

III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

ANTI-TROP2

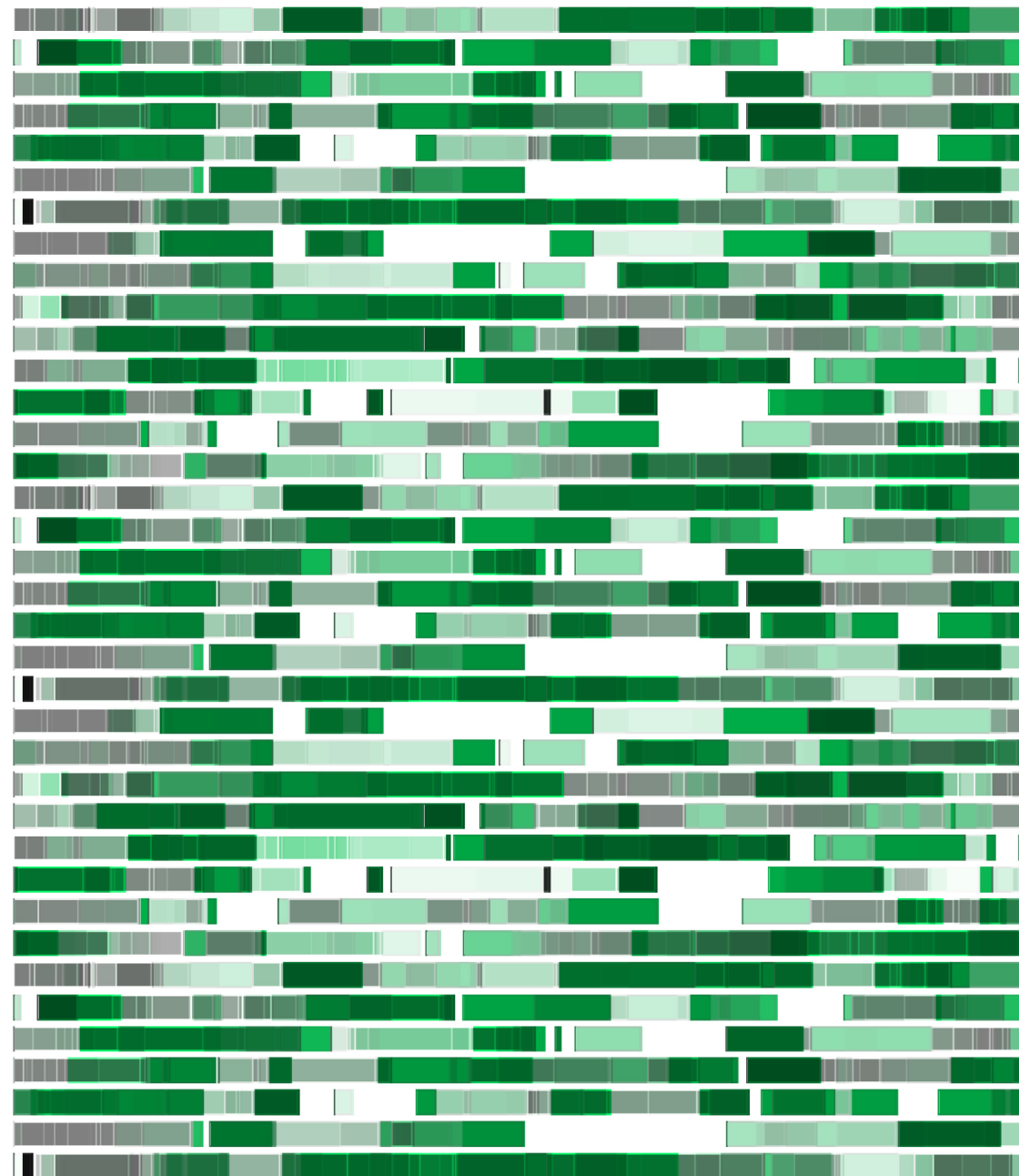
NUEVA POSIBILIDAD EN EL TRATAMIENTO DEL CÁNCER
DE PULMÓN

David Vicente Baz

Hospital Universitario Virgen Macarena. Sevilla

Organizador por:

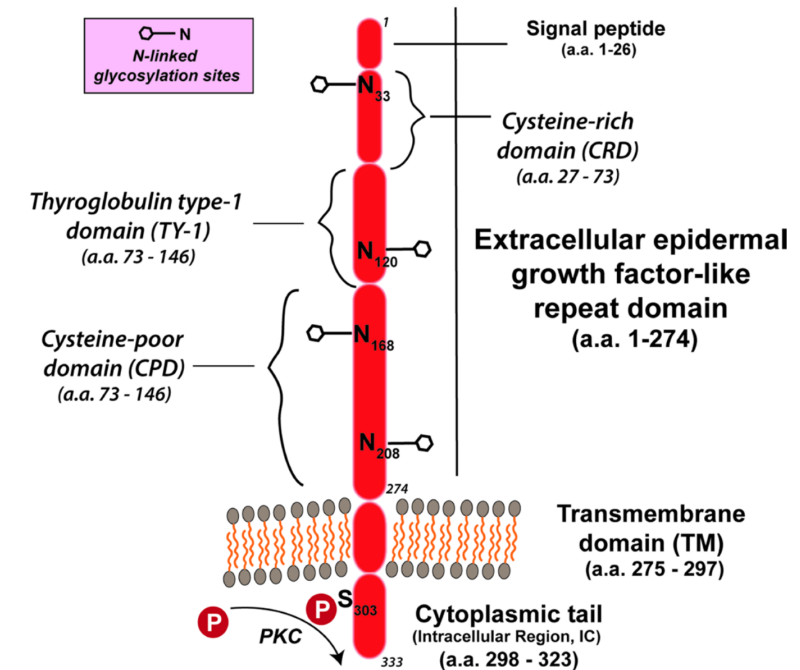
HENDERE HEALTHCARE





TROP-2 UNSELECTED BIOMARKER. LUNG CANCER

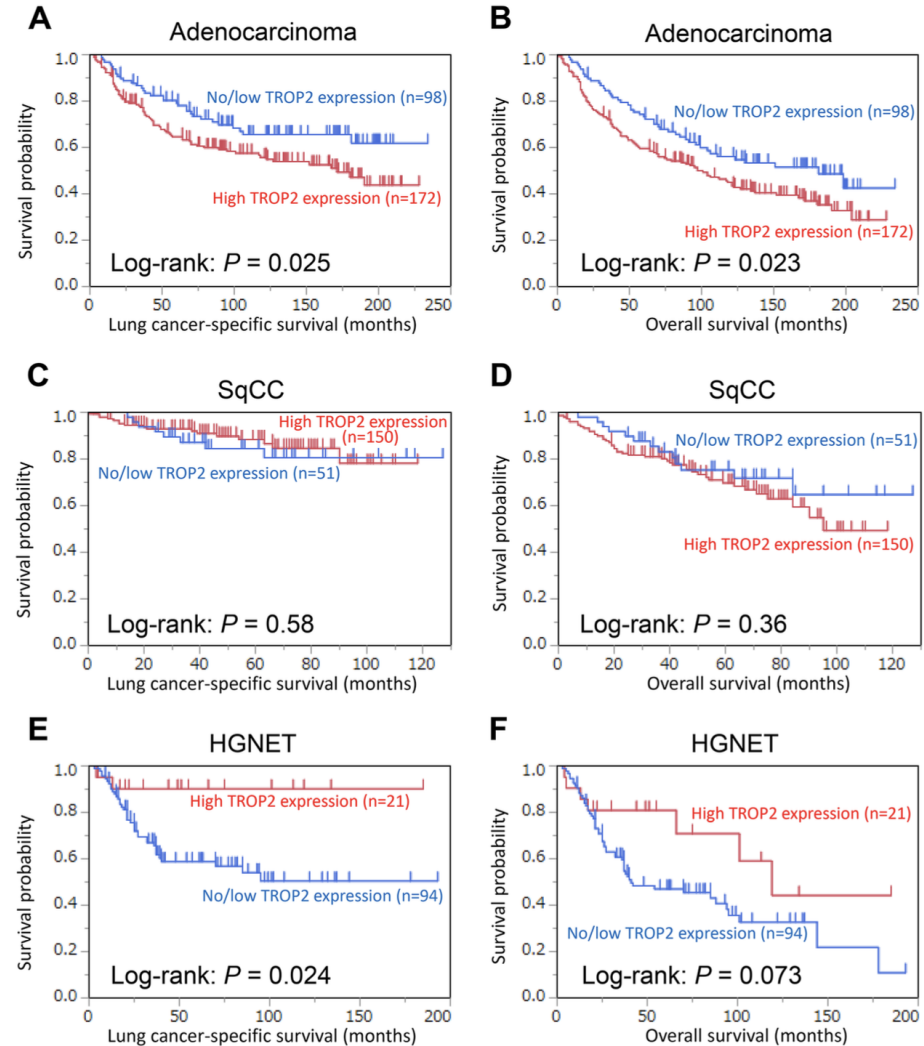
- The efficacy of TROP-2 ADC appears unrelated to TROP-2 expression
- Outcomes have also been less encouraging than other tumours
 - Differences in internalization efficiency
 - Lysosomal proteases
 - Sensitivity off cancer cells to payload
 - Unkown





