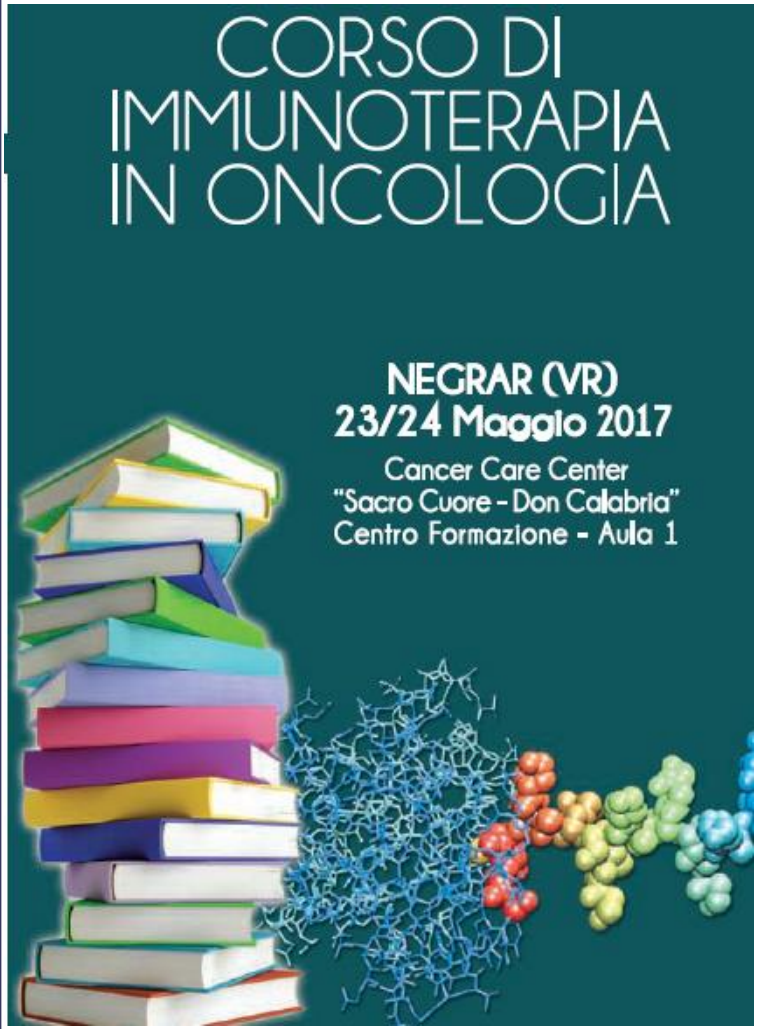


NSCLC: immunotherapy as a first-line treatment

Paolo Bironzo

Oncologia Polmonare – AOU S. Luigi Gonzaga

Orbassano (To)

The 800-pound gorilla

Platinum-based chemotherapy is the SOC for 1st-line therapy in advanced NSCLC without oncogenic drivers : ~ 85% caucasians

Platinum-based CT

NSCLC

No oncogenic-driver | EGFR or ALK

SCC | Non-SQUAMOUS

Platinum-doublet
+/- bev in non-SCC

1st line platinum-based chemotherapy is **not** the big Gorilla in EGFR mutant and ALK rearranged NSCLC only.

Group discussion

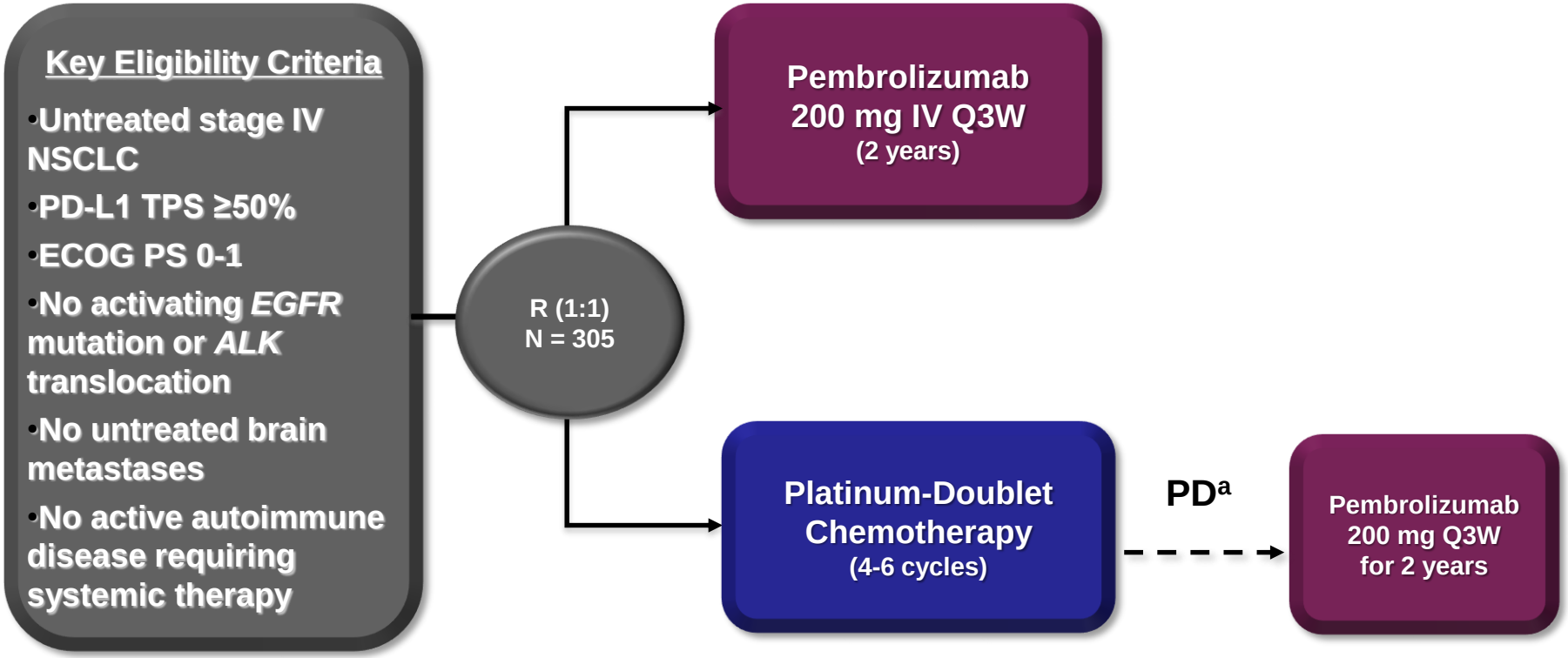
What are the evidences for single-agent front-line checkpoint inhibition? → We've got 2 phase 3 trials!

Are other strategies promising? → Platinum-doublets + PD-1 inhibitors (Ph2)

Can immune checkpoint inhibitors occupy this sit?

