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Salvage Therapy for Advanced NSCLC: Reasons for Hope?

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Disclosures

Consultant with honoraria to self: Amgen, AstraZeneca, Blueprint, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Lilly, Novocure, Novartis, Mirati.

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Background

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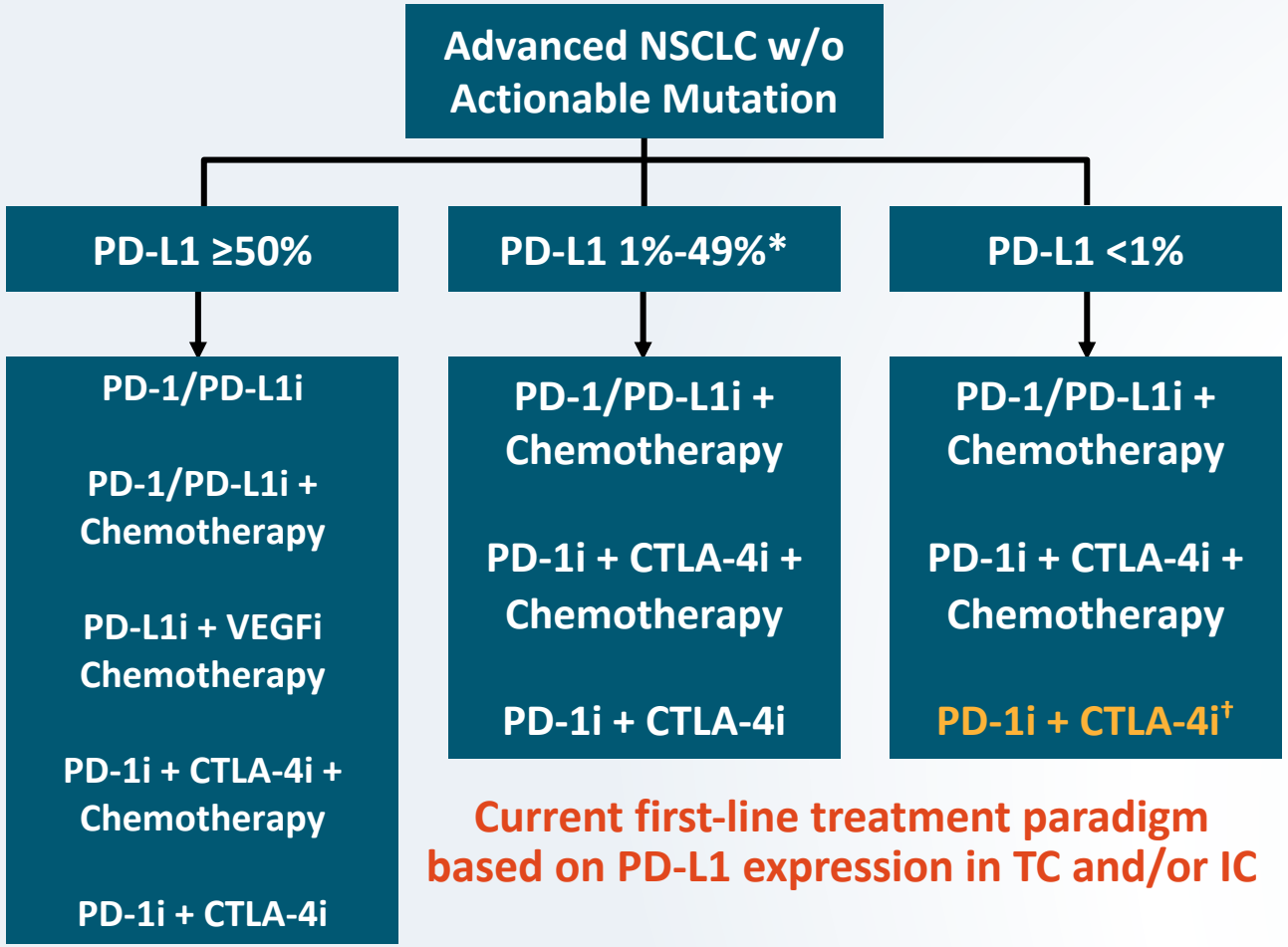
2024 Paradigm for Immunotherapy in Advanced NSCLC Without an Actionable Mutation



Current first-line treatment paradigm based on PD-L1 expression in TC and/or IC

- ICI monotx: pembrolizumab,* atezolizumab, cemiplimab (Sq/Nsq)
- ICI + chemotherapy
  - Pembrolizumab/platinum/pemetrexed (Nsq)
  - Atezolizumab/carboplatin/paclitaxel/bevacizumab (Nsq)
  - Atezolizumab/carboplatin/nab-paclitaxel (Nsq)
  - Pembrolizumab/carboplatin/taxane (Sq)
  - Cemiplimab + plt-based CT‡ (Sq/Nsq)
  - Nivolumab/ipilimumab + 2 cycles of plt-based CT‡ (Sq/Nsq)
  - Durvalumab/tremelimumab + plt-based CT‡ (Sq/Nsq)
- ICI combination: nivolumab/ipilimumab (Sq/Nsq)

*Single-agent pembrolizumab also approved for ≥1% PD-L1 but not broadly recommended by experts; guideline recommended for PD-L1 1%-49% if poor PS or contraindications to combining with CT. †Not an FDA-approved indication but guideline recommended. ‡Per histology.

NCCN. Clinical practice guidelines in oncology: NSCLC. v.10.2024. nccn.org.

Clinical Impact of IO in Early-Stage NSCLC on Treatment of Advanced Disease

Parameter	CheckMate 816: Neoadj Nivo/CT (N = 358)[1]	IMpower010: Adj Atezo (N = 1280)[2]	PEARLS/ KEYNOTE-091: Adj Pembro† (N = 1177)[3]	KEYNOTE-671: Neoadj Pembro/CT > Adj Pembro (N = 797)[4]	AEGEAN: Neoadj Durva/CT > Adj Durva (N = 802)[5]	PACIFIC: Consolidation Durva Post cCRT (N = 713)[6]
Disease setting	Stage IB-III, resectable	Stage IB-IIIA, resected	Stage IB-IIIA, resected	Stage II-IIIB, resectable	Stage II-IIIB, resectable	**Stage III, unresectable**
Median survival, mo	EFS: NR vs 21.1 (HR: 0.68)	DFS*: NE vs 35.3 (HR: 0.66)	DFS: 53.6 vs 42.0 (HR: 0.76)	EFS: 47.2 vs 18.3 (HR: 0.59)	EFS: NR vs 30.0 (HR: 0.68)	PFS: 16.9 vs 5.6 (HR: 0.55)
Patients with relapse within 2 yr, %	**35**	**25***	**33**	**38**	**35**	**55**

*For patients with PD-L1 ≥1%, the FDA-approved indication for adjuvant atezolizumab. †Adjuvant chemotherapy not mandatory.

1. Girard. ELCC 2023. Abstr 840. 2. Felip. Lancet. 2021;398:1344. 3. O'Brien. Lancet Oncol. 2022: 23:1274-1286. 4. Spicer. ESMO 2023. Abstr LBA56. 5. Heymach. NEJM 2023: 389; 1672-84. 6. Spigel. JCO. 2022;40:1301.

Types of Immunotherapy Resistance

Primary resistance: tumor does not initially respond to immunotherapy

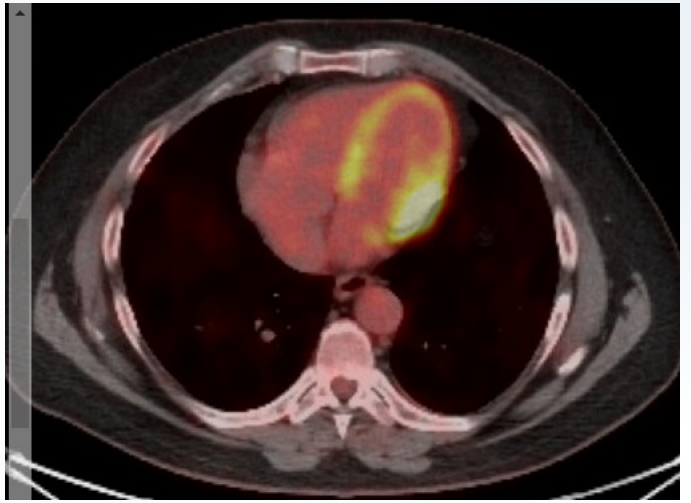
Includes hyperprogression

Acquired resistance: tumor initially responds effectively to immunotherapy but subsequently progresses

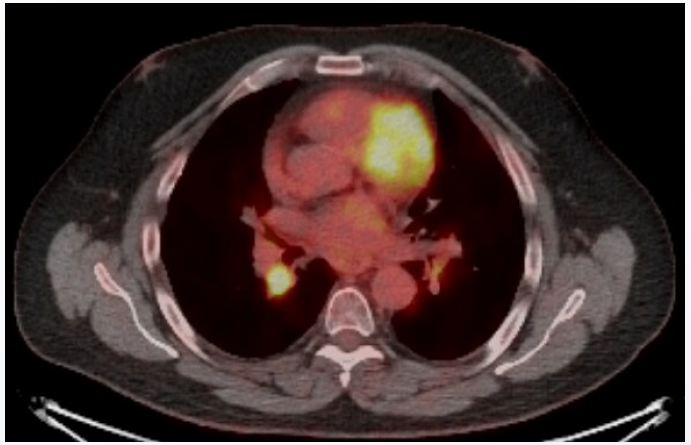
Bai. Front Oncol. 2020;10:1290.

Patient Case 1

- 68-yr-old male with 40 pack-yr smoking history (quit 10 yr ago) diagnosed with stage cT4N3M1c SCC
- IHC TTF1 negative, Napsin-A negative, p40 positive
- PET/CT with uptake in RUL, bilateral lung nodules, hilar and mediastinal LN, left adrenal gland, bone (L3, L iliac, R sacrum)
- MRI brain normal
- PD-L1 20%; NGS negative for actionable alterations
- ECOG PS 1
- He received carboplatin, nab-paclitaxel, and pembrolizumab with response followed by maintenance pembrolizumab
- After 18 mo of maintenance therapy, progression in hilar LN, liver and left adrenal gland identified



Tumor Response



Progression

Treatment options following chemotherapy and ICI

- Currently have minimal treatment options
- Current SoC therapy options following platinum-doublet chemotherapy

Regimen	Median PFS, Mo	Median OS, Mo
Docetaxel[1]	3.0	9.1
Gemcitabine[2]	--	5.7
Pemetrexed[3]	2.9	8.3
Docetaxel + nintedanib[4]	3.4	10.1
Docetaxel + ramucirumab[1]	4.5	10.5

- Role of radiation for oligometastatic disease

1. Garon. Lancet. 2014;384:665. 2. Anderson. Br J Cancer. 2000;83:447.
3. Hanna. JCO. 2023;41:2682. 4. Reck. Lancet Oncol. 2014;15:143.

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ICI and VEGF inhibition

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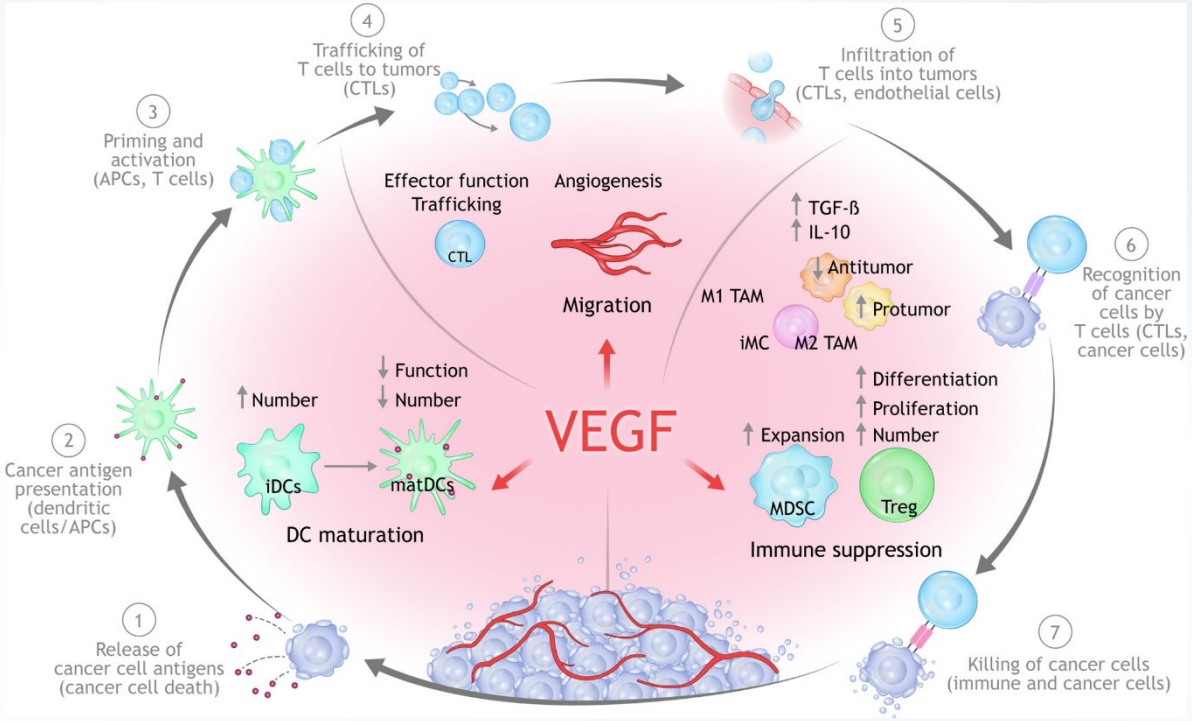
Angiogenesis-Modulating Factors on the Immune System

- VEGF modulates tumor microenvironment—inhibition can restore many of these phenotypes[1]
- Induces PD-L1 on dendritic cells, suppresses maturation
- Impedes T-cell extravasation
- Inhibits proliferation, cytotoxicity of cytotoxic T lymphocytes
- Stimulates proliferation of T-regulatory cells
- Mediates effects on myeloid-derived suppressor cells



VEGF is Important to Modulating Tumor Microenvironment[1,4]

- VEGFR2 inhibition ↓ infiltration of suppressive immune cells while ↑ maturation of dendritic cells[2]
- Combination blockade of PD-1 and VEGFR may overcome resistance by reducing tumor neovascularization with upregulation of proinflammatory cytokines[3]

1. Rivera. Trends Immunol. 2015;36:240. 2. Roland. PLoS One. 2009;4:e7669.
3. Yasuda. Clin Exp Immunol. 2013;172:500. 4. Hack. Front Immunol. 2020;11:598877.

