Immunotherapy for Advanced Non-Small Cell Lung Cancer

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Disclosures

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The speaker will directly disclose the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

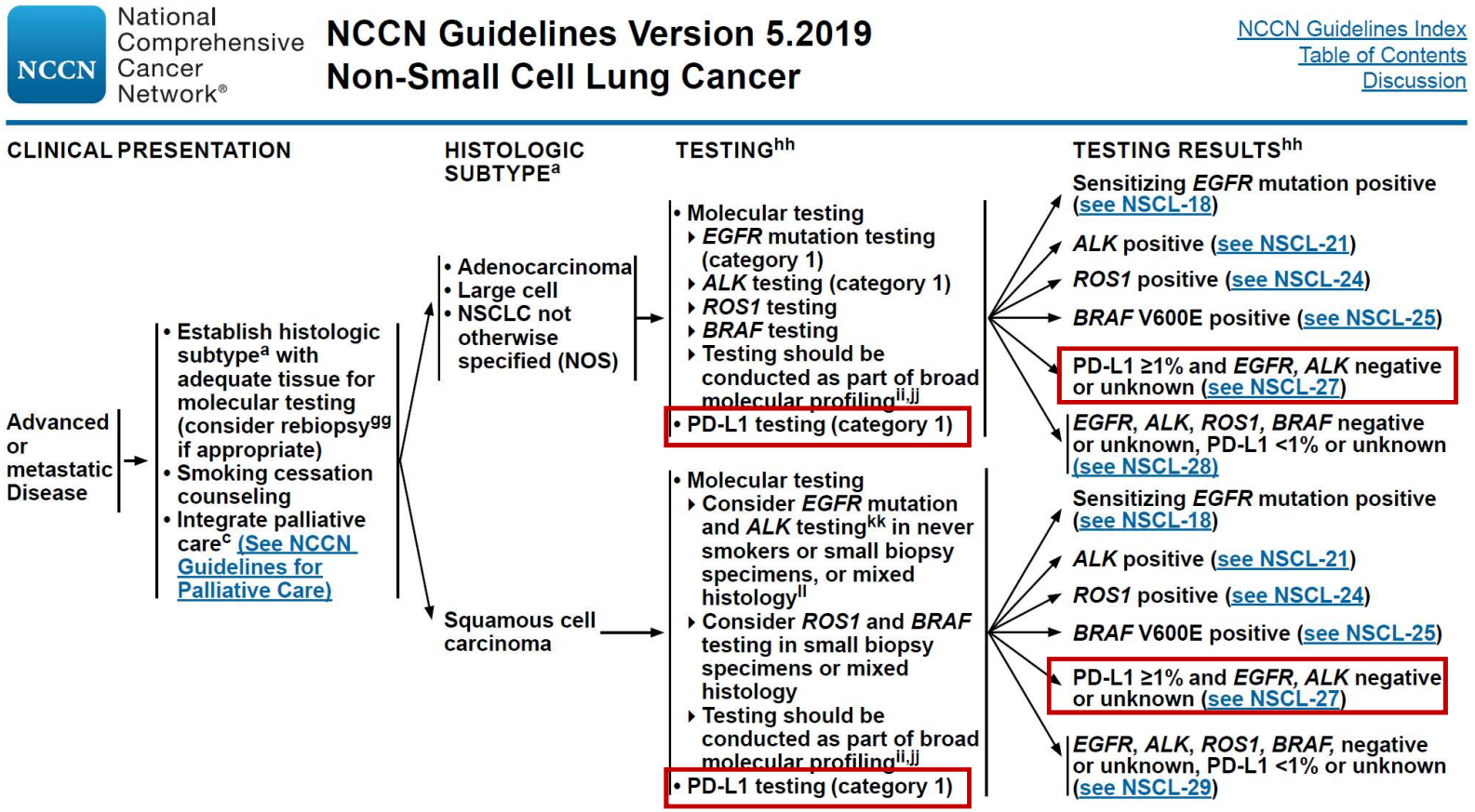
Objectives

- Current use of Immunotherapy in advanced NSCLC
- Role of 2L+ Immunotherapy
- Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy
- Biomarkers (and combination immunotherapy)
- Problem Areas

Objectives

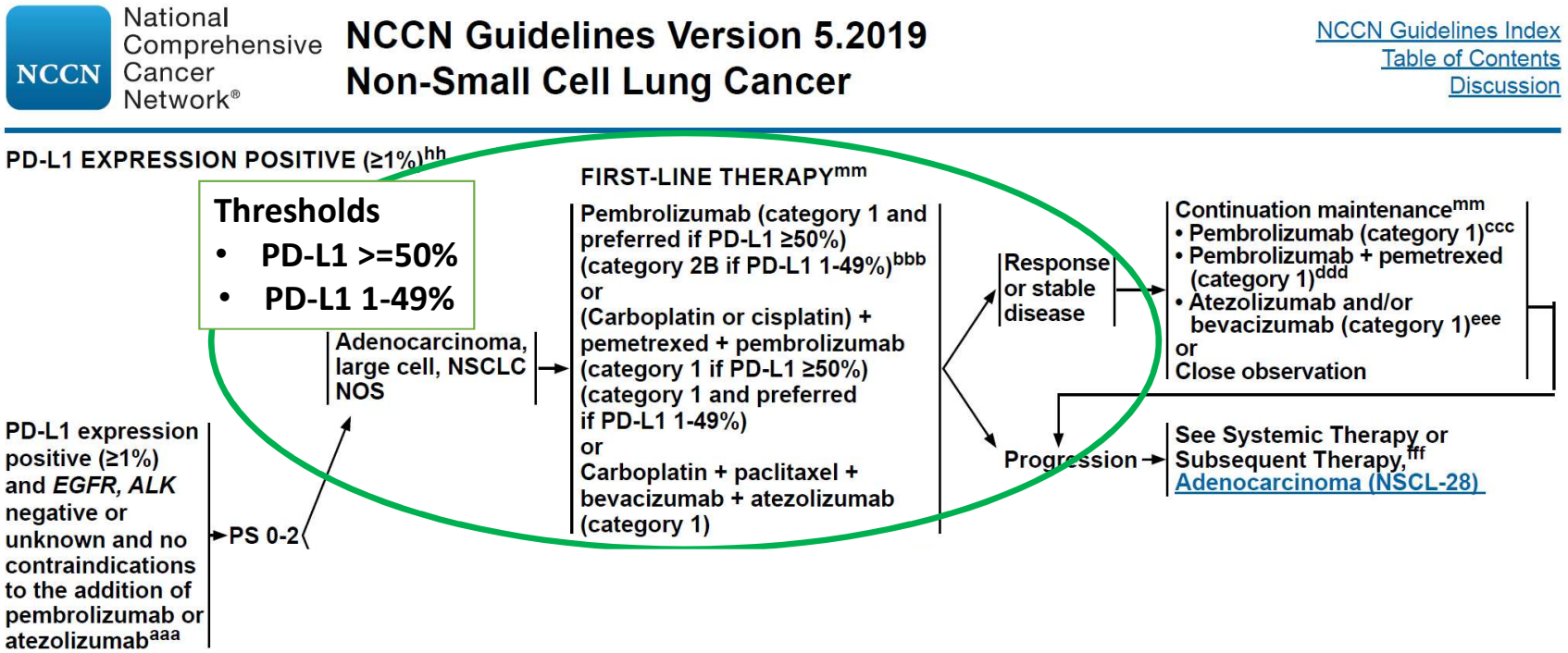
- **Current use of Immunotherapy in advanced NSCLC**
  - **Overview of NCCN guidelines**
- Role of 2L+ Immunotherapy
- Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy
- Biomarkers (and combination immunotherapy)
- Problem Areas

PD-L1 (IHC) is a critical upfront biomarker in NSCLC



NCCN v 5.2019

NSCLC adenocarcinoma PD-L1>=1%, *EGFR/ALK* WT



NCCN v 5.2019

NSCLC squamous cell PD-L1>=1%, *EGFR/ALK* WT

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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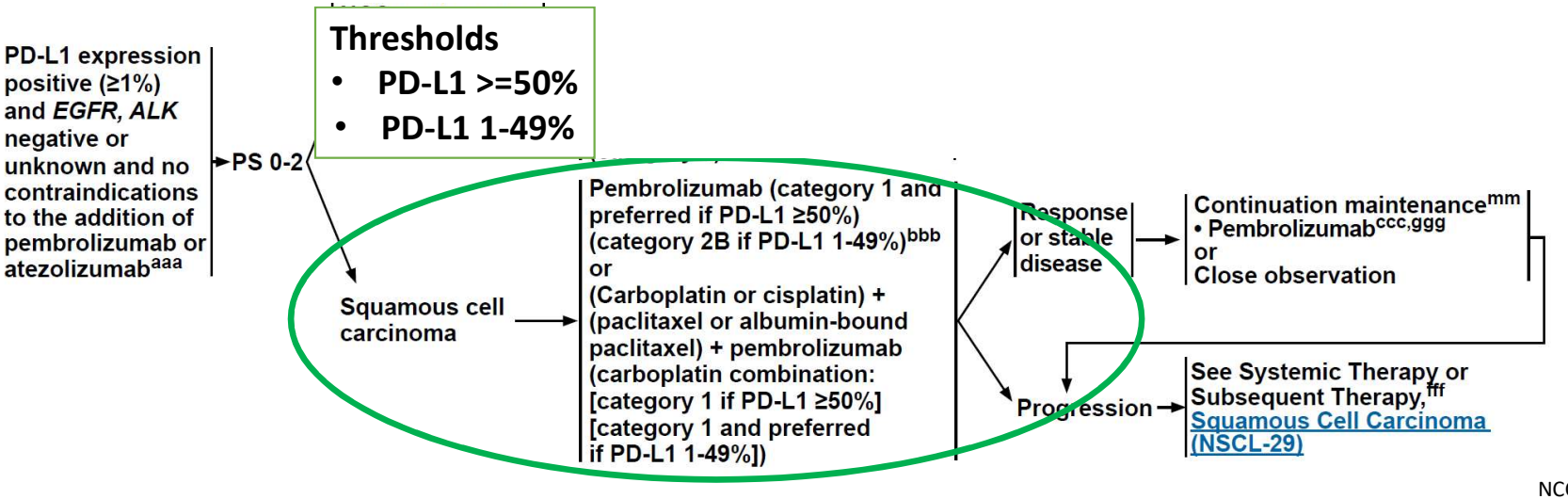
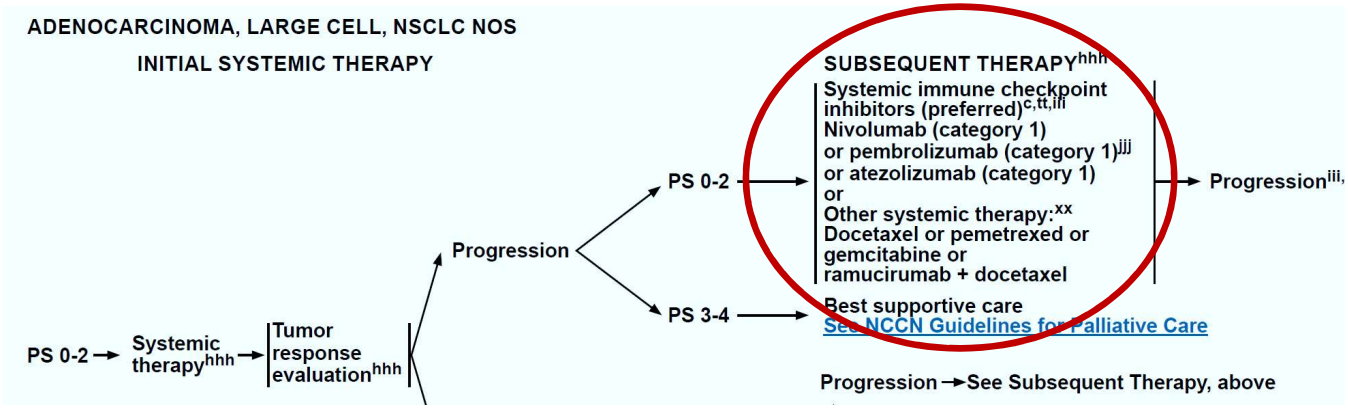
Discussion

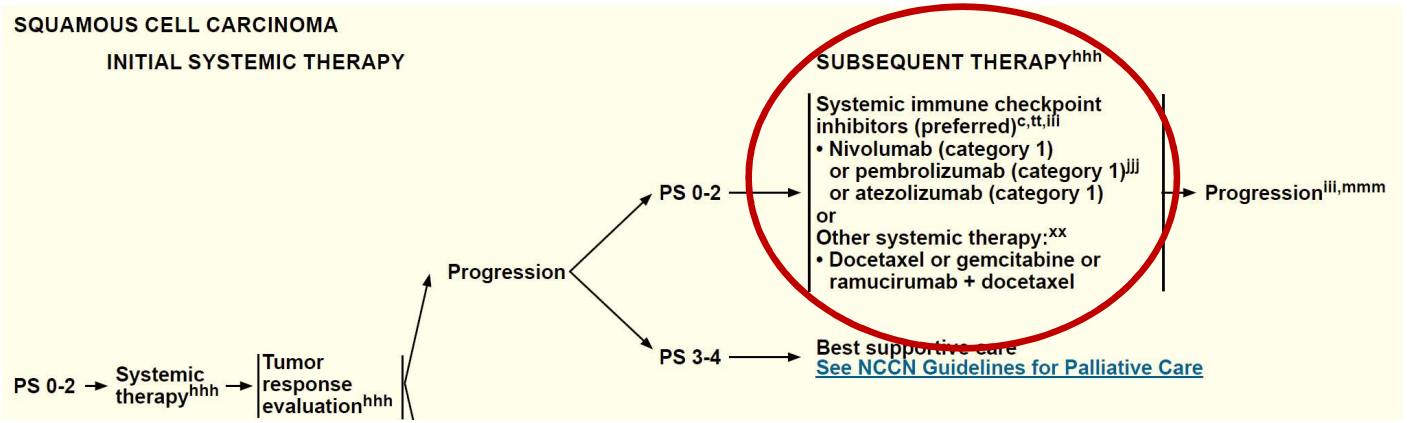
PD-L1 EXPRESSION POSITIVE (≥1%)[hh]



NCCN v 5.2019

NSCLC adenoca and squamous: 2L+ Immunotherapy (if not received in 1L setting)





