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Updates in Immunotherapy in Lung Cancer

Strategies for frontline immunotherapy

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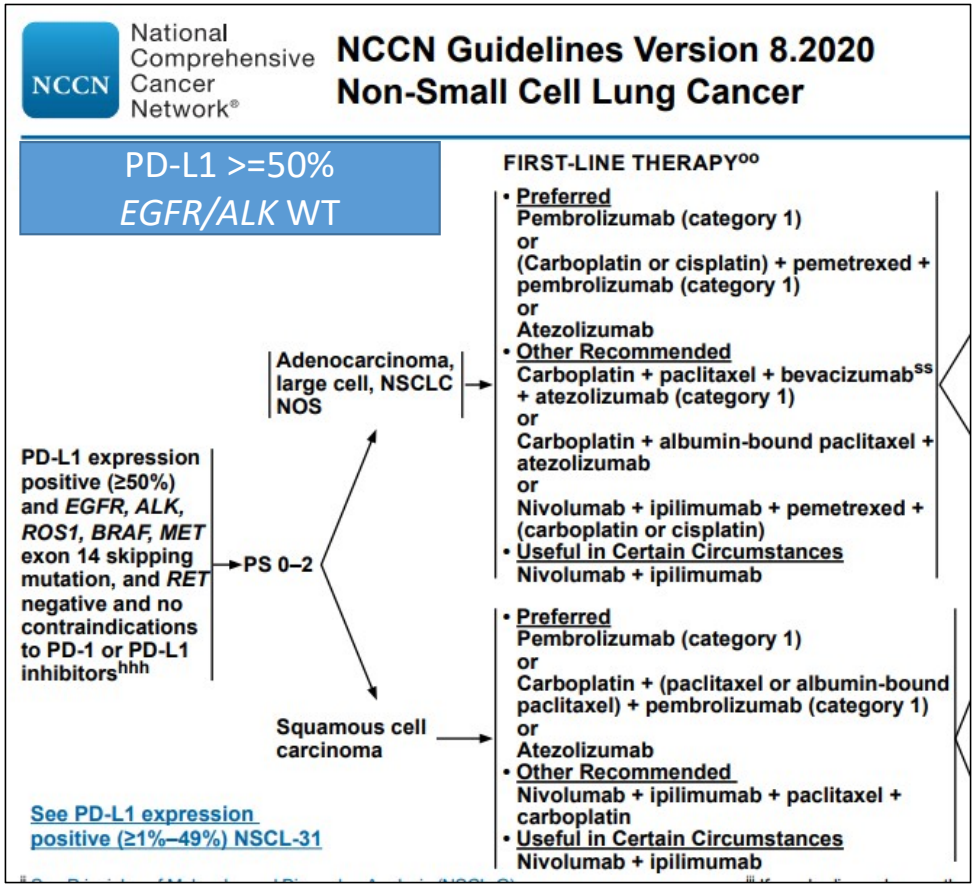
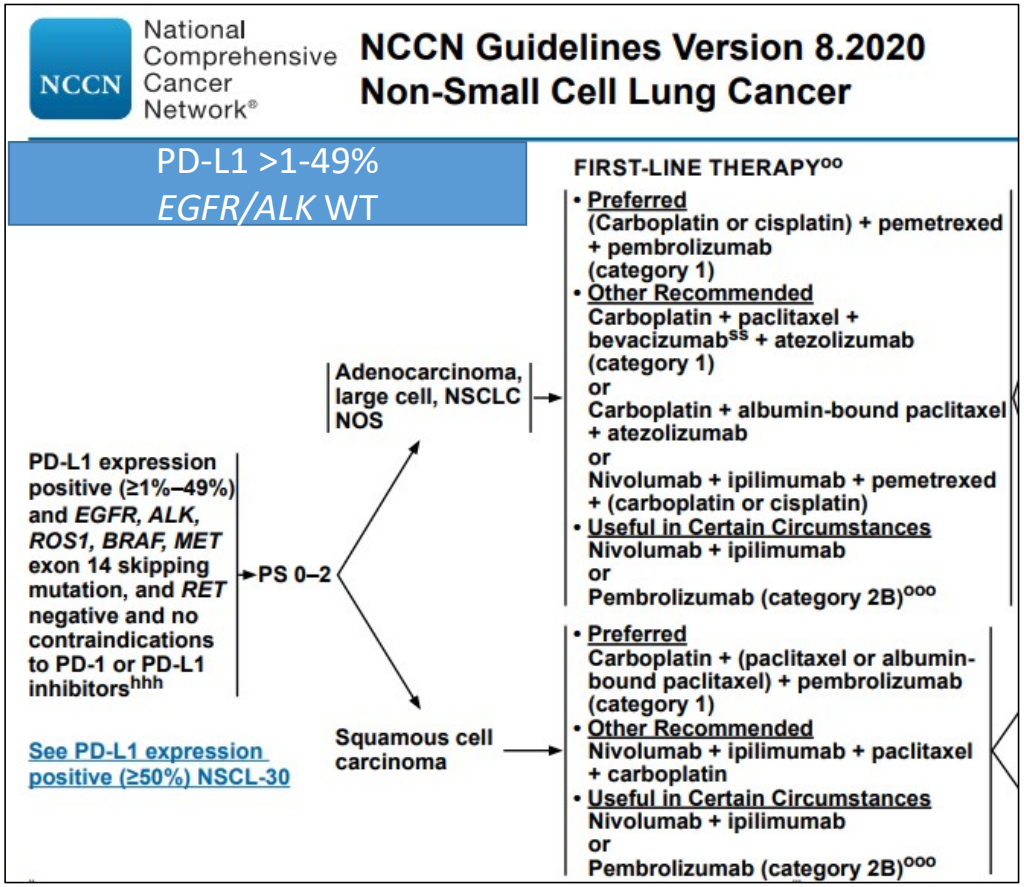
Guidelines- an increasingly complex flow diagram





Guidelines- an increasingly complex flow diagram

PD-L1 <1% Non-squamous
***EGFR/ALK* WT**

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]
- Nivolumab + ipilimumab[5,d]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)[6,d]

PD-L1 <1% Squamous
***EGFR/ALK* WT**

Preferred
- Pembrolizumab/carboplatin/paclitaxel[34,d] (category 1)
- Pembrolizumab/carboplatin/albumin-bound paclitaxel[34,d] (category 1)

Other recommended
- Nivolumab + ipilimumab[5,d]
- Nivolumab + ipilimumab + paclitaxel + carboplatin[6,d]

Outline –Strategies for Frontline Immunotherapy

- Single agent immunotherapy
- Combination chemo-immunotherapy
- Combination immunotherapy

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***Strategies in this talk assume *EGFR/ALK* wild type**

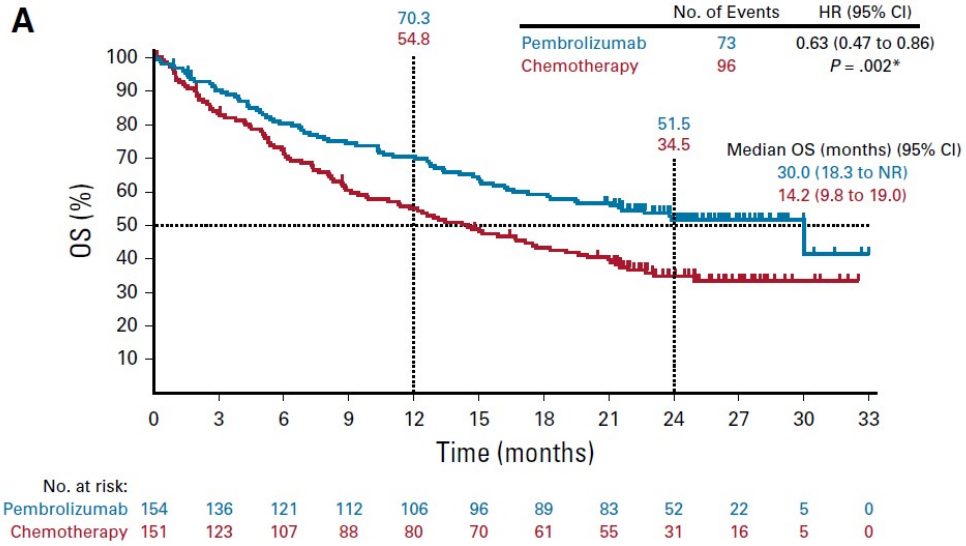
Outline –Strategies for Frontline Immunotherapy

- **Single agent immunotherapy**
  - **KN-024: Pembrolizumab PD-L1 >=50%– updated OS**
  - **KN-042: Pembrolizumab PD-L1 >=1%– updated OS**
  - **IMpower110: Atezolizumab PD-L1 High TC >=50% or IC>=10%– new data, new approval**

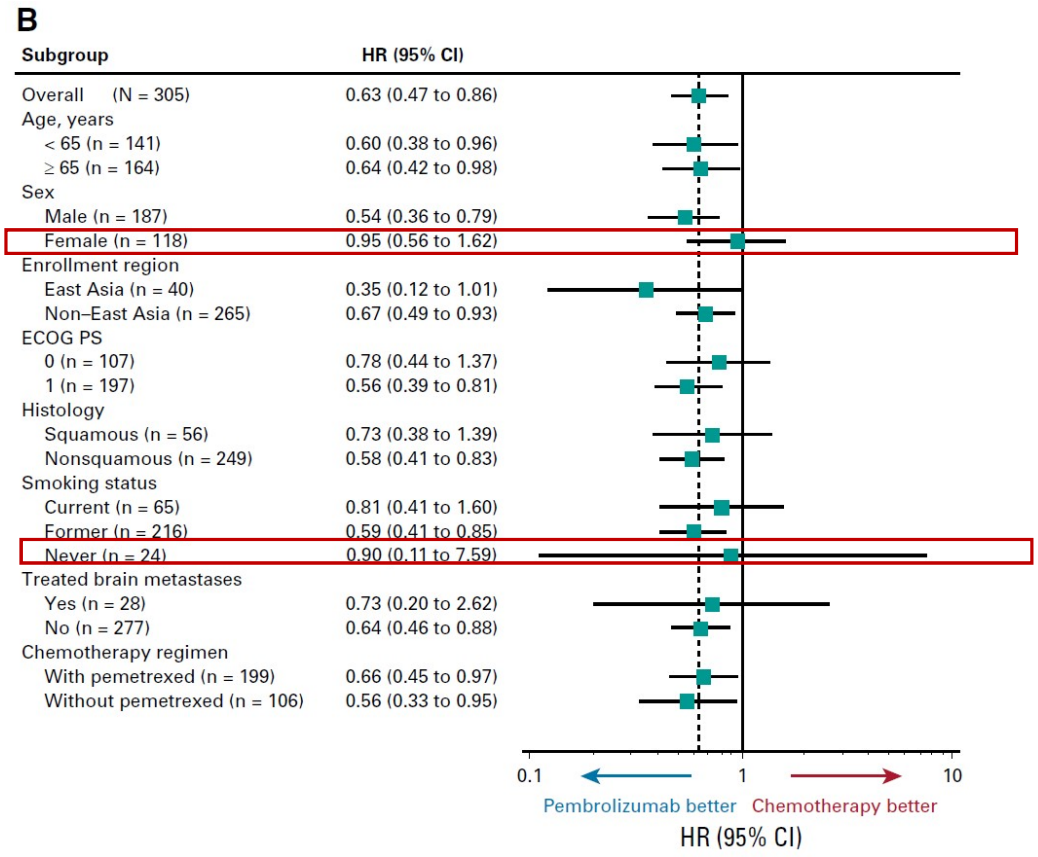
- Combination chemo-immunotherapy
- Combination immunotherapy

SP1

Pembrolizumab improves OS over platinum-doublet chemotherapy in PD-L1 high (>=50%), *EGFR/ALK* WT NSCLC (*KEYNOTE-024*)



- **OS HR 0.63** (0.47-0.86); P=0.002
  - HR adjusted for crossover 0.49 (95% CI 0.34-0.69); **54%** crossover rate
- **PFS HR 0.50**; p <0.001; 10.3 mo vs. 6.0 mo
- **ORR** 44.6% vs. 27.8%



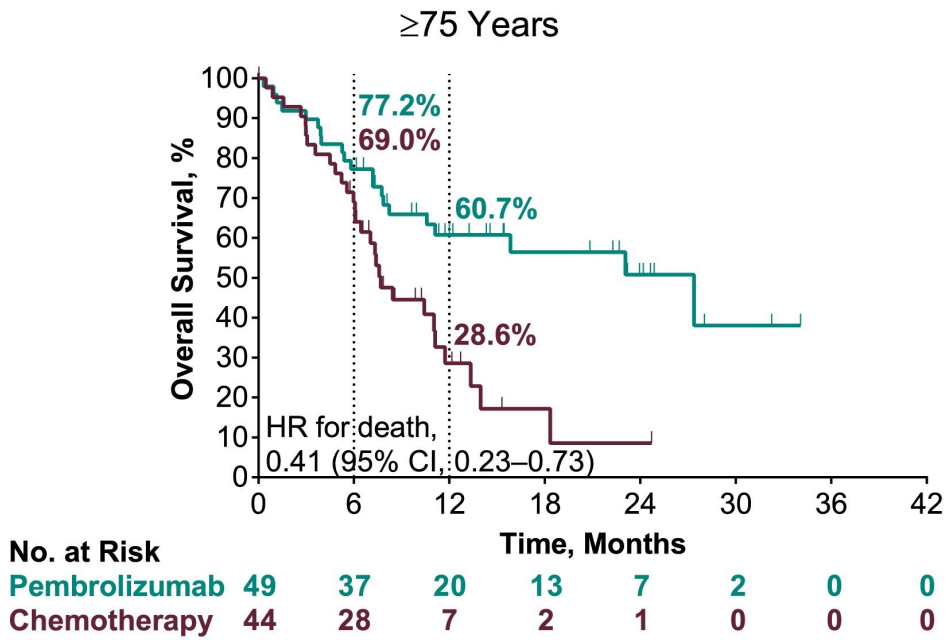
*median f/u 25.2 months

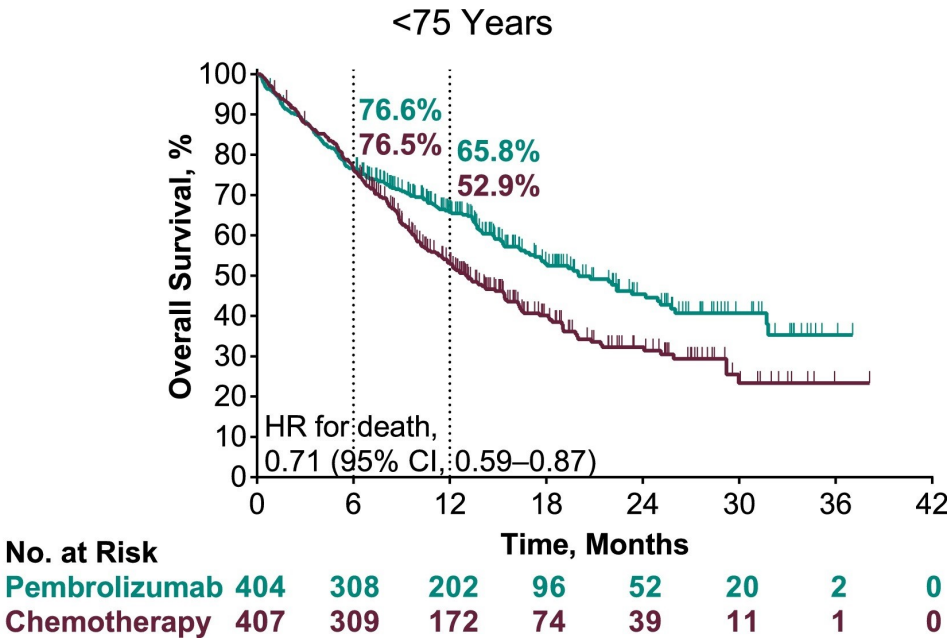
Reck M. N Engl J Med. 2016 Nov 10;375(19):1823-1833. Reck M et al. J Clin Oncol. 2019 Mar 1;37(7):537-546.

Slide 7

SP1 I will update with ESMO 2020 study once I get access to slides: Julie Brahmer
KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50% Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
Sukhmani Padda, 10/20/2020

Elderly patients (>= 75 years-old) with PD-L1>=50% NSCLC benefit from frontline pembrolizumab (pooled KN-042 and KN-024 studies)





Age >=75 years

- **OS HR 0.41** (95% CI 0.23-0.73)

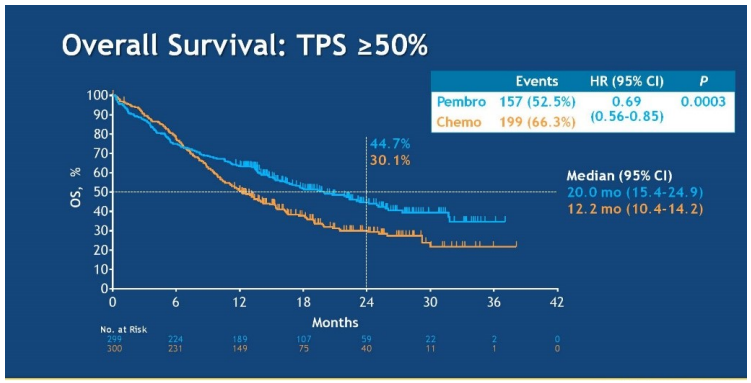
Age < 75 years

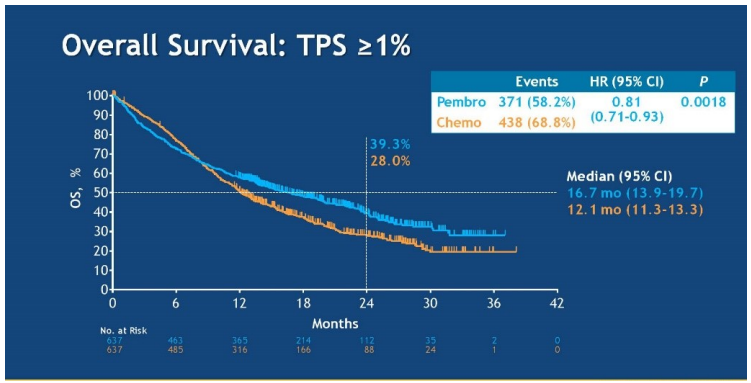
- **OS HR 0.71** (95% CI 0.59-0.87)

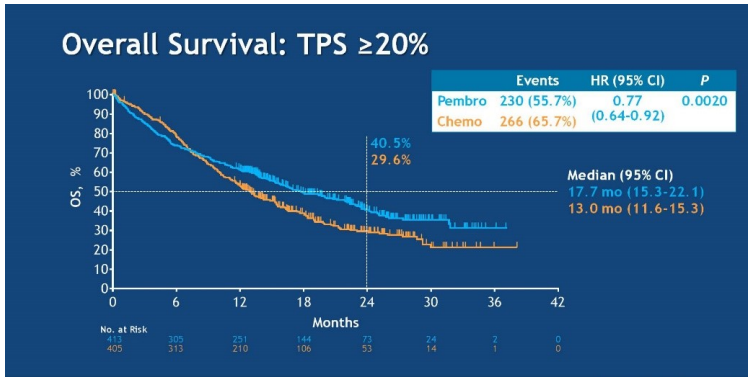
Nosaki K et al. Lung Cancer. 2019 Sep;135:188-195.

