IO-chemotherapy Combinations

November 9, 2019

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Ensign Professor of Medicine
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YaleNewHavenHealth
Smilow Cancer Hospital

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Disclosures: Roy S. Herbst, MD, PhD

Consulting

Abbvie Pharmaceuticals, ARMO Biosciences, AstraZeneca, Biodesix, Bristol-Myers Squibb, Eli Lilly and Company, EMD Serrano, Genentech/Roche, Genmab, Heat Biologics, Loxo Oncology, Merck and Company, Nektar, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Tesaro, Tocagen

Research Support

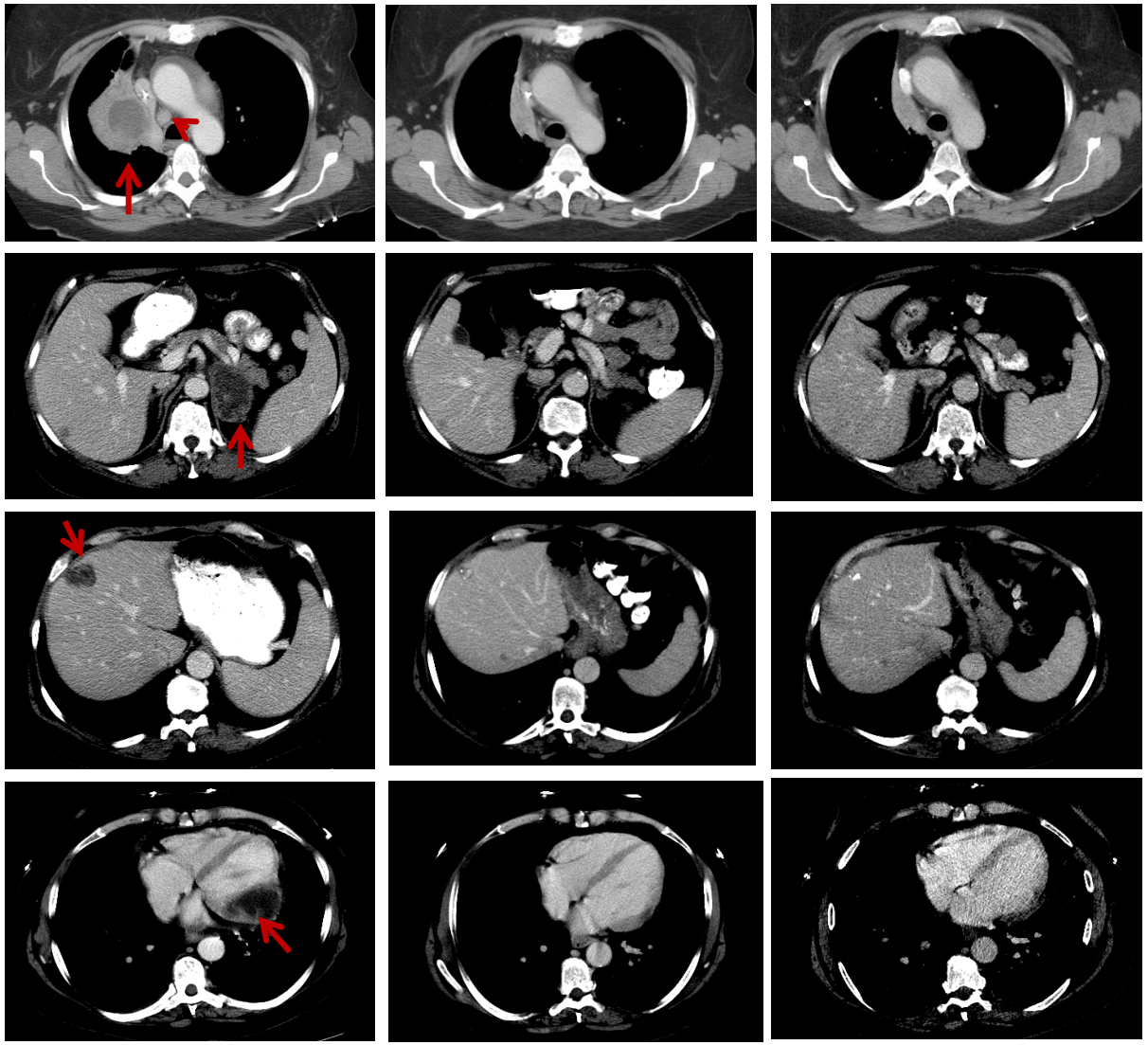
AstraZeneca, Eli Lilly and Company, Merck and Company

Scientific Advisory Boards

Neon Therapeutics, Infinity Pharmaceuticals, NextCure

Board Member (non-executive/ independent)

Junshi Pharmaceuticals



Pre- Nivolumab | 2 Years on Nivolumab | year 8: > 6 Years off Nivolumab

One of the very first lung patients
on MDX-1106 (Nivolumab)
3X Chemo-Refractory
Squamous Cell NSCLC
June 2010

Cure?

15% of Patients

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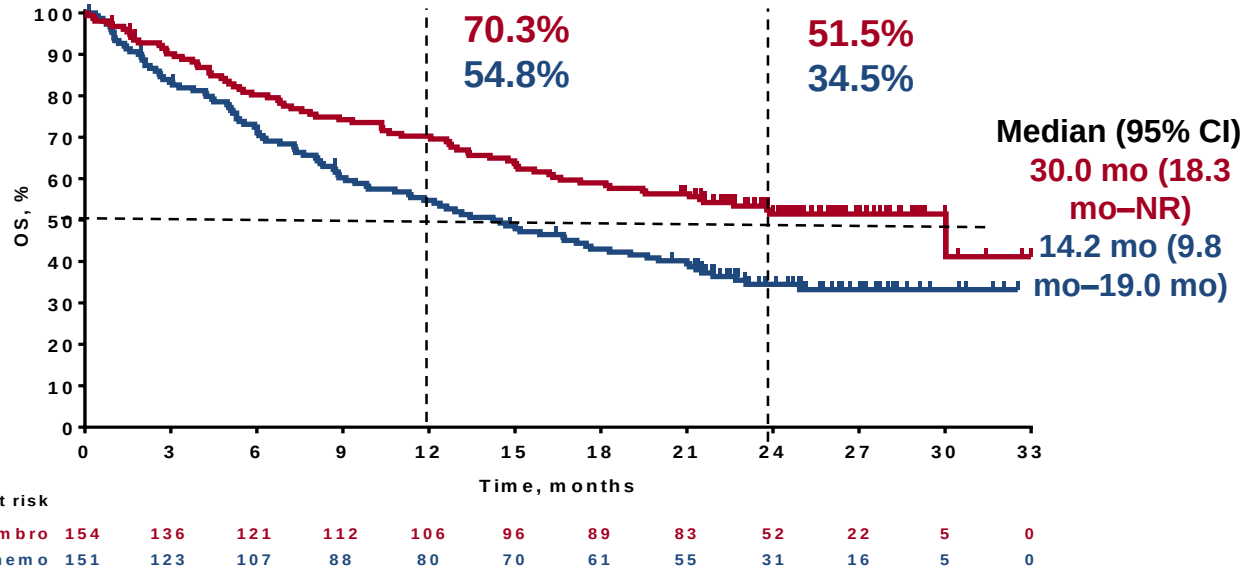
Courtesy of Scott Gettinger, Yale Centerpoint

KEYNOTE 024
Overall Survival: Pembrolizumab PDL-1 score > 50%

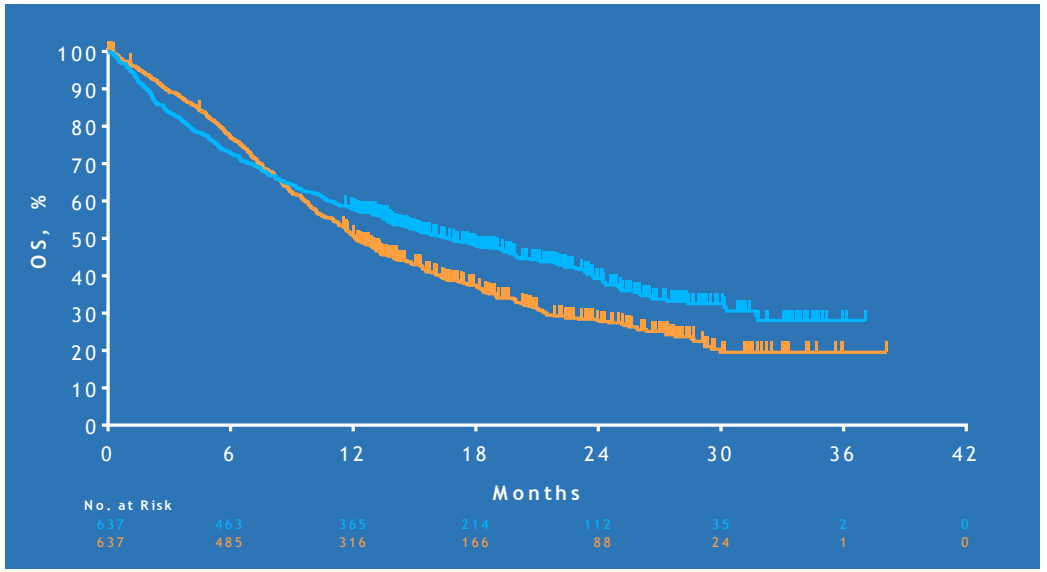
	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86)
Chemotherapy	96	*P* = 0.002[b]



[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

KEYNOTE 042
Overall Survival: Pembrolizumab PDL-1 score ≥1%

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



Data cutoff: Feb 26, 2018.
Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study.