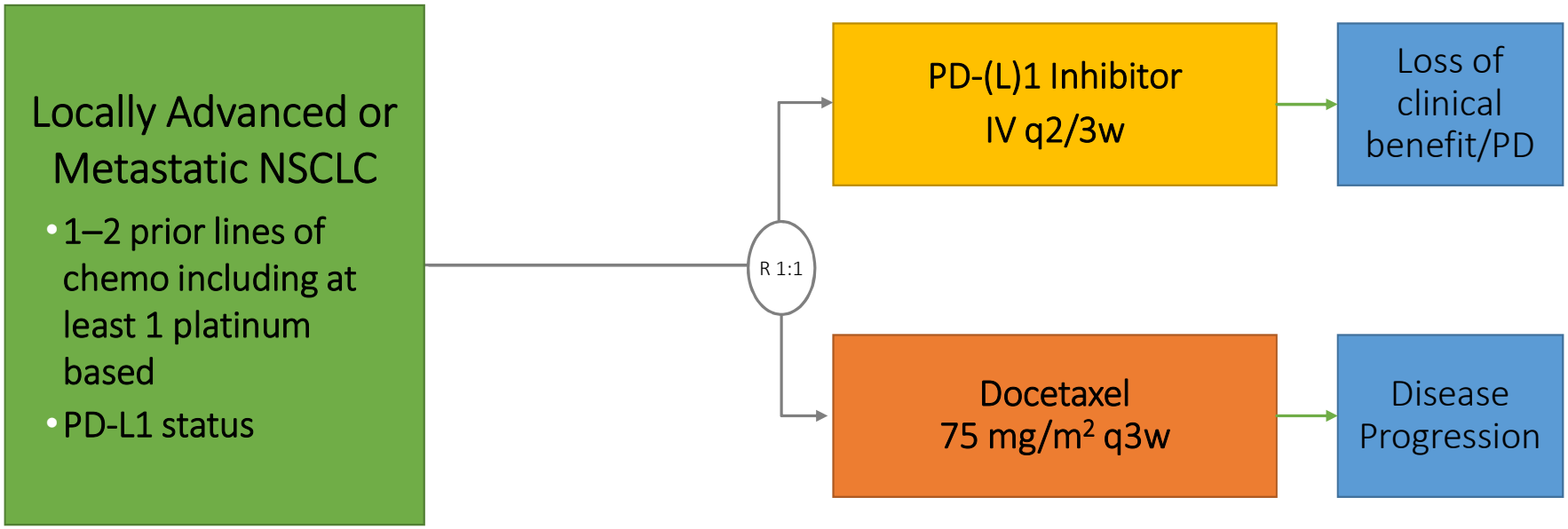
PD-L1 use only linked to pembrolizumab in 2L+ setting

NCCN v 5.2019

Objectives

- Current use of Immunotherapy in advanced NSCLC
- **Role of 2L+ Immunotherapy**
  - **Overview of major phase III randomized studies compared to docetaxel**
    - **Nivolumab: CM-017 (squamous) and CM-057 (non-squamous)**
    - **Pembrolizumab: KN-010**
    - **Atezolizumab: OAK**
- Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy
- Biomarkers (and combination immunotherapy)
- Problem Areas

PHASE III – 2ND LINE NSCLC PD-(L)1 VS. DOCETAXEL

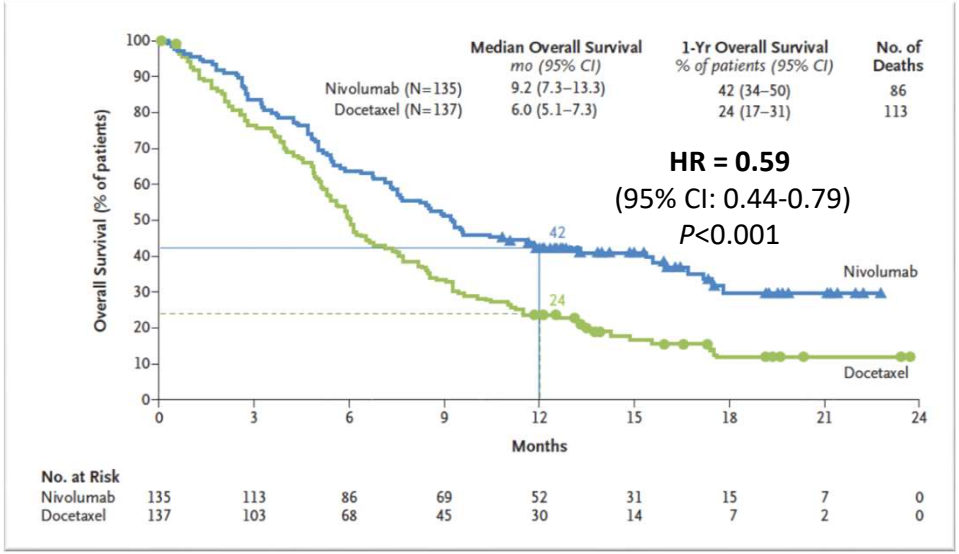


Primary Endpoints:

- OS in the ITT population
- OS in patients with PD-L1 expression
- Secondary Endpoints: ORR, PFS, DoR, Safety

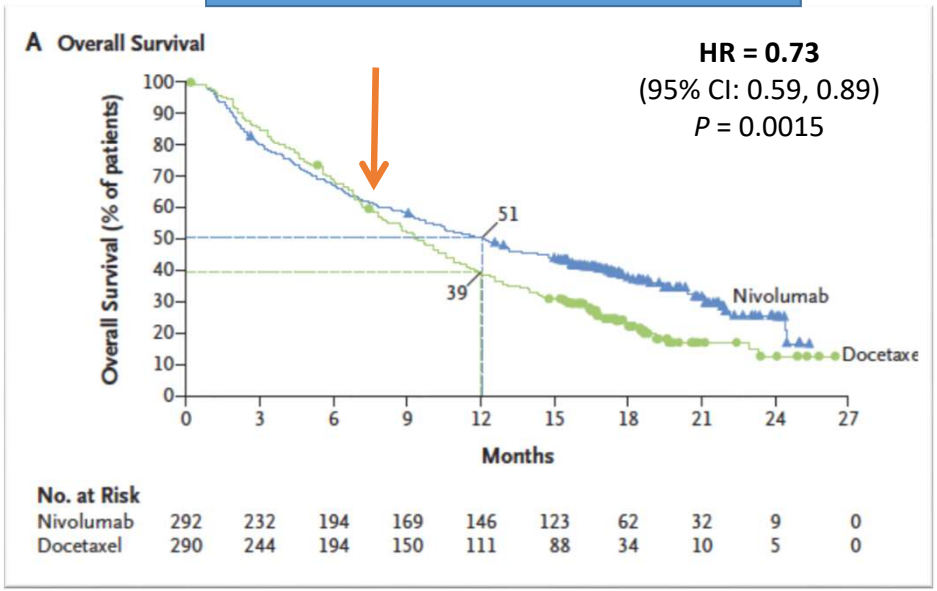
All second line immunotherapy studies showed an improvement in overall survival

CM-017
Nivolumab Squamous NSCLC



Brahmer. N Engl J Med. 2015 Jul 9;373(2):123-35.

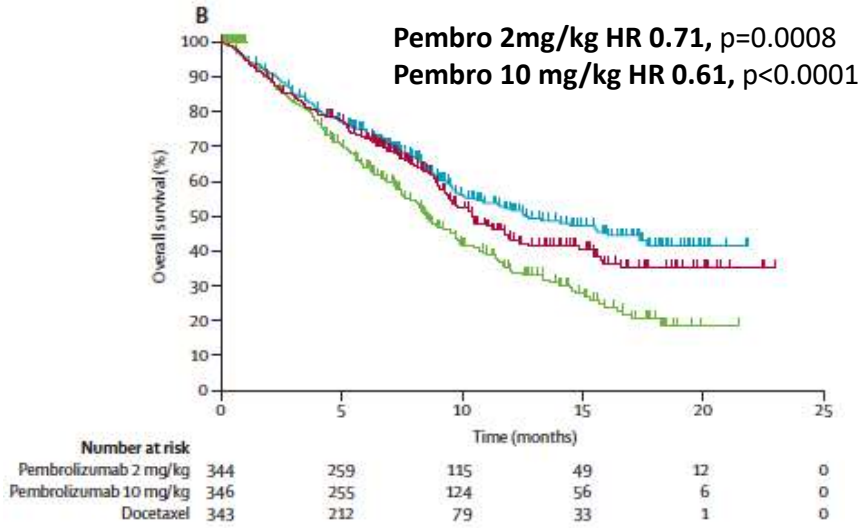
CM-057
Nivolumab Non- squamous NSCLC



Borghaei H. N Engl J Med. 2015 Oct 22;373(17):1627-39.

All second line immunotherapy studies showed an improvement in overall survival

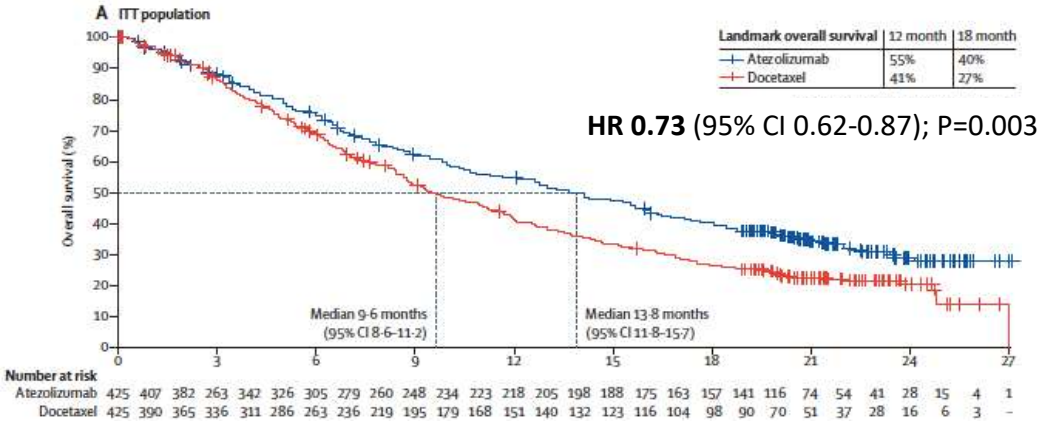
KN-010 (PD-L1 >=1%)
Pembrolizumab
Squamous and Non-squamous NSCLC



Pembro 2mg/kg HR 0.71, p=0.0008
Pembro 10 mg/kg HR 0.61, p<0.0001

Herbst et al. Lancet. 2016 Apr 9;387(10027):1540-50.

OAK (ITT)
Atezolizumab
Squamous and Non-squamous NSCLC



HR 0.73 (95% CI 0.62-0.87); P=0.003

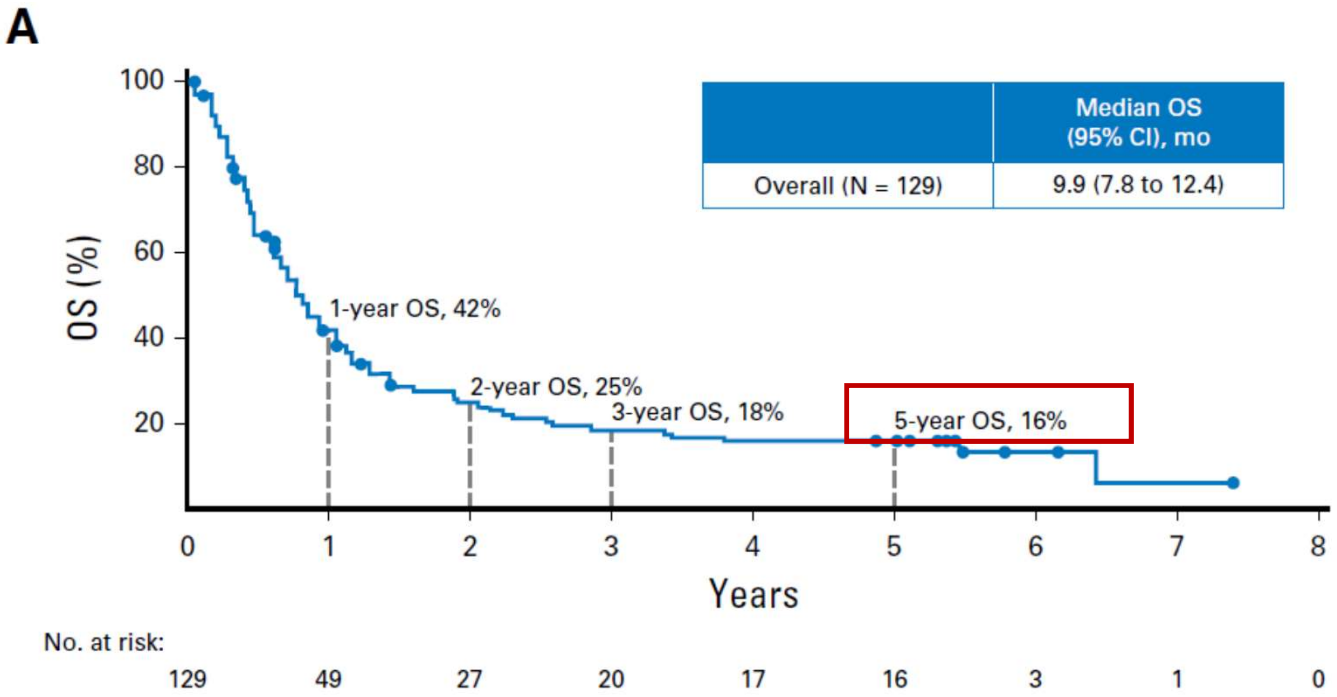
Rittmeyer et al. Lancet. 2017 Jan 21;389(10066):255-265.

Summary 2nd line Checkpoint Inhibitors in NSCLC

Trial	Primary Endpoint OS	median OS	1-year OS rate	mPFS	ORR	PD-L1+ matter?
Nivo: squam CM017	**HR = 0.59** (95% CI: 0.44,0.79)	9.2 vs 6.0 mo	42% vs 24%	3.5 vs. 2.8 mo	20% vs. 9% *P* = 0.008	NO
Nivo: non-sq CM057	**HR = 0.73** (95% CI: 0.59,0.89)	12.2 vs 9.4 mo	51% vs 39%	2.3 vs. 4.2 mo	19% vs.12% *P* = 0.025	**YES**
Pembro: KN010 TPS≥1%	**P2:HR = 0.71** (95% CI: 0.58,0.88) **P10:HR = 0.61** (95% CI 0.49,0.75)	10.4 (P2) vs 12.7 (P10) vs 8.5 mo (D)	43% vs 52% vs 35%	~4.0 mo all 3 groups	18% (P2) vs 18% (P10) vs 9% D; *P*=.0005	**YES**
Atezo: OAK	**HR = 0.73** (95% CI:0.62,0.87)	13.8 vs 9.6 mo	55% vs 41%	2.8 vs 4.0 mo	14% vs. 13% NS	**YES**

Long term-survival documented in 2L+ immunotherapy studies

Nivolumab CA209-003

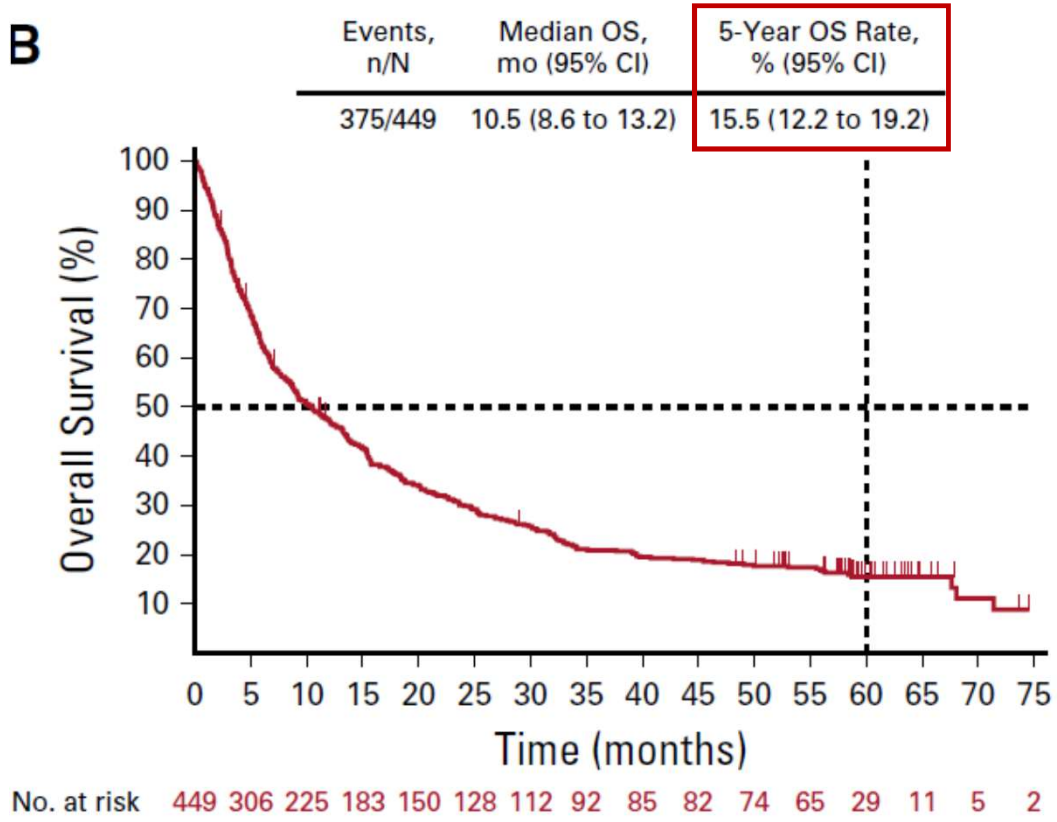


	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8 to 12.4)

Gettinger. J Clin Oncol. 2018 Jun 10;36(17):1675-1684.

