MaTOS™
Masters in Thoracic Oncology Summit
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Emerging Strategies in Immunotherapy (IO) Resistant NSCLC

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Introduction

- With clinically meaningful survival benefits, durable responses, and favorable safety profile versus chemotherapy, immune checkpoint inhibitors have become the standard of care for patients with NSCLC without driver mutations in the front-line setting.
- Resistance to immunotherapy may be different depending on prior line of immunotherapy containing regimen (+/- CTL4 inhibitor, +/- anti-angiogenic therapy).

Schoenfeld AJ, Hellmann MD. Cancer Cell. 2020;37:443–455.

Addressing IO resistance in NSCLC

- Despite multiple trials, no new approved agents or combinations in this space.
- Definition immunotherapy resistance is evolving.

Organization	ICI exposure requirement	Best response	Continuity of treatment	Confirmatory scan for PD requirement	Confirmatory scan timeframe
SITC	≥ 6 months	CR, PR, SD for >6 months	N/A	Yes	At least 4 weeks after initial disease progression
ESMO (NSCLC)	Prior ICI treatment	OR (SD excluded); no DOR threshold	Progression occurs ≤ 6 months of last treatment	No	NA
LUNG-MAP	≥84 days	CR, PR, SD for >84 days	N/A	No	NA

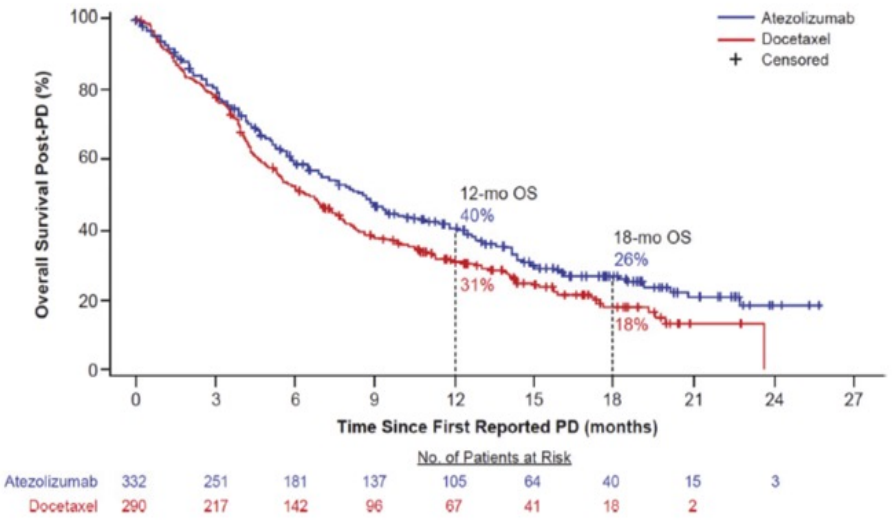
Kluger, et al. J Immunother Cancer, 2020. 8(1); Schoenfeld, A.J., et al. Ann Oncol, 2021. 32(12): p. 1597-1607.

Post-Progression: Immunotherapy Resistance

- Immunotherapy treatment beyond progression (TBP) outcomes have been reported for multiple tumor types, including NSCLC showing that a subset of patients may derive benefit
- Treatment with PD-1/PD-L1 blockade beyond progression is not a standard approach
- Post-progression prolongation of survival has been observed with immunotherapy and further research is warranted

