First line treatment: pembrolizumab monotherapy

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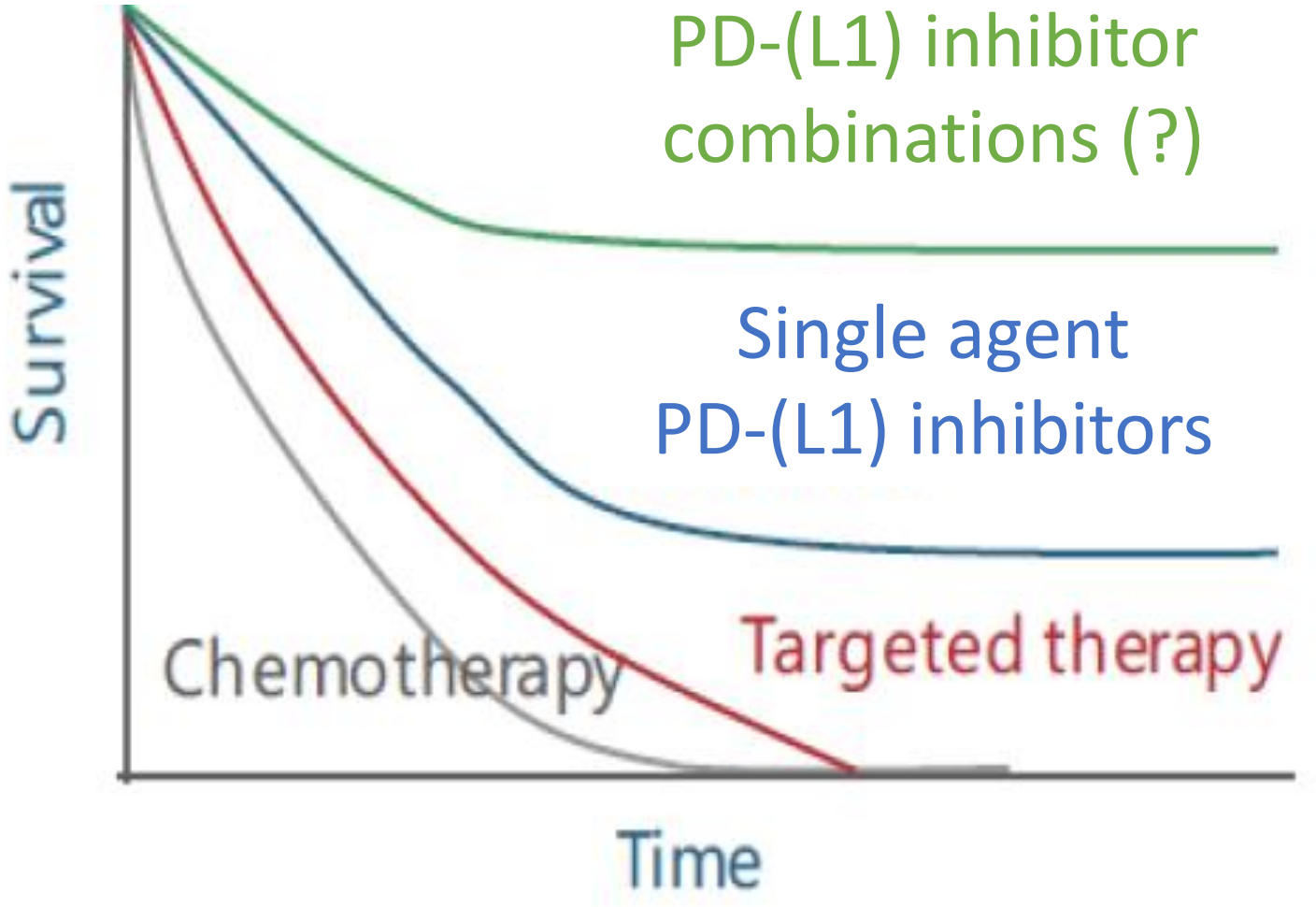
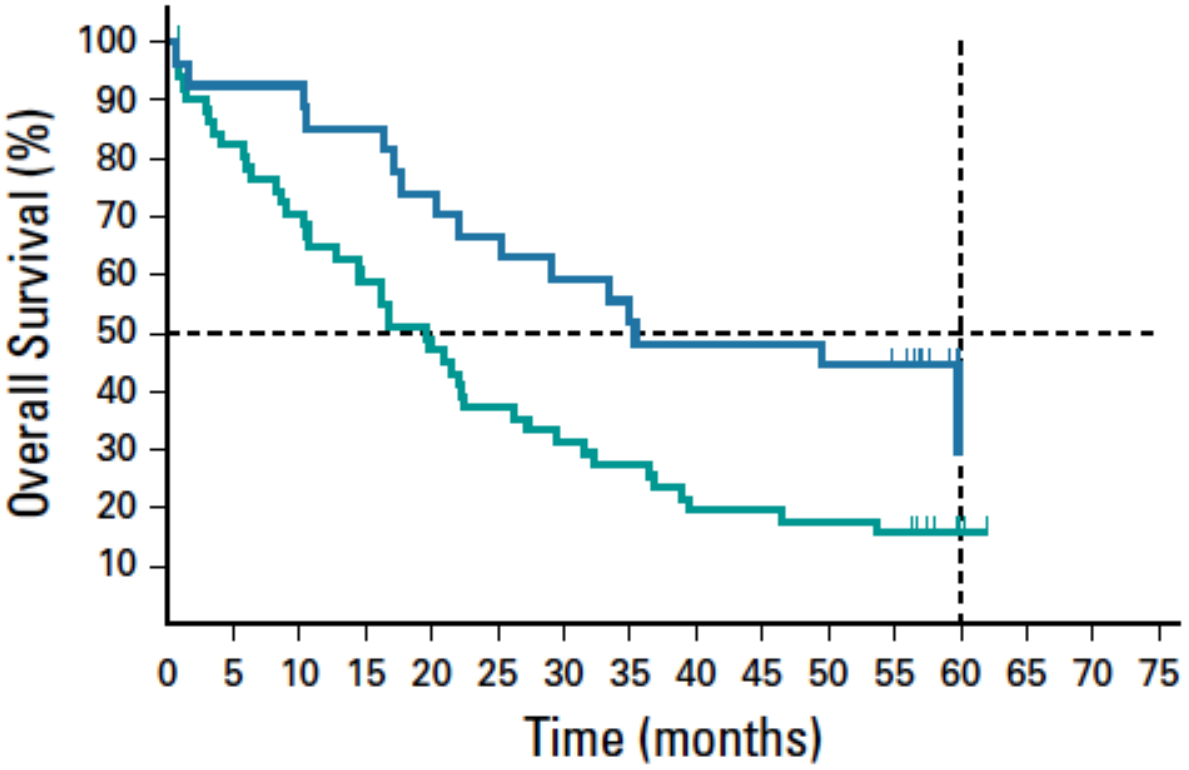
Disclosures

