Immunotherapy in Advanced NSCLC: Initial Therapy and How to Overcome Resistance

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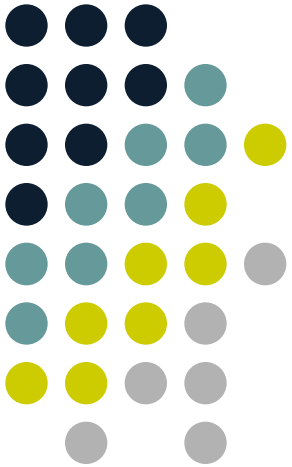
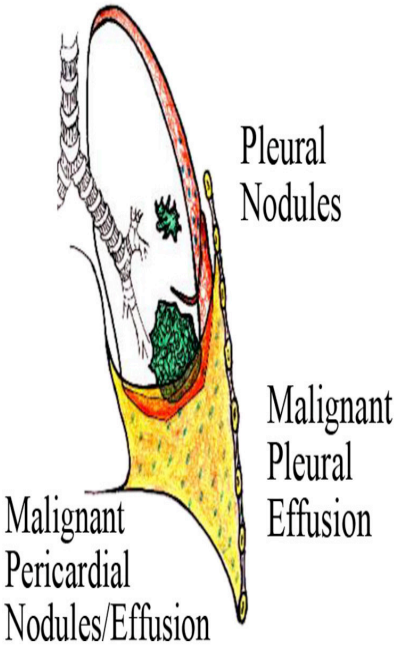


AJCC 8: Stage IVA and IVB

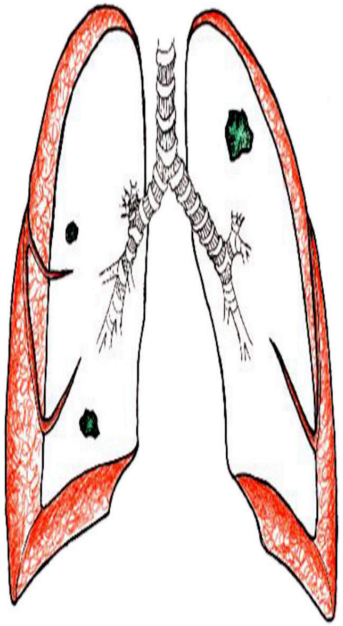
Stage IVA

Stage IVB

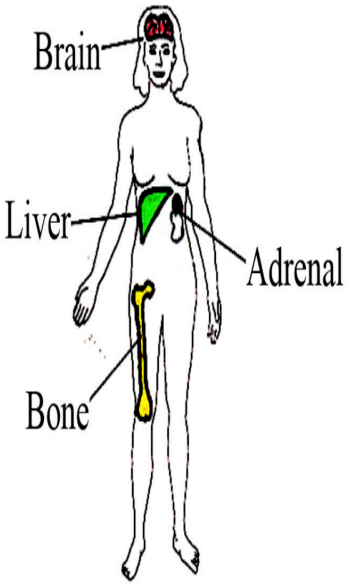
M1a Pl Dissem



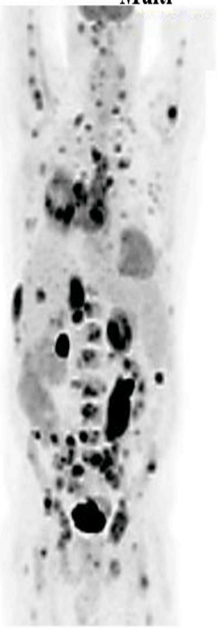
M1a Contra Nod



M1b Single



M1c Multi

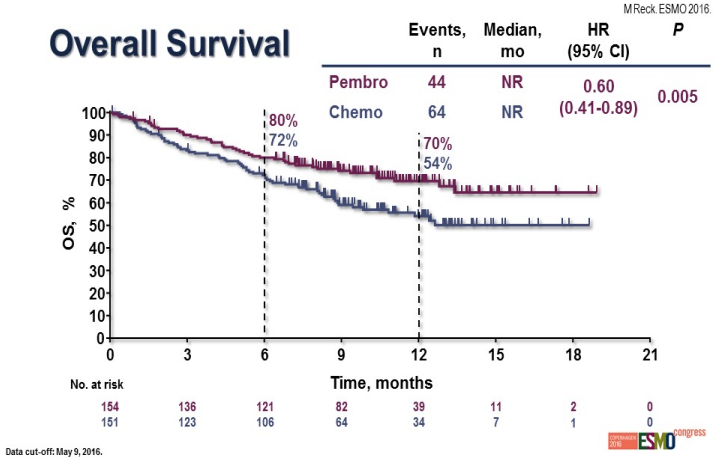


Key Phase III Studies in NSCLC

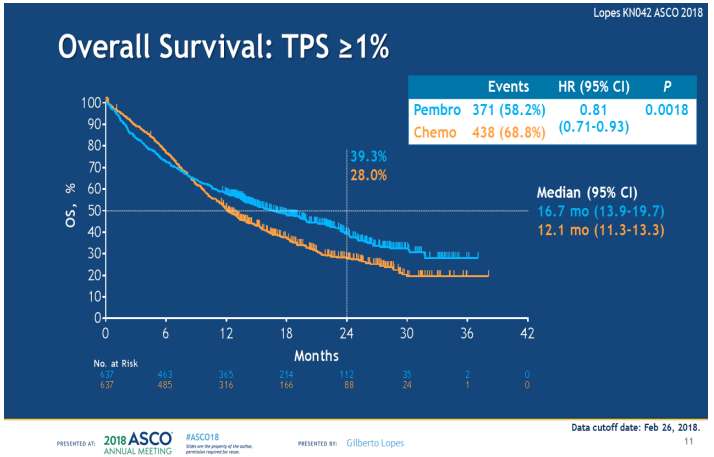
Phase III IO trials in Advanced-NSCLC

	Pathology	PDL-1	Arm I (OS)	Arm II (OS)	HR
KEYNOTE-024	squamous (18%) and nonsquamous (82%)	≥50%	Pembro	Chemotherapy	
			30 months	14.2 months	0.63
KEYNOTE-042	squamous (38%) and nonsquamous (62%)	≥1%	Pembro	Chemo	
			16.7 months	12.1 months	0.81
KEYNOTE-189	nonsquamous	Any level	Pembro/Pem/Plat	Plat/Pem	
			22 months	10.7 month	0.56
KEYNOTE-407	squamous	Any level	Pembro/Carbo/Tax	Carbo/Taxane	
			15.9 months	11.3 months	0.64
CHECKMATE-227	squamous (28%) and nonsquamous (72%)	Any level ≥1% <1%	Ipi/Nivo	Chemotherapy	
			17.1 months	14.9 months	0.79
			17.2 months	12.2 months	0.62
CHECKMATE 9LA	squamous and nonsquamous	Any level	Ipi/Nivo/Chemo	Plat/Pem or Taxane	
			15.6 months	10.9 months	0.66
IMpower110	squamous (25%) and nonsquamous (75%)	≥50%	Atezo	Plat/Pem or Gem	
			20.2 months	13.1 months	0.59
IMpower130	non-squamous	Any level	Atezo/Carbo/NbT	Carbo/NbT	
			18.6 months	13.9 months	0.79
IMpower150	non-squamous	Any level	Atezo/Bev/Carbo/Pac	Bev/Carbo/Pac	
			19.8 months	14.9 months	0.76

