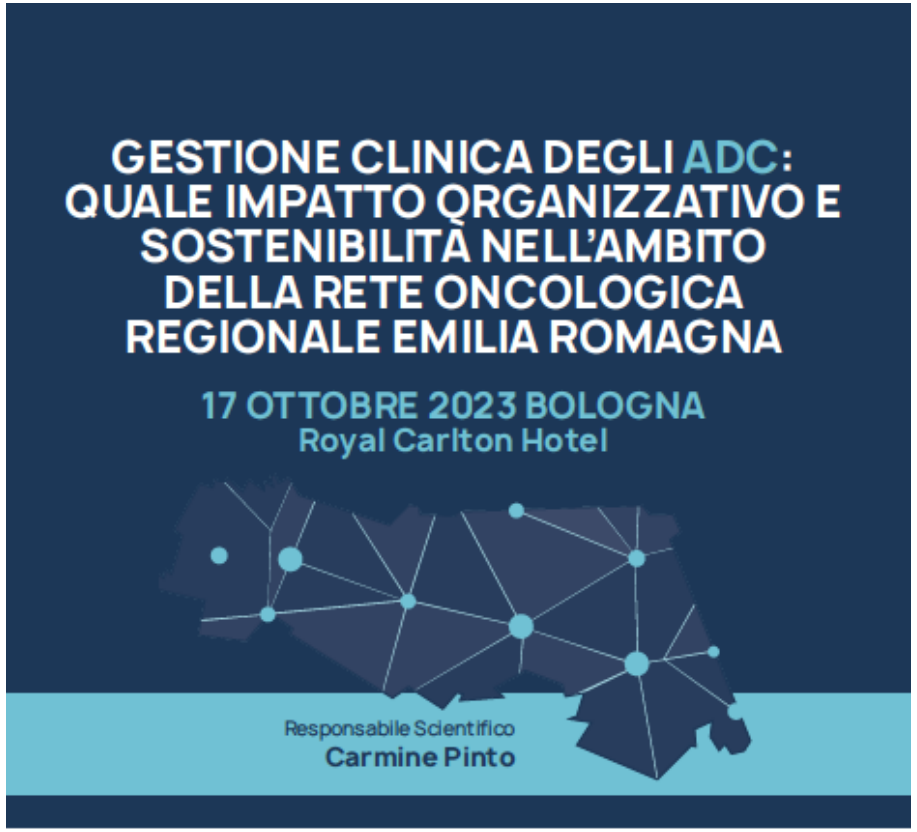

ADC prospettive future: Neoplasie polmonari

Marcello Tiseo

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Disclosures

- **Advisory boards and speakers' fee**
  - AstraZeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Merck, Amgen, Sanofi
- **Research Grant:**
  - Astrazeneca
  - Boehringer Ingelheim
  - AIRC
  - Cariparma

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Agenda

- Introduzione
- ADC anti-HER2
- ADC anti-HER3
- ADC anti-MET
- ADC anti-Trop2
- ADC anti-B7-H3
- Considerazioni e conclusioni

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Agenda

- Introduzione
- ADC anti-HER2 (primo approvato FDA in lung cancer)
- ADC anti-HER3 (fase III in corso)
- ADC anti-MET (fase III in corso)
- ADC anti-Trop2 (risultati fase III ESMO 2023)
- ADC anti-B7-H3 (risultati promettenti nel SCLC)
- Considerazioni e conclusioni

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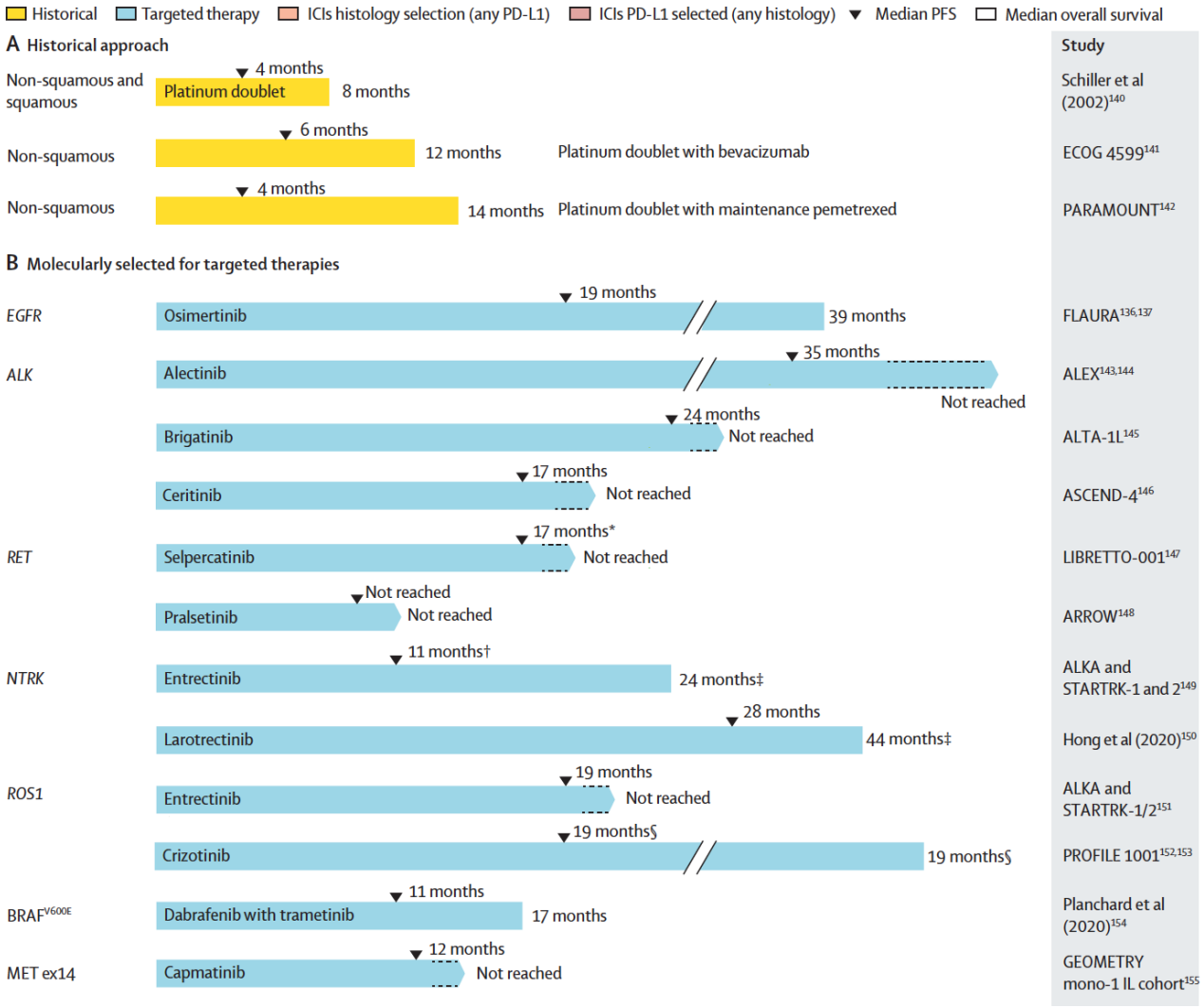
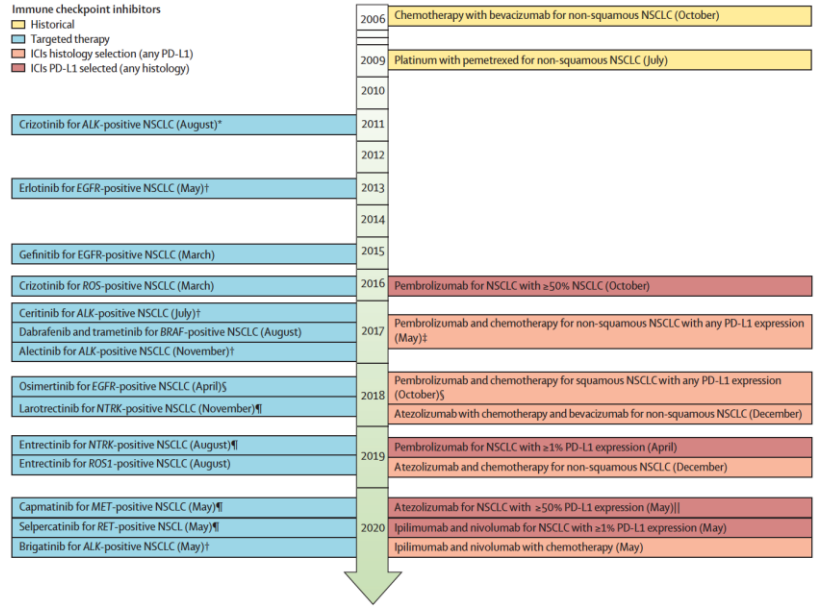
2 Mondi, 2 Rivoluzioni nel NSCLC

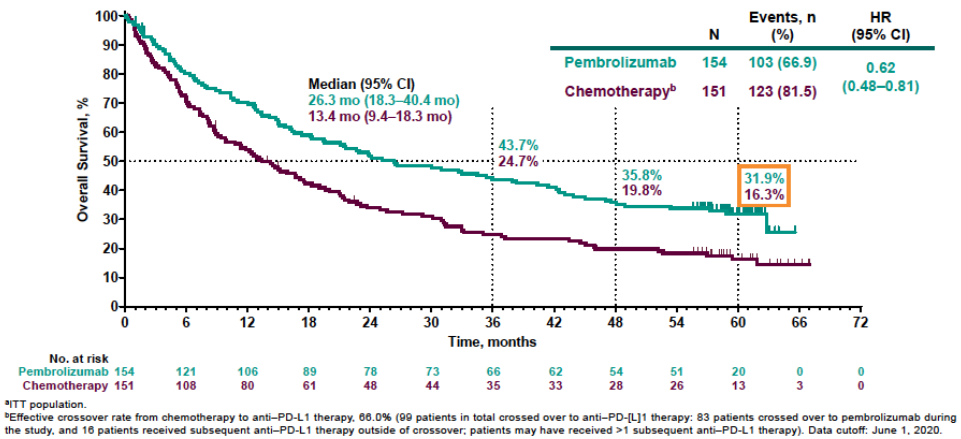
NSCLC oncogene-addicted

NSCLC NON-oncogene-addicted

NSCLC avanzato:
Evoluzione dei trattamenti e vantaggio in OS







[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). Data cutoff: June 1, 2020.

