Lung Cancer UPDATES
ASCO HIGHLIGHTS
31 MAYO-04 JUNIO 2024
Chicago, USA

Iniciativa científica de:
GECP lung cancer research

CNMP AVANZADO SIN MUTACIONES ACCIONABLES

XABIER MIELGO-RUBIO, MD

Unidad de Oncología

Hospital Universitario Fundación Alcorcón

KEY-HOME MESSAGES

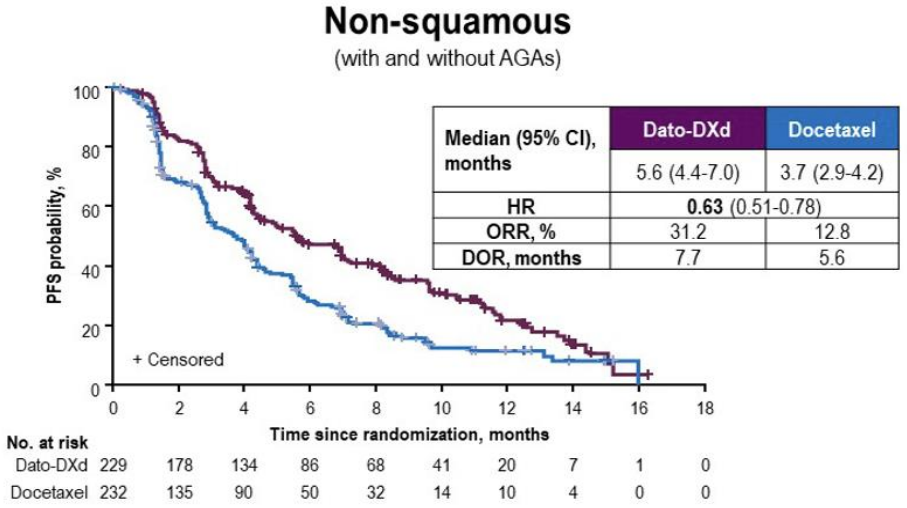
- ADC
  - TROP-2 ADC's in 2nd line not superior to SoC CT (Docetaxel)
  - (TROP-2) ADC's + ICB combo in 1L NSCLC promising!!!
  - Need more studies of biomarkers to better understand MoA and resistance
  - cMET directed Teliso-V: promising results in IHC+ pts, Will beat Docetaxel?
  - IB6 directed ADC: promising results in ph1. Tryng to beat Docetaxel irrespective of IHC
- Oligometastatic disease
  - First randomized ph II/III study evaluating LCT after 1L IO-based systemic régimen NEGATIVE (no PFS Benefit)
  - Further investigation required
- 1L immunotherapy
  - Confirmation of double IO + short CT regimen as an efficient alternative in advanced NSCLC with similar proportion of long survivors, with higher proportion in PD-L1 negative pts
- TTFields

ADC

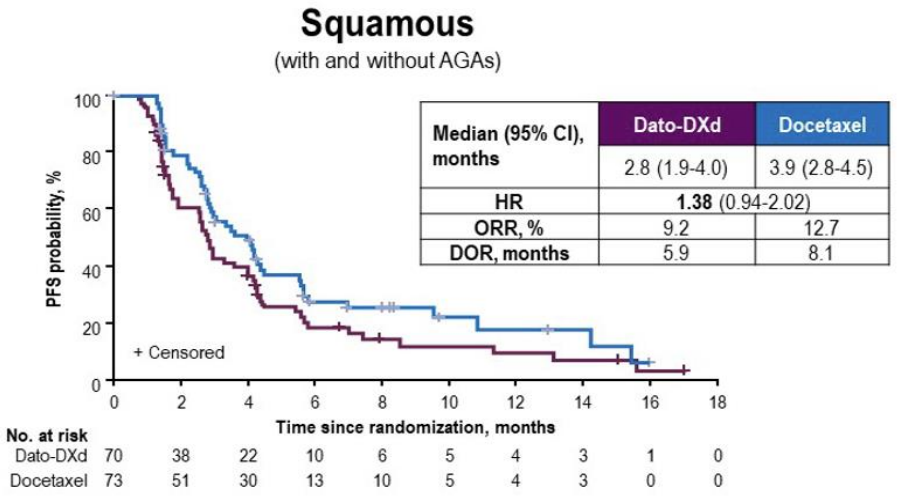
TROP-2

- Overexpressed in aprox 80% NSCLC
- High TROP-2 expression worse prognosis in adenocarcinomas (not sq)

- Phase 3 TROPION-Lung01 study: demonstrated significant improvement in PFS with Dato-DXd over Docetaxel (HR 0.75, p=0.004) in 2L NSCLC and clinically meaningful OS in non-sq histology



Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

ADC

TROP-2: EVOKE-01 - SACITUZUMAB GOVITECAN

Iniciativa científica de: GECP lung cancer research

2024 ASCO ANNUAL MEETING

2024 ASCO Annual meeting, May 31 – June 4, 2024, Chicago, IL, USA

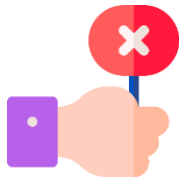
Abstract LBA8500

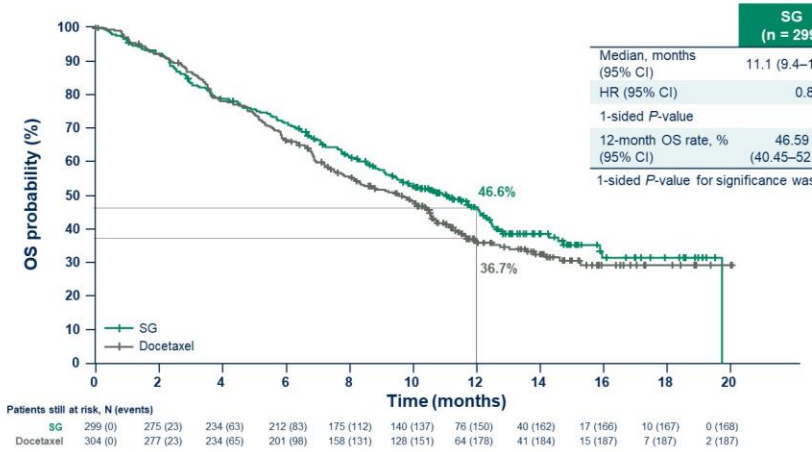
Sacituzumab Govitecan vs Docetaxel in Patients With Metastatic Non-small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy and PD-(L)1 Inhibitors: Primary Results From the Phase 3 EVOKE-01 Study

Luis G. Paz-Ares, MD, PhD,[1] Oscar Juan-Vidal, MD,[2] Giannis S. Mountzios, MD, PhD,[3] Enriqueta Felip, MD, PhD,[4] Niels Reinmuth, MD,[5] Filippo de Marinis, MD, PhD,[6] Nicolas Girard, MD, PhD,[7] Vipul M. Patel, MD,[8] Takayuki Takahama, MD, PhD,[9] Scott P. Owen, MD,[10] Douglas M. Reznick, MD,[11] Firas B. Badin, MD,[12] Irfan Cicin,MD,[13] Sabeen Mekan, MD,[14] Riddhi Patel, PharmD,[14] Eric Zhang, PhD,[14] Divyadeep Karumanchi, PharmD,[14] Marina Chiara Garassino, MD[15]

[1]Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Complutense University and Ciberoncse University and Ciberonc, Madrid, Spain; [2]Hospital Universitari i Politécnic La Fe de Valencia, Valencia, Spain; [3]Henry Dunant Hospital Center, Athens, Greece; [4]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Asklepios Lung Clinic, German Center for Lung Research (DZL), Munich-Gauting, Germany; [6]European Institute of Oncology IRCCS, Milan, Italy; [7]Institut du Thorax Curie Montsouris, Institut Curie, Paris, France; [8]Florida Cancer Specialists and Research Institute, Ocala, FL, USA; [9]Kindai University, Osaka, Japan; [10]McGill University Health Centre, Montreal, Quebec, Canada; [11]Rocky Mountain Cancer Center, Aurora, CO, USA; [12]Baptist Health Medical Group, Lexington, KY, USA; [13]Istinye University, Medical Center, Istanbul, Turkey; [14]Gilead Sciences, Inc, Foster City, CA, USA; [15]University of Chicago Comprehensive Cancer Center, Chicago, IL, USA

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 $P \leq 0.0223$

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

N = 603

R 1:1

- **Sacituzumab govitecan** 10 mg/kg on Days 1 and 8 of 21-day cycles[d]
- **Docetaxel** 75 mg/m² on Day 1 of 21-day cycles[d]

End points

Primary

- OS

Secondary

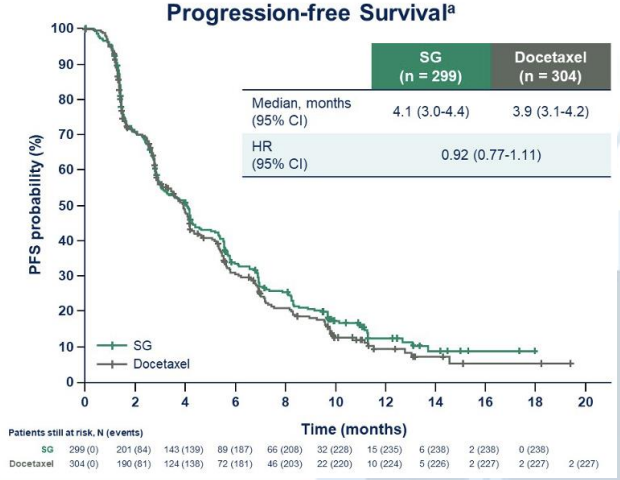
- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

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)

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)

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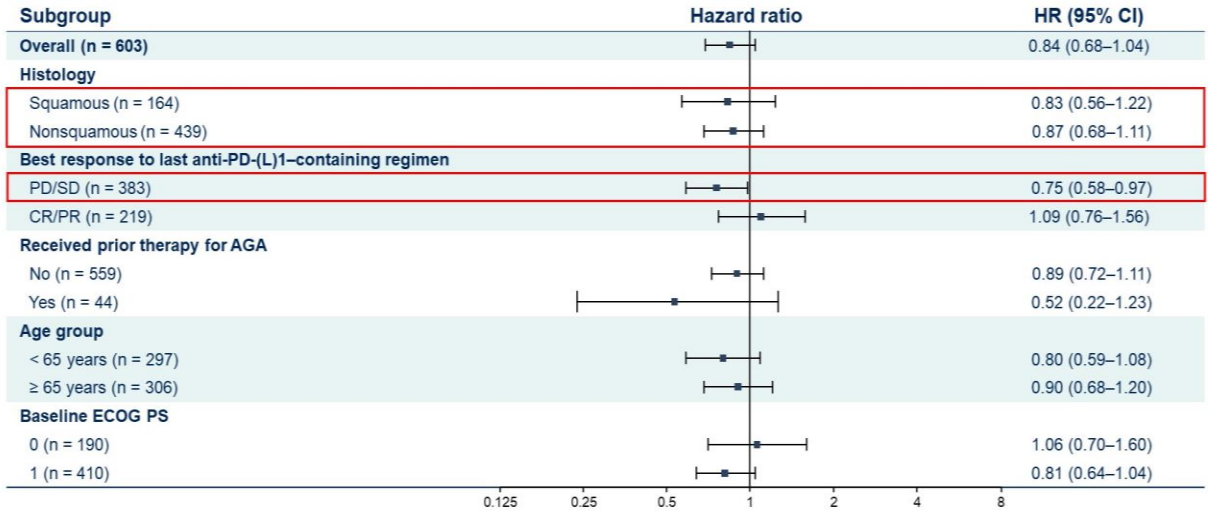
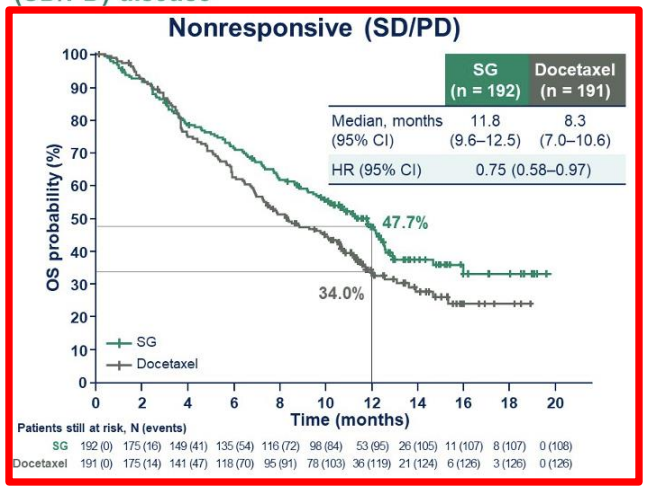
TROP-2: EVOKE-01 - SACITUZUMAB GOVITECAN

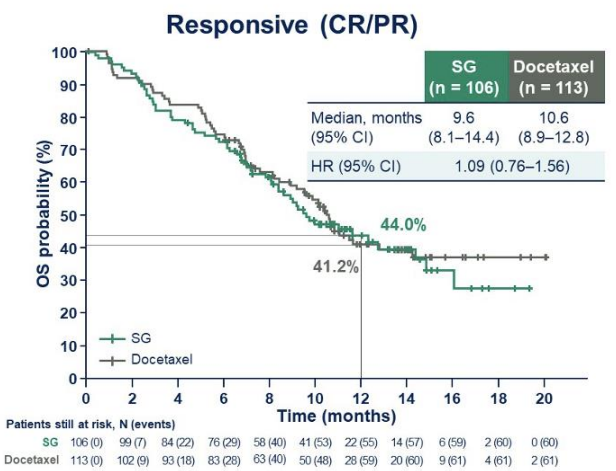
Iniciativa científica de: GECP lung cancer research