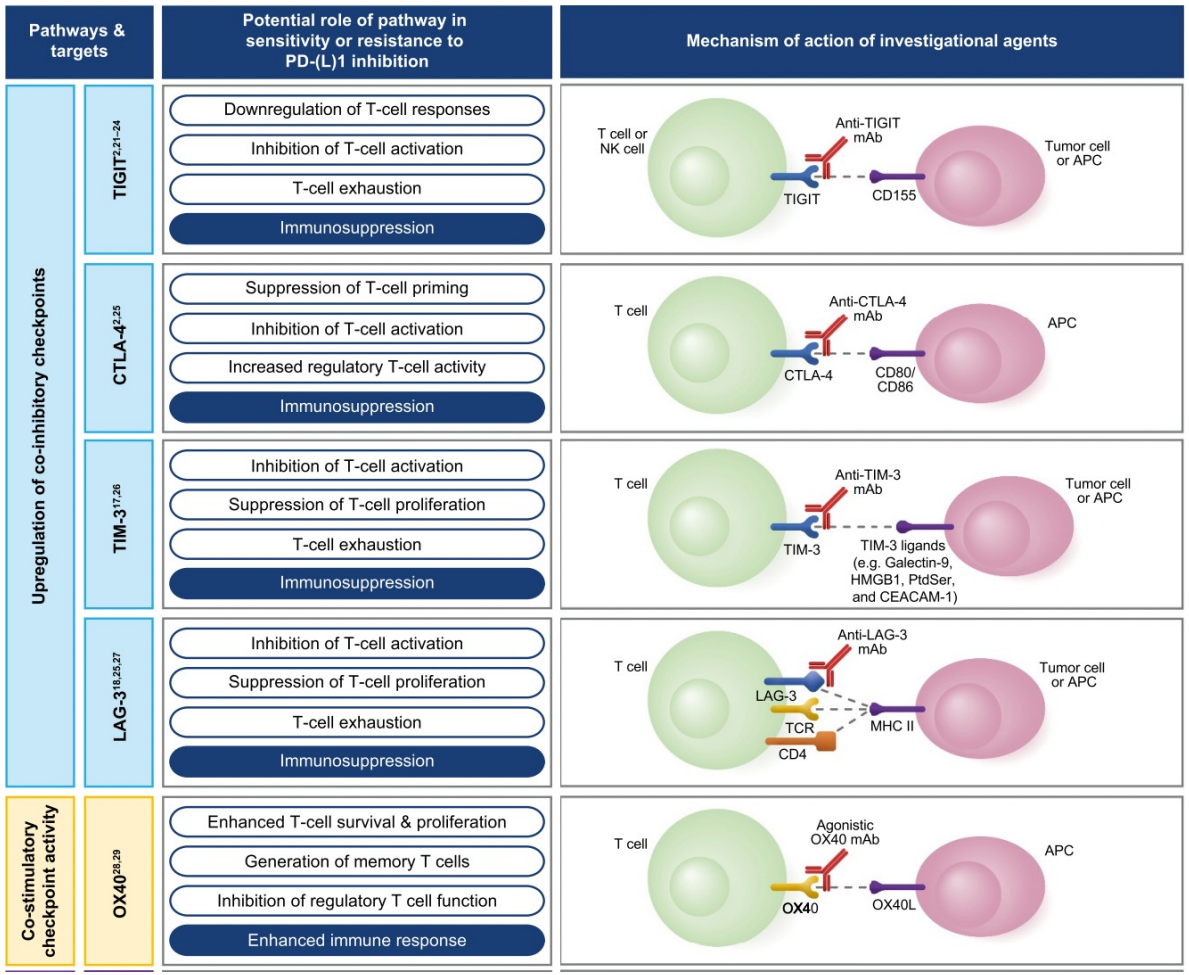
OAK Study

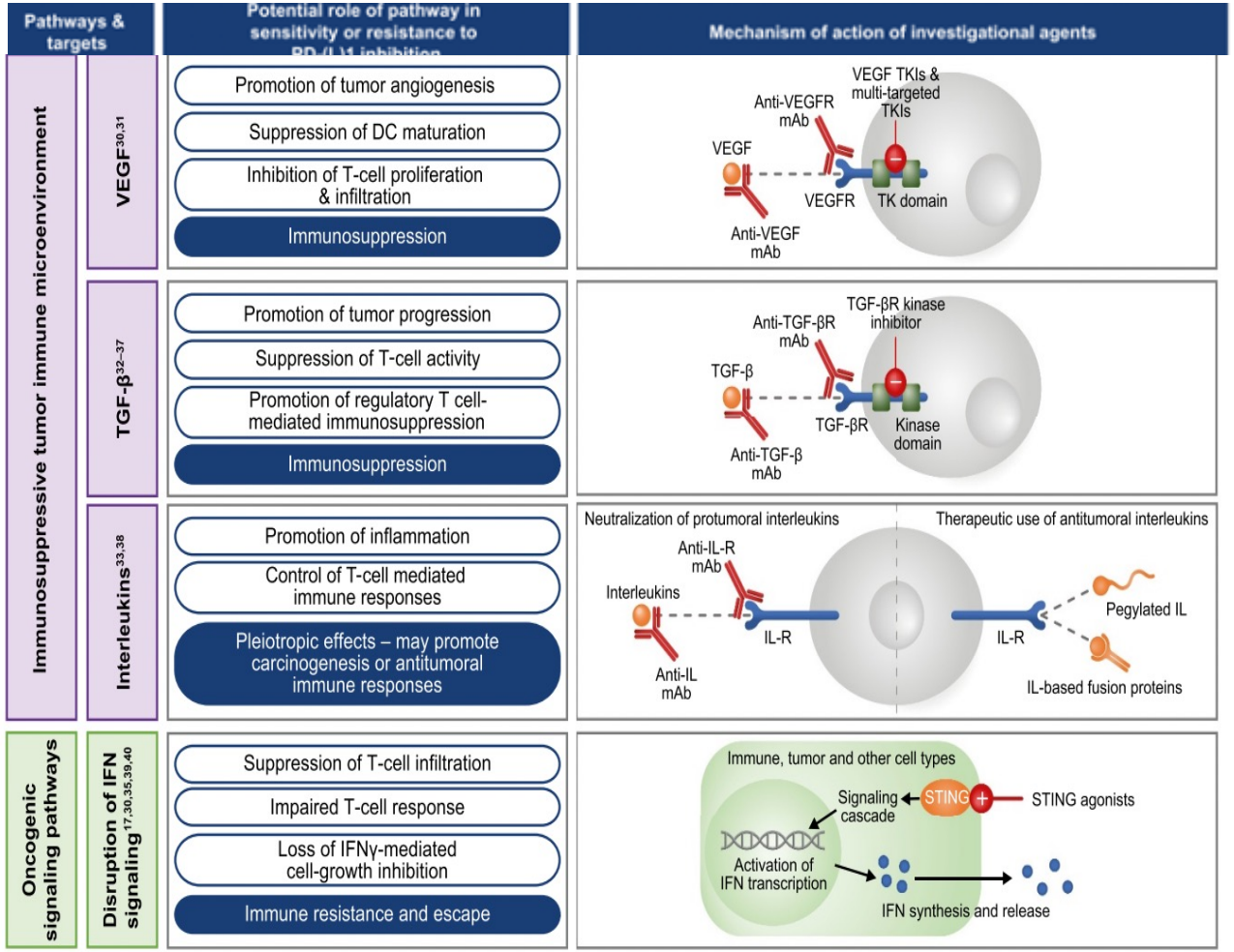
Post-PD OS



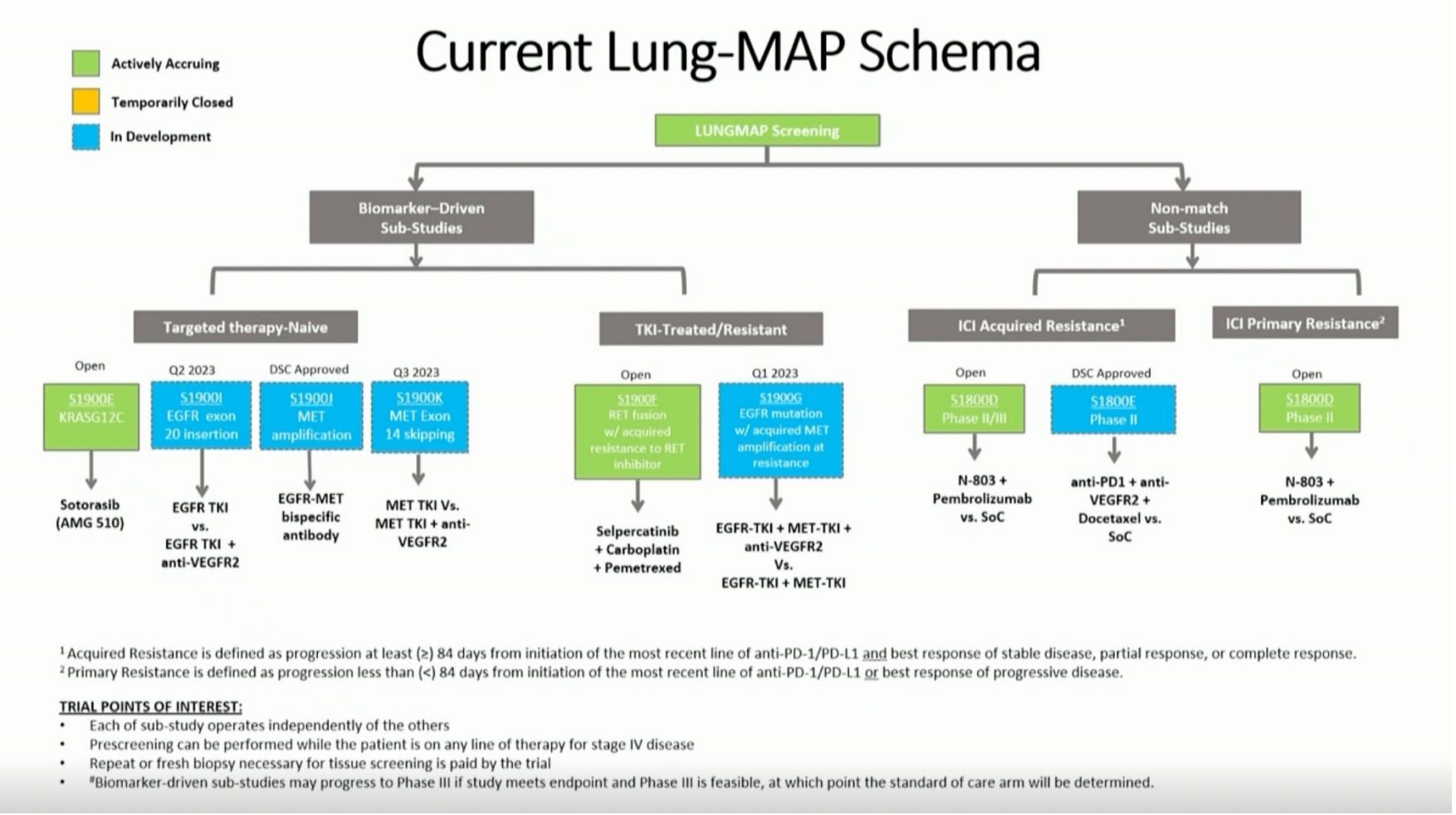
Necchi et al, 2017; George et al, 2016; Long et al, 2017; Gandara et al, 2018; Escudier et al, 2016.

Potential pathways contributing to sensitivity and resistance to PD-(L)1 inhibitors in NSCLC





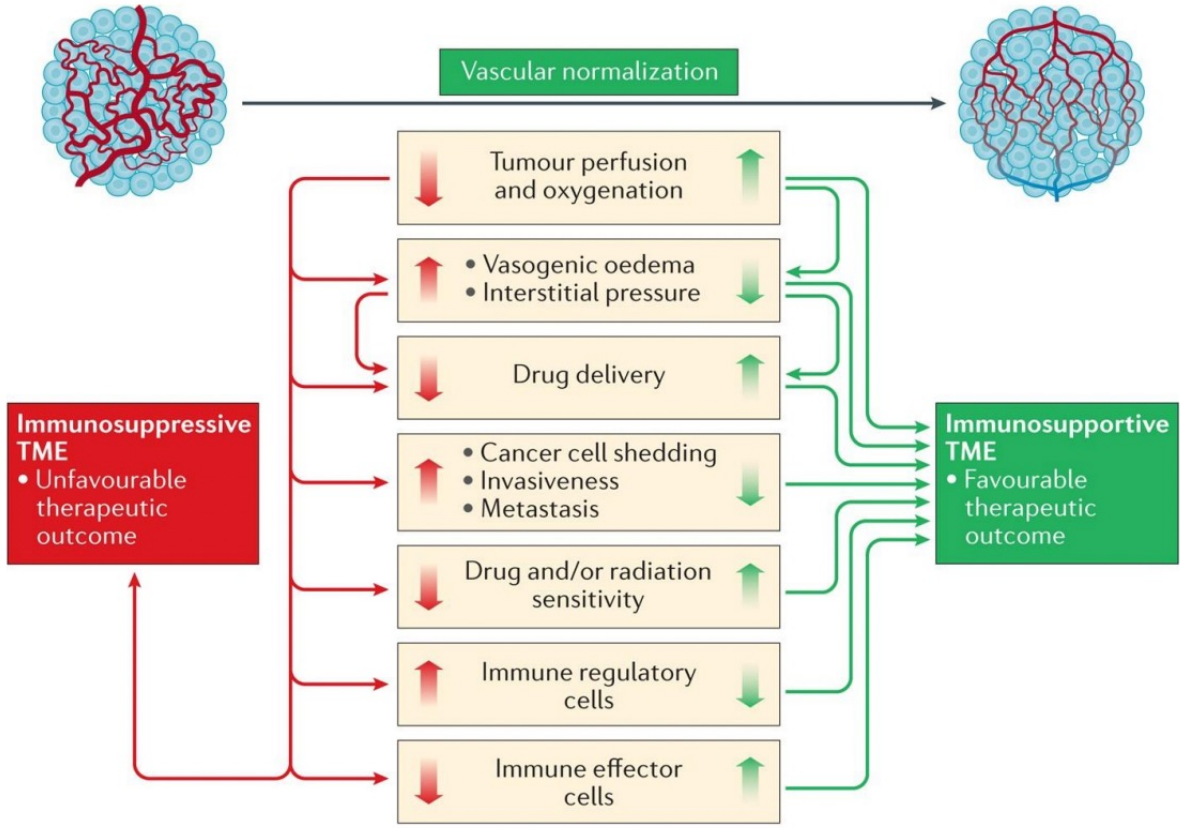
LUNG MAP

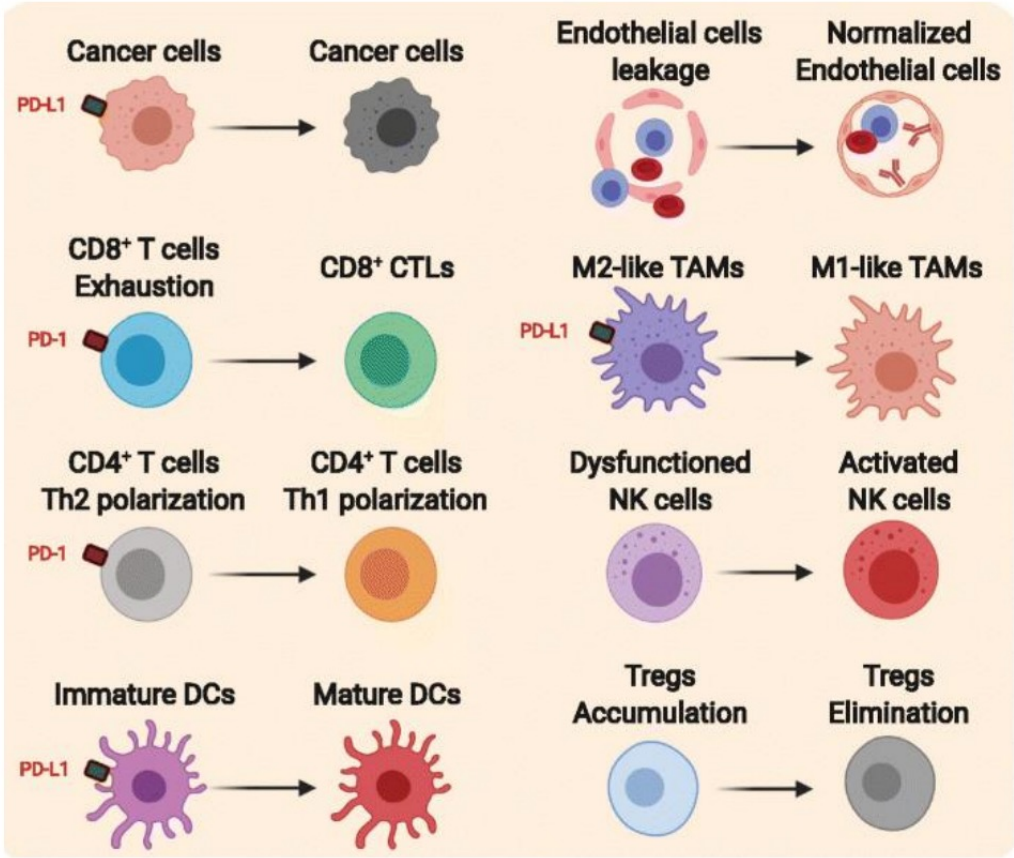


Herbst. TTCL 2023.

Herbst. TTCL 2023.