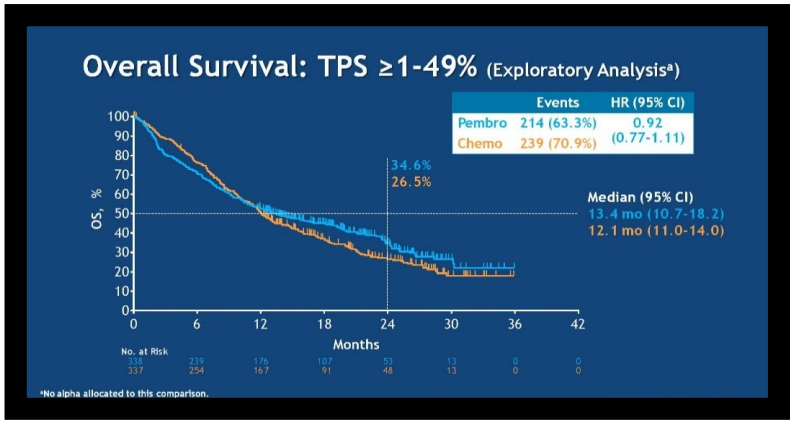
SP2

Pembrolizumab improves OS over platinum-doublet chemotherapy in PD-L1 positive (>=1%), *EGFR/ALK* WT NSCLC (*KEYNOTE-042*)









PFS significantly improved for TPS>=50% but not >=20% or >=1%
ORR 27% (TPS>=1%), 33% (TPS>=20%), 39% (TPS>=50%)
DOR ~ 20 months in all PD-L1 subgroups

Median f/u 12.8 months
Of note, no crossover@PD

Mok. Lancet. 2019 May 4;393(10183):1819-1830.

Slide 9

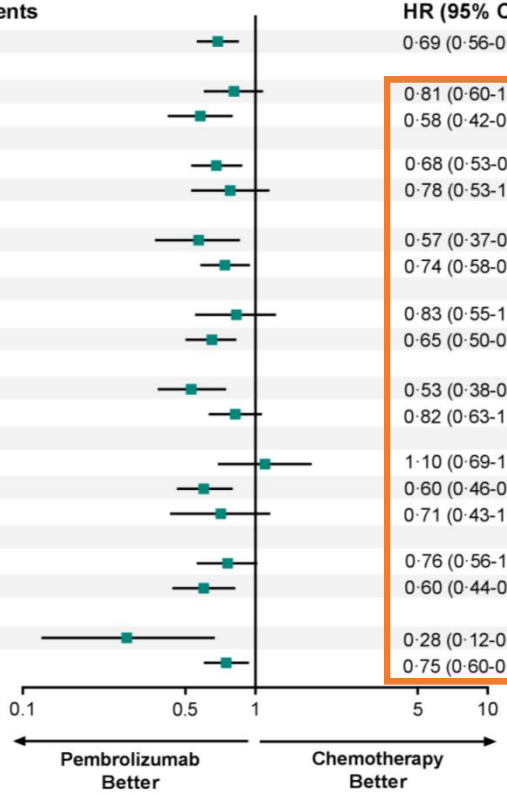
SP2 I willl update with final analysis once I have slides from ESMO 2019: Mok et al. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1–positive locally advanced/metastatic NSCLC. ESMO 2019

Sukhmani Padda, 10/20/2020

Pembrolizumab benefits majority of subgroups at TPS >=50% threshold and TPS >=1% threshold (*KEYNOTE-042*)

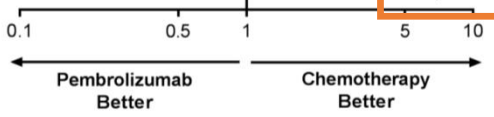
TPS >=50%

Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	356/599	0·69 (0·56-0·85)
Age		
<65 yr	189/328	0·81 (0·60-1·08)
≥65 yr	167/271	0·58 (0·42-0·80)
Sex		
Male	248/415	0·68 (0·53-0·88)
Female	108/184	0·78 (0·53-1·15)
ECOG performance status		
0	94/187	0·57 (0·37-0·86)
1	262/412	0·74 (0·58-0·95)
Geographic region		
East Asia	97/186	0·83 (0·55-1·23)
Rest of world	259/413	0·65 (0·50-0·83)
Histologic features		
Squamous	144/221	0·53 (0·38-0·75)
Nonsquamous	212/378	0·82 (0·63-1·07)
Smoking status		
Never	73/131	1·10 (0·69-1·75)
Former	208/352	0·60 (0·46-0·80)
Current	75/116	0·71 (0·43-1·16)
Chemotherapy regimen		
Pemetrexed and carboplatin	179/319	0·76 (0·56-1·02)
Paclitaxel and carboplatin	177/280	0·60 (0·44-0·82)
Disease status		
Locally advanced	34/62	0·28 (0·12-0·67)
Metastatic	322/537	0·75 (0·60-0·94)



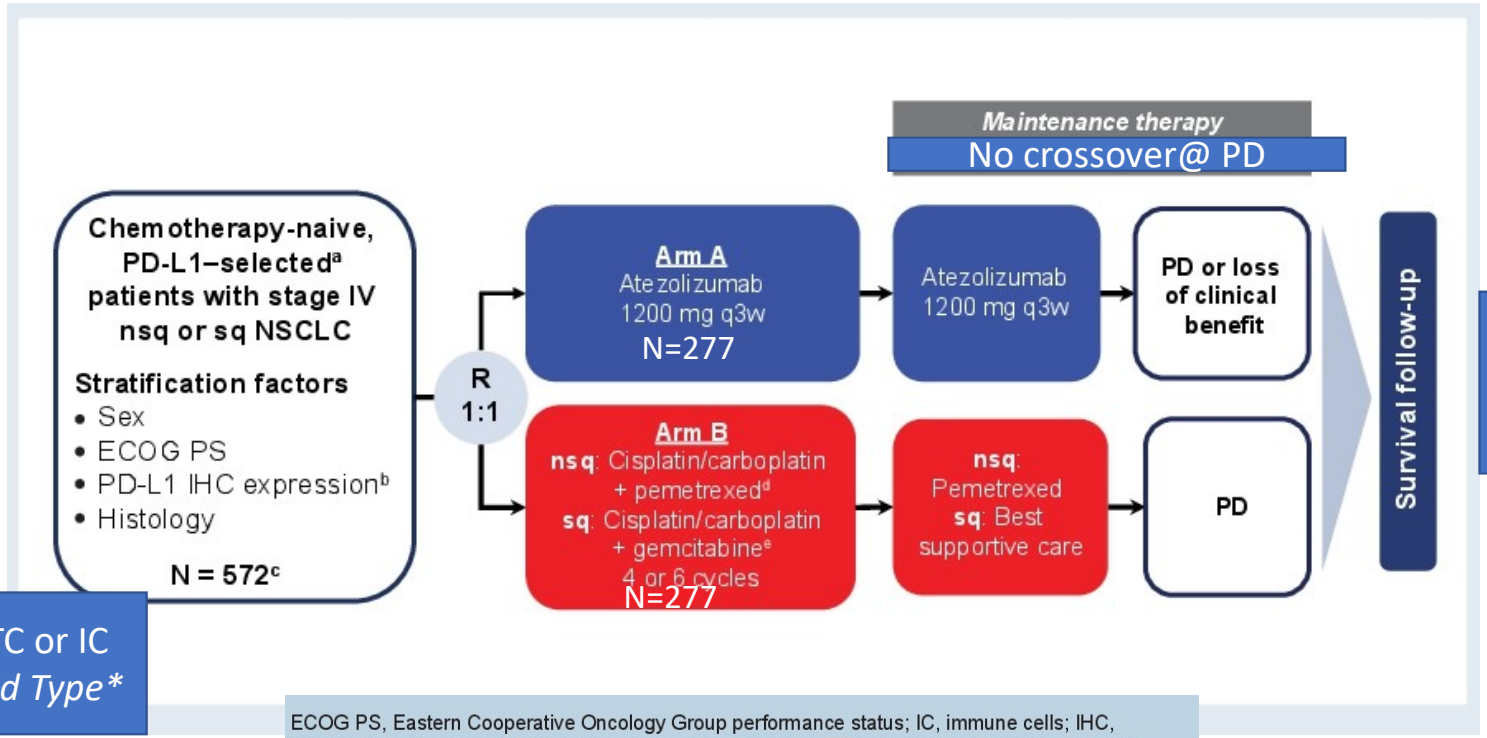
TPS >=1%

Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	809/1274	0·81 (0·71-0·93)
Age		
<65 yr	444/707	0·81 (0·67-0·98)
≥65 yr	365/567	0·82 (0·66-1·01)
Sex		
Male	584/902	0·80 (0·68-0·94)
Female	225/372	0·89 (0·68-1·17)
ECOG performance status		
0	215/390	0·77 (0·59-1·05)
1	594/884	0·83 (0·71-0·98)
Geographic region		
East Asia	196/370	0·79 (0·59-1·05)
Rest of world	613/904	0·82 (0·70-0·96)
Histologic features		
Squamous	343/492	0·75 (0·60-0·93)
Nonsquamous	466/782	0·86 (0·72-1·03)
Smoking status		
Never	163/282	1·00 (0·73-1·37)
Former	471/721	0·71 (0·59-0·86)
Current	175/271	0·95 (0·70-1·29)
Chemotherapy regimen		
Pemetrexed and carboplatin	371/636	0·87 (0·71-1·07)
Paclitaxel and carboplatin	438/638	0·74 (0·61-0·90)
Disease status		
Locally advanced	98/160	0·74 (0·49-1·13)
Metastatic	711/1114	0·83 (0·71-0·96)



Mok. Lancet. 2019 May 4;393(10183):1819-1830.

Atezolizumab in frontline PD-L1 positive NSCLC (*Schema for IMpower110*)



PD-L1 >=1% TC or IC
*EGFR /ALK Wild Type**

*18 with *EGFR* or *ALK* excluded from efficacy analysis

Primary endpoint: overall survival
*hierarchical testing starting with high PD-L1

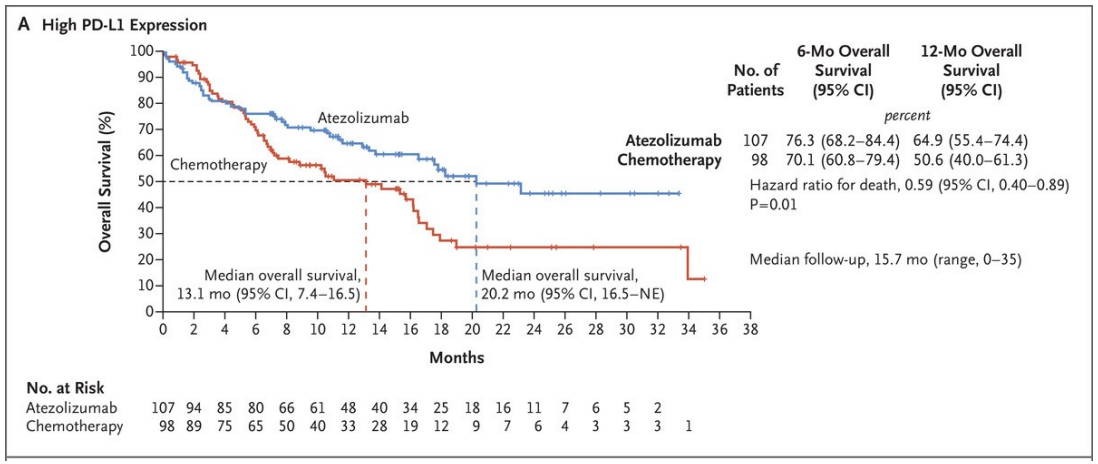
ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cells; IHC, immunohistochemistry; IV, intravenous; nsq, nonsquamous; PD, progressive disease; q3w, every 3 weeks; sq, squamous; TC, tumor cells; WT, wild-type.

[a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. Categories are defined as follows: TC0 and IC0, PD-L1 <1% TC and IC; TC1/2/3 or IC1/2/3, PD-L1 ≥ 1% by TC or IC; TC2/3 or IC2/3, PD-L1 ≥ 5% by TC or IC; TC3 or IC3, PD-L1 ≥ 50% by TC or ≥ 10% by IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] WT population, n = 554 patients. [d] Cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m^2 IV q3w. [e] Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 or carboplatin AUC 5 + gemcitabine 1000 mg/m^2 IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

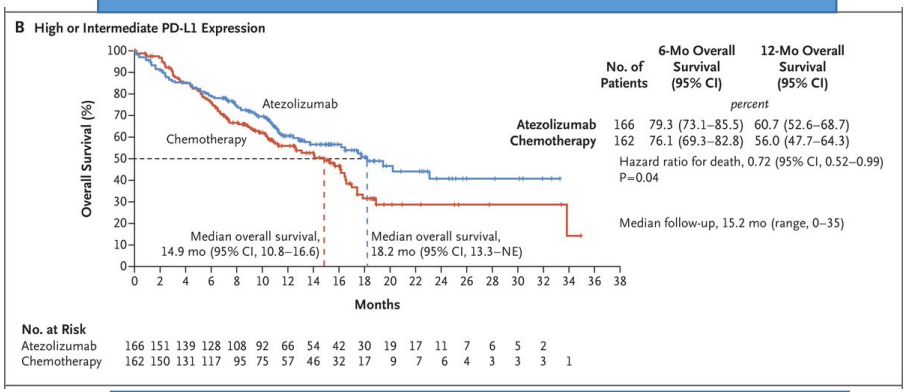
Interim analysis shows improved OS with atezolizumab over platinum chemotherapy in high-PD-L1 / *EGFR + ALK WT* (*IMpower110*)

TC >=50% or IC >=10%

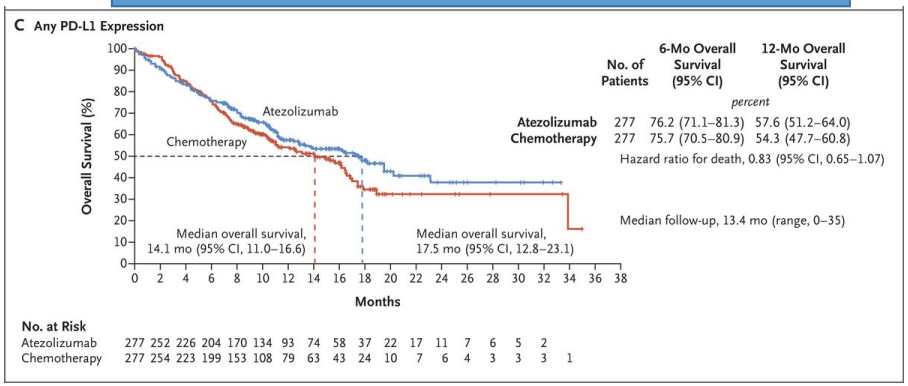


- **High PD-L1: HR 0.59** (95% CI 0.40-0.89); P=0.01
  Median 20.2 mo vs. 13.1 mo
- **Intermediate PD-L1: HR 0.72** (95% CI 0.52-0.99); P=0.04 (NS)
  Median 18.2 mo vs. 14.9 mo
- **Any: HR 0.83 (95% CI 0.65-1.07)**
  Median 17.5 mo vs. 14.1 mo

TC >=5% or IC >=5%

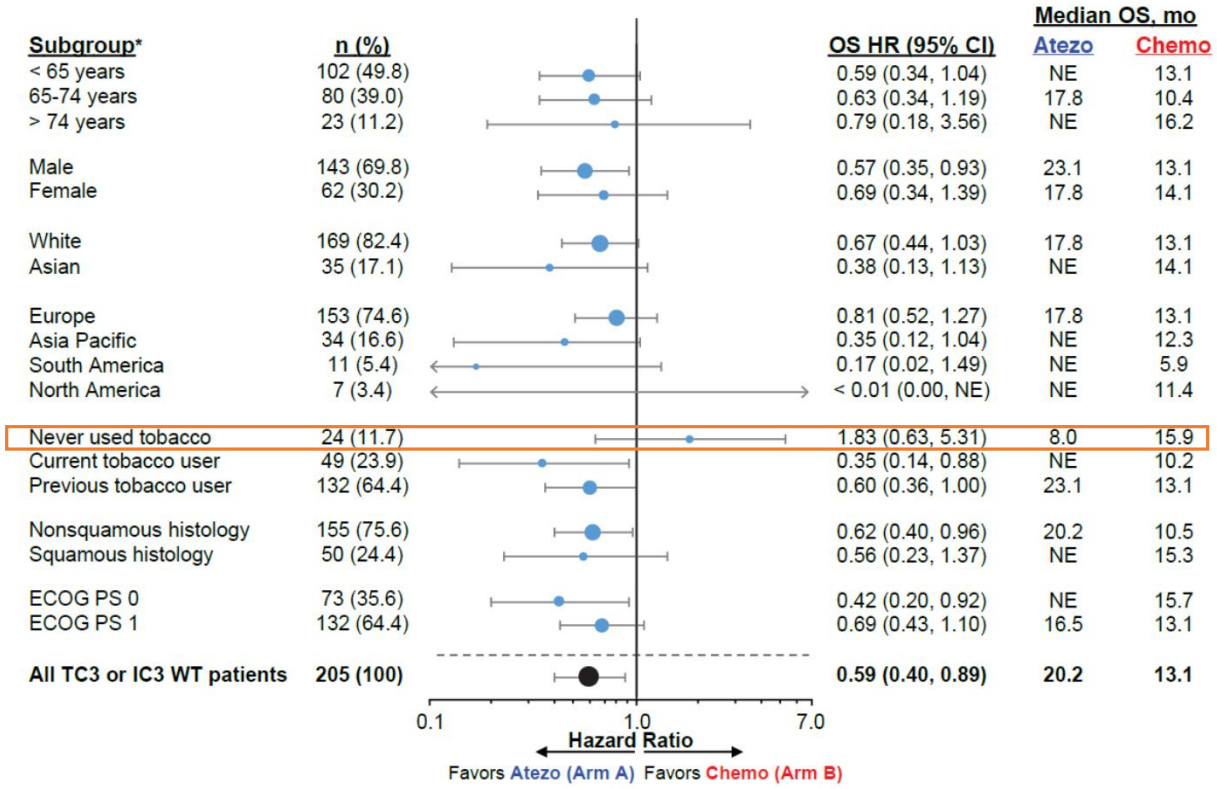


TC >=1% or IC >=1%



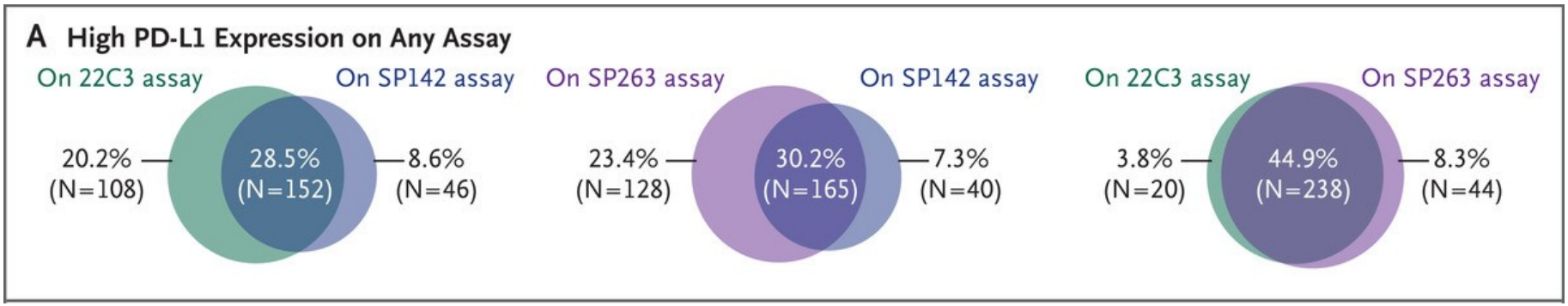
Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

