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Antibody Drug Conjugates and Bispecific Inhibitors in Lung Cancer

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

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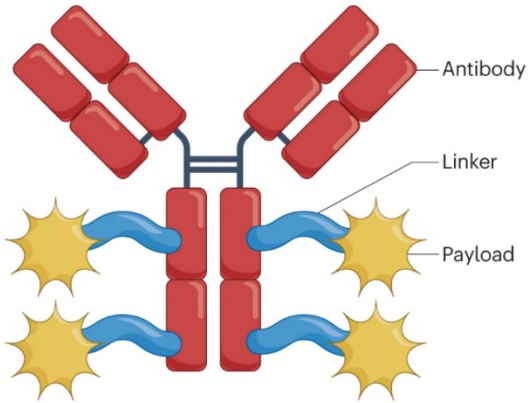
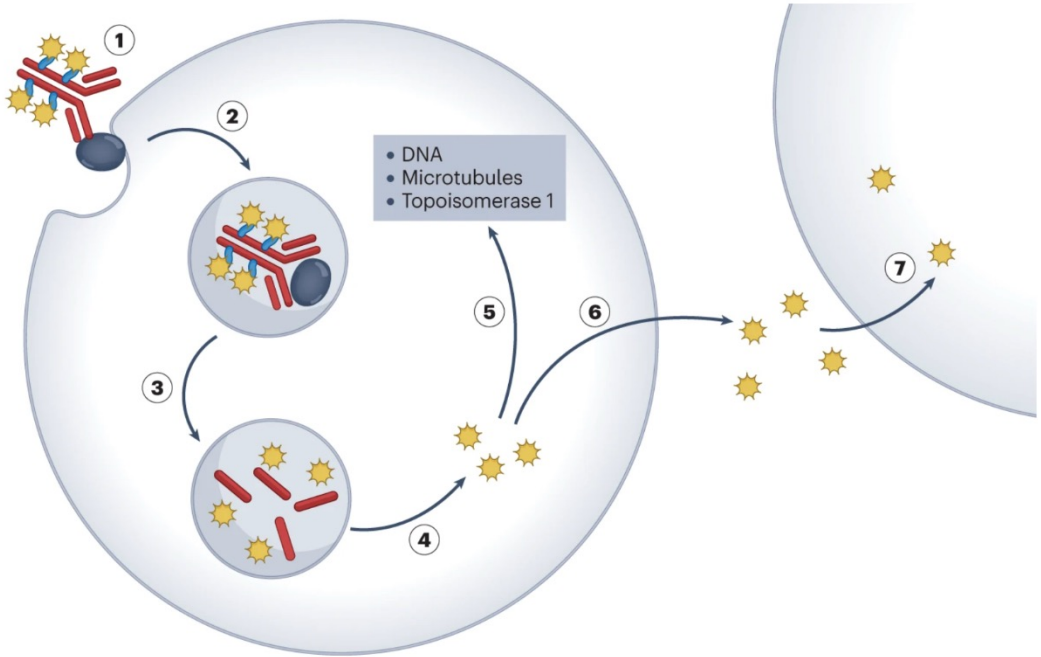
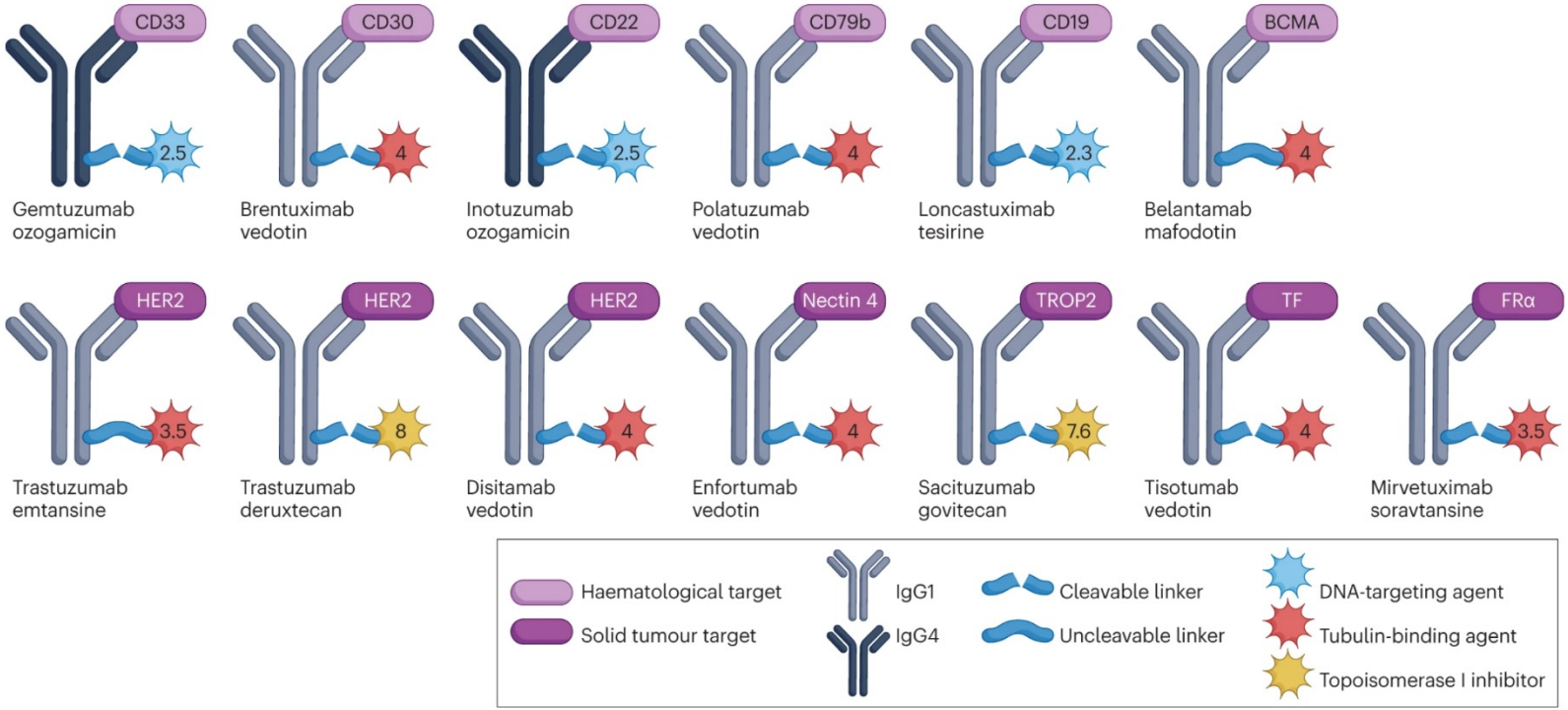
Structure and Mechanism of Action of Conventional ADCs





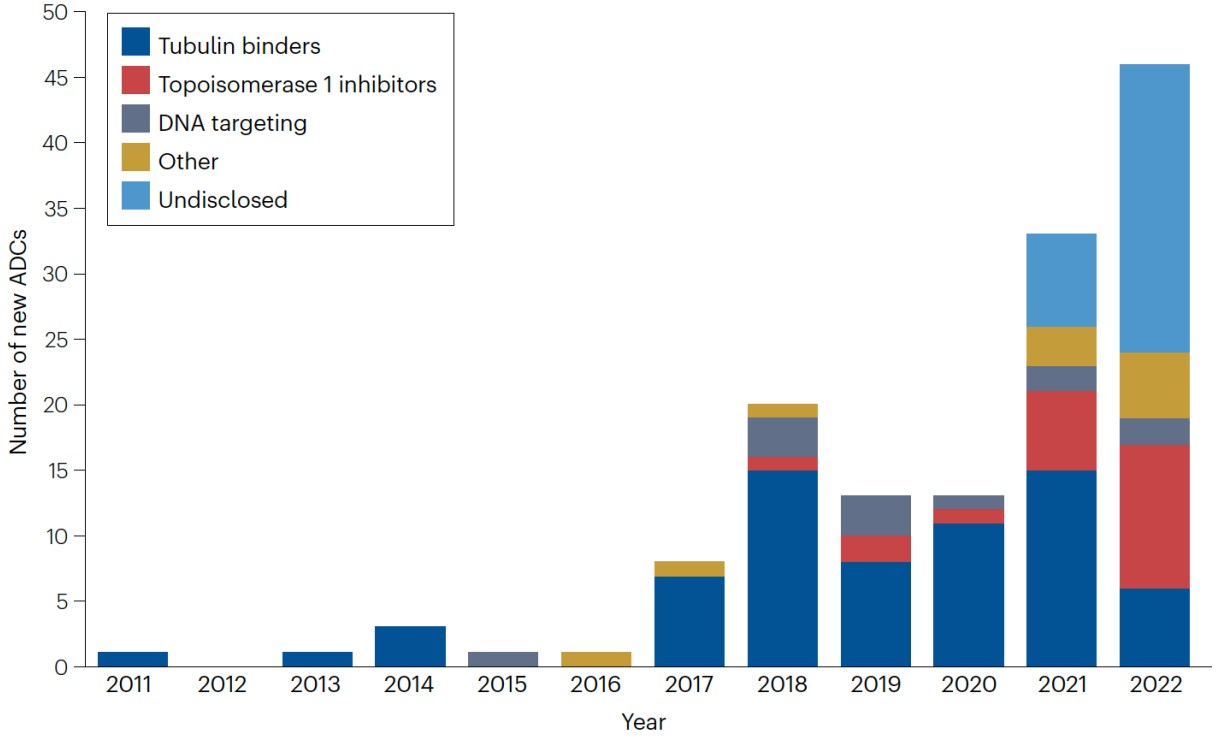
Dumontet et al. *Nat Rev Drug Discov* 2023

Main Characteristics of Approved ADCs



Dumontet et al. *Nat Rev Drug Discov* 2023

Number of ADCs Reaching Clinical Trials Between 2012 and 2022



Dumontet et al. *Nat Rev Drug Discov* 2023

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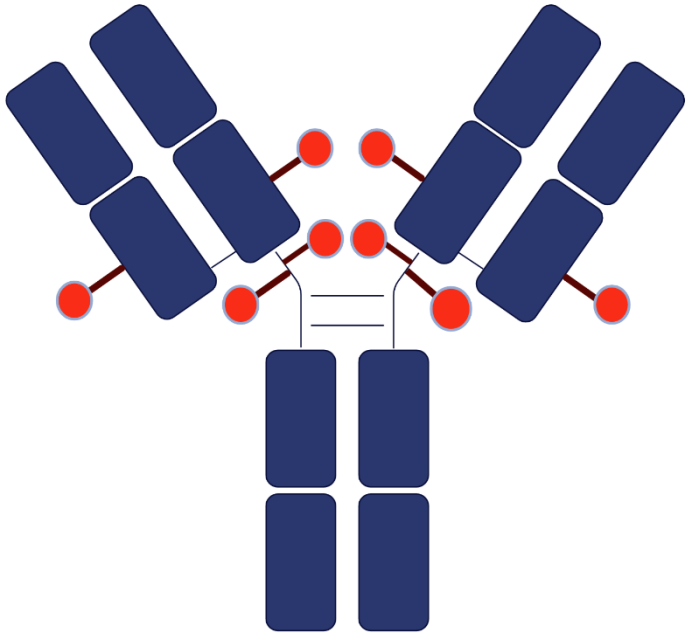
FDA-approved ADCs