Targeting angiogenesis to overcome ICI resistance





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

S1800A: Pembrolizumab + Ramucirumab

- Advanced NSCLC
- Previously received PD-(L)1 inhibitor and platinum doublet chemotherapy
- PD after ≥ 84 days of ICI
- ECOG 0-1

R
1:1

Investigator's choice
SOC
Docetaxel/ram
Docetaxel
Gemcitabine
Pemetrexed (nonSq)

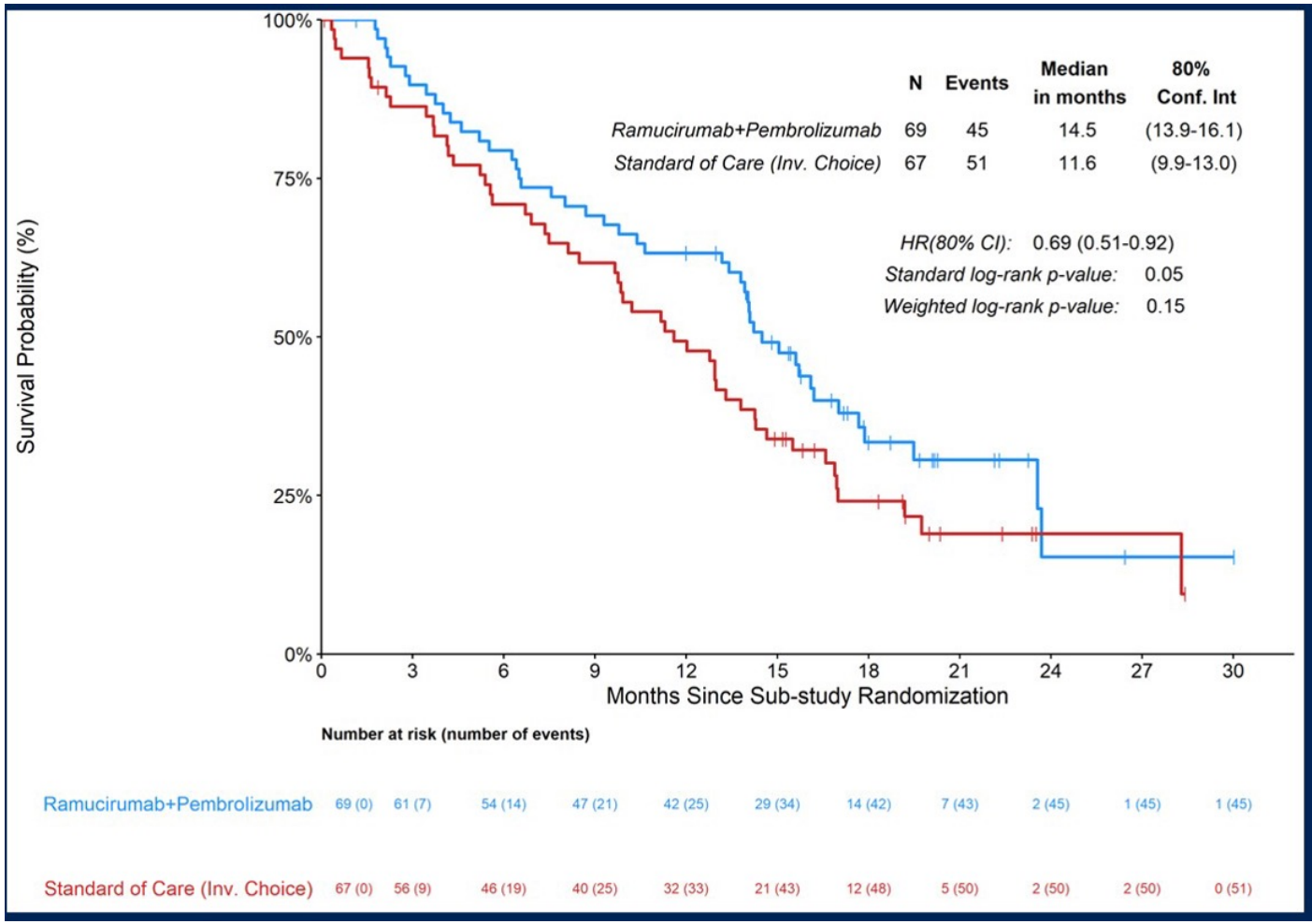
Pembrolizumab
+
Ramucirumab

Primary endpoint: OS
Secondary endpoints: RR, DCR, DoR, PFS, tox

Stratified by:
1) PD-L1 expression
2) Histology
3) Intent to give ram in SOC arm

Reckamp et al JCO 2022. Leal, Ramalingam et al. JCO 2022

S1800A: Pembrolizumab + Ramucirumab



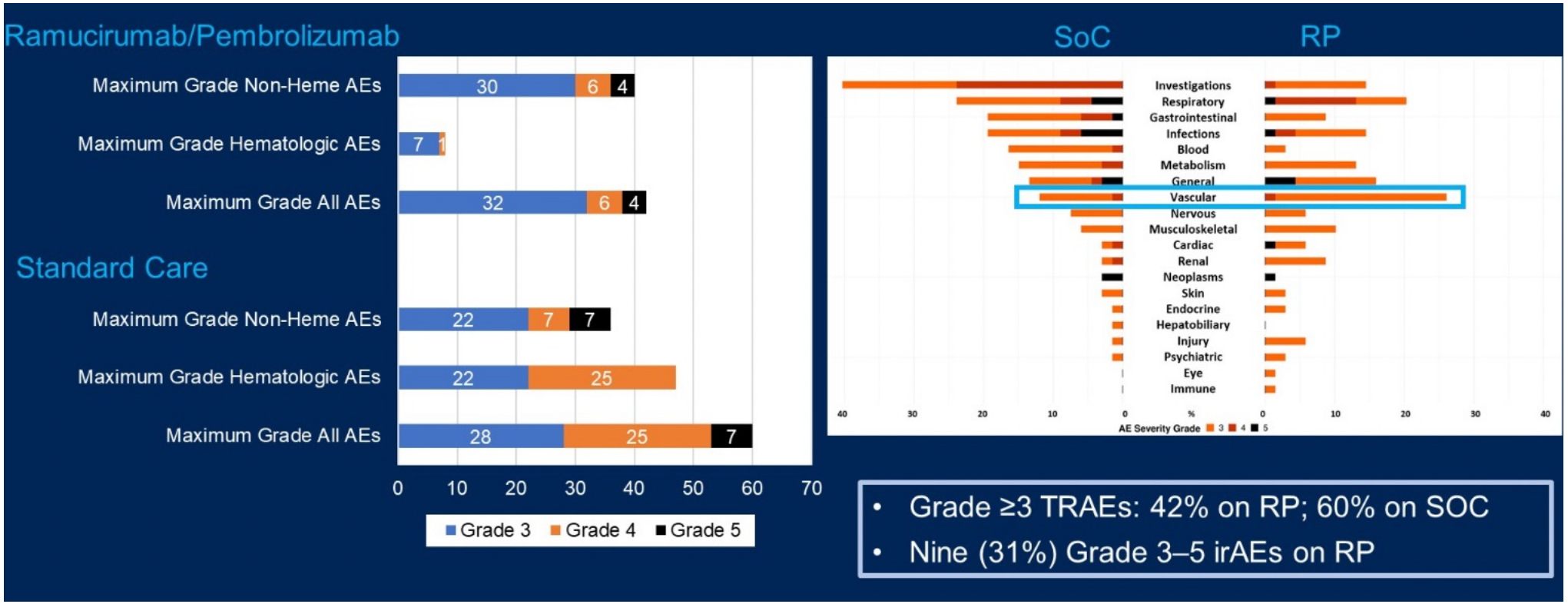
- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

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

Reckamp et al JCO 2022. Leal, Ramalingam et al. JCO 2022

S1800A: Safety Summary



Reckamp et al JCO 2022. Leal, Ramalingam et al. JCO 2022

Project Pragmatica-Lung

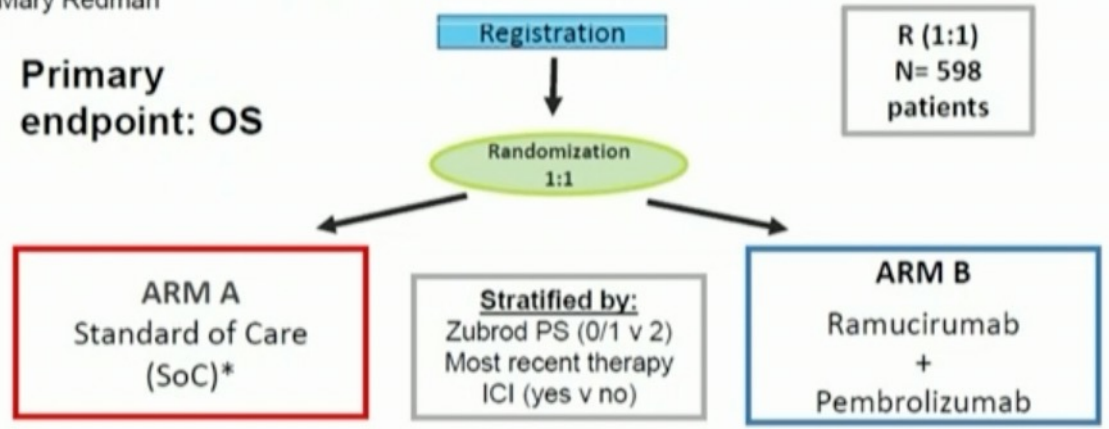
Phase III Rationale

- Effective therapy following frontline ICI for NSCLC is needed with limited FDA-approved options.
- We propose a pragmatic clinical trial design to promote diversity and inclusion in clinical trials.
- The aim of the trial is to validate the improvement in overall survival demonstrated in S1800A.
- The purpose is to empower investigators to treat patients as would be done in real world practice.
- The design is novel and potentially paradigm-changing to decrease barriers to enrollment and minimize the data collection burden.