Pembrolizumab, a new standard (at least for some patients)

Phase 3 Keynote 024 Study Design



Primary: **PFS**

Secondary: OS, ORR, safety

Exploratory (prespecified): DOR, patient-reported outcomes

[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, NEJM 2016

1934 patients entered screening

500 TPS ≥ 50% (30%)

305 patients randomly allocated[a]

Pembrolizumab
- 154 allocated
- 154 treated

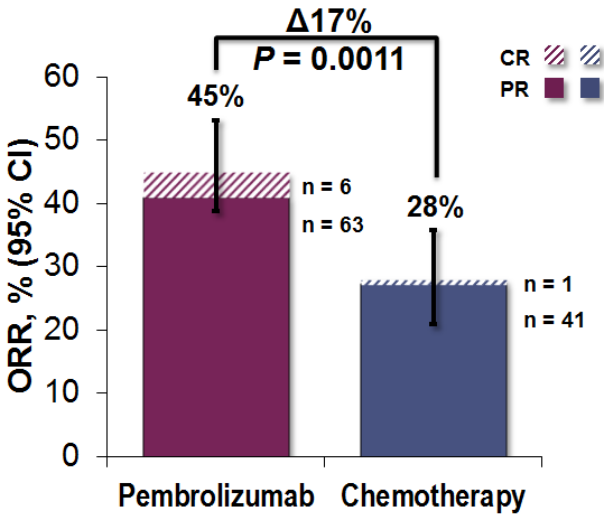
Chemotherapy
- 151 allocated
- 150 treated

- 74 ongoing
- 80 discontinued
  - 51 progressive disease
  - 17 AEs
  - 6 deaths
  - 4 patient withdrawal
  - 1 physician decision
  - 1 complete response

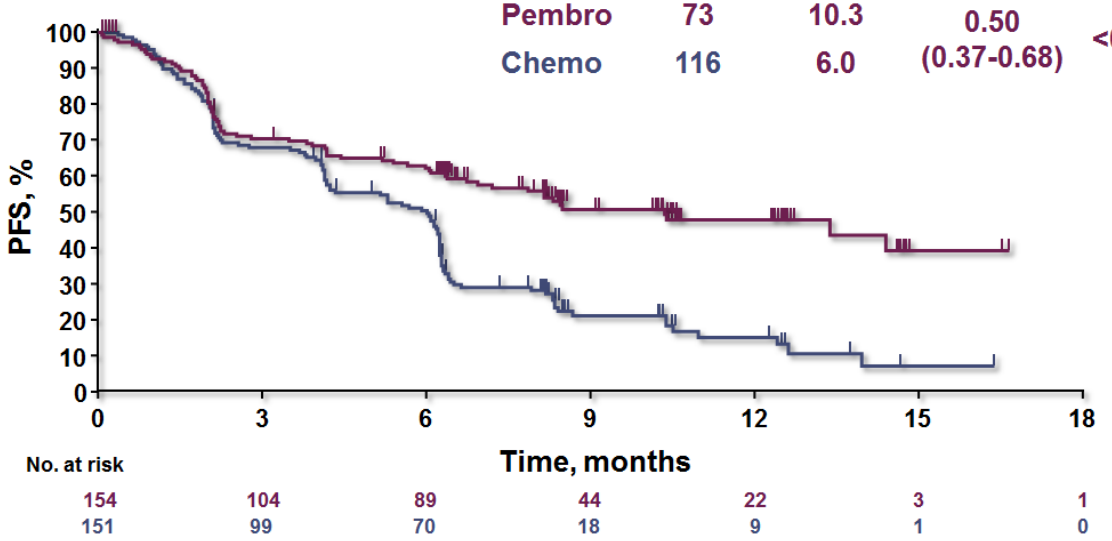
66/151 (44%) crossed over to pembrolizumab in study[b]

- 15 ongoing
- 106 discontinued
  - 69 progressive disease
  - 16 AEs
  - 9 deaths
  - 5 patient withdrawal
  - 7 physician decision
- 29 completed treatment

Reck M, NEJM 2016



Progression-Free Survival



	Events, n	Median, mo	HR (95% CI)	P
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		

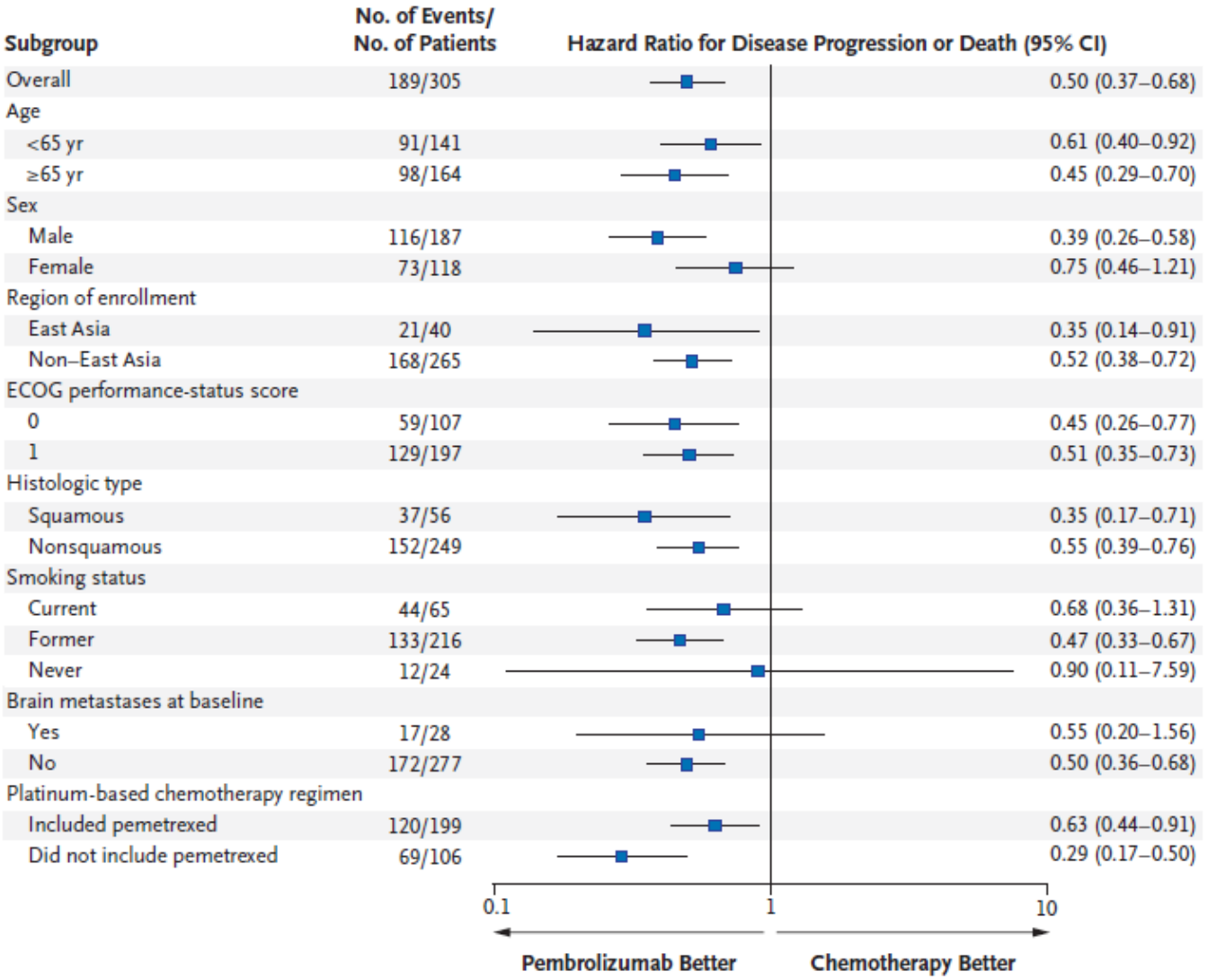
→ ORR is improved, with a control arm that performs as expected (from other phase III trials)

