Metastatic NSCLC Immunotherapy Updates

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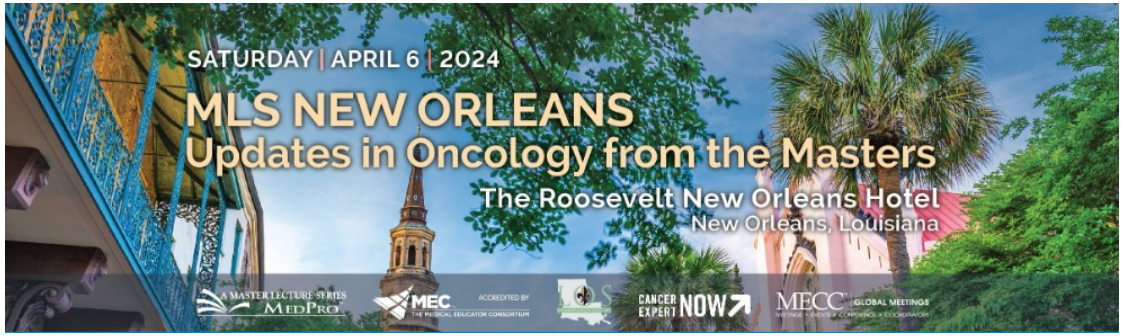

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE Florida HEALTH

FAU I-HEALTH Florida Atlantic University

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC and SQCC:

- Cemiplimab/Chemotherapy [Empower Lung-3]
- Durvalumab +Tremelimumab/Chemotherapy [Poseidon 3]

IO single Agent (NSQCC OR SQCC)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

EMPOWER

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c[†], IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases[‡]

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Follow-up

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

[†]Patient not a candidate for definitive chemoradiation. [‡]Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). [§]For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. Lancet 2021;397:592–604.

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EMPOWER

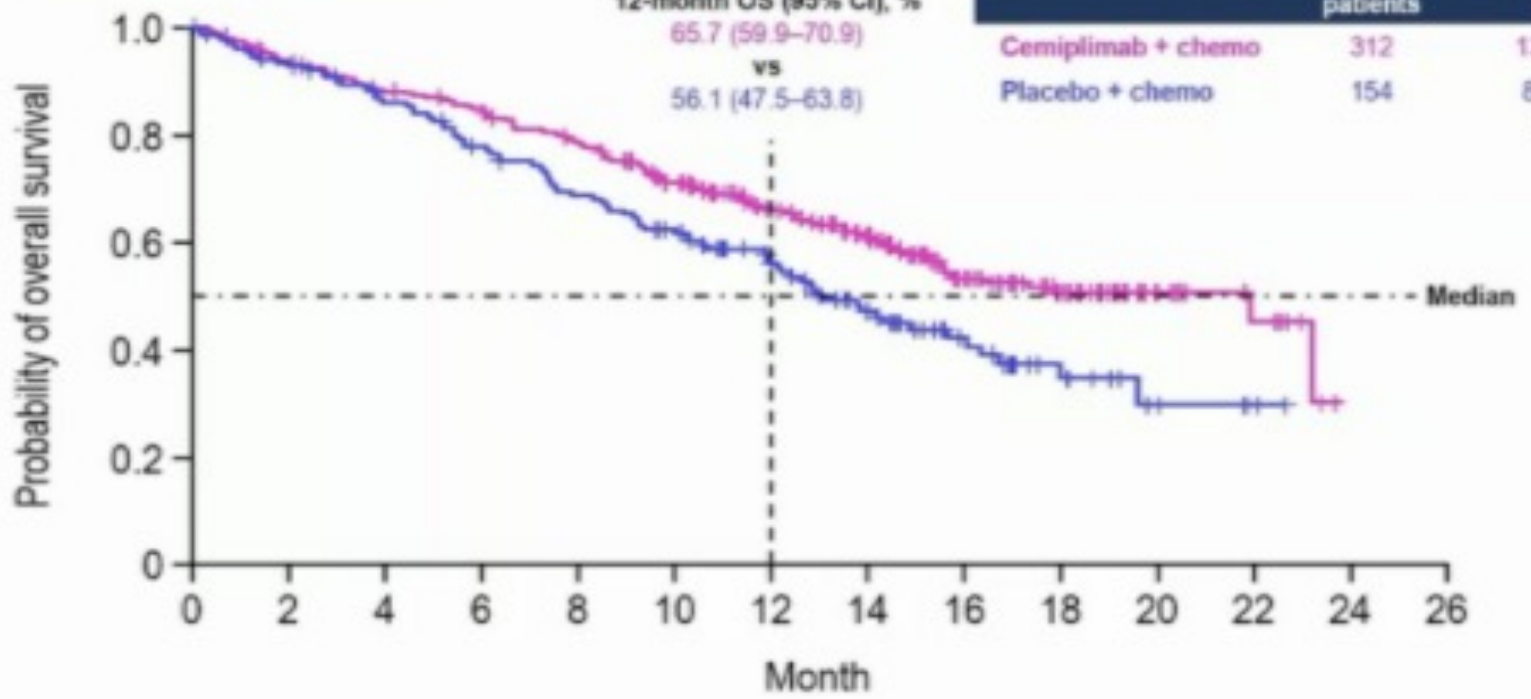
Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014

12-month OS (95% CI), %
65.7 (59.9–70.9)
vs
56.1 (47.5–63.8)



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

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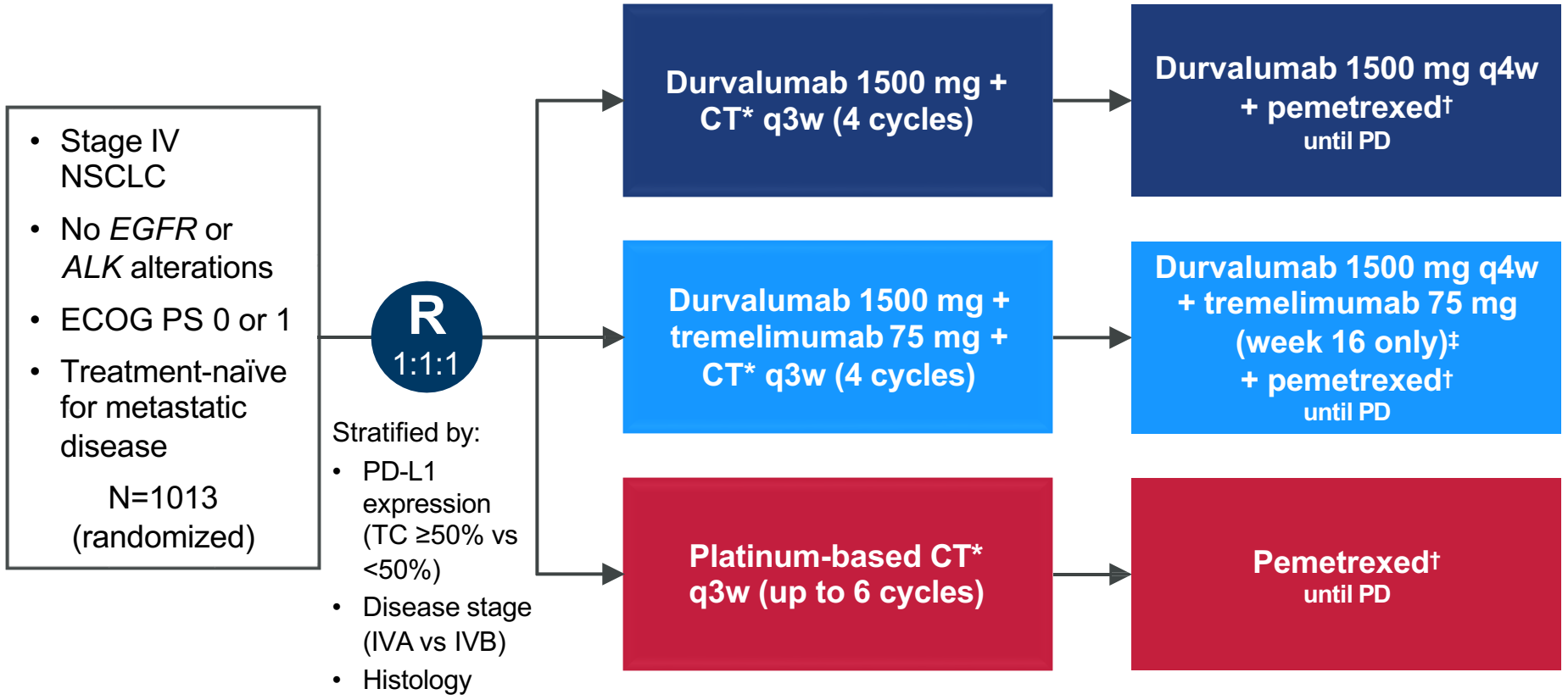
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off date:
14 June 2021

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

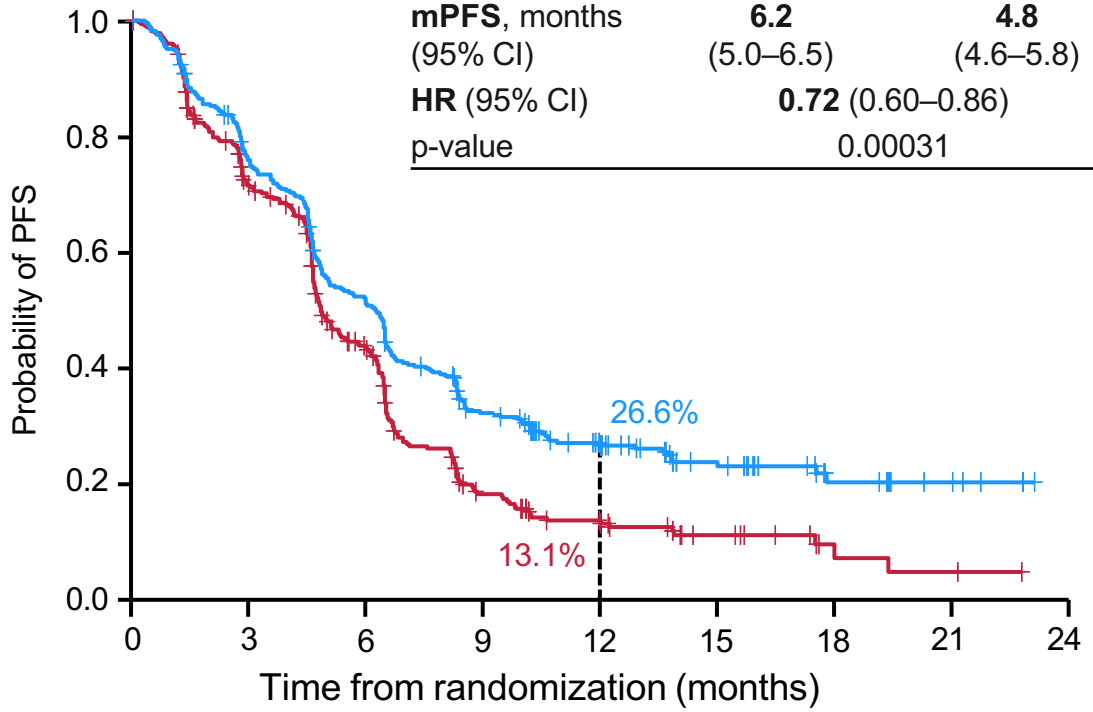
*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

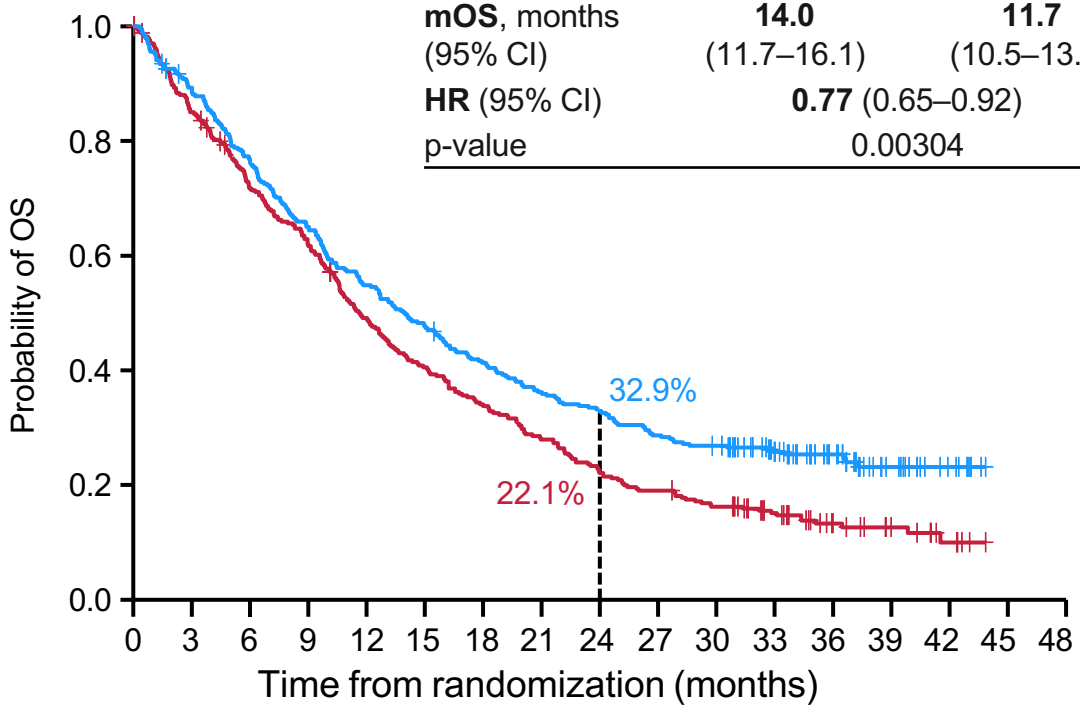


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk																	
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

