### Updates in Immunotherapy for Metastatic NSCLC

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The Winship Cancer Institute of Emory University July 23, 2022

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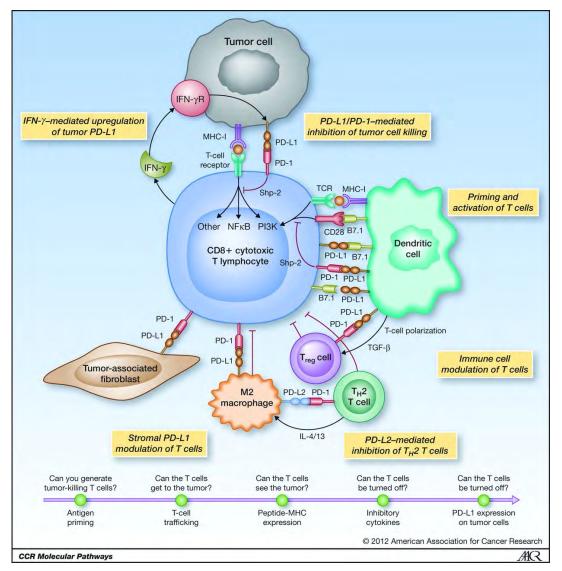
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# **Disclosures**

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



# PD-1/PD-L1 Pathway



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WINSHIP CANCER INSTITUTE Chen et al. CCR 2012

# **Approved Immunotherapeutic Agents in NSCLC**

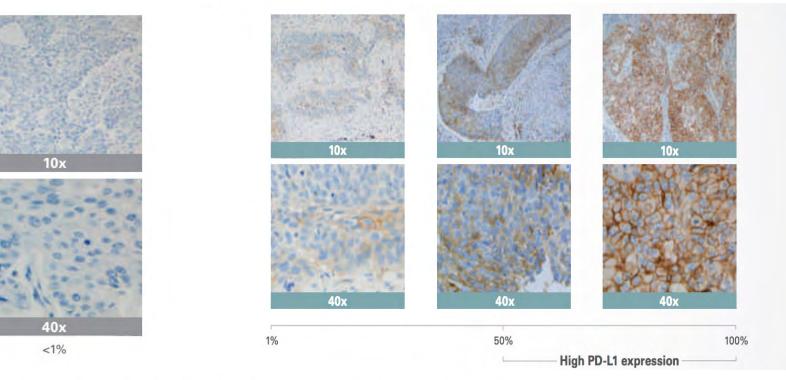
- Metastatic disease
  - 1<sup>st</sup> Line
    - Pembrolizumab with or without chemotherapy
    - Atezolizumab with chemotherapy and bevacizumab
    - Nivolumab and Ipilimumab with or without chemotherapy
    - Cemiplimab
  - 2<sup>nd</sup> line
    - Pembrolizumab
    - Nivolumab
    - Atezolizumab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

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- 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:

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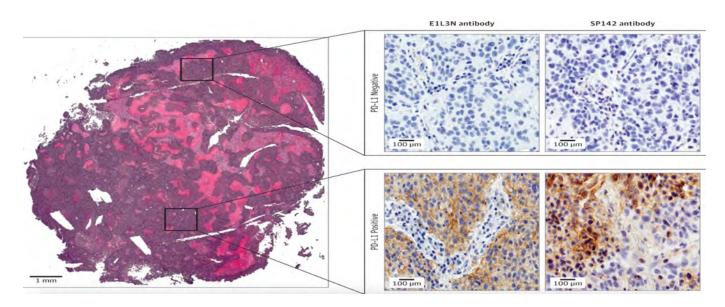
PD-L1 DAKO 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer 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