Atezolizumab improved OS in most subgroups compared to platinum chemotherapy (*IMpower110*- high-PD-L1)



Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

Imperfect overlap of “High PD-L1” on any assay (*IMpower110*)

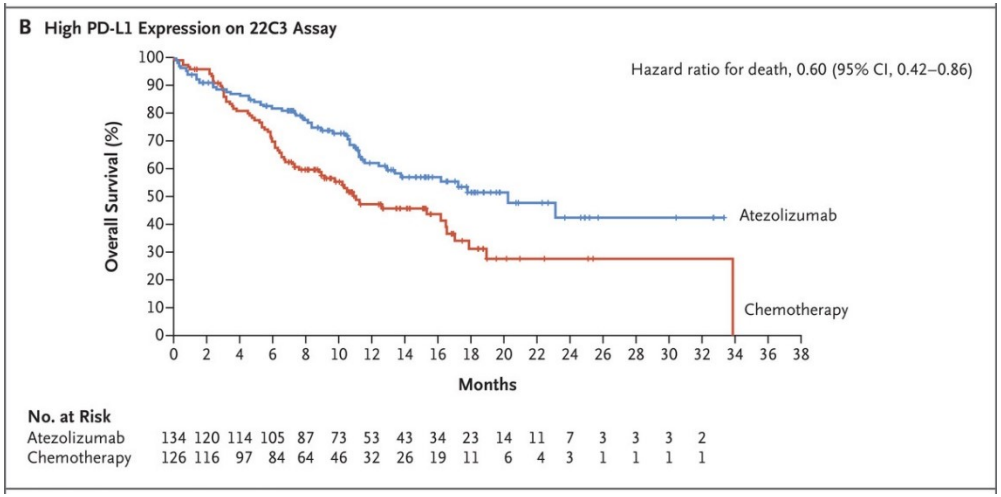


- 534 patients for the 22C3 and SP142
  - 22C3 PD-L1 >=50% tumor cells
  - SP142 PD-L1 >=50% TC or >=10% IC
- 546 for the SP263 and SP142
  - SP263 PD-L1 >=50% TC
  - SP142 PD-L1 >=50% TC or >=10% IC
- 530 for the 22C3 and SP263
  - SP263 PD-L1 >=50% TC
  - 22C3 PD-L1 >=50% TC

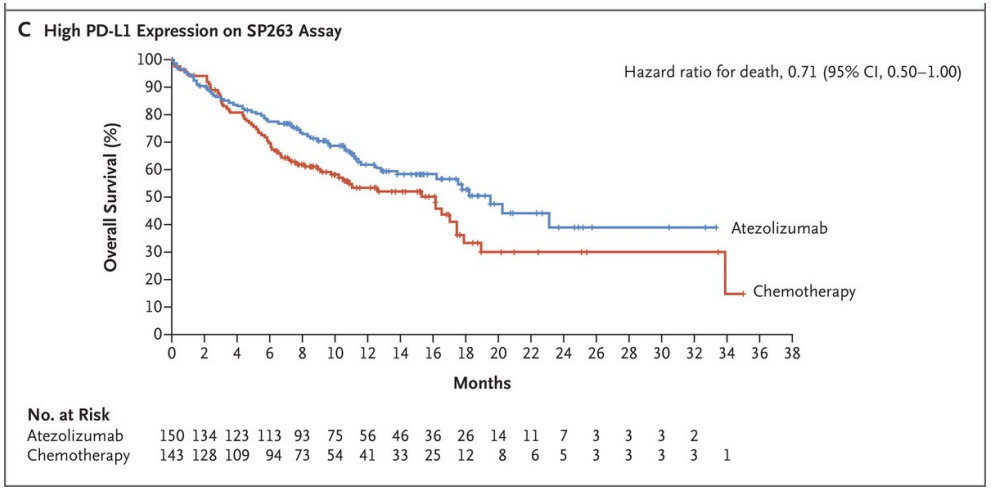
Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

PD-L1 high as measured by 22C3 and SP263 IHC also show OS benefit with atezolizumab over platinum doublet chemotherapy (*IMpower110*)

22C3: TC >=50%
HR 0.60 (95% CI 0.42-0.86)



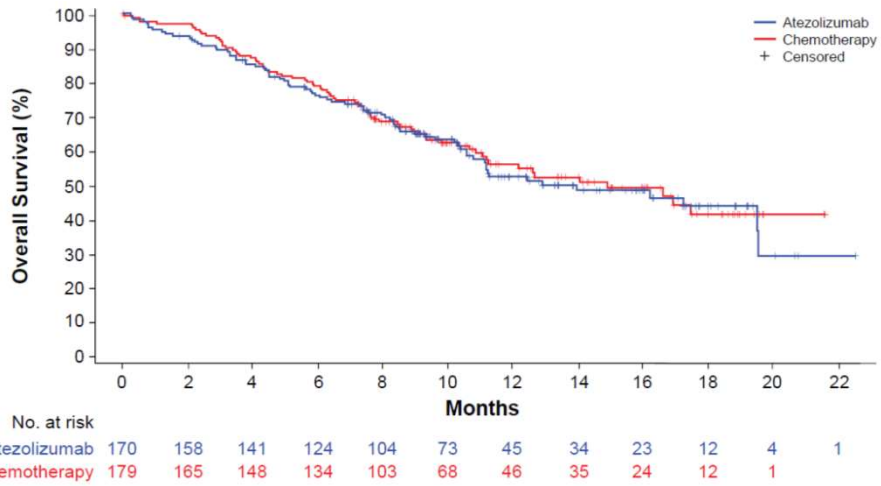
SP263: TC >=50%
HR 0.71 (95% CI 0.50-1.00)



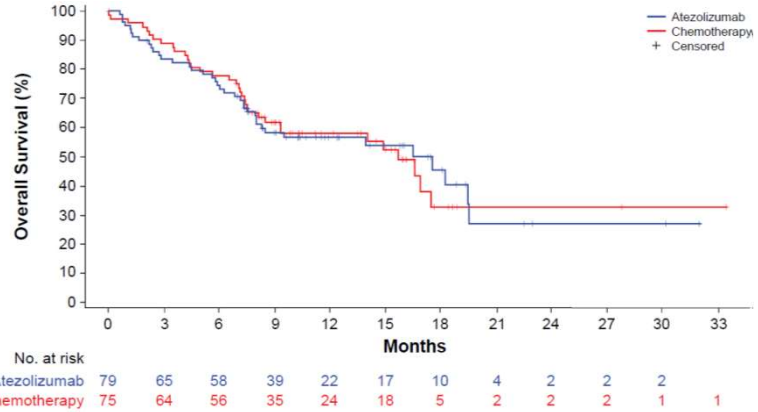
Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

No clear improvement in OS of atezolizumab in PD-L1 intermediate subgroups defined by varied IHC assays (*IMpower110*)

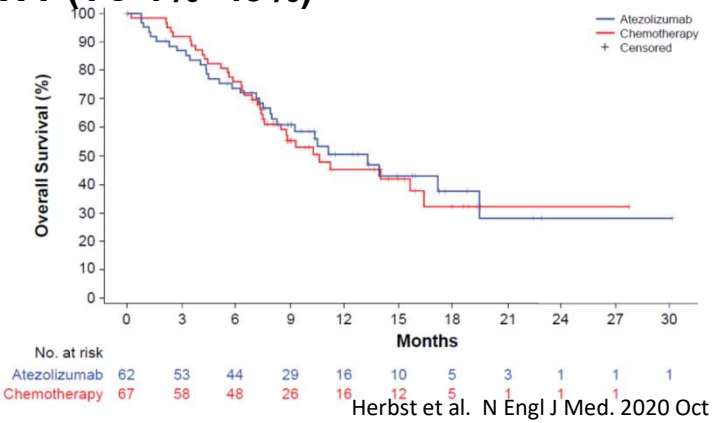
SP142 (TC1/2 or IC1/2 WT)



22C3 WT (TPS 1%–49%)

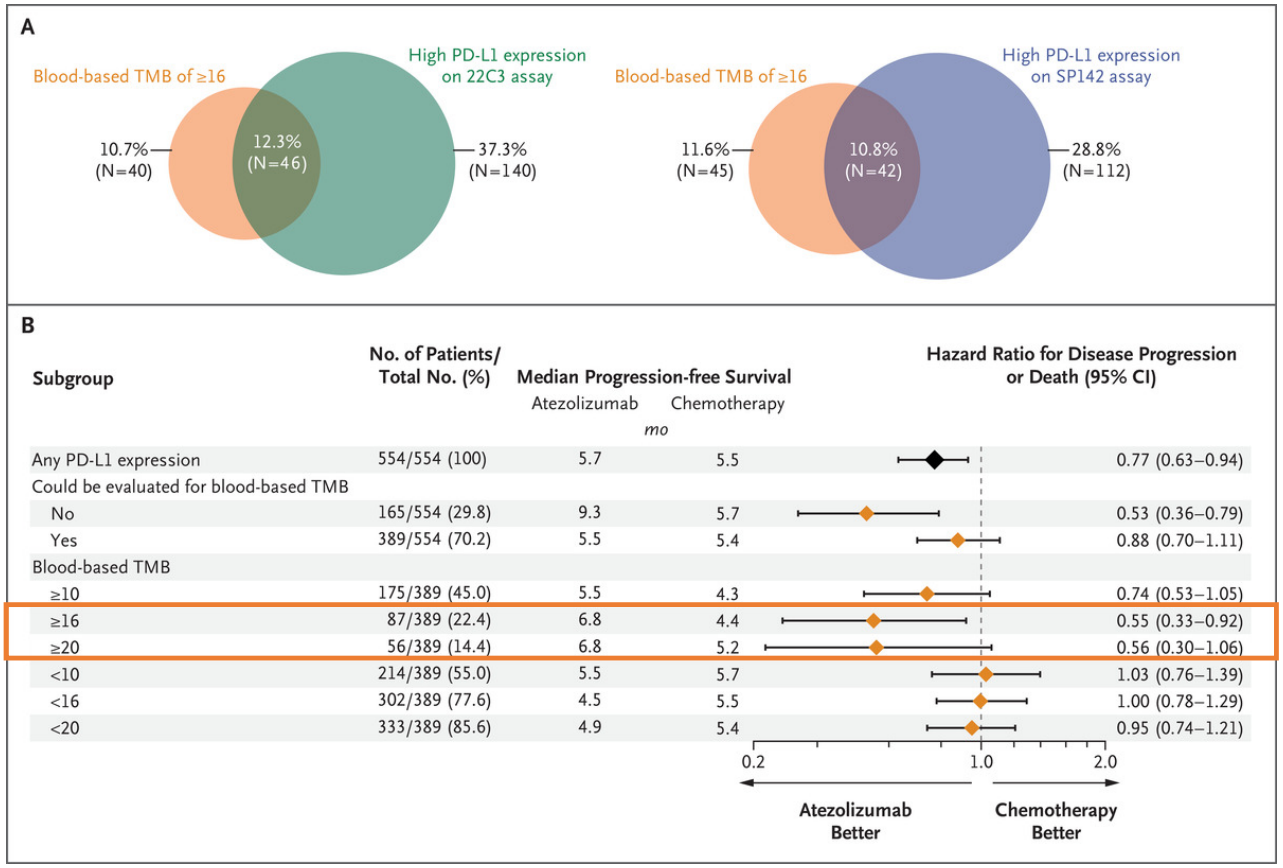


SP263 WT (TC 1%–49%)



Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

Blood TMB enhances PFS benefit with atezolizumab and benefit plateaus ~16 mut/Mb (*IMpower110*)



165 not evaluable for blood TMB: 88 max somatic allele frequency <1%, 39 samples failed quality control or had a median exon coverage of <800. *38 patients had not provided a baseline plasma sample.

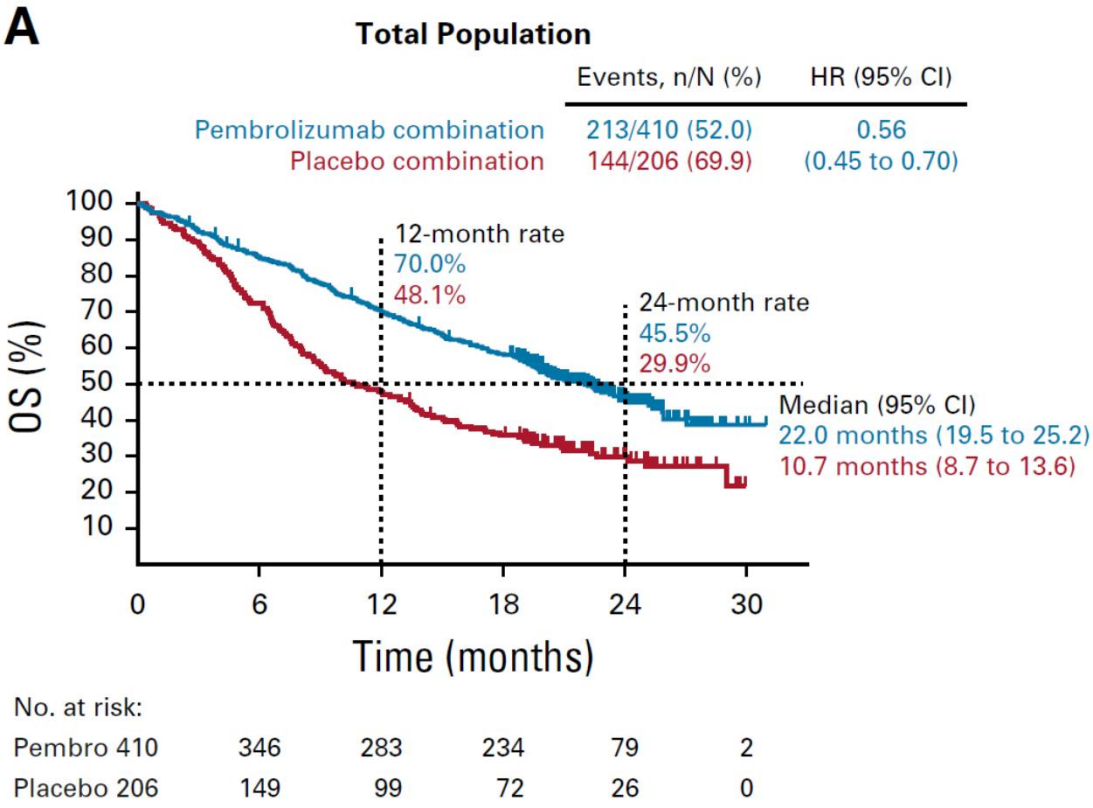
Herbst et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339.

