Northwestern Medicine®
Feinberg School of Medicine

The Era of Antibody Drug Conjugates and Bi-Specifics

Jyoti D. Patel, MD FASCO
Professor of Medicine
Vice Chair of Clinical Research, Department of Medicine
Medical Director, Thoracic Oncology
Lurie Comprehensive Cancer Center

Disclosures

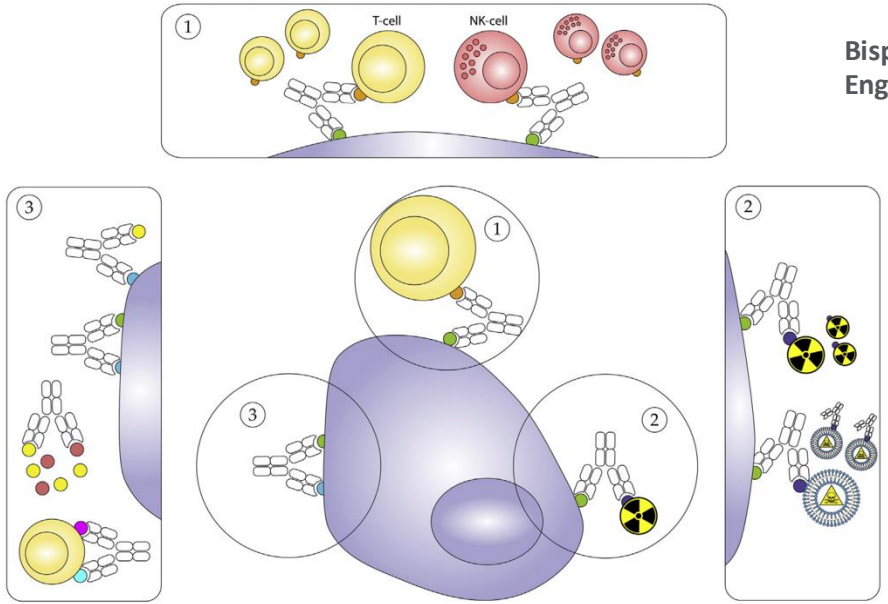
AbbVie, Anheart, AstraZeneca, Black Diamond, Blueprint, Boehringer-Ingelheim, Genentech, Gilead, Guardant, Johnson and Johnson, Lilly Sanofi, Takeda, Tempus

Key Takeaways: ADC and Bispecifics

- Are revolutionizing cancer therapeutics across solid and liquid tumors
- Provide an advantage of selectively targeting tumor cell and sparing some of the traditional side effects of chemotherapy
- Significant challenges remain about biomarker selection, toxicity, resistance and sequencing

Bispecific Antibodies and Antibody Drug Conjugates

Bispecific antibodies
Engagement of immune cells



Bispecific antibodies
Blocking Signaling

Antibody Drug Conjugates

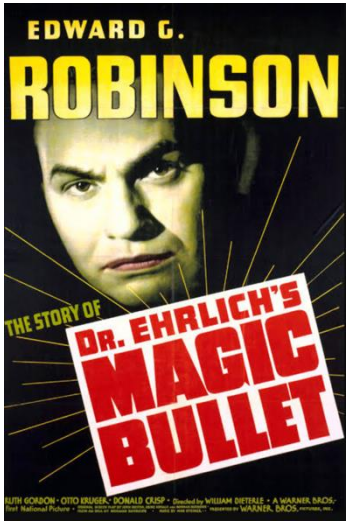
F.V. Suurs et al. / Pharmacology & Therapeutics 201 (2019) 103–119

