Updates in Immunotherapy for Metastatic NSCLC

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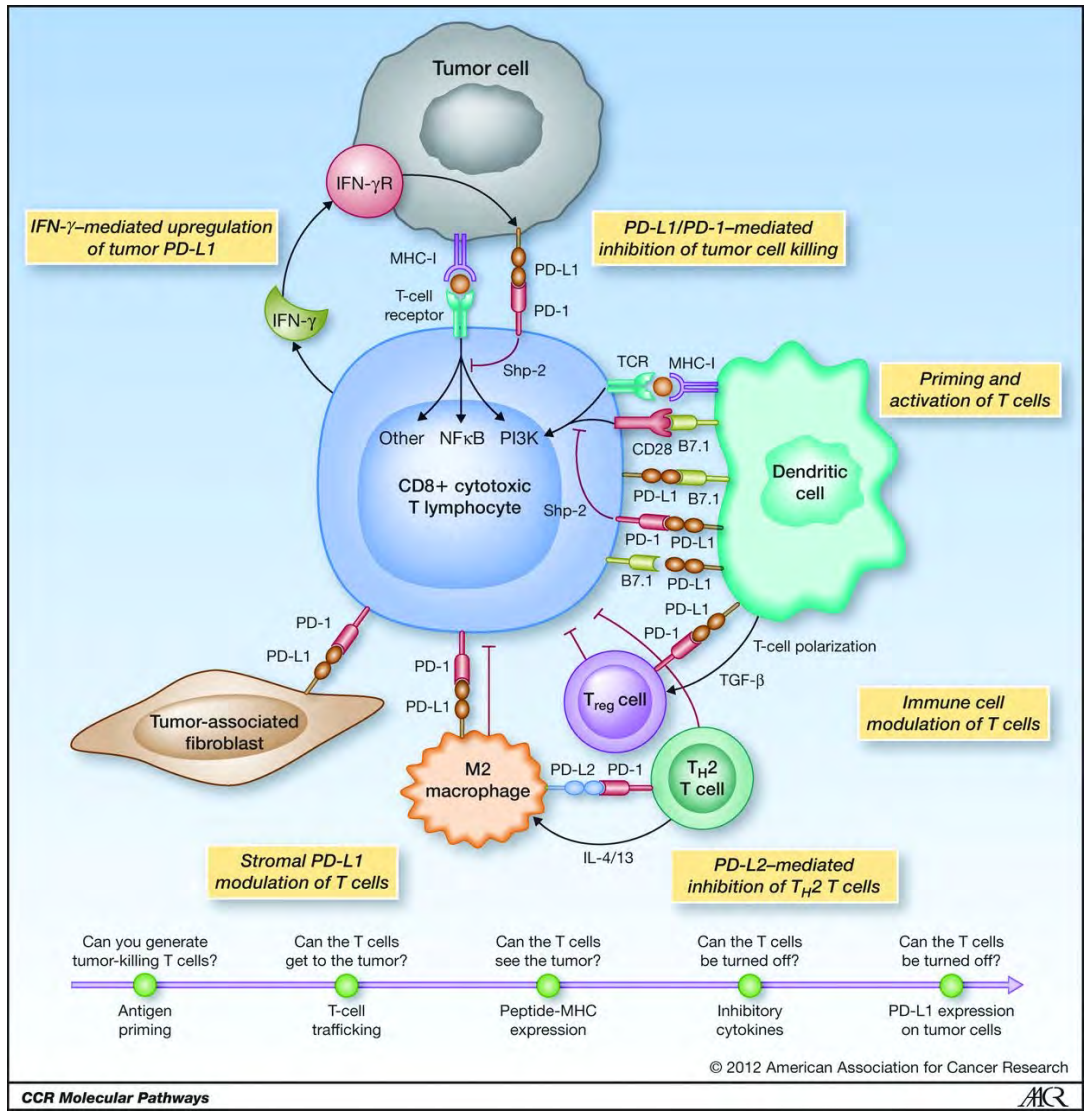
Disclosures

- Received honoraria for AbbVie, Merck, Bergen Bio, Armo, Mirati, Caris, Sanofi/Regeneron

PD-1/PD-L1 Pathway

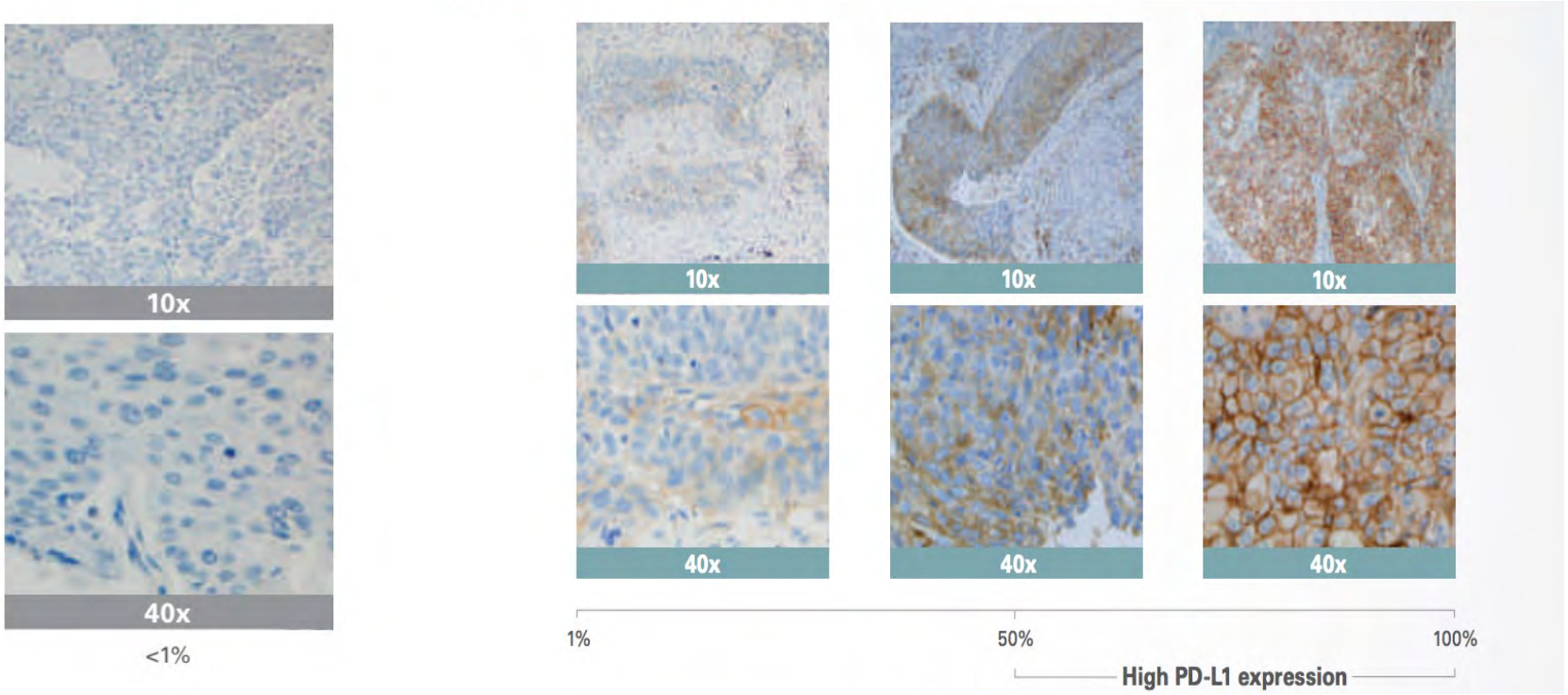


Chen et al. CCR 2012

Approved Immunotherapeutic Agents in NSCLC

- Metastatic disease
  - 1st Line
    - Pembrolizumab with or without chemotherapy
    - Atezolizumab with chemotherapy and bevacizumab
    - Nivolumab and Ipilimumab with or without chemotherapy
    - Cemiplimab
  - 2nd line
    - Pembrolizumab
    - Nivolumab
    - Atezolizumab
- Adjuvant Therapy
  - Atezolizumab
  - Pembrolizumab (soon?)
- Stage III after Chemo-RT
  - Durvalumab
- Neoadjuvant Therapy
  - Chemotherapy plus Nivolumab

Examples of PD-L1 Staining



PD-L1 (DAKO 22C3 pharmDx) testing on this tumor (Block A1) was requested by Dr. Vannostrand.

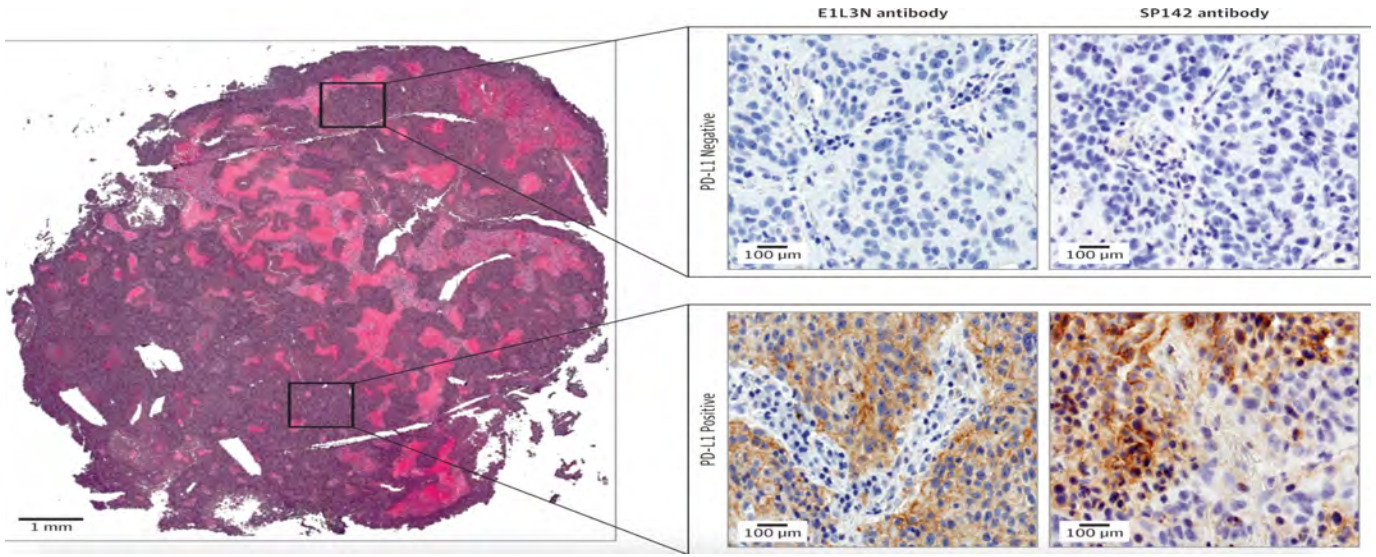
Result

HIGH PD-L1 EXPRESSION: Partial or complete cell membrane staining (≥ 1+) in ≥ 50% of viable tumor cells.