Antibody Drug Conjugate	Target	Antibody Isotype	Payload	Payload MoA	Drug Antibody Ratio	Approved Disease Type(s)	Initial Year of Approval
Gemtuzumab ozogamicin	CD33	IgG4	N-acetyl-γ-calicheamicin	DNA double strand break	2-3	AML	2000
Brentuximab vedotin	CD30	IgG1	MMAE	Microtubule inhibitor	4	ALCL, Hodgkin lymphoma, PTCL	2011
Ado-trastuzumab emtansine	HER2	IgG1	DM1	Microtubule inhibitor	3.5	Breast cancer	2013
Inotuzumab ozogamicin	CD22	IgG4	N-acetyl-γ-calicheamicin	DNA double strand break	6	ALL	2017
Moxetumomab pasudotox*	CD22	IgG1	PE38	Immunotoxin	-	Hairy cell leukemia	2018
Fam-trastuzumab deruxtecan-nxki (T-DXd)	HER2	IgG1	DXd (exatecan derivative)	Topoisomerase 1 inhibitor	7.7	Breast cancer, NSCLC, gastric or gastroesophageal (GEJ) adenocarcinoma	2019
Polatuzumab vedotin-piiq	CD79	IgG1	MMAE	Microtubule inhibitor	3.5	DLBCL	2019
Sacituzumab govitecan	TROP-2	IgG1	SN-38	Topoisomerase 1 inhibitor	7.6	Breast cancer, urothelial cancer	2020
Enfortumab vedotin-ejfv	Nectin 4	IgG1	MMAE	Microtubule inhibitor	3.8	Urothelial cancer	2020
Tisotumab vedotin-tftv	Tissue factor	IgG1	MMAE	Microtubule inhibitor	4	Cervical cancer	2021
Loncastuximab tesirine-lpyl	CD20	IgG1	SG3199	DNA cleavage	2.3	Large B-cell lymphoma	2021
Mirvetuximab soravtansine	Folate receptor α	IgG1	DM4	Microtubule inhibitor	3.5	Ovarian, fallopian tube, or primary peritoneal cancer	2022

Trastuzumab Deruxtecan (T-DXd): Anti-HER2 ADC

Humanized anti-HER2 IgG1 antibody



Topoisomerase I inhibitor (DXd)

- Derivative of camptothecin analog exatecan
- Drug:antibody ratio: 7.7:1

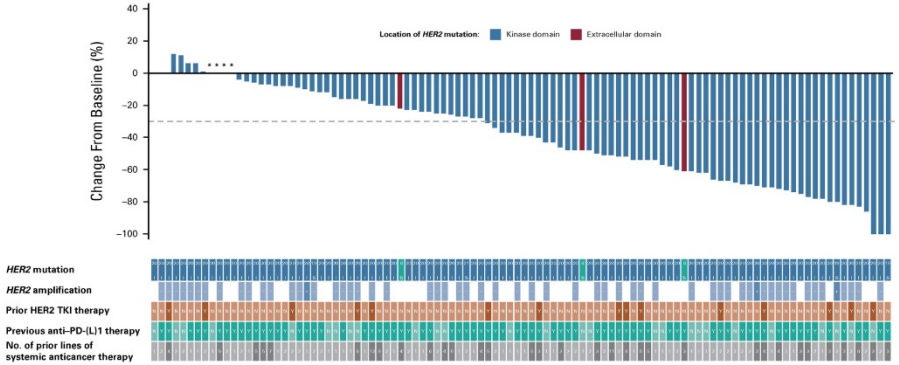
Linker

- Tetrapeptide-based cleavable linker
- Payload linked to cysteine residues of the antibody

Joubert et al. *Pharmaceuticals* 2020

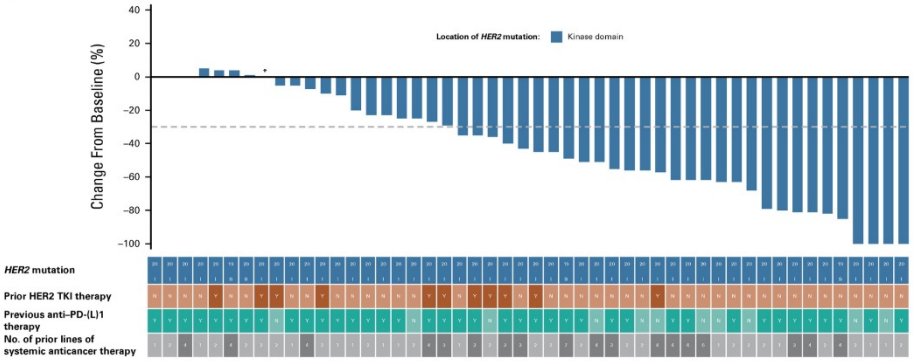
DESTINY-Lung02: Trastuzumab Deruxtecan in Previously Treated *HER2*-mutant NSCLC

T-DXd 5.4 mg/kg (n=102)



ORR=49.0%
DOR=16.8 months

T-DXd 6.4 mg/kg (n=50)



ORR=56.0%
DOR=NE

Responses were consistent regardless of 1) *HER2* mutation type, 2) *HER2* amplification status, 3) presence or absence of baseline CNS metastases, 4) prior treatment.

Goto et al. *J Clin Oncol* 2023

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DESTINY-Lung02: Safety Profile

5.4 mg/kg dose associated with better safety profile

TRAEs, %	T-DXd 5.4 mg/kg (n=101)	T-DXd 6.4 mg/kg (n=50)
Any grade	96.0	100
Grade ≥3	38.6	58.0
Led to drug discontinuation	13.9	20.0
Led to drug reduction	16.8	32.0
Led to drug interruption	26.7	48.0
Leading to death	1	2

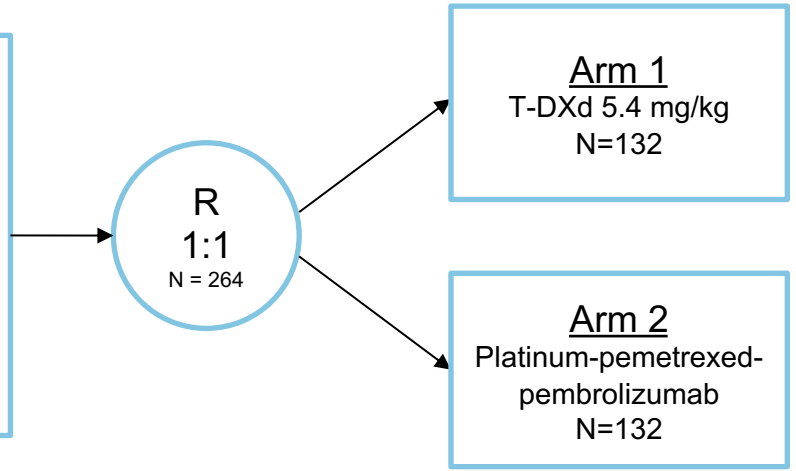
Adjudicated drug-related ILD, n (%)	T-DXd 5.4 mg/kg (n=101)	T-DXd 6.4 mg/kg (n=50)
Any grade	13 (12.9)	14 (28.0)
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Goto et al. *J Clin Oncol* 2023

DESTINY-Lung04

Study population

- Unresectable, locally advanced or metastatic non-squamous NSCLC with *HER2* exons 19 or 20 mutations
- Treatment naïve for advanced disease
- LVEF ≥ 50%
- ECOG 0-1

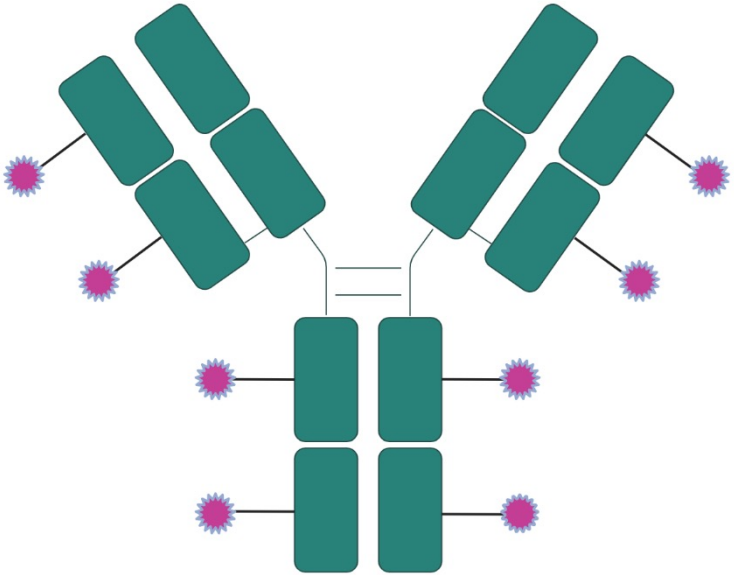


Clinicaltrials.gov (NCT05048797)

Patritumab Deruxtecan: Anti-HER3 ADC

Humanized anti-HER3 IgG1 antibody

- Targets HER3, an antigen expressed in 83% of NSCLC tumors, 85-100% of tumors harboring an activating *EGFR* mutation



Topoisomerase I inhibitor (DXd)

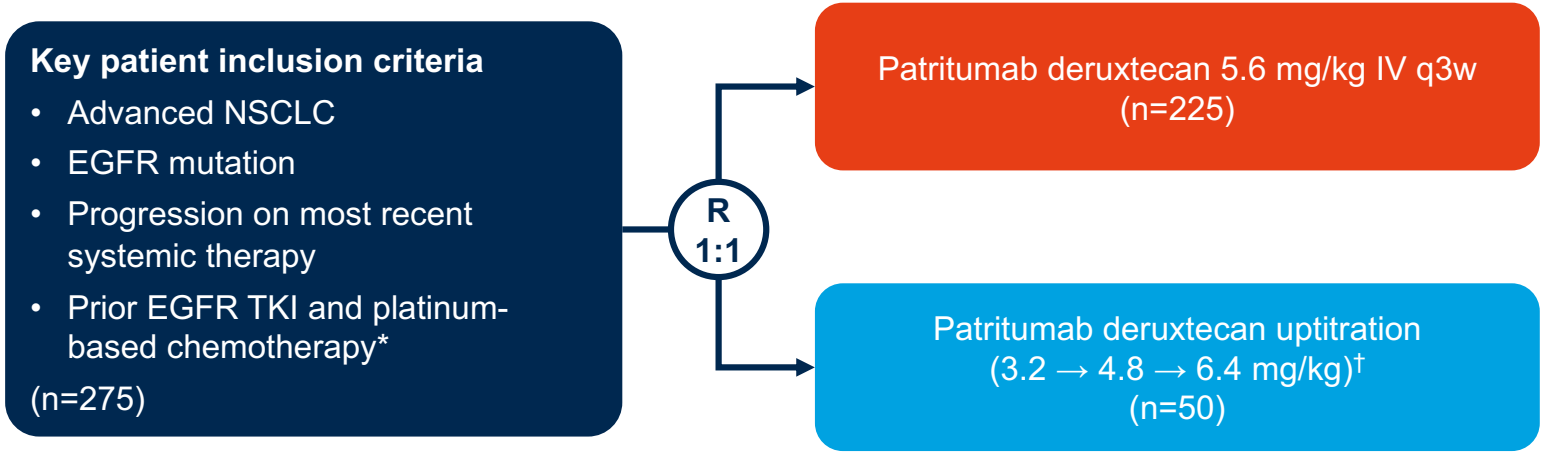
- Derivative of camptothecin analog exatecan
- Drug:antibody ratio: 8:1

