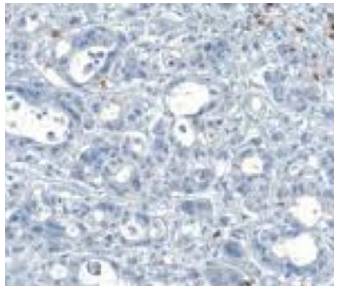

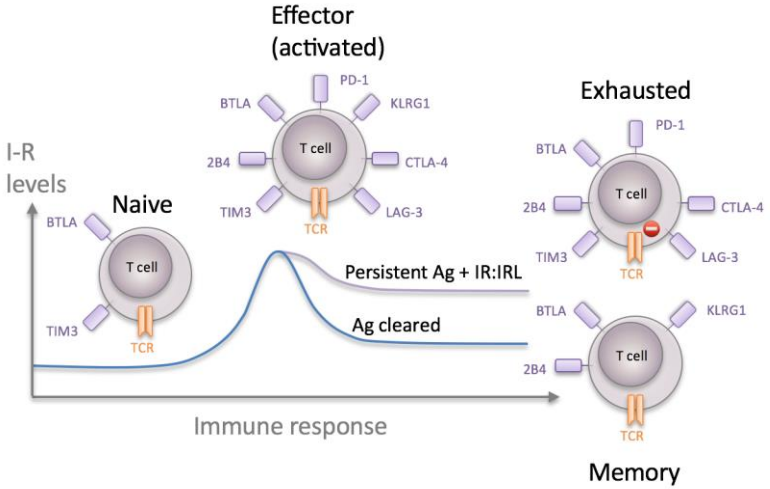

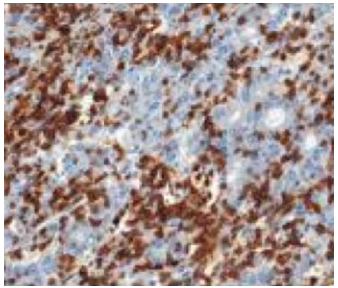

In high PD-L1, should monotherapy pembrolizumab or combinations be used?

Pr Solange Peters, MD-PhD
Lausanne University Hospital & Ludwig Institute
Switzerland

Disclosure information – Solange Peters

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria:

- **Consultation / Advisory role:** Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda

- **Talk in a company's organized public event**: AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Takeda

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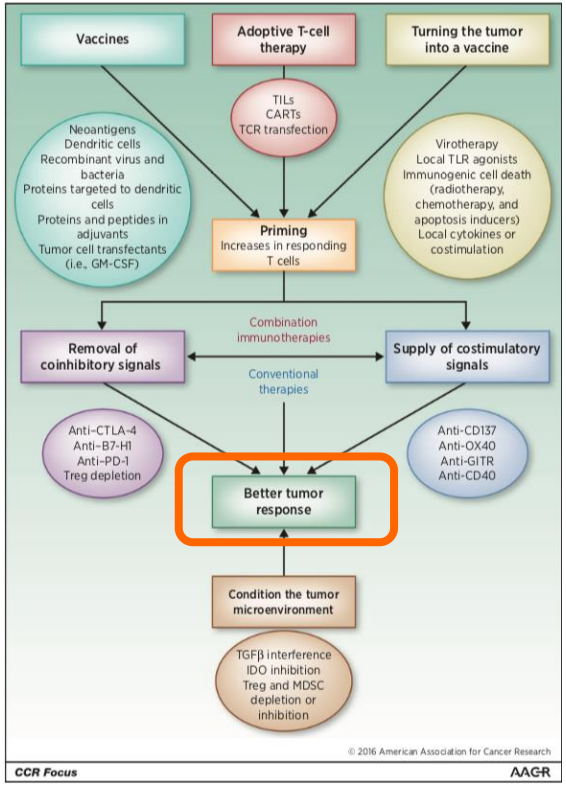
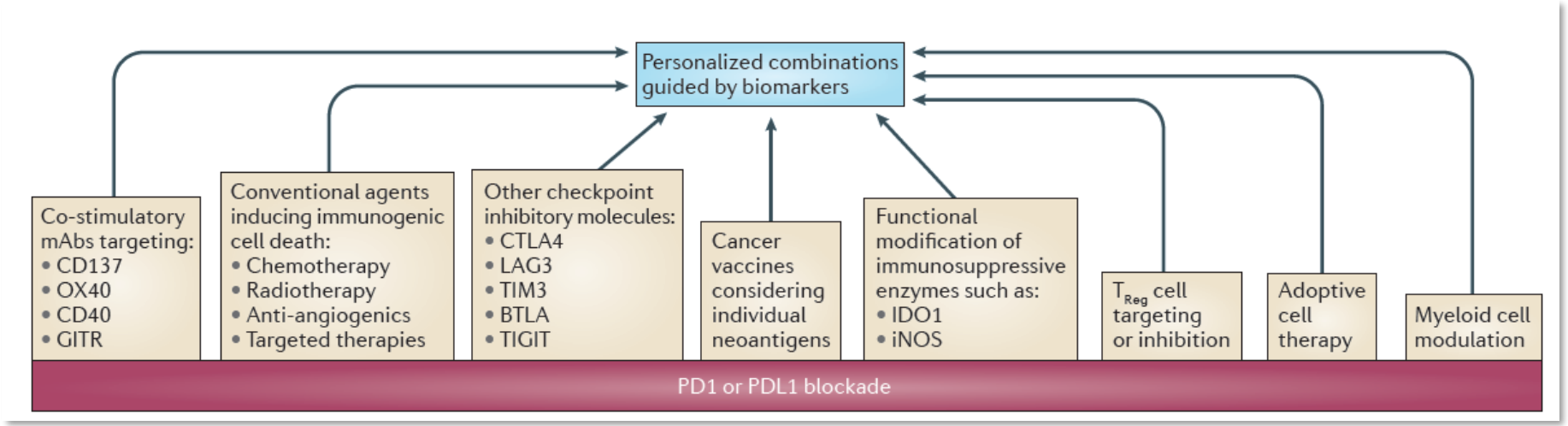
The Concept of IO
Four pillars of promise

- Enhancement of T-cell priming
- Removal of coinhibitory signals
- Supply of costimulatory signals
- Conditioning the tumor microenvironment
  - ➢ Optimising Durable Tumor Control
  - ➢ Cure?



Reck, ESMO 2018; Whiteside, Clin Cancer Res 2016

Most combinations keep anti-PD1/PD-L1 as backbone



Galluzzi, Cancer Immunol Res 2016;
Lanitis, Curr Opinion in Immunology 2015

How to decide for frontline immunotherapy?

General picture of frontline treatment strategies

- Landscape of new evidence-based data
- Biomarker-driven subgroups (PD-L1, TMB)
- Standards for ≥ 50% PD-L1 TC NSCLC

Specific subgroups and related treatment preferences

Long term survival

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Trial		PFS / OS (months)	Treatment-Related AEs, Grade 3-5 (* *All toxicities*)
KEYNOTE-024	PD-L1 TPS ≥50%	Pembrolizumab: 10.3 / 30.0 Plat/Pem or Gem or Pacli: 6.0 / 14.2	31% vs 53%
CheckMate 026	PD-L1 ≥5%	Nivolumab: 4.2 / 14.4 Plat/Pem or Gem or Pacli: 5.9 / 13.2	18% vs 52%
KEYNOTE-042	PD-L1 TPS ≥1%	Pembrolizumab: 5.4 / 16.7 Plat/Pem or Pacli: 6.5 / 12.1	18% vs 41%
IMpower150	Nonsquamous	Atezolizumab + Beva + Plat/Pacli: 8.3 / 19.2 Beva + Plat/Pacli: 6.8 / 14.7	59% vs 50%
KEYNOTE-189	Nonsquamous	Pembrolizumab + Plat/Pem: 8.8 / NR Placebo + Plat/Pem: 4.9 / 11.3	67% vs 66%*
IMpower132	Nonsquamous	Atezolizumab + Plat/Pem: 7.6 / 18.1 Plat/Pem: 5.2 / 13.6	57% vs 42%
IMpower130	Nonsquamous	Atezolizumab + Carbo/nabPacli: 7.0 / 18.6 Carbo/nabPacli: 5.5 / 13.9	75% vs 61%
KEYNOTE-407	Squamous	Pembrolizumab + Plat/Tax: 6.4 / 15.9 Placebo + Plat/Tax: 4.8 / 11.3	70% vs 68%*
IMpower131	Squamous	Atezolizumab + Carbo/nabPacli: 6.3 / 14.0 Carbo/nabPacli: 5.6 / 13.9	69% vs 58%
CheckMate 227	PD-L1 neg (*only PFS*)	Nivolumab + Plat/Pem or Gem: 5.6 Plat/Pem or Gem: 4.7	54% vs 38%
CheckMate 227	TMB ≥10 mut/Mb	Nivolumab + Ipilimumab: 7.2 / 23.0 Plat/Pem or Gem: 5.5 / 16.7	32% vs 37%
MYSTIC	PD-L1 ≥25%	Durvalumab: 4.7 / 16.3 Plat/Pem or Gem or Pacli: 5.4 / 12.9	15% vs 35%
MYSTIC	PD-L1 ≥25%	Durvalumab + Tremelimumab: 3.9 / 11.9 Plat/Pem or Gem or Pacli: 5.4 / 12.9	24% vs 35%
MYSTIC	TMB ≥16 mut/Mb (*only OS*)	Durvalumab + Tremelimumab: 16.5 Plat/Pem or Gem or Pacli: 10.5	24% vs 35%

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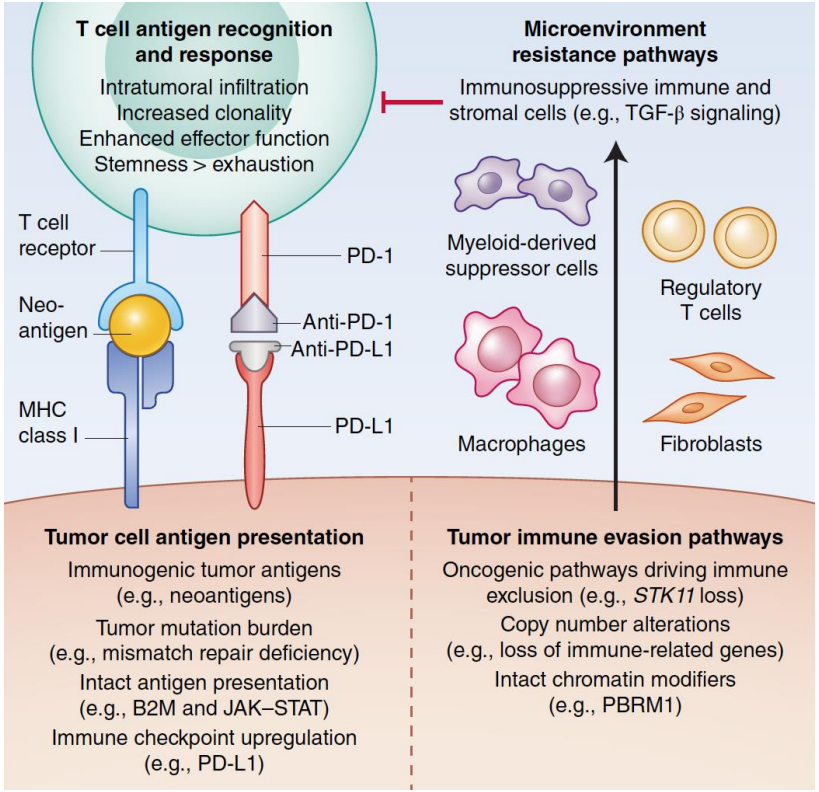
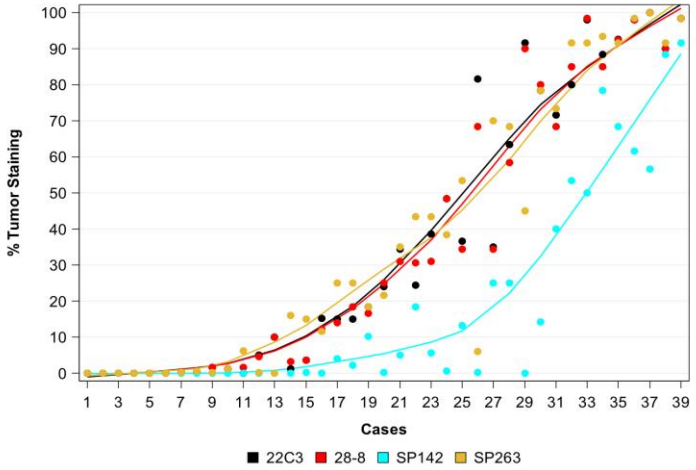
The parameters for IO success: defining biomarkers

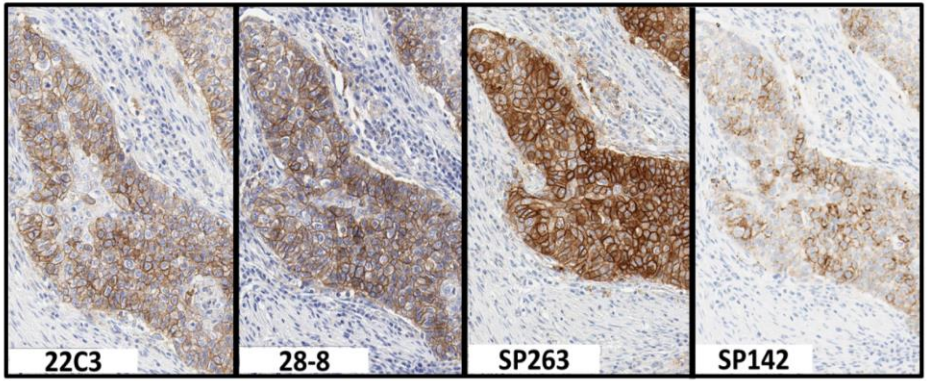


Keenan, Nat Med 2019

PD-L1 expression on TC & predictive ability



Each dot represents the mean score of 3 pathologists



3 assays showed similar staining characteristics for PD-L1 staining on tumor cells, but SP142 comparatively showed less tumor cells stained