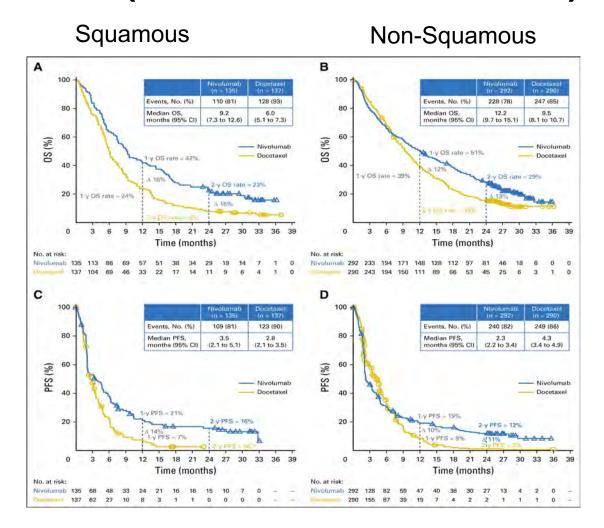
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McLaughlin et al. Jama Onc 2016 Grigg and Rizvi, JITC 2016

### Combined Analysis of Nivolumab vs. Docetaxel, 2<sup>nd</sup> line NSCLC, (CheckMate 17 and 57)



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WINSHIP CANCER INSTITUTE 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

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• Secondary endpoints: OS, ORR, Safety

# Keynote 24

• 305 patients enrolled

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

# Keynote 24

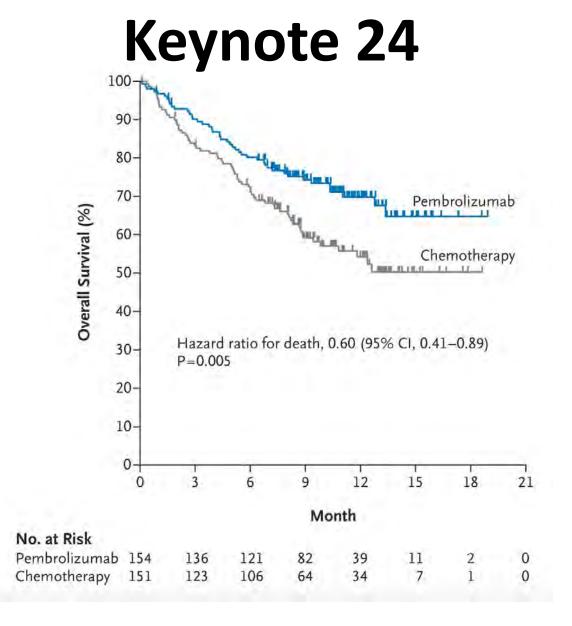
Treatment	ORR	PFS	OS (HR)
Chemotherapy	27.8%	6.0 mo	14.2 mo
Pembrolizumab	44.8%	10.3 mo	30.2 mo

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Reck et al. NEJM 2016

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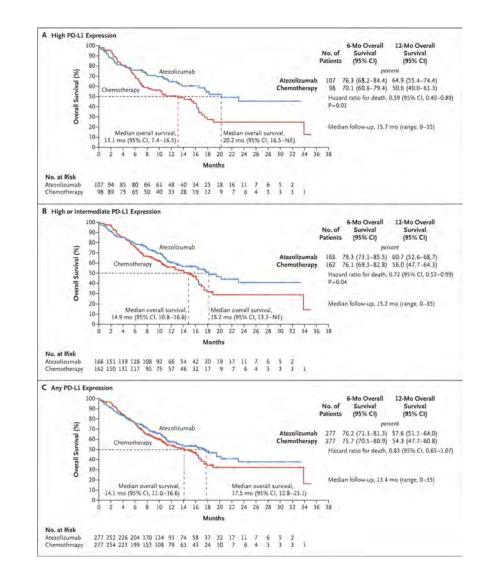
# IMpower110

• Similar to Keynote-024, but utilized atezolizumab

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- 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



# **EMPOWER-Lung 1**

- Similar to Keynote-024, but utilized cemiplimab
- 710 patients

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- 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

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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