Thai et al, Lancet 2021

Reck et al, JCO 2021

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2 Mondi, 2 Rivoluzioni nel NSCLC

NSCLC oncogene-addicted

Resistenza
Nuovi Target

NSCLC NON-oncogene-addicted

Beneficio in circa il 20-30% a lungo termine

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ADC in lung cancer

IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Antibody Drug Conjugates:
The Next Tsunami

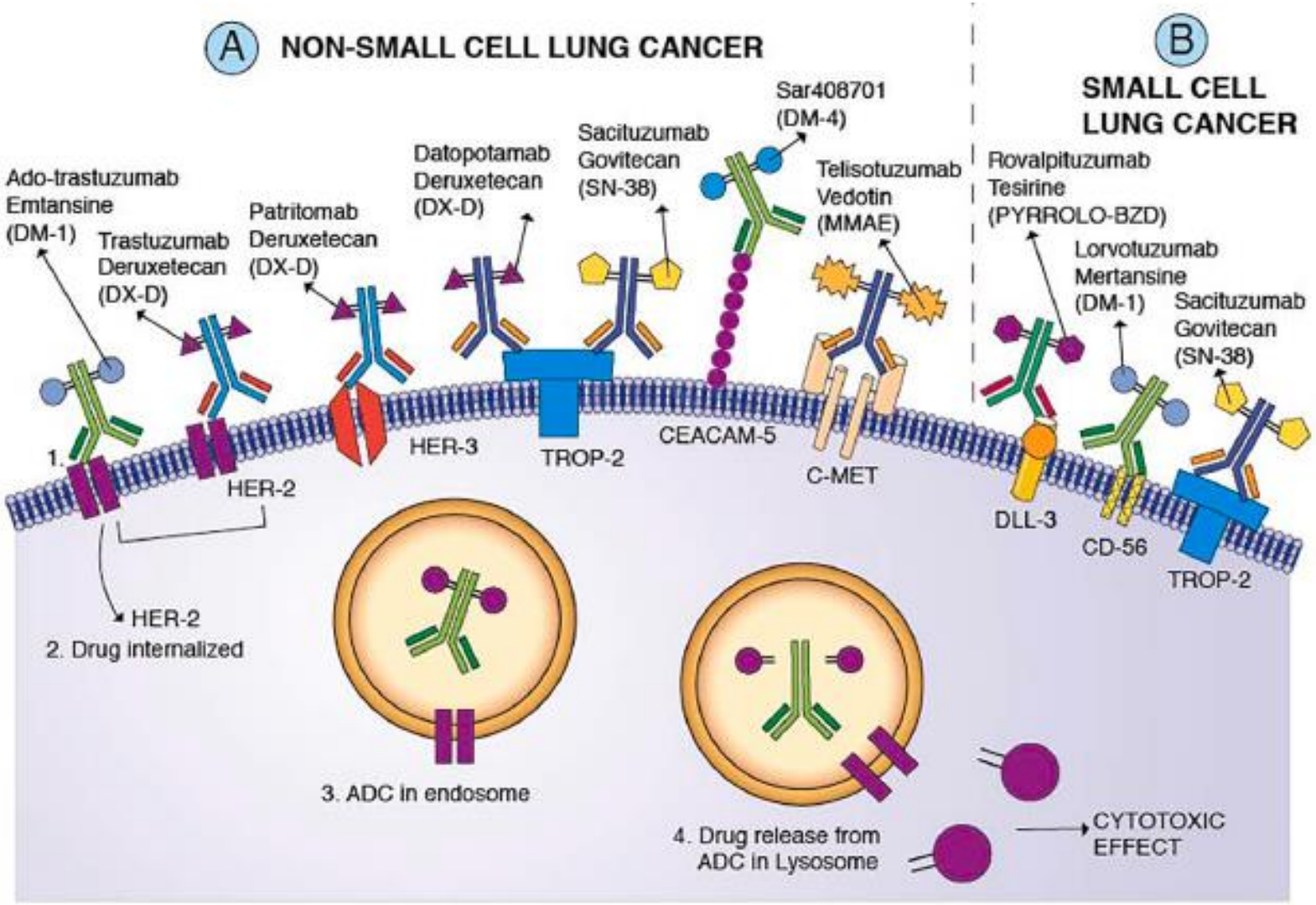
ADCs in advanced NSCLC – where we are today

- ✓**HER-2 mutant NSCLC: Trastuzumab-DXd,** FDA accelerated approval for pretreated patients (Aug 2022)
  - ✓DESTINY-Lung01 trial *(Li et al. NEJM 2022; 386:241)*
  - ✓DESTINY-Lung02 trial *(Goto et al. ESMO 2022)*
- ✓**EGFR-mutant NSCLC: Patritumab-DXd**, FDA Breakthrough Therapy Designation, after failure of 3rd generation TKI and platinum-based chemotherapy
- ✓**c-MET overexpressing NSCLC: Telisotuzumab vedotin**, FDA Breakthrough Therapy Designation, after failure of platinum-based chemotherapy

- ✓Numerous early-phase trials assessing various ADCs (monotherapy or in combinations)

Adapted from Linardou H, WCLC 2023

ADC in lung cancer



Desai et al, Lung Cancer 2022

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ADC in lung cancer

Target	Drug	Payload	Linker	RP2D and Schedule	DAR
HER2	Trastuzumab-DM1	DM1	Noncleavable (thioether)	3.6 mg/kg, once every 3 weeks	3.1
	Trastuzumab-DXd	Deruxtecan	Cleavable (tetrapeptide)	6.4 mg/kg, once every 3 weeks	8
HER3	Patritumab-DXd	Deruxtecan	Cleavable (tetrapeptide)	5.6 mg/kg, once every 3 weeks	8
TROP2	Datopotamab-DXd	Deruxtecan	Cleavable (tetrapeptide)	6 mg/kg, once every 3 weeks	4
	Sacituzumab govitecan	SN-38	Cleavable (carbonate)	10 mg/kg on day 1 and 8, once every 3 weeks	7.6
CEACAM5	Tusamitamab ravtansine	DM4	Cleavable (SPDB)	100 mg/m^2, once every 2 weeks	3.8
c-MET	Telisotuzumab vedotin	MMAE	Cleavable (valine-citrulline)	2.7 mg/kg, once every 3 weeks	3.1
B7-H3	I-DXd (DS-7300a)	Deruxtecan	Cleavable (tetrapeptide)	TBD	4
	MGC018	DUBA	Cleavable (valine-citrulline)	TBD	2.7
CD56	Lorvotuzumab mertansine	DM1	Cleavable (disulfide)		–
AXL	Enapotamab vedotin	MMAE	Cleavable (protease)	2.2 mg/kg, once every 3 weeks	–
	Mecbotamab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	–
PK7	Cofetuzumab pelidotin	Auristatin-0101	Cleavable (valine-citrulline)	TBD	4
PVRL4	Enfortumab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
TF	Tisotumab-vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
EGFR	MRG003	MMAE	Cleavable (valine-citrulline)	2.0 mg/kg, once every 3 weeks	4
ROR2	Ozuriftamab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
NaPi2b	Upifitamab rilsodotin	AF-HPA	Cleavable (protease)	TBD	12-15
	Lifastuzumab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	3-4

Passaro et al, JCO 2023

NSCLC HER2 mutato (circa 2%): Trastuzumab Deruxtecan – Destiny Lung 01

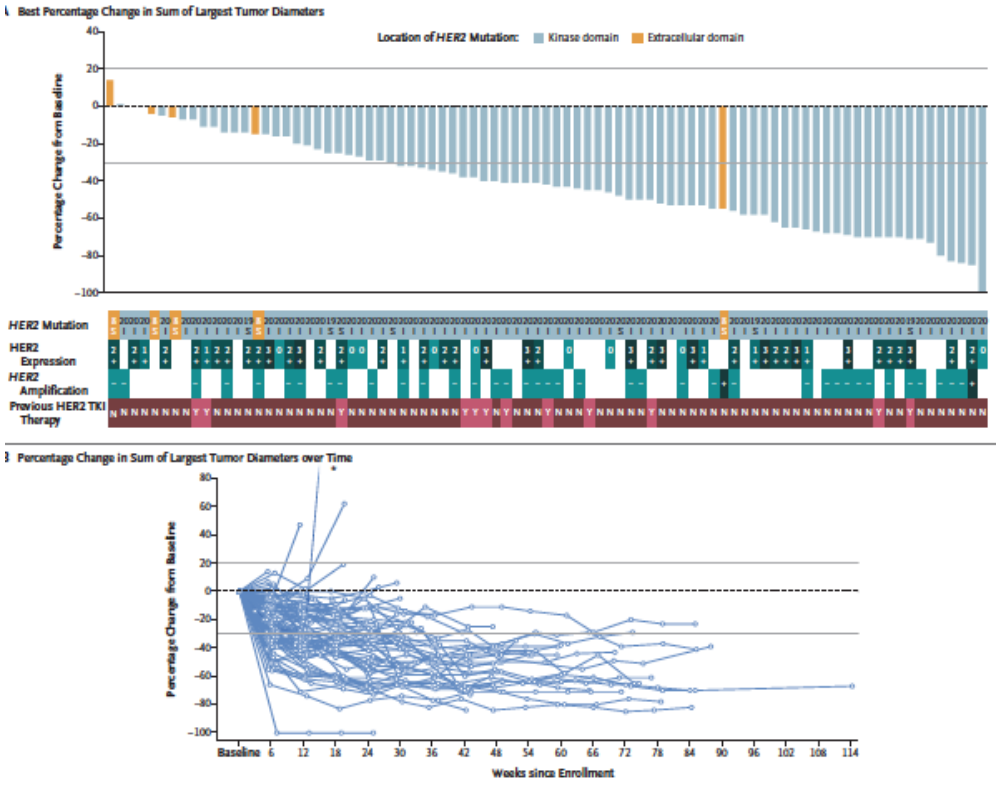
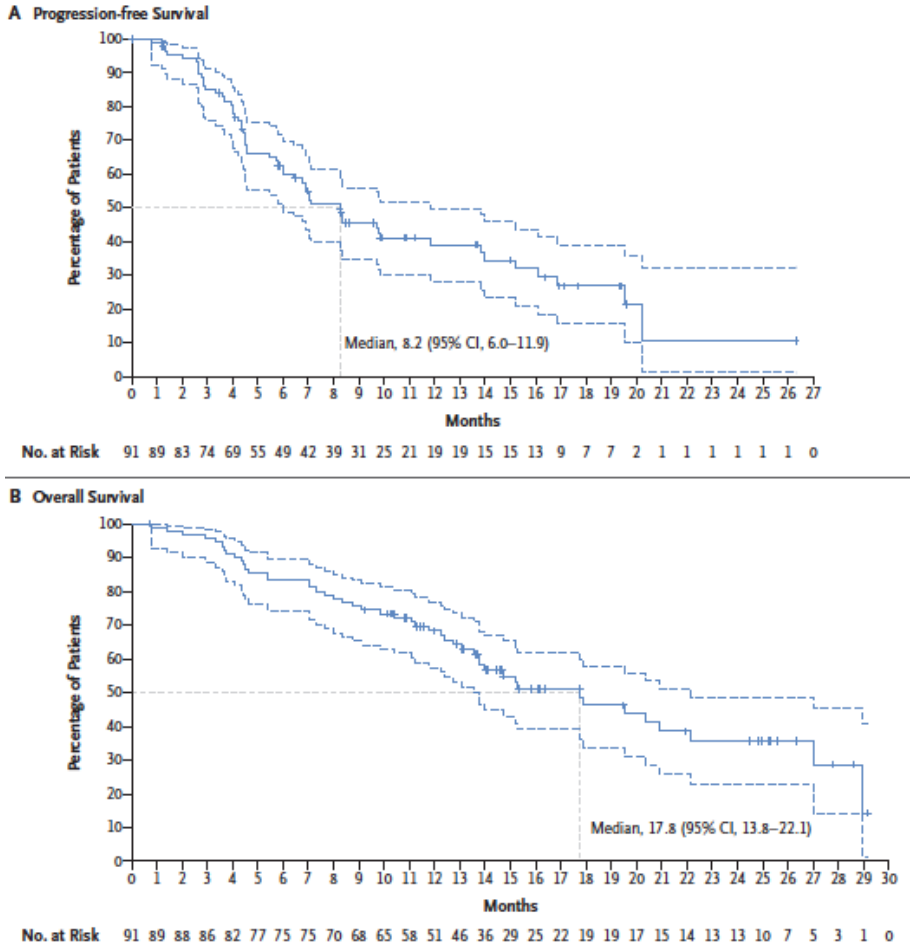