Lung-MAP S1800A: Ramucirumab + Pembrolizumab vs SoC CT in Advanced NSCLC After ICI and Platinum CT

Multicenter, open-label, randomized phase II trial

Stratified by PD-L1 tumor status (<1% vs ≥1% or unknown), tumor histology (squamous vs nonsquamous), planned ramucirumab if assigned to SoC (yes vs no)

Stage IV/recurrent NSCLC previously treated with ≥1 line of anti–PD-1/PD-L1 tx for stage III/IV/ recurrent disease, in sequence or combined with platinum-based CT; PD ≥84 days after starting anti–PD-(L)1 tx; ECOG PS 0/1
(N = 136)

Ramucirumab 10 mg/kg IV + **Pembrolizumab** 200 mg IV Q21D
(n = 69)

SoC Chemotherapy* Q21D
(n = 67)

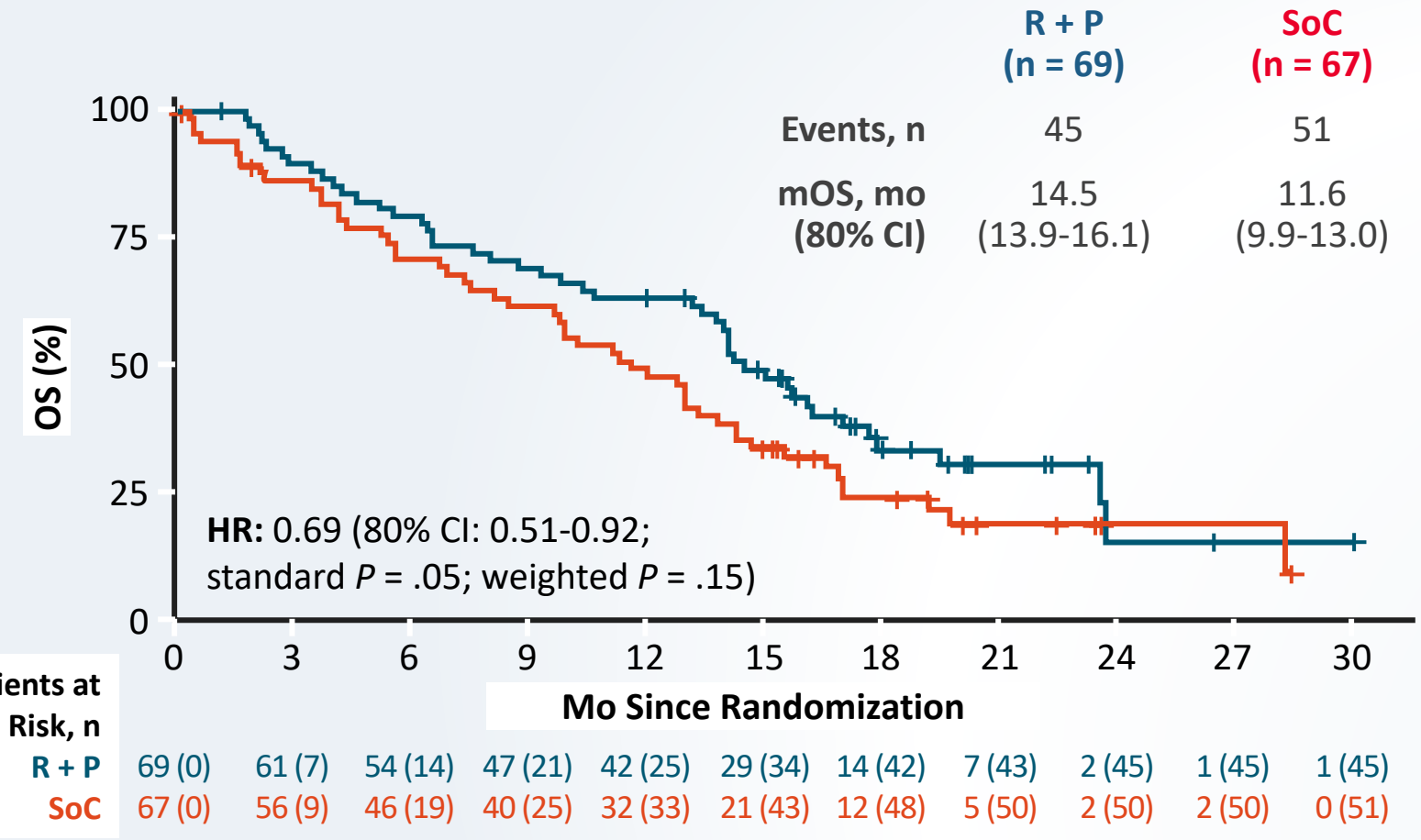
Until PD per RECIST v1.1, symptomatic deterioration, unacceptable toxicity, tx delay >84 days, patient choice

*Investigator's choice: docetaxel 75 mg/m^2 IV ± ramucirumab 10 mg/kg IV; gemcitabine 1000 mg/m^2 on Days 1 and 8; nonsquamous only, pemetrexed 500 mg/m^2.

- **Primary endpoint:** OS
- **Secondary endpoints:** ORR, DCR, DoR, PFS, safety

Reckamp. JCO. 2022;40:2295. Reckamp. ASCO 2022. Abstr 9004. NCT03971474.

S1800A: OS in mITT (Primary Endpoint)

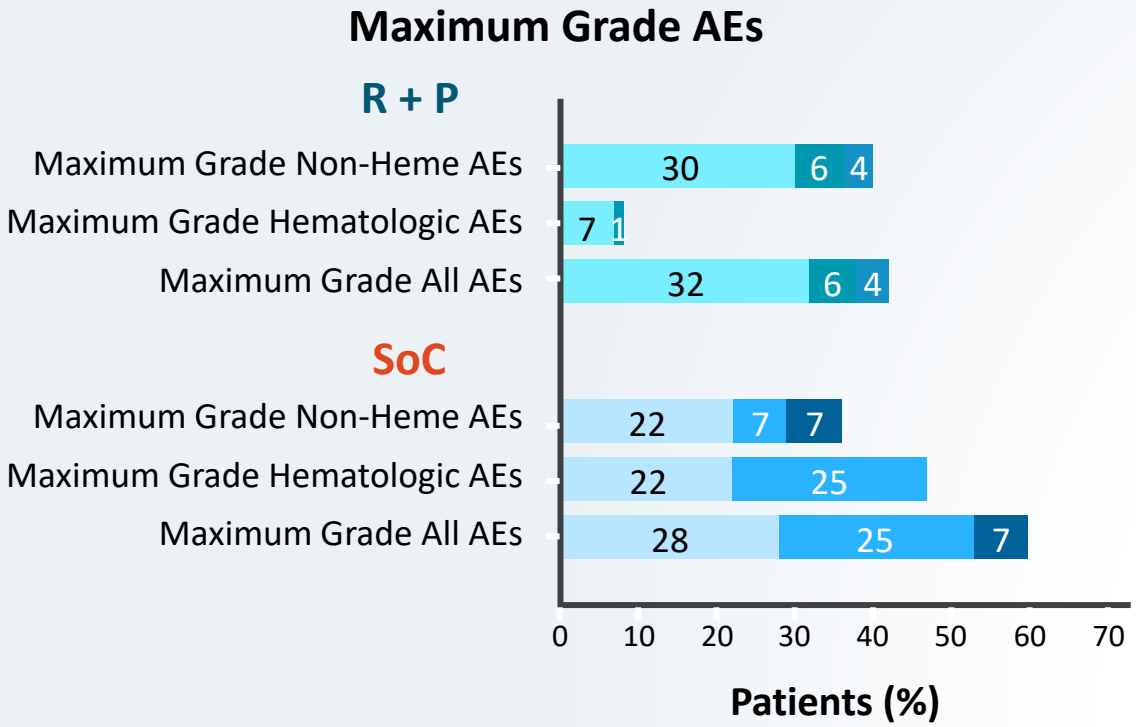


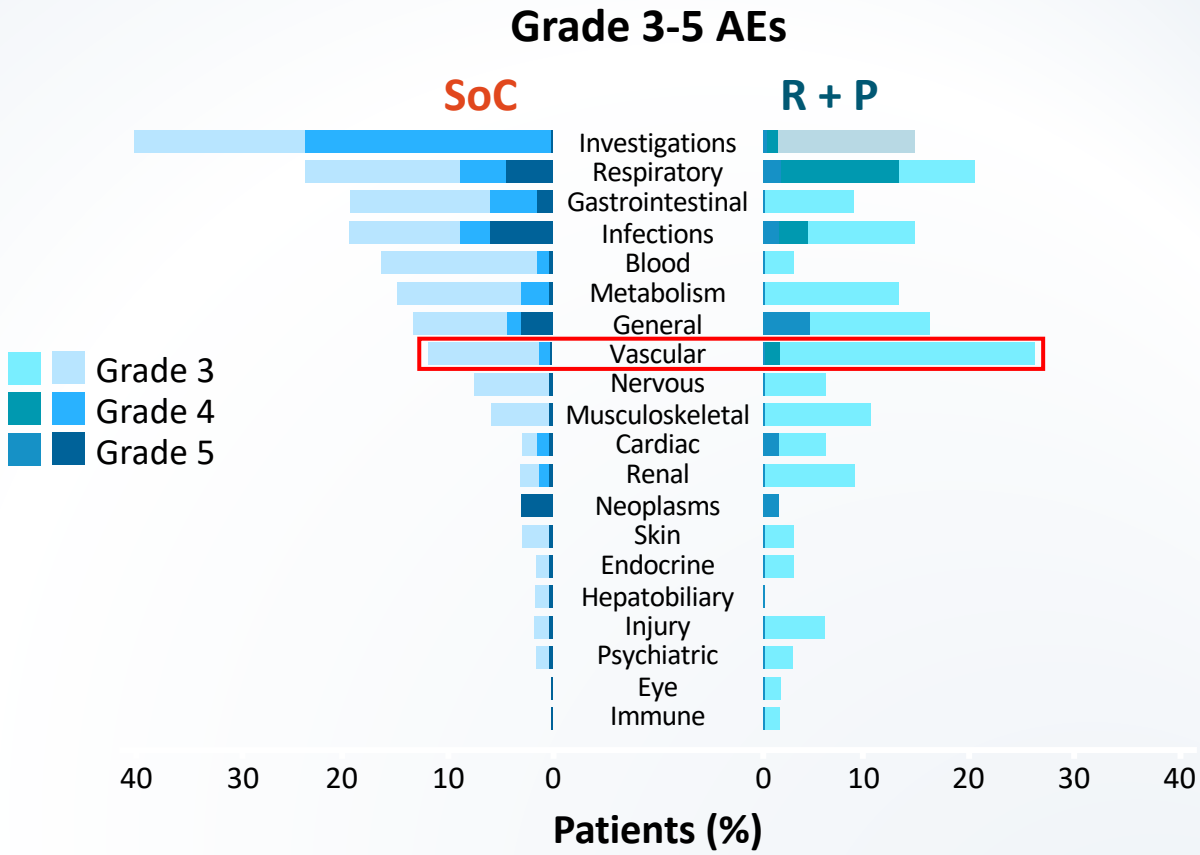
SoC therapy received:

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

Reckamp. JCO. 2022;40:2295. Reckamp. ASCO 2022. Abstr 9004.

S1800A: Safety Summary—Percentage of Patients With Grade 3-5 AEs





Grade 3-5 TRAEs reported in 42% with RP vs 60% with SoC

Of TRAEs in RP arm, 31% were classified as irAEs

Reckamp. JCO. 2022;40:2295. Reckamp. ASCO 2022. Abstr 9004.