→ **45% ORR is the best RR ever reported in 1st line setting in Ph III trials (and with a monotherapy !)**

→ Time to Response is identical between Pembro and Chemo (2.2 months)

Reck M, NEJM 2016

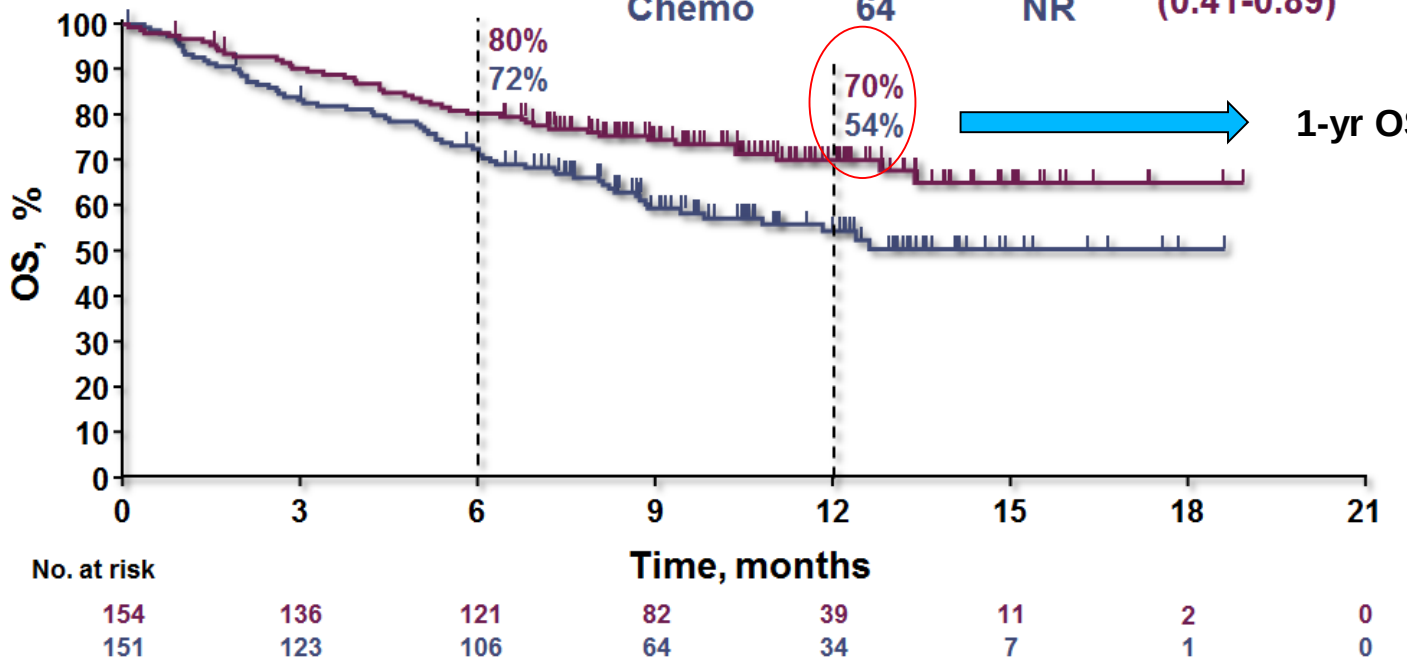
Subgroup analyses



Reck M, NEJM 2016

Overall Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



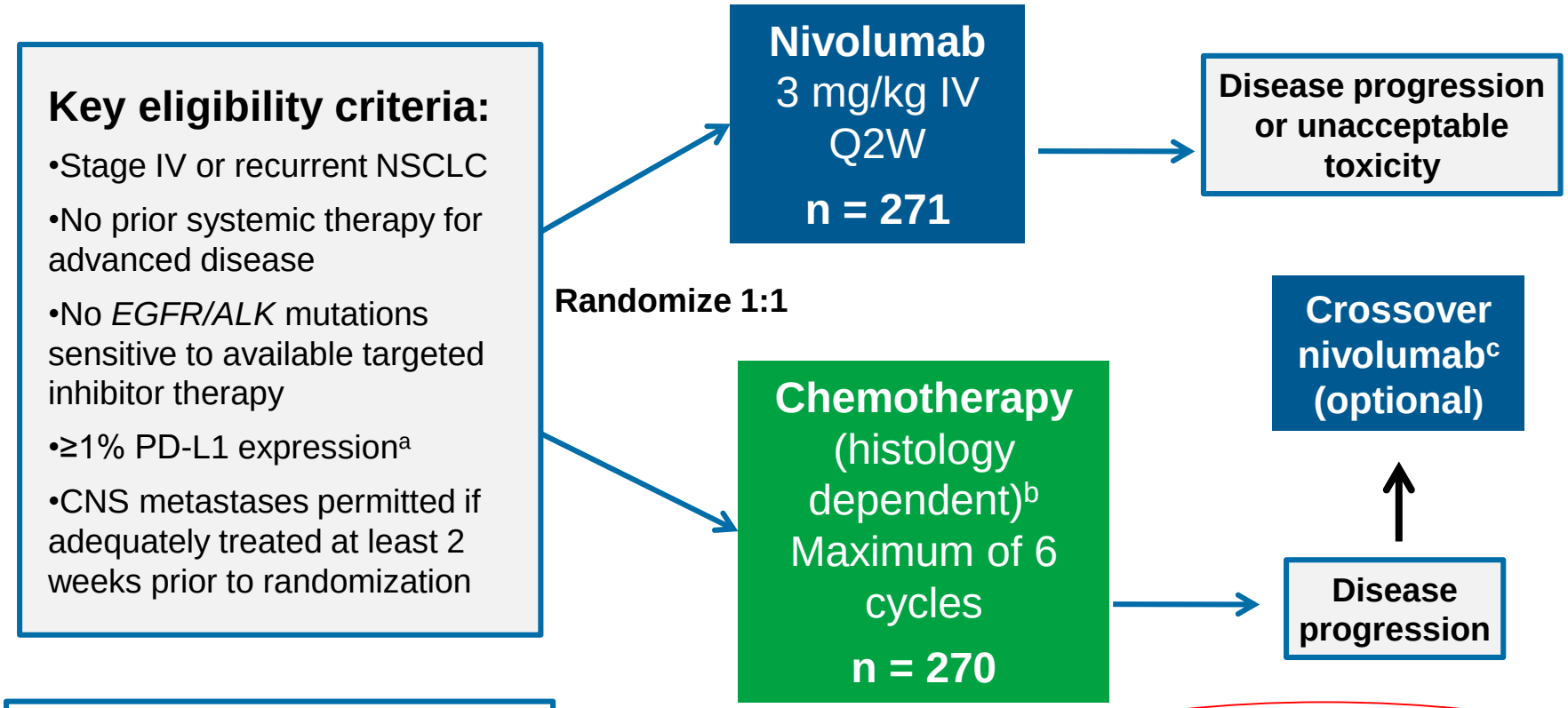
1-yr OS 70% vs 54%

FDA approval: October 24th, 2016
EMA approval: December 15th, 2016
AIFA reimbursement: May 19th 2017