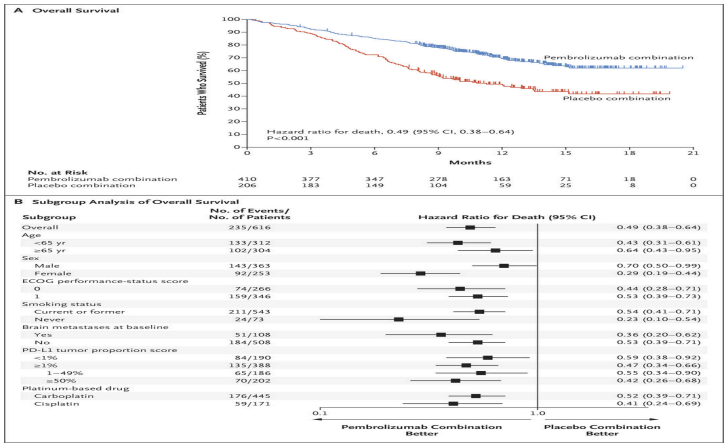
KN-24



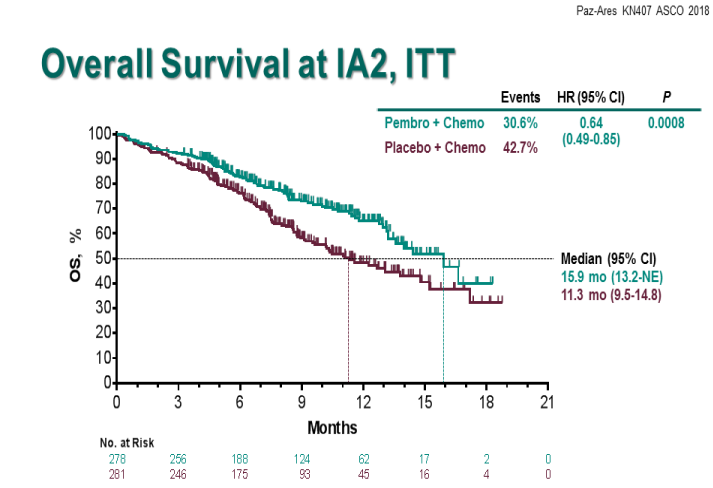
KN-42



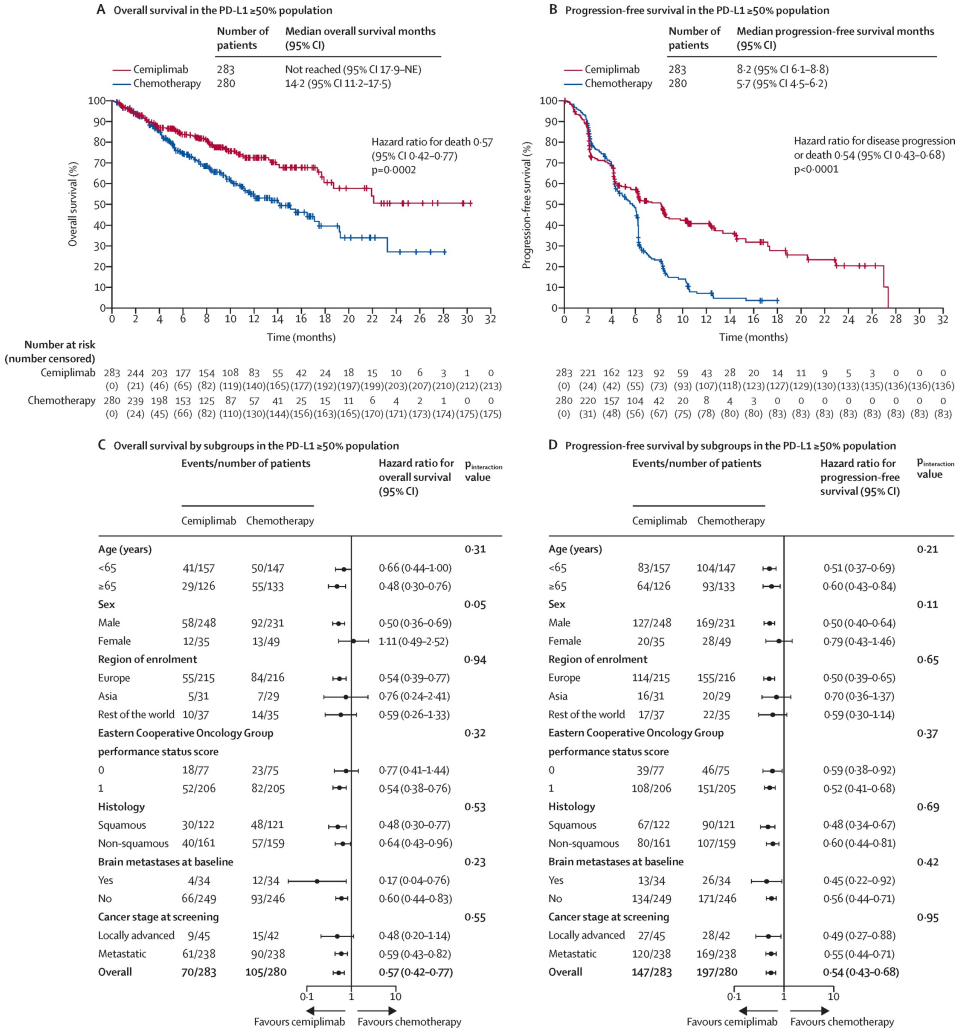
KN-189

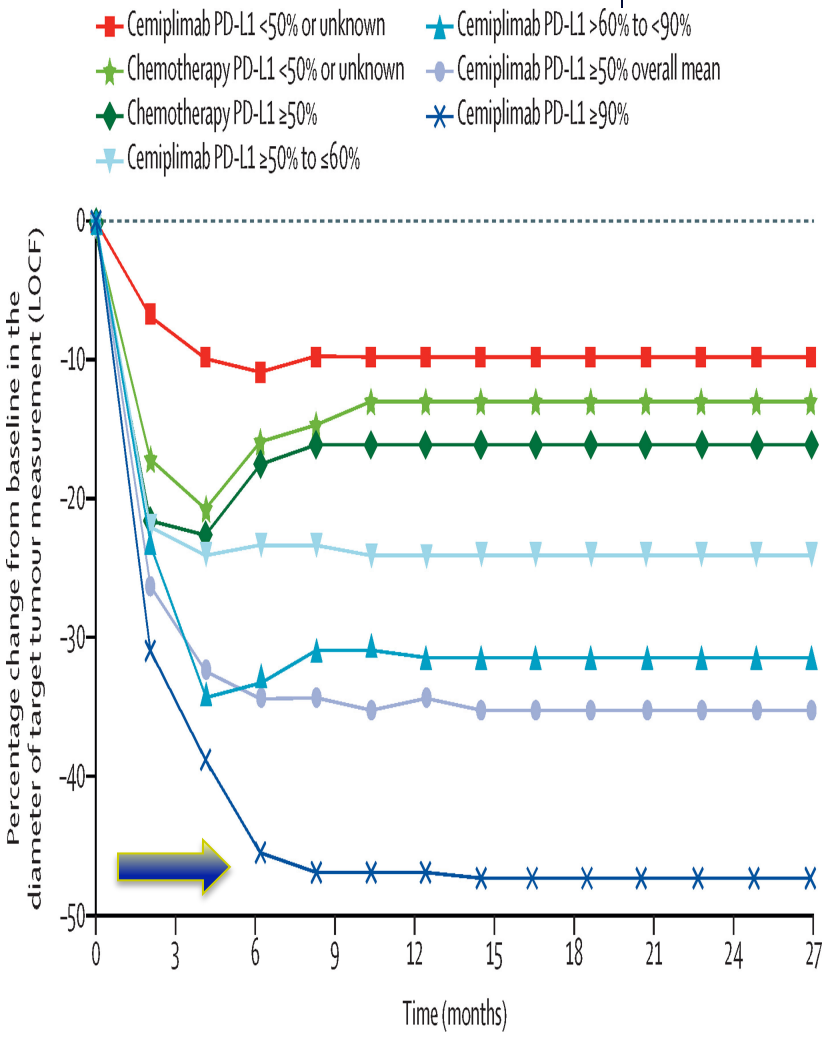


KN-407



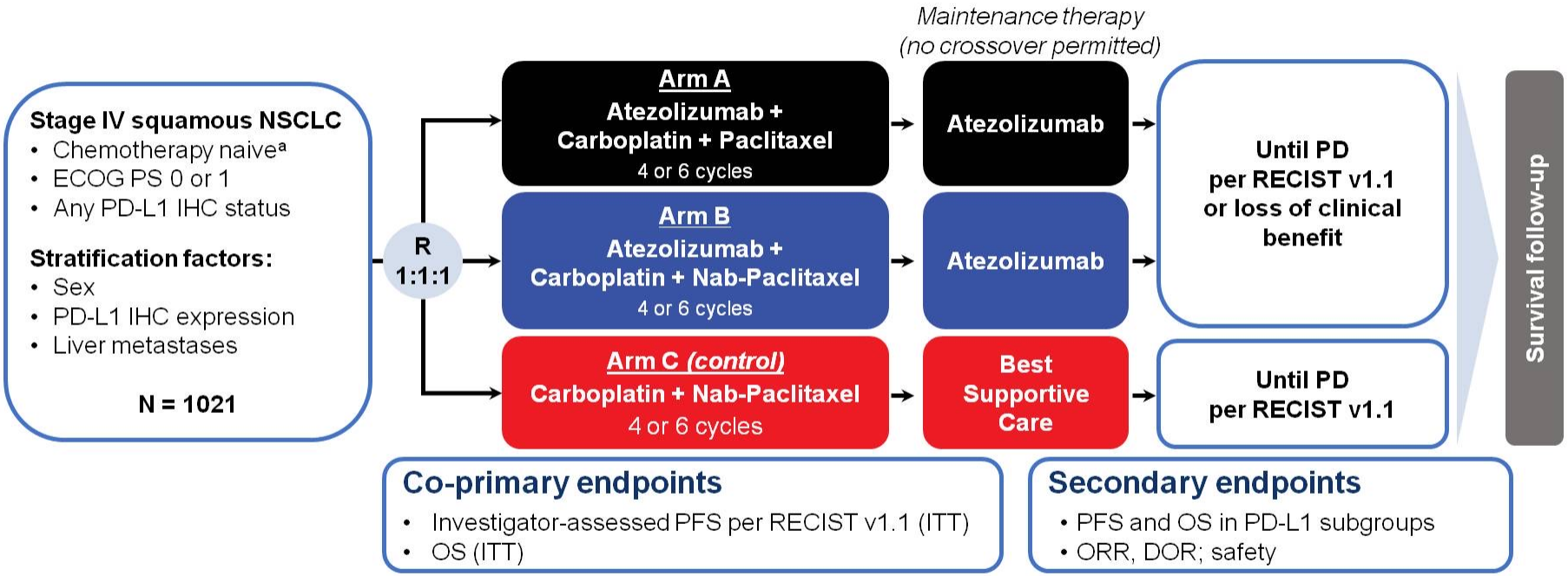
EMPOWER-Lung1
Cemiplimab Vs. Chemo: PD-L1 ≥ 50%





Lancet. February 13, 2021DOI:https://doi.org/10.1016/S0140-6736(21)00228-2

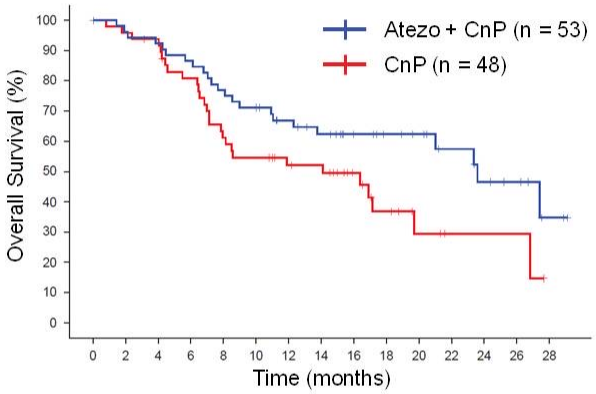
IMpower131: Study Design



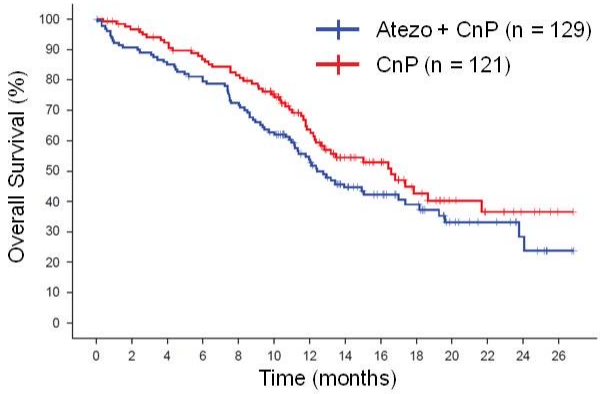
Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

First Interim OS in PD-L1 Subgroups (Arm B vs Arm C)

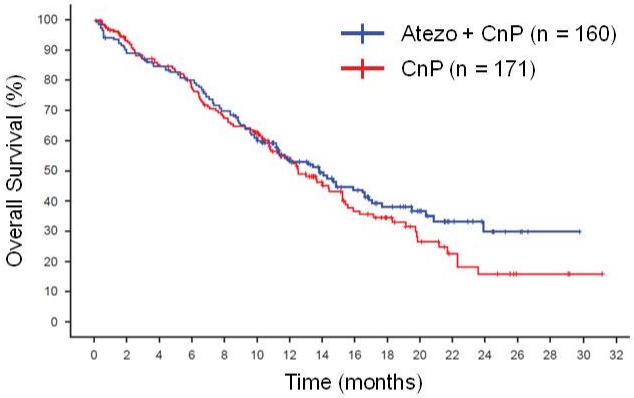
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0



	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month OS	67%	52%	54%	64%	53%	53%
24-month OS	47%	30%	28%	37%	30%	16%
Median OS, mo	23.6	14.1	12.4	16.6	13.8	12.5
HR[a] (95% CI)	0.56 (0.32, 0.99)		1.34 (0.95, 1.90)		0.86 (0.65, 1.15)	

Data cutoff: January 22, 2018.
[a] Unstratified HR.

PERLE: Randomized Phase II study

	PDL1 < 1%	PDL! 1 to 49%	PDL1> 50%	All patients
	DCP v PCP	DCP v PCP	DCP v PCP	DCP v PCP
RR	28% v 33%	50% v 34%	74% v 48%	46% v 37%
mPFS months	7.0 v 6.9 HR – 0.77	9 v 6.7 HR – 0.67	10.4 v 6.7 HR – 0.60	8.8 v 6.7; HR – 0.70

D=Dostarlimab; CP = Carbo+Pemetrexed; P - Pembrolizumab

(FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors. News release. FDA. August 17, 2021. GARNET Trial - NCT02715284)

Peters S, et al. Presented at ESMO Immuno-Oncology Congress 2022; December 7-9, 2022; Geneva, Switzerland

2022 ASCO® ANNUAL MEETING

FDA

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

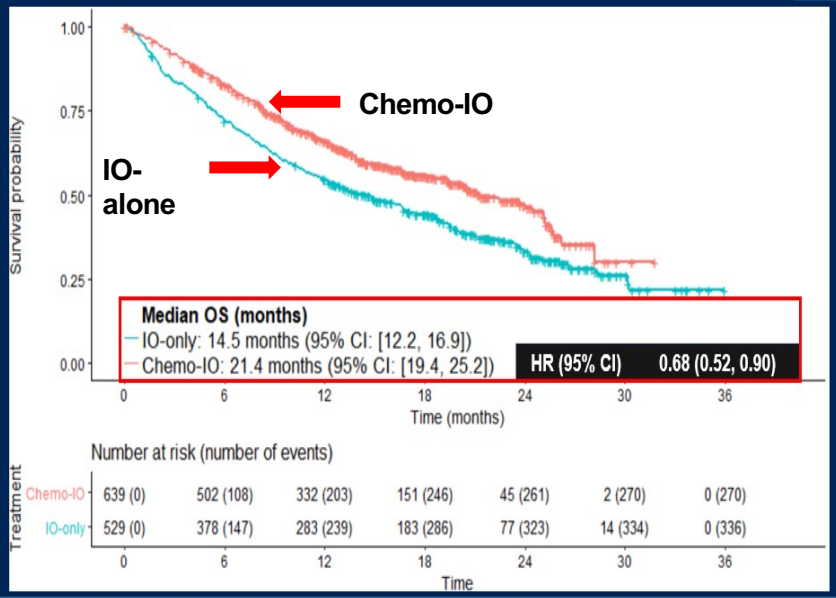
Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

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

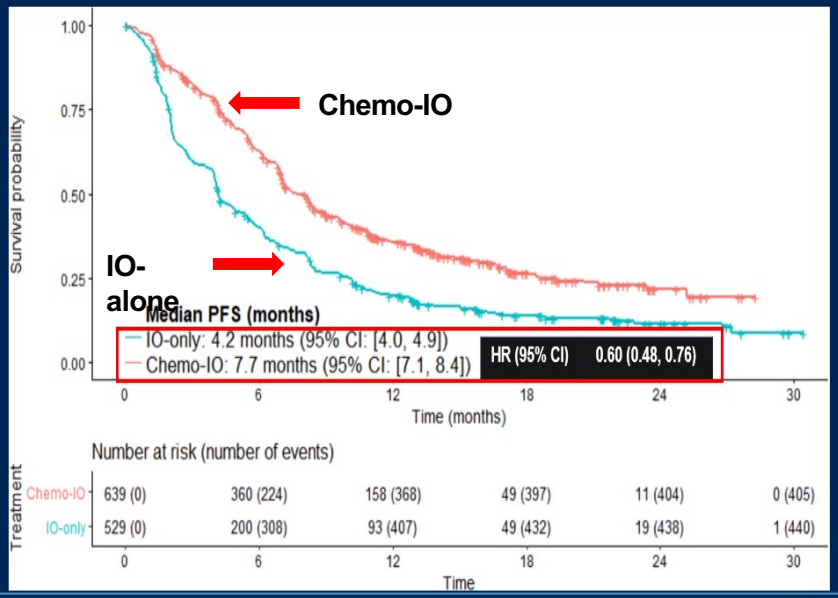
[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