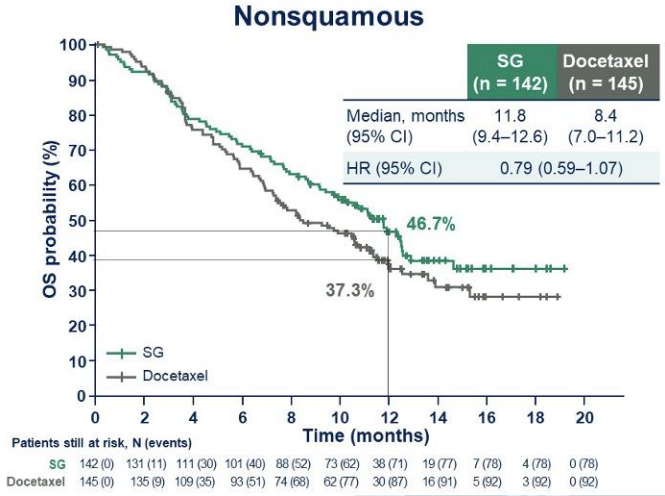
Overall Survival: Subgroup Analyses

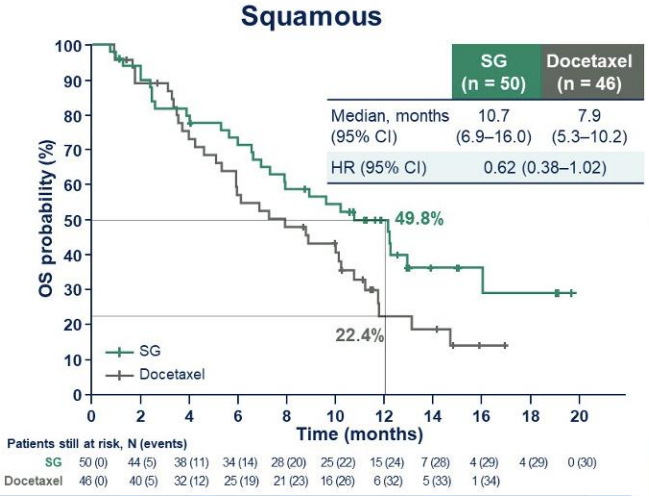


SG had a 3.5-month median OS improvement over docetaxel among subgroups with nonresponsive (SD/PD) disease









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TROP-2: EVOKE-01 - SACITUZUMAB GOVITECAN

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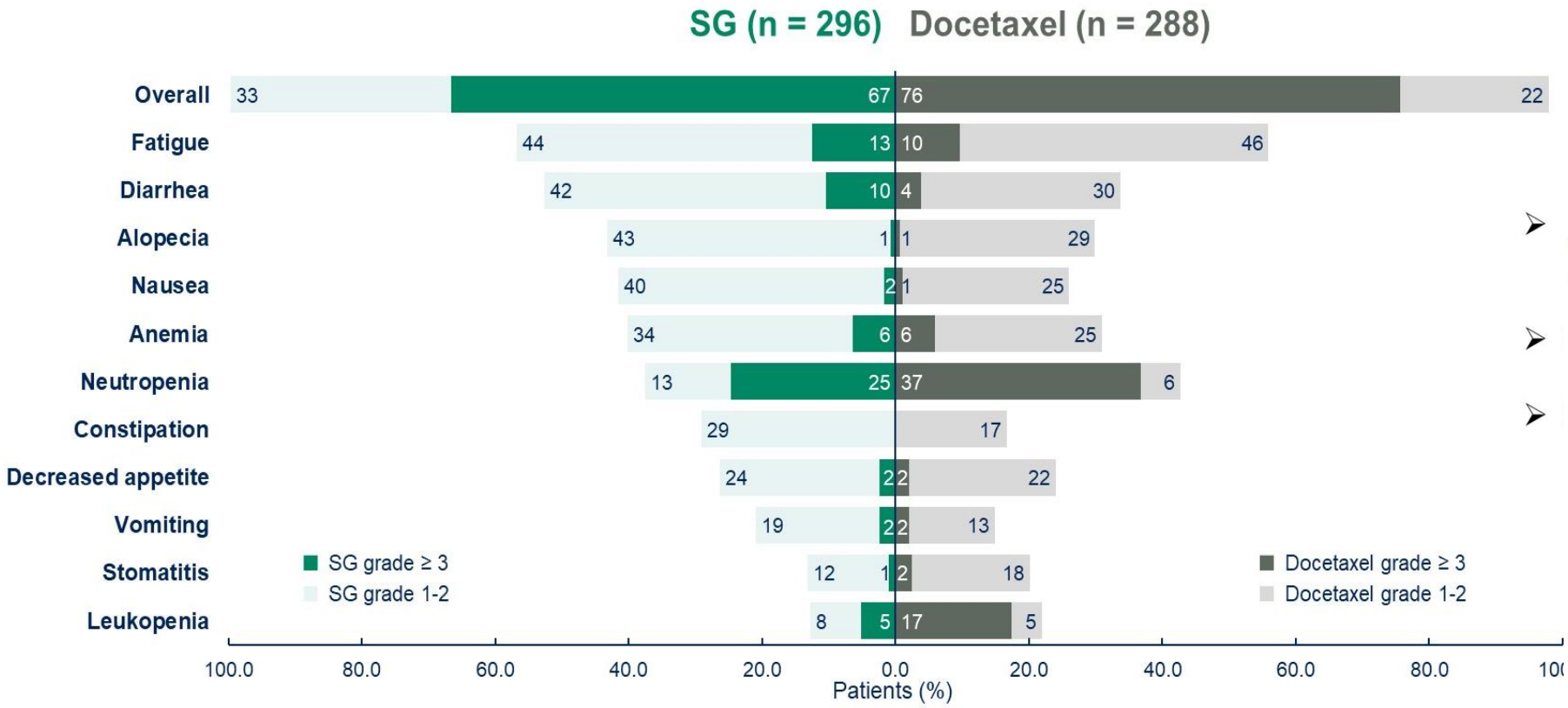
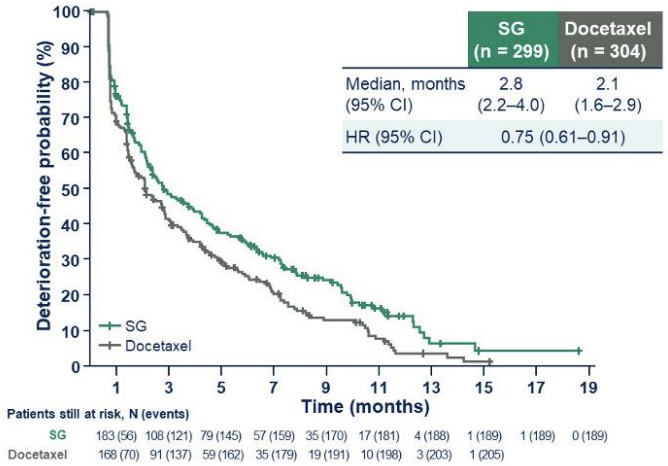
Treatment-Emergent Adverse Events

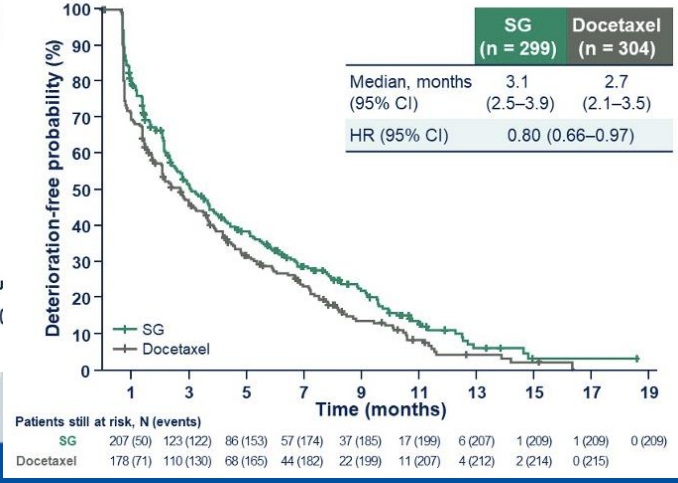
In ≥ 20% of patients receiving SG or docetaxel



TTD in shortness-of-breath domain



TTD in NSCLC-SAQ total score



ADC

TROP-2: OptiTROP-Lung01 – SACITUZUMAB TIMUROTECAN + ICB

Iniciativa científica de: GECP lung cancer research

2024 ASCO ANNUAL MEETING

Sacituzumab Tirumotecan (sac-TMT; Also Known as SKB264/MK-2870) in Combination With KL-A167 (Anti–PD-L1) as First-Line Treatment for Patients With Advanced NSCLC From the Phase II OptiTROP-Lung01 Study

Wenfeng Fang,[1] Qiming Wang,[2] Ying Cheng,[3] Yongzhong Luo,[4] Xiujuan Qu,[5] Haibo Zhu,[6] Zhenyu Ding,[7] XingYa Li,[8] Lin Wu,[4] Yan Wang,[9] Sheng Hu,[10] Enwen Wang,[11] AnWen Liu,[12] Yuping Sun,[13] Yun Fan,[14] Feng Ye,[15] Kaihua Lu,[16] Yalan Yang,[17] Junyou Ge,[17] Li Zhang[1]

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Henan Cancer Hospital, Zhengzhou, China; [3]Jilin Cancer Hospital, Changchun, China; [4]Hunan Cancer Hospital, Changsha, China; [5]The First Hospital of China Medical University, Shenyang, China; [6]Shanxi Cancer Hospital, Taiyuan, China; [7]West China Hospital of Sichuan University, Chengdu, China; [8]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [9]Harbin Medical University Cancer Hospital, Harbin, China; [10]Hubei Cancer Hospital, Wuhan, China; [11]Chongqing University Cancer Hospital, Chongqing, China; [12]The Second Affiliated Hospital of Nanchang University, Nanchang, China; [13]Shandong Cancer Hospital, Jinan, China; [14]Zhejiang Cancer Hospital, Hangzhou, China; [15]The First Affiliated Hospital of Xiamen University, Xiamen, China; [16]Jiangsu Province Hospital, Nanjing, China; [17]Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China

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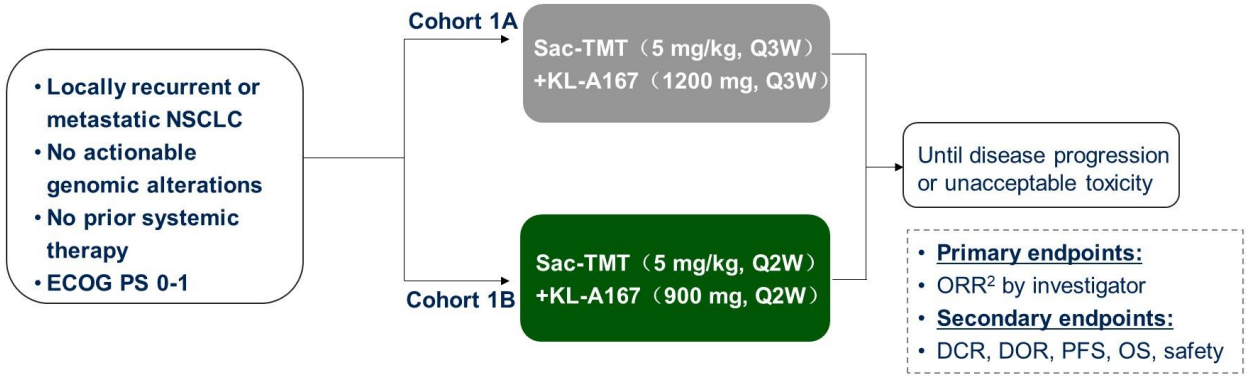
OptiTROP-Lung01: non-randomized, phase 2 study[1]

The first study evaluating sac-TMT + KL-A167 in locally recurrent or metastatic NSCLC without actionable genomic alterations.



[1] NCT05351788

[2] Tumor assessment was performed every 6 weeks per RECIST v1.1

ECOG PS: Eastern Cooperative Oncology Group performance status; DCR: disease control rate; DOR: duration of response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors.

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TROP-2: SACITUZUMAB TIMUROTECAN + ICB

45% non-squamous

54% non-squamous

Iniciativa científica de: GECP lung cancer research

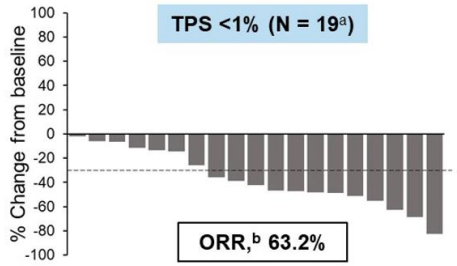
Efficacy in ITT population

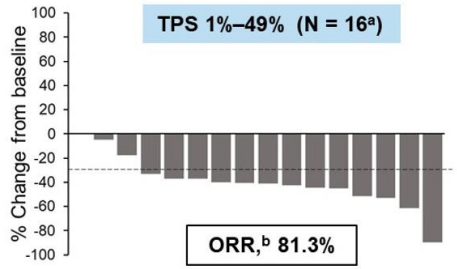
	Cohort 1A Sac-TMT (5 mg/kg Q3W) + KL-A167 (1200 mg Q3W) N = 40	Cohort 1B Sac-TMT (5 mg/kg Q2W) + KL-A167 (900 mg Q2W) N = 63
Median follow-up, mo	14.0	6.9
ORR,[a] n/N (%) [95% CI]	18/37 (48.6) [31.9, 65.6]	45/58 (77.6) [64.7, 87.5]
PR, n (%)	18 (48.6)	45 (77.6)
Confirmed PR, n (%)	16 (43.2)	40 (69.0)
SD, n (%)	17 (45.9)	13 (22.4)
PD, n (%)	2 (5.4)	0
DCR,[b] n/N (%)	35/37 (94.6)	58/58 (100.0)
Median DOR (95% CI), mo	NR (8.3, NE)	NR (6.6, NE)
Median PFS (95% CI), mo	15.4 (6.7, NE)	NR (8.4, NE)
6-mo PFS rate (95% CI), %	69.2 (51.2, 81.6)	84.6 (71.4, 92.1)