- Virtually every trial has shown a predictive ability of PD-L1 expression
- PD-L1 expression is a biological continuum
- FNA, biopsy, large block can be used : heterogeneity is the background

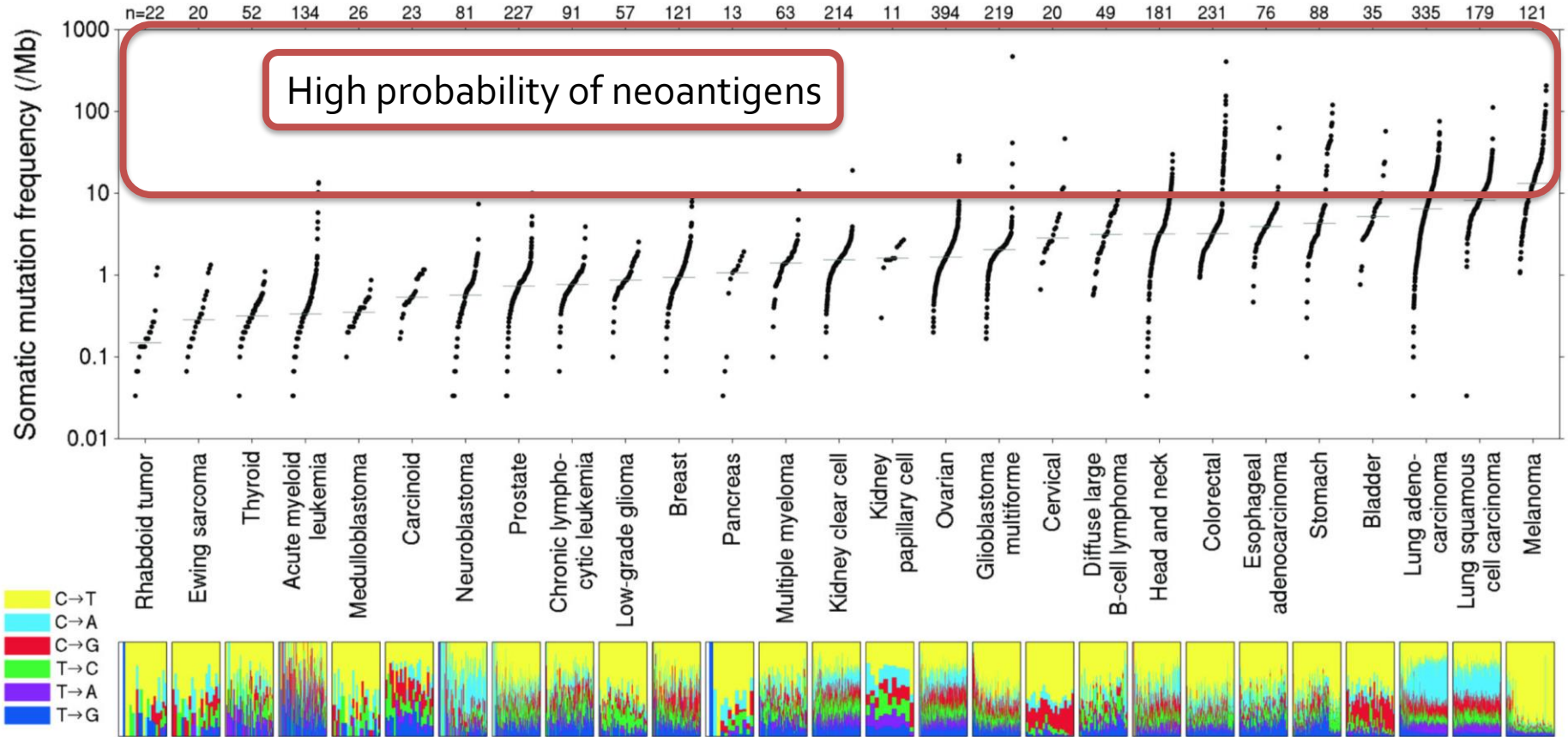
Kerr, JTO 2017 and WCLC 2018

	KN-024[1,2] Pembro vs CT (N = 305, PD-L1 TC ≥50%, 1:1)	KN-042[3] Pembro vs CT (N = 1274, PD-L1 TC ≥1%, 1:1)	CM-026[4] Nivo vs CT (N = 423, PD-L1 TC ≥5%, 1:1)	MYSTIC Durva vs CT (N = 568, PD-L1 TC ≥1%, 1:1)
Exp Arm Numbers	TC ≥50% n = 305	TC ≥50% n = 299	TC ≥50%* n = 214	TC ≥50%* n = 118
Median OS, mos **HR**	30 vs 14.2 **0.63**	20.0 vs 12.2 **0.69**	15.9 vs 13.9 **0.90**	18.3 vs 12.7 **0.76**
Median PFS, mos **HR**	10.3 vs 6.0 **0.50**	7.1 vs 6.4 **0.81**	5.4 vs 5.8 **1.07**	-
12-mo PFS, %	-	37.4 vs 27.3	-	-
ORR, %	45.5 vs 29.8	39.5 vs 32.0	34 vs 39	-

*exploratory analysis
TC, tumour cell

1. Brahmer et al; WCLC 2017 2. Reck et al 2016; NEJM 375;19 3. Lopes et al. ASCO 2018
4. Carbone al 2017; NEJM 376;2415-2426.

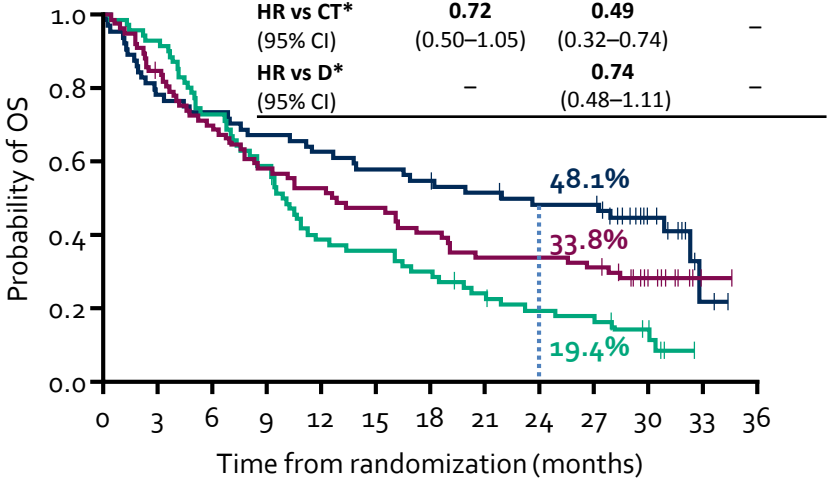
Cancer is characterized by the accumulation of mutations increasing its likelihood to be recognized as foreign



Overall Survival in Blood TMB ≥20 and <20 mut/Mb

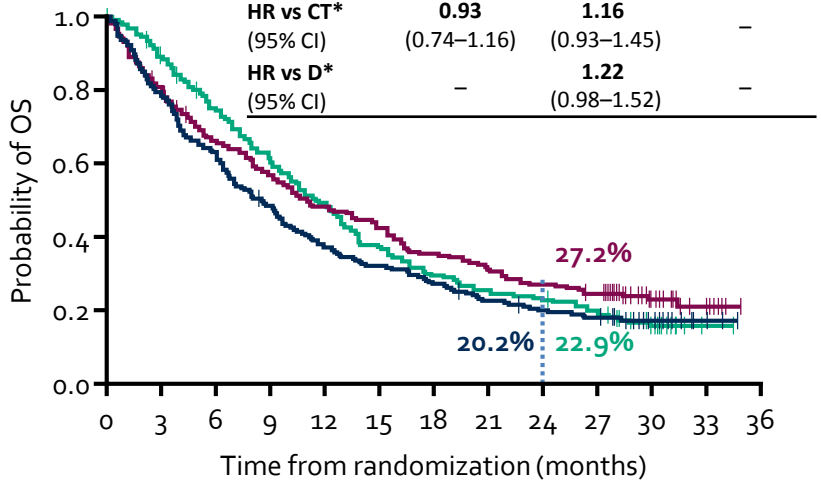
bTMB ≥20 mut/Mb

	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)	–



bTMB <20 mut/Mb

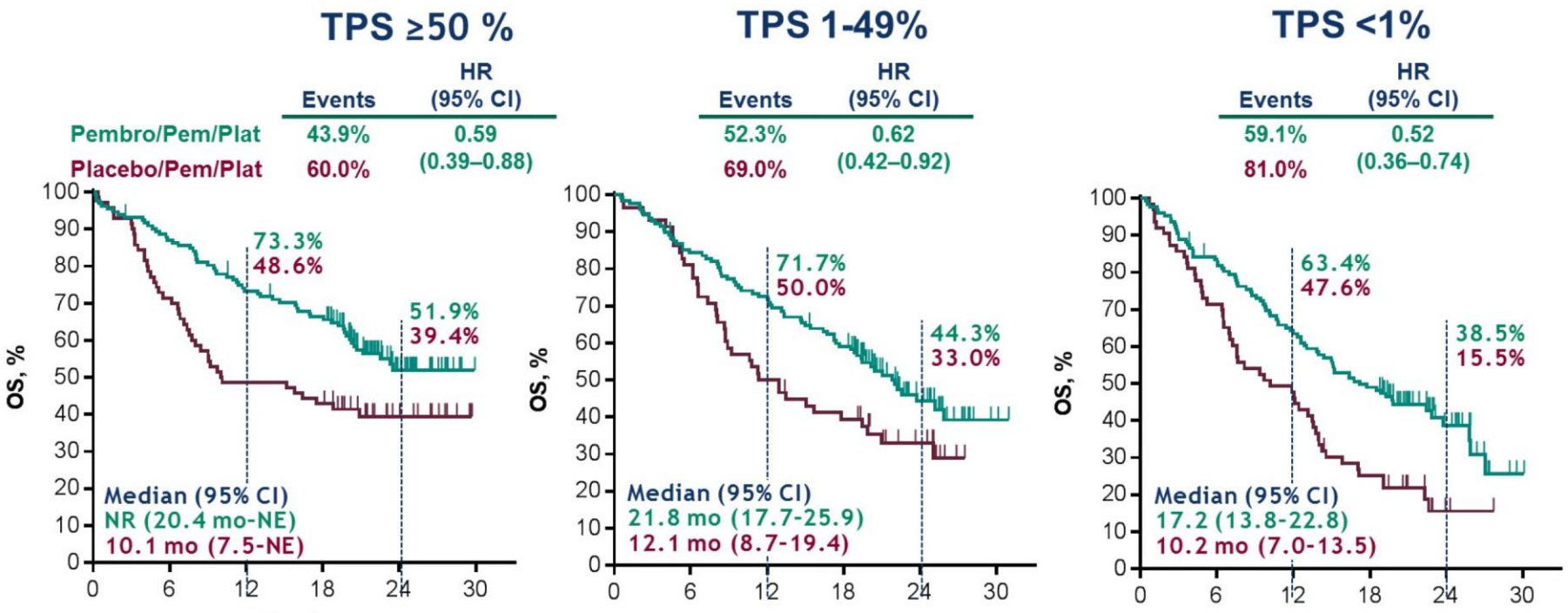
	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	**11.0** (8.9–14.9)	**8.5** (6.7–9.8)	**11.6** (9.6–13.1)
HR vs CT* (95% CI)	**0.93** (0.74–1.16)	**1.16** (0.93–1.45)	–
HR vs D* (95% CI)	–	**1.22** (0.98–1.52)	–



- bTMB was evaluated with the GuardantOMNI platform comprised of a 500-gene panel (1.0 Mb DNA footprint)
- The large bTMB dataset included baseline samples from 809 patients (72.4% of ITT) in the MYSTIC trial

Peters, AACR 2019

Platinum/pemetrexed/pembrolizumab is superior to platinum/pemetrexed irrespective of PD-L1 (and TMB?)