Reck M, NEJM 2016

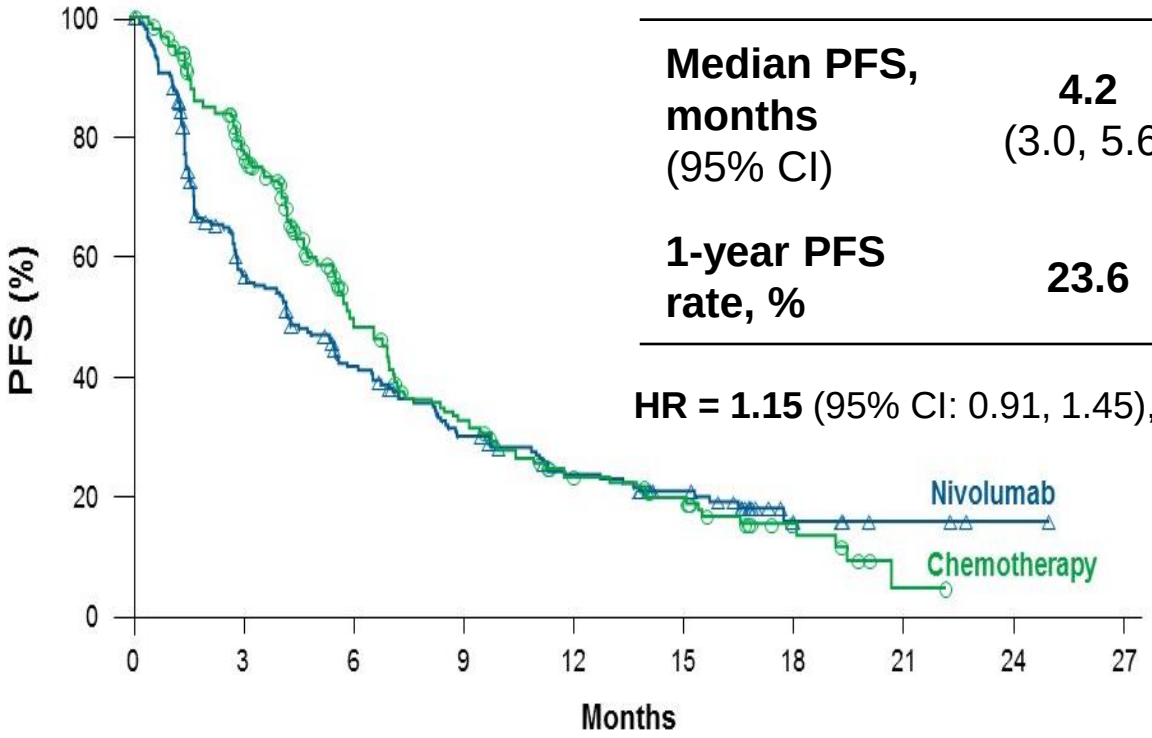
Nivolumab…a different story

Phase 3 CheckMate 026 Study Design



Socinski M, ESMO 2016

CheckMate 026: Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**

No. of patients at risk:

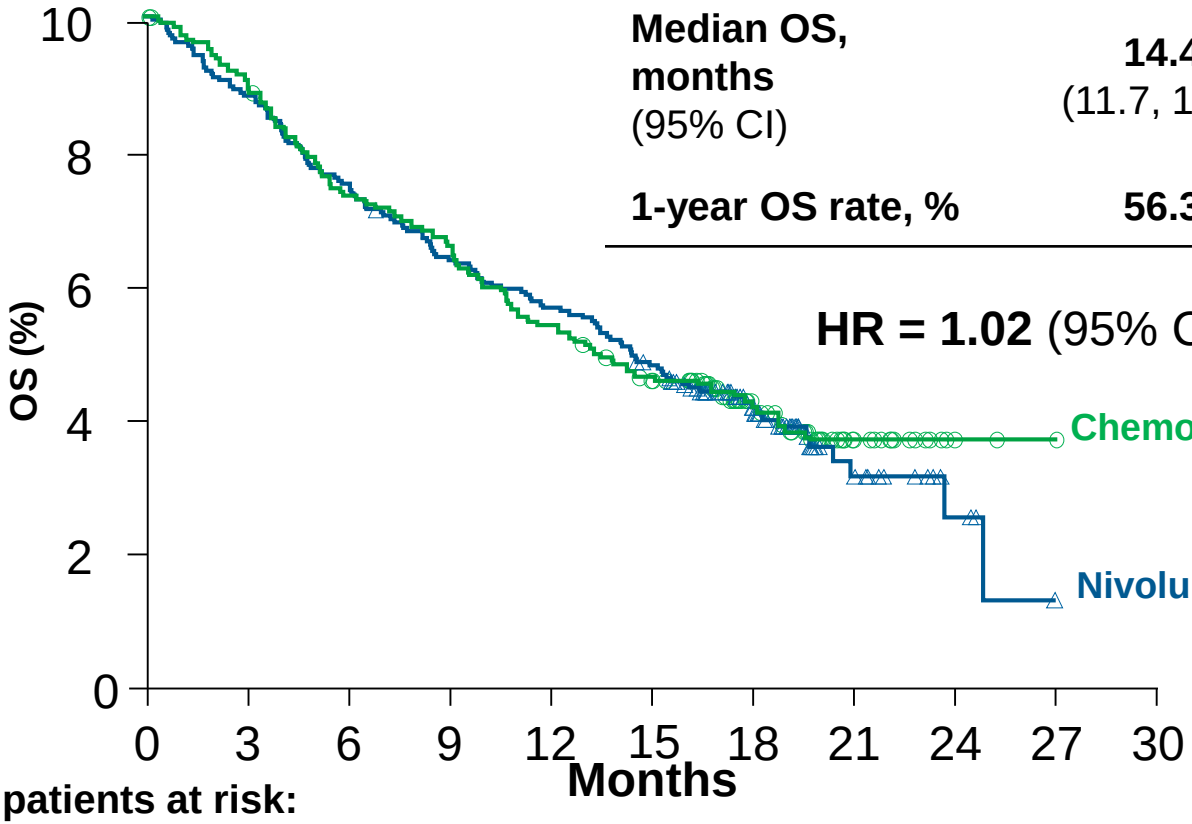
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemo	212	144	74	47	28	21	8	1	0	0

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

Socinski M, ESMO 2016

CheckMate026: OS (≥5% PD-L1+)

	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**



No. of patients at risk:

Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemo	212	186	153	137	112	91	50	15	3	1	0

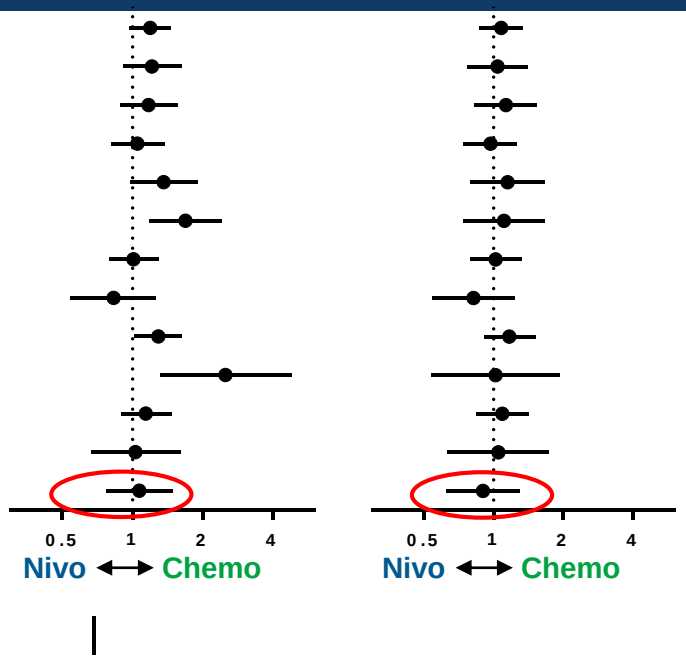
All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