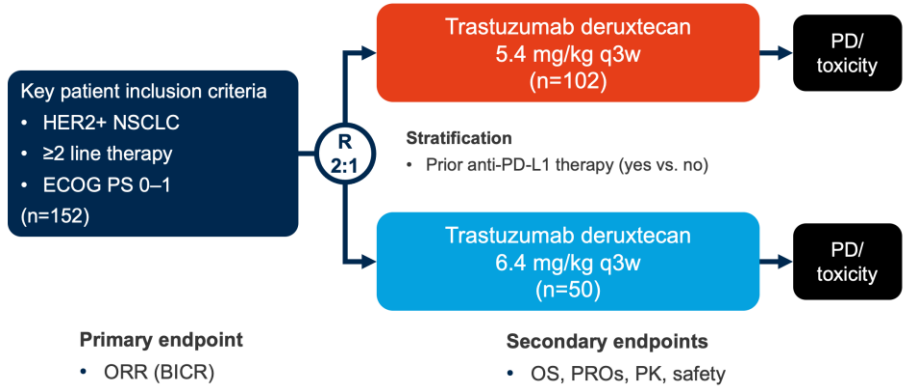
Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N= 91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo†	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo†	9.3 (5.7–14.7)



Li et al, N Engl J Med 2021

NSCLC HER2 mutato (circa 2%):
Trastuzumab Deruxtecan - Destiny Lung 02



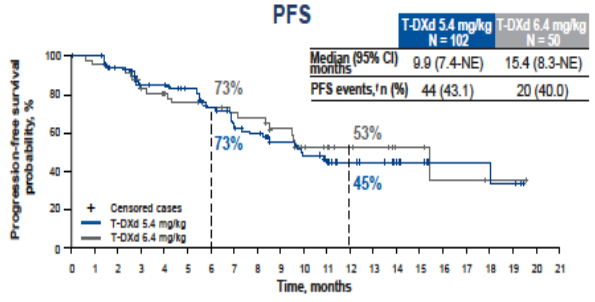
Baseline Characteristics and Efficacy Summary

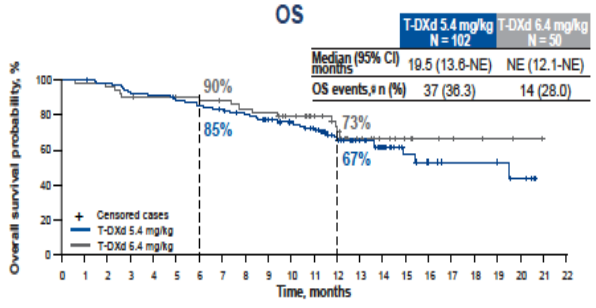
Baseline Characteristics

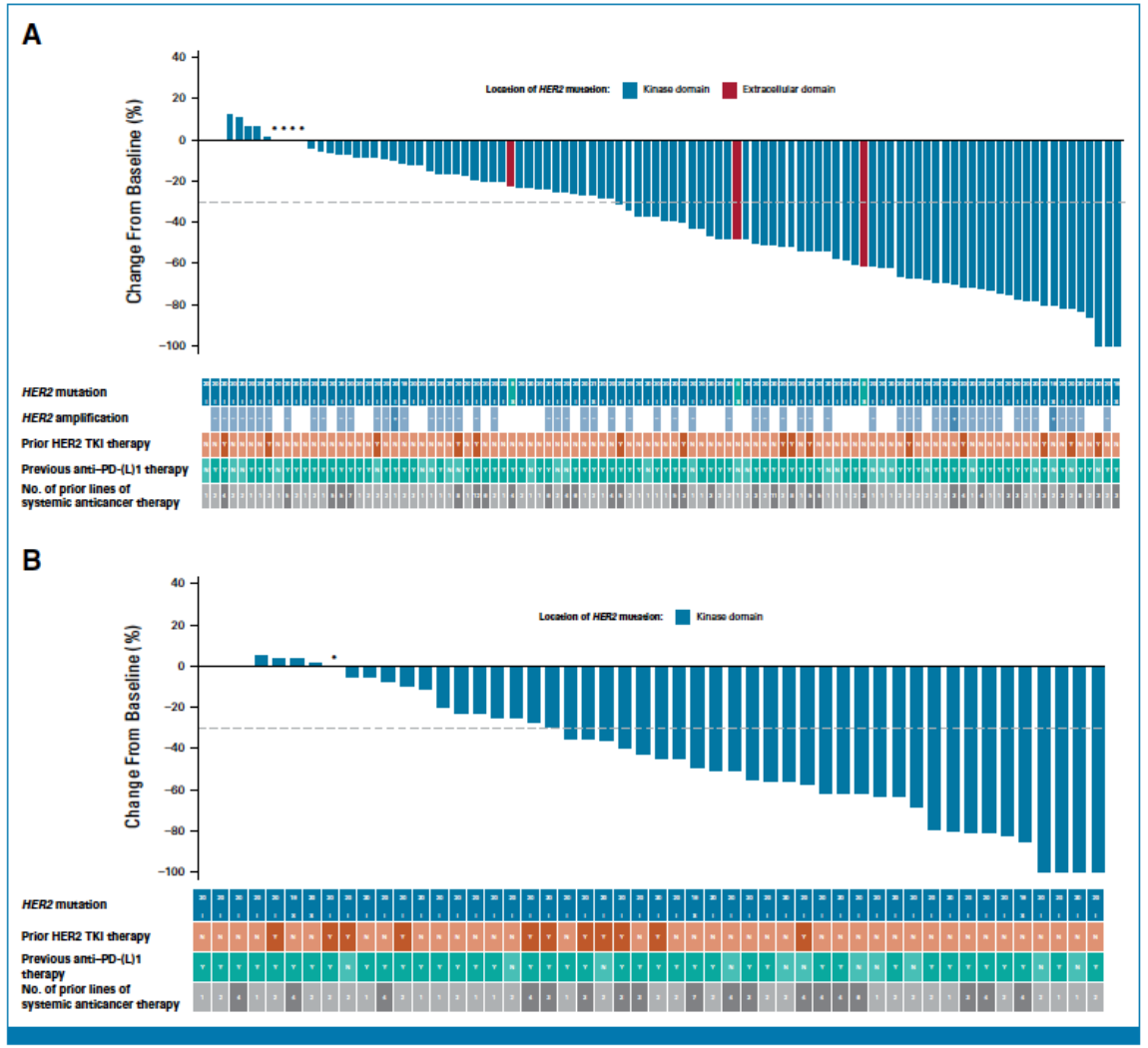
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	50 (49.0) [39.0-59.1]	28 (56.0) [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)





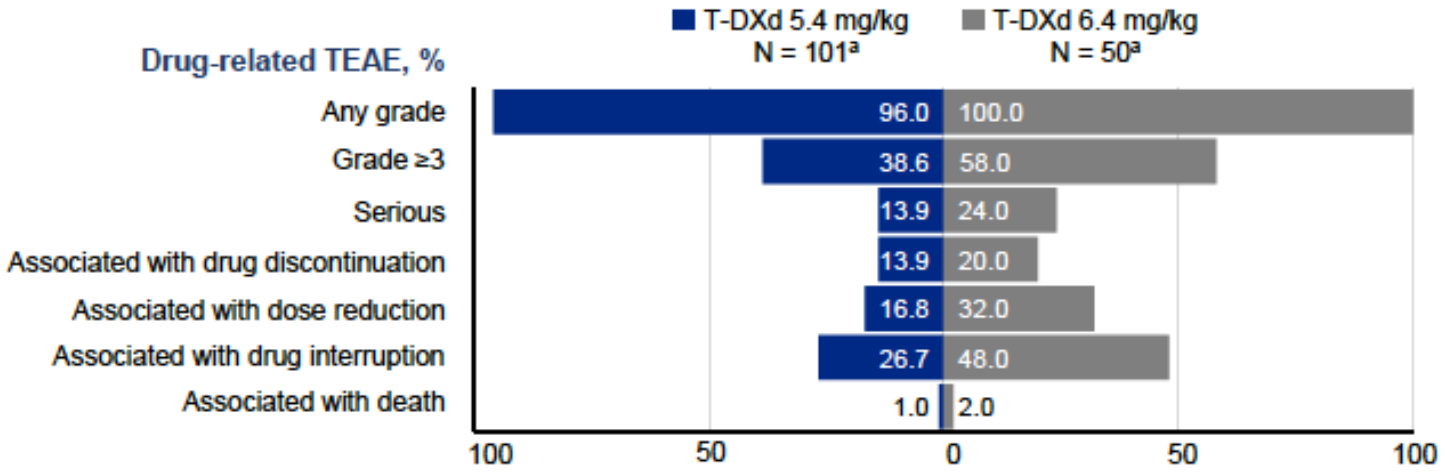


Janne et al, WCLC 2023 and Goto et al, JCO 2023

NSCLC HER2 mutato (circa 2%): Trastuzumab Deruxtecan - Destiny Lung 02

Overall Safety Summary

Overall Safety



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

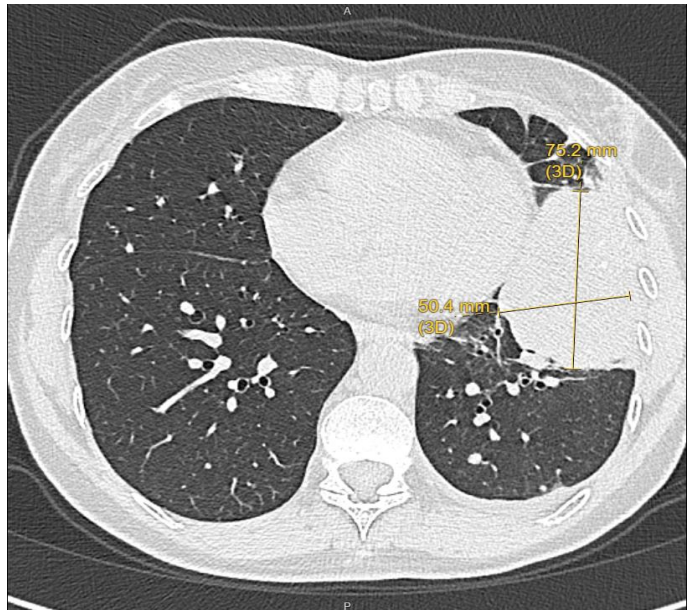
- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

ILD, interstitial lung disease; TEAE, treatment emergent adverse event; T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.