Linker

- Tetrapeptide-based cleavable linker

Yu et al. *J Clin Onc* 2023; Image created with BioRender.com

HERTHENA-Lung01



Primary endpoint

- ORR (BICR, RECIST v1.1)

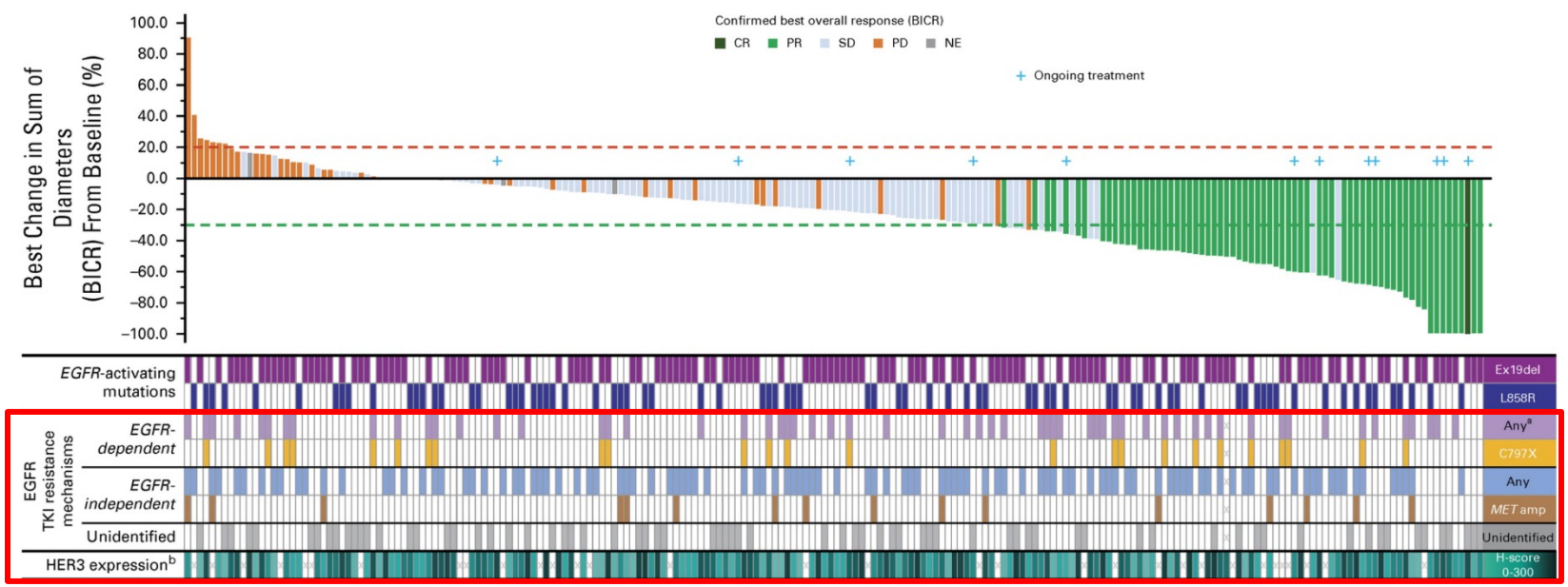
Secondary endpoints

- DoR

† Closed early based on prespecified assessment of data from the phase I U31402-A-U102 trial

Yu et al. WCLC 2023

Patritumab deruxtecan demonstrated antitumor activity after EGFR-TKI and platinum-doublet chemotherapy



- ORR=29.8%, mDOR=6.4 months
  - mPFS: 5.5 months
  - mOS: 11.9 months

Yu et al. *J Clin Onc* 2023

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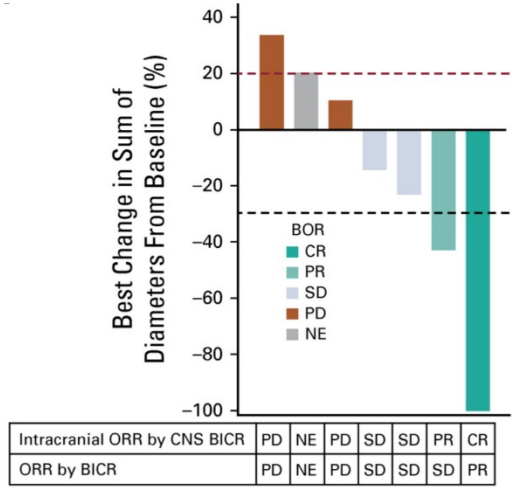
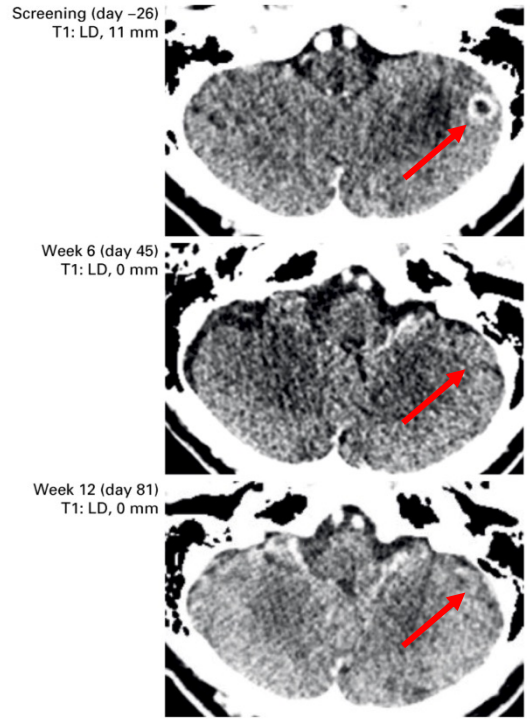
CNS Activity of Patritumab Deruxtecan



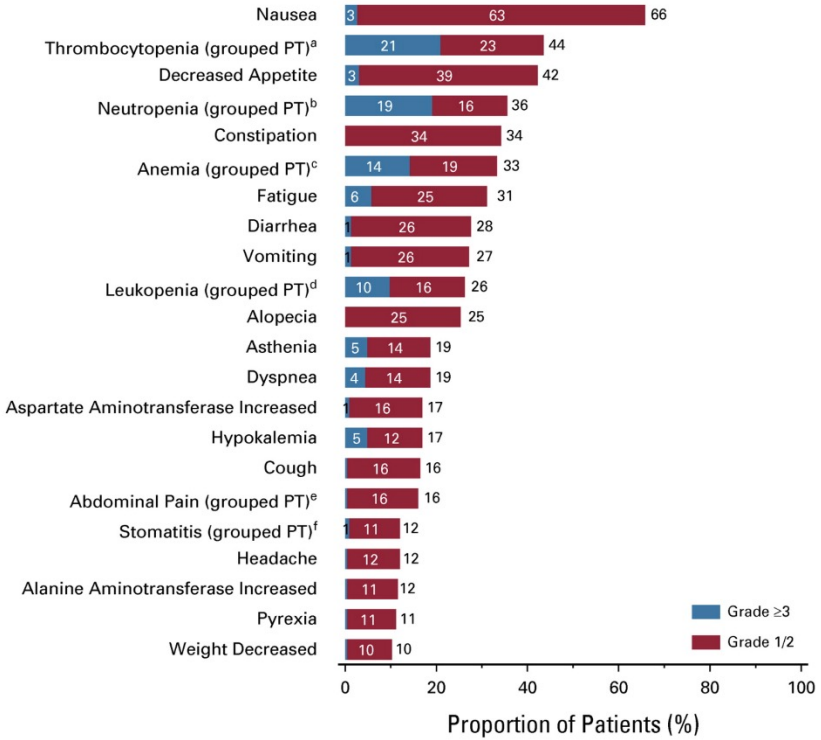
Patients with measurable target brain lesions

Result	Patients with brain metastasis at baseline (n=30)
cORR, No. (%)	10 (33.3)
CR, No. (%)	9 (30.0)
PR, No. (%)	1 (3.3)
SD, No. (%)	13 (43.3)
PD, No. (%)	4 (13.3)
NE, No. (%)	3 (10.0)
DOR (95% CI)	8.4 (5.8-9.2)



Yu et al. *J Clin Onc* 2023

Safety Profile of Patritumab Deruxtecan

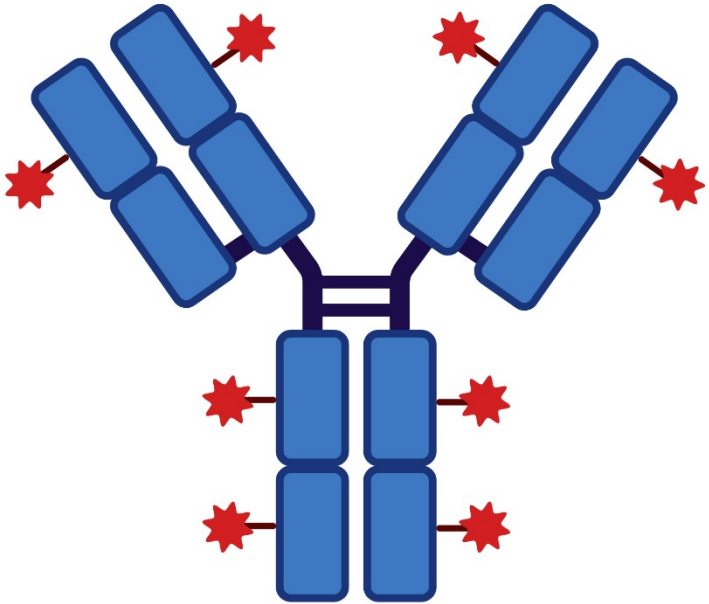


Adjudicated as drug-related ILD n (%)	HER3-DXd 5.6 mg/kg (n=225)
Any grade	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

Yu et al. *J Clin Onc* 2023

Sacituzumab Govitecan: Anti-TROP-2 ADC

Humanized anti-Trop-2 IgG1 antibody
- Targets Trop-2, an antigen expressed in many cancers
- High expression associated with poor outcomes