TROP-2 UNSELECTED BIOMARKER. LUNG CANCER

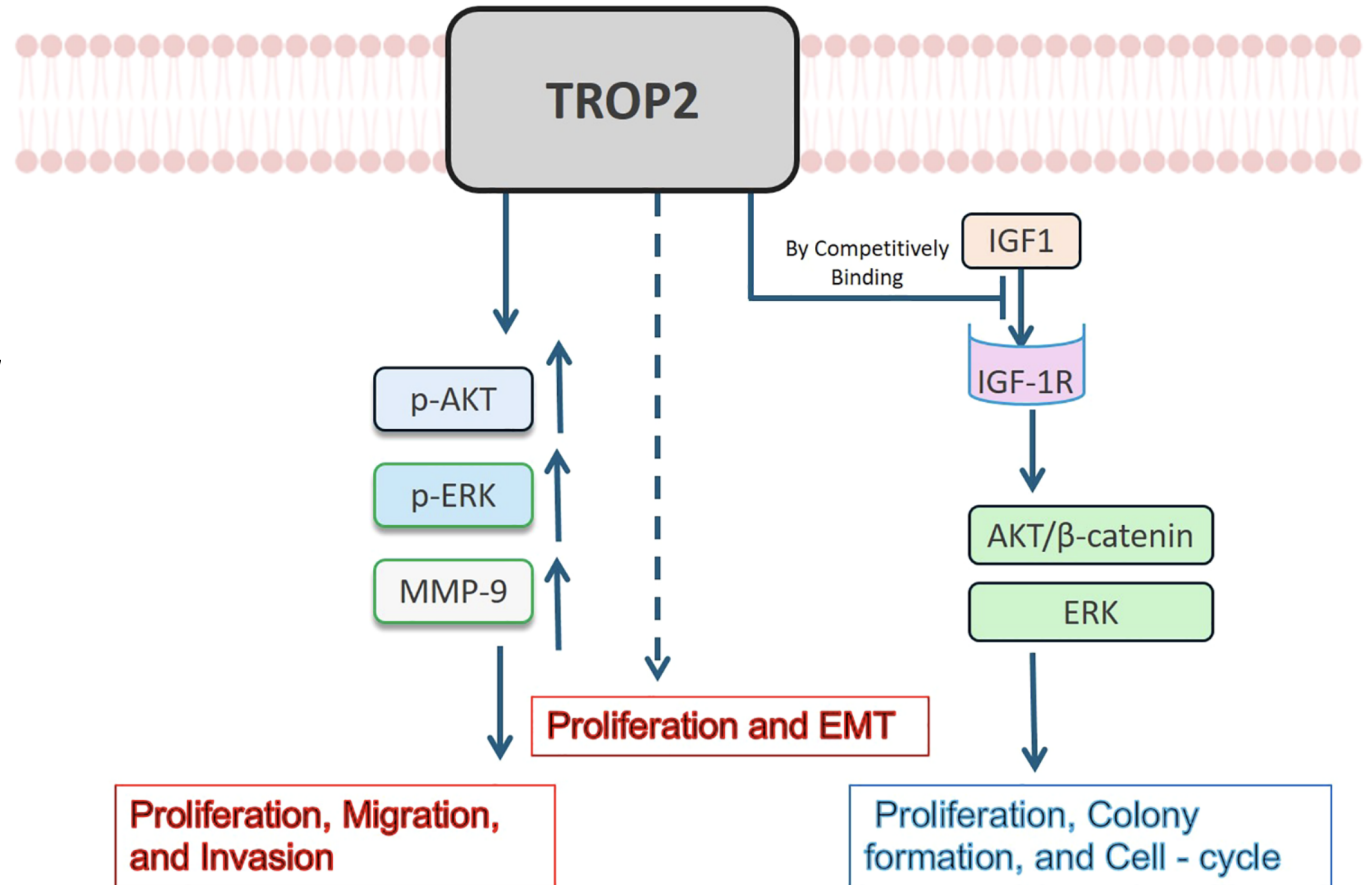
Association of tumour TROP-2 expression with prognosis varies among lung cancer subtypes





TROP-2 BIOLOGICAL EFFECTS IN LUNG CANCER

The exact function in the regulation of cancer progression might be organ and cancer type dependent



Zheng WP. Front Oncol 2020;10:1304529

Lin JC. Oncotarget 2017;8:28725-3

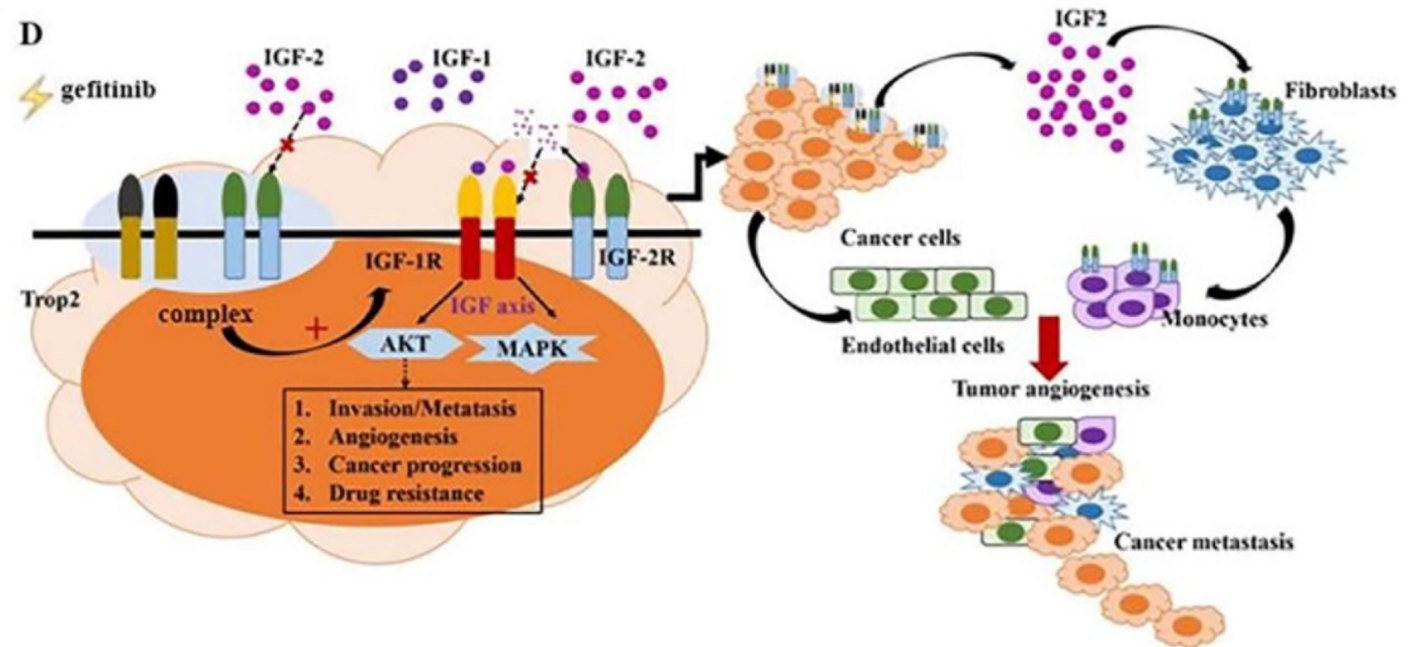
Liu R. Front Oncol 2025,15:1638054



TROP-2 BINDING IGF2R INDUCES GEFITINIB RESISTANCE

TROP2 physically interacted with IGF2R

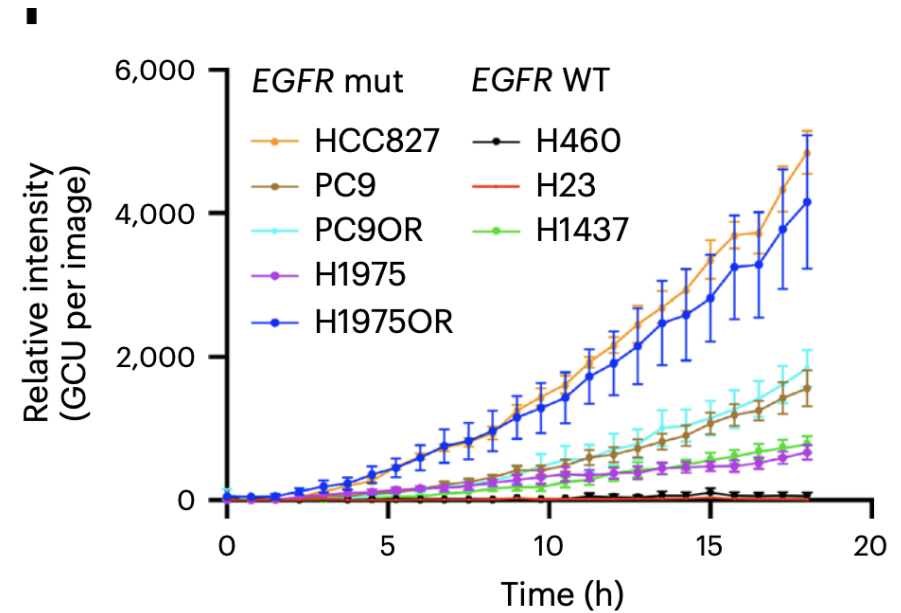
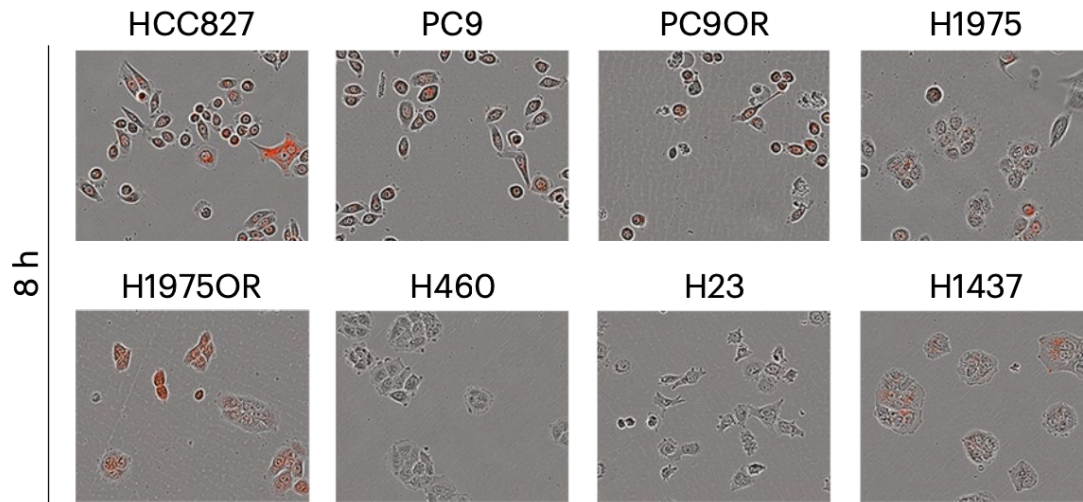
TROP2 increased the IGF2-IGF1R-Akt axis to promote EGFR-TKI resistance and remodeling the TME





