Check Mate-026

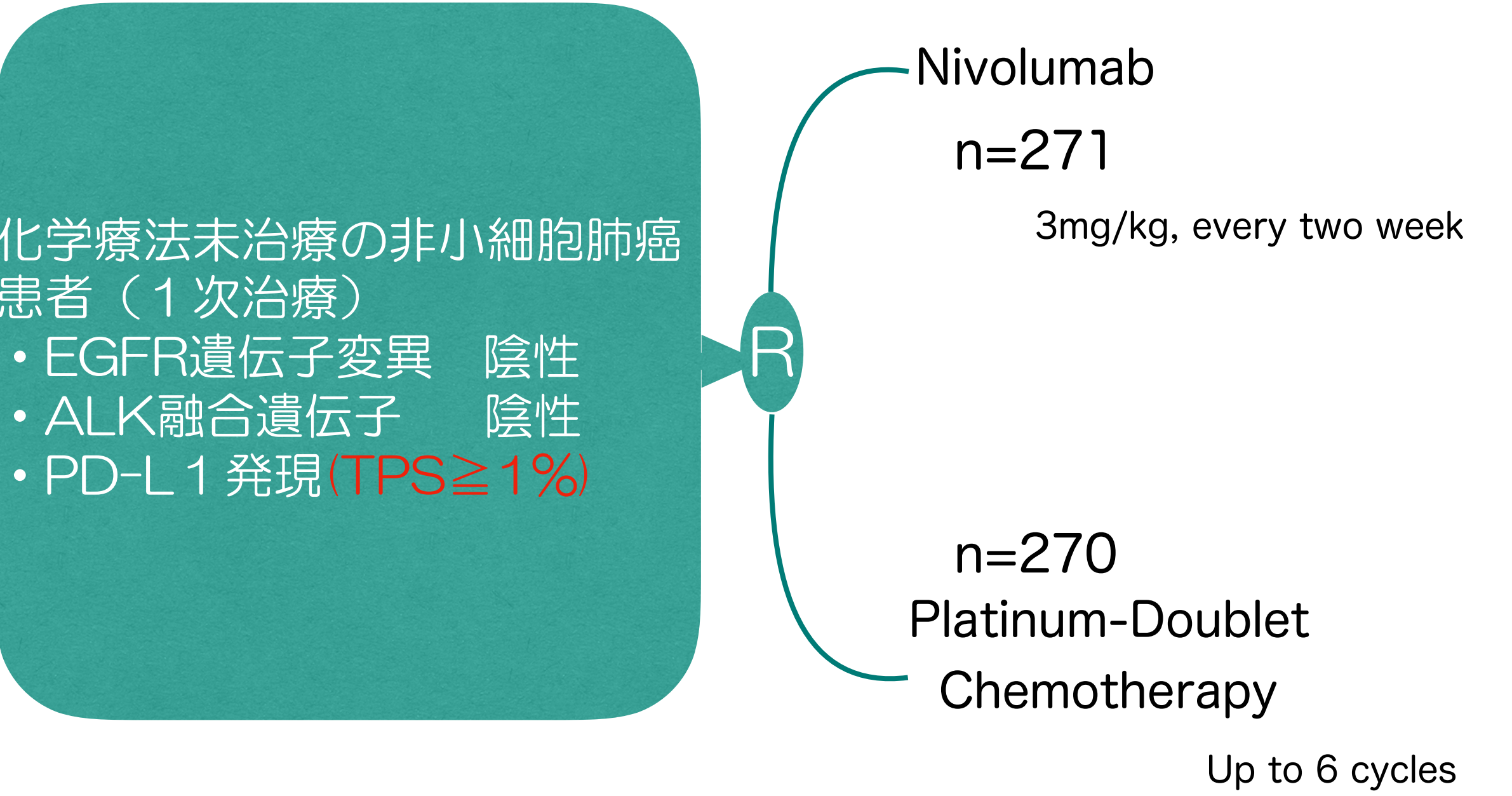# Check Mate-026

Primary Endpoint: PFS per BIRC (TPS≧5%)

Secondary Endpoint: PFS per BIRC (TPS≧1%), OS, ORR

非小細胞肺癌患者

All comer（腺癌、扁平上皮癌）

化学療法未治療の非小細胞肺癌患者（１次治療）
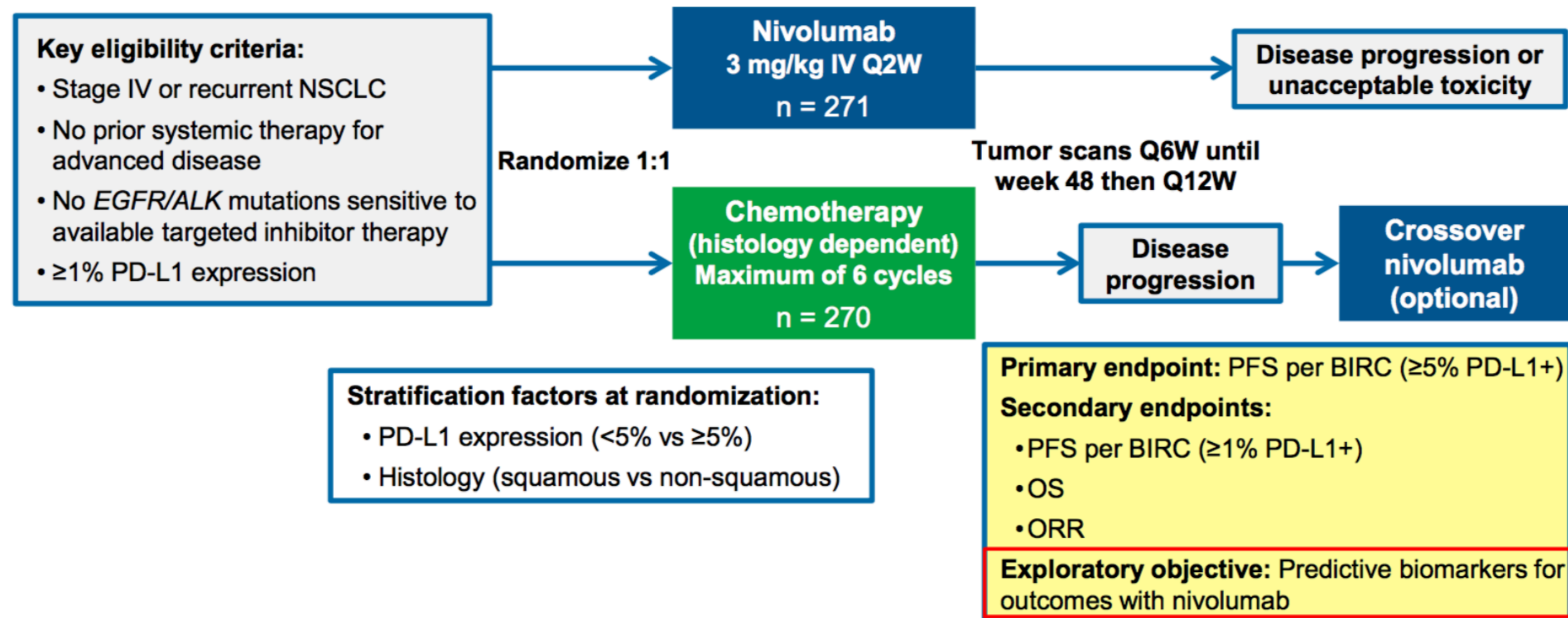• EGFR遺伝子変異　陰性
• ALK融合遺伝子　　陰性
• PD-L１発現(TPS≧1%)