Randomized Trials of VEGF(R)i + IO in 2L NSCLC

Parameter	Ph III REVEL[1]		Ph III CONTACT-01[2]		Ph III SAPPHIRE[3,4]		Ph II Lung-MAP S1800A[5]		Ph III LEAP-008[6]	
	Doc + Pbo (n = 625)	Doc + Ramu (n = 628)	Doc (n = 180)	Atezo + Cabo (n = 186)	Doc (n = 284)	Nivo + Sitravatinib (n = 293)	SoC CT (n = 67)	Pembro + Ramu (n = 69)	Doc (n = 189)	Pembro + Len (n = 185)
Tx line	2L		2L-3L		2L-3L		≥2L (19% ≥4L)	≥2L (16% ≥4L)	2L-3L	
Prior ICI, %	0	0	100	100	100	100	100	100	100	100
Duration of prior ICI	NA	NA	62% ≥6 mo	59% ≥6 mo	8.3	8.5	100% ≥84 days; 70% ≥6 mo; 26% ≥12 mo		NR	NR
ORR, %	14	23	13.3	11.8	17.2	15.6	28	22	22.7	14.3
mDoR, mo	NR	NR	4.3	5.6	7.1	7.4	5.6	12.9	6.9	6.8
mPFS, mo	3.0	4.5	4.0	4.6	5.4	4.4	5.2	4.5	4.2	5.6
mOS, mo	9.1	10.5	10.5	10.7	10.6	12.2	11.6	14.5	12.0	11.3

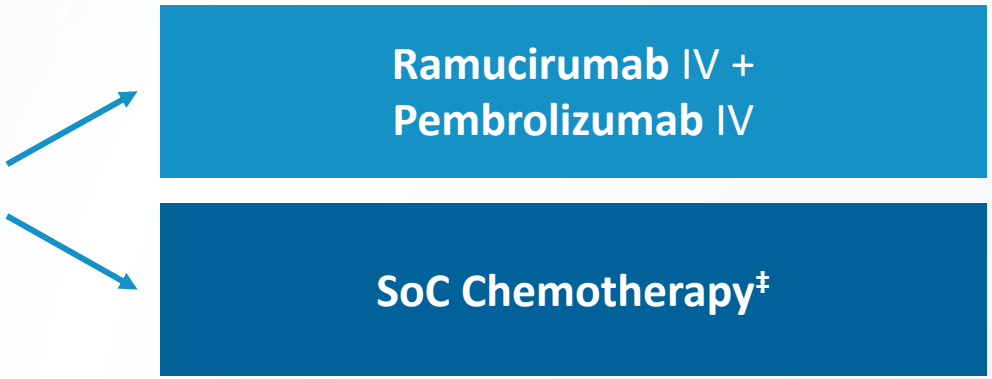
1. Garon. Lancet. 2014;384:665. 2. Neal. ELCC 2023. Abstr 6O. 3. Borghaei. Ann Oncol. 2023;[Epub]. 4. Borghaei. ESMO 2023. Abstr LBA63. 5. Reckamp. JCO. 2022;40:2295. 6. Leighl et al ESMO IO 2023.

S2302 Pragmatica-Lung: Ramucirumab + Pembrolizumab vs SoC for Stage IV/Recurrent NSCLC Following ICI and CT

Multicenter, open-label, randomized phase III trial

Stratified by Zubrod PS (0/1 vs 2) most recent therapy ICI (yes vs no)

Adult patients with stage IV/recurrent NSCLC, previously treated with platinum-based CT and experienced PD; previously received anti–PD-1/PD-L1 tx for any disease stage* and experienced PD ≥84 days from initiation; if sensitizing genomic alteration,† must have received ≥1 approved targeted tx; ECOG PS 0-2
(planned N = 800)

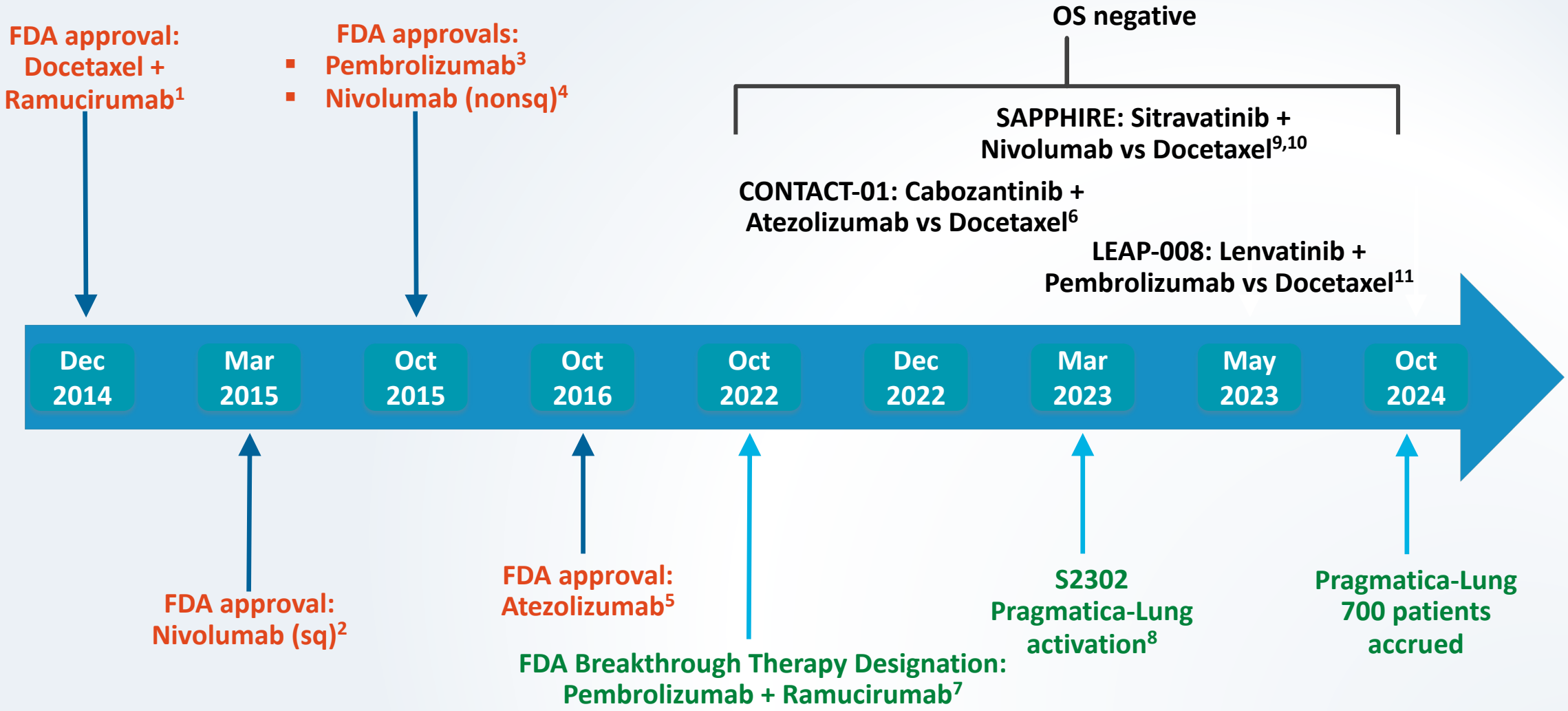


*Alone or in combination. If for stage IV/recurrent disease, must have received only 1 line and achieved SD/PR/CR. If only as neo/adjuvant or consolidation tx, must have experienced PD ≤365 d from initiation. †*EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS* G12C*, HER2, MET*ex14. ‡Investigator's choice per clinical guidelines.

- **Primary endpoint:** OS
- **Secondary endpoint:** incidence of grade ≥3 TRAEs

NCT05633602. Reckamp et al ASCO 2024.

Second-line Therapy for Advanced NSCLC

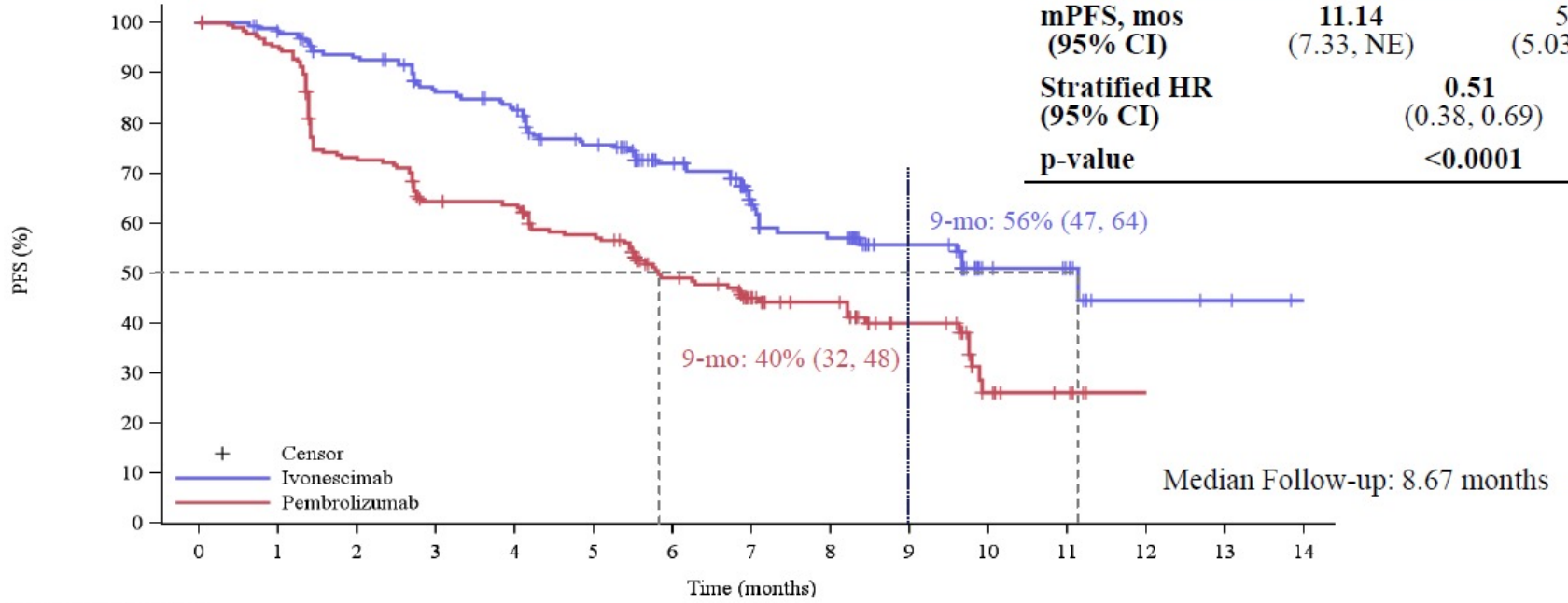


1. Larkins. Oncologist. 2015;20:1320. 2. Raedler. Am Health Drug Benefits. 2015;8(Spec Feature):180. 3. Pai-Scherf. Oncologist. 2017;22:1392. 4. Kazandjian. Oncologist. 2016;21:634. 5. Weinstock. Clin Cancer Res. 2017;23:4534. 6. Neal. ELCC 2023. Abstr 6O. 7. https://cancerletter.com/clinical/20221202_1/. 8. NCT05633602. 9. Borghaei. ESMO 2023. Abstr LBA63. 10. Borghaei. Ann Oncol. 2023;[Epub]. 11. Leighl et al Ann Oncol 2023.

HARMONi-2: Frontline Ivonescimab versus Pembrolizumab in advanced NSCLC with PD-L1 ≥1%

Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

Zhou et al WCLC 2024 PL02.04

LATIFY: Ceralasertib + Durvalumab vs Docetaxel in Advanced NSCLC After ICI + Platinum-Based CT

International, randomized, open-label phase III trial—ATR inhibition

Stratified by histology (nonsquamous vs squamous), resistance to prior anti–PD-(L)1 (primary vs acquired), TC PD-L1 (<1% vs ≥1%), region (N America/W Europe vs RoW)

Adults with stage III/IV NSCLC; locally documented *EGFR/ALK* WT; PD on 1 line of prior anti–PD-1/PD-L1 with platinum-based CT (in sequence or combined); stable brain mets or spinal cord compression permitted; ECOG PS 0/1
(N = 580)

Ceralasertib 240 mg PO BID Days 1-7 + **Durvalumab** 1500 mg Day 8
28-day cycle

Docetaxel 75 mg/m^2 IV Day 1
21-day cycles

Until PD, unacceptable toxicity, consent withdrawal, or d/c criteria met

- **Primary endpoint:** OS
- **Secondary endpoints:** Inv-assessed PFS, ORR, DoR, TTR, DCR per RECIST v1.1; time to second progression/death; 12-mo OS rate; safety/tolerability; QoL; PK

Besse. ASCO 2023. Abstr TPS9161. NCT05450692.