Long term-survival documented in 2L+ immunotherapy studies

Pembrolizumab KEYNOTE-001



Garon E et al. J Clin Oncol. 2019 (Epub)

Conclusions 2L+ Immunotherapy

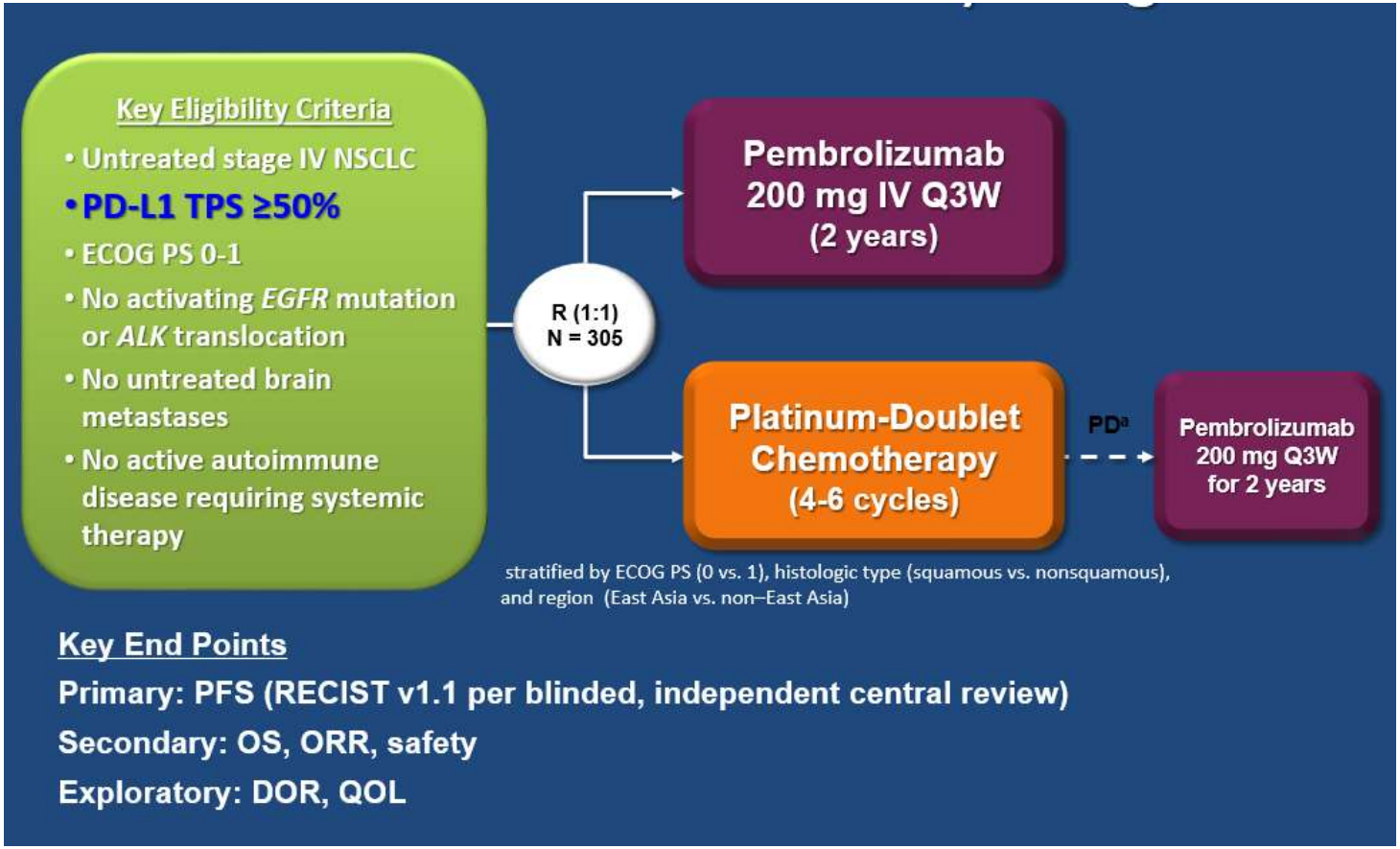
- All 2L+ immunotherapy studies showed an improvement in overall survival compared to docetaxel
- Long-term survivors observed with 2L+ immunotherapy
- Uncommonly used in 2L+ setting as immunotherapy has moved to the 1L setting

Objectives

- Current use of Immunotherapy in advanced NSCLC
- Role of 2L+ Immunotherapy
- **Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy**
  - **Immunotherapy single agent: Pembrolizumab KN-024 (>=50% PD-L1); KN-042 (>=1% PD-L1)**
  - **Chemo-immunotherapy: KN-189 nonsquamous (carbo/pemetrexed/pembro); KN-407 squamous (carbo/pac or nab-pac/pembro); IMPower150 (carbo/pac/atezo/bev)**
- Biomarkers (and combination immunotherapy)
- Problem Areas

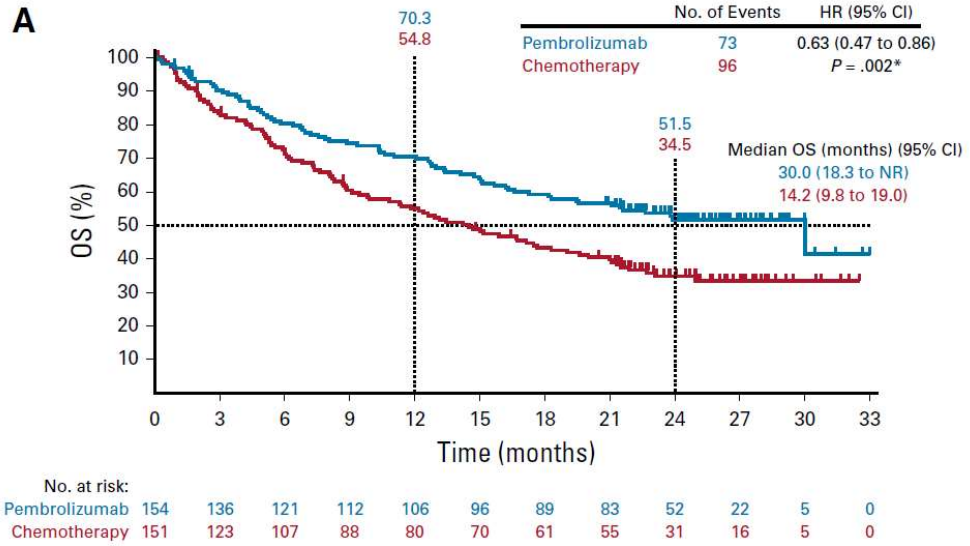
1L Pembrolizumab in PD-L1 high (>=50%), *EGFR/ALK* WT NSCLC

PH III KEYNOTE-024 Study

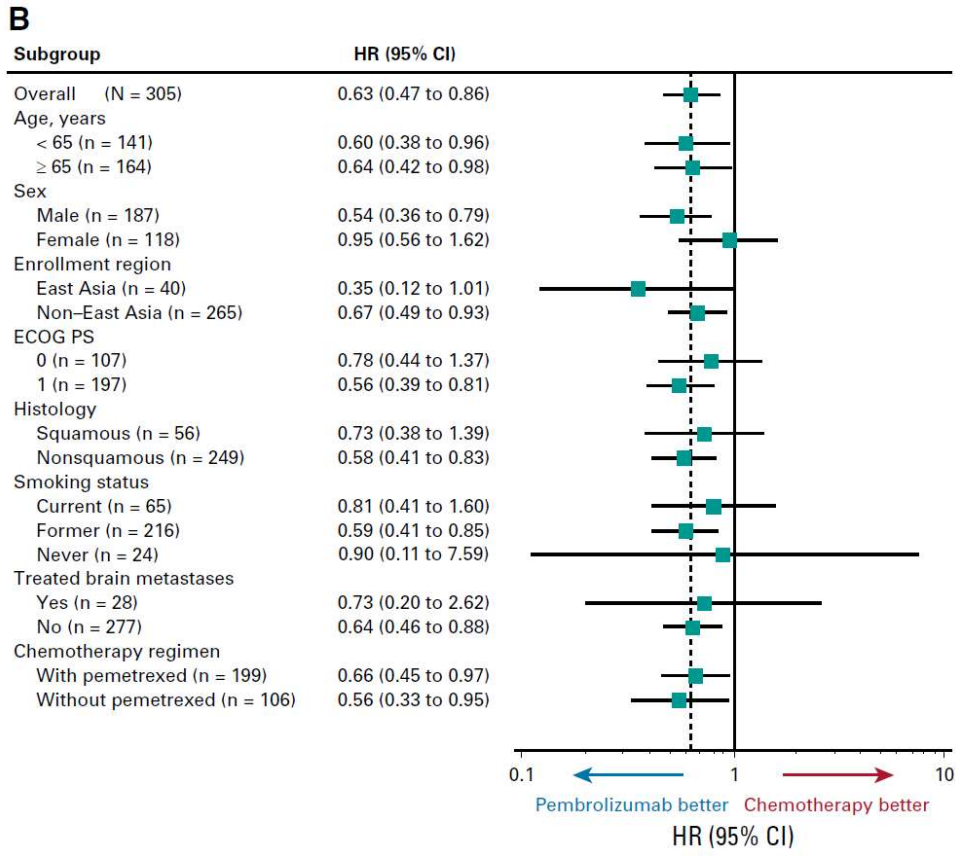


Reck M. N Engl J Med. 2016 Nov 10;375(19):1823-1833.

1L Pembrolizumab improves overall survival in PD-L1 high (>=50%), *EGFR/ALK* WT NSCLC



- **OS HR 0.63**; P=0.002
  - HR adjusted for crossover 0.49 (95% CI 0.34, 0.69)
- **PFS HR 0.50**; p <0.001
- **ORR** 44.6% vs. 27.8%

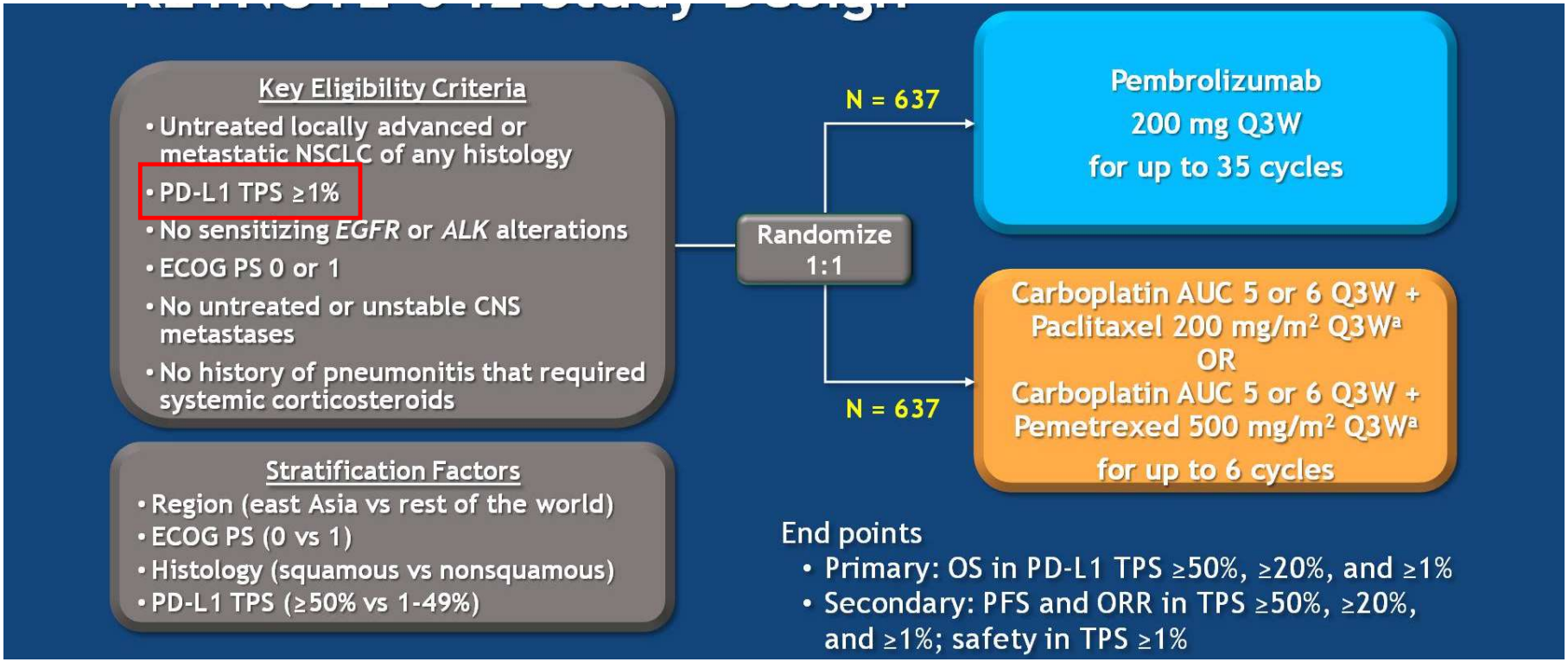


*median f/u 25.2 months

Reck M. N Engl J Med. 2016 Nov 10;375(19):1823-1833.