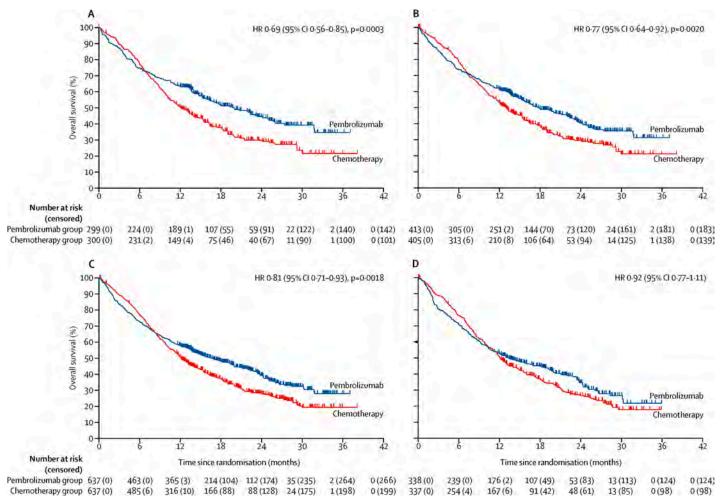


# Keynote-042

- Phase 3 study comparing pembrolizumab vs platinumbased 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

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### **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.

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WINSHIP CANCER INSTITUTE 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

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# Combination Studies Chemo-IO IO-IO Hybrid

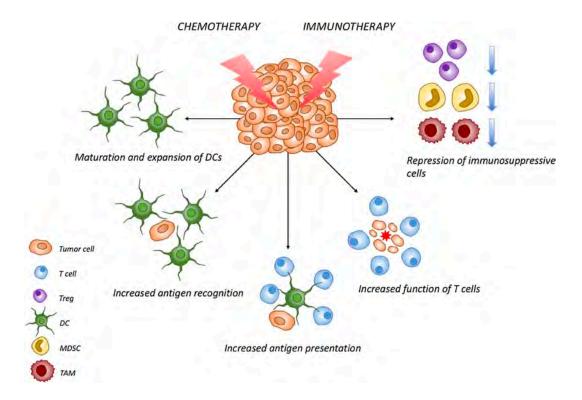


# Clear Biological Rationale for Chemo/IO

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

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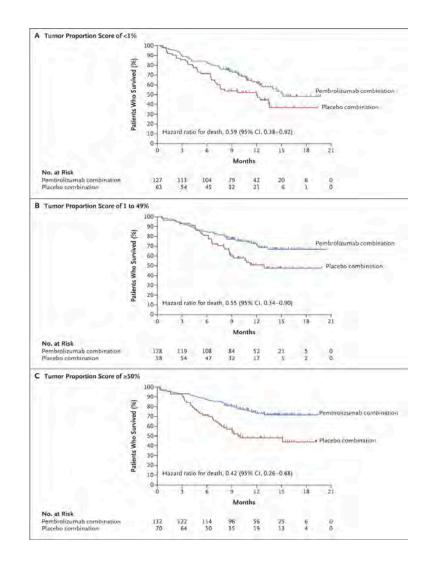


# Chemo + IO- Keynote 189

- 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

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# Keynote 189



L Gandhi et al. N Engl J Med 2018

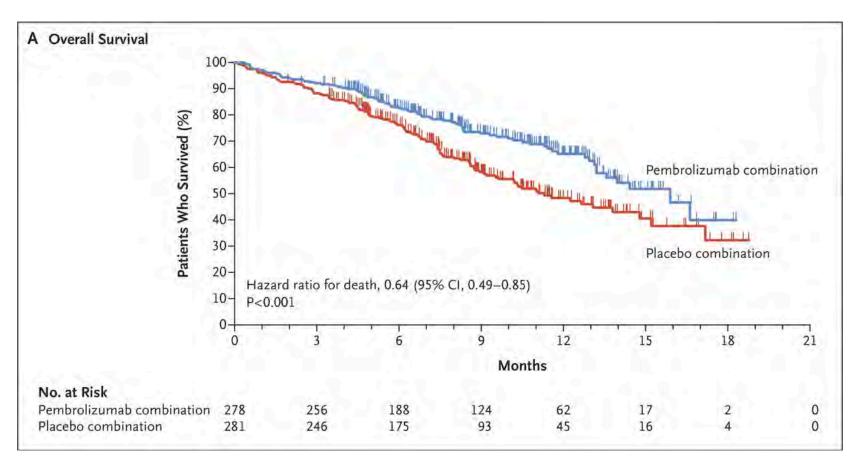
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# Keynote 407