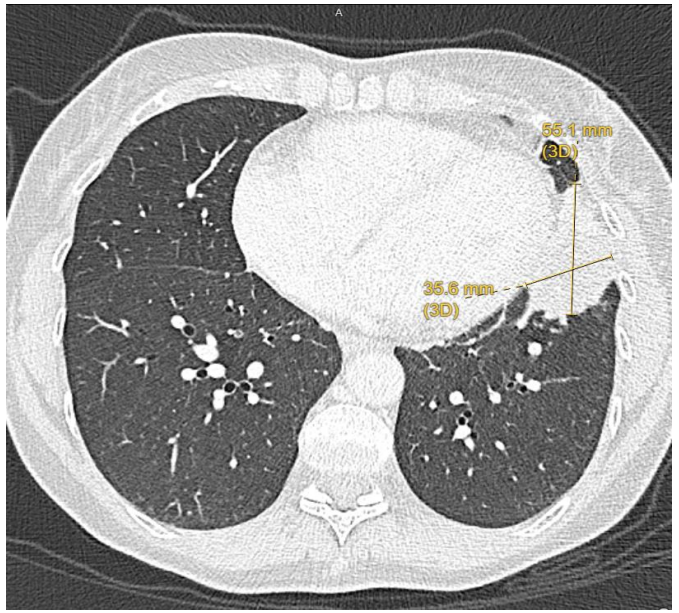
Janne et al, WCLC 2023 and Goto et al, JCO 2023

NSCLC HER2 mutato (circa 2%): Trastuzumab Deruxtecan - Destiny Lung 04

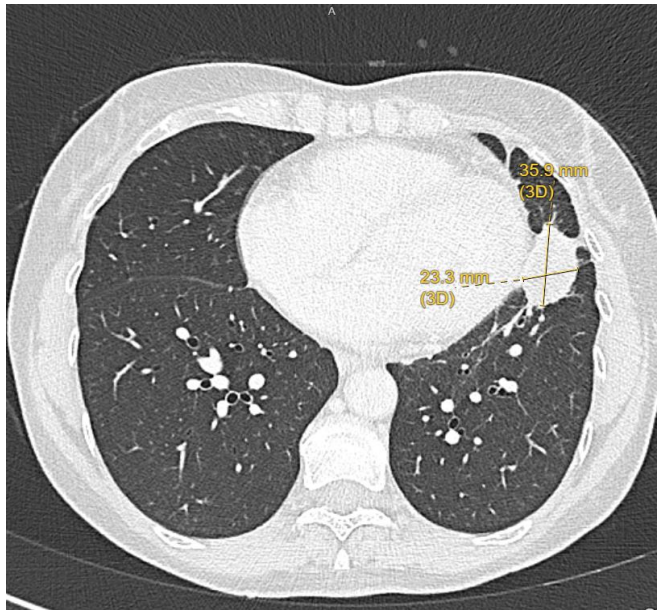
- F, 61 anni
- Dicembre 2022: diagnosi di adenocarcinoma polmonare stadio IV (polmone, linfonodi, osso, encefalo)
- NGS: HER2 mut. Esone 20
- 13/02/2023 avvia trastuzumab deruxtecan (studio Destiny-Lung04)
- 28/03/2023 TC dopo 2 cicli: PR; neutropenia G2, nausea e vomito G1, astenia G1
- 12/09/2023 TC dopo 10 cicli: ulteriore PR



Basale 7/02/2023



Prima rivalutazione 28/03/2023



Attuale 12/09/2023

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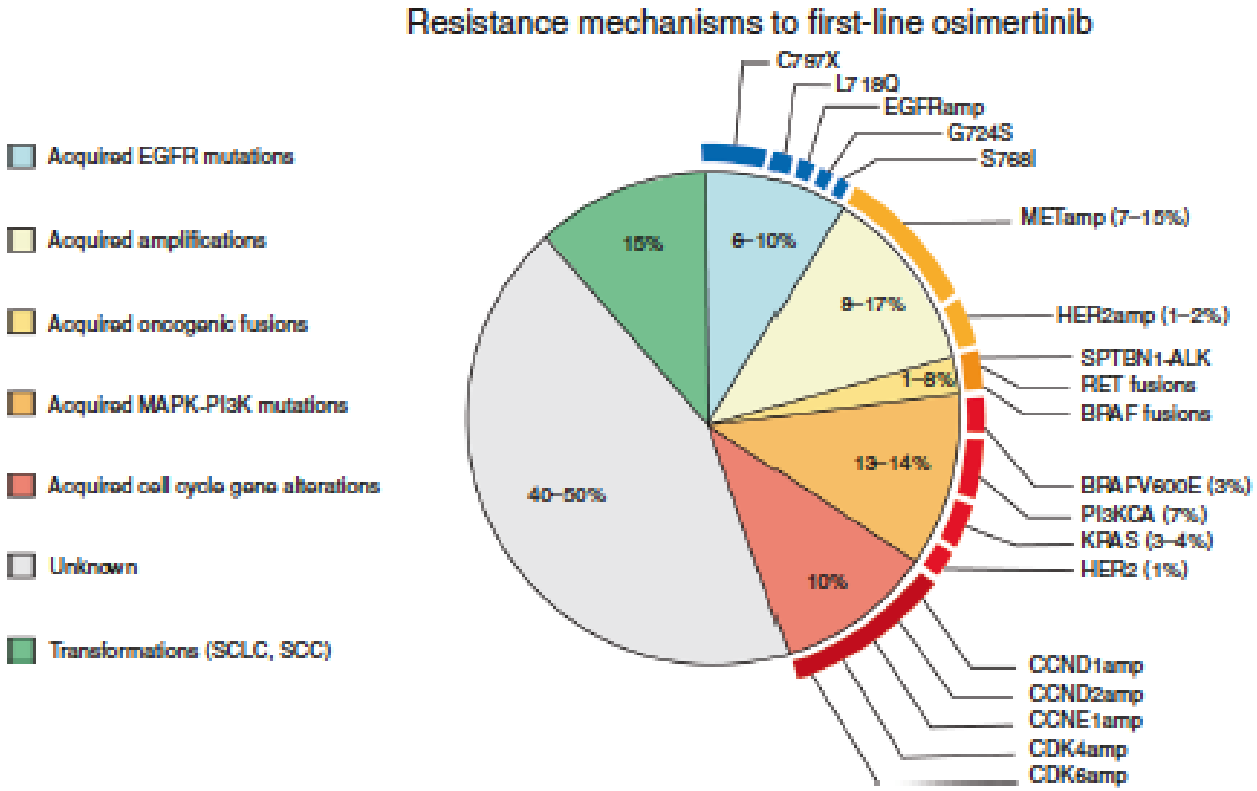
Osimertinib resistance in first-line EGFR mutated NSCLC

- Mostly unknown
- Highly eterogeneous
- Sometimes overlapping
- Not always targetable