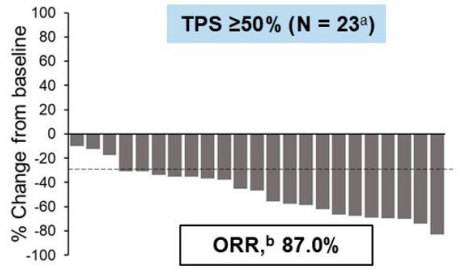
Efficacy by subgroups

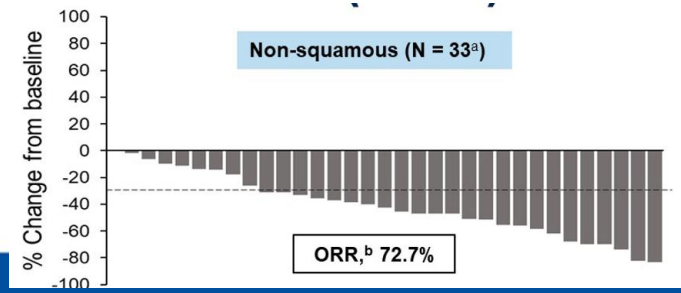
- PD-L1 <1%/1-49%/≥ 50%

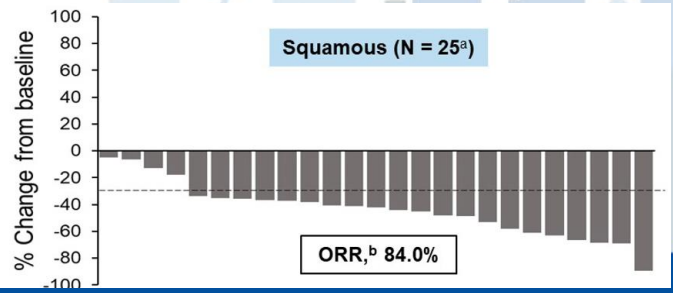
- Non-sq / Squamous











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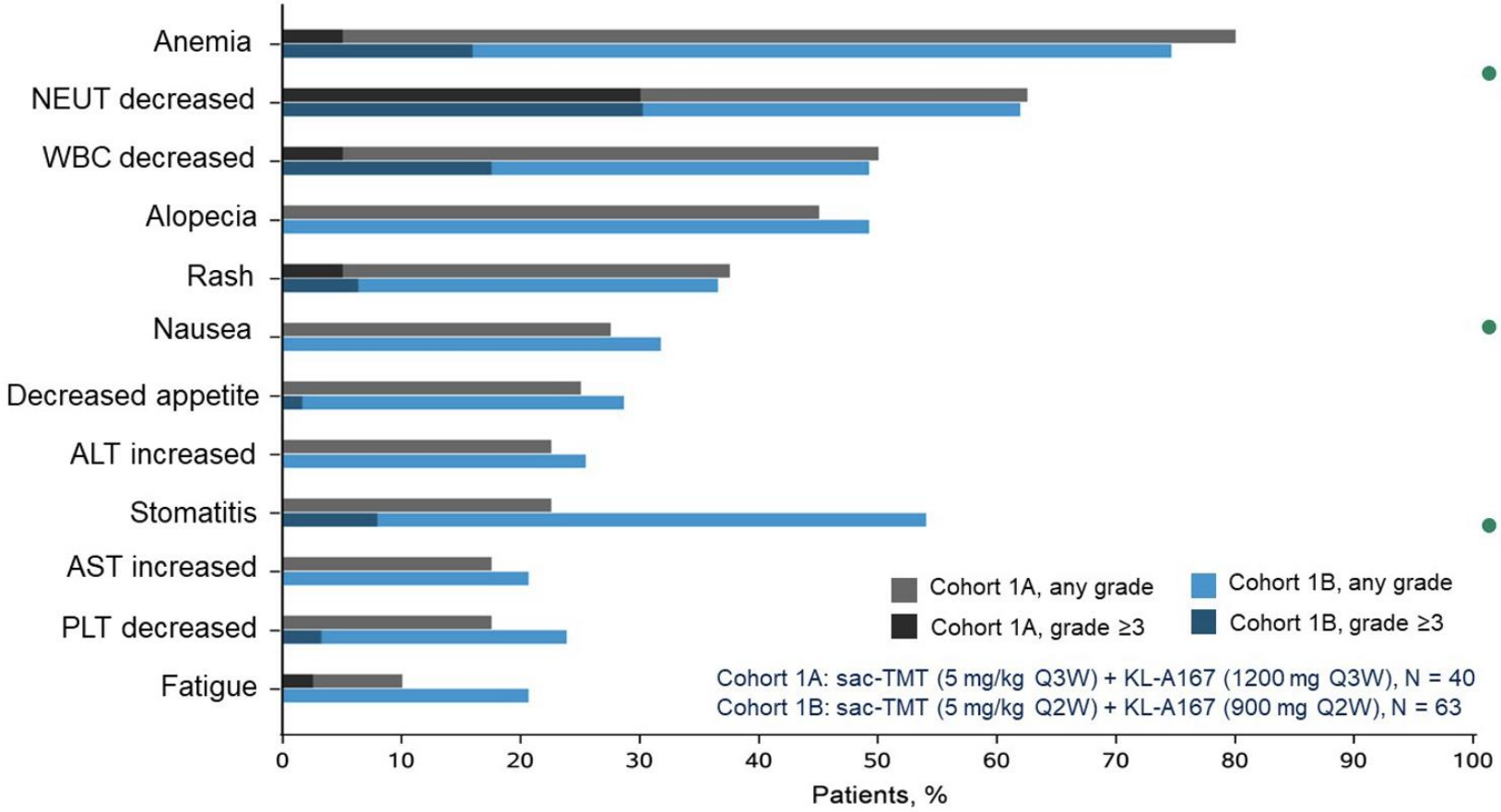
TROP-2: SACITUZUMAB TIMUROTECAN + ICB

Iniciativa científica de: GECP lung cancer research

Toxicity facts



- ILD only in 1 patient of cohort B (G2)
- >= G3 TREAs in cohort 1B 54%
- TRAEs leading to discontinuation were rare (3,2%)

3 pase III studies of SAC-TMT + pembrolizumab are ongoing in different settings

ADC

TROP-2: ICARUS-LUNG01 - DATOPOTAMAB DERUXTECAN

Iniciativa científica de: GECP lung cancer research

2024 ASCO ANNUAL MEETING

ICARUS-LUNG01: A phase 2 Study of Dato-DXd in patients with previously treated advanced NSCLC, with sequential tissue biopsies and biomarkers analysis to predict treatment outcome

D. Planchard[1,2], N. Cozic[3], M. Wislez[4], C. Chouaid[5], H. Curcio[6], S. Cousin[7], C. Mascaux[8], J. Cadranel[9], M. Geier[10], M. R. Ghigna[11], G. Nachabeh[12], R. Zwirtes[13], R. Chiaverelli[13], R. Cheikh-Hussin[14], N. Corcos[14], F. Mosele[1,15], F. André[1,2,15], G. Montagnac[14], B. Pistilli[1,14]

1Department of Medical Oncology, Gustave Roussy, Villejuif, France; 2Faculty of Medicine, Paris-Saclay University, Paris, France; 3Department of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France; 4Department of Pulmonology-Thoracic Oncology, Cochin Hospital, Paris, France; 5Department of Pulmonology, Centre Hospitalier Intercommunal de Créteil, Créteil, France; 6Department of Medical Oncology, Centre François Baclesse, Caen, France; 7Department of Medical Oncology, Institut Bergonié, Regional Comprehensive Cancer, Bordeaux, France; 8Department of Pulmonology, Nouvel Hopital Civil, Strasbourg University Hospital, Strasbourg, France; 9Sorbonne University, Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Service de pneumologie et Centre Constitutif des Maladies Pulmonaires Rares, Paris, France; 10Department of Medical Oncology, Regional University Hospital, Brest, France; 11Department of Pathology, Gustave Roussy, Villejuif, France; 12Projects and Promotion Division, Gustave Roussy, Villejuif, France; 13Daiichi-Sankyo Inc, NJ, USA; 14INSERM U1279, Gustave Roussy, Villejuif, France; 15INSERM U981, Gustave Roussy, Villejuif, France

ICARUS

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

2024 ASCO ANNUAL MEETING #ASCO2

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Study Design

Multi-center, single-arm, phase 2 study (NCT04940325)

KEY ELIGIBILITY CRITERIA

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- Progressed on prior 1-3 lines:
  - Without known mutations: anti PD-1/PDL-1 containing therapy and a platinum-doublet regimen
  - With known EGFR, BRAF, MET ALK, ROS1, RET, NTRK alterations: one line of an approved targeted agent and one platinum-doublet regimen
- Asymptomatic brain metastases

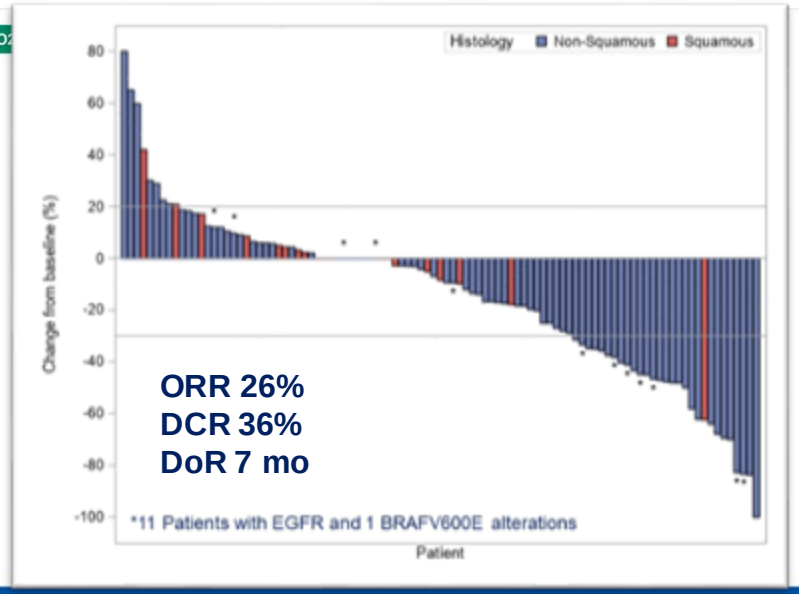
Dato-DXd 6 mg/kg Q3W until PD or unacceptable toxicity

Primary Endpoint:
- Investigator-assessed ORR*

Secondary Endpoints:
- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory sample collection :
- Tumor biopsy (1 Frozen + 3 FFPE)
- Blood (5 to 69 ml)

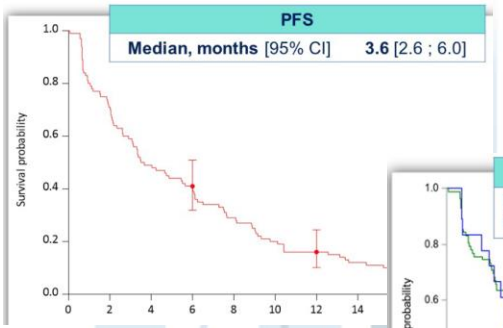
Exploratory Endpoints:
- Predictors of response/resistance
- Dynamics of TROP2 expression before and after treatment
- CTCs levels during treatment