S2302 Treatment/Schema

S2302, PROJECT PRAGMATICA: A PROSPECTIVE RANDOMIZED STUDY OF RAMUCIRUMAB (NSC 749128) PLUS PEMBROLIZUMAB (MK-3475; NSC 776864) VERSUS STANDARD OF CARE FOR PARTICIPANTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER

Chair: Karen Reckamp, MD; Co-chair: Konstantin Dragnev, MD; TBD
Statistician: Mary Redman

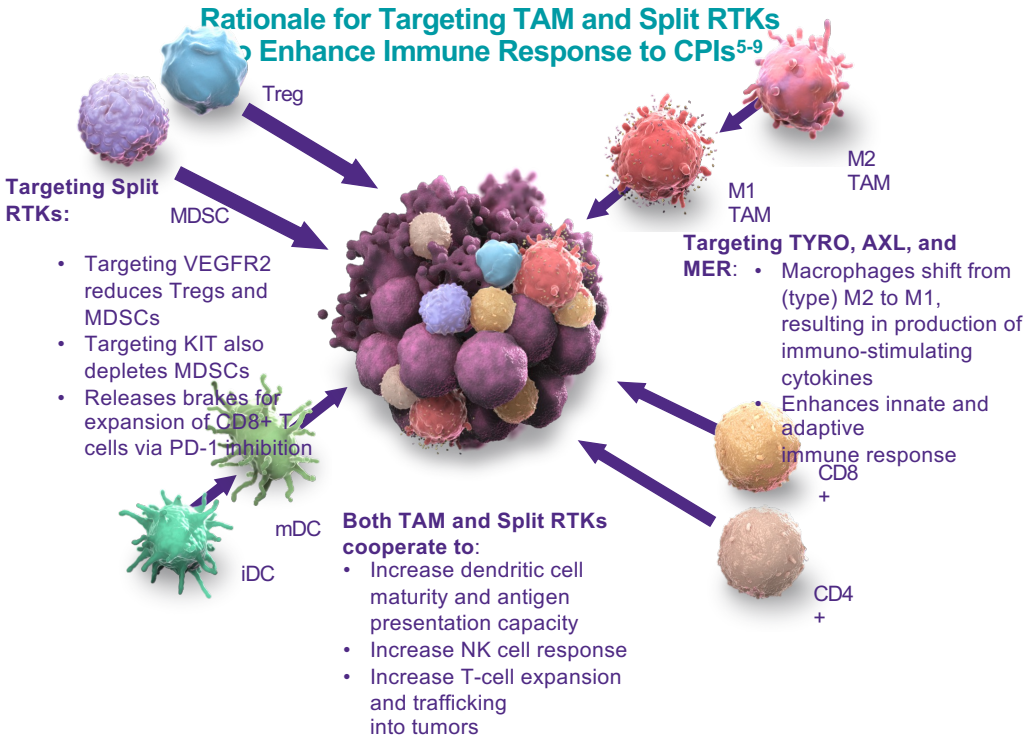


*SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

2021 ESMO congress

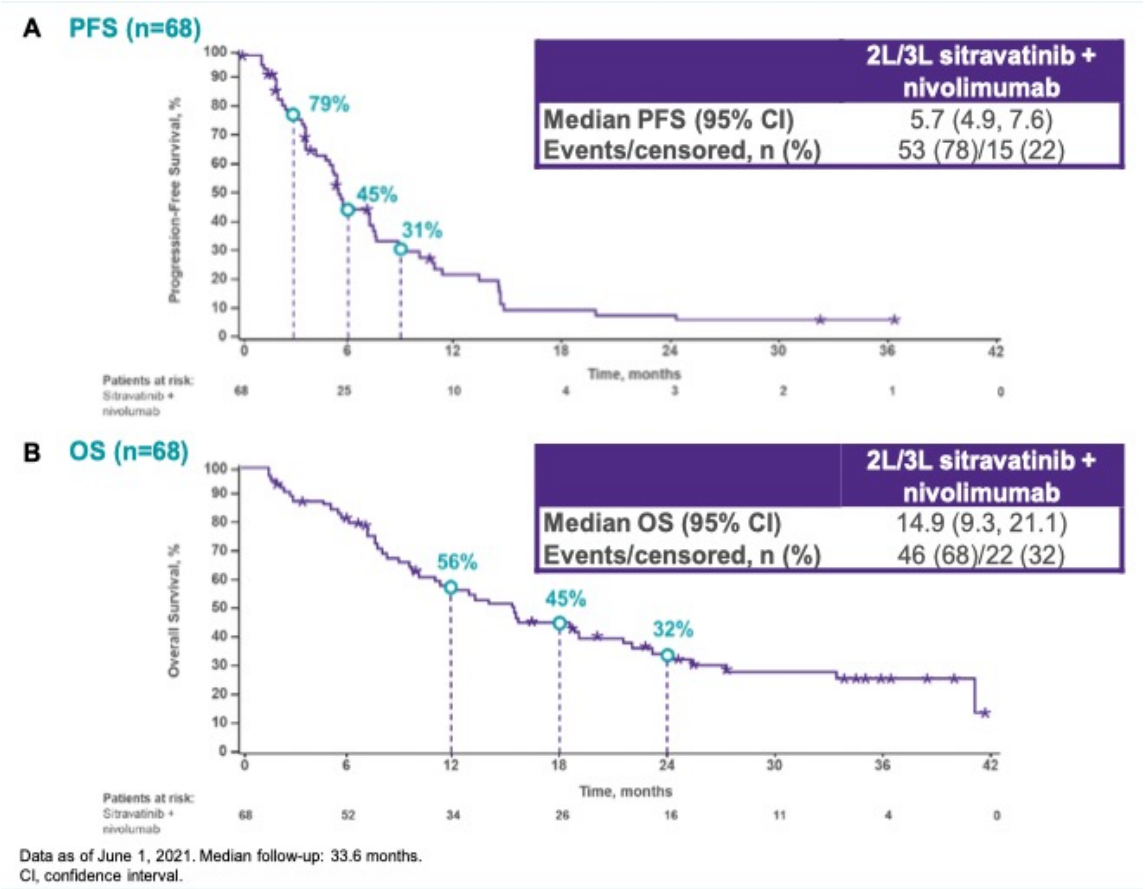
MRTX-500: Phase 2 Trial of Sitravatinib + Nivolumab in Patients With Nonsquamous Non–Small-Cell Lung Cancer Progressing on or After Prior Checkpoint Inhibitor Therapy

Ticiana A. Leal[1], David Berz[2], Igor I. Rybkin[3], Wade T. Iams[4], Debora S. Bruno[5], Collin M. Blakely[6], Alexander I. Spira[7], Manish R. Patel[8], David M. Waterhouse[9], Donald A. Richards[10], Anthony Pham[11], Robert Jotte[12], Edward B. Garon[13], David S. Hong[14], Ronald Shazer[15], Xiaohong Yan[15], Lisa Latven[15], Kai He[16]



Kai H, …, Leal T. JTO 2023.

MRTX-500: Study design



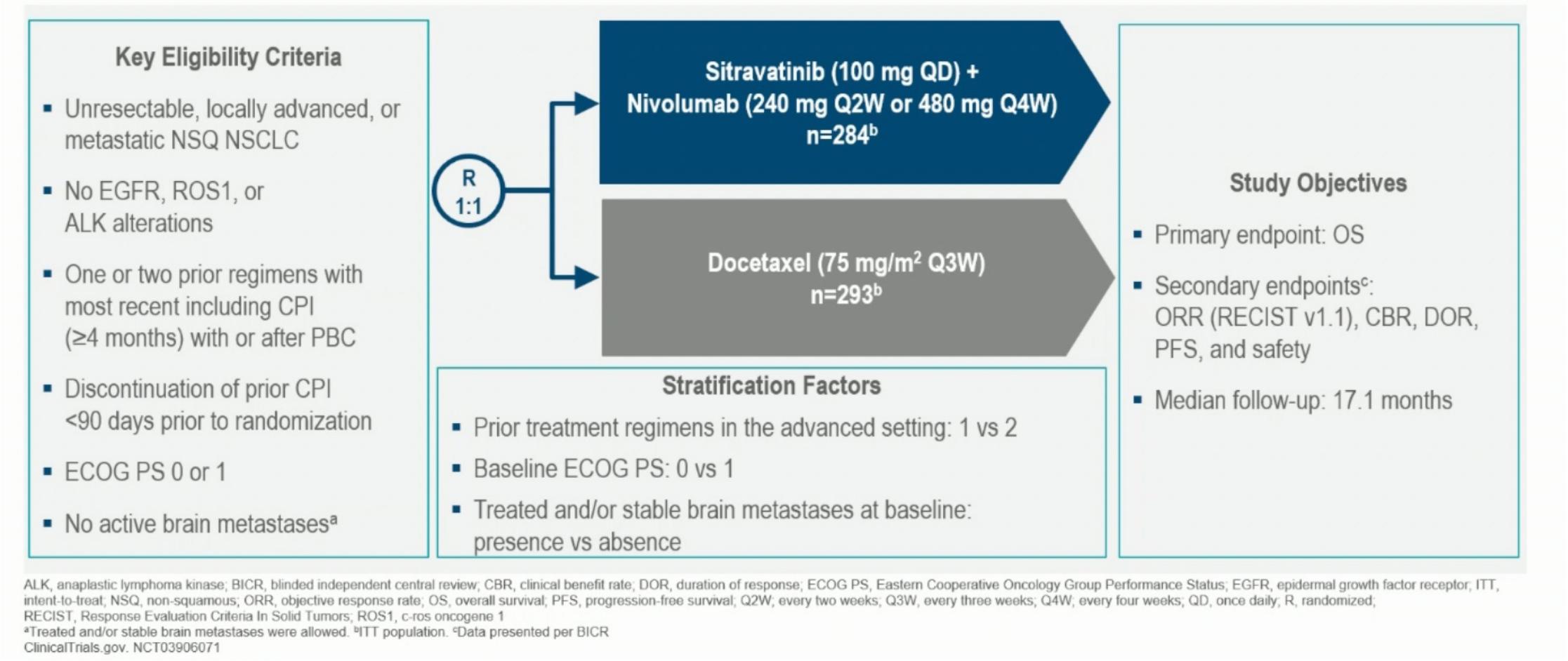
Data as of June 1, 2021. Median follow-up: 33.6 months.
CI, confidence interval.

Most frequent (≥15%) TRAEs (n=68)	2L/3L sitravatinib + nivolumab	
TRAEs, %	**Any Grade**	**Grade 3–4**
Any TRAEs	93	66
Most frequent TRAEs, %		
Diarrhea	62	16
Fatigue	52	4
Nausea	44	2
Hypertension	40	22
Decreased appetite	35	0
Weight decreased	31	9
Vomiting	31	0
Hypothyroidism	22	0
Dysphonia	19	0
ALT increase	18	2
AST increase	16	0
Stomatitis	15	2
PPE syndrome	15	3
Dehydration	15	3

One grade 5 TRAE (cardiac arrest) occurred in the CPI-naive cohort.