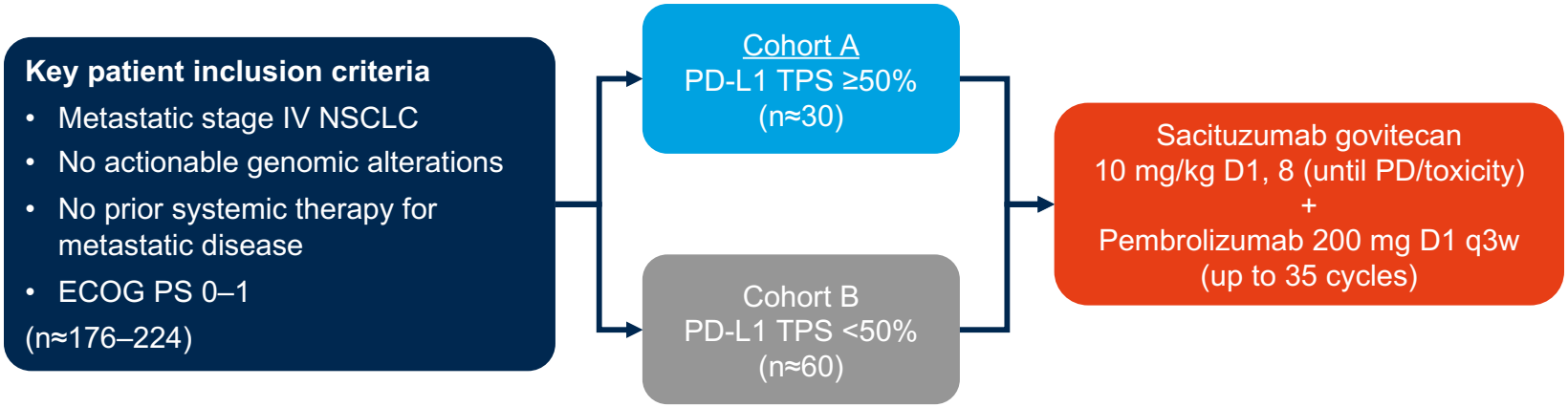


SN-38 payload
- Active metabolite of irinotecan
- More potent than parent compound irinotecan

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive hydrolysable linker for rapid release of payload at or inside tumor

Spring et al. *Oncologist* 2021; Created with BioRender.com

EVOKE-02: Sacituzumab Govitecan and Pembrolizumab in 1L Metastatic NSCLC



Primary endpoints

- ORR, DLTs

Secondary endpoints

- DCR, DoR, PFS, OS, safety

Cho et al. WCLC 2023

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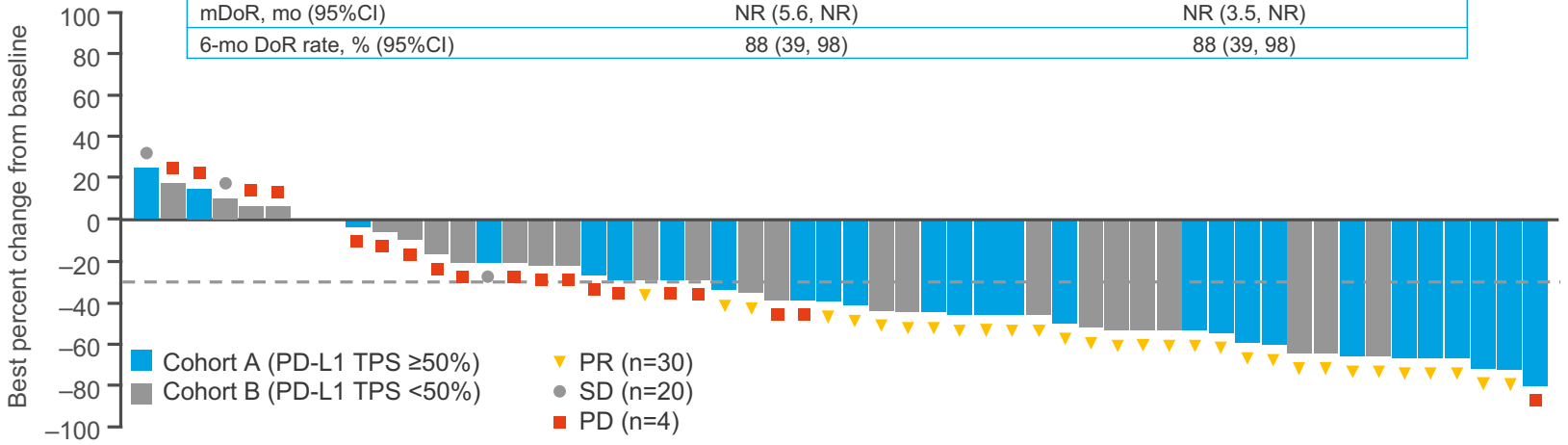
Antitumor Activity of 1L Sacituzumab Govitecan and Pembrolizumab

Efficacy	Cohort A (PD-L1 TPS ≥50%) Sacituzumab govitecan + pembrolizumab (n=29)	Cohort B (PD-L1 TPS <50%) Sacituzumab govitecan + pembrolizumab (n=32)
ORR, % (95%CI)	69 (49, 85)	44 (26, 62)
PR / cPR, n (%)	20 (69) / 18 (62)	14 (44) / 12 (38)
SD, n (%)	5 (17)	11 (34)
PD, n (%)	3 (10)	2 (6)
DCR, % (95%CI)	86 (68, 96)	78 (60, 91)
mDoR, mo (95%CI)	NR (5.6, NR)	NR (3.5, NR)
6-mo DoR rate, % (95%CI)	88 (39, 98)	88 (39, 98)



Cho et al. WCLC 2023

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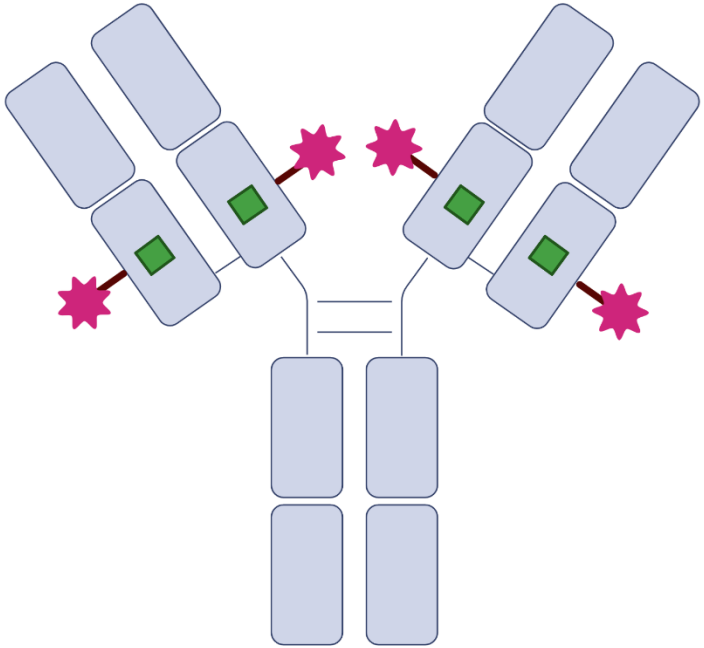
Datopotamab Deruxtecan: Anti-TROP-2 ADC

Humanized anti-Trop-2 IgG1 antibody
- Targets Trop-2, an antigen expressed in many cancers
- High expression associated with poor outcomes



Topoisomerase I inhibitor (DXd)
- Derivative of camptothecin analog exatecan
- Drug:antibody ratio: 4:1

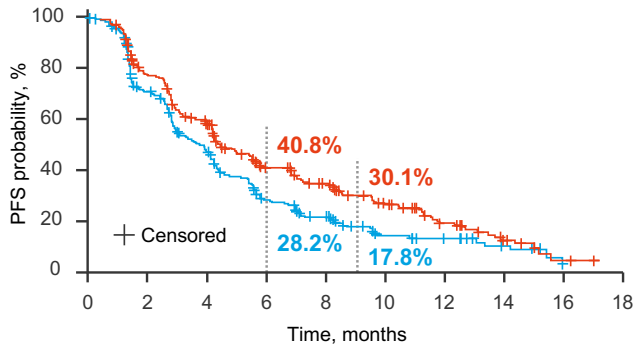
Linker
- Tetrapeptide-based cleavable linker
- Payload linked to cysteine residues of the antibody

Okajima et al. *Mol Cancer Ther* 2021; Image created with BioRender.com

TROPION-Lung01: Dato-DXd vs. Docetaxel

- Randomized phase III trial of Dato-DXd vs. docetaxel in previously treated advanced NSCLC

Progression-free survival

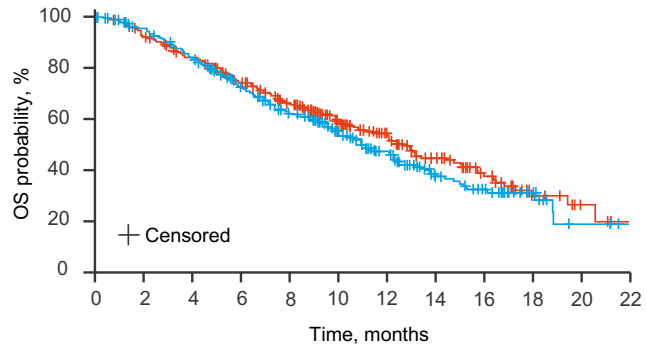


No. at risk

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

	Dato-DXd	Docetaxel
mPFS, mo (95%CI)	4.4 (4.2, 5.6)	3.7 (2.9, 4.2)
HR (95%CI); p-value	0.75 (0.62, 0.91); 0.004	
Prespecified boundary (2-sided)	0.008	

Interim overall survival



No. at risk

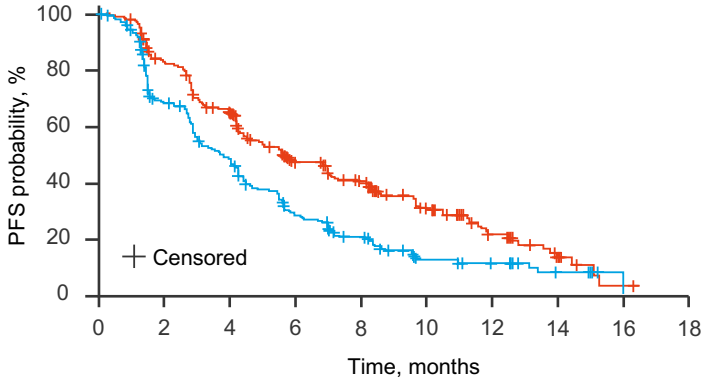
Dato-DXd	299	273	243	201	166	121	85	56	33	14	6	1
Docetaxel	305	273	239	193	156	115	76	42	29	13	4	1

	Dato-DXd	Docetaxel
mOS, mo (95%CI)	12.4 (10.8, 14.8)	11.0 (9.8, 12.5)
HR (95%CI)	0.90 (0.72, 1.13)	