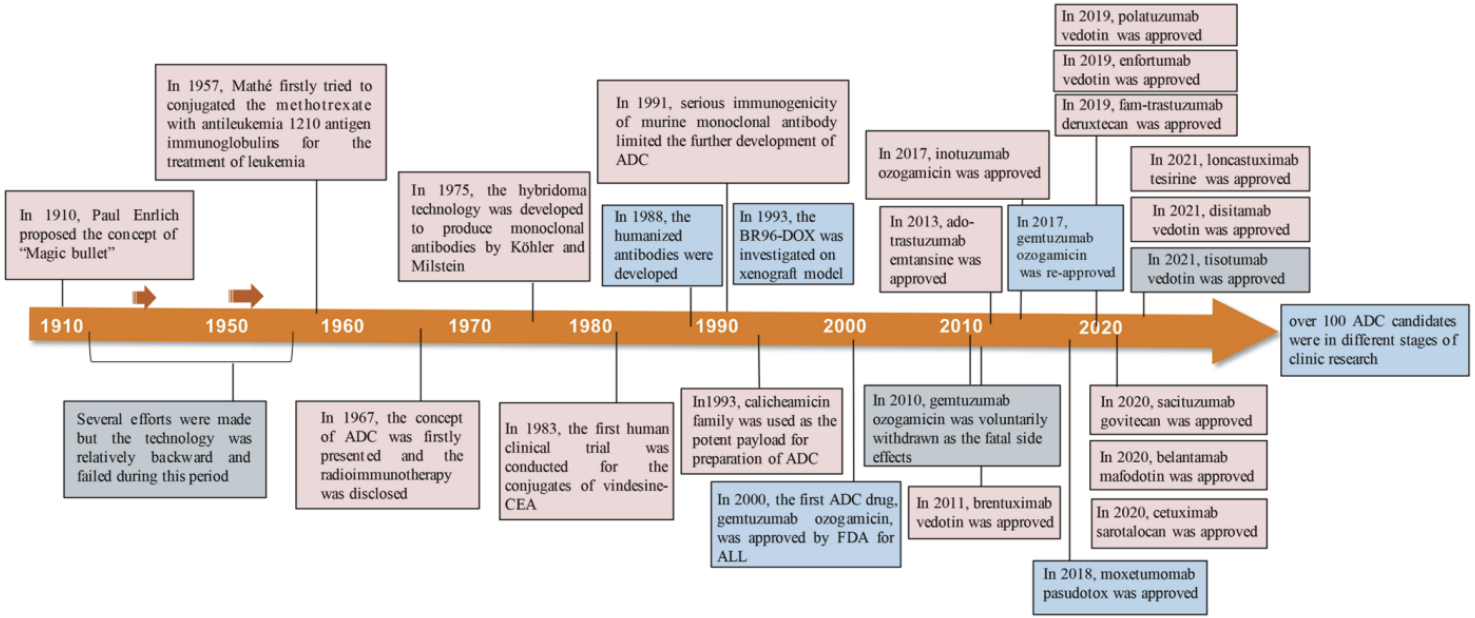
ADCs

A brief history

Paul Ehrlich was the father of hematology, a revolutionary immunologist, and the creator of the field of chemotherapy.