Kai H, …, Leal T. JTO 2023.

SAPPHIRE: Phase 3, Randomized, Open-Label Trial of 2L/3L Sitravatinib + Nivolumab vs Docetaxel After Progression on or Following CPI in Advanced NSCLC



ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; ITT, intent-to-treat; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every two weeks; Q3W, every three weeks; Q4W, every four weeks; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors; ROS1, c-ros oncogene 1

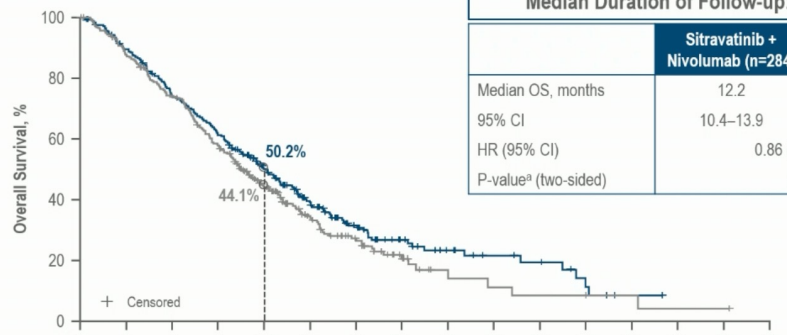
[a]Treated and/or stable brain metastases were allowed. [b]ITT population. [c]Data presented per BICR

ClinicalTrials.gov. NCT03906071

Borgahei et al. ESMO 2023.

SAPPHIRE: Efficacy Endpoints

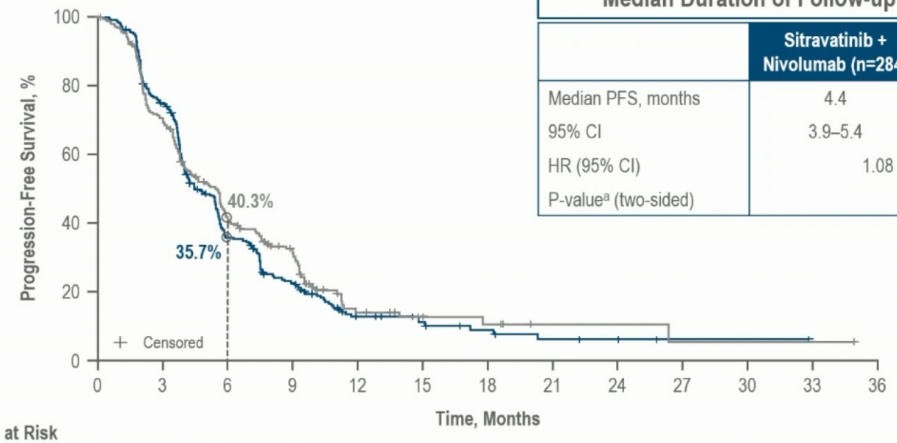
Overall Survival



Median Duration of Follow-up: 17.1 Months		
	Sitravatinib + Nivolumab (n=284)	Docetaxel (n=293)
Median OS, months	12.2	10.6
95% CI	10.4–13.9	9.4–12.3
HR (95% CI)	0.86 (0.70–1.05)	
P-value[a] (two-sided)	0.144	

CI, confidence interval; HR, hazard ratio
[a]P-value is based on the log-rank test
Censoring rate, n (%): sitravatinib plus nivolumab, 98 (35%); docetaxel, 102 (35%)
Data as of March 20, 2023

Progression-Free Survival



Median Duration of Follow-up: 17.1 Months		
	Sitravatinib + Nivolumab (n=284)	Docetaxel (n=293)
Median PFS, months	4.4	5.4
95% CI	3.9–5.4	3.9–5.8
HR (95% CI)	1.08 (0.89–1.32)	
P-value[a] (two-sided)	0.452	

Borgahei et al. ESMO 2023.

SAPPHIRE: Safety

	Sitravatinib + Nivolumab (n=281)	Docetaxel (n=273)
Any TRAEs, n (%)[a]	268 (95)	259 (95)
Grade 3–4, n (%)	148 (53)	179 (66)
Grade 5, n (%)[b]	1 (<1)	3 (1)
Most common TRAEs, all grades, n (%)[c]		
Diarrhea	158 (56)	97 (36)
Nausea	88 (31)	88 (32)
Decreased appetite	80 (29)	68 (25)
Hypothyroidism	79 (28)	0 (0)
Fatigue	74 (26)	97 (36)
Hypertension	70 (25)	1 (<1)
Vomiting	57 (20)	44 (16)
Asthenia	40 (14)	65 (24)
Anemia	9 (3)	57 (21)
Alopecia	4 (1)	84 (31)
Neutrophil count decreased	2 (<1)	87 (32)
Neutropenia	0 (0)	71 (26)
Leading to discontinuation, n (%)	44 (16)[d] / 18 (6)[e]	32 (12)
Leading to dose reduction, n (%)	137 (49)[d] / 0 (0)[e]	85 (31)
Leading to dose interruption, n (%)	152 (54)[d] / 55 (20)[e]	45 (17)

- Immune-related AEs of any grade occurred in 46% of patients treated with sitravatinib + nivolumab; the most frequent were hypothyroidism (14%) and diarrhea (12%)

Borgahei et al. ESMO 2023.

CONTACT-01: Phase III study of atezolizumab + cabozantinib vs docetaxel in pts with mNSCLC previously treated with checkpoint inhibitors and chemotherapy

- Histologically or cytologically confirmed NSCLC (nonsquamous and squamous)
- ECOG PS 0-1
- Progression on or after immune checkpoint inhibitor and platinum-based chemotherapy
- Any PD-L1 status[a]
- Absence of sensitizing *EGFR* mutation or *ALK* fusion oncogene

N=366

R 1:1

Atezolizumab 1200 mg Q3W + **Cabozantinib** 40 mg QD → PD or loss of clinical benefit

No crossover allowed

Docetaxel (75 mg/m² Q3W) → PD

Stratification factors

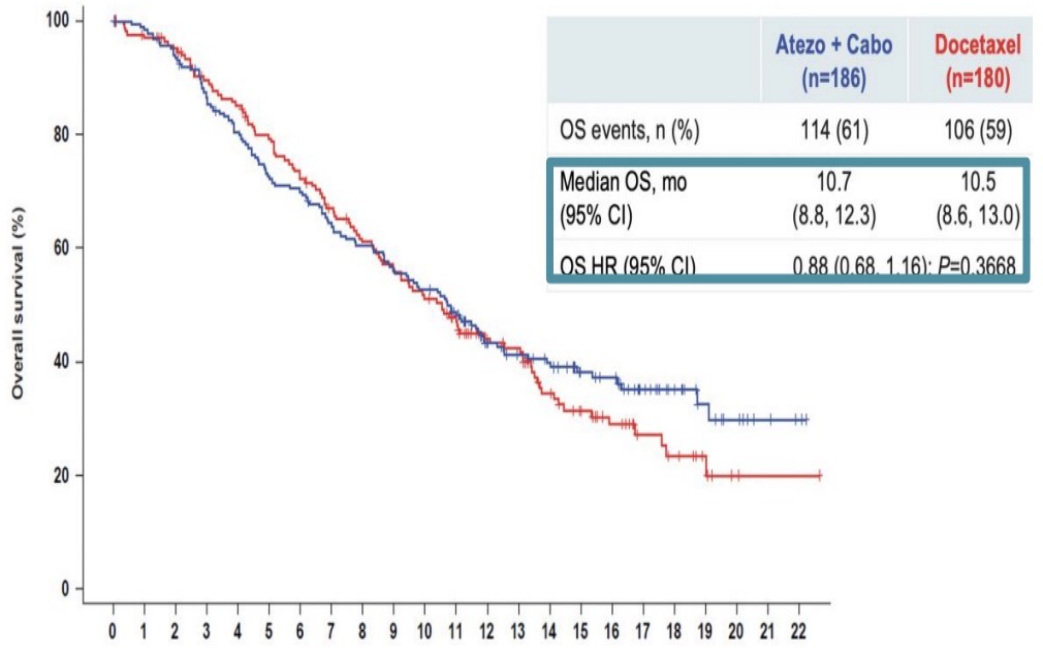
- Histology (nonsquamous vs squamous)
- Prior NSCLC treatment regimen(s):
  - Concurrent platinum-based chemotherapy + anti-PD(L)1
  - Platinum-based chemotherapy, then anti-PD(L)1 monotherapy
  - Anti-PD(L)1 monotherapy, then platinum-based chemotherapy
  - Anti-PD(L)1 monotherapy, then platinum-based chemotherapy added at progression

Primary endpoint

- Overall survival (OS)

Key secondary endpoints[b]

- Investigator-assessed PFS per RECIST 1.1
- Confirmed ORR per RECIST 1.1
- DOR
- Safety



	Atezo + Cabo (n=186)	Docetaxel (n=180)
OS events, n (%)	114 (61)	106 (59)
Median OS, mo (95% CI)	10.7 (8.8, 12.3)	10.5 (8.6, 13.0)
OS HR (95% CI)	0.88 (0.68, 1.16); *P*=0.3668	

Neal et al. ELCC 2023.