Lisberg et al. ESMO 2023

TROPION-Lung01: PFS by Histology

Nonsquamous

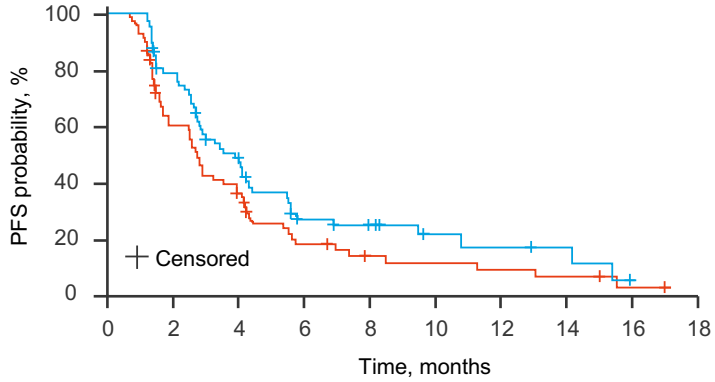


No. at risk

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

	Dato-DXd	Docetaxel
mPFS, mo (95%CI)	5.6 (4.4, 7.0)	3.7 (2.9, 4.2)
HR (95%CI)	0.63 (0.51, 0.78)	
ORR, %	31.2	12.8
DoR, mo	7.7	5.6

Squamous



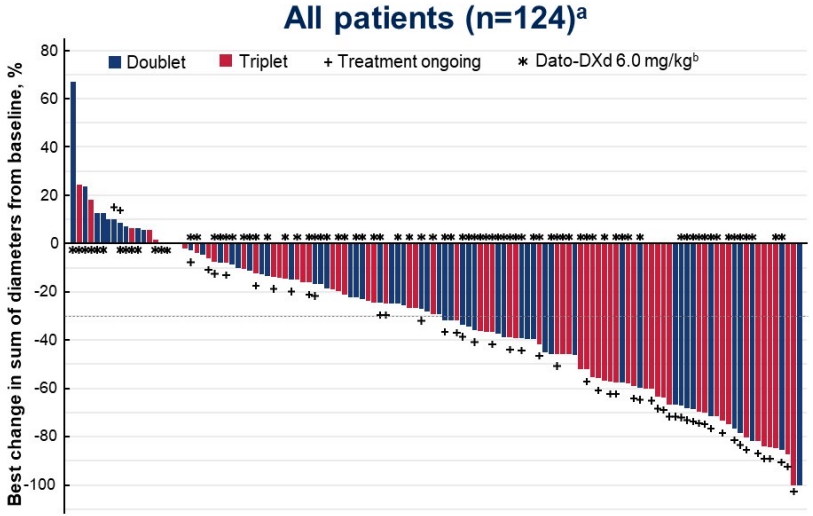
No. at risk

Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

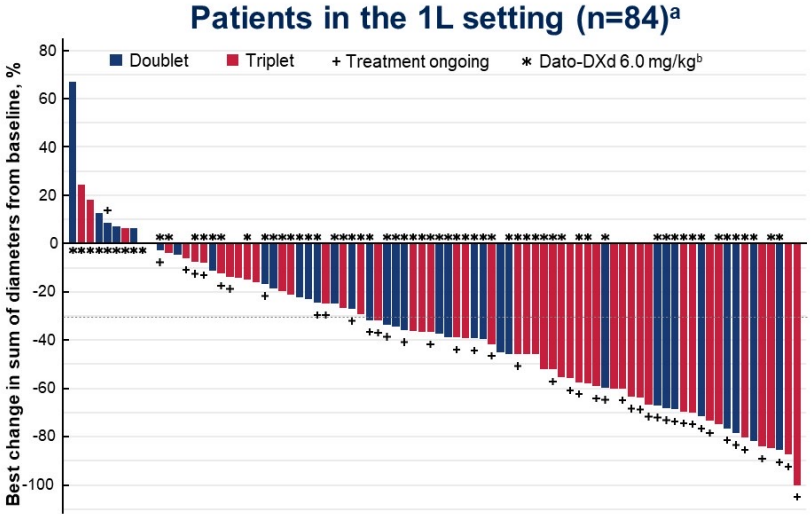
	Dato-DXd	Docetaxel
mPFS, mo (95%CI)	2.8 (1.9, 4.0)	3.9 (2.8, 4.5)
HR (95%CI)	1.38 (0.94, 2.02)	
ORR, %	9.2	12.7
DoR, mo	5.9	8.1

Lisberg et al. ESMO 2023

TROPION-Lung02: Dato-DXd + pembrolizumab +/- platinum CT



ORRs
- Doublet=38%
- Triplet=49%



ORRs
- Doublet=50%
- Triplet=57%

Goto et al. ASCO 2023

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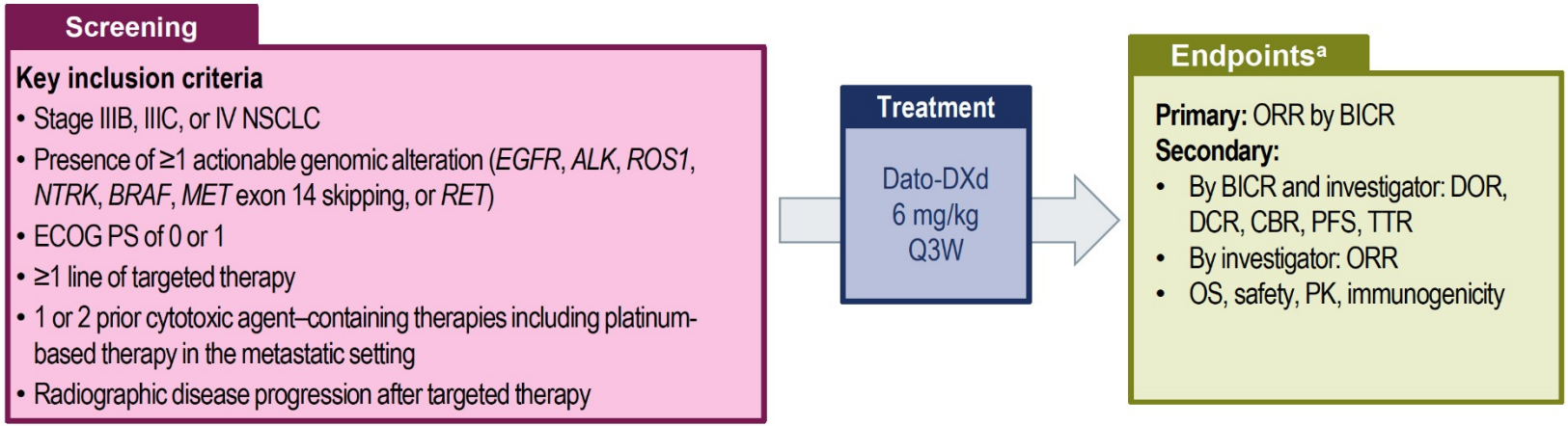
TROPION-Lung05: Dato-DXd in NSCLC with Actionable Genomic Alterations

- Phase 2, single-arm study evaluating Dato-DXd in previously treated advanced NSCLC with actionable genomic alterations