Note:
PD-L1 DAKO 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer Link 48. This assay is indicated as an aid in identifying NSCLC patients for treatment with pembrolizumab

But…PD-L1 is Not Perfect

- Even in Keynote-024, RR was only ~45%. EGFR TKIs ORR 60-80%
- Reasonable concordance between both synchronous and metachronous PD-L1 expression in the range of 75–90 %, but tx (chemo, RT) can alter expression
- Tumor heterogeneity

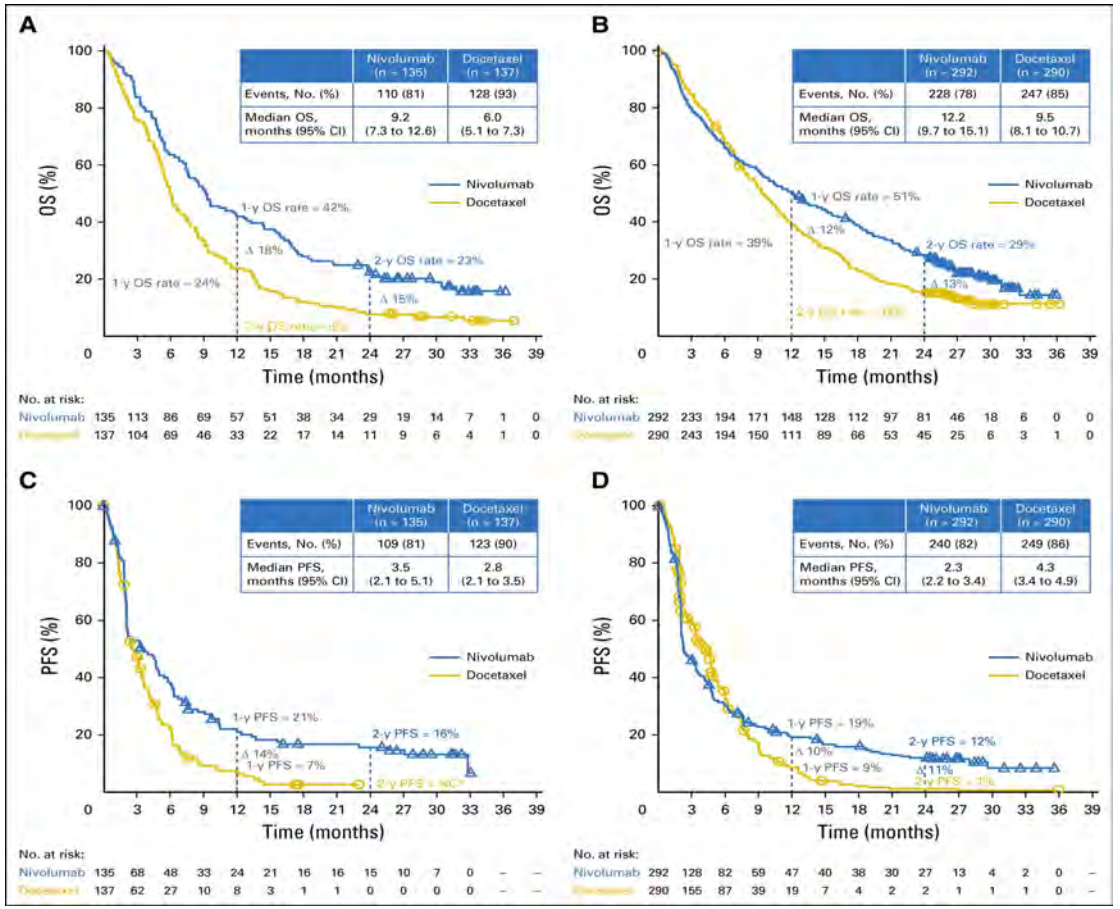


McLaughlin et al. Jama Onc 2016
Grigg and Rizvi, JITC 2016

Combined Analysis of Nivolumab vs. Docetaxel, 2nd line NSCLC, (CheckMate 17 and 57)

Squamous

Non-Squamous



Horn et al. JCO 2017

- First-line, non-driver mutation metastatic NSCLC can now be thought of in 2-3 main boxes based on PD-L1 status; PD-L1 high (IHC expression greater than 50%), and PD-L1 Low (1%-49%)/PD-L1 negative

- Not perfect, and there is overlap, but helps to think of these “boxes” when deciding on a treatment plan for a patient or designing clinical trials

PD-L1 High - Keynote 24

- Phase 3 randomized trial
- Compared pembrolizumab 200mg q3week vs investigator choice chemotherapy in first line NSCLC
- Patients needed to have 50% or greater PD-L1 staining in tumor cells using PD-L1 IHC 22C3 pharmDx assay to be enrolled
- This biomarker cutoff was predefined
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, Safety

Reck et al. NEJM 2016

Keynote 24

- 305 patients enrolled
- Approximately 30% of patients tested had PD-L1 greater than 50%
- ~20% squamous, 80% non-squamous
- Most common chemotherapy regimen was carboplatin and pemetrexed

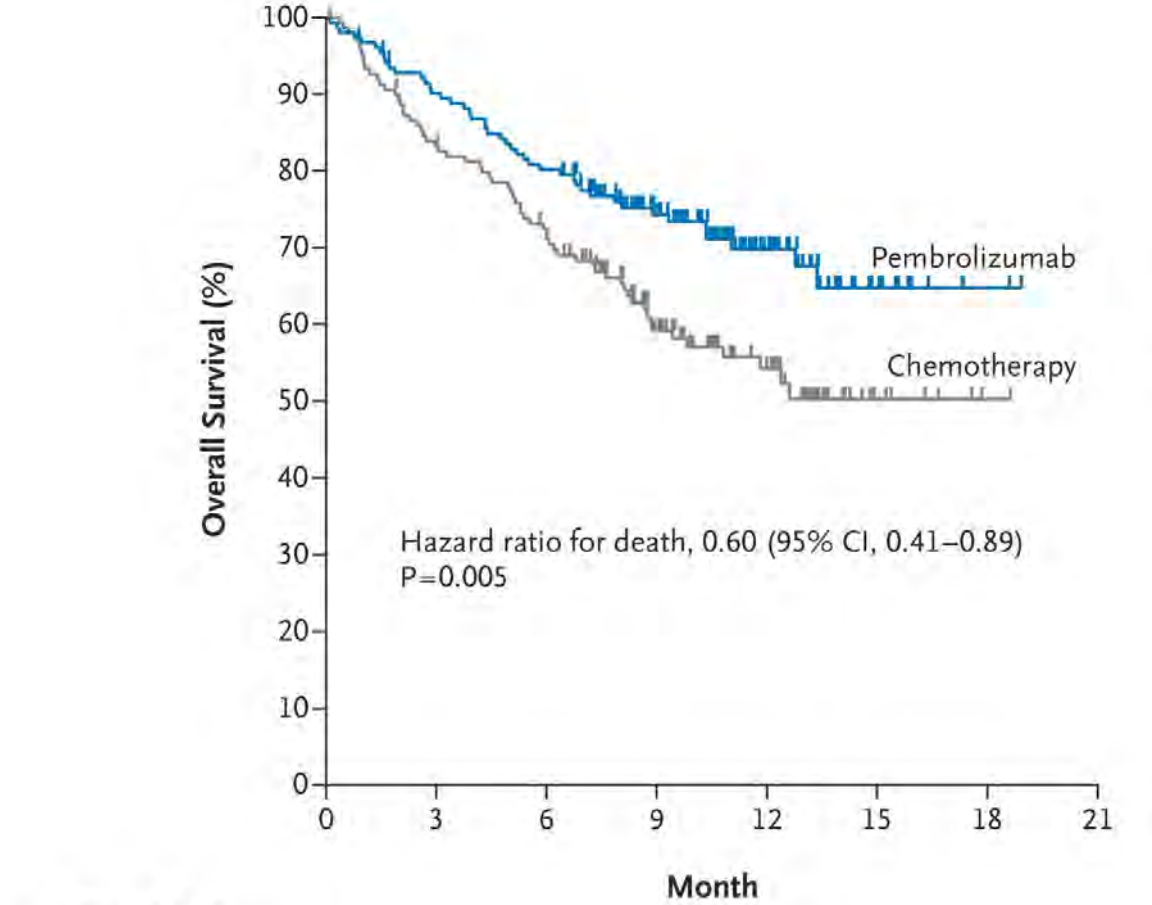
Reck et al. NEJM 2016

Keynote 24

Treatment	ORR	PFS	OS (HR)
Chemotherapy	27.8%	6.0 mo	14.2 mo
Pembrolizumab	44.8%	10.3 mo	30.2 mo