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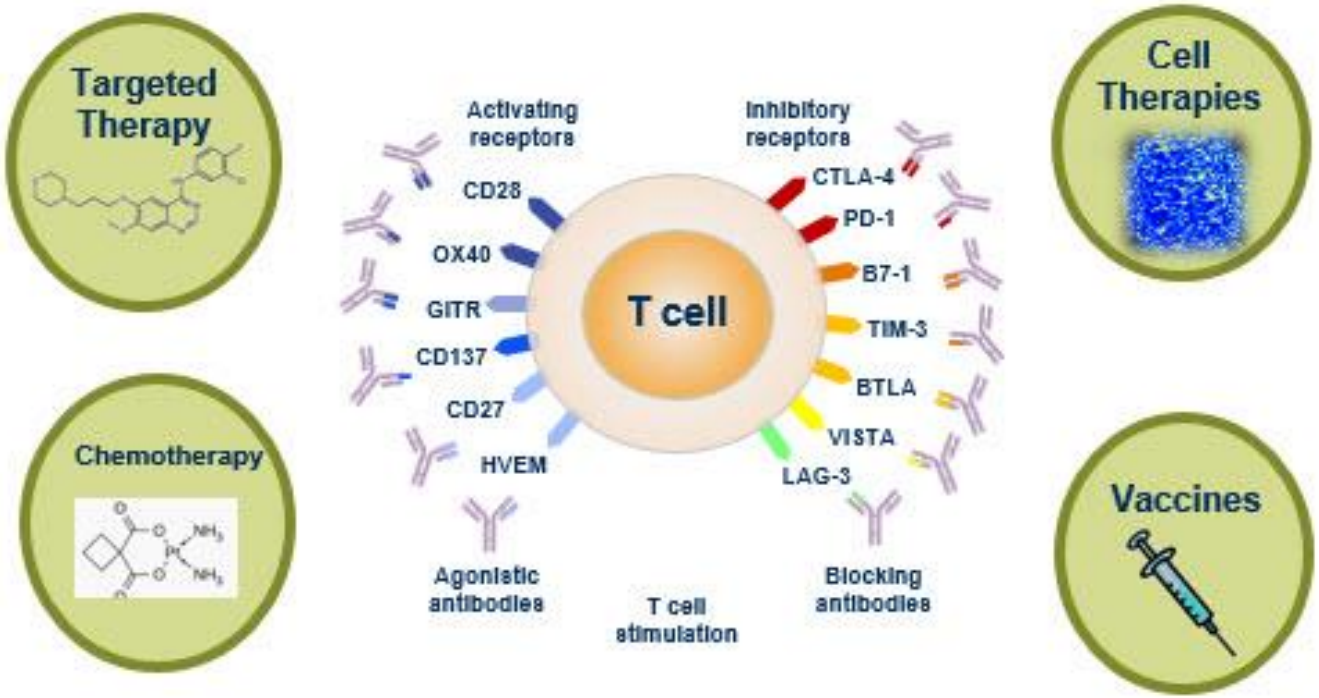
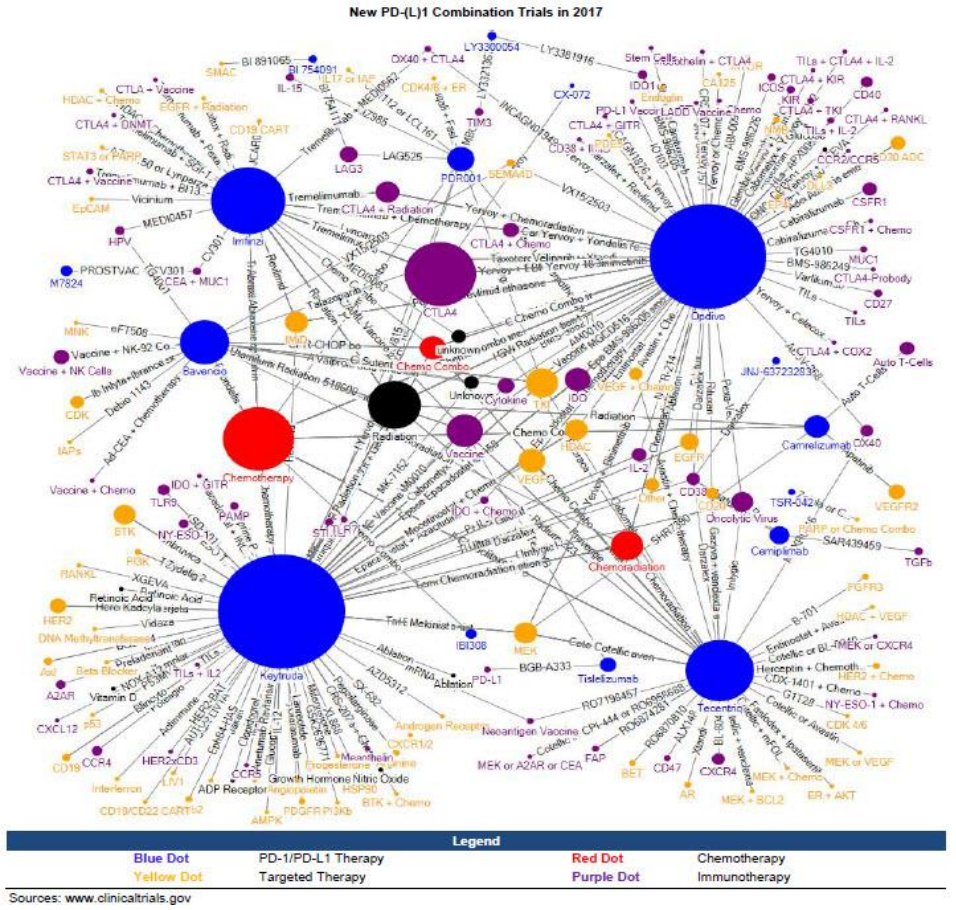
Reck et al. N Engl J Med 2016 Nov 10;375(19):1823-1833.; Brahmer et al. WCLC 2017; Lopes G. et al. J Clin Oncol 36, 2018 (suppl; abstr LBA4)

There is clearly a population who will do incredibly well with IO therapy alone!

- Need to understand why- ie. Yale Lung SPORE exceptional responder project
- Identify biomarkers
- This group should get single agent IO

The Search for New Combinations and Personalized Immunotherapy Continues





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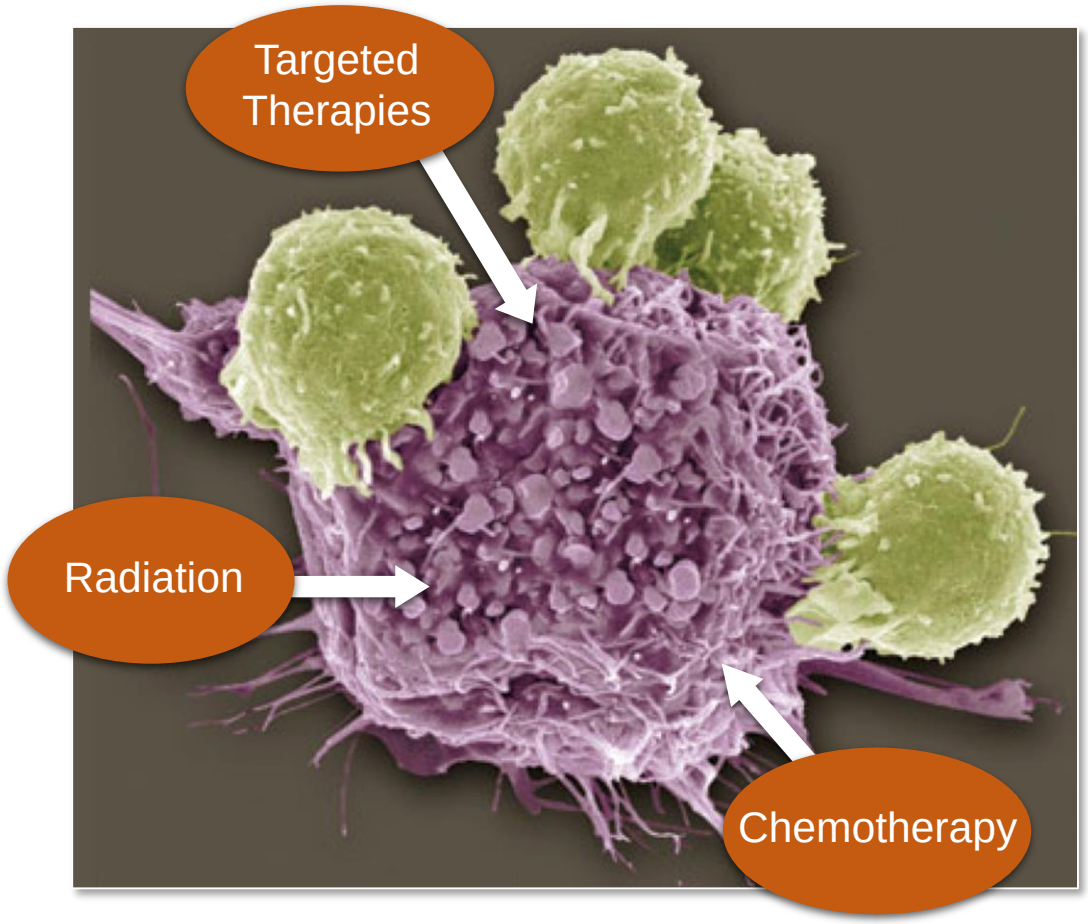
Mellman I et al. *Nature* 2011 Dec 21;480(7378):480-9.
M. Philips, *Equity Research* 2018