SACITUZUMAB TIRUMOTECAN

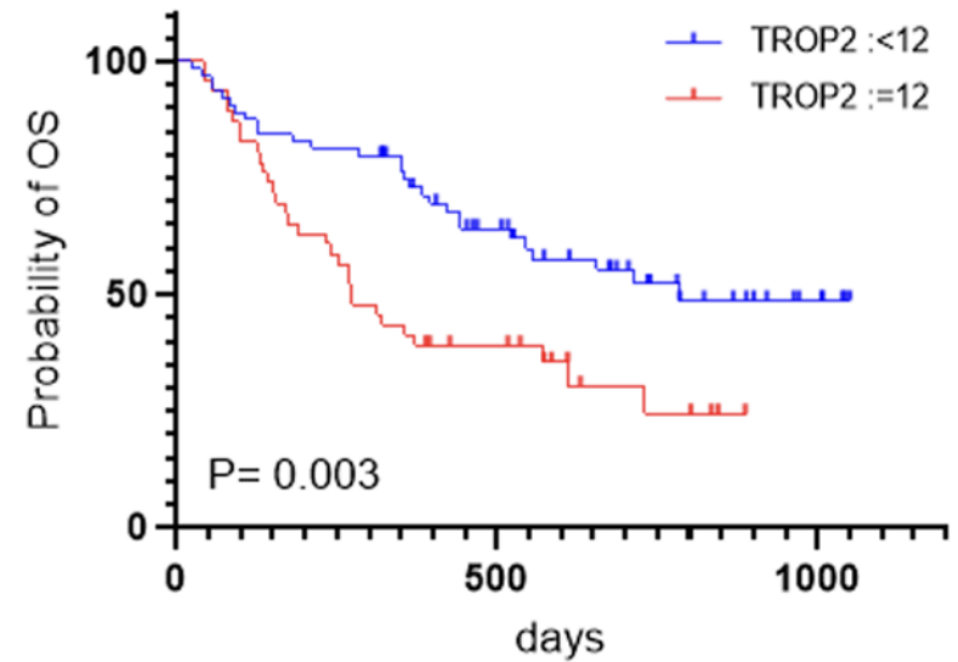
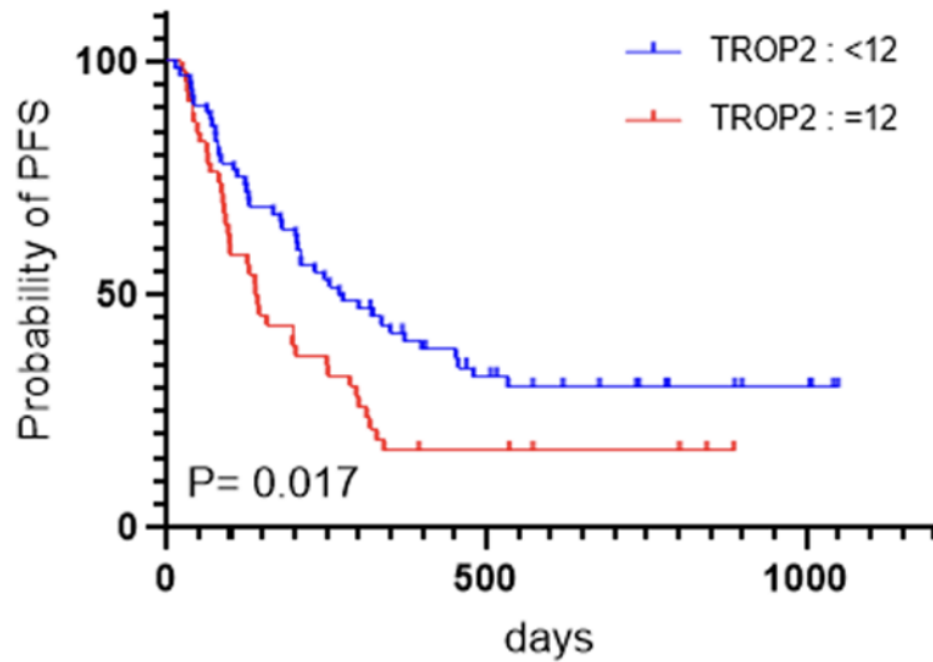
The presence of EGFR-activating mutations increases the internalization and activity of sac-TMT





PROGNOSTIC RELEVANCE OF TROP2 EXPRESIÓN IN PATIENTS WITH NSCLC RECEIVING IMMUNOTHERAPY

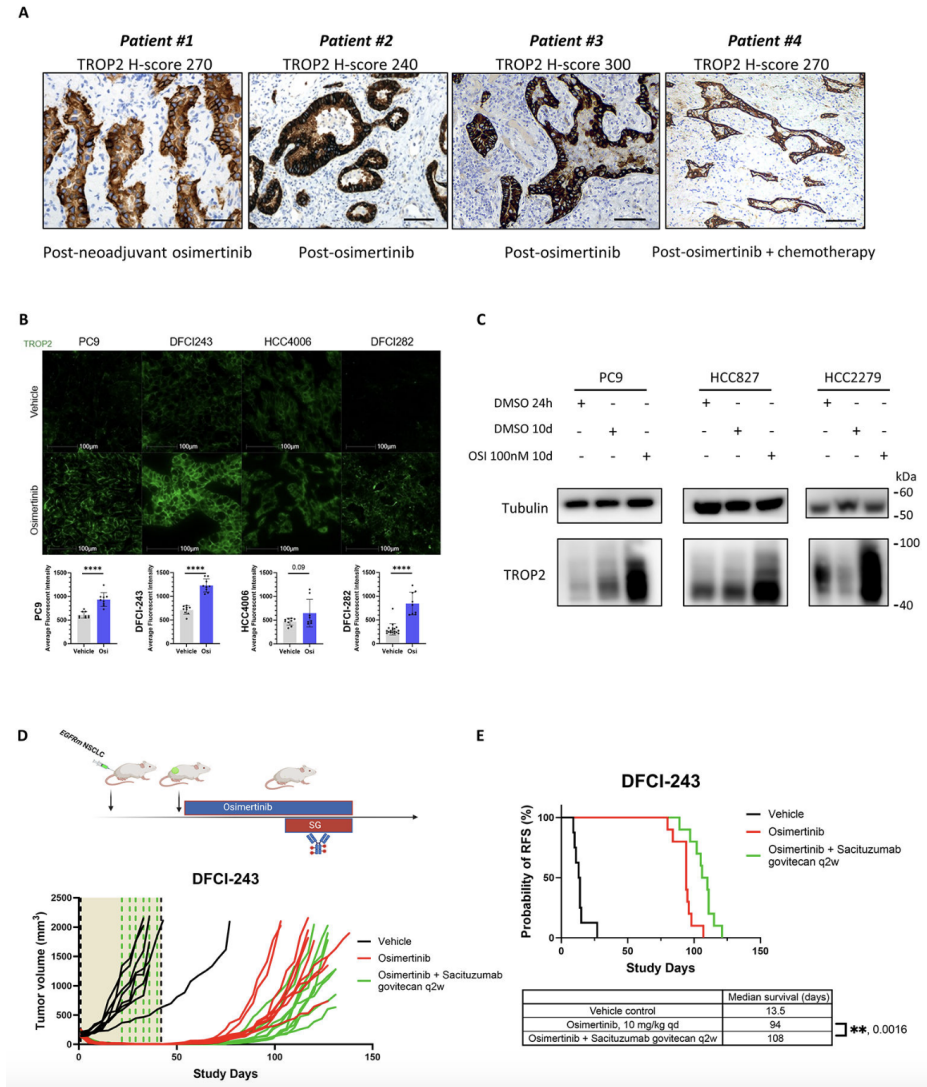
TROP2 overexpression as an independent prognostic predictor for PFS and OS