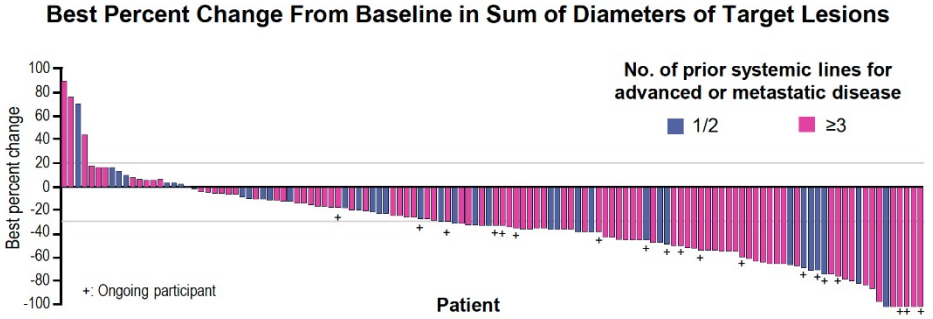
Paz-Ares et al. ESMO 2023

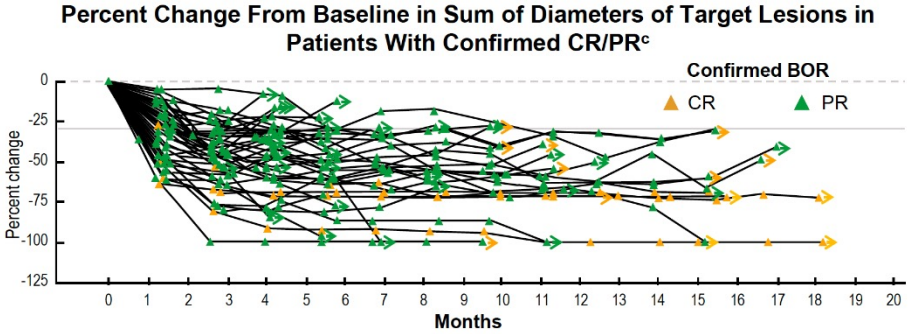
TROPION-Lung05: Efficacy Summary

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib





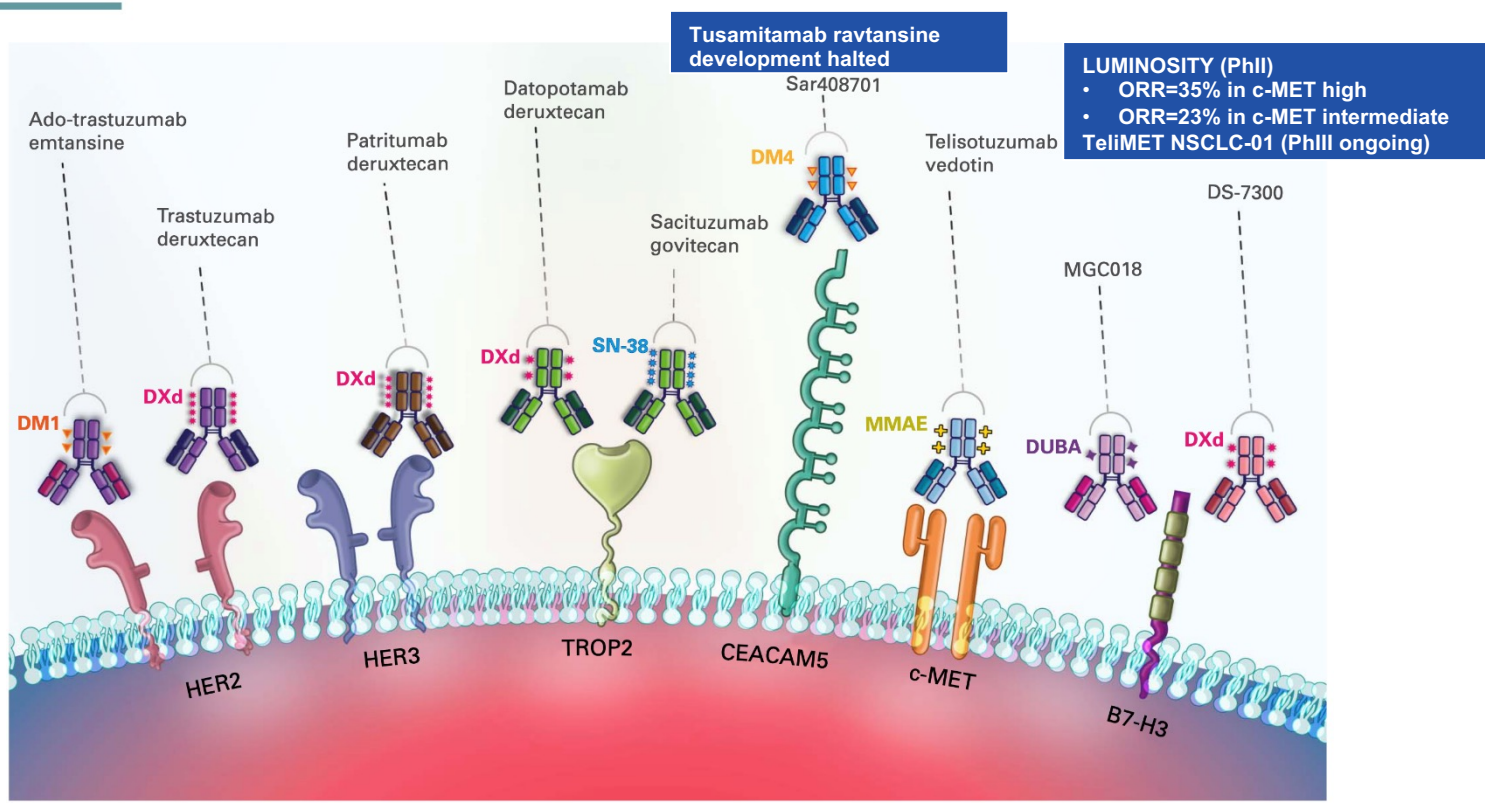
Paz-Ares et al. ESMO 2023

Randomized Trials of anti-TROP-2 ADCs in NSCLC

Trial Name	Study treatment	Comparator	Phase	Disease type	NCT
EVOKE-1	Sacituzumab Govitecan	Docetaxel	III	NSCLC	NCT05089734
EVOKE3 (KEYNOTE D46)	SacituzumabGovitecan Pembrolizumab	Pembrolizumab	III	NSCLC	NCT05609968
TROPION-Lung07	Dato-DXd Pembrolizumab Platinum	Pembrolizumab Pemetrexed Platinum	III	NSCLC	NCT05555732
AVANZAR	Dato-DXd Durvalumab Carboplatin	Pembrolizumab Platinum-based chemotherapy	III	NSCLC	NCT05687266

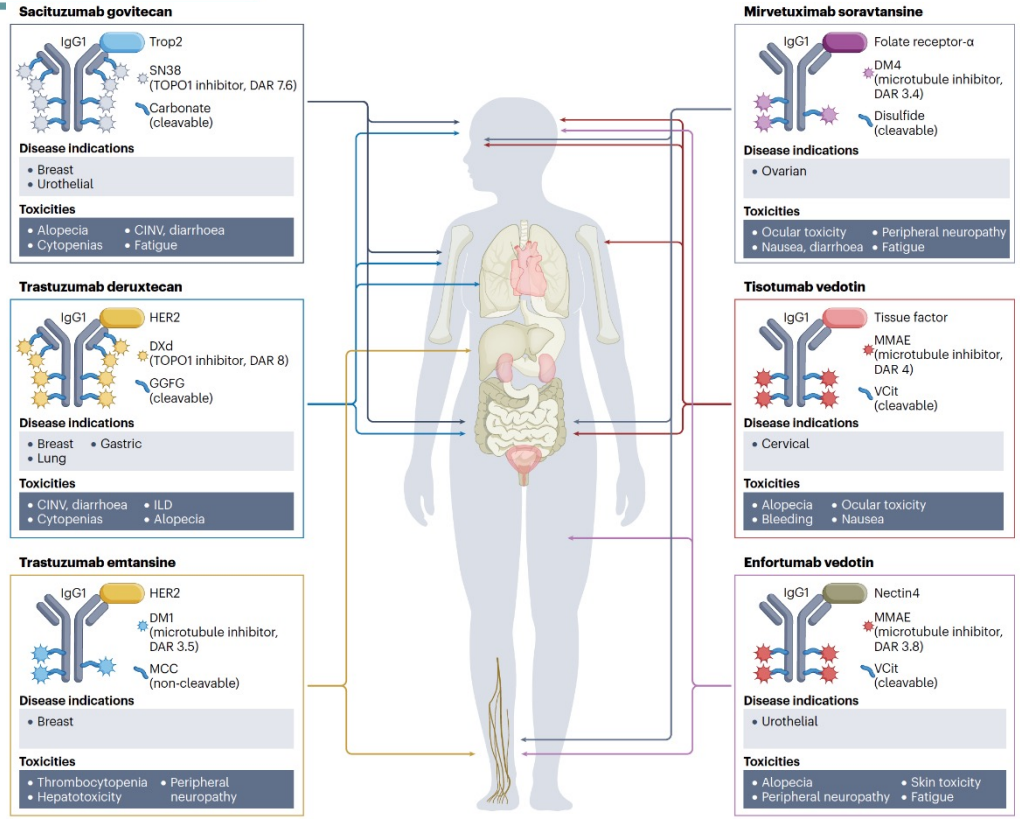
Clinicaltrials.gov

Expanding List of New Targets



Passaro et al. *J Clin Oncol* 2023

Toxicities of Antibody Drug Conjugates



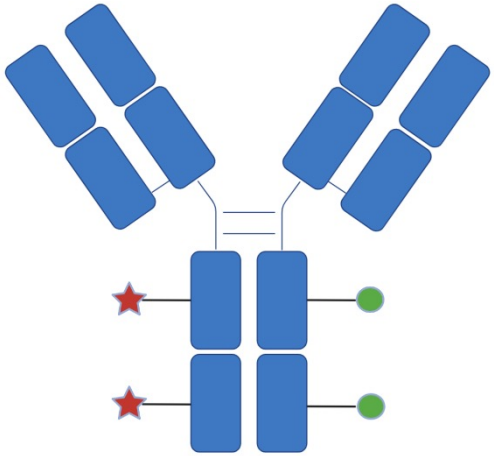
! Boxed warnings

ADCs used in solid tumors	Toxicity
Trastuzumab emtansine	Hepatotoxicity, reduction in LVEF, fetal harm
Trastuzumab deruxtecan	ILD and pneumonitis, embryo-fetal harm
Enfortumab vedotin	Skin reactions
Sacituzumab govitecan	Neutropenia, diarrhea
Tisotumab vedotin	Ocular toxicity
Mirvetuximab soravtansine	Ocular toxicity

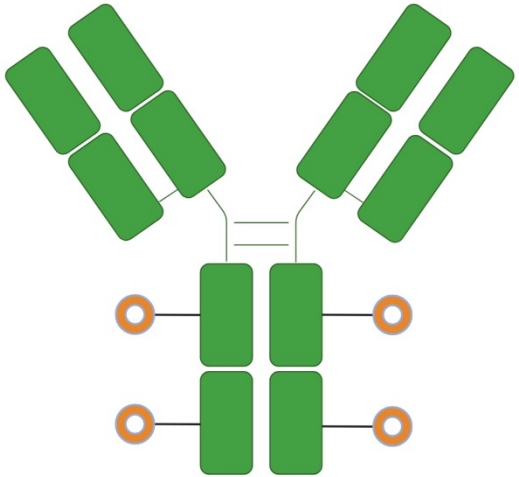
Tarantino et al. *Nat Rev Clin Oncol* 2023; FDA labels

Enhanced and Novel Payloads

Dual-payload ADCs



ADCs with immune stimulating payloads (e.g. TLR agonists, STING)



Radionuclide-conjugated ADCs

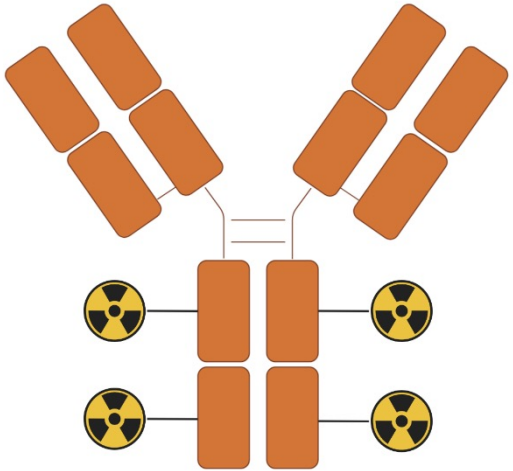
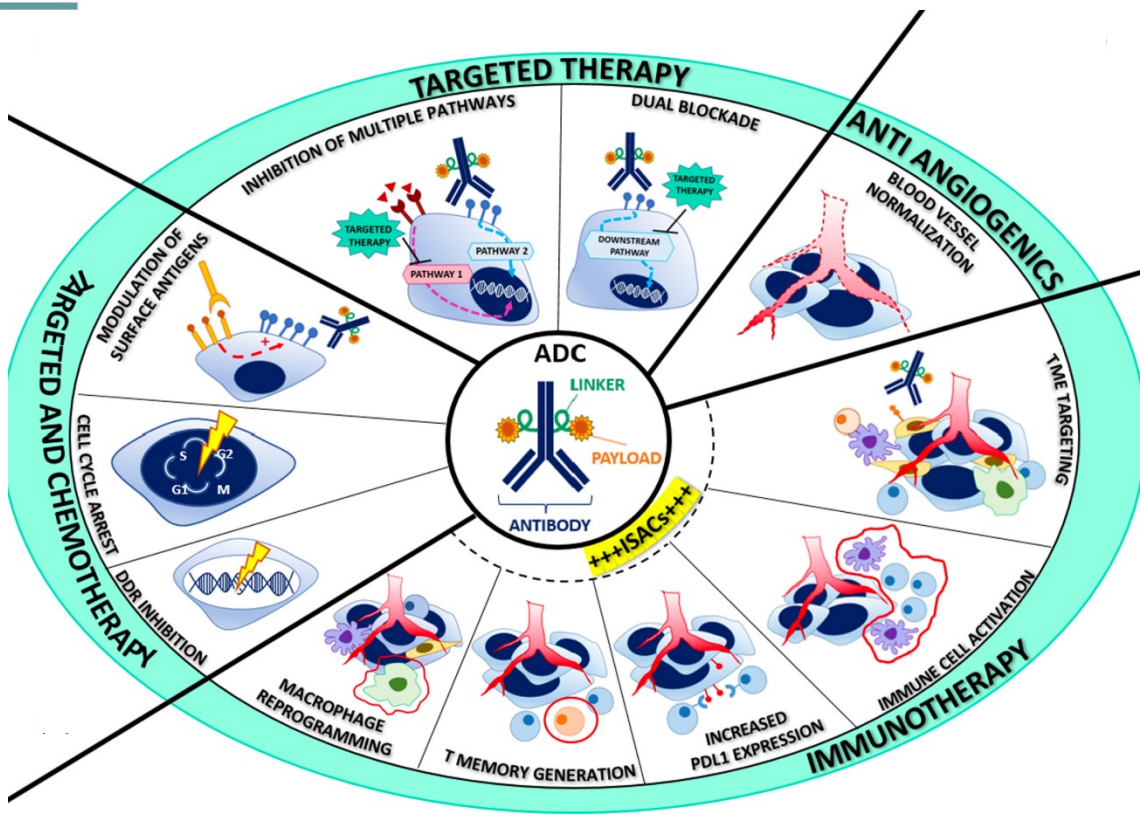