- Personal financial interests:
  - Advisory board: AbbVie, AstraZeneca, BMS, EMD Serono, Genentech, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron
  - Leadership role: Bellicum (clinical advisory board), Gritstone (co-founder and scientific advisory board member), Neogenomics and Apricity (scientific advisory board)
  - Stock or stock options: Gritstone, Bellicum, Brooklyn ImmunoTherapeutics
  - Royalties related to patent filed by MSKCC, determinants of cancer response to immunotherapy, (PCT/US2015/062208): PGDX
- Institutional research funding:
  - AstraZeneca, BMS, Genentech, GSK, Merck, Regeneron

Goals for immunotherapy



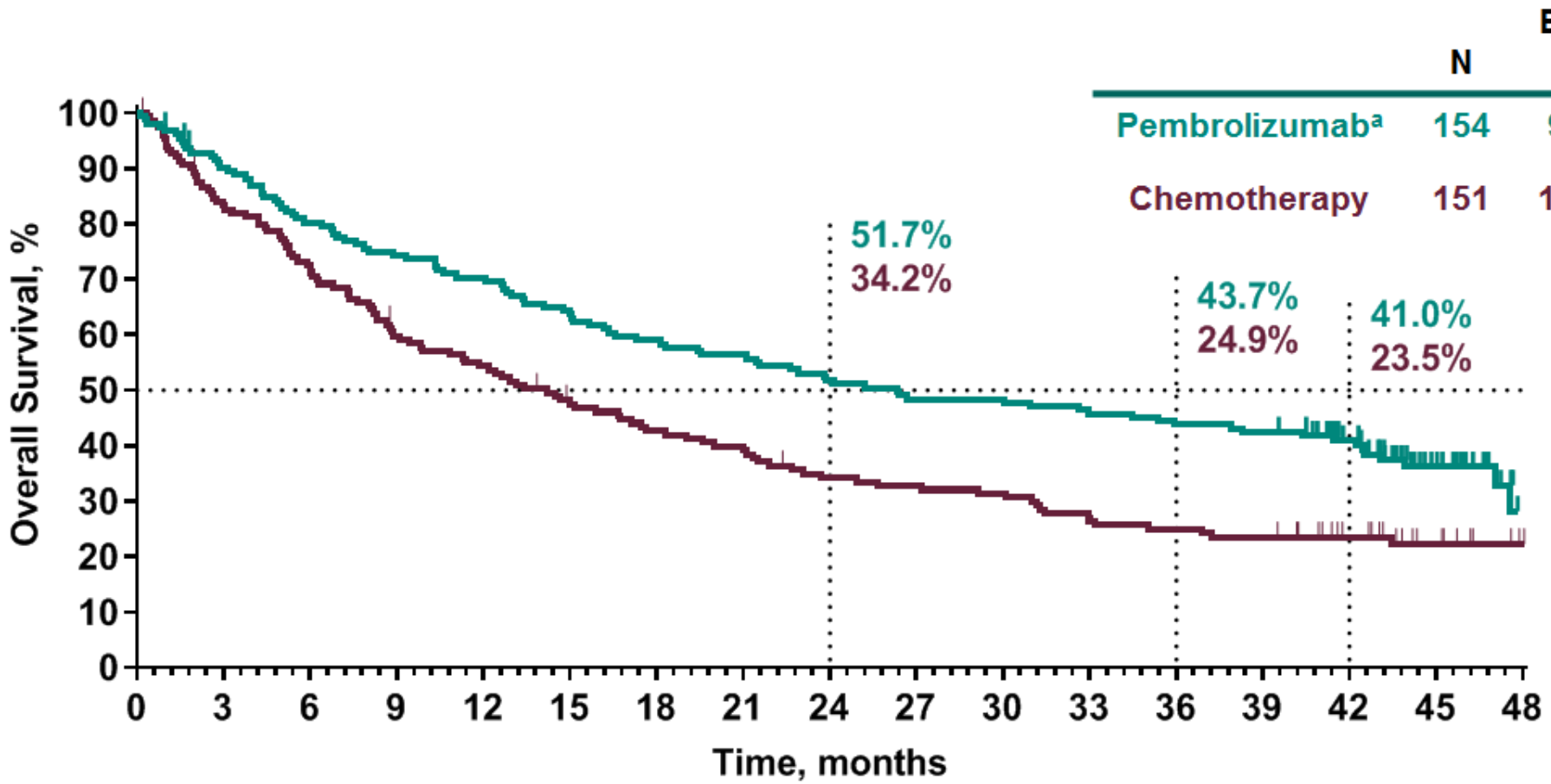
KN001 pembrolizumab monotherapy
5 year survival (chemotherapy naïve)



	Events, n/N	Median OS, mo (95% CI)	5-Year OS Rate, % (95% CI)
TPS ≥ 50%	17/27	35.4 (20.3 to 63.5)	29.6 (7.7 to 56.1)
TPS 1–49%	43/52	19.5 (10.7 to 26.3)	15.7 (7.3 to 26.9)

Garon et al, JCO 2019

KN024 pembrolizumab 3 year survival



	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) *P* = 0.001[b]
Chemotherapy	151	113 (75)	

Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

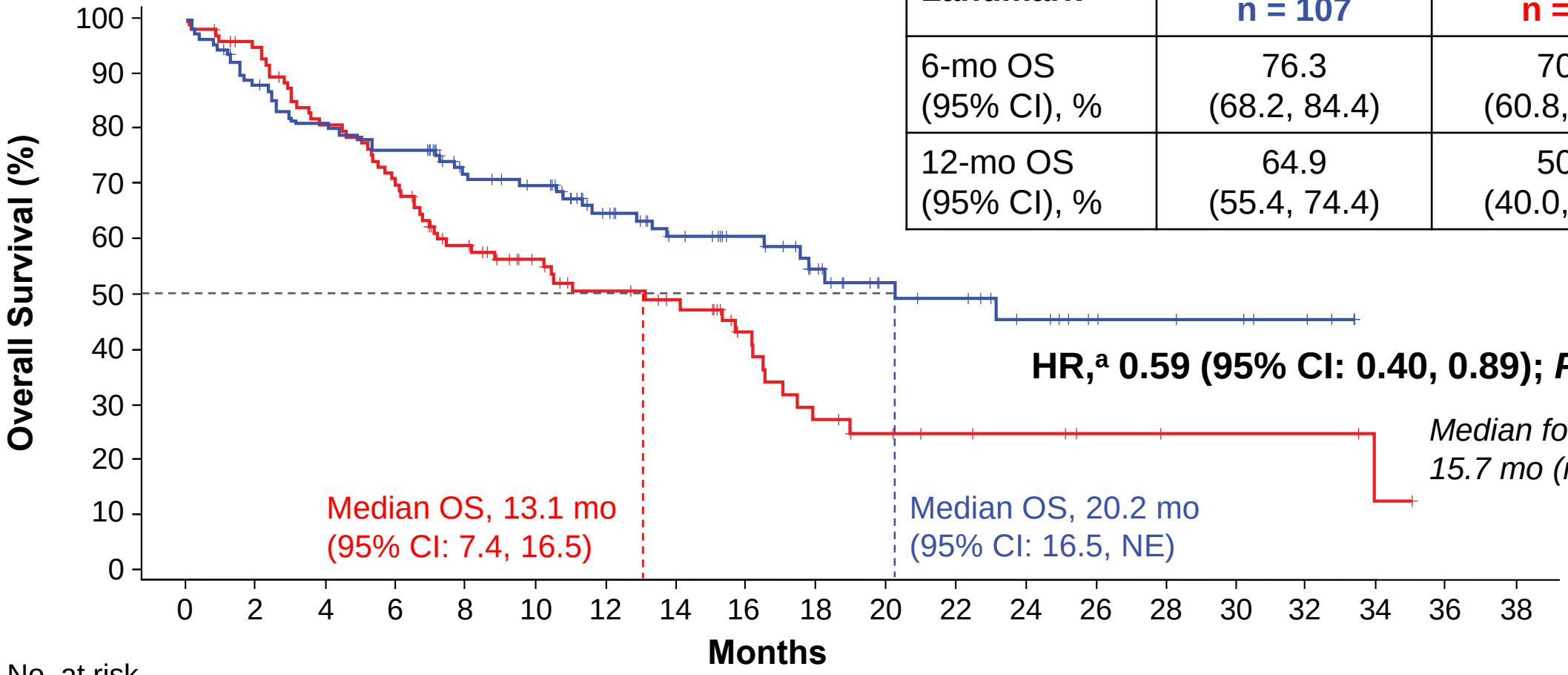
No. at risk

Pembrolizumab	154	136	121	112	106	96	89	85	78	73	73	69	66	64	50	24	5
Chemotherapy	151	124	108	88	80	69	61	56	48	46	44	37	35	33	24	14	6

[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal *P* value.
Data cutoff: February 15, 2019.