CELL THERAPY TO ELIMINATED EGFR DRUG TOLERANT PERSISTER CELLS

Residual tumor cells express high level of TROP2

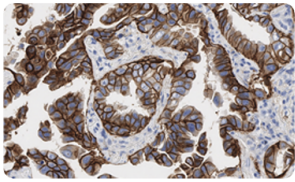





TROP 2 NORMALIZED MEMBRANE RATIO (NMR) MEASURED BY QUANTITATIVE CONTINUOUS SCORING

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

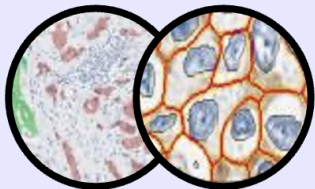
1 **IHC with TROP2 Assay**



2 **Whole Slide Imaging**



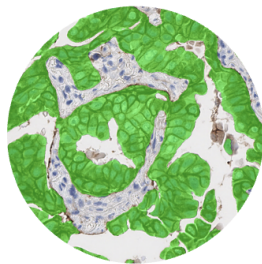
3 **Automated Image Analysis (QCS)**



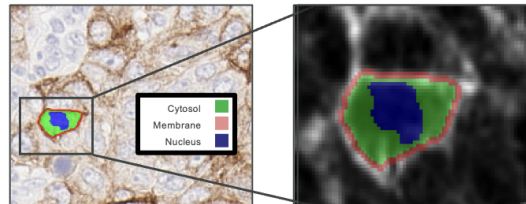
4 **Patient Biomarker Status Determination**

- +** $\geq 75\%$ of tumor cells with TROP2 NMR ≤ 0.56
- $< 75\%$ of tumor cells with TROP2 NMR $\leq 0.56^*$

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

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

Lower NMR \rightarrow higher cytoplasm proportion



SELECTED LATE-STAGE TRIALS OF ANTI-TROP2 ADCS

	Sacituzumab Govitecan	Sacituzumab Tirumotecan	Datopotamab Deruxtecan
3rd line TNBC	Ascent	OptiTROP-Breast01	NA
	Approved in US	Approved in China	
3rd-line (post-TKI) NSCLC	NA	OptiTROP-Lung03	Tropion-Lung05
		Filed in China	Filed in US
2nd-line NSCLC	EVOKE-01	OptiTROP-Lung04 (EGFRm postTKI)	Tropion-Lung01
	US filing plan abandoned	Filed in China	US filling withdrawn

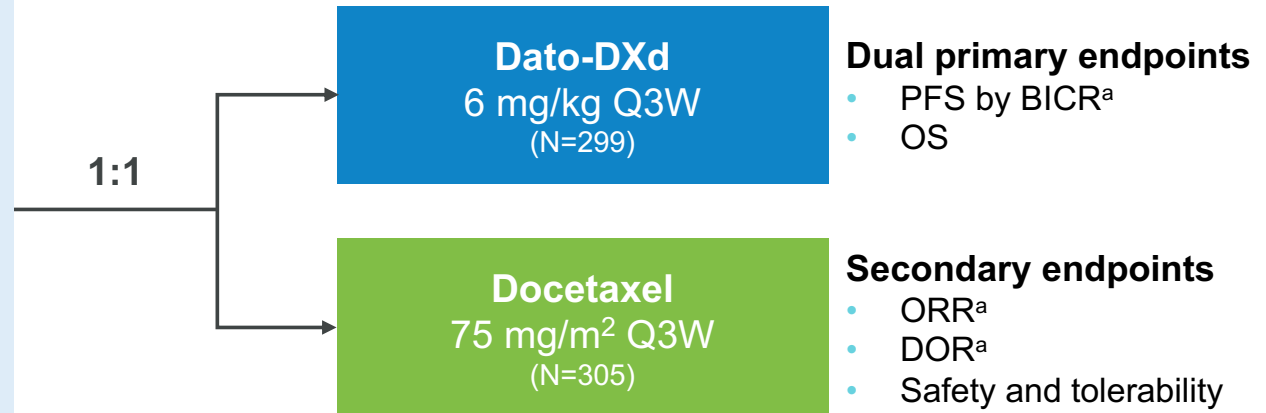


Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

- NSCLC (stage IIIB, IIIC, or IV)
 - ECOG PS of 0–1
 - No prior docetaxel
- Without actionable genomic alterations**
- One to two prior lines, including platinum-based CT and anti-PD-(L)1 mAb therapy
- With actionable genomic alterations**
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
 - One to two prior approved targeted therapies + platinum-based CT, and ≤ 1 anti-PD-(L)1 mAb



Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,^b anti-PD-(L)1 mAb included in most recent prior therapy, and geography^c

Statistical considerations: Study is deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was $\alpha=0.045$

^aEvaluated per RECIST v1.1. ^bPresence vs absence. ^cUnited States/Japan/Western Europe vs rest of world.

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; kg, kilogram; m, meter; mAb, monoclonal antibody; mg, milligram; *MET*, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study

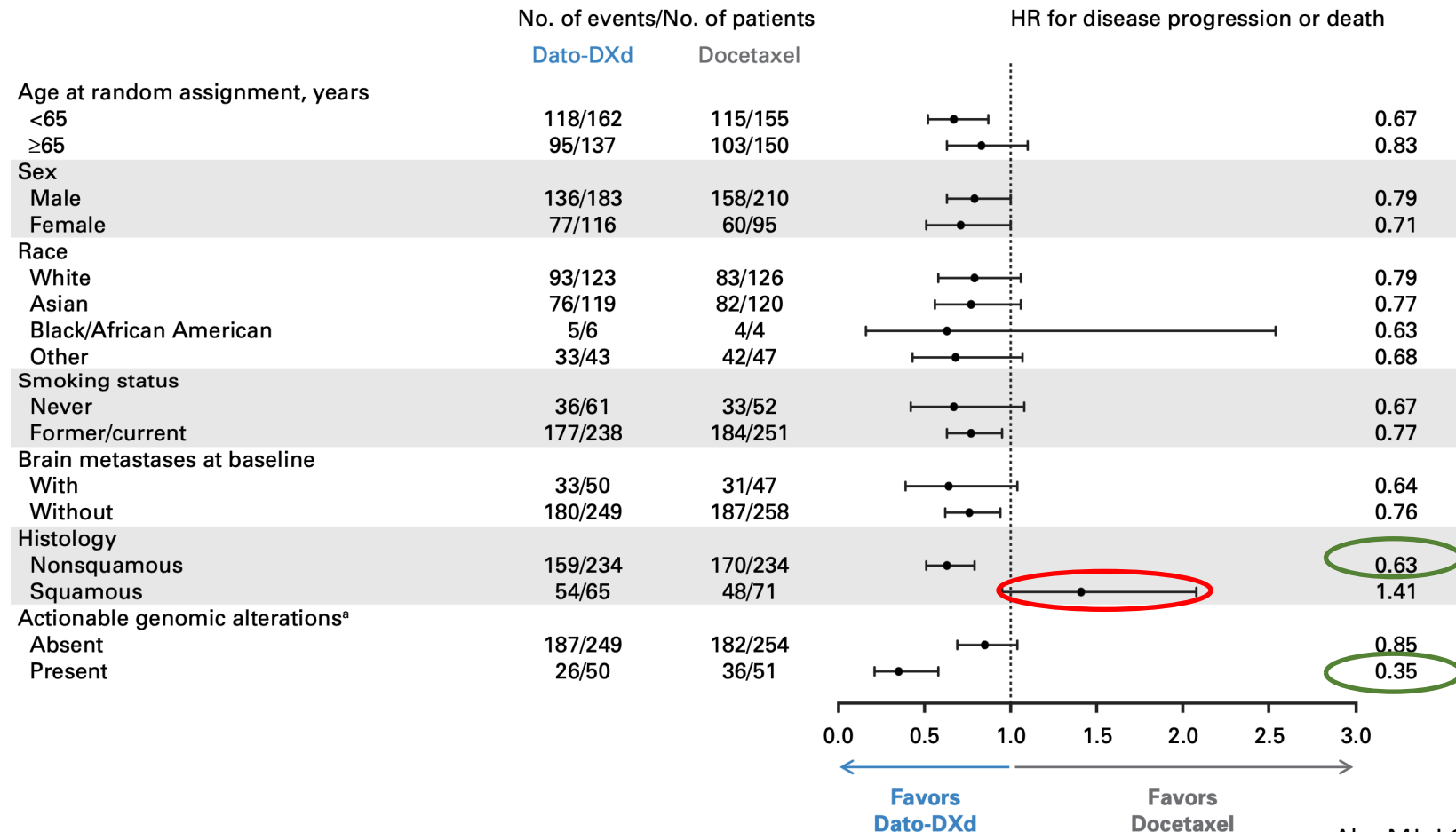
Myung-Ju Ahn, MD, PhD¹; Kentaro Tanaka, MD, PhD²; Luis Paz-Ares, MD, PhD³; Robin Cornelissen, MD, PhD⁴; Nicolas Girard, MD, PhD⁵; Elvire Pons-Tostivint, MD, PhD⁶; David Vicente Baz, MD⁷; Shunichi Sugawara, MD, PhD⁸; Manuel Cobo, MD, PhD⁹; Maurice Pérol, MD¹⁰; Céline Mascoux, MD, PhD¹¹; Elena Poddubskaya, MD¹²; Satoru Kitazono, MD, PhD¹³; Hidetoshi Hayashi, MD, PhD¹⁴; Min Hee Hong, MD¹⁵; Enriqueta Felip, MD¹⁶; Richard Hall, MD¹⁷; Oscar Juan-Vidal, MD, PhD¹⁸; Daniel Brungs, MBBS¹⁹; Shun Lu, MD, PhD²⁰; Marina Garassino, MD²¹; Michael Chargualaf, PharmD²²; Yong Zhang, MSc²³; Paul Howarth, MD²⁴; Deise Uema, MD²⁵; Aaron Lisberg, MD²⁶; and Jacob Sands, MD²⁷; for the TROPION-Lung01 Trial Investigators