Reck et al. NEJM 2016

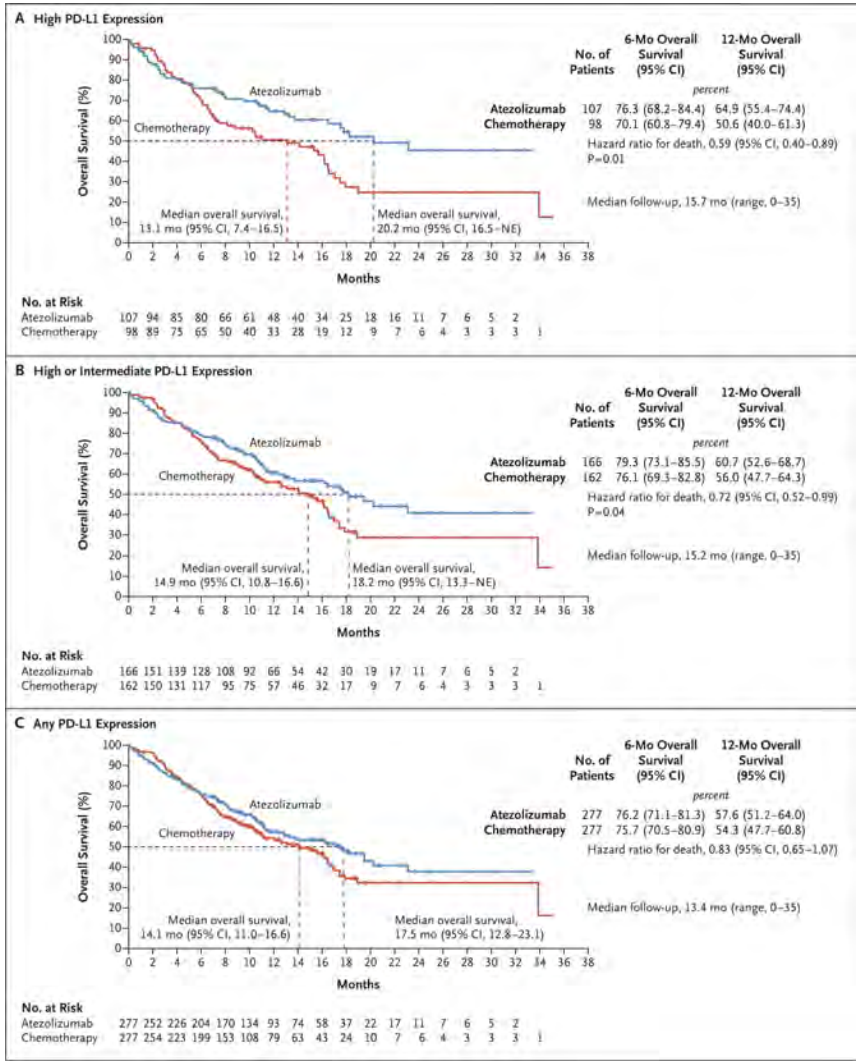
Keynote 24



Reck et al. NEJM 2016

IMpower110

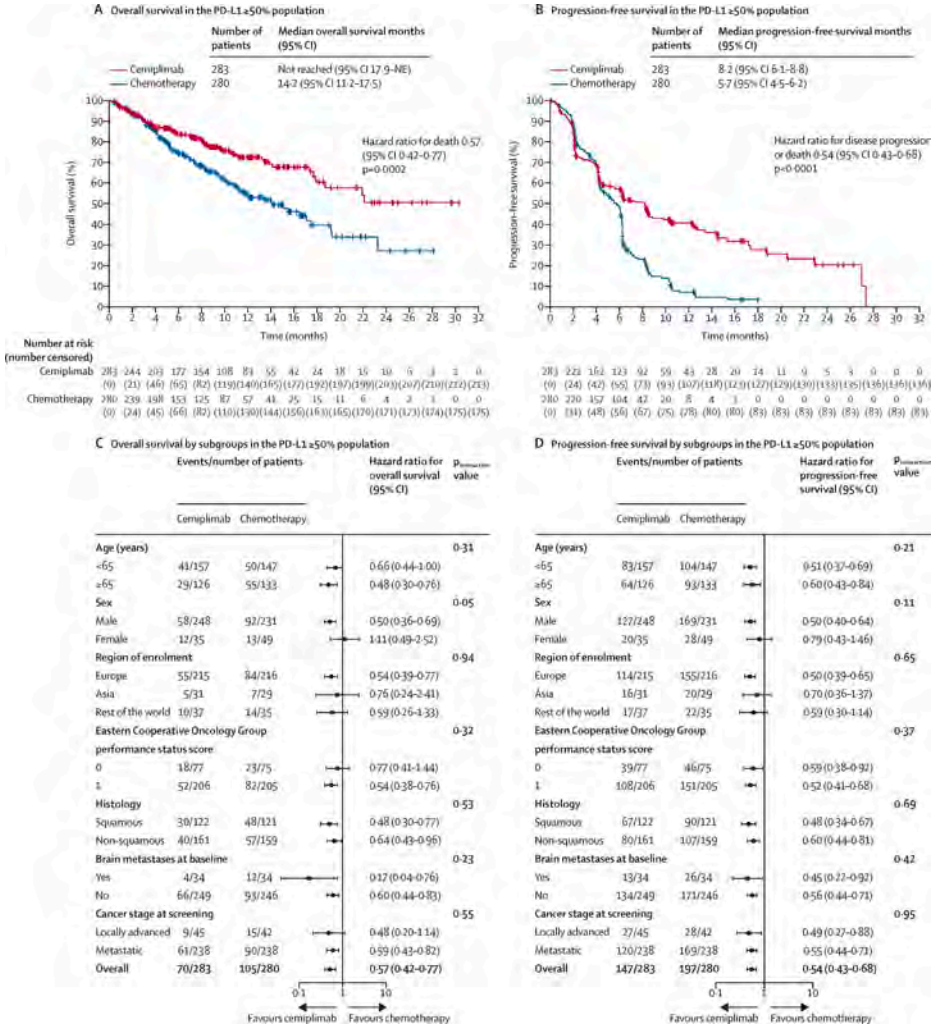
- Similar to Keynote-024, but utilized atezolizumab
- 572 patients PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells covering at least 1% of the tumor area as determined by the SP142 assay was required
- For patients who had the highest expression of PD-L1 (≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells) (205 patients), the median overall survival was 20.2 months for atezolizumab vs.13.1 months for chemotherapy; HR 0.59



Herbst et al. NEJM 2020

EMPOWER-Lung 1

- Similar to Keynote-024, but utilized cemiplimab
- 710 patients
- Median OS was not reached with cemiplimab vs 14.2 months with chemotherapy, HR 0.57
- Median progression-free survival was 8.2 months with cemiplimab versus 5.7 months with chemotherapy, HR 0.54



Sezer et al. Lancet 2021

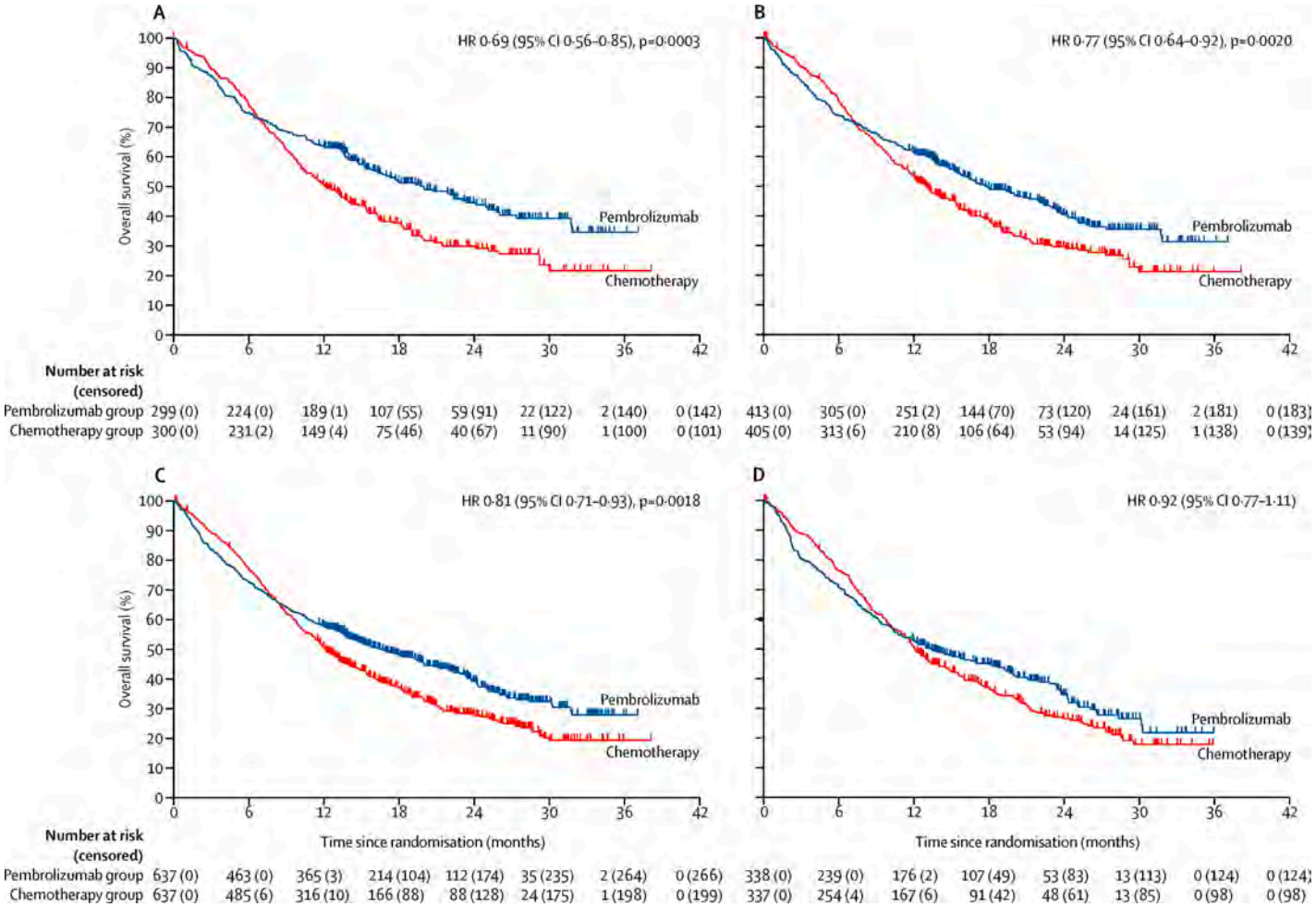
For PD-L1 High (PD-L1 expression ≥50%), immunotherapy as a single agent is a clear-cut treatment option, providing survival and toxicity benefits over chemotherapy alone

Keynote-042

- Phase 3 study comparing pembrolizumab vs platinum-based chemotherapy for metastatic NSCLC
- Tumors must express PD-L1 at 1% or higher
- Primary endpoints were overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater, assessed sequentially
- 1274 patients enrolled

Mok et al. Lancet 2019

Keynote-042



(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. (D) PD-L1 TPS 1–49% population (exploratory analysis). Tick marks indicate censoring of the data at the last time the patient was known to be alive.

Mok et al. Lancet 2019

Keynote-042 was a positive trial and led to FDA approval for pembrolizumab for PD-L1 positive patients. However, the data is weak for PD-L1 1-49% (HR 0.92), and unless a frail patient, do not favor immuno-monotherapy for this patient population

Not Every IO study in Metastatic is Positive!