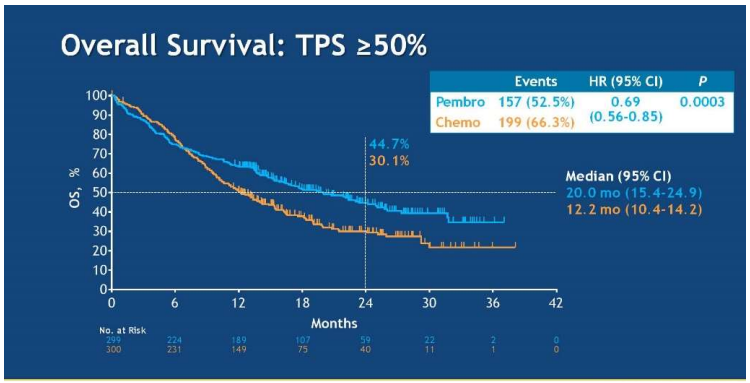
1L Pembrolizumab in PD-L1 positive (>=1%), *EGFR/ALK* WT NSCLC

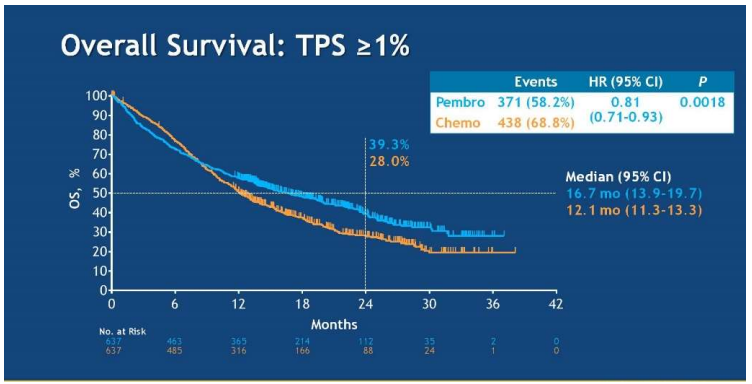
PH III KEYNOTE-024 Study

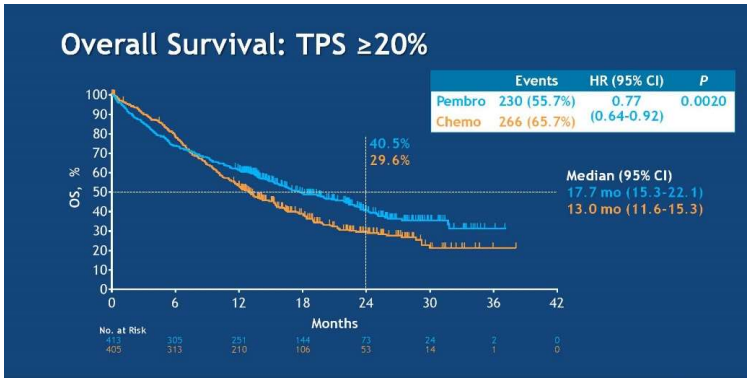


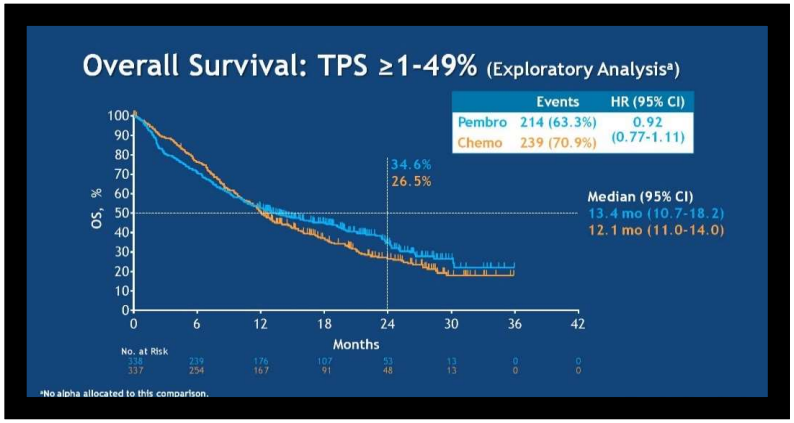
Mok. Lancet. 2019 May 4;393(10183):1819-1830.

Is 1L Pembrolizumab good enough in PD-L1 1-49%?





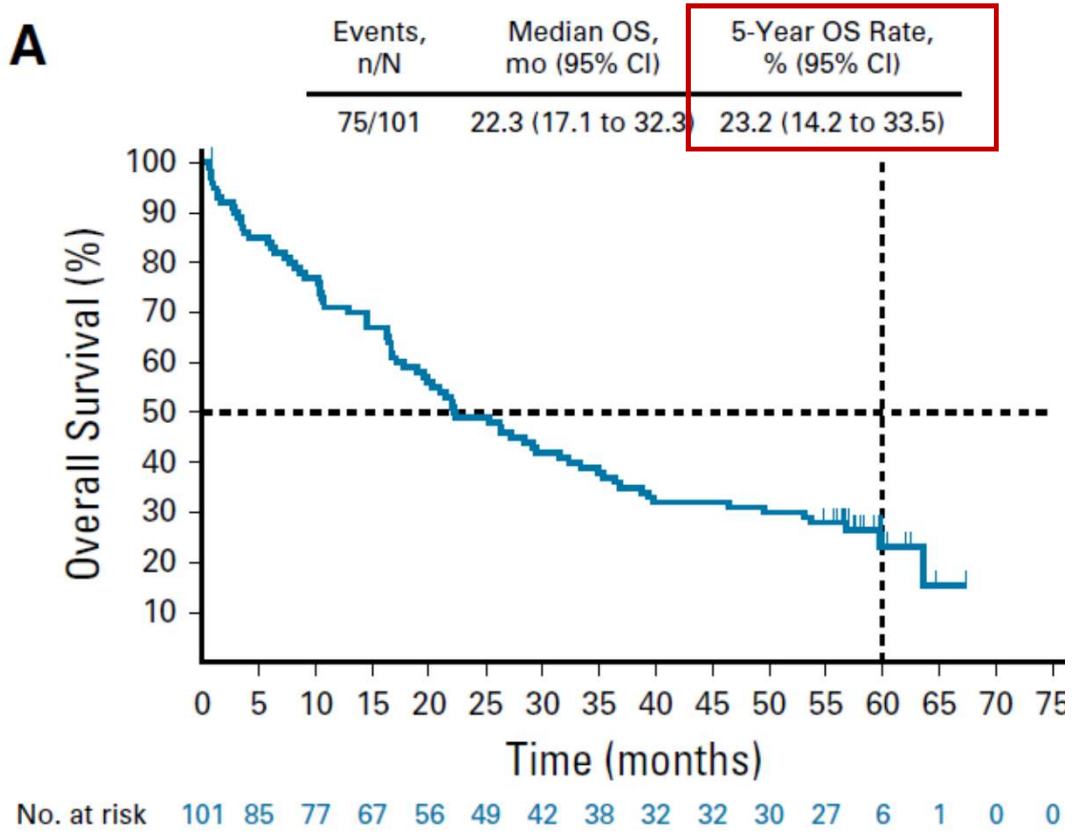




Mok. Lancet. 2019 May 4;393(10183):1819-1830.

Long term-survival documented in treatment-naïve NSCLC

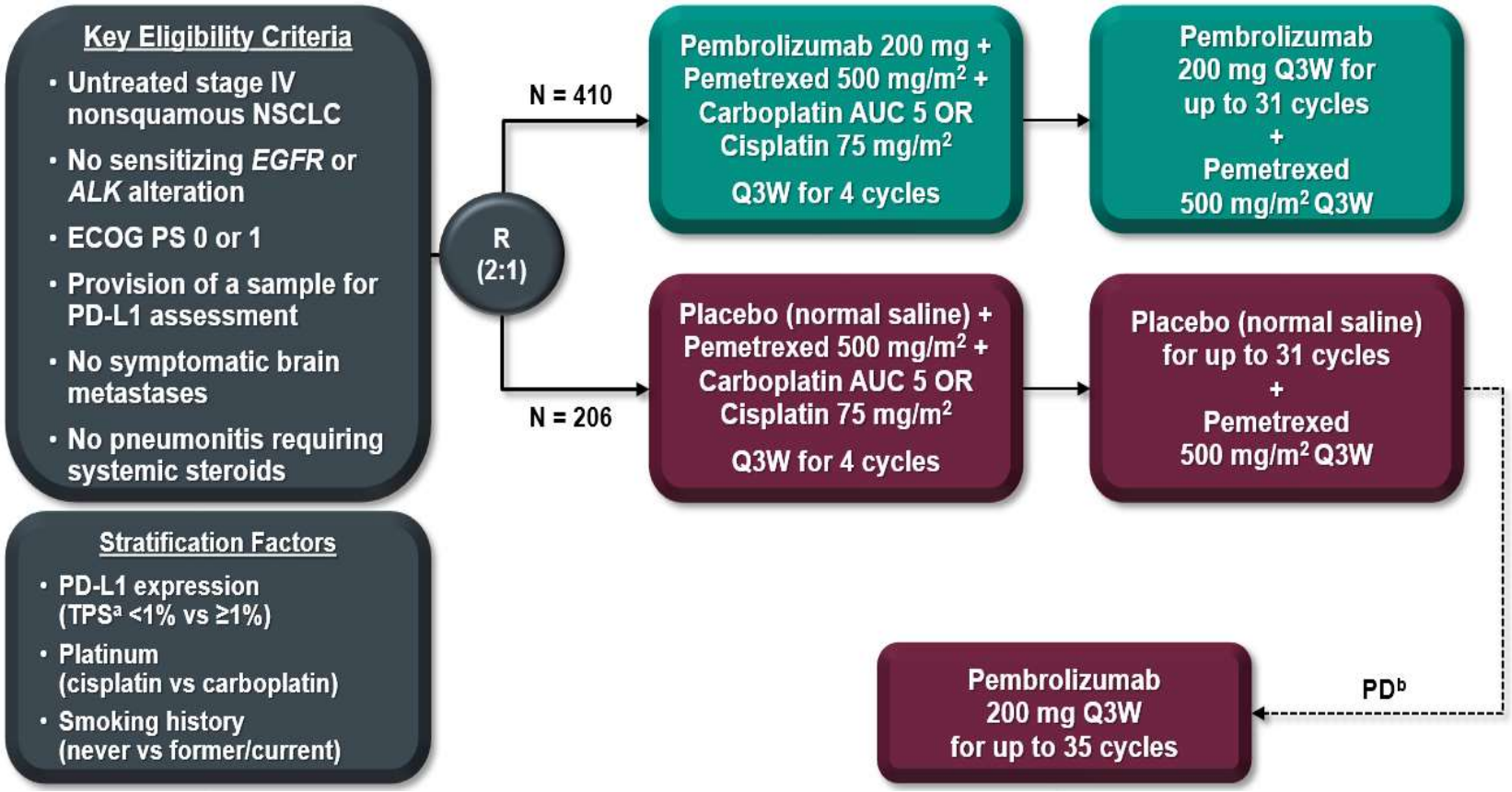
Pembrolizumab KEYNOTE-001



Garon E et al. J Clin Oncol. 2019 (Epub)

1L Pembrolizumab + Chemotherapy Non-squamous NSCLC

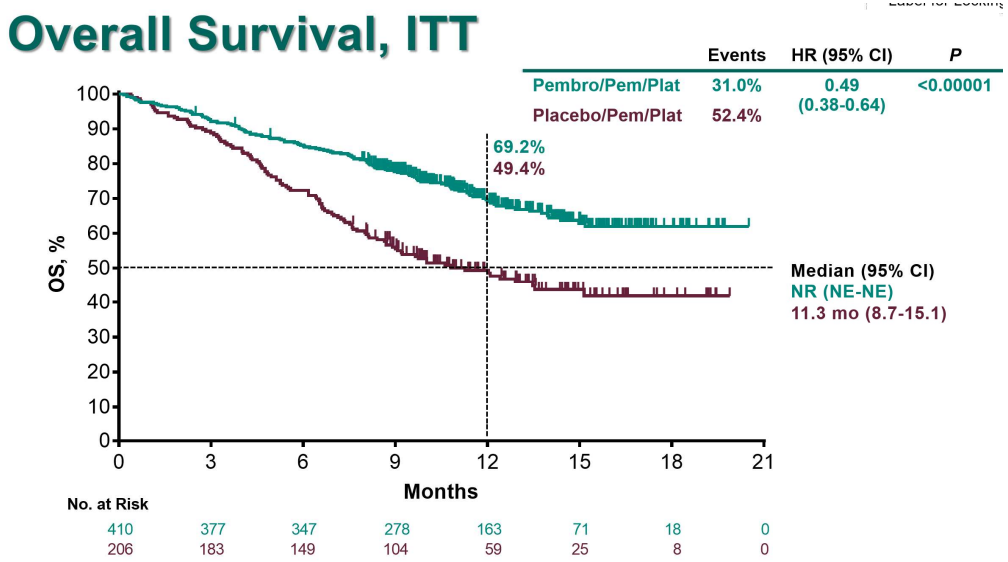
Ph III KEYNOTE-189 Study Design

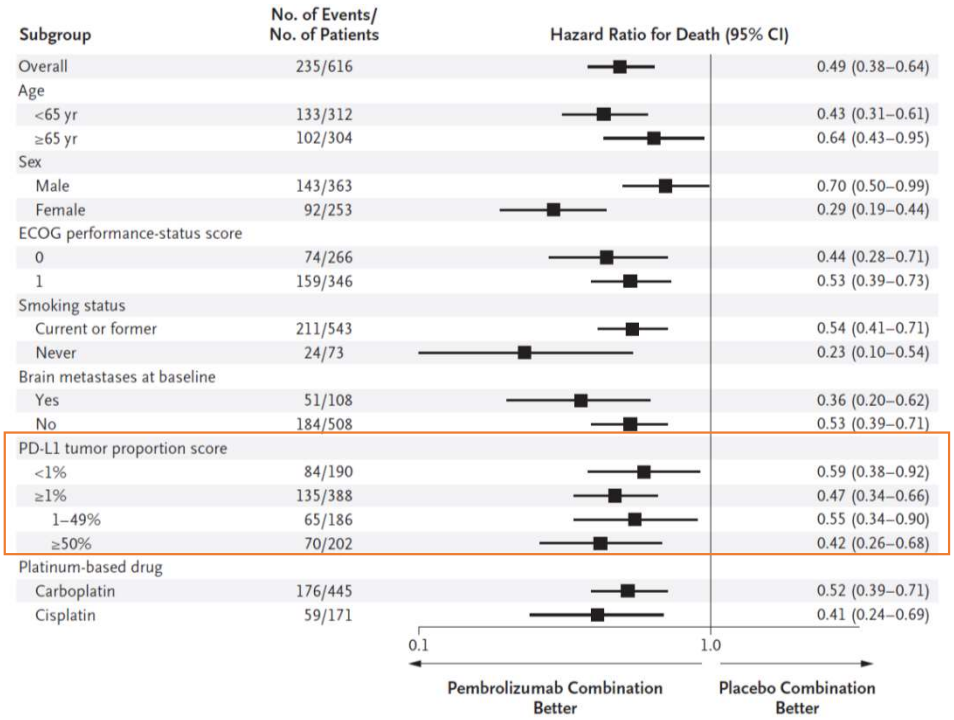


Gandhi L et al. N Engl J Med. 2018 May 31;378(22):2078-2092.