TROPION LUNG 01

Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study

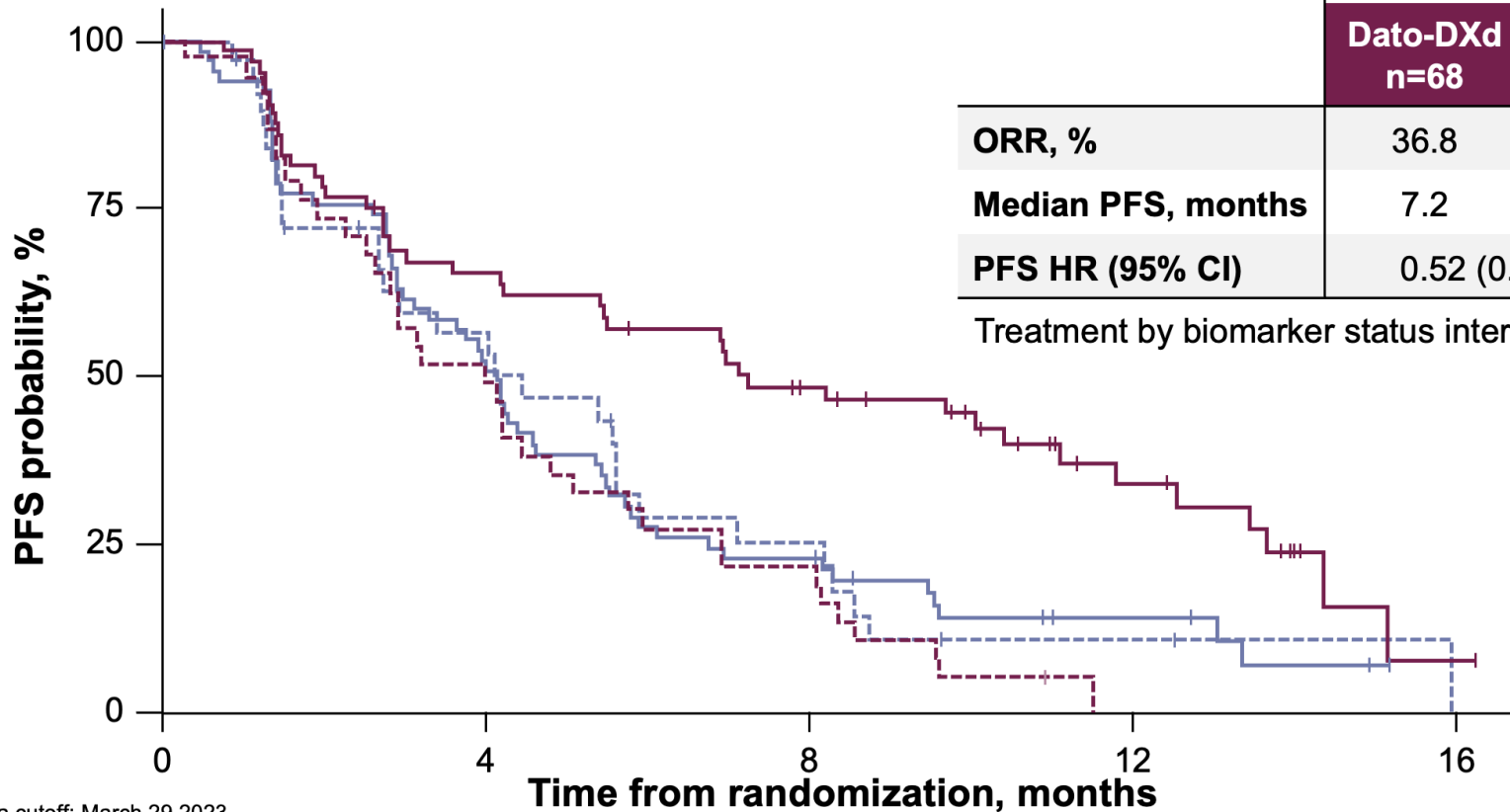
Myung-Ju Ahn, MD, PhD¹; Kentaro Tanaka, MD, PhD²; Luis Paz-Ares, MD, PhD³; Robin Cornelissen, MD, PhD⁴; Nicolas Girard, MD, PhD⁵; Elvire Pons-Tostivint, MD, PhD⁶; David Vicente Baz, MD⁷; Shunichi Sugawara, MD, PhD⁸; Manuel Cobo, MD, PhD⁹; Maurice Pérol, MD¹⁰; Céline Masciaux, MD, PhD¹¹; Elena Poddubskaya, MD¹²; Satoru Kitazono, MD, PhD¹³; Hidetoshi Hayashi, MD, PhD¹⁴; Min Hee Hong, MD¹⁵; Enriqueta Felip, MD¹⁶; Richard Hall, MD¹⁷; Oscar Juan-Vidal, MD, PhD¹⁸; Daniel Brungs, MBBS¹⁹; Shun Lu, MD, PhD²⁰; Marina Garassino, MD²¹; Michael Chargualaf, PharmD²²; Yong Zhang, MSc²³; Paul Howarth, MD²⁴; Deise Uema, MD²⁵; Aaron Lisberg, MD²⁶; and Jacob Sands, MD²⁷; for the TROPION-Lung01 Trial Investigators





TROPION LUNGO1 NON-SQUAMOUS/NON-AGA EFFICACY BY TROP2 QCS-NMR STATUS

NSQ/non-AGA BEP, n=221



	TROP2 QCS-NMR+		TROP2 QCS-NMR-	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

Data cutoff: March 29 2023

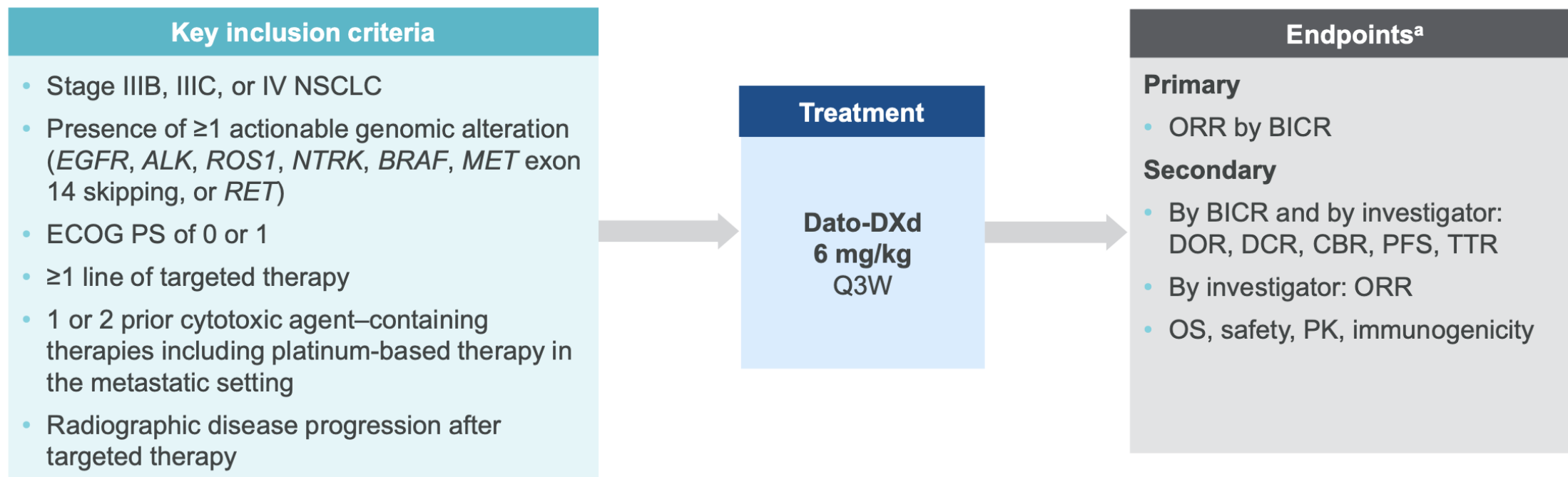
PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.40 [0.25-0.64]; Docetaxel: 0.94 [0.60-1.49]

AGA, actionable genomic alterations; BEP, biomarker evaluable population; Dato-DXd, datopotamab deruxtecán; HR, hazard ratio; NMR, normalized membrane ratio; NSQ, non-squamous; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; SQ, squamous; TROP2, trophoblast cell-surface antigen 2.