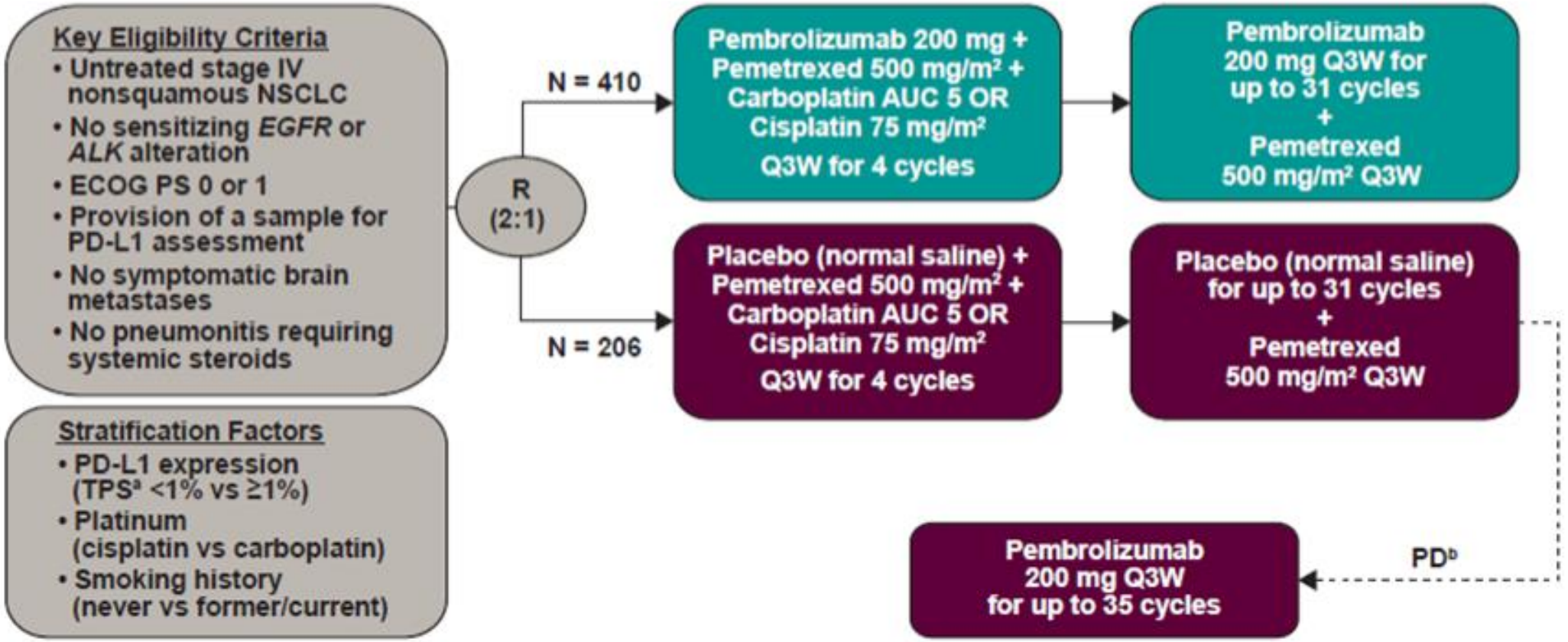
Rationale for Combination Therapy



- Reduces tumor bulk – Improves T-cell: tumor target ratio
- Separate mechanism of kill – ‘synergize’ with T-cell mechanism of killing
- Reduces T-cell inhibitory substances produced by tumor
- Alters tumor barriers (vasculature/pressure) to T-cell penetration
- Kills tumor cells in a manner that increases their recognition by T-cells and APC (vaccination)
- Alters T-cell signaling/gene expression to produce T-cell attractants

Adapted from M. Sznol, Yale Cancer Center

KEYNOTE-189 Study Design

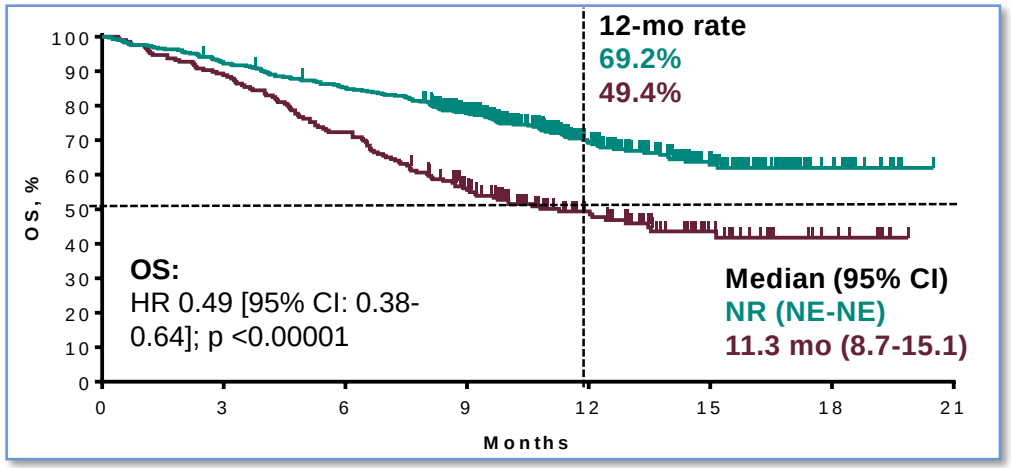


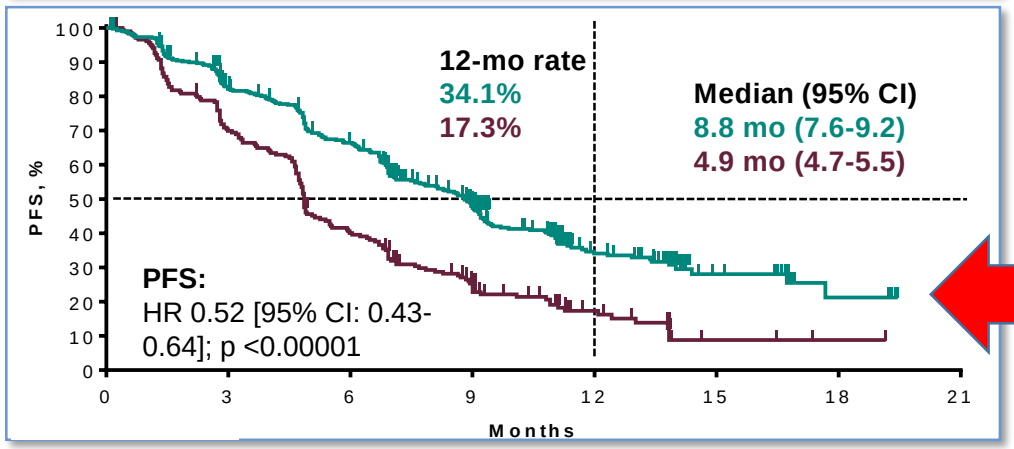
AUC, area under the concentration–time curve; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; Q3W, every 3 weeks; R, randomized.

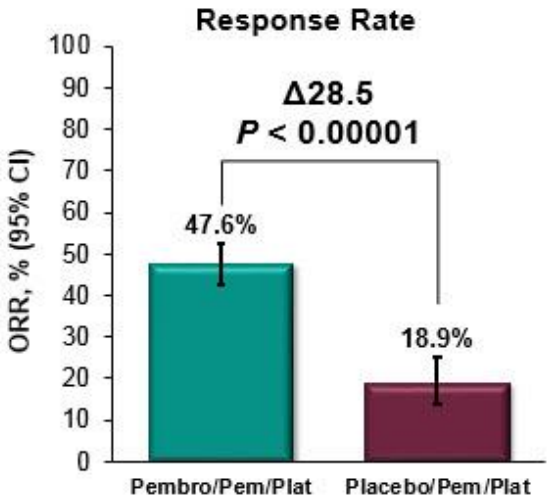
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.

[b]Patients could cross over 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

Keynote 189: Pembrolizumab (PD1 plus Chemotherapy) Met All Primary Endpoints







Subgroup Analyses

OS: Positive across all subgroups

PFS: Positive across all subgroups except for PD-L1 TPS <1%

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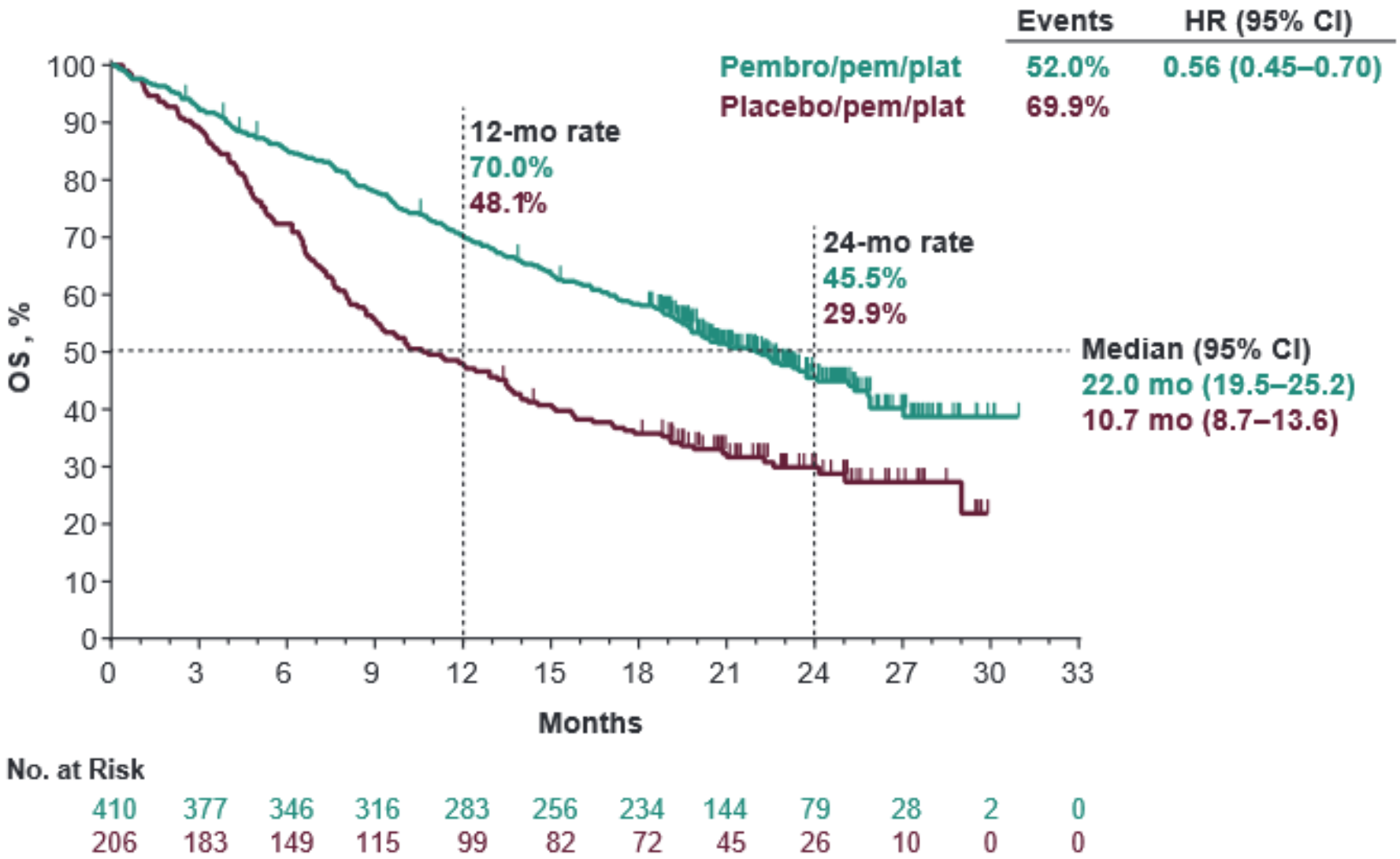
Gandhi et al, *N Engl J Med* 2018; 378:2078-2092