R

Nivolumab
n=271
3mg/kg, every two week

n=270
Platinum-Doublet
Chemotherapy
Up to 6 cycles

（PD後のNivolumab Cross Over許容）

	TPS≧5%			TMB	
				High	Low
	ORR	mPFS	OS	OR	PFS
Nivolumab	26%	4.2ヶ月	14.4ヶ月	47%	9.7ヶ月
		HR=1,15	HR=1,02		
Chemotherapy	33%	5.9ヶ月	13.2ヶ月	28%	5.8ヶ月

Table S4. Chemotherapy Study Treatments (All Treated Patients).

Study treatments, n (%)	Chemotherapy n = 263
Pemetrexed/carboplatin	115 (43.7)
Pemetrexed/cisplatin	86 (32.7)
Gemcitabine/carboplatin	33 (12.5)
Gemcitabine/cisplatin	13 (4.9)
Paclitaxel/carboplatin	16 (6.1)
Maintenance pemetrexed, n (%)	100 (38.0)

（PD1／PDL1-105）

CHECKMATE 026: FIRST-LINE NIVOLUMAB VERSUS CHEMOTHERAPY

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W
n = 271

Chemotherapy
(histology dependent)
Maximum of 6 cycles
n = 270

Tumor scans Q6W until week 48 then Q12W

Disease progression or unacceptable toxicity

Disease progression

Crossover nivolumab (optional)

Stratification factors at randomization:
- PD-L1 expression (<5% vs ≥5%)
- Histology (squamous vs non-squamous)

Primary endpoint: PFS per BIRC (≥5% PD-L1+)
Secondary endpoints:
- PFS per BIRC (≥1% PD-L1+)
- OS
- ORR

Exploratory objective: Predictive biomarkers for outcomes with nivolumab

- An exploratory analysis was conducted in CheckMate 026 to test the hypothesis that patients with high TMB may derive enhanced benefit from nivolumab
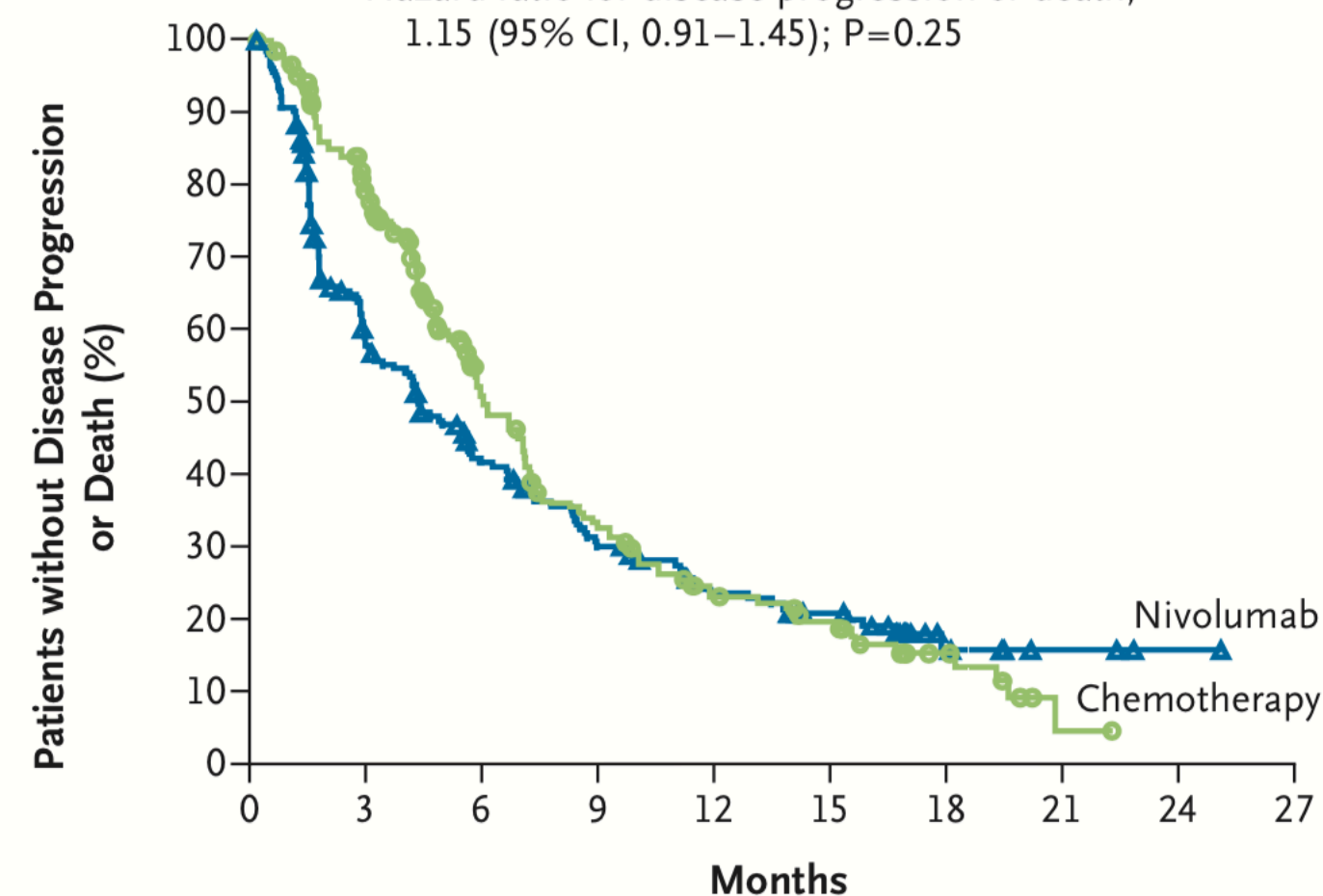
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PD1/PDL1-105