TROPION-Lung05: Phase 2 Study

TROPION-Lung05 ([NCT04484142](https://clinicaltrials.gov/ct2/show/study/NCT04484142)) is a **phase 2**, single-arm, open-label study in heavily pretreated patients **with advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy





TROPION LUNG 05

Datopotamab Deruxtecan in Advanced or Metastatic Non-Small Cell Lung Cancer With Actionable Genomic Alterations: Results From the Phase II TROPION-Lung05 Study

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Variable	Overall (N = 137)	EGFR Mutations (n = 78)
Confirmed ORR, No. (%)	49 (35.8)	34 (43.6)
95% CI ^a	27.8 to 44.4	32.4 to 55.3
CR, No. (%)	4 (2.9)	4 (5.1)
PR, No. (%)	45 (32.8)	30 (38.5)
SD, No. (%)	56 (40.9)	27 (34.6)
PD, No. (%)	19 (13.9)	10 (12.8)
Non-CR/non-PD, No. (%)	3 (2.2)	3 (3.8)
NE for BOR, No. (%)	10 (7.3)	4 (5.1)
DCR, No. (%)	108 (78.8)	64 (82.1)
95% CI ^a	71.0 to 85.3	71.7 to 89.8
DOR, months, median	7.0	7.0
95% CI ^b	4.2 to 9.8	4.2 to 10.2
CBR, No. (%)	64 (46.7)	42 (53.8)
95% CI ^b	38.1 to 55.4	42.2 to 65.2
Time to response, months, median	1.5	1.5
Range	1.1-11.3	1.2-11.3
PFS, months, median ^b	5.4	5.8
95% CI ^b	4.7 to 7.0	5.4 to 8.3

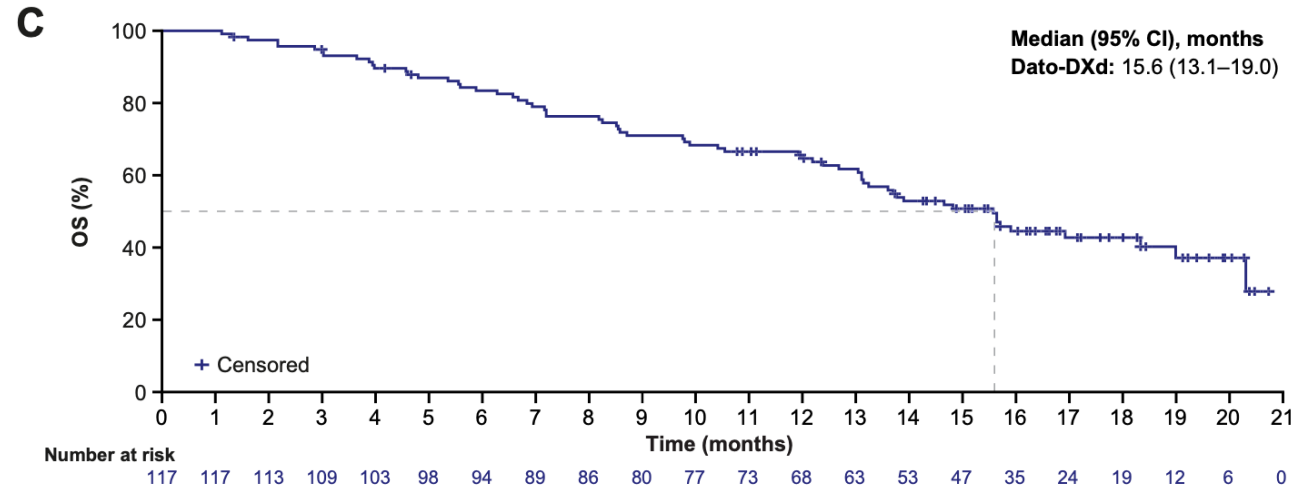
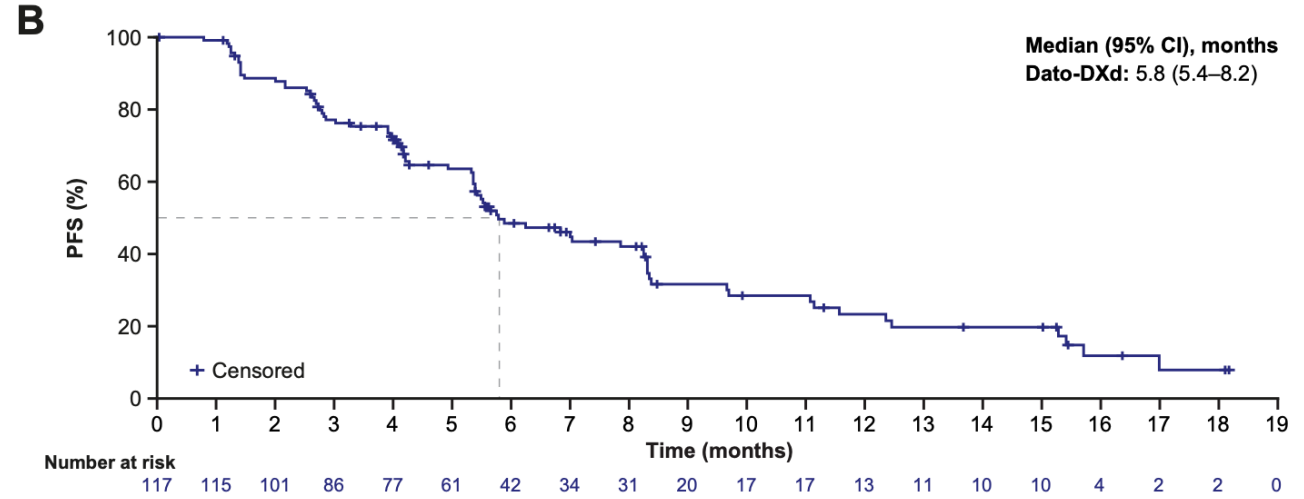
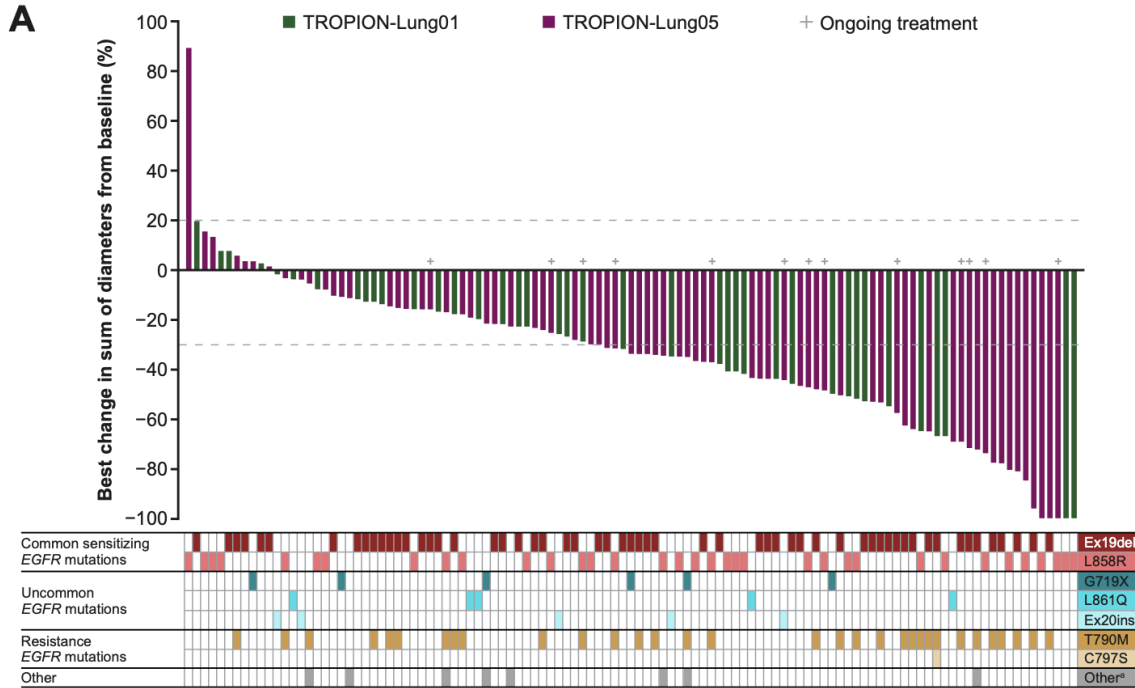


A Pooled Analysis of Datoipotamab Deruxtecan in Patients With EGFR-Mutated NSCLC

Check for updates

Myung-Ju Ahn, MD, PhD,^{a,†} Aaron Lisberg, MD,^b Yasushi Goto, MD, PhD,^c
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Jong-Seok Lee, MD, PhD,ⁿ Rebecca S. Heist, MD, PhD,^o Robin Cornelissen, MD, PhD,^p
Wen-Cheng Chang, MD,^q Dariusz Kowalski, MD, PhD,^r Hong Zebger-Gong, MD, PhD,^s
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Paul Howarth, MD,^w Richard Joseph, MD,^x Isamu Okamoto, MD, PhD^y

POOLED ANALYSIS





POOLED ANALYSIS

Table 2. Exploratory Efficacy Outcomes in *EGFR*-Mutated Patient Subsets From TROPION-Lung05 and TROPION-Lung01

Efficacy Outcome	<i>EGFR</i> m Pool	TROPION-Lung05	TROPION-Lung01	
	Dato-DXd (N = 117)	Dato-DXd (n = 78)	Dato-DXd (n = 39)	Docetaxel (n = 45)
Confirmed ORR, ^{a,b} % (95% CI)	43 (34-52)	44 (32-55)	41 (26-58)	9 (3-21)
Best overall response, n (%)				
CR	5 (4)	4 (5)	1 (3)	0
PR	45 (38)	30 (38)	15 (38)	4 (9)
SD	48 (41)	27 (35)	21 (54)	18 (40)
Non-CR or non-PD	3 (3)	3 (4)	0	0
PD	12 (10)	10 (13)	2 (5)	10 (22)
NE	4 (3)	4 (5)	0	13 (29)
Median DOR, ^a mo (95% CI)	7.0 (4.2-9.8)	7.0 (4.2-10.2)	6.9 (2.9-NE)	NE (3.6-NE)
DCR, ^{a,c} % (95% CI)	86 (79-92)	82 (72-90)	95 (83-99)	49 (34-64)
Median PFS, ^a mo (95% CI)	5.8 (5.4-8.2)	5.8 (5.4-8.3)	6.8 (4.2-8.2)	2.7 (1.5-4.4)
Median OS, mo (95% CI)	15.6 (13.1-19.0)	18.3 (12.4-NE)	15.6 (12.0-16.9)	12.8 (6.9-17.2)