Outline –Strategies for Frontline Immunotherapy

- Single agent immunotherapy
- Combination chemo-immunotherapy
  - **KN-189 (non-sq): Carboplatin/pemetrexed/pembrolizumab– updated OS**
  - **IMpower130 (non-sq): Carboplatin/nab-paclitaxel/atezolizumab– new approval**
  - **IMpower150 (non-sq): Carboplatin/paclitaxel/bevacizumab/atezolizumab– updated data in subgroups (*EGFR* mutation, brain mets)**
  - **KN-407 (sq): Carboplatin/paclitaxel or nab-paclitaxel/pembrolizumab– final analysis**
- Combination immunotherapy

Combination chemo-IO (carboplatin/ pem/ pembro) improves OS compared to platinum-doublet chemo alone in non-squamous NSCLC (*KN-189 updated OS analysis*)

Median follow-up 23.1 mo
HR 0.56 (95% CI 0.45-0.70)
- last reported median follow-up only 10.5 months HR 0.49 95% CI 0.38-0.64; P < 0.001



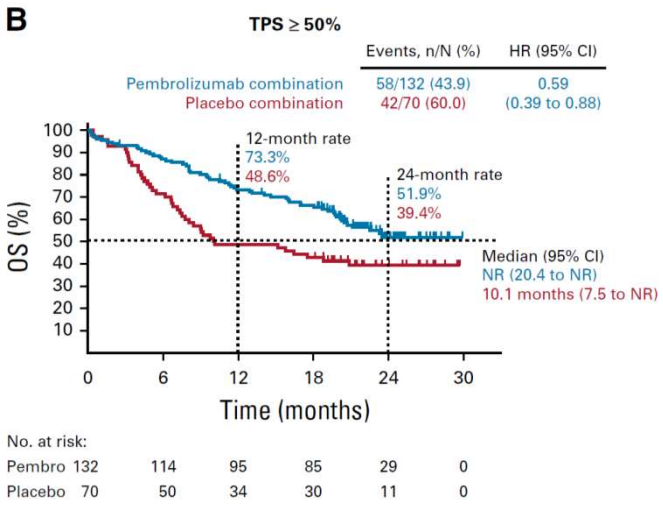
54% of patients in the chemotherapy arm crossed over to pembrolizumab monotherapy or other PD-1/PD-L1 inhibitors

PFS HR 0.48; (95% CI 0.40-0.58); median 9.0 mo vs. 4.9 mo
ORR 48% vs. 19.4%; median DOR 12.4 vs. 7.1 mo

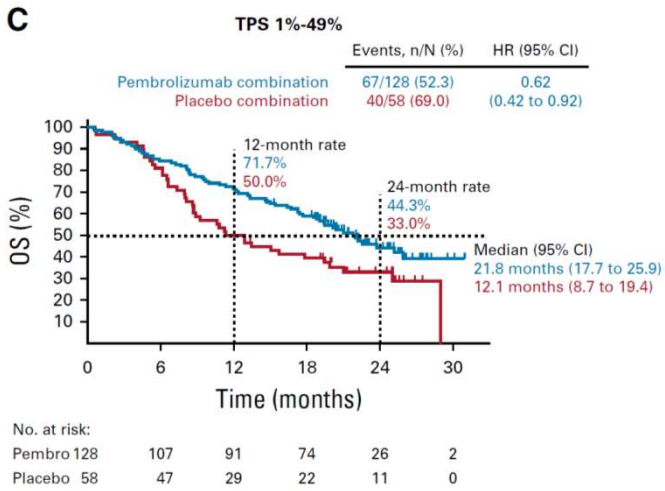
Gadgeel S et al. J Clin Oncol. 2020 May 10;38(14):1505-1517.

Combination chemo-IO (carbo/pem/pembro) improves OS (*and PFS*) irrespective of PD-L1 level (*KN-189*)

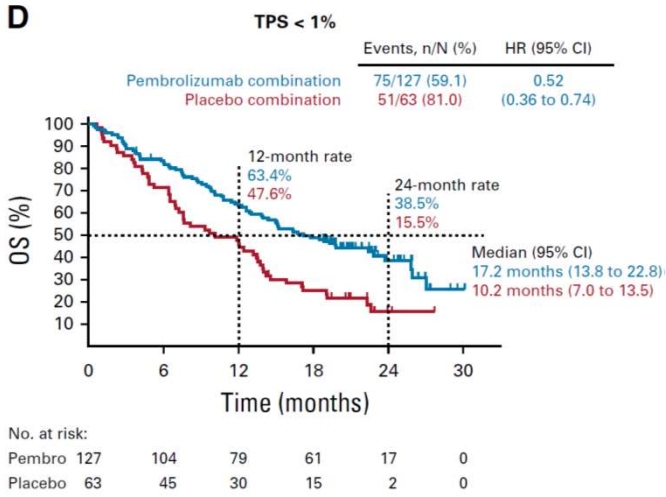
PD-L1 >=50%
HR 0.59 (95% 0.39-0.88)



PD-L1 1-49%
HR 0.62 (95% 0.42-0.92)



PD-L1 <1%
HR 0.52 (95% 0.36-0.74)



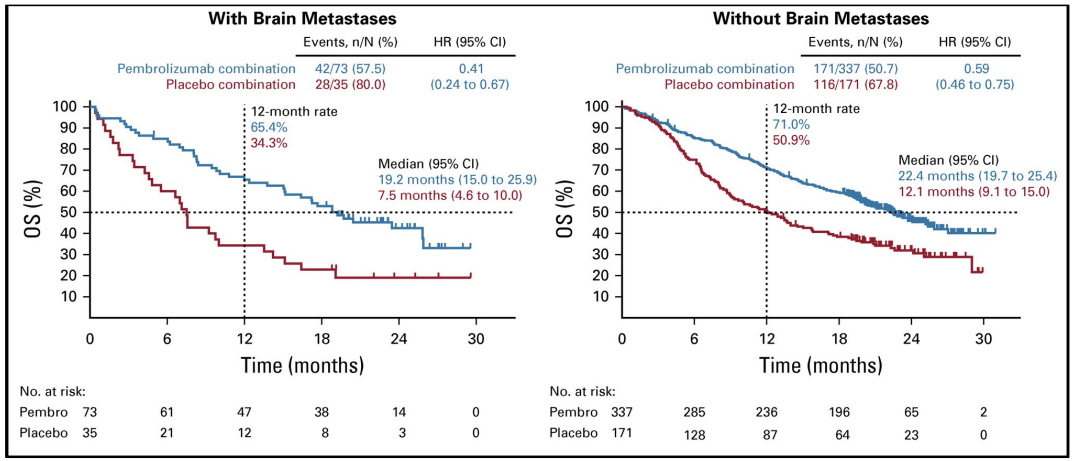
Response Rate: 62.1% TPS>=50%
49.2% TPS 1-49%
32.1% TPS >1%

Gadgeel S et al. J Clin Oncol. 2020 May 10;38(14):1505-1517.

Combination chemo-IO (carbo/pem/pembro) improves OS irrespective of presence of liver or brain metastases (*KN-189*)

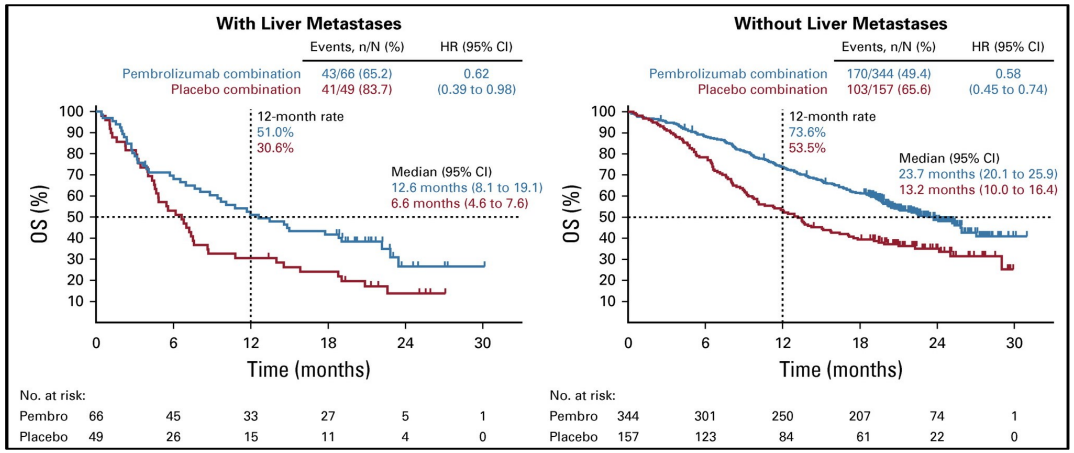
Brain Mets

With: HR 0.41 (95% CI 0.24-0.67)
Without: HR 0.59 (95% CI 0.46-0.75)



Liver Mets

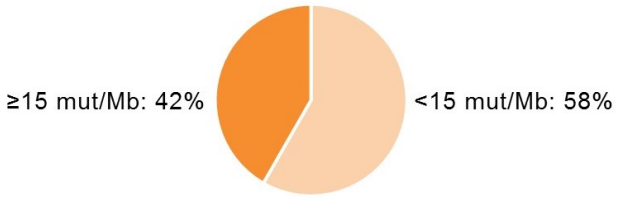
With: HR 0.62 (95% CI 0.39-0.98)
Without: HR 0.58 (95% CI 0.45-0.74)



Gadgeel S et al. J Clin Oncol. 2020 May 10;38(14):1505-1517.

Blood TMB (similar to tissue TMB) does not enhance magnitude of benefit of chemo-IO in KN-189

Prevalence by bTMB Cutpoint

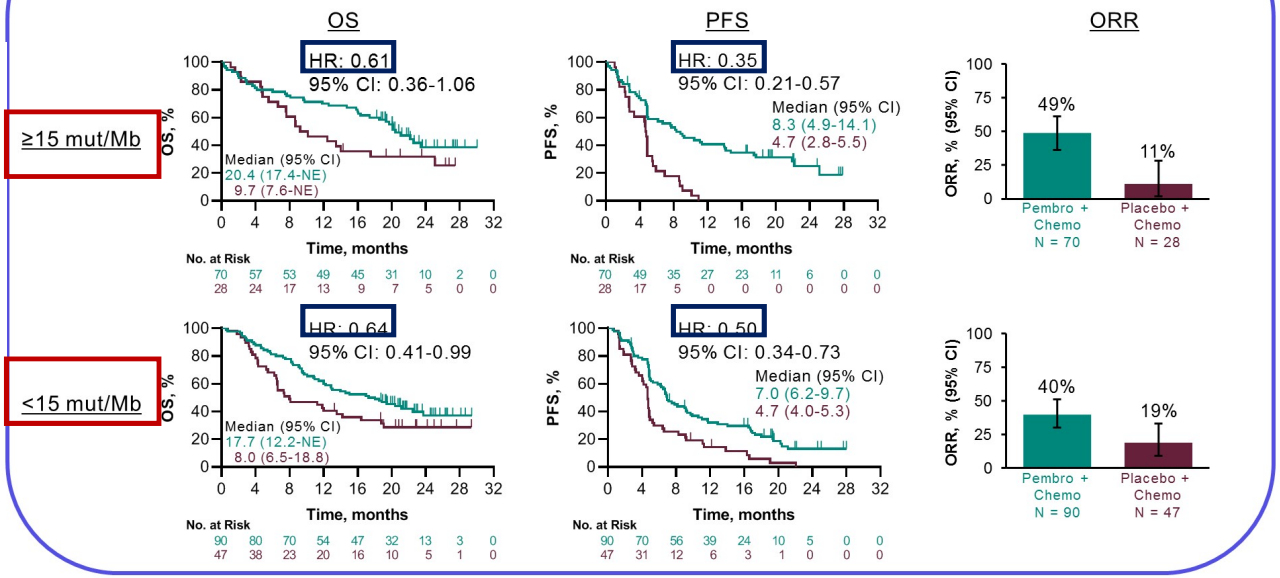


tTMB ≥175/ bTMB <15 **15%**	tTMB ≥175/ bTMB ≥15 **33%**
tTMB <175/ bTMB <15 **43%**	tTMB <175/ bTMB ≥15 **9%**

- 178 (76%) had concordant bTMB and tTMB
- 57 (24%) had discordant bTMB and tTMB

Clinical Utility of Prespecified bTMB Cutpoint of 15 mut/Mb

- Pembro + chemo improved OS, PFS, and ORR vs placebo + chemo for bTMB ≥15 and <15 mut/exome

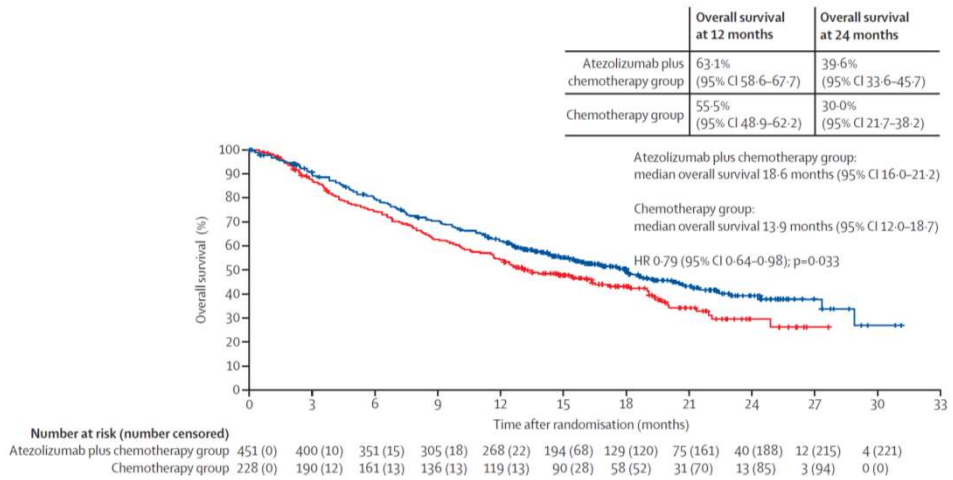


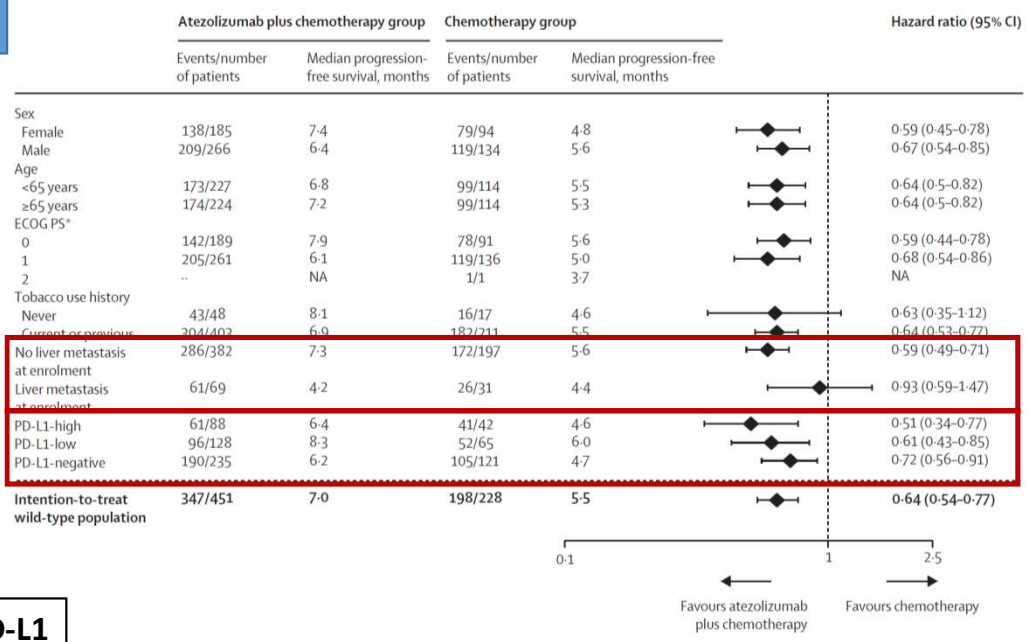
Data cutoff date: Sep 21, 2018.

Garassino M et al. ASCO 2020. Abstr #9521

Combination chemo-IO (carbo/nab-pac/atezolizumab) improves OS over platinum chemotherapy in non-squamous NSCLC (*IMpower130*)

OS HR 0.79 (95% CI 0.64-0.98); p=P=0.033
Median 18.6 mo vs. 13.9 mo (f/u ~18-19 mo)





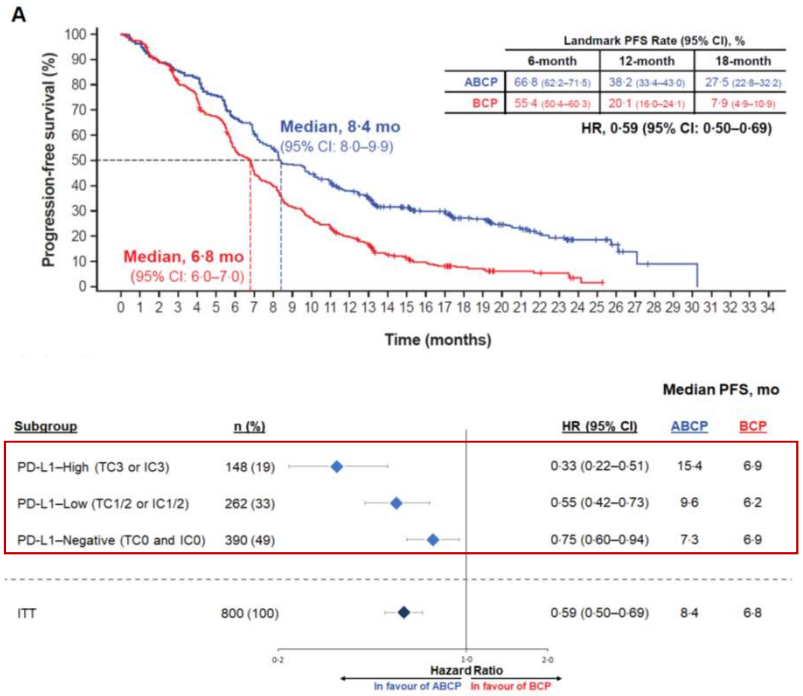
~60% of patients in the chemotherapy arm crossed over to PD-1/PD-L1 inhibitors
PFS HR 0.64 (95% CI 0.54–0.77) P<0.0001; median 7.0 mo vs. 5.5 mo
ORR 49.2% vs. 31.9%

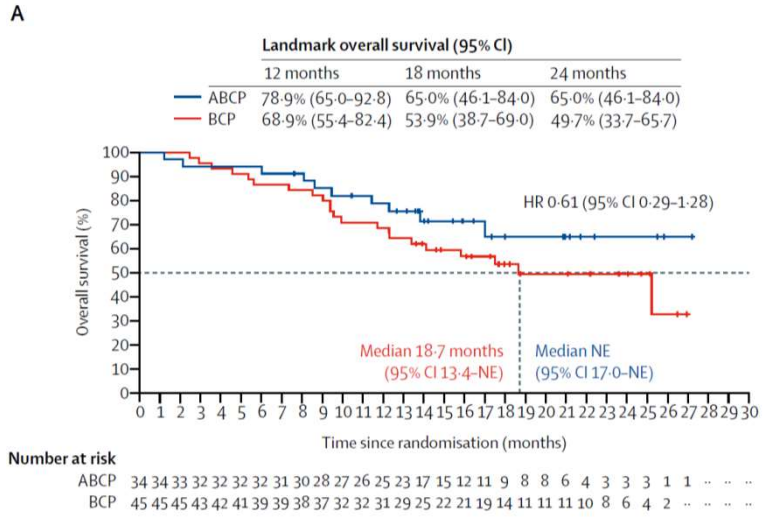
West H et al. Lancet Oncol. 2019 Jul;20(7):924-937.