Gadgeel, ASCO 2019

Co-primary endpoints PFS/OS, crossing over 54%, 1/3 no second line therapy

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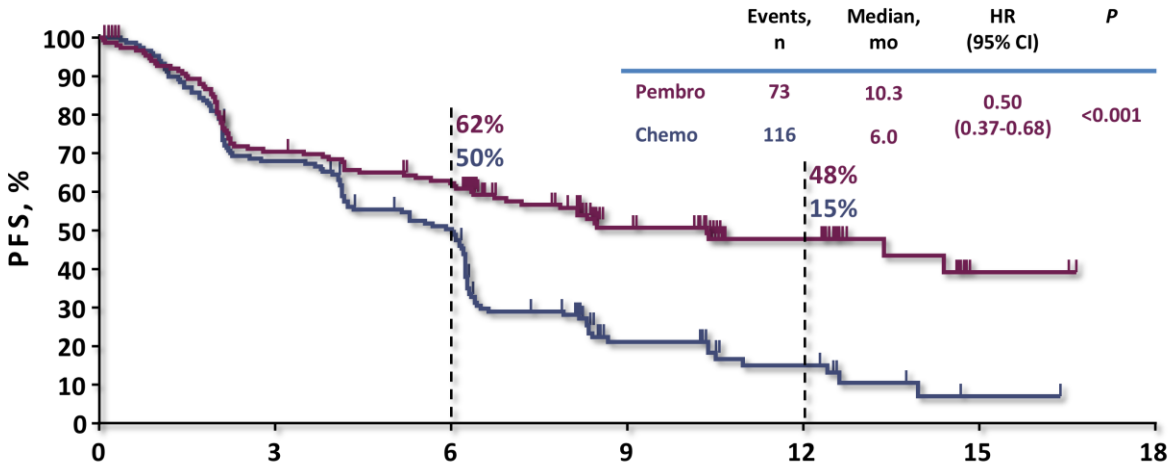
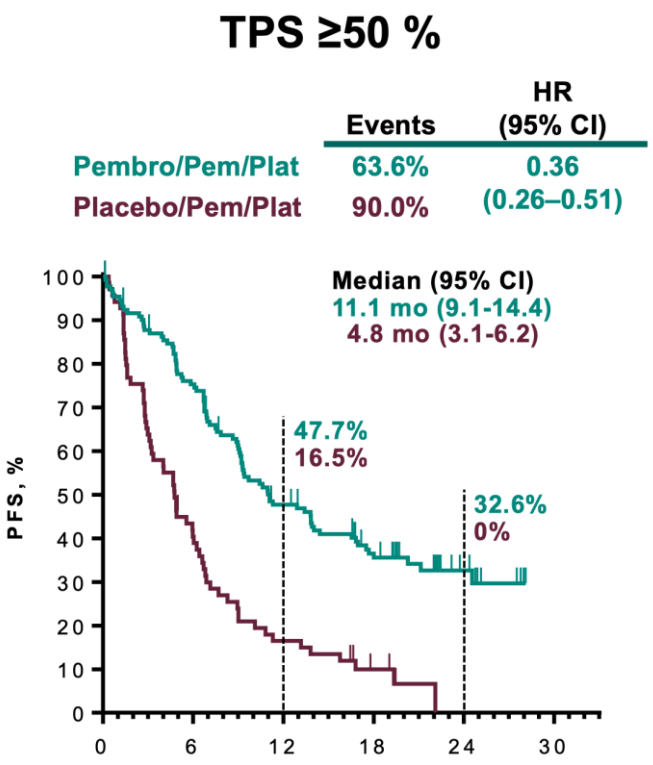
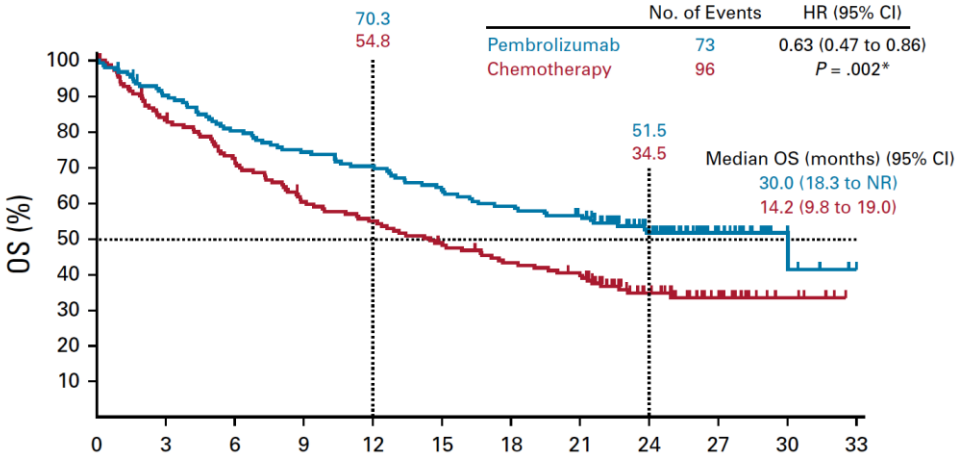
Current standards in PD-L1 ≥50%: PFS

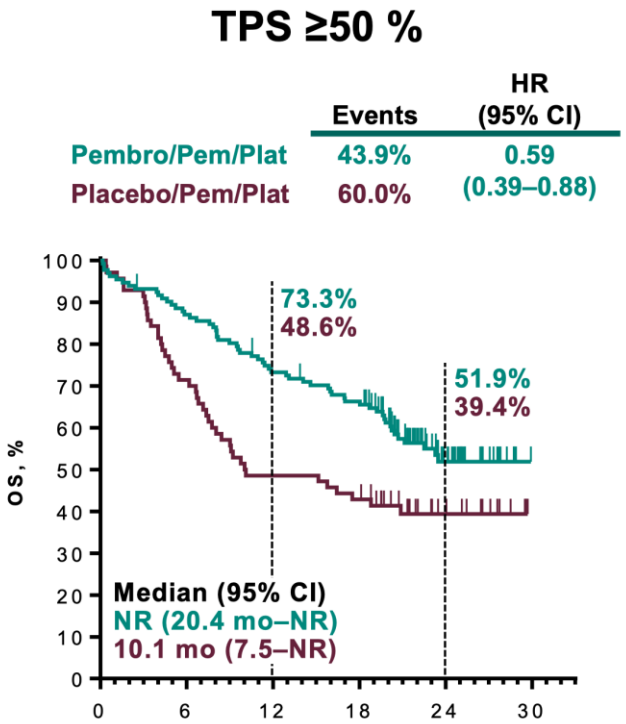




Current standard in PD-L1 ≥50%: OS

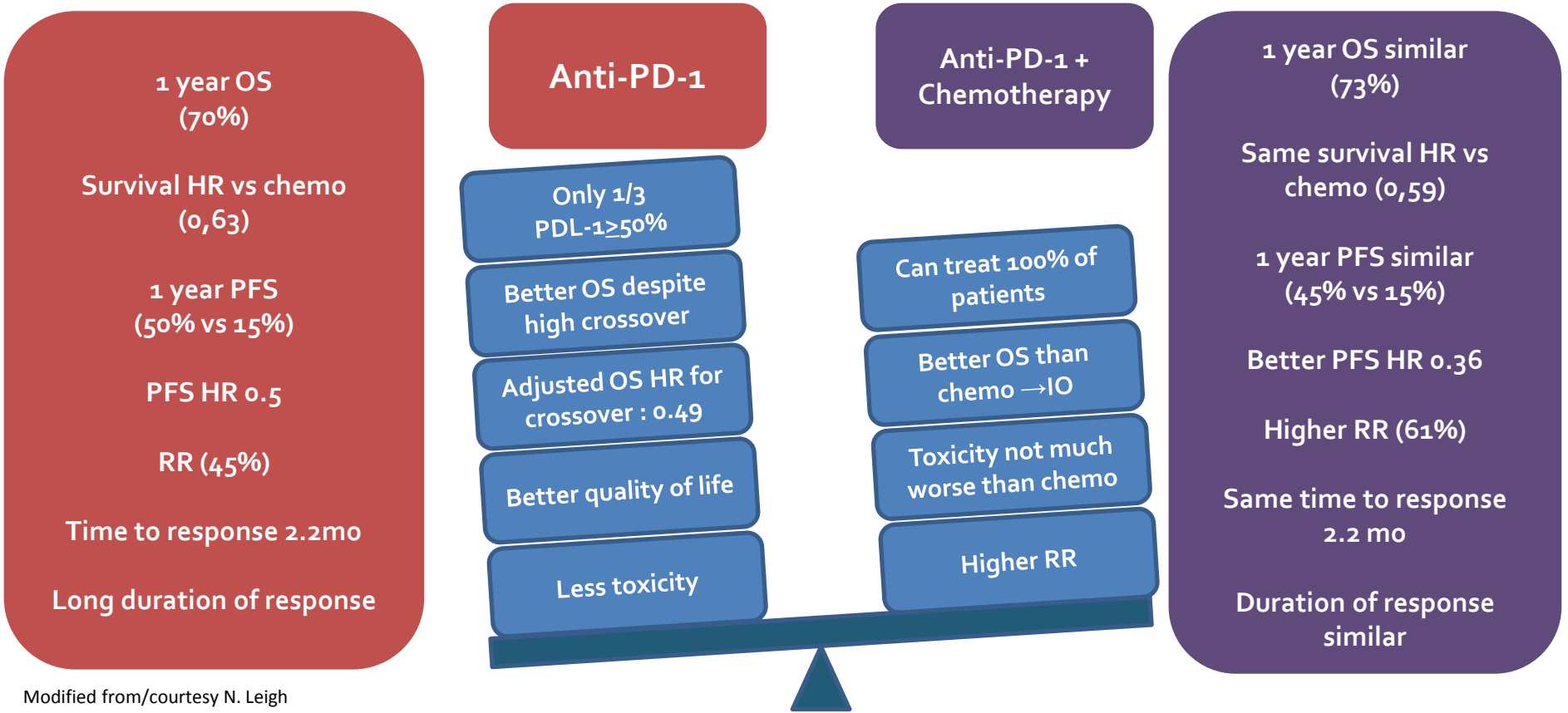


Effective crossover rate of 65.1%
(97 of 149 patients)



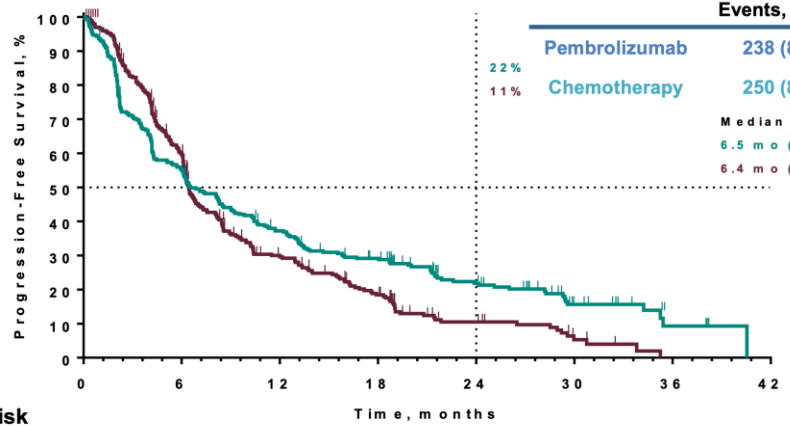
Effective crossover rate of 52.9%
(37 of 70 patients)

Can we compare IO monotherapy vs IO+Chemo in high PD-L1?



Modified from/courtesy N. Leigh

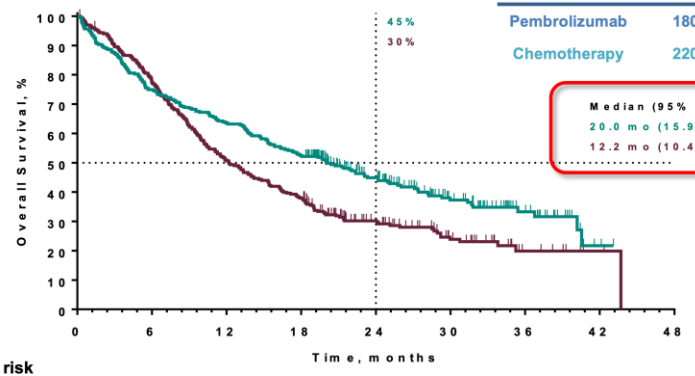
Crossing of the curves in PD-L1 ≥50%: KEYNOTE-042



	Events, n (%)	HR (95% CI)
Pembrolizumab	238 (80)	0.83[a] (0.69–1.00)
Chemotherapy	250 (83)	

Median (95% CI)
6.5 mo (5.9–8.5)
6.4 mo (6.2–7.2)

No. at risk								
Pembro/Pem/Plat	299	164	107	79	42	17	4	0
Placebo/Pem/Plat	300	169	75	42	15	5	0	0



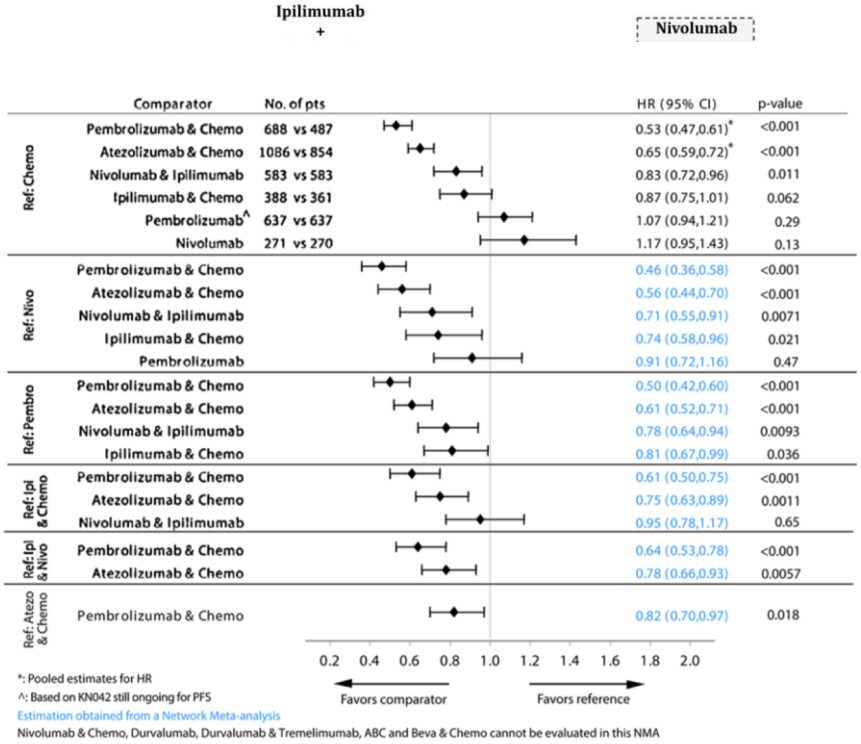
	Events, n (%)	HR (95% CI)
Pembrolizumab	180 (60)	0.70 (0.58–0.86)
Chemotherapy	220 (73)	