Exploratory OS: NSCLC PDL1 1-49%



Exploratory PFS: NSCLC PDL1 1-49%



Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

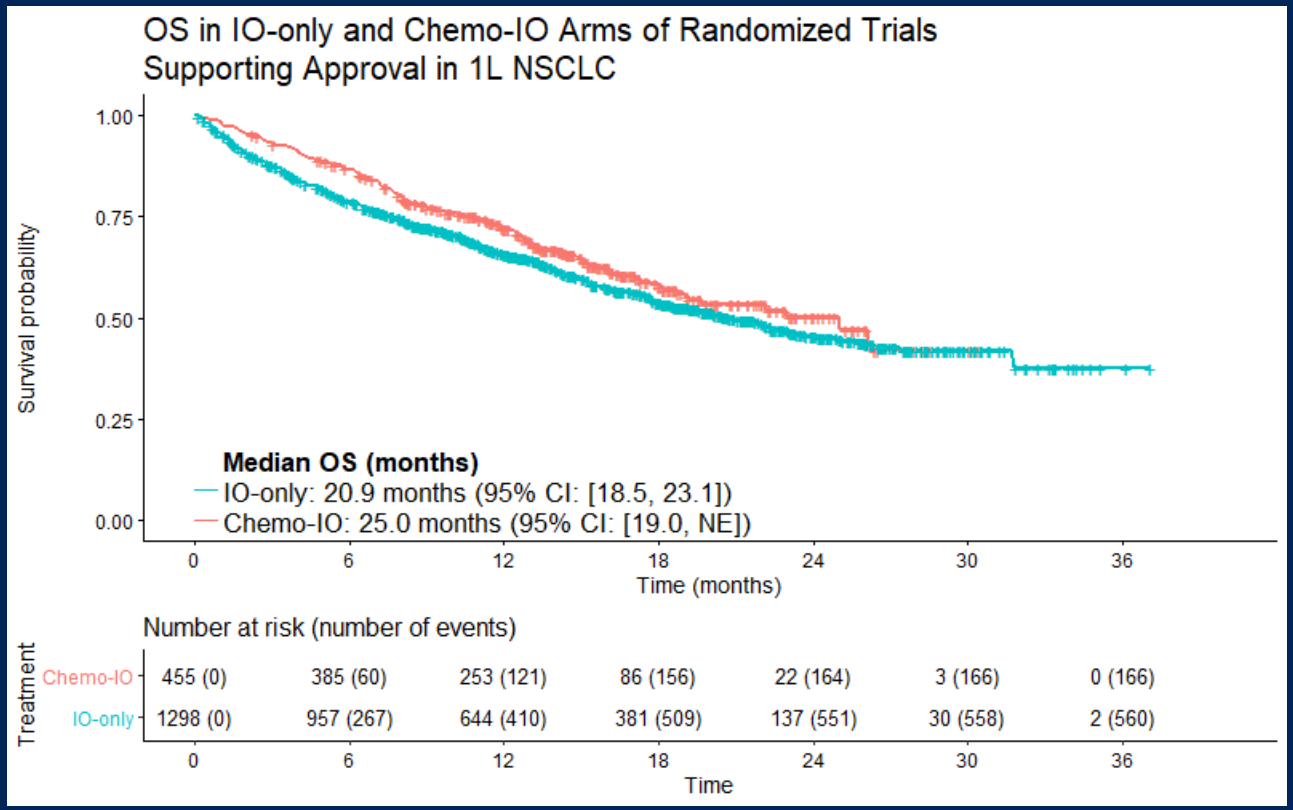
Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

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)	

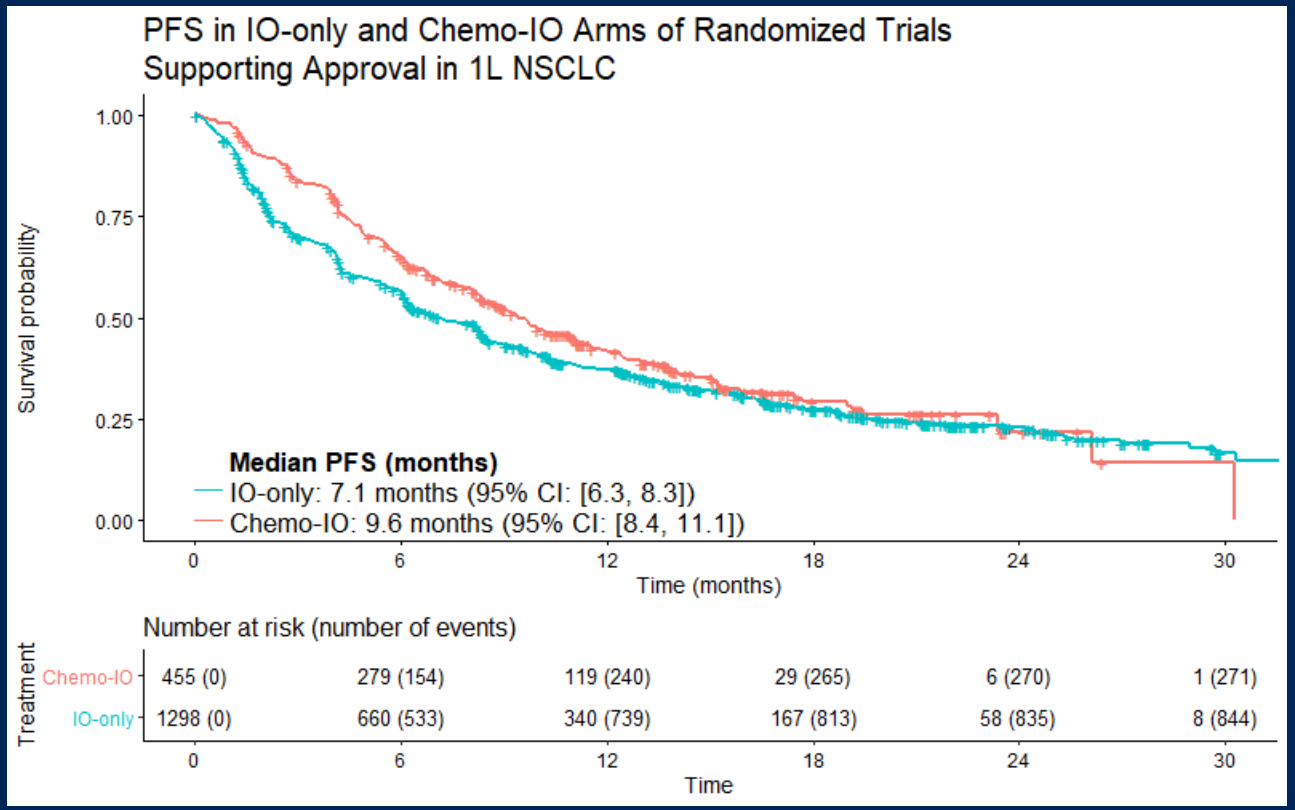
Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free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

Exploratory OS: Chemo-IO vs IO in NSCLC PD-L1 ≥50%



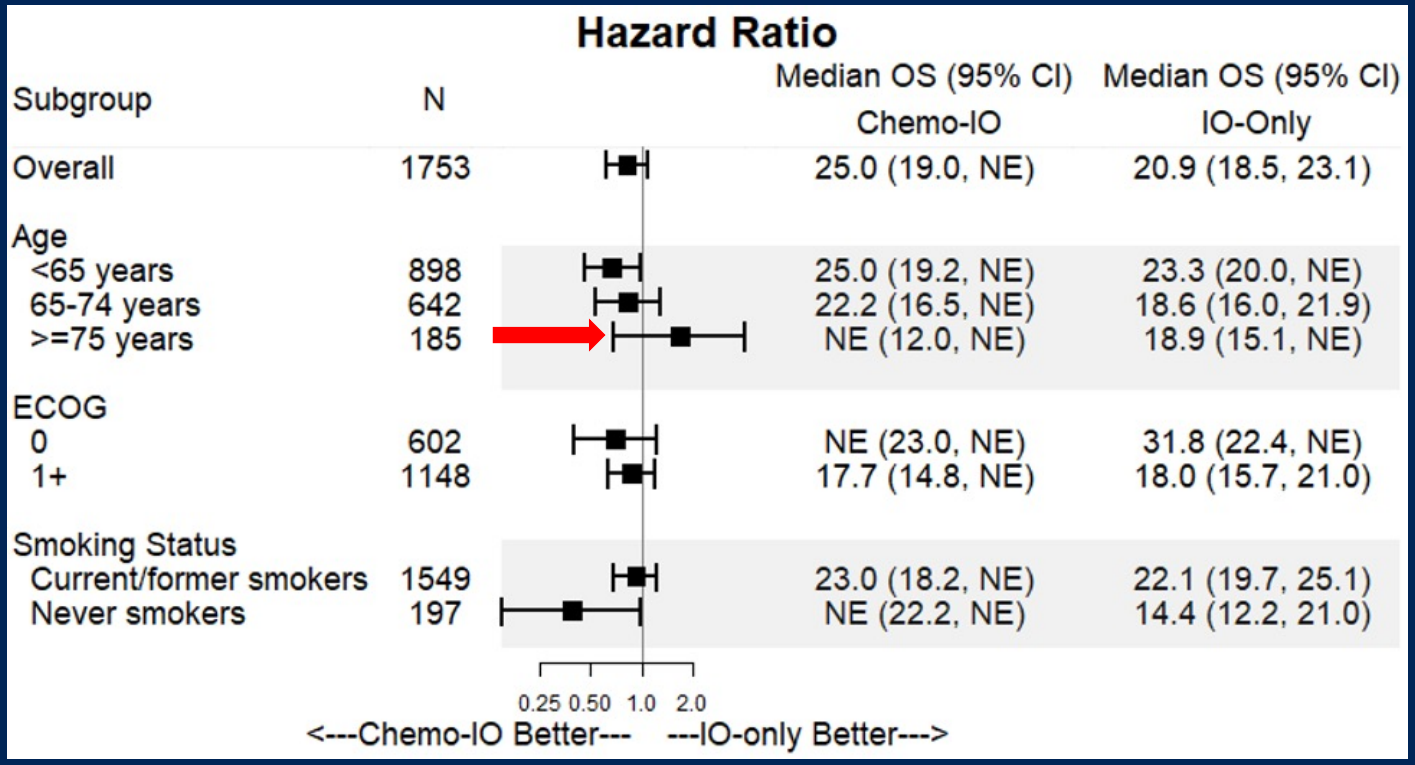
Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR=hazard ratio; IO=immunotherapy; NE=not estimable; NSCLC=non-small-cell lung cancer; OS=overall survival; PD-L1=programmed death ligand-1.

Exploratory PFS: Chemo-IO vs IO in NSCLC PD-L1 ≥50%



Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI-confidence interval; HR=hazard ratio; IO=immunotherapy; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1; PFS=progression-free survival.

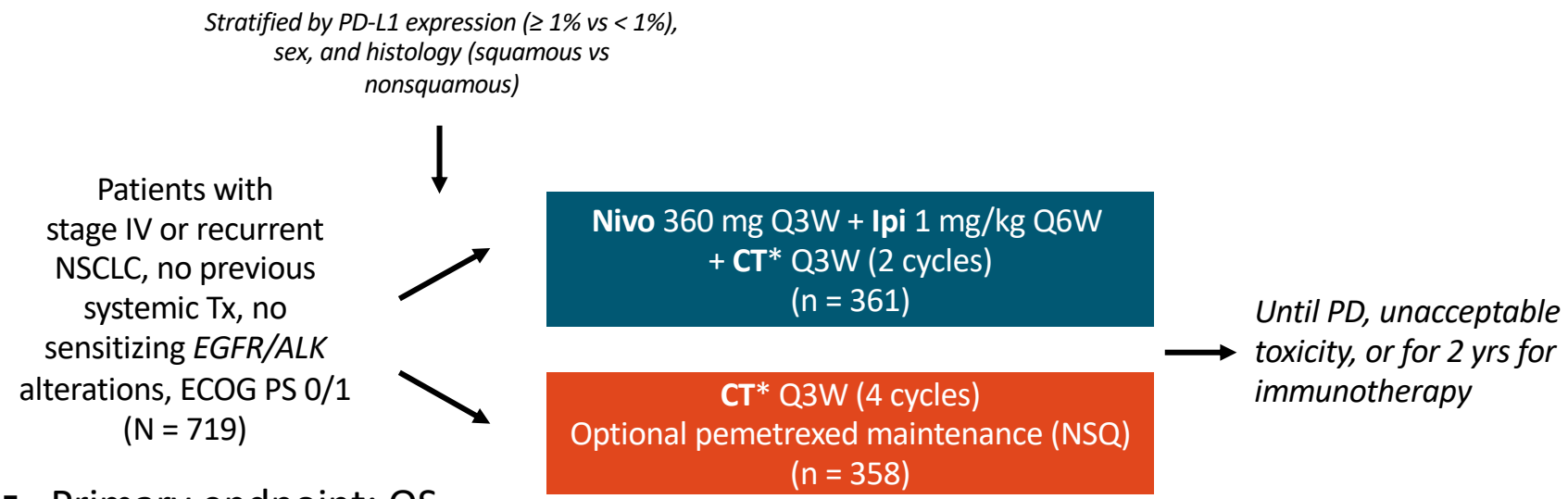
OS in NSCLC PD-L1 ≥50% in selected subgroups



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.

CheckMate 9LA: Study Design

- Randomized, open-label, phase III study



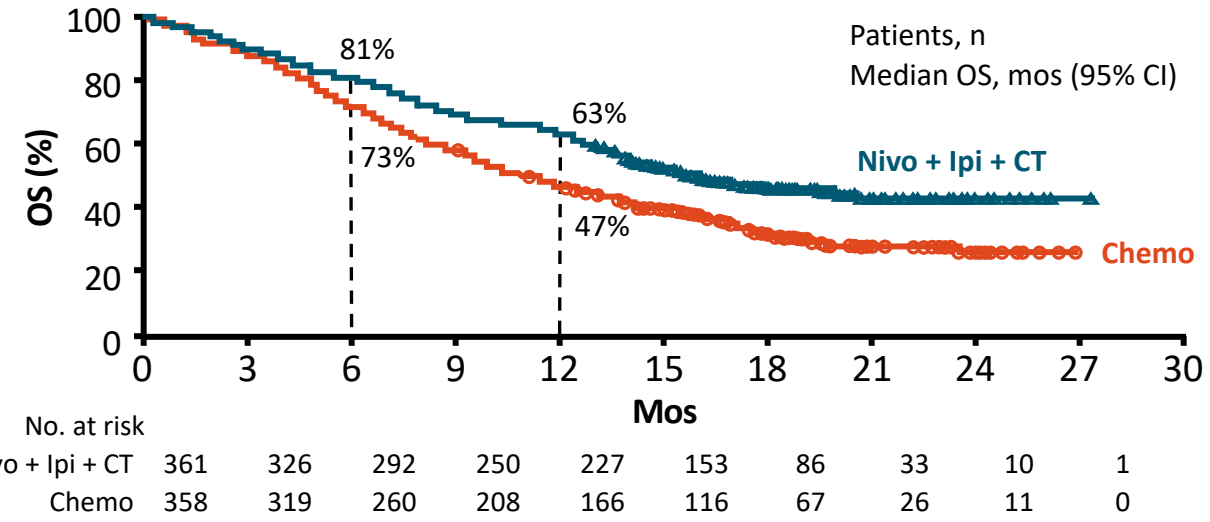
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, efficacy by tumor PD-L1 expression

*Pts with NSQ: pemetrexed + cisplatin or carboplatin; pts with SQ: paclitaxel + carboplatin.