Combination chemo + atezolizumab + bevacizumab improves OS compared to chemo-bev in non-squamous NSCLC (*IMpower150*)

Median f/u ~19.6 months

- **PFS HR 0.59** (95% CI 0.50-0.69); median 8.4 vs. 6.8 mo
- **Interim OS HR 0.61** (95% CI 0.29-1.28); median NE (95% CI 17.0-NE) vs. 18 mo



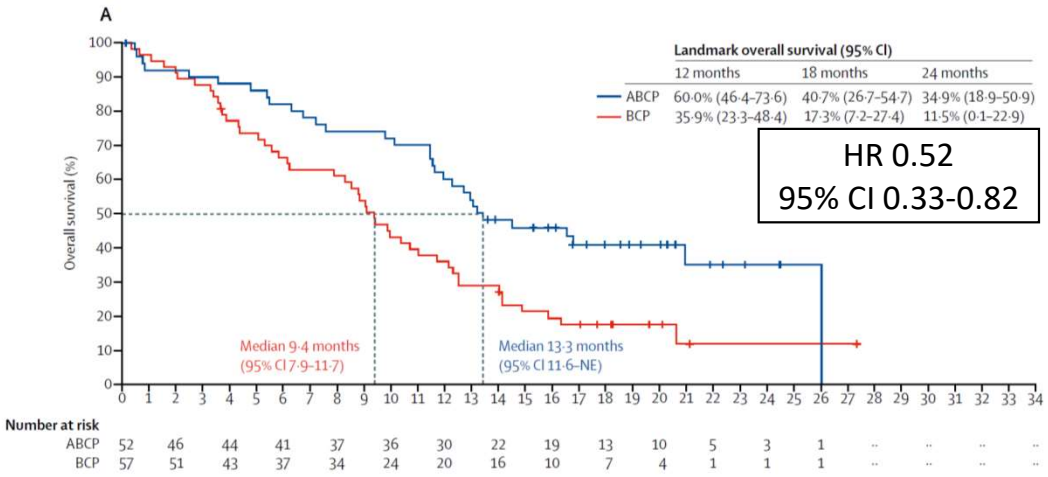


ORR 56.4% vs. 40.2%

Socinski MA et al. N Engl J Med. 2018 Jun 14;378(24):2288-2301. Reck et al. Lancet Respir Med. 2019 May;7(5):387-401.

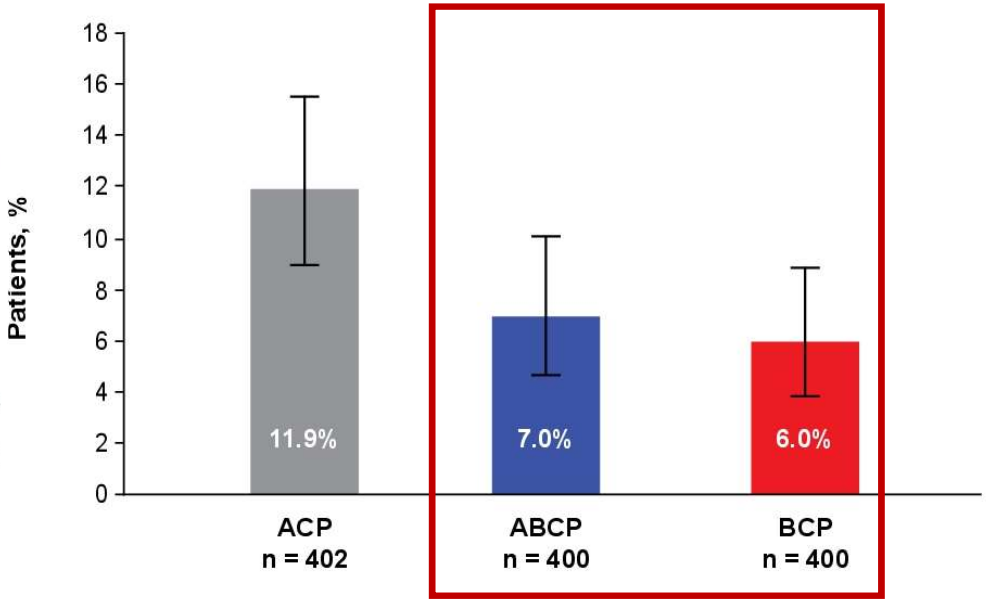
Combination chemo + atezolizumab + bevacizumab improves OS compared to chemo-bev – clinical factors of efficacy (*IMpower150*)

Liver metastases OS ABCP vs. BCP



Interaction test trend improved PFS/OS in liver mets
Not seen with ACP vs. BCP HR 0.87 (95% CI 0.57-1.32)

Rate of New Brain Metastases



Median time to discontinuation- trend toward in ABCP vs. BCP arm HR 0.68 85% CI 0.39-1.19

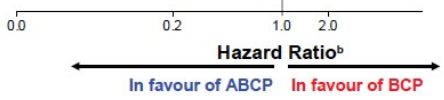
Socinski MA et al. Abstr #9012. ASCO 2019. Capuzzo F et al. Abstr #9587. ASCO 2020. Reck et al. Lancet Respir Med. 2019 May;7(5):387-401.

What is known about frontline chemo-IO in *EGFR* mutated NSCLC?
Synergy for Bev-Atezo IMpower150

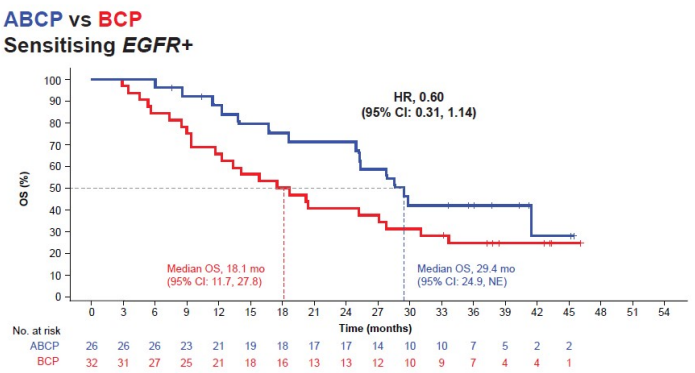
PFS

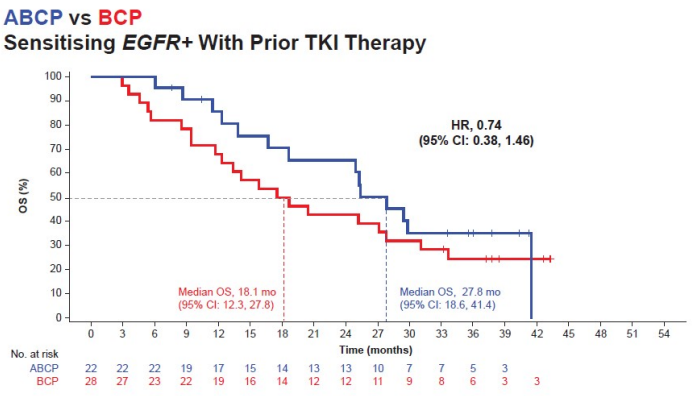
ABCP vs BCP

Subgroup	n	HR (95% CI)	Median PFS, months ABCP	BCP
EGFR mutation	78	0.56 (0.34, 0.91)	10.2	7.1
Sensitising *EGFR* mutation[a]	58	0.38 (0.21, 0.68)	10.3	6.1
Received prior TKI therapy	50	0.39 (0.20, 0.74)	9.7	6.1



OS



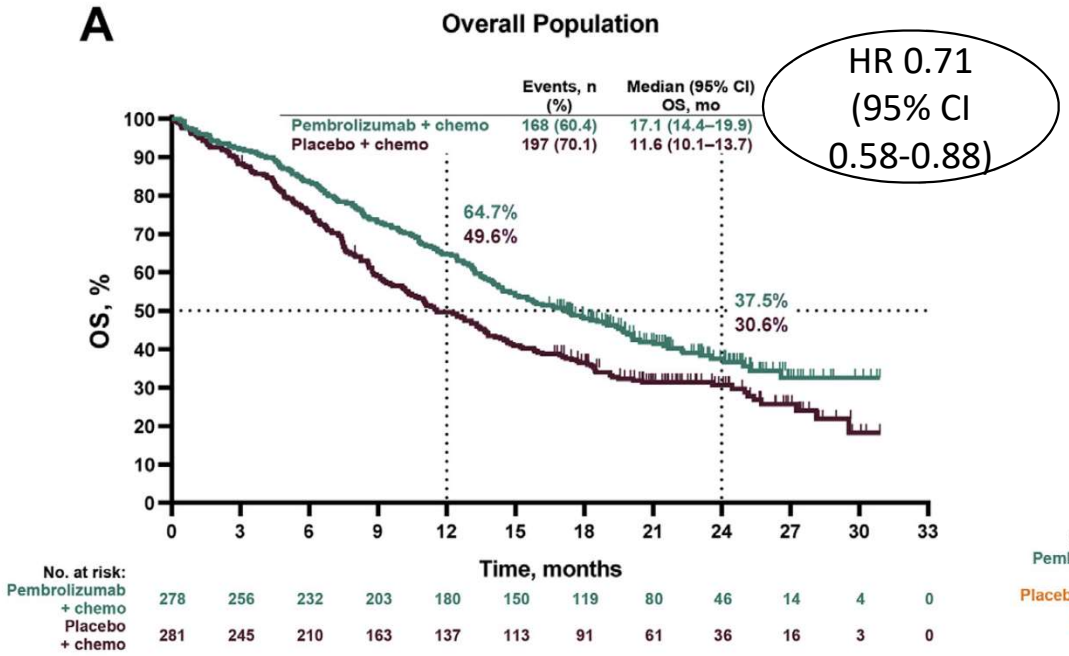


EGFR OS HR 0.91 95% CI 0.53-1.59

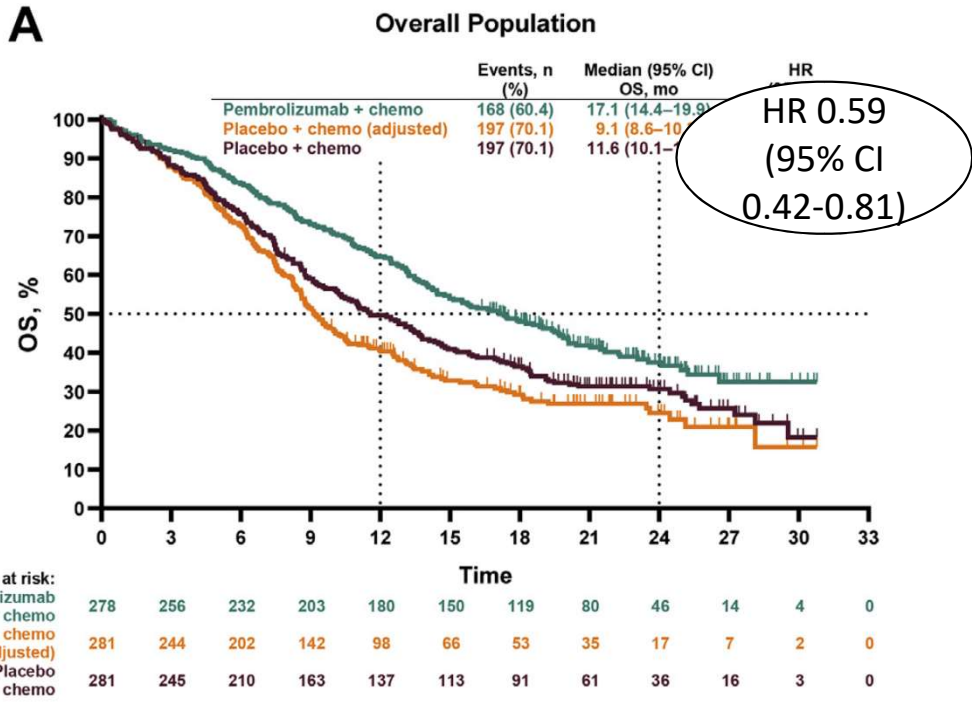
Additional f/u 20 months; post-progression therapies → BCP arm 79.1%, ABCP 45.5%, ACP 70.5%

Reck et al. ESMO 2020.

Combination chemo-IO (carbo /taxane/ pembrolizumab) improves OS over platinum chemo in squamous NSCLC (*KN-407*)



Median follow-up 14.3 months
last reported median follow-up only 7.8 months
HR 0.64 95% CI 0.49-0.85; P < 0.001



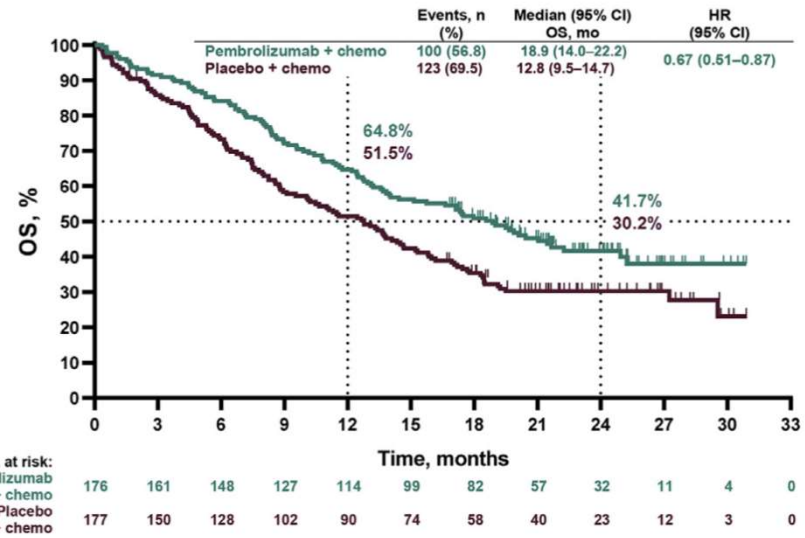
~50% of patients in the chemotherapy arm crossed over to pembrolizumab monotherapy or other ICIs; adjusted HR reported

PFS HR 0.57 (95% CI: 0.47–0.69); median 8.0 vs. 5.1 mo
ORR 62.6% vs. 38.4%

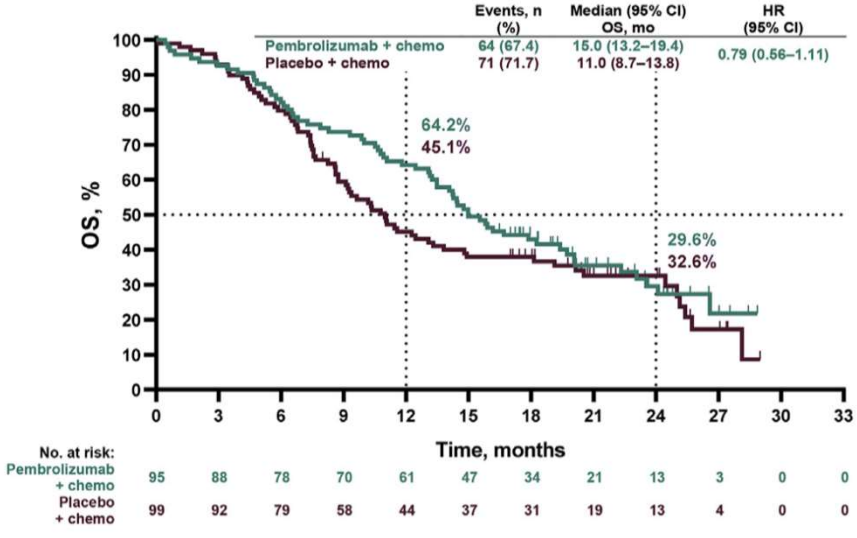
Paz Ares et al. J Thorac Oncol. 2020 Oct;15(10):1657-1669.

Combination chemo-IO (carbo /taxane/ pembrolizumab) improves OS over chemo irrespective of PD-L1 status (*KN-407*)

PD-L1 >=1%
HR 0.67 (95 % CI 0.51-0.87)



PD-L1 <1%
HR 0.79 (95% 0.56-1.11)



Paz Ares et al. J Thorac Oncol. 2020 Oct;15(10):1657-1669.