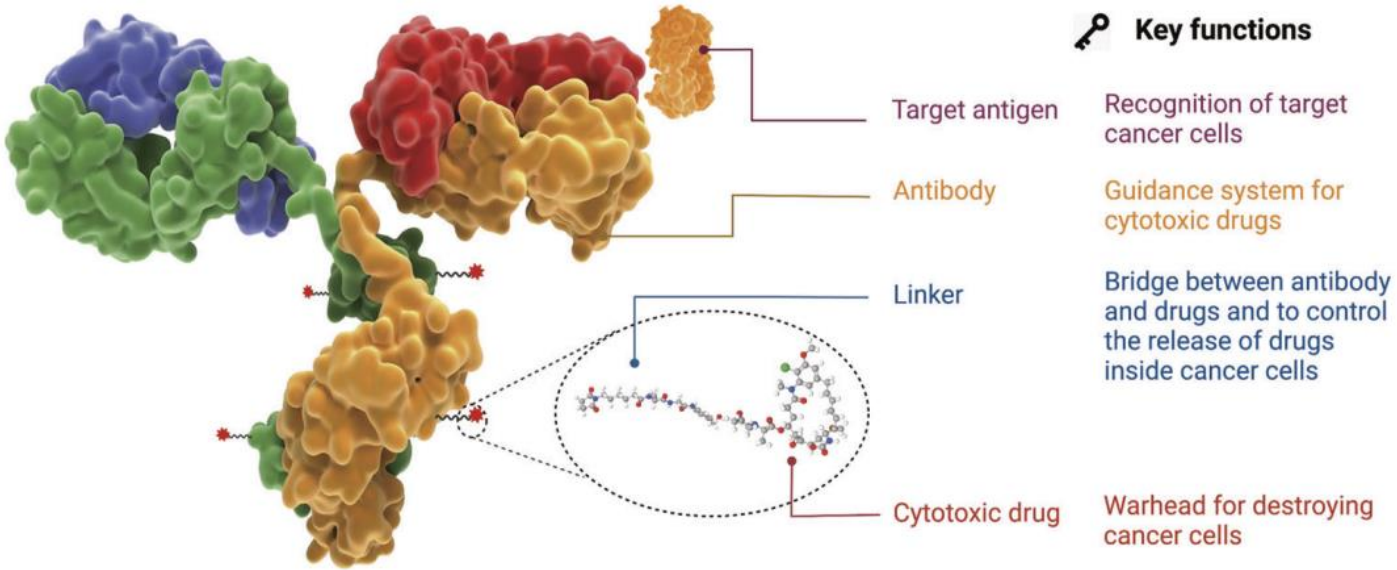
Ehrlich's dream of the “magic bullet” — his term — that would seek out and specifically destroy invading microbes or tumor cells is now not only a reality but a major aspect of clinical medicine.





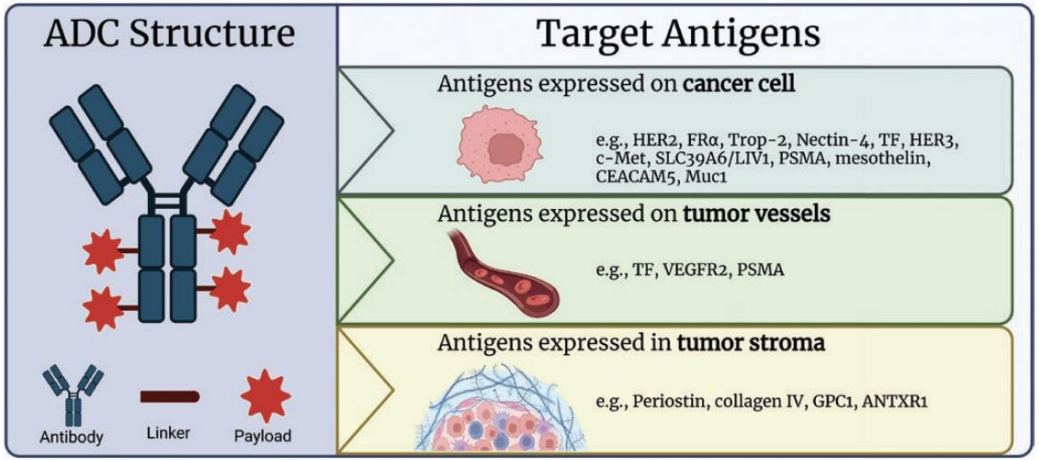
Fu et al,Signal Transduction and Targeted Therapy (2022) 7:93