Reck. ASCO 2020. Abstr 9501.

CheckMate 9LA: Updated OS Results

- Interim analysis (minimum FU 8.1 mos) median OS, Nivo + Ipi + CT vs CT: 14.1 vs 10.7 mos; HR: 0.69 (95% CI: 0.55-0.87); *P* = .0006; met primary endpoint
- Updated results (minimum FU 12.7 mos)



	Nivo + Ipi + CT	CT
Patients, n	361	358
Median OS, mos (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)

HR: 0.66 (95% CI: 0.55-0.80)

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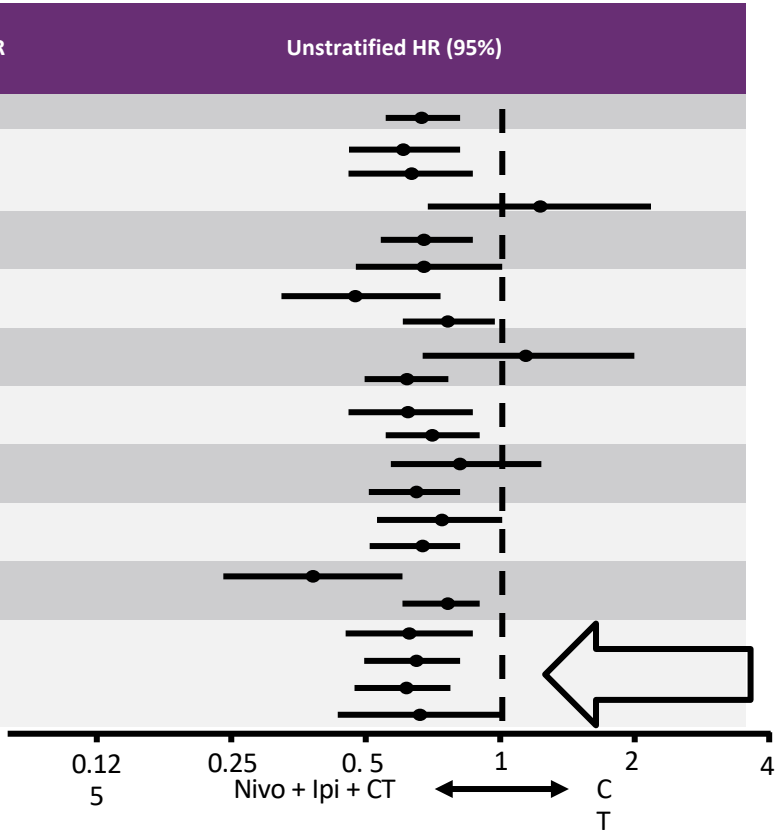
CheckMate 9LA: OS Subgroup Analysis

Subgroup	Median OS, mos		Unstratified HR
	Nivo + Ipi + CT n = 361	CT n = 358	
All randomized (N = 719)	15.6	10.9	0.66*
< 65 yrs (n = 354)	15.6	10.7	0.61
65 to < 75 yrs (n = 295)	19.4	11.9	0.62
≥ 75 yrs (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
PDL-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 mos

*Stratified HR; unstratified HR: 0.67 (95% CI: 0.55-0.81)

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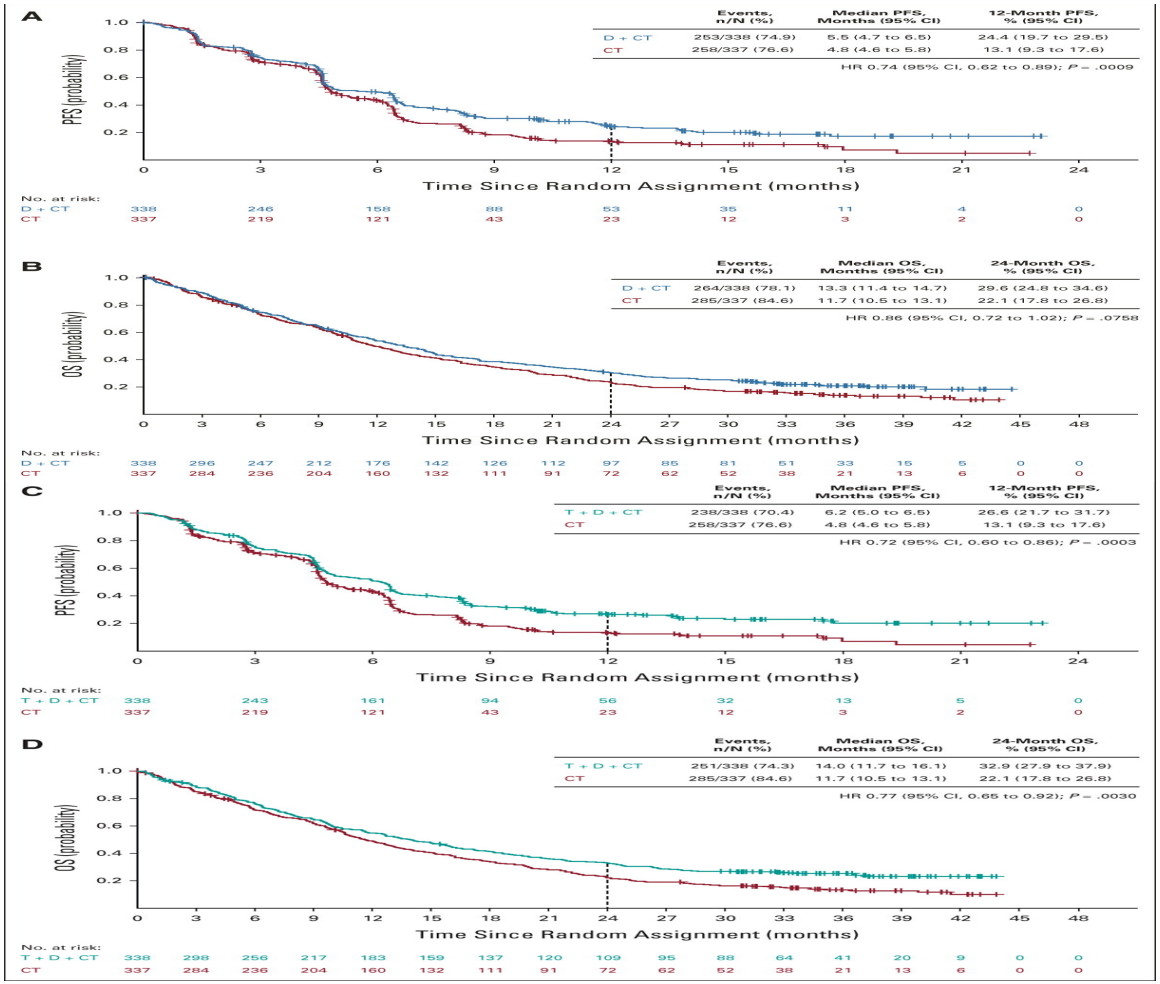
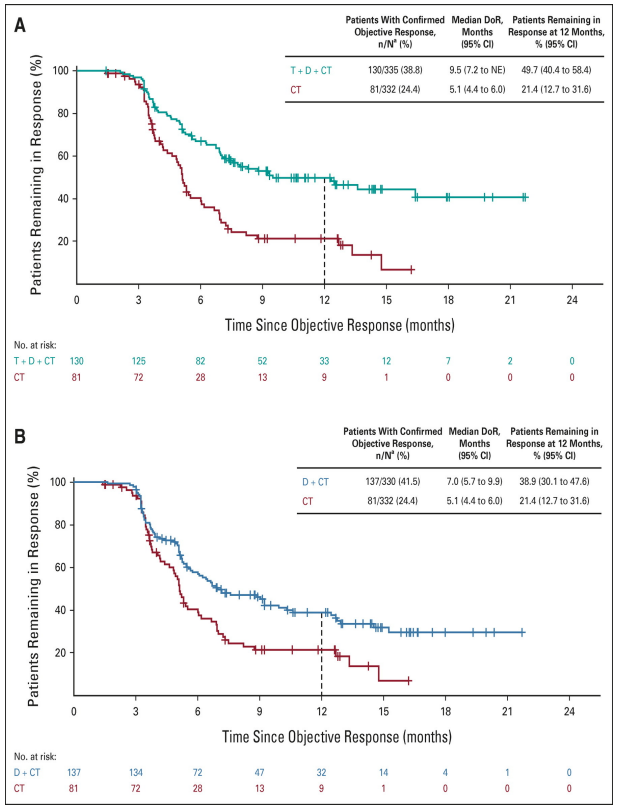
D +/- T in Combination With CT as First-Line Therapy for Metastatic NSCLC
The Phase III POSEIDON Study
(N – 1,013 - (1:1:1)

Journal of Clinical Oncology 2023 411213-1227.DOI: 10.1200/JCO.22.00975

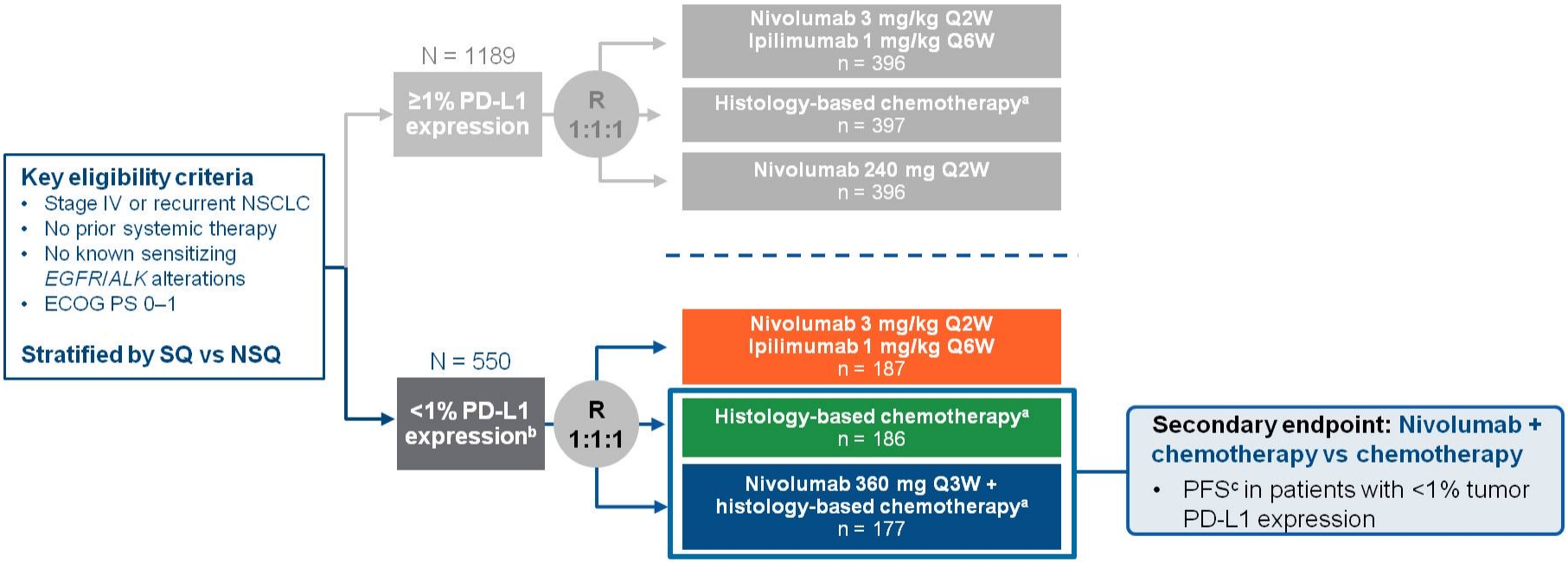




D+CT vs CT PFS -HR, 0.74; *P* = **.0009 (**Median, 5.5 *v* 4.8 months); OS HR, 0.86; *P* = **.0758** (Median, 13.3 *v* 11.7 months).