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

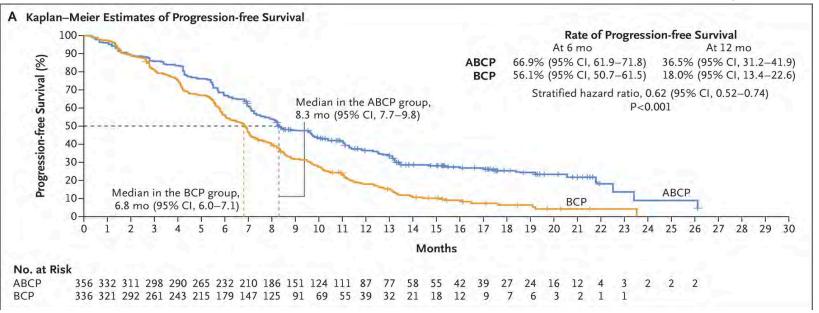


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WINSHIP CANCER INSTITUTE L Paz-Ares et al. N Engl J Med 2018

# 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)



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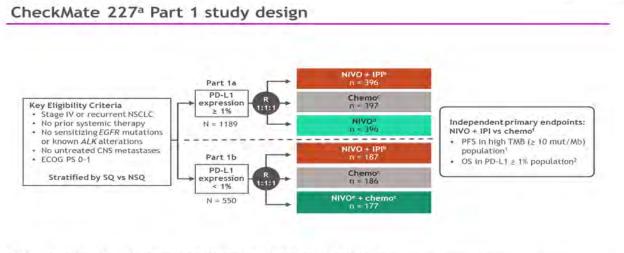
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# Checkmate-227

- 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 CheckMate 227: 3-year update

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Database lock: February 28, 2020; minimum / median follow-up for 05: 37.7 months / 43.1 months. Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immuntherapy; NCT02477826: MIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); NSQ: pemetrexed - cisplatin or carboplatin, Q3W for 4 cycles; with optional pemetrexed maintenance following chemo or NIVO - pemetrexed maintenance following therapetre distance or Divor - pemetrexed maintenance following therapetre distance for the divort of the distance or Divor - pemetrexed maintenance following therapetre distance for the distance for the distance of the divort of the distance or Divor - pemetrexed maintenance following therapetre distance or Divor - pemetrexed maintenance following therapetre previously reported. 1. Helimaim M0, et al. N Engl J Med 2019;3812(3):2003-2014; J Heliman M0, et al. N Engl J Med 2019;3812(3):2003-2031.