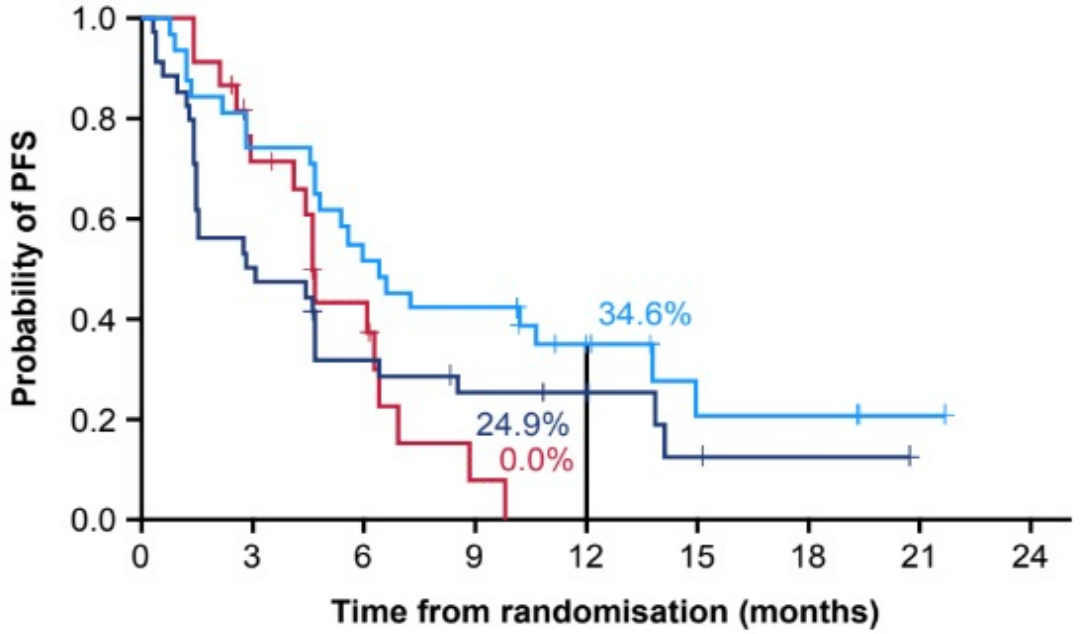
- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

PFS and Response in *STK11*m Subgroup

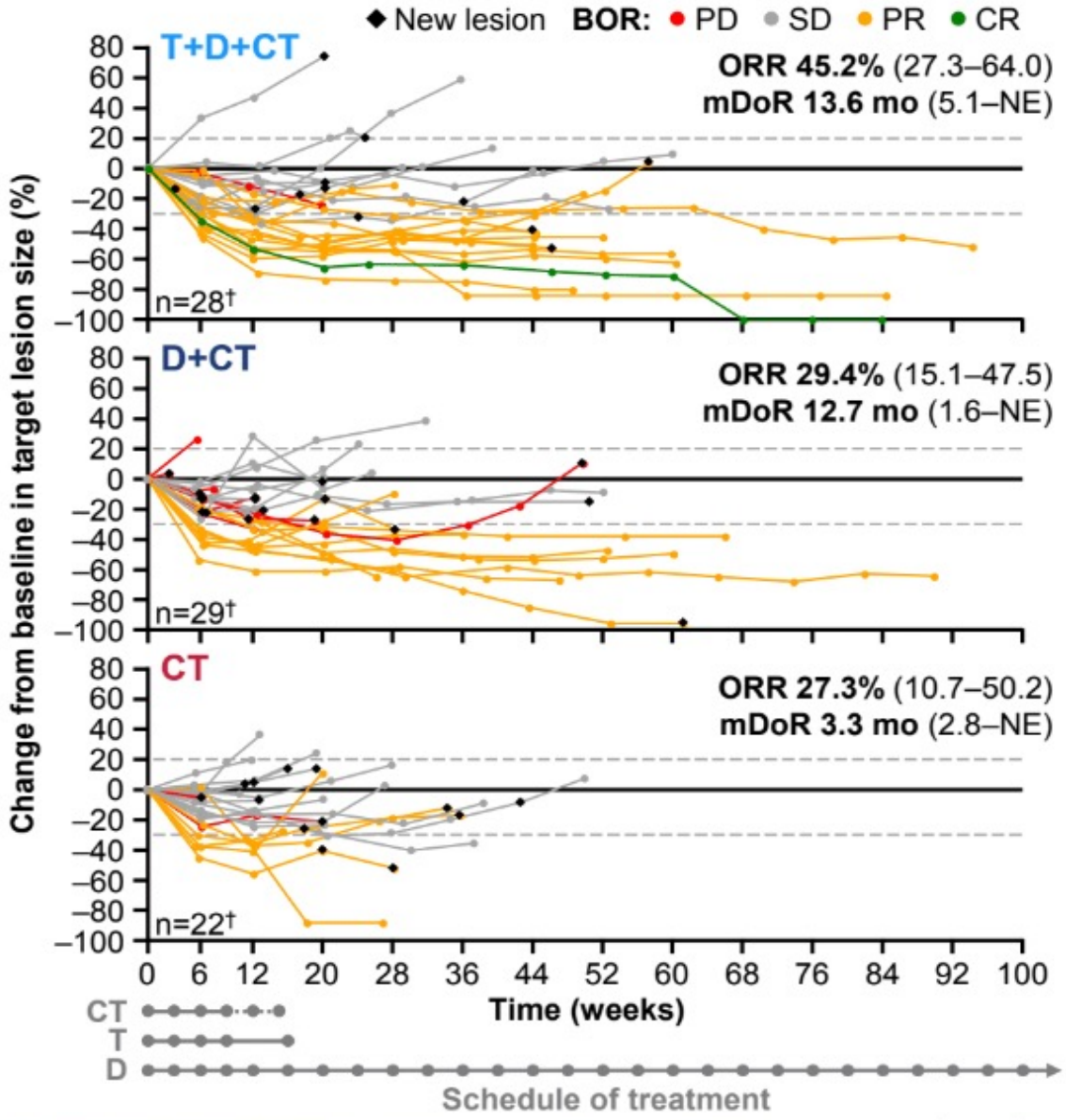
PFS

	T+D+CT	D+CT	CT
Events, n/N	22/31	27/34	17/22
mPFS, mo (95% CI)	**6.4** (4.7–13.8)	**2.9** (1.4–4.7)	**4.6** (2.9–6.4)
HR* (95% CI)	**0.47** (0.23–0.93)	**1.02** (0.55–1.93)	–



No. at risk

T+D+CT	31	23	16	13	7	3	3	1	0
D+CT	34	17	10	7	5	2	1	0	0
CT	22	14	7	1	0	0	0	0	0



BOR, best objective response; CR, complete response; mDoR; median duration of response; mPFS, median PFS; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

*HR <1 favours D (± T) + CT versus CT (unstratified analysis); †Patients who have both a baseline and post-baseline target lesion measurement
Assessed by BICR among mutation-evaluable patients with NSQ tumour histology; confirmed objective responses are shown; DCO, 24 Jul 2019

Conclusions

- In POSEIDON, PFS was significantly improved with first-line durvalumab + CT vs CT in patients with mNSCLC, with a positive trend for OS that did not reach statistical significance
  - PFS HR 0.74 (95% CI 0.62–0.89; p=0.00093)
  - OS HR 0.86 (95% CI 0.72–1.02; p=0.07581)
- First-line durvalumab + tremelimumab + CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS vs CT in patients with mNSCLC
  - PFS HR 0.72 (95% CI 0.60–0.86; p=0.00031)
  - OS HR 0.77 (95% CI 0.65–0.92; p=0.00304)
  - OS and PFS benefit were more prominent among patients with non-squamous (than squamous) histology
- Overall, the safety profile was similar across all three arms, with no new safety signals identified. Adding tremelimumab to durvalumab + CT did not lead to a meaningful increase in treatment discontinuation
  - TRAE discontinuation rate 15.5% and 14.1% with D+T+CT and D+CT, respectively
- **Durvalumab + tremelimumab + CT represents a potential new first-line treatment option for mNSCLC**

TRAE, treatment-related adverse event

First Line Lung Cancer Therapy with no actionable genes

Chemotherapy/IO Combinations

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]
- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]
- Cemiplimab/Chemotherapy [Empower Lung-3]
- Durvalumab + Tremelimumab/Chemotherapy [Poseidon 3]

IO single Agent (PDL1>50%)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

ORR slightly in favor of combination chemo+IO

	KN 24 (TPS > 50%)	KN 42 (TPS > 50%)	IMPW 10 TC3/IC3 (>50% and >10%)	KN 407 (TPS > 50%)	KN 189 (TPS > 50%)
ORR	45%	39.5%	30.7%	60.3%	61.4%
DOR	Nr (1.8-20.6 m)	20.2 m	Nr (1.8-29.3m)	7.7 m (all patients)	11.2 m (all patients)

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Adverse Events more prevalent with Chemo/IO

	KN-42		KN-24		KN-189		KN-407	
	Pembro	CT	Pembro	CT	Pembro + CT	CT	Pembro + CT	CT
All TRAE (%)	62.7%	89.9%	76.6%	90.0%	99.8%	99.0%	98.2%	97.9%
Grade 3-5 TRAE (%)	17.8%	41%	31.2%	53.3%	67.2%	65.0%	69.8%	68.2%
Discontinuation rate (any) (%)	9%	9.4%	13.6%	10.7%	27.7%	14.9%	23.4%	11.8%
Led to death	0.2%	0%	1.3%	2.0%	6.7%	5.9%	8.3%	6.4%

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

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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

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

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

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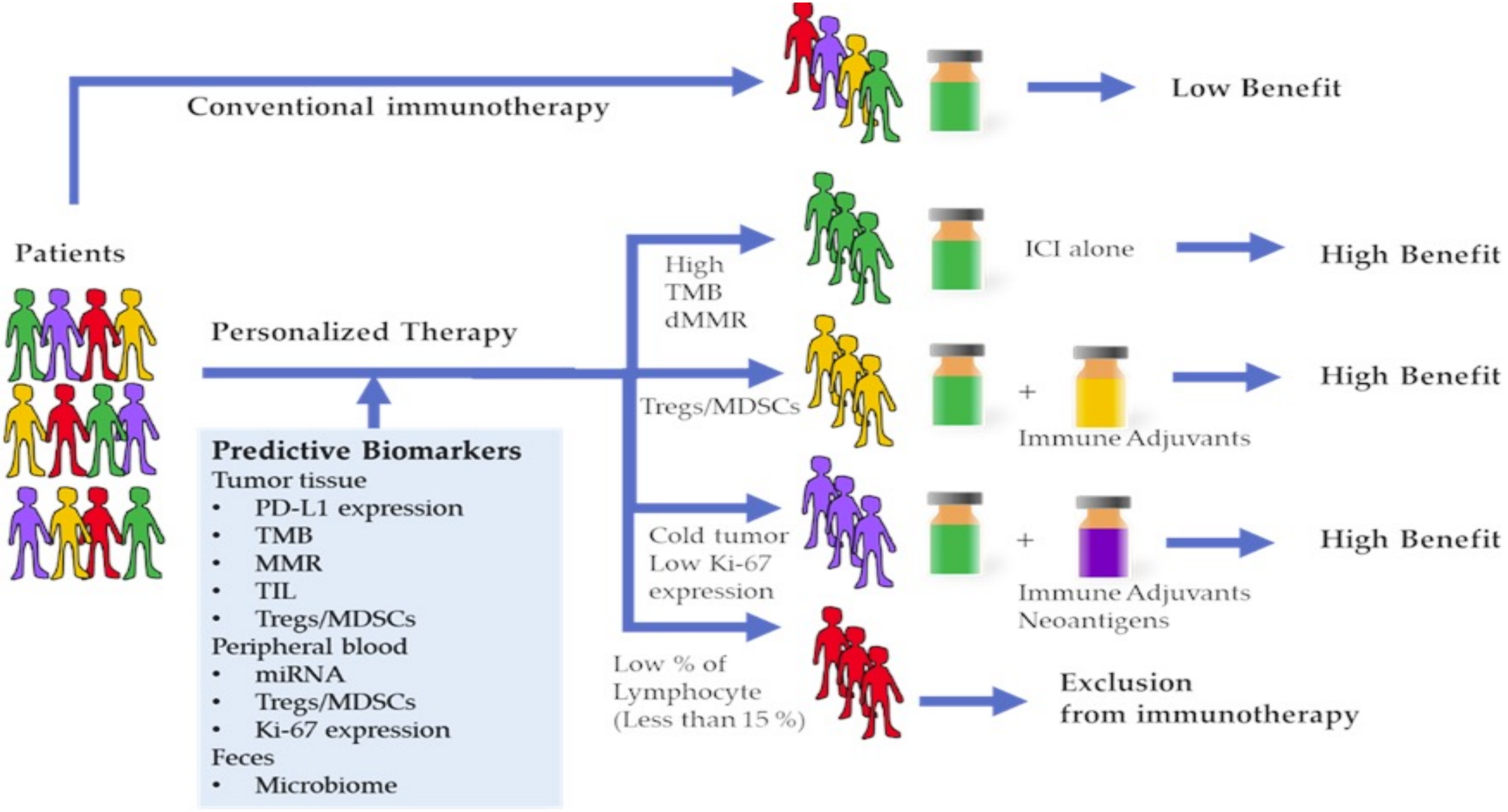
Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	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.