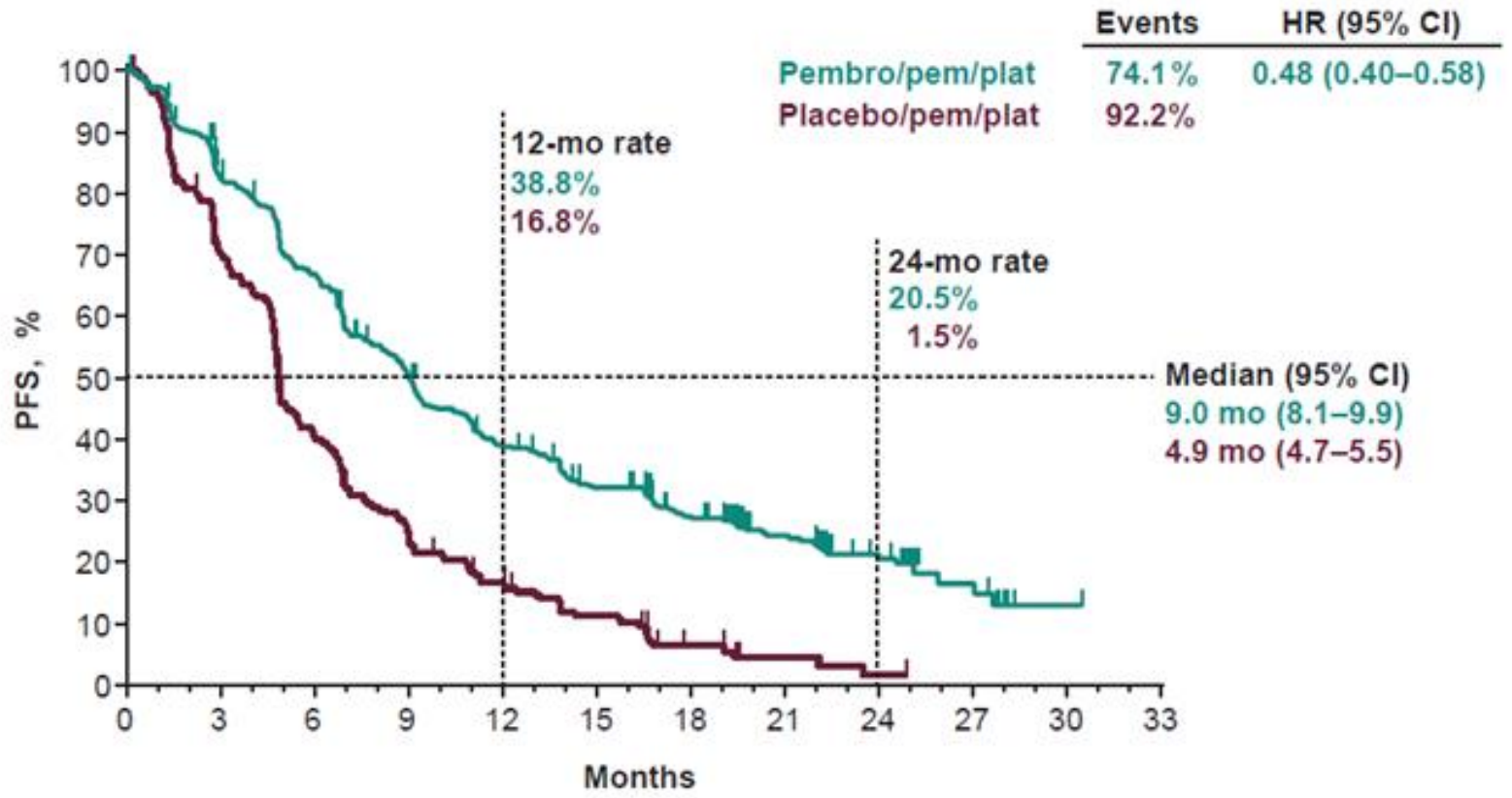
Summary of Adverse Events

	Pembro/Pem/Platinum N = 405	Placebo/Pem/Platinum N = 202
All cause	404 (99.8%)	200 (99.0%)
Grade 3-5	272 (67.2%)	133 (65.8%)
Led to death	27 (6.7%)	12 (5.9%)
Led to discontinuation		
All treatment[a]	56 (13.8%)	16 (7.9%)
Any treatment	112 (27.7%)	30 (14.9%)
Immune mediated	92 (22.7%)	24 (11.9%)
Grade 3-5	36 (8.9%)	9 (4.5%)
Led to death	3 (0.7%)	0

Figure 3. Kaplan-Meier Estimates of OS in the Total Population (ITT)

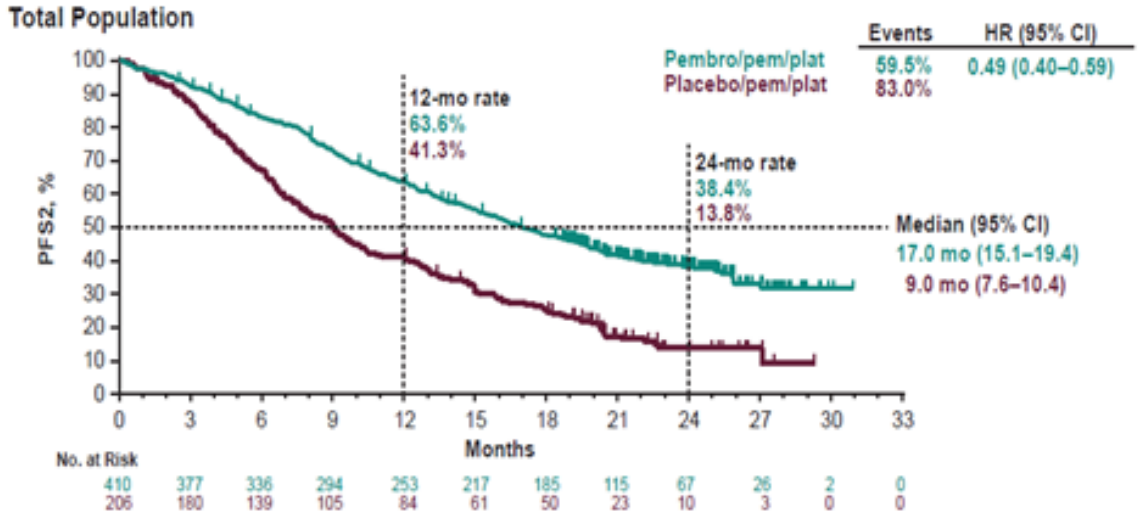


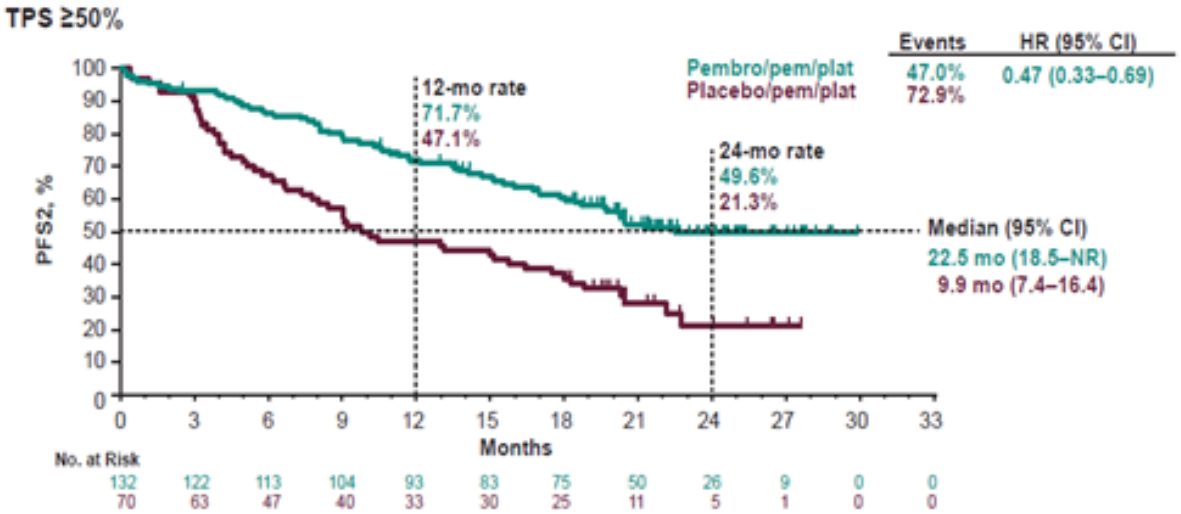
Kaplan-Meier Estimates of PFS in the Total Population (ITT)

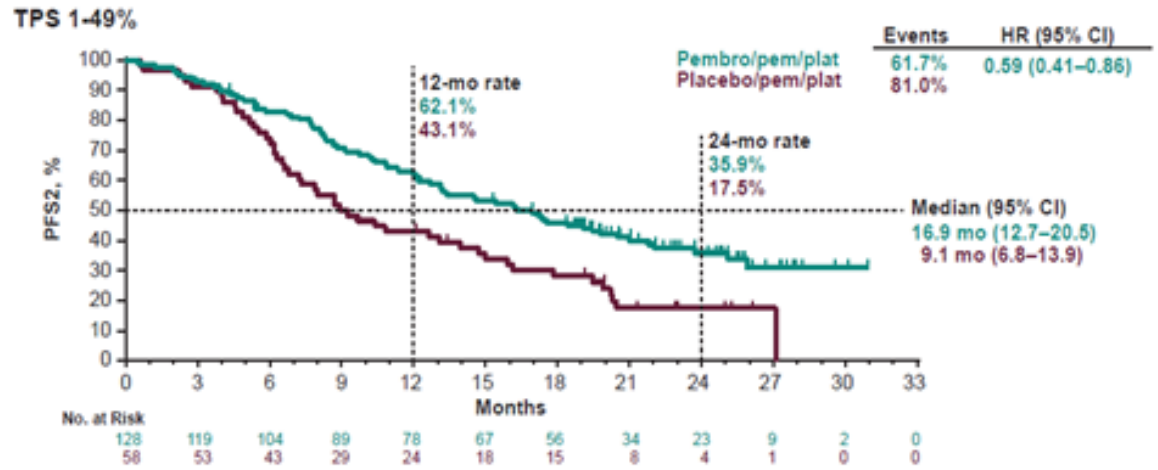


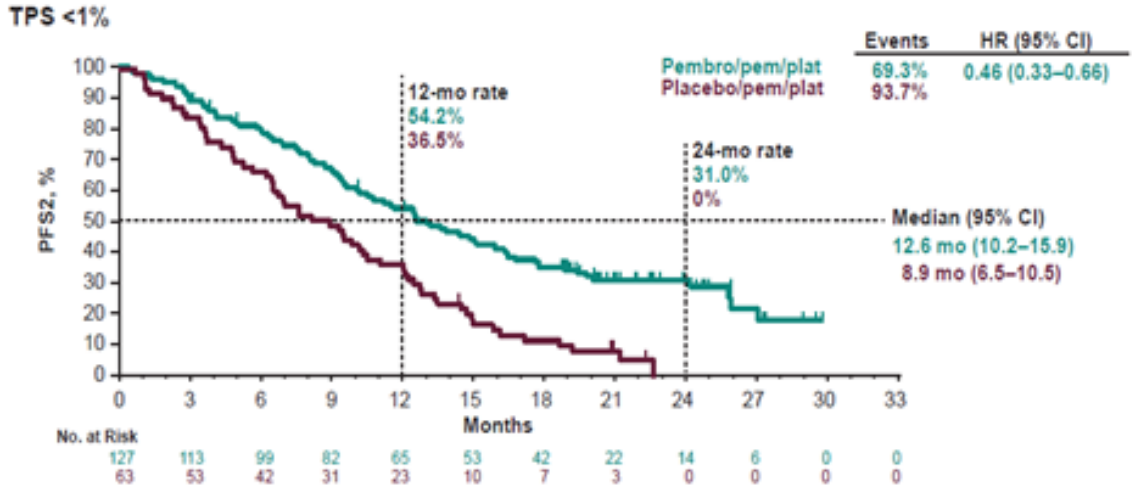
Assessed per RECIST v1.1 by blinded, independent central review.