Antibody Drug Conjugate Structure

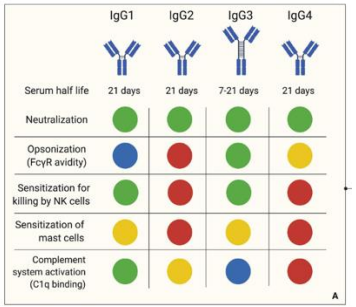


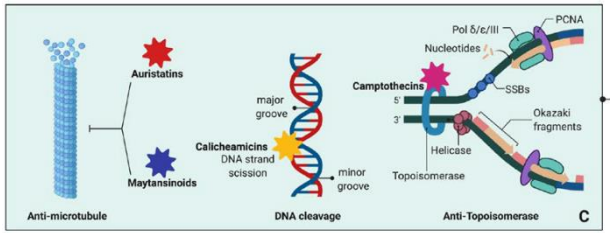
Fu et al, Signal Transduction and Targeted Therapy (2022) 7:93

ADCs: Key Parameters



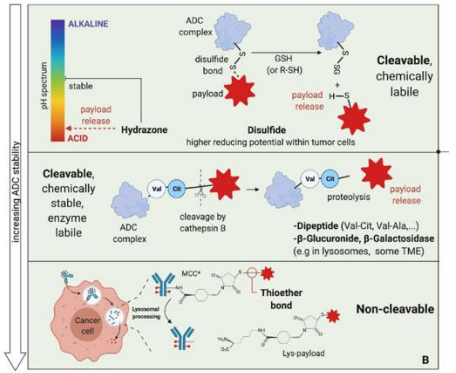
Antibody





Payload

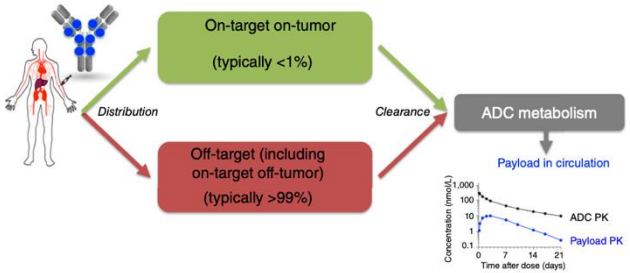
Linker

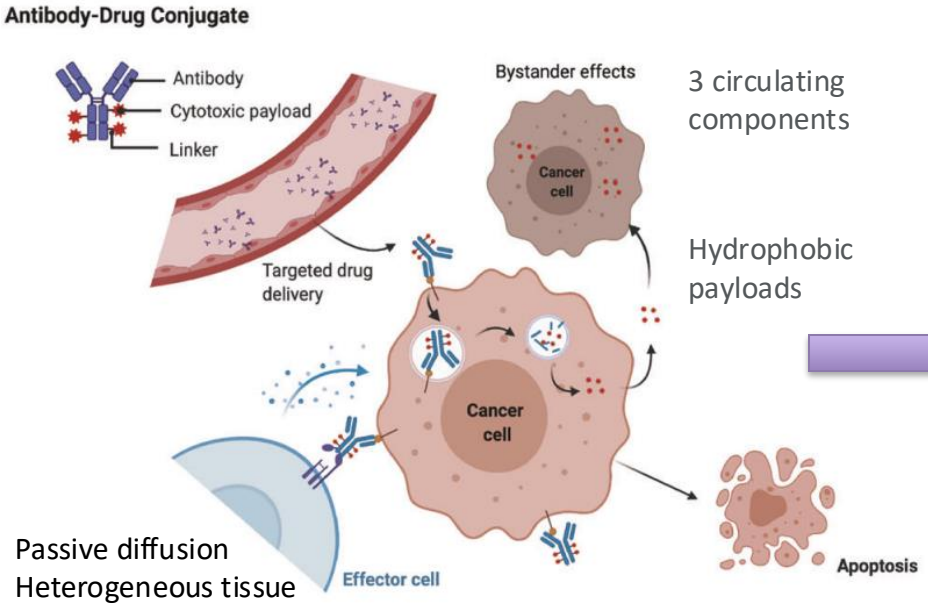


Tarantino, CA CANCER J CLIN 2022;72:165–182; Ascione, The Oncologist, 2023

ADCs

”Smarter” chemotherapy delivery