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Antibody Drug Conjugates

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TROPION-Lung01: Datopotamab Deruxtecan vs Docetaxel for Previously Treated Adv/Metastatic NSCLC

Global, randomized, open-label phase III trial

Stratified by histology (squamous vs nonsquamous), actionable genomic alteration (present vs absent), geography (US/Japan/Western Europe vs rest of world), anti–PD-1/PD-L1 mAb in most recent prior therapy

Patients with previously treated*
stage IIIB, IIIC, or IV NSCLC;
no prior docetaxel; ECOG PS 0-1;
+/- actionable genomic alterations
(N = 604)

Dato-DXd 6 mg/kg Q3W
(n = 299)

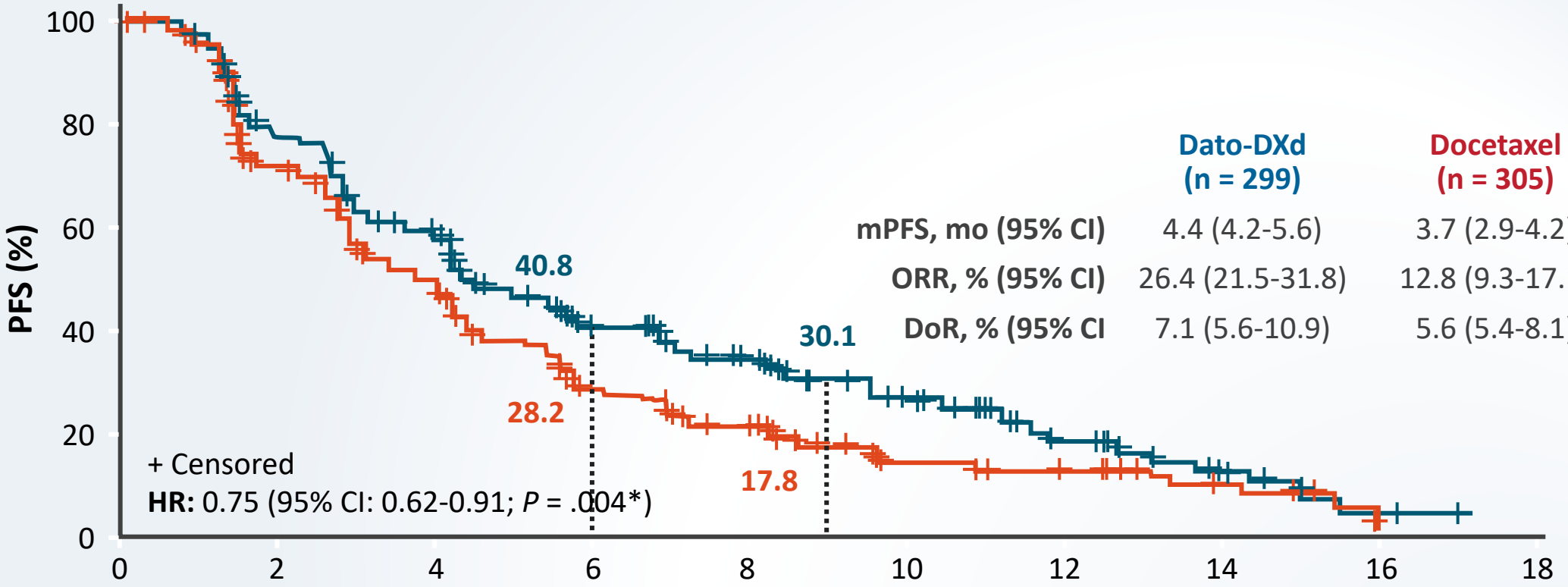
Docetaxel 75 mg/m^2 Q3W
(n = 305)

*Patients without actionable genomic alterations: 1-2 lines, including plt-based CT and anti–PD-1/PD-L1 mAb; patients with actionable genomic alterations (*EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET*ex14, or *RET)*: 1-2 prior approved targeted therapies and/or plt-based CT with ≤1 anti–PD-1/PD-L1 mAb.

- **Dual primary endpoints**: PFS (BICR), OS
- **Secondary endpoints**: ORR (BICR), DoR (BICR), safety

Lisberg. ESMO 2023. Abstr LBA12. Ahn et al J Clin Oncol 2024.

TROPION-Lung01: PFS (ITT)



	Dato-DXd (n = 299)	Docetaxel (n = 305)
mPFS, mo (95% CI)	4.4 (4.2-5.6)	3.7 (2.9-4.2)
ORR, % (95% CI)	26.4 (21.5-31.8)	12.8 (9.3-17.1)
DoR, % (95% CI	7.1 (5.6-10.9)	5.6 (5.4-8.1)

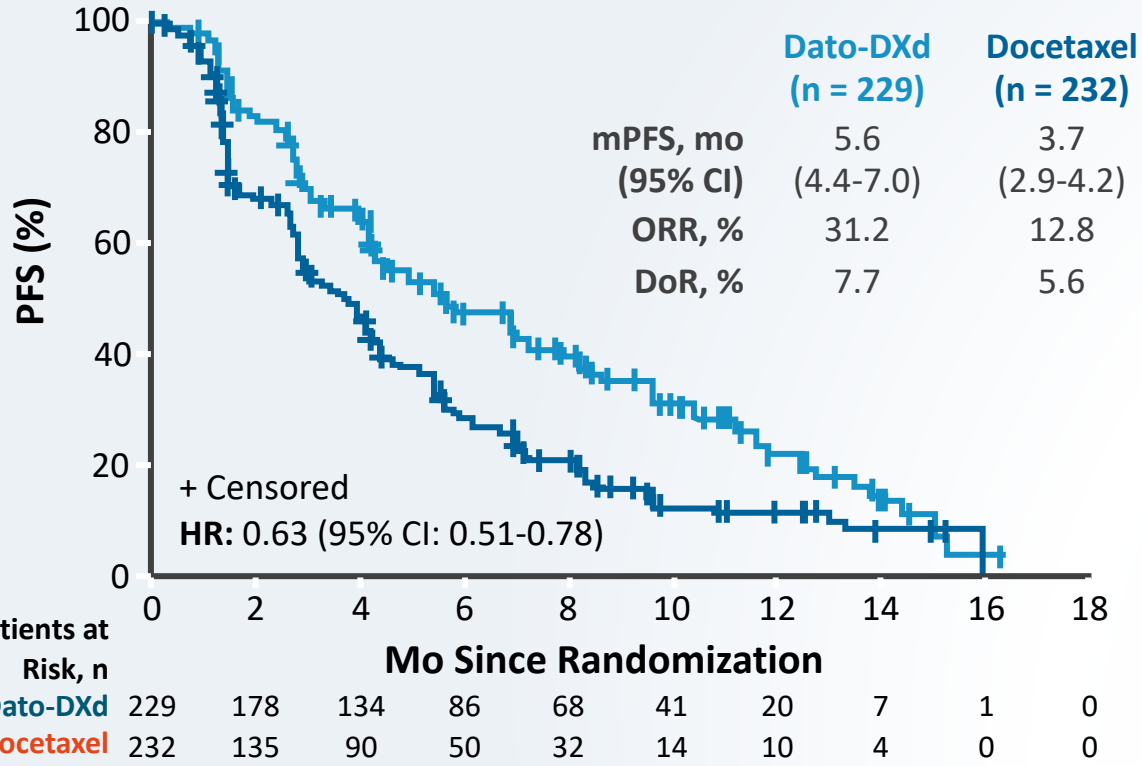
Patients at Risk, n										
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

*Prespecified boundary (2-sided): *P* = .008

Lisberg. ESMO 2023. Abstr LBA12. Ahn et al J Clin Oncol 2024.

TROPION-Lung01: PFS by Histology

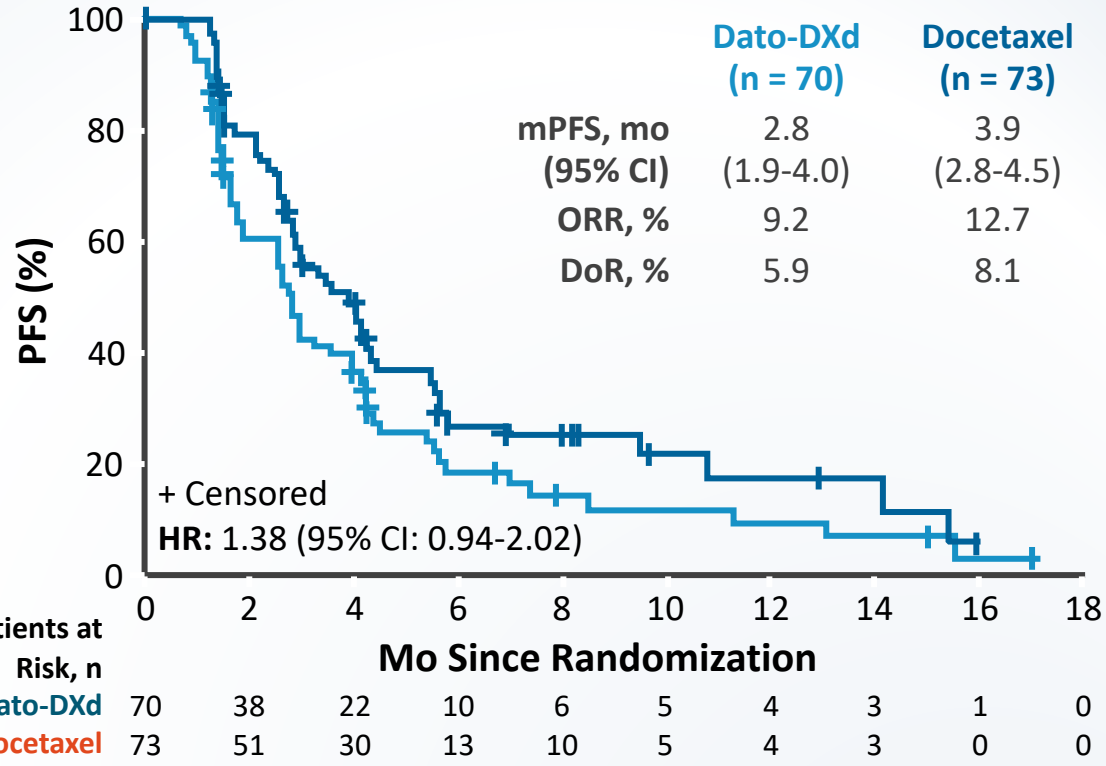
Nonsquamous* (n = 461)



	Dato-DXd (n = 229)	Docetaxel (n = 232)
mPFS, mo (95% CI)	5.6 (4.4-7.0)	3.7 (2.9-4.2)
ORR, %	31.2	12.8
DoR, %	7.7	5.6

Patients at Risk, n										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous* (n = 143)



	Dato-DXd (n = 70)	Docetaxel (n = 73)
mPFS, mo (95% CI)	2.8 (1.9-4.0)	3.9 (2.8-4.5)
ORR, %	9.2	12.7
DoR, %	5.9	8.1

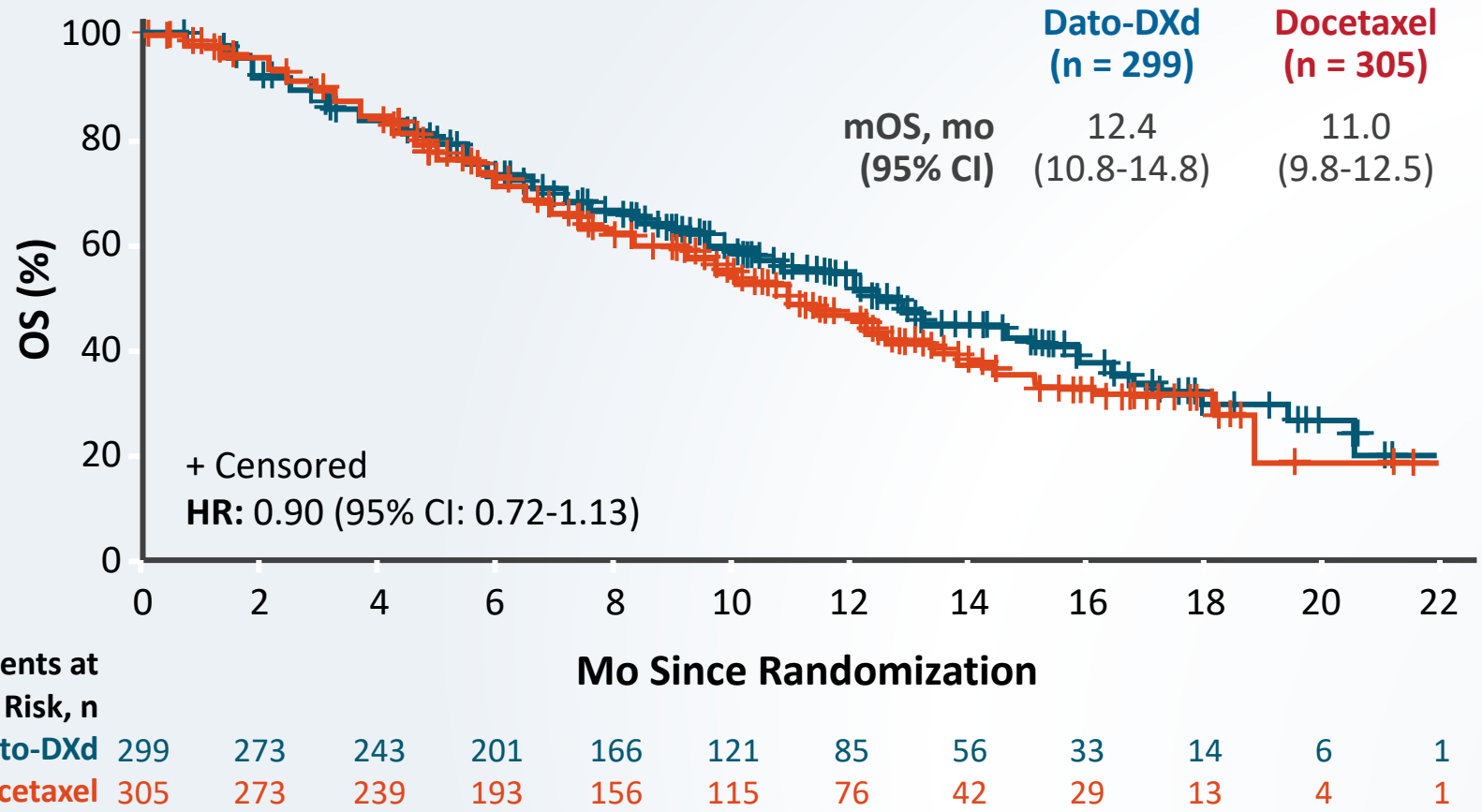
Patients at Risk, n										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for nonsquamous without AGAs: 0.71 (95% CI: 0.56-0.91)

Lisberg. ESMO 2023. Abstr LBA12. Ahn et al J Clin Oncol 2024.