- CheckMate 026 -nivolumab vs. chemotherapy for NSCLC patients with PD-L1 expression ≥ 5%, but failed to meet its primary endpoint of PFS, HR 1.15

- MYSTIC study-durvalumab (+/- tremelimumab) vs chemotherapy for NSCLC PD-L1 ≥ 25% did not meet its primary end points of improved OS or PFS

Carbone et al. NEJM 2017
Rizvi et al. JAMA Onc 2020

Combination Studies

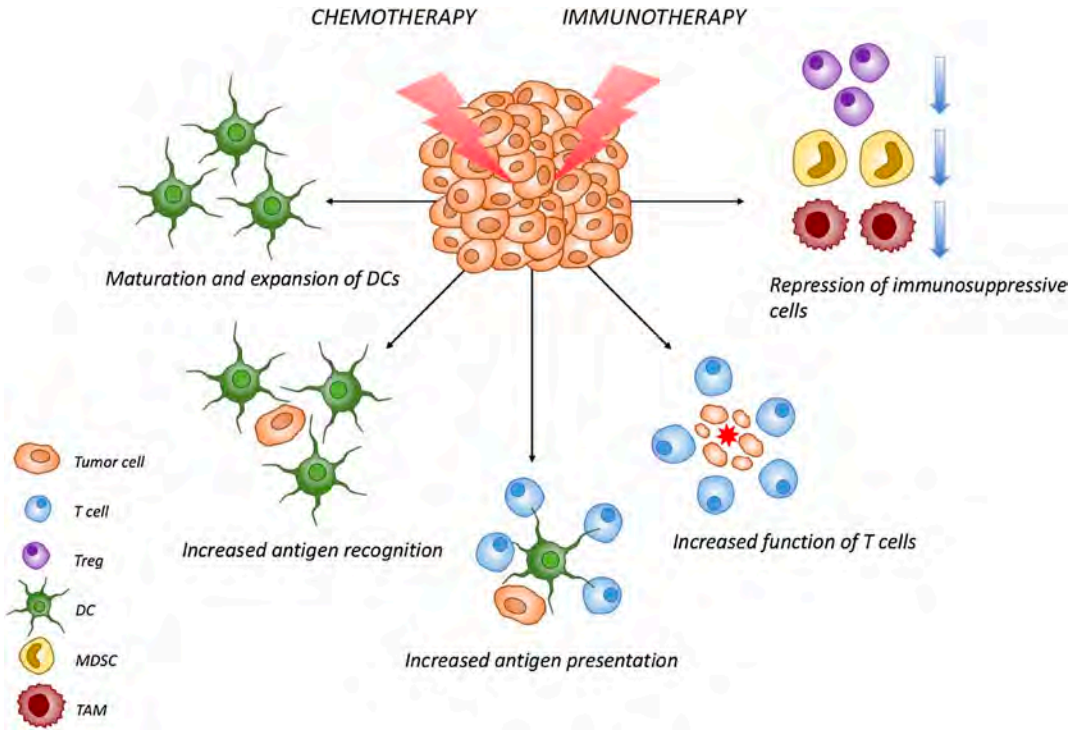
Chemo-IO

IO-IO

Hybrid

Clear Biological Rationale for Chemo/IO

- Initial response rates higher for chemotherapy addition
- Increases recognition of tumor cells by host immune system
- Reduces immunosuppressive environment



Leonetti et al. Drug Resistance Updates 2019

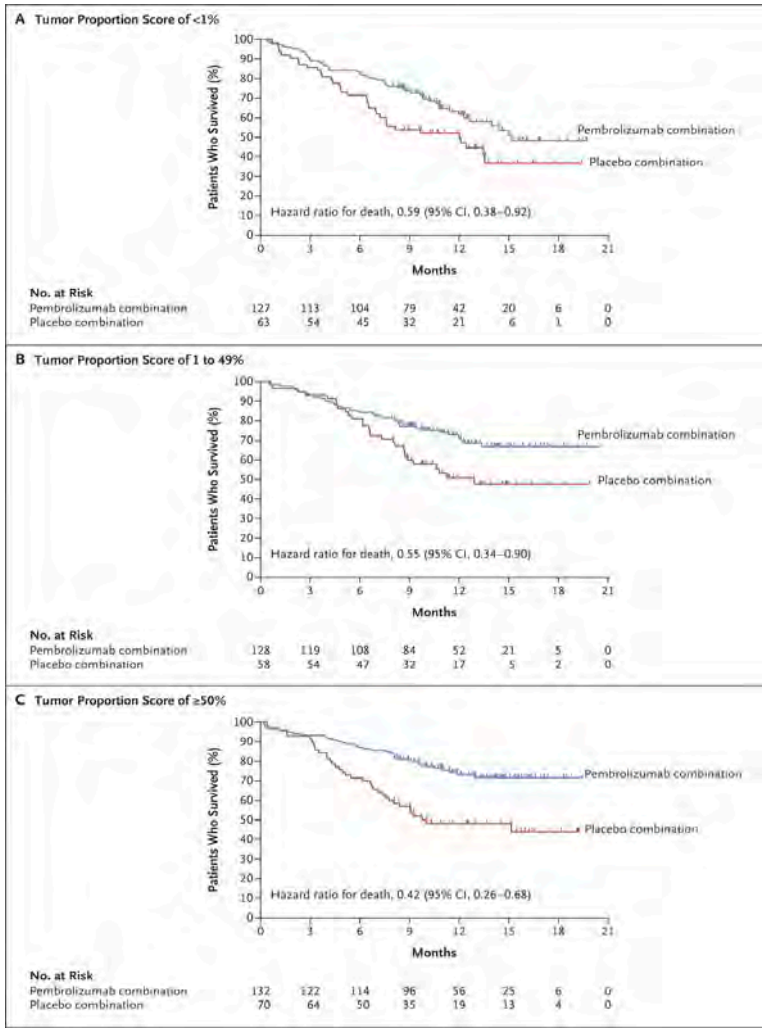
Chemo + IO- Keynote 189

- Phase 3 randomized trial
- Compared pembrolizumab 200mg q3week + platinum and pemetrexed vs chemotherapy in first line non-squamous NSCLC
- All PD-L1 staining allowed on study, stratified by PD-L1 by 1% or higher
- Primary endpoint: OS and PFS
- 616 enrolled

L Gandhi et al. N Engl J Med 2018

Keynote 189

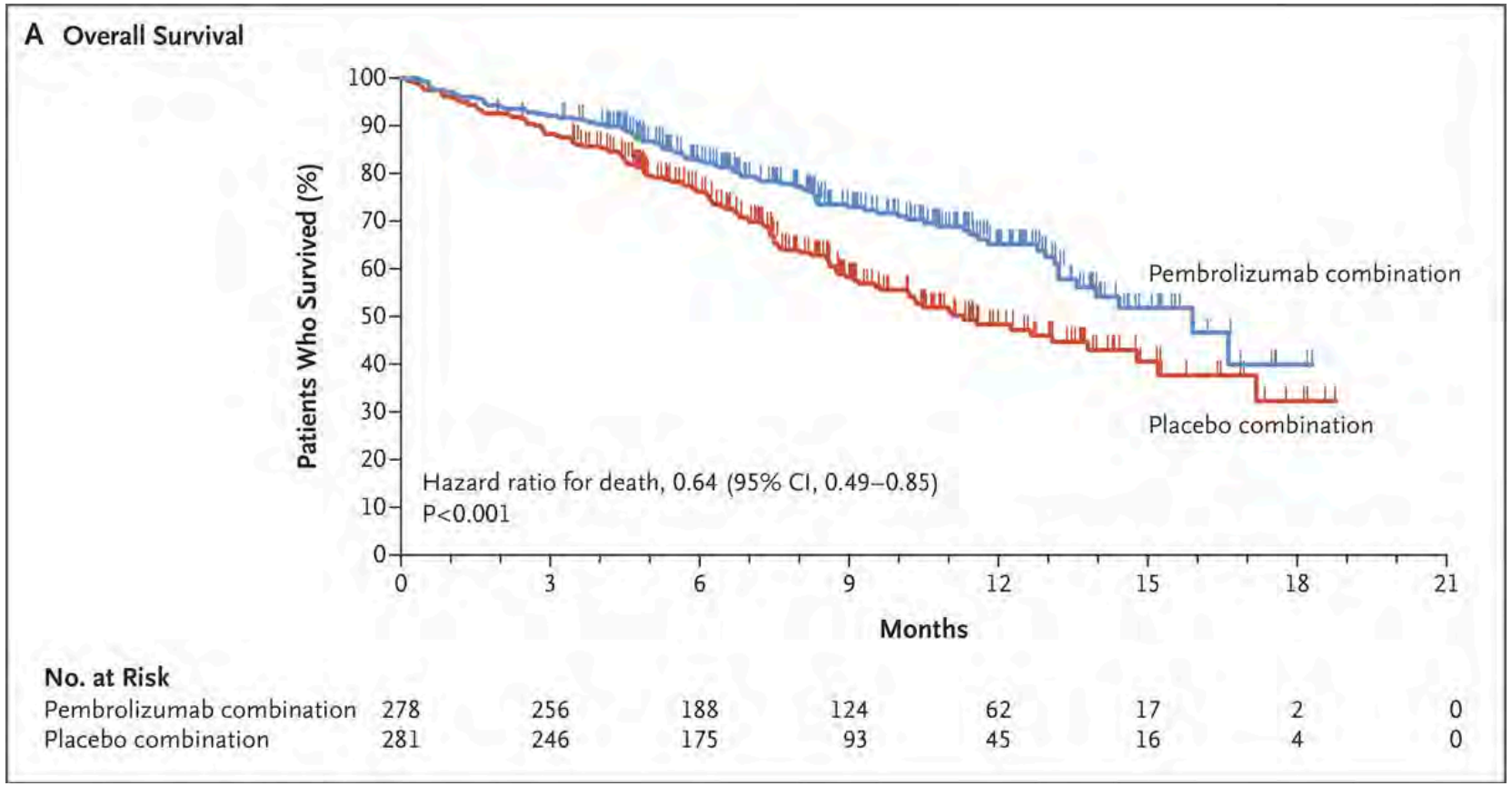
OS



L Gandhi et al. N Engl J Med 2018

Keynote 407

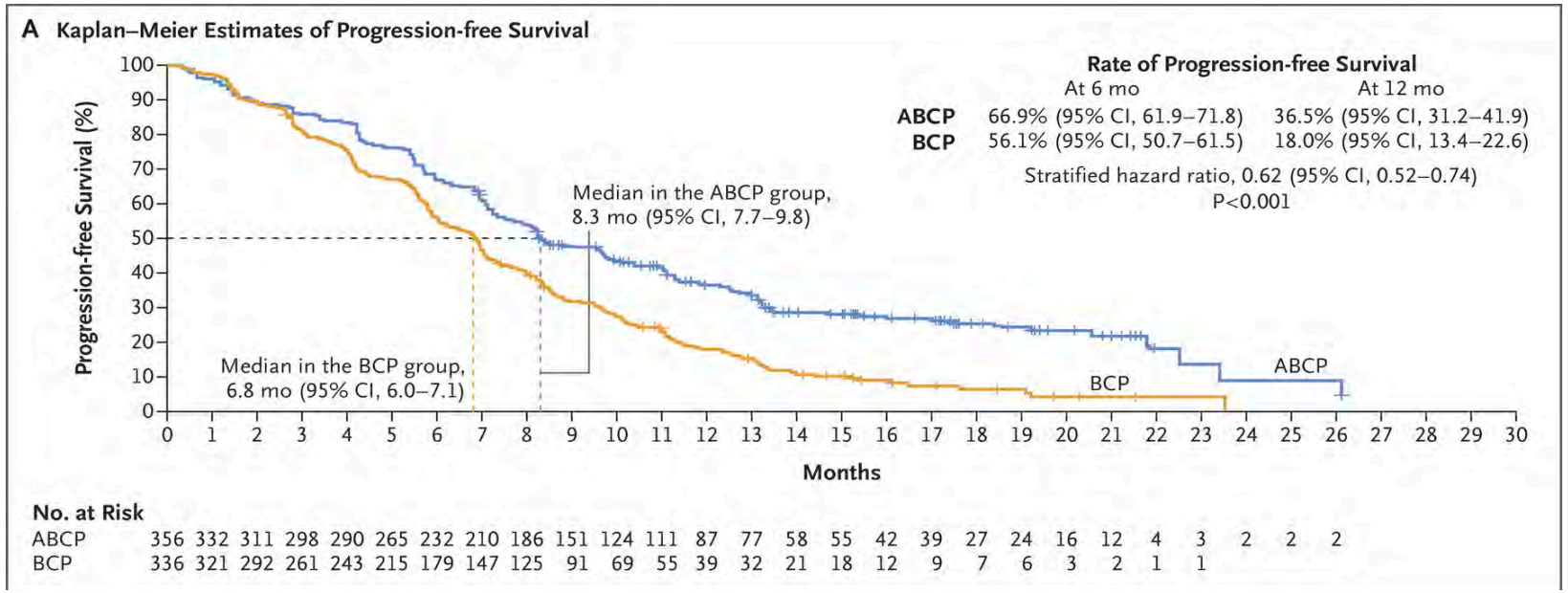
Platinum + Taxane + Pembrolizumab vs. Chemotherapy alone in SCC NSCLC