Median (95% CI)
20.0 mo (15.9–24.2)
12.2 mo (10.4–14.6)

No. at risk									
Pembro/Pem/Plat	299	224	190	157	94	50	21	1	0
Placebo/Pem/Plat	300	231	151	113	59	31	8	2	0

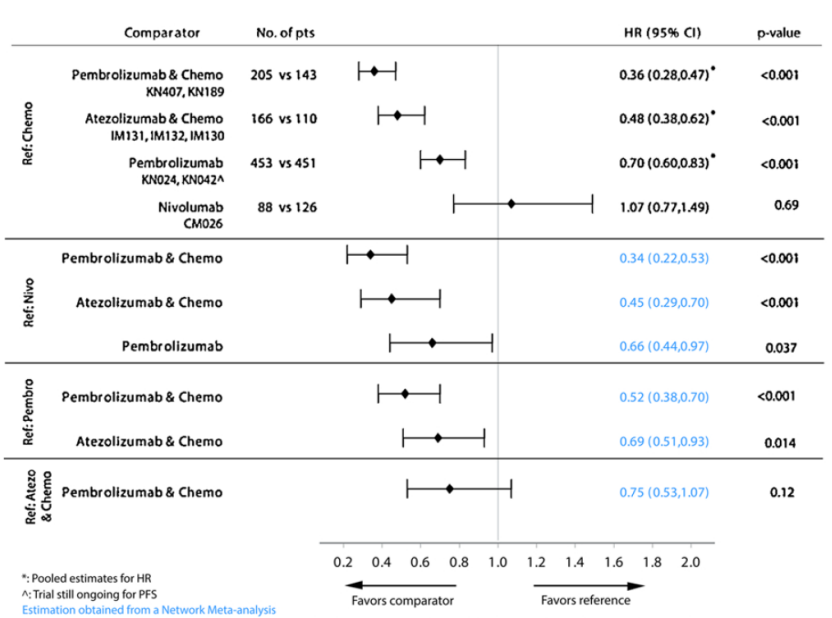
Network Meta-analysis and PFS

i



*: Pooled estimates for HR
^: Based on KN042 still ongoing for PFS
Estimation obtained from a Network Meta-analysis
Nivolumab & Chemo, Durvalumab, Durvalumab & Tremelimumab, ABC and Beva & Chemo cannot be evaluated in this NMA

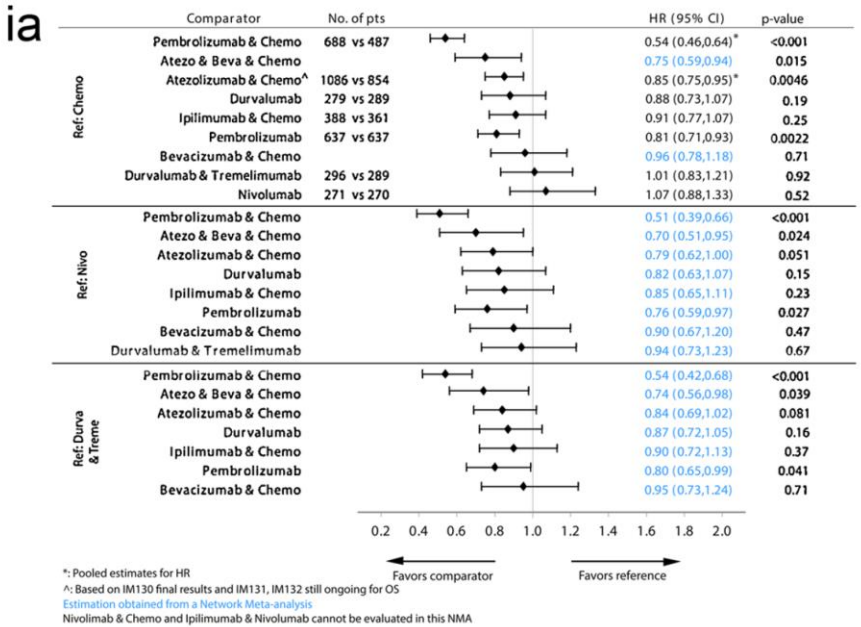
iii



*: Pooled estimates for HR
^: Trial still ongoing for PFS
Estimation obtained from a Network Meta-analysis
Nivolumab & Ipilimumab, Ipilimumab & Chemo, Nivolumab & Chemo, Durvalumab, Durvalumab & Tremelimumab, ABC and Beva & Chemo cannot be evaluated n this NMA

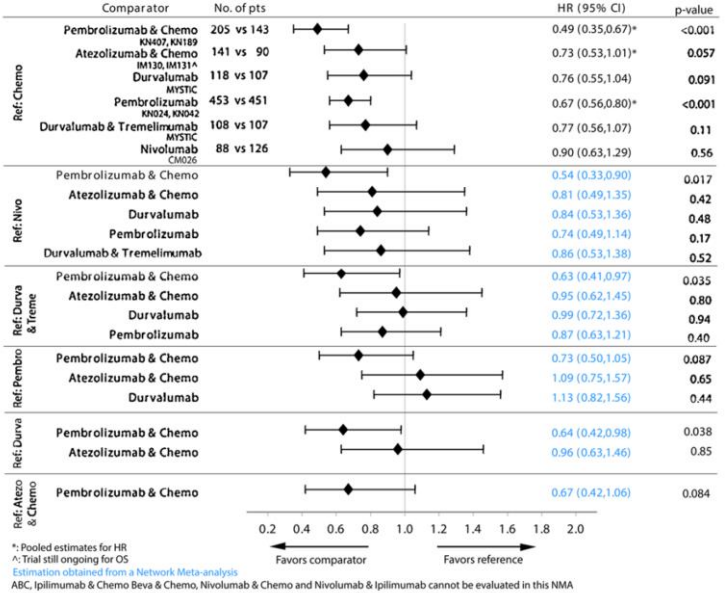
Network Meta-analysis: OS

ia



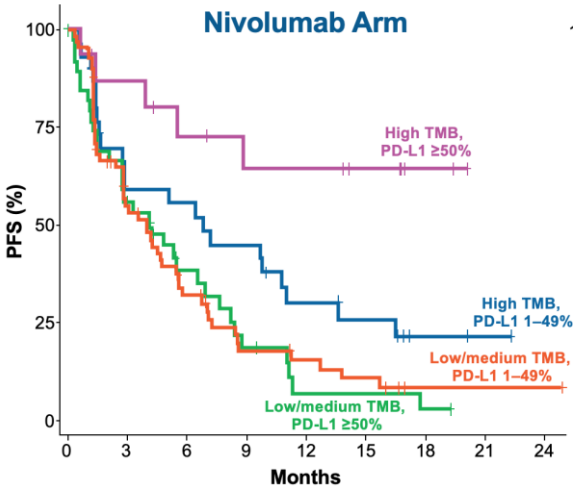
*: Pooled estimates for HR
^: Based on IM130 final results and IM131, IM132 still ongoing for OS
Estimation obtained from a Network Meta-analysis
Nivolimab & Chemo and Ipilimumab & Nivolumab cannot be evaluated in this NMA

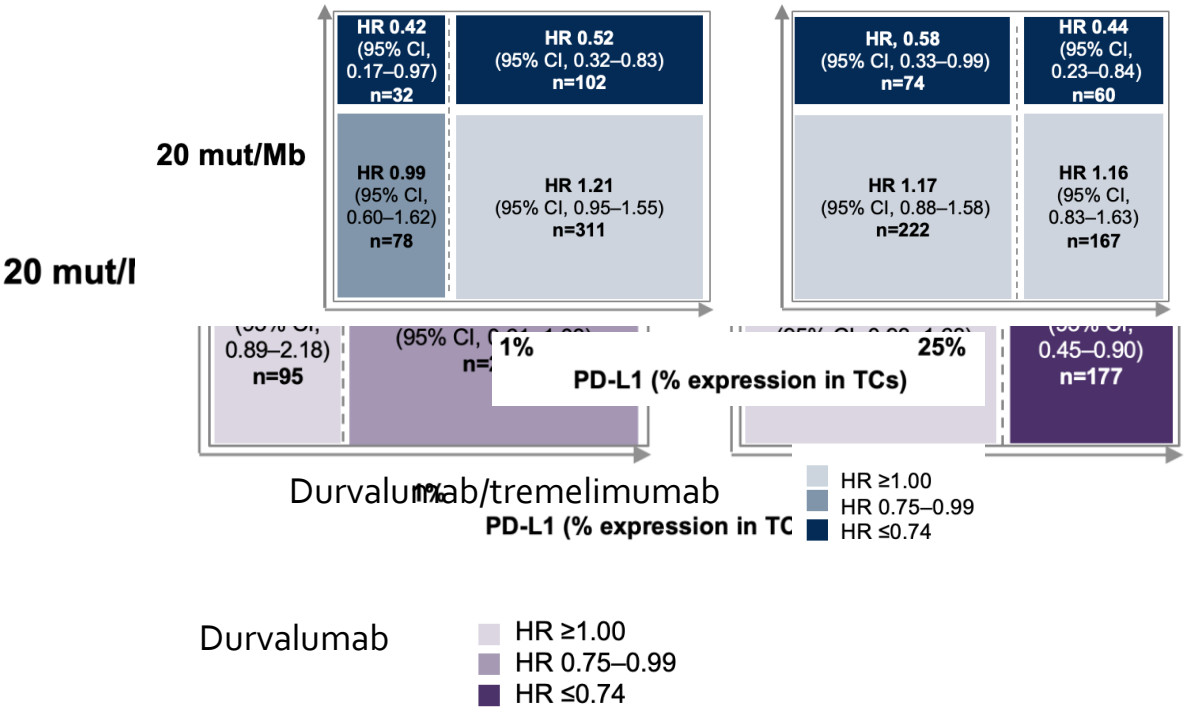
iii



*: Pooled estimates for HR
^: Trial still ongoing for OS
Estimation obtained from a Network Meta-analysis
ABC, Ipilimumab & Chemo Beva & Chemo, Nivolumab & Chemo and Nivolumab & Ipilimumab cannot be evaluated in this NMA

Would IO/IO be a better option in high TMB high PD-L1?





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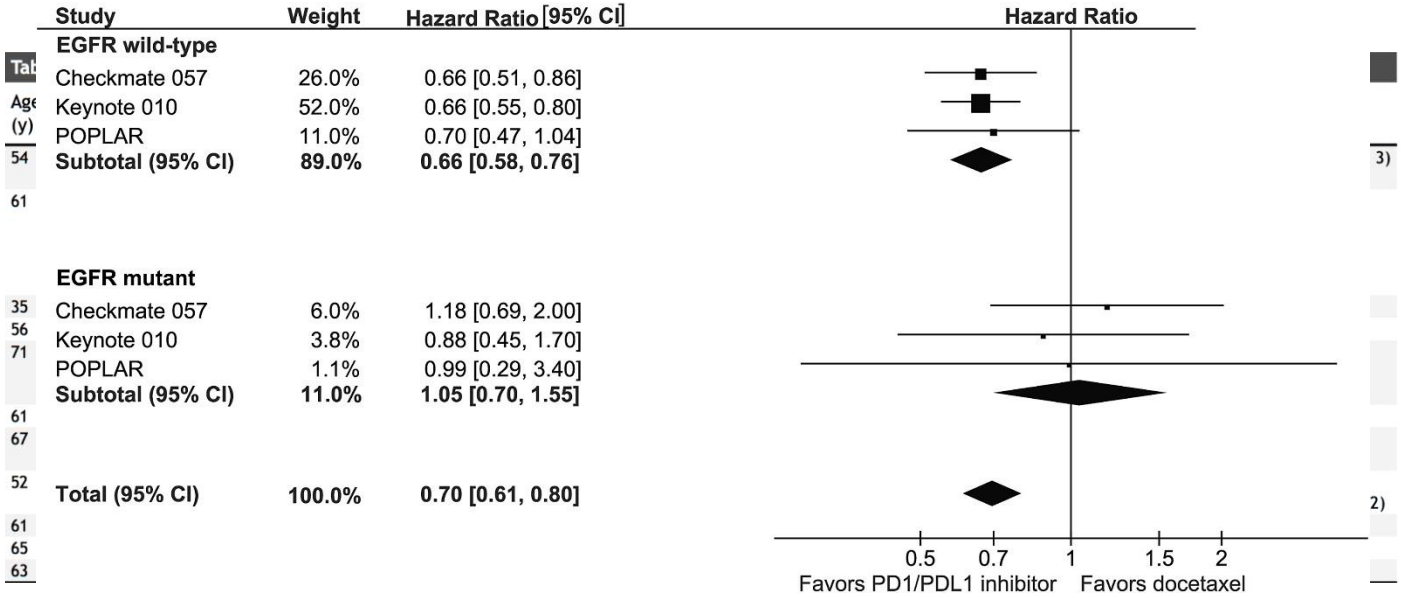
Shouldn't high PD-L1 EGFR M+ receive frontine IO ?

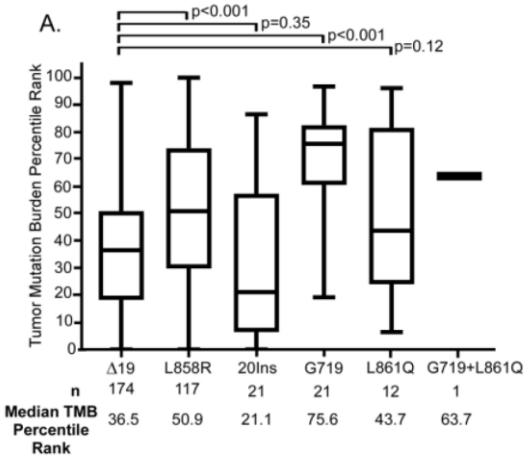


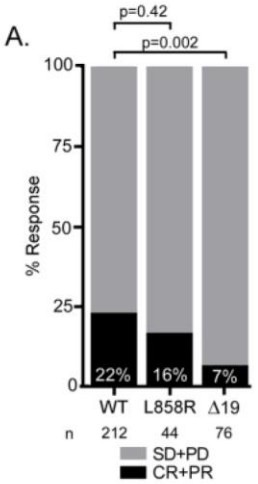
- The lack of an objective response in 10 PD-L1–positive, EGFR-mutant patients, inclusive of 7 with PD-L1 expression >50% was sobering
- Do not omit molecular testing!