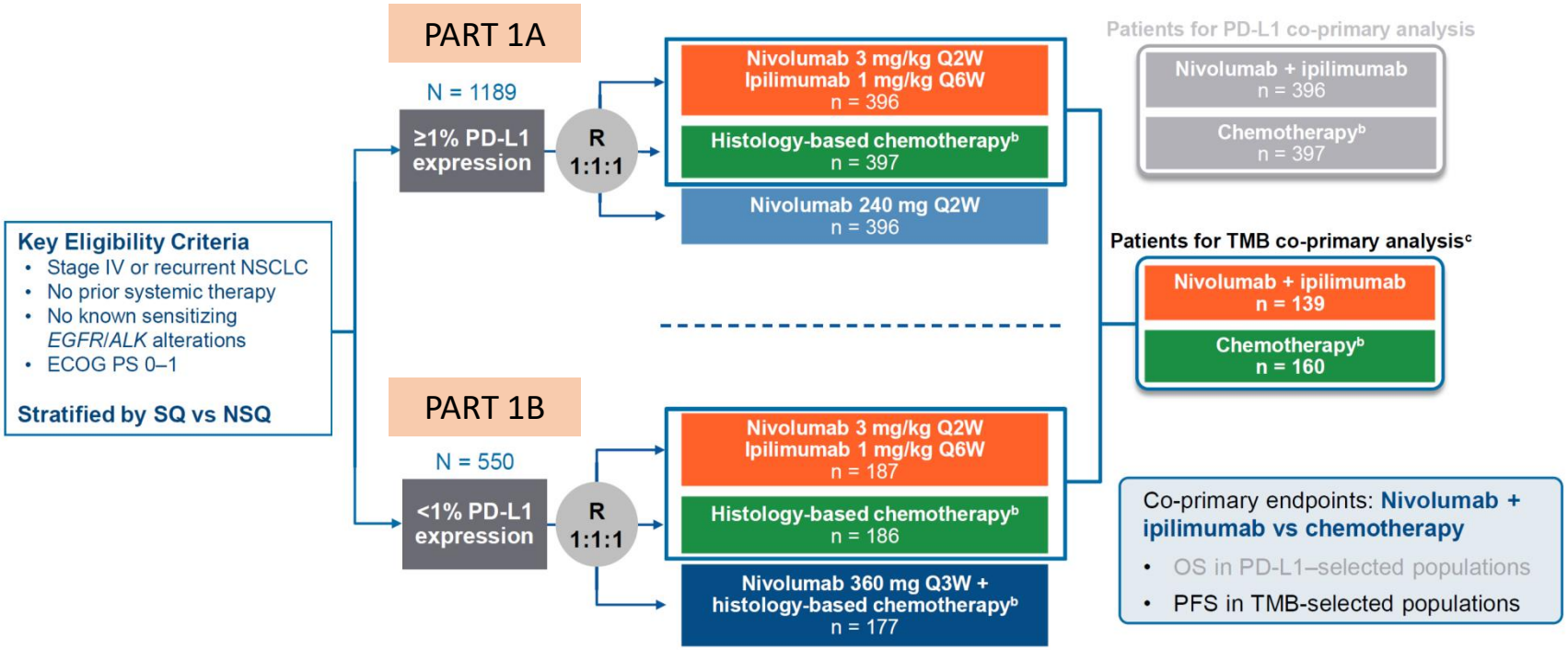
Outline –Strategies for Frontline Immunotherapy

- Single agent immunotherapy
- Combination chemo-immunotherapy

- Combination immunotherapy
  - **CheckMate-227 – new approval, updated data**
  - **CheckMate-9LA – new approval, new data**

Nivolumab + ipilimumab NSCLC CM-227 schema

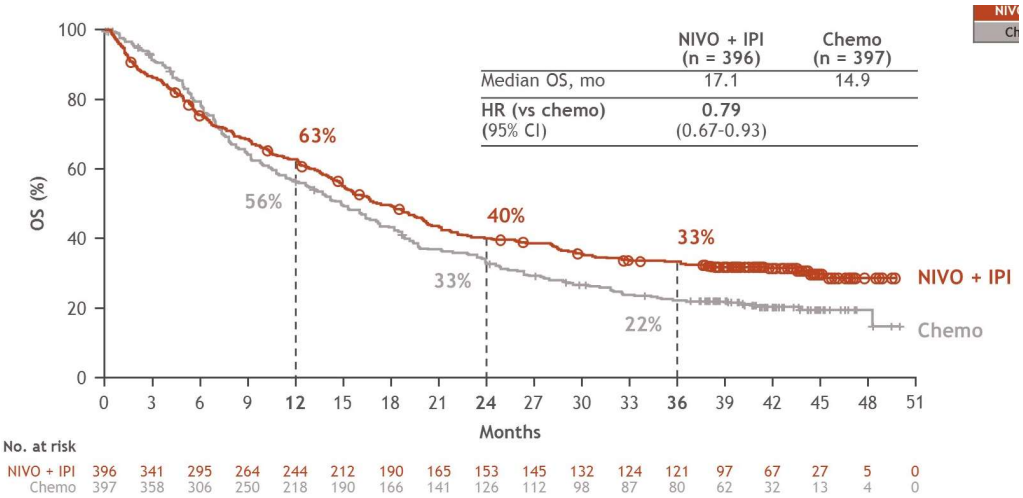
PART 2: Nivo+chemo vs. chemo non-squamous regardless of PD-L1



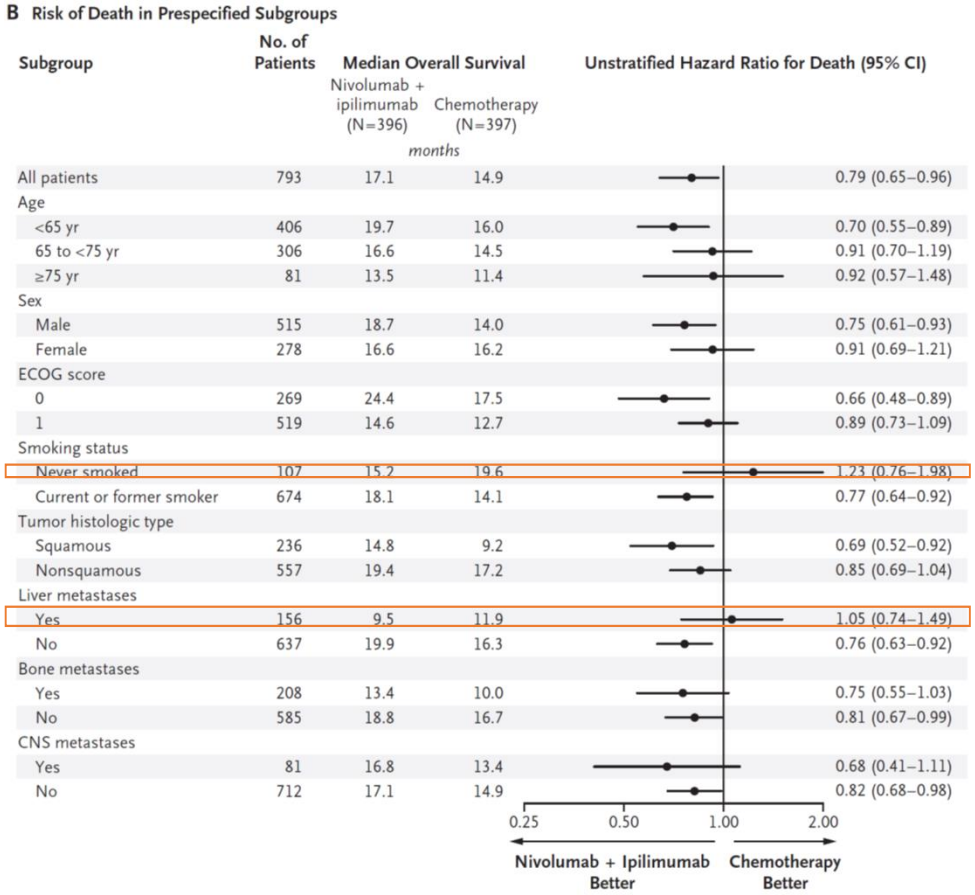
Co-primary endpoints: PFS in high TMB >=10 mut/Mb population and OS in PD-L1 >=1% population

Hellmann MD et al. N Engl J Med. 2018 May 31;378(22):2093-2104.

Nivolumab + ipilimumab NSCLC improves OS over platinum chemotherapy in PD-L1 >=1% NSCLC (*CM-227*)



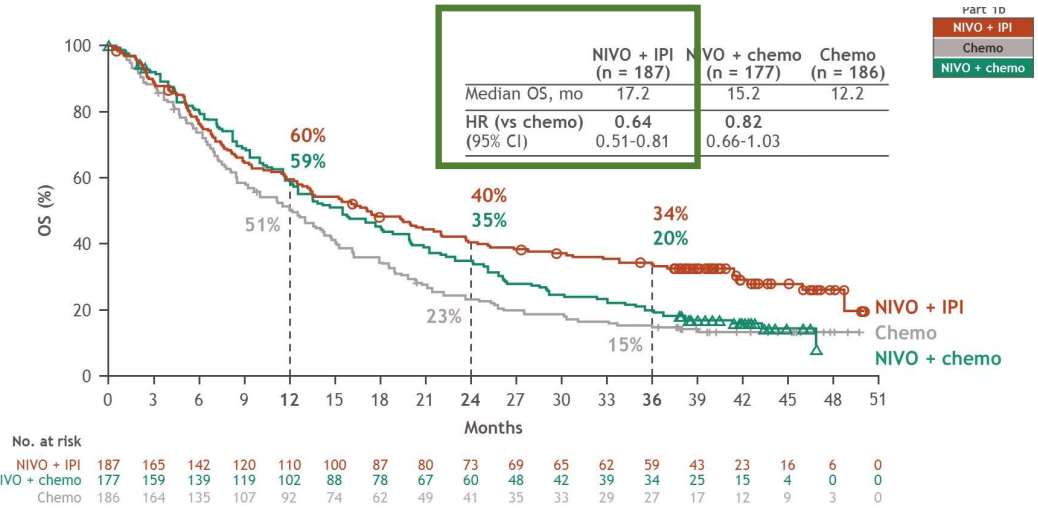
- **OS HR 0.79*** (95% CI 0.67-0.93)
- **PFS HR 0.81*** (95% CI 0.69-0.96); median 5.1 vs. 5.6 mo



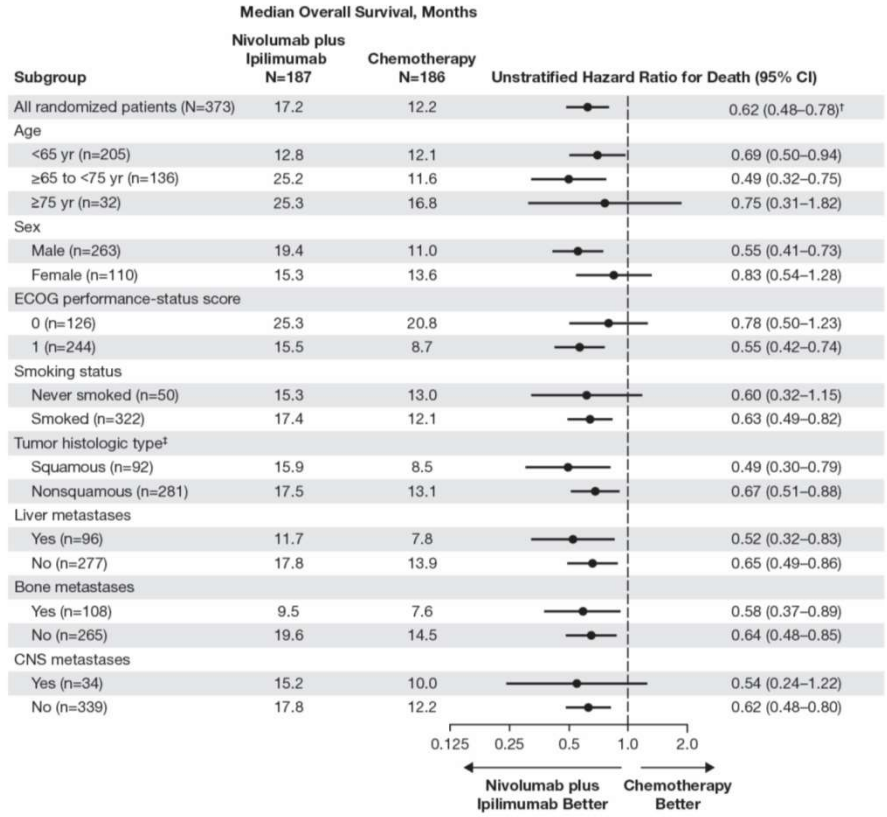
*3-year OS follow-up data presented by Ramalingam S et al. ASCO 2020
Biomarkers: PD-L1>=50%: 51.8% N+I vs. 61% chemo; TMB >= 10 mut/Mb 42.1% N+I vs. 61.0% chemo
43% in chemotherapy arm received subsequent ICIs and 31.6% in N/I arm received subsequent chemotherapy

Hellmann MD et al. N Engl J Med. 2019 Nov 21;381(21):2020-2031.
Ramalingam S et al. Abstr #9500. ASCO 2020

Nivolumab + ipilimumab NSCLC improves OS over chemotherapy in PD-L1 <1% NSCLC (*CM-227*)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

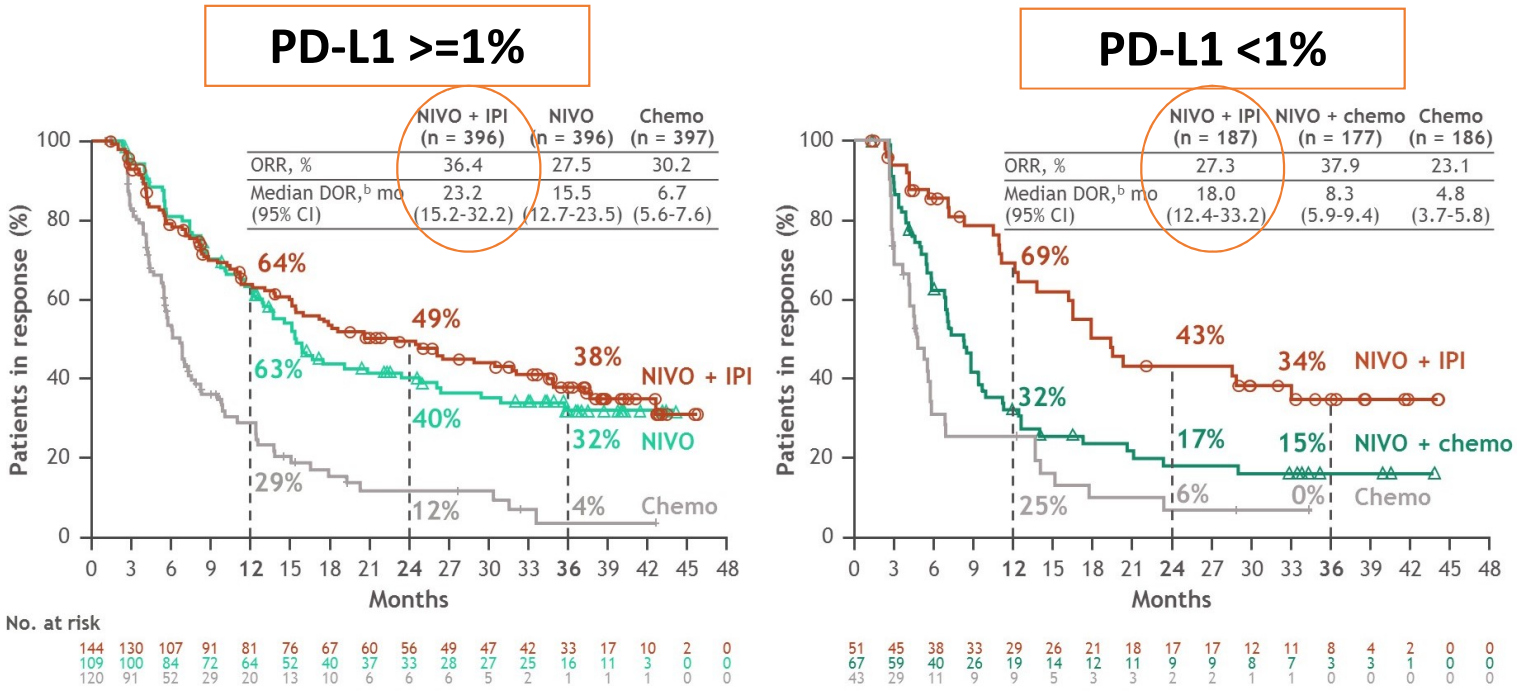


- **OS HR 0.64** (95% CI 0.51-0.81)
- **PFS HR 0.75** (95% CI 0.59-0.95); median 5.1 vs. 4.7 mo

36.0% in chemotherapy arm received subsequent ICI and 42.2 % in N/I arm received subsequent chemotherapy

Hellmann MD et al. N Engl J Med. 2019 Nov 21;381(21):2020-2031.
Ramalingam S et al. Abstr #9500. ASCO 2020

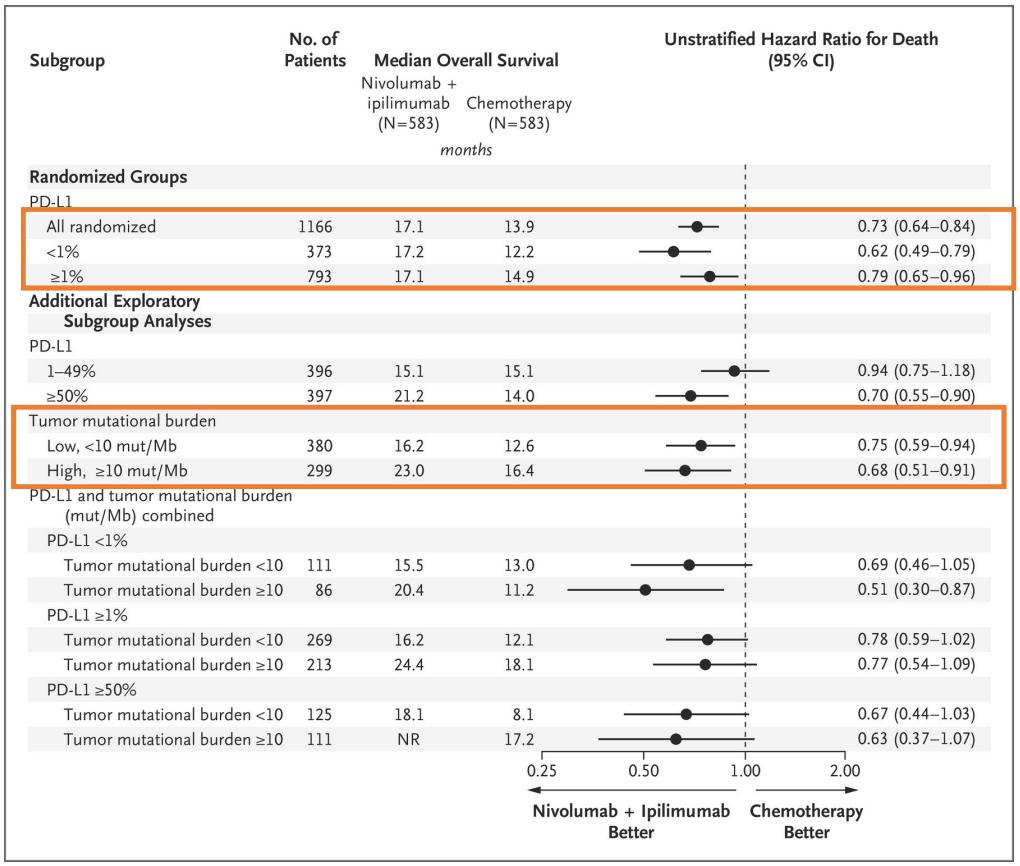
Nivolumab + ipilimumab has potential for prolonged duration of response irrespective of PD-L1 status in NSCLC (*CM-227*)



Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W), and NIVO (360 mg Q3W) + chemo. [a]ORR and DOR were assessed by blinded independent central review; [b]DOR was reported for responders only in each treatment arm.