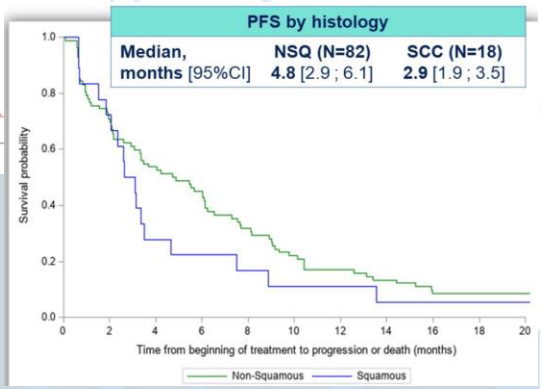


ORR

Non-sq 30,5% / Sq 5,6%

EGFR/BRAF+ 50% / 23,2%





ADC

TROP-2: ICARUS-LUNG01 - DATOPOTAMAB DERUXTECAN

Iniciativa científica de: GECP lung cancer research

Exploratory biomarker analyses

ICARUS LUNG

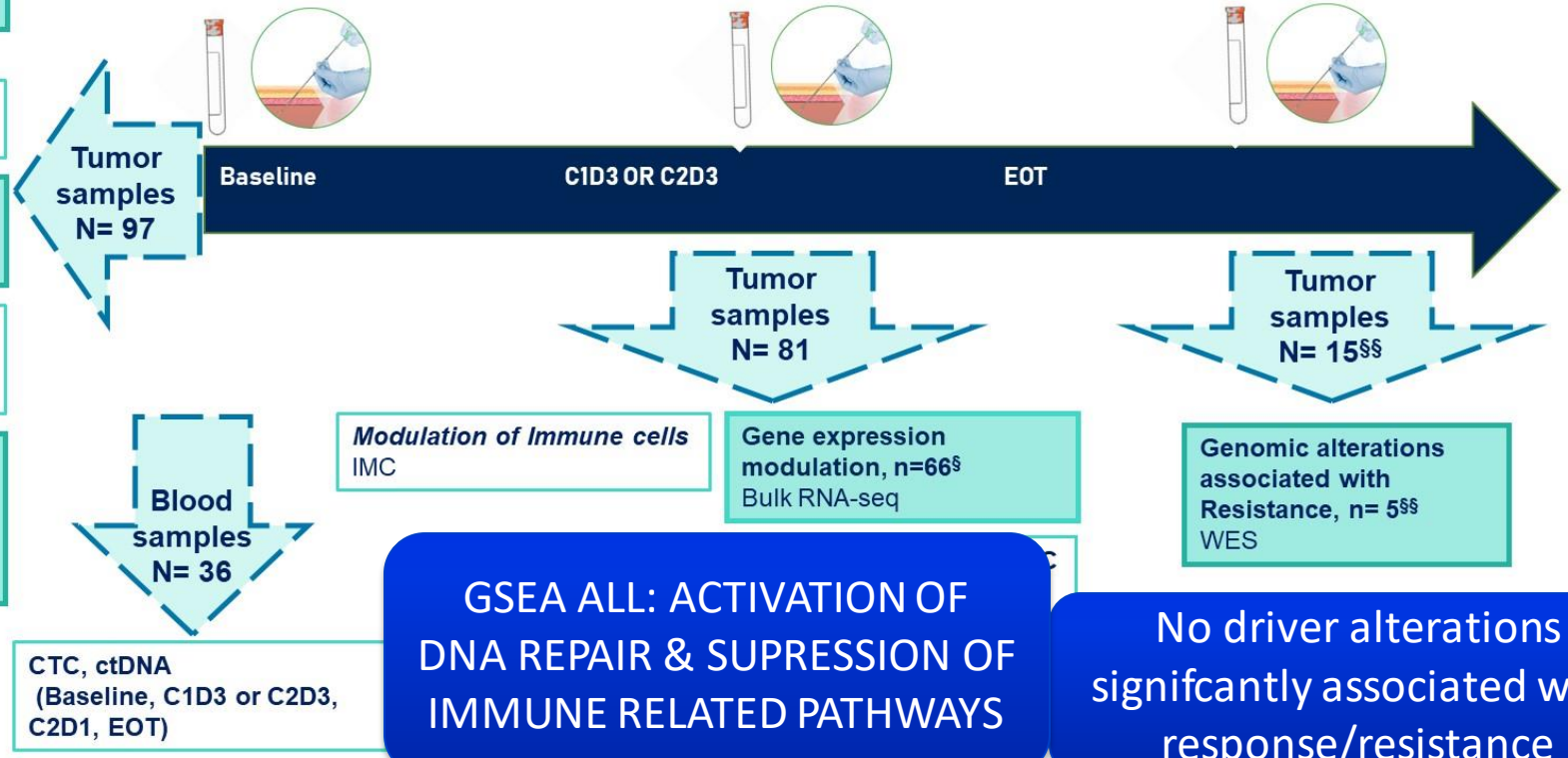
TROP2 expression by IHC, n=78*

TROP2 spatial distribution
Machine learning analysis

Gene expression modulation, n= 71**
Bulk RNA-seq

Modulation of Immune cells
IMC

Genomic alterations associated with Response/Resistance n= 71***
WES



GSEA ALL: ACTIVATION OF DNA REPAIR & SUPRESSION OF IMMUNE RELATED PATHWAYS

No driver alterations signifcantly associated with response/resistance

IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing

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ADC

cMET: LUMINOSITY PH II - TELISOTUZUMAB VEDOTIN

Iniciativa científica de: GECP lung cancer research

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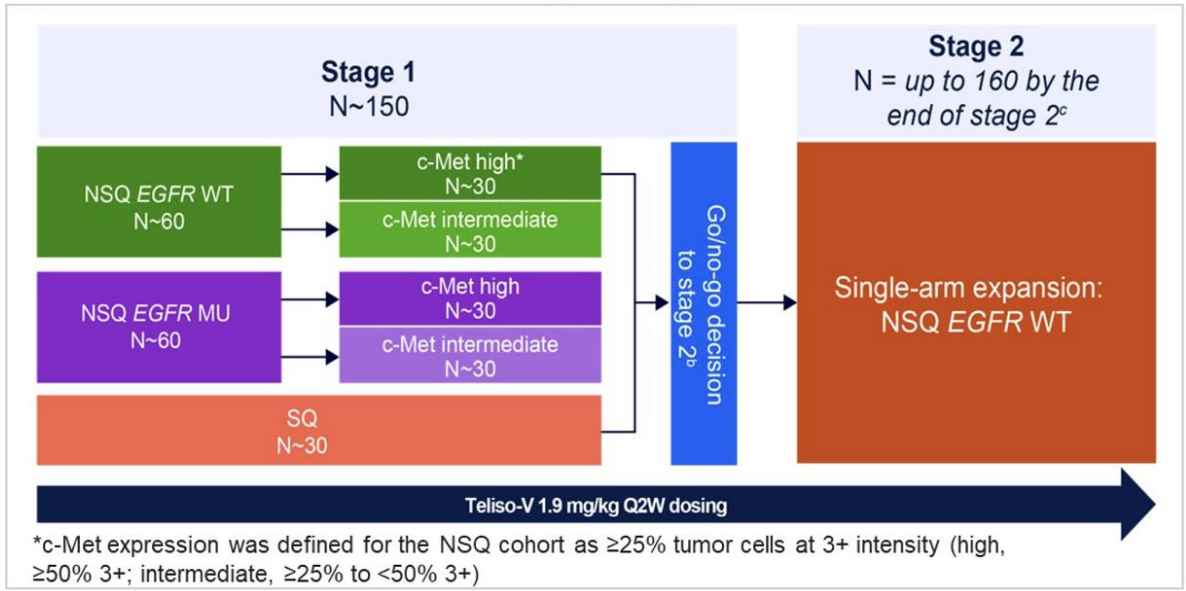
Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met–Overexpressing Non-Squamous *EGFR* Wildtype Advanced NSCLC: Primary Analysis of the LUMINOSITY Trial

D. Ross Camidge, MD, PhD[1], Jair Bar, MD MD[4], Fedor Moiseenko, MD, PhD[5], Elena I Nathalie Daaboul, MD[9], Chunling Liu, MD Moskovitz, MD[12], Nuran Katgi, MD[13], Pas Christine Ratajczak, PhD[16], Martha

Eligible Patients
- ≥18 years
- Advanced/metastatic NSCLC
- c-Met OE by IHC[a]
- Received ≤2 prior lines of systemic therapy in the advanced/metastatic setting, including cytotoxic CTx (≤1 line), immunotherapy (sequential or combined with CTx), and therapy targeting driver gene alterations (if eligible)

Primary Endpoint
- ORR assessed by ICR per RECIST v1.1

Secondary Endpoints
- DCR, DOR, PFS, and OS



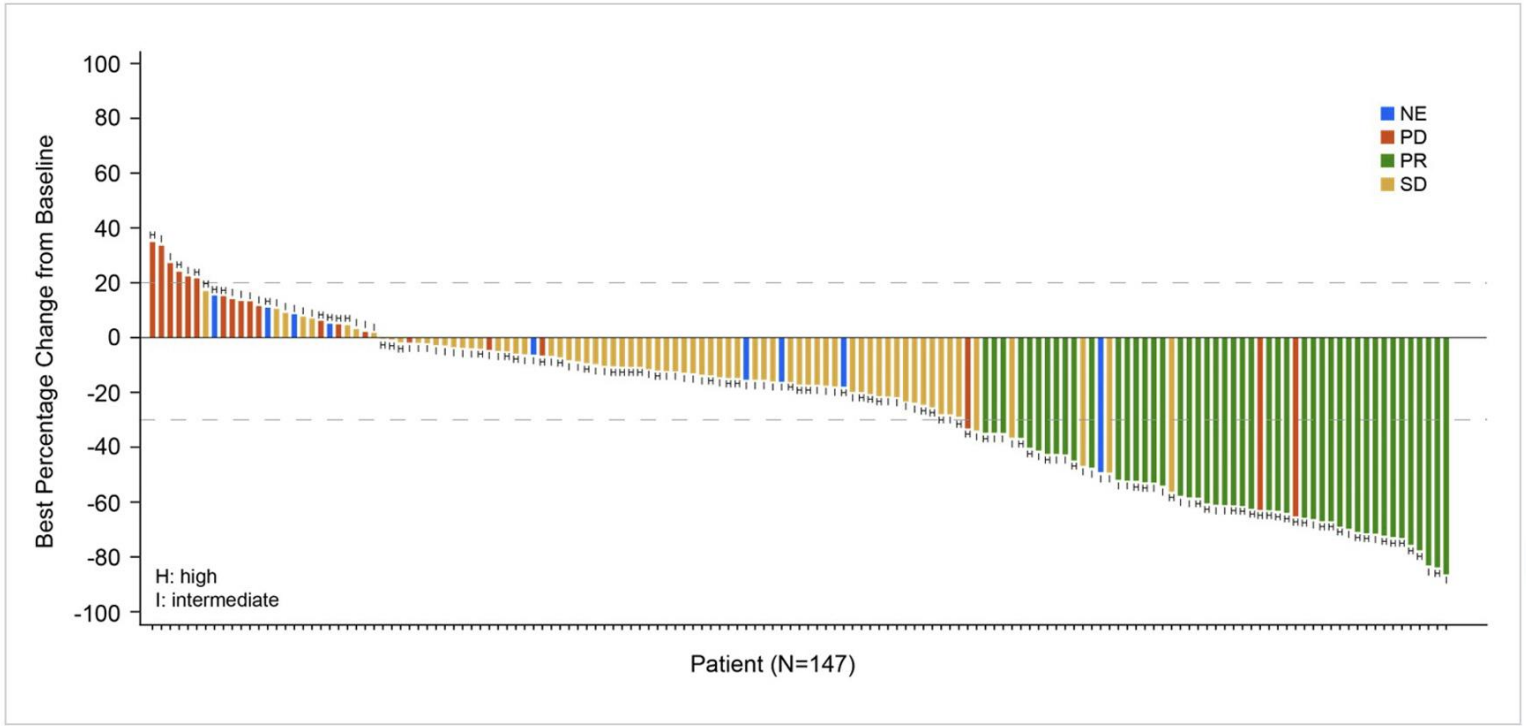
*c-Met expression was defined for the NSQ cohort as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, ≥25% to <50% 3+)

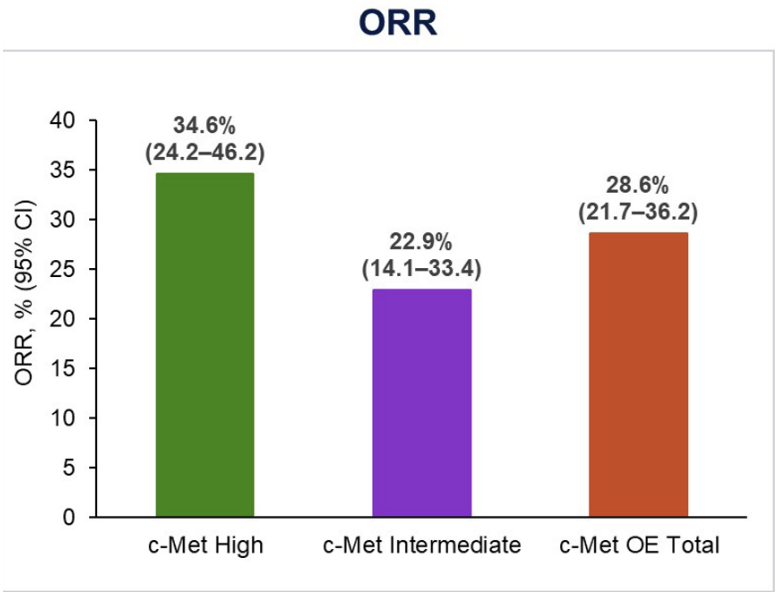
- The SQ and *EGFR* MU NSQ cohorts met stopping criteria
- The *EGFR* WT NSQ cohort met criteria for expansion in stage 2

ADC

cMET: LUMINOSITY PH II – TELISOTUZUMAB VEDOTIN

Iniciativa científica de: GECP lung cancer research





- DCR was 60.3% (c-Met high), 57.8% (c-Met intermediate), and 59.0% (c-Met OE total)

	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Number of responders	27	19	46
Median DOR, months [95% CI]	9.0 [4.2, 13.0]	7.2 [5.3, 11.5]	8.3 [5.6, 11.3]
DOR ≥6 months, n (%)	17 (63.0)	9 (47.4)	26 (56.5)

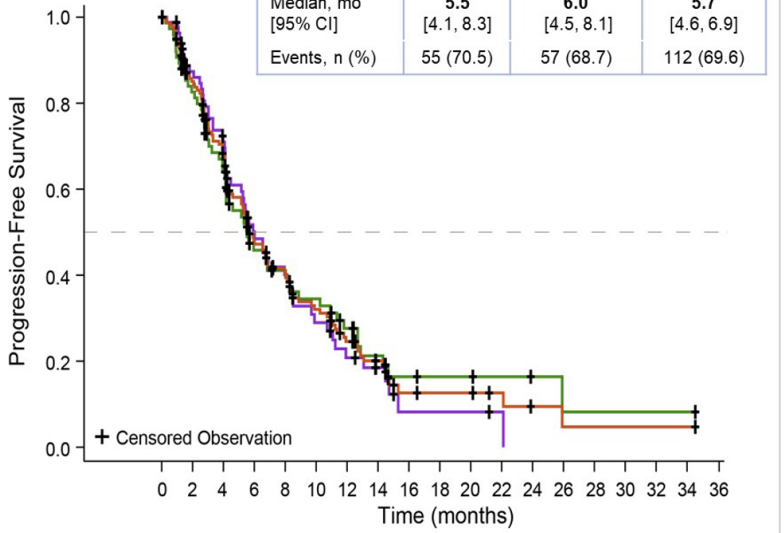
ADC

cMET: LUMINOSITY PH II – TELISOTUZUMAB VEDOTIN

Iniciativa científica de: GECP lung cancer research

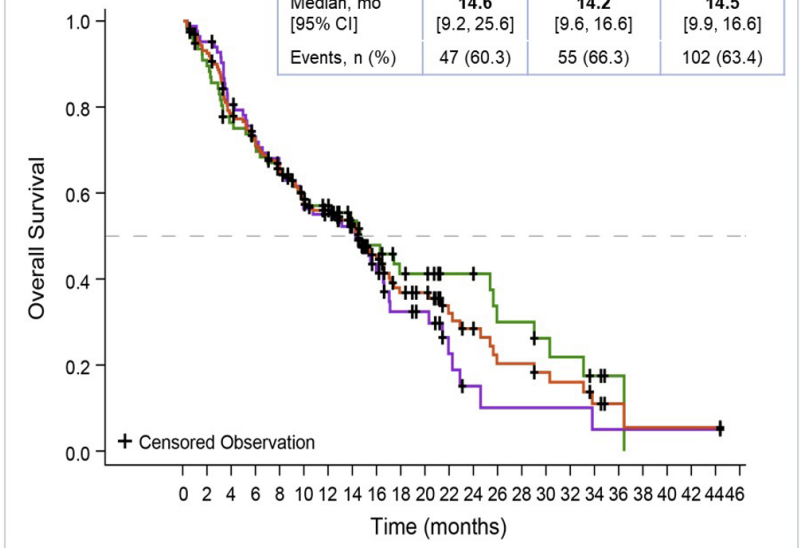
Progression-Free Survival

	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Median, mo [95% CI]	5.5 [4.1, 8.3]	6.0 [4.5, 8.1]	5.7 [4.6, 6.9]
Events, n (%)	55 (70.5)	57 (68.7)	112 (69.6)

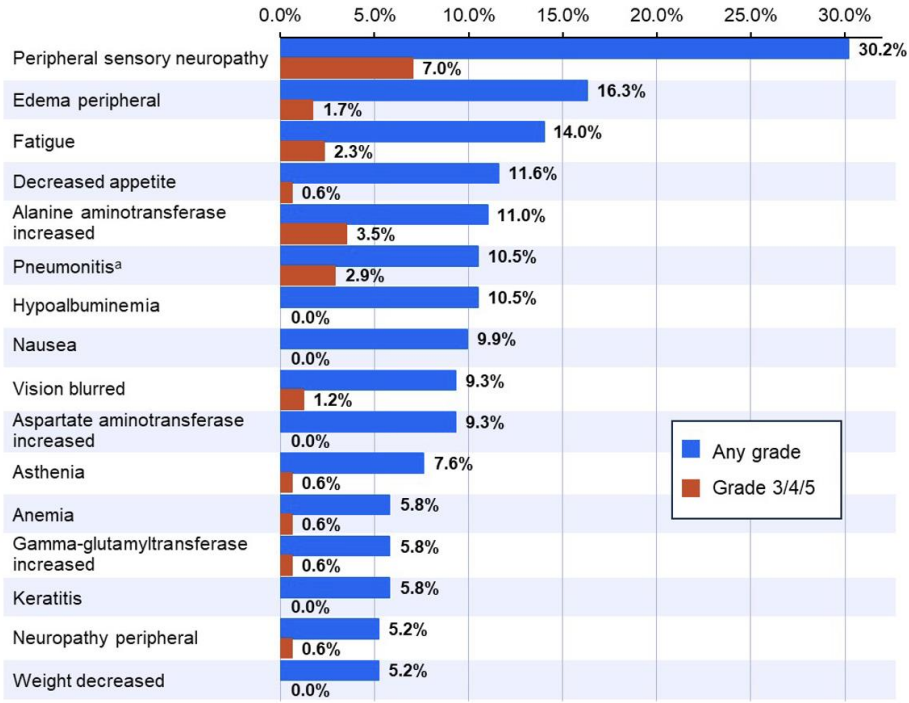


Overall Survival

	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Median, mo [95% CI]	14.6 [9.2, 25.6]	14.2 [9.6, 16.6]	14.5 [9.9, 16.6]
Events, n (%)	47 (60.3)	55 (66.3)	102 (63.4)



TRAEs



- 66 (41.0%) of patients received a subsequent systemic therapy after Teliso-V discontinuation

