Lung Cancer UPDATES
WCLC HIGHLIGHTS
San Diego, USA
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Iniciativa científica de:
GECP
lung cancer research

CPNM enfermedad avanzada sin driver

Dr. Joaquim Bosch Barrera

ICO Girona, Hospital Universitari Dr Josep Trueta

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1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

Iniciativa científica de: GECP lung cancer research

2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: HARMONi-2

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1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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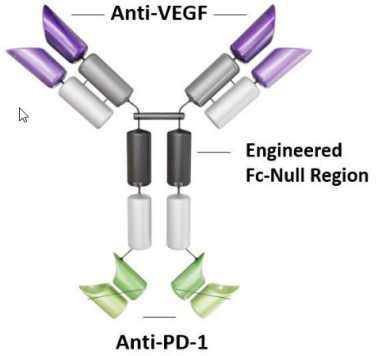

HARMONi-2 (AK112-303) Study Design

A randomized, double-blind, phase 3 study[a]

Patient Population

- Stage IIIB-IV aNSCLC
- No prior systemic therapy
- No *EGFR* mutations or *ALK* rearrangements
- ECOG PS 0 or 1
- PD-L1 TPS ≥1%

R 1:1

N=398

Ivonescimab
20 mg/kg Q3W (N=198)

Pembrolizumab
200 mg Q3W (N=200)

Treatment until no clinical benefit, unacceptable toxicity or up to 24 months

Stratification

- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

Endpoints

Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

[a] Patients were randomized from November 2022 to August 2023. Data cut off: January 29, 2024.

Abbreviations: aNSCLC, advanced non-small cell lung cancer; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; R, randomization; SQ, squamous cell carcinoma; Q3W, every three weeks; PFS, progression-free survival; IRRC, independent radiology review committee; OS, overall survival; INV, investigator; ORR, overall response rate; DoR, duration of response; TTR, time to response; QoL, quality of life.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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Baseline Characteristics

Characteristics, n (%)		Ivonescimab (n = 198[a])	Pembrolizumab (n = 200[a])	Total (n = 398[a])
Age (years)	<65	97 (49.0)	85 (42.5)	182 (45.7)
	≥65	101 (51.0)	115 (57.5)	216 (54.3)
Sex	Male	164 (82.8)	169 (84.5)	333 (83.7)
	Female	34 (17.2)	31 (15.5)	65 (16.3)
ECOG PS	0	25 (12.6)	26 (13.0)	51 (12.8)
	1	173 (87.4)	174 (87.0)	347 (87.2)
Smoker	Never	39 (19.7)	38 (19.0)	77 (19.3)
	Current	39 (19.7)	42 (21.0)	81 (20.4)
	Former	120 (60.6)	120 (60.0)	240 (60.3)
Clinical stage	IIIB/C	15 (7.6)	16 (8.0)	31 (7.8)
	IV	183 (92.4)	184 (92.0)	367 (92.2)
Pathology	SQ	90 (45.5)	91 (45.5)	181 (45.5)
	Tumor centrally located[b]	65 (72.2)	57 (62.6)	122 (67.4)
	Tumor with cavitation/necrosis[b]	9 (10.0)	7 (7.7)	16 (8.8)
	Tumor encasing large blood vessel[b]	6 (6.7)	1 (1.1)	7 (3.9)
	Non-SQ	108 (54.5)	109 (54.5)	217 (54.5)
PD-L1 TPS	≥50%	83 (41.9)	85 (42.5)	168 (42.2)
	1-49%	115 (58.1)	115 (57.5)	230 (57.8)
Liver metastases	Yes	25 (12.6)	28 (14.0)	53 (13.3)
	No	173 (87.4)	172 (86.0)	345 (86.7)
Brain metastases	Yes	33 (16.7)	39 (19.5)	72 (18.1)
	No	165 (83.3)	161 (80.5)	326 (81.9)

[a] Patients who received randomization. [b] In 181 patients with SQ.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; SQ, squamous cell carcinoma.

Realizado en China

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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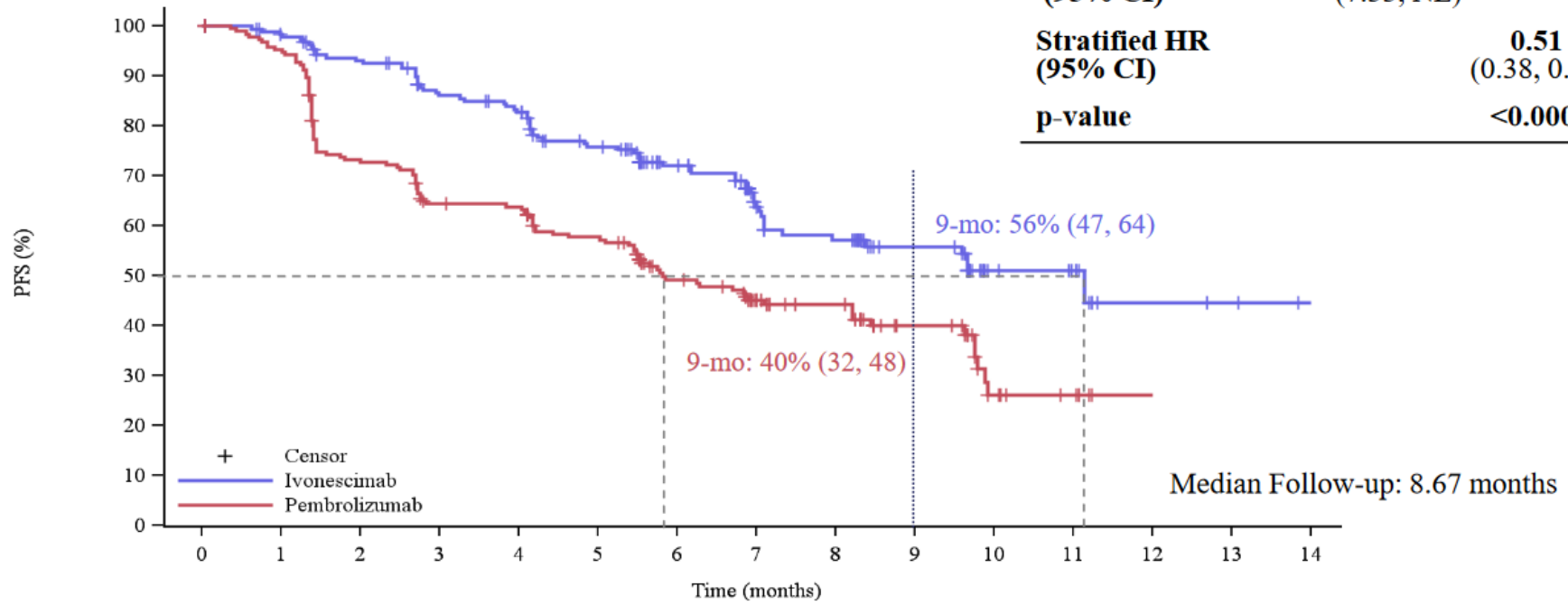
Primary endpoint: PFS per IRRC

	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.

Abbreviations: mPFS, median progression-free survival; IRRC, independent radiology review committee; mo, month; NE, not estimable; HR: hazard ratio; CI, confidence interval.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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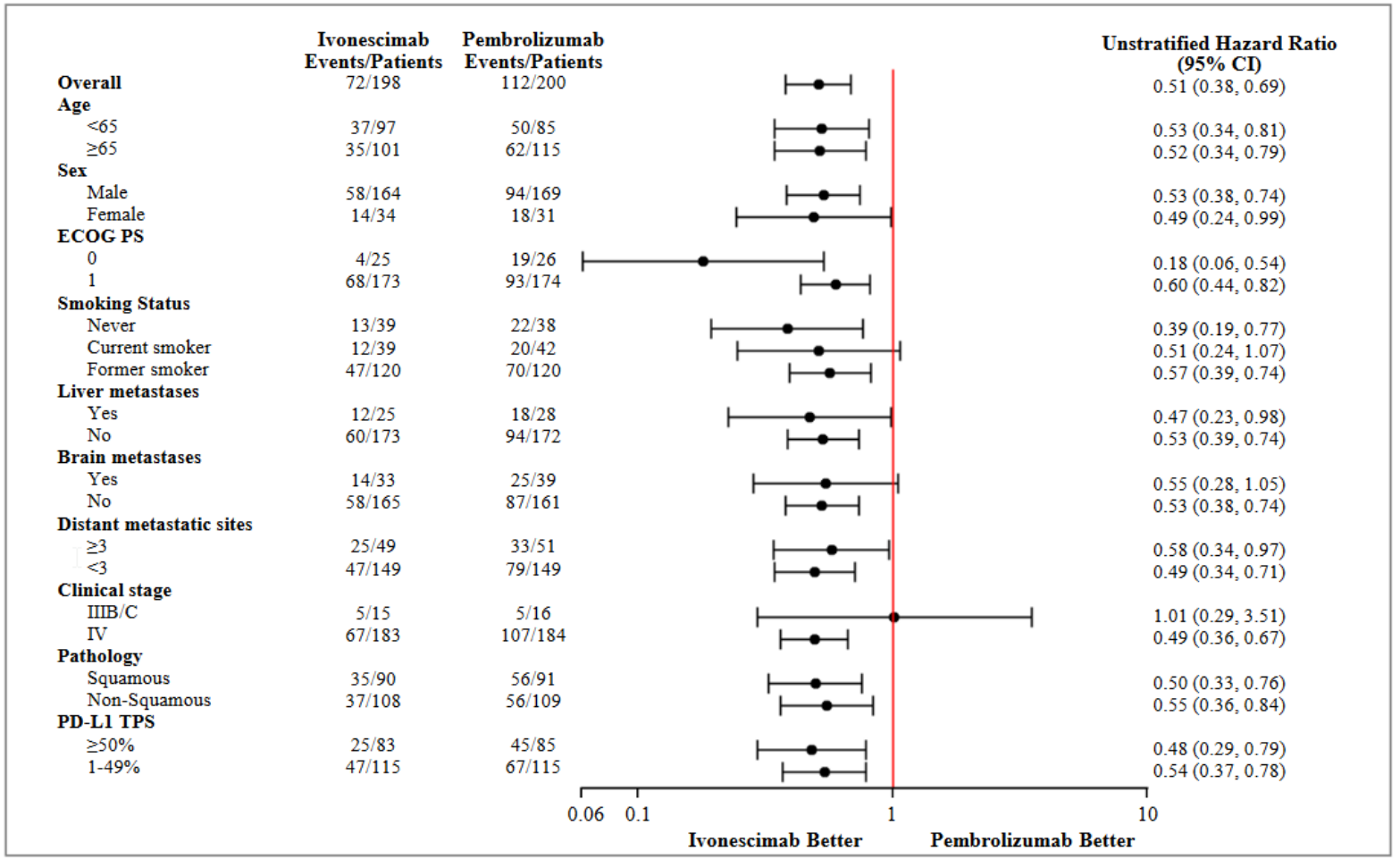
PFS Subgroup Analyses



Abbreviations: PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; SQ, squamous cell carcinoma; CI, confidence interval; aNSCLC, advanced non-small cell lung cancer.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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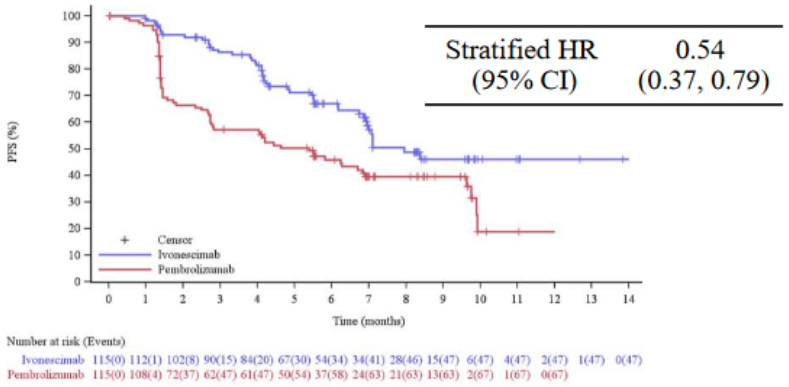
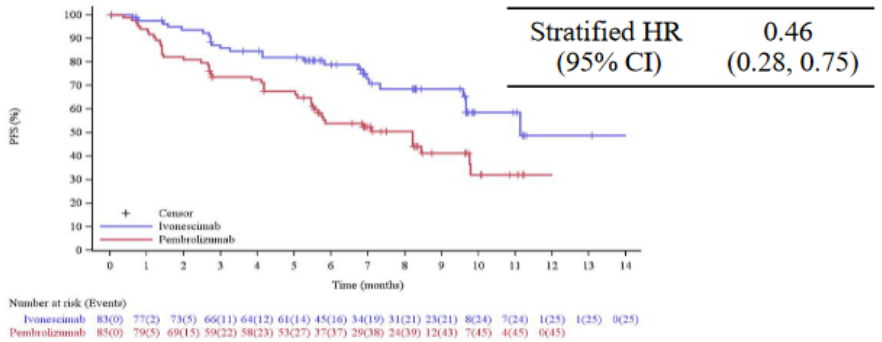
Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

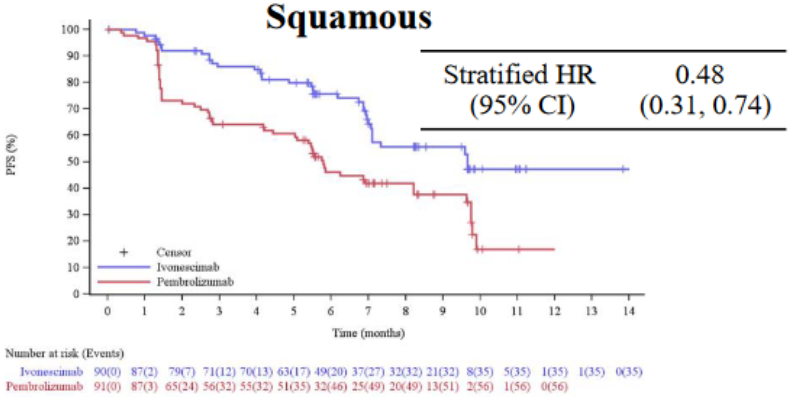


PD-L1 High (TPS ≥50%)

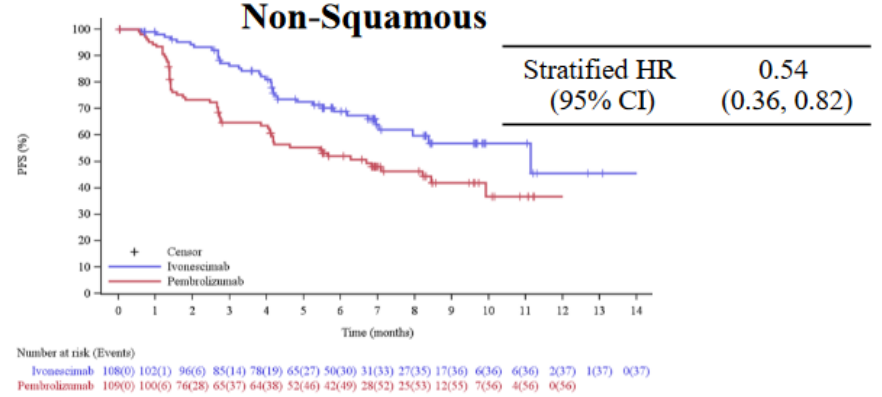


NSCLC Histology

Squamous



Non-Squamous



Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Abbreviations: PFS, progression-free survival; PD-L1, programmed death ligand 1; TPS, tumor proportion score; HR: hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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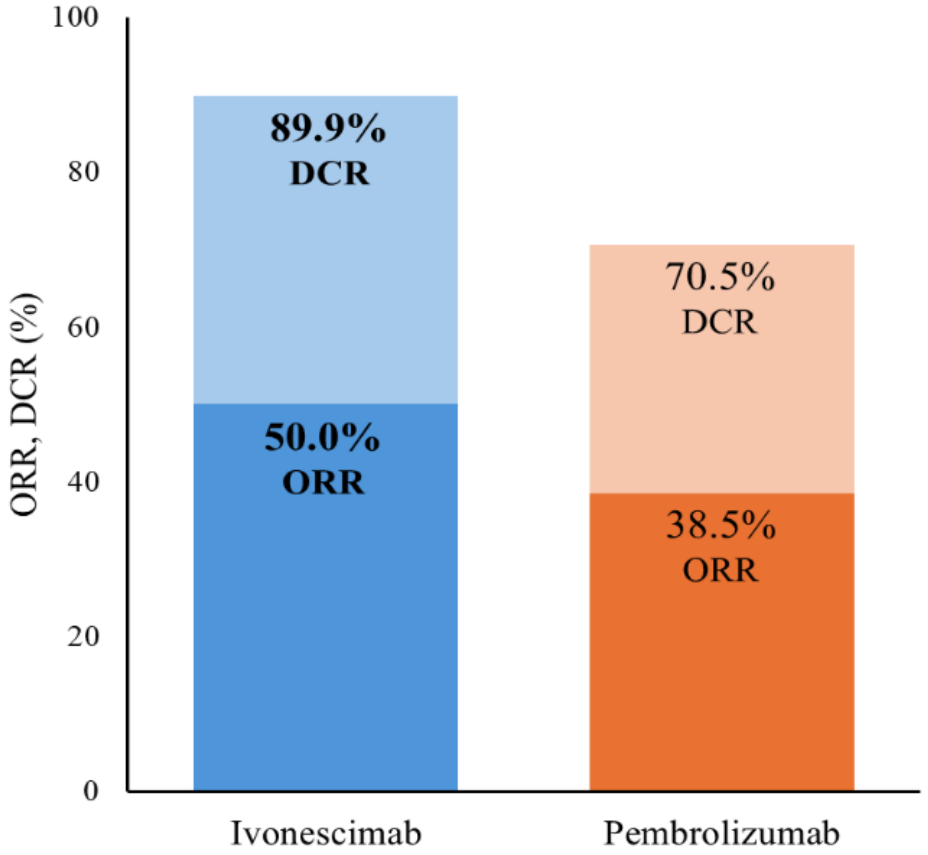
ORR, DCR and DoR per IRRC



	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
ORR, % **(95% CI)**	**50.0** (42.8, 57.2)	38.5 (31.7, 45.6)
DCR, % **(95% CI)**	**89.9** (84.8, 93.7)	70.5 (63.7, 76.7)
Median DoR, mos **(95% CI)**	**NR** (NE, NE)	NR (8.28, NE)

ORR and DCR were higher with ivonescimab vs. pembrolizumab.