Platinum-pemetrexed +/- Pembrolizumab

KN189 Non-squamous NSCLC 1L (PD-L1 unselected)





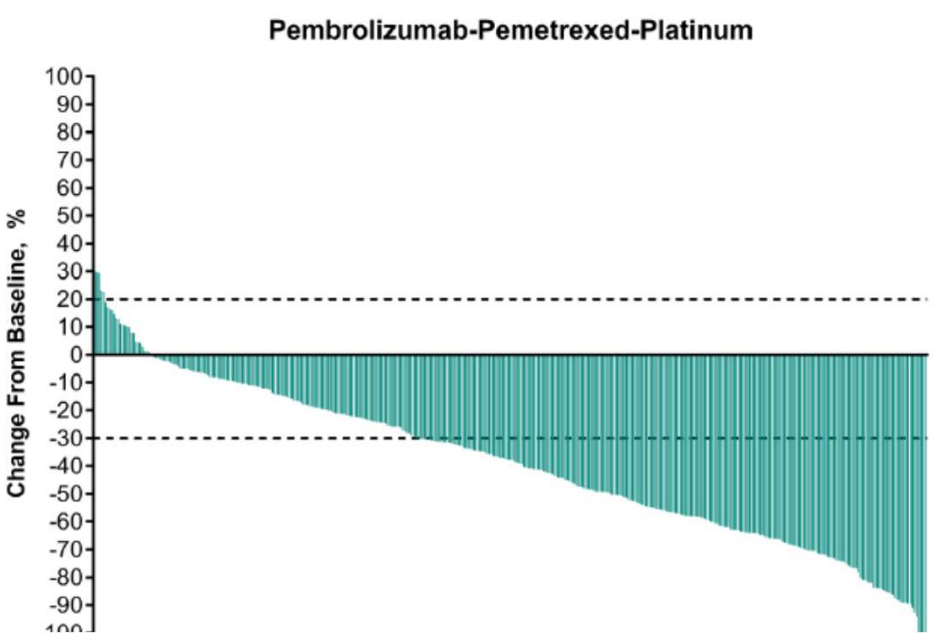
- **OS HR 0.49***; P<0.00001
- PFS HR 0.52; P<0.001
- ORR 47.6% vs. 18.9%

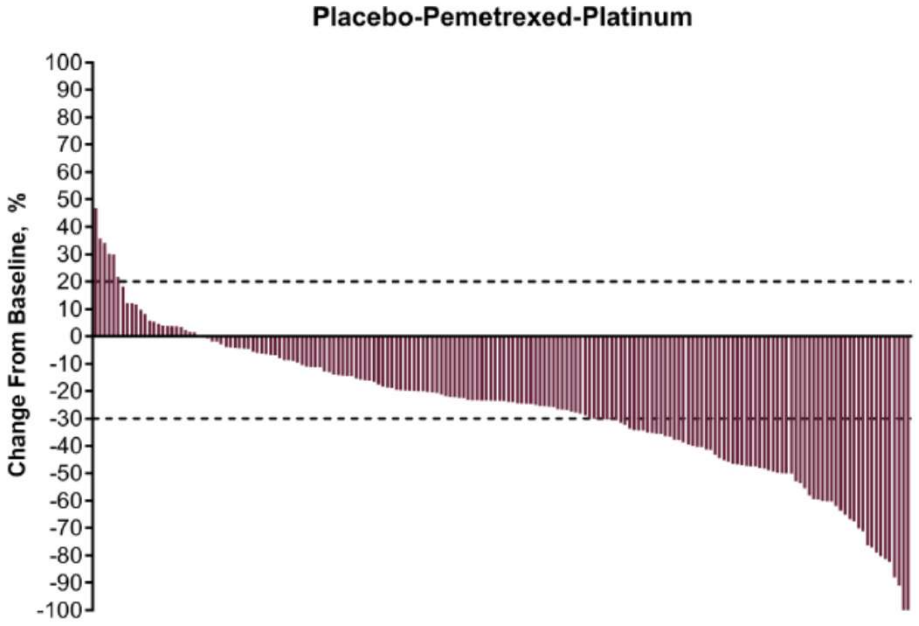
*median follow-up of 10.5 months; 1/3 cross-over

Gandhi L et al. N Engl J Med. 2018 May 31;378(22):2078-2092.

Platinum-pemetrexed +/- Pembrolizumab

KN189 Non-squamous NSCLC 1L (PD-L1 unselected)

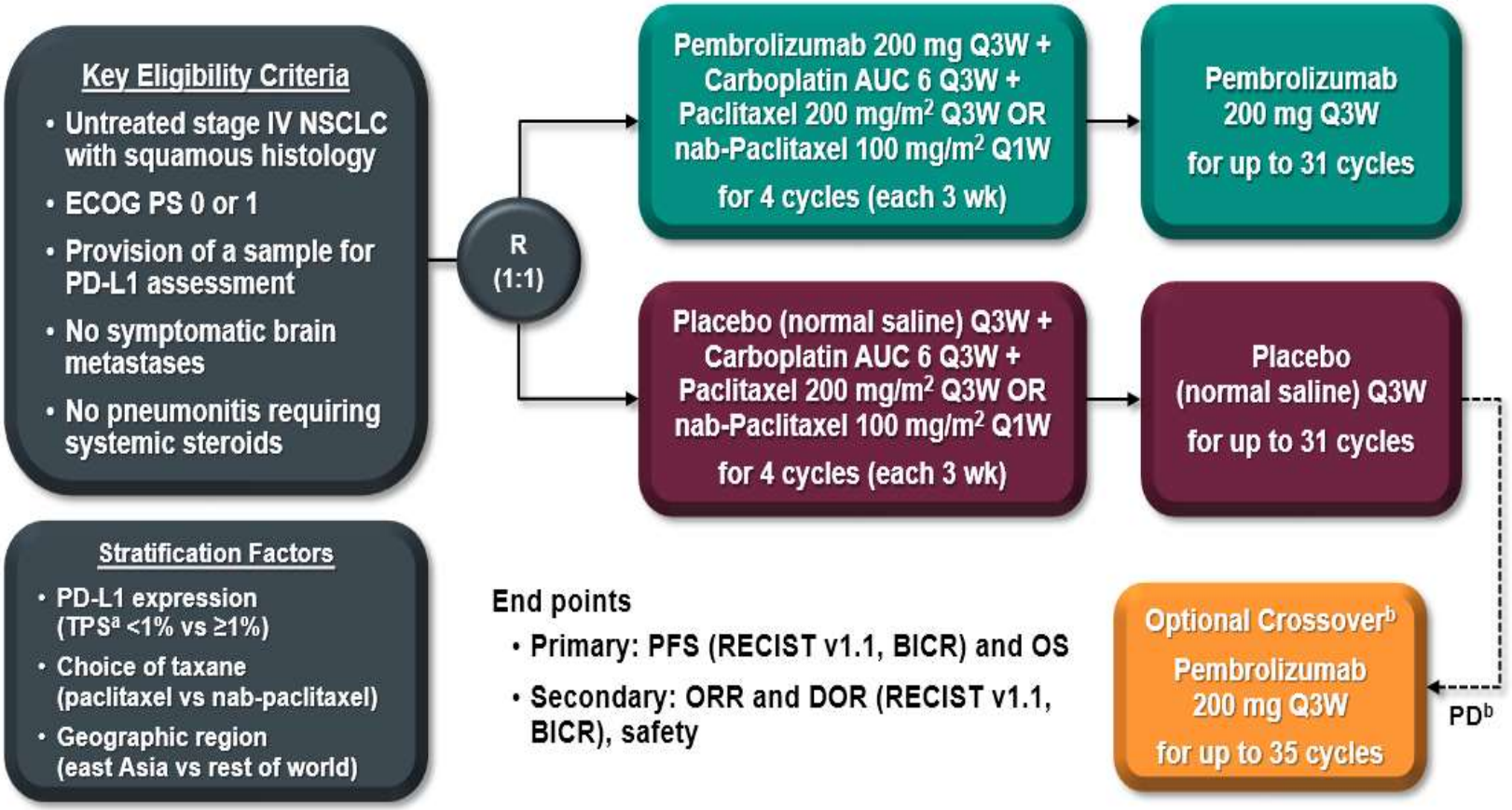




Gandhi L et al. N Engl J Med. 2018 May 31;378(22):2078-2092.

1L Carboplatin/taxane (pac/nab-pac) +/- Pembrolizumab Squamous NSCLC

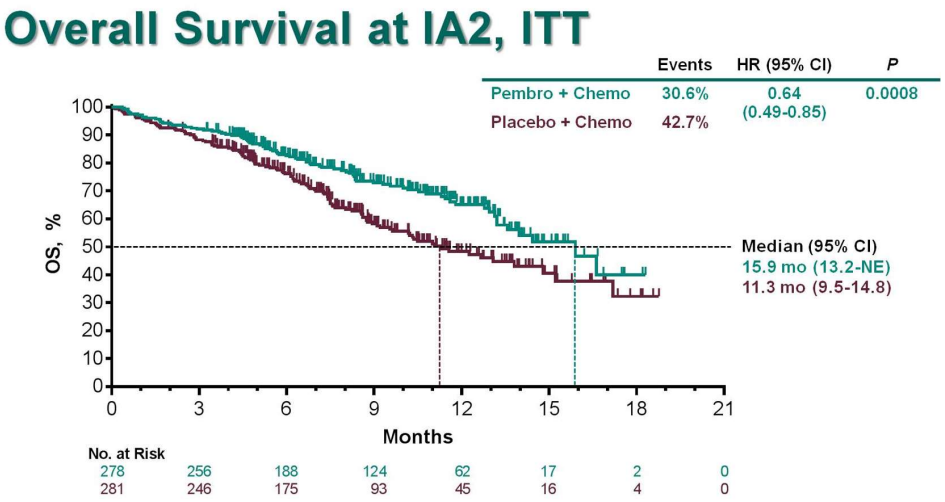
Ph III Keynote-407 Study Design



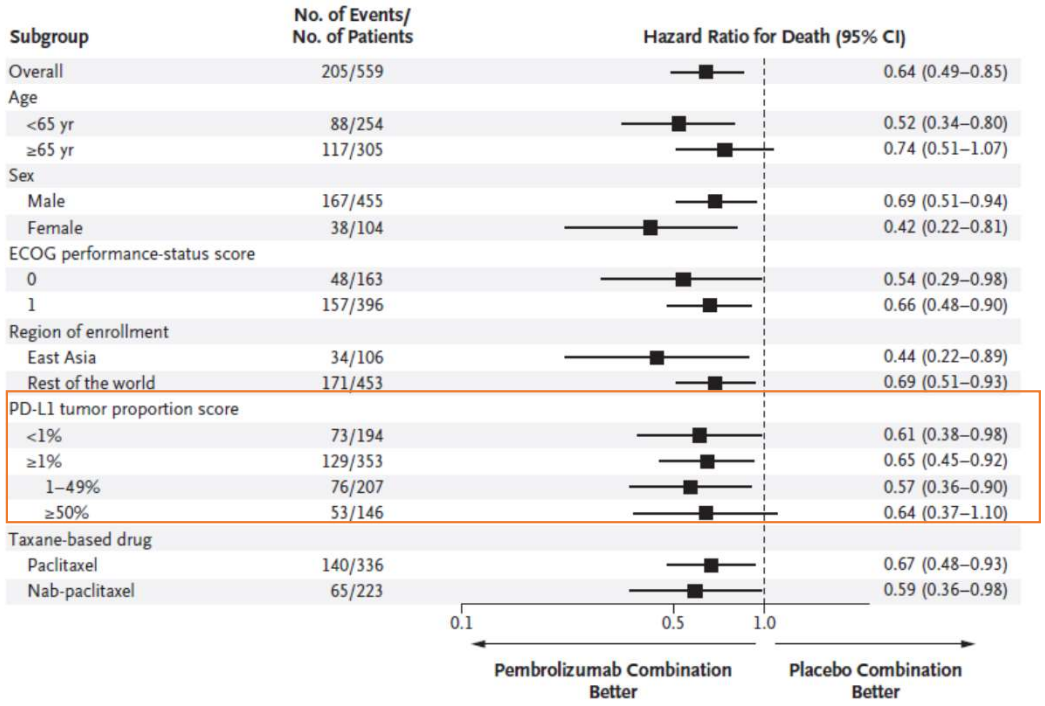
Paz-Ares et al. N Engl J Med. 2018 Nov 22;379(21):2040-2051.

Carboplatin/taxane (pac/nab-pac) +/- Pembrolizumab

KN407 Squamous NSCLC 1L (PD-L1 unselected)



- **OS HR 0.64***; p=0.0008
- PFS HR 0.56; p<0.0001
- ORR 58% vs. 38%

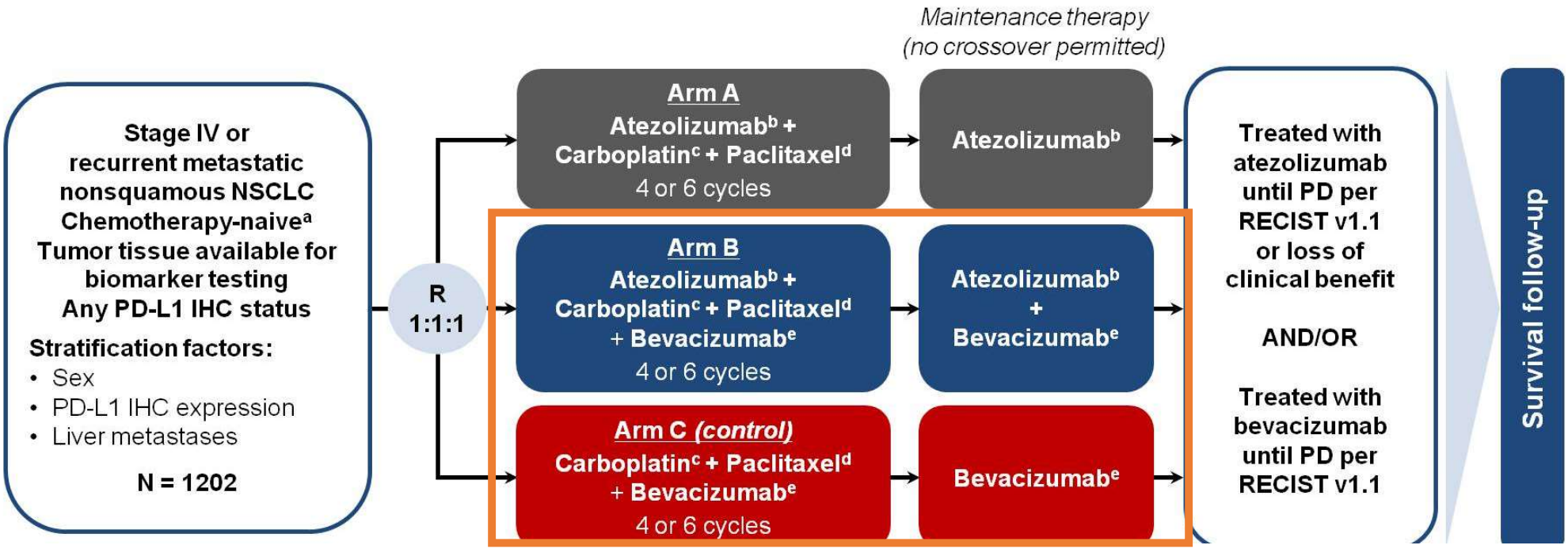


*median f/u 7.8 months; 27% crossover

Paz-Ares et al. N Engl J Med. 2018 Nov 22;379(21):2040-2051.