TRAEs ≥ G3 27,9%
TRAEs leading to discontinuation 21,5%
Death 1,2%

ADC

INTEGRIN BETA 6 - SIGVOTATUG VEDOTIN

Iniciativa científica de: GECP

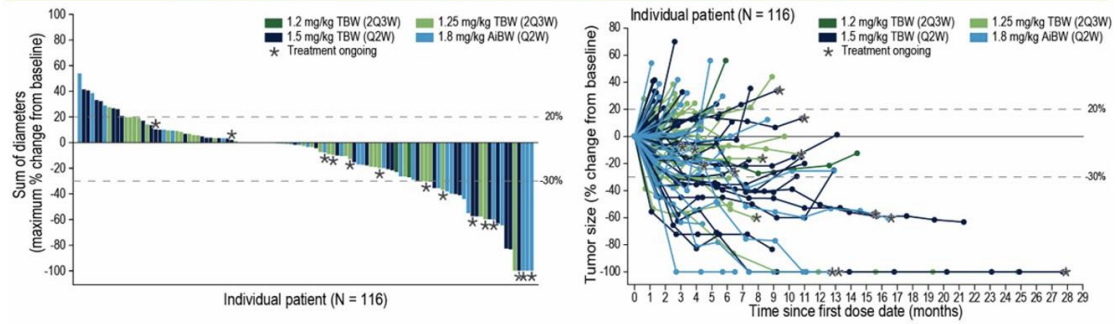
EFFICACY AND SAFETY OF SIGVOTATUG VEDOTIN, AN INVESTIGATIONAL ADC, IN NSCLC: UPDATED PHASE 1 RESULTS (SGNB6A-001)

Solange Peters, MD, PhD[1]; Antoine Hollebecque, MD[2]; Kartik Sehgal, MD[3]; Juanita Suzanne Lopez, PhD, MRCP[4]; Emiliano Calvo, MD[5]; Afshin Dowlati, MD[6]; Bruno Bockorny, MD[7]; Cesar Augusto Perez, MD[8]; Rachel E. Sanborn, MD[9]; Amita Patnaik, MD, FRCPC[10]; Elisa Fontana, MD, PhD[11]; Vladimir Galvao, MD, MSc[12]; Ed Kingsley, MD[13]; Gabriela Patilea-Vrana, PhD[14]; Tianhua Wang, PhD[15]; Scott Knowles, MD, PhD[14]; Sarina A. Piha-Paul, MD[16]

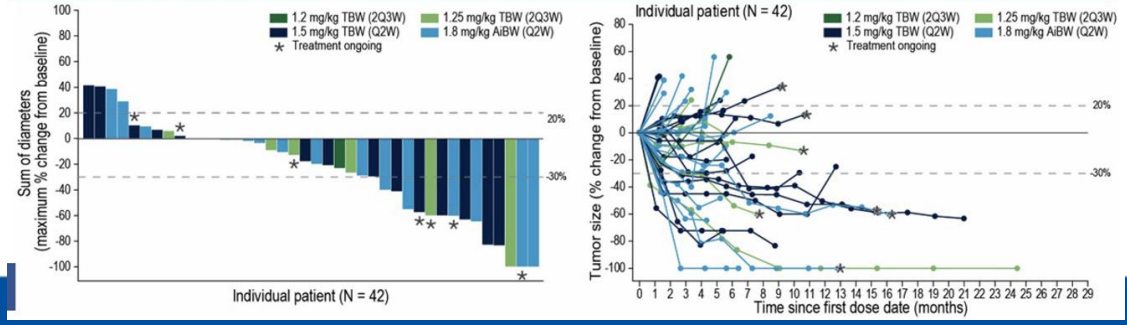
SV Monotherapy

Part A	Part B
Complete	Ongoing
	Disease-specific expansion cohorts
NSCLC	
Other Advanced Solid Tumors	1,8 mg/kg AiBW Q2W

Antitumor Activity in All NSCLC Dose Groups (N = 116)[a]



Antitumor Activity in Non-Squamous, Taxane Naive NSCLC (N = 42)



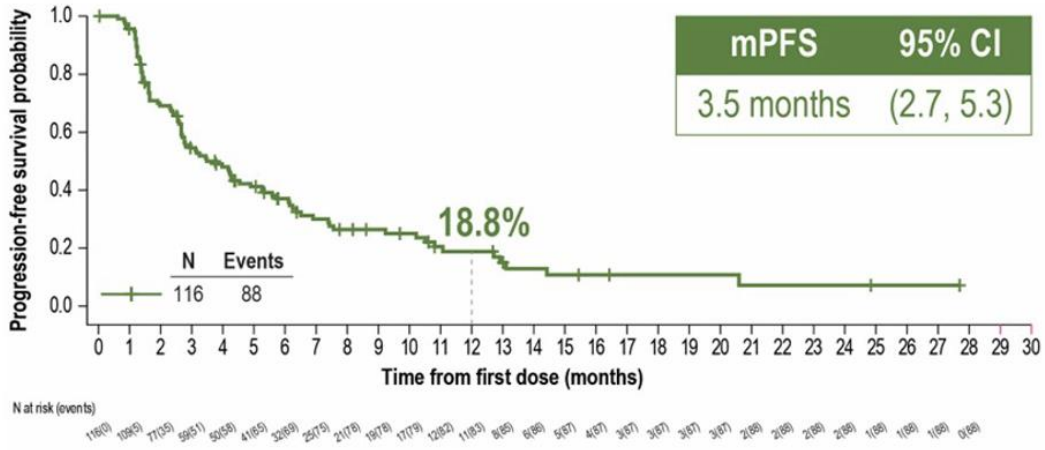
NSCLC efficacy evaluable set	NSCLC – all dose groups[a] (N = 116)	Non-squamous, taxane naive NSCLC – all dose groups (N = 42)
Confirmed ORR, % (95% CI)	19.0 (12.3, 27.3)	31.0 (17.6, 47.1)
Confirmed BOR,[b] n (%)		
CR	3 (2.6)	2 (4.8)
PR	19 (16.4)	11 (26.2)
SD	58 (50.0)	21 (50.0)
PD	29 (25.0)	6 (14.3)
mDOR, months (range)	11.3 (2.4, 24.9+)	11.6 (2.4, 24.2+)
DCR, % (95% CI)	69.0 (59.7, 77.2)	81.0 (65.9, 91.4)

ADC

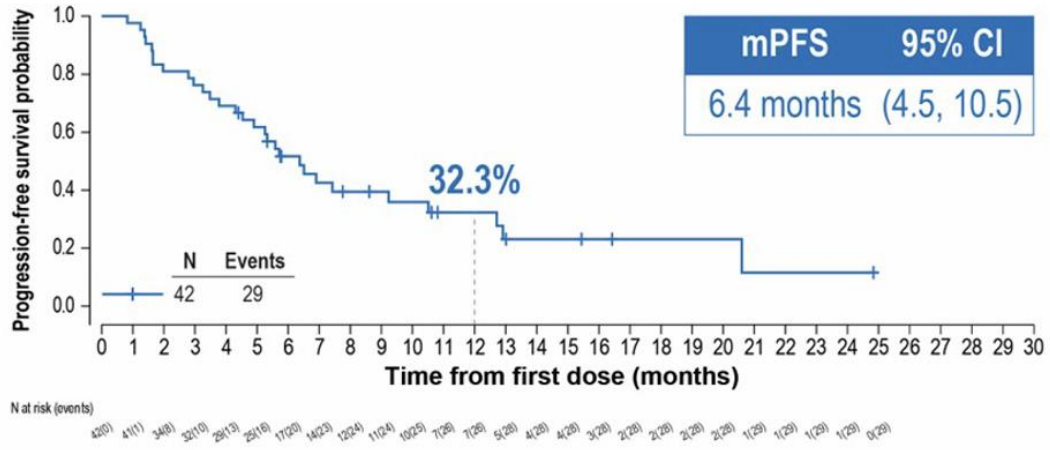
INTEGRIN BETA 6 - SIGVOTATUG VEDOTIN

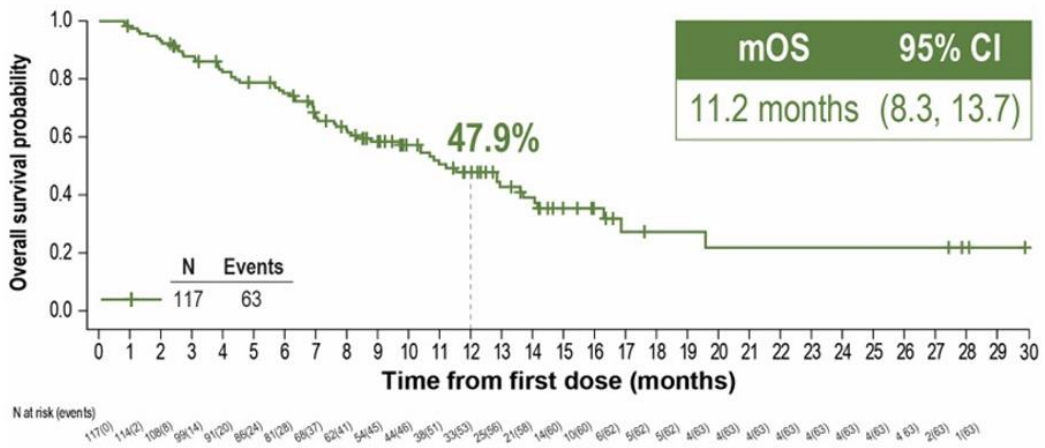
Iniciativa científica de: GECP lung cancer research

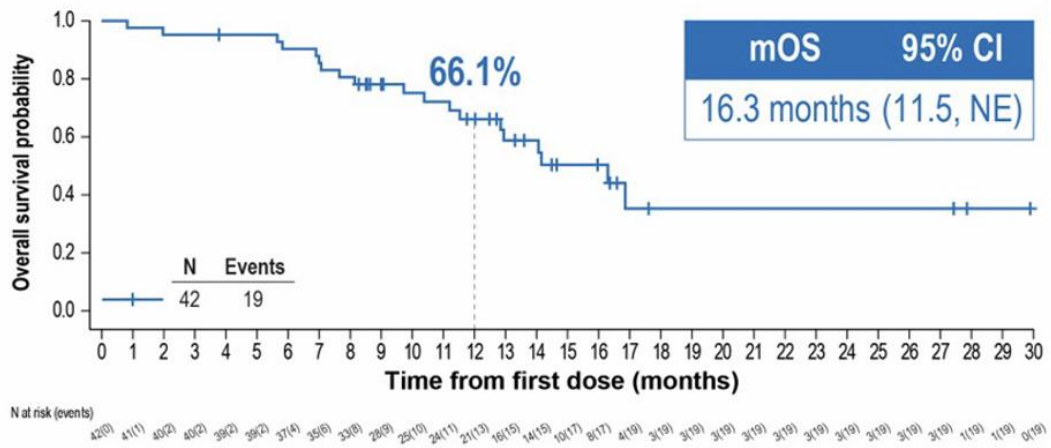
NSCLC – All Dose Groups[a]



Non-Squamous, Taxane Naive NSCLC – All Dose Groups







Encouraging initial PFS and OS observed in patients with non-squamous, taxane-naive NSCLC

ADC

INTEGRIN BETA 6 - SIGVOTATUG VEDOTIN

Iniciativa científica de: GECP lung cancer research

Treatment-Emergent Adverse Events

Constitutional symptoms, gastrointestinal-related TEAEs, and neuropathy were the most frequent types of TEAEs observed.

Dose escalation and expansion Most common TEAEs, n (%) • ≥15% Any grade[a] • ≥3% grade ≥3[b]	NSCLC – all dose groups (N = 117)		1.8 mg/kg AiBW Q2W – NSCLC (N = 31)	
Fatigue				
Peripheral sensory neuro				
Nausea				
Diarrhea				
Decreased appetite				
Dyspnea				
Alopecia				
Cough				
Weight decreased				
Vomiting				
Constipation	19 (16.2)	0	7 (22.6)	0
Anemia	13 (11.1)	5 (4.3)	2 (6.5)	1 (3.2)
Neutropenia	12 (10.3)	7 (6.0)	4 (12.9)	2 (6.5)
Hypomagnesemia	8 (6.8)	4 (3.4)	3 (9.7)	1 (3.2)
Pneumonia	8 (6.8)	4 (3.4)	3 (9.7)	2 (6.5)
Pulmonary embolism	6 (5.1)	6 (5.1)	1 (3.2)	1 (3.2)

Data cutoff: 06 Mar 2024

Adverse Events of Interest by Composite Term

TEAEs, n (%)	NSCLC – all dose groups (N = 117)	1.8 mg/kg AiBW Q2W – NSCLC (N = 31)
Peripheral neuropathy[a]		
Any grade	51 (43.6)	16 (51.6)
Grade ≥3	0	0

Be6A Lung-01 Study (NCT06012435)

Key eligibility criteria

- Stage IIIB, IIIC, or Stage IV (M1a, M1b, or M1c) non-squamous 2L+ NSCLC
- No prior treatment with antimicrotubule agents

R 1:1 N=600

- Sigvotatug vedotin 1.8 mg/kg AiBW 28-day cycle (Q2W)
- Docetaxel 21-day cycle (Q3W)

Events identified using the following SMQ search strategies:

[a] Peripheral neuropathy
[b] Oropharyngeal conditions (excl neoplasms, infections and allergies)
[c] Hematopoietic leukopenia
[d] Cholestasis and jaundice of hepatic origin, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, Liver related investigations, signs and symptoms and Hepatitis, non-infectious
[e] Interstitial lung disease

AiBW, adjusted ideal body weight; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks (Day 1 and Day 15 on a 28-day cycle); SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

1,8 mg/kg Q2W subset

TEAEs ≥ G3 **35,5%**

TEAEs leading to discontinuation **12,9%**

No deaths

OLIGOMETASTATIC

PROSPECTIVE PHASE II/III of LCT IN IO ERA

Iniciativa científica de: GECP lung cancer research

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG-LU002: *Randomized Phase II/III Trial Of Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC)*

Puneeth Iyengar, MD, PhD, Chen Hu, PhD, Daniel Gomez, MD, Robert Timmerman, MD, Charles Simone, MD, Clifford Robinson, MD, David Gerber, MD, Saiama N Waqar, MBBS, MSCI, Jessica S Donington, MD, Stephen G Swisher, MD, Michael Weldon, MSc, Jackie Wu, PhD, Bryan Faller, MD, Sawsan Rashdan, MD, Kevin L Stephans, MD, Pamela Samson, MD, Kristin A Higgins, MD, Ryan Nowak, MD, Jessica A Lyness, MS, Jeffrey D Bradley, MD

Puneeth Iyengar, MD, PhD; Attending and Director, Metastatic Service,
Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

@IyengarPuneeth

@NRGonc

ASCO 2024

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

OLIGOMETASTATIC

PROSPECTIVE PHASE II/III of LCT IN IO ERA

Iniciativa científica de: GECP lung cancer research

Metastatic NSCLC

0-3 metastatic lessions AFTER 4 cycles of induction

SBRT to all lessions (hypofractionated RT/surgery to primary permitted)

Patients with metastatic NSCLC having completed at least 4 cycles or courses* of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited metastatic disease (0-3 discrete extracranial sites), all of which must be amenable to SBRT/ radiation +/- Surgery A minimum of one disease site (metastasis or primary) needs to be present after first-line/induction systemic therapy and treatable with local consolidative therapy	**STRATIFY**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy-containing Induction Regimens vs. Cytotoxic Chemotherapy Only Induction Regimens**	**RANDOMIZE**	**Arm 1**: Maintenance systemic therapy alone** **Arm 2:** SBRT/radiation or SBRT/ radiation and Surgery to all sites of metastases (0-3 discrete sites) and/or irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation*** If a metastatic site is best treated with hypofractionated radiation, this will be permitted if SBRT or surgery not indicated *** **As noted in Section 5**

NRG-LU002
218 patients
68 sites enrolled at least 1 pt

2:1 randomization in favor of LCT arm.