Data cut off: January 29, 2024.
Abbreviations: ORR, overall response rate; DCR, disease control rate; DoR, duration of response; IRRC, independent radiology review committee; CI, confidence interval; mo, month; NR, not reached; NE, not estimable.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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Safety Summary

TRAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

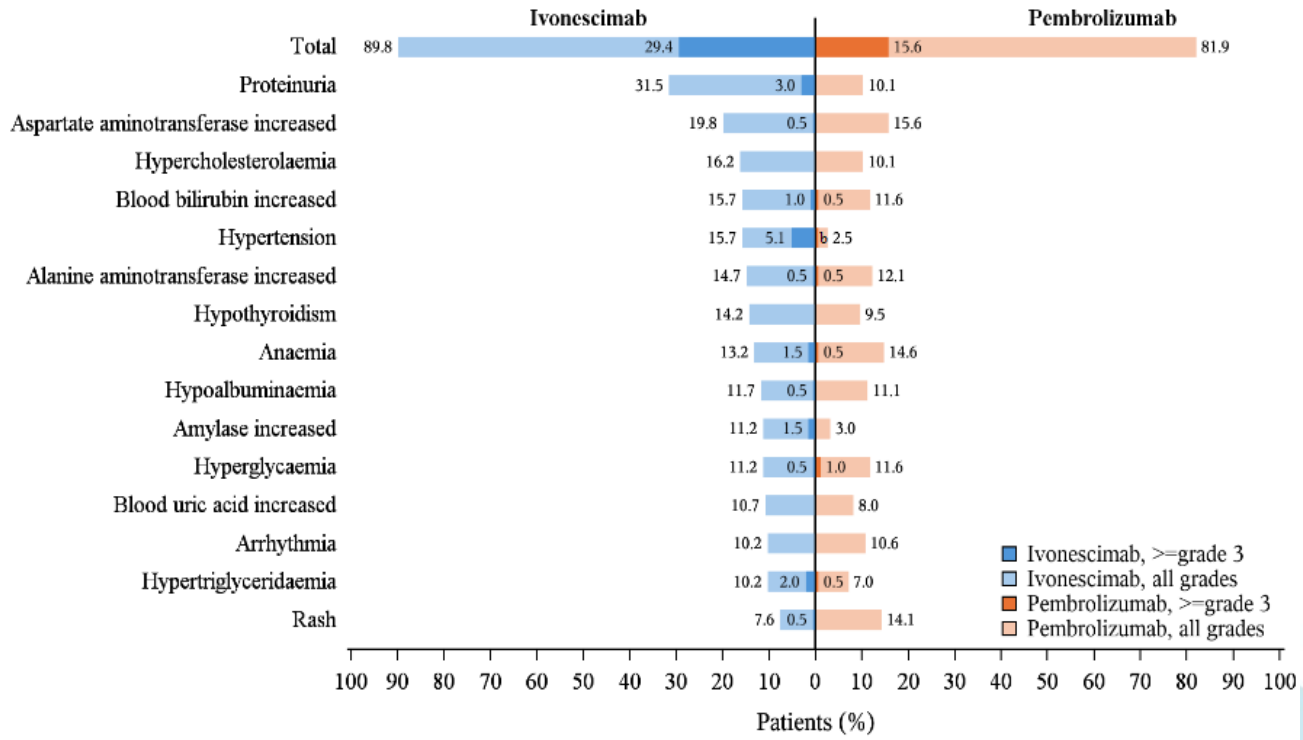
Ivonescimab showed a manageable safety profile, which was consistent with previous studies.

TRAEs in SQ Subgroup

Safety Summary, n (%)	Ivonescimab (n = 90[a])	Pembrolizumab (n = 91[a])
TRAEs (all grades)	77 (85.6)	73 (80.2)
Grade≥3	20 (22.2)	17 (18.7)
Serious TRAEs	17 (18.9)	17 (18.7)
Leading to discontinuation	2 (2.2)	3 (3.3)
Leading to death	0	1 (1.1)

Ivonescimab also demonstrated a tolerable safety profile in SQ patients.

The Most Common TRAEs (incidence ≥10%)



The differences in AEs were predominantly proteinuria, hypertension, and laboratory abnormalities.

[a] Patients who received ≥1 dose of study treatment. [b] The incidence of ≥grade 3 Hypertension was 0.5%.
Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events; SQ, squamous cell carcinoma.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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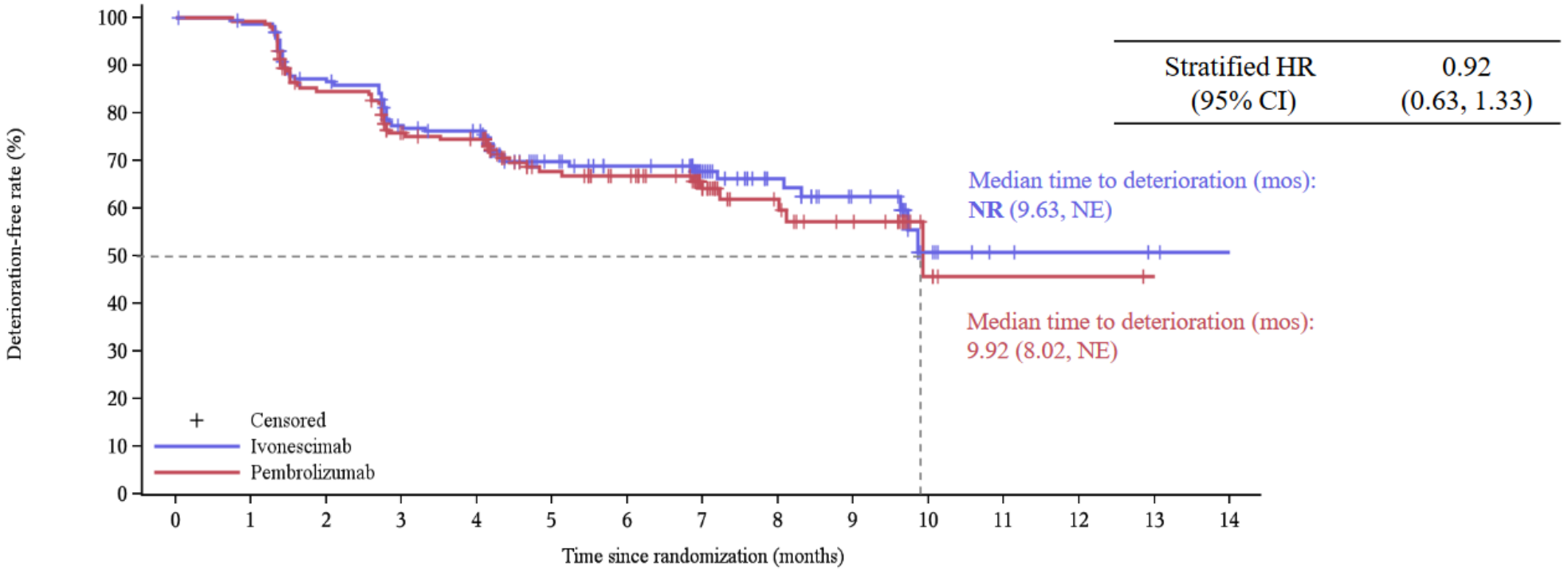
Global Health Status – EORTC QLQ-C30

Time to deterioration of global health status – EORTC QLQ-C30[a]



Stratified HR (95% CI)	0.92 (0.63, 1.33)

Number at risk (events)

Ivonescimab	177(0)[b]	173(2)	146(22)	125(38)	120(40)	80(49)	72(50)	48(51)	35(52)	25(54)	8(57)	3(57)	2(57)	1(57)	0(57)
Pembrolizumab	174(0)[b]	173(1)	137(26)	115(40)	110(42)	72(50)	65(51)	38(53)	26(54)	19(56)	4(57)	1(57)	1(57)	0(57)	

Ivonescimab was associated with comparable, numerically better time to deterioration of global health status.

[a] Deterioration of global health status/quality of life (QoL) refers to a decrease of 10 points or greater from the baseline in standardized score. Time to deterioration is defined as the time from the date of randomization to the date of first occurrence of deterioration. [b] Patients who completed EORTC QLQ-C30.
Abbreviations: mo, month; NR, not reached; NE, not estimated; HR: hazard ratio; CI, confidence interval.

1a Linea PD-L1 positivo

Ivonescimab vs Pembrolizumab

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Conclusions

- First-line ivonescimab significantly improve IRRC-assessed PFS in patients with aNSCLC and PD-L1 TPS ≥1%, compared with pembrolizumab (**median PFS (mos), 11.14 vs. 5.82; HR, 0.51; *p*<0.0001**).
- PFS benefit with ivonescimab were consistent across major clinical subgroups:
  - TPS ≥50%, HR = 0.46 (0.28, 0.75); TPS 1-49%, HR = 0.54 (0.37, 0.79)
  - SQ, HR = 0.48 (0.31, 0.74); non-SQ, HR = 0.54 (0.36, 0.82)
- Higher ORR (50.0% vs. 38.5%) and DCR (89.9% vs. 70.5%) were observed with ivonescimab vs. pembrolizumab.
- OS was not matured at this time; the OS analysis is event-driven and will be reported in the future.
- The safety profile of ivonescimab was consistent with prior studies and well tolerated, including in patients with SQ-NSCLC.
- HRQoL with ivonescimab was comparable to pembrolizumab.

This is the first randomized phase 3 study to demonstrate a clinically significant improvement in efficacy with a novel drug compared to pembrolizumab in aNSCLC.

Ivonescimab is a novel 1st line treatment for patients with aNSCLC and positive PD-L1(TPS ≥1%).

Ivonescimab is an investigational therapy in this setting worldwide; ivonescimab is approved in 2L EGFRm NSCLC in China.
Abbreviations: IRRC, independent radiology review committee; PFS, progression-free survival; aNSCLC, advanced non-small cell lung cancer; PD-L1, programmed death ligand 1; TPS, tumor proportion score; mo, month; HR: hazard ratio; CI, confidence interval; SQ, squamous cell carcinoma; ORR, overall response rate; DCR, disease control rate; OS, overall survival.

1a L PD-L1 high

Galaxies lung-201, anti-TIGIT (Belrestotug)

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BARCELONA 2024 ESMO congress

Interim Analysis of GALAXIES Lung-201: Phase 2, Randomized, Open-label Platform Study of Belrestotug Plus Dostarlimab in Patients With Previously Untreated Locally Advanced/Metastatic PD-L1 High (TPS ≥50%) Non-Small Cell Lung Cancer

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Dr. David R. Spigel

Barcelona, Spain, 14 September 2024

1a L PD-L1 high

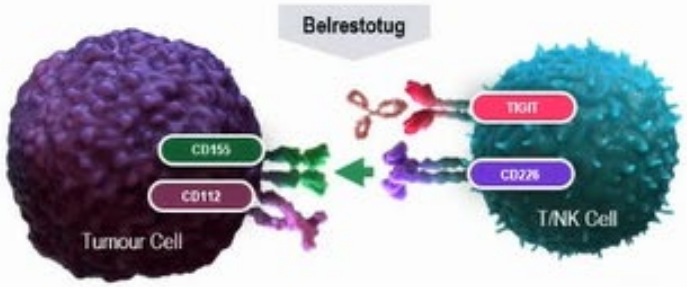
Galaxies lung-201

Iniciativa científica de: GECP lung cancer research

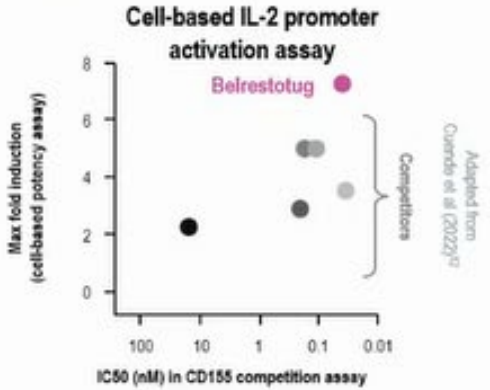
Background

- Current 1L treatment options for patients with PD-L1 high (expression ≥50%), locally advanced/metastatic NSCLC include single-agent immunotherapy; however, less than half of patients respond, necessitating new treatment approaches[1–3]
- Dostarlimab, an anti–PD-1 antibody approved for the treatment of endometrial cancer,[4,5] demonstrated comparable clinical activity to pembrolizumab in 1L NSCLC in the PERLA trial, a randomized, double-blind, head-to-head Phase 2 study of dostarlimab + chemotherapy vs standard of care pembrolizumab + chemotherapy[6]
- Anti-tumour activity with PD-(L)1 inhibitors may be further amplified through combination with novel anti-TIGIT inhibitory immune checkpoint agents, such as belrestotug[7–9]

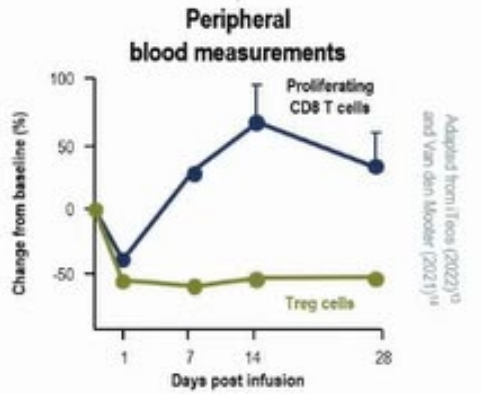
Belrestotug is an **Fcγ-receptor enabled mAb**[10,11] with two key mechanisms of action



Belrestotug demonstrated **higher potency** relative to other anti-TIGIT mAbs[12]



Belrestotug treatment leads to increases in proliferating CD8+ T-cells and a **marked reduction in Tregs** in patients[13,14]



1L, first line; IC50, 50% inhibitory concentration; IL, interleukin; mAb, monoclonal antibody; NK, natural killer; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein (ligand) 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain; Treg, regulatory T cell.

1. Reck, et al. J Clin Oncol 2021;39:2339–49; 2. Walsh, Soo. Ther Adv Med Oncol 2020;12:1–22; 3. Guo, et al. Medicine 2024;103:e38861; 4. GSK, Jemperli SmPC (2024) available from https://www.ema.europa.eu/en/documents/product-information/jemperli-epar-product-information_en.pdf; [accessed Aug 2024]; 5. GSK, JEMPERLI® (dostarlimab) US prescribing information (2024) available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761174s000lbl.pdf; [accessed Aug 2024]; 6. Lim, et al. Nat Commun 2023;14(1):7301; 7. Mittal, et al. Cancer Immunol Res 2019;7(4):559–71; 8. Sanchez-Correa, et al. Cancers (Basel) 2019;11(8):877; 9. Qin, et al. Mol Cancer 2019;18(1):155; 10. Preillon, et al. Mol Cancer Ther 2021;20(1):121–31; 11. Nguyen, et al. Presented at AACR 2020 (Abstract 3720), 22–24 Jun, online; 12. Cuende, et al. Poster #LB189 presented at: AACR; 8–13 Apr 2022; Philadelphia, PA; 13. iTeos corporate presentation (2022) available from https://investors.iteostherapeutics.com/static-files/f2ecce47-6d47-473c-93b3-7203f222af72 [accessed Aug 2024]; 14. Van den Mooter, et al. Presented at AACR (Poster CT118), 10–15 Apr and 17–21 May 2021; Philadelphia, PA.