Socinski M, ESMO 2016

Subgroup analyses

CheckMate 026: PFS and OS Subgroup Analyses (All Randomized Patients)

	Patients, n		Unstratified HR	
Subgroup	Nivolumab	Chemo	PFS	OS
Overall	271	270	1.19	1.08
≥65 years	123	137	1.21	1.04
<65 years	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Non-squamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥50% PD-L1+	88	126	1.07	0.90



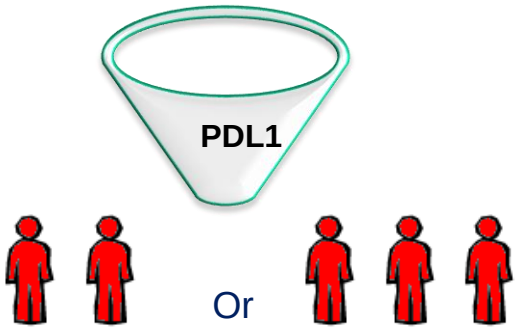
Why such divergent results in phase 3 trials ?

- Is nivolumab less active than pembrolizumab? **Unlikely** (see previous Ph2 and Ph3 studies in NSCLC)…
- Are enrolled patients different? 11% of non-smokers in CM vs 3% in KN; prior radiation: 37.6% in CM vs none* in KN
- Is PD-L1 the issue? Different threshold, antibodies, time of specimens collection (archival in CM vs fresh in KN).
- Different performances of control arms? **Not at all…**

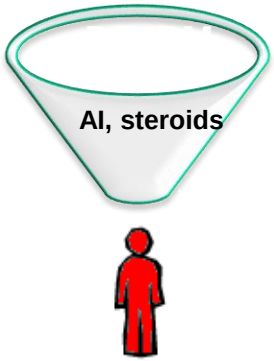
* No prior RT if performed < 6 months before starting immunotherapy and with less than 30 Gy

So pembro as a first line…but how many patients would be elegible in our dailiy clinical practice?

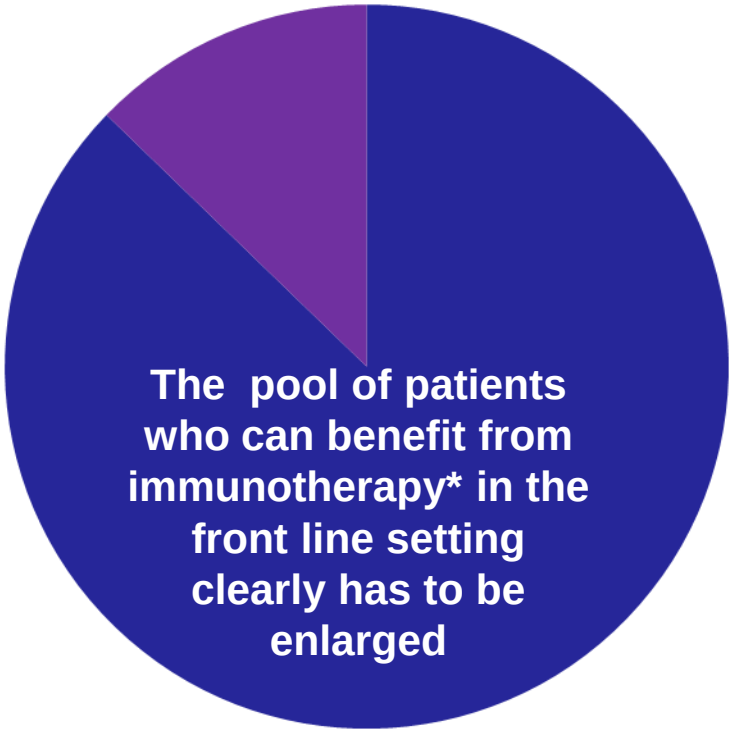
NSCLC patients in daily practice



NSCLC patients with PD-L1 ≥ 50%



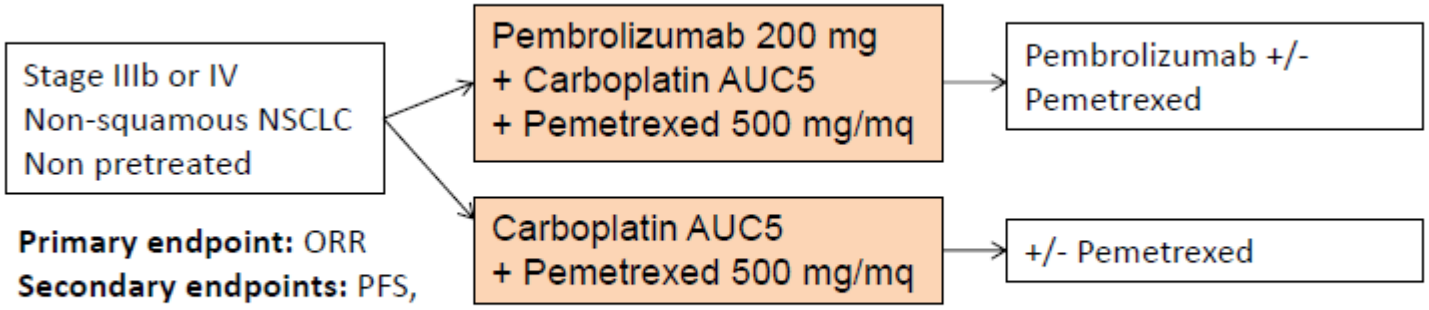
PS 0/1, no untreated BM, no AI, no steroids



* Pembrolizumab

How about combining treatments?