A Progression-free Survival

|	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

B Overall Survival

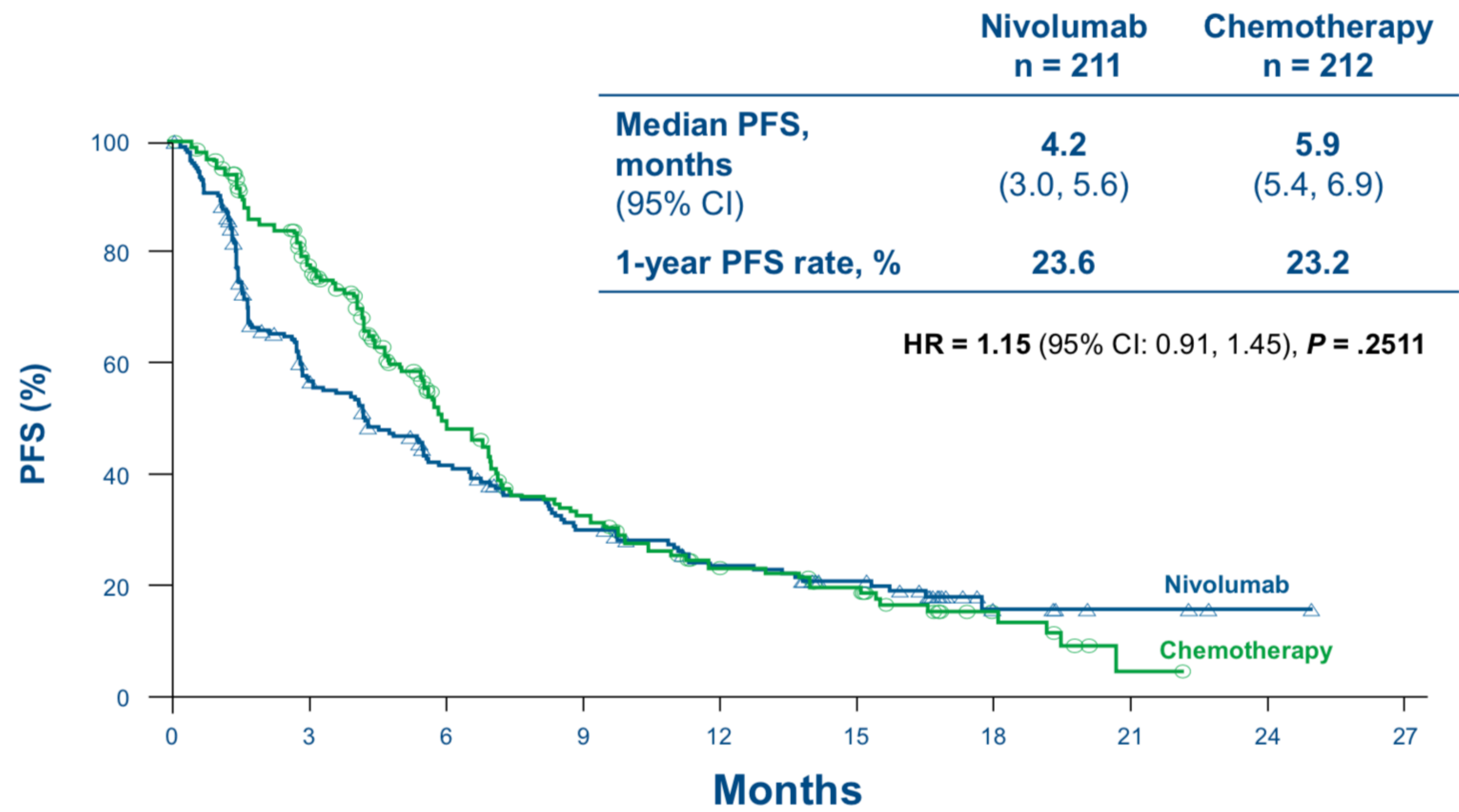