1a L PD-L1 high

Galaxies lung-201

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GALAXIES Lung-201: A Phase 2, Open-label, Randomized Platform Study[1]

- This study is designed to assess the efficacy and safety of belrestotug + dostarlimab combinations in NSCLC
- Additional follow-up and recruitment will determine dose optimization, contribution of components, and comparisons to current standard of care (pembrolizumab monotherapy)

Key Eligibility Criteria:

- Previously untreated, unresectable, locally advanced/metastatic NSCLC
- PD-L1 high (TPS ≥50%; determined locally or centrally by DAKO 22C3 or VENTANA SP263 assay)
- EGFR/ALK wild-type, no actionable driver mutations
- Current or former smoker
- Asymptomatic and treated brain metastases are eligible

R

Stratification: Squamous vs non-squamous

Substudy 1

- Pembrolizumab 200 mg Q3W
- Dostarlimab 500 mg Q3W
- A: Belrestotug 100 mg + dostarlimab 500 mg Q3W
- B: Belrestotug 400 mg + dostarlimab 500 mg Q3W
- C: Belrestotug 1000 mg + dostarlimab 500 mg Q3W

Substudy 2

- Belrestotug + dostarlimab + nelistotug[2] Q3W

Substudies to be added by amendment

Study initiation timeline

Primary Endpoint:

ORR per RECIST 1.1 by investigator assessment

Key Secondary Endpoints:

- PFS
- OS
- DoR
- Safety
- PK
- ADA

- **This follow-up interim analysis reports preliminary efficacy and safety (mITT ≥5.6 months follow-up)**
- **At data cut-off (7 June 2024), a total of 124 patients were included, with an overall median follow-up of 7.3 months**

[1]NCT05585378; EudraCT 2021-005115-32; [2]nelistotug is a CD96 mAb. ADA, antidrug antibodies; ALK, anaplastic lymphoma kinase; DoR, duration of response; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; mITT, modified intention-to-treat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TPS, tumour positive score.

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Dr David R. Spigel

1a L PD-L1 high

Galaxies lung-201

Iniciativa científica de: GECP lung cancer research

Primary Efficacy Endpoint: Investigator Assessment of ORR per RECIST 1.1

Belrestotug + dostarlimab combinations were associated with a clinically meaningful improvement in ORR vs dostarlimab monotherapy

Response measure in mITT	Dostarlimab N=32	A: Belrestotug 100 mg + dostarlimab N=30	B: Belrestotug 400 mg + dostarlimab N=32	C: Belrestotug 1000 mg + dostarlimab N=30
Median follow-up, months (range)[1]	7.0 (0.2–16.6)	8.5 (0.3–14.3)	8.5 (0.4–16.2)	6.7 (2.4–9.7)
ORR,[2,3] % n (95% CI)	**37.5%** n=12 (21.1–56.3)	**63.3%** n=19 (43.9–80.1)	**65.6%** n=21 (46.8–81.4)	**76.7%** n=23 (57.7–90.1)
Complete response, n (%)	0	0	0	0
Partial response, n (%)	12 (37.5%)	19 (63.3%)	21 (65.6%)	23 (76.7%)
Stable disease, n (%)	14 (43.8%)	5 (16.7%)	4 (12.5%)	5 (16.7%)
Progressive disease, n (%)	2 (6.3%)	4 (13.3%)	3 (9.4%)	2 (6.7%)
Not evaluable/no assessment,[4] n (%)	4 (12.5%)	2 (6.7%)	4 (12.5%)	0
Confirmed ORR,[3,5] % n (95% CI)	**28.1%** n=9 (13.7–46.7)	**60.0%** n=18 (40.6–77.3)	**59.4%** n=19 (40.6–76.3)	**63.3%** n=19 (43.9–80.1)

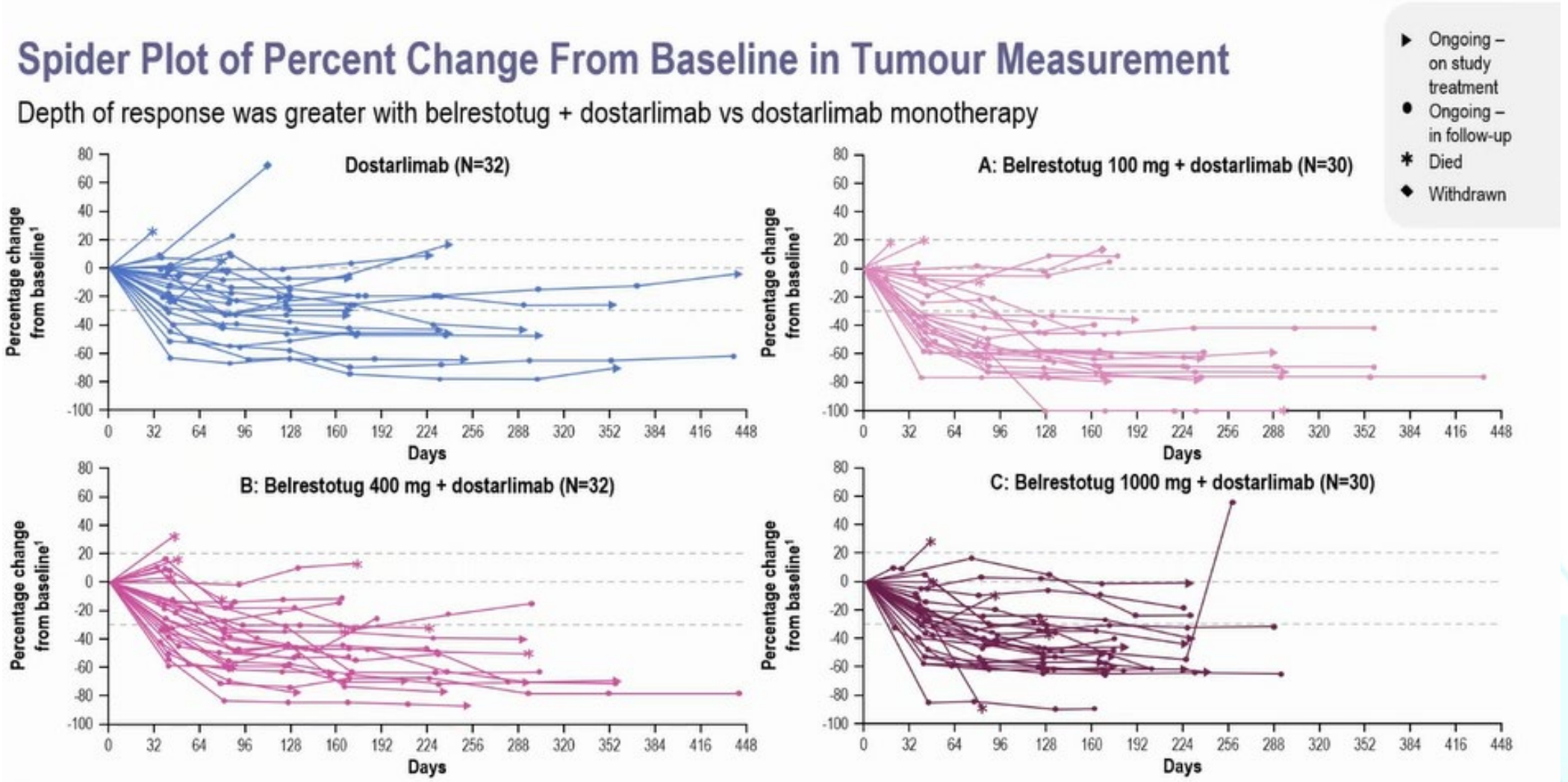
[1]As of data cut 7 Jun 2024, 65% of patients remained in ongoing follow-up and 33% of patients remained on study treatment; [2]unconfirmed ORR; [3]PD-L1 high (TPS ≥50%) was determined locally or centrally by DAKO 22C3 or VENTANA SP263 assay; [4]patients who only had "not evaluable" post-baseline assessments, those who had a best response of "not evaluable" per RECIST 1.1 by investigator assessment, or those where no post-baseline tumour assessment was performed; [5]complete or partial response confirmed by repeat imaging ≥4 weeks after response criteria first met.
CI, confidence interval; mITT, modified intention-to-treat; ORR, objective response rate; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumours; TPS, tumour positive score.

1a L PD-L1 high

Galaxies lung-201

Spider Plot of Percent Change From Baseline in Tumour Measurement

Depth of response was greater with belrestotug + dostarlimab vs dostarlimab monotherapy



[1]Investigator assessed percentage change from baseline per RECIST 1.1 by investigator assessment. RECIST, Response Evaluation Criteria in Solid Tumours.

1a L PD-L1 high

Galaxies lung-201

Iniciativa científica de: GECP lung cancer research

Overall Safety Profile

The combination regimen led to an increase in immune-related adverse events compared to dostarlimab monotherapy

Event, n (%)	Dostarlimab (N=32)	A: Belrestotug 100 mg + dostarlimab (N=30)	B: Belrestotug 400 mg + dostarlimab (N=32)	C: Belrestotug 1000 mg + dostarlimab (N=30)
TEAE	29 (91%)	29 (97%)	31 (97%)	30 (100%)
Grade 3+ TEAE	14 (44%)	19 (63%)	16 (50%)	16 (53%)
TRAE	19 (59%)	24 (80%)	27 (84%)	29 (97%)
Grade 3+ TRAE	5 (16%)	10 (33%)	7 (22%)	13 (43%)
Serious TRAE	3 (9%)	10 (33%)	8 (25%)	11 (37%)
Grade 5 serious TRAE	0	2 (7%)	1 (3%)	0
TRAE leading to discontinuation	2 (6%)	7 (23%)	5 (16%)	12 (40%)
TR-irAE[1]	6 (19%)	20 (67%)	18 (56%)	22 (73%)
Grade 3+ TR-irAE	4 (13%)	9 (30%)	5 (16%)	11 (37%)
Infusion-related reactions[2]	4 (13%)	8 (27%)	3 (9%)	7 (23%)

- The most common TRAEs overall (≥15%) were skin and subcutaneous tissue disorders (50%) and endocrine disorders (26%)
- The most common TEAEs leading to discontinuation were skin and subcutaneous tissue disorders (6%) and respiratory, thoracic and mediastinal disorders (6%)
- Fatal serious TRAEs include immune-mediated lung disease (N=1), immune-mediated hepatitis (N=1) and immune-mediated myocarditis (N=1)

[1]Immune-related AEs are events of potential immunologic aetiology, including irAEs; irAEs are identified as any Grade 2+ AEs (or AEs of unknown grade) based on a prespecified search list of preferred terms using the most recent MedDRA version identified by a custom MedDRA query (CMQ) using GSK Terms of Interest codes; [2]infusion-related reactions are drug component–related AEs which occurred ≤1 day after drug component infusion and are identified based on a prespecified search list of preferred terms and most recent MedDRA version.
AE, adverse event; irAE, immune-related AE; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TR, treatment-related; TRAE, treatment-related treatment-emergent adverse event.

1a L PD-L1 high

Galaxies lung-201

Iniciativa científica de: GECP lung cancer research

Conclusion

- GALAXIES Lung-201 is the largest presented prospectively designed, randomized, dose-ranging, Phase 2 study in patients with previously untreated, unresectable locally advanced/metastatic PD-L1 high NSCLC assessing anti-TIGIT + anti–PD-1 combinations
- Belrestotug is a differentiated anti-TIGIT mAb with multiple mechanisms of action
- A clinically meaningful improvement in ORR was observed in all combination cohorts compared with dostarlimab monotherapy
- The combination regimen had an increase in immune-related adverse events, which were considered generally manageable
- Ongoing recruitment in the reported arms and additional follow-up will better characterise the long-term efficacy and safety of belrestotug + dostarlimab. Follow-up of this study will inform the future development of belrestotug

Data support the ongoing **GALAXIES Lung-301 Phase 3 study** (NCT06472076) of belrestotug + dostarlimab in patients with previously untreated, unresectable locally advanced/metastatic PD-L1 high NSCLC

mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-(L)1, programmed cell death protein (ligand) 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

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Nivolumab plus relatlimab with platinum-doublet chemotherapy vs nivolumab plus platinum-doublet chemotherapy as first-line treatment for stage IV or recurrent NSCLC: results from the randomized phase 2 **RELATIVITY-104** study

Nicolas Girard,[1] Mauricio Burotto,[2] Luis G. Paz-Ares,[3] Martin Reck,[4] Michael Schenker,[5] Alejo Lingua,[6] Francisco Orlandi,[7] Jarushka Naidoo,[8,9] Emma K. Beardsley,[10] Vamsidhar Velcheti,[11] Gaston Lucas Martinengo,[12] Enriqueta Felip,[13] Yan Zhang,[14] Priyanka Kasbekar,[14] Marzana Chowdhury,[14] Thomas Spires,[14] Amol Tendolkar,[14] Manuel Cobo[15]

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Presentation number LBA53

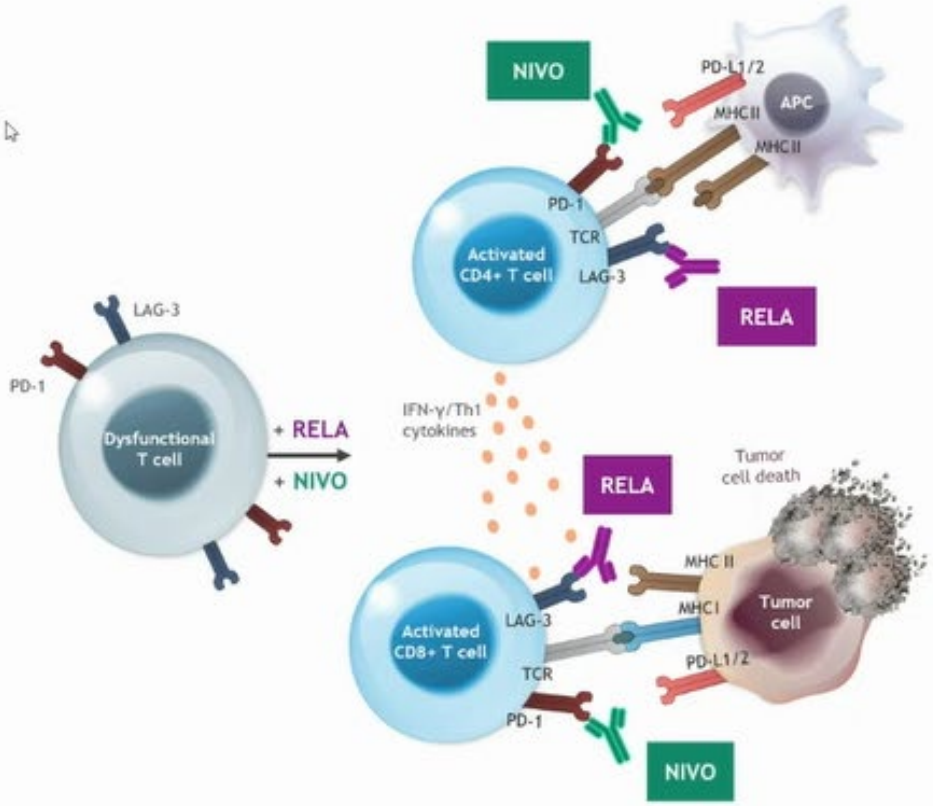
1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

Background

- Relatlimab (RELA) is a human LAG-3-blocking antibody that restores effector T-cell function[1]
  - NIVO 480 mg + RELA 160 mg Q4W was approved for the treatment of advanced melanoma (**RELATIVITY-047**)[2]
- **RELATIVITY-104** is the first randomized phase 2 study to evaluate a LAG-3-blocking antibody-containing regimen as a 1L treatment for metastatic NSCLC
  - In Part 1 (n = 159), safety of NIVO 360 mg + RELA 360 mg + PDCT and NIVO 360 mg + RELA 720 mg + PDCT was demonstrated
  - Here, we report results from the randomized Part 2 evaluating NIVO 360 mg + RELA 360 mg + PDCT vs NIVO + PDCT to help identify patient populations with metastatic NSCLC who might benefit from the addition of RELA



1. Khair DO, et al. *Front Immunol* 2019;10:453-453; 2. Tawbi H, et al. *N Engl J Med* 2022;386:24-34.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

RELATIVITY-104 Part 2 study design

Key eligibility criteria
- 1L stage IV/recurrent NSCLC
- No prior systemic therapy for metastatic disease
- No *EGFR*, *ALK*, *ROS-1* mutations[a]
- ECOG PS 0-1

N = 309

R 1:1

NIVO 360 mg + RELA 360 mg Q3W + PDCT[c] (4 cycles)

Prophylactic myeloid growth factor was mandatory for patients aged ≥ 60 years[d] according to guidelines[1,2]

NIVO 360 mg Q3W + PDCT[c] (4 cycles)

Stratified by tumor PD-L1[b] (≥ 1% vs < 1%), histology (NSQ vs SQ), and ECOG PS (0 vs 1)

Primary endpoint
- ORR (BICR)

Secondary endpoints
- PFS (BICR)
- Safety
- ORR and PFS by PD-L1
- DOR (BICR)

Database lock date: June 28, 2024; median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.