OS: TC3 or IC3 WT

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



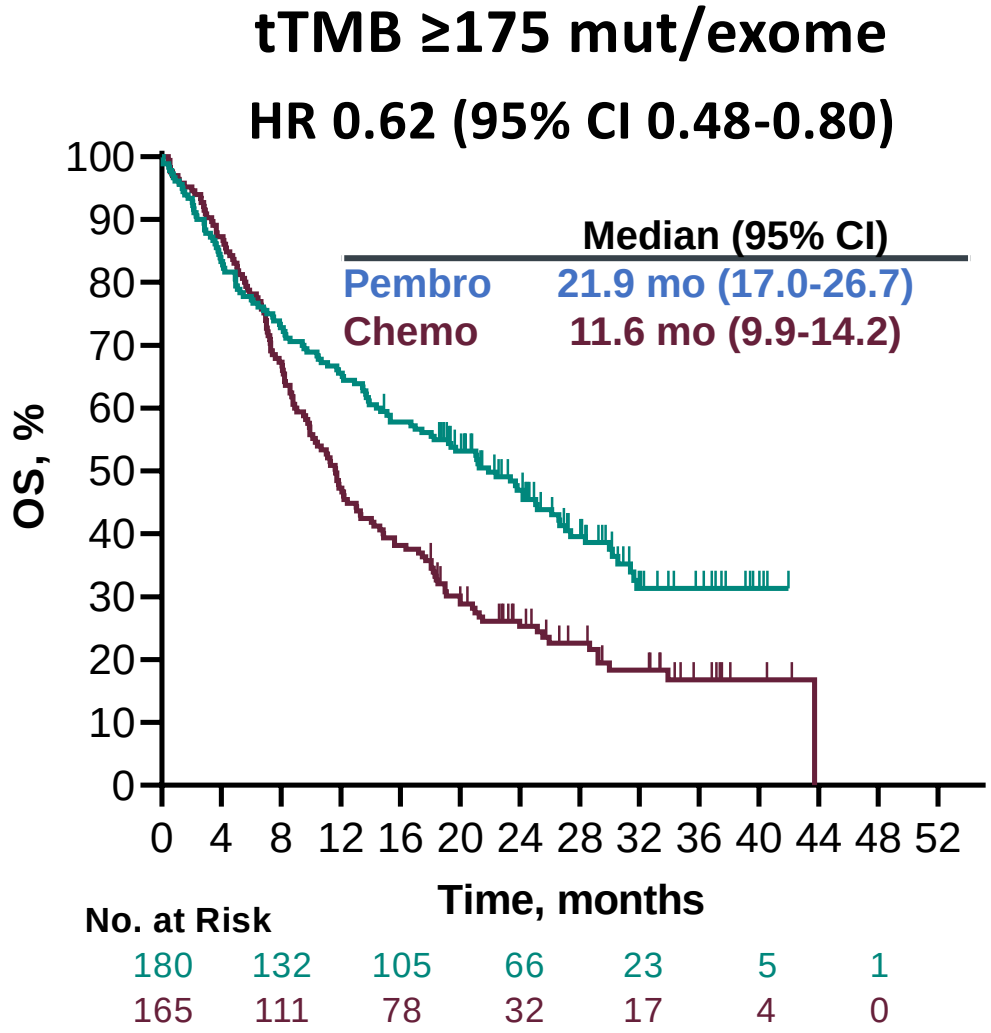
No. at risk

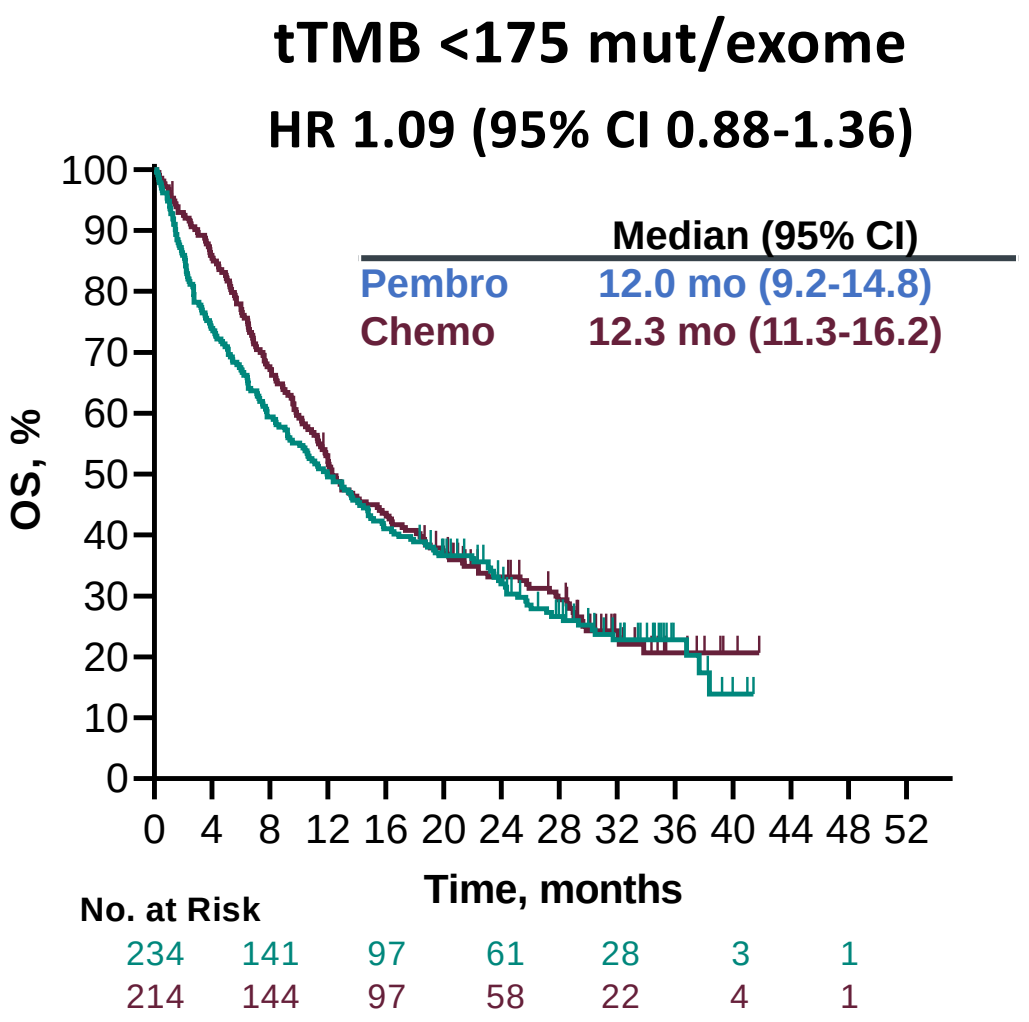
Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel et al, ESMO 2019