*With and without AGAs.

TROPION-Lung01: OS (ITT)



- Fraction of required events/total events at interim analysis: 74%
- OS HR for nonsquamous: 0.77 (95% CI: 0.59-1.01)
- OS HR for squamous: 1.32 (95% CI: 0.87-2.00)

Lisberg. ESMO 2023. Abstr LBA12. Ahn et al J Clin Oncol 2024.

TROPION-Lung01: Safety

AE of Special Interest, n (%)	Dato-DXd (n = 297)	Docetaxel (n = 290)
Stomatitis/oral mucositis*		
▪ All grade	160 (54)	59 (20)
▪ Grade ≥3	19 (6)	4 (1)
Ocular events†		
▪ All grade	57 (19)	27 (9)
▪ Grade ≥3	5 (2)‡	0
Adjudicated drug-related ILD		
▪ All grade	25 (8)	12 (4)
▪ Grade ≥3	10 (3)	4 (1)
▪ Grade 5	7 (2)	1 (0.3)
TRAE associated with d/c	**23 (8)**	**34 (12)**

- Investigator-assessed cause of deaths:
  - Dato-DXd: ILD/pneumonitis (n = 2), sepsis (n = 1)
  - Docetaxel: ILD/pneumonitis, septic shock (n = 1 each)

TRAEs in ≥10%, n (%)	Dato-DXd (n = 297)		Docetaxel (n = 290)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Blood and lymphatic system				
▪ Anemia	43 (15)	11 (4)	59 (20)	11 (4)
▪ Neutropenia	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
▪ Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
▪ Nausea	100 (34)	7 (2)	48 (17)	3 (1)
▪ Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
▪ Constipation	29 (10)	0	30 (10)	0
▪ Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
General				
▪ Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
▪ Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
▪ Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and SC				
▪ Alopecia	95 (32)	0	101 (35)	1 (0.3)*
▪ Rash	36 (12)	0	18 (6)	0
▪ Pruritus	30 (10)	0	12 (4)	0

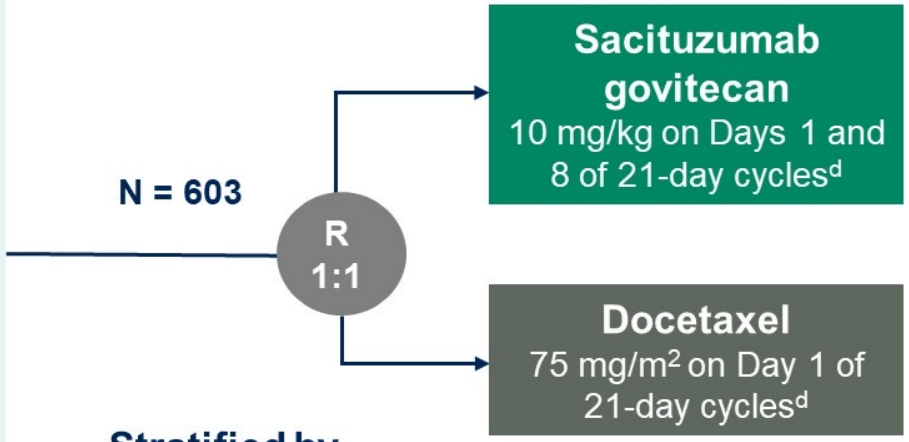
*Includes event incorrectly reported as grade 3.

Lisberg. ESMO 2023. Abstr LBA12. Ahn et al J Clin Oncol 2024.

EVOKE-01: Global, Randomized, Open-Label, Phase 3 Study

Key eligibility criteria

- Measurable stage IV NSCLC
- ECOG PS 0–1
- Radiographic progression after platinum-based and anti-PD-(L)1–containing regimen[a]
- In addition, patients with known AGAs must have received ≥ 1 approved TKI[b]
  - *EGFR/ALK* test required. Testing of other AGAs recommended[c]
- Previously treated stable brain metastases were included
- No prior treatment with Topo-1 inhibitors, Trop-2–targeted therapies, or docetaxel



End points

Primary

- OS

Secondary

- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

Stratified by

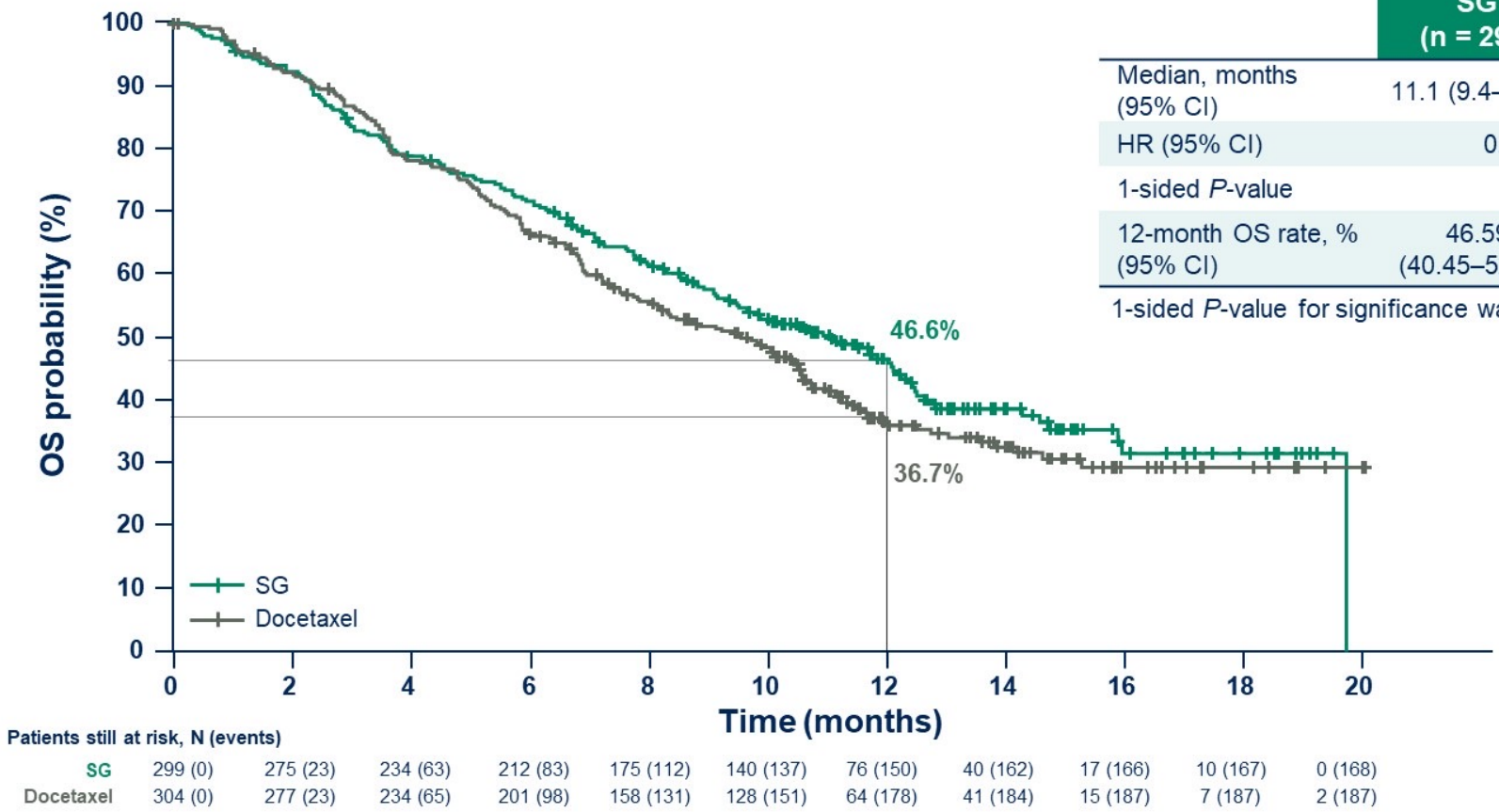
- **Histology** (squamous vs nonsquamous)
- **Response to last anti-PD-(L)1–containing regimen** (responsive [best response CR/PR] vs nonresponsive [PD/SD])
- **Received prior targeted therapy for AGA** (yes vs no)

At data cutoff (29 November 2023), the study median follow-up was 12.7 months (range, 6.0–24.0)

[a](Neo)adjuvant therapy counted if progression within 6 months of platinum treatment and while on maintenance with checkpoint inhibitor agent. [b]If local approval exists for targeted therapy to that genomic alteration. [c]Based on local SOC and availability of testing/approved targeted agent. [d]Until PD or unacceptable toxicity. AGA, actionable genomic alteration; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; NSCLC, non-small cell lung cancer; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; PR, partial response; QoL, quality of life; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOC, standard of care; TKI, tyrosine kinase inhibitor; Topo-1, topoisomerase-1; Trop-2, trophoblast cell surface antigen 2.

Paz-Ares et al ASCO 2024; Paz-Ares et al. J Clin Oncol 2024.

Primary End Point: Overall Survival (ITT)



	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	11.1 (9.4–12.3)	9.8 (8.1–10.6)
HR (95% CI)	0.84 (0.68–1.04)	
1-sided *P*-value	0.0534	
12-month OS rate, % (95% CI)	46.59 (40.45–52.50)	36.72 (30.88–42.57)

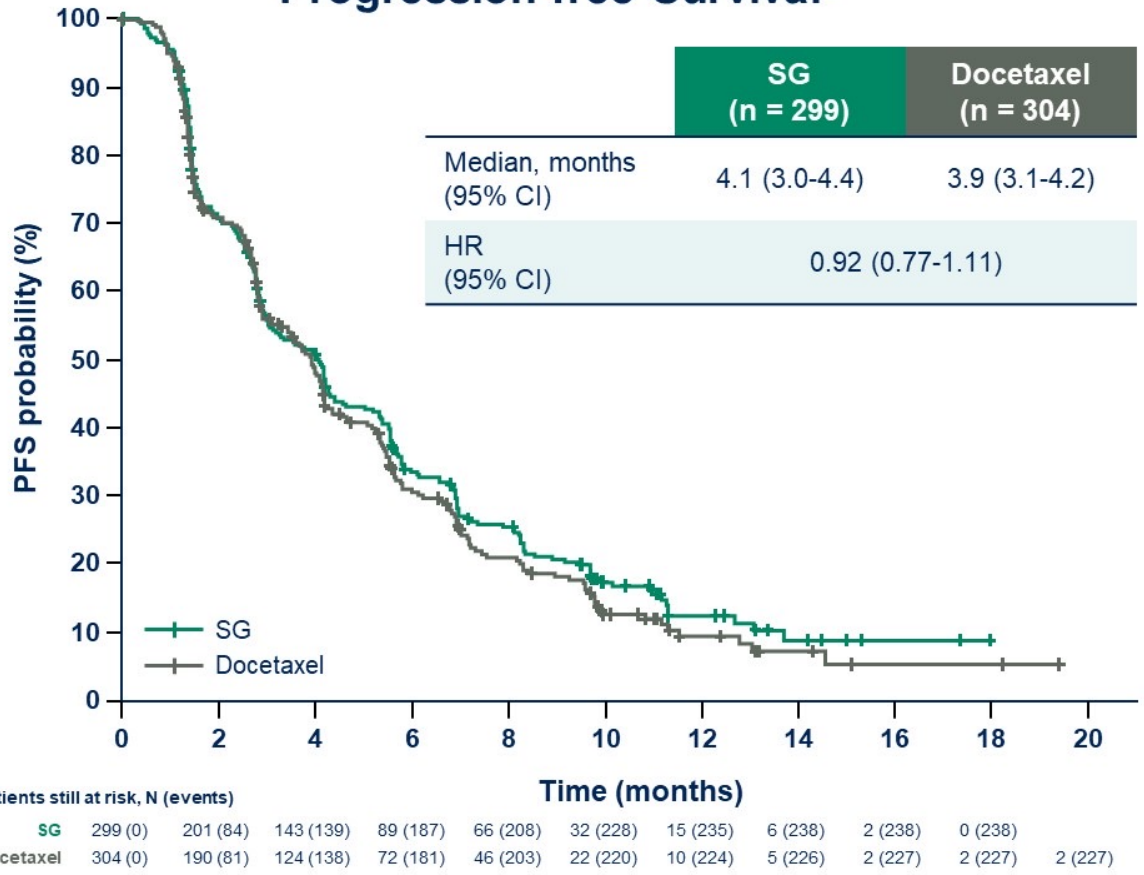
1-sided *P*-value for significance was $P \leq 0.0223$

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; SG, sacituzumab govitecan.