D+T+CT vs CT PFS (HR, 0.72; *P* = **.0003 (**Median, 6.2 *v* 4.8 months)**;** OS (HR, 0.77;***P* = .003** (Median, 14.0 *v* 11.7 months)

CheckMate 227 Part 1 Study Design



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

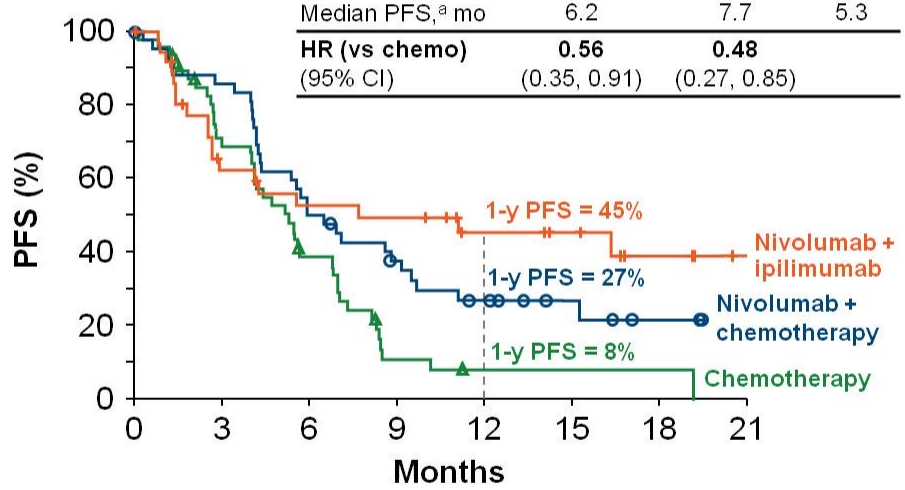
Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

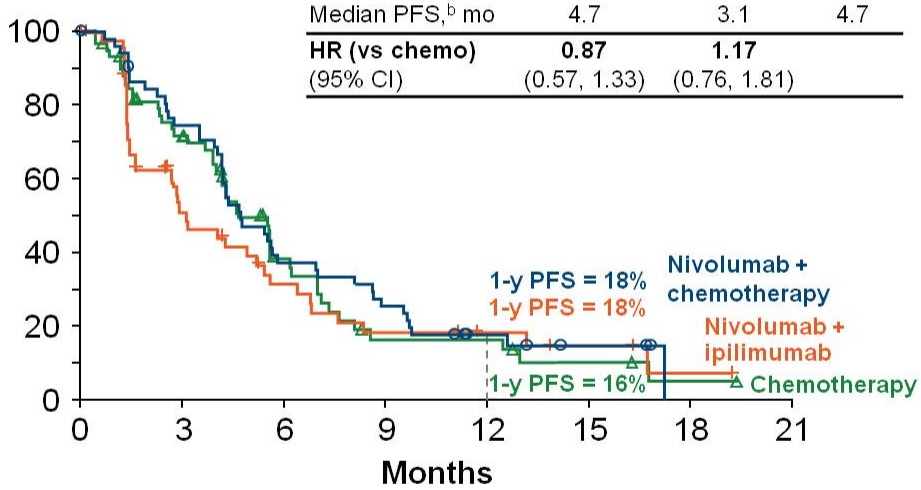
	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	



No. at risk								
Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 54)	Nivo + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo) (95% CI)	**0.87** (0.57, 1.33)	**1.17** (0.76, 1.81)	



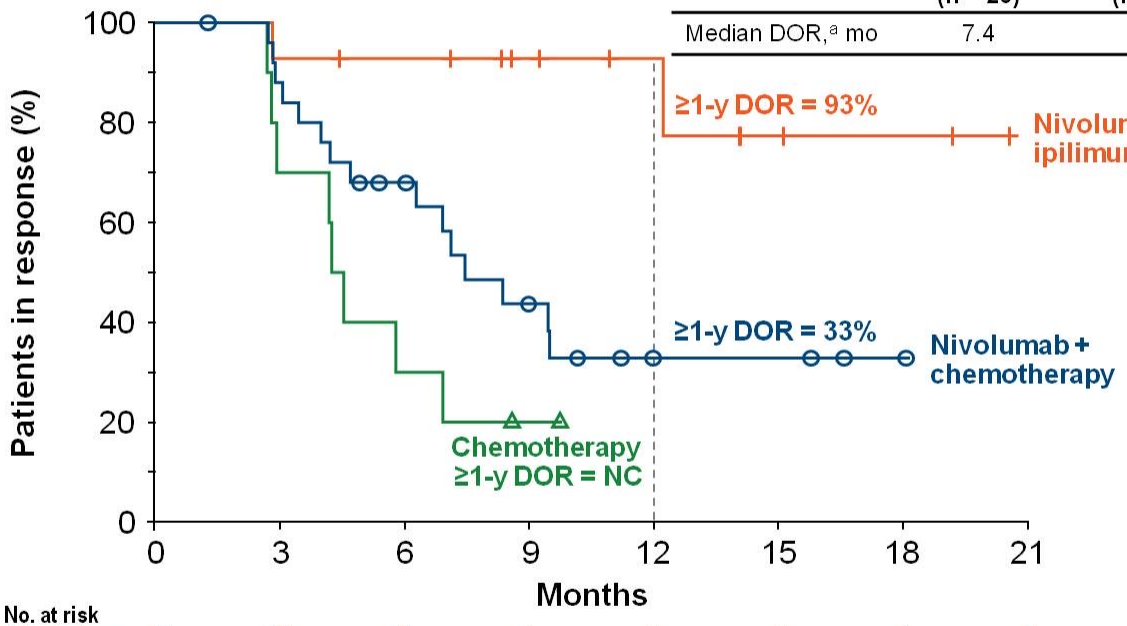
No. at risk								
Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

Exploratory analysis

[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

DOR: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 26)	Nivo + ipi (n = 14)	Chemo (n = 10)
Median DOR,[a] mo	7.4	NR	4.4

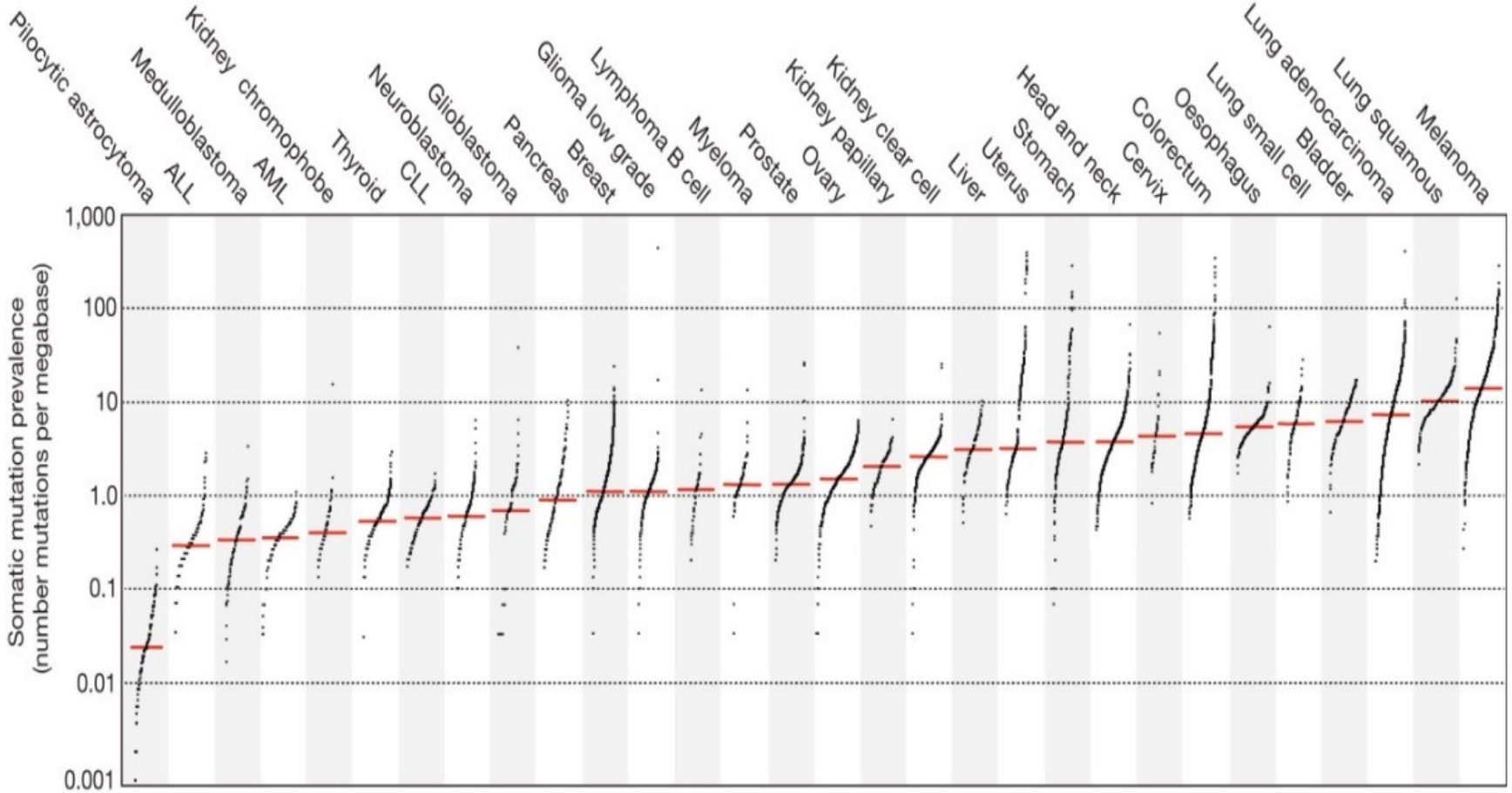


- ORR was 60.5% with nivo + chemo, 36.8% with nivo + ipi, and 20.8% with chemo

Exploratory analysis

[a]95% CI: nivo + chemo (4.6, NR mo), nivo + ipi (12.2, NR mo), chemo (2.7, 6.9 mo)

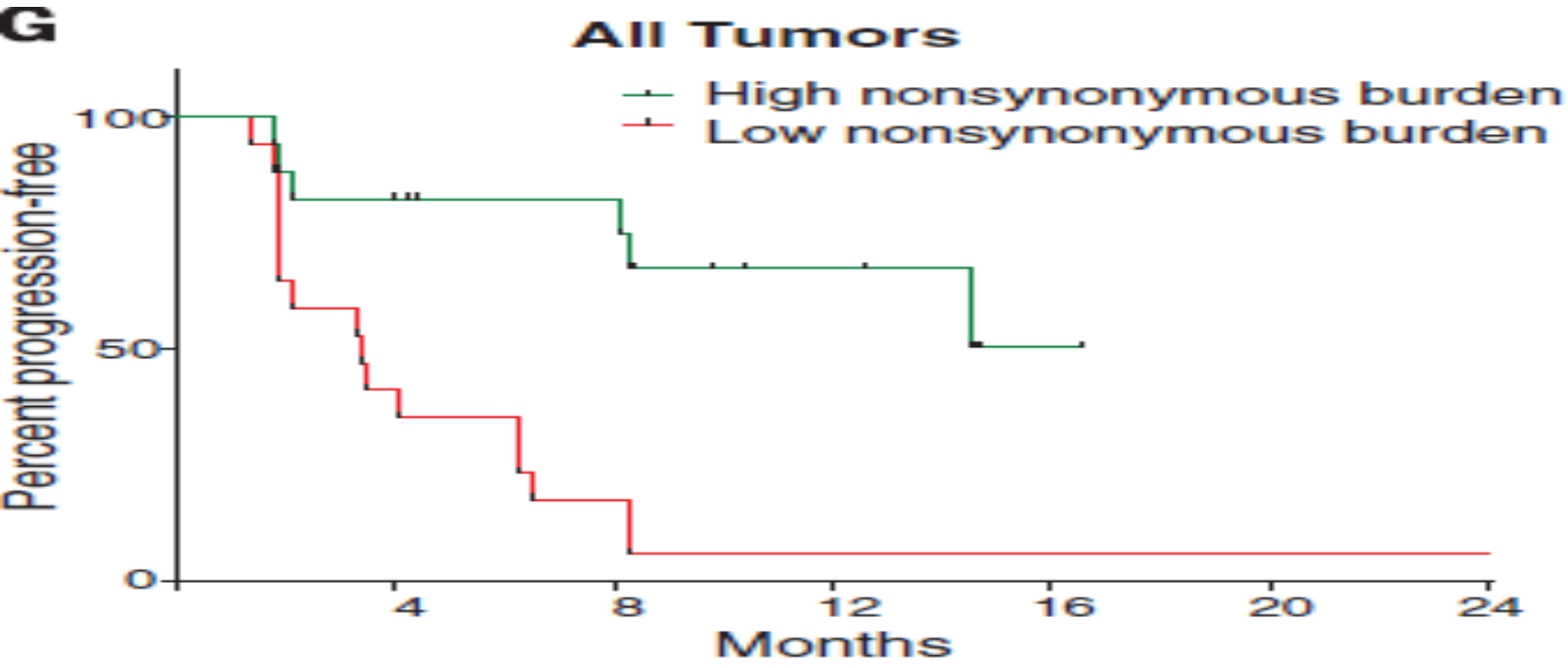
Mutational Load and Correlation with NSCLC Histology