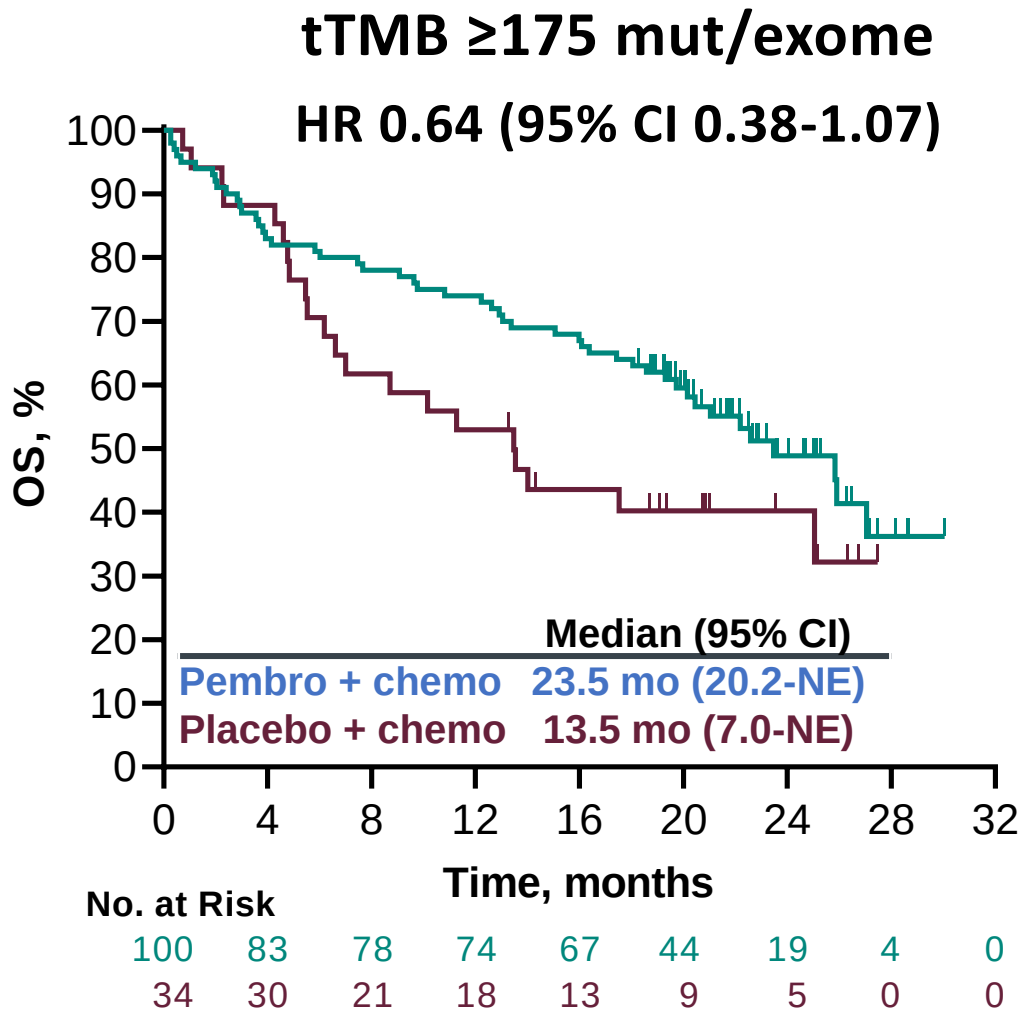
Clinical Utility for OS (KEYNOTE-042): tTMB Cutpoint of 175 mut/exome