[a]*EGFR, ALK and ROS-1* testing was mandatory in all patients with NSQ histology (using US FDA/local health authority-approved assays). [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Histology-based platinum doublets: SQ - carboplatin AUC 6 and paclitaxel 200 mg/m^2; NSQ - carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (maintenance permitted). [d]During the first 4 cycles of treatment (PDCT period) for patients aged ≥ 60 years; or during the remaining PDCT treatment for patients aged < 60 years who had a grade ≥ 3 neutropenic AE. 1. Smith TJ et al. *J Clin Oncol* 2015;33:3199; 2. Klastersky J, et al. *Ann Oncol* 2016;27:v111.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

Baseline characteristics

	Part 2	
	NIVO + RELA 360 mg + PDCT n = 158	NIVO + PDCT n = 151
Median age, years (range)	65 (40-85)	65 (33-86)
Male, n (%)	103 (65)	94 (62)
ECOG PS, n (%)		
0	57 (36)	53 (35)
1	101 (64)	98 (65)
Histology, n (%)		
NSQ	107 (68)	104 (69)
SQ	51 (32)	47 (31)
Smoking status, n (%)		
Current/former	145 (92)	134 (89)
Never	13 (8)	17 (11)
Tumor PD-L1 expression,[a] n (%)		
< 1%	70 (44)	67 (44)
≥ 1%	79 (50)	71 (47)
1-49%	47 (30)	32 (21)
≥ 50%	32 (20)	39 (26)
Tumor LAG-3 expression,[b] n (%)		
< 1%	51 (32)	52 (34)
≥ 1%	94 (60)	76 (50)

Percentages may not total 100 due to rounding. [a]9 (NIVO + RELA 360 mg + PDCT) and 13 patients (NIVO + PDCT) were not evaluable. [b]LAG-3 expression on immune cells was measured using an analytically validated IHC assay.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

Safety summary

	Part 2			
	NIVO + RELA 360 mg + PDCT n = 158		NIVO + PDCT n = 149[a]	
Ongoing treatment,[b] n (%)	38 (24)		44 (30)	
Safety[c]	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
All-cause AEs, n (%)	158 (100)	112 (71)	148 (99)	104 (70)
TRAEs, n (%)	147 (93)	86 (54)	138 (93)	82 (55)
Serious TRAEs	37 (23)	33 (21)	36 (24)	32 (22)
TRAEs leading to discontinuation	21 (13)	12 (8)	21 (14)	13 (9)
TRAEs leading to death	6 (4)		5 (3)	

- Grade ≥3 treatment-related neutropenic AEs[d] occurred in 6% (NIVO + RELA 360 mg + PDCT) vs 14% (NIVO + PDCT)
- TRAEs leading to death:
  - NIVO + RELA 360 mg + PDCT: neutropenic sepsis (n = 2), febrile neutropenia (n = 1), pneumonitis (n = 2), pneumonia (n = 1)
  - NIVO + PDCT: febrile neutropenia, sepsis, septic shock, asthenia, lung disorder (n = 1 each)
- Most common TRAEs (≥ 20%) with NIVO + RELA 360 mg + PDCT: anemia, nausea, neutropenia, thrombocytopenia, fatigue

[a]2 patients were randomized but not treated. [b]Median number of I-O doses received: 9 NIVO + RELA 360 mg + PDCT and 9 NIVO + PDCT. [c]AEs were graded per CTCAE v5.0 and MedDRA v27.0. Includes events reported between the first dose and 30 days after the last dose of study treatment. [d]Includes neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, neutrophil count decreased, neutrophil percentage decreased, pancytopenia, sepsis, septic shock.

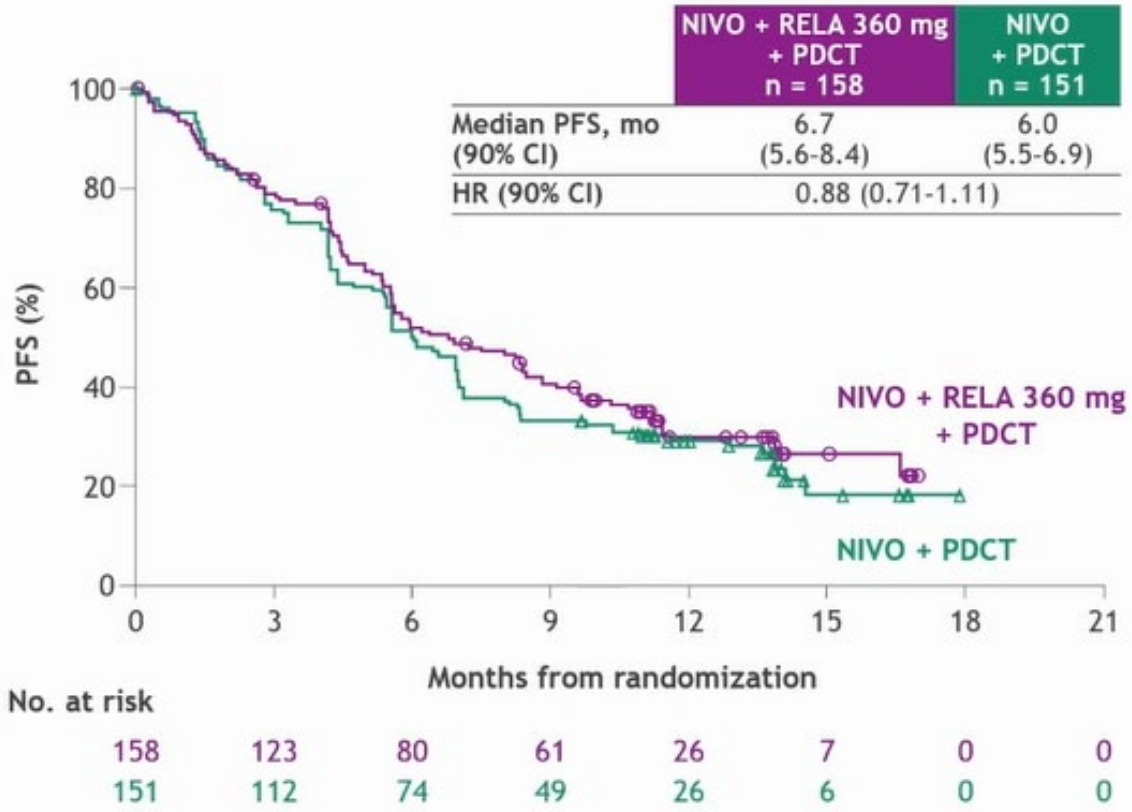
1a L quimio-inmuno + anti-LAG3

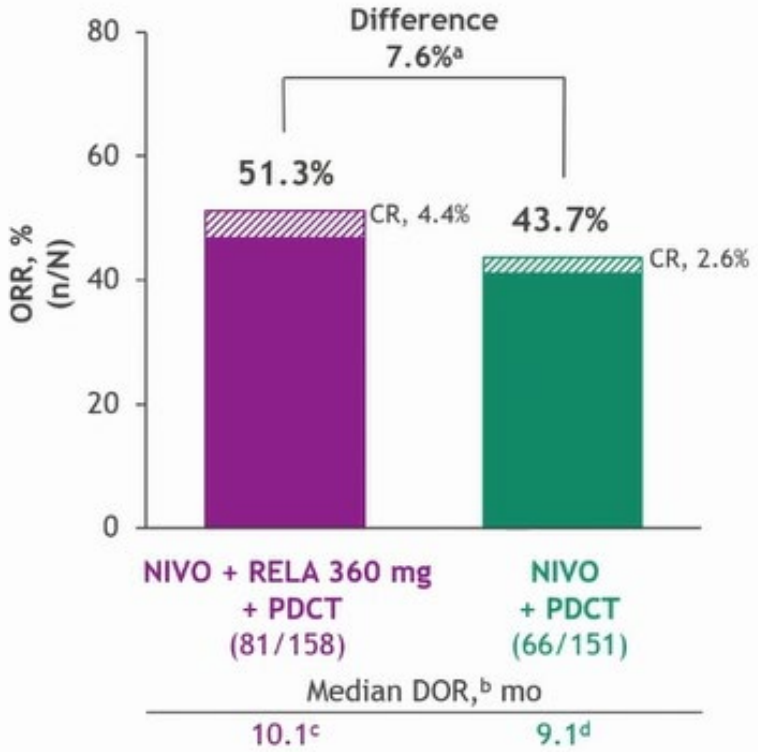
Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

RELATIVITY-104: 1L NIVO + RELA + PDCT in metastatic NSC

All randomized patients: PFS and ORR per BICR





Median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.
[a]90% CI: −1.3-16.6. Calculated using the stratified Cochran-Mantel-Haenszel method. [b]Calculated using the Kaplan-Meier method. [c,d]90% CI: [c]7.4-NR; [d]6.7-13.4.

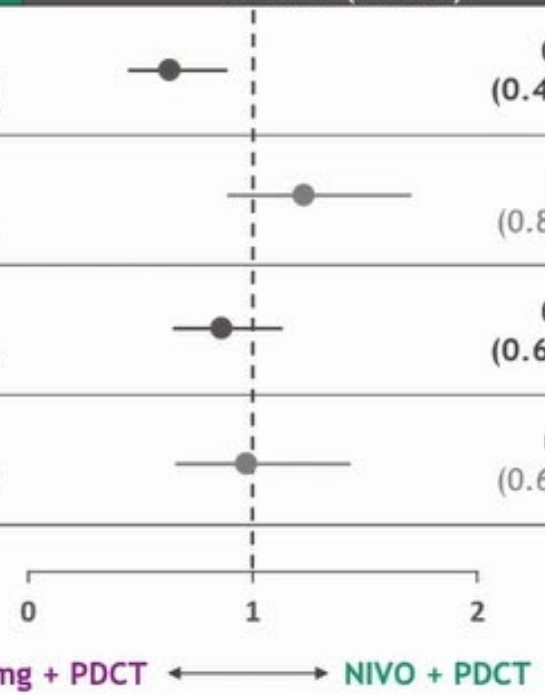
1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

Stratified[a] patient subgroups: PFS and ORR per BICR

Subgroup, n[b]	mPFS, mo (90% CI) NIVO + RELA 360 mg + PDCT	mPFS, mo (90% CI) NIVO + PDCT	PFS HR (90% CI)	ORR, % (90% CI) NIVO + RELA 360 mg + PDCT	ORR, % (90% CI) NIVO + PDCT
PD-L1 ≥ 1% (n = 79, 71)	**9.8 (5.9-13.8)**	**6.1 (4.2-7.0)**	**0.63 (0.45-0.88)**	**53.2 (43.3-62.8)**	**40.8 (31.0-51.3)**
PD-L1 < 1% (n = 70, 67)	5.6 (5.3-7.0)	5.8 (5.4-7.0)	1.23 (0.89-1.70)	50.0 (39.6-60.4)	44.8 (34.4-55.5)
NSQ (n = 107, 104)	**8.3 (5.6-9.8)**	**6.0 (4.6-7.0)**	**0.86 (0.65-1.13)**	**46.7 (38.5-55.1)**	**38.5 (30.5-47.0)**
SQ (n = 51, 47)	5.6 (5.3-8.2)	5.8 (5.4-7.1)	0.97 (0.66-1.43)	60.8 (48.3-72.3)	55.3 (42.3-67.8)



Median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.
[a]ECOG PS was also a stratified patient subgroup that is not shown. [b]Number of patients in the NIVO + RELA 360 mg + PDCT and NIVO + PDCT arms, respectively.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

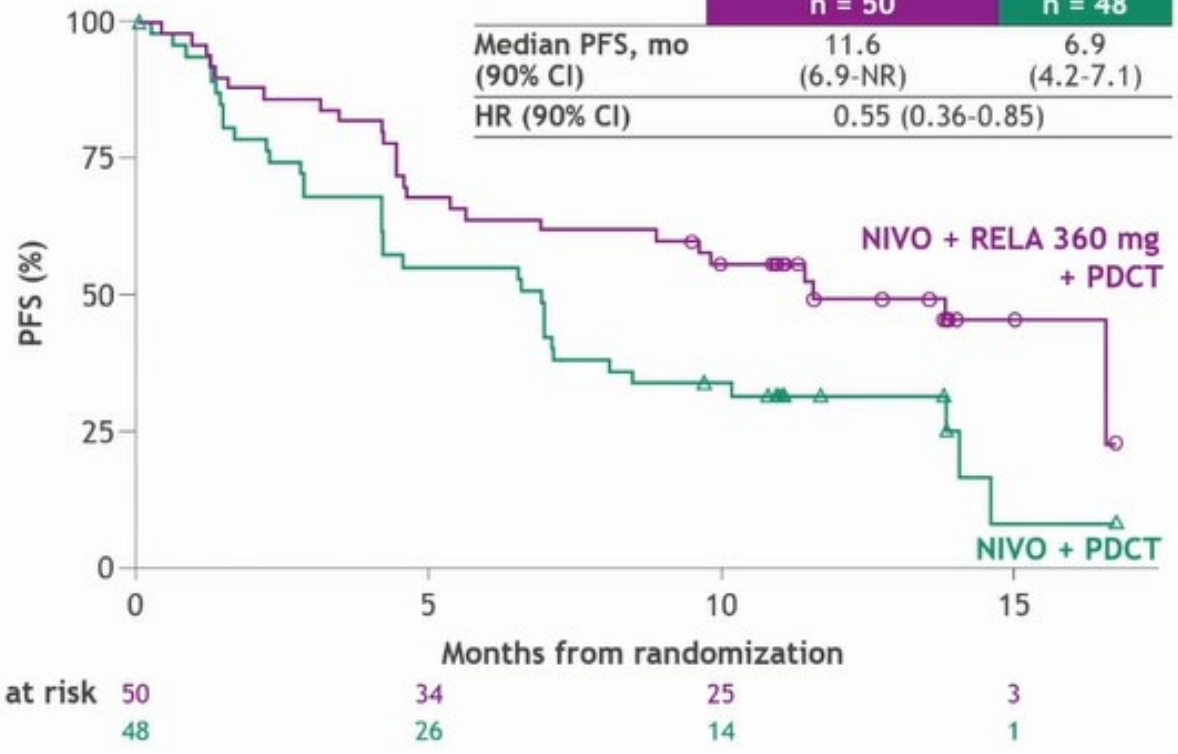
Iniciativa científica de: GECP lung cancer research

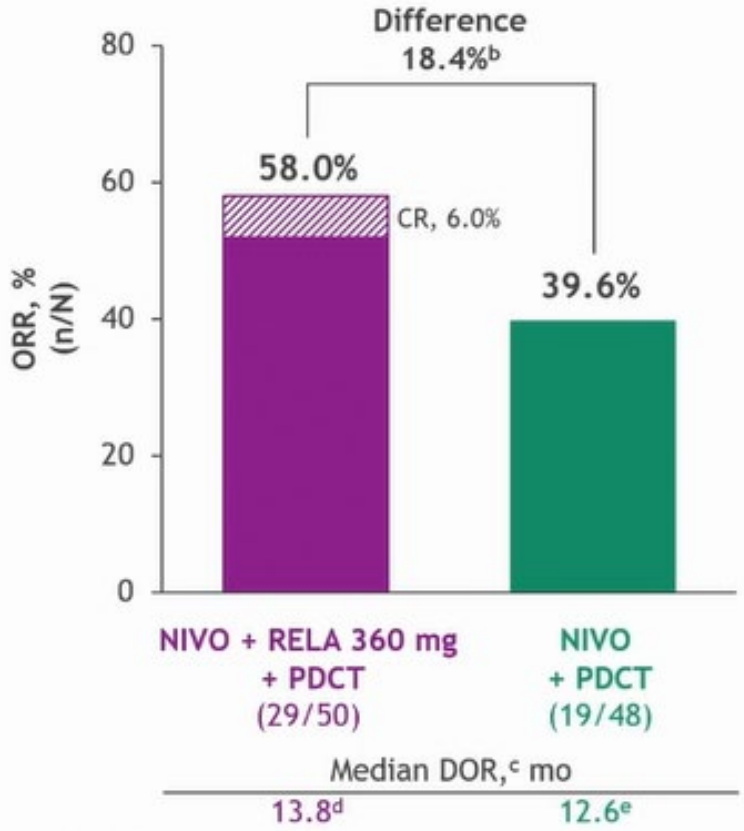
RELATIVITY-104: 1L NIVO + RELA + PDCT in metastatic NS

PD-L1 expression ≥ 1% and NSQ: PFS and ORR[a]

- PD-L1 ≥ 1% and NSQ are two strata in this study; subgroup analysis by PD-L1 expression and histology were pre-specified

	NIVO + RELA 360 mg + PDCT n = 50	NIVO + PDCT n = 48
Median PFS, mo (90% CI)	11.6 (6.9-NR)	6.9 (4.2-7.1)
HR (90% CI)	0.55 (0.36-0.85)	





Median follow-up (range) for Part 1 (RELA 360mg & 720mg doses): 16.5 (0.0-36.1) months and Part 2: 10.7 (0.0-18.6) months.
[a]Part 1 RELA 360mg dose in PD-L1 ≥ 1% & NSQ (n = 22): mPFS 10.9 months, ORR 50.0%, mOS 22.0 months.
[b]90% CI: 0.4-34.9. Calculated using the stratified Cochran-Mantel-Haenszel method. [c]Calculated using the Kaplan-Meier method. [d-e]90% CI: [d]12.2-NR; [e]7.1-NR.