Randomized clinical trials in 2L

	Doc *vs*	doc+nintedanib[1]	Doc *vs*	doc+ramu[2]	SoC *vs*	pembro+ramu[*3]	Doc *vs*	atezo+cabo[4]
N	**659**	**655**	**625**	**628**	**67**	**69**	**180**	**186**
Treatment line	2L		2L		2-3L 19% ≥ 3L	2-3L 16% ≥ 3L	2-3L	
Prior ICI	0	0	0	0	100%	100%	100%	100%
Duration of prior ICI treatment	NA	NA	NA	NA	100% ≥ 84 days ≥ 6 mo 69% (26% ≥12 mo)	100% ≥ 84 days ≥ 6 mo 69% (26% ≥12 mo)	≥ 6 mo 62%	≥ 6 mo 59%
ORR	3.3%	4.4%	14%	23%	28%	22%	13.3%	11.8%
mDoR	NA	NA	NA	NA	5.6 mo	12.9 mo	4.3 mo	5.6 mo
mPFS	2.7 mo	3.4 mo	3.0 mo	4.5 mo	5.2 mo	4.5 mo	4.0 mo	4.6 mo
mOS	**9.1 mo**	**10.1 mo**	**9.1 mo**	**10.5 mo**	**11.6 mo**	**14.5 mo**	**10.5 mo**	**10.7 mo**

Felipe ELLC 2023; 1. Reck Lancet Oncol 14, 2. Garon Lancet 14, 3. Reckamp JCO 22, 4. Neal ELCC 23

TIGIT

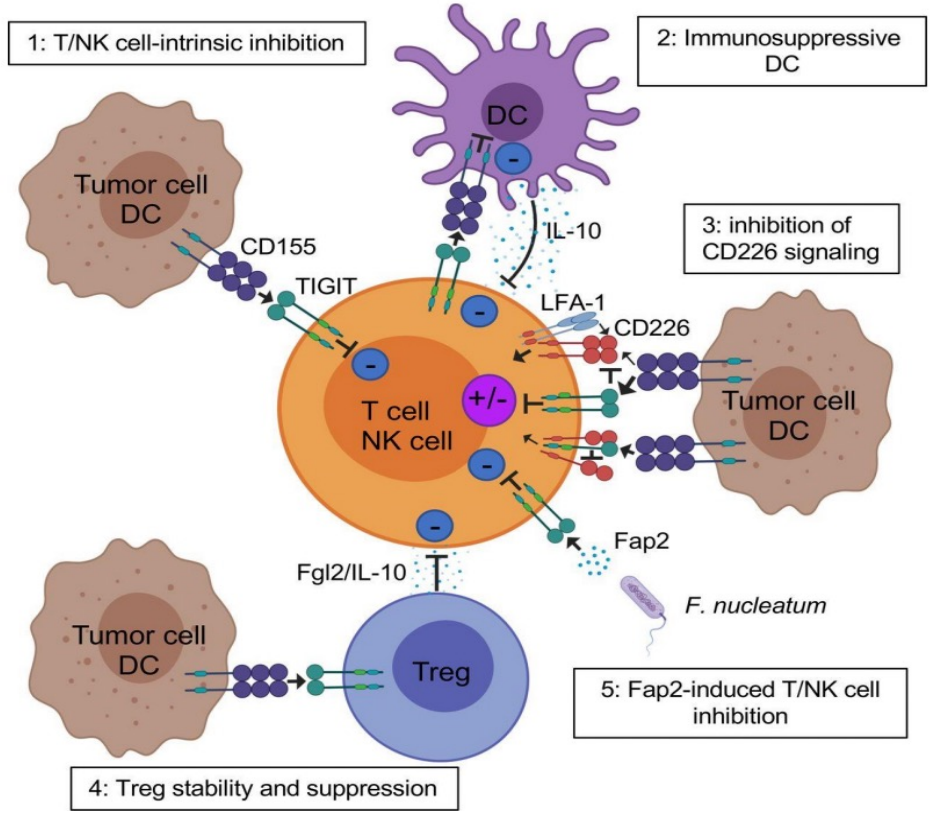
- **TIGIT/CD155**:
- Directly inhibits T cells

- 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

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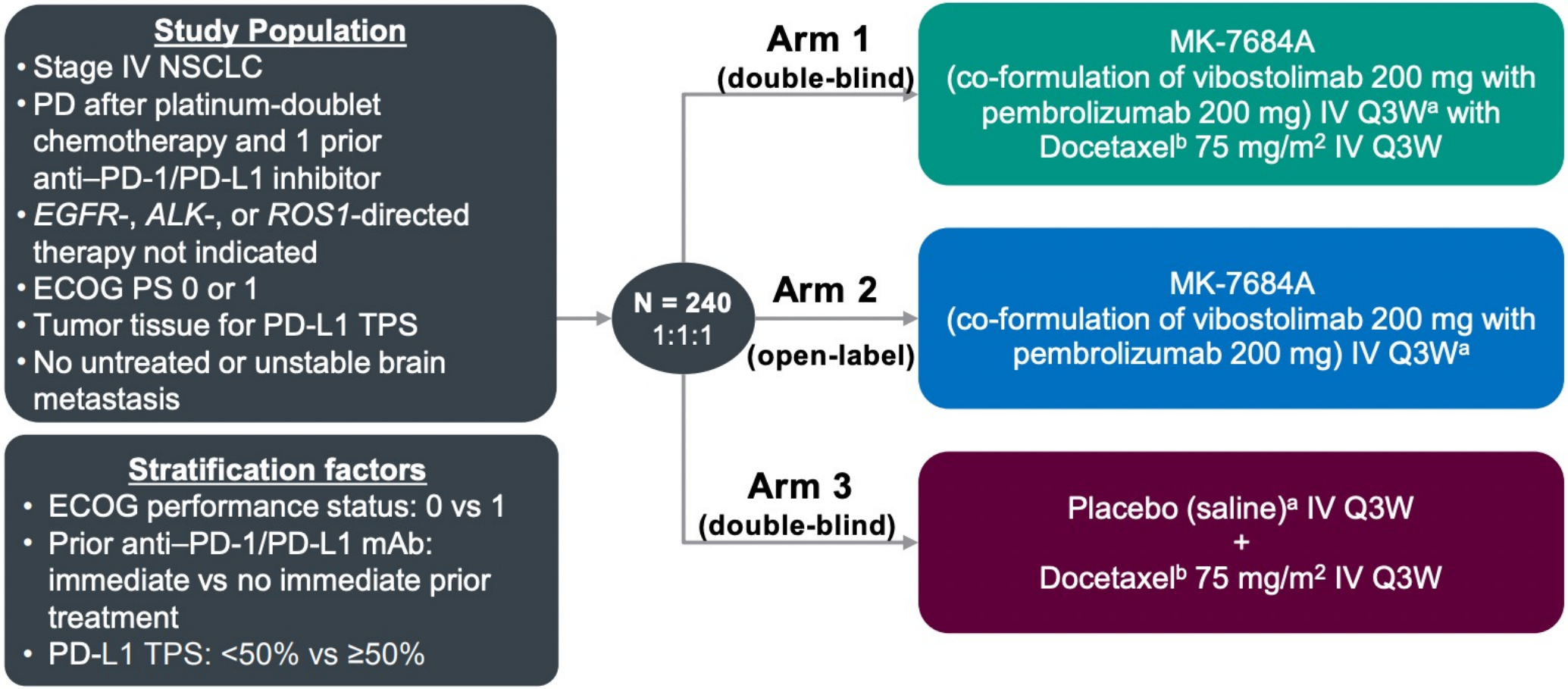
Journal for ImmunoTherapy of Cancer

KEYVIBE-002



NCT04725188

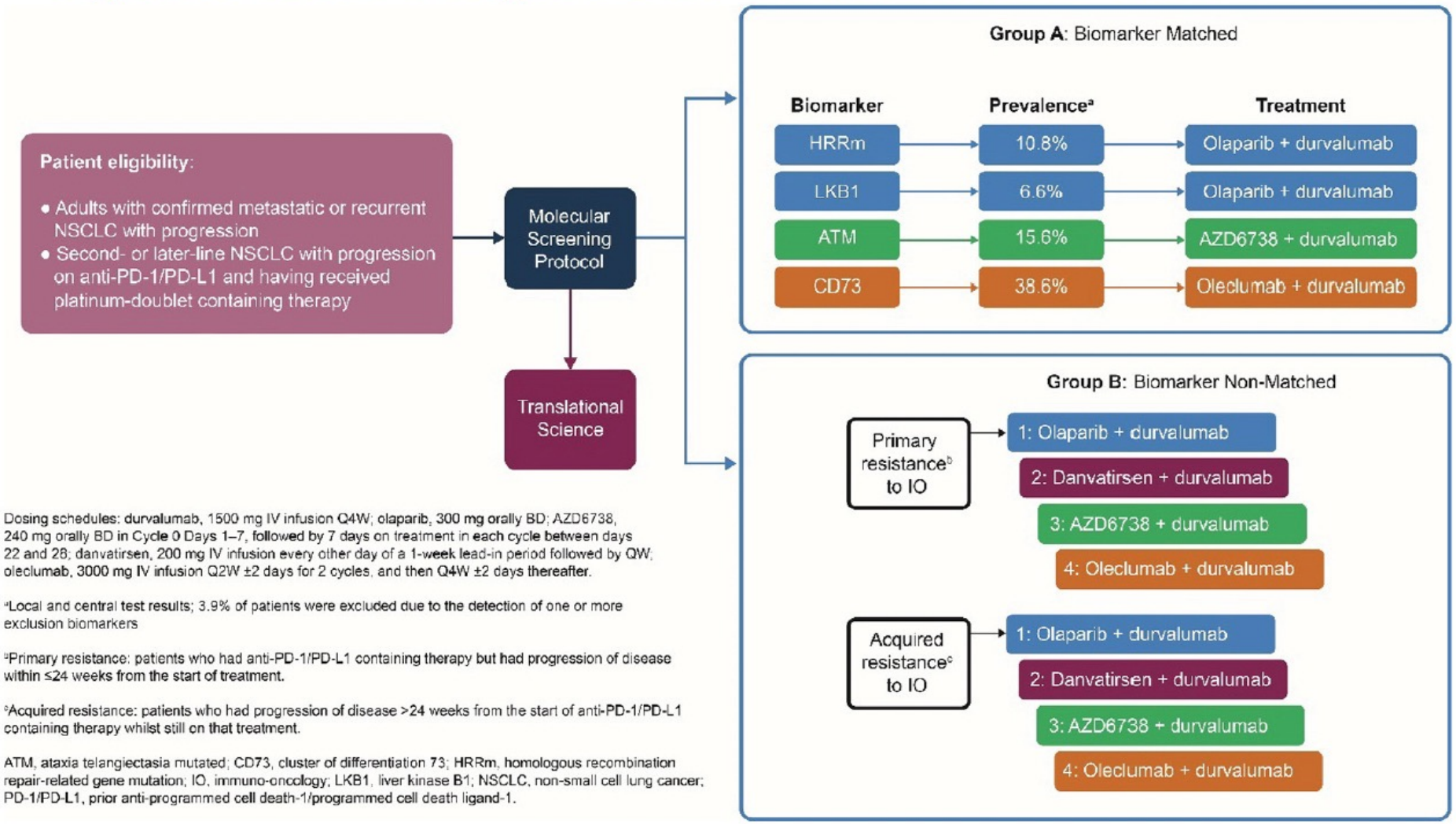
KEYVIBE-002: Press Release March 16, 2023

- A coformulation of pembrolizumab and vibostolimab (MK-7684A) did not elicit a statistically significant improvement in progression-free survival (PFS) vs docetaxel in pretreated patients with metastatic non–small cell lung cancer (NSCLC), according to results from the open-label portion of the phase 2 KeyVibe-002 trial.