1L Chemo + Atezolizumab + Bevacizumab

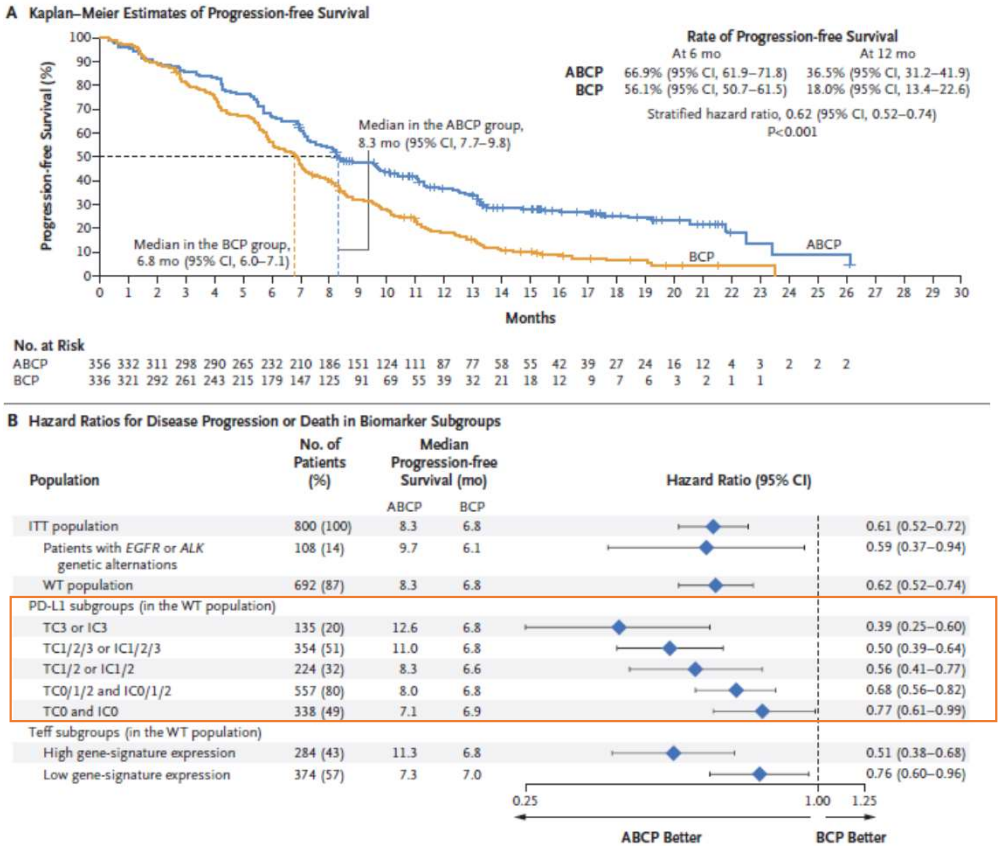
IMpower150 Non-squamous NSCLC 1L (PD-L1 unselected)



Socinski MA et al. N Engl J Med. 2018 Jun 14;378(24):2288-2301.

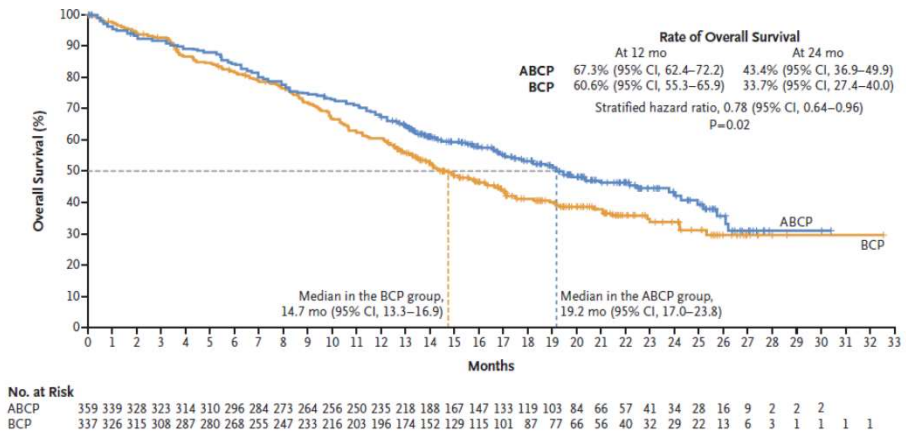
Chemo + Atezolizumab + Bevacizumab

IMpower150 Non-squamous NSCLC 1L (PD-L1 unselected)



PFS HR 0.62 (95% CI 0.52-0.74); median 8.3 mo vs. 6.8 mo

Interim OS HR 0.78 (95% CI 0.64-0.96); median 19.2 mo vs. 14.7 mo



Socinski MA et al. N Engl J Med. 2018 Jun 14;378(24):2288-2301.

Conclusions- 1L Immunotherapy vs. Chemo-Immunotherapy

- **Non-squamous NSCLC High PD-L1 >=50%; *EGFR/ALK*(-)**
  - Pembrolizumab monotherapy
  - Platinum-pemetrexed-pembrolizumab combination therapy, especially if high tumor burden, high symptom burden, good performance status, limited comorbidity
  - IMPower150 regimen also an option if bevacizumab eligible

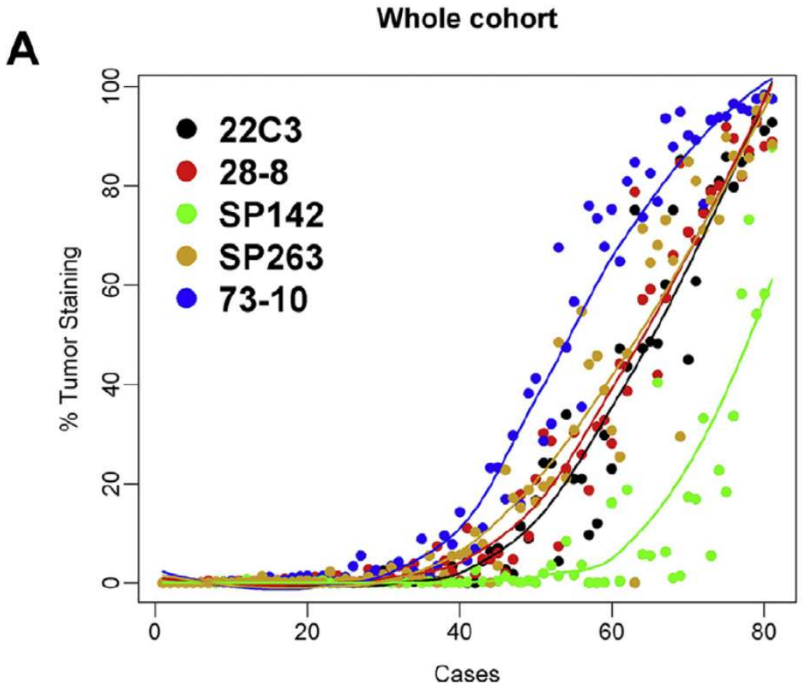
- **Squamous NSCLC High PD-L1 >=50%; *EGFR/ALK*(-)**
  - Pembrolizumab monotherapy
  - Platinum-(nab)paclitaxel-pembrolizumab combination therapy, especially if high tumor burden, high symptom burden, good performance status, limited comorbidity

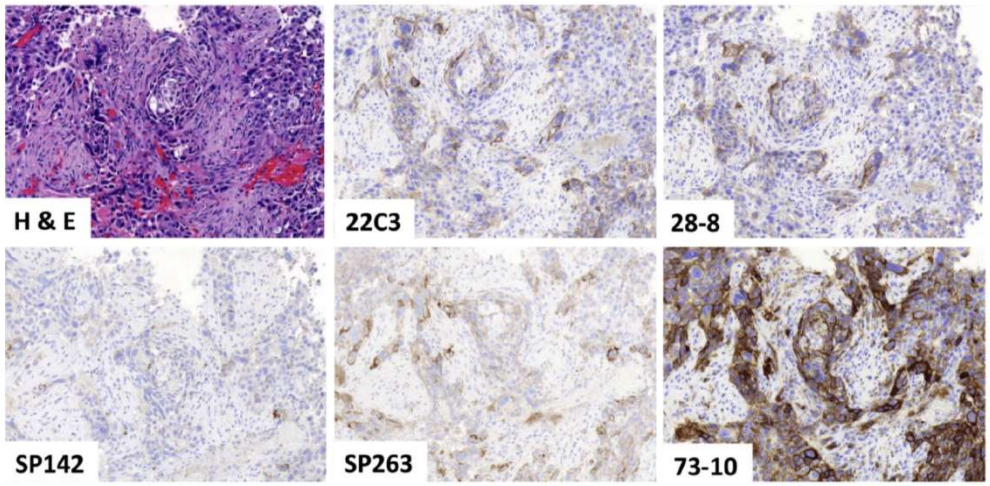
- **Non-squamous/squamous NSCLC PD-L1 0-49%, *EGFR/ALK*(-)**
  - Chemo-immunotherapy (preferred)
  - Immunotherapy PD-L1 1-49% if not a chemotherapy candidate but ? benefit

Objectives

- Current use of Immunotherapy in advanced NSCLC
- Role of 2L+ Immunotherapy
- Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy
- **Biomarkers (and combination immunotherapy)**
  - **PD-L1 (IHC)- premier biomarker for the moment…**
  - **Tumor mutation burden in context of PD-1/CTLA-4 inhibition (CheckMate-227 and MYSTIC)**
- Problem Areas

Blueprint Project PD-L1 IHC Assays- some differences



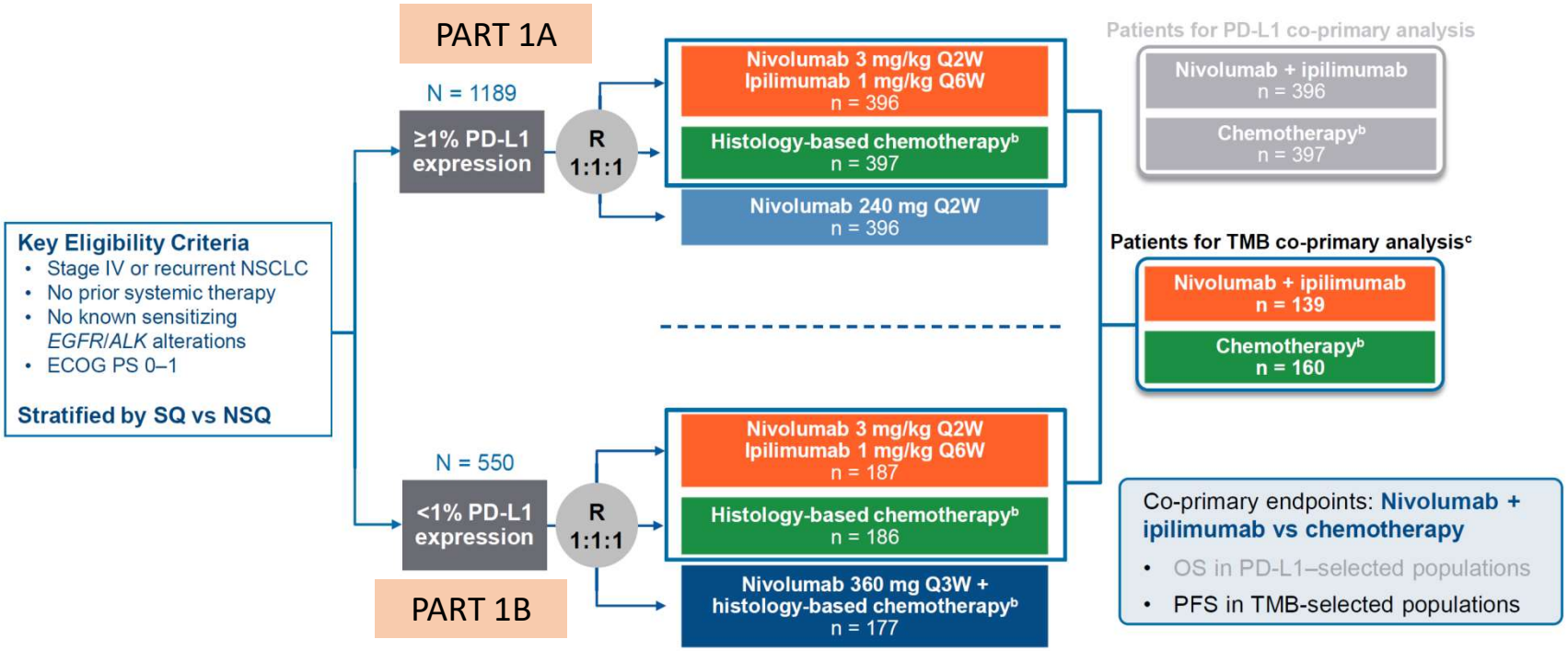


Tsao MS. J Thorac Oncol. 2018 Sep;13(9):1302-1311

Nivolumab + ipilimumab NSCLC

CM227 NSCLC 1L

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



Co-primary endpoints: OS in PD-L1–selected populations (Part 1A) and PFS in TMB-selected populations (Part 1A and 1B) treated with nivolumab + ipilimumab vs chemotherapy

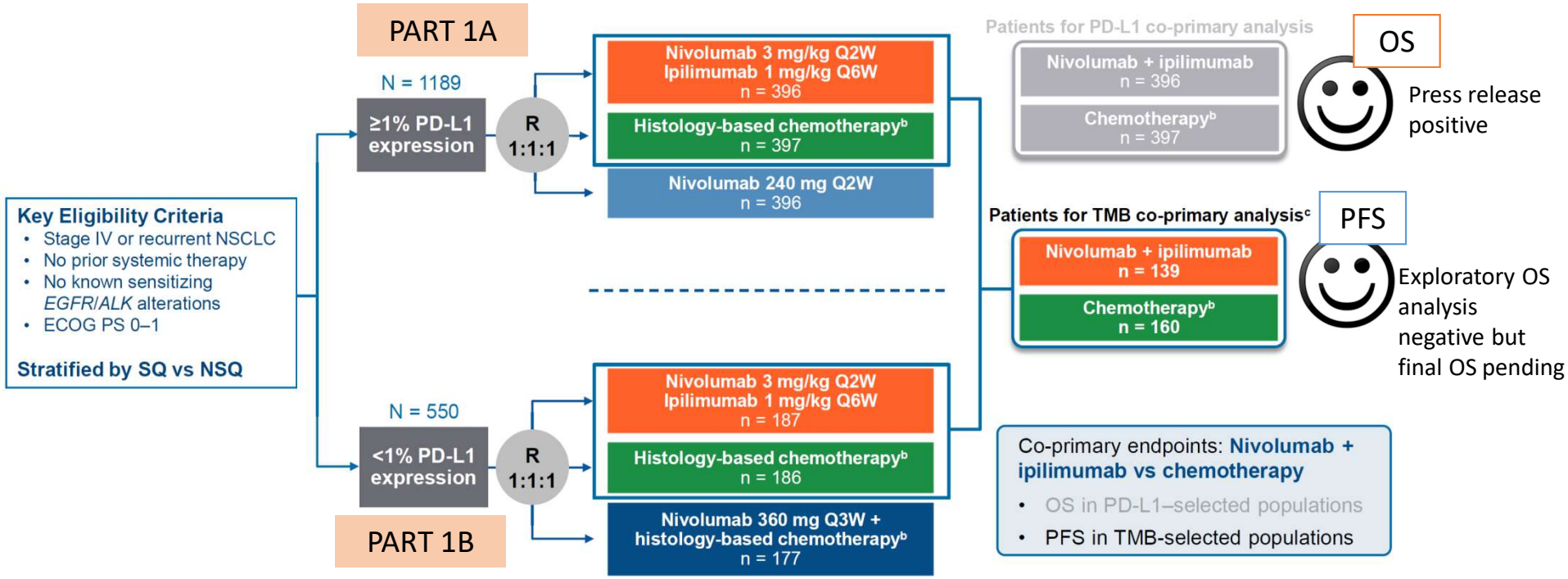
Hellmann MD et al. N Engl J Med. 2018 May 31;378(22):2093-2104.