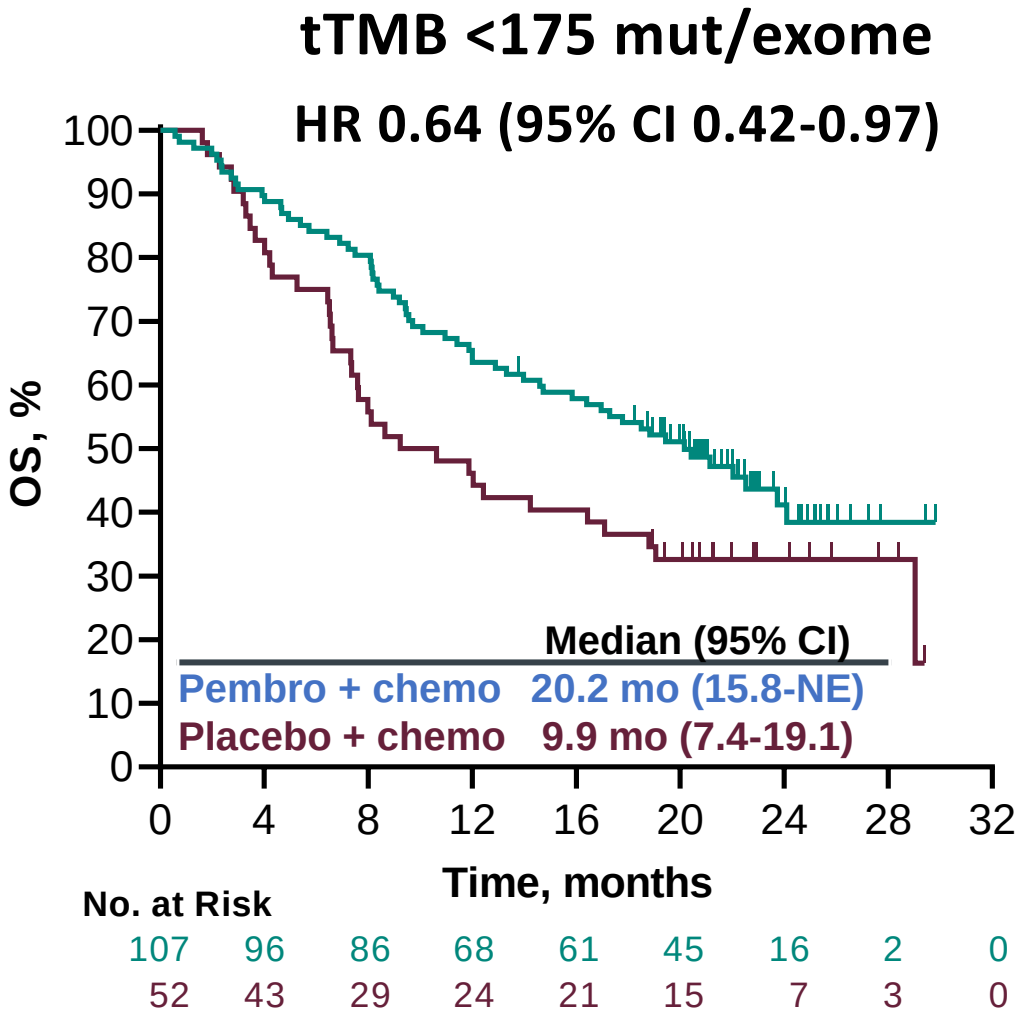




Herbst et al, ESMO 2019

Clinical Utility for OS in KEYNOTE-189: tTMB Cutpoint of 175 mut/exome



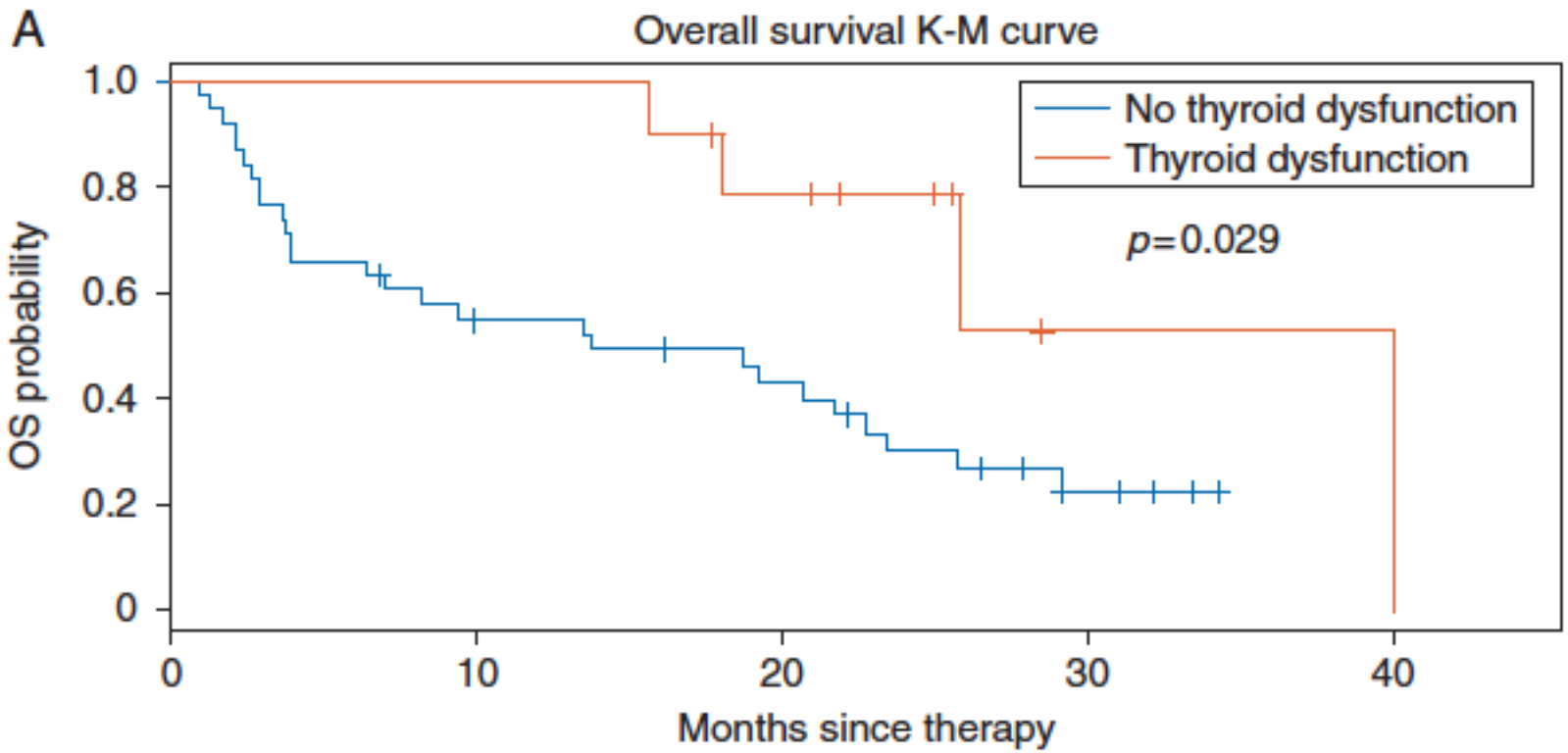


Herbst et al, ESMO 2019

What does chemotherapy add in TMB high?

Cancer	Trial and treatment	PD-L1	Method	Threshold Defined	Prevalence	RR	PFS	OS	Ref.
KN 042	Pembrolizumab (n=180)	≥1%	WES	175 mutations	43.5%	34.4%	6.3 mo.	21.9 mo.	Herbst et al, ESMO 2019
KN189	Pembrolizumab Chemotherapy (non-squamous)	NA	WES	175 mutations	46%	50%	9.2 mo.	23.5 mo.	Paz-Ares et al, ESMO 2019
KN407	Pembrolizumab Chemotherapy (squamous)	NA	WES	175 mutations	52%	59%	8.3 mo.	17.1 mo.	Paz-Ares et al, ESMO 2019