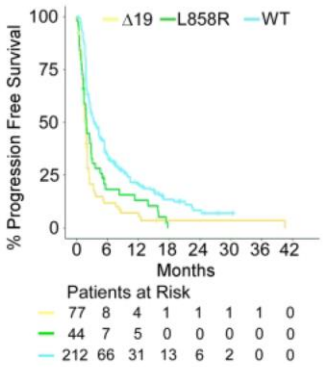
Lee, JTO 2017
Lisberg, JTO 2018

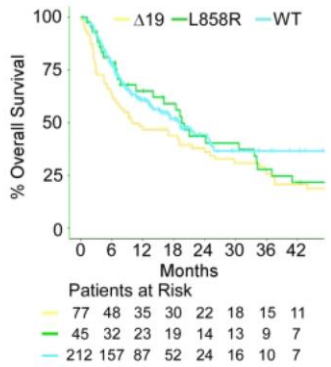
EGFR mutations are not equal

EGFR T790M (n=27)	21 (77.8%)	5 (18.5%)	1 (3.7%)
EGFR exon19 (n=21)	18 (85.7%)	1 (4.8%)	2 (9.5%)
EGFR other (n=34)	19 (55.9%)	11 (32.4%)	4 (11.8%)
EGFR exon21 (n=24)	14 (58.3%)	5 (20.8%)	5 (20.8%)



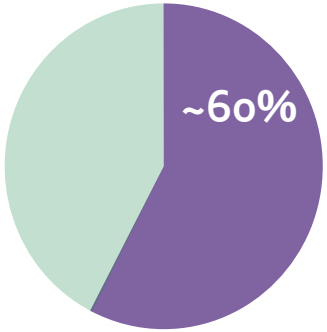




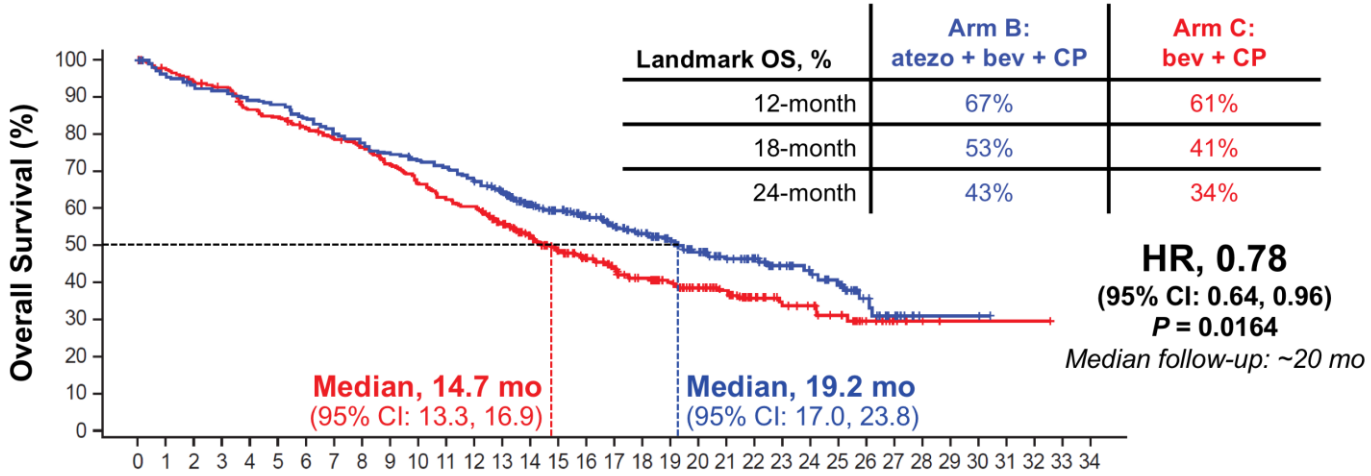


Mazieres and Gautschi, ASCO and WCLC 2018; Hastings, Ann Oncol 2019

Carboplatin/paclitaxel/atezolizumab/bevacizumab IMpower150



Non-squamous NSCLC

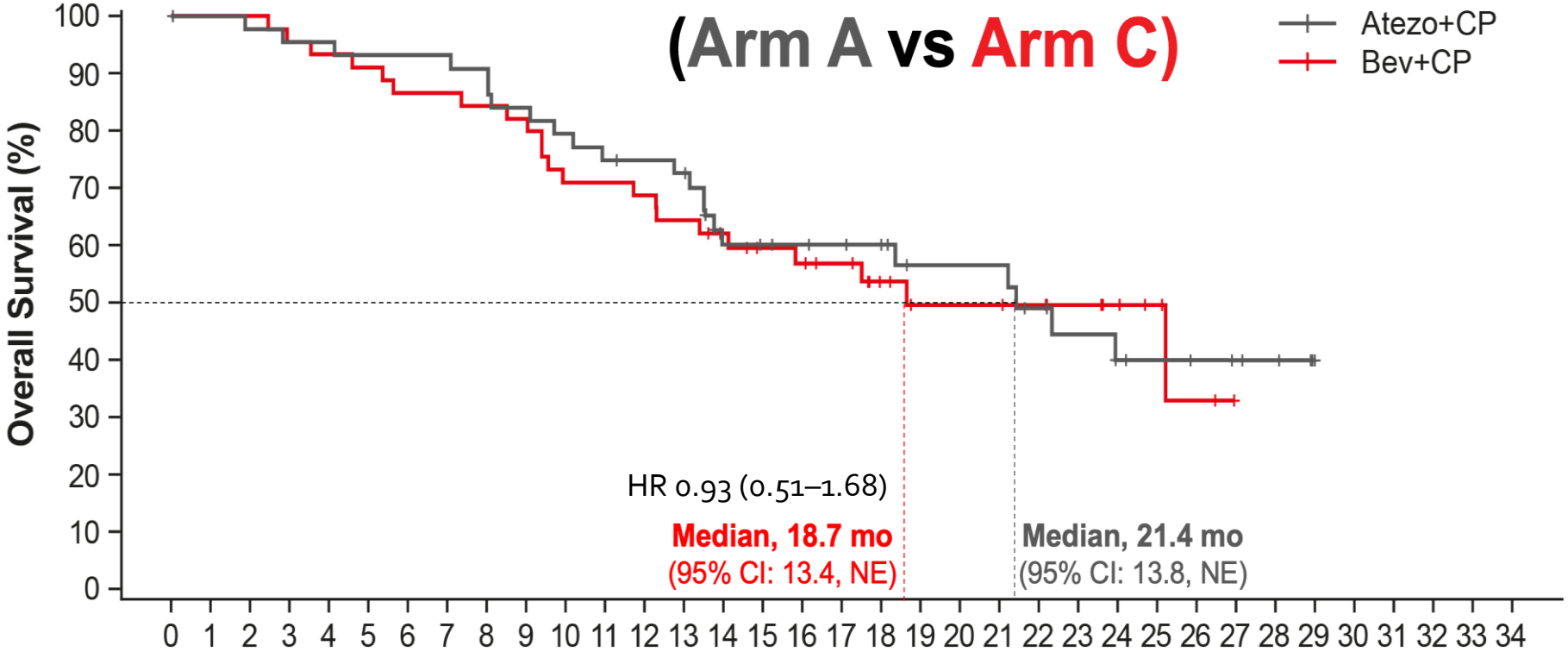


Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

HR, 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

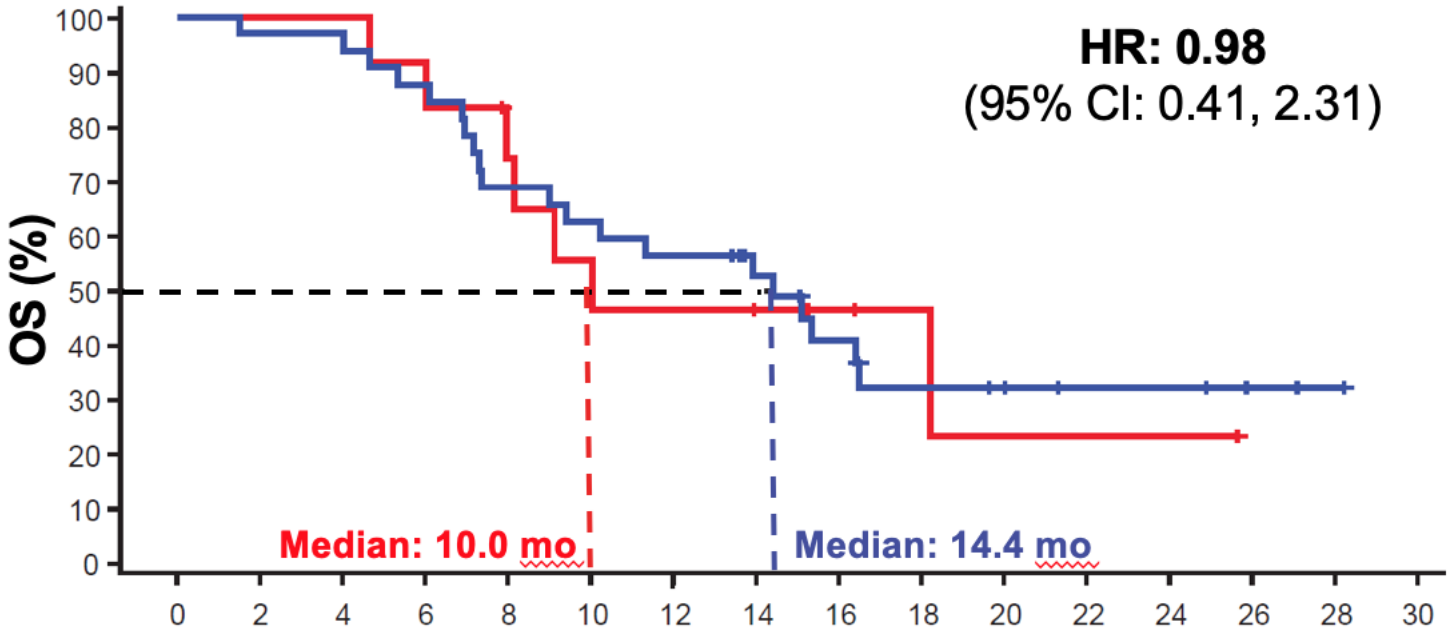
Reck, ESMO IO 2017; Socinski ASCO 2018

OS in *EGFR*-mt patients (Arm B vs Arm C)