Nivolumab + ipilimumab NSCLC

CM227 NSCLC 1L

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

OS



OS

Press release positive

PFS

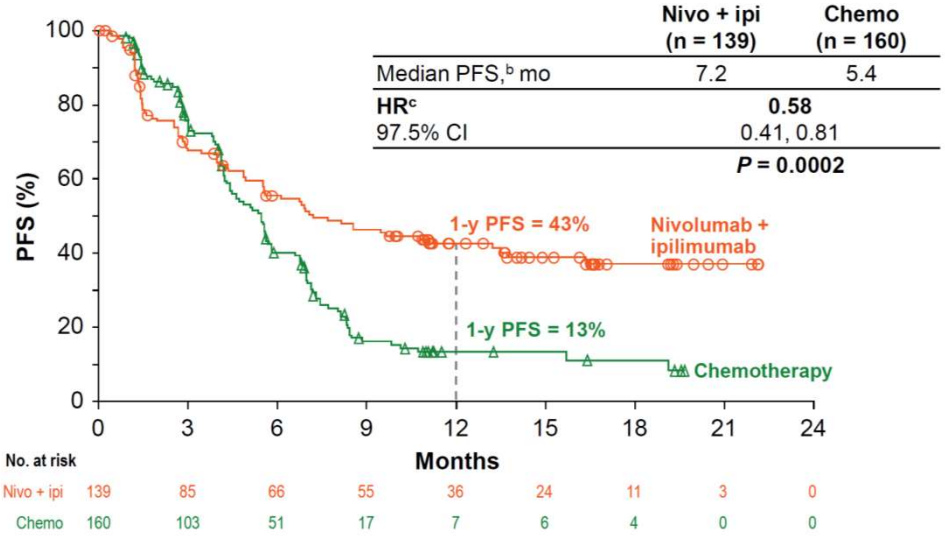
Exploratory OS analysis negative but final OS pending

Co-primary endpoints: OS in PD-L1–selected populations and PFS in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

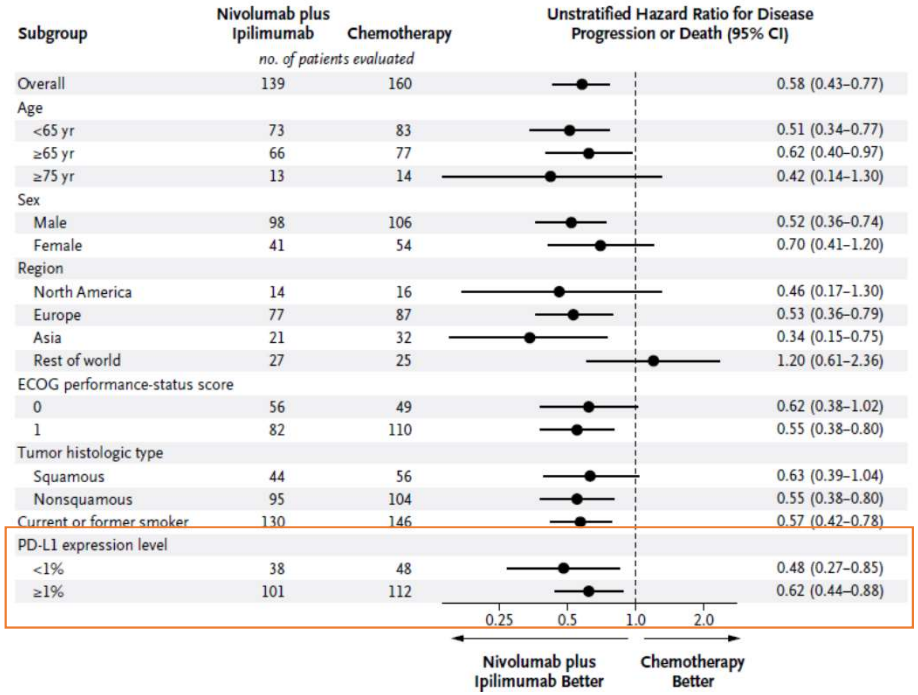
Hellmann MD et al. N Engl J Med. 2018 May 31;378(22):2093-2104.

Nivolumab + ipilimumab NSCLC

CM227 NSCLC 1L High TMB (≥10 mutations per megabase)



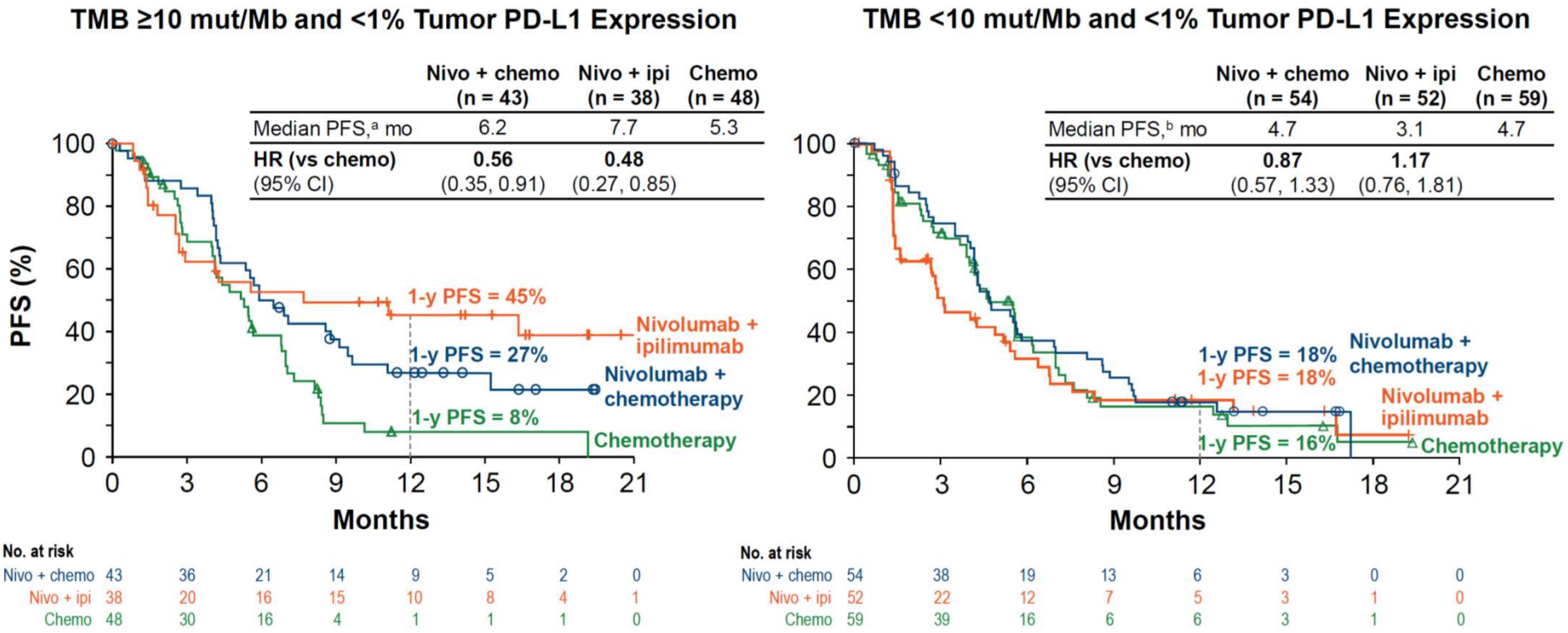
ORR 45.3% vs. 26.9%



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

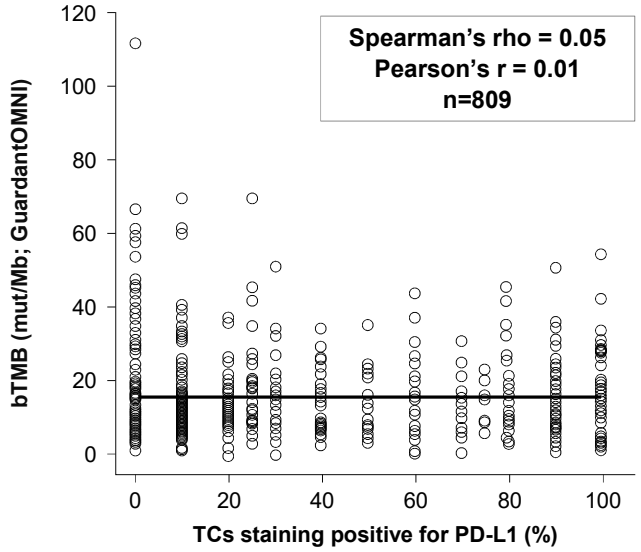
Nivolumab + ipilimumab NSCLC

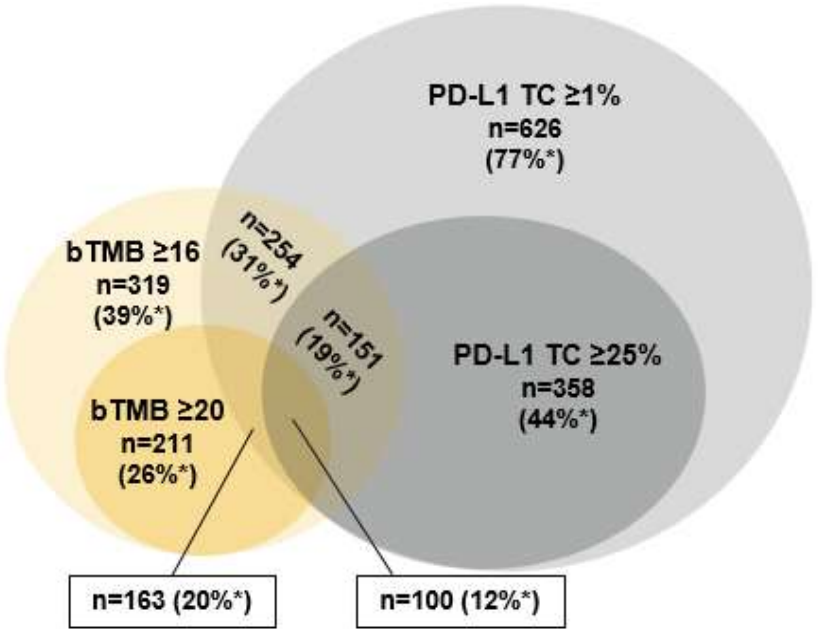
CM227 NSCLC 1L TMB at 10 mutations per megabase threshold & **PD-L1<1%**



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

MYSTIC Trial (durvalumab/tremelimumab) overall negative but blood tumor mutation burden potential independent biomarker





Rizvi. Journal of Clinical Oncology 37, no. 15_suppl (May 20 2019) 9016-9016.

Conclusions- Biomarkers

- PD-L1 IHC remains the “premier” biomarker in selection for immunotherapy in advanced NSCLC
- Tumor mutation burden (including blood-based) potential independent biomarker of PD-L1 IHC, particularly for PD-1/CTLA-4 combination

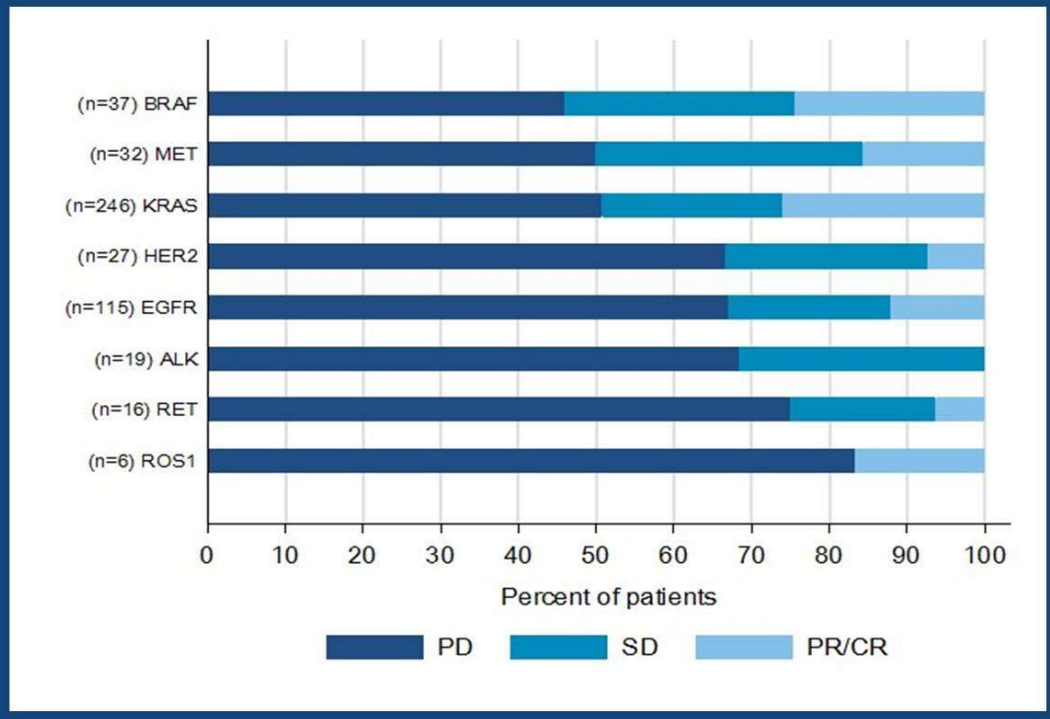
Objectives

- Current use of Immunotherapy in advanced NSCLC
- Role of 2L+ Immunotherapy
- Role of 1L Immunotherapy vs. 1L Chemo-Immunotherapy
- Biomarkers (and combination immunotherapy)
- **Problem Areas**
  - **Oncogenic drivers *EGFR, ALK***
  - **Emerging oncogenic drivers *KEAP1, STK11***