Ramalingam S et al. Abstr #9500. ASCO 2020

Any PD-L1 (threshold 1%) and TMB (threshold 10 mut/Mb) show OS benefit with nivo/ipi over chemo (*CM-227*)



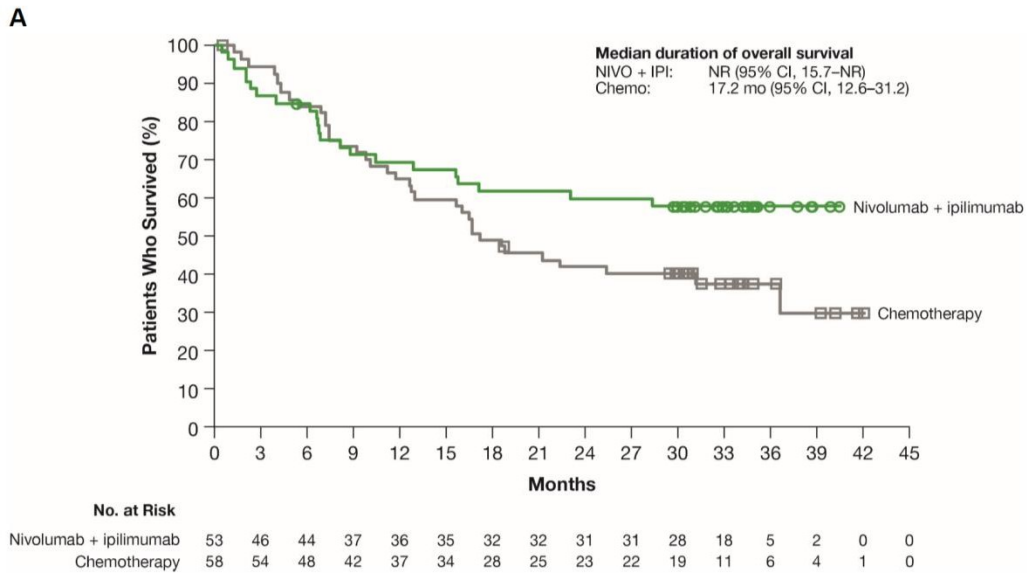
Subgroup	No. of Patients	Median Overall Survival (months): Nivolumab + ipilimumab (N=583)	Median Overall Survival (months): Chemotherapy (N=583)	Unstratified Hazard Ratio for Death (95% CI)
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)

No clear subgroup combining 2 key biomarkers with increased magnitude of benefit with nivo/ipi vs. chemo

Hellmann MD et al. N Engl J Med. 2019 Nov 21;381(21):2020-2031.

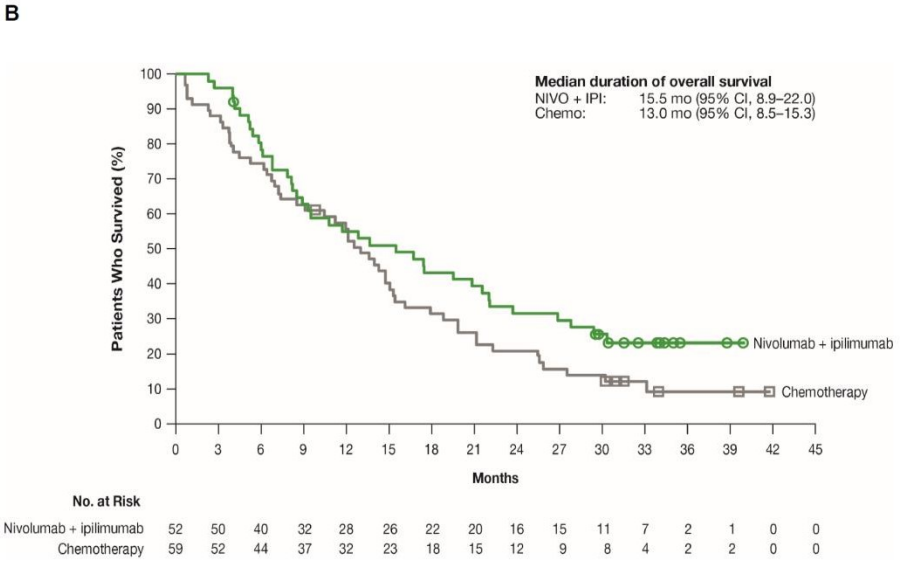
Any PD-L1 (threshold 1%) and TMB (threshold 10 mut/Mb) show OS benefit with nivo/ipi over chemo (*CM-227*)

PD-L1 >=50%/TMB >=10 mut/Mb



HR 0.63 (95% CI 0.37-1.07)

PD-L1 <1%/TMB < 10 mut/Mb



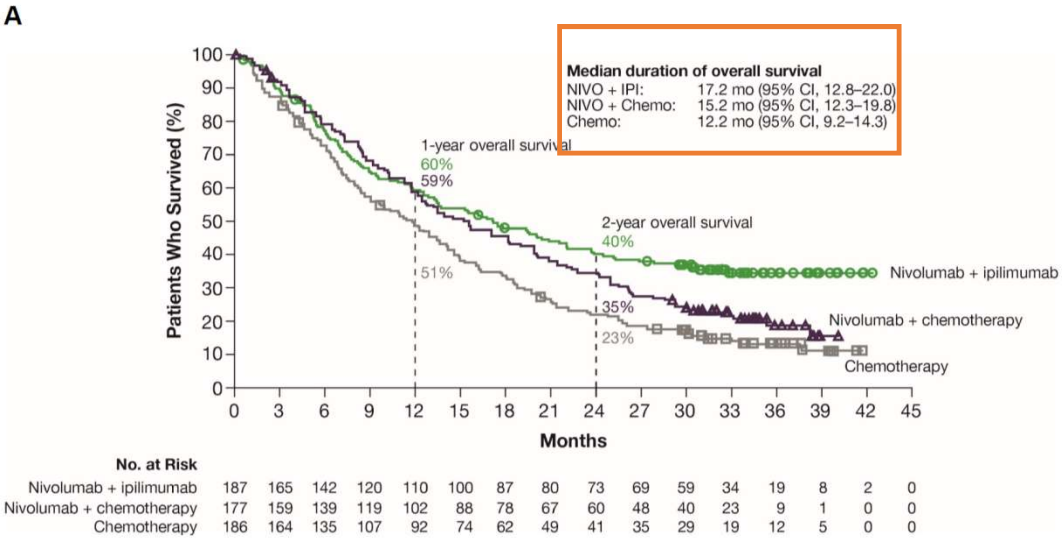
HR 0.69 (95% CI 0.30-0.87)

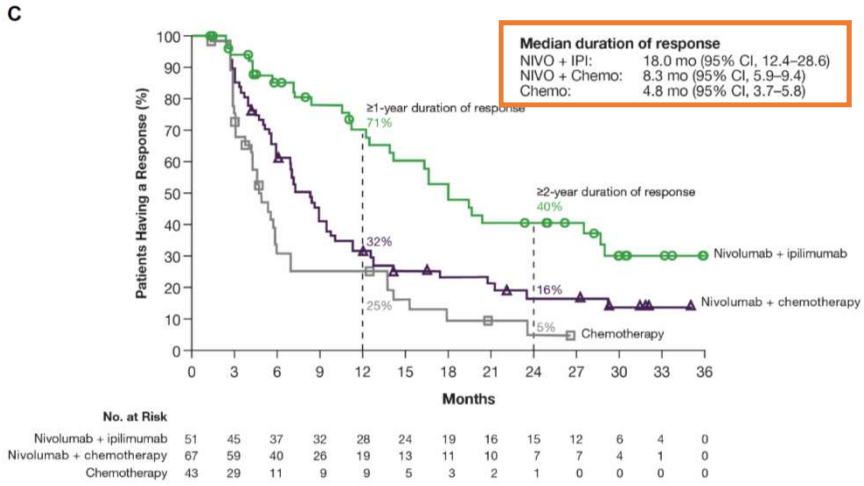
Hellmann MD et al. N Engl J Med. 2019 Nov 21;381(21):2020-2031.

PD-L1 <1%: Combination immunotherapy (nivo/ipi) vs. combination chemo-immunotherapy (nivo + chemo)? (*CM-227*)

OS

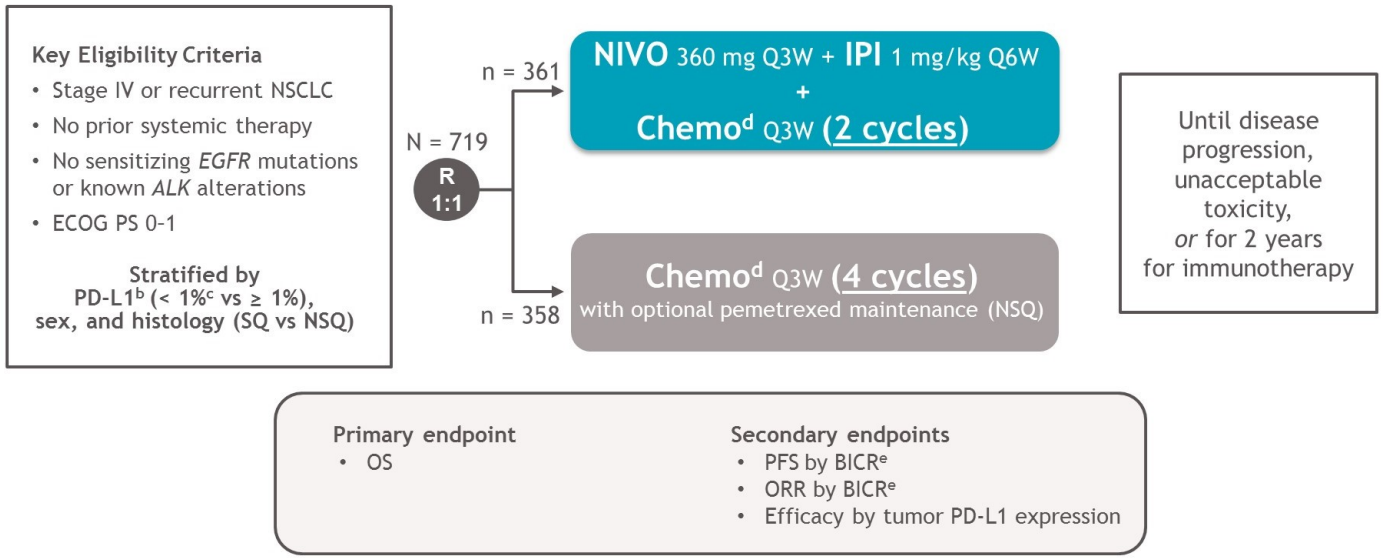
DOR





Hellmann MD et al. N Engl J Med. 2019 Nov 21;381(21):2020-2031.

How does the addition of limited chemo help nivo/ipi in the frontline? (*CM-9LA*)

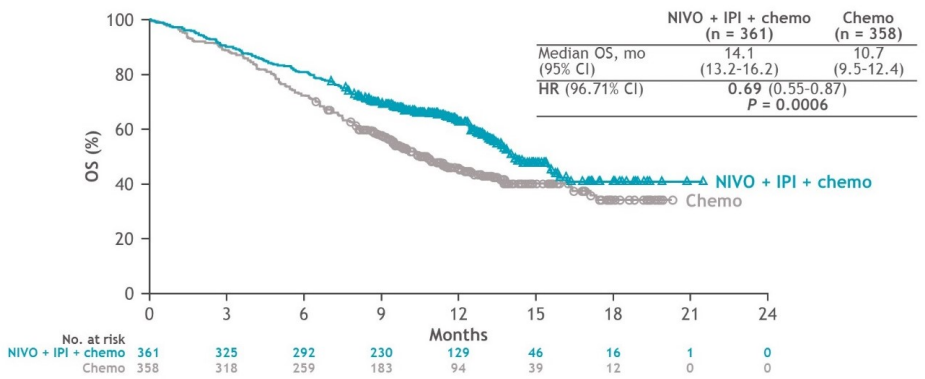


Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.
[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Reck M et al. Abstr #9501. ASCO 2020.

Nivo/ipi/limited chemo improves OS over chemo alone at interim analysis (*CM-9LA*)

Interim: HR 0.69 (95% CI 0.55-0.87)
Min f/u 8.1 mo



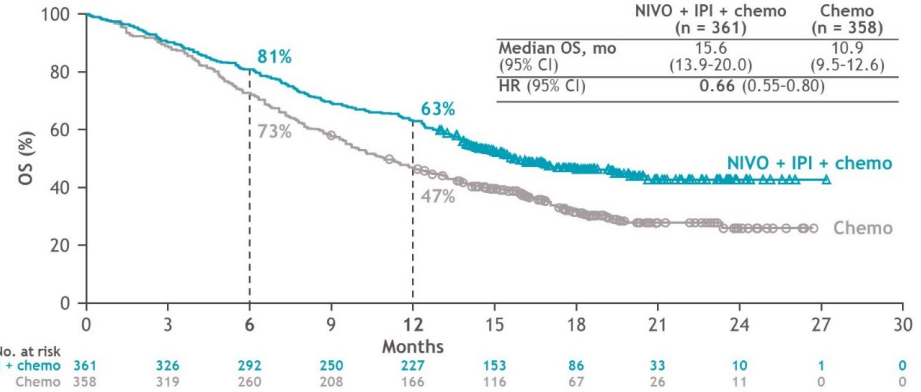
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	14.1 (13.2-16.2)	10.7 (9.5-12.4)
HR (96.71% CI)	0.69 (0.55-0.87) P = 0.0006	

- PFS and ORR were also significantly improved with NIVO + IPI + chemo vs chemo[b]

Minimum follow-up: 8.1 months for OS; 6.5 months for PFS / ORR.

[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 57% of patients in the NIVO + IPI + chemo arm and 46% of patients in the chemo arm were censored; [b]Median PFS was 6.8 mo versus 5.0 mo, respectively, HR 0.70 (97.48% CI, 0.57-0.86; *P* = 0.0001), and ORR was 38% versus 25%, respectively, *P* = 0.0003.

Updated: HR 0.66 (95% CI 0.55-0.80)
Min f/u 12.7 mo



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

Minimum follow-up: 12.7 months.

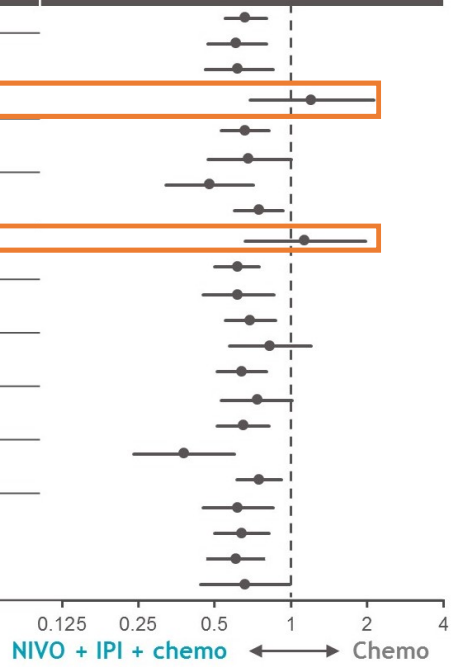
[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively

PFS: HR 0.68 (95% CI 0.57-0.82); median 6.7 vs. 5.0 mo

Reck M et al. Abstr #9501. ASCO 2020.

Nivo/ipi/limited chemo improves OS over chemo alone in majority of subgroups (*CM-9LA*)

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



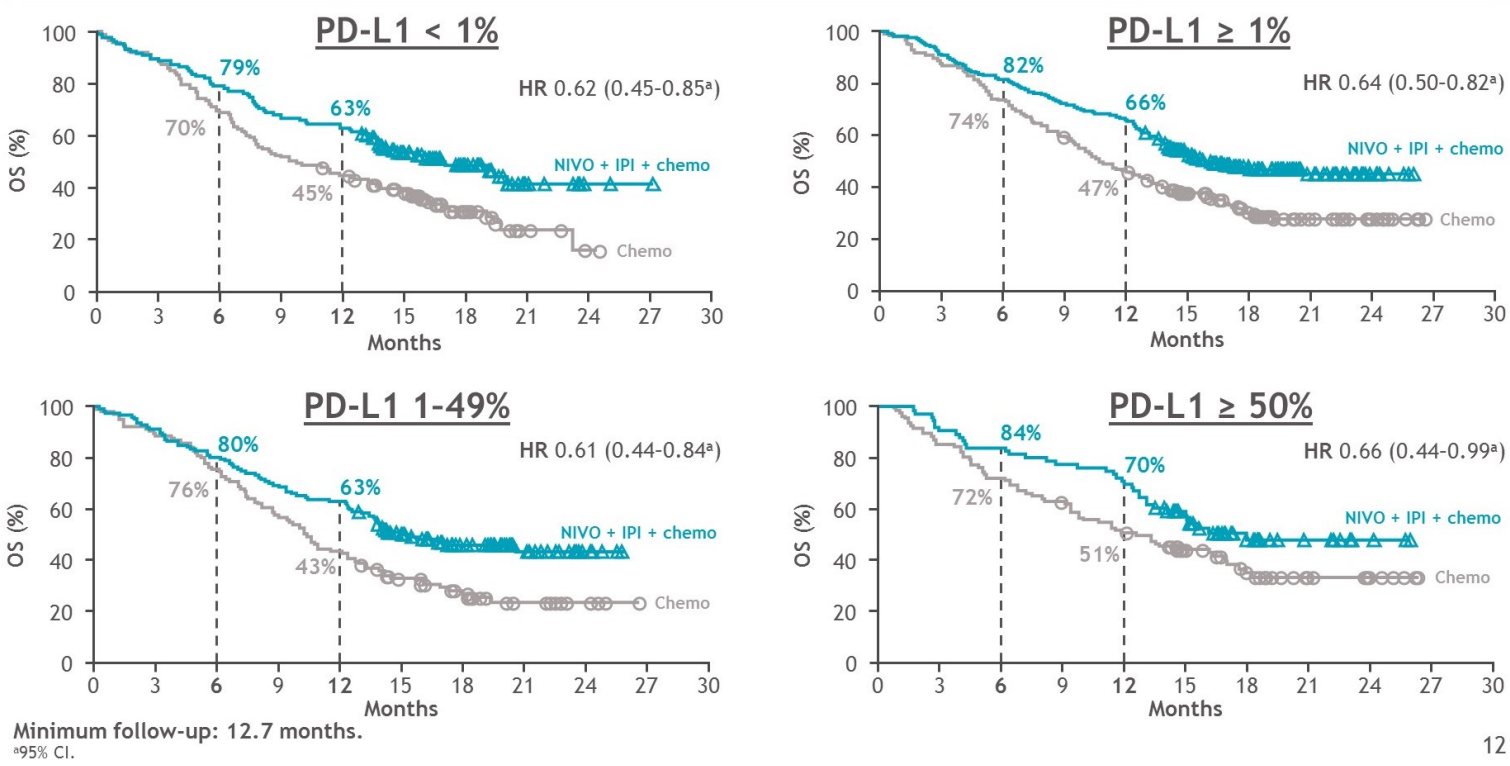
Minimum follow-up: 12.7 months.

[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

Benefit seen in liver mets, bone mets, and CNS mets

Reck M et al. Abstr #9501. ASCO 2020.

Nivo/ipi/limited chemo improves OS over chemo alone in irrespective of PD-L1 status (*CM-9LA*)



Reck M et al. Abstr #9501. ASCO 2020.