L Paz-Ares et al. N Engl J Med 2018

IMpower 150

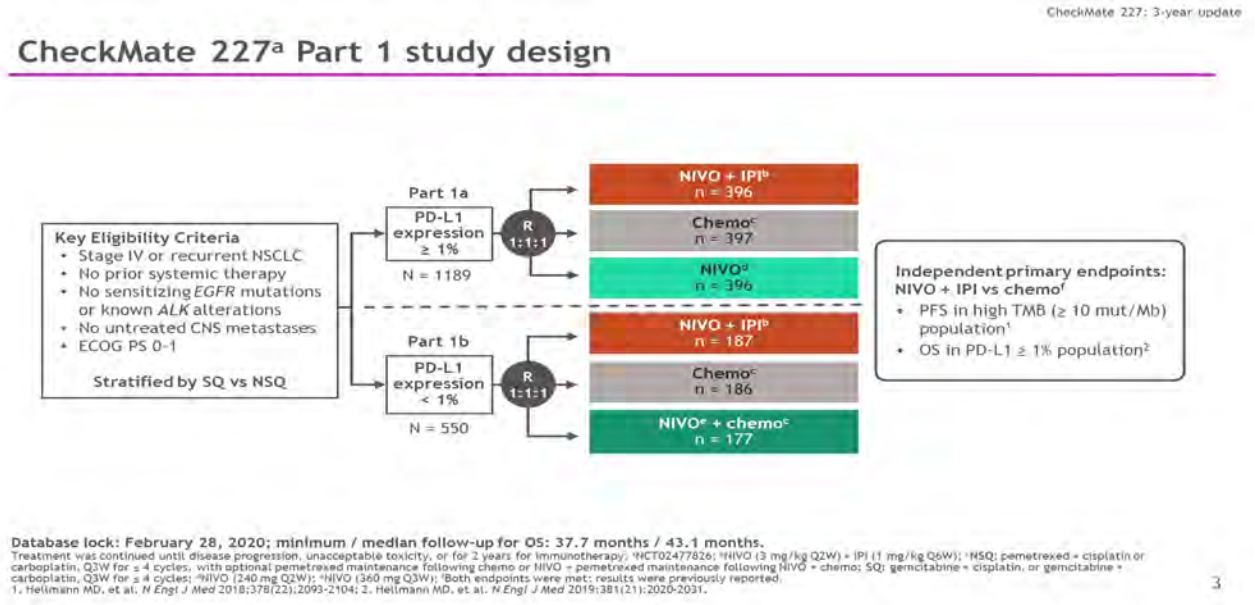
- Phase 3 study comparing atezolizumab with chemotherapy and the VEGF inhibitor bevacizumab (ABCP) vs. atezolizumab with chemotherapy alone (ACP) vs. the control arm of chemotherapy with bevacizumab (BCP) for non-SCC NSCLC
- ABCP was shown to improve overall survival vs. BCP (HR 0.78)



Socinski et al. NEJM 2018

Checkmate-227

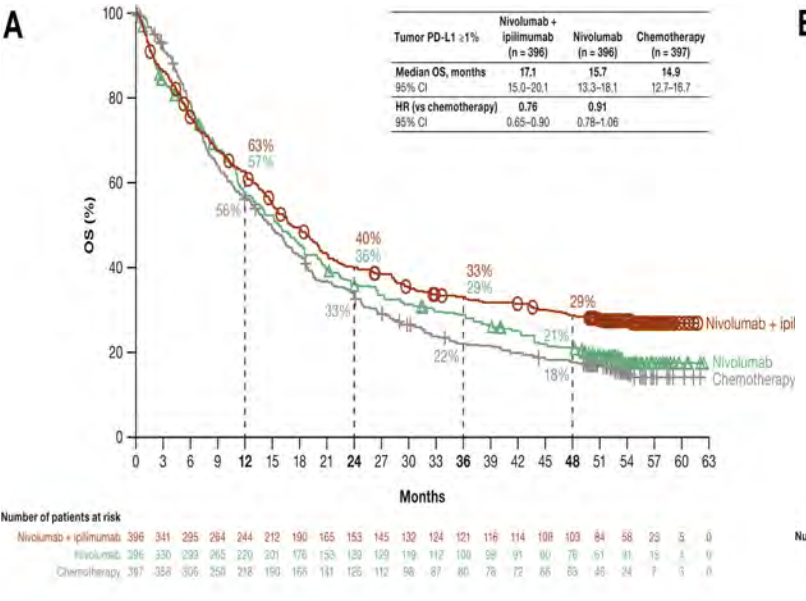
- Multicenter phase 3 randomized study of Nivolumab and Ipilimumab vs SOC chemotherapy
- Independent primary endpoint PFS in high TMB patients, OS in PD-L1 ≥ 1%
- First line therapy for squamous or non-squamous histology, no activating mutations

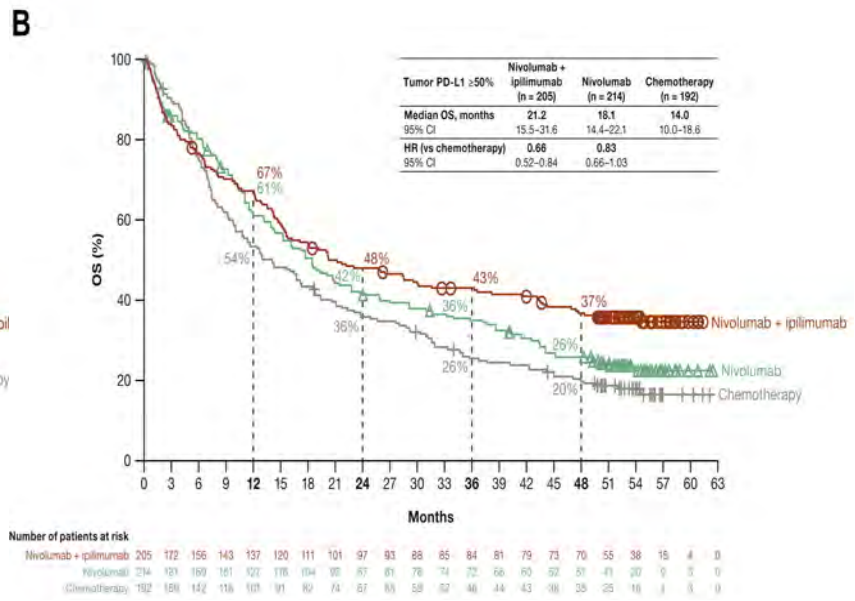


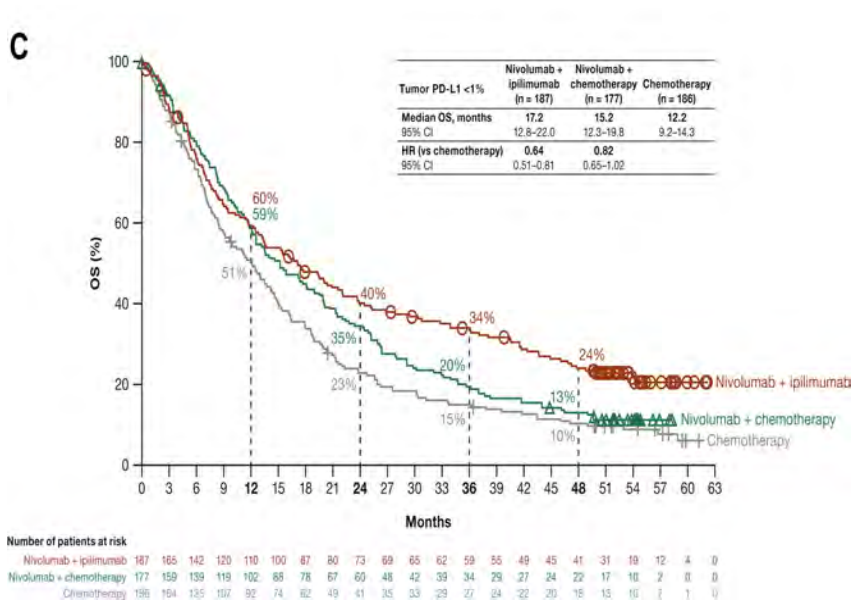
Ramalingam et al. ASCO 2020

Checkmate-227, 4-Year Update

- 1739 patients enrolled overall
- 4-year OS rate with nivolumab plus ipilimumab versus chemotherapy was 29% versus 18% (PD-L1 ≥1%); and 24% versus 10% (PD-L1 <1%)
- All patients off immunotherapy for 2 years