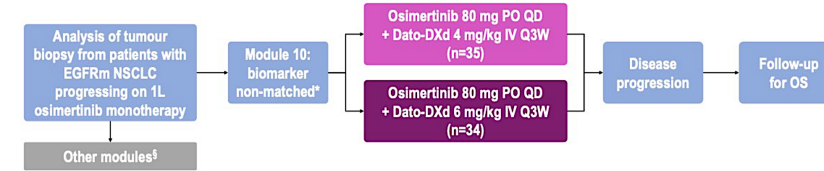


	OptiTROP-Lung04	OptiTROP-Lung03	Pooled TL05/TL01
	Phase 3 (N=376)¹	Phase 2 (N=137)³	Pts from Phase 2 & 3 (N=117)^{3,4}
	vs PBC	vs TXT	After TKI and PBC
Patient population	188 in SAC-TMT arm	91 in Sac-TMT	117
Setting	≥1 EGFR TKI	≥1 EGFR TKI and PBC	1 PBC and 1–2L EGFR TKI
mPFS, months (95% CI)	8,3 (6,7 – 9,9) HR 0,49	6.9 (5.4, 8.2) HR 0,30 p < 0,0001	5.8 (5.4, 8.2)
mOS, months (95% CI)	NR (21,5 – NE) HR 0,60 p = 0,0006	NR (NE, NE) HR 0,49 p = 0,0070	15.6 (13.1, 19.0)
ORR, % (95% CI)	60,6 (53.3 – 67,7)	45.1 (34.6, 55.8)	43.0 (34.0, 52.0)
mDOR, months (95% CI)	8,3 (6,2 – 10,0)	7.0 (5.4, 9.1)	7.0 (4.2, 9.8)



ORCHARD

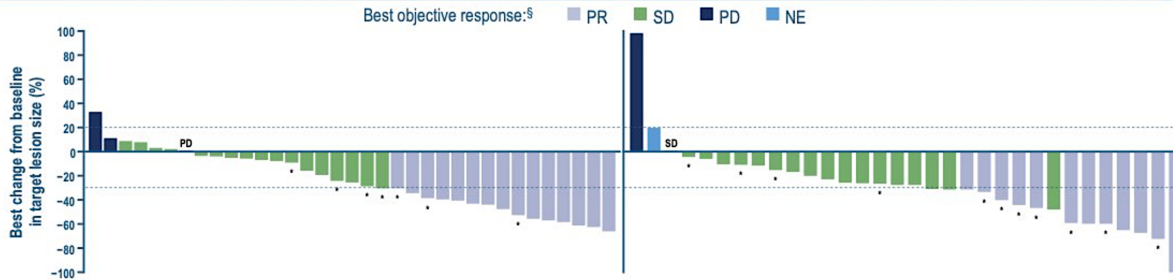
ORCHARD module 10 study design



- **Primary endpoint:** ORR based on RECIST v1.1 by investigator assessment
- **Key secondary endpoints:** PFS[§], DoR[§], OS, AEs, SAEs

ORR was similar between the two cohorts

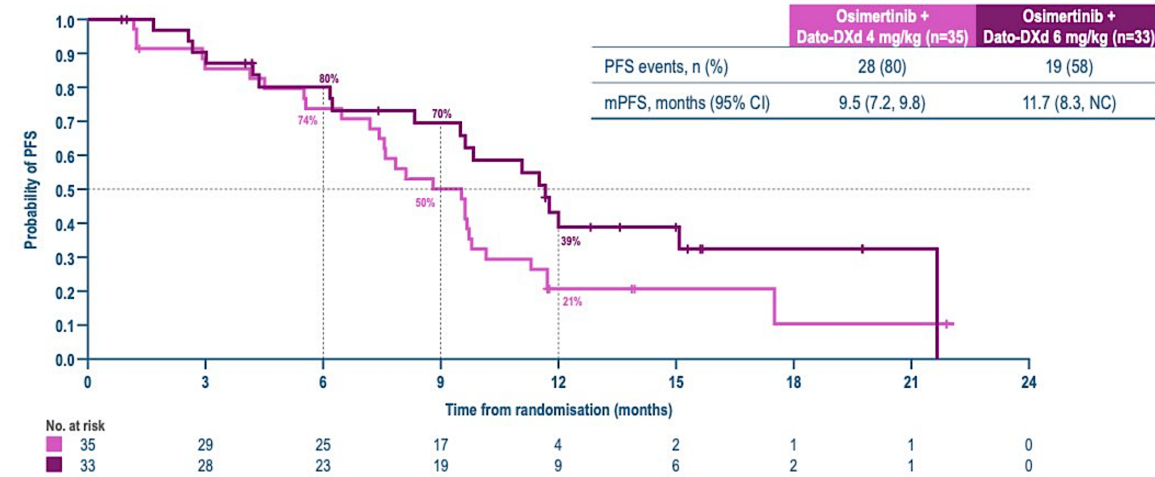
	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
ORR, % (80% CI)	43 (31, 55)	36 (25, 49)
Median time to onset of response, months (Q1, Q3)	2.7 (1.5, 4.1)	1.4 (1.2, 2.1)

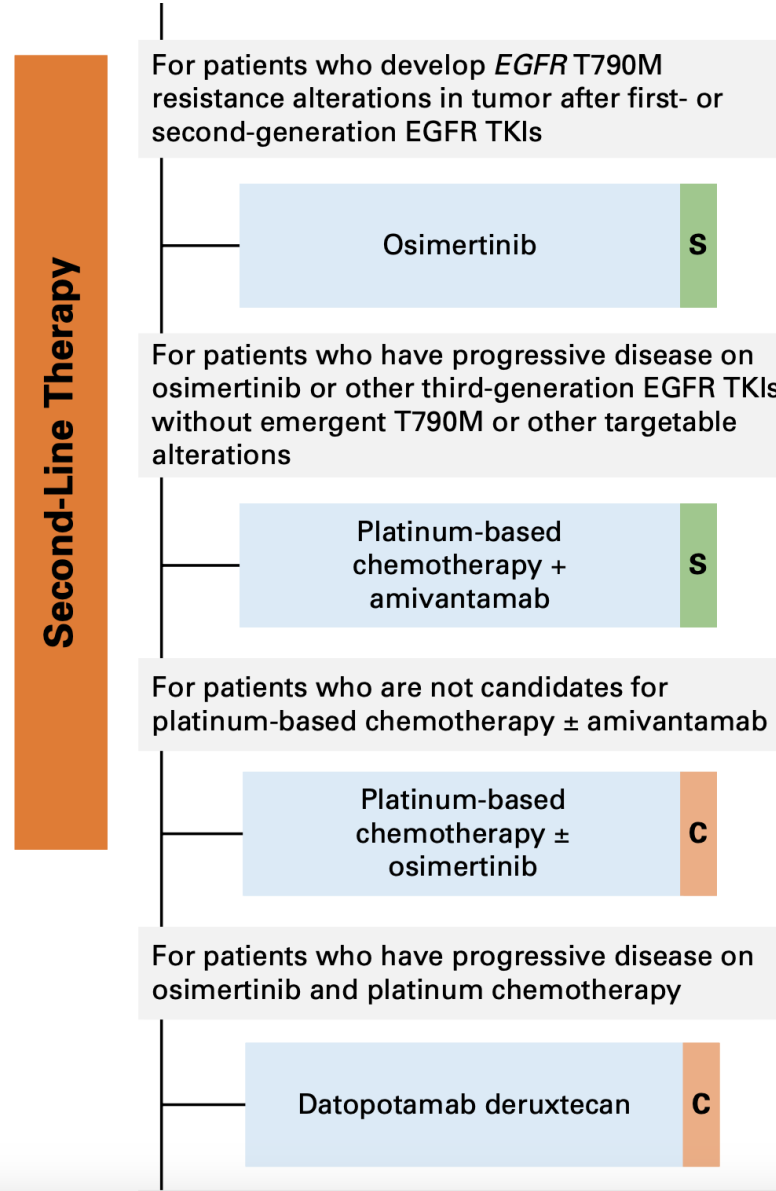
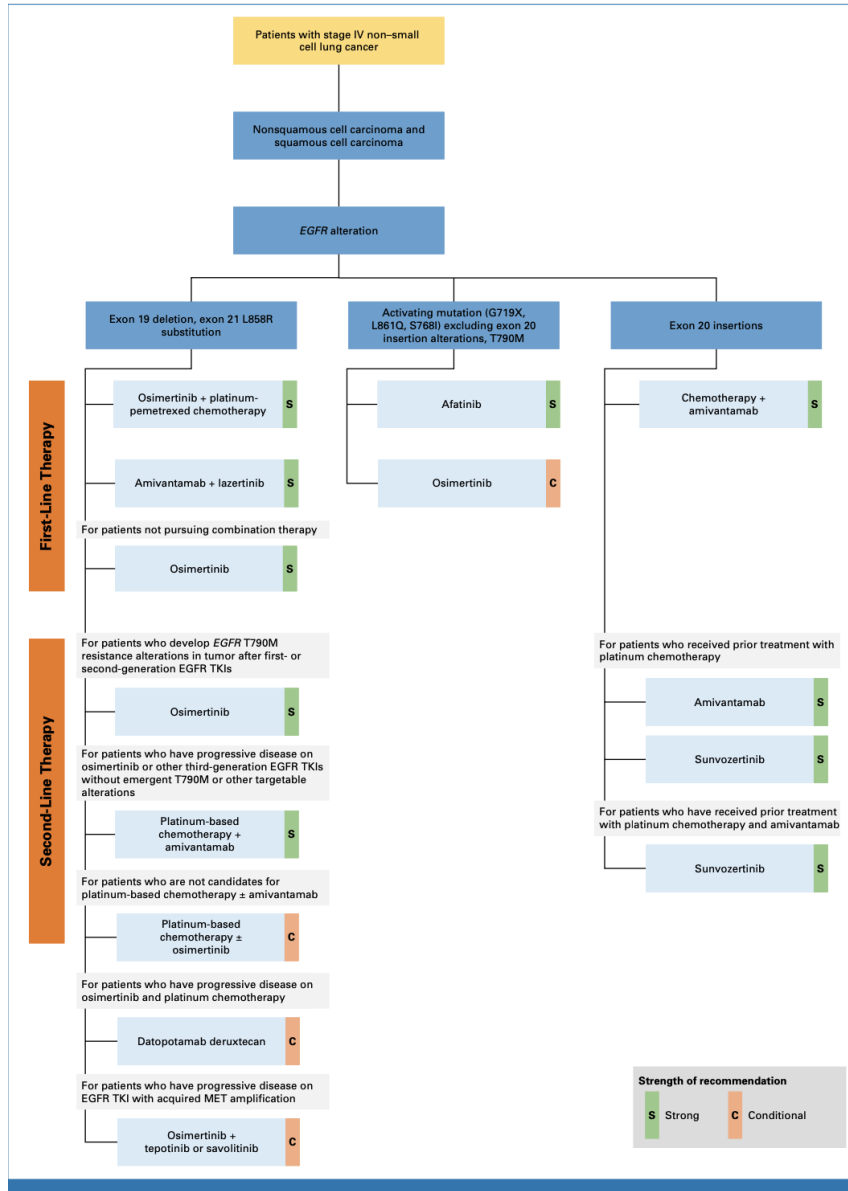