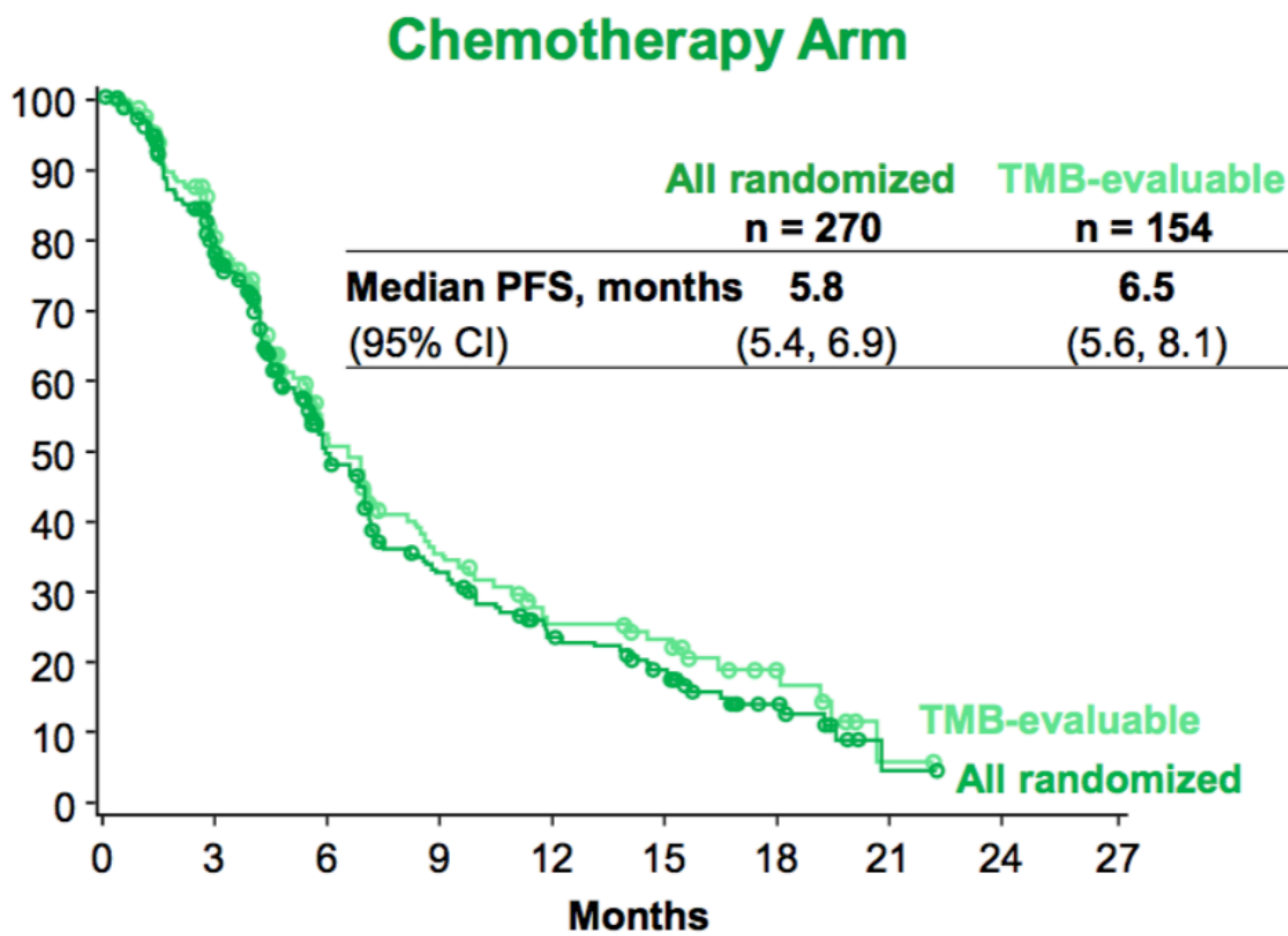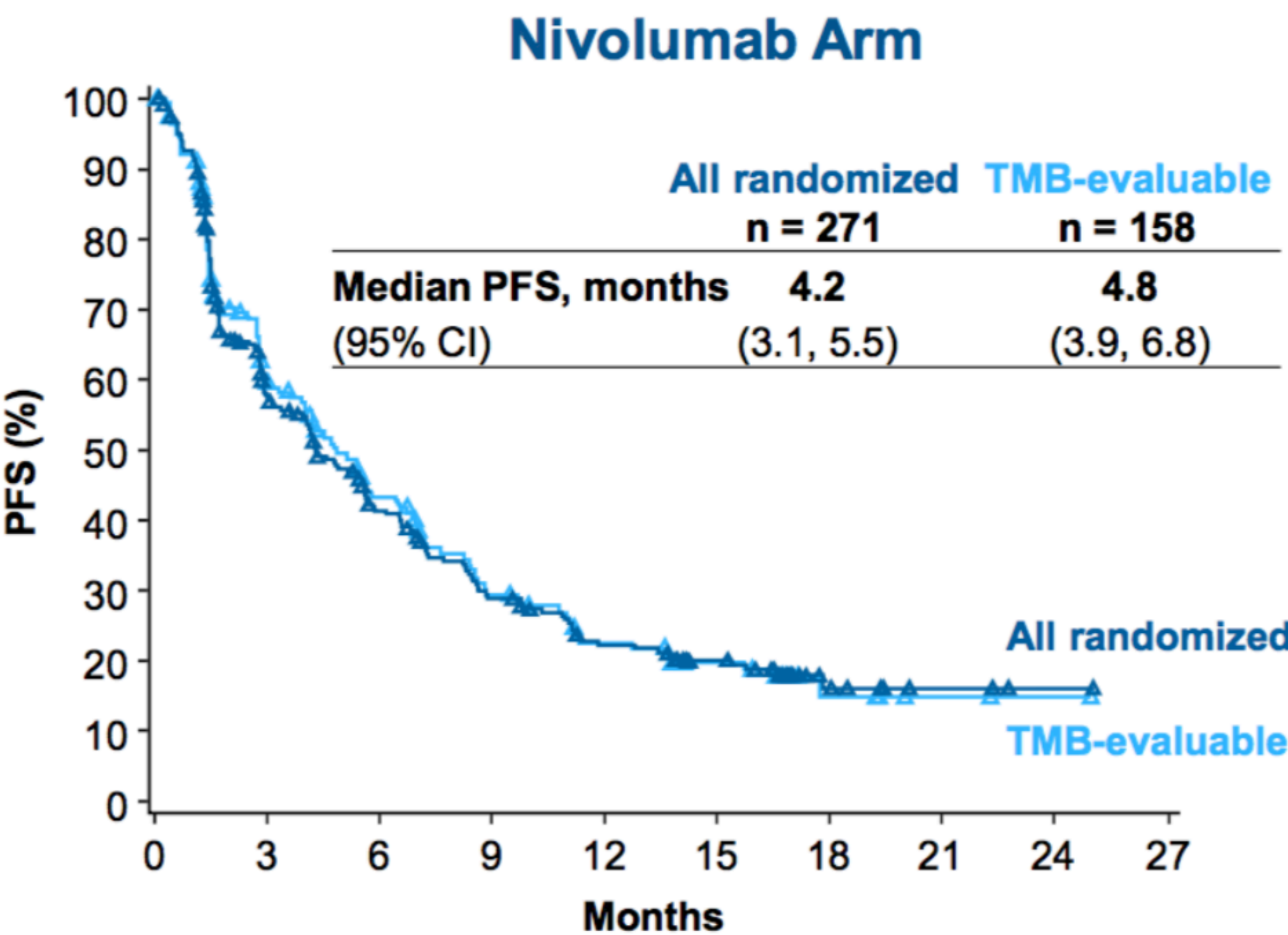|	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