- The blinded arms of the study will continue to further evaluate MK-7684A with docetaxel versus docetaxel alone. The safety profile of MK-7684A was consistent with that observed for vibostolimab and pembrolizumab in previously reported studies, with no new safety signals observed. Results will be presented at an upcoming medical meeting once further data from the blinded study arms are available.

NCT04725188

HUDSON Umbrella Study of Durvalumab with Novel Anticancer Agents After Progression on an Anti-PD-1/PD-L1-Containing Therapy



Dosing schedules: durvalumab, 1500 mg IV infusion Q4W; olaparib, 300 mg orally BD; AZD6738, 240 mg orally BD in Cycle 0 Days 1–7, followed by 7 days on treatment in each cycle between days 22 and 28; danvatirsen, 200 mg IV infusion every other day of a 1-week lead-in period followed by QW; oleclumab, 3000 mg IV infusion Q2W ±2 days for 2 cycles, and then Q4W ±2 days thereafter.

[a]Local and central test results; 3.9% of patients were excluded due to the detection of one or more exclusion biomarkers

[b]Primary resistance: patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease within ≤24 weeks from the start of treatment.

[c]Acquired resistance: patients who had progression of disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

ATM, ataxia telangiectasia mutated; CD73, cluster of differentiation 73; HRRm, homologous recombination repair-related gene mutation; IO, immuno-oncology; LKB1, liver kinase B1; NSCLC, non-small cell lung cancer; PD-1/PD-L1, prior anti-programmed cell death-1/programmed cell death ligand-1.

ORR

Olaparib HRRm 9.5%

Ceralasertib (AZD6738) 11.1%

Oleclumab 0

Ceralasertib (AZD6738) 10.5%

no other responses with other agents

Olaparib 4.3%

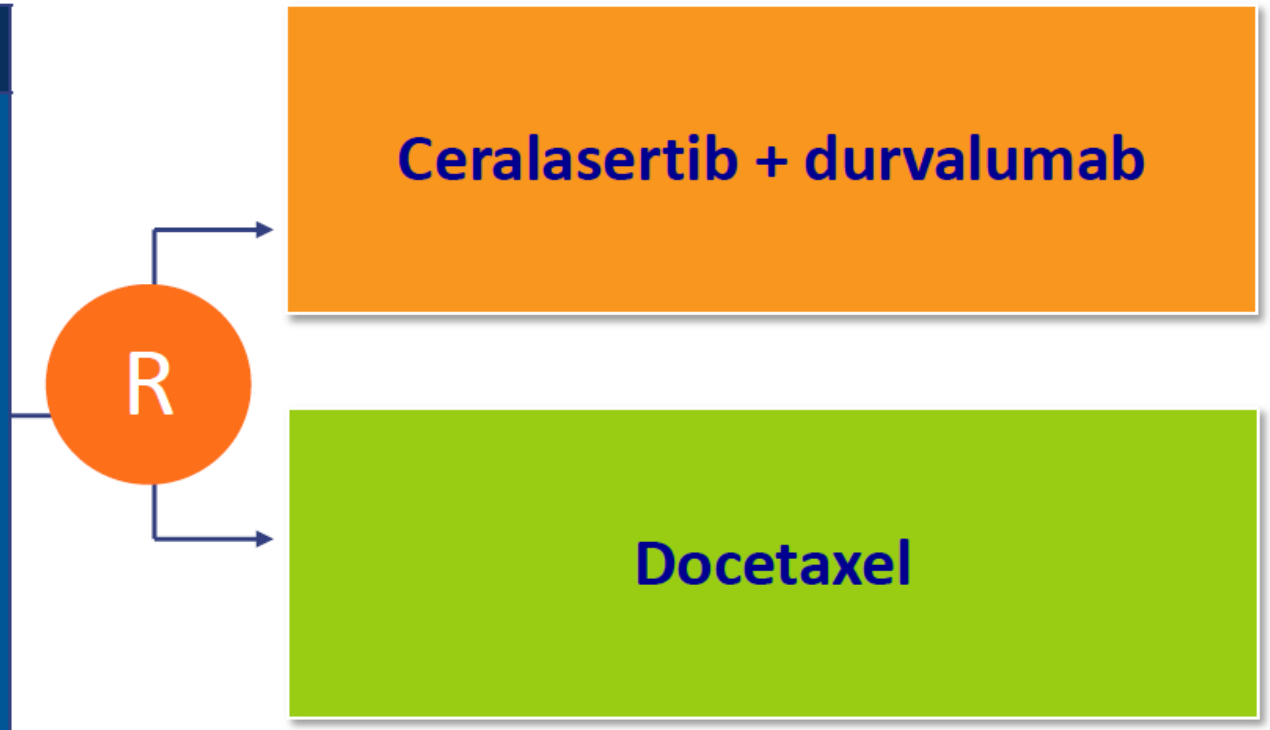
Ceralasertib (AZD6738) 8.3%

Oleclumab 4.2%

LATIFY Phase III Trial Schema

Estimated enrollment: N = 580

- Locally advanced or metastatic NSCLC with documented radiological progression on most recent treatment regimen
- EGFR and ALK wild type gene status
- Eligible for second-line or third-line therapy
- Prior treatment with an anti-PD-(L)1 therapy and a platinum doublet-containing therapy either separately or in combination



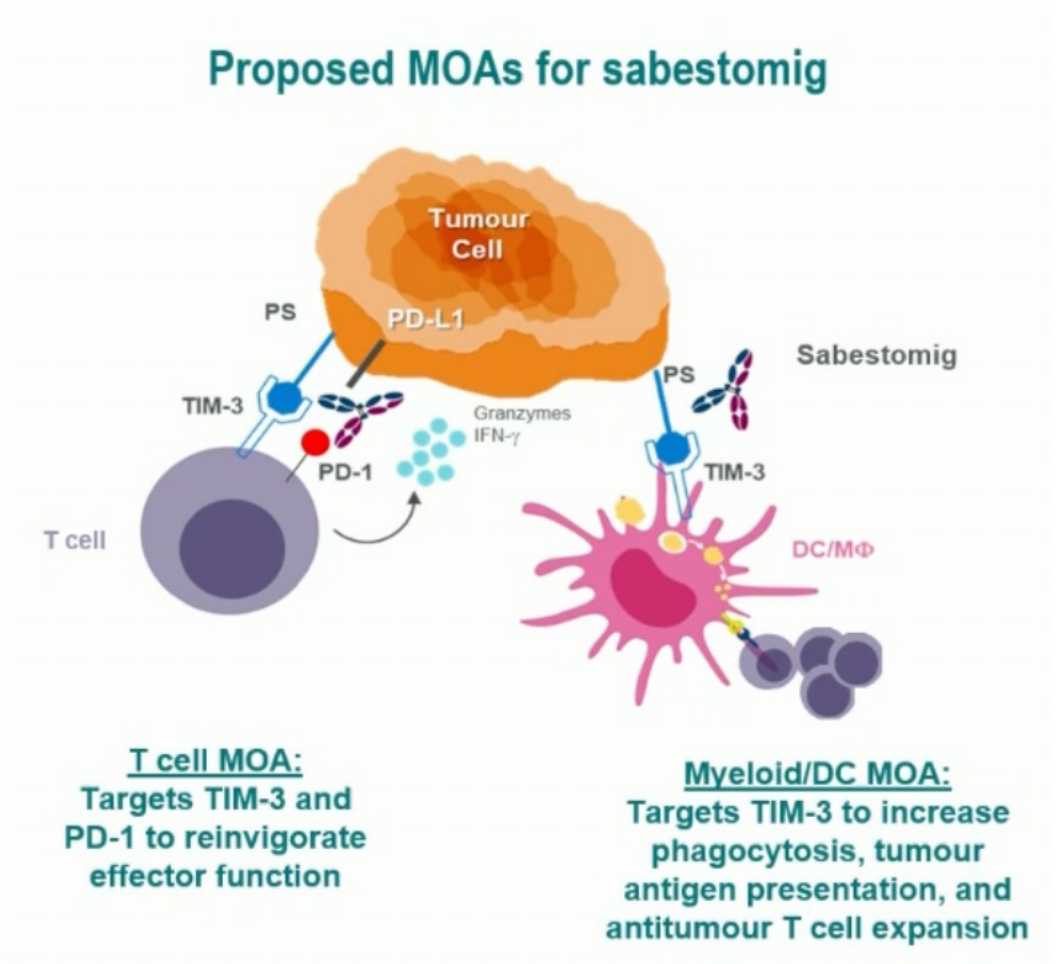
Primary endpoint: Overall survival

Secondary endpoints include PFS, objective response rate, duration of response time and adverse events

www.clinicaltrials.gov. NCT05450692. Accessed June 2023.