PH.II PRIMARY OBJECTIVE: PFS

PH.III PRIMARY OBJECTIVE: OS

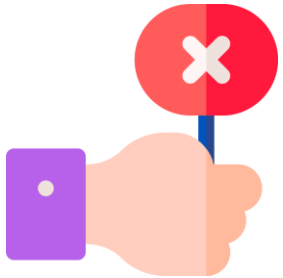
SECONDARY OBJECTIVES: QoL/ctDNA

77% non-squamous NSCLC

90% immunotherapy-containing regimen

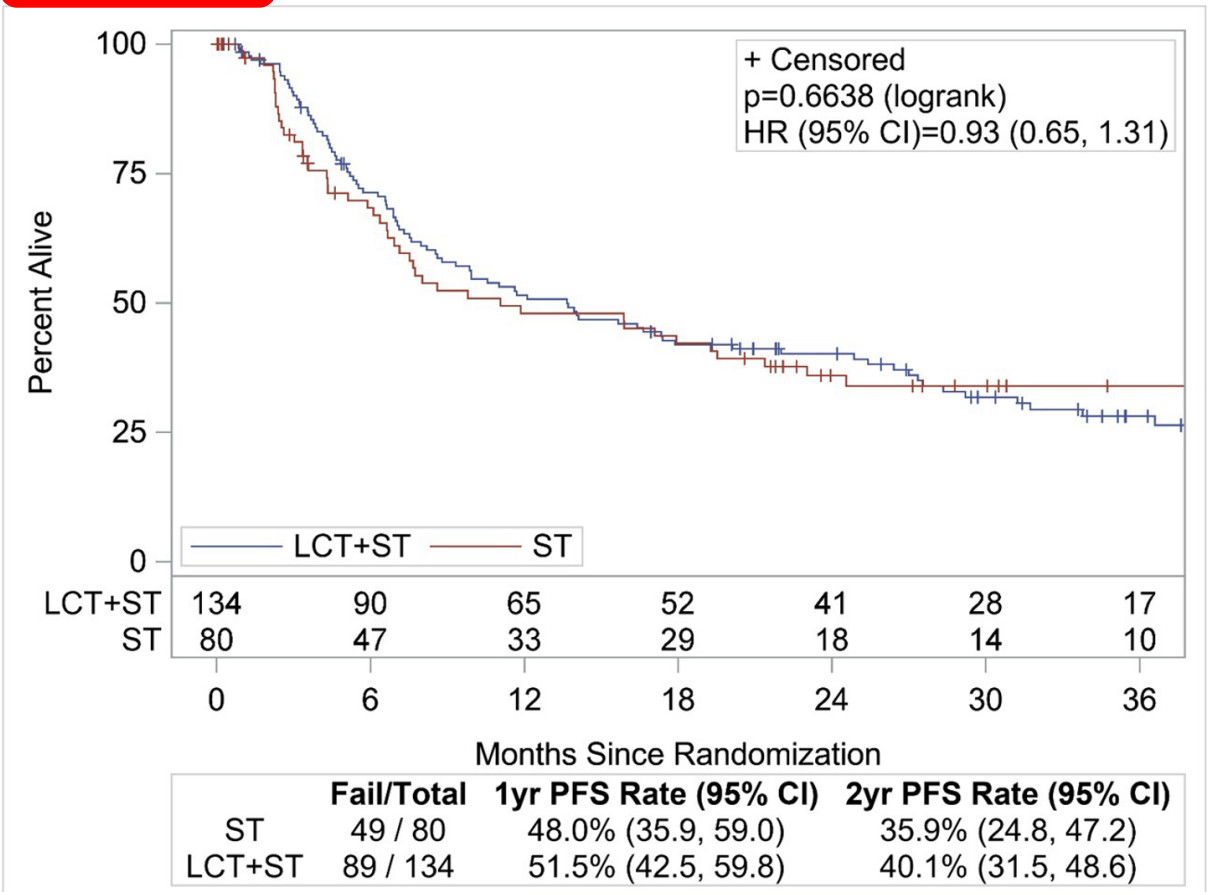
OLIGOMETASTATIC

PROSPECTIVE PHASE II/III of LCT IN IO ERA



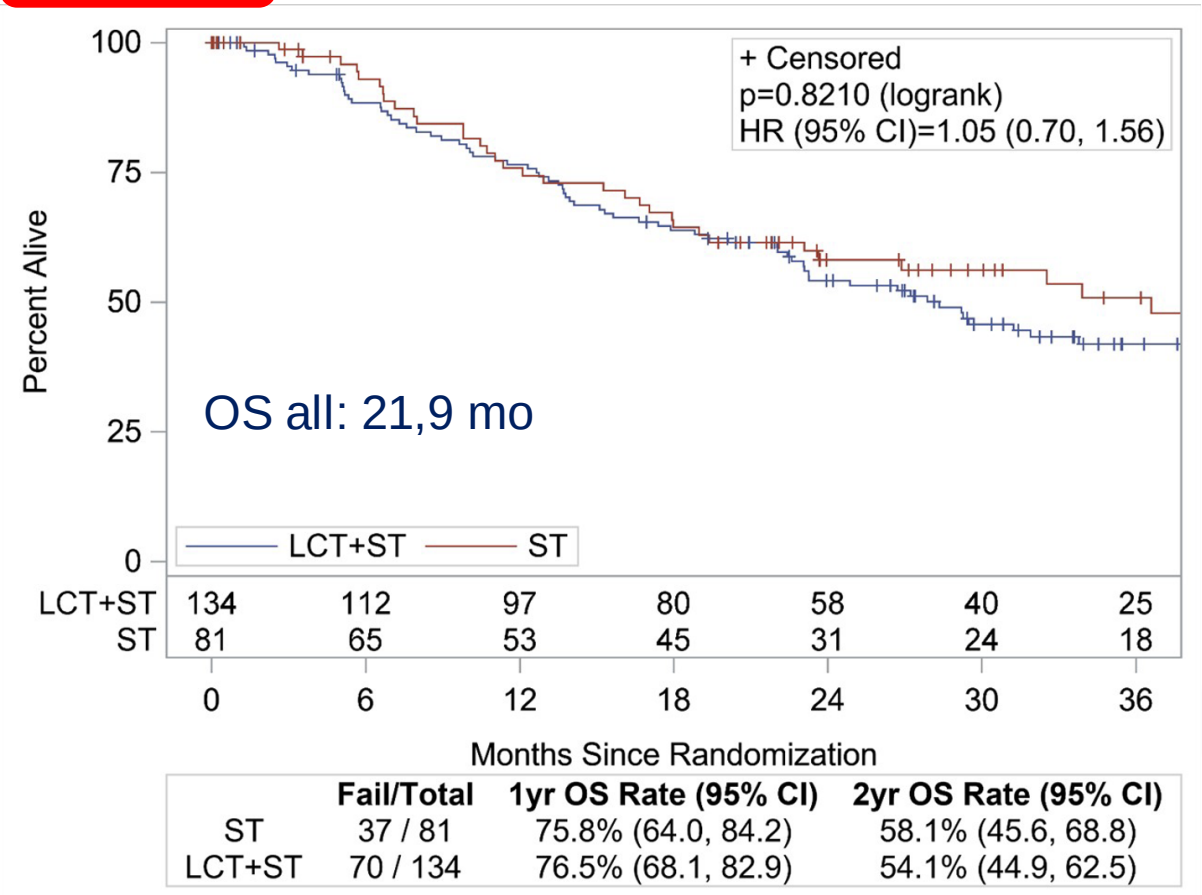
Iniciativa científica de: GECP lung cancer research

PFS



	Fail/Total	1yr PFS Rate (95% CI)	2yr PFS Rate (95% CI)
ST	49 / 80	48.0% (35.9, 59.0)	35.9% (24.8, 47.2)
LCT+ST	89 / 134	51.5% (42.5, 59.8)	40.1% (31.5, 48.6)

OS



	Fail/Total	1yr OS Rate (95% CI)	2yr OS Rate (95% CI)
ST	37 / 81	75.8% (64.0, 84.2)	58.1% (45.6, 68.8)
LCT+ST	70 / 134	76.5% (68.1, 82.9)	54.1% (44.9, 62.5)

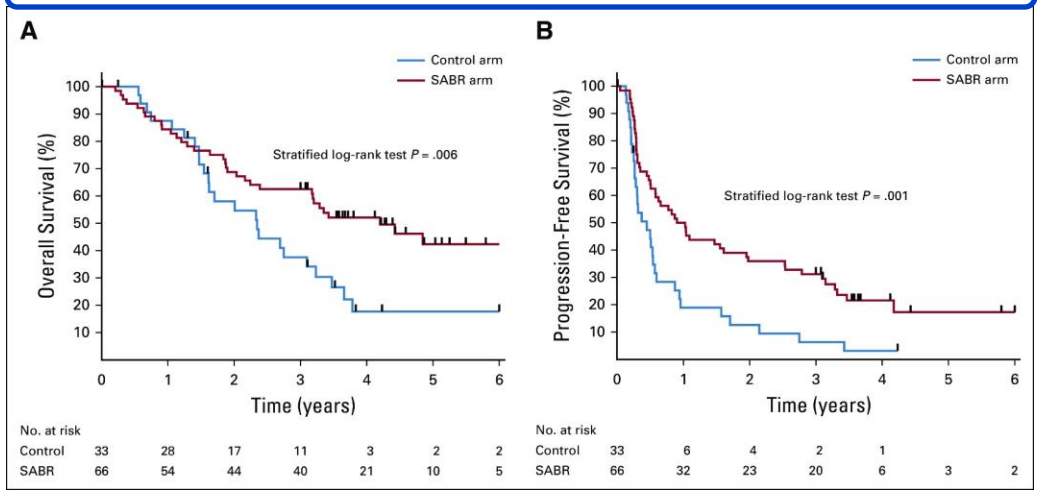
HR were similar in the group of patients who received immunotherapy

OLIGOMETASTATIC

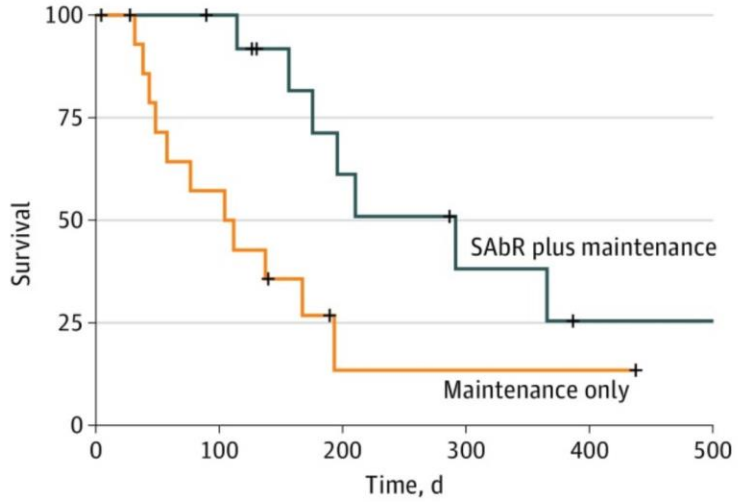
PREVIOUS POSITIVE PH II RANDOMIZED TRIALS

Iniciativa científica de: GECP lung cancer research

SABR-COMET



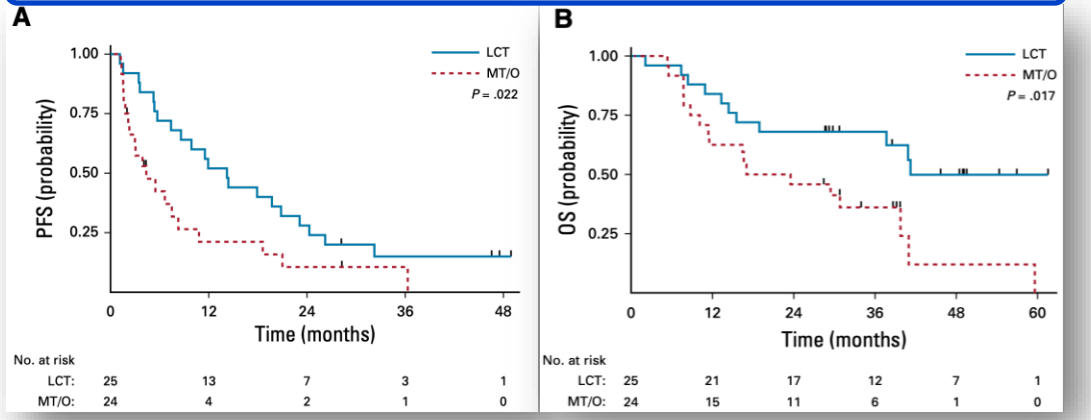
IYENGAR



No. at risk

SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

"OLIGOMEZ"



Palma A et al, J Clin Oncol 2020; Gomez et al, Lancet Oncol 2016; Gomez et al, J Clin Oncol 2019; Iyengar, JAMA Oncol 2018

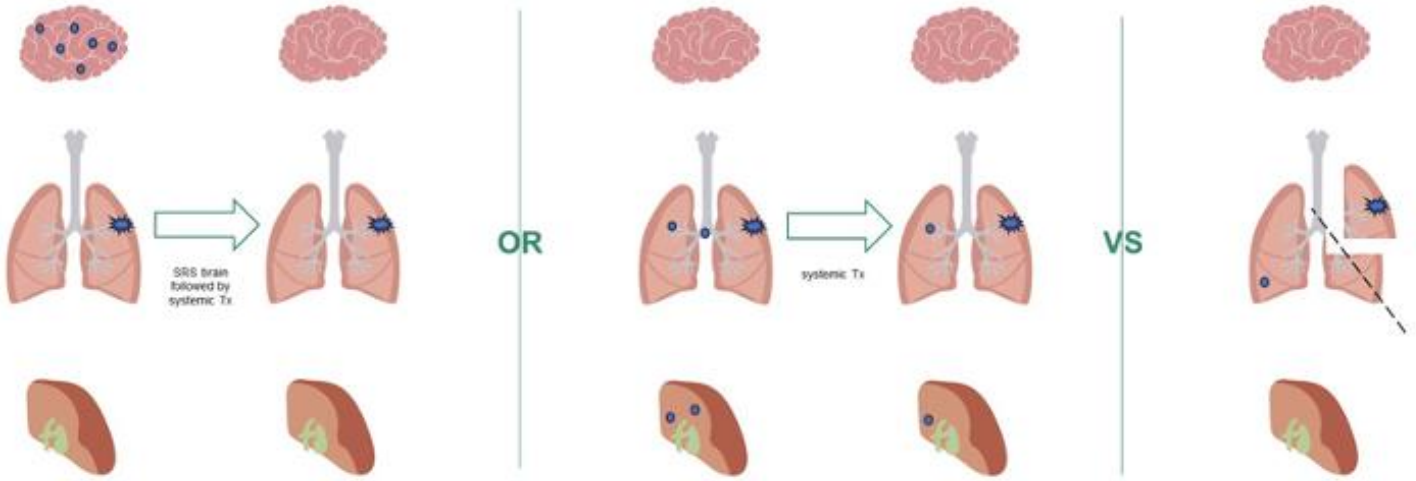
OLIGOMETASTATIC

NRG-LU002

Iniciativa científica de: GECP lung cancer research

Why negative???