Is combo better than chemo?
Keynote-021 phase 2 trial cohort G

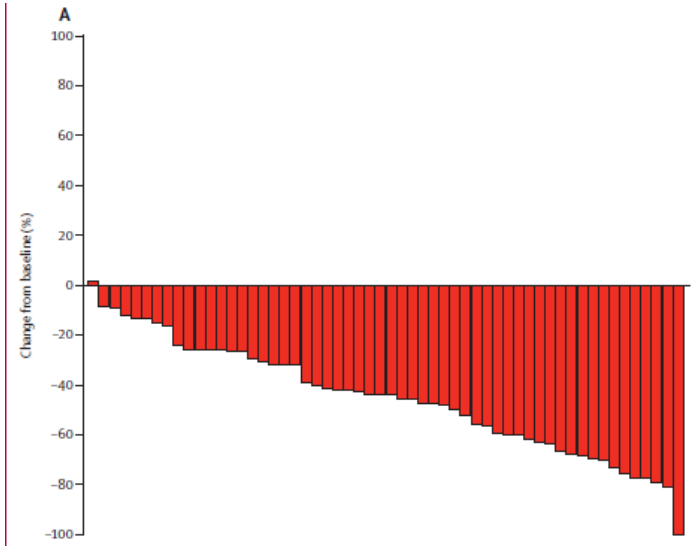


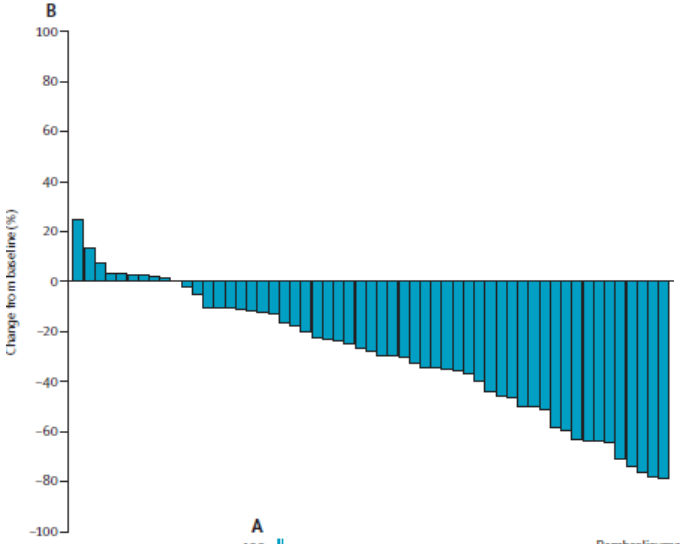
Primary endpoint: ORR
Secondary endpoints: PFS, OS, activity and PD-L1 correlation

Characteristics N(%)	Pembro plus chemo N = 60	Chemo N = 63
Adenocarcinoma	58 (97%)	55 (87%)
Current o former	45 (75%)	54 (86%)
PD-L1 < 1%	21 (35%)	23 (37%)
PD-L1 1-49%	19 (32%)	23 (37%)
PD-L1 > 50%	23 (33%)	17 (27%)

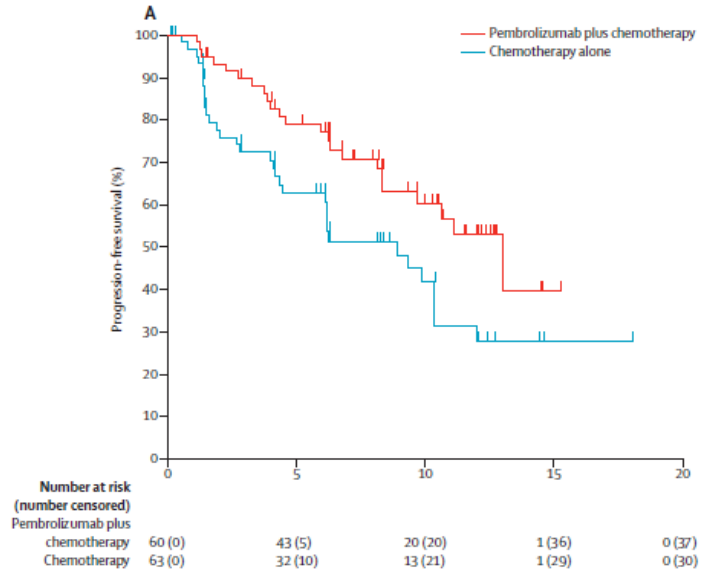
Langer CJ, Lancet Oncol 2016

Is combo better than chemo?
Keynote-021 phase 2 trial cohort G





Results	Pembro + Chemo	Chemo	HR	p value
ORR %	55%	29%	-	0.0016
PFS	13 months	8.9 months	0.53	0.010



Langer CJ, Lancet Oncol 2016

Is combo better than chemo?
Keynote-021 phase 2 trial cohort G

	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Related to treatment*								
Any	32 (54%)	18 (31%)	4 (7%)	1 (2%)	40 (65%)	12 (19%)	2 (3%)	2 (3%)
Serious	2 (3%)	10 (17%)	3 (5%)	1 (2%)	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Led to discontinuation	1 (2%)	4 (7%)	0	1 (2%)	5 (8%)	1 (2%)	0	2 (3%)
Led to death	0	0	0	1 (2%)	0	0	0	2 (3%)
Of interest based on a presumed immunological mechanism of action†‡								
Any	11 (19%)	1 (2%)	1 (2%)	0	6 (10%)	1 (2%)	0	0
Hypothyroidism	9 (15%)	0	0	0	3 (5%)	0	0	0
Hyperthyroidism	5 (8%)	0	0	0	1 (2%)	0	0	0
Pneumonitis	2 (3%)	1 (2%)	0	0	0	0	0	0
Infusion reactions	1 (2%)	0	1 (2%)	0	2 (3%)	0	0	0
Severe skin reactions	0	1 (2%)	0	0	0	1 (2%)	0	0

Data are presented as n (%). *As attributed by the investigator. Events are listed in order of descending frequency in the pembrolizumab plus chemotherapy group. †Listed in order of descending frequency in the total population. ‡Events include related terms, are provided regardless of attribution to study treatment by the investigator, and are listed in order of descending frequency in the pembrolizumab group.

Table 3: Adverse events in the as-treated population

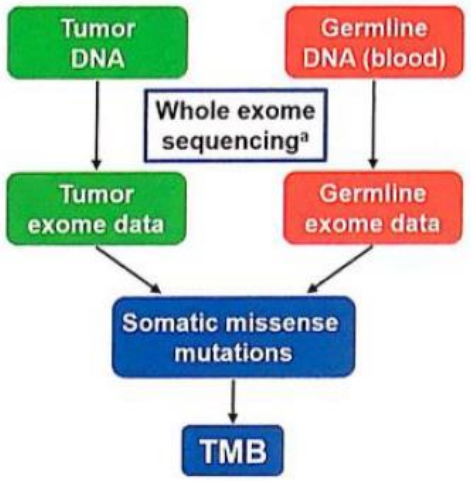
Grade 3 or worse AEs: 39% vs 26%

Selected AEs with high rate of incidence: fatigue, nausea, anaemia.

AEs with ≥ 10% difference between arms: rash (27% vs 15%), alopecia (14% vs 3%)

Langer CJ, Lancet Oncol 2016

Improve patients selection: TMB?



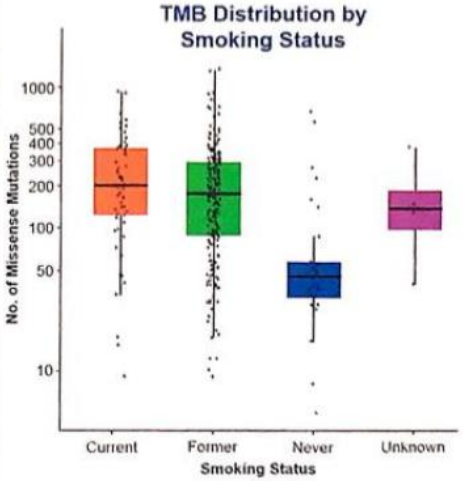
[a]DNA was sequenced on the Illumina HiSeq 2500 using 2 × 100-bp paired-end reads; an average of 84 and 89 million reads were sequenced per tumor and germline sample, respectively (average 84.6 × and 93 × the mean target coverage, respectively)

Characteristic	Nivolumab (n = 158)	Chemotherapy (n = 154)
Median age, years (range)	65 (32, 89)	64 (34, 87)
Female, %	33.5	46.8
ECOG PS, %		
0	29.1	35.1
1/2	69.6/0.6	63.6/1.3
Smoking status, %		
Current/former smoker	15.2/73.4	20.8/69.5
Never smoker	10.1	8.4
Tumor histology, %		
Squamous	22.8	22.7
Non-squamous	77.2	77.3
PD-L1 expression level, %		
≥5%	79.1	82.5
≥50%	36.1	47.4
TMB tertile, %		
Low	39.2	26.6
Medium	31.0	34.4
High	29.7	39.0

58% of randomized patients.