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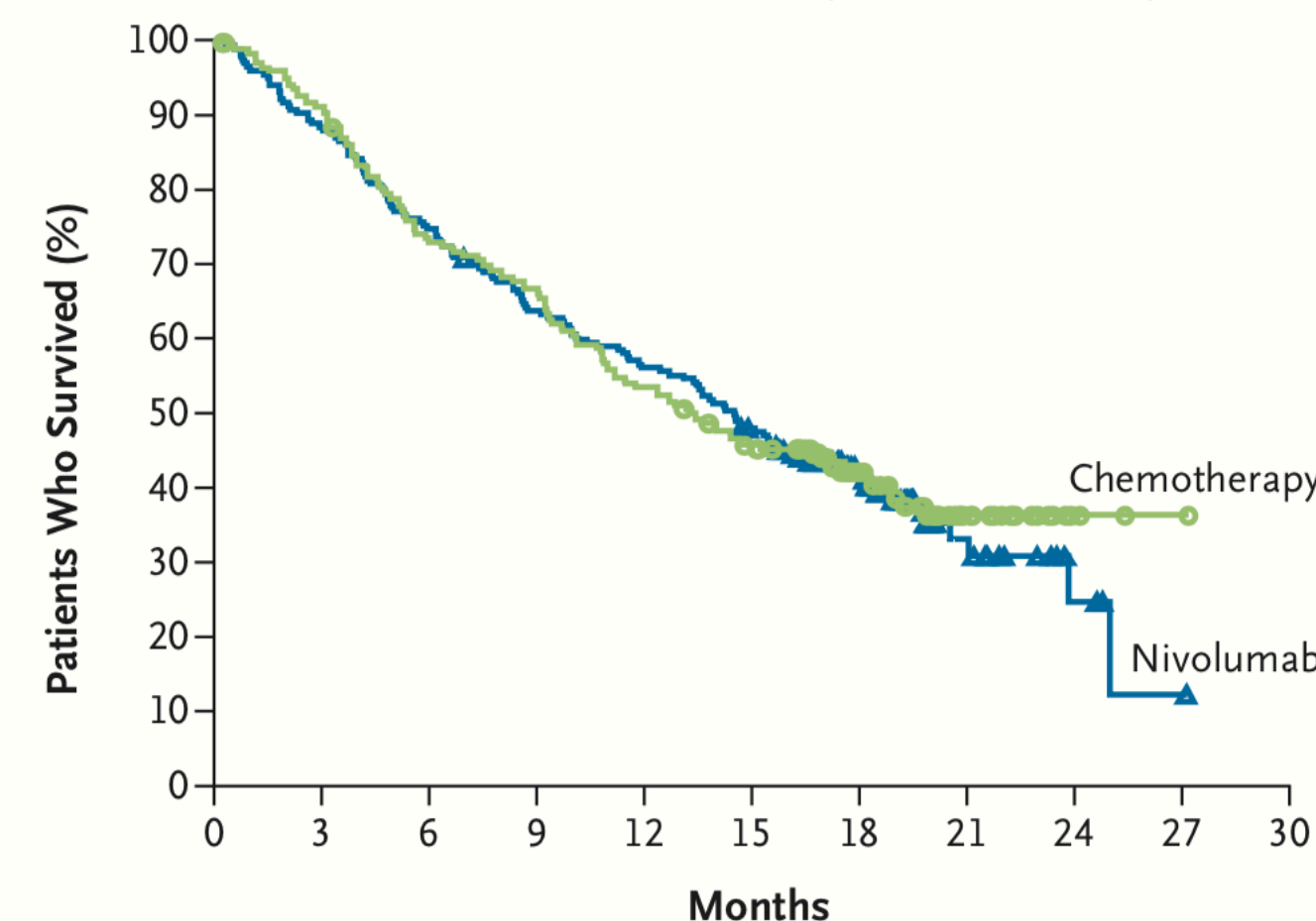
CONCLUSIONS

Nivolumab was not associated with significantly longer progression-free survival than chemotherapy among patients with previously untreated stage IV or recurrent NSCLC with a PD-L1 expression level of 5% or more. Overall survival was similar between groups. Nivolumab had a favorable safety profile, as compared with chemotherapy, with no new or unexpected safety signals. (Funded by Bristol-Myers Squibb and others; CheckMate 026 ClinicalTrials.gov number, NCT02041533.)

PFS (≥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 = .2511**

CHECKMATE 026: PFS

Nivolumab Arm

	All randomized n = 271	TMB-evaluable n = 158
Median PFS, months	4.2	4.8
(95% CI)	(3.1, 5.5)	(3.9, 6.8)