Alexandrov, Nature 2013

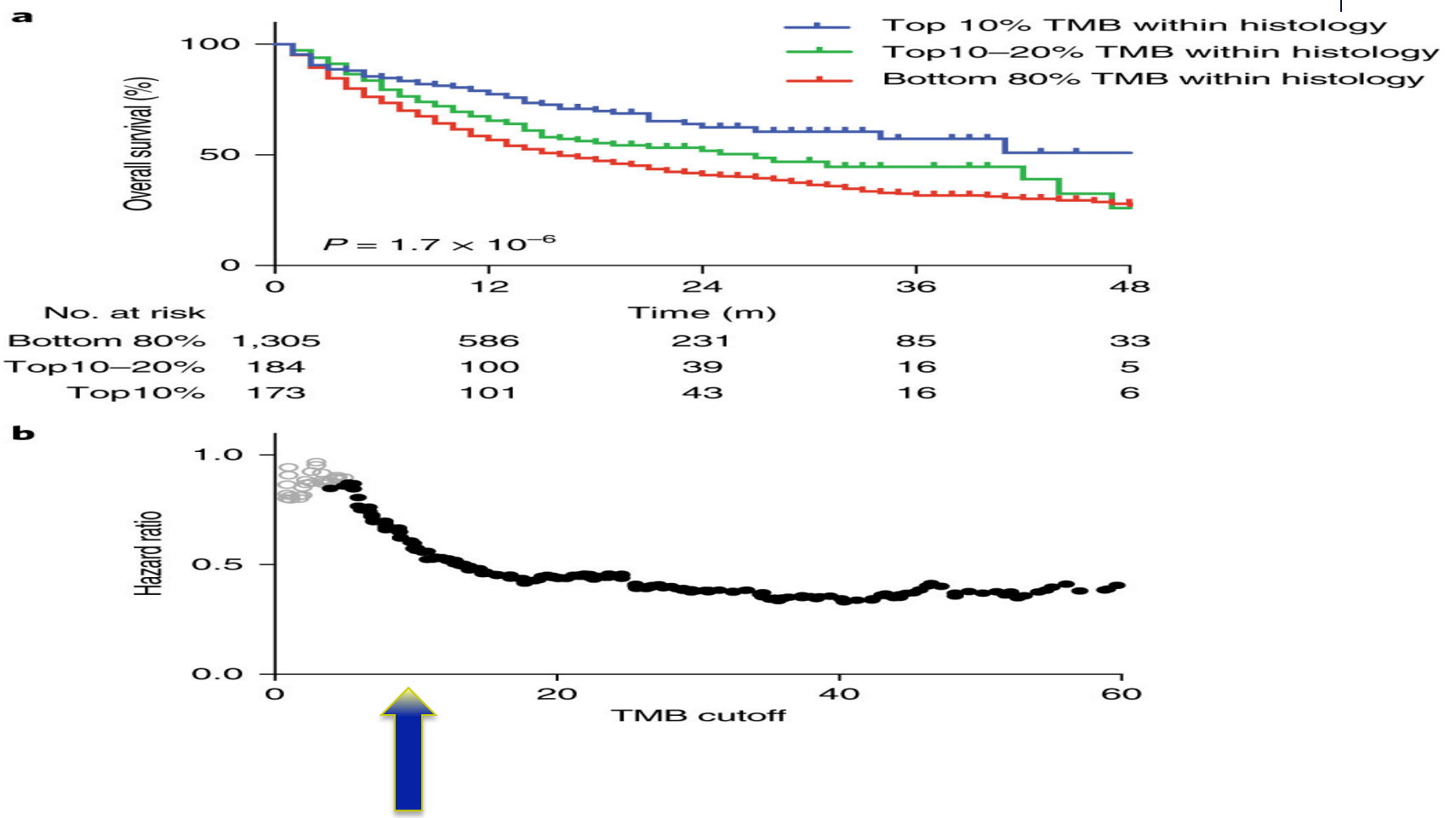
Heavy Mutational Load Associated with Better Outcomes to Immuno-Oncology Agents

Outcomes with pembrolizumab



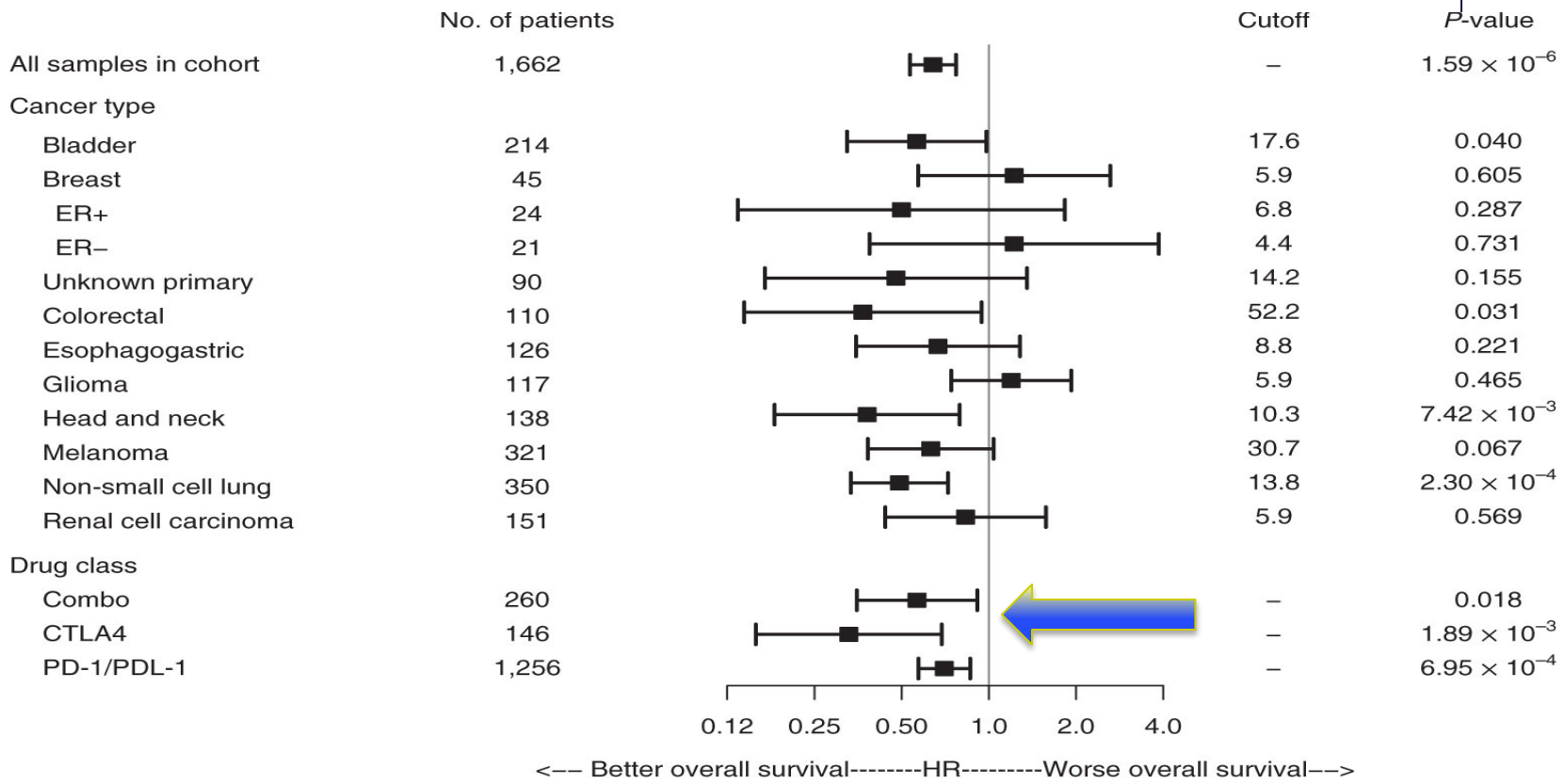
Rizvi, Science 2015

Effect of mutational load on overall survival after ICI treatment.



https://doi.org/10.1038/s41588-018-0312-8

Effect of nonsynonymous mutational load on overall survival after ICI treatment, by cancer subtype and drug class.



Do we need a PD1/PDL1 inhibitor along with a CTLA-4 inhibitor + Chemotherapy in the PD-L1 negative setting?

https://doi.org/10.1038/s41588-018-0312-8

FDA approves pembrolizumab for adults and children with TMB-H solid tumors

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab [illegible] the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Today, the FDA also approved the FoundationOneCDx assay [illegible] as a companion diagnostic for pembrolizumab.

Efficacy was investigated in a prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) in patients who have received at least one dose of pembrolizumab as assessed by blinded independent central review according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A total of 102 patients (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb. The ORR for these patients was 29% (95% CI: 21,39), with a 4% complete response rate and 25% partial response rate. The median DoR was not reached, with 57% of patients having response durations ≥12 months and 50% of patients having response durations ≥24 months.

Incidence of MSI High in various tumors

Cancer	Match	Foundation	Caris
Gastroesophageal	7/142 (4.9%)	6/400 (1.5%)	
Esophageal SCC	1/19 (5.3%)		
Gastric/GEJ Adenoca	4/79 (5.1%)		6/91 (6.2%)*
Esophageal Adenoca	2/44 (4.5%)		9/91 (0%)**
CRC	20/723 (2.8%)	42/1185 (3.5%)	38/888 (4.1%)
Rectal Adenoca	1/205 (0.5%)		
Colon Adenoca	19/518 (3.7%)		
Small bowel Adenoca	1/27 (3.7%)	6/70 (8.6%)	1/35 (2.8%)***
Panceatic Adenoca	1/267 (0.4%)	1/459 (0.2%)	7/316 (2.2%)
Uterine	34/237 (14.3%)	39/277 (14.1%)	62/365 (14.5%)
Prostate	7/122 (5.7%)	11/178 (6.2%)	3/128 (2.3%)
Breast	8/566 (1.4%)	2/1459 (0.1%)	2/705 (0.3%)
NSCLC	2/244 (0.8%)	5/2112 (0.2%)	9/1042 (0.9%)
SCLC	2/65 (3.1%)		1/52 (0.9%)
Hepatobiliary	4/166 (2.4%)	9/389 (2.3%)	
Gallbladder	1/37 (2.7%)		
Cholangiocarcinoma	3/129 (2.3%)		3/89 (3.3%)
HCC			0/30 (0%)
GBM	1/47 (2.1%)		2/431 (0.5%)
Neuroendocrine NOS	1/99 (1%)	1/431 (0.2%)	3/124 (2.4%)
Panc Neuroendocrine	2/28 (7.1%)		
CUP		22/815 (2.7%)	6/421 (1.4%)

FDA-approved regimens for advanced/metastatic NSCLC not harboring tumor genomic alterations

PD-L1 level	Regimen	Histology	Approval endpoint
≥ 50%	**Pembrolizumab**	NSCLC	**OS** & PFS
	Atezolizumab [a]	NSCLC	**OS**
	Cemiplimab	NSCLC	**OS** & PFS
≥ 1%	**Pembrolizumab**	NSCLC	**OS**
	Nivolumab + Ipilimumab	NSCLC	**OS**
None	**Pembrolizumab** + Platinum + Pemetrexed [b]	NSq-NSCLC	**OS** & PFS
	Pembrolizumab + Carboplatin + Paclitaxel	Sq-NSCLC	**OS** & PFS
	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	NSq-NSCLC	**OS** & PFS
	Atezolizumab + Carboplatin + Nab-paclitaxel	NSq-NSCLC	**OS** & PFS
	Nivolumab + Ipilimumab + Platinum doublet	NSCLC	**OS**
	Durvalumab + Tremelimumab + Platinum doublet	NSCLC	**OS & PFS**

Abbreviations: NSCLC=non-small cell lung cancer; Nsq=non-squamous; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; Sq=squamous.
[a] PD-L1 high population for atezolizumab defined as PD-L1 staining ≥ 50% of tumor cells or tumor-infiltrating immune cells covering ≥ 10% of the tumor area.
[b] Initial Accelerated approval in 2017 based on PFS.

2022 ASCO® ANNUAL MEETING

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

Acquired Resistance

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

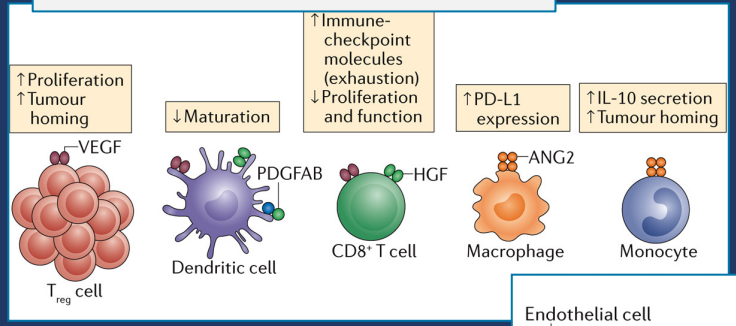
Karen L. Reckamp, M.D.[1], Mary W. Redman, PhD[2], Konstantin H. Dragnev, M.D.[3], Liza Villaruz, M.D.[4], Bryan Faller, MD[5]; Tareq Al Baghdadi, MD[6], Susan Hines, MD[7], Lu Qian, M.S.[2], Katherine Minichiello, M.S.[2], David R. Gandara, M.D.[8], Karen Kelly, MD[8], Roy S. Herbst, M.D., Ph.D.[9]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]SWOG Statistics and Data Management Center & Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH/Alliance for Clinical Trials in Cancer; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center; [5]Missouri Baptist Medical Center, St. Louis, MO/Heartland NCORP; [6]IHA Hematology Oncology Consultants-Ann Arbor/Michigan CRC NCORP; [7]Novant Health Cancer Institute - Mount Airy/Southeast Clinical Oncology Research Consortium NCORP); [8]UC Davis Comprehensive Cancer Center, Sacramento, CA; [9]Yale University, New Haven, CT