Association of thyroid dysfunction and pembrolizumab benefit

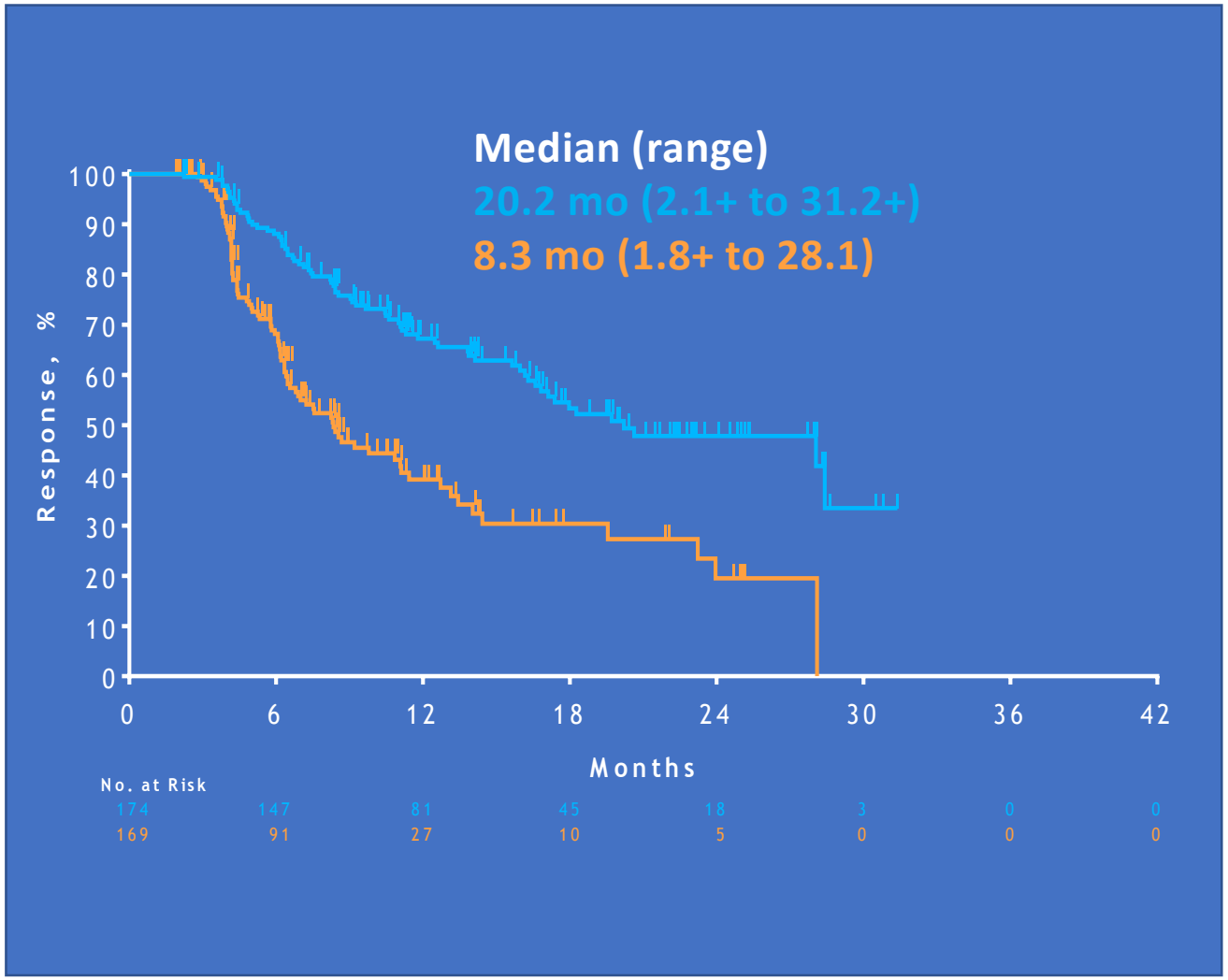


Osorio et al, Annals of Oncology. 2017

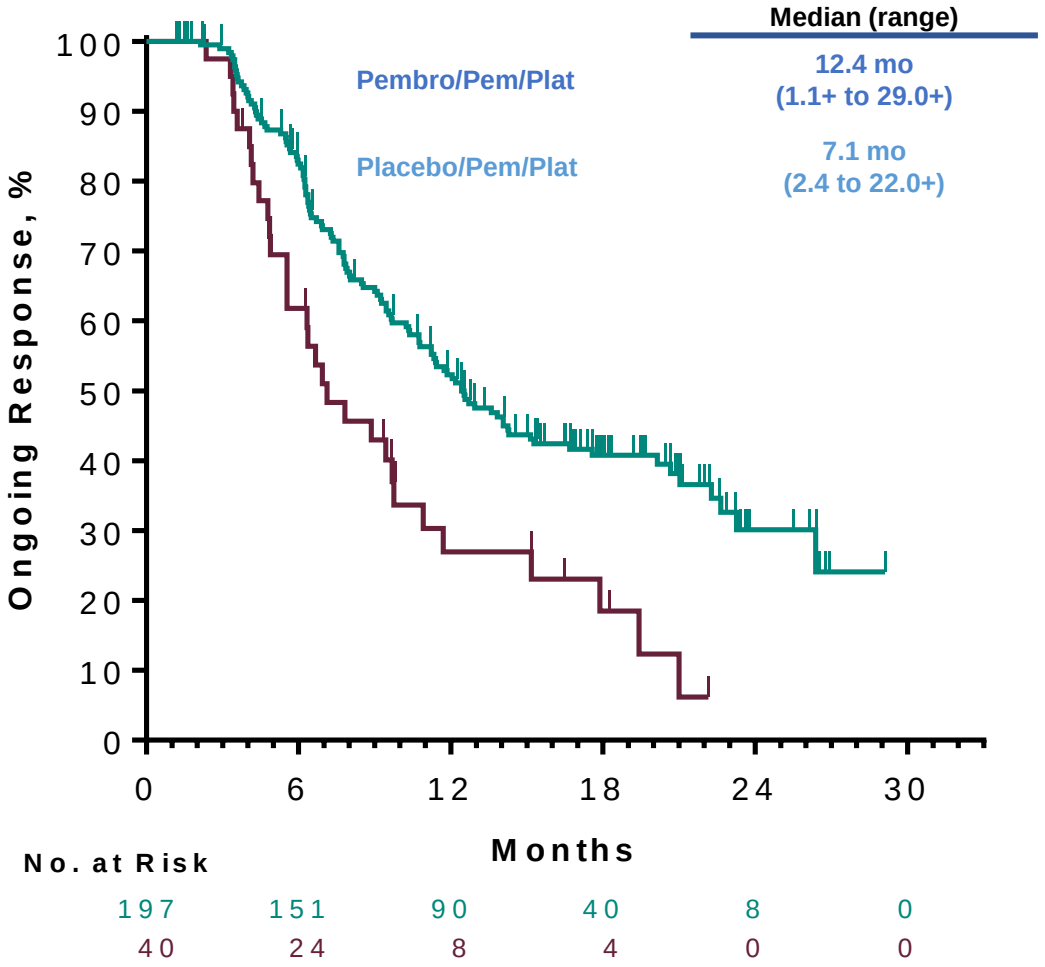
Thyroid dysfunction: pembrolizumab monotherapy vs. chemotherapy combination

	KN024	KN042	KN189	KN407
All	19.5%	20%	10.9%	16.2%
Hypothyroidism	9.1	12	6.7	7.9
Hyperthyroidism	7.8	6	4.0	7.2
Thyroiditis	2.6	2	0.2	1.1

KN042: Pembrolizumab monotherapy DOR (TPS ≥1%)



KN189: Pembro/chemo DOR (all-comers)