Leonetti et al, Br J Cancer 2019

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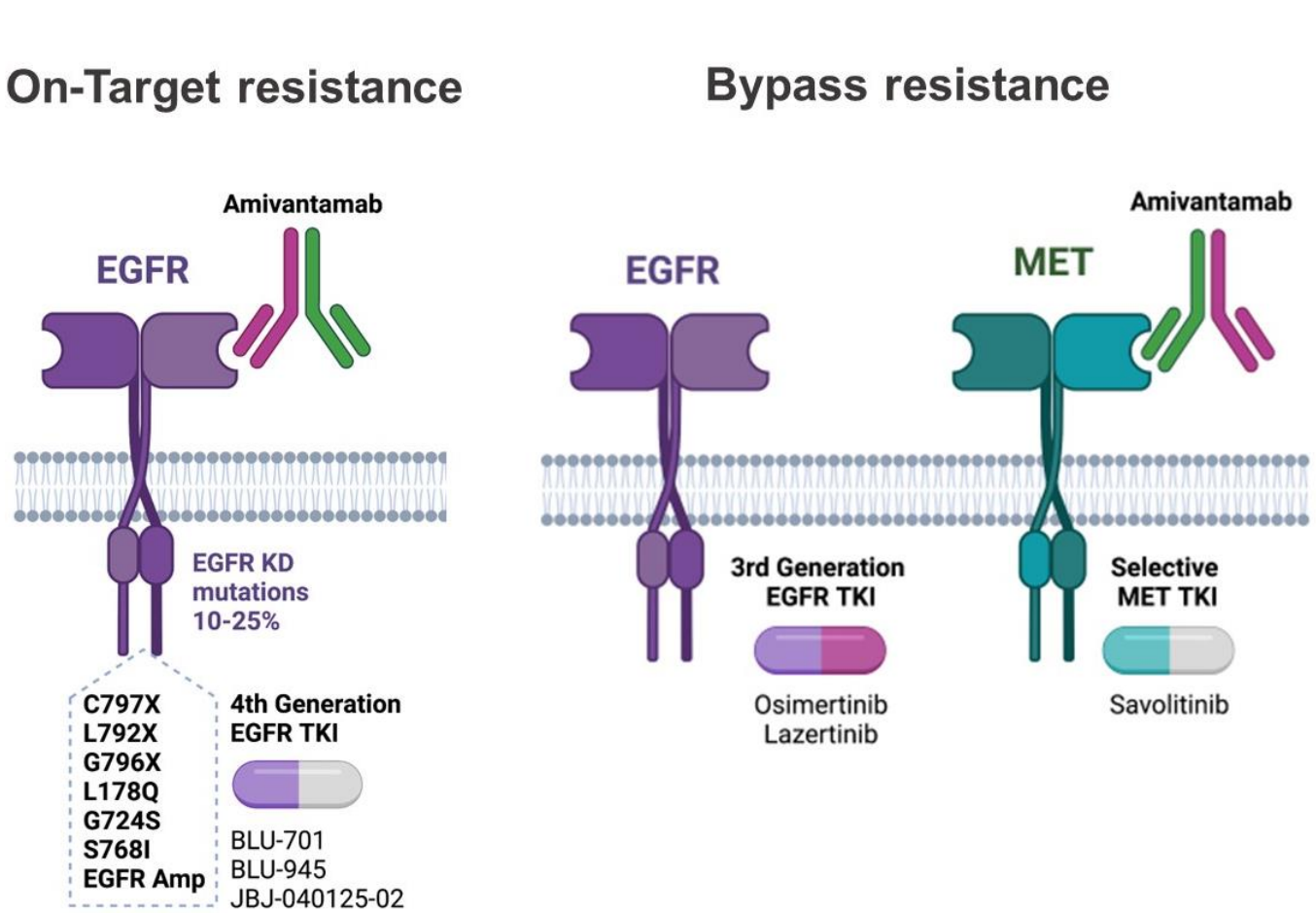
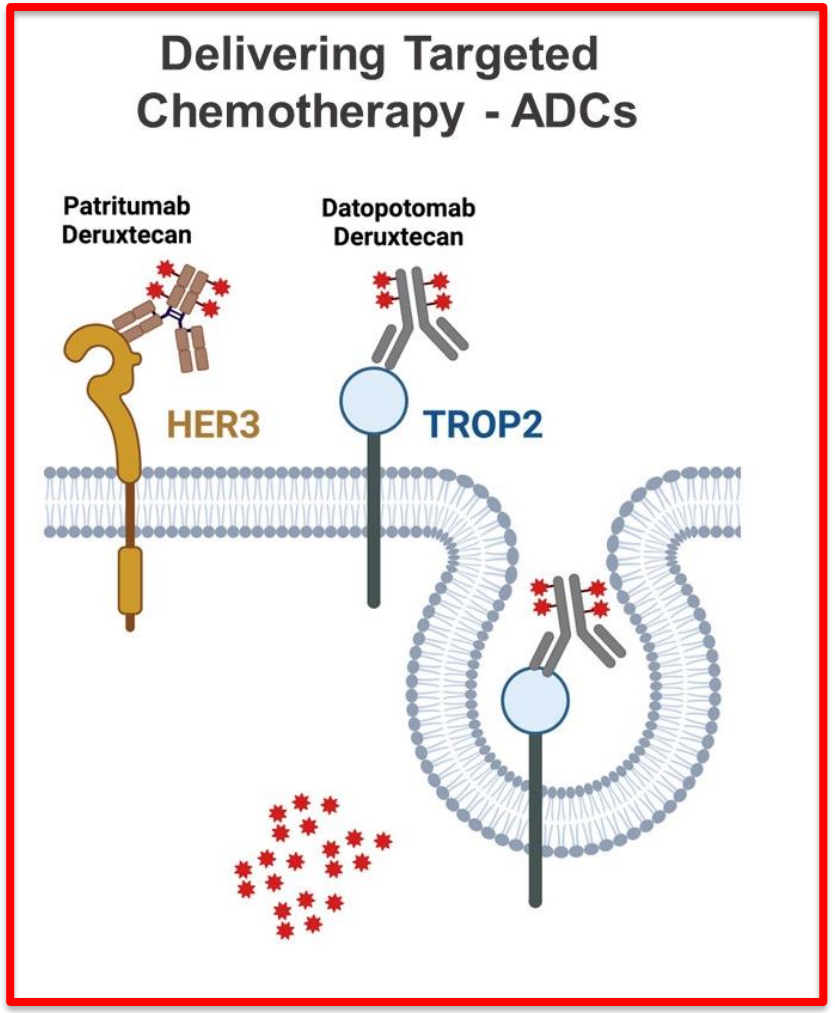
Investigational Treatment Strategies to Overcome Osimertinib-Resistance





Adapted from Recondo ASCO 2022

NSCLC EGFR mutato dopo TKI

Patritumab Deruxtecan – HERTENA Lung 01

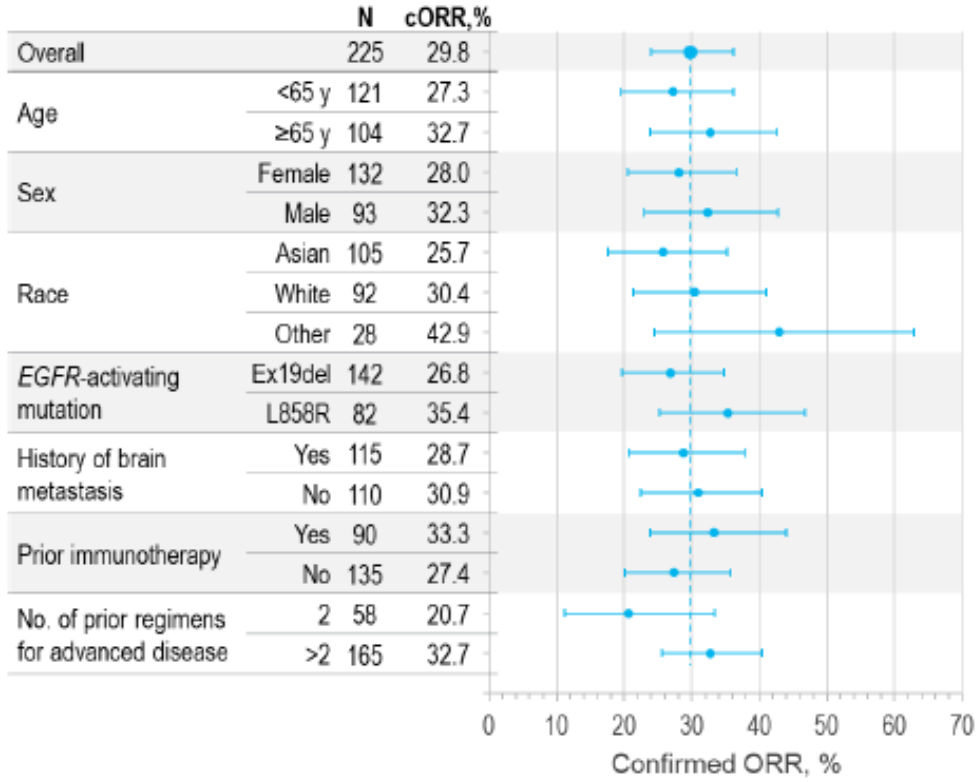
Patritumab Deruxtecan
HERTHENA-Lung01

Clinically Meaningful Efficacy Was Observed in the Overall Population and Across Subgroups

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

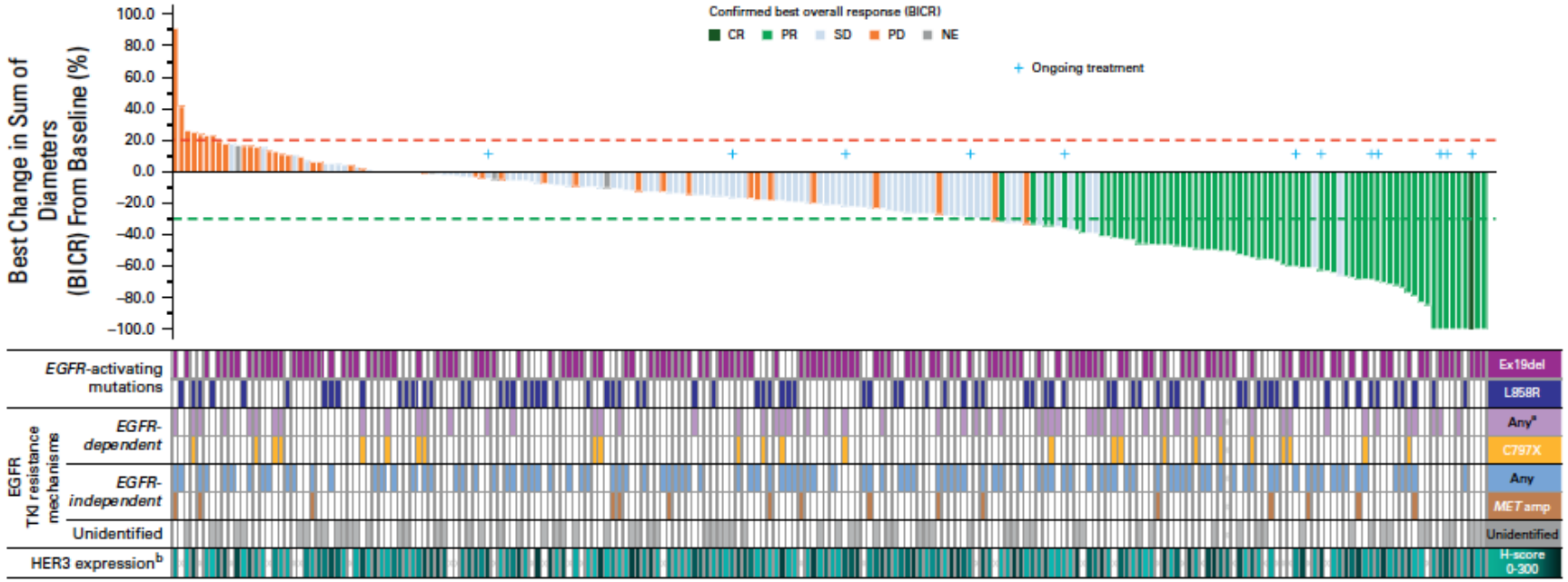
cORR by Patient and Disease Characteristics at Study Entry



Yu et al, WCLC 2023 and JCO 2023

NSCLC EGFR mutato dopo TKI

Patritumab Deruxtecan – HERTENA Lung 01



Intracranial response by CNS BICR per CNS RECIST	Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a]
Confirmed ORR (95% CI), %	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
NE, n (%)	3 (10.0)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

Toxicity: chemo-like AEs, haematological early and transient, 45.3% Gr ≥3 TEAEs, but low discontinuation rate (7%), managed with dose interruption and relatively low ILD rate (5.3%)