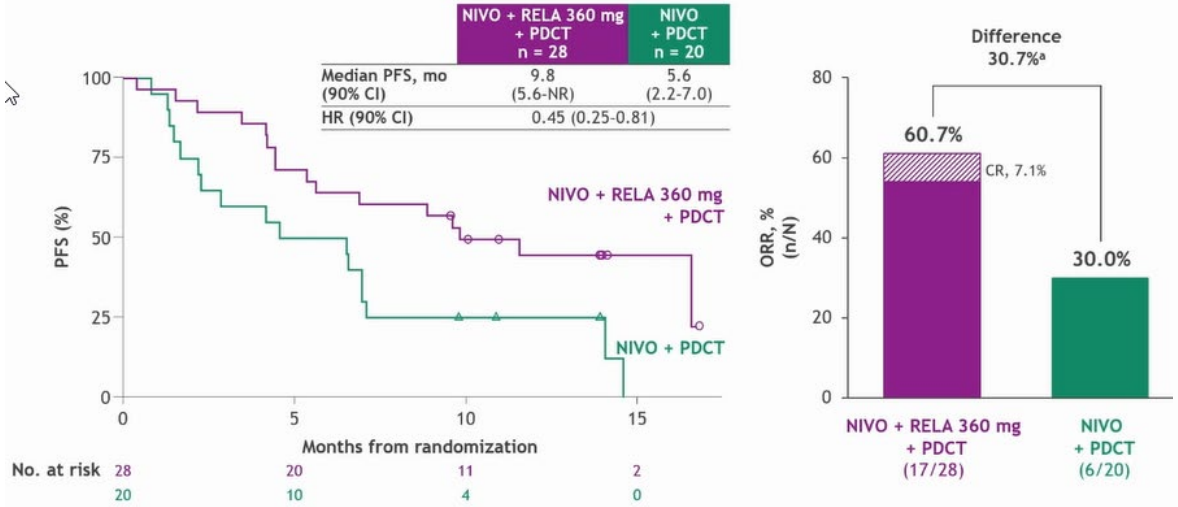
1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

RELATIVITY-104: 1L NIVO + RELA + PDCT in metastatic NSCLC

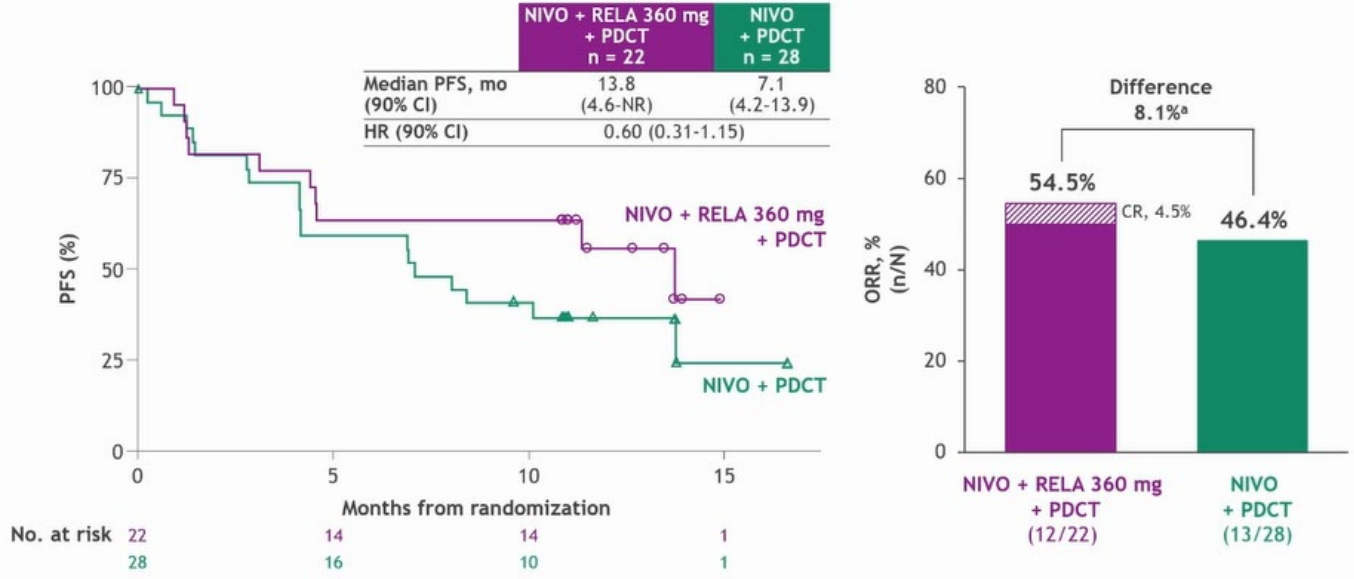
PD-L1 expression 1-49% and NSQ: PFS and ORR



Median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.
a90% CI: 3.7-52.3. Calculated using the stratified Cochran-Mantel-Haenszel method.
Historical controls for I-O + PDCT for PD-L1 1-49% NSQ: Gandhi L, et al. *N Engl J Med* 2018;378:2078-2092; Velcheti V, et al. *Sci Rep* 2021;11:9222.

RELATIVITY-104: 1L NIVO + RELA + PDCT in metastatic

PD-L1 expression ≥ 50% and NSQ: PFS and ORR



Median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.
a90% CI: −17.3-32.2. Calculated using the stratified Cochran-Mantel-Haenszel method.

1a L quimio-inmuno + anti-LAG3

Fase 2, RELATIVITY-104, relatlimab

Iniciativa científica de: GECP lung cancer research

Summary: nivolumab + relatlimab 360 mg in metastatic NSCLC

- **RELATIVITY-104** is the first proof-of-concept randomized phase 2 study in metastatic NSCLC that demonstrated improved clinical benefit from the addition of LAG-3 inhibition to anti-PD-1 + chemo in the PD-L1 ≥ 1% stratified and pre-specified patient subgroup, which was further enriched with NSQ histology
- The safety profile of nivolumab + relatlimab 360 mg + PDCT was consistent with the known profile of the individual components of the combination, and showed no increase in AE rates vs nivolumab + PDCT
- **RELATIVITY-1093** (NCT06561386) is an open-label, randomized, phase 3 study evaluating nivolumab + relatlimab 360 mg + PDCT vs standard-of-care pembrolizumab + PDCT as 1L treatment for patients with metastatic NSCLC having PD-L1 expression 1-49% and NSQ histology
- An additional phase 3 study for patients with metastatic NSCLC having PD-L1 ≥ 50% and NSQ histology is currently under development

1a Linea immunoterapia

Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

BARCELONA 2024 ESMO congress

Low-dose versus standard dose pembrolizumab for treatment of advanced-stage non-small cell lung carcinoma (NSCLC)

Results of the pre-planned interim analysis of the NVALT-30 clinical trial

Michel M van den Heuvel[1], Berber Piet[1], Vincent van der Noort[2], Nicole Barlo[3], Yvonne Berk[4], Annette Bijsmans[5], Niels Claessens[6], Emanuel Citgez[7], Daphne Dumoulin[8], Wouter van Geffen[9], Erica Geraedts[10], Lizza Hendriks[11], Judith Herder[12], Jeroen Hiltermann[13], Wouter Jacobs[14], Joost Jansen[15], Antoinette Kroeze[16], Way-Yee Lam-Wong[17], Ernst Lammers[18], Keetie van Loenhout[19], Femke van der Meer[20], Arthur Mulders[21], Suzy Samii[22], Arthur Smit[23], Marijn Smits[24], Jeske Staal[25], Christi Steendam[26], Svitlana Tarasevych[27], Quincy de Waard[28], Nicolaas van Walree[29], Maggy Youssef[30], Rob ter Heine[1].

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1a Linea immunoterapia

Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

Background

Rationale dosing pembrolizumab

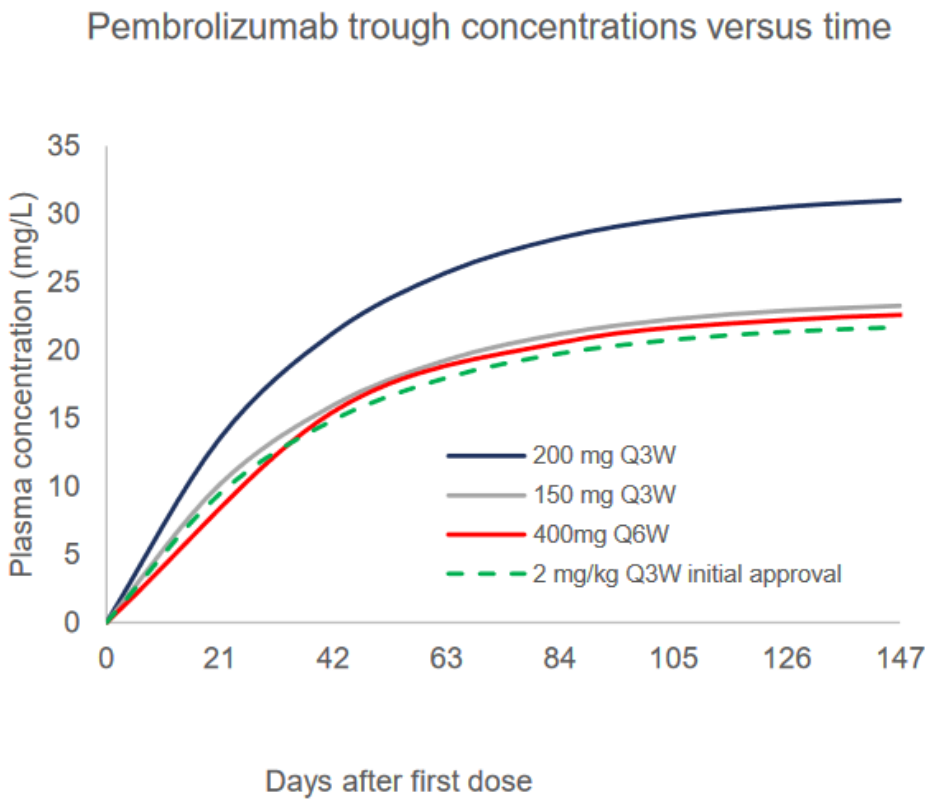
Improved overall survival NSCLC due to immune checkpoint blockade

Limitations:

1. Response rate approx. 50%
2. Toxicity
3. Limited data on optimal dosing

→ Redundant healthcare costs

→ Redundant exposure to pembrolizumab



Pembrolizumab - Patnaik et al. Clin. Cancer Res. 21, 4286–4293 (2015); Elassaiss-Schaap et al. CPT Pharmacometrics Syst Pharmacol . 2017 Jan;6(1):21-28.

1a Linea immunoterapia

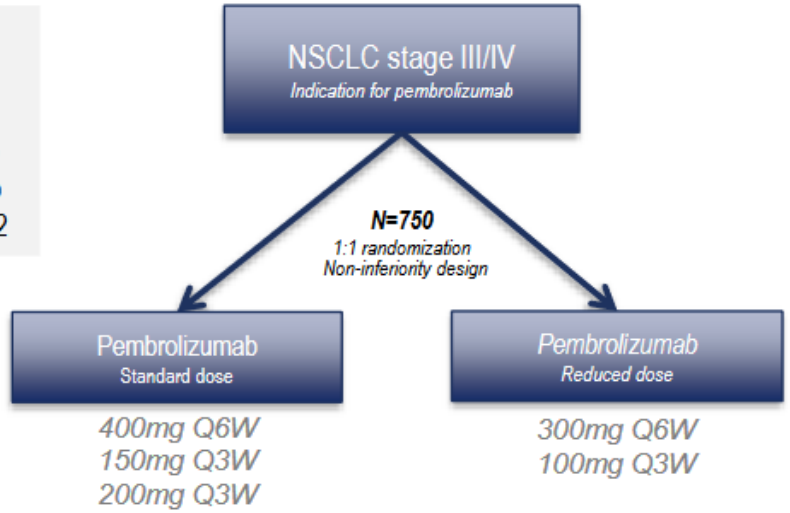
Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

Design

DEDICATION-1 trial (NVALT-30)

Stratification factors:
- Type of treatment:
  - Pembrolizumab
  - Pemetrexed / platinum / pembrolizumab
  - Carboplatin / paclitaxel / pembrolizumab
- Smoking, PDL1 status, Gender, PS 0/1 vs 2



Primary objective:

To investigate the non-inferiority of reduced dose pembrolizumab vs. standard dose for treatment of advanced stage NSCLC in terms of overall survival

Secondary objectives:
- DCR, PFS, OS, 1yr-DCR, ORR
- To develop, assess, and validate immune checkpoint inhibitor response biomarkers

Interim analysis:

A difference of 10% between arms in one-year overall survival (OS) is considered clinically relevant and set as stopping criterion for the interim analysis

1a Linea immunoterapia

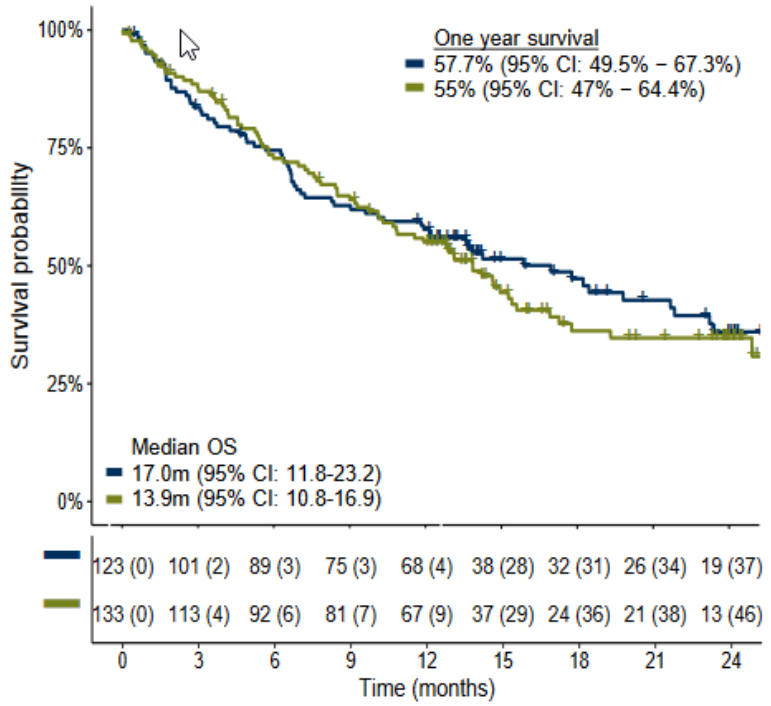
Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

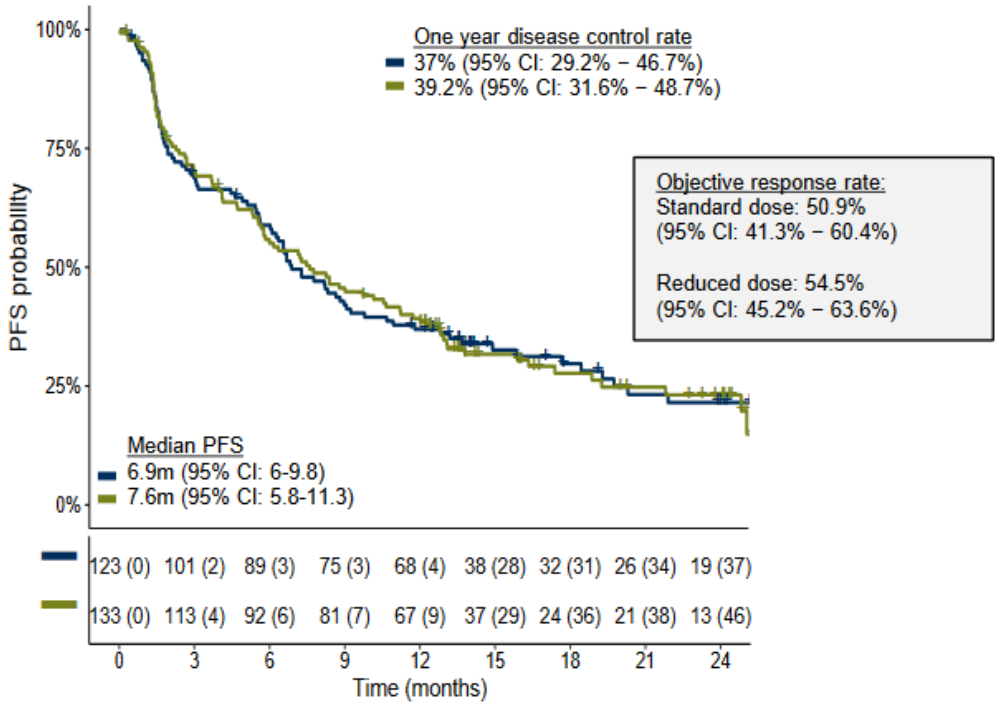
Survival analysis

DEDICATION-1 trial (NVALT-30)

Overall survival



Progression free survival



BARCELONA 2024 ESMO congress

Standard dose

Reduced dose

DEDICATION

1a Linea immunoterapia

Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

Conclusion

DEDICATION-1 trial (NVALT-30)

- The one-year survival (2.7%) difference meets the predetermined criterion for continuing inclusion
- Trials on optimization of dosing, duration, and personalization of treatment are underrepresented in current research
- Real world efficacy (chemo)immunotherapy (NVALT30 vs KN189):
  - One-years OS: 58 vs. 70%
  - Median OS: 17 vs. 22 months

Gadgeel et al, J Clin Oncol. 2020. doi: 10.1200/JCO.19.03136.