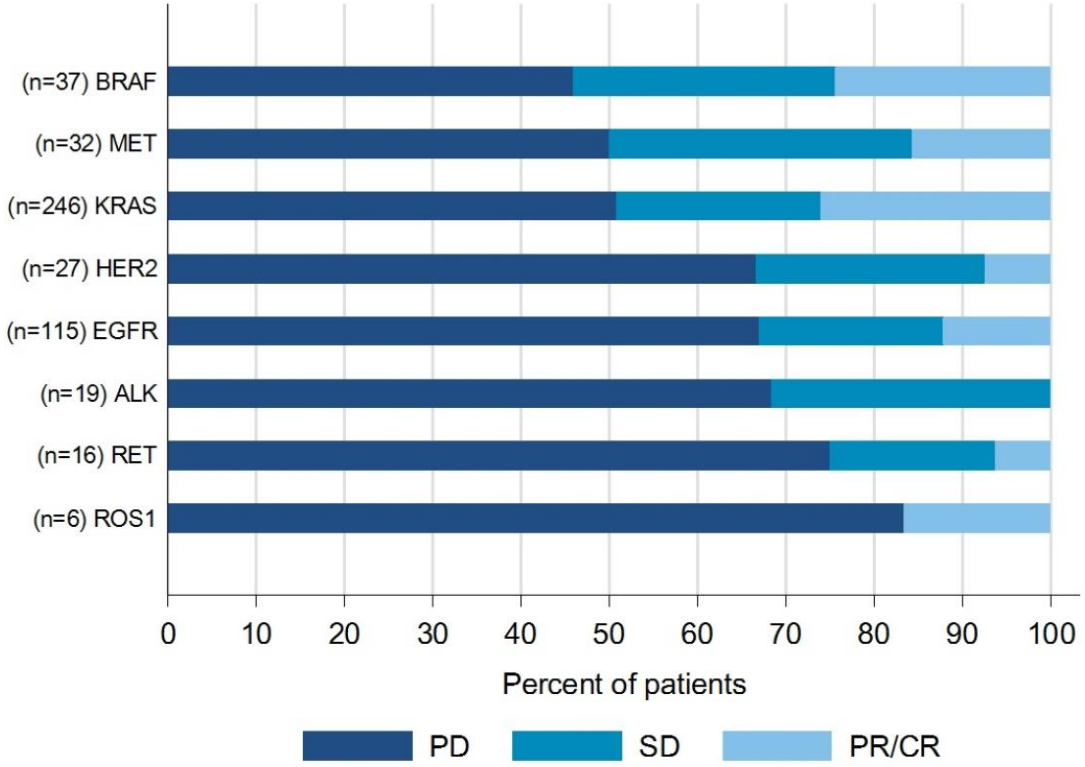
Reck, ELCC 2019

IMpower 130: carboplatin - NabP +/- atezo



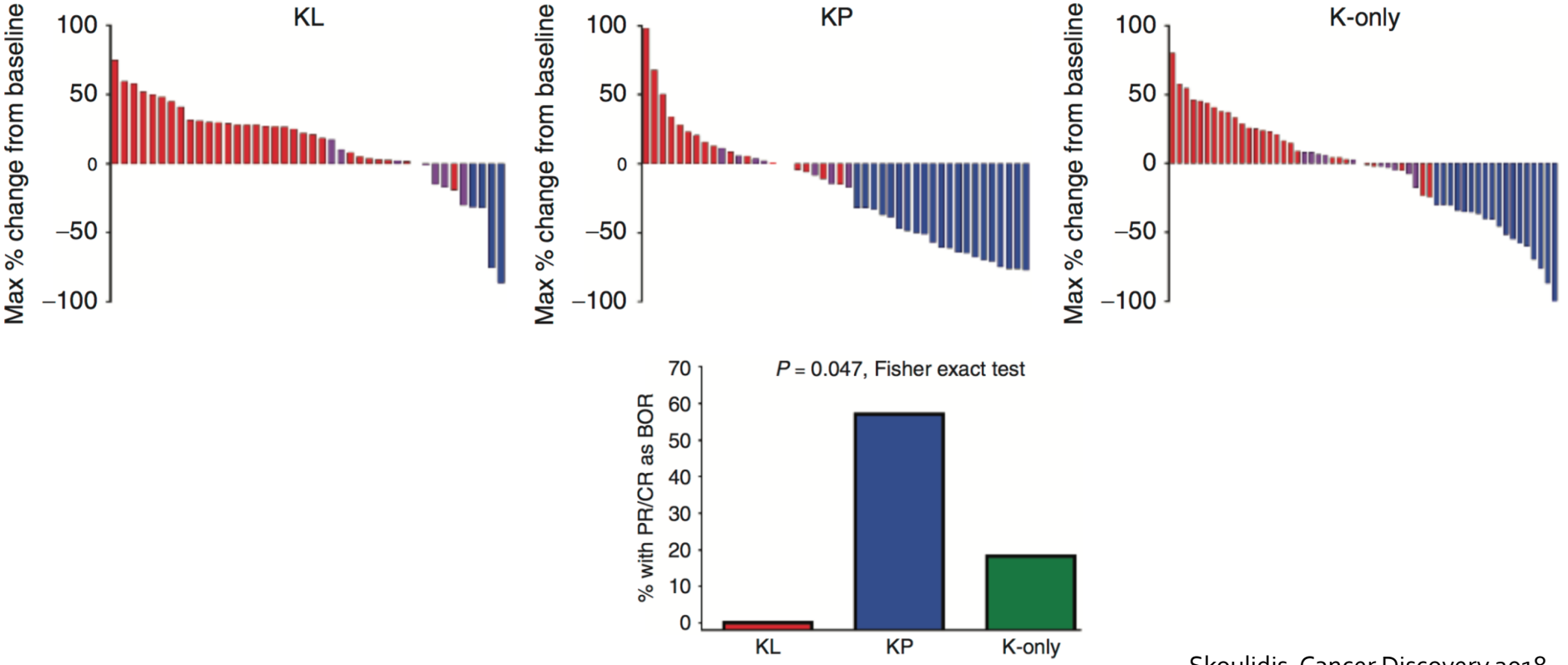
Cappuzzo, ESMO 2018

What about other mutations?



Mazieres and Gautschi, ASCO and WCLC 2018

STK11/LKB1 alterations drive primary resistance to PD-1 axis inhibitors in *KRAS*-mutant lung adenocarcinoma

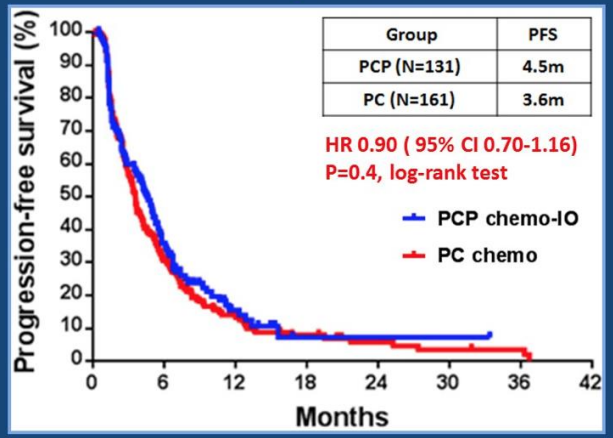


Skoulidis, Cancer Discovery 2018

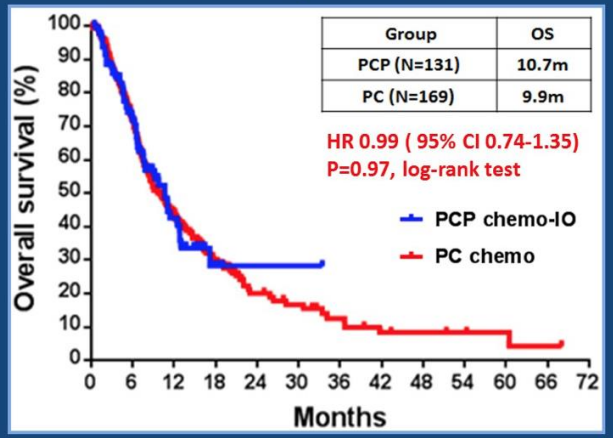
Chemo-IO in STK11/LKB1 and/or KEAP-1 alterations

Lack of benefit from addition of pembrolizumab to CP chemotherapy in *STK11* and/or *KEAP1*-mutant non-squamous NSCLC

***STK11*^{MUT} and/or *KEAP1*^{MUT}**

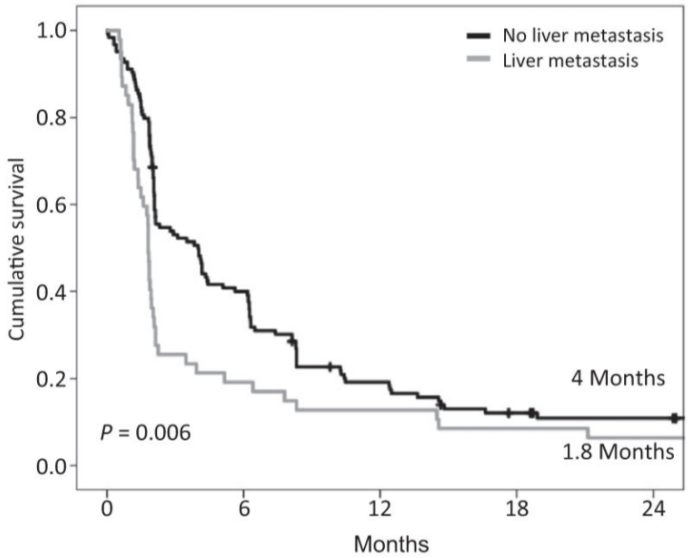


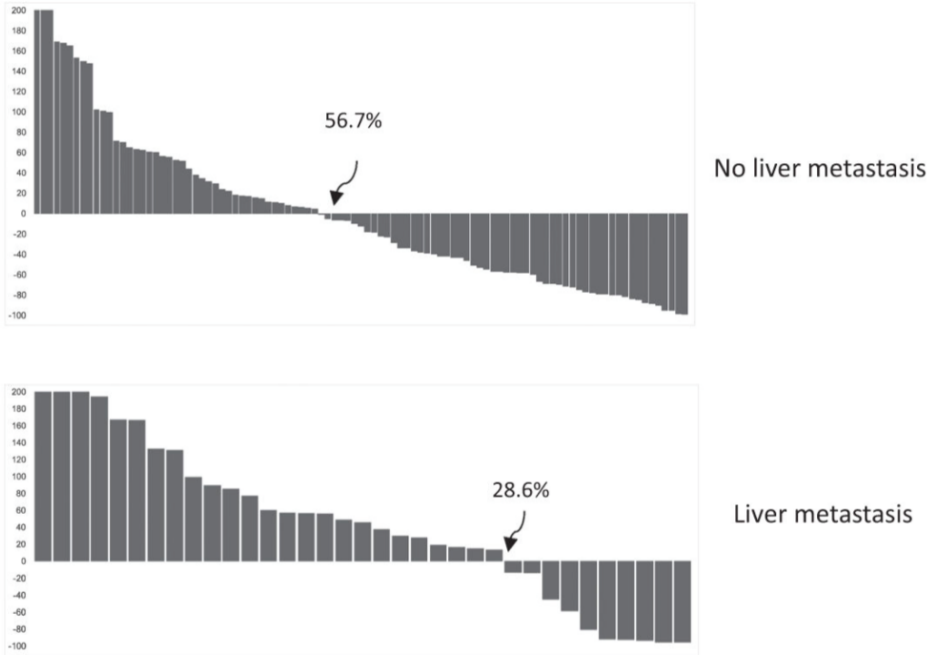
***STK11*^{MUT} and/or *KEAP1*^{MUT}**



Skoulidis, ASCO 2019

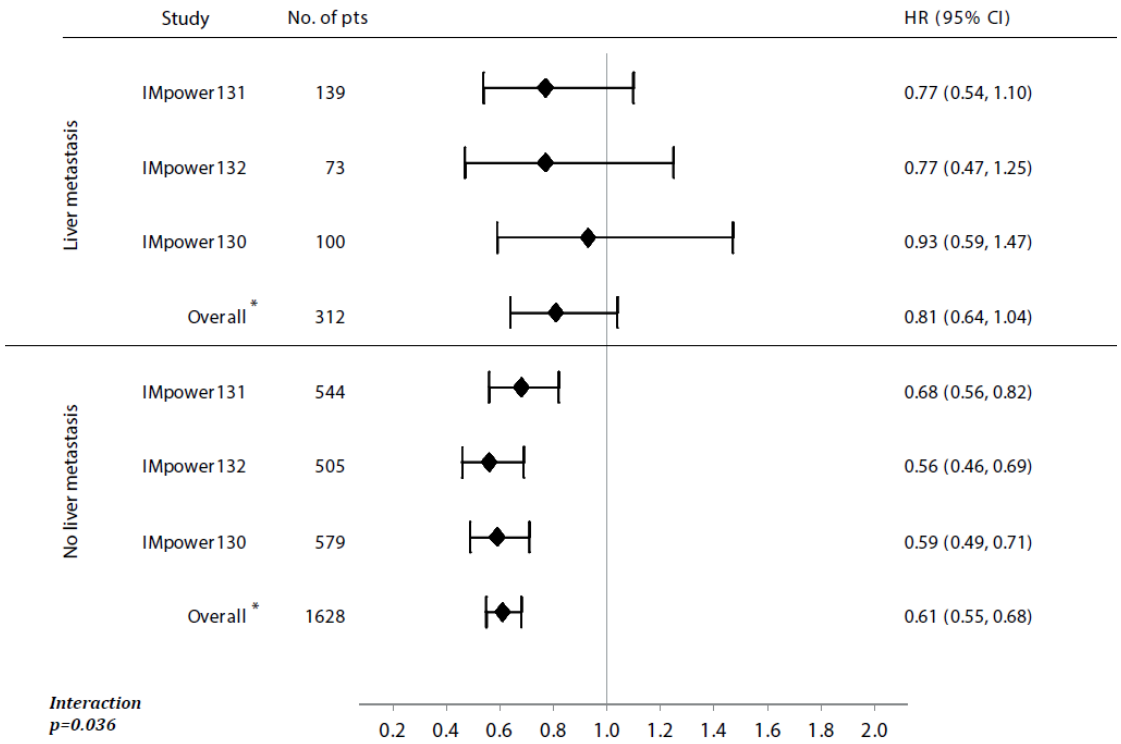
Liver metastases define a negative predictive factor for IO monotherapy





Tumeh, Cancer Immunol Res 2017

Liver metastases in NSCLC

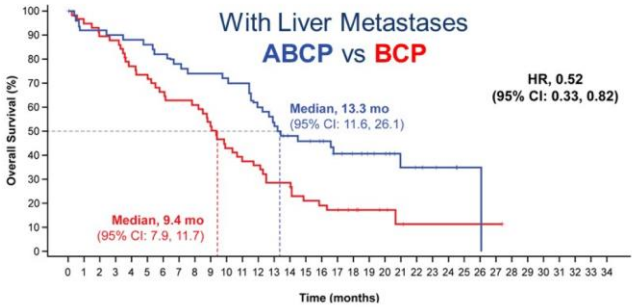


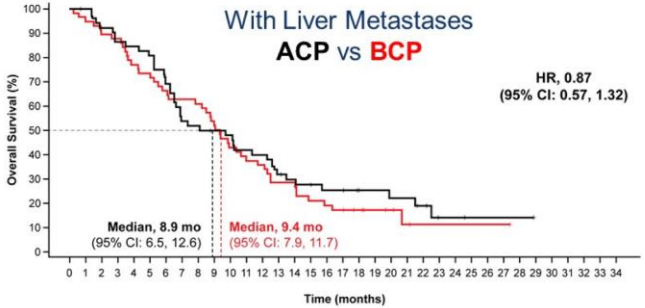
*Estimates of HR (95% CI) based on fixed effect model