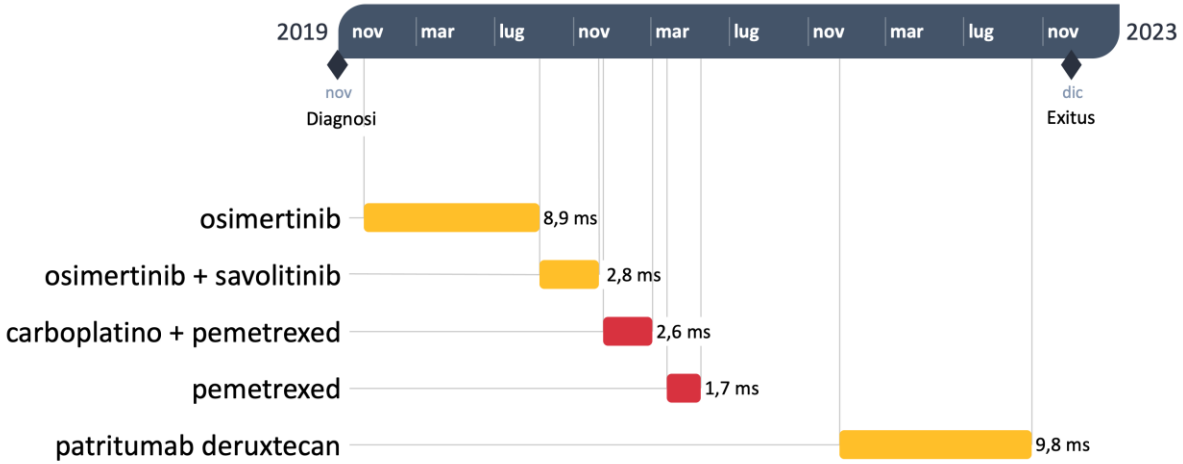
Yu et al, WCLC 2023 and JCO 2023

NSCLC EGFR mutato dopo TKI

Patritumab Deruxtecan – HERTENA Lung 01 e 02

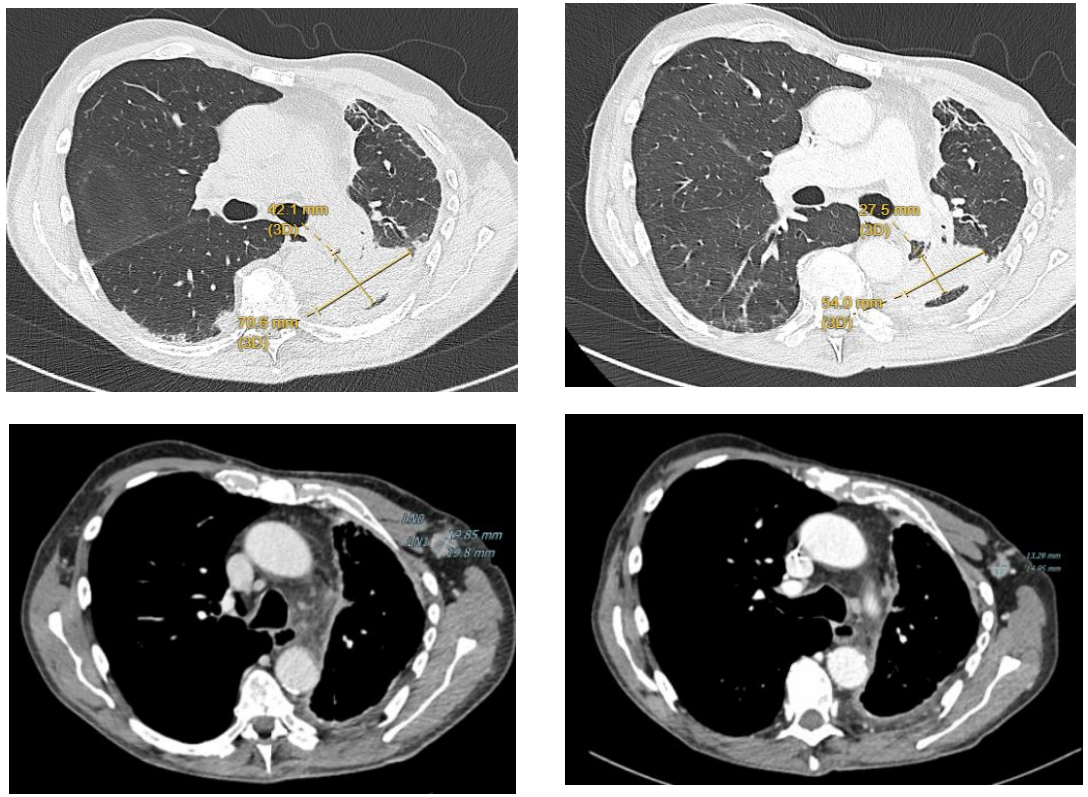
Hertena Lung 01

Decorso clinico: Nov ‘19 – Dic ‘22



Hertena Lung 02

M, 72 anni, in PD dopo 12 mesi di Osimertinib, Met non amplificato



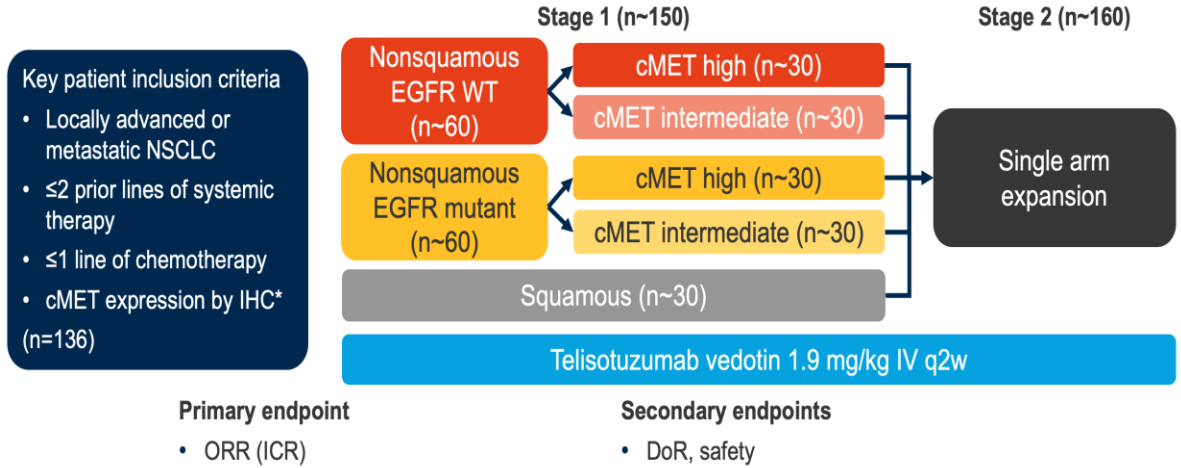
Basale 14/07/2023

Dopo 2 cicli 5/09/2023

Anti-MET Telisotuzumab Vedotin

Luminosity Trial

– To evaluate the efficacy and safety of telisotuzumab vedotin in previously treated patients with NSCLC and cMET overexpression in the LUMINOSITY trial



Cohort	ORR n/N	ORR % (95%CI)	DoR n/N	DoR mo (95%CI)
NSQ EGFR WT				
All	19/52	36.5 (23.6, 51.0)	8/19	6.9 (4.1, NR)
cMET high	12/23	52.2 (30.6, 73.2)	5/12	6.9 (2.4, NR)
cMET intermediate	7/29	24.1 (10.3, 43.5)	3/7	NR (4.1, NR)
NSQ EGFR mutant				
All	5/43	11.6 (3.9, 25.1)	2/5	NR (3.0, NR)
cMET high	5/30	16.7 (5.6, 34.7)	2/5	NR (3.0, NR)
cMET intermediate	0/13	0	-	-
Squamous	3/27	11.1 (2.4, 29.2)	2/3	4.4 (3.0, NR)

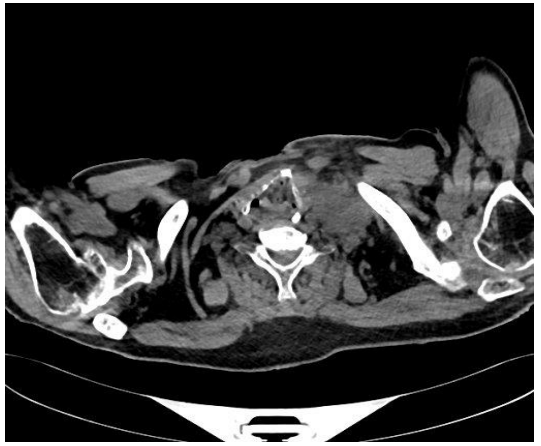
Cohort	Prior platinum n/N	Prior platinum ORR, %	Prior platinum + immune checkpoint inhibitor n/N	Prior platinum + immune checkpoint inhibitor ORR, %
NSQ EGFR WT				
All	18/50	36.0	15/37	40.5
cMET high	11/21	52.4	9/16	56.3
cMET intermediate	7/29	24.1	6/21	28.6

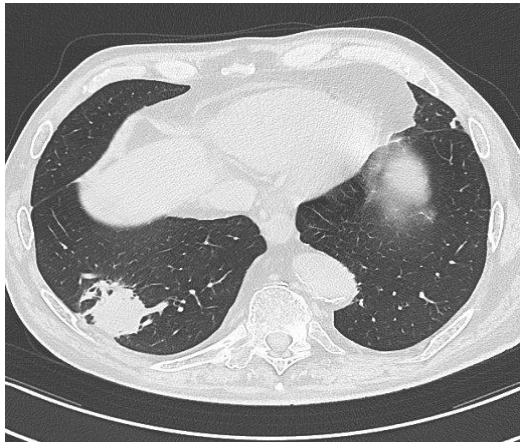
Camidge et al, ASCO 2022

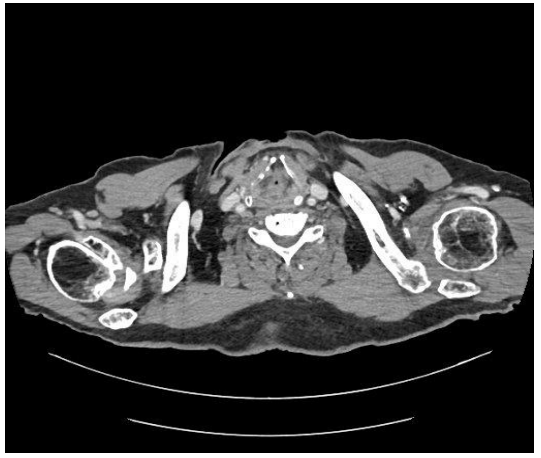
Anti-MET Telisotuzumab Vedotin

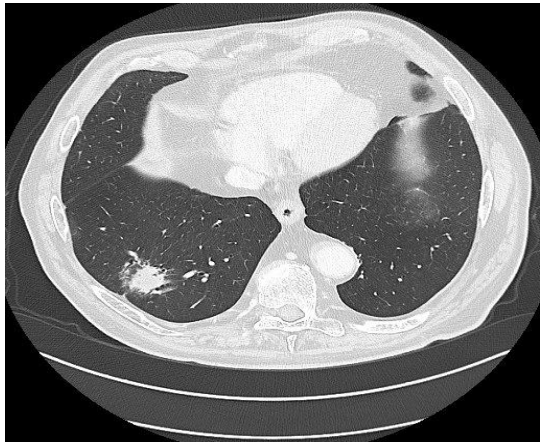
Luminosity Trial

- 75 anni ex-fumatore
- Maggio 2020: diagnosi di ADK T2N2 multistazione PDL1 5%, MET amplificato
- CT-RT e durvalumab
- In corso di durvalumab comparsa di adenopatia LC sx e PD polmonare
- Arruolato studio Luminosity
- 23.9.21: inizio telisotuzumab vedotin
- RP polmone e RC su N
- Terapia in corso, ben tollerata salvo parestesie G2