Conventional immunotherapy
Low Benefit
Patients
Personalized Therapy
High
TMB
dMMR
ICI alone
High Benefit
Tregs/MDSCs
+
Immune Adjuvants
High Benefit
Cold tumor
Low Ki-67
expression
+
Immune Adjuvants
Neoantigens
High Benefit
Low % of
Lymphocyte
(Less than 15 %)
Exclusion
from immunotherapy
Predictive Biomarkers
Tumor tissue
• PD-L1 expression
• TMB
• MMR
• TIL
• Tregs/MDSCs
Peripheral blood
• miRNA
• Tregs/MDSCs
• Ki-67 expression
Feces
• Microbiome

Co-mutational status (STK11, KEAP, TP53) and PD-L1 expression in *KRAS* mutant non-small cell lung cancer (NSCLC)

- Molecular profiles of 27748 NSCLC tumors were tested with next-generation sequencing (Caris Life Sciences, Phoenix, AZ) and classified by *KRAS* mt.
- PD-L1 IHC (22C3) was reported as TPS.
- Co-occurring genomic alterations, tumor mutational burden (TMB) and PD-L1 IHC (22C3, TPS score) were analyzed by *KRAS* mt type.
- Real-world post-immunotherapy (IO) overall survival (OS) was obtained from insurance claims and calculated from start of an immune check-point inhibitor (with or without chemotherapy) to the last day of follow-up.
- Prognosis was evaluated by rwOS calculated from tissue collection to last contact
- Molecular groups including K-only, KP, KL, KK and KKL were defined based on distinct mutational status of four genes as described below.

	Gene mutations			
Molecular Groups	**KRAS**	**STK11**	**TP53**	**KEAP1**
K-only	MT	WT	WT	WT
KP	MT	WT	MT	WT
KL	MT	MT	WT	WT
KK	MT	WT	WT	MT
KKL	MT	MT	WT	MT

Table 1: Molecular sub-groups

End point: Median rwOS (Tissue collection to Last Contact)		
	mrwOS (m)	95% CI
K-only	23.1	20.9-25.3
KP	17.7	16.2-19.35
KL	19.1	16.6-21.2
KK	9.7	7.4-14.2
KKL	8.0	6.6-9.0

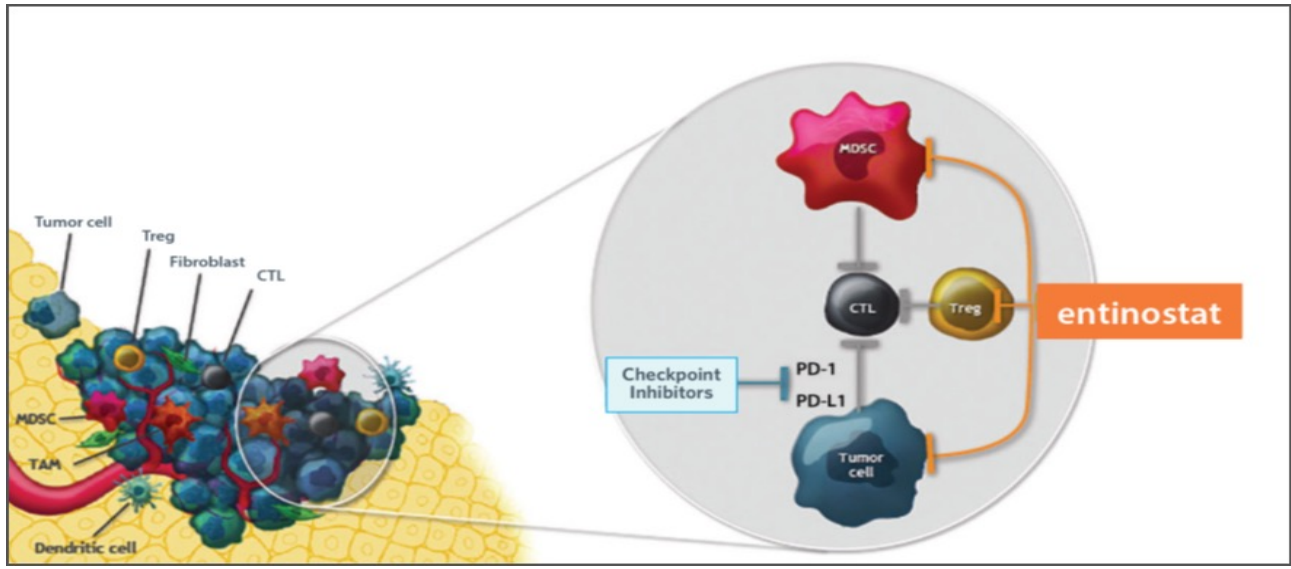
- We report a large real-world dataset evaluating outcomes with check-point inhibitors in NSCLCs with *KRAS* and specific co-mts. Across the subgroups, KKL (KRAS mt/STK-11 mt/KEAP-1 mt) demonstrated universally poor outcomes in all *KRAS* subtypes; irrespective of PD-L1 expression.

Khan, H (Raez LE) et al. J Clin Oncol 41, 2023 (suppl 16; abstr 9038)

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti-PD-(L)1 Therapy

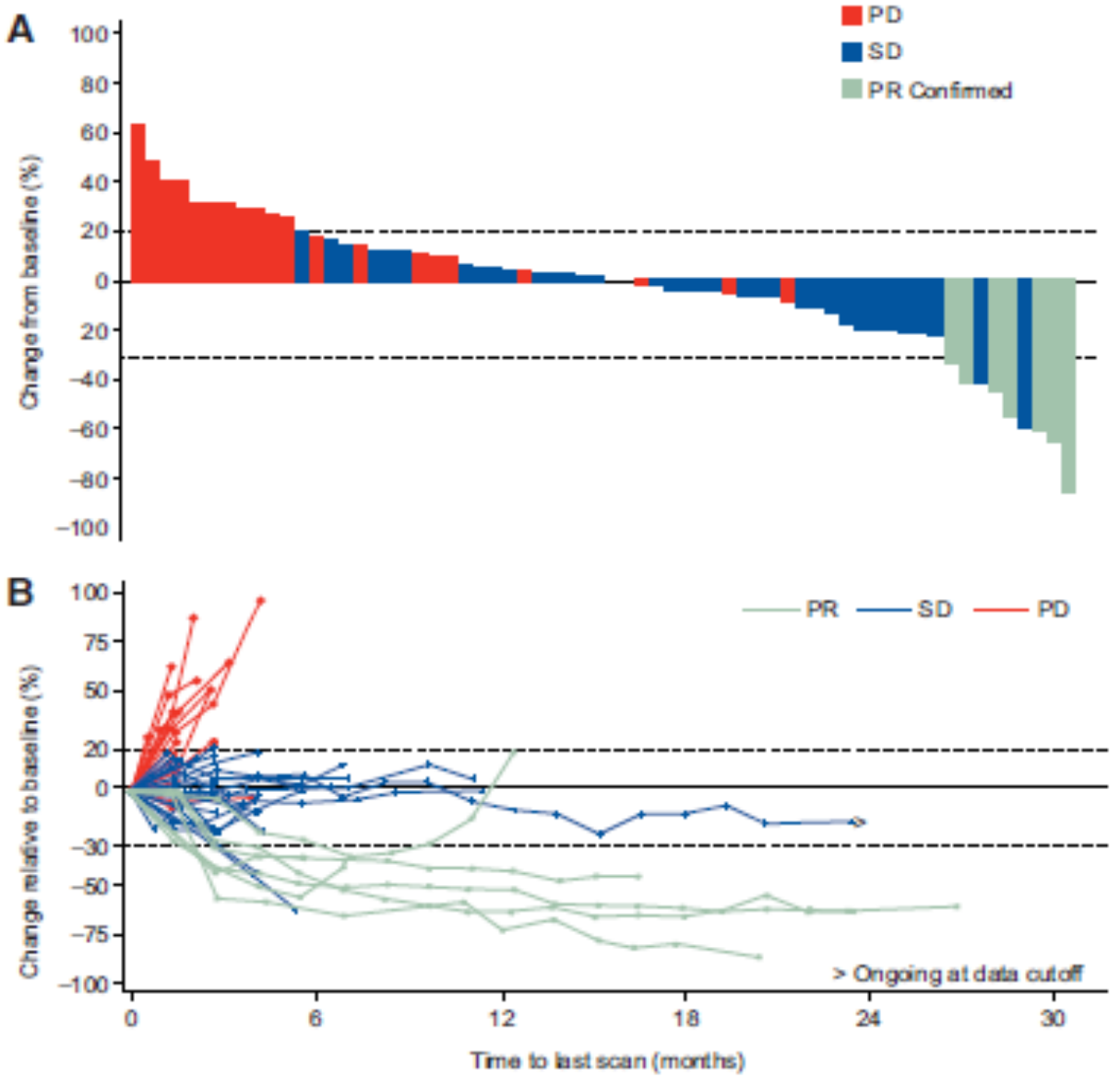
Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry I. Gabrilovich[6], Fang Wang[6], Jane B. Trepel[7], Min-Jung Lee[7], Akira Yuno[7], Sunmin Lee[7], Susan Brouwer[8], Serap Sankoh[8], Lei Wang[8], David Tamang[8], Emmett V. Schmidt[9], Michael L. Meyers[8], Suresh S. Ramalingam[10], Elaine Shum[11], and Peter Ordentlich[8]



- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD1 inhibition in preclinical models
- Promising activity shown in combination with pembrolizumab in patients with melanoma and lung cancer

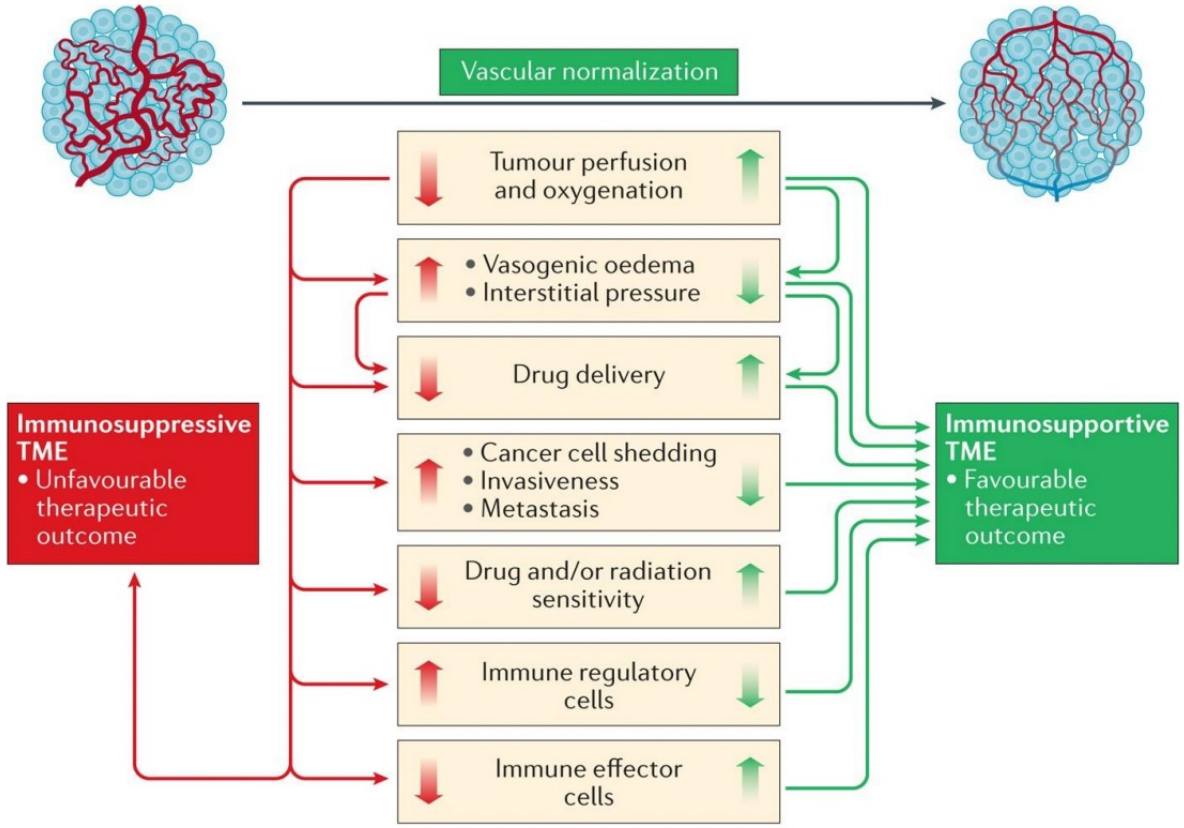
Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