Led To FDA approval for Nivo-IPI ≥ 1%

Paz-Ares et al. JTO 2021

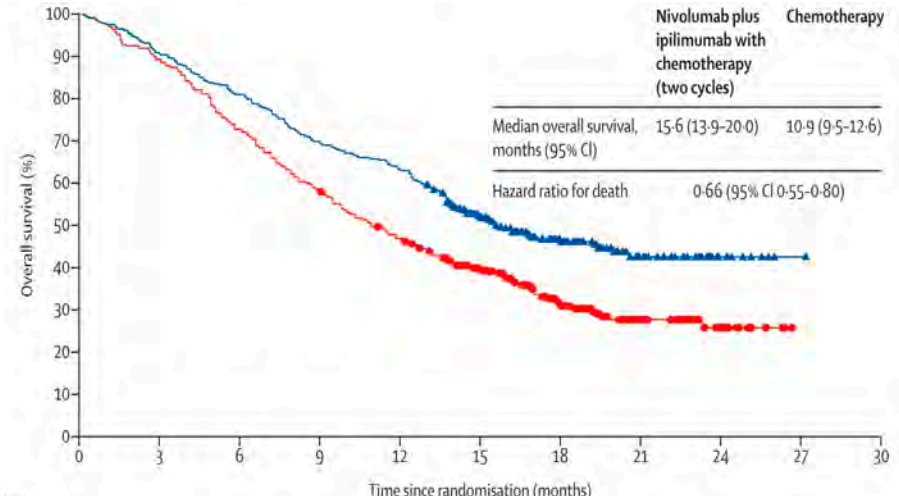
Checkmate 9LA

- Phase 3 study examining Nivo-IPI combined with chemotherapy (for only 2 cycles) vs SOC chemotherapy for untreated metastatic NSCLC
- 719 patients randomized
- Primary endpoint was overall survival
- OS favored IO-IO combination(15.6 months vs 10.9 months in the control group (HR 0.66)
- 40% of patients had PD-L1 < 1%

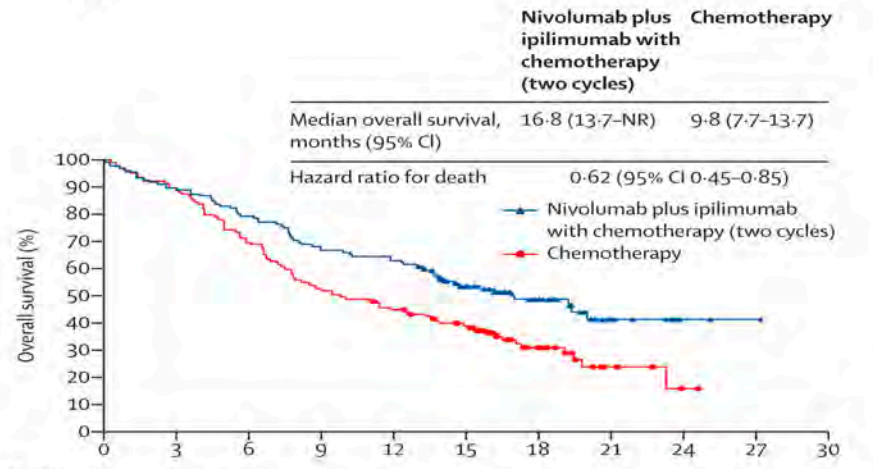
Paz-Ares Lancet Onc. 2021

Checkmate 9LA

Overall Population



PD-L1 < 1% Population



Paz-Ares Lancet Onc. 2021

Chemo–IO and IO-IO are reasonable options regardless of PD-L1 status for metastatic NSCLC

How to choose between the options, especially for PD-L1 high patients?

Chemo IO vs IO

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

Study Design

Pooled Analysis Population

- Advanced NSCLC
- PD-L1 TPS ≥50%
  - Excluded staining by tumor-infiltrating immune cells
- No sensitizing *EGFR* mutations or *ALK* alterations
- Clinical trial supported FDA approval of IO-based regimen

Chemo-IO

IO-only

Exploratory Primary Outcome measure

- OS

Other exploratory outcome measures

- PFS
- ORR

Sub-group analyses

- Age (yrs): *<65 vs 65-75 vs ≥75*
- ECOG PS: *0 vs. ≥ 1*
- Smoking history: *Never vs. Ever*

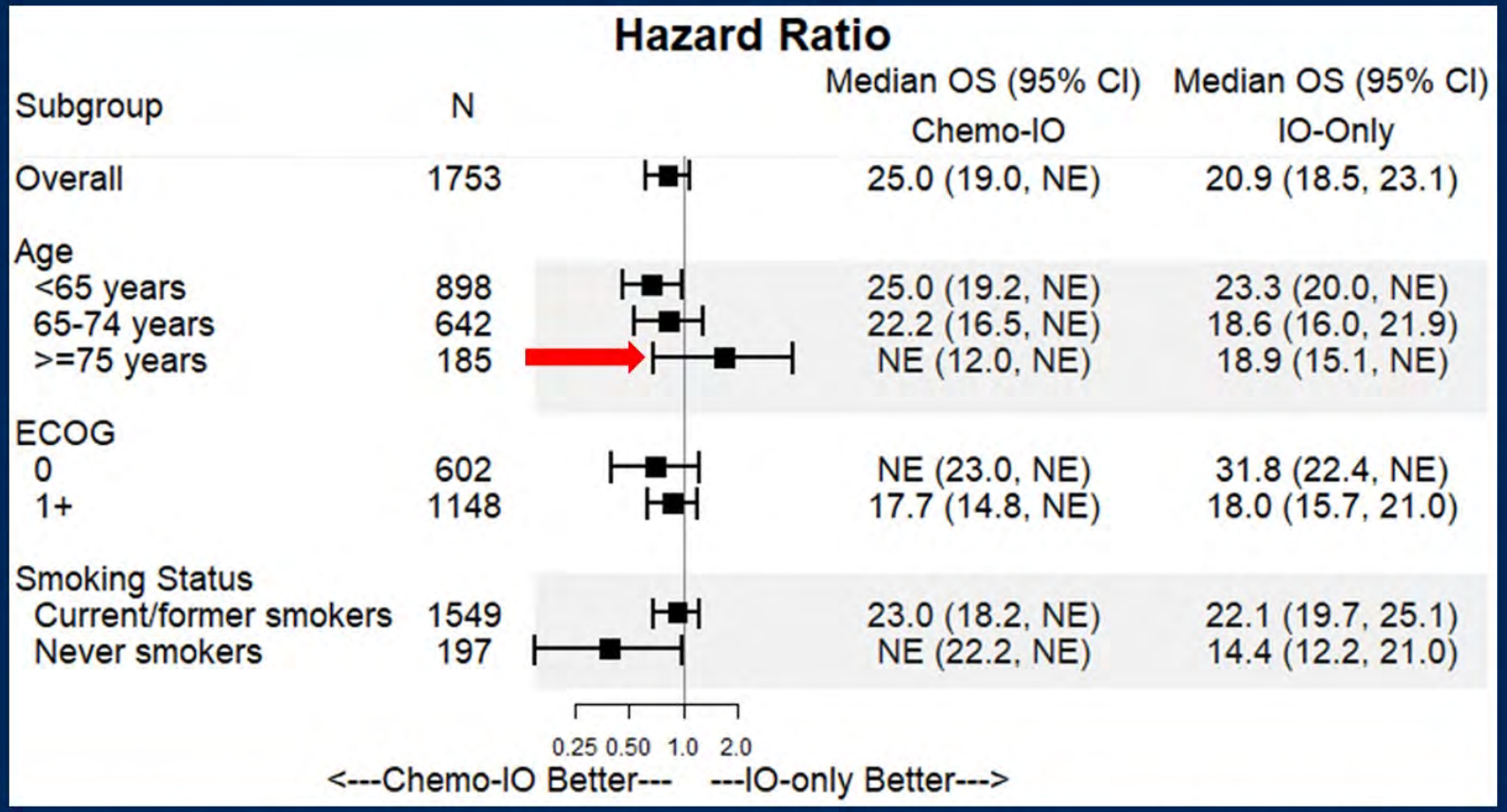
Abbreviations: *ALK*=anaplastic lymphoma kinase gene; Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; *EGFR*=epidermal growth factor receptor gene; FDA=U.S. Food and Drug Administration; IO=immunotherapy; NSCLC=non-small-cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; TPS=tumor proportion score; yrs=years.

Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

OS in NSCLC PD-L1 ≥50% in selected subgroups



Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group Performance Status; IO=immunotherapy; NE=not estimable; NSCLC=non-small-cell lung cancer; OS=overall survival; PD-L1=programmed death ligand-1.

Toxicity- IO alone is the clear winner

	Keynote 24	Keynote 42	Keynote 189	Keynote 407
Toxicity	IO alone	IO alone	Chemo-IO	Chemo-IO
% of pts with any TRAE	73.4%	63%	99.8%	98.2%
% of pts with grade 3-5 TRAEs	26.6%	18%	67.2%	69.8%
Discontinuation due to TRAE	7.1%	9%	13.8%	13.3%
TRAE leading to death	1/154 (<1%)	13/636 (2%)	27/405 (6.7%)	8.3%
Most common AEs	Diarrhea (14.3%) Fatigue (10.4%) Pyrexia (10.4%)	Hypothyroidism (11%) Fatigue (8%) Pruritus (7%)	Nausea (55.6%) Anemia (46.2%) Fatigue (40.7%)	Anemia (53.2%) Alopecia (46%) Neutropenia (37.8%)
Most common grade 3 and above AEs	Skin reaction (3.9%) Diarrhea (3.9%) Pneumonitis (2.6%)	Pneumonitis (3%) ALT/AST increase (1%) Diarrhea (1%)	Anemia (16.3%) Neutropenia (15.8%) Thrombocytopenia (7.9%)	Neutropenia (22.7) Anemia (15.5%) Thrombocytopenia (6.8%)
IRAEs	29.2%	28%	22.7%	28.8%
Grade 3 or above IRAEs	9.7%	8%	8.9%	10.8%

Reck et al. NEJM 2016, Mok et al. Lancet 2019, Paz-Ares et al. NEJM 2018, Gandhi et al. NEJM 2018

Increased Needs Chemo-IO

- Infusion time
  - Pembrolizumab-2 hours
  - Carboplatin and pembrolizumab and pembrolizumab- 3 hours
  - Carboplatin and Paclitaxel and pembrolizumab- 5-6 hours