Chemotherapy Arm

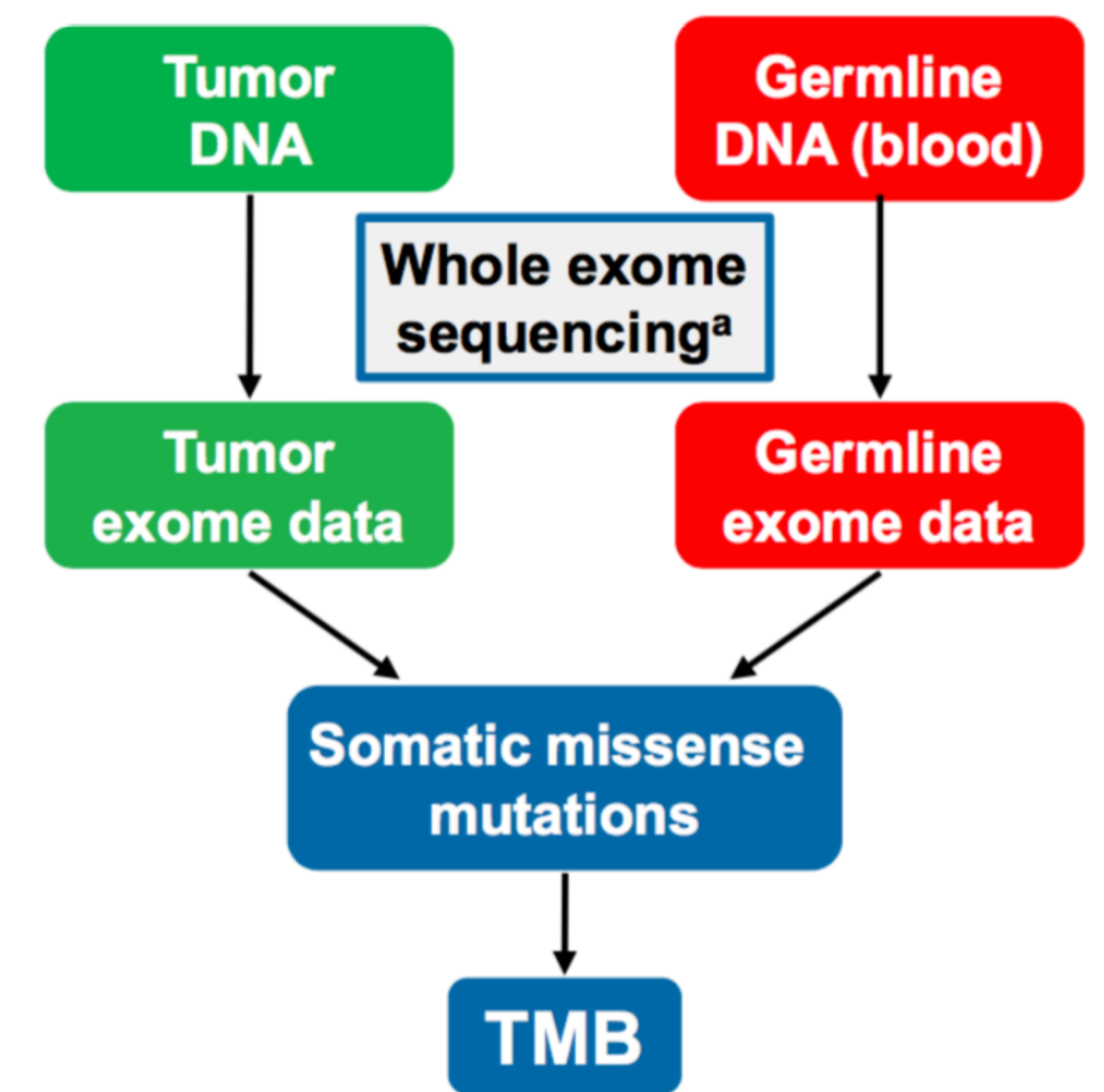|	All randomized n = 270	TMB-evaluable n = 154
Median PFS, months	5.8	6.5
(95% CI)	(5.4, 6.9)	(5.6, 8.1)

- OS in each treatment arm was also similar in patients with evaluable TMB data and all randomized patients

CHECKMATE 026: FIRST-LINE NIVOLUMAB VERSUS CHEMOTHERAPY

Tumor DNA	Germline DNA (blood)

Whole exome sequencing[a]

Tumor exome data	Germline exome data

Somatic missense mutations

TMB

Sample size throughout TMB determination		
Patients, n (%)	**Tumor DNA**	**Germline DNA**
Randomized	541 (100)	541 (100)
Samples available for DNA extraction[a]	485 (90)	452 (84)
DNA available for sequencing	408 (75)	452 (84)
Successful preparation of next-generation sequencing library	402 (74)	452 (84)
Passed internal quality control[b]	320 (59)	432 (80)
Matched tumor-germline exome sequences for TMB analysis[c]	312 (58)	

[a]Samples were not available for various reasons, including but not limited to lack of patient pharmacogenetic consent, samples exhausted for PD-L1 testing, or poor tissue sampling
[b]Internal quality control failure included factors such as discordance between tumor and germline DNA, too few sequence reads, and low or uneven target region coverage
[c]8 patients with available tumor DNA sequences did not have matched germline DNA sequences

[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)