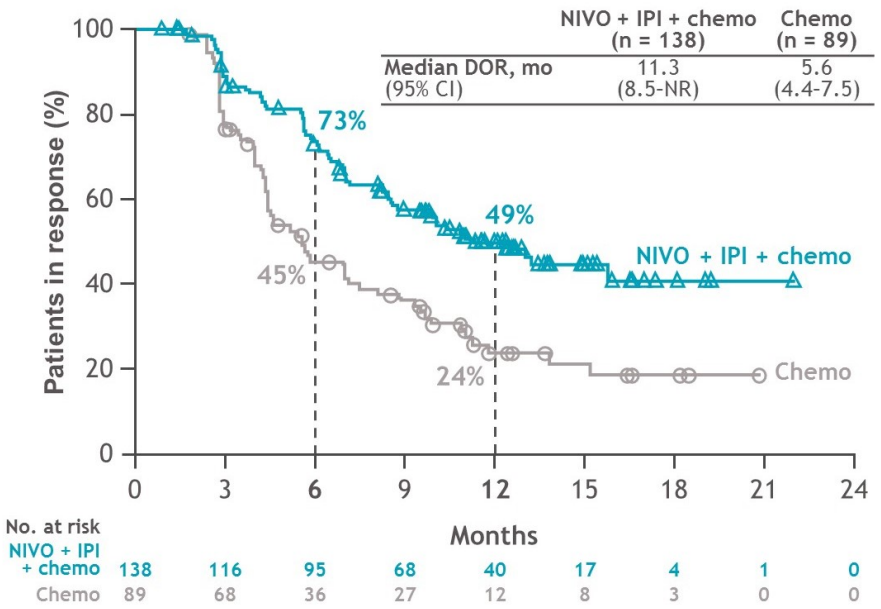
Nivo/ipi/limited chemo decreases proportion of progression as best response while maintaining improved duration of response (*CM-9LA*)

Response rates

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)

Minimum follow-up: 12.2 months.

Duration of response



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Nivo/ipi (CM-227) PD rates 21.5-24.1%
G3-4 AEs 47% vs. 38% for N/I/chemo vs. chemo

Reck M et al. Abstr #9501. ASCO 2020.

Summary of Treatment

PD-L1 >=50%	PD-L1 1-49%	PD-L1 <1%
Single agent immunotherapy, sometimes combination chemotherapy + immunotherapy	**Combination chemotherapy + immunotherapy,** sometimes single agent immunotherapy	**Combination chemotherapy + immunotherapy**
Pembrolizumab, Atezolizumab	<u>Non-squamous:</u> Carbo/pem/pembro Carbo/nab-pac/atezo Carbo/pac/atezo/bev ?Nivo/ipi + chemo <u>Squamous:</u> Carbo/nab-pac or pac/atezo ?Nivo/ipi + chemo	<u>Non-squamous:</u> Carbo/pem/pembro Carbo/nab-pac/atezo Carbo/pac/atezo/bev ?Nivo/ipi + chemo <u>Squamous:</u> Carbo/nab-pac or pac/atezo ?Nivo/ipi + chemo

Summary of Treatment

PD-L1 >=50%	PD-L1 1-49%	PD-L1 <1%
Single agent immunotherapy, sometimes combination chemotherapy + immunotherapy	**Combination chemotherapy + immunotherapy,** sometimes single agent immunotherapy	**Combination chemotherapy + immunotherapy**

- **Where does nivo/ipi fit in (CM-227)?**
  - PD-L1 <1%?
- **Where does nivo/ipi + 2 platinum cycles fit in?**
  - Does this data provide “some” reassurance to discontinue pemetrexed maintenance at an earlier timepoint in combination with pembrolizumab in non-squamous NSCLC?
- **Will there ever be a standard role for blood or tumor TMB?**

- THANK YOU!

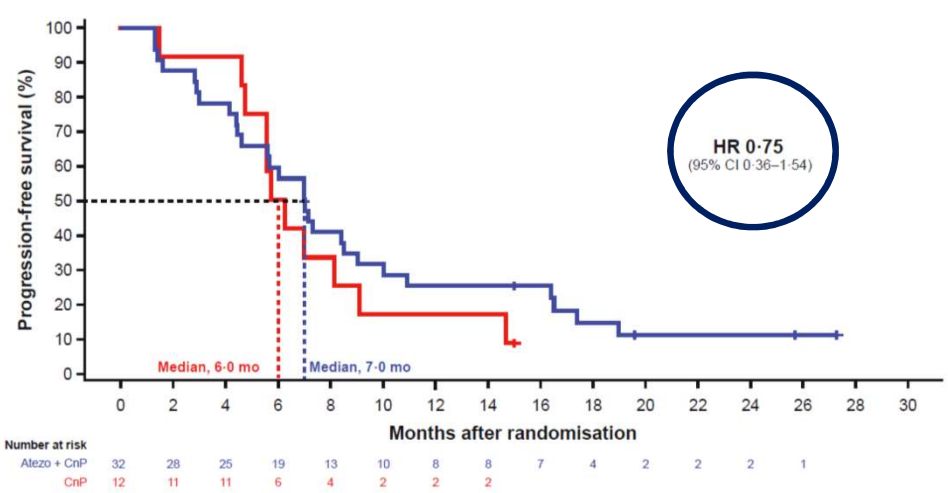
Outline –Strategies for Frontline Immunotherapy

- Single agent immunotherapy
- Combination chemo-immunotherapy
- Combination immunotherapy
- Bonus
  - *EGFR*
  - Duration of Treatment

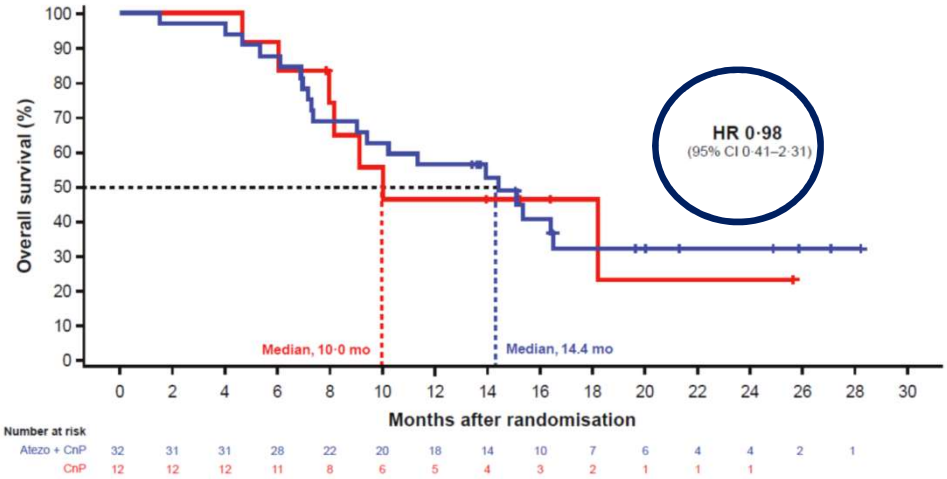
What is known about frontline chemo-IO in *EGFR* mutated NSCLC?

IMpower130 – no effect but small sample size

PFS HR 0.75 (95% CI 0.36-1.54)



OS HR 0.98 (95% CI 0.41-2.31)



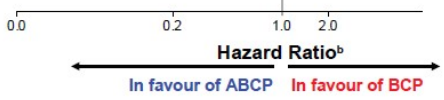
West H et al. Lancet Oncol. 2019 Jul;20(7):924-937.

What is known about frontline chemo-IO in *EGFR* mutated NSCLC?
Synergy for Bev-Atezo IMpower150

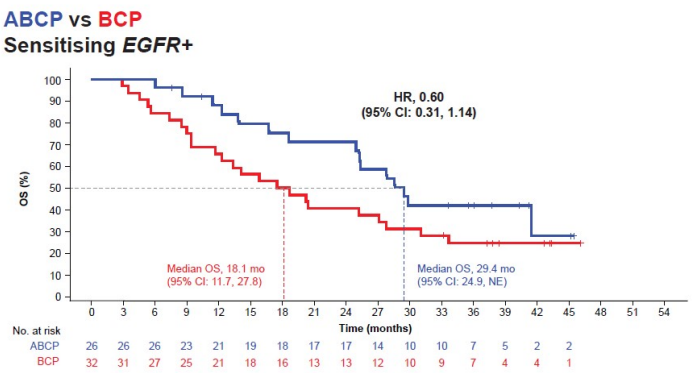
PFS

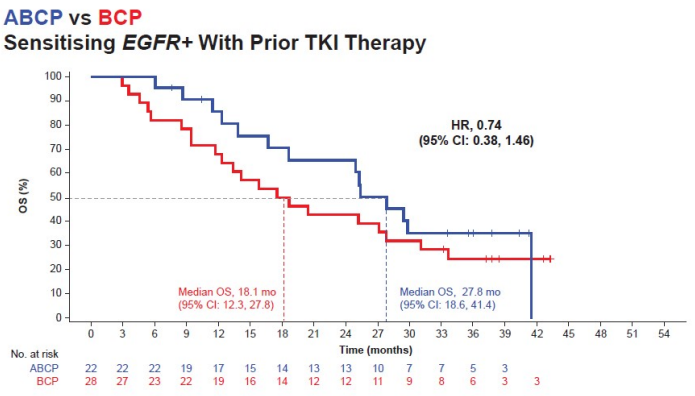
ABCP vs BCP

Subgroup	n	HR (95% CI)	Median PFS, months ABCP	BCP
EGFR mutation	78	0.56 (0.34, 0.91)	10.2	7.1
Sensitising *EGFR* mutation[a]	58	0.38 (0.21, 0.68)	10.3	6.1
Received prior TKI therapy	50	0.39 (0.20, 0.74)	9.7	6.1



OS





EGFR OS HR 0.91 95% CI 0.53-1.59

Additional f/u 20 months; post-progression therapies → BCP arm 79.1%, ABCP 45.5%, ACP 70.5%

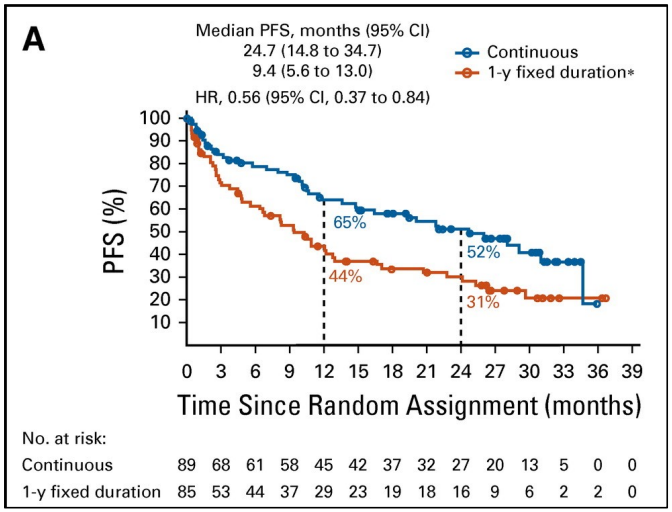
Reck et al. ESMO 2020.

Duration of first line immunotherapy treatment in NSCLC unknown

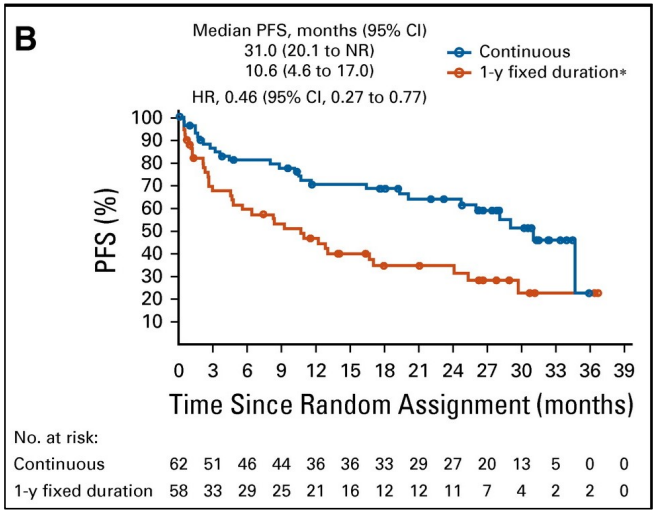
Trial	Duration
KEYNOTE-189 (non-squamous)	Pembrolizumab for up to a total of **35 cycles (2 years)**
KEYNOTE-407 (squamous)	Pembrolizumab for up to a total of **35 cycles (2 years)**
IMpower130 (non-squamous)	Atezolizumab until investigator-assessed loss of clinical benefit or toxicity **(no pre-defined limit)**
IMpower110 (all NSCLC)	Atezolizumab until investigator-assessed loss of clinical benefit **(no pre-defined limit)**
KEYNOTE-024 (all NSCLC)	Pembrolizumab for up to a total of **35 cycles (2 years)**
KEYNOTE-042 (all NSCLC)	Pembrolizumab for up to a total of **35 cycles (2 years)**
CheckMate 227 (all NSCLC)	Nivolumab/ipilimumab for **up to 2 years**
CheckMate 9LA (all NSCLC)	Nivolumab/ipilimumab for **up to 2 years**

Continuous 2nd line nivolumab improves PFS (and OS), especially in responders (*CM-153*)

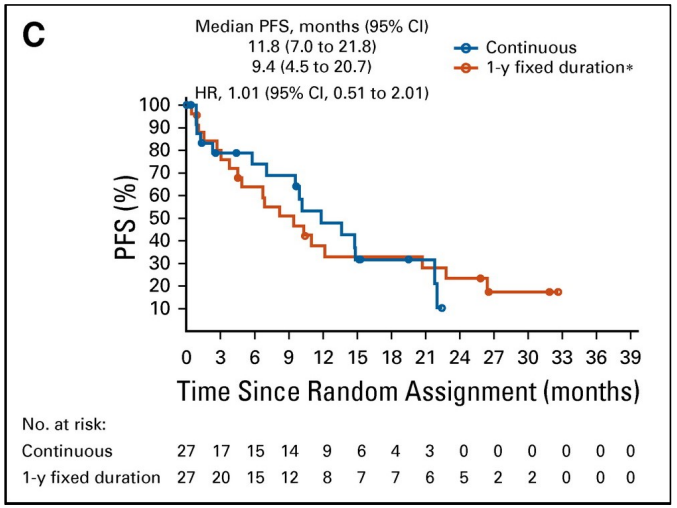
Overall



CR/PR

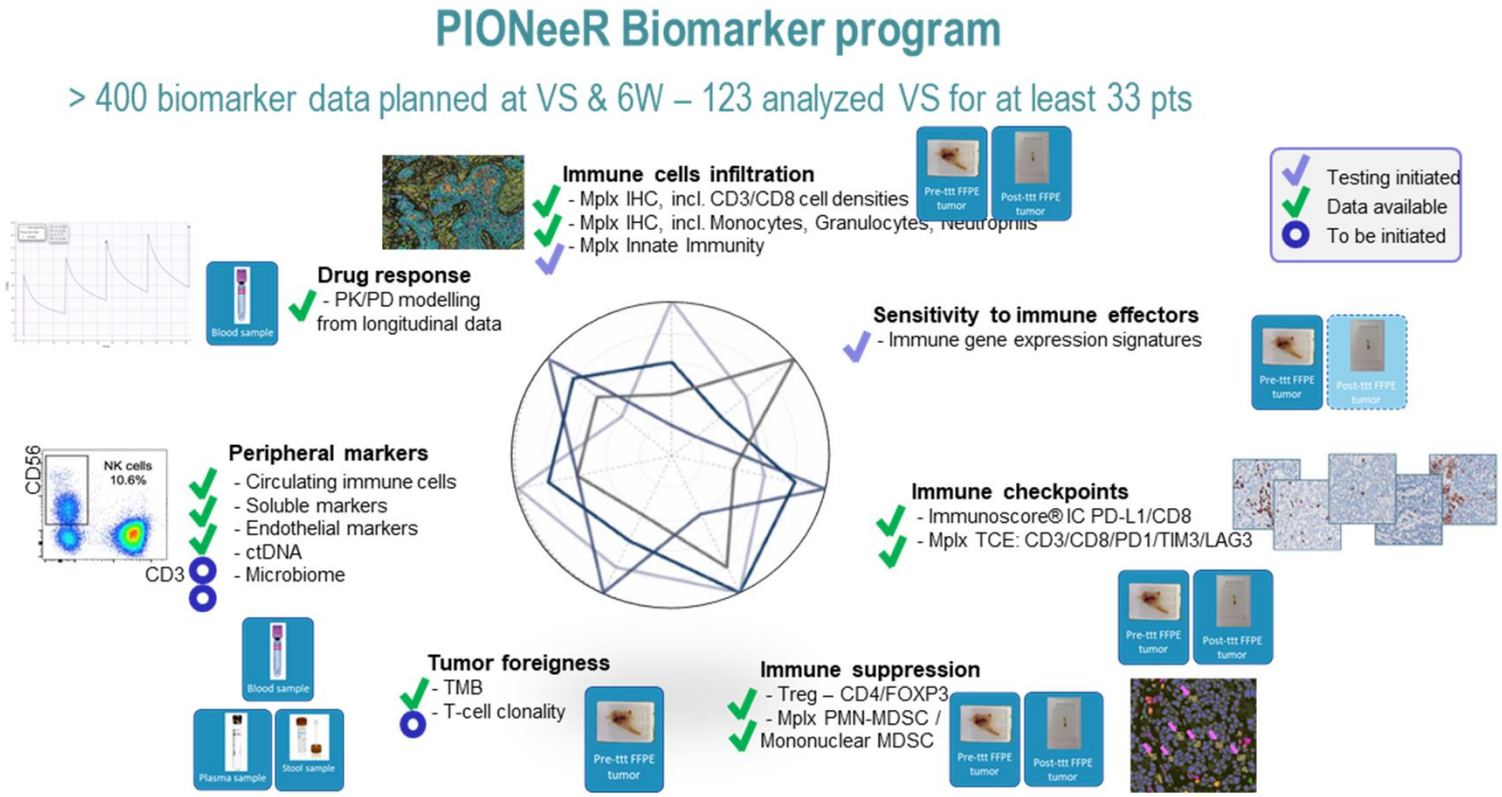


SD



Waterhouse DM et al. J Clin Oncol. 2020 Sep 10:JCO2000131.

Will more biomarkers & computational modeling be necessary for more nuanced selection for immunotherapy in the future?



Barlesi F et al. LBA53. ESMO 2020.