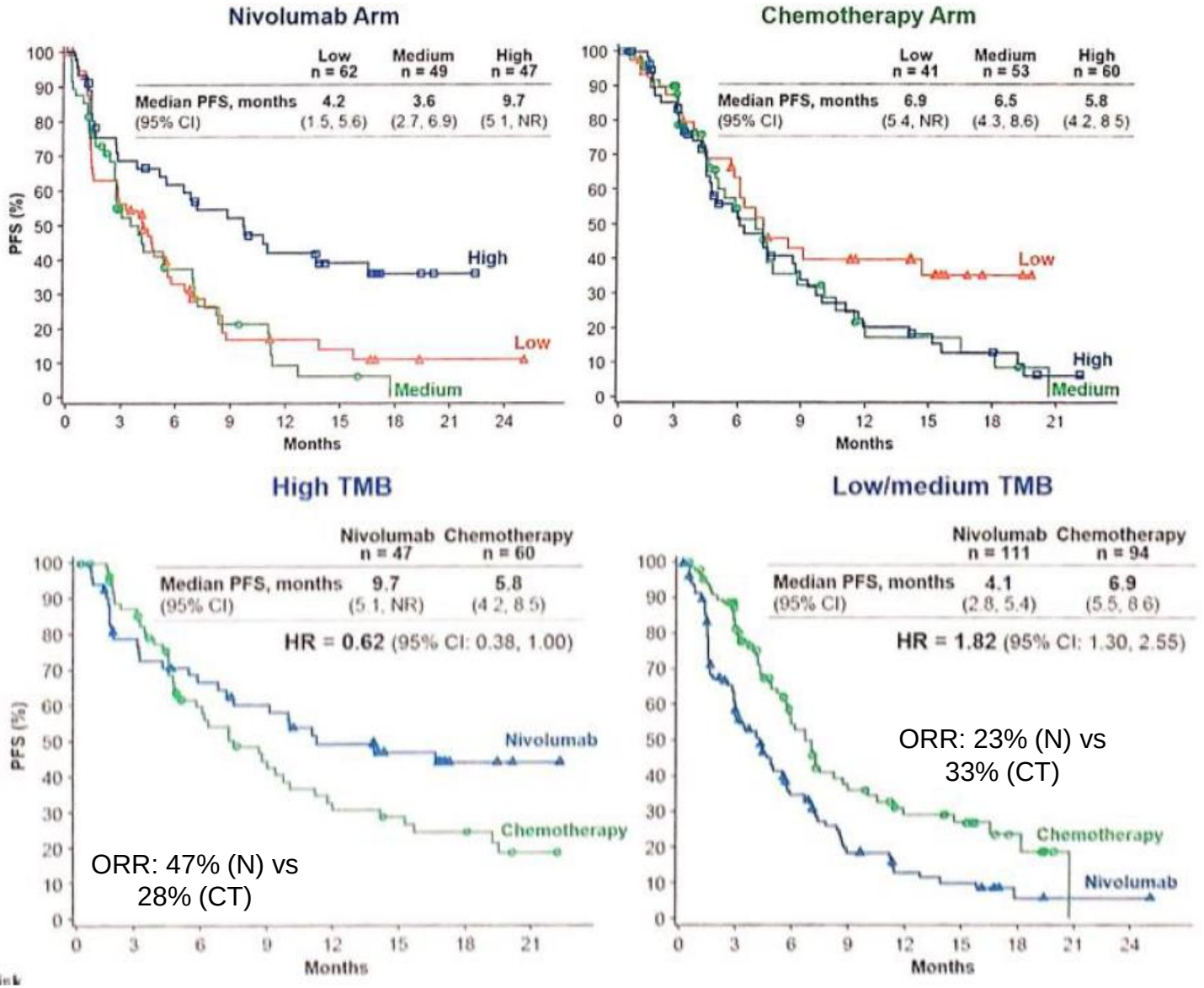
TMB subgroups divided according to tertile distribution

Characteristic	High TMB (n = 107)	Low/medium TMB (n = 205)
Median age, years (range)	65 (40, 87)	65 (32, 89)
Female, %	36.4	42.0
ECOG PS, %		
0	31.8	32.2
1/2	67.3/0.9	66.3/1.0
Smoking status, %		
Current smoker	22.4	15.6
Former smoker	73.8	70.2
Never smoker	2.8	12.7
Disease stage, %		
Stage IV	91.6	94.1
Recurrent	7.5	5.9
Tumor histology, %		
Squamous	29.0	19.5
Non-squamous	71.0	80.5
PD-L1 expression level, %		
≥5%	77	83
≥25%	60	59
≥50%	45	40