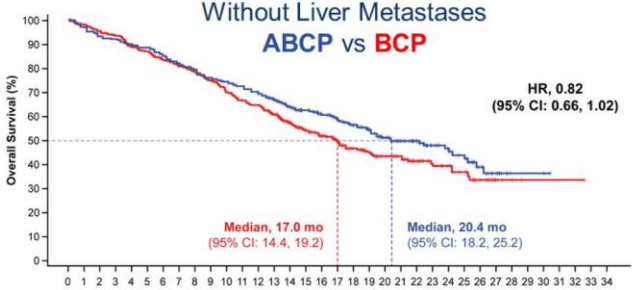
Dafni and Peters, in press

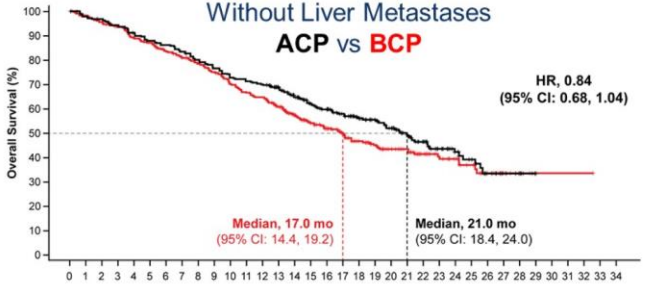
Carboplatin/nabPaclitaxel/atezolizumab in liver metastatic patients (stratification factor)

Abstract 9012: IMpower150: Analysis of efficacy in patients with liver metastases: Overall Survival







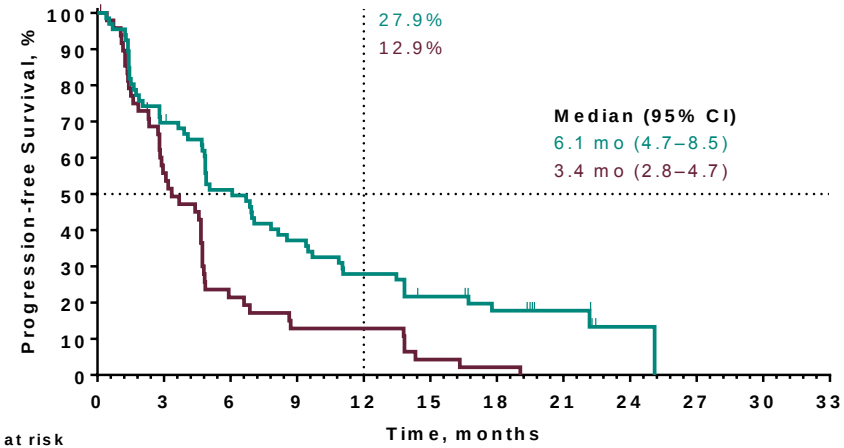


Reck, ESMO IO 2017 and ASCO 2019

KEYNOTE 189 : PFS and Liver Metastases

With Liver Metastases

	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	55 (83.3)	0.52 (0.34–0.81)
Placebo/Pem/Plat	47 (95.9)	

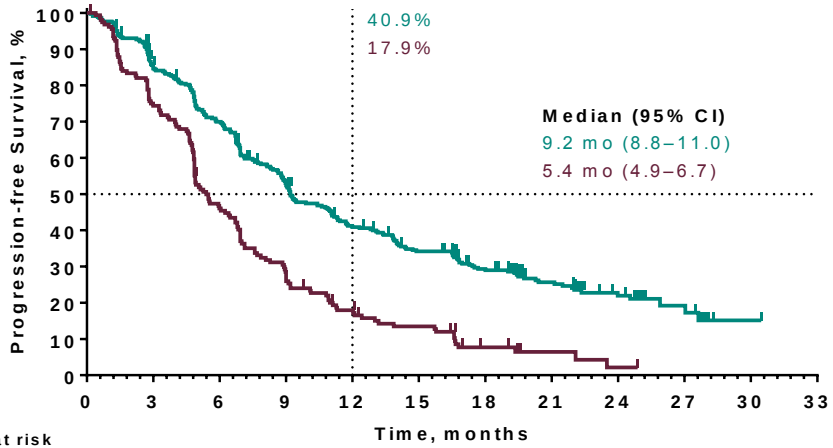


No. at risk

Pembro/Pem/Plat	66	45	33	24	18	13	9	5	1	0	0	0
Placebo/Pem/Plat	49	26	10	6	6	2	1	0	0	0	0	0

Without Liver Metastases

	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	249 (72.4)	0.48 (0.39–0.59)
Placebo/Pem/Plat	143 (91.1)	



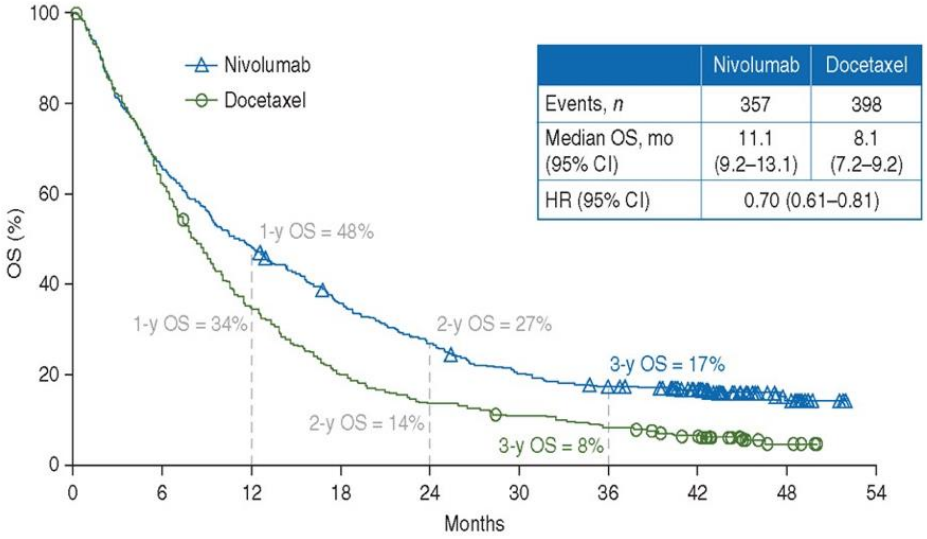
No. at risk

Pembro/Pem/Plat	344	283	233	173	131	106	82	49	27	10	1	0
Placebo/Pem/Plat	157	116	71	44	25	18	7	3	1	0	0	0

Garassino, AACR 2019

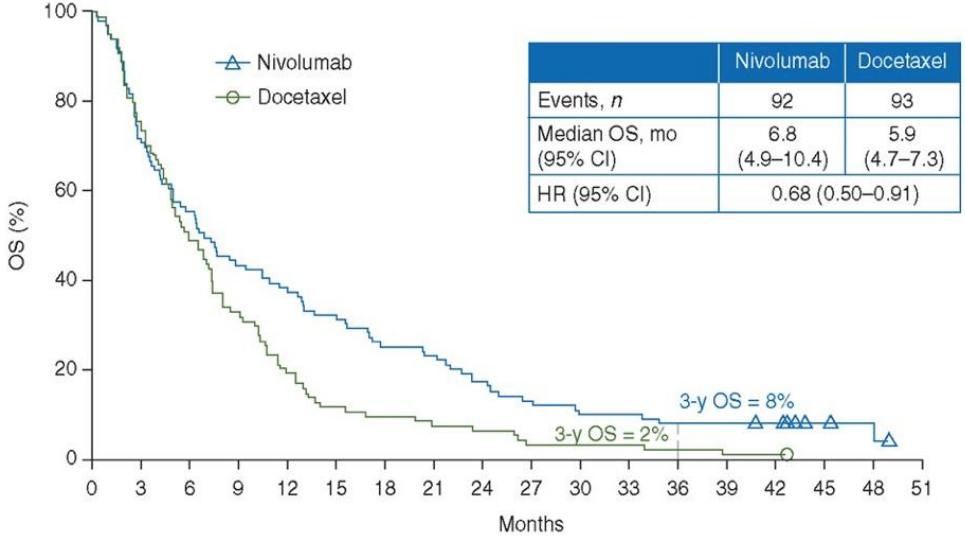
CheckMate 017/057: Similarly, nivolumab demonstrated an OS benefit in liver metastases

Overall Study Population



	Nivolumab	Docetaxel
Events, *n*	357	398
Median OS, mo (95% CI)	11.1 (9.2–13.1)	8.1 (7.2–9.2)
HR (95% CI)	0.70 (0.61–0.81)	

Patients with Liver Metastases



	Nivolumab	Docetaxel
Events, *n*	92	93
Median OS, mo (95% CI)	6.8 (4.9–10.4)	5.9 (4.7–7.3)
HR (95% CI)	0.68 (0.50–0.91)	

Vokes, Ann Oncol 2018

Immune evasion beyond and independent of the PD-1 axis

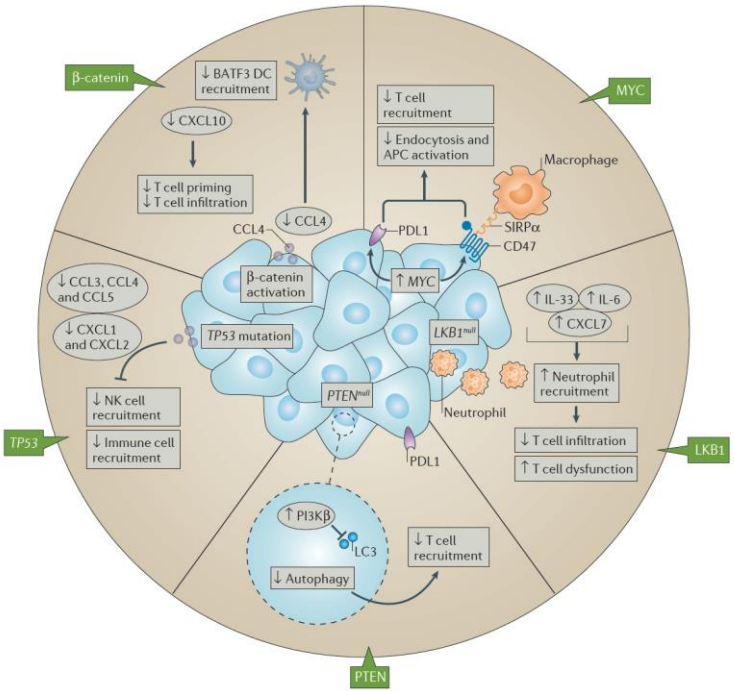


Table 1 | Genomic correlates of response and resistance organized by primary location

Primary location	Response category	Defining characteristics or examples
T cell	Intratumoral infiltration[85,115,135–137,139]	Transcriptional signatures of cytotoxic lymphocytes infiltrating the tumor core
	Enhanced effector function[62,134,141]	Increased expression of *PRF1*, *GZMA/B*, *CD8A*, and *IFNG*
	Increased clonality[14,144,41]	Ranging from 0 to 1, with 1 indicating a monoclonal population
	Greater stemness[147,150]	Express chemokine receptor CXCR5 and transcription factor TCF7; lack TIM-3/CD39
	Reduced exhaustion[147,150]	Express co-inhibitory receptor TIM-3 and ectonucleotidase CD39; lack CXCR5/TCF7
Tumor cell (response mechanisms)	Tumor antigens[31,32,34–40,54,57,65,67]	Neoantigens, viral antigens
	Increased tumor mutation burden[9,37,48]	Mismatch repair deficiency
	Immunogenic alterations[159]	Inactivating mutations in *SERPINB3* and *SERPINB4*
	Mutational signatures[39,53,108]	Smoking, ultraviolet light, alkylating agent therapy, APOBEC
	Genomic upregulation of PD-L1 (refs. [50,92–94,97–100])	*PDL1* amplification and loss of *CDK4*, *SPOP*, and *CMTM4* and *CMTM6*
	Chromatin modifier loss[152,154,157,158]	Inactivating mutations in *PBRM1*, *ARID1A*, and *SMARCA4*
Tumor cell (resistance mechanisms)	Tumor antigens[68]	Cancer/testis antigens similar to self and less immunogenic
	Deficient antigen presentation[37,53]	Inactivating mutations in *B2M*, *HLA*, JAK/STAT, and IFN-γ response genes
	Oncogenic pathways[45,113–115,117,118,124,125,129,130,133]	Inactivating *STK11* and *PTEN* mutations, WNT/β-catenin, *EGFR* and *KRAS* mutations
	Immune evasion alterations[141]	Increased expression of *SERPINB9*
	CNAs[144,160]	High levels of copy-number loss, chromosome arm and whole-chromosome CNAs
Microenvironment	Immunosuppressive stromal cells[115,123,126,140]	Transcriptional signatures of fibroblasts, endothelial cells, and TGF-β signaling
	Immunosuppressive immune cells[136,141]	Transcriptional signatures of myeloid-derived suppressor cells and regulatory T cells

Spranger, Nat Rev Cancer 2018
Keenan, Nat Med 2019

How to decide for frontline immunotherapy?