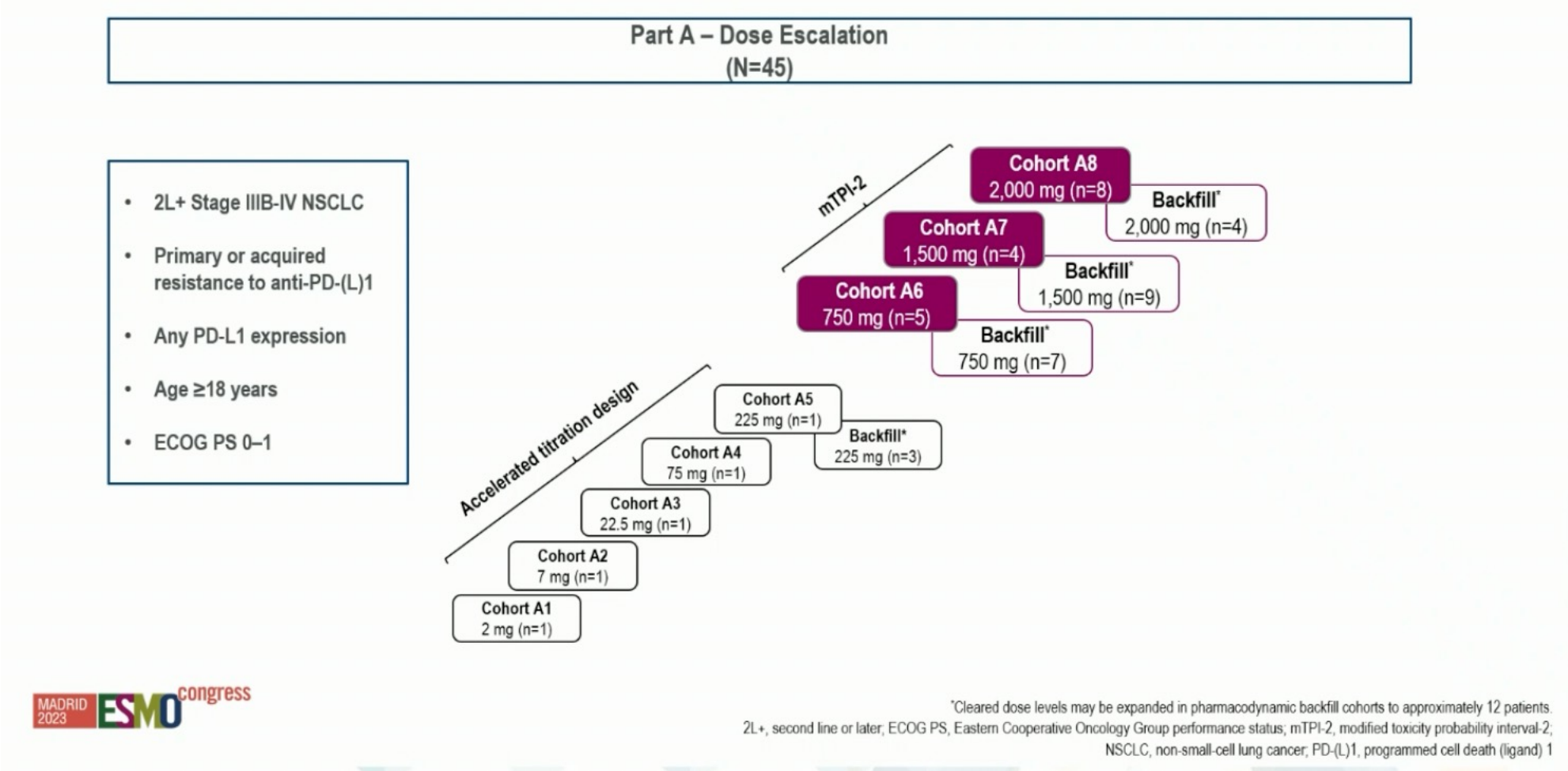
Safety and prelim efficacy of sabestomig in IO previously treated NSCLC

- Mechanism of action: PD-1/TIM-3 bispecific antibody
- TIM-3 is highly expressed in NSCLC and may eb a resistance mechanism to PD-1 blockade.



Besse et al. ESMO 2023.

Phase I /IIa FIH study of sabestomig (NCT0431654)



Besse et al. ESMO 2023.

Phase I /IIa FIH study of sabestomig: Safety

n (%)	Cohort A1 2 mg (n=1)	Cohort A2 7 mg (n=1)	Cohort A3 22.5 mg (n=1)	Cohort A4 75 mg (n=1)	Cohort A5 225 mg (n=4)	Cohort A6 750 mg (n=12)	Cohort A7 1,500 mg (n=13)	Cohort A8 2,000 mg (n=12)	Total 2–2,000 mg (N=45)
Any Grade AE	0	1 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)	12 (100.0)	12 (92.3)	12 (100.0)	43 (95.6)
Grade ≥3 AE	0	1 (100.0)	0	0	1 (25.0)	5 (41.7)	5 (38.5)	6 (50.0)	18 (40.0)
Treatment-emergent SAE	0	1 (100.0)	0	0	1 (25.0)	5 (41.7)	5 (38.5)	3 (25.0)	15 (33.3)
Immune-mediated AE	0	1 (100.0)	0	0	2 (50.0)	2 (16.7)	5 (38.5)	6 (50.0)	16 (35.6)
Related any Grade AE	0	1 (100.0)	1 (100.0)	0	2 (50.0)	6 (50.0)	9 (69.2)	8 (66.7)	27 (60.0)
Related Grade ≥3 AE	0	0	0	0	0	0	1 (7.7)	0	1 (2.2)
Related treatment-emergent SAE	0	0	0	0	0	0	1 (7.7)	0	1 (2.2)

- No dose-limiting toxicities or deaths
- No Grade 4 or 5 treatment-related AEs.
- No discontinuation of sabestomig due to AEs.

MADRID 2023 ESMO congress

AE, adverse event; NSCLC, non-small-cell lung cancer; PD-(L)1-resistant, resistant to prior anti-programmed cell death (ligand)-1 therapy; SAE, serious AE

Besse et al. ESMO 2023.

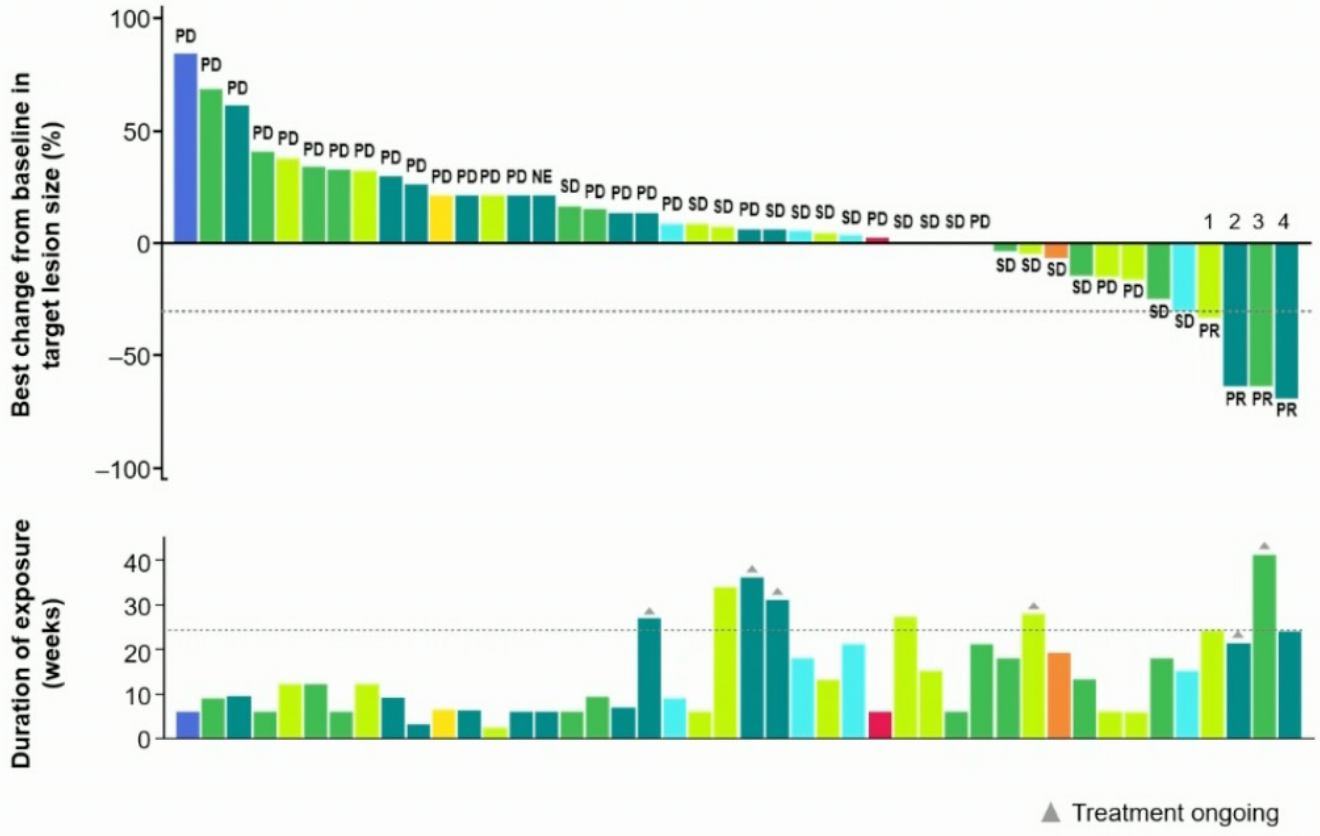
Phase I /IIa FIH study of sabestomig: Treatment emergent AEs and IRAEs

TEAEs ≥15% any grade or ≥4% Grade 3	Any Grade n (%)	Grade ≥3 n (%)
Decreased appetite	11 (24.4)	1 (2.2)
Nausea	11 (24.4)	0
Blood creatinine increased	11 (24.4)	0
Fatigue	10 (22.2)	1 (2.2)
Cough	8 (17.8)	0
Anaemia	7 (15.6)	2 (4.4)
Dyspnoea	6 (13.3)	2 (4.4)
Asthenia	6 (13.3)	2 (4.4)
Haemoglobin decreased	4 (8.9)	3 (6.7)

- Investigator-assessed immune-mediated AEs were observed and were mostly low grade, including:
  - Rash (n=4), increased creatinine (n=3), diarrhoea (n=2), increased lipase (n=2), nausea (n=2)
  - 3 patients required steroids

Besse et al. ESMO 2023.

Prelim efficacy



- Responses seen at biologically active doses (≥750 mg, n=36)
- 4 pts had a confirmed PR, including heavily pretreated pts, IO nonresponders, and those with PD-L1 <1%

1 6 prior lines SD to prior IO PD-L1 ≥1%	2 3 prior lines Unk to prior IO PD-L1 <1%
3 4 prior lines SD to prior IO PD-L1 <1%	4 2 prior lines PR to prior IO PD-L1 ≥50%

- 8 pts had duration of exposure ≥24 weeks, and several are ongoing

Cohort

- A1 (2 mg) (n=1)
- A2 (7 mg) (n=1)
- A3 (22.5 mg) (n=1)
- A4 (75 mg) (n=1)
- A5 (225 mg) (n=4)
- A6 (750 mg) (n=12)
- A7 (1,500 mg) (n=12*)
- A8 (2,000 mg) (n=12)

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*One patient in cohort A7 (n=13) did not have an on-treatment scan as of the data cutoff

IO, immunotherapy; NE, not evaluable; NSCLC, non-small-cell lung cancer; PD, progressive disease; PD-L1, programmed cell death ligand-1; PD-(L)1-resistant, resistant to prior anti-PD-(L)1 therapy; PR, partial response; pts, patients; SD, stable disease; Unk, unknown

Besse et al. ESMO 2023.

Take Home Messages

- Immunotherapy resistance in the setting of recurrent or metastatic NSCLC is heterogeneous and better therapies are needed.
- Definition immunotherapy resistance is evolving and studies are needed to better define mechanisms of resistance which could impact salvage therapies.
- Pembrolizumab + ramucirumab in patients with immunotherapy-resistant advanced NSCLC improved OS compared to SOC.