- Many patients with less favorable disease for LCT?



- Were ther imbalances in treatment arms?
  - < pts in the LCT received maintenance (93 vs 87%)
  - > pts with favorable immunotherapy biomarkers in control arm (PD-L1)

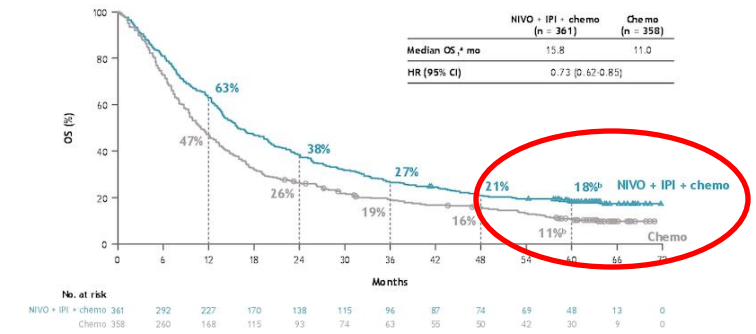
- No need of LCT with long-term immunotherapy benefits?

NSCLC 1L IMMUNOTHERAPY

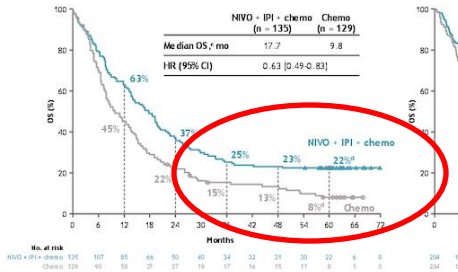
CheckMate 9LA: 5-year-OS update

Iniciativa científica de: GECP lung cancer research

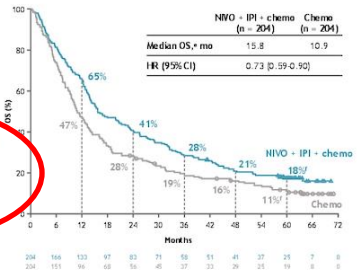
A. All randomized



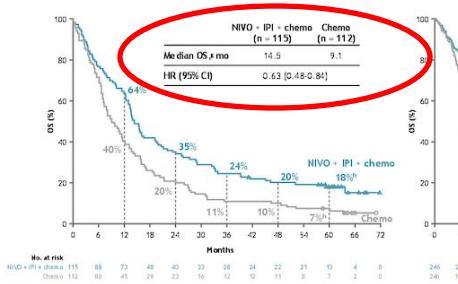
B. PD-L1 < 1%



C. PD-L1 ≥ 1%



D. SQ



E. NSQ

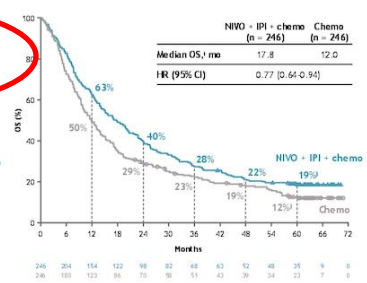


Figure 4. OS in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]

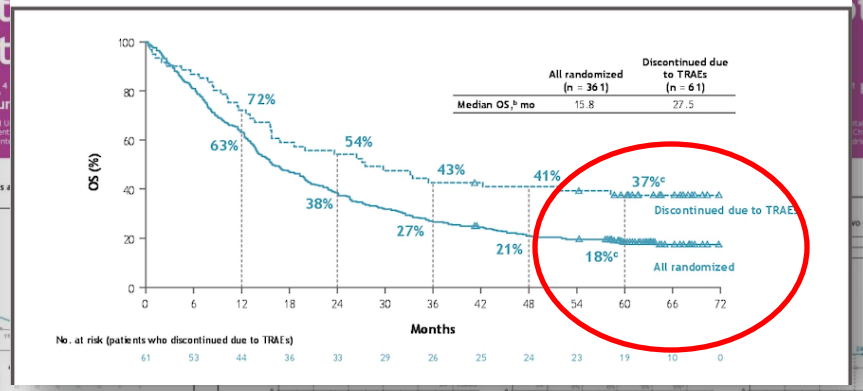


Table 2. Efficacy in 5-year survivors

	NIVO + IPI + chemo (n = 48)	Chemo (n = 30)
Median PFS, months (95% CI)	NR (44.8-NR)	16.8 (7.1-NR)
HR (95% CI)	0.52 (0.26-1.02)	
5-year PFS rate, % (95% CI)	55 (39-69)	38 (19-58)
ORR, n (%) [95% CI]	35 (73) [58-85]	18 (60) [41-77]
Median DOR, months (95% CI)	NR (51.1-NR)	35.8 (9.6-NR)
Ongoing response at 5 years, % (95% CI)	59 (35-76)	46 (20-69)
Median TFI,[a] months (95% CI)	NR (52.2-NR)	9.1 (1.8-NR)
TFI rate,[a] % (95% CI)		
36 months	85 (72-93)	44 (25-62)
48 months	81 (65-90)	44 (25-62)
60 months	72 (47-87)	35 (15-56)

Table 3. IMAEs[a] among 5-year survivors in the NIVO + IPI + chemo arm by number of IPI doses received[b]

Patients, n (%)		1-5 doses of IPI (n = 12)		6-15 doses of IPI (n = 12)		16-18 doses of IPI (n = 24)	
		Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Non-endocrine IMAE	Rash	2 (17)	2 (17)	5 (42)	0	2 (8)	0
	Diarrhea/ colitis	0	0	4 (33)	1 (8)	0	0
	Hepatitis	3 (25)	3 (25)	1 (8)	1 (8)	0	0
	Pneumonitis	2 (17)	1 (8)	1 (8)	1 (8)	0	0
	Nephritis and renal dysfunction	1 (8)	0	1 (8)	1 (8)	0	0
Endocrine IMAE	Hypothyroidism	1 (8)	0	3 (25)	0	11 (46)	0
	Hyperthyroidism	2 (17)	0	3 (25)	0	4 (17)	0
	Adrenal insufficiency	1 (8)	1 (8)	1 (8)	1 (8)	3 (12)	1 (4)
	Thyroiditis	1 (8)	0	1 (8)	0	0	0

therapy vs 8560

Hideaki Mizutani,[12] David P. Carbone,[13]

Safety summary

- At this 5-year update, patients had been off immunotherapy treatment for ≥ 3 years, and safety in all treated patients was consistent with previous reports
- The incidence of grade 3-4 immune-mediated adverse events (IMAEs) in 5-year survivors in the NIVO + IPI + chemo arm was generally low, regardless of the number of IPI doses

Exploratory analyses in patients who discontinued treatment

- In patients who discontinued all components of NIVO + IPI + chemo due to TRAEs (n = 61), median OS was 27.5 months, the 5-year OS rate was 37% (Figure 4), and the 5-year TFI rate was 22%

References

Acknowledgments

Email: m.reck@lungenclinic.de

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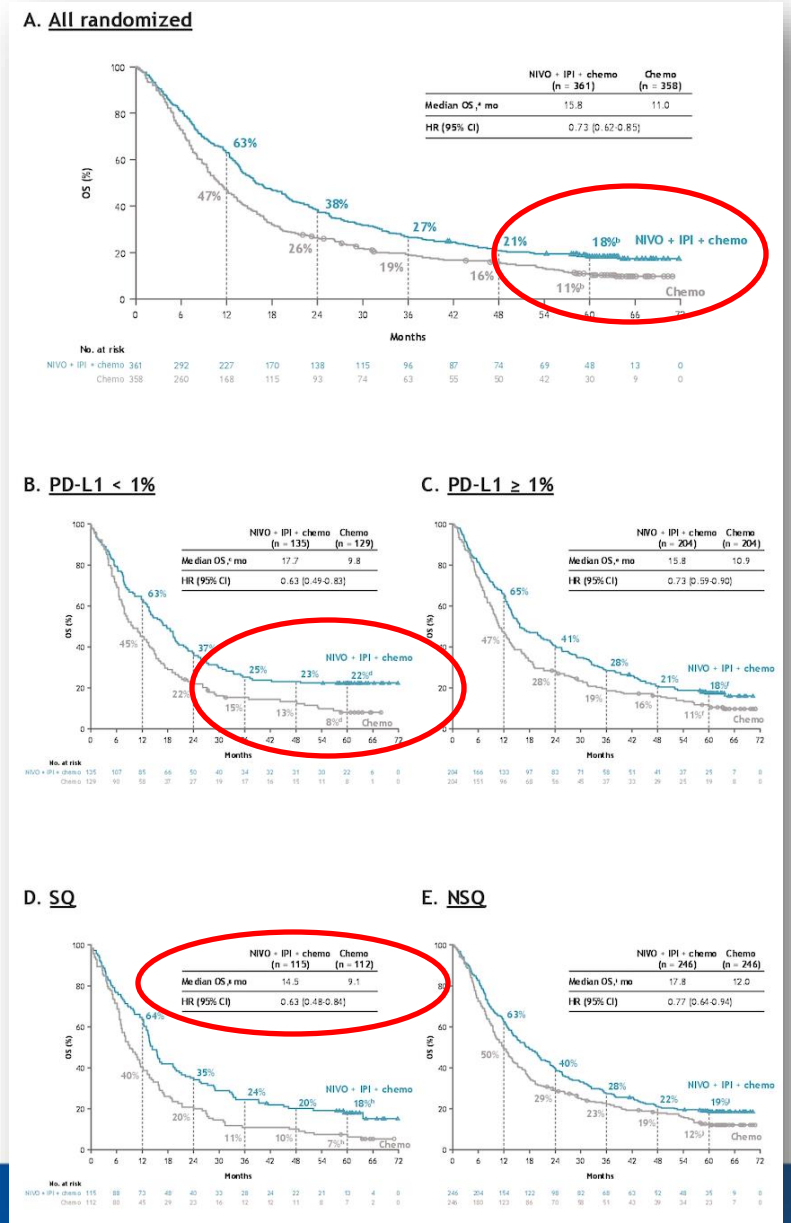
NSCLC 1L IMMUNOTHERAPY

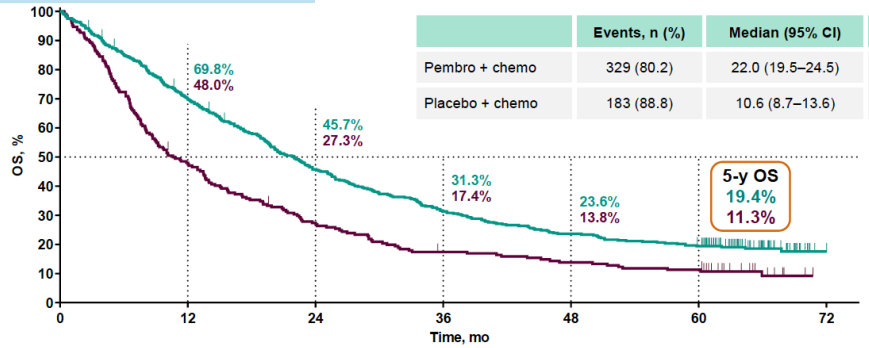
CheckMate 9LA: 5-year-OS update



18% vs 11%
ITT
HR 0,73

22% vs 8%
PD-L1 <1%
HR 0,63

KeyNote 189



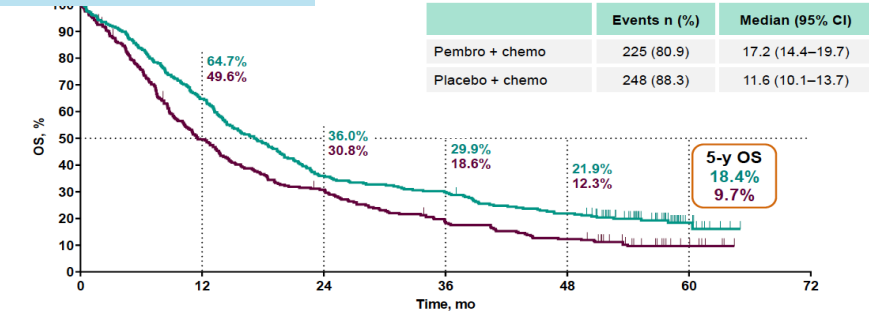
	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	