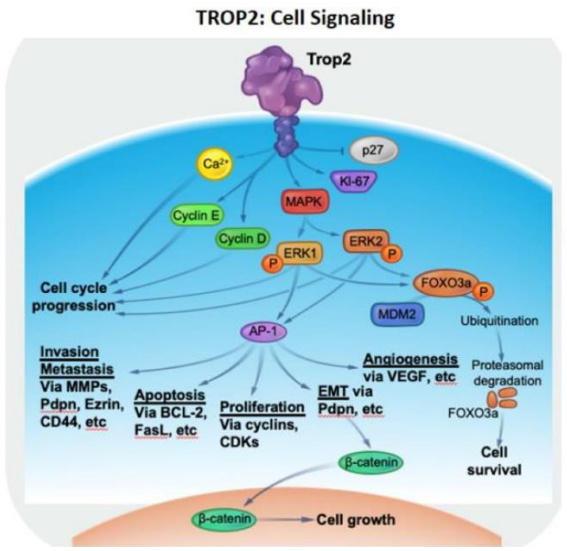




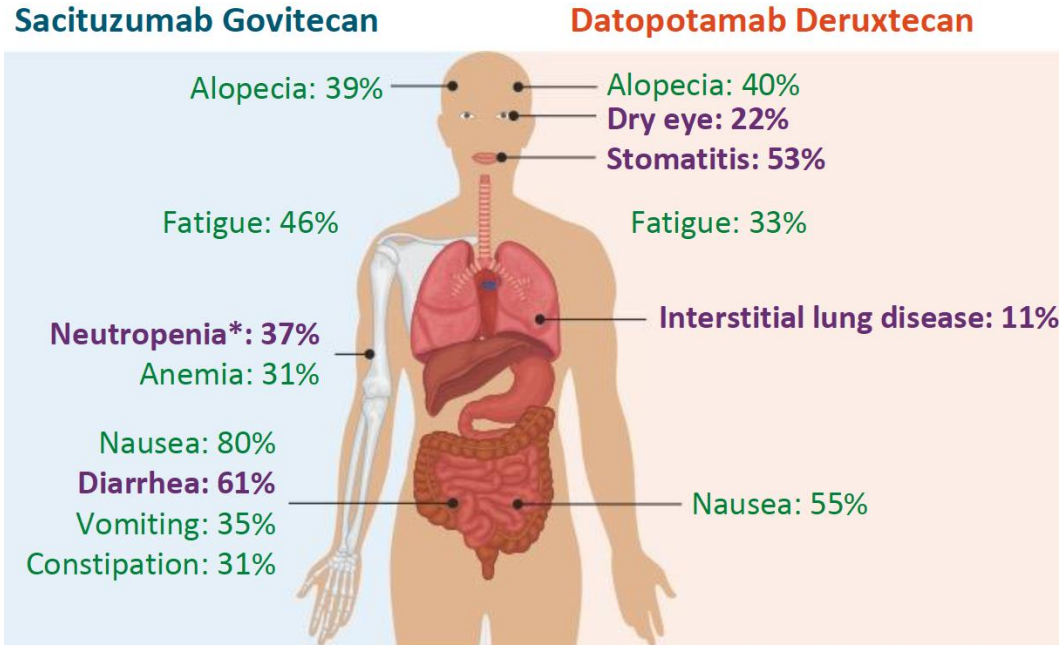


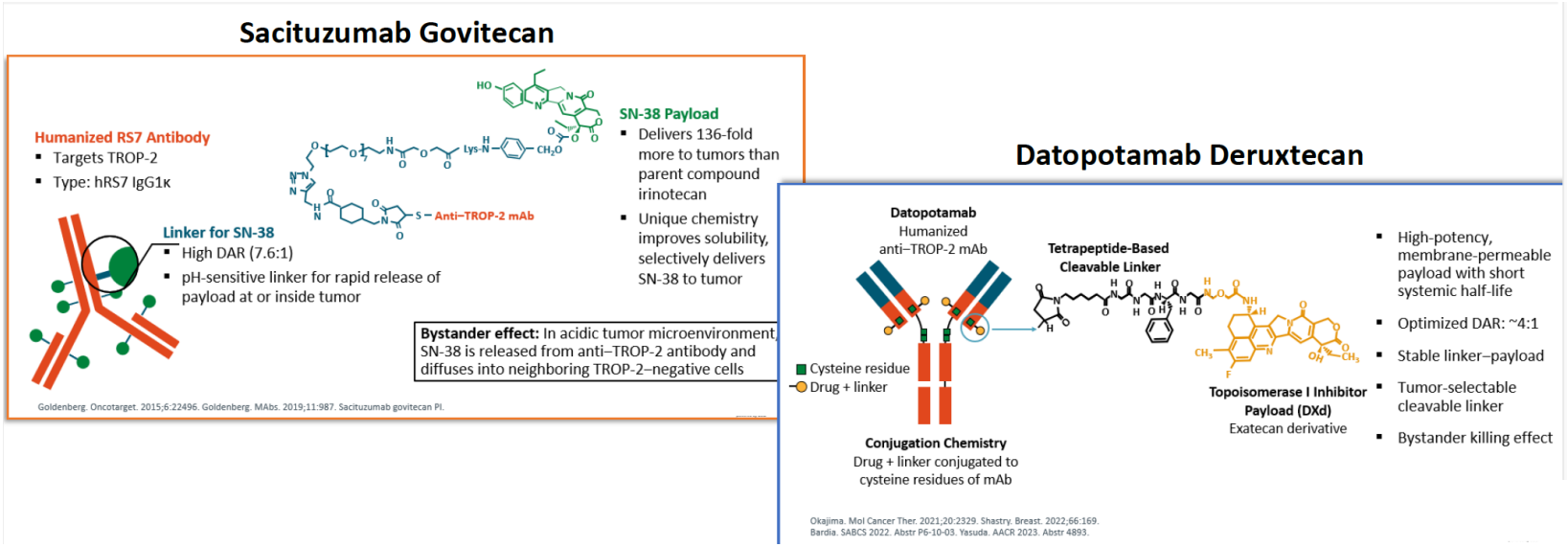


Anti-TROP2 in NSCLC



- Trophoblast cell-surface antigen 2 (TROP-2) is a transmembrane glycoprotein overexpressed in solid tumors including TNBC and NSCLC, associated with poor survival
- **NSCLC overexpression in 64% of AC and 75% of SCC**
- TROP-2 is an epithelial adhesion molecule and regulates stem cell marker–associated cell regeneration





Adapted from Linardou H, WCLC 2023

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Anti-TROP2 in NSCLC

- **Dato-DXd:** An ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase-I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- **Pre-clinical data:** Dato-DXd enhances antitumor response to PD-1/PD-L1 inhibitors[2]
- **Phase 1 data:** Dato-DXd showed encouraging early clinical efficacy and manageable safety in patients with advanced or metastatic NSCLC:[3,4]

TROPION-PanTumor01 study[3,a]

ORR (confirmed): 26%

with Dato-DXd 6 mg/kg monotherapy in heavily pre-treated NSCLC

TROPION-Lung02 study[4,b]

ORR (confirmed and pending): 50% and 57%

with Dato-DXd + pembro and Dato-DXd + pembro + platinum-based chemotherapy, respectively, in 1L NSCLC

- **Phase 3 data:** Dato-DXd 6 mg/kg monotherapy demonstrated a statistically significant improvement in PFS versus docetaxel in previously treated advanced or metastatic NSCLC (TROPION-Lung01 study)[5]

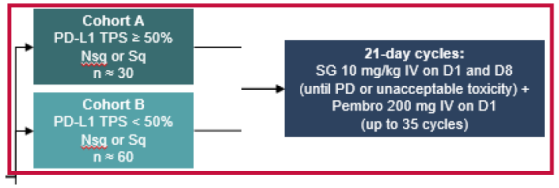
[a] N=50 patients in the Dato-DXd 6 mg/kg cohort with an ORR of 26% (95% CI: 14.6, 40.3). [b] N=34 patients in the doublet cohort with an ORR of 50% (95% CI: 32, 68). N=53 patients in the triplet cohort with an ORR of 57% (95% CI: 42, 70).
1L, first-line; ADC, antibody-drug conjugate; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; Ig, immunoglobulin; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS: progression-free survival; TROP2, trophoblast cell surface protein 2.

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 2. Okajima D, et al. Poster 2932. Presented at AACR 2023; 3. Shimizu T, et al. J Clin Oncol 2023;10.1200/JCO.23.00059:ePub; 4. Goto Y, et al. Oral 9004. Presented at ASCO 2023; 5. AstraZeneca Press Release. Datopotamab deruxtecan met dual primary endpoint of progression-free survival in patients with advanced non-small cell lung cancer in TROPION-Lung01 Phase III trial. Available at: https://www.astrazeneca.com/media-centre/press-releases.html (accessed July 2023).

Waqar et al, WCLC 2023

Anti-TROP2 combo in NSCLC

EVOKE-02: An Open-Label, Multicohort Phase 2 Study, 1st Line



Efficacy by Investigator Assessment

Efficacy by INV[a]	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 29	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 32	Total SG + Pembro n = 61
ORR[b] (95% CI), %	69 (49-85)	44 (26-62)	56 (42-69)
PR, n (%) – confirmed and unconfirmed	20 (69)	14 (44)	34 (56)
Confirmed PR, n (%)	18 (62)	12 (38)	30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR[c] (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR[d,e] (95% CI), months	NR (5.6-NR)	NR (3.5-NR)	NR (7.9-NR)
DOR rate at 6 months[d,e] (95% CI), %	88 (39-98)	88 (39-98)	87 (58-97)

KEYNOTE 189: ORR: 62.1% (TPS≥50%), 50% (TPS 1-49%), 48.3% all comers

The safety profile of SG + Pembro was manageable and consistent with the known safety of each agent
- –The most common any-grade TEAEs were diarrhea, anemia, and asthenia
- –TEAEs leading to treatment discontinuation were low (18%)

TROPION-Lung04 is investigating Dato-DXd in combination with different immunotherapy agents ± carboplatin across 11 cohorts. This interim analysis reports the first data from Cohorts 2 and 4

Cohort 2 (Doublet): Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)

Cohort 4 (Triplet): Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)

Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		7 (50.0)	10 (76.9)[b]
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		13 (92.9)	12 (92.3)
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

Data cut-off: March 6 2023
All subjects must have had at least one scan (6 weeks of follow-up) to be included in the ORR interim analysis set. The 2-sided 95% CIs are exact Clopper-Pearson intervals. [a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.
CI, confidence interval.