1a Linea immunoterapia

Low dose pembrolizumab

Iniciativa científica de: GECP lung cancer research

How to decrease exposure to Pembrolizumab?

Same frequency (q3w) BUT

Lower dose: 100 mg flat dose or 2 mg/kg or even less…

Same dose (200 mg) BUT

Lower frequency: q6w, q9w, q12w…

Mariana Brandão, MD/PhD

Datopotamab-Deruxtecan, TROPION-Lung01

Datos finales OS

Iniciativa científica de: GECP lung cancer research

2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Datopotamab Deruxtecan vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

Jacob Sands,[1] Aaron Lisberg,[2] Isamu Okamoto,[3] Luis Paz-Ares,[4] Robin Cornelissen,[5] Nicolas Girard,[6] Elvire Pons-Tostivint,[7] David Vicente Baz,[8] Shunichi Sugawara,[9] Manuel Cobo Dols,[10] Maurice Pérol,[11] Céline Mascaux,[12] Elena Poddubskaya,[13] Satoru Kitazono,[14] Hidetoshi Hayashi,[15] Min Hee Hong,[16] Enriqueta Felip,[17] Richard Hall,[18] Oscar Juan-Vidal,[19] Daniel Brungs,[20] Shun Lu,[21] Marina Garassino,[22] Ekaterine Alexandris,[23] Yong Zhang,[23] Paul Howarth,[23] Deise Uema,[23] Myung-Ju Ahn[24]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA; [3]Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [4]Hospital Universitario 12 de Octubre, Madrid, Spain; [5]Erasmus MC, Rotterdam, Netherlands; [6]Institut Curie, Paris, France; [7]University Hospital of Nantes, Nantes, France; [8]Hospital Universitario Virgen Macarena, Sevilla, Spain; [9]Sendai Kousei Hospital, Sendai, Japan; [10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [11]Centre Léon Bérard, Lyon, France; [12]Hopitaux Universitaire de Strasbourg, Strasbourg, France; [13]VitaMed LLC, Moscow, Russia; [14]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [15]Kindai University Hospital, Osaka, Japan; [16]Yonsei Cancer Center, Severance Hospital, Seoul, Republic of Korea; [17]Vall d'Hebron Hospital Campus, Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Spain; [18]University of Virginia Health System, Charlottesville, VA, USA; [19]Hospital Universitari i Politecnic La Fe, Valencia, Spain; [20]Southern Medical Day Care Centre, University of Wollongong, Wollongong, Australia; [21]Shanghai Lung Cancer Center, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [22]Department of Medicine, Hematology-Oncology Section, Thoracic Oncology Program, The University of Chicago Medicine & Biological Sciences, Chicago, IL, USA; [23]Daiichi Sankyo, Basking Ridge, NJ, USA; [24]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Datopotamab-Deruxtecan, TROPION-Lung01

Datos finales OS

Iniciativa científica de: GECP lung cancer research

Study Design

TROPION-Lung01

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

1:1

- **Dato-DXd** 6 mg/kg Q3W (N=299)
- **Docetaxel** 75 mg/m² Q3W (N=305)

Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

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 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 α=0.045

[a]Evaluated per RECIST v1.1. [b]Presence vs absence. [c]United States/Japan/Western Europe vs rest of world.
BICR, blinded independent central review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

Datopotamab-Deruxtecan, TROPION-Lung01

Datos finales OS

Iniciativa científica de: GECP lung cancer research

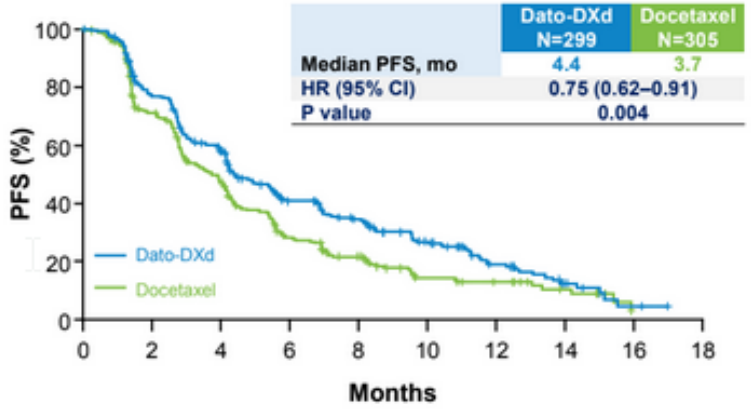
2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Background

TROPION-Lung01

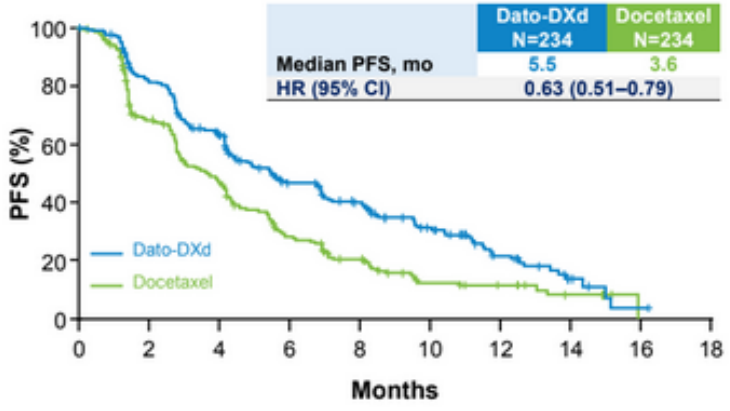
- Survival outcomes for patients with advanced NSCLC on docetaxel-based regimens in the second-line setting and beyond remain poor, and multiple trials of novel treatment regimens have failed in this setting, underscoring a high unmet need[1,2]
- **TROPION-Lung01** met its dual primary endpoint of **PFS with a statistically significant improvement** in favor of **datopotamab deruxtecan** (**Dato-DXd**) vs docetaxel[3]; a 37% reduction in relative risk of progression and more than doubling of response rate were seen in the NSQ subgroup[4]

ITT

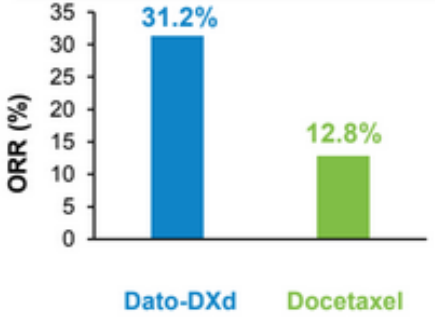


	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

NSQ



	Dato-DXd N=234	Docetaxel N=234
Median PFS, mo	5.5	3.6
HR (95% CI)	0.63 (0.51–0.79)	



	Dato-DXd N=234	Docetaxel N=234
Median DOR, mo	7.7	5.6

- Differential PFS outcomes by histology for Dato-DXd have been independently reported in two other NSCLC trials[5,6]

Here, we report the final analysis of the dual primary endpoint of overall survival for TROPION-Lung01

1. Fossella FV, et al. *J Clin Oncol* 18:2354-2362, 2000; 2. Reck M, et al. *Lancet Oncol* 15:143-155, 2014; 3. Ahn M-J, et al. Presented at ESMO 2023, Madrid, Spain, October 20–24, 2023 (Abstract 509MO);
4. Girard N, et al. Presented at ELCC 2024, Prague, Czech Republic, March 20–23, 2024 (Poster 59P); 5. Planchard D, et al. *J Clin Oncol* 42:8501, 2024; 6. Sun Y, et al. *J Clin Oncol* 42:8548, 2024.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; mo, months; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; PFS, progression-free survival.

Datopotamab-Deruxtecan, TROPION-Lung01

Datos finales OS

Iniciativa científica de: GECP lung cancer research

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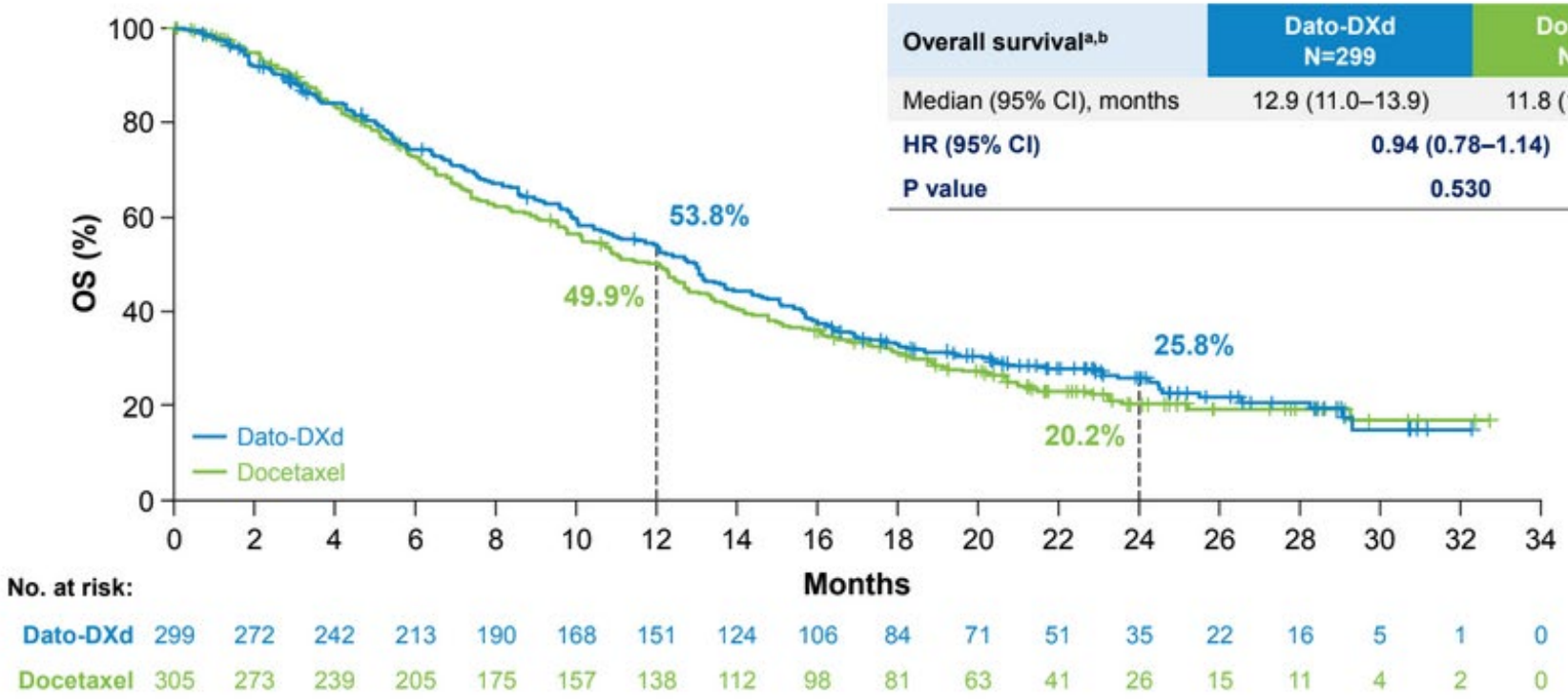
Overall Survival: ITT

TROPION-Lung01



Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	0.94 (0.78–1.14)	
P value	0.530	

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

Datopotamab-Deruxtecan, TROPION-Lung01

Datos finales OS

Iniciativa científica de: GECP lung cancer research

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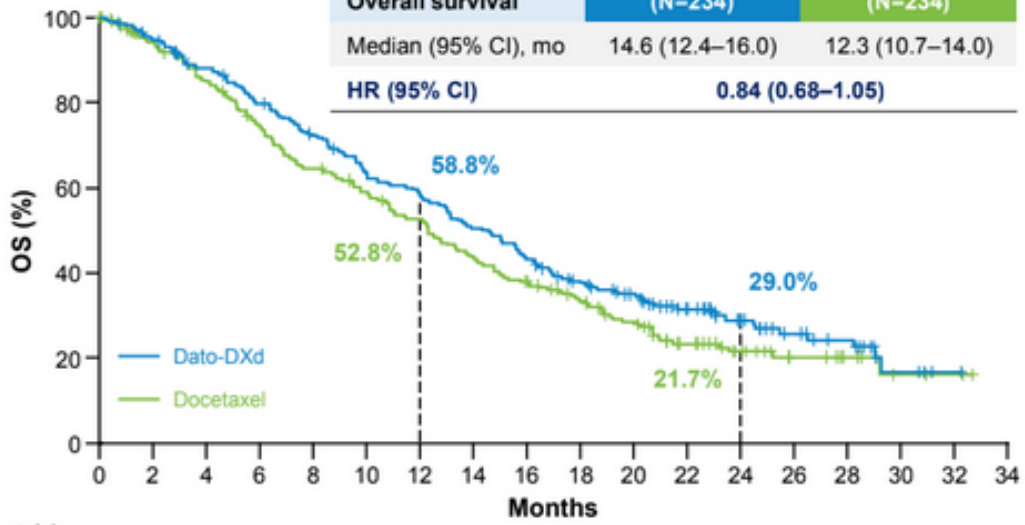
Overall Survival by Histology

TROPION-Lung01

Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

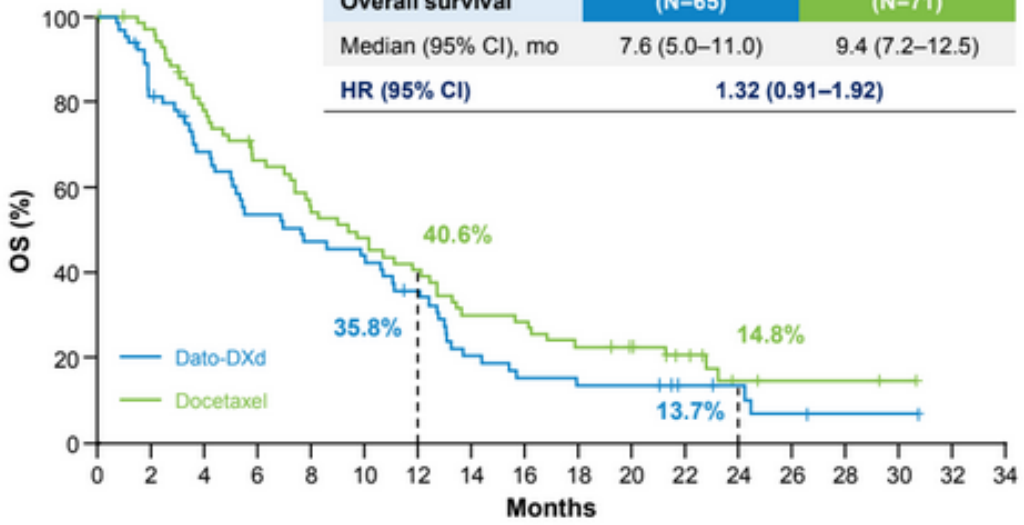


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.