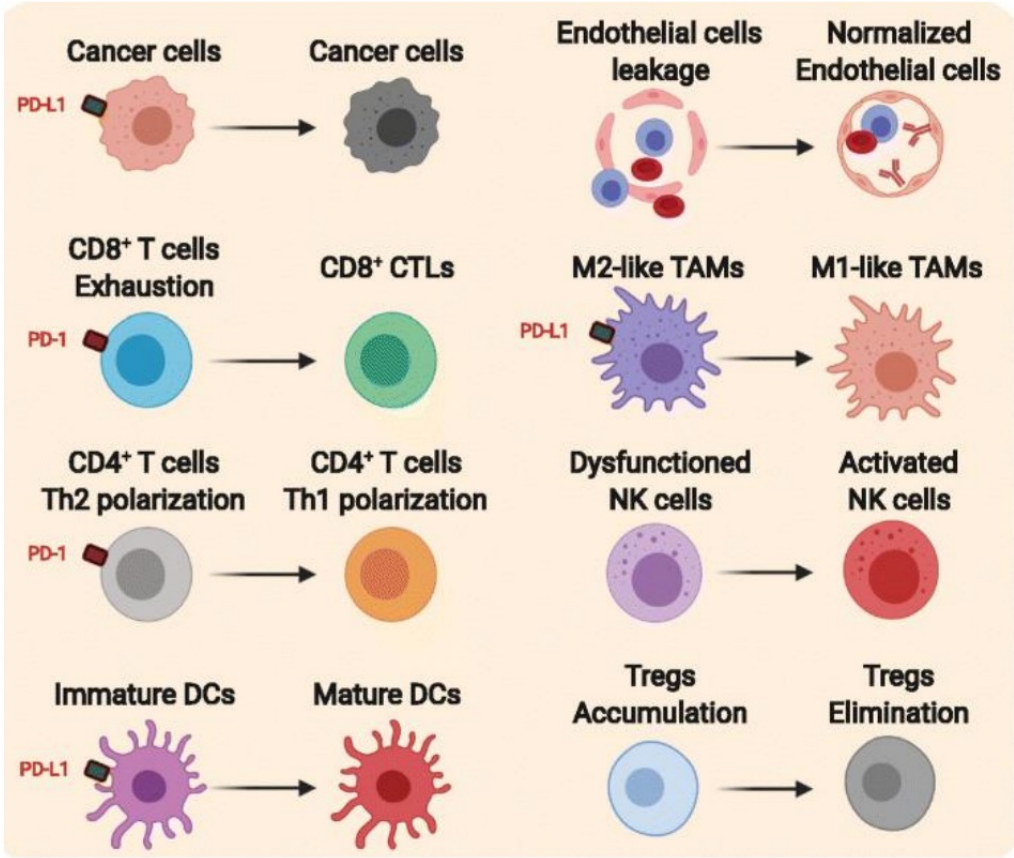
- **Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)**
  - **Median duration of response was 5.3 months**
  - **An additional 50% of patients achieved disease stabilization**
- **Median progression-free survival = 2.8 months (95% CI: 2.1-4.1)**



Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

Targeting angiogenesis to overcome ICI resistance





Fukumura et al., *Nat Rev Clin Oncol* 2018; Chen et al., *Biomarker Res* 2021

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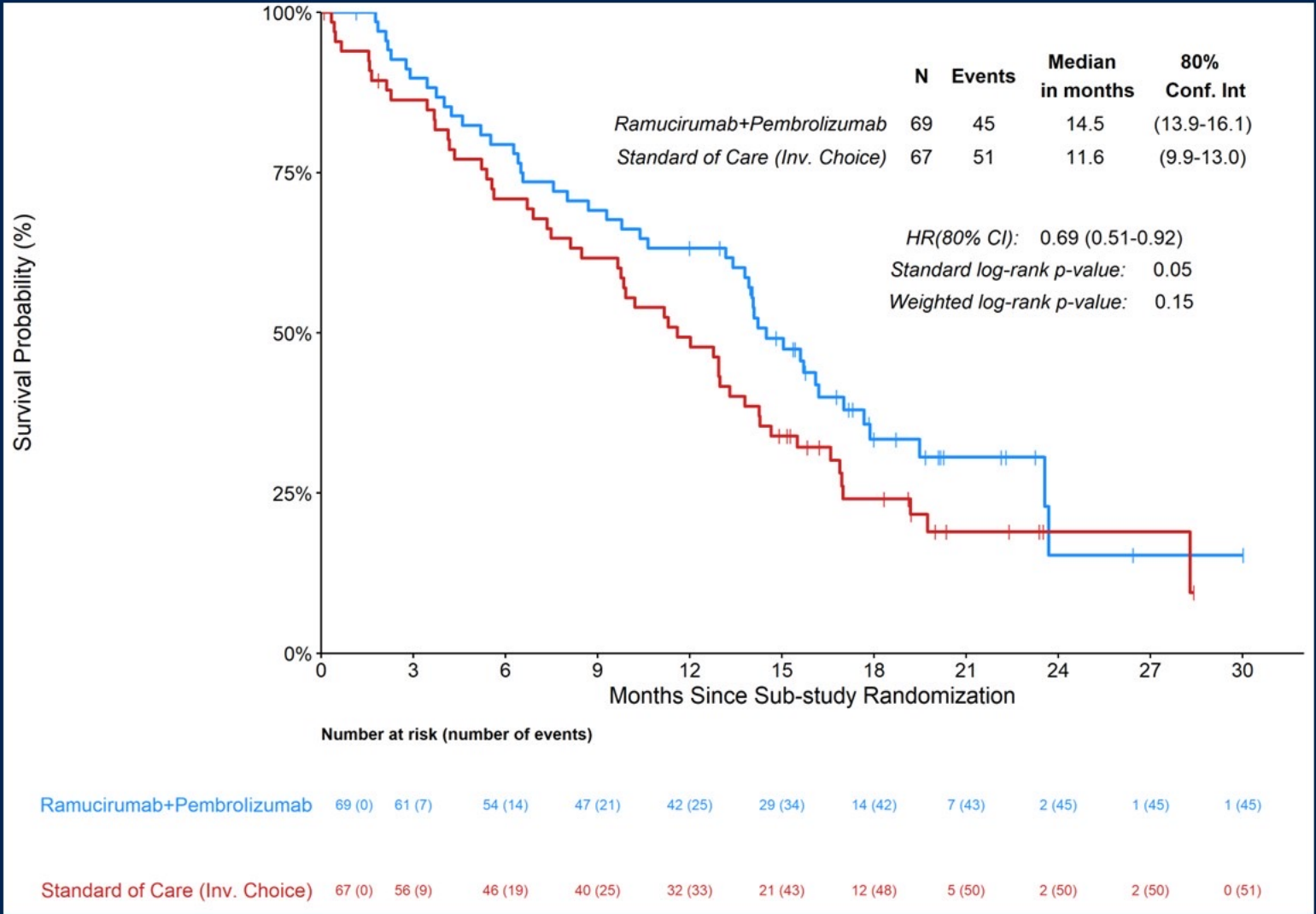
SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

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

Overall survival

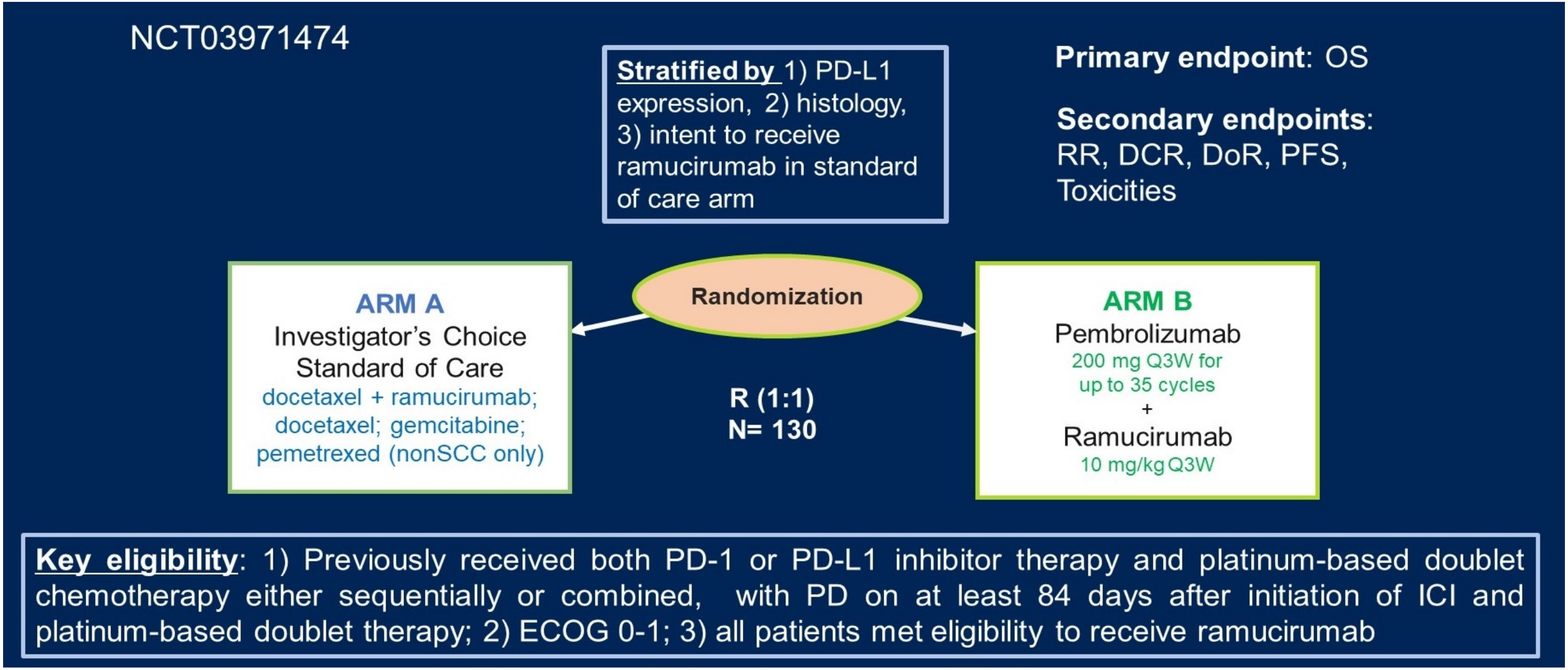


- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

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

PRAGMATICA LUNG, Phase 3 trial ongoing……..



Reckamp KL, et al. Presented at: ASCO;2022. Abstract 9004.