- Faster time to response and greater target lesion shrinkage in the 6 mg/kg cohort

PFS favoured the 6 mg/kg cohort

- mPFS: 11.7 months with osimertinib + Dato-DXd 6 mg/kg







TROPION LUNGO2. FIRST LINE

- Phase 1b study of Dato-DXd + pembrolizumab ± Pt-CT in a/mNSCLC without actionable genomic alterations^a

Key eligibility criteria	1L patients only				Objectives	
<ul style="list-style-type: none"> <u>a/mNSCLC</u> Dose <u>escalation</u>^b: ≤2 lines of prior <u>therapy</u>^c Dose expansion <ul style="list-style-type: none"> ≤1 line of Pt-CT (cohorts 1 and 2)^c Treatment-naïve (cohort 2)^{c,d} Treatment-naïve (cohorts 3–6)^c 	Dato-DXd IV Q3W	+ Pembrolizumab IV Q3W	+ Pt-CT IV Q3W		<p>Primary: Safety and tolerability</p> <p>Secondary: Efficacy</p>	
	Cohort 1 (n=2):	4 mg/kg	+ 200 mg			Doublet
	Cohort 2 (n=40):	6 mg/kg	+ 200 mg			
	Cohort 3 (n=14):	4 mg/kg	+ 200 mg	+ Carboplatin AUC 5		Triplet
	Cohort 4 (n=26):	6 mg/kg	+ 200 mg	+ Carboplatin AUC 5		
	Cohort 5 (n=8):	4 mg/kg	+ 200 mg	+ Cisplatin 75 mg/m ²		
Cohort 6 (n=6):	6 mg/kg	+ 200 mg	+ Cisplatin 75 mg/m ²			

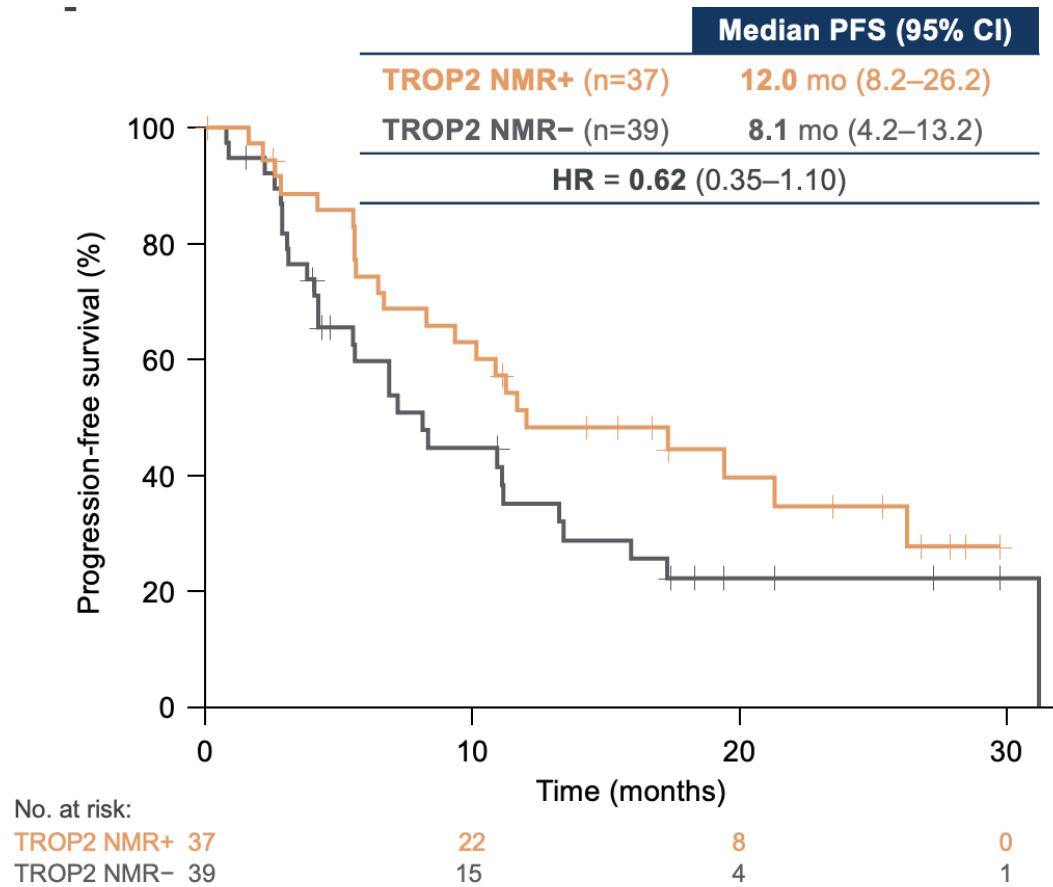


TROPION LUNGO2. EFFICACY BY PD-L1 STATUS

	Doublet		Triplet	
	PD-L1 <50%	PD-L1 ≥50%	PD-L1 <50%	PD-L1 ≥50%
N	30	5	40	10
ORR,% (95% CI)	53.3% (34.3–71.7)	100% (47.8–100)	55.0% (38.5–70.7)	60.0% (26.2–87.8)
BoR (%)				
CR	3.3%	0	2.5%	10.0%
PR	50%	100%	52.5%	50.0%
DOR, months (95% CI)	12.0 (8.0–NE)	NE (5.5–NE)	14.6 (5.3–NE)	NE 4.1–NE
DCR (%) (95% CI)	96.7 (82.8–99.9)	100 (47.8–100)	87.5 (73.2–95.8)	90.0 (55.5–99.7)
Median PFS, months (95% CI)	11.1 (7.2–13.3)	NE (8.3–NE)	6.4 (5.5–13.2)	6.8 (0.8–NE)
Median OS, months (95% CI)	NE (19.2–NE)	NE (12.6–NE)	13.3 (7.7–NE)	NE (0.8–NE)

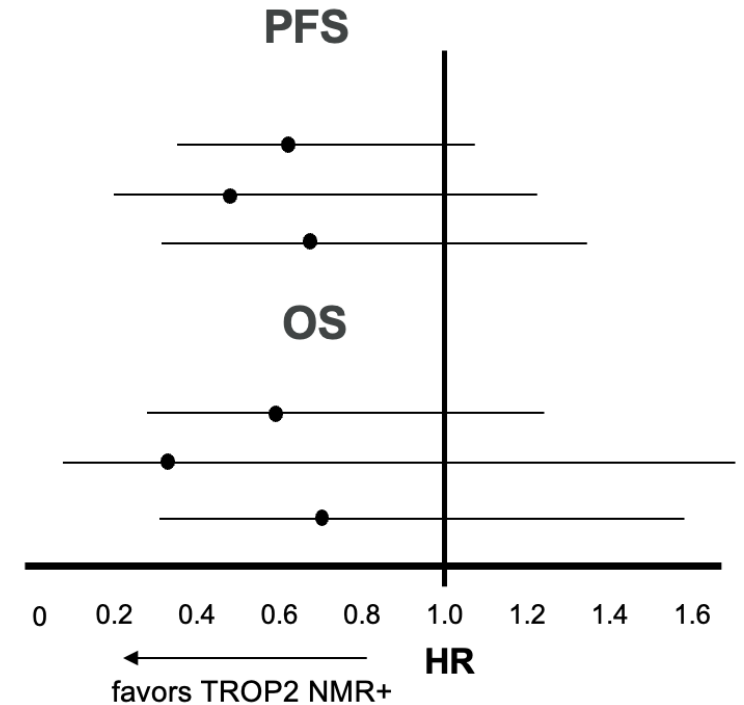


TROPION LUNGO2. EFFICACY BY TROP2 NMR. 1ST LINE BIOMARKER EVALUABLE POPULATION



BEP (n=76)
 Doublet (n=32)
 Triplet (n=44)

BEP (n=76)
 Doublet (n=32)
 Triplet (n=44)





TAKE HOME

- The preliminary work describing TROP-2 as a biomarker in NSCLC was not sufficiently developed
- TROP2 specific ADCs have been evaluated in the second line setting for NSCLC with better results for EGFR mutated patients
- New clinical trials are coming

GRACIAS!

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