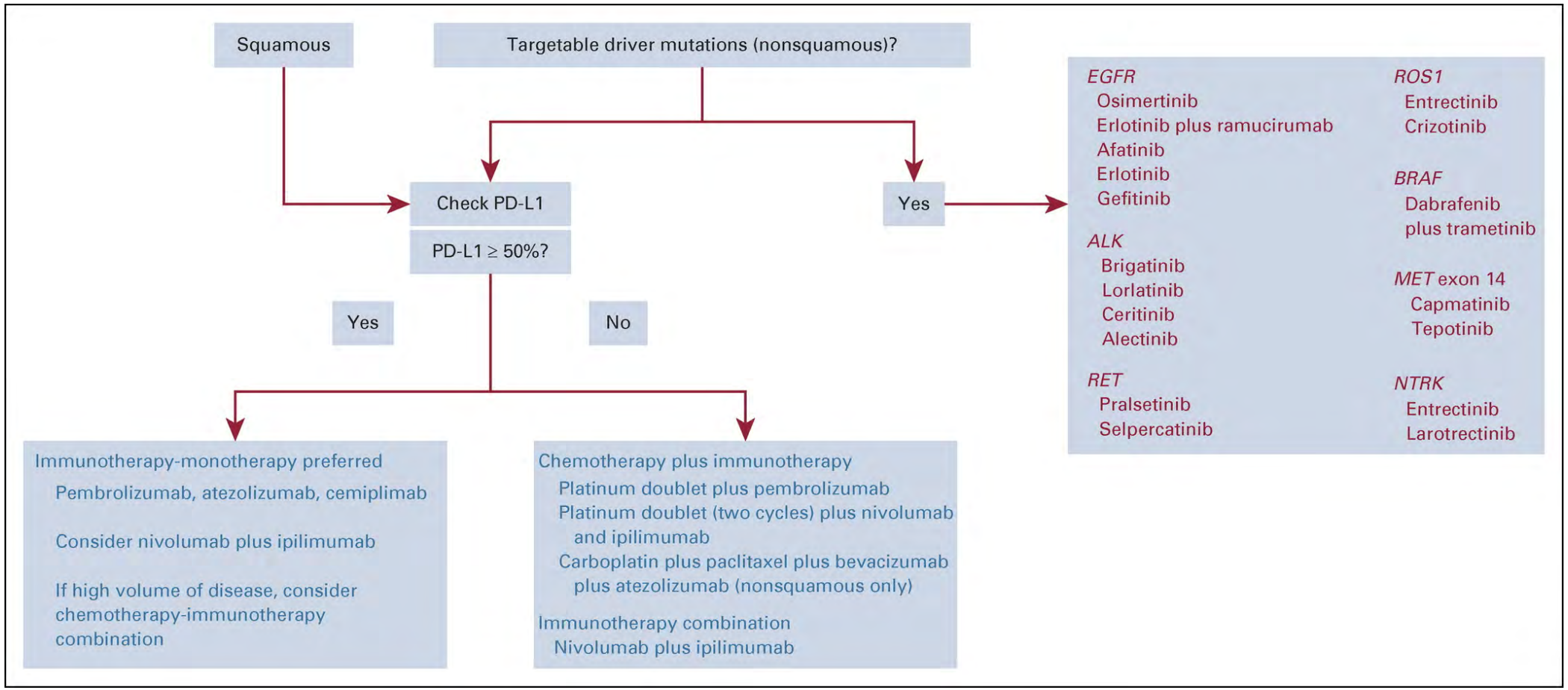
- Premeds
  - Pembrolizumab-none
  - Carbo/Pem/Pem-Dex 12mg, ondansetron 16mg, fosaprepitant 150mg
  - Carbo/Paclitaxel/Pem-Dex 12mg, ondansetron 16mg, fosaprepitant 150mg, famotidine 20mg, diphenhydramine 50mg

- Support medications chemo - antiemetics, steroids, b12 and folate

Some important questions:

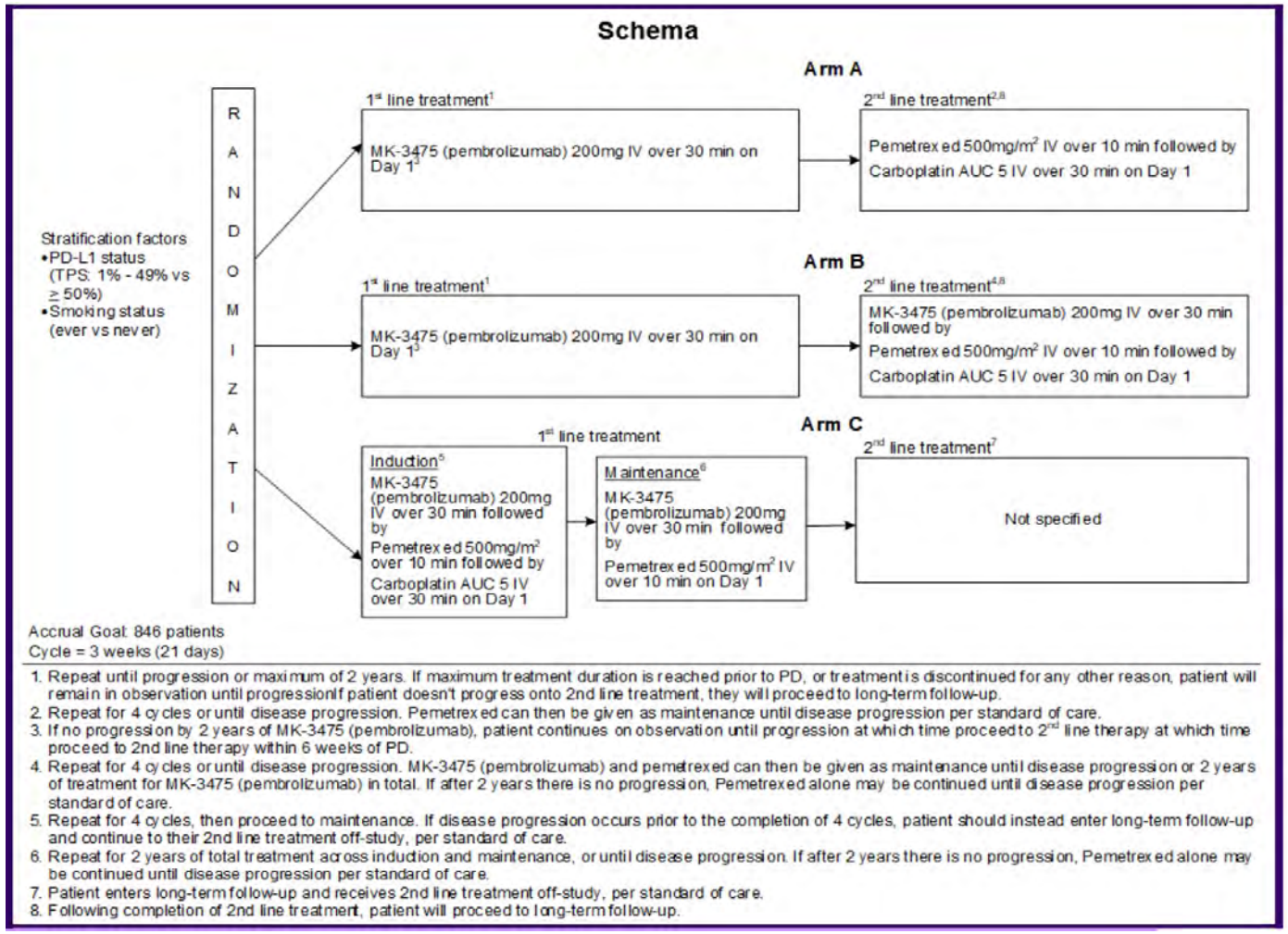
- What is the PD-L1?
- How fit is the patient? Age, PS, comorbidities etc.
- How much is a more immediate response needed?
- What is the patient preference?

Basic Metastatic NSCLC Algorithm



Steuer et al. JOP 2021

Insignia Clinical Trial



https://ecog-acrin.org/wp-content/uploads/2021/03/EA5163-physician-fact-sheet.pdf

Immunotherapy for Driver Mutations

- With few exceptions, NSCLC patients with driver mutations do not respond well to immuno-monotherapy

TABLE 2. Best Overall Response Rate Among Patients With NSCLC by Driver Mutation by Treatment Options and Levels of Evidence

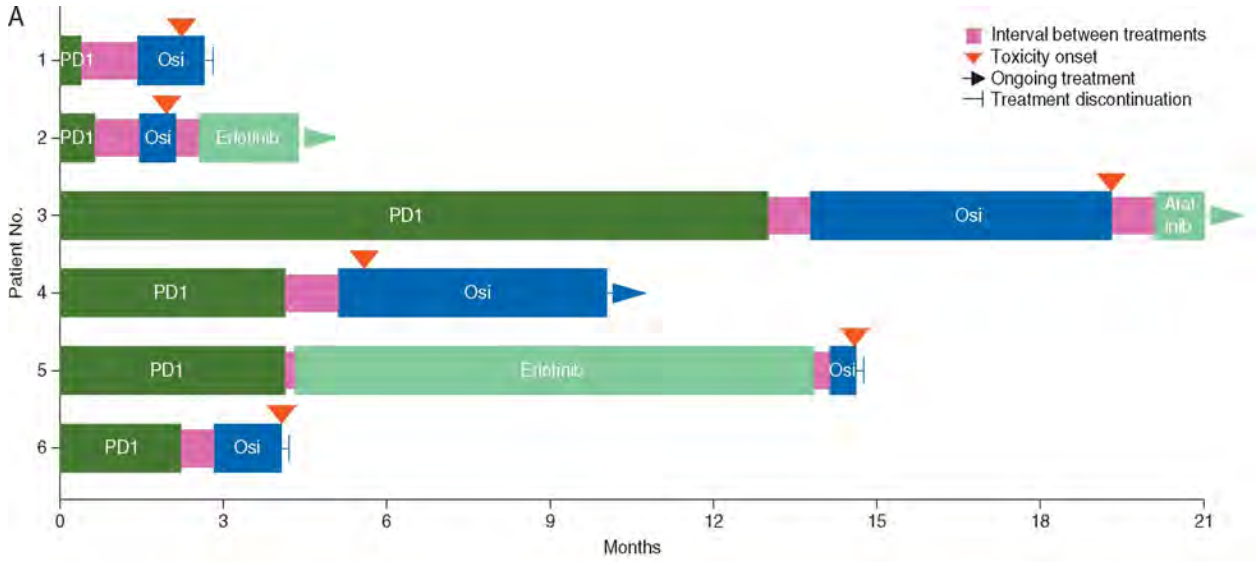
	EGFR	*ALK*	*ROS1*	*BRAF*	*KRAS*	*HER2*	*MET*	*RET*	*NTRK*
Targeted therapy	**80%**[a]	**83%**	*77%*	*64%*	*54%*[b]	*55%*	*71%*	*68%*	*75%*
ICI	**11%**	**4%**	**14%**	**24%**	**57%**[c]	**15%**	**23%**	**11%**	**NA**
					25%				
ICI + targeted therapy	*75%*[d]	*81%*[d]							
Chemotherapy + ICI	***81%***[a]	**NA**			***41%***				

NOTE. The following key refers to data source: bold, randomized phase III clinical trials; italic, phase I or II single-arm clinical trials; bold and italic, subgroup analysis of phase III clinical trials; bold and underline, pooled analysis of retrospective series. For EGFR and ALK, data from phase II noncomparative trials and subgroup analysis of phase III clinical trials are also available. For KRAS, data from subgroup analysis of phase II or III clinical trials are also available.
Abbreviations: ICI, immune checkpoint inhibitor.
[a]In sensitizing mutations.
[b]Specific *KRAS* G12C inhibitor.
[c]In first line.
[d]Increased grade ≥ 3 toxicities.