19,4% vs 11,3%
HR 0,6

9,6% vs 5,3%
HR 0,55
PD-L1 <1%

KeyNote 407



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7

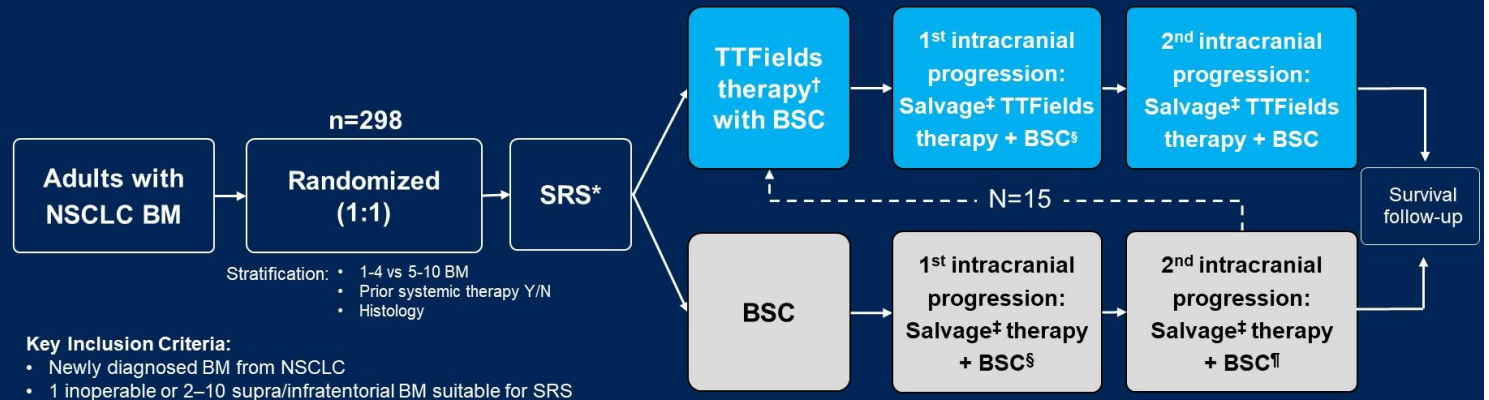
18,4% vs 9,7%
HR 0,71

10,7% vs 13,1%
HR 0,83 ns
PD-L1 <1%

TTFields

METIS TRIAL: NSCLC with brain metastasis

METIS Trial: Study Design



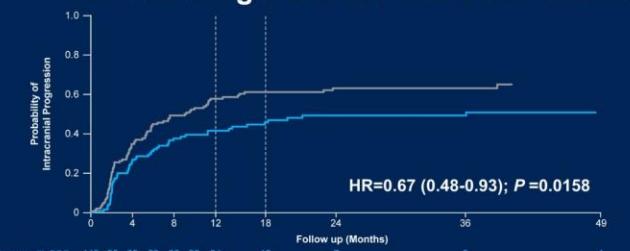
Key Inclusion Criteria:
- Newly diagnosed BM from NSCLC
- 1 inoperable or 2–10 supra/infratentorial BM suitable for SRS
- KPS ≥70
- Receive systemic NSCLC treatment

Key Exclusion Criteria:
- Known mutations with available targeted agents (ALK, EGFR, ROS-1, and B-RAF genes)
- Prior WBRT
- Leptomeningeal or recurrent BM

Study sites: 78 (enrolled; 298 pts randomized)
Enrollment: October 2016–March 2023

Data cut off: 5th December 2023
Registration number: NCT02831959

Primary Endpoint: Time to First Intracranial Progression or Neurologic Death Favors TTFields Arm



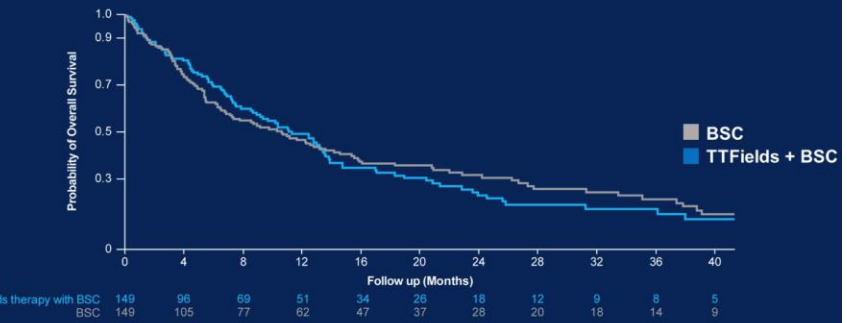
	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Time to Intracranial Progression* (95% CI), months	21.9 (8.3–NE)	11.3 (7.6–NE)	0.0158
Progression rate at 12 months (95% CI)	41.6% (32.4–50.5)	57.8% (49.0–65.7)	0.005
Progression rate at 18 months (95% CI)	46.9% (37.3–56.0)	61.2% (52.3–68.9)	0.0132

*Primary endpoint measured as per RANO-BM over course of study based on independent radiology review

	TTFields + BSC (n=149)	BSC (n=149)
Neurologic deaths, n	9	10
Deaths from other reasons, n	53	44

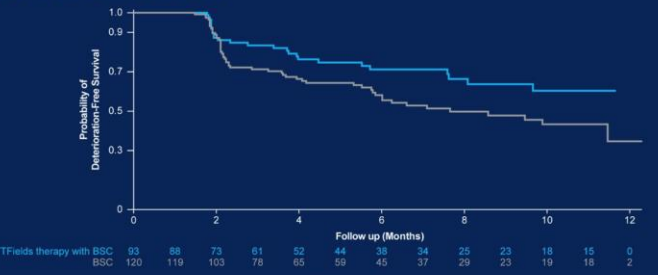
BSC, best supportive care; patients in both arms could receive systemic NSCLC treatment; CI, confidence interval; HR, hazard ratio; NE, not evaluable; TTFields, Tumor Treating Fields.

Median Overall Survival: No Difference



	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Overall Survival (95% CI), months	11.3 (8.5–13.5)	10.6 (6.8–14.1)	0.7796

EQ-5D Deterioration-Free Survival & Time to Deterioration Favor TTFields Arm



	TTFields + BSC (n=93)	BSC (n=120)	*P*-value
Median Time to EQ5D Deterioration (95% CI), months	NR (9.7–NR)	7.7 (5.8–NR)	0.0375
Median EQ-5D DFS (95% CI), months	8.08 (5.717–11.3)	5.32 (3.91–6.242)	0.0361

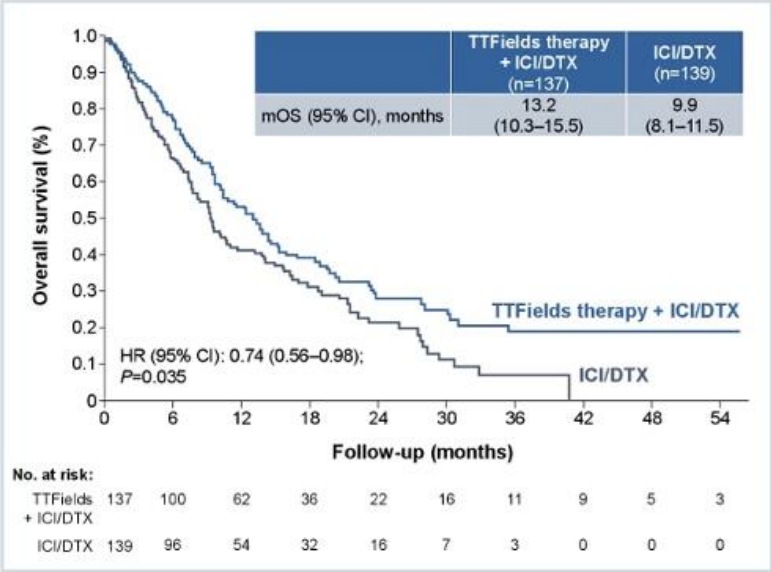
- EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) derived from mapping of EORTC QLQ-C30

TTFields

Iniciativa científica de:

GECP lung cancer research

Figure 2. LUNAR (EF-24): OS in the intention-to-treat population[6]



LUNAR-2: Pivotal, Randomized, Open-Label Study of Tumor Treating Fields (TTFields, 150 kHz) Concomitant with Pembrolizumab and Platinum-Based Chemotherapy for the Treatment of Metastatic Non-Small Cell Lung Cancer

TPS8665

Michael Eaton,[1] Manuel Cobo,[2] Li Zhang,[3] Maximilian Hochmair,[4] Corey J. Langer[5]

[1]Franciscan Health Indianapolis, Indianapolis, IN, USA; [2]Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [3]Sun Yat-sen University Cancer Center, Guangzhou, China; [4]Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Department of Respiratory and Critical Care Medicine, Krankenhaus Nord, Klinik Floridsdorf, Vienna, Austria; [5]University of Pennsylvania, Philadelphia, PA, USA

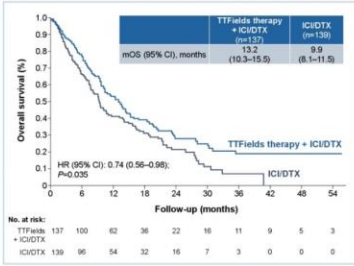
Background

- Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell viability and tumor progression[1–3]
- TTFields therapy is delivered noninvasively to the tumor site via a portable medical device and two pairs of skin-placed arrays on the torso (**Figure 1**)[4,5]
- TTFields therapy is approved for the treatment of glioblastoma and pleural mesothelioma in combination with standard therapies[4,5]

Figure 1. The TTFields device components

- The pivotal, phase 3 LUNAR study (EF-24; NCT02973789) found a statistically significant and clinically meaningful 3.3-month improvement in overall survival (OS) with TTFields therapy when added to an immune checkpoint inhibitor (ICI) or docetaxel vs an ICI or docetaxel alone (**Figure 2**) in patients with metastatic non-small cell lung cancer (mNSCLC) progressing on/after platinum-based therapy[6]
  - The OS benefit was especially pronounced in the subgroup assigned an ICI by the investigator (median OS 18.5 vs 10.8 months [HR 0.63; *P*=0.03])[6]
- During the study, there were no added systemic toxicities and no clinically significant difference in quality of life between treatments[6]
- Given the OS benefit seen for TTFields therapy in a second-line setting, particularly in patients receiving an ICI, it is relevant to evaluate this treatment modality in a front-line setting in treatment-naïve patients with mNSCLC initiating combination chemotherapy and ICI[6]

Figure 2. LUNAR (EF-24): OS in the intention-to-treat population[6]

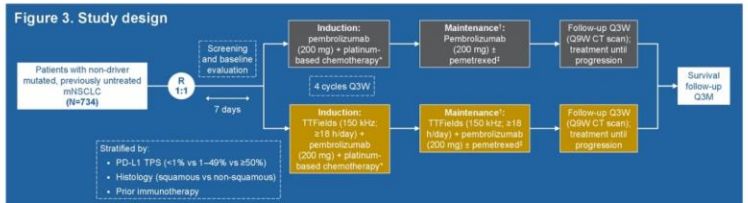


CI, confidence interval; DTX, docetaxel; HR, hazard ratio; ICI, immune checkpoint inhibitor; m, median; OS, overall survival.
Figure adapted from Leal et al., 2023[6], copyright (2023), with permission from Elsevier.

Study design

- LUNAR-2 (EF-44; NCT06216301) is a global, pivotal, randomized study assessing the efficacy and safety of TTFields therapy concomitant with pembrolizumab and platinum-based chemotherapy in patients with mNSCLC[7] (**Figure 3**)

Figure 3. Study design



AUC, area under the curve; CT, computed tomography; mNSCLC, metastatic non-small cell lung cancer; PD-L1; programmed death-ligand 1; Q3M, every 3 months; Q3W, every 3 weeks; Q9W, every 9 weeks, R, randomization; TPS, tumor proportion score.
*Non-squamous histology: cisplatin (75 mg/m²)/carboplatin (AUC-time curve: 5 mg/mL/min) + pemetrexed (500 mg/m²). Squamous histology: carboplatin (AUC-time curve: 6 mg/mL/min) + paclitaxel (200 mg/m²)/nab-paclitaxel (100 mg/m²). †Pembrolizumab to be administered for a maximum of 35 cycles (including induction). ‡Pemetrexed only for non-squamous histology per investigator's discretion.

Table 1. Select inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
• Histologically/cytologically confirmed stage IV NSCLC • No prior systemic treatment for mNSCLC • Evaluable (measurable or non-measurable) disease in the thorax per RECIST v1.1 • ≥18 years old (≥22 years in the US) • ECOG PS 0–1	• Mixed small-cell and NSCLC histology • Untreated/symptomatic CNS metastases and/or carcinomatous meningitis • Eligible/planning to receive targeted therapy for NSCLC with any of the following oncogenes: *EGFR* sensitizing mutation, *ALK* translocation, *ROS1*, *RET* targetable gene rearrangement, METex14 skipping mutation, *NTRK1/2* gene fusion directed therapy • Active autoimmune disease requiring systemic treatment in the past 2 years

ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor; *METex14*, MET exon 14; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer; *NTRK1/2*, neurotrophic tropomyosin receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Select study endpoints

Endpoints	
Primary*	• OS and PFS per RECIST v1.1 as assessed by a BICR
Secondary	• OS and PFS (by histology and PD-L1 TPS) per RECIST v1.1 as assessed by BICR • ORR, DoR, and DCR (all per RECIST v1.1 as assessed by BICR and by investigator) • PFS rates at 6, 12, 24 and 36 months per RECIST v1.1 as assessed by BICR • 1-, 2-, and 3-year survival rates • Safety profile
Exploratory	• PFS and OS according to in-field or out-of-field location of the disease

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.
*Primary endpoints are independent of each other.

Sample size and statistical considerations

- Assuming approximately 12% drop-out rate, a sample size of 734 patients is estimated to achieve 80% power and detect a hazard ratio of 0.75 for OS using a 2-sided log-rank test (with an overall alpha of 0.05)

Study status

- LUNAR-2 is currently enrolling patients and has a planned enrollment of 734 patients at approximately 130 sites globally[7]

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1. Mun EJ et al. *Clin Cancer Res*. 2018;24(2):266–275. **2.** Giladi M et al. *Sci Rep*. 2015;5:18046. **3.** Voloshin T et al. *Cancer Immunol Immunother*. 2020;69(7):1191–1204. **4.** Optune Gio™. Instructions for Use. Novocure; US 2023. Accessed May 2024. **5.** Optune Lua™. Instructions for Use for Unresectable Malignant Pleural Mesothelioma. Novocure; US 2021. Accessed May 2024. **6.** Leal T et al. *Lancet Oncol*. 2023;24:1002–1017. **7.** ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06216301. Accessed May 2024.

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For further information, please contact Michael Eaton at meaton@cancercaregroup.com

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KEY-HOME MESSAGES

- ADC
  - TROP-2 ADC's in 2nd line not superior to SoC CT (Docetaxel)
  - (TROP-2) ADC's + ICB combo in 1L NSCLC promising!!!
  - Need more studies of biomarkers to better understand MoA and resistance
  - cMET directed Teliso-V: promising results in IHC+ pts, Will beat Docetaxel?
  - IB6 directed ADC: promising results in ph1. Tryng to beat Docetaxel irrespective of IHC
- Oligometastatic disease
  - First randomized ph II/III study evaluating LCT after 1L IO-based systemic régimen NEGATIVE (no PFS Benefit)
  - Further investigation required
- 1L immunotherapy
  - Confirmation of double IO + short CT regimen as an efficient alternative in advanced NSCLC with similar proportion of long survivors, with higher proportion in PD-L1 negative pts
- TTFields
  - METIS trial: Time to intracranial progression and QoL benefit. No OS benefit

ASCO 2024

Lung Cancer Updates - GECP

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GECP lung cancer research