Paz-Ares et al ASCO 2024; Paz-Ares et al. J Clin Oncol 2024.

Secondary End Points (ITT)

Progression-free Survival[a]



	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	4.1 (3.0-4.4)	3.9 (3.1-4.2)
HR (95% CI)	0.92 (0.77-1.11)	

Objective Response Rate[a]

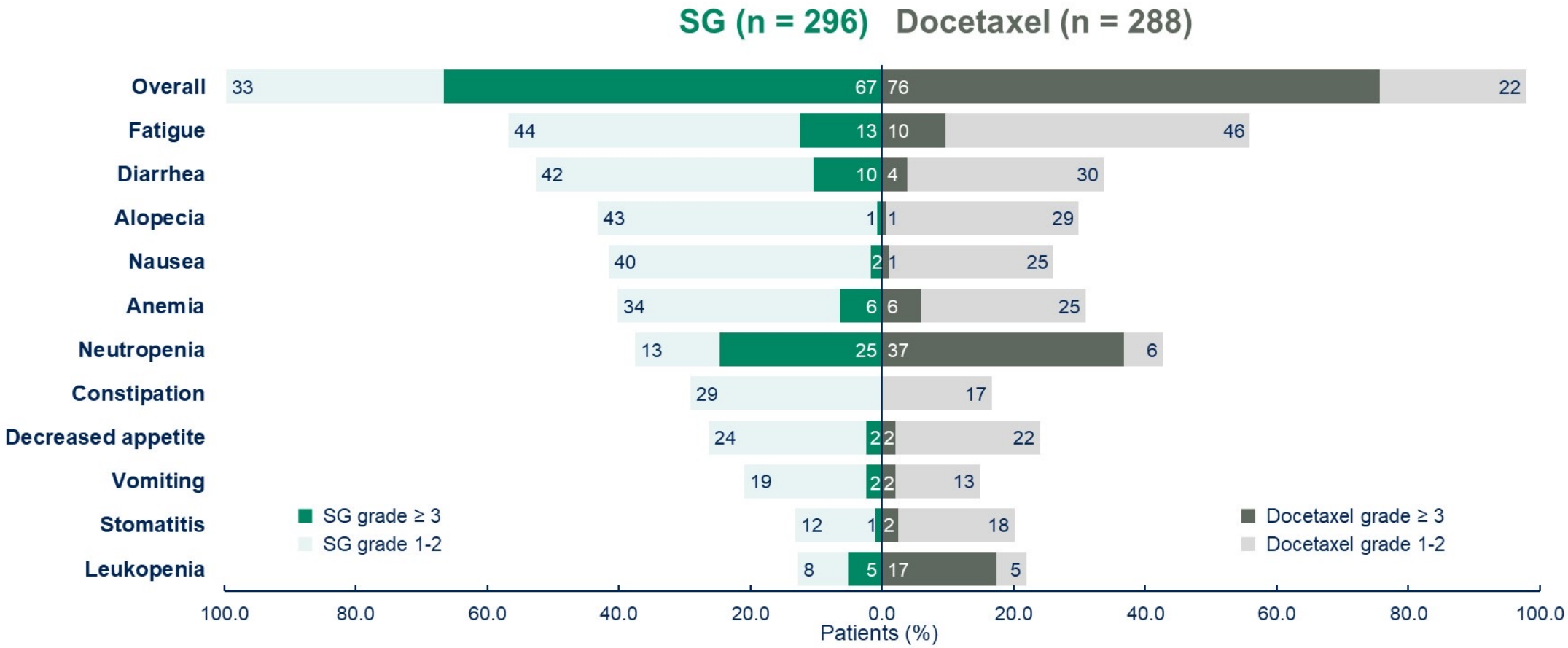
	SG (n = 299)	Docetaxel (n = 304)
ORR, % (95% CI)	13.7 (10.0–18.1)	18.1 (13.9–22.9)
DCR, % (95% CI)	67.6 (61.9–72.8)	67.1 (61.5–72.4)
Median DOR, months (95% CI)	6.7 (4.4–9.8)	5.8 (4.1–8.3)
DOR rate at 6 months, % (95% CI)	52.5 (35.6–66.9)	46.5 (31.9–59.8)

[a]By INV assessment. CI, confidence interval; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; INV, investigator; ITT, intent-to-treat; ORR, objective response rate; PFS, progression-free survival; SG, sacituzumab govitecan.

Paz-Ares et al ASCO 2024; Paz-Ares et al. J Clin Oncol 2024.

Treatment-Emergent Adverse Events

In ≥ 20% of patients receiving SG or docetaxel



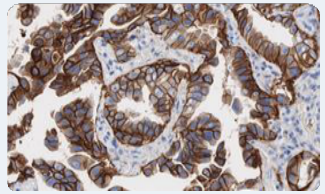
SG, sacituzumab govitecan.

Paz-Ares et al ASCO 2024; Paz-Ares et al. J Clin Oncol 2024.

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

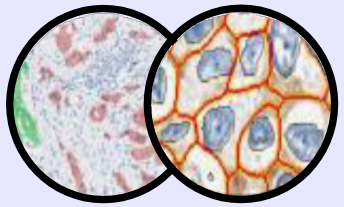
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

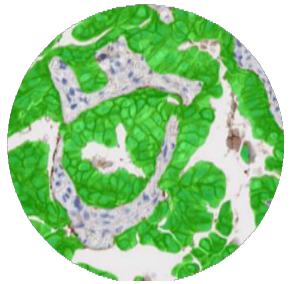


4 Patient Biomarker Status Determination

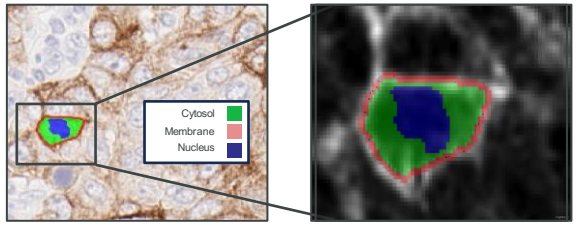
\+ ≥75% of tumor cells with TROP2 NMR ≤0.5585

\- <75% of tumor cells with TROP2 NMR ≤0.5585

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

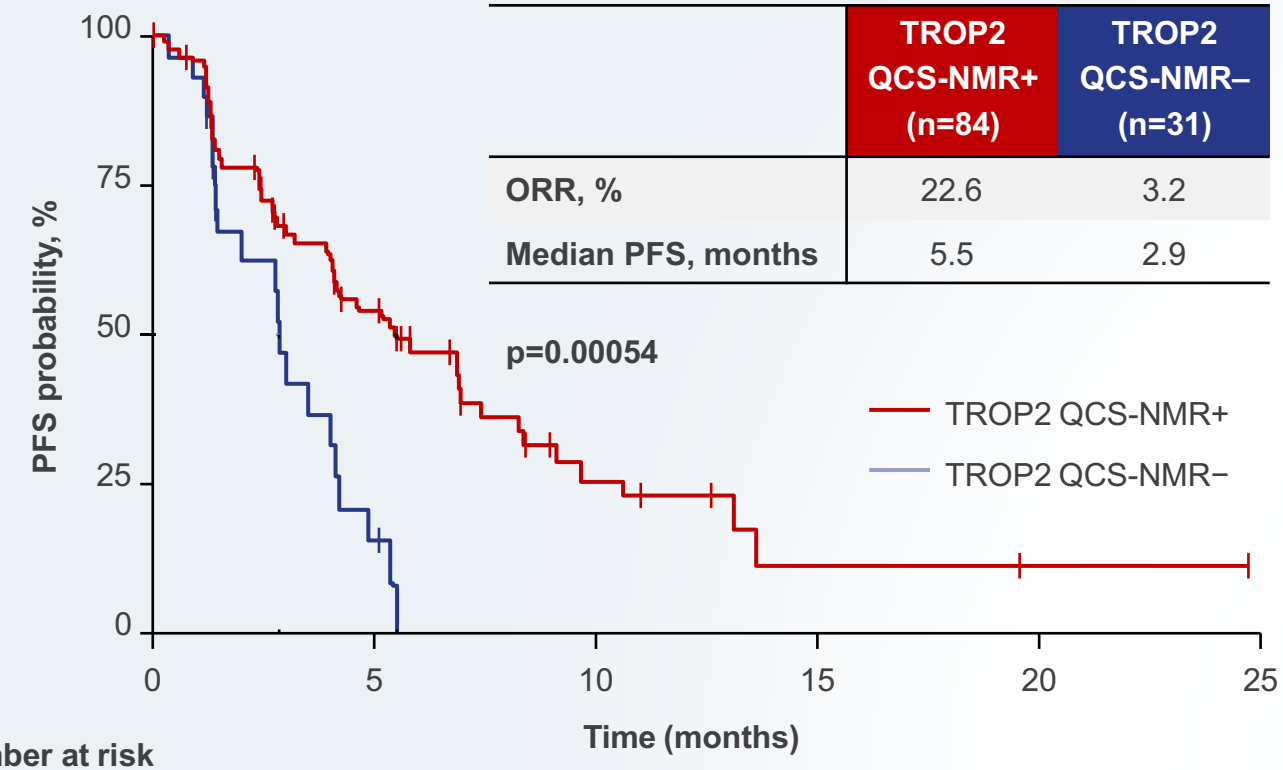
Lower NMR → higher cytoplasm proportion

Garassino et al WCLC 2024 PL02.11

OD, optical density (a measure of staining intensity).

Biomarker Discovery: Identification of QCS-NMR

TROPION-PanTumor01 (NCT03401385)*



	TROP2 QCS-NMR+ (n=84)	TROP2 QCS-NMR– (n=31)
ORR, %	22.6	3.2
Median PFS, months	5.5	2.9

Number at risk

QCS-NMR+	84	33	9	2	1	0
QCS-NMR–	31	3	0	0	0	0

- **Population:** 115 biomarker-evaluable patients out of 180 patients with NSCLC who received Dato-DXd (4, 6, and 8 mg/kg q3w) in dose-expansion cohorts from TROPION-PanTumor01
- **Methods:** A hypothesis-free exploration of multiple QCS features linked with PFS was completed

TROP2 QCS-NMR was identified as the most promising QCS feature based on correlation with PFS

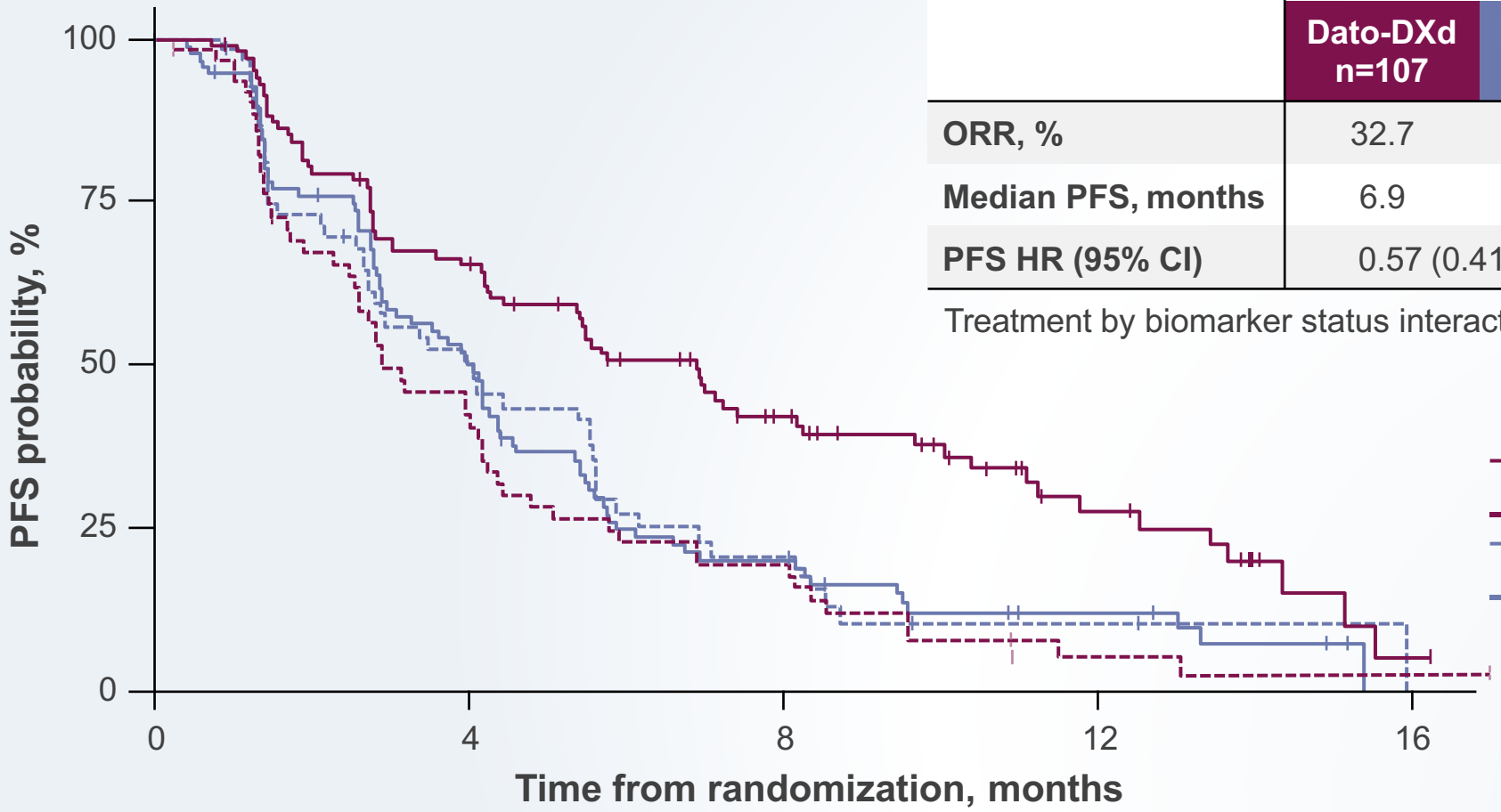
Garassino et al WCLC 2024 PL02.11

Spitzmueller A, Schmidt G, Triltsch N & Kapil A, 2023: A scoring method for an anti-TROP2 antibody-drug conjugate therapy. International Patent Application No. PCT/IB2023/052428.
*Analysis based on a Research Use Only IHC assay and early version of the QCS algorithm with alternate cut-points.
NMR, normalized membrane ratio; ORR, objective response rate; q3w, every 3 weeks; QCS, quantitative continuous scoring.

Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Garassino et al WCLC 2024 PL02.11

Data cutoff: March 29 2023

18th Annual

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Tumor Treating Fields

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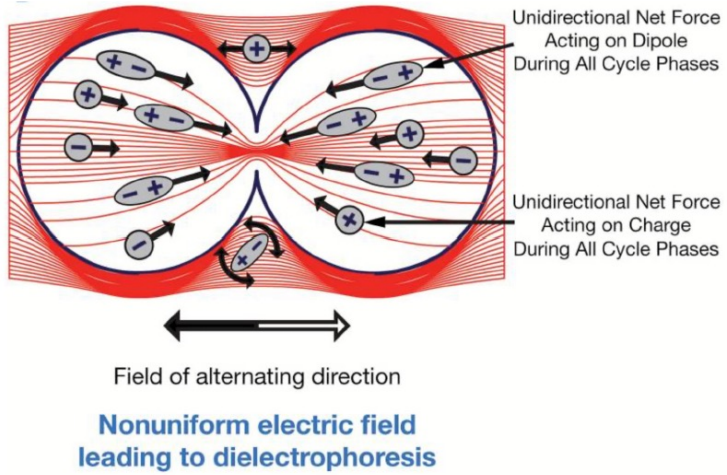
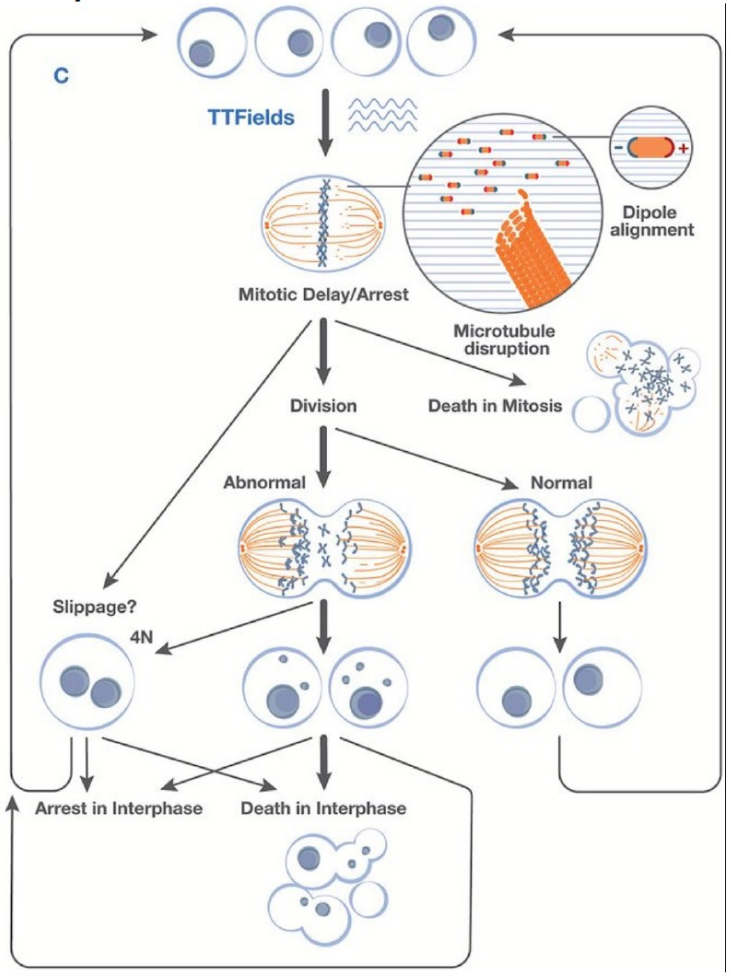
Tumor Treating Fields (TTFields): Mechanism of Action

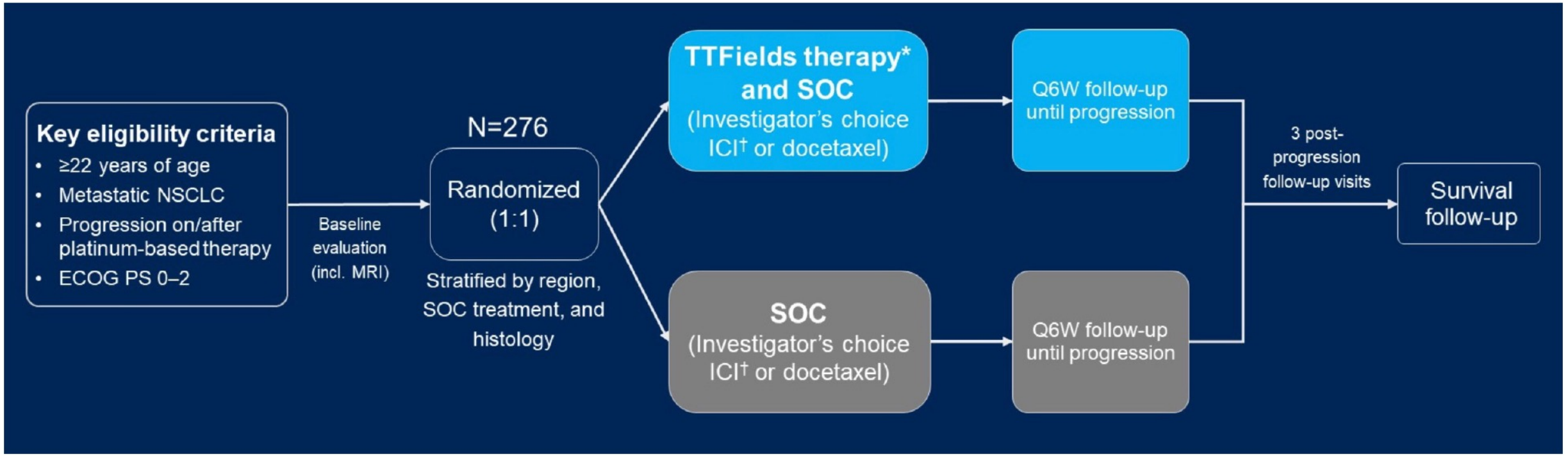




Hottinger AF et al. *Neuro Oncol* 2016;18(10):1338-49.

- Inhibit tumor growth by disrupting cell division
- Induce cell death through apoptosis, autophagy, pyroptosis, and cell cycle arrest
- Disrupt DNA repair, cell permeability, and immunological responses

LUNAR: A Phase III Study of TTFields for Metastatic Non-Small Cell Lung Cancer (mNSCLC) with Progression on/after Platinum

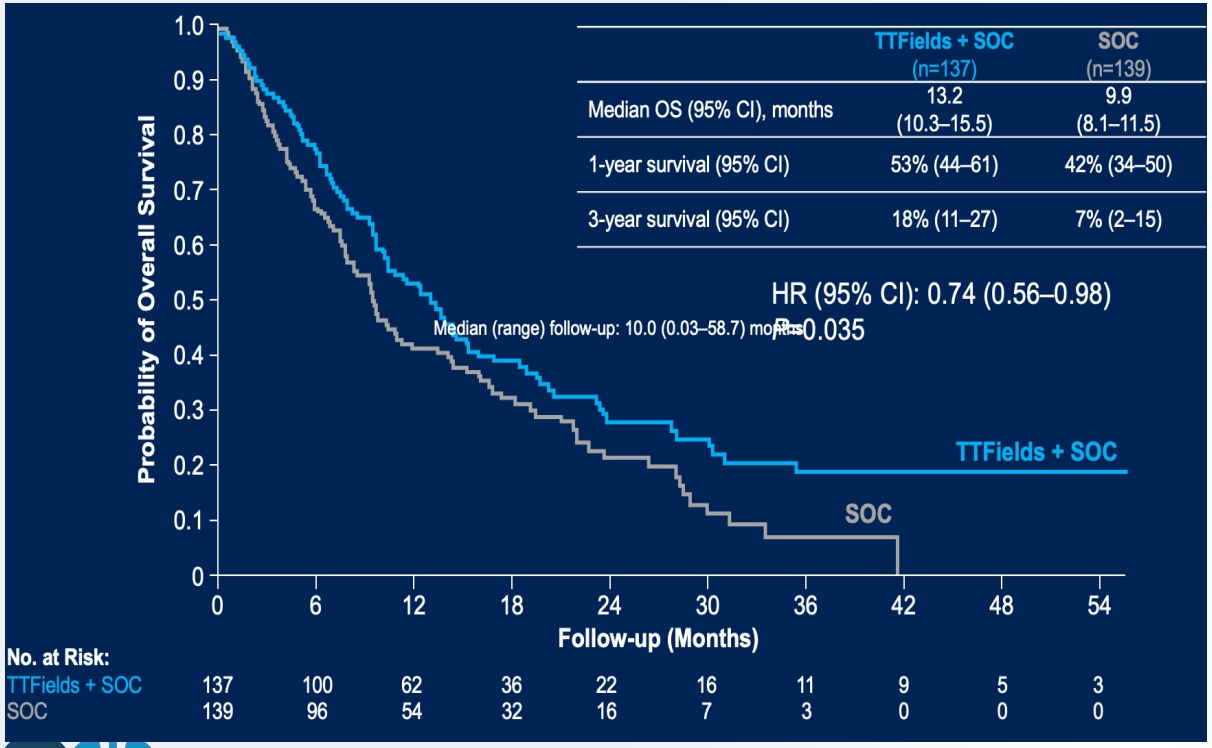


SOC = standard of care; ICI = immune checkpoint inhibitor

Leal T et al. ASCO 2023;Abstract LBA9005.
Leal T et al. Lancet Oncol 2023;24(9):1002-17.

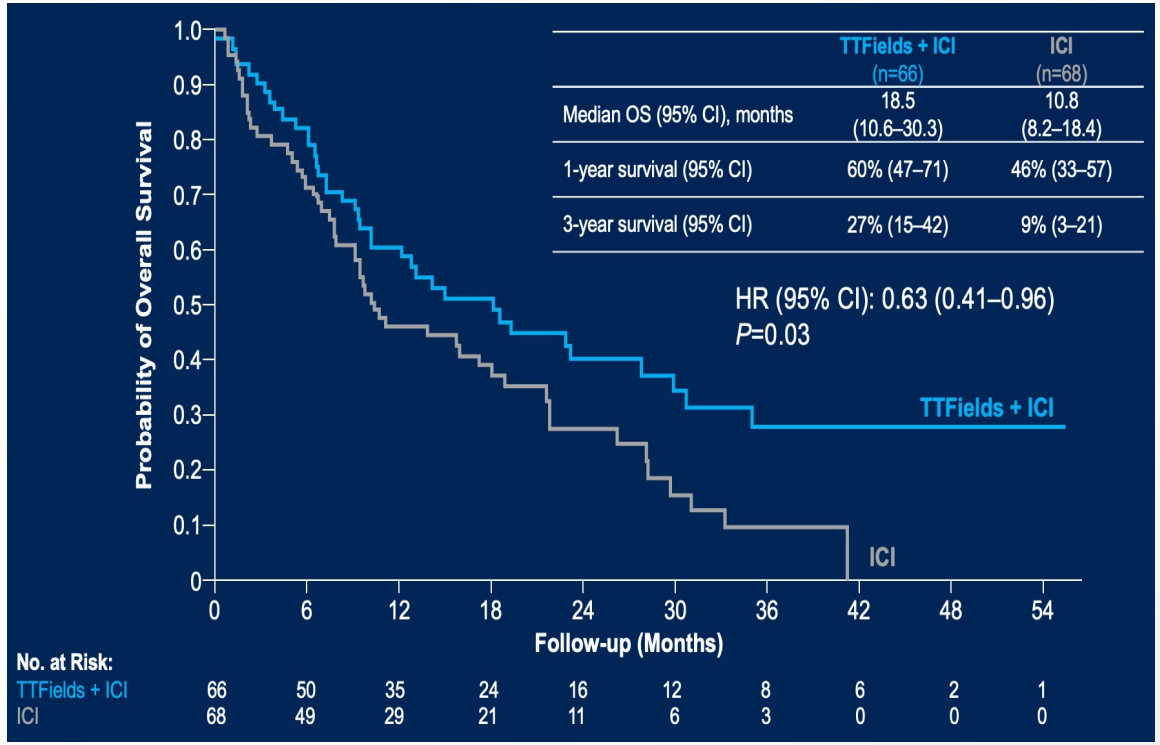
LUNAR: Efficacy

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)