2021 ESMO congress

MRTX-500: Phase 2 Trial of Sitravatinib + Nivolumab in Patients With Nonsquamous Non–Small-Cell Lung Cancer Progressing on or After Prior Checkpoint Inhibitor Therapy

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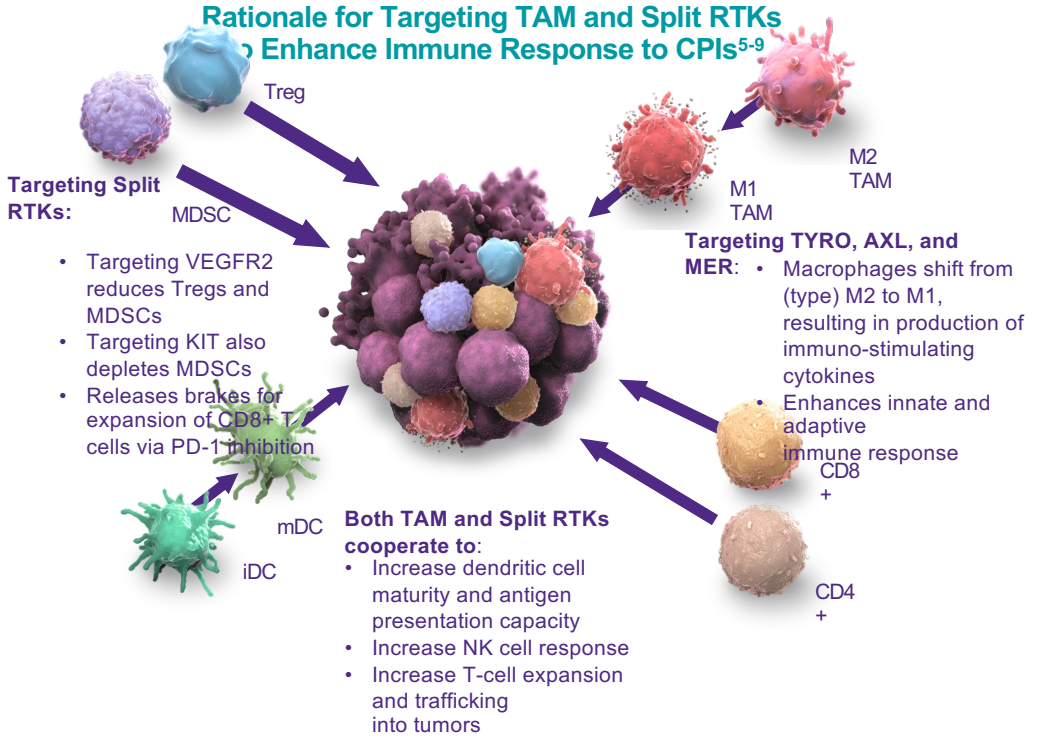
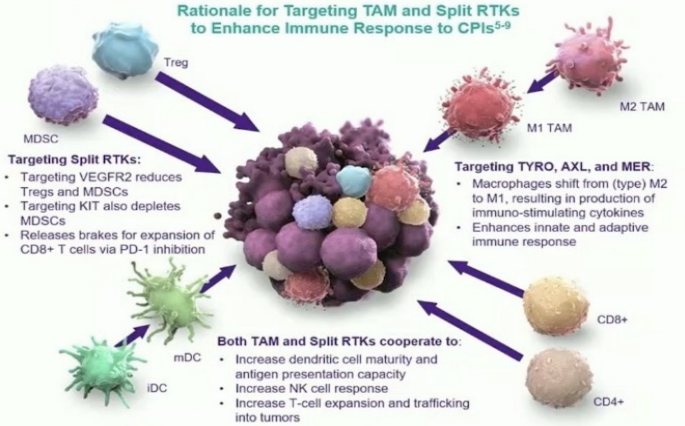
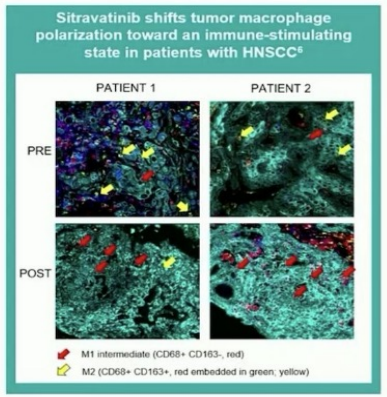


Kai H, …, Leal T. JTO 2023.

Sitravatinib Is a TKI That Targets TAM Receptors (TYRO3, AXL, MERTK) and Split-Family Receptors (eg, VEGFR2)





Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

MRTX-500: Phase 2, Open-Label Study of Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From Checkpoint Inhibitor Therapy

Key Eligibility Criteria
(n=68)

- Advanced/metastatic nonsquamous NSCLC[a]
- No actionable driver mutations
- Anti–PD-1/L1 must be the most recent line of therapy
- Prior Clinical Benefit (PCB) to CPI: CR, PR, or SD ≥12 weeks from prior CPI therapy
- No uncontrolled brain metastases
- ECOG PS 0-2

→ **Sitravatinib** 120 mg QD + nivolumab

Primary Endpoint:
- Objective Response Rate[b] (ORR), as defined by RECIST 1.1

Secondary Endpoints:
- Safety and tolerability
- DOR
- CBR
- PFS
- OS
- 1-year survival rate

Here we report updated efficacy and safety with sitravatinib + nivolumab in the 2L or 3L setting in patients with nonsquamous NSCLC who have experienced clinical benefit on a prior CPI and subsequent disease progression

Data as of 1 June 2021

[a]Additional cohorts included a CPI-experienced cohort that did not receive prior clinical benefit from CPI therapy (radiographic progression of disease ≤12 weeks after initiation of treatment with CPI) and a CPI-naive cohort in patients that were previously treated with platinum-based chemotherapy. [b]Objective response rate based on investigator assessment. Dosing: sitravatinib free base formulation; nivolumab, 240 mg Q2W or 480 mg Q4W. Treatment discontinuation could be due to (but is not limited to) disease progression, global health deterioration, AEs, protocol violation, lost to follow-up, refusal of further treatment, study termination, or death.

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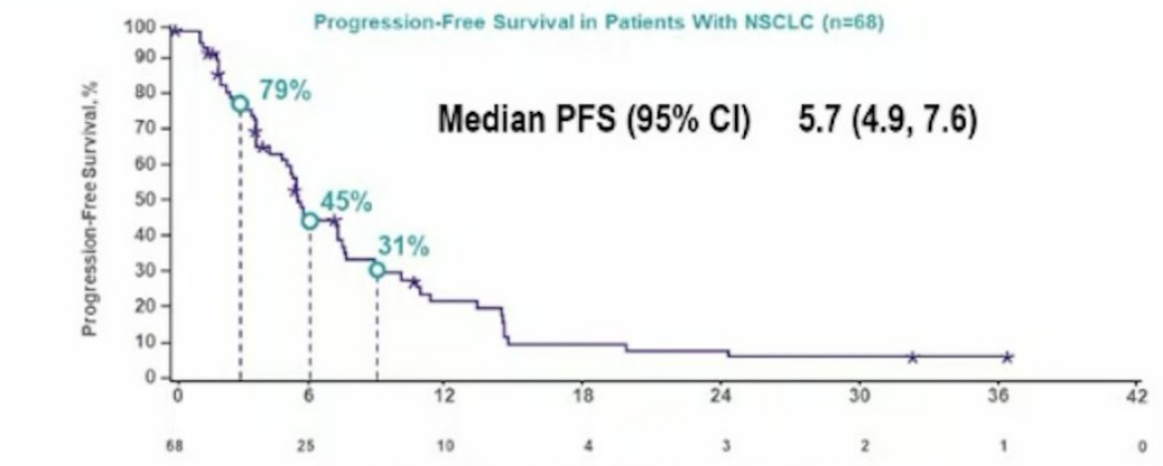
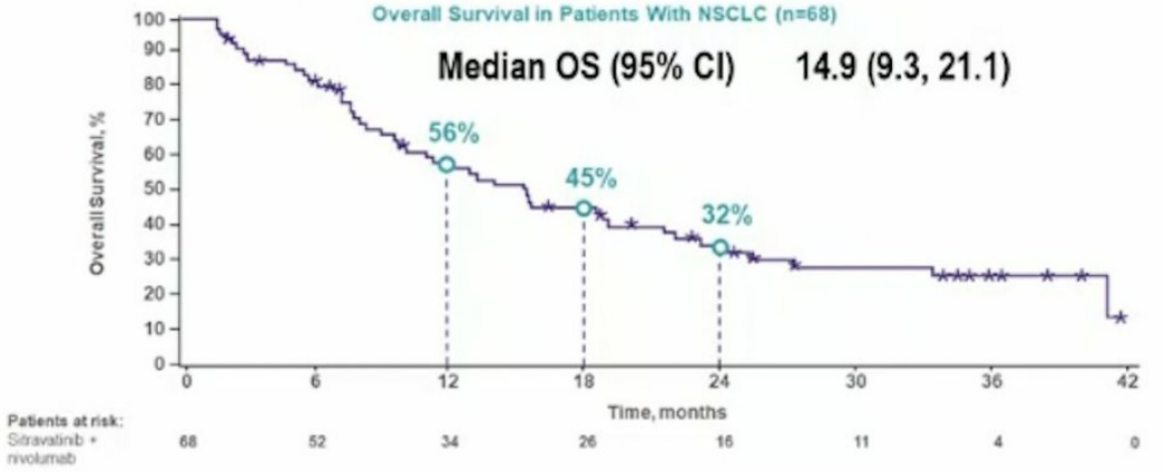




Ticiana Leal. ESMO 2021.

TIGIT

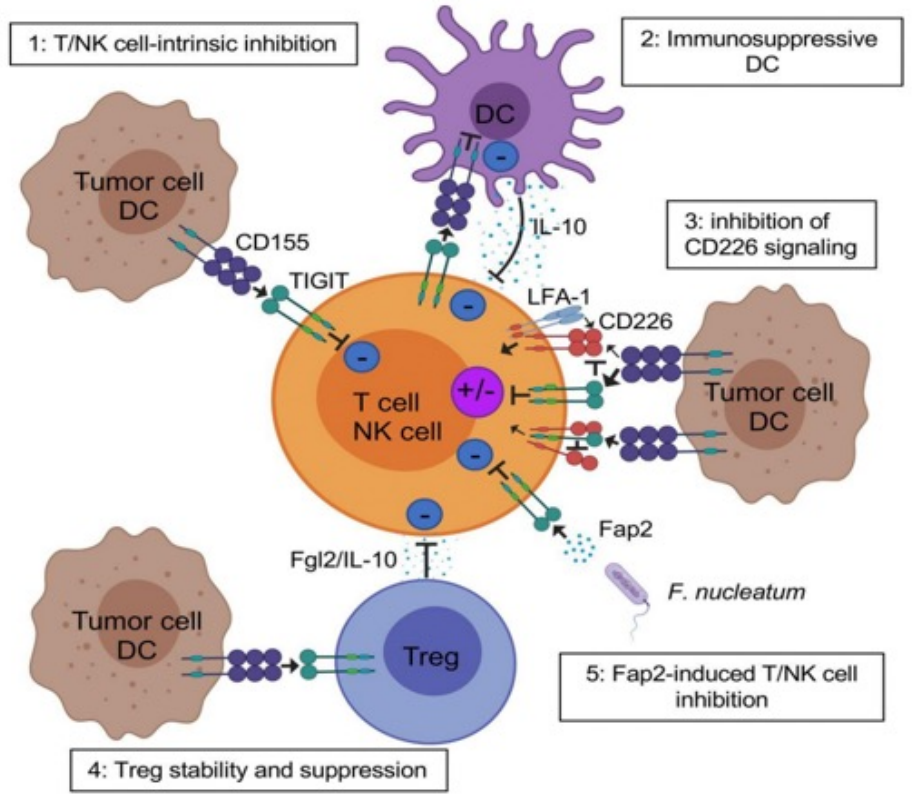
- **TIGIT/CD155**:
- Directly inhibits T cells

- Triggers **IL-10** production, **IL-12** decrease from **APCs** = Indirectly inhibits T cells

- Enhances immunosuppressive **Treg** function

- Interaction with **gut microbiome**: Binds with Fusobacterium nucleatum = Inhibitory signaling

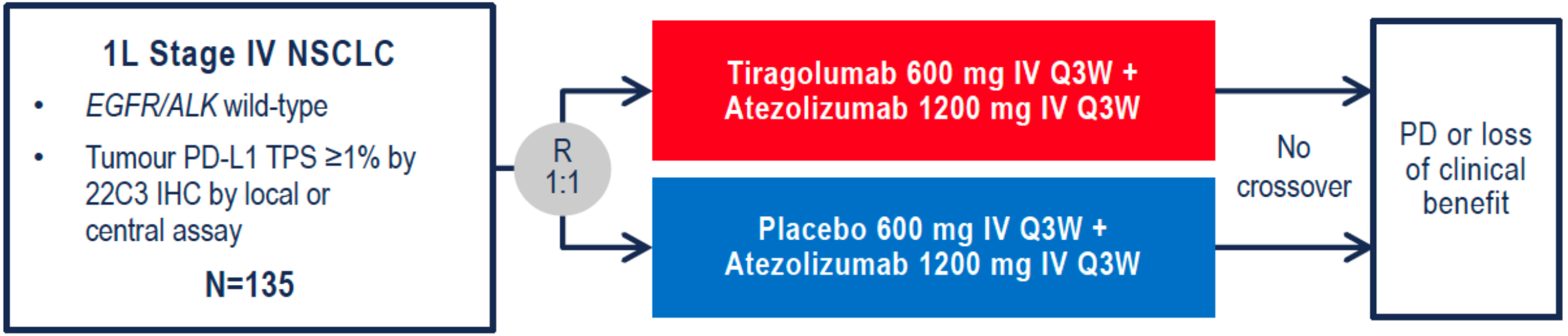
Mechanisms of TIGIT inhibition of T cells in TME