- In the 1L setting, ORRs were **50.0%** for Cohort 2 and **76.9%**[b] for Cohort 4
- In the overall population (1L/2L+), ORRs were **47.4%** for Cohort 2 (N=19) and **71.4%**[b] for Cohort 4 (N=14)
- Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

Safety

No new safety signals were observed in Cohort 2 and Cohort 4 investigating Dato-DXd in combination with durvalumab ± carboplatin, throughout dose escalation and dose expansion

The most frequent TEAEs of any grade were stomatitis, alopecia and nausea. In general, Grade ≥3 TEAEs were more frequently observed with the triplet versus the doublet combination, which was mainly driven by more hematological events. There were four cases of ILD adjudicated as drug-related, three of which were Grade 1 or 2

The Phase 3 AVANZAR trial in 1L is ongoing

Adapted from Linardou H, WCLC 2023

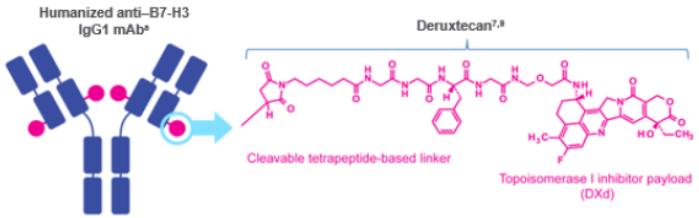
Anti-B7-H3 in SCLC

DS7300-A-J101 Study Design (NCT04145622)

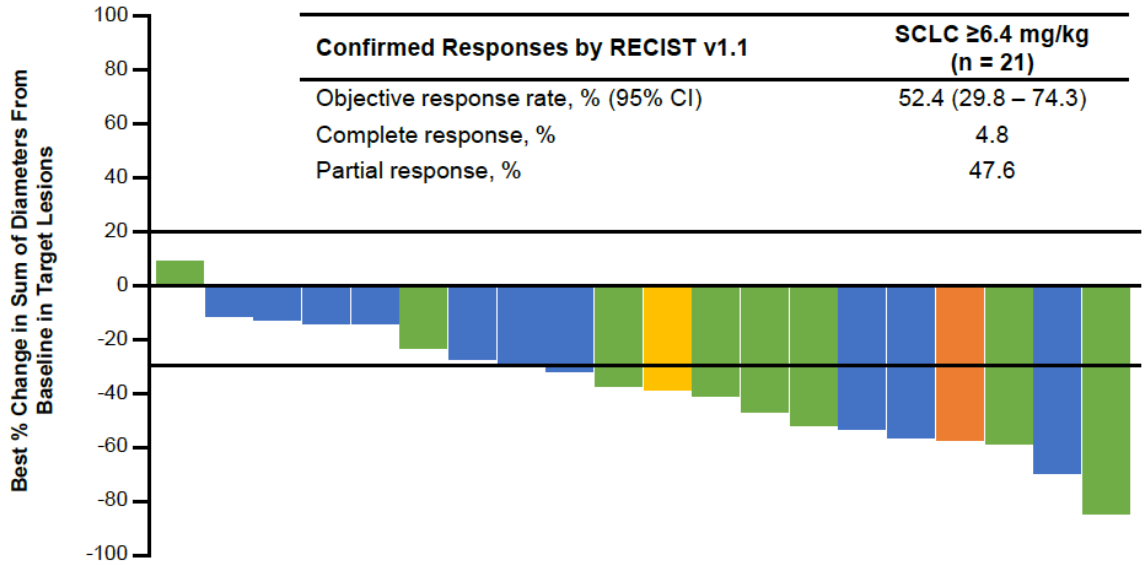
- **We present a subgroup analysis of patients with SCLC (N = 22) from part 1 treated with I-DXd at all doses studied**

Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]



Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6

- **52% ORR, 5.9 months mDOR, 5.6 months mPFS, and 12.2 months mOS**
- Nausea was the most common TEAE, and antiemetic prophylaxis is now required for all I-DXd studies, ILD 13.6% (Gr1-2)

Johson et al, WCLC 2023; adapted from Linardou WCLC 2023

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ADC in lung cancer: main ongoing trials

Drug	Target	Trial No.	Phase	Setting	Treatments	Primary End Point
Trastuzumab-DXd	HER2	NCT04644237 (DESTINY-Lung02)	II	Pretreated HER2 mutant NSCLC	T-DXd 5.4 or 6.4 mg/kg	ORR
		NCT05048797 (DESTINY-Lung04)	III	First-line HER2 mutant NSCLC	T-DXd *v* platinum-pemetrexed-pembrolizumab	PFS
		NCT04042701	Ib	HER2-expressing NSCLC who had not received any prior treatment with anti–PD-1, anti–PD-L1, or HER2	T-DXd plus pembrolizumab	DLTs ORR
		NCT04686305 (DESTINY-Lung03)	Ib	HER2 overexpressing nonsq NSCLC (first-line and pretreated)	T-DXd plus platinum pemetrexed and durvalumab	AEs
		NCT05246514 (DESTINY-Lung05)	II	Pretreated HER2-mutant NSCLC	T-DXd	ORR
		NCT05650879	Ia	Pretreated HER2-mutant NSCLC arm	T-DXd plus ELVN-002	DLTs safety
A166	HER2	NCT03602079	I/II	HER2-expressing tumors	A166 monotherapy	DLTs
XMT-1522	HER2	NCT02952729	I/II	HER2-expressing tumors	XMT-1522 monotherapy	DLTs
Patritumab-DXd	HER3	NCT04619004 (HERTHENA-Lung01)	II	Pretreated EGFR-mutant NSCLC	HER3-DXd	ORR
		NCT05338970 (HERTHENA-Lung02)	III	Pretreated EGFR-mutant NSCLC	HER3-DXd *v* platinum doublet	PFS
		HERTHENA-Lung03	III	First-line EGFR-mutant NSCLC	HER3-Dxd plus osimertinib *v* osimertinib	PFS
		NCT04676477	I/II	First-line and pretreated EGFR-mutant NSCLC	HER3-DXd plus osimertinib	DLTs ORR
		NCT03260491	I	NSCLC multiple cohorts	HER3-DXd	DLTs ORR
Datopotamab-DXd	TROP2					
		NCT03401385 [TROPION-PanTumor01]	I	NSCLC (multiple cohorts) Pretreated SCLC	Dato-DXd	DLTs AEs
		NCT05460273 (TROPION-PanTumor02)	I/II	Pretreated (≥2L) NSCLC without AGA in Chinese patients	Dato-DXd	ORR
		NCT04612751 (TROPION-Lung04)	I	First-line and pretreated NSCLC without AGA	Dato-DXd plus ICI (different agents) ± carboplatin	DLTs
		NCT04656652 (TROPION-Lung01)	III	Pretreated NSCLC with or without AGA	Dato-DXd *v* docetaxel	PFS OS
		NCT04484142 (TROPION-Lung05)	II	Pretreated NSCLC with AGA	Dato-DXd	ORR
		NCT04940325 (ICARUS-Lung01)	II	Pretreated NSCLC with or without AGA	Dato-DXd	ORR
		NCT04526691 (TROPION-Lung02)	I	NSCLC without AGA (≤two prior lines)	Dato-DXd plus pembrolizumab ± platinum chemotherapy	DLTs
		NCT05215340 (TROPION-Lung08)	III	First-line NSCLC with PD-L1 ≥50% (no AGA)	Dato-DXd plus pembrolizumab *v* pembrolizumab monotherapy	PFS OS
		NCT05555732 (TROPION-Lung07)	III	First-line NSCLC with PD-L1 <50% (no AGA)	Dato-DXd plus pembrolizumab +/- platinum-doublet *v* platinum-doublet plus pembrolizumab	PFS OS

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ADC in lung cancer: main ongoing trials

Drug	Target	Trial No.	Phase	Setting	Treatments	Primary End Point
Sacituzumab govitecan (SG)	TROP2	NCT03337698 (Morpheus-Lung)	Ib/II	(Multiarm) NSCLC Pretreated cohort	Atezolizumab plus SG	ORR
		NCT05633667 (VELOCITY-Lung)	II	NSCLC without AGA	1L: Zimberelimab (ZIM) + SG + domvanalimab (DOM) Previous CTx and ICI: SG + ZIM + etrumadenant	ORR
		NCT05609968 (EVOKE-03)	III	First-line NSCLC with PD-L1 ≥50% (no AGA)	Pembrolizumab *v* pembrolizumab + SG	PFS OS
		NCT05186974 (EVOKE-02)	II	First-line NSCLC without AGA	SG plus pembrolizumab or SG plus pembrolizumab plus platinum	ORR DLTs
		NCT05089734 (EVOKE-01)	III	Pretreated NSCLC with/without AGA (previous CTx and ICI)	SG *v* docetaxel	OS
		NCT04826341	I/II	Pretreated SCLC cohort	SG + berzosertib (PARPinh)	MTD ORR
Tusamitamab ravtansine (TUSA)	CEACAM5	NCT04154956 (CARMEN-LC03)	III	Pretreated nonsq NSCLC CEACAM5+ (previous CTx and ICI)	TUSA *v* docetaxel	PFS OS
		NCT04524689 (CARMEN-LC05)	II	First-line and pretreated nonsq NSCLC nonsq without AGA, CEACAM5+	TUSA plus pembrolizumab or TUSA plus pembrolizumab plus platinum ± pemetrexed	DLTs
		NCT05245071 (CARMEN-LC06)	II	Pretreated NSCLC nonsq CEACAM5 0-2+ High circulating CEA levels (previous CTx and ICI)	TUSA	ORR
		NCT04394624 (CARMEN-LC04)	II	Pretreated NSCLC nonsq CEACAM5 ≥2+ (previous CTx and ICI)	TUSA plus ramucirumab	DLTs ORR
Telisotuzumab vedotin (Teliso-V)	c-MET	NCT03539536	II	NSCLC c-MET+ (IHC) ≤two prior lines	Teliso-V	ORR AEs
		NCT05513703	II	First-line NSCLC c-MET amplified	Teliso-V	ORR
		NCT04928846	III	Pretreated NSCLC c-MET+ (IHC)	Teliso-V *v* docetaxel	PFS OS
Ifinatamab Deruxtecan (I-DXd)	B7-H3	NCT05280470	II	Pretreated ES-SCLC	I-DXd 8 or 12 mg/kg	ORR
Vobramitamab duocarmazine (MGC018)	B7-H3	NCT03729596	I/II	NSCLC cohort	MGC018	AEs DLTs
Mecbotamab vedotin (BA3011)	AXL	NCT04681131	II	NSCLC	BA3011 monotherapy or plus anti–PD-1	ORR AEs
Cofetuzumab pelidotin	PK7	NCT04189614	I	Pretreated NSCLC PK7+ (IHC)	Cofetuzumab pelidotin	ORR
Enfortumab vedotin	PRVL4	NCT04225117	II	Pretreated NSCLC cohorts	Enfortumab vedotin	ORR
Tisotumab vedotin	TF	NCT03485209	II	Pretreated sq NSCLC	Tisotumab vedotin	ORR

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ADC in lung cancer: conclusions

- ADCs for lung cancer treatment have demonstrated encouraging results
- Several target (HER2, HER3, TROP2, c-MET, CEACAM5, B7-H3) have been evaluated with their specific ADCs
- Some ADCs could be represent the next standard of care in different settings in the of NSCLC
- Promising results have been obtained also in SCLC
- Other target antigens of interest are under investigation with novel ADCs currently in early phase clinical trials
- Appropriate patient selection and drug development approaches will help improve toxicity profiles, as well as strategies to overcome acquired ADC resistance

Grazie per l'attenzione

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