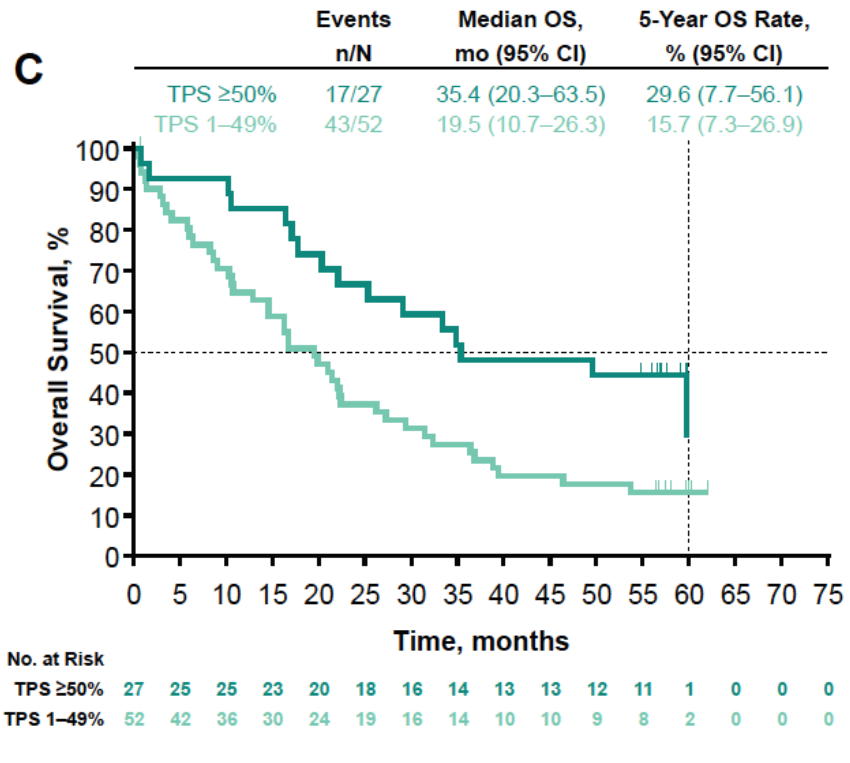
General picture of frontline treatment strategies

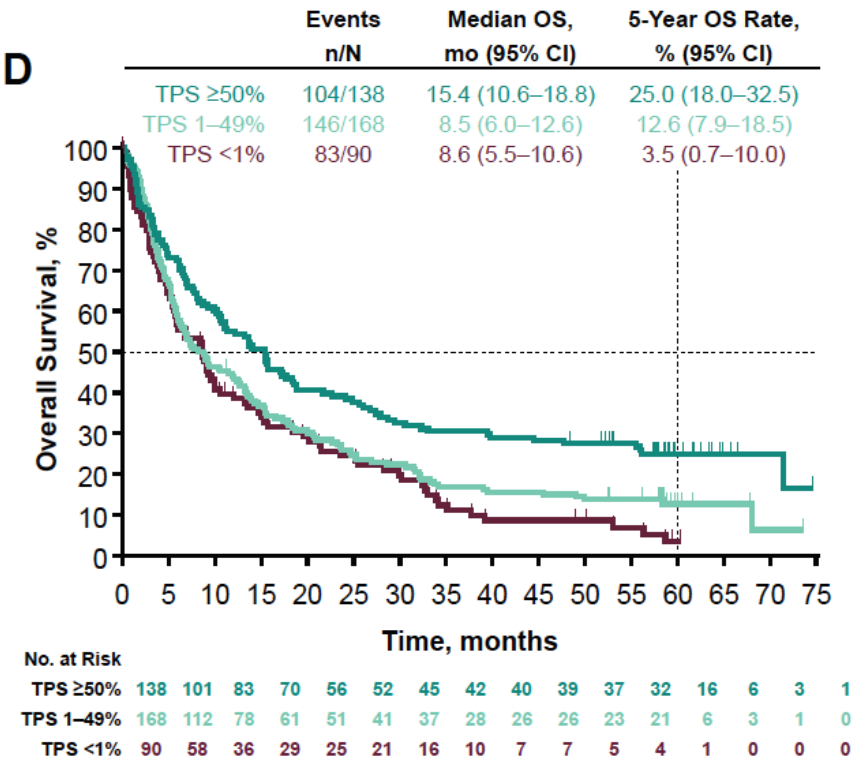
- Landscape of new evidence-based data
- Biomarker-driven subgroups (PD-L1, TMB)
- Standards for ≥ 50% PD-L1 TC NSCLC

Specific subgroups and related treatment preferences

Long term survival

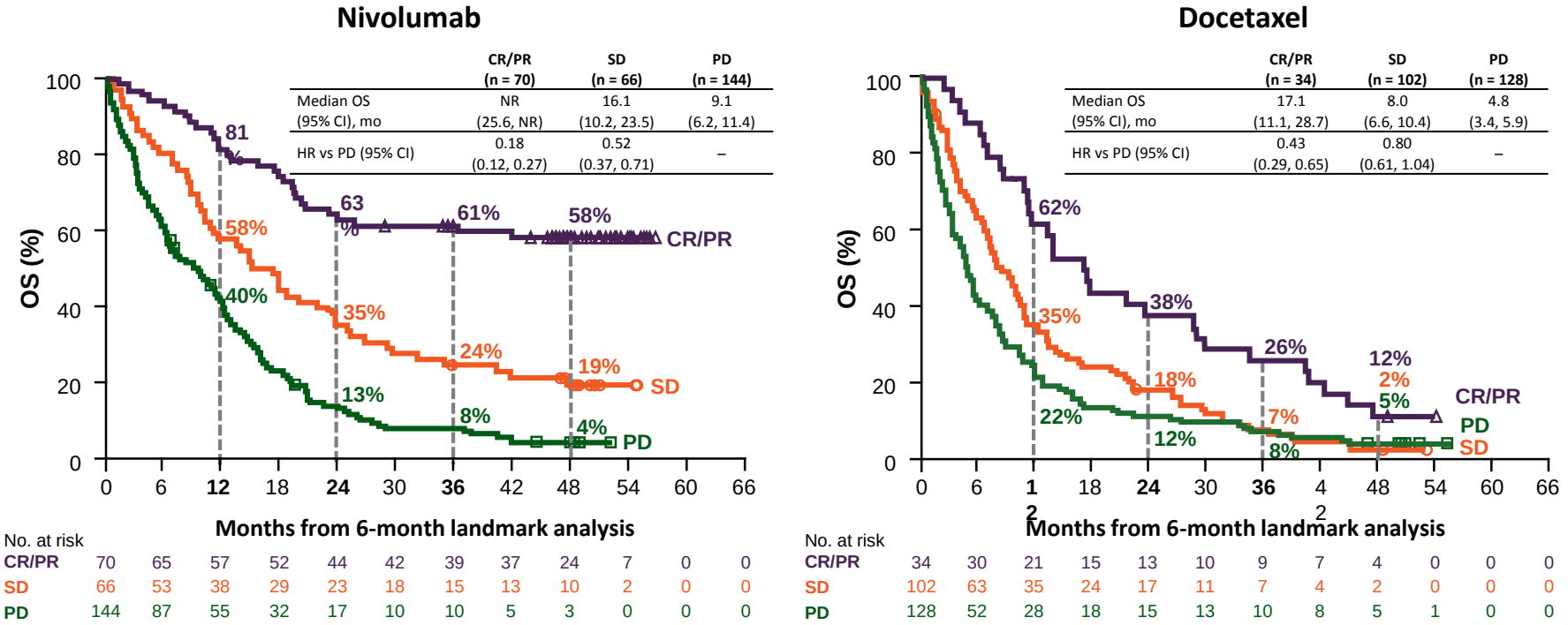
Long term survivors exist





Brahmer, AACR 2018; Garon, ASCO 2019

Landmark analysis of OS by response category status at 6 months in CheckMate 017/ 057

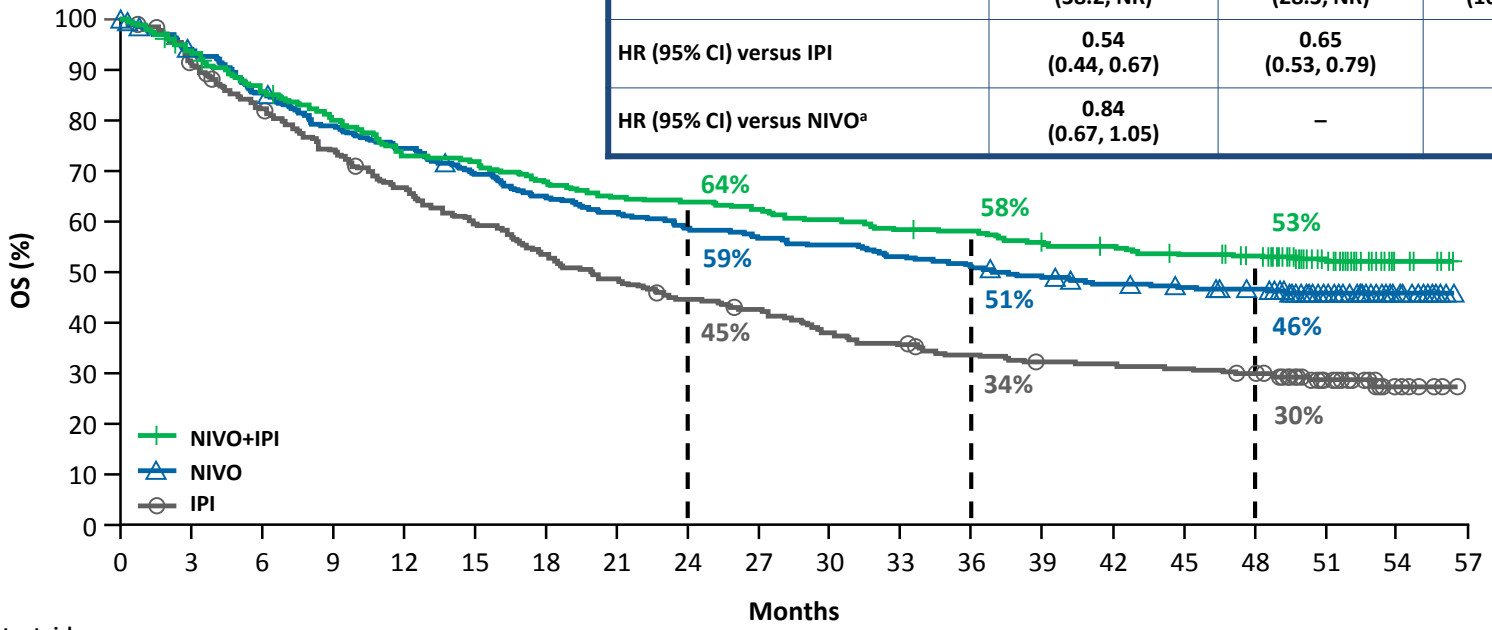


Brains mets, EGFR mutants, never smokers are also found among survivors

Brahmer, AACR 2019

Higher probability when a CTLA-4 component is included?

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–

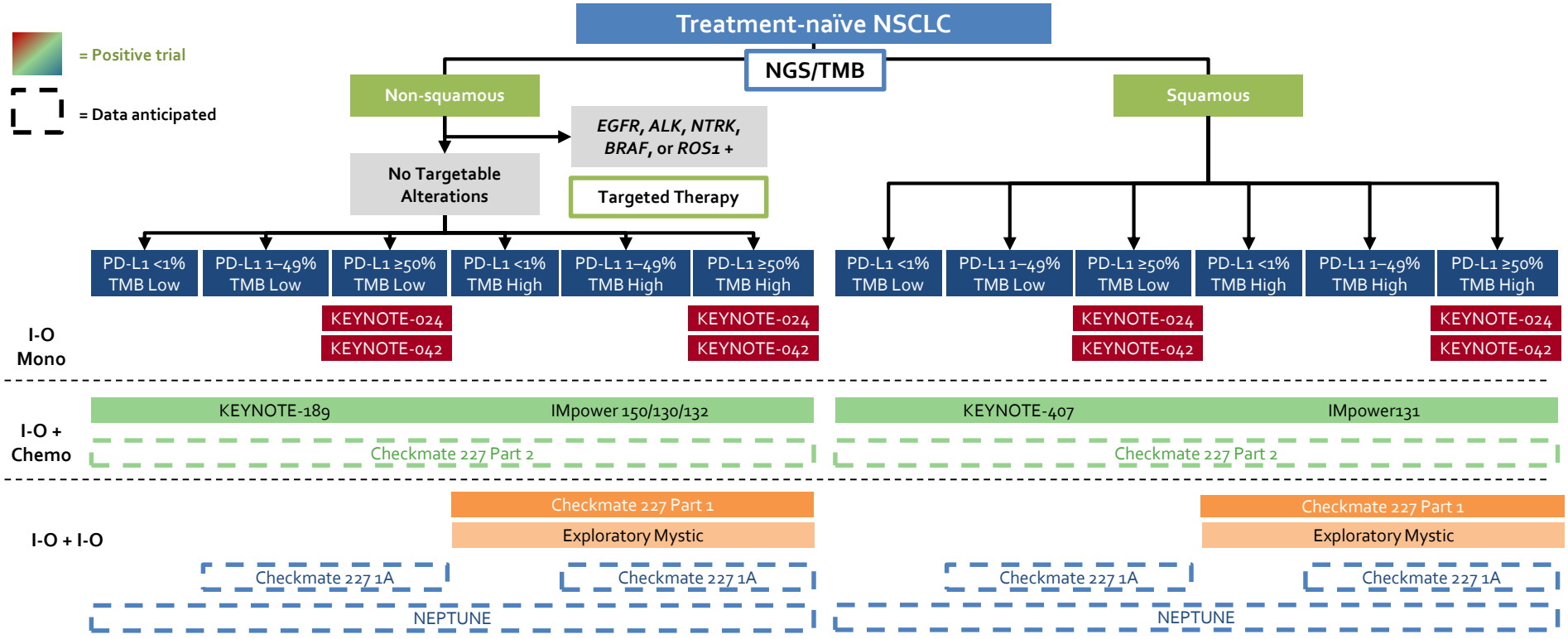


Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

Hodi, ESMO 2018 CheckMate 067

Evolving treatment options frontline in advanced NSCLC



Mono, combos IO/IO and IO/chemo
How should we choose?

- Patient Safety ✓
- Patient Preference ✓
- Tumour PDL-1 ✓
- TMB ✓
- Comorbidities ✓
- Smoking ✗ (or by default)
- Age ✗
- Sex ✗

- Favor class of / a specific drug?
- Disease Burden ?
- Liver metastases ?
- Genetic alterations?
- HLA?
- Other biomarkers ?

➢ **Impact on long term OS**

Thanks for your kind attention