Joe-Marc Chauvin, and Hassane M Zarour J Immunother Cancer 2020;8:e000957

Journal for ImmunoTherapy of Cancer

CITYSCAPE: Randomized Phase 2 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

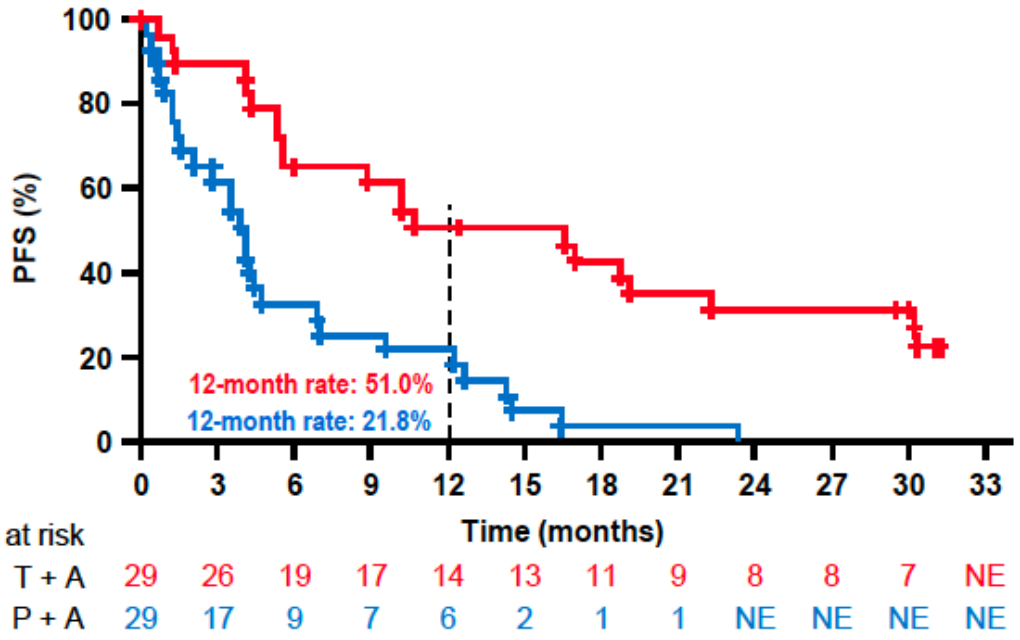
IHC, immunohistochemistry; PROs, patient-reported outcomes; TPS, tumor proportion score.

Rodriguez-Abreu D, et al. Presented at: ASCO;2020.

Investigator-Assessed PFS: PD-L1 Subgroups

PD-L1 TPS ≥50% (n=58)

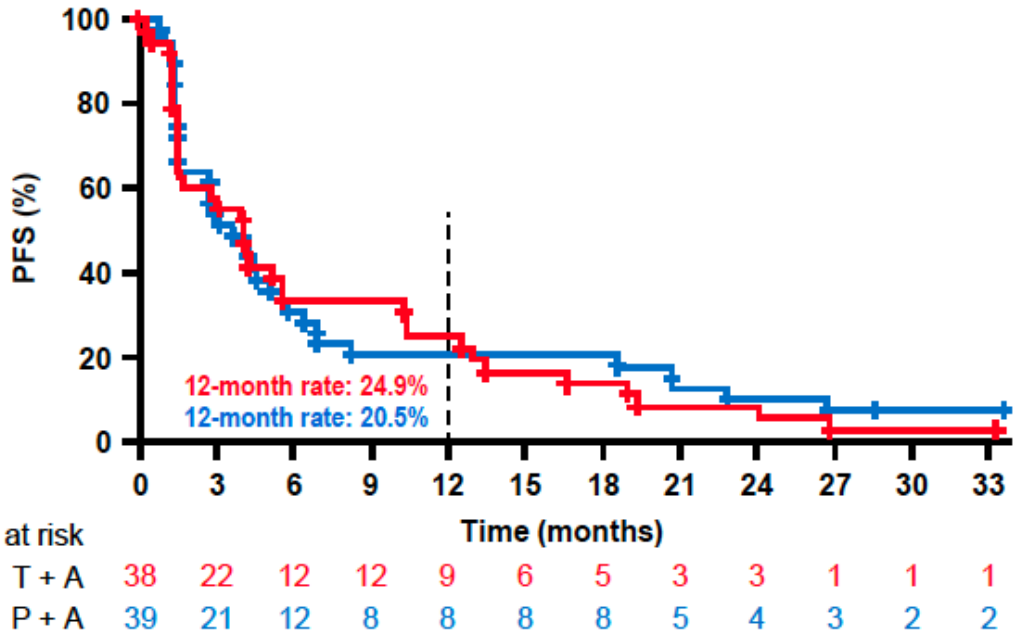
	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	21 (72.4)	16.6 (5.5–22.3)	0.29* (0.15–0.53)	69.0	15.7 (9.1–NE)
Placebo + atezo	28 (96.6)	4.1 (2.1–6.8)		24.1	8.2 (5.6–10.4)



No. at risk												
T + A	29	26	19	17	14	13	11	9	8	8	7	NE
P + A	29	17	9	7	6	2	1	1	NE	NE	NE	NE

PD-L1 TPS 1–49% (n=77)

	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	36 (94.7)	4.0 (1.6–5.6)	1.07* (0.67–1.71)	15.8	17.8 (8.3–24.2)
Placebo + atezo	36 (92.3)	3.6 (1.4–5.5)		17.9	18.8 (15.9–22.8)

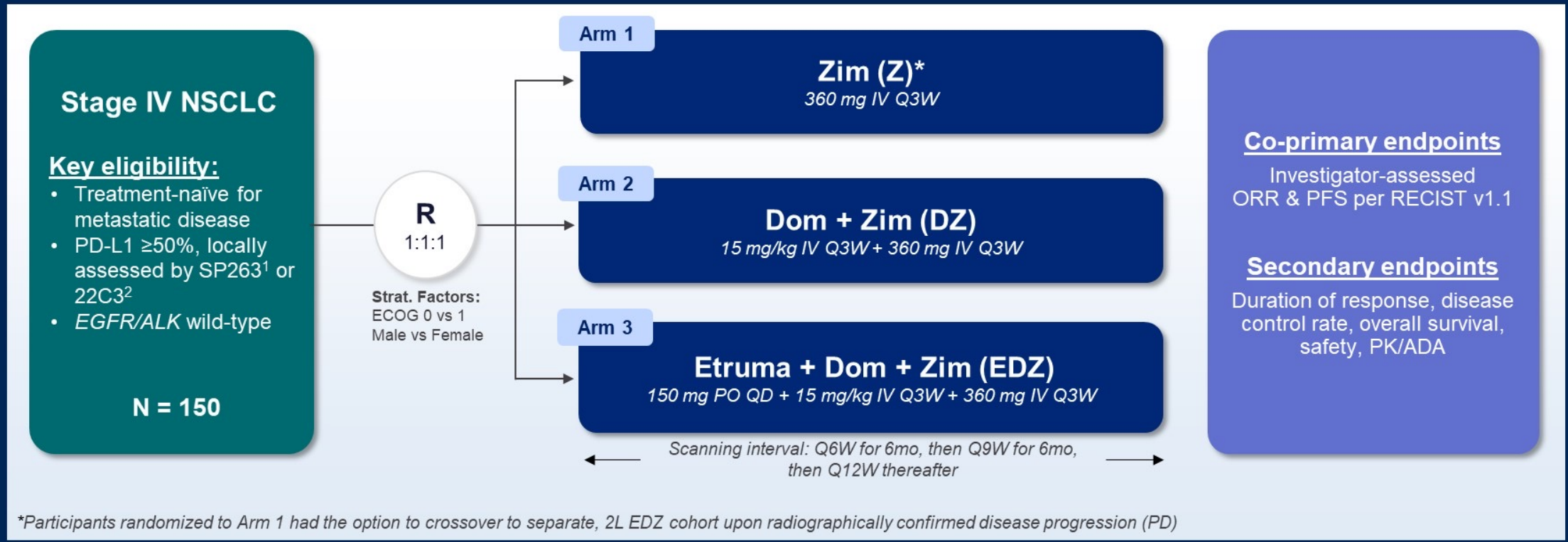


No. at risk												
T + A	38	22	12	12	9	6	5	3	3	1	1	1
P + A	39	21	12	8	8	8	8	5	4	3	2	2

*Unstratified.
Updated analysis data cut-off: 16 August 2021 (median follow-up: 30.4 months)
PD-L1 status determined by 22c3 IHC assay.

Rodriguez-Abreu D, et al. Presented at: ASCO;2020.

ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



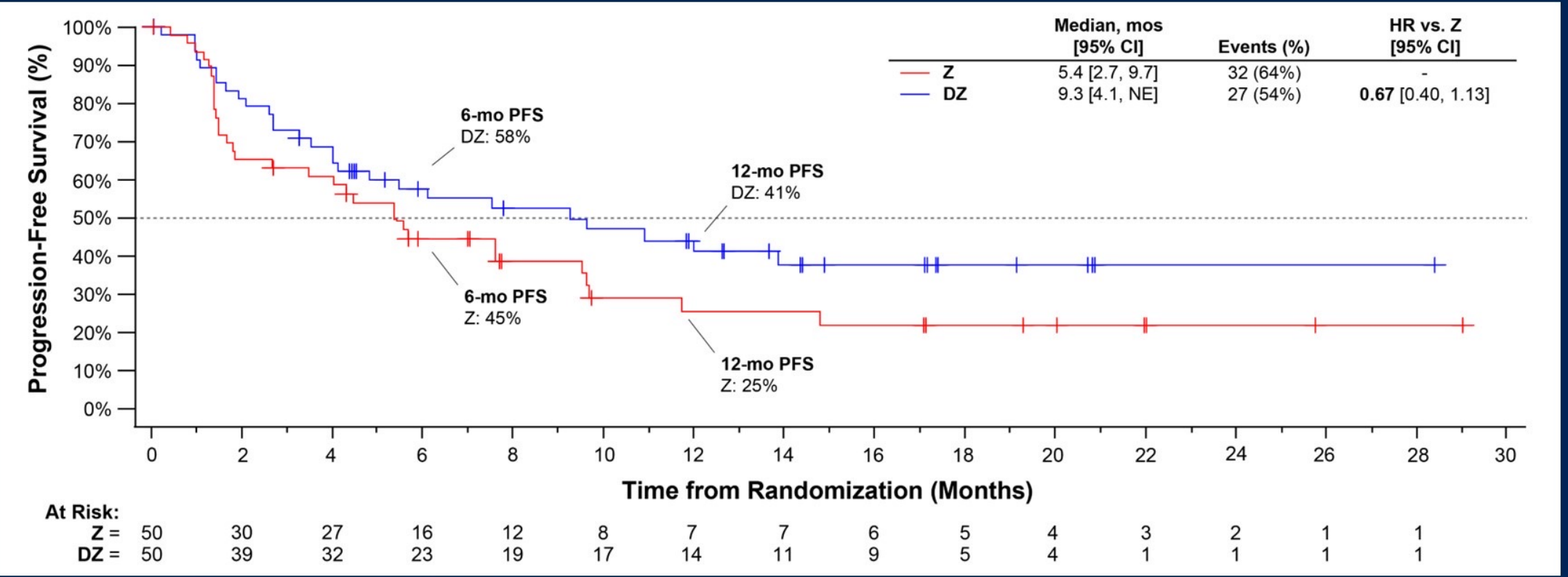
*Participants randomized to Arm 1 had the option to crossover to separate, 2L EDZ cohort upon radiographically confirmed disease progression (PD)

ADA: anti-drug antibody, Dom: domvanalimab, Etruma: etrumadenant, ORR: objective response rate, PFS: progression-free survival, PK: pharmacokinetics; R: randomized; Zim: zimberelimab; Q3W: every three weeks
[1]Ventana SP263 assay; [2]PharmDx 22C3 assay

PRESENTED BY: Melissa Johnson, MD, Director Lung Cancer Research
Sarah Cannon Research Institute at Tennessee Oncology
@MLJohnsonMD2

Progression-Free Survival (mITT)

Zim Monotherapy vs. Dom + Zim Doublet



CI: confidence interval; HR: hazard ratio; Mos: months; NE: not evaluable

Addition of dom to zim resulted in 33% reduction in risk of progression or death as compared to zim alone

PRESENTED BY: Melissa Johnson, MD, Director Lung Cancer Research Sarah Cannon Research Institute at Tennessee Oncology
@MLJohnsonMD2