Kaplan-Meier Estimates of PFS2 in the Total Population and PD-L1 TPS Subgroups (ITT)

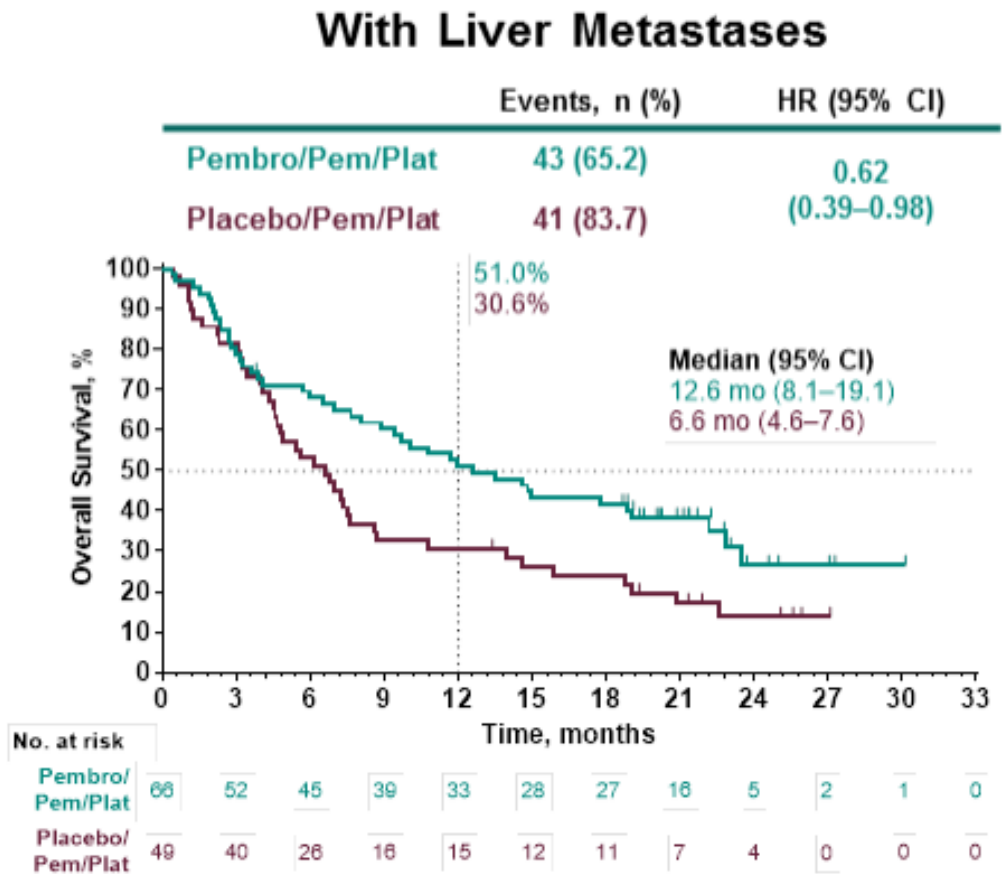


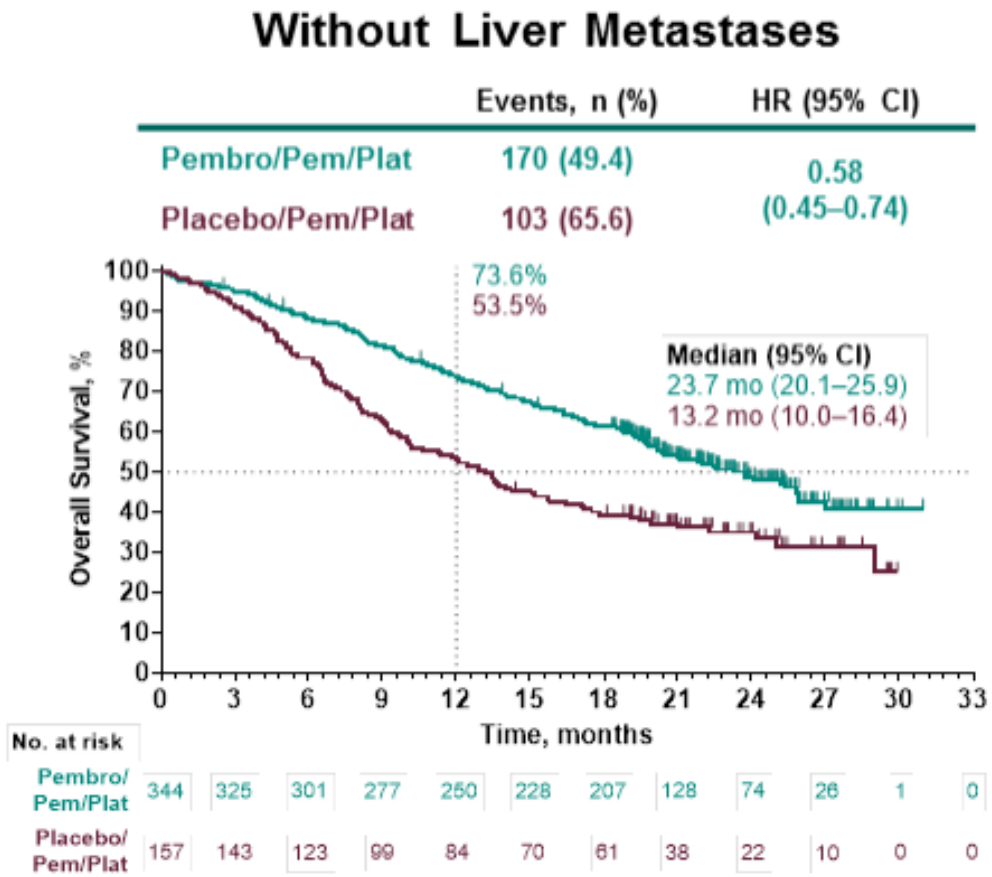






Overall Survival: Liver Metastases



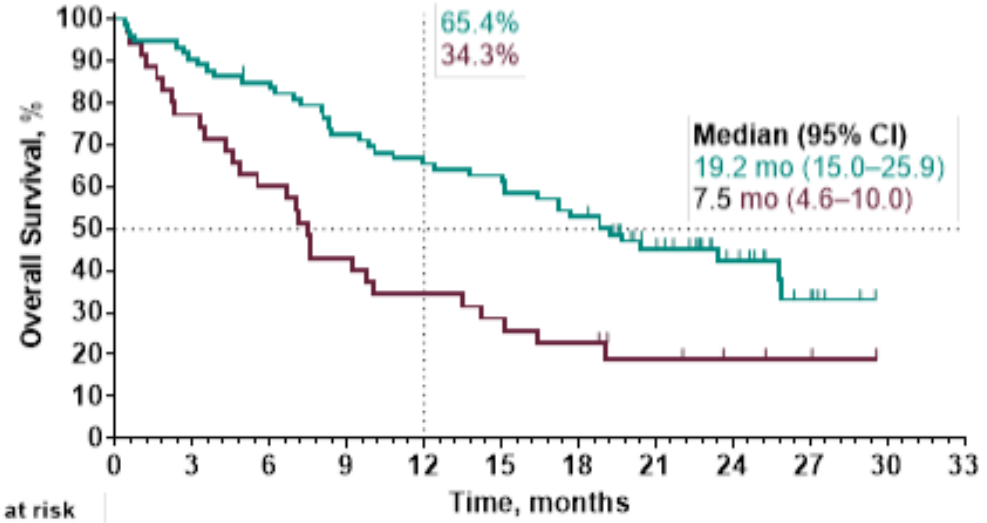


Data cutoff date: September 21, 2018.