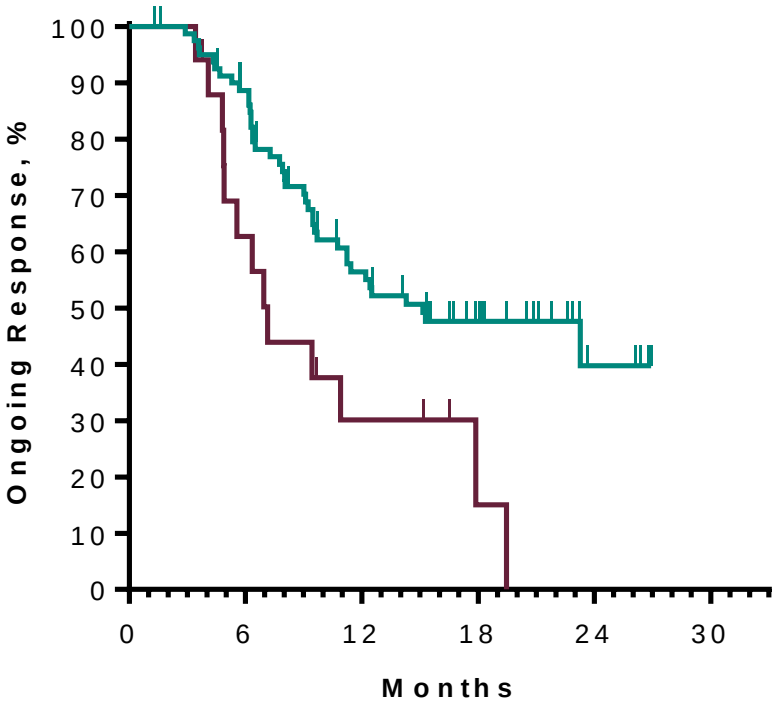
Gadgeel et al, ASCO 2019

Response Duration by PD-L1 TPS (RECIST v1.1, BICR)

Gadgeel et al, ASCO 2019

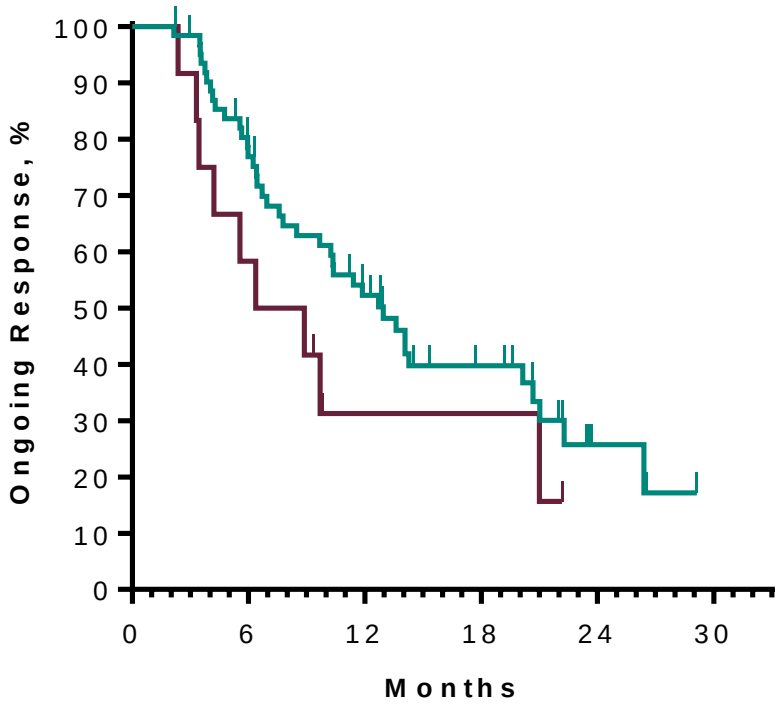
TPS ≥50 %

	Median
Pembro/Pem/Plat	15.1 mo
Placebo/Pem/Plat	7.1 mo



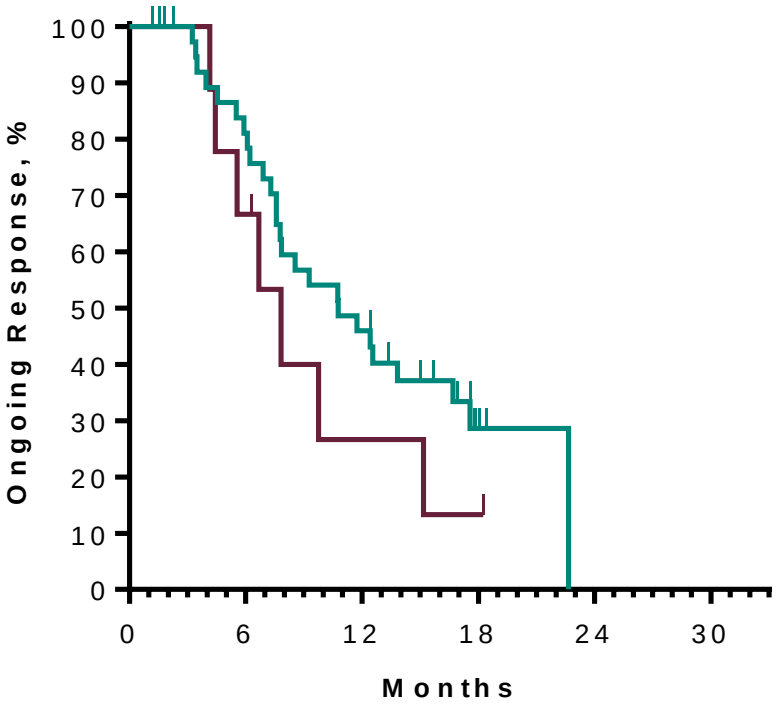
TPS 1-49%

	Median
Pembro/Pem/Plat	12.9 mo
Placebo/Pem/Plat	7.6 mo



TPS <1%

	Median
Pembro/Pem/Plat	10.8 mo
Placebo/Pem/Plat	7.8 mo



BICR, blinded, independent central review. Data cutoff date: Sep 21, 2018.

Conclusion

- Pembrolizumab monotherapy treatment of choice for biomarker selected NSCLC population (PD-L1 > 50% or TMB high)
- Less toxicity with pembrolizumab monotherapy vs. combination treatment
- Potentially less immunosuppressive effects with pembrolizumab monotherapy
- Potentially more durable benefit with pembrolizumab monotherapy
- No clear superiority to tail of curve with combination treatment (in biomarker selected population)