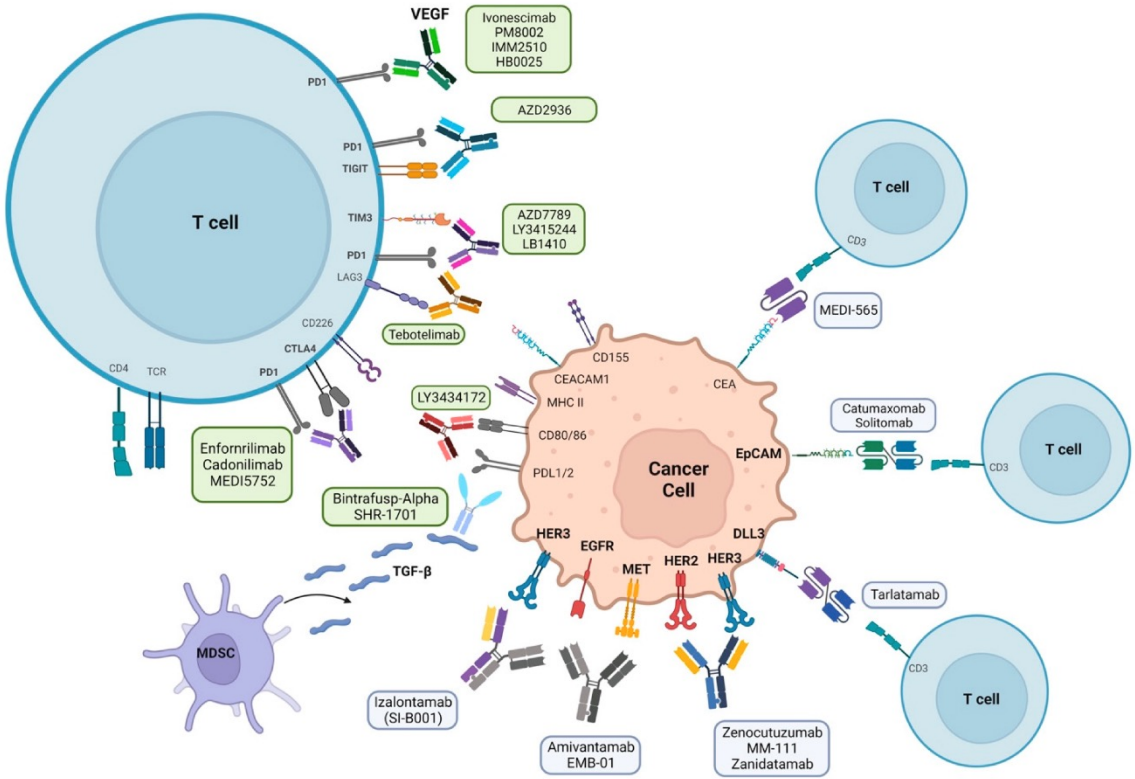
Figure modified from Tarantino et al. *CA Cancer J Clin* 2022

Combination Approaches



Fuentes-Antras et al. *Trends Cancer* 2023

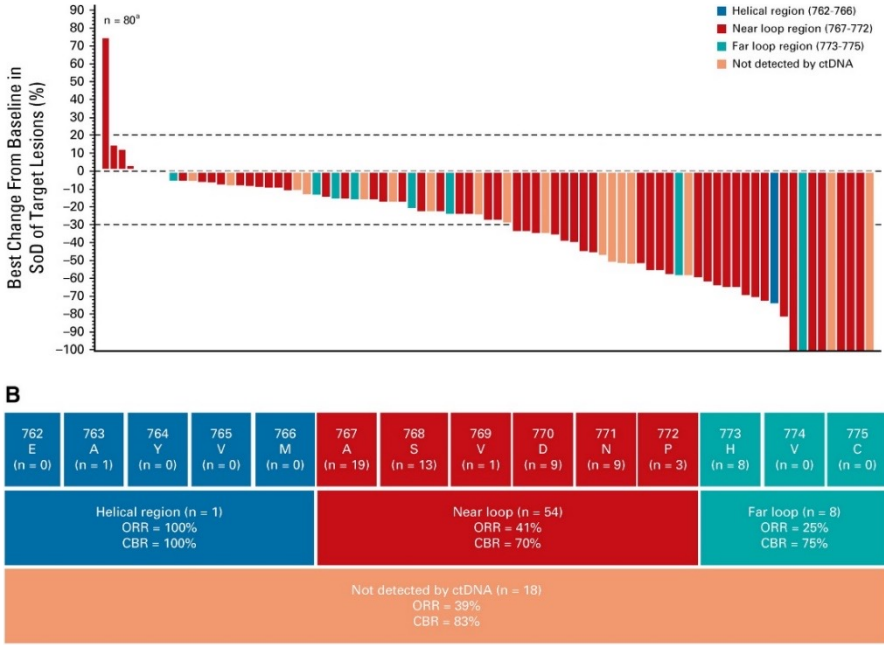
Bispecific Antibodies in Lung Cancer Therapeutics



Khosla et al. *Pharmaceuticals* 2023

Amivantamab in *EGFR* exon 20 insertion positive NSCLC

- CHRYSALIS
  - Efficacy population (n=81)
    - ORR: 40%
      - Response seen regardless of location of the mutation
    - mDOR: 11.1 months
    - mPFS: 8.3 months
    - mOS: 22.8 months
  - Safety population (n=114)
    - Most common AEs: rash (86%), infusion-related reactions (66%), and paronychia (45%)
  - FDA accelerated approval in May 2021



Park et al. *J Clin Onc* 2021

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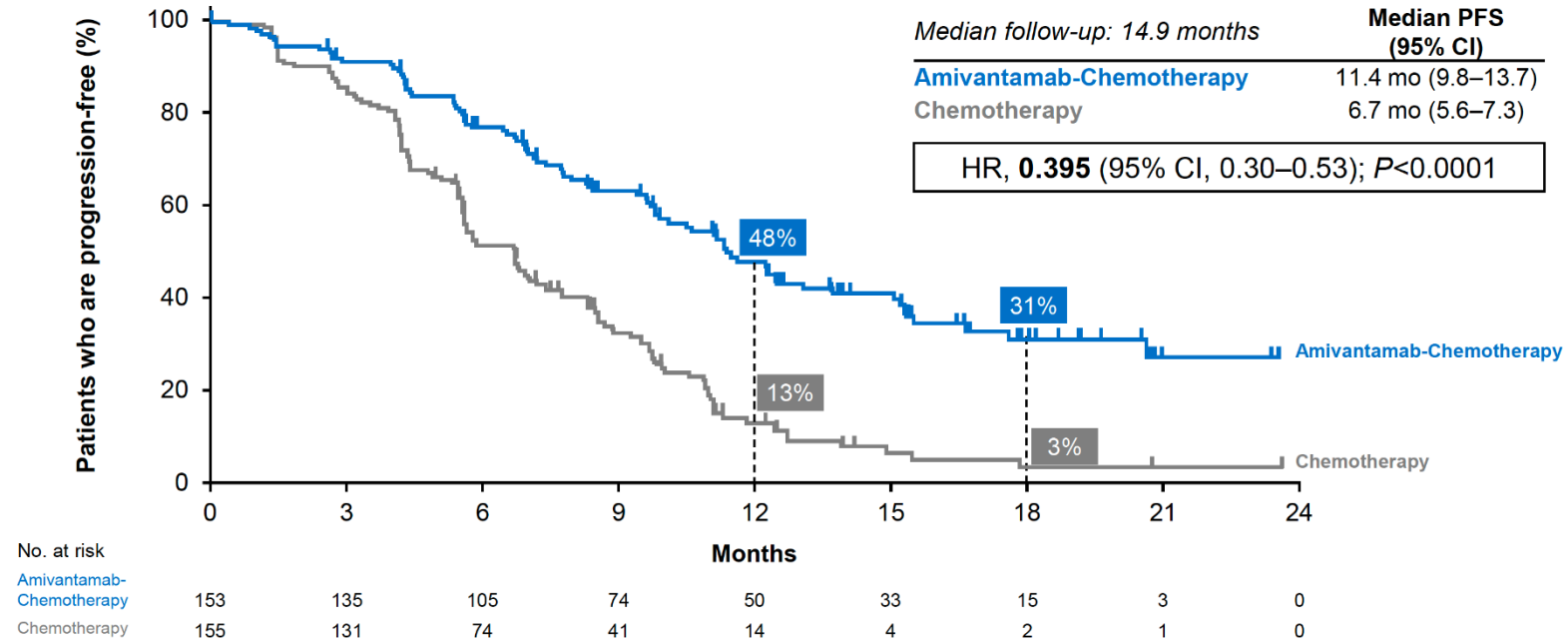
PAPILLON – Improved PFS with Amivantamab plus Chemotherapy

Amivantamab-chemotherapy reduced risk of progression or death by 60%



Girard et al. ESMO 2023

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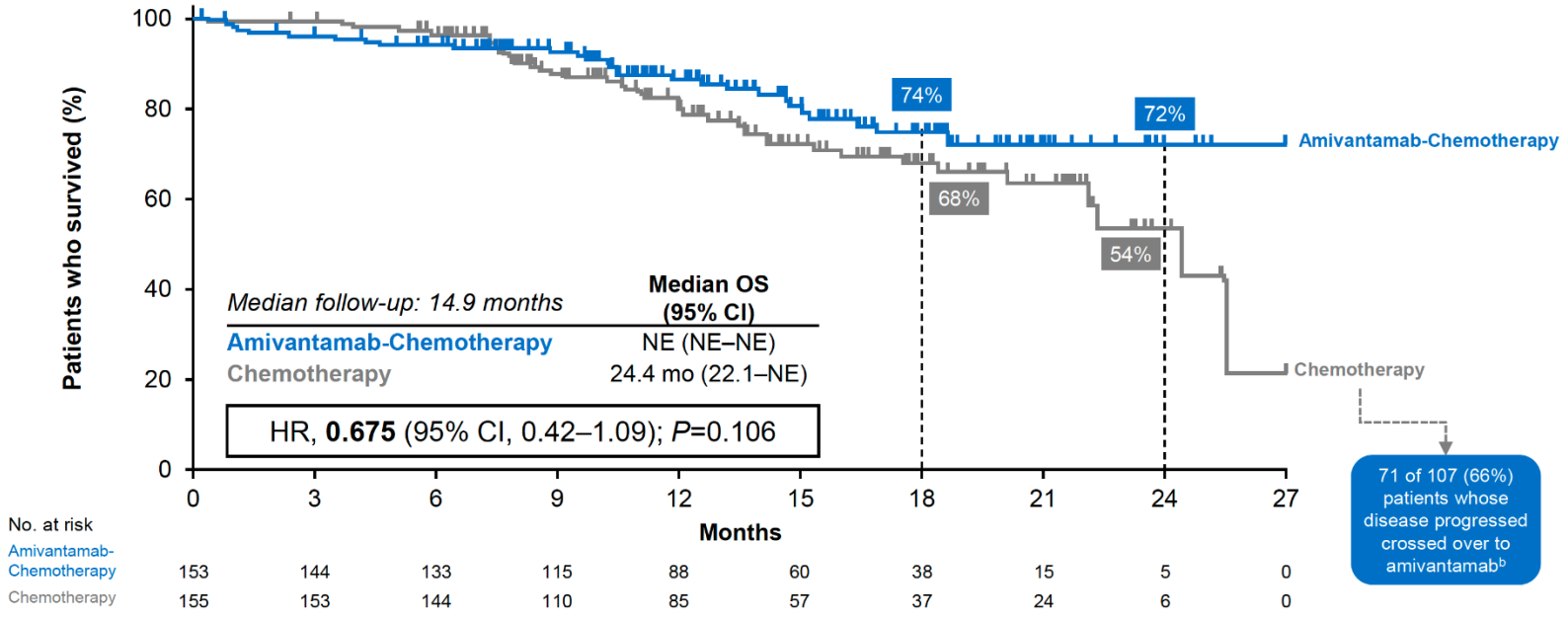
PAPILLON – Interim OS