Overall Survival: Brain Metastases

With Brain Metastases

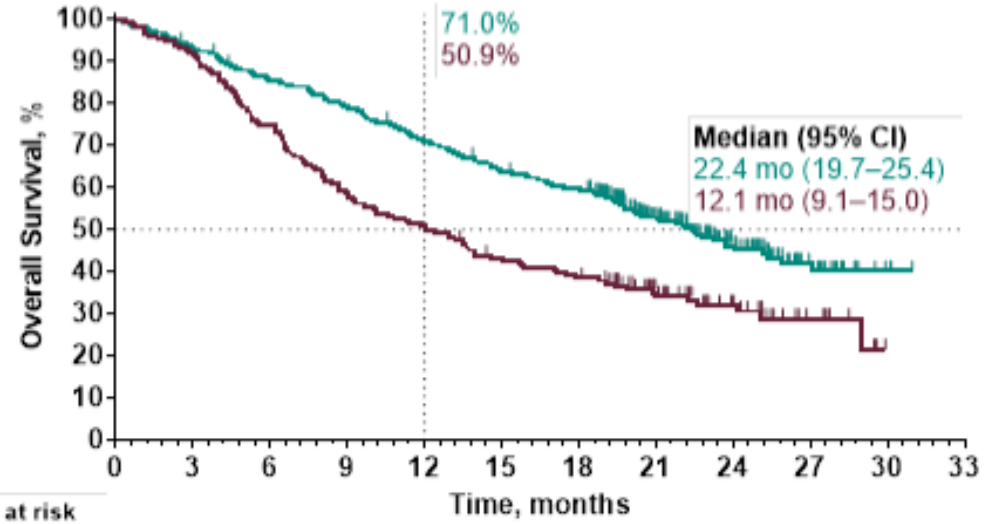
	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	42 (57.5)	0.41 (0.24–0.67)
Placebo/Pem/Plat	28 (80.0)	



No. at risk												
Pembro/Pem/Plat	73	66	61	52	47	45	38	25	14	5	0	0
Placebo/Pem/Plat	35	27	21	15	12	10	8	5	3	1	0	0

Without Brain Metastases

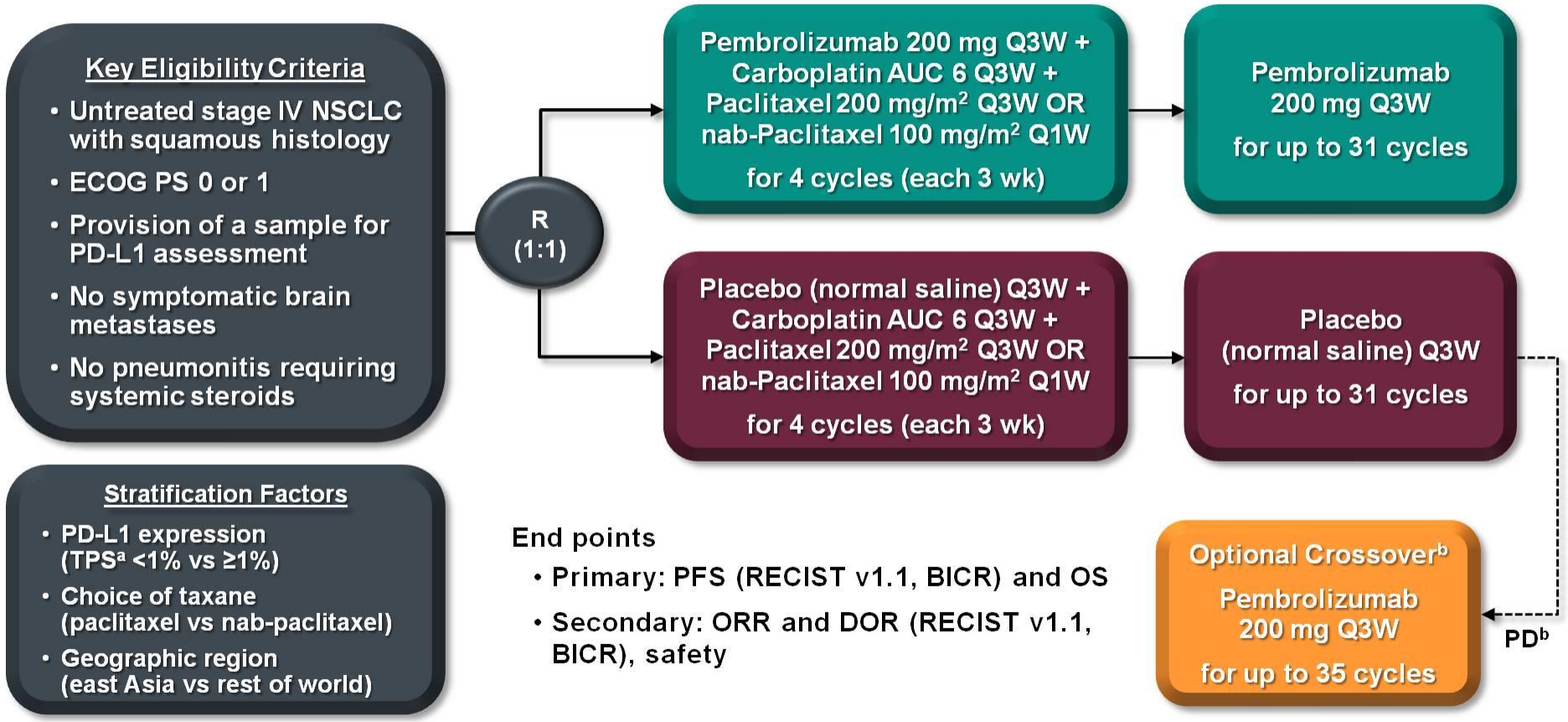
	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	171 (50.7)	0.59 (0.46–0.75)
Placebo/Pem/Plat	116 (67.8)	



No. at risk												
Pembro/Pem/Plat	337	311	285	264	236	211	196	119	65	23	2	0
Placebo/Pem/Plat	171	156	128	100	87	72	64	40	23	9	0	0

Data cutoff date: September 21, 2018.

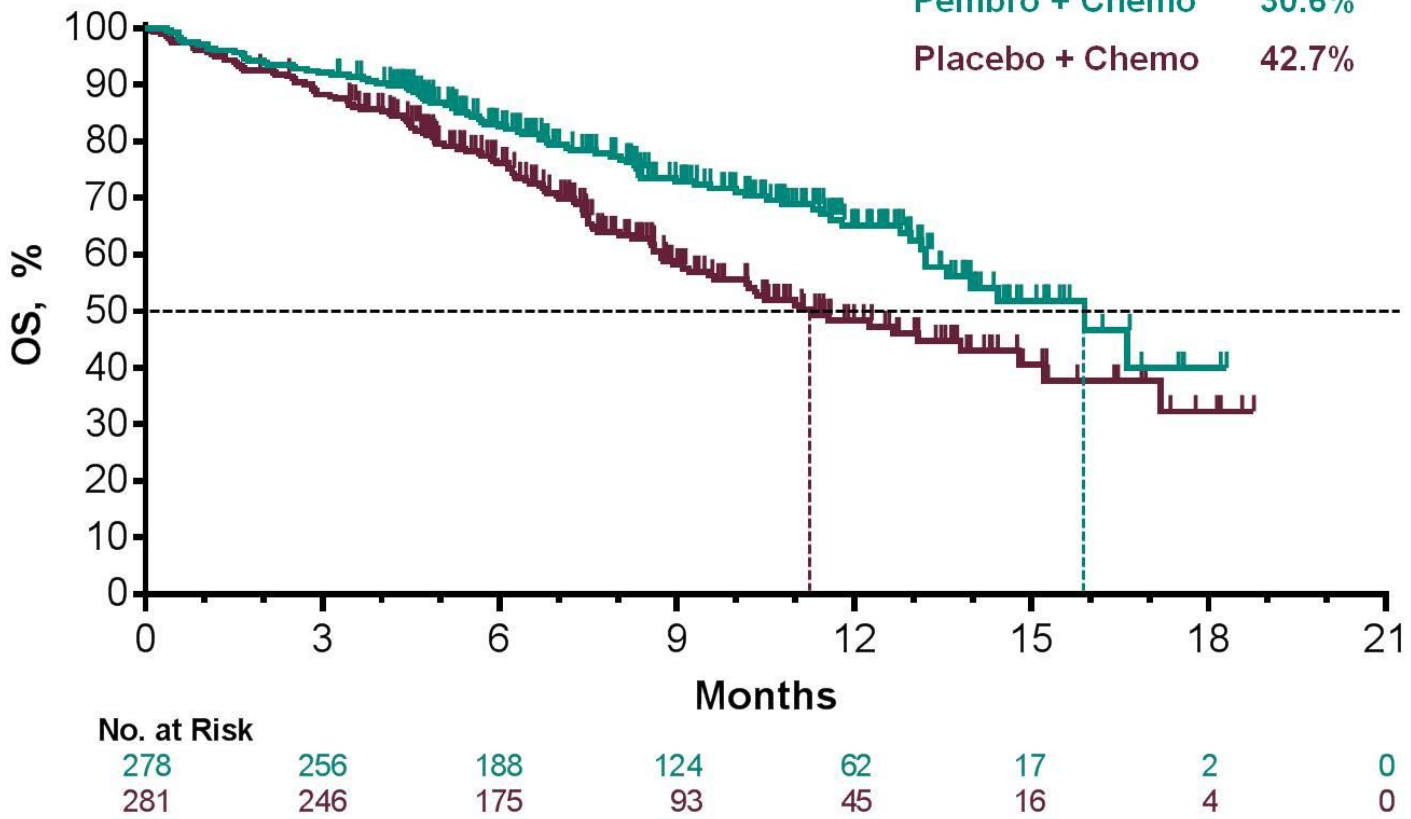
KEYNOTE-407 Study Design (NCT02775435)