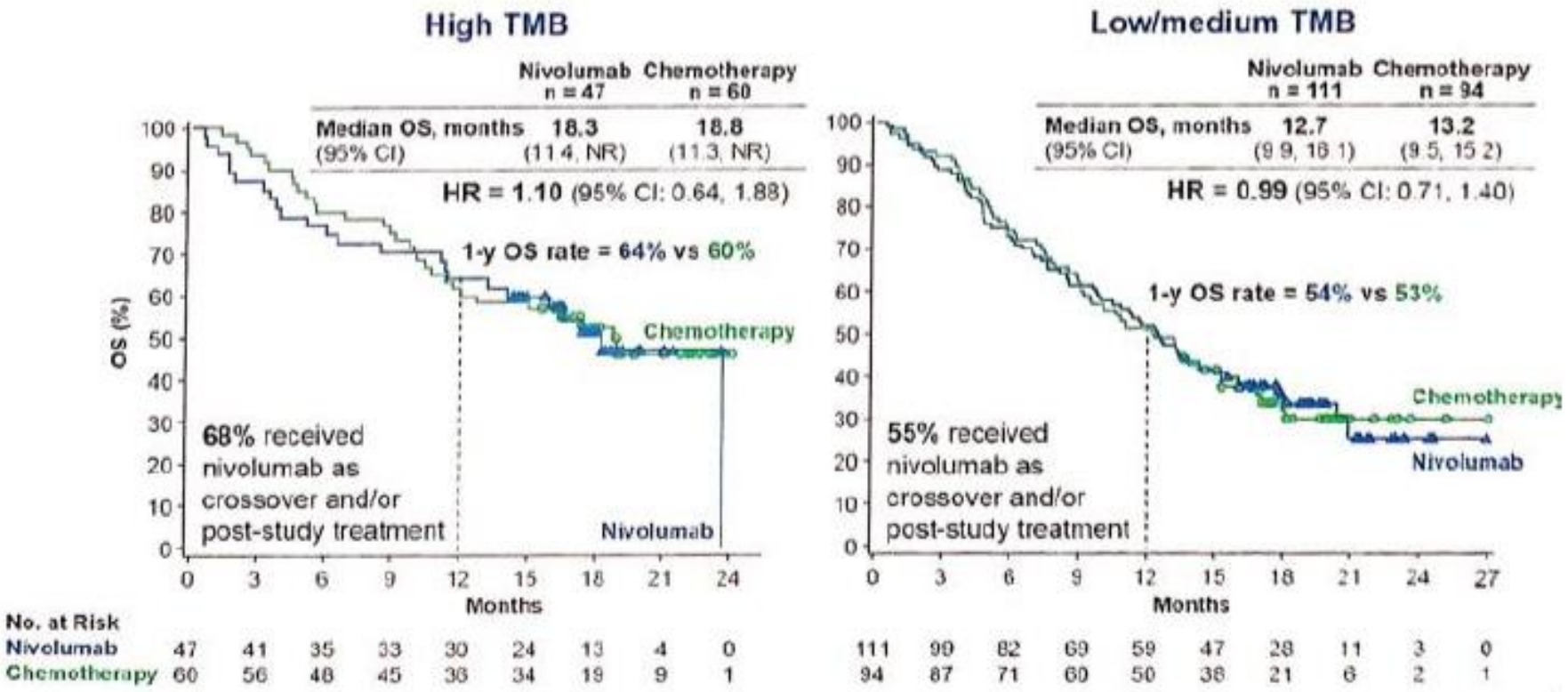
Peters S, AACR 2017C

PFS by subgroups



Peters S, AACR 2017C

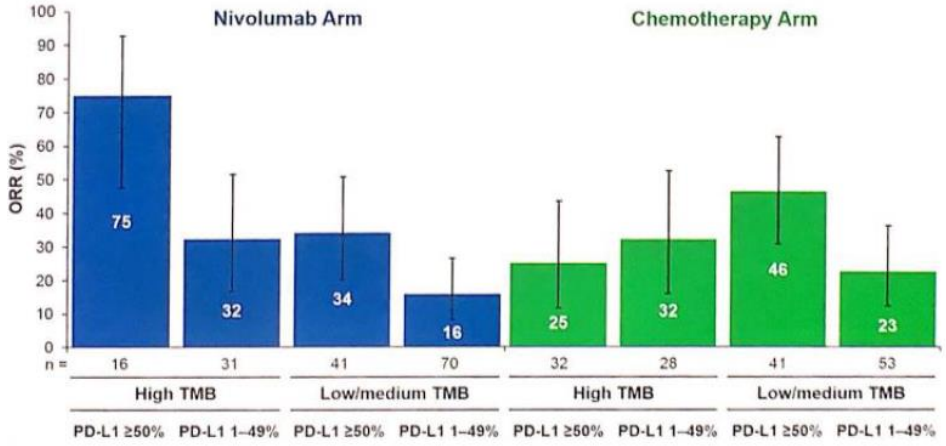
OS by subgroups

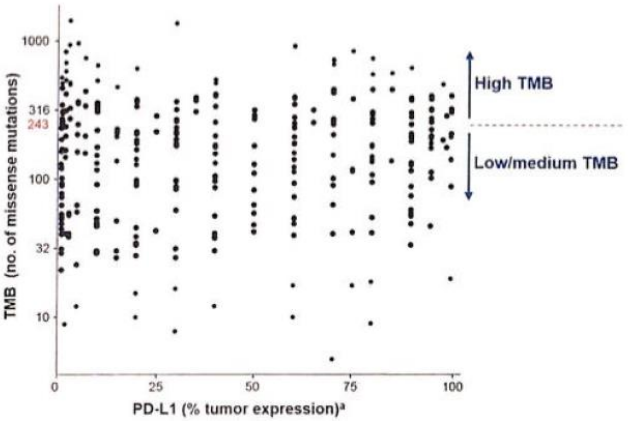


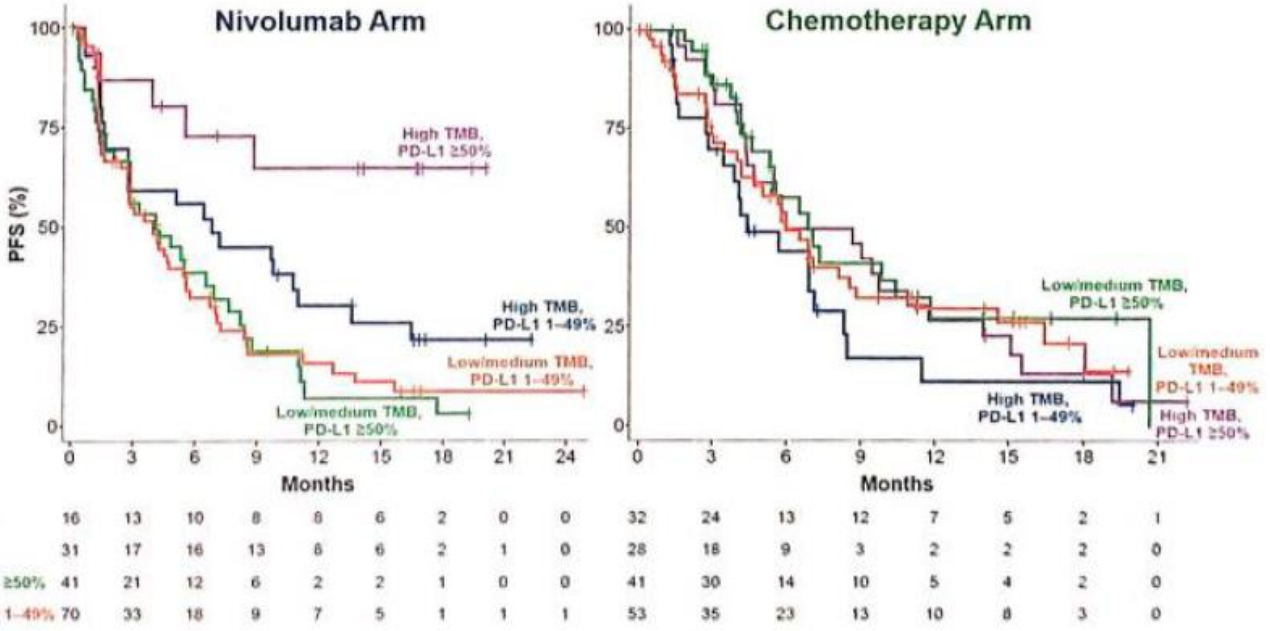
Peters S, AACR 2017C

PD-L1 and TMB

NO association between TMB and PD-L1 expression in patients with >1% of PD-L1







Peters S, AACR 2017C

Still many questions to be answered…

- Is the role of PD-L1 expression so sure for front-line single agent immunotherapy patients selection? Waiting for **Keynote 042**
- How to enlarge Keynote 024 population? The issue of PS 2 patients.
- How can we select patients for checkpoint inhibition in first-line setting? Going beyond PD-L1…TMB?
- Will combinations keep promises? Waiting for phase 3 data…
- If so, are combinations better than single-agent checkpoint inhibitors in all patients?
- And are they better than sequences?

And now, what should we do in daily clinical practice?

- Pembrolizumab is the first line treatment for advanced NSCLC with PD-L1 expression ≥50% without uncontrolled autoimmune disease and high dose steroids
- Testing PD-L1 will become mandatory at diagnosis