Girard et al. ESMO 2023

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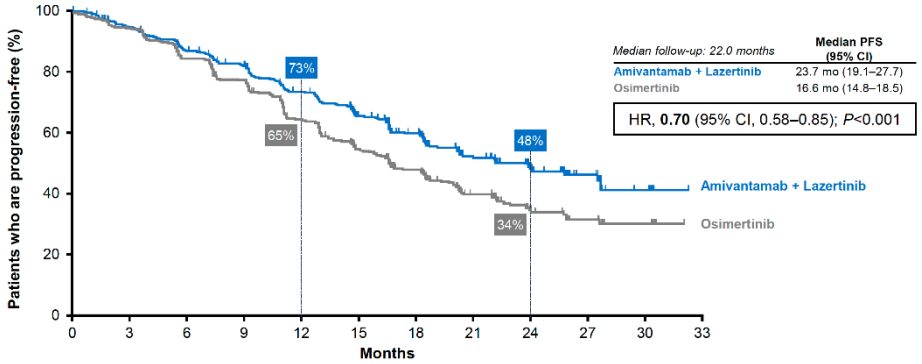
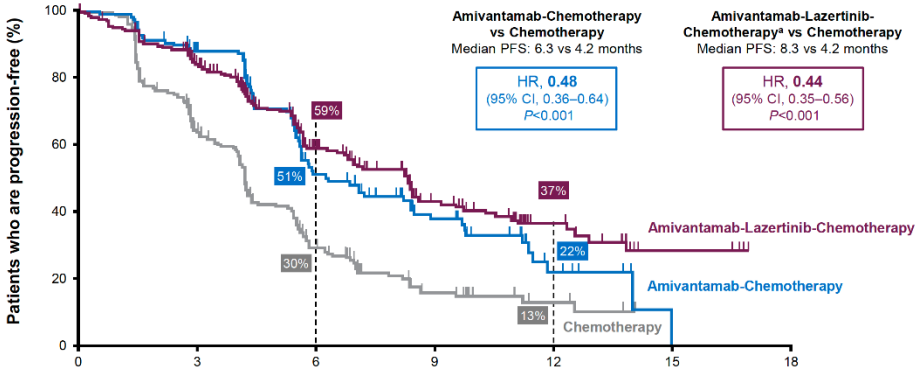
Combination Treatment with Amivantamab in 1L and 2L *EGFR*-mutant NSCLC

MARIPOSA



MARIPOSA-2



Cho et al. ESMO 2023; Passaro et al. ESMO 2023

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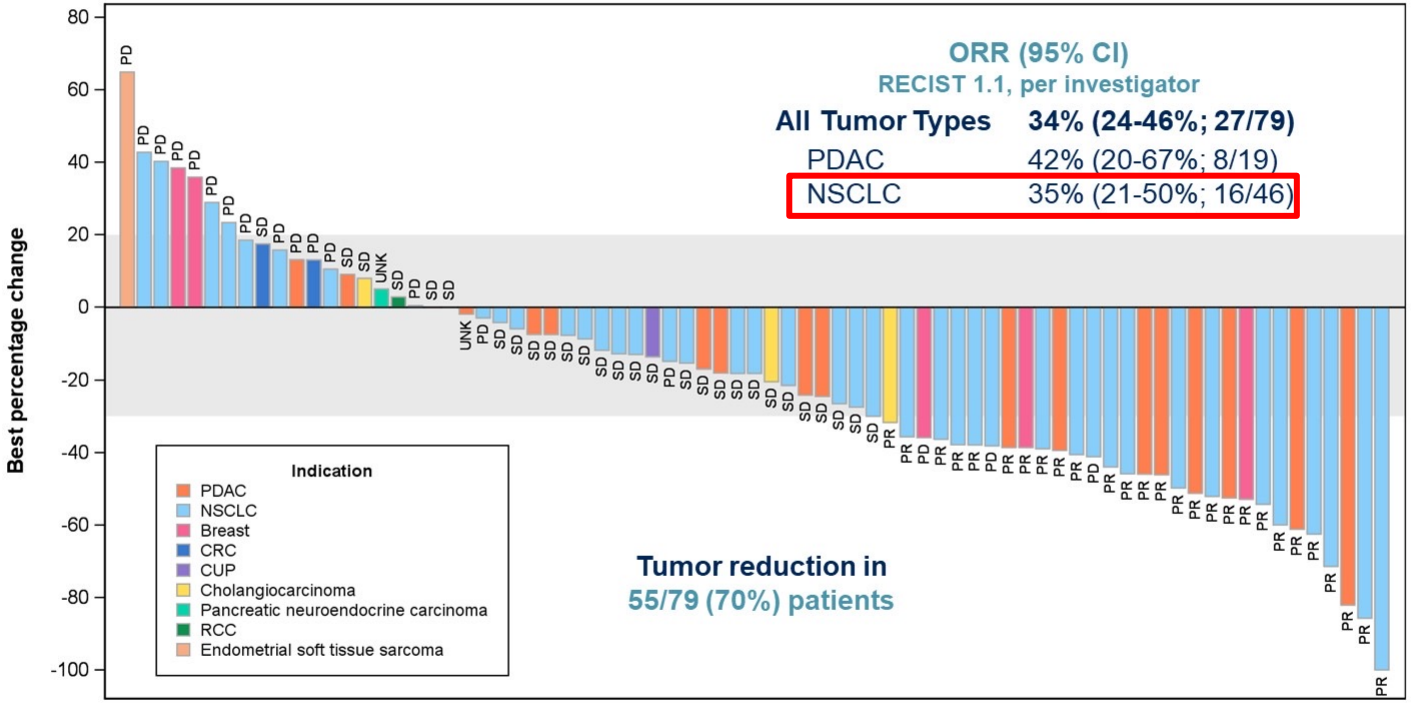
Zenocutuzumab – HER2 x HER3 Bispecific Antibody



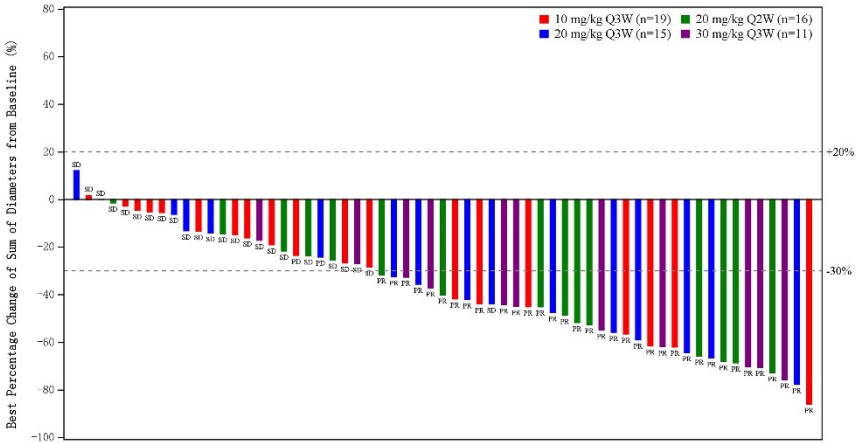
ESMO 2023
ORR in 79 patients with NSCLC = 37.2%

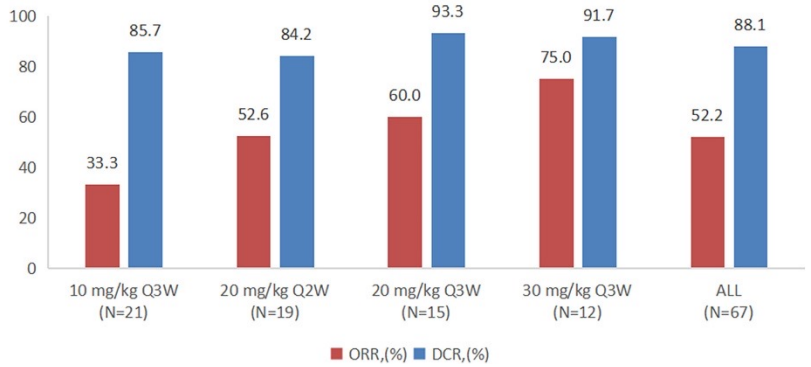
Schlam et al. ASCO 2022, ESMO 2023

Ivonescimab - PD-1/VEGF Bispecific Antibody

HARMONi-5: Phase Ib study of ivonescimab as first- or second-line monotherapy in patients with advanced immunotherapy-naive NSCLC

Antitumor activity in patients with first-line advanced/metastatic NSCLC with PD-L1–positive tumors





Ongoing phase III trials in the U.S.

- **HARMONi:** Phase 3 study of ivonescimab + chemotherapy vs. placebo + chemotherapy in EGFR-mutant NSCLC after EGFR-TKI
- **HARMONi-3**: Phase 3 study of ivonescimab + chemotherapy vs. pembrolizumab + chemotherapy for the first-line treatment of metastatic squamous NSCLC

Wang et al. J Thorac Onc 2023

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Conclusions

- ADCs and bispecific antibodies are reshaping the lung cancer treatment landscape, with trastuzumab deruxtecan and amivantamab currently being FDA-approved therapeutics in advanced NSCLC.
  - We will see more drugs in these categories entering the clinic in the near future.
  - Use of these drugs in early-stage lung cancer will increasingly be investigated.
- Optimizing patient selection, mitigating side effects, and unraveling resistance mechanisms are imperative.
- Further research is needed to explore novel targets, develop new payloads (for ADCs), and investigate combination approaches, all of which have the potential to enhance treatment outcomes.

Thank you for your attention

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