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

Overall Survival at IA2, ITT

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		

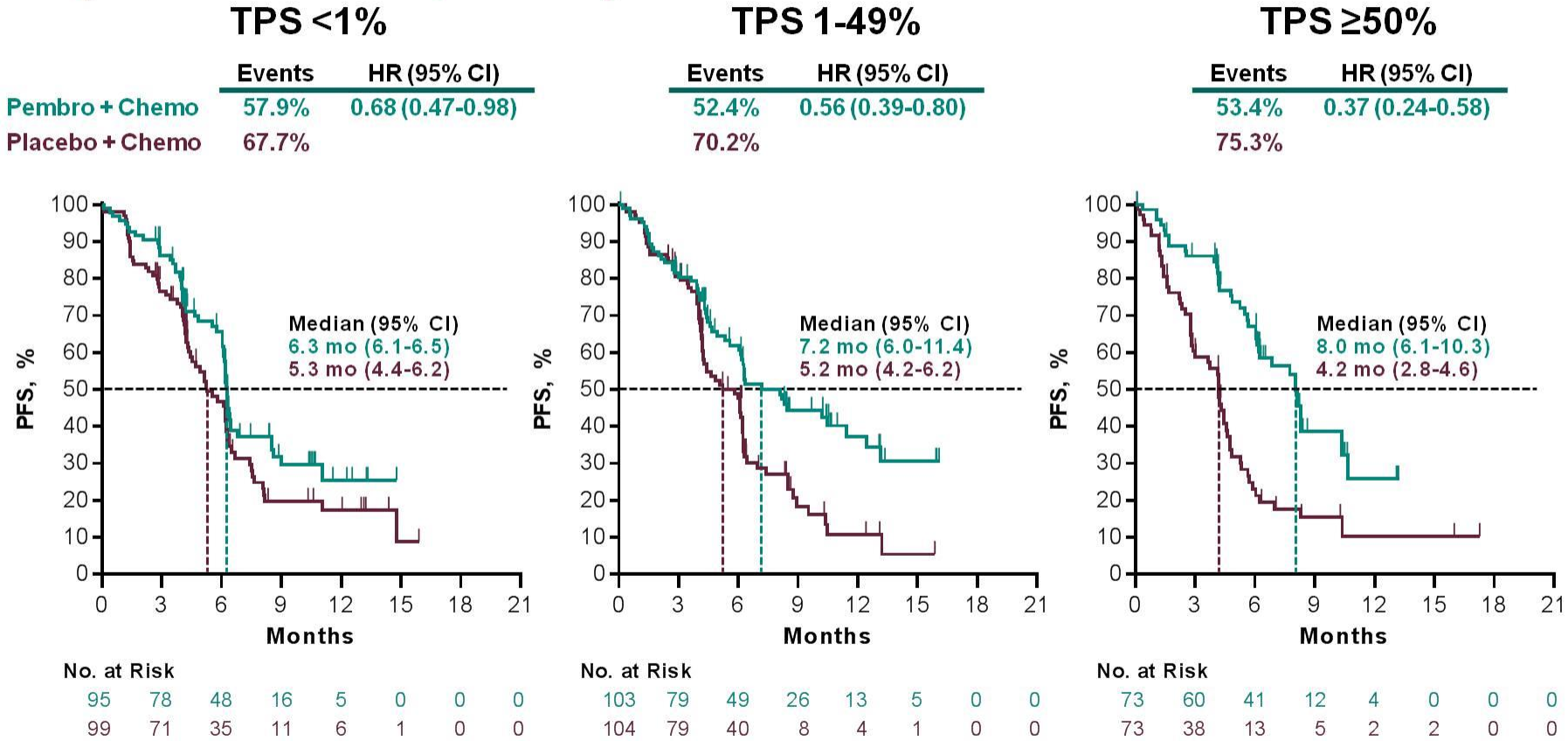


No. at Risk

278	256	188	124	62	17	2	0
281	246	175	93	45	16	4	0

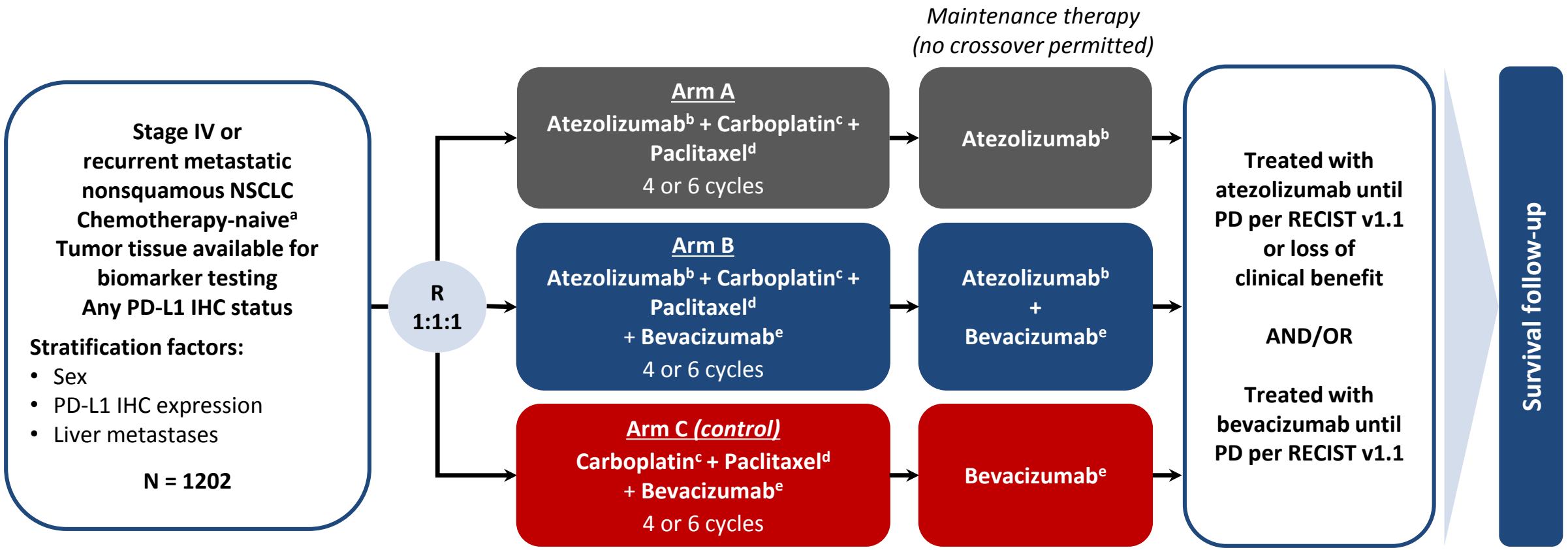
Data cutoff date: Apr 3, 2018.

Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)



BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

IMpower150 Study Design



Socinski M, et al. NEJM

NSCLC: First Line Chemotherapy vs. Chemoimmunotherapy Randomized Trials

Study	Author	Year	Selection	N	Control	Experimental Arm	OS :Control (PFS)	OS: Exp (PFS)	HR
KN021 (cohort G)	Langer (Lancet Oncol)	2017	Nonsquam	123	Carbo/Pem (maint)	Carbo/Pem/Pembro	20.9	NR	0.54 (p=0.0067
KN189	Gandhi (NEJM)	2018	Nonsquam Any PD-L1	616 (2:1)	Carbo/Pem (maint)	Carbo/Pem/Pembro	11.3 (4.9)	NR (8.8)	0.49 (p<.00001)
IM150	Socinski	2018	Nonsquam	1202	CPac+bev	CP+bev+atezo CP+atezo (NR)	14.4	19.2	HR =0.775 (p=.026)
IM131	Jotte (NEJM)	2018	Squamous	1021	CPac or CnabPac	Cpac/nabPac + Atezo	13.9 (5.6) PFS12mo =12%	14 (6.3) PFS12mo= 24.7%	.96 (.72) (p<.0001)
KN407	Paz-Ares (NEJM)	2018	Squamous Any PD-L1	559	CPac or CnabPac	CP/nabP + Pemb	11.3	15.9	.64, p<.001
IM 132	Papadimitrakopoulou	2018	Nonsquam	578	CisPem or Carbo/Pem (maint)	CisPem or Carbo/Pem + Atezo	(5.2)	(7.6)	OS HR = 0.81 (p=.08) (PFS HR = 0.60)

KN = Keynote CM = CheckMate IM = IMpower

Bristol-Myers Squibb

Press Release

CheckMate -9LA, a Phase 3 Trial Evaluating Opdivo (nivolumab) Plus Low-Dose Yervoy (ipilimumab) Combined with Chemotherapy, Meets Primary Endpoint Demonstrating Superior Overall Survival Compared to Chemotherapy Alone in First-Line Lung Cancer

Study evaluated Opdivo plus low-dose Yervoy given concomitantly with two cycles of chemotherapy vs. chemotherapy alone for the first-line treatment of advanced non-small cell lung cancer

CATEGORY: CORPORATE/FINANCIAL NEWS

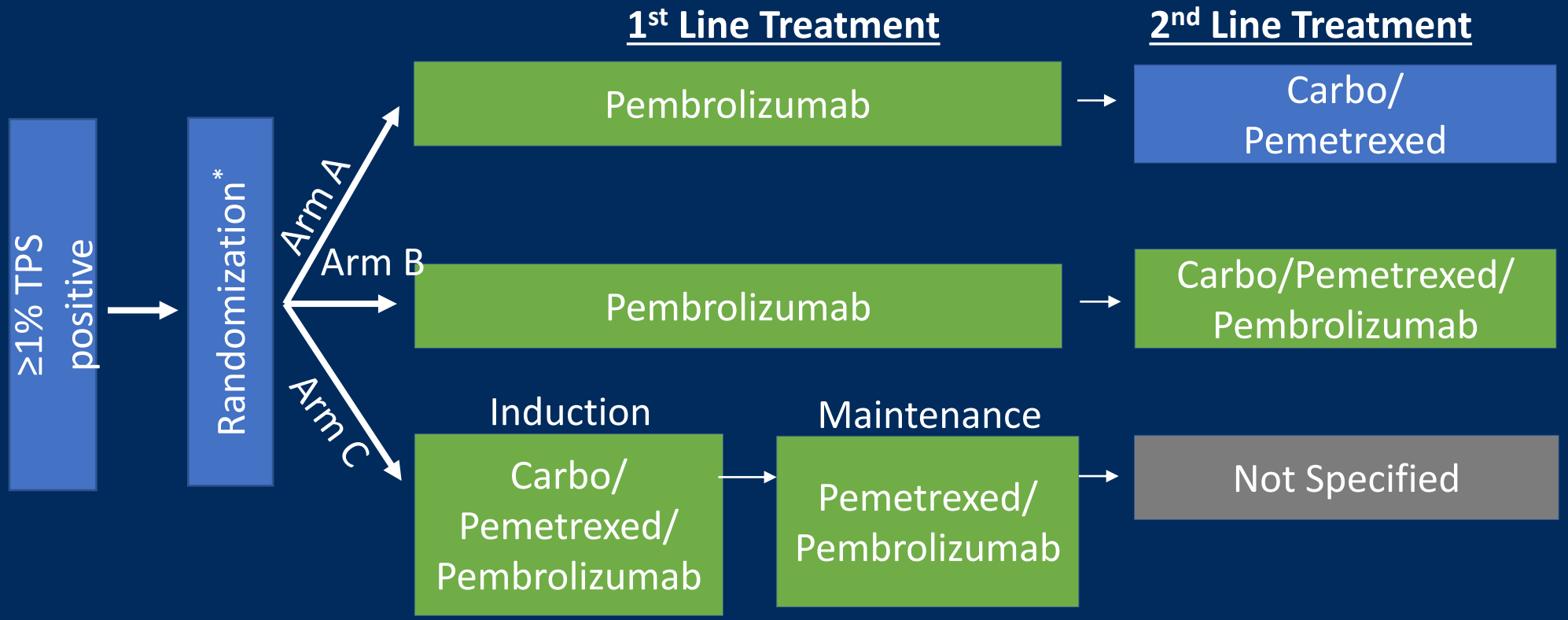
TUESDAY, OCTOBER 22, 2019 6:59 AM EDT

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY)

$BMY announces positive topline results in

Sequential vs Combination Therapy: INSIGNA

A Randomized, Phase III Study of First line **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis



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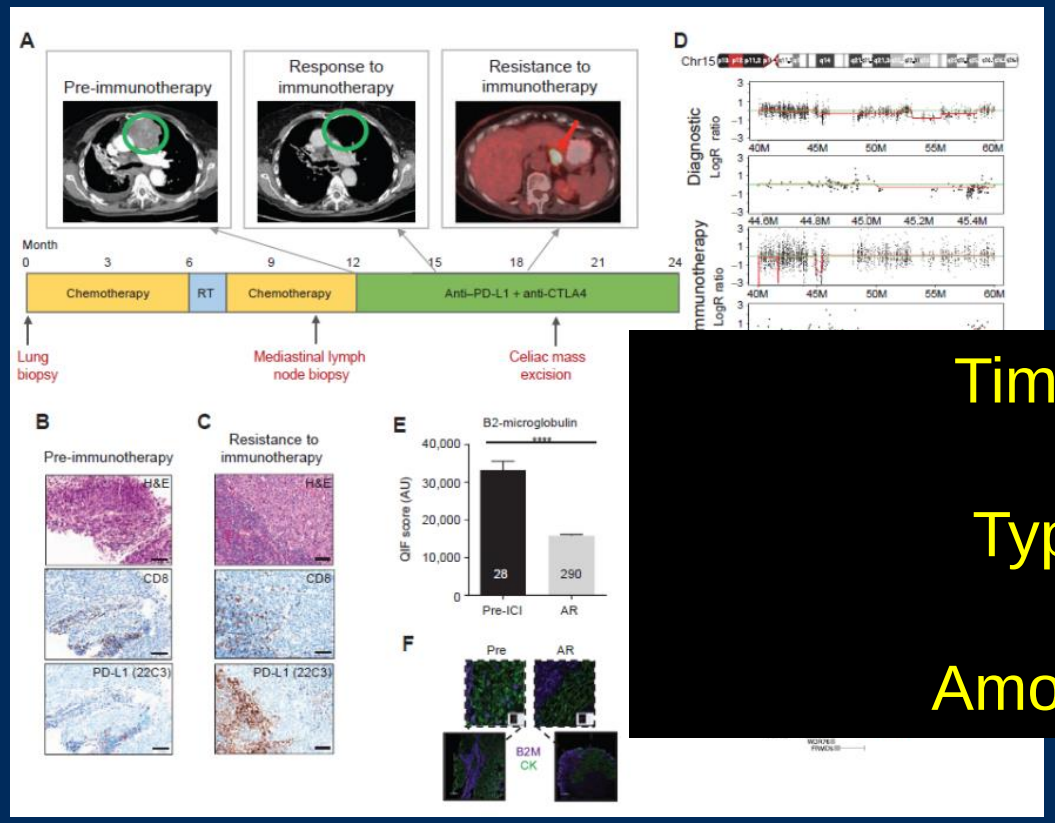
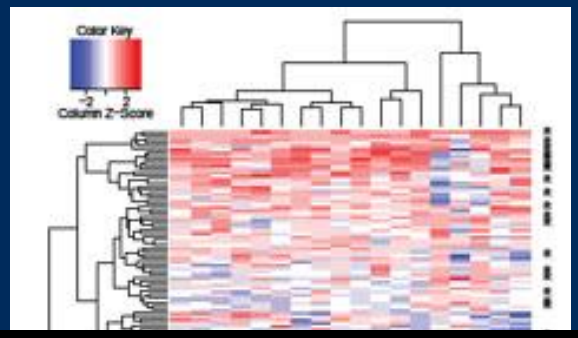
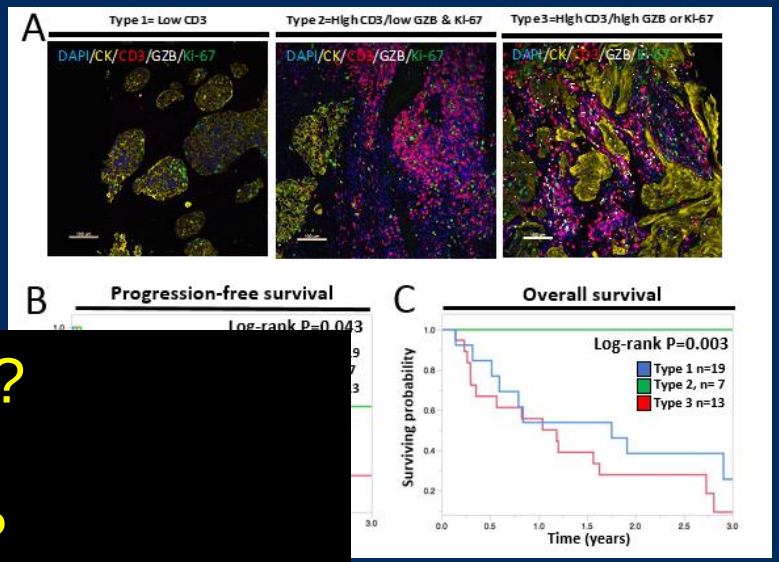
SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

We need to consider evolving biomarkers (How is it working)



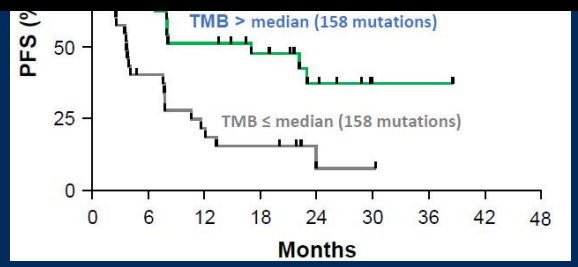


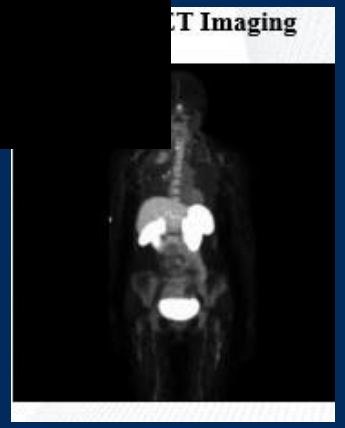


Timing of chemotherapy?

Type of Chemotherapy?

Amount of Chemotherapy?





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S. Ramalingam AACR 2018 CT 078, K. Schalper et al. Manuscript Accepted; Gettinger et al. Cancer Discovery 2017:7(12):1420-35)

Brahmer et al. Journal for ImmunoTherapy of Cancer (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

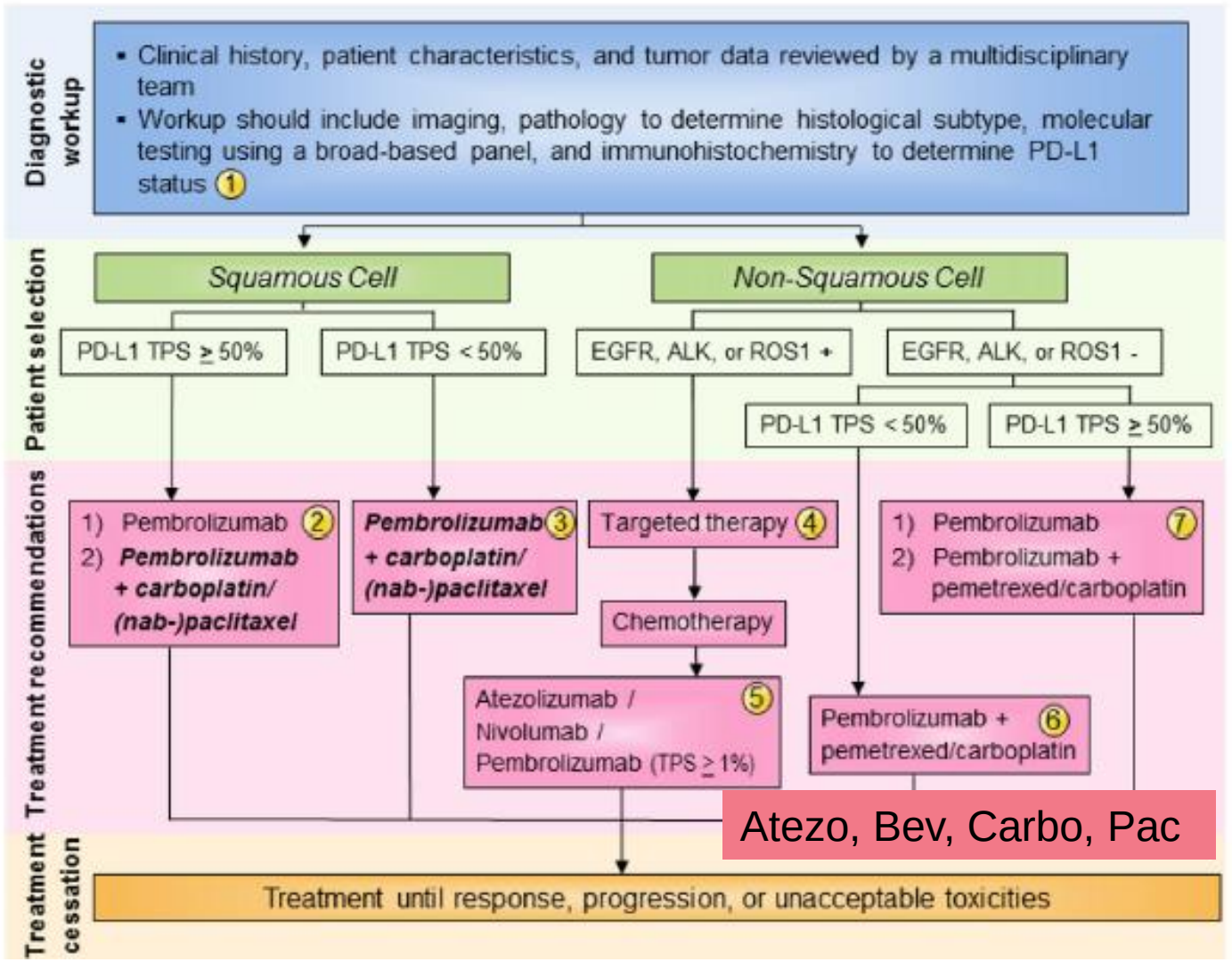
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

Julie R. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki A. Papadimitrakopoulou[15], David L. Rimm[16], Lawrence H. Schwartz[17], Boris Sepesi[18], Beow Yong Yeap[19], Naiyer A. Rizvi[20] and Roy S. Herbst[21*]

Time for an update??

Where does Ipilimumab and Nivolumab get placed???

Its all about the tail!



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