Calles et al. ASCO. Educational Book 2020

Using Immunotherapy Before NGS Results

- Case series from MSK detailing 126 EGFR mutant NSCLC patients who were treated with IO and osimertinib
- 6/41 (15%) patients that were treated with PD-L1 followed by osimertinib developed severe IRAEs. The reverse was not true.
- 4/6 of these were Grade 3 pneumonitis.
- **Therefore, if the rare need should arise to start systemic therapy immediately, I would use chemotherapy alone. Can add immunotherapy later if appropriate**.



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Patient No.	IO regimen	Time on IO	Time interval between IO and Osimertinib	Time to onset of toxicity after 1st dose of Osimertinib	Toxicity	Toxicity grade	Need for hospitalization?	Response to steroids?
1	nivolumab	14 days	29 days	24 days	Pneumonitis	3	yes	yes
2	carboplatin, pemetrexed, pembrolizumab	21 days	23 days	15 days	Pneumonitis	3	no	yes
3	ipilimumab, nivolumab	392 days	22 days	167 days	Pneumonitis	3	yes	yes
4	pembrolizumab	126 days	28 days	14 days	Colitis	3	yes	no
5	pembrolizumab	126 days	314 days	15 days	Pneumonitis	3	yes	yes
6	nivolumab	68 days	39 days	39 days	Hepatitis	4	yes	no

Schoenfeld et al. Ann Onc. 2019

CITYSCAPE: randomised Phase II study of tiragolumab + atezolizumab in PD-L1+ patients with NSCLC

Stratification factors
- PD-L1 TPS (1–49% vs ≥50%)
- Histology (non-squamous vs squamous)
- Tobacco use (yes vs no)

Co-primary endpoints
- ORR and PFS

Key secondary endpoints
- Safety, DOR, OS

Exploratory endpoints
- Efficacy analysis by PD-L1 status, PROs

Primary analysis[1]
- Cut-off date of 30 June 2019
- Median follow-up of 5.9 months

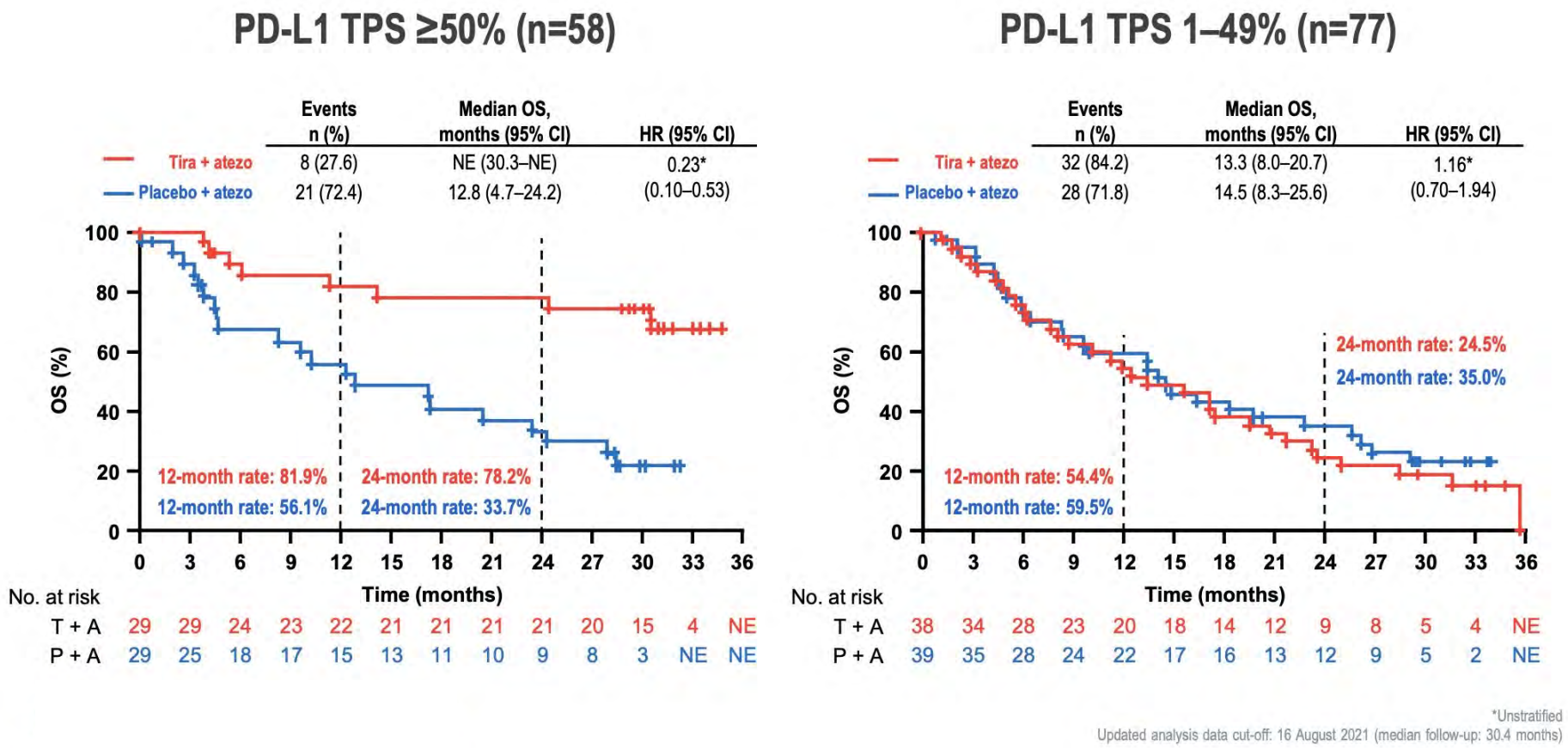
Updated analysis
- Follow-up performed to assess safety and efficacy
- Cut-off date of 16 August 2021
- Median follow-up of 30.4 months

1. Rodriguez-Abreu et al. ASCO 2020

DOR, duration of response; IHC, immunohistochemistry; ORR, confirmed overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; TPS, tumour proportion score

Cho et al. ESMO 2021

Overall survival: PD-L1 subgroups



- But press release reports that phase 3 SKYSCRAPER-01 failed to meet its endpoint

Cho et al. ESMO 2021

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

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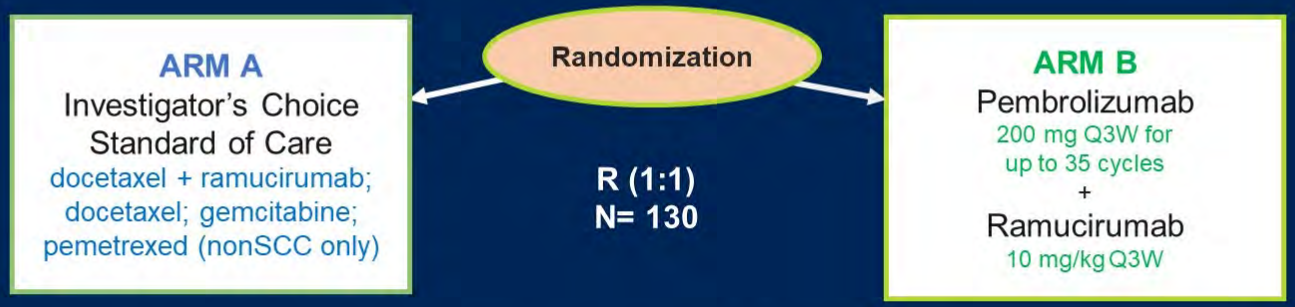
S1800A Schema—Randomized Phase II trial

NCT03971474

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

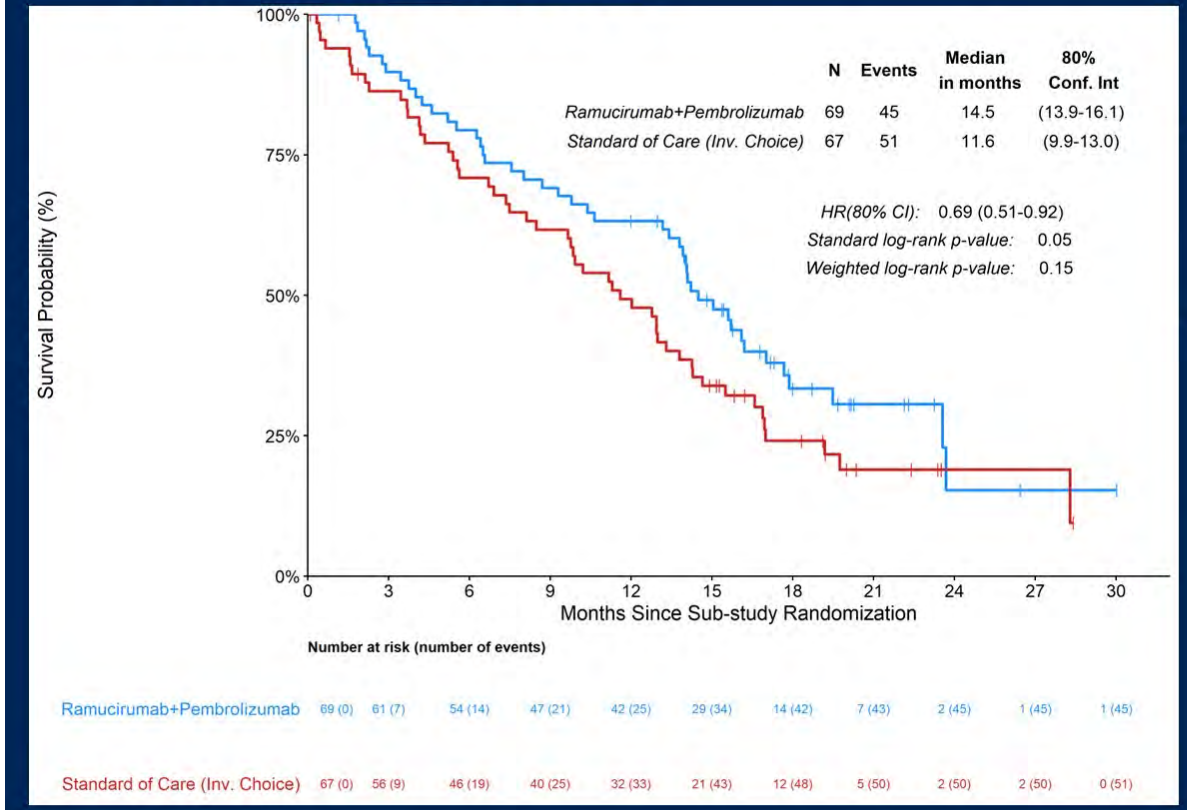
Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities



Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

Overall survival



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Thank you!