CHECKMATE 026: BASELINE CHARACTERISTICS

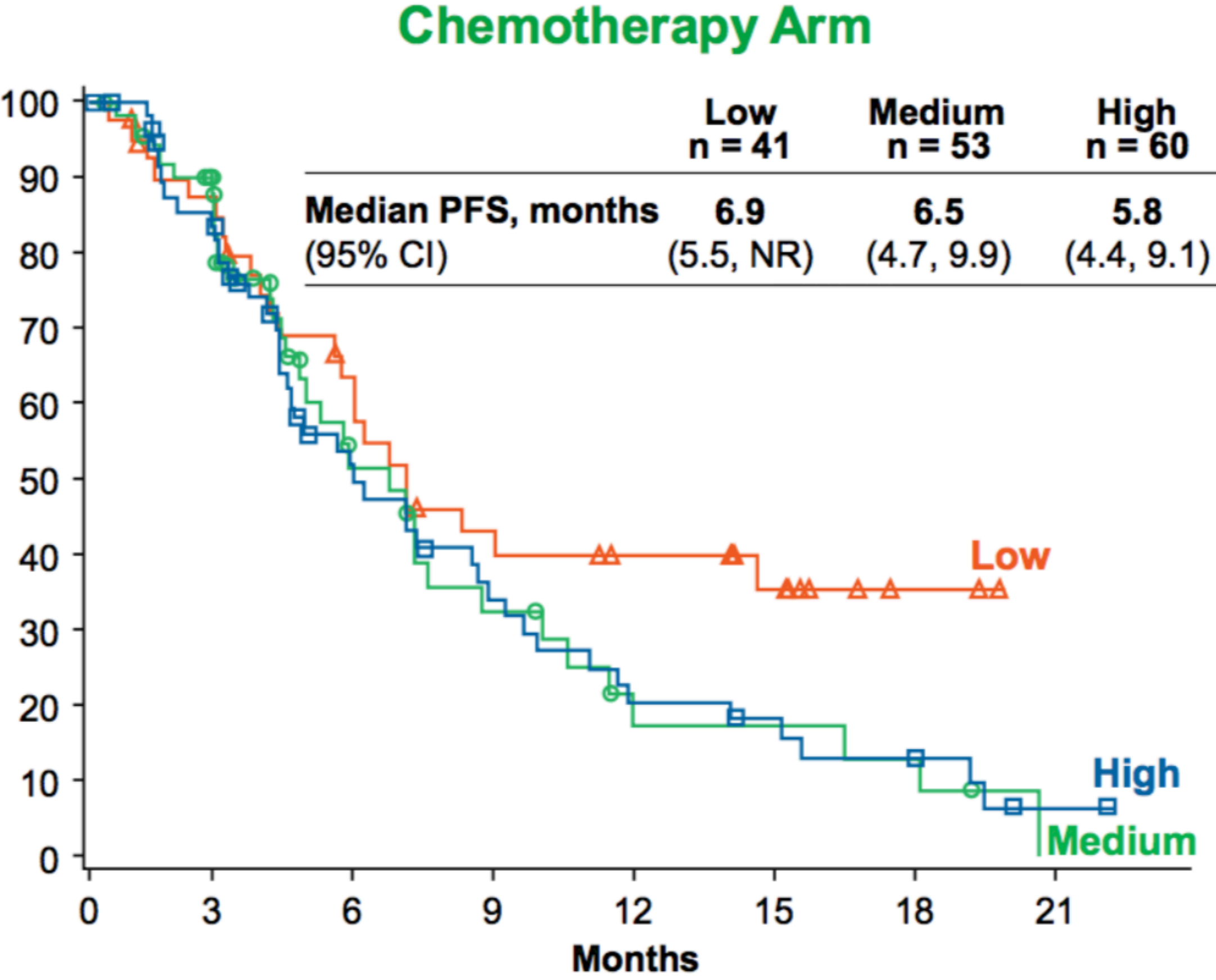| Characteristic	All randomized patients (n = 541)	TMB-evaluable patients (n = 312)
Median age, years (range)	64 (29, 89)	65 (32, 89)
Female, %	38.6	40.1
ECOG PS, %		
0	32.9	32.1
1/2	66.0/0.9	66.7/1.0
Smoking status, %		
Current/former smoker	19.8/68.0	17.9/71.5
Never smoker	10.9	9.3
Disease stage, %		
Stage IV	92.2	93.3
Recurrent	7.6	6.4
Tumor histology, %		
Squamous	24.0	22.8
Non-squamous	76.0	77.2
PD-L1 expression level, %		
≥5%	77.3	80.8
≥50%	39.6	41.7

CHECKMATE 026: EXPLORATORY ANALYSIS
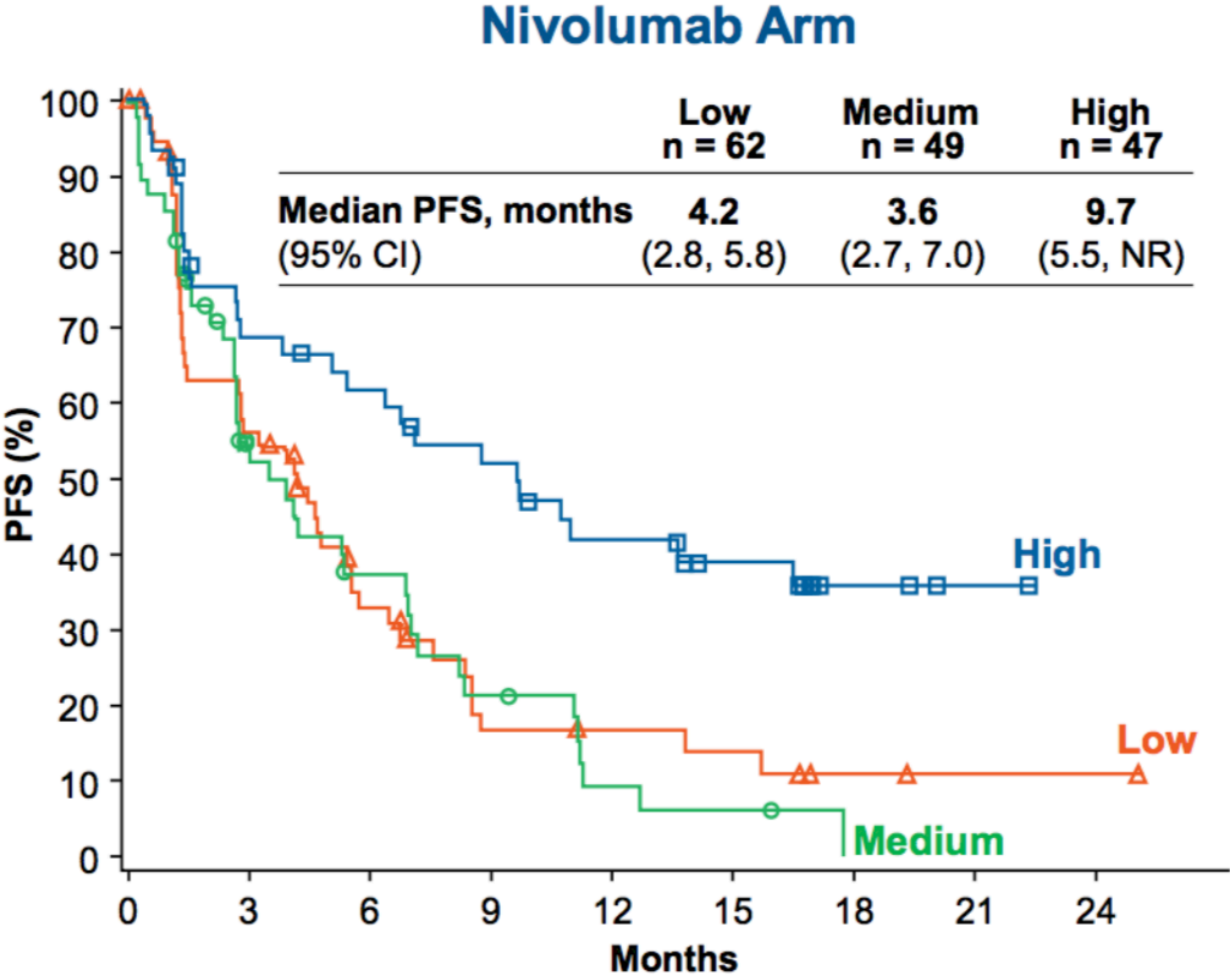
- For initial exploratory analyses, patients were divided into 3 subgroups based on TMB tertile distribution