[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

Sacituzumab-Govitecan, EVOKE 01

Impacto enfermedad no responedora a 1a línea

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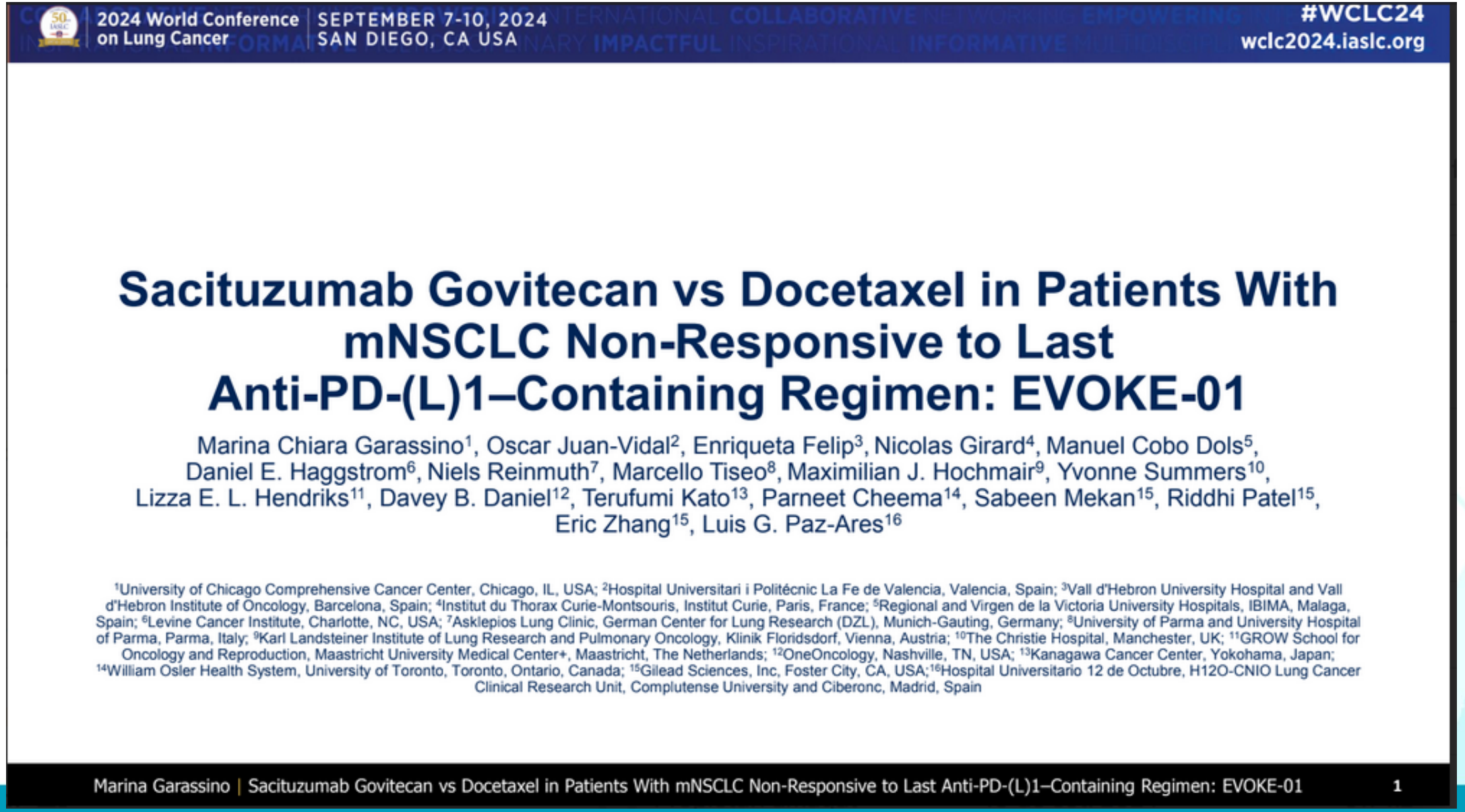

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Sacituzumab Govitecan vs Docetaxel in Patients With mNSCLC Non-Responsive to Last Anti-PD-(L)1–Containing Regimen: EVOKE-01

Marina Chiara Garassino[1], Oscar Juan-Vidal[2], Enriqueta Felip[3], Nicolas Girard[4], Manuel Cobo Dols[5], Daniel E. Haggstrom[6], Niels Reinmuth[7], Marcello Tiseo[8], Maximilian J. Hochmair[9], Yvonne Summers[10], Lizza E. L. Hendriks[11], Davey B. Daniel[12], Terufumi Kato[13], Parneet Cheema[14], Sabeen Mekan[15], Riddhi Patel[15], Eric Zhang[15], Luis G. Paz-Ares[16]

[1]University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; [2]Hospital Universitari i Politécnic La Fe de Valencia, Valencia, Spain; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [5]Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain; [6]Levine Cancer Institute, Charlotte, NC, USA; [7]Asklepios Lung Clinic, German Center for Lung Research (DZL), Munich-Gauting, Germany; [8]University of Parma and University Hospital of Parma, Parma, Italy; [9]Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; [10]The Christie Hospital, Manchester, UK; [11]GROW School for Oncology and Reproduction, Maastricht University Medical Center+, Maastricht, The Netherlands; [12]OneOncology, Nashville, TN, USA; [13]Kanagawa Cancer Center, Yokohama, Japan; [14]William Osler Health System, University of Toronto, Toronto, Ontario, Canada; [15]Gilead Sciences, Inc, Foster City, CA, USA;[16]Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Clinical Research Unit, Complutense University and Ciberonc, Madrid, Spain

Sacituzumab-Govitecan, EVOKE 01

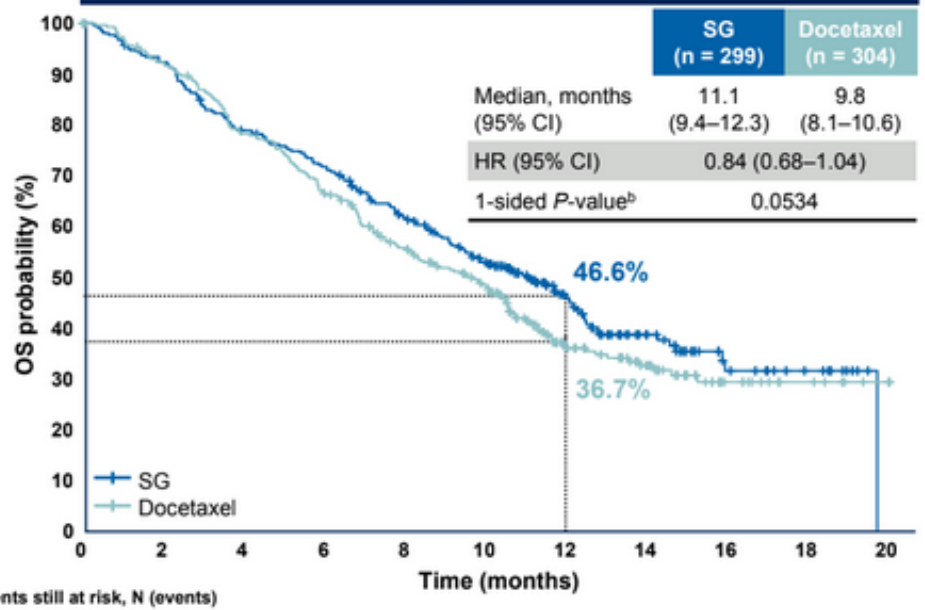
Impacto enfermedad no responedora a 1a línea

Iniciativa científica de: GECP lung cancer research

Background: EVOKE-01 Primary Results[1]

- There was a clinically meaningful OS improvement favoring SG over docetaxel in patients with mNSCLC that was non-responsive (SD/PD) to their last anti-PD-(L)1–containing regimen[a]
  - — Here we discuss this subgroup

OS: ITT



Patients still at risk, N (events)

SG	299 (0)	275 (23)	234 (63)	212 (83)	175 (112)	140 (137)	76 (150)	40 (162)	17 (166)	10 (167)	0 (168)
Docetaxel	304 (0)	277 (23)	234 (65)	201 (98)	158 (131)	128 (151)	64 (178)	41 (184)	15 (187)	7 (187)	2 (187)

OS: Key subgroups

Subgroup	HR	HR (95% CI)
Overall (N = 603)		0.84 (0.68–1.04)
Histology		
Squamous (n = 164)		0.83 (0.56–1.22)
Non-squamous (n = 439)		0.87 (0.68–1.11)
Best response to last anti-PD-(L)1–containing regimen[a]		
SD/PD (n = 383, 63.5%)		0.75 (0.58–0.97)
CR/PR (n = 219)		1.09 (0.76–1.56)
Received prior therapy for AGA		
No (n = 559)		0.89 (0.72–1.11)
Yes (n = 44)		0.52 (0.22–1.23)
Age group		
< 65 years (n = 297)		0.80 (0.59–1.08)
≥ 65 years (n = 306)		0.90 (0.68–1.20)
Baseline ECOG PS		
0 (n = 190)		1.06 (0.70–1.60)
1 (n = 410)		0.81 (0.64–1.04)

[a]Investigator-assessed. [b]One-sided *P*-value for significance was $P \leq 0.0223$.

AGA, actionable genomic alteration; **CR**, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HR**, hazard ratio; **ITT**, intent-to-treat; **mNSCLC**, metastatic non-small cell lung cancer; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PR**, partial response; **SD**, stable disease; **SG**, sacituzumab govitecan.

1. Paz-Ares LG, et al. *J Clin Oncol*. Published online May 31, 2024. doi:10.1200/JCO.24.00733.

Sacituzumab-Govitecan, EVOKE 01

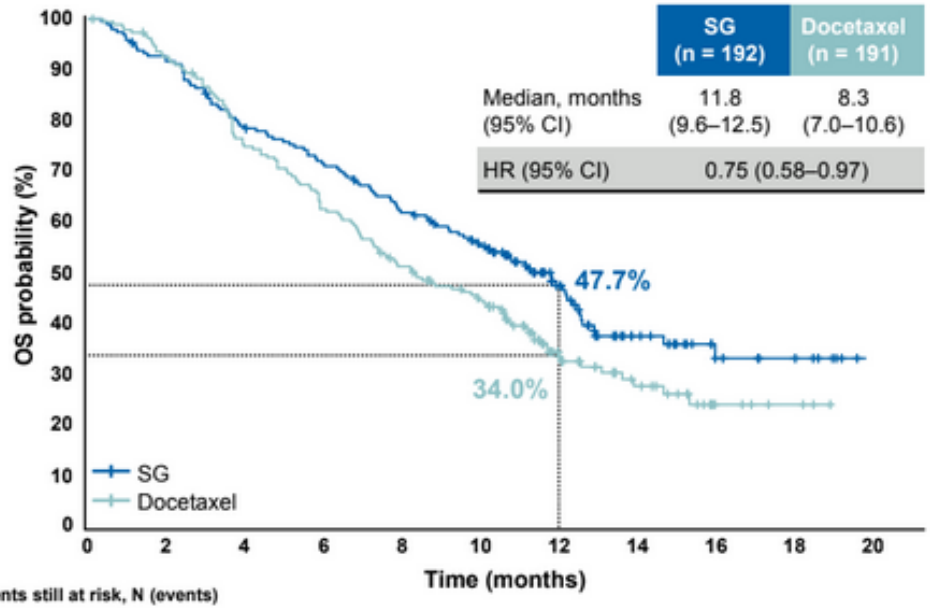
Impacto enfermedad no responedora a 1a línea

Iniciativa científica de: GECP lung cancer research

Efficacy: Non-Responsive (SD/PD) to Last Anti-PD-(L)1–Containing Regimen

SG had a 3.5-month median OS improvement over docetaxel among the subgroup of patients with non-responsive (SD/PD) disease

OS[1]

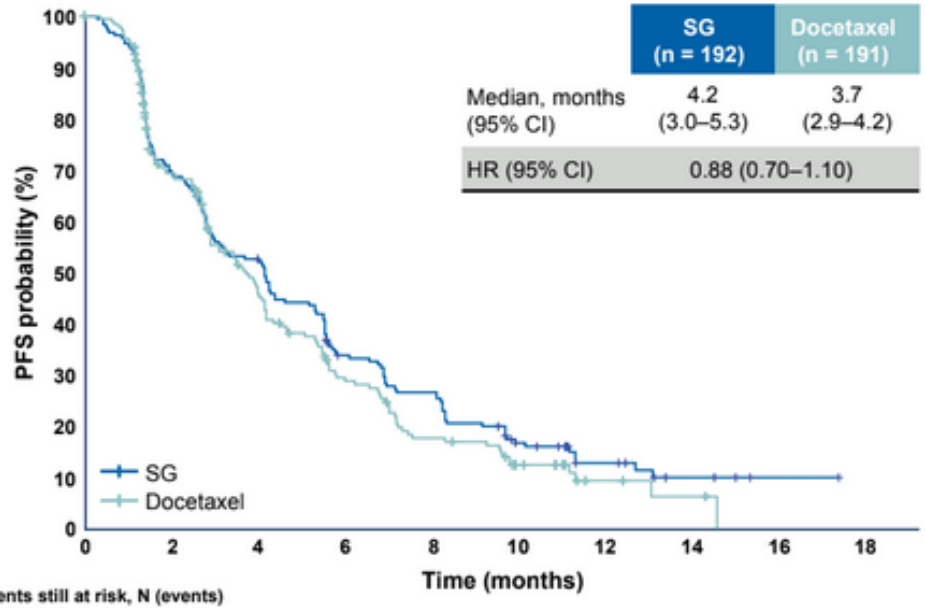


	SG (n = 192)	Docetaxel (n = 191)
Median, months (95% CI)	11.8 (9.6–12.5)	8.3 (7.0–10.6)
HR (95% CI)	0.75 (0.58–0.97)	

Patients still at risk, N (events)

SG	192 (0)	175 (16)	149 (41)	135 (54)	116 (72)	98 (84)	53 (95)	26 (105)	11 (107)	8 (107)	0 (108)
Docetaxel	191 (0)	175 (14)	141 (47)	118 (70)	95 (91)	78 (103)	36 (119)	21 (124)	6 (126)	3 (126)	0 (126)

PFS[a]



	SG (n = 192)	Docetaxel (n = 191)
Median, months (95% CI)	4.2 (3.0–5.3)	3.7 (2.9–4.2)
HR (95% CI)	0.88 (0.70–1.10)	

Patients still at risk, N (events)

SG	192 (0)	127 (56)	94 (87)	56 (120)	44 (132)	23 (148)	11 (152)	4 (154)	1 (154)	0 (154)	
Docetaxel	191 (0)	116 (54)	74 (90)	43 (117)	25 (134)	13 (141)	4 (143)	2 (144)	0 (145)		

[a]By investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1.

HR, hazard ratio; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PFS**, progression-free survival; **SD**, stable disease; **SG**, sacituzumab govitecan.