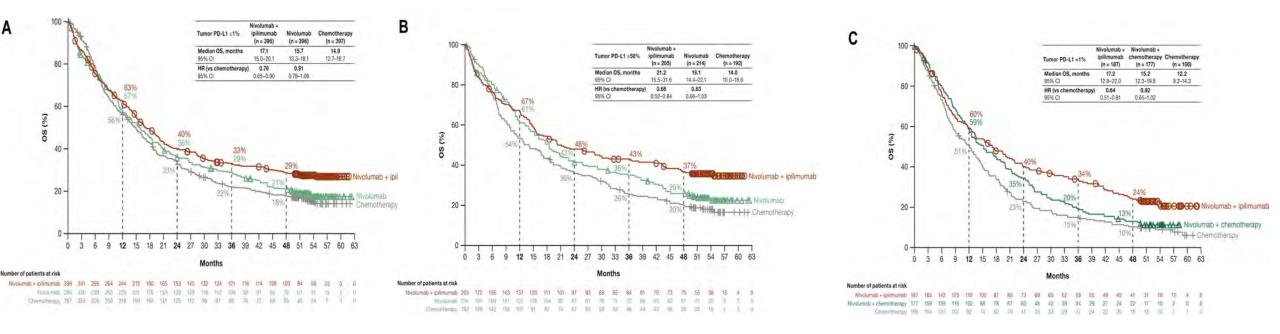
# Checkmate-227, 4-Year Update

• 1739 patients enrolled overall

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



Led To FDA approval for Nivo-IPI  $\geq$  1%

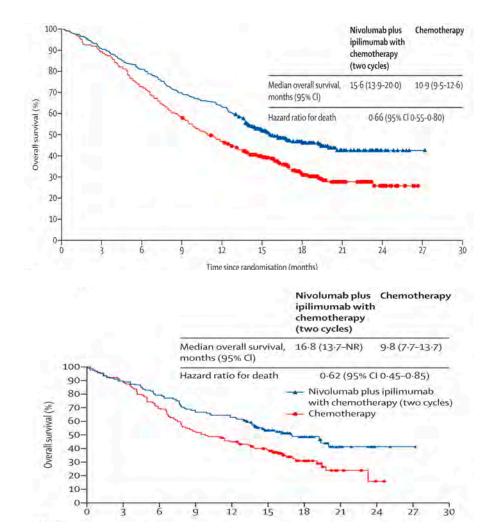
Paz-Ares et al. JTO 2021

## **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%

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# **Checkmate 9LA**



**Overall Population** 

PD-L1 < 1% Population

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

<sup>1</sup>Center for Drug Evaluation and Research, U.S. Food and Drug Administration

<sup>2</sup>Oncology Center of Excellence, U.S. Food and Drug Administration

#### Oladimeji Akinboro, MD, MPH



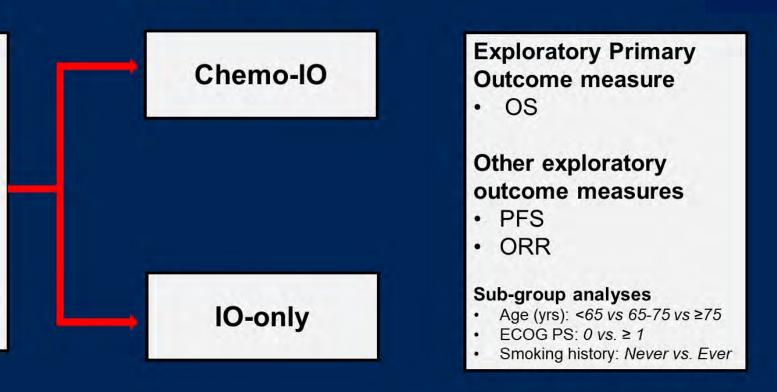
### **Study Design**

#### **Pooled Analysis Population**

- Advanced NSCLC
- PD-L1 TPS ≥50%
  - Excluded staining by tumorinfiltrating immune cells
- No sensitizing EGFR mutations or ALK alterations

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 Clinical trial supported FDA approval of IO-based regimen



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 ( <i>N</i> =455)	IO-alone ( <i>N</i> =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)					

cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.