Conclusions

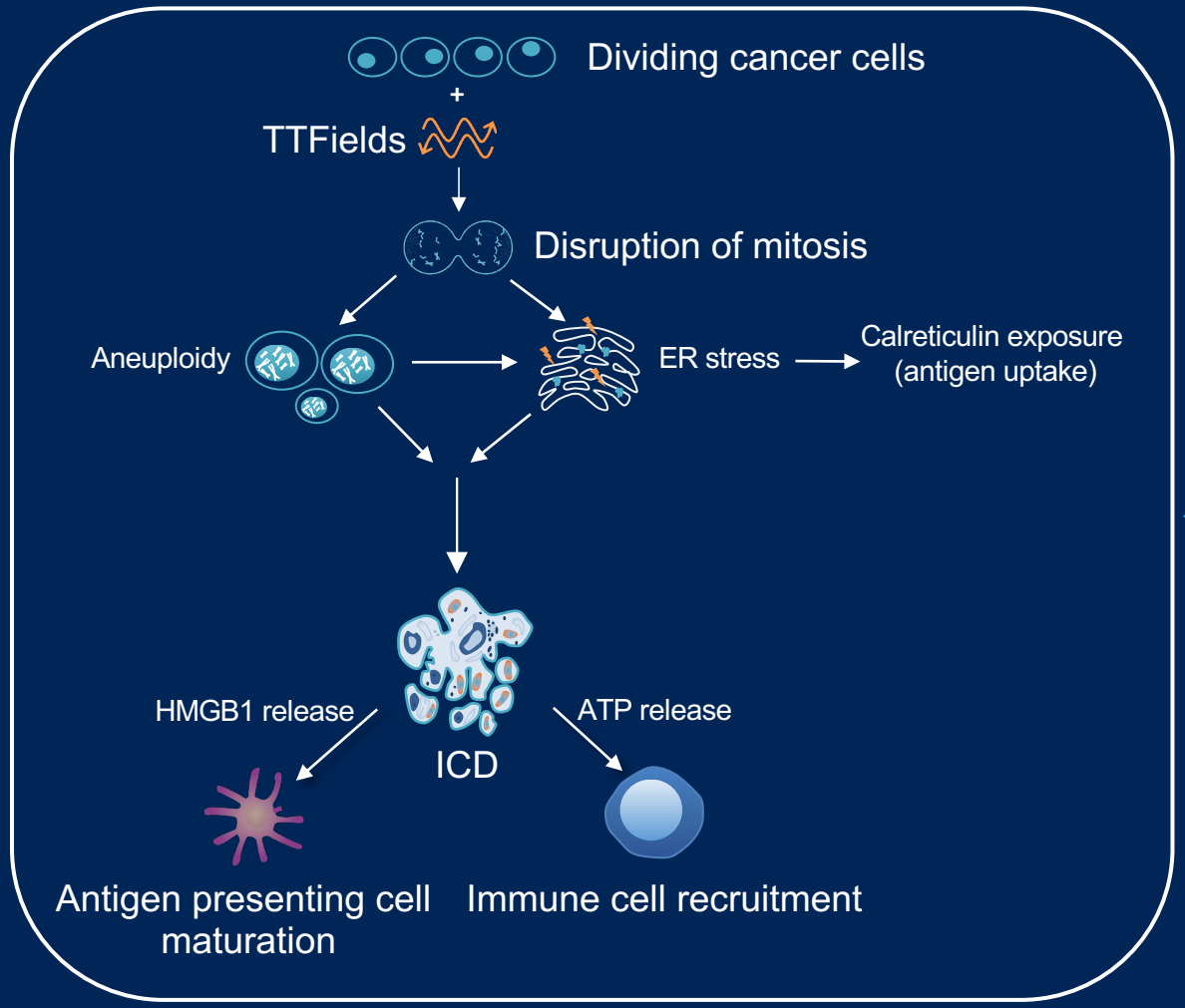
- In an updated analysis of ARC-7, with longer median follow-up of 18.5 months, dom-containing arms continued to demonstrate clinically meaningful improvement in ORR and PFS as compared to zim monotherapy. Specifically, TIGIT combinations resulted in:
  - Greater ORR, Δ: +10 to 14%, compared to zim alone
  - Approximately 30% reduction in risk of progression or death compared to zim alone
- Clinical activity and safety of zim performed as expected with agents in the anti-PD-1 class
- Dom + zim combinations with or without etruma were generally well-tolerated with similar, manageable safety profiles across all arms
  - Rates of infusion-related reactions were low across dom-containing arms (4 – 12%), as intended with the Fc-silent design of dom
- The data presented support the ongoing phase 3 studies with domvanalimab: ARC-10 (NCT04736173), STAR-121 (NCT05502237), STAR-221 (NCT05568095) and PACIFIC-8 (NCT05211895)

Current trials in Stage IV NSCLC targeting TIGIT

	VELOCITY-Lung	STAR-121	ARC-7	KEYVIBE-007	KEYVIBE-003	SKYSCRAPER-01	CITYSCAPE
	NCT05633667	NCT05502237	NCT04262856	NCT05226598	NCT04738487	NCT04294810	NCT03563716
Anti-TIGIT	Domvanalimab (DOM)	Domvanalimab (DOM)	Domvanalimab	Vibostolimab*	Vibostolimab*	Tiragolumab	Tiragolumab
Immunotherapy	Zimberelimab (ZIM)	Zimberelimab (ZIM)	Zimberelimab (ZIM)	Pembrolizumab*	Pembrolizumab*	Atezolizumab	Atezolizumab
Additional Tx	Sacituzumab govitecan (SG)/ Etrumadenant (ETRUMA)	Chemotherapy	Etrumadenant (ETRUMA)	Chemotherapy	n/a	n/a	n/a
Control Arm	SOC	Pembrolizumab + CT	Zimberelimab	Pembrolizumab + CT	Pembrolizumab	Placebo + Atezolizumab	Placebo + Atezolizumab
Line of Therapy	1 L	1L	1L	1L	1L	1L	1L
Histology	NSQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ
Patient Population	Non-AGA	No EGFR/ALK	PD-L1 >50% No EGFR/ALK	Non-AGA	No EGFR/ALK/ROS1 PD-L1 ≥1%	Non-AGA PD-L1 ≥50%	CT Naïve
Start Date	Not Yet Recruiting	October 2022	May 2020	March 2022	April 2021	March 2020	August 2018
Estimated Completion Date	January 2027	December 2027	February 2024	September 2025	April 2026	February 2025	June 2019
Primary Outcome	ORR	PFS/OS	ORR/PFS	PFS/OS	OS	PFS/OS	ORR: 31.3% PFS: 5.4 months
Trial Type	Phase II	Phase III	Phase II	Phase III	Phase III	Phase III	Phase II

*Coformulation (MK-7684A)

Tumor Treating Fields (TTFields) Mechanism of Action



- TTFields are electric fields that exert physical forces on electrically charged components in dividing cancer cells, leading to an antimitotic effect[1,2]

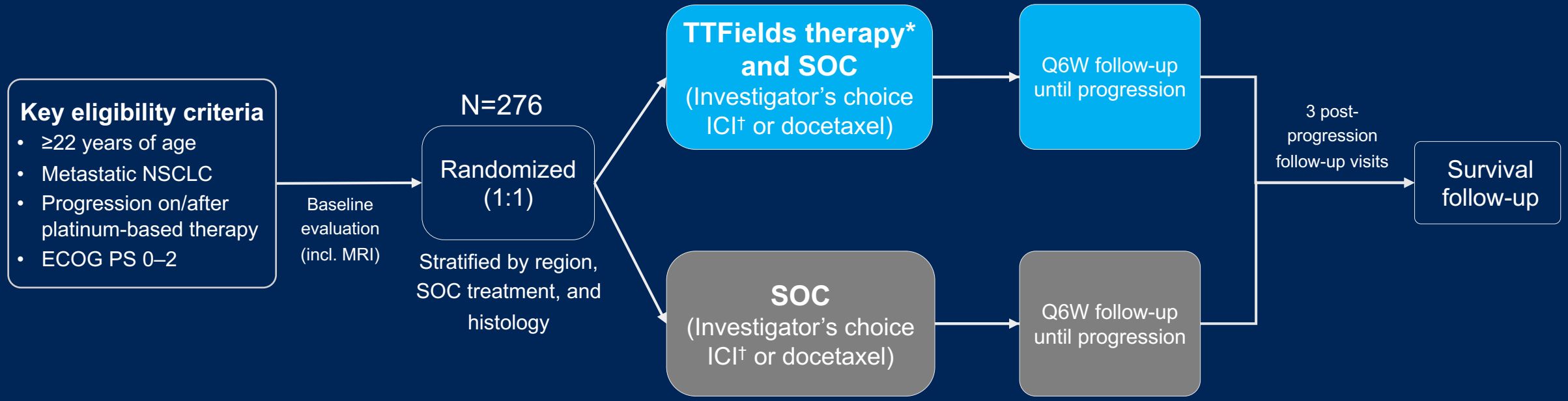
- Downstream effects include cell stress-induced immunogenic cell death (ICD), triggering a systemic anti-tumor immune response[3,4]

ATP, adenosine triphosphate; ER, endoplasmic reticulum; HMGB1, high mobility group box 1 protein; ICD, immunogenic cell death; TTFields, Tumor Treating Fields.

1. Mun EJ et al. *Clin Cancer Res.* 2018;24(2):266–275; **2**. Giladi M et al. *Sci Rep.* 2015;5:18046; **3**. Voloshin T et al. *Cancer Immunol Immunother.* 2020;69(7):1191–1204; **4**. Barsheshet Y et al. *Int J Mol Sci*. 2022;23(22):14073. Figure adapted from: Shteingauz A et al. *Cell Death Dis.* 2018;9(11):1074.

LUNAR Phase 3 Study Design

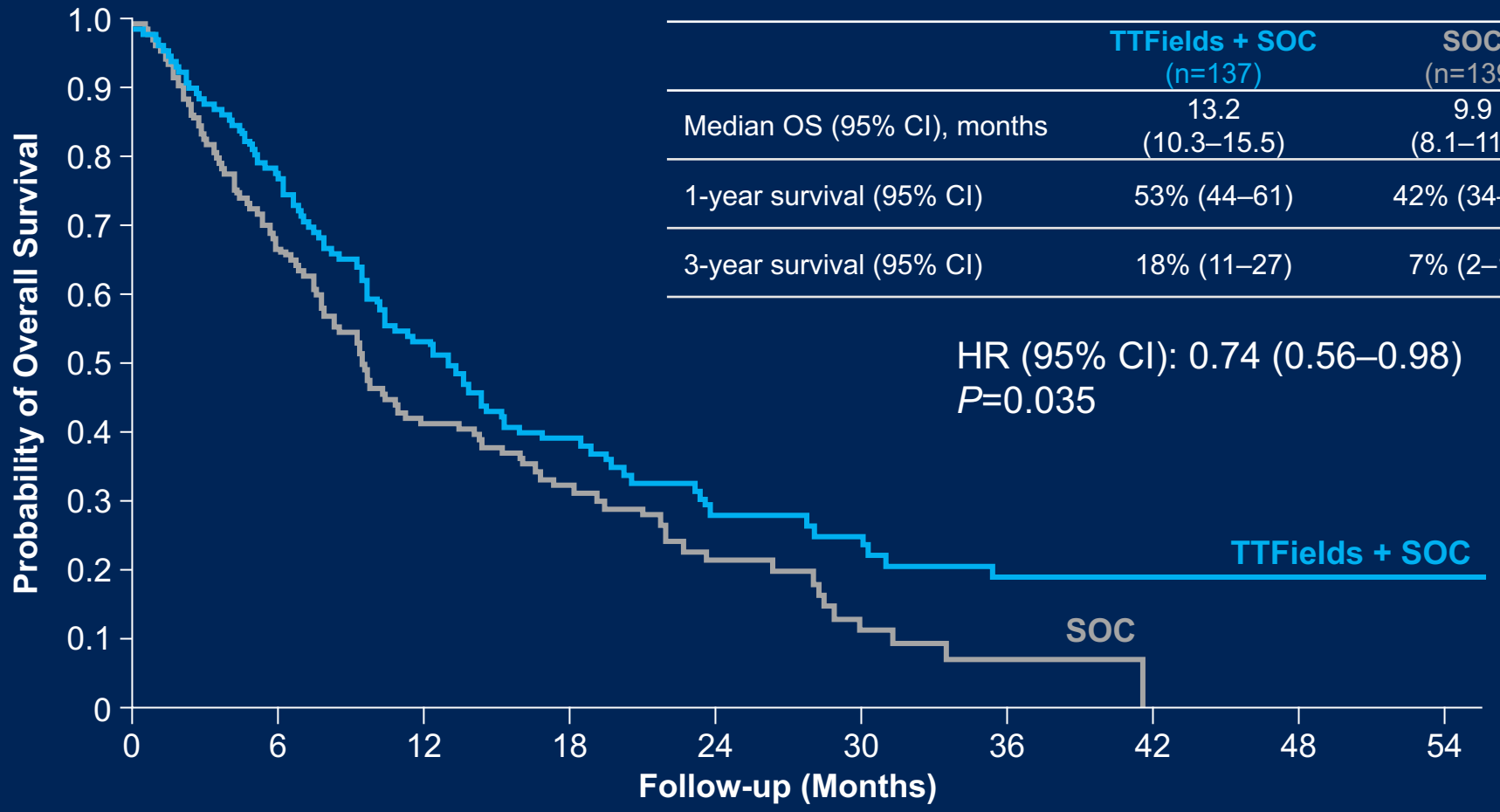
Objective: To evaluate safety and efficacy of TTFields therapy with standard of care (SOC) compared to SOC alone in metastatic NSCLC progressing on or after platinum-based therapy



Data cut-off: November 26, 2022
Study sites: 124 in 17 countries (North America, Europe, Asia)

*150 kHz; ≥18 h/day; †pembrolizumab, nivolumab, or atezolizumab.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; Q6W, every 6 weeks; SOC, standard of care; TTFields, Tumor Treating Fields.