1. Paz-Ares LG, et al. *J Clin Oncol*. Published online May 31, 2024. doi:10.1200/JCO.24.00733.

Sacituzumab-Govitecan, EVOKE 01

Impacto enfermedad no responedora a 1a línea

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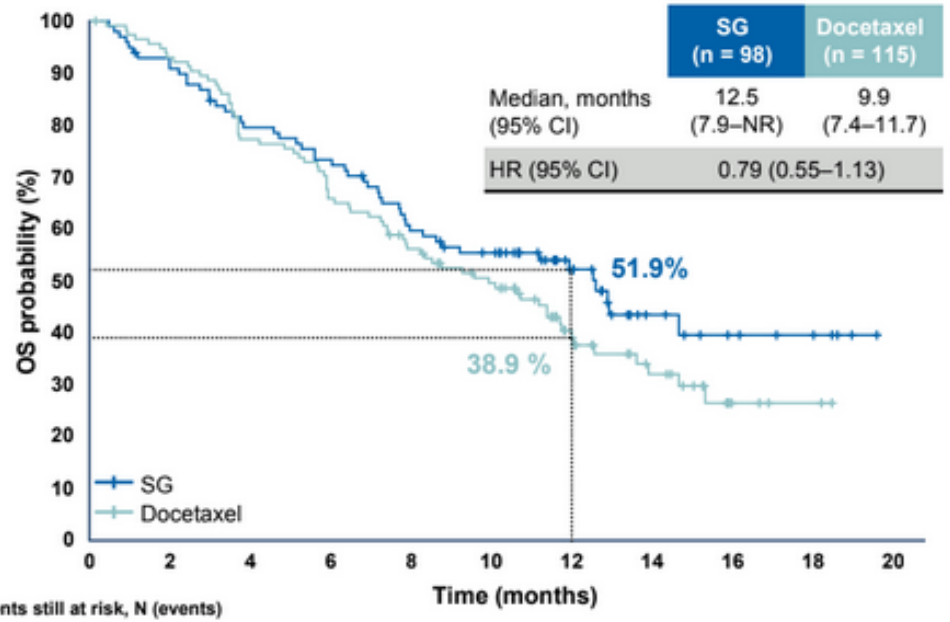
Overall Survival: SD or PD as Best Response to Last Anti-PD-(L)1–Containing Regimen

SG showed an OS improvement over docetaxel in both SD and PD subgroups

SD[a]

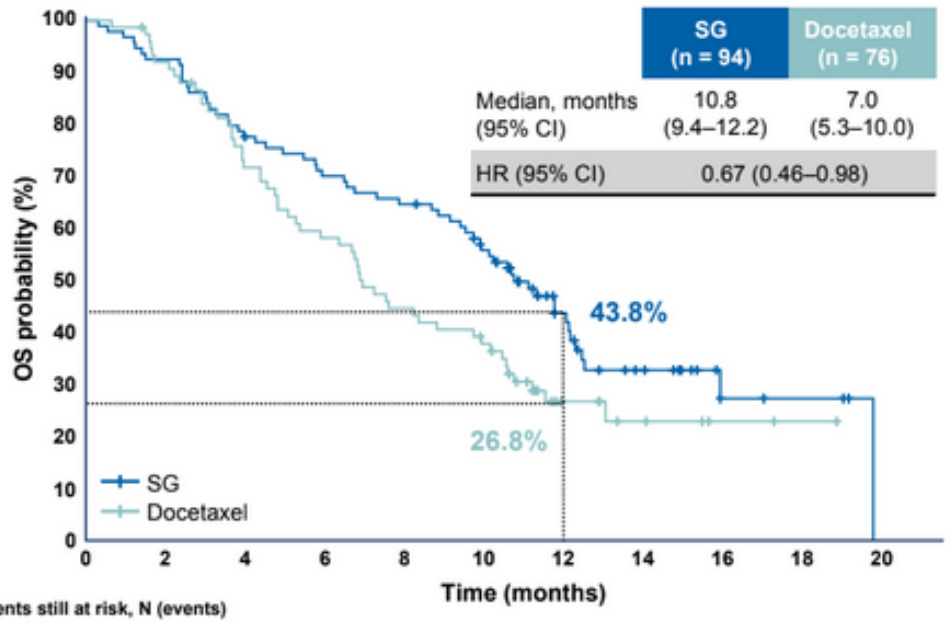


	SG (n = 98)	Docetaxel (n = 115)
Median, months (95% CI)	12.5 (7.9–NR)	9.9 (7.4–11.7)
HR (95% CI)	0.79 (0.55–1.13)	

Patients still at risk, N (events)

SG	98 (0)	88 (9)	76 (20)	70 (26)	56 (39)	49 (43)	28 (45)	12 (49)	7 (50)	5 (50)	0 (50)
Docetaxel	115 (0)	106 (8)	88 (26)	75 (39)	62 (50)	51 (57)	27 (66)	16 (70)	4 (72)	2 (72)	

PD[a]



	SG (n = 94)	Docetaxel (n = 76)
Median, months (95% CI)	10.8 (9.4–12.2)	7.0 (5.3–10.0)
HR (95% CI)	0.67 (0.46–0.98)	

Patients still at risk, N (events)

SG	94 (0)	87 (7)	73 (21)	65 (28)	60 (33)	49 (41)	25 (50)	14 (56)	4 (57)	3 (57)	0 (58)
Docetaxel	76 (0)	69 (6)	53 (21)	43 (31)	33 (41)	27 (46)	9 (53)	5 (54)	2 (54)	1 (54)	

[a]Best response to last anti-PD-(L)1–containing regimen.

HR, hazard ratio; **NR**, not reached; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **SD**, stable disease; **SG**, sacituzumab govitecan.

Sacituzumab-Govitecan, EVOKE 01

Impacto enfermedad no responedora a 1a línea

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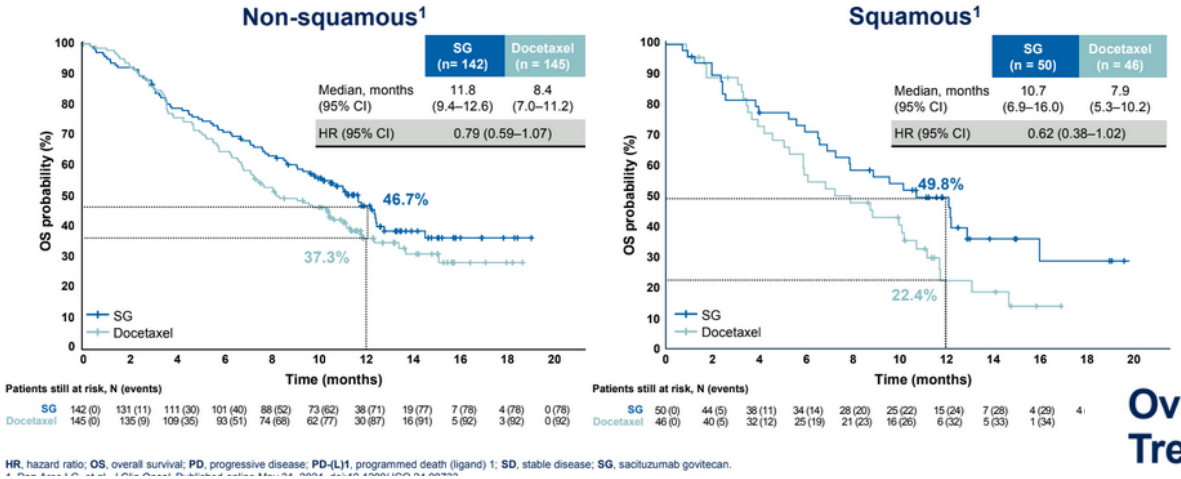
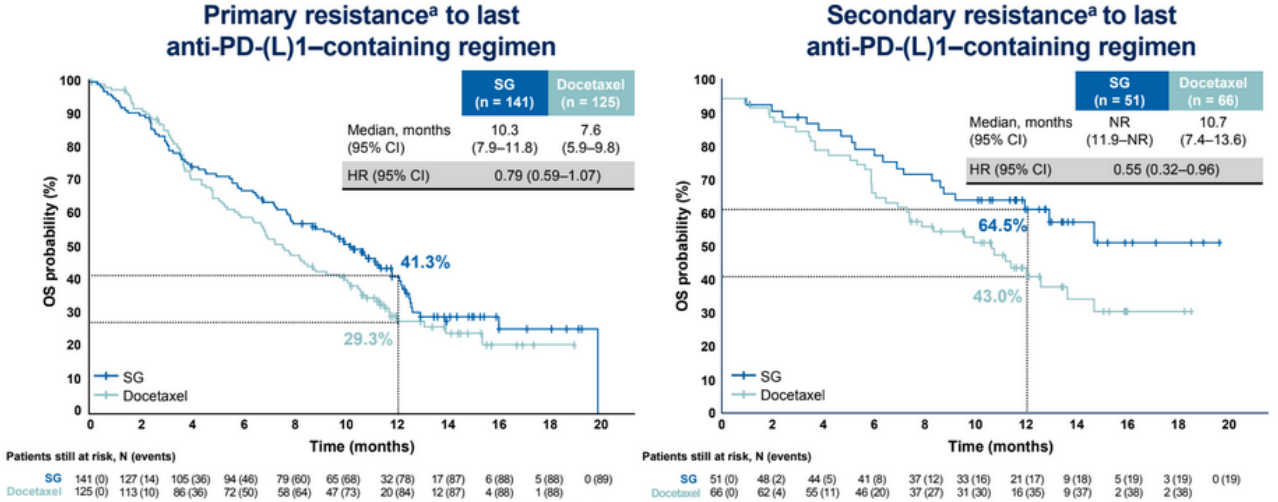
Overall Survival: Non-Responsive (SD/PD) to Last Anti-PD-(L)1–Containing Regimen, by Histology

SG showed an OS improvement over docetaxel in both non-squamous and squamous histologies



HR, hazard ratio; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; SD, stable disease; SG, sacituzumab govitecan.

Overall Survival Analysis: Primary or Secondary Resistance to Treatment With Last Anti-PD-(L)1–containing Regimen (SD/PD)



[a]Primary resistance per SITC-based criteria for PD-(L)1 inhibitors: patients with PD or SD (< 6 months on treatment); secondary resistance SD (≥6 months on treatment), no patients in subgroup had CR or PR.[1]

CR, complete response; **HR**, hazard ratio; **NR**, not reached; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PR**, partial response; **SD**, stable disease; **SITC**, Society for Immunotherapy of Cancer; **SG**, sacituzumab govitecan.

1. Kluger HM, et al. *J Immunother Cancer*. 2023;11:e005921.

Datopotanamab-deruxtecan (Biomarker)

Normalized membrane ratio TROP2

Iniciativa científica de: GECP lung cancer research

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Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

Marina Chiara Garassino,[1] Jacob Sands,[2] Luis Paz-Ares,[3] Aaron Lisberg,[4] Melissa Johnson,[5] Maurice Pérol,[6] Danielle Carroll,[7] Ansh Kapil,[8] Vincent Haddad,[7] Deise Uema,[9] Hadassah Sade,[8] Myung-Ju Ahn,[10]

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Datopotanamab-deruxtecan (Biomarker)

Normalized membrane ratio TROP2

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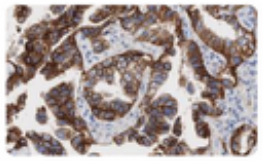
TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

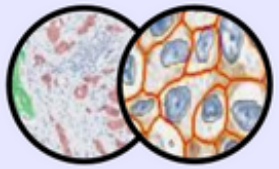
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

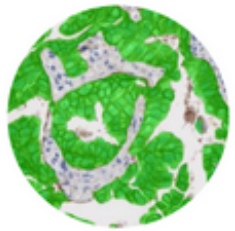


4 Patient Biomarker Status Determination

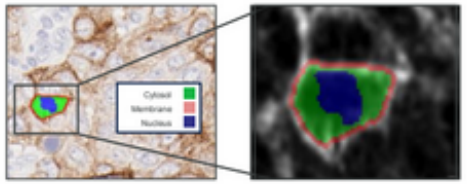
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

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

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

Lower NMR → higher cytoplasm proportion

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OD, optical density (a measure of staining intensity).
*Or >25% of cells with an NMR >0.56

Datopotanamab-deruxtecan (Biomarker)

Normalized membrane ratio TROP2

Iniciativa científica de: GECP lung cancer research

TROPION-Lung01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
– 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
– Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
– 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

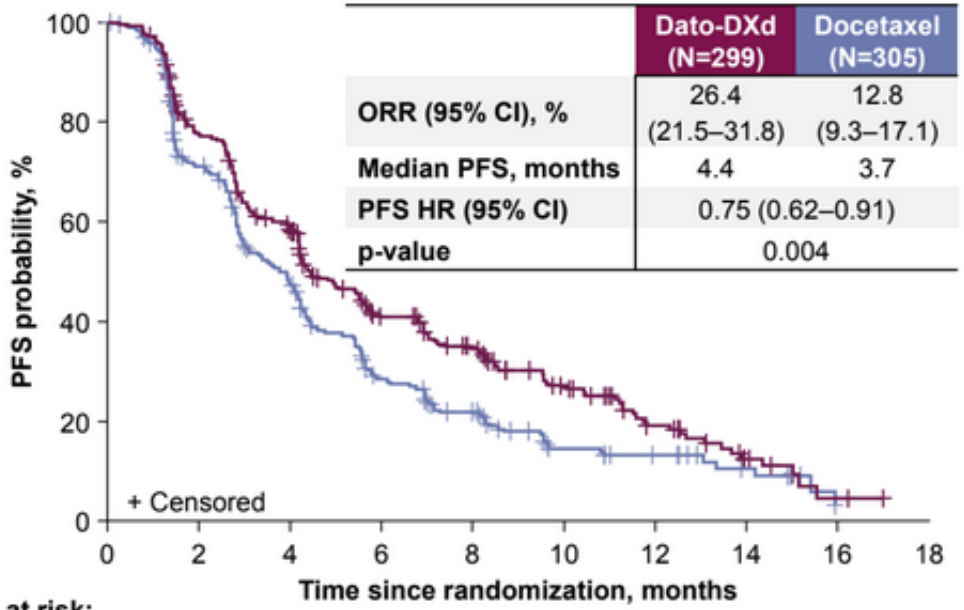
R 1:1

- **Dato-DXd** 6 mg/kg q3w N=299
- **Docetaxel** 75 mg/m² q3w N=305

Stratified by: Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR[1]



	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

No. at risk:

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

1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).
Enrollment period: February 19, 2021, to November 7, 2022. Data cutoff: March 29, 2023.
AGA, actionable genomic alterations; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; q3w, every 3 weeks; R, randomized.
*Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. †Squamous vs non-squamous. ‡Presence vs absence. §United States/Japan/Western Europe vs other geographic regions.

Datopotanamab-deruxtecan (Biomarker)

Normalized membrane ratio TROP2

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Prevalence

Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
Biomarker-evaluable population, n=352	
NSQ	66% (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	76% (39/51)
SQ	44% (35/80)

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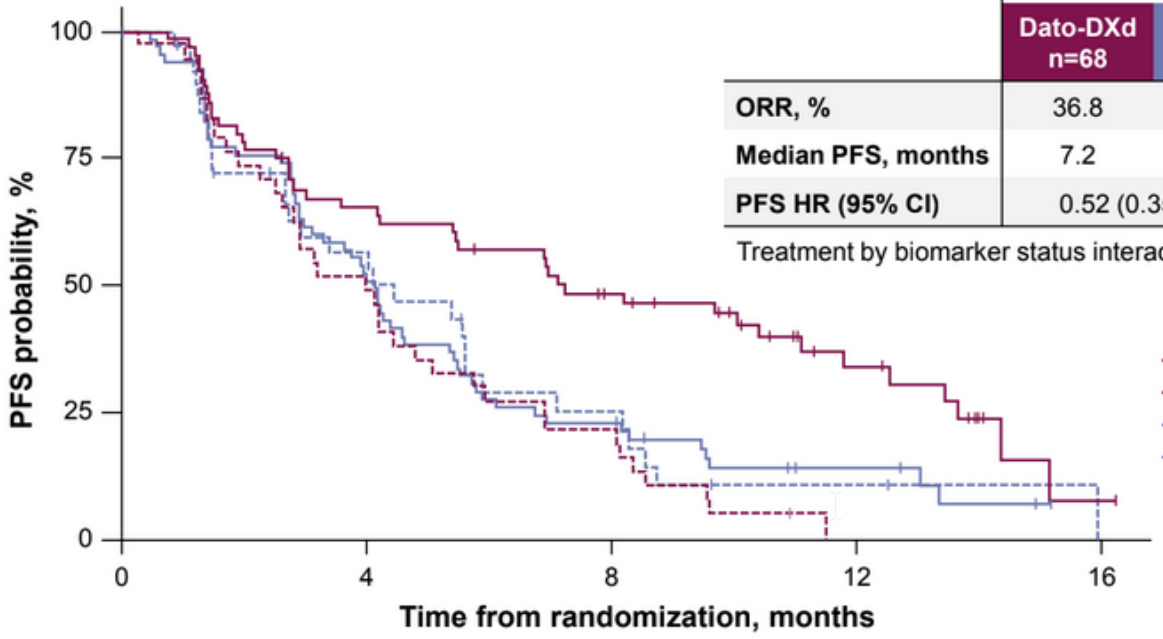
NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

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

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

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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]

Datopotanamab-deruxtecan (Biomarker)

Normalized membrane ratio TROP2

Iniciativa científica de: GECP lung cancer research

Conclusions

- TROP2 normalized membrane ratio (NMR) as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm) and predicts outcomes in an exploratory TROPION-Lung01 analysis:
  - TROP2 QCS-NMR+ was more prevalent in patients with NSQ vs SQ histology (66% vs 44%)
  - Patients receiving Dato-DXd who were TROP2 QCS-NMR+ had a higher ORR and longer PFS compared with those who were TROP2 QCS-NMR–
  - Overall/grade 3+ adverse event rates with Dato-DXd were similar regardless of TROP2 QCS-NMR status
- Further investigation of this promising biomarker is ongoing in the first-line advanced/metastatic NSCLC trials AVANZAR (NCT05687266) and TROPION-Lung 10 (NCT06357533)

TROP2 QCS-NMR has the potential to be the first TROP2 biomarker and the first computational pathology biomarker for predicting clinical response to Dato-DXd in NSCLC

Conclusiones

- 1a Línea monoterapia, PD-L1 ≥1%: fase 3, ivonescimab vs pembrolizumab
- -> positivo, pero en China (molécula muy prometedora)
- 1a Linea combo, PD-L1 ≥ 50%: fase 2, anti-TIGIT + dostarlimab
- 1a Línea combo: fase 2, QT-IO +/- anti LAG3
- -> prometedor, ayudarán a definir los fase 3
- 1a Línea, fase 3: low dose pembro vs Standard dose (interim analaysis)
- -> clínicamente muy relevante, pendientes datos estudio completo
- 2a Línea: ADCs TROP2: dato-deruxtecan (TROPION1-lung), sacituzumab-govitecan (EVOKE-01)
- -> no beneficio OS, biomarcador o selección pacientes