TMB tertile	Total missense mutations, no.
Low	0 to <100
Medium	100 to 242
High	≥243

- ROC curves were generated and suggested TMB has predictive power
  - Additional analyses to help further refine potential optimal cutpoints are ongoing

CHECKMATE 026: PFS

Nivolumab Arm

	Low n = 62	Medium n = 49	High n = 47
Median PFS, months (95% CI)	4.2 (2.8, 5.8)	3.6 (2.7, 7.0)	9.7 (5.5, NR)

Chemotherapy Arm

	Low n = 41	Medium n = 53	High n = 60
Median PFS, months (95% CI)	6.9 (5.5, NR)	6.5 (4.7, 9.9)	5.8 (4.4, 9.1)

- Data for patients with low and medium TMB were pooled in subsequent analyses

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CHECKMATE 026: PFS

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median PFS, months (95% CI)	9.7 (5.5, NR)	5.8 (4.4, 9.1)

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

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median PFS, months (95% CI)	4.1 (2.8, 5.4)	6.9 (5.6, 8.8)

HR = 1.82 (95% CI: 1.30, 2.55)
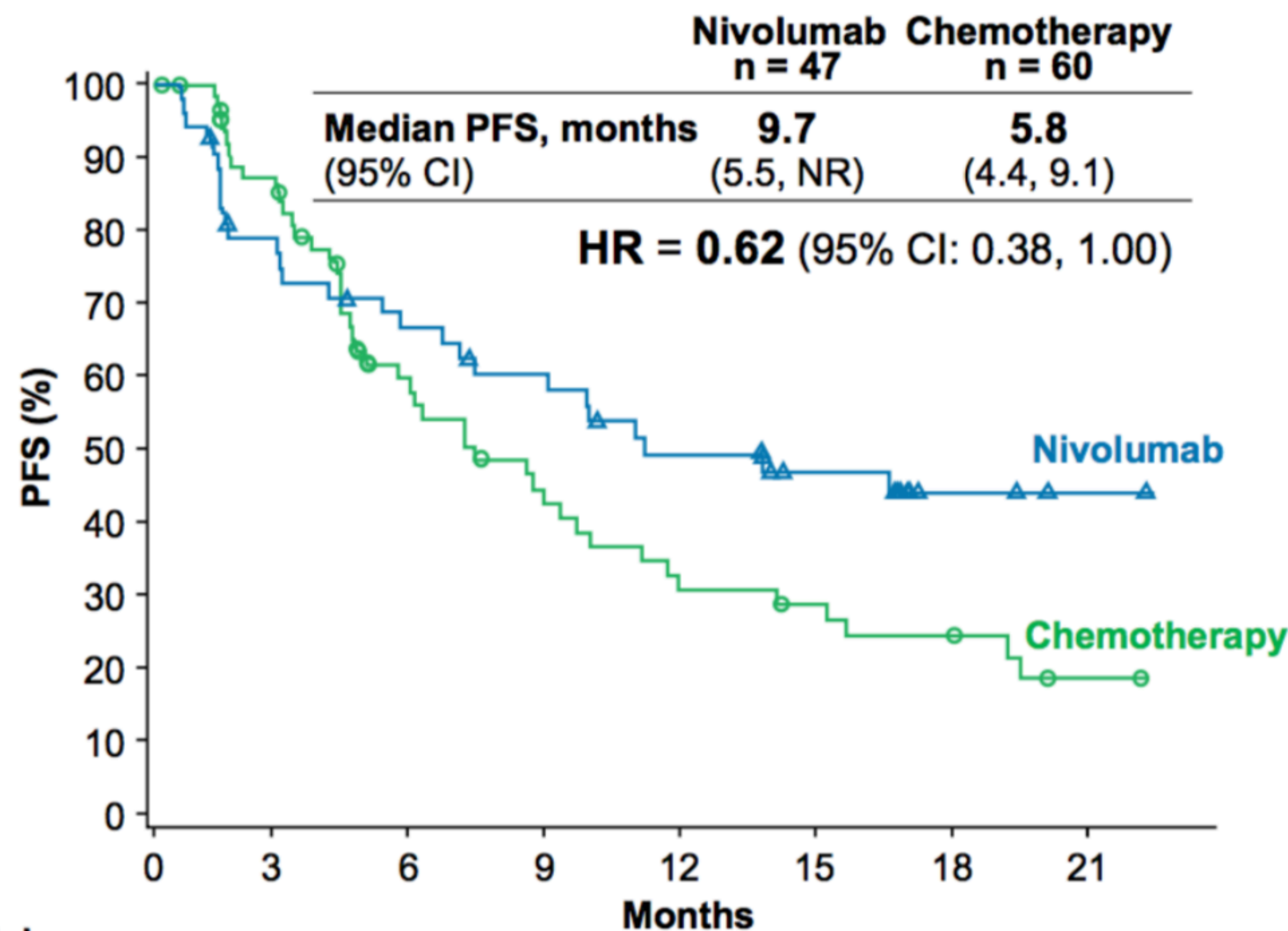
No. at Risk

Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

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

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CHECKMATE 026: OS

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median OS, months (95% CI)	18.3 (13.2, NR)	18.8 (12.0, NR)

HR = 1.10 (95% CI: 0.64, 1.88)

1-y OS rate = 64% vs 60%

68% received nivolumab as crossover and/or post-study treatment

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median OS, months (95% CI)	12.7 (10.5, 17.7)	13.2 (9.5, 17.0)

HR = 0.99 (95% CI: 0.71, 1.40)

1-y OS rate = 54% vs 53%

55% received nivolumab as crossover and/or post-study treatment

No. at Risk
Nivolumab 47 ... 11 3 0
Chemotherapy 60 ... 6 2 1

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CHECKMATE 026: ORR