Overall Survival in the ICI Population



	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)

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

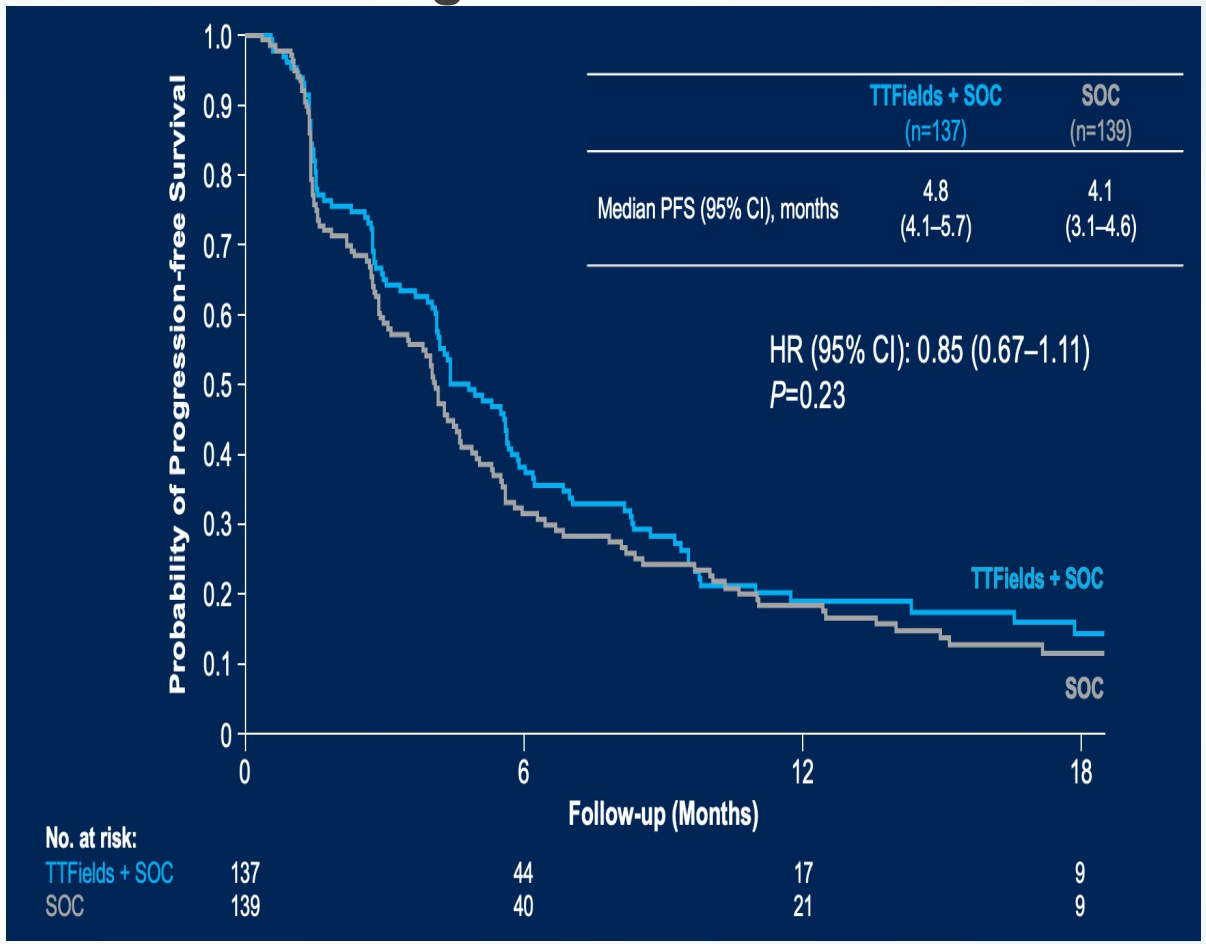
Leal et al Lancet Oncol 2023

LUNAR: Efficacy

Response rate

	TTFields + SOC (n=137)	SOC (n=139)
Patients with a follow-up scan	n=122	n=127
ORR, % (95% CI)	20% (14–28)	17% (11–25)
Difference in ORR, % (95% CI)	3% (-8.5–15.0) *P*=0.5	
Best overall response, %		
Complete response	3%	1%
Partial response	18%	17%
Stable disease	49%	47%
Progressive disease	18%	26%
Not evaluable	2%	1%

Progression-free survival

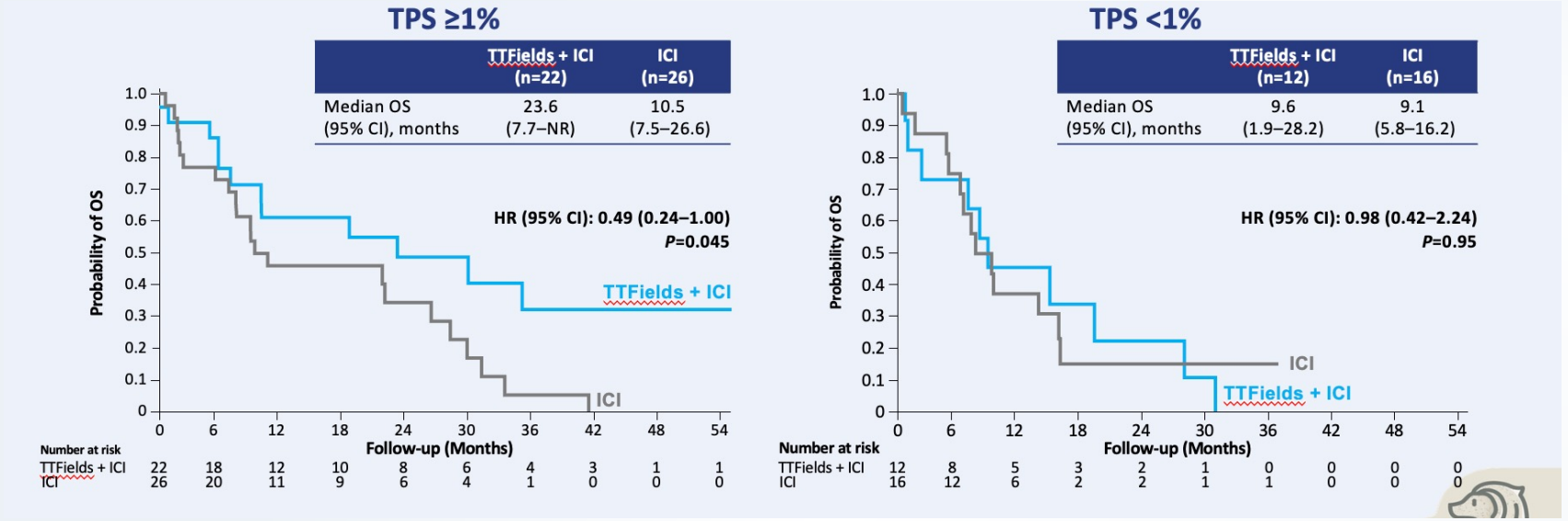


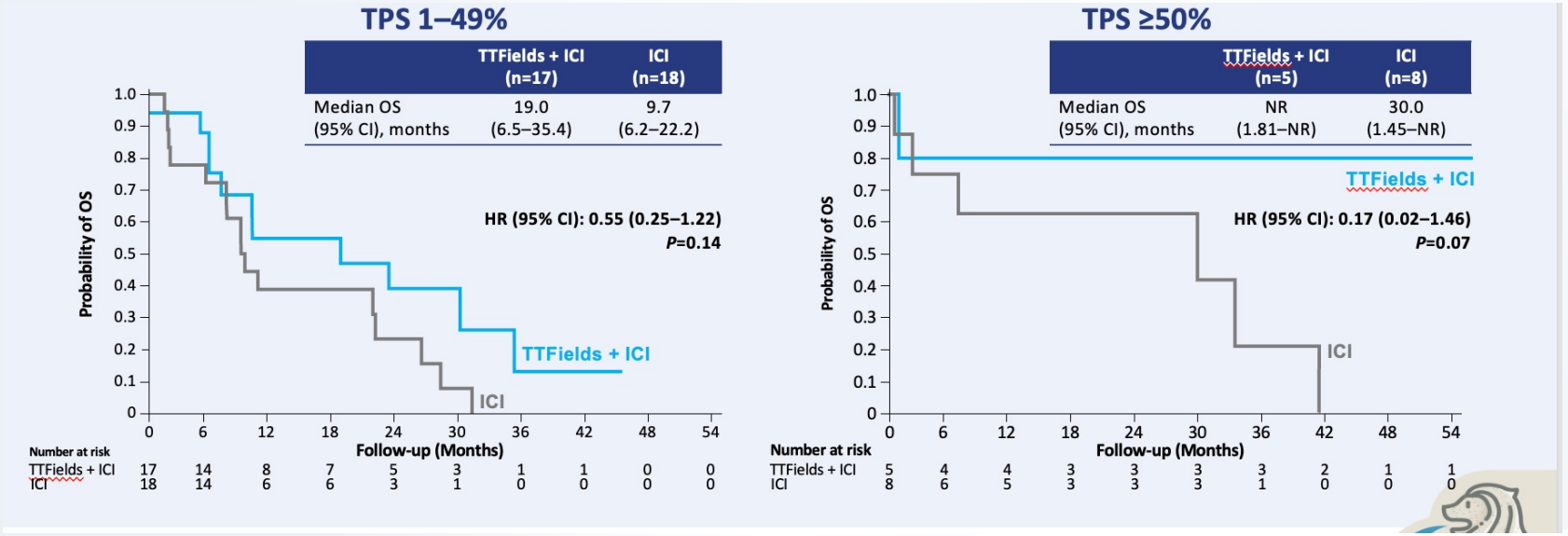
	TTFields + SOC (n=137)	SOC (n=139)
Median PFS (95% CI), months	4.8 (4.1–5.7)	4.1 (3.1–4.6)

- All 5 complete responses occurred in patients receiving an ICI
  - 4 with TTFields therapy
  - 1 with ICI alone

Leal et al Lancet Oncol 2023

OS in the ICI Subgroup by PD-L1 Tumor Expression





LUNAR: Safety

	TTFields + SOC (n=133)		SOC (n=134)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE*	97%	59%	91%	56%
Most frequent AEs				
Dermatitis	**43%**	**2%**	**2%**	**0%**
Fatigue	28%	4%	37%	8%
Musculoskeletal pain	36%	3%	27%	4%
Dyspnea	20%	7%	25%	3%
Anemia	23%	8%	22%	8%
Diarrhea	19%	2%	19%	0%
Cough	18%	0%	19%	1%
Nausea	19%	0%	16%	1%
Leukopenia	17%	14%	18%	14%
Pneumonia	15%	11%	17%	11%
Alopecia	10%	0%	17%	1%
Respiratory tract infection	15%	3%	16%	0%
Localized edema	15%	1%	16%	2%
Any serious AE	53%		38%	
Any AE leading to discontinuation	36%		20%	
Any AE leading to death	10%		8%	

TTFields Adverse Device Effects (ADEs)

Preferred term	TTFields + ICI (n=67)	TTFields + DTX (n=66)
Any ADE*	73.1%	69.7%
ADEs grade ≥3	4.5%	7.6%
Dermatitis	1.5%	3.0%
Pruritus	0	1.5%
Skin ulcer	0	1.5%
Pain	1.5%	0%
Skin infection	0	1.5%
Bronchopleural fistula	1.5%	0%
Serious ADEs	1.5%	4.5%
Dermatitis	0	3.0%
Skin ulcer	0	1.5%
Skin infection	0	1.5%
Bronchopleural fistula	1.5%	0
ADEs leading to device discontinuation	11.9%	16.7%
Dermatitis	6.0%	7.6%
Skin ulcer	3.0%	3.0%
Rash	0	3.0%
Pain	1.5%	1.5%
Maculopapular rash	0	1.5%
Skin infection	0	1.5%
Bronchopleural fistula	1.5%	0
ADEs leading to death	0	0

Leal et al Lancet Oncol 2023

FDA approval October 15, 2024

- FDA Approved Tumor Treating Fields for the Treatment of Metastatic Non-Small Cell Lung Cancer

- For use concurrently with PD-1/PD-L1 inhibitors or docetaxel in adult patients with metastatic NSCLC who progressed on or after a platinum-based regimen

Conclusions

- Immune-based and targeted therapies have led to improved survival in NSCLC
- Frontline ICI is a part of most therapies for advanced NSCLC without actionable alterations and improved survival with long-term benefits for some
- Movement of ICI therapy to earlier stages increases the need for therapies following the development of resistance
- Few options are approved in the second-line setting
- OS benefit was seen with ramucirumab and pembrolizumab
- Trop2 ADCs may provide another option for patients
- TTF approved in combination with ICI or docetaxel
- Novel therapies with biomarkers for selection are needed to improve outcomes

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