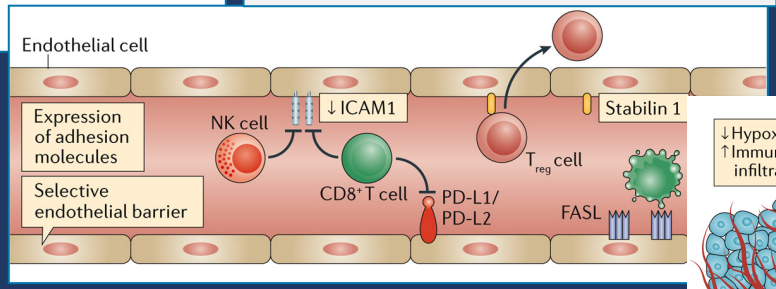
LUNG-MAP

Effects of angiogenesis-modulating factors on the immune system

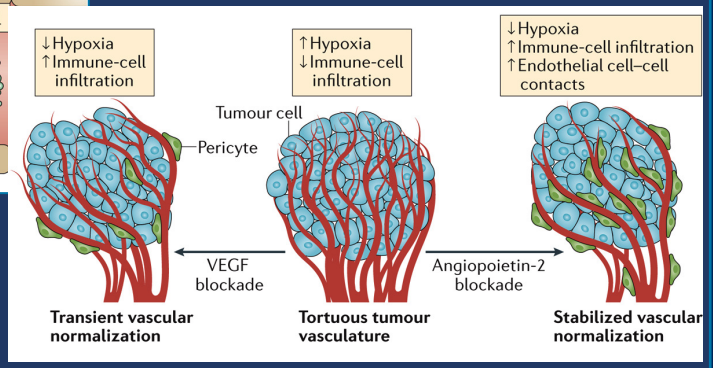
Direct effects on immune cells



Indirect effects on endothelium

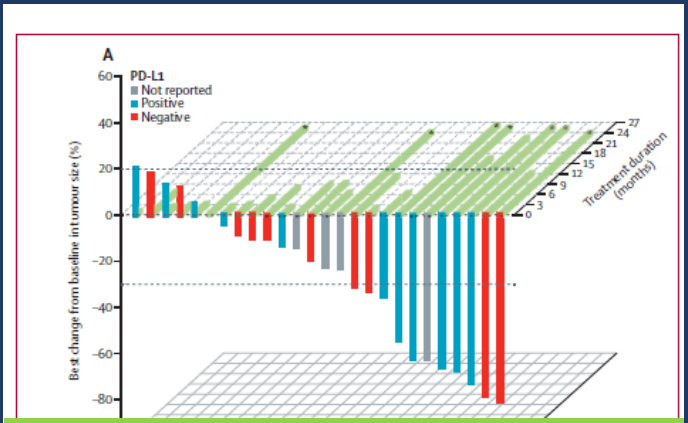


Indirect physical effects

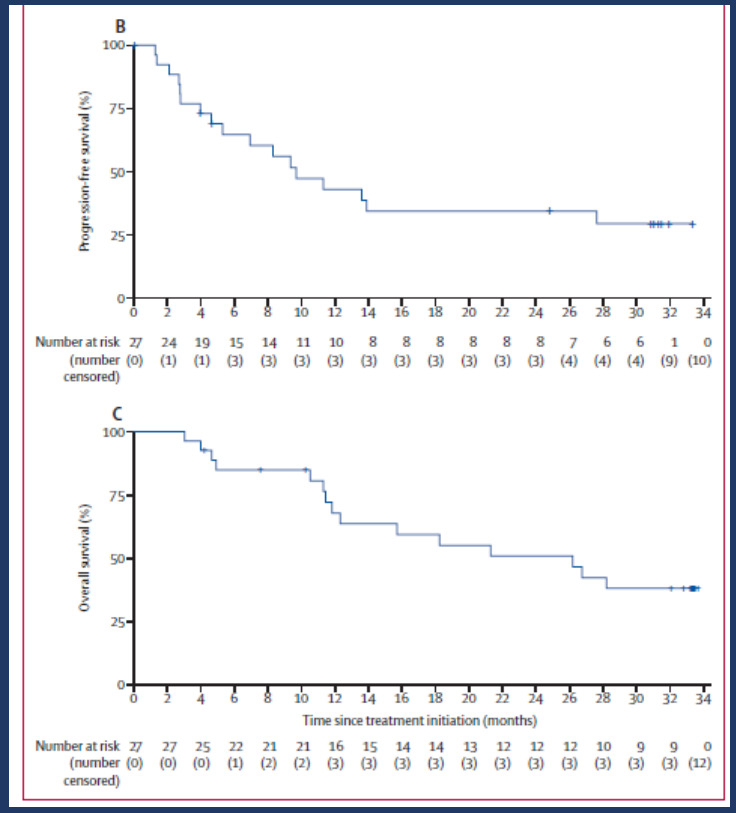


Khan, K. A. & Kerbel, R. S. (2018) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2018.9

Ramucirumab and pembrolizumab in previously treated, IO-naïve advanced NSCLC

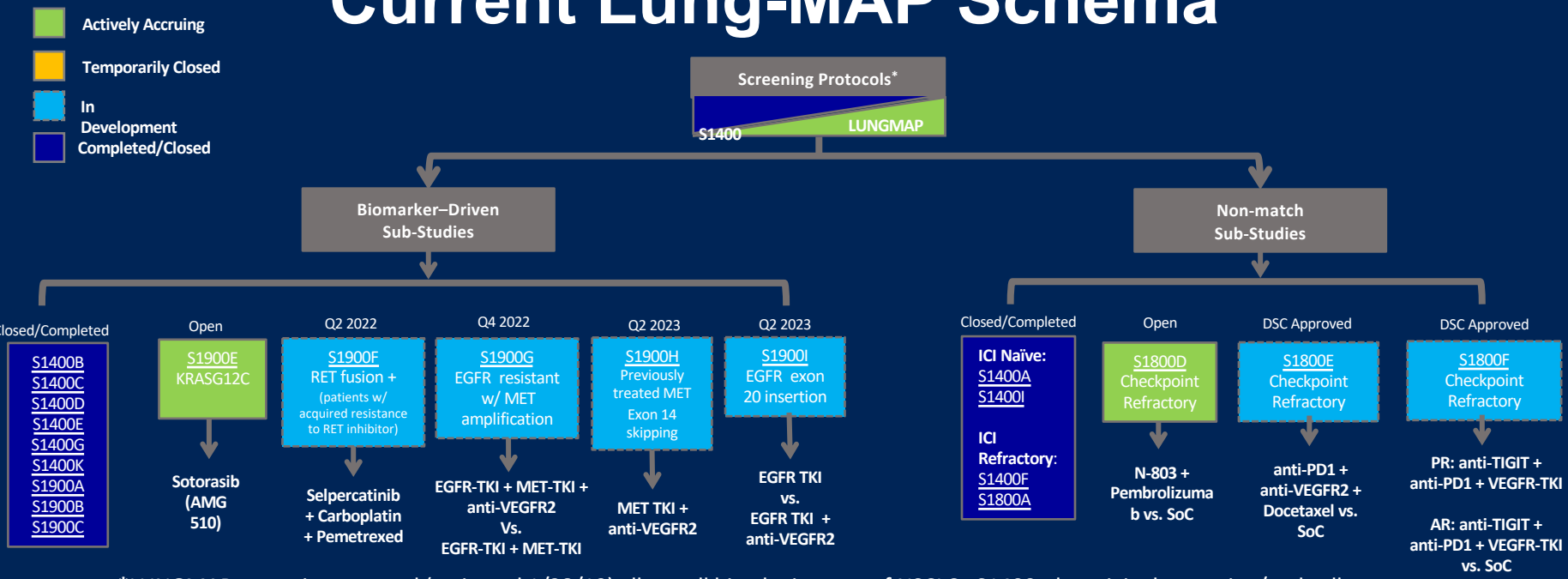


	NSCLC (N = 27)
ORR, % (95% CI)	**30 (13.8-50.2)**
▪ CR	1 (4%)
▪ PR	7 (26%)
▪ SD	15 (56%)
▪ PD	3 (11%)
DCR, % (95% CI)	85% (66.3-95.8)
PFS, median mos (95%CI)	9.7 (4.6-27.6)
OS, median mos (95%CI)	26.2 (11.8-NR)



Herbst et al Lancet Oncol 2019

Current Lung-MAP Schema



*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

TRIAL POINTS OF INTEREST:

- Each of sub-study operates independently of the others
- Prescreening can be performed while the patient is on any line of therapy for stage IV disease
- Repeat or fresh biopsy necessary for tissue screening is paid by the trial
- **#Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.**

- Karen L. Reckamp, MD, MS

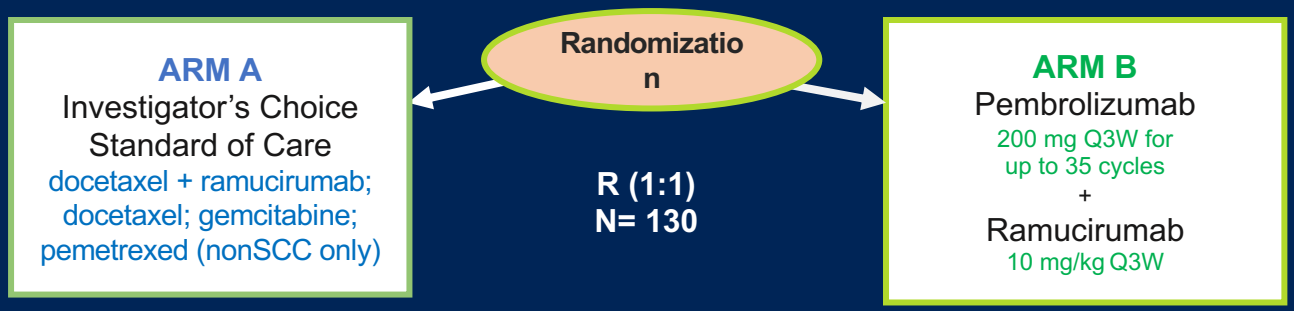
LUNG-MAP

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

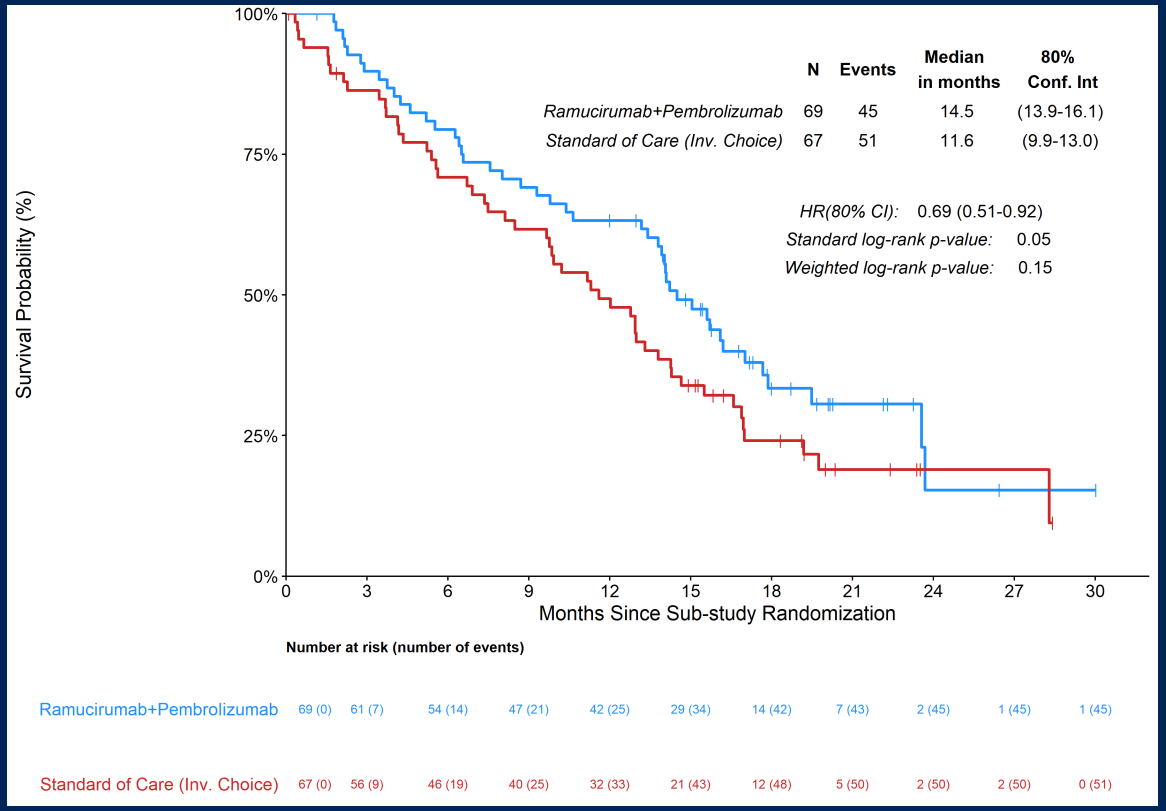


Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

LUNG-MAP

PRESENTED BY:
Karen L. Reckamp, MD, MS

Overall survival



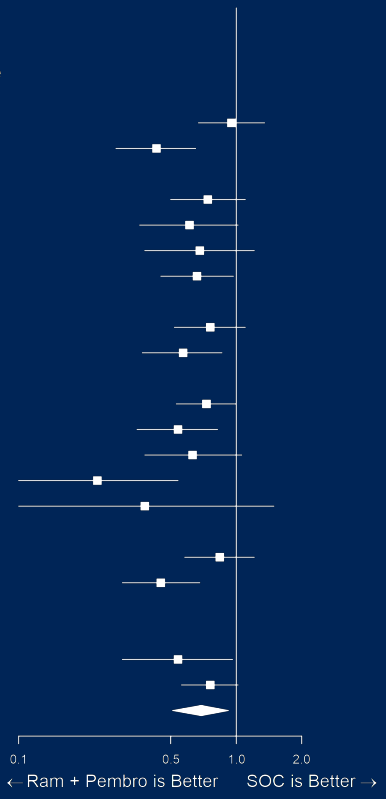
- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

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

Overall survival—subgroup analysis

	Ram+ Pembro Events/N	SOC Events/N	HR (80% CI)	P-value
HISTOLOGY				
Non-Squamous	27/40	27/39	0.95 (0.67,1.35)	0.43
Squamous/Mixed	18/29	24/28	0.43 (0.28,0.65)	0.005
PD-L1				
PD-L1 0	21/29	21/26	0.74 (0.50,1.10)	0.16
PD-L1 1-49	11/21	15/22	0.61 (0.36,1.02)	0.11
PD-L1 50+	8/12	12/16	0.68 (0.38,1.21)	0.20
PD-L1 1+	19/33	27/38	0.66 (0.45,0.97)	0.08
TMB				
TMB <10	23/32	28/38	0.76 (0.52,1.10)	0.17
TMB 10+	18/33	20/25	0.57 (0.37,0.86)	0.04
BIOMARKER				
TP53	31/48	35/48	0.73 (0.53,1.00)	0.10
CDKN2A	18/27	21/24	0.54 (0.35,0.82)	0.03
KRAS	12/21	13/16	0.63 (0.38,1.06)	0.13
STK11	4/7	10/10	0.23 (0.10,0.54)	0.01
KEAP1	1/3	7/10	0.38 (0.10,1.49)	0.18
PRIOR TREATMENT				
IO+CHEMO COMBO	20/32	32/42	0.84 (0.58,1.21)	0.27
CHEMO->IO	25/36	18/23	0.45 (0.30,0.68)	0.006
PERFORMANCE STATUS				
PS 0	15/23	8/9	0.54 (0.30,0.96)	0.08
PS 1	30/46	43/58	0.76 (0.56,1.02)	0.12
OVERALL	**45/69**	**51/67**	**0.69 (0.51,0.92)**	**0.05**



- All subgroup HRs < 1
- HRs by PD-L1 does not appear to vary
- Pronounced benefit in SCC/mixed histology
- Benefit seen with PS 0 and 1
- Co-mutations did not affect OS improvement

LUNG-MAP

PRESENTED BY:
Karen L. Reckamp, MD, MS

First line Treatment strategy for NSCLC without Driver Mutations (2023) (It is going to be out of state soon!)