Overall Survival in the ITT Population



	TTFields + SOC (n=137)	SOC (n=139)
Median OS (95% CI), months	13.2 (10.3–15.5)	9.9 (8.1–11.5)
1-year survival (95% CI)	53% (44–61)	42% (34–50)
3-year survival (95% CI)	18% (11–27)	7% (2–15)

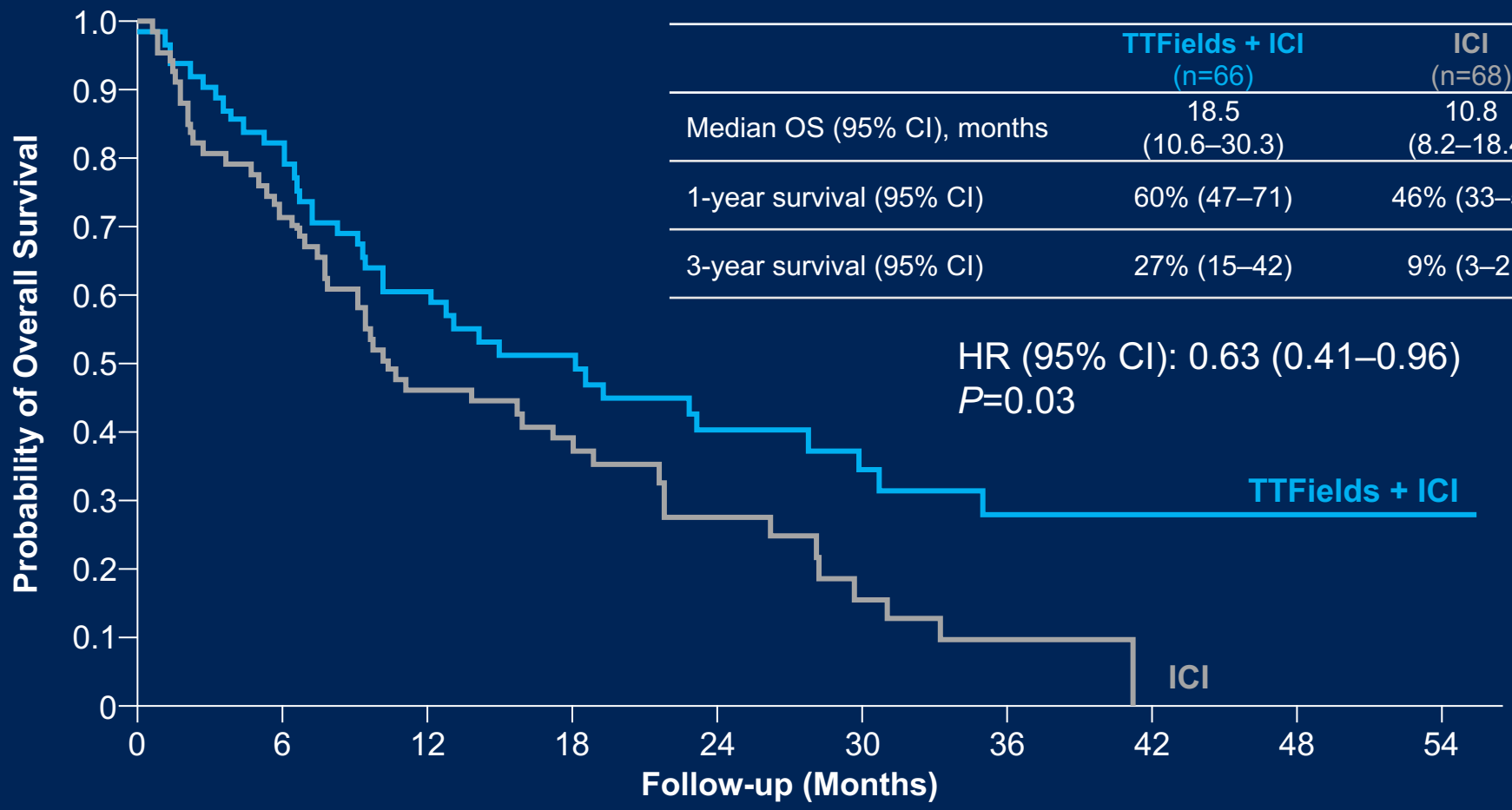
HR (95% CI): 0.74 (0.56–0.98)
P=0.035

No. at Risk:										
TTFields + SOC	137	100	62	36	22	16	11	9	5	3
SOC	139	96	54	32	16	7	3	0	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; SOC, standard of care; TTFields, Tumor Treating Fields.

Median (range) follow-up: 10.0 (0.03–58.7) months

Overall Survival in ICI-Treated Patients



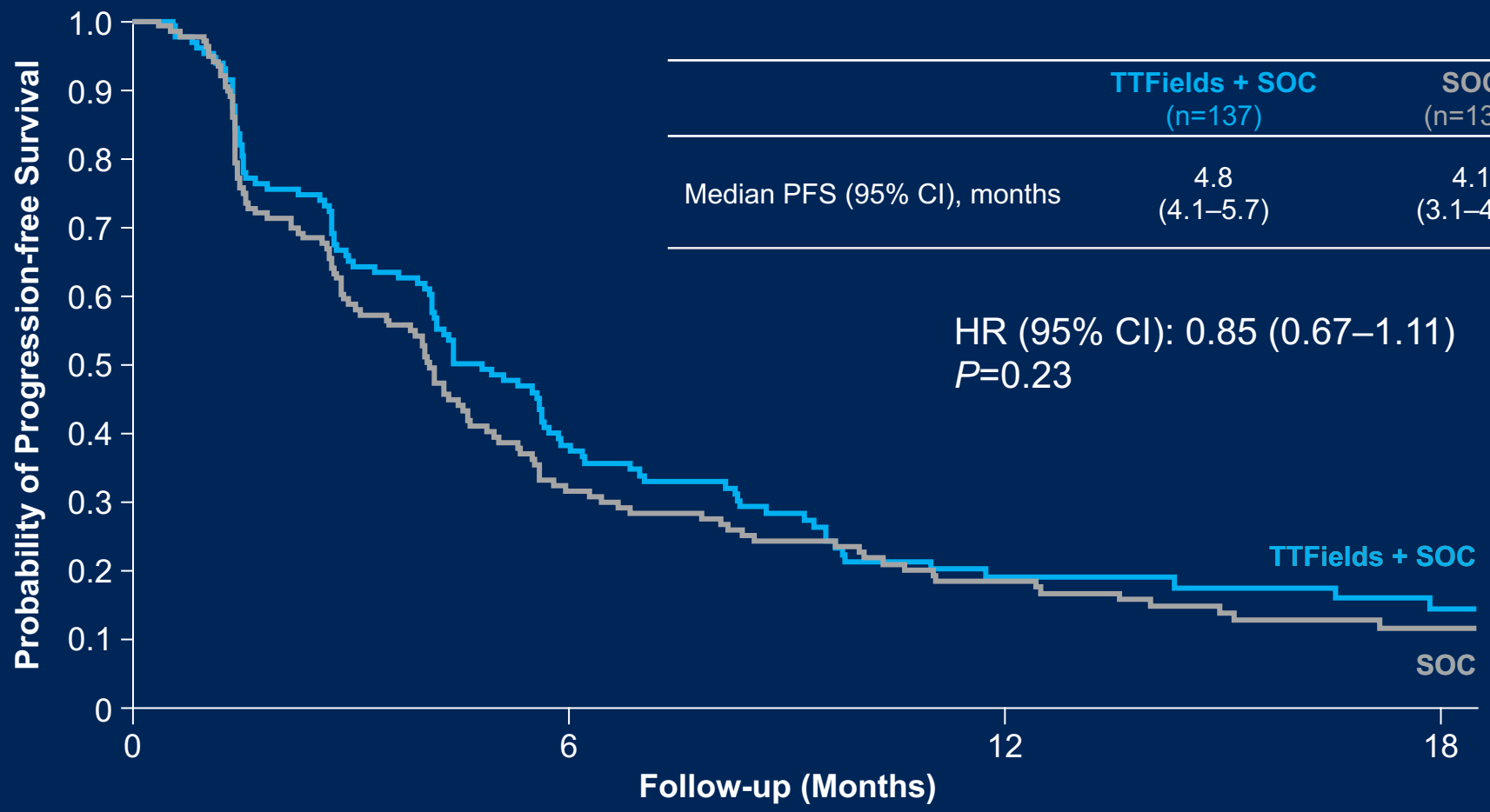
	TTFields + ICI (n=66)	ICI (n=68)
Median OS (95% CI), months	18.5 (10.6–30.3)	10.8 (8.2–18.4)
1-year survival (95% CI)	60% (47–71)	46% (33–57)
3-year survival (95% CI)	27% (15–42)	9% (3–21)

HR (95% CI): 0.63 (0.41–0.96)
P=0.03

No. at Risk:										
TTFields + ICI	66	50	35	24	16	12	8	6	2	1
ICI	68	49	29	21	11	6	3	0	0	0

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; TTFields, Tumor Treating Fields.

Progression-free Survival in the ITT Population



	TTFields + SOC (n=137)	SOC (n=139)
Median PFS (95% CI), months	4.8 (4.1–5.7)	4.1 (3.1–4.6)

HR (95% CI): 0.85 (0.67–1.11)
P=0.23

No. at risk:				
TTFields + SOC	137	44	17	9
SOC	139	40	21	9

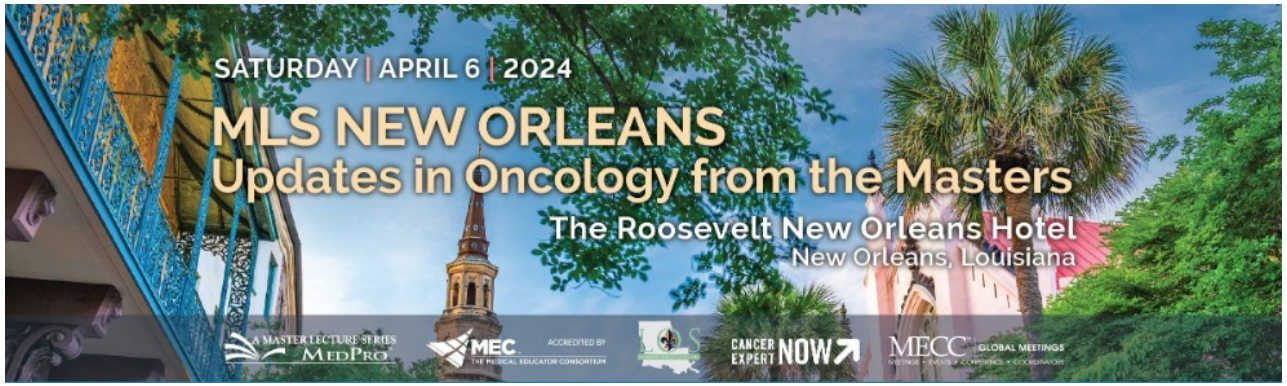
PFS was defined as the time from date of randomization until date of disease progression, or death by any cause.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival; SOC, standard of care; TTFields, Tumor Treating Fields.

Conclusions

- Pivotal, phase 3 LUNAR study met its primary endpoint
- TTFields therapy with SOC provided a statistically significant and clinically meaningful 3-month improvement in median OS vs SOC (HR: 0.74, *P*=0.035) with no added systemic toxicities
  - Statistically significant ~8-month increase in median OS (from 10.8 to 18.5 months) was demonstrated with TTFields therapy and an ICI (HR: 0.63, *P*=0.030)
  - There was a 2.4-month difference in median OS (from 8.7 to 11.1) for TTFields therapy and docetaxel vs docetaxel alone (HR: 0.81, *P*=0.28)
- TTFields therapy should be considered part of SOC for metastatic NSCLC following progression on or after platinum-based therapy
- Additional studies evaluating TTFields therapy with current SOC for first-line metastatic and locally advanced NSCLC are underway
- TTFields therapy is a potentially paradigm shifting new treatment modality

HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; SOC, standard of care; TTFields; Tumor Treating Fields.

Thanks



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