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

		Hazard Ra	tio	1
Subgroup	Ν	1	Median OS (95% CI) Chemo-IO	Median OS (95% CI) IO-Only
Overall	1753	F∎ł	25.0 (19.0, NE)	20.9 (18.5, 23.1)
Age <65 years 65-74 years >=75 years	898 642 185		25.0 (19.2, NE) 22.2 (16.5, NE) NE (12.0, NE)	23.3 (20.0, NE) 18.6 (16.0, 21.9) 18.9 (15.1, NE)
ECOG 0 1+	602 1148	⊦-æ-i ⊦æi	NE (23.0, NE) 17.7 (14.8, NE)	31.8 (22.4, NE) 18.0 (15.7, 21.0)
Smoking Status Current/former smokers Never smokers	1549 197		23.0 (18.2, NE) NE (22.2, NE)	22.1 (19.7, 25.1) 14.4 (12.2, 21.0)
<c< td=""><td>hemo-IO</td><td>0.25 0.50 1.0 2.0 BetterIO-on</td><td>ly Better&gt;</td><td></td></c<>	hemo-IO	0.25 0.50 1.0 2.0 BetterIO-on	ly Better>	

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.

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# **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

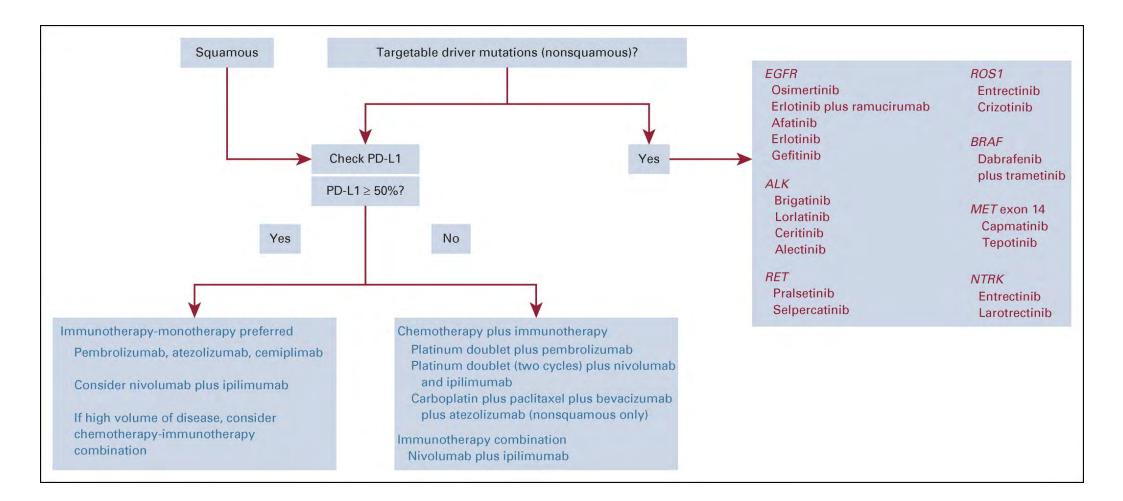


# Some important questions:

- 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**



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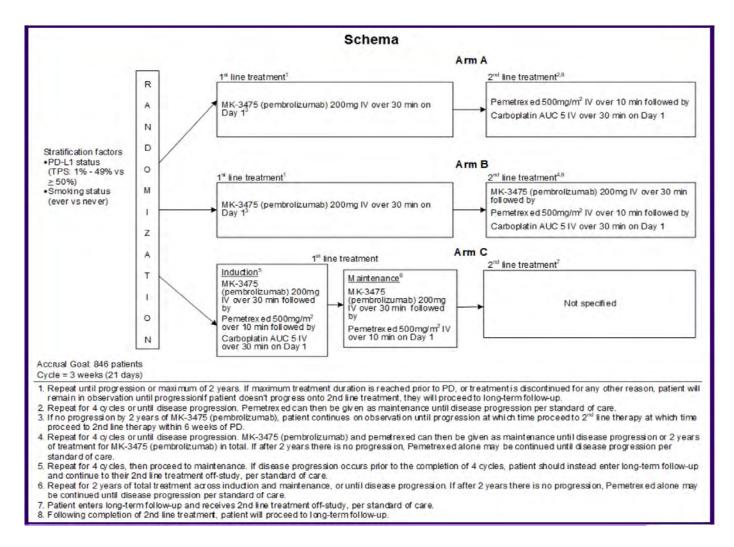
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#### **Insignia Clinical Trial**

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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

2.0.111	EGFR	ALK	ROS1	BRAF	KRAS	HER2	MET	RET	NTRK
Targeted therapy	80%"	83%	77%	64%	54 % <sup>b</sup>	55%	71%	68%	75%
ICI	11%	4%	14%	24%	57% <sup>c</sup>	15%	23%	11%	NA
					25%				
ICI + targeted therapy	75% <sup>a</sup>	81 % <sup>d</sup>			199				
Chemotherapy + ICI	81%	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.

\*In sensitizing mutations.

<sup>b</sup>Specific KRAS G12C Inhibitor.

CIn first line.

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<sup>d</sup>Increased grade ≥ 3 toxicities.

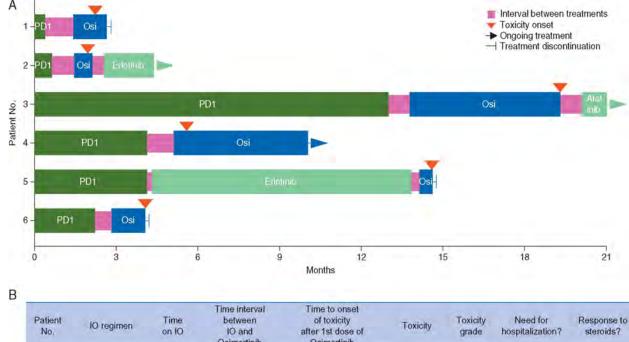
# **Using Immunotherapy Before NGS Results**

- 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.

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• Therefore, if the rare need should arise to start systemic therapy immediately, I would use chemotherapy alone. Can add immunotherapy later if appropriate.



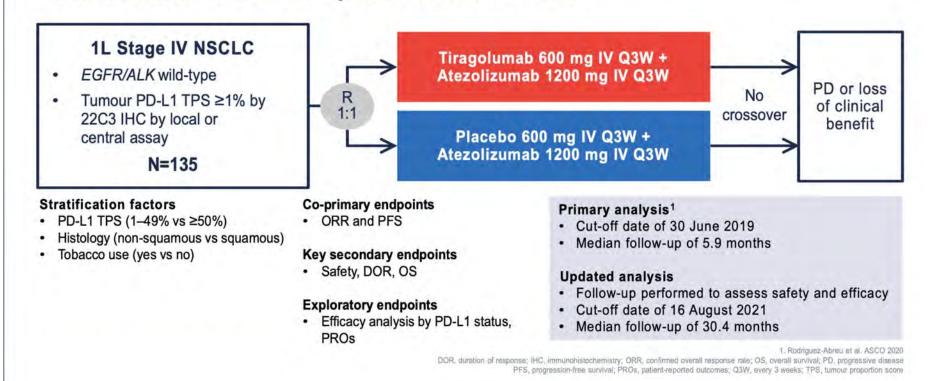
Patient No.	IO regimen	Time on IO	between IO and Osimertinib	of toxicity after 1st dose of Osimertinib	Toxicity	Toxicity grade	Need for hospitalization?	Response to steroids?
1	nivolumab	14 days	29 days	24 days	Pneumonitis	3	yes	yes
2	carboplatin, pemetrexed, pembrolizumab	21 days	23 days	15 days	Pneumonitis	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

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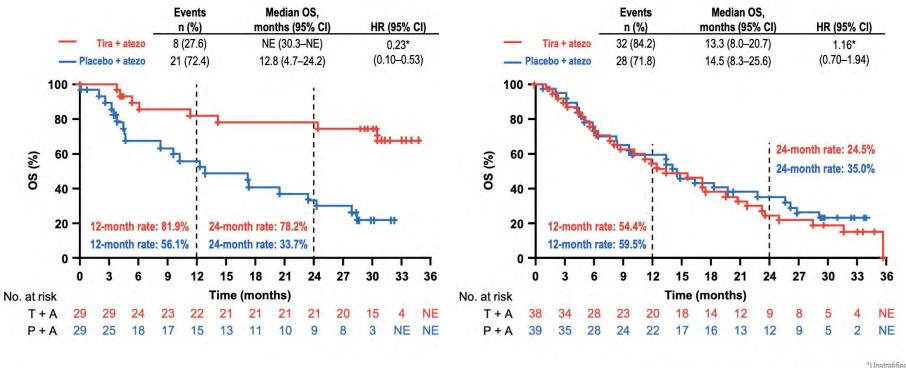
Cho et al. ESMO 2021

### **Overall survival: PD-L1 subgroups**

#### PD-L1 TPS ≥50% (n=58)

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WINSHIP CANCER INSTITUTE PD-L1 TPS 1-49% (n=77)



Updated analysis data cut-off: 16 August 2021 (median follow-up: 30.4 months)

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

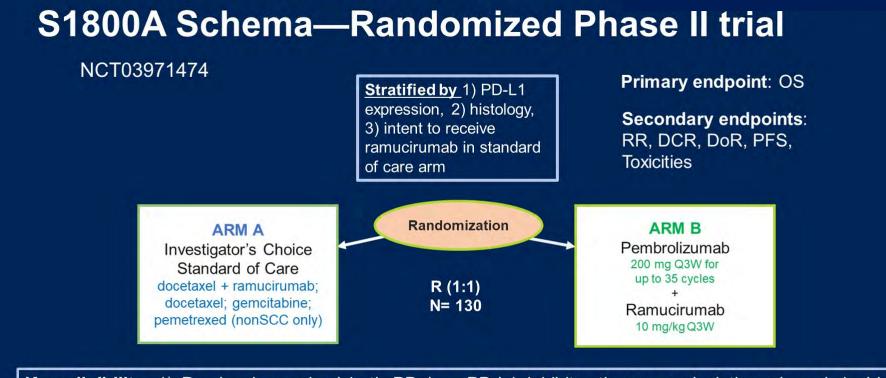
Cho et al. ESMO 2021

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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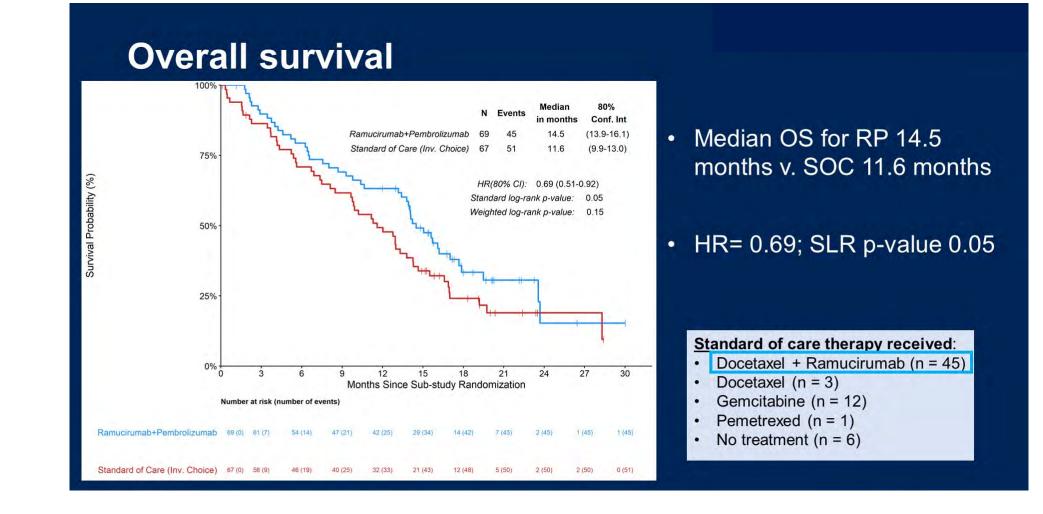




<u>Key eligibility</u>: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive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

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# Thank you!