	PD-L1 < 1% (35%)	PD-L1 = 1 to 49% (39%)	PD-L1 - 50% to 80%	PD-L1 ≥ 90%
Non-Sq				
TMB – H (38%)	IN or K	K or CPK or CTA/B	K or A or L	K or A or L
TMB – L (62%)	CPIN CPDT	CPK or CTA±B	K or A or L > 75ys CPK or K or A or L < 70ys	K or A or L
Sq				
TMB – H (38%)	IN or K	K or A or L	K or A or L	K or A or L
TMB – L (62%)	CTIN CTDTr	CTK or CTA	K or A or L	K or A or L

C = Cis/Carbo; P = Pemetrexed; K = Pembro; A = Atezo ; B = Bevacizumab
T = Taxane; I = Ipi; N = Nivo; L = Cemiplimab; D = Durva; Tr = Treme; H = High; L = Low

ARC-7
Rand Ph II – ANSCLC; PDL1 ≥ 50%

Efficacy Population	Z (n = 44)	DZ (n = 44)	EDZ (n = 45)
Confirmed ORR n (%) [95% CI]	12 (27) [15.0, 42.8]	18 (41) [26.3, 56.8]	18 (40) [25.7, 55.7]
Median PFS (mo) [95% CI]	5.4 [1.8, 9.6]	12.0 [5.5, NE]	10.9 [4.8, NE]
PFS Hazard Ratio vs Z [95% CI]	-	**0.55 [0.31, 1.0]**	0.65 [0.37, 1.1]
6-mo PFS % (95% CI)	**43 (27, 59)**	**65 (49, 80)**	63 (48, 78)
Safety Population	**Z (n = 50)**	**DZ (n = 49)**	**EDZ (n = 50)**
IRAEs, n (%)	24 (48)	23 (47)	30 (60)
Infusion-related reactions	2 (4)	2 (4)	5 (10)
Rash	6 (12)	5 (10)	9 (18)

NE: Not Evaluable IRAE: Immune-related adverse events; D = Domvanalimab (anti-TIGIT); Z = Zimberelimab (Anti – PD1) Etrumadenant (E)

•Journal of Clinical Oncology >Volume 40, Issue 36_suppl . Abstr # 397600, 12/2022

Artificial Intelligence Based Predictive Platforms (1)

Spatial Analyses of Tissue.

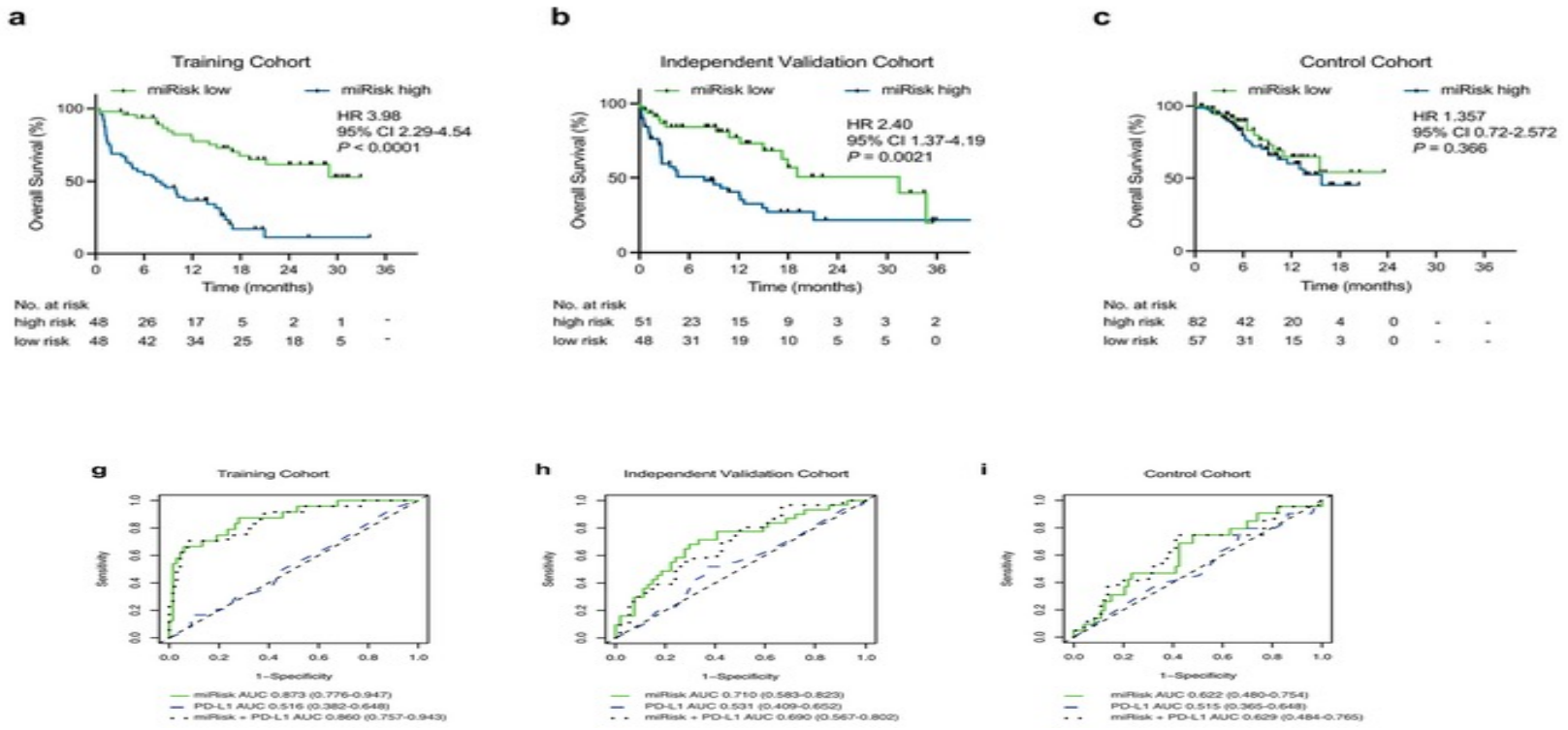
Artificial Intelligence–Powered Spatial Analysis of Tumor-Infiltrating Lymphocytes as Complementary Biomarker for Immune Checkpoint Inhibition in Non–Small-Cell Lung Cancer

Sehhoon Park, MD, PhD et al

ascopubs.org/journal/JCO on March 10, 2022
DOI https://doi.org/10.1200/JCO.21.02010

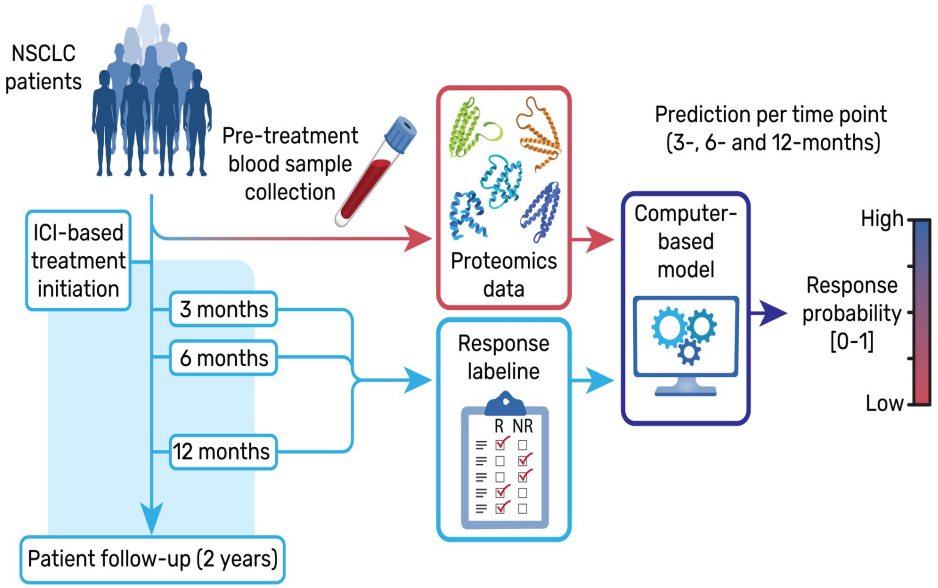
AI (2)
Hummingbird's MicroRNA profile

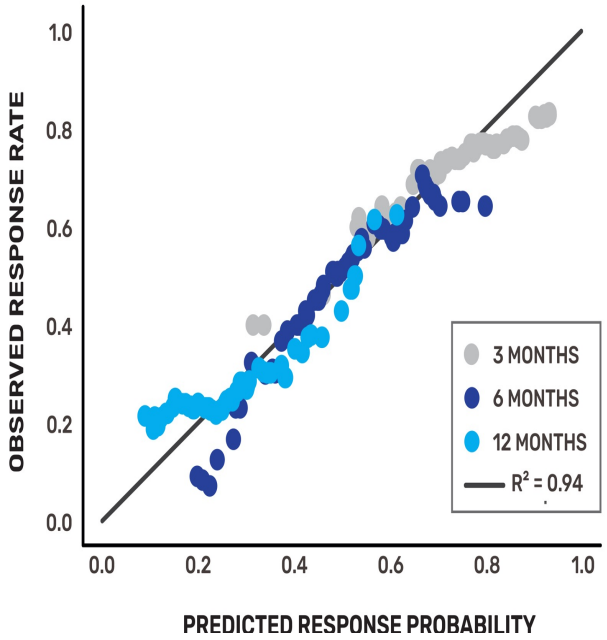
Hummingbird's MiRisk Profile



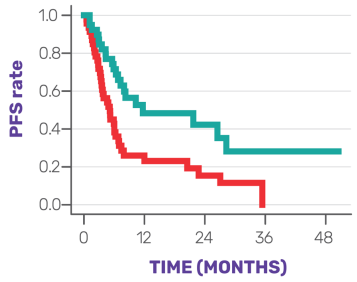
NPJ Precision Oncology (2022) 6:19 ; https://doi.org/10.1038/s41698-022-00262-y

AI (3)
OncoHost – Proteomic Platform





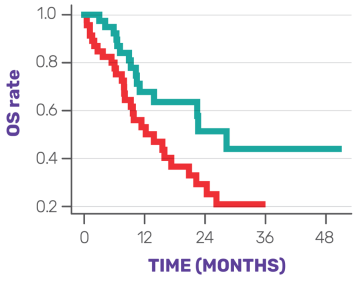
PROGRESSION FREE SURVIVAL (PFS)



HAZARD RATIO=0.45
(95% CI: 0.26-0.76)
p = 0.002

- Favorable long-term outcome population (n=39)
- Unfavorable long-term outcome population (n=46)

OVERALL SURVIVAL (OS)



HAZARD RATIO=0.5
(95% CI: 0.27-0.94)
p = 0.027

- Favorable long-term outcome population (n=39)
- Unfavorable long-term outcome population (n=46)

AI (4)
OncAI: Radiomics & Multimodal Platform

Predicting 3-month multi-lesion response to PD-1/PD-L1 immune checkpoint inhibitor therapy in stage IV NSCLC: A radiomics-based multi-modal model

PD-1/PD-L1 immunotherapy response performance (ROC-AUC) of 3-months PFS per RECIST 1.1.			
Biomarker	First-line ICI Monotherapy (N = 91)	All-lines ICI Monotherapy (N=138)	All-lines ICI + Chemotherapy (N=114)
Multi-modal	0.81 (0.xx-0.xx)	0.72 (0.xx-0.xx)	0.71 (0.xx-0.x)
CT radiomics	0.71 (0.xx-0.xx)	0.61 (0.xx-0.xx)	0.62 (0.xx-0.xx)
PD-L1 IHC	0.61 (0.xx-0.xx)	0.60 (0.xx-0.xx)	0.58 (0.xx-0.xx)

Simon et al; AACR 2023

Conclusions

1. The optimal strategy for the treatment of Driver Mutation Negative Advanced NSCLC continues to evolve.

2. Resistance remains a problem

More Qs than As

1. Optimal treatment strategy for the Elderly?
2. Optimal way to predict benefit to PD1/L1 inhibitors? Role of AI platforms?
3. Place of TIGIT inhibitors in the therapeutic landscape?
4. Newer PD-1 inhibitors Vs. Older PD-1 Inhibitors?
5. Optimal treatment strategy for initial responders who develop resistance?

Thank YOU!

Gracias!