Oncogenic Drivers matter for immunotherapy in NSCLC

IMMUNOTARGET COHORT: Response

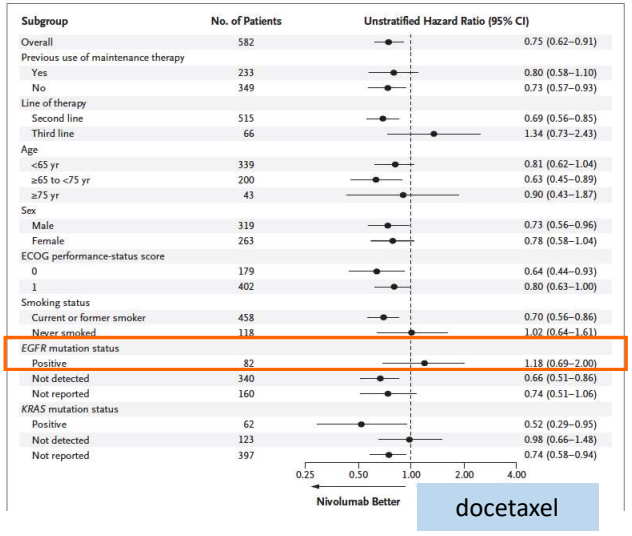
Driver	PD	SD	CR/PR
BRAF	46%	30%	24%
MET	50%	34%	16%
KRAS	51%	23%	26%
HER2	67%	26%	7%
EGFR	67%	21%	12%
ALK	68%	32%	0
RET	75%	19%	6%
ROS1	83%	0	17%
TOTAL	57%	24%	19%



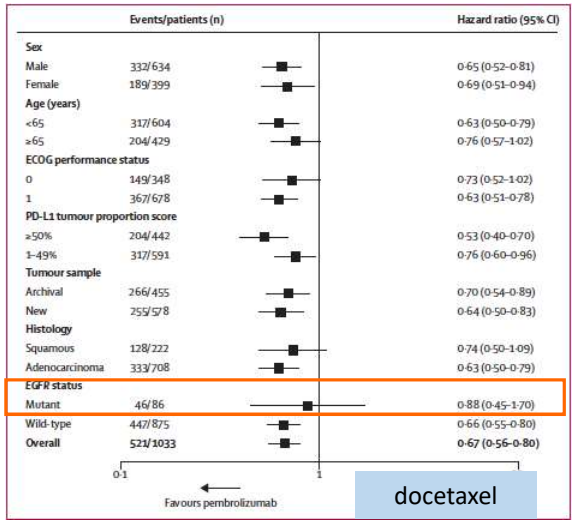
Mazieres ASCO 2018.Ann Oncol. 2019 May 24.

EGFR mutated subgroups did not have benefit in 2L+ immunotherapy studies compared to docetaxel

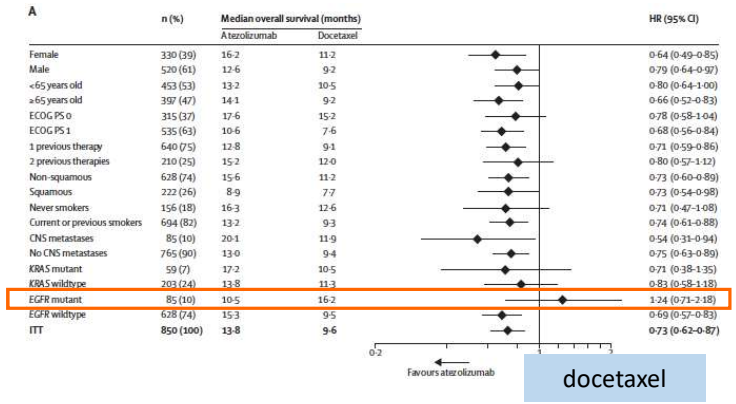
CM-057 Nivo Non-Squamous



KN-010 Pembro

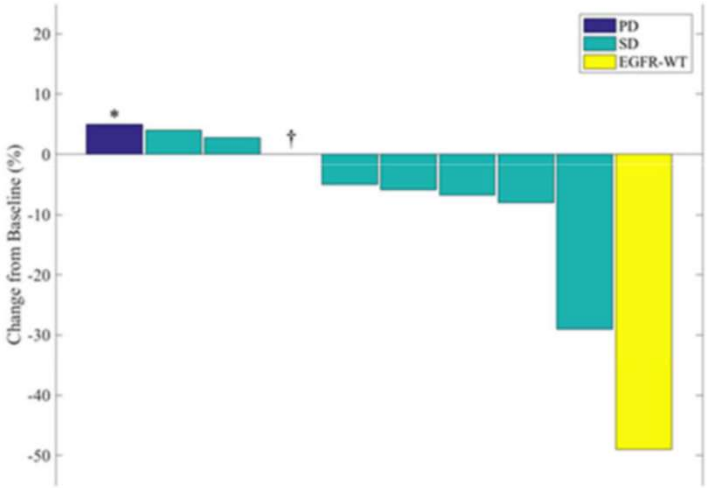


OAK Atezo



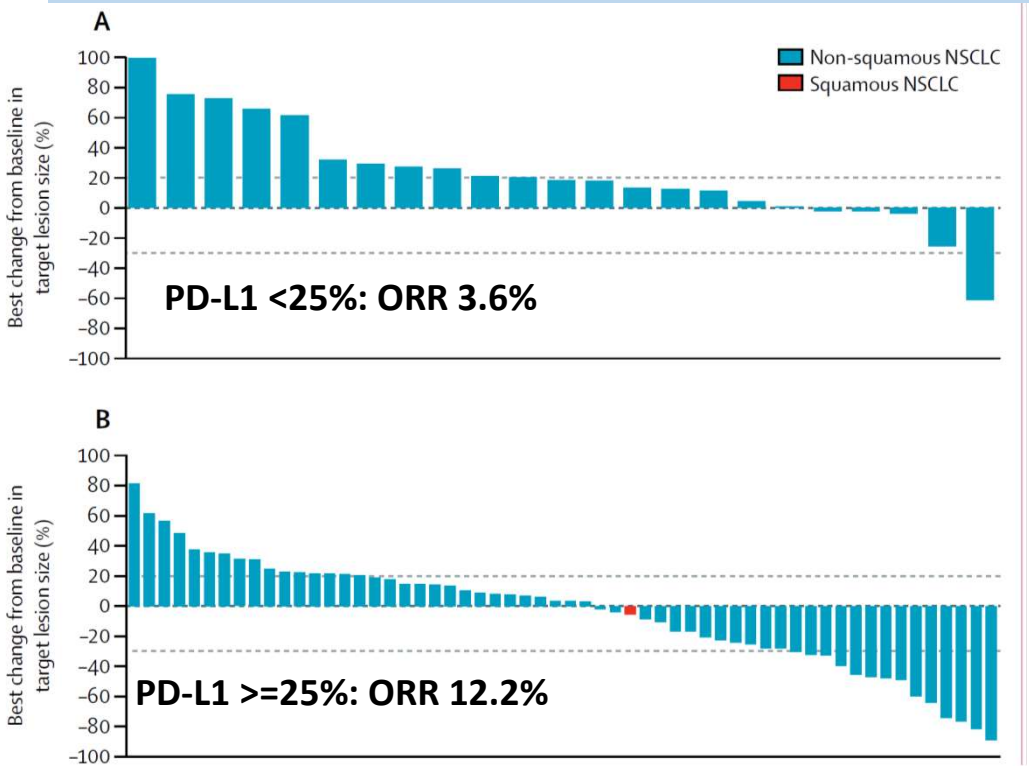
An Immunotherapy Challenge: oncogene drivers *EGFR, ALK*

Pembrolizumab 1L PD-L1+
***EGFR* mutant**



Lisberg. J Thorac Oncol. 2018 Aug;13(8):1138-1145.

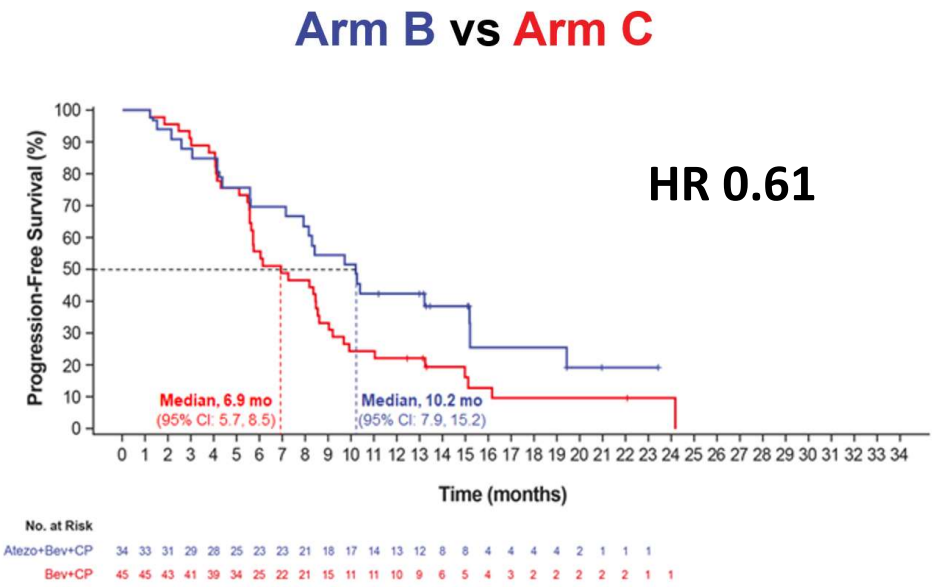
Durvalumab 3L
***EGFR/ALK* mutant/rearranged**

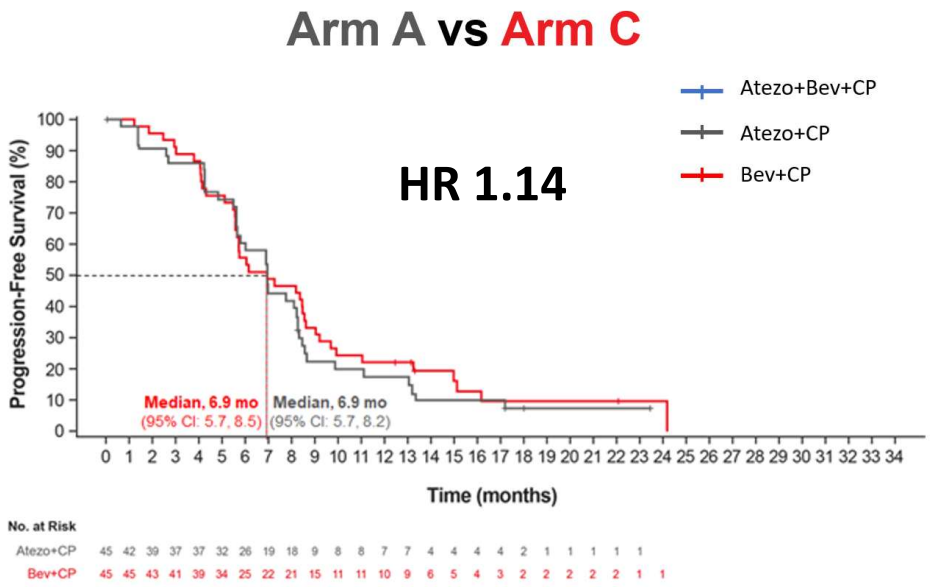


Garassino MC. Lancet Oncol. 2018 Apr;19(4):521-536.

Bev + Atezo > Bev in *EGFR* mutated NSCLC

IMpower150 Non-squamous NSCLC 1L (PD-L1 unselected)





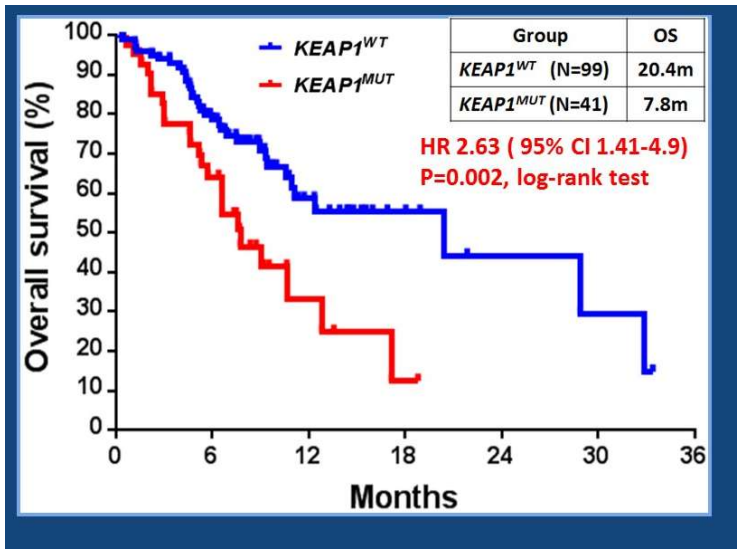
Arm A/B/C ORR: 36%/**71%**/42% and DOR mo 5.6/**11.1**/4.7

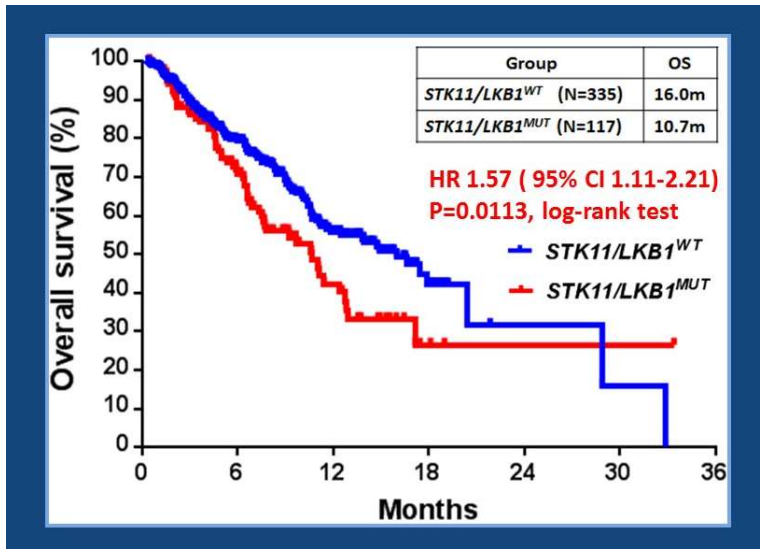
Mok T et al. *Ann Oncol* 29(Suppl 9); 483.0081

Emerging problem targets- *KEAP1*, *STK11* mutations

Worse outcomes with chemo-immunotherapy

KEAP1 mutant	*STK11* mutant





- Immunotherapy does not add to chemotherapy in these subgroups
- High TMB or PD-L1 do NOT improve outcomes for these subgroups

Skoulidis ASCO 2019.

Conclusions

- *EGFR* mutant*/ALK* rearranged NSCLC have limited efficacy with immunotherapy and these subgroups were excluded from chemo-immunotherapy studies

- Chemo-immunotherapy + antiangiogenic agent bevacizumab may be useful for the *EGFR* mutated NSCLC

- Emerging oncogenic mutations such as *STK11*, *KEAP1* also pose a problem for immunotherapy efficacy

Overall Conclusions

- Most NSCLC patients without “actionable” oncogenic drivers will receive immunotherapy as part of their first line standard of care, either as monotherapy or in combination with chemotherapy
- PD-L1 remains an important biomarker, with tumor mutation burden emerging
- Future directions involve overcoming cold tumor immune microenvironments created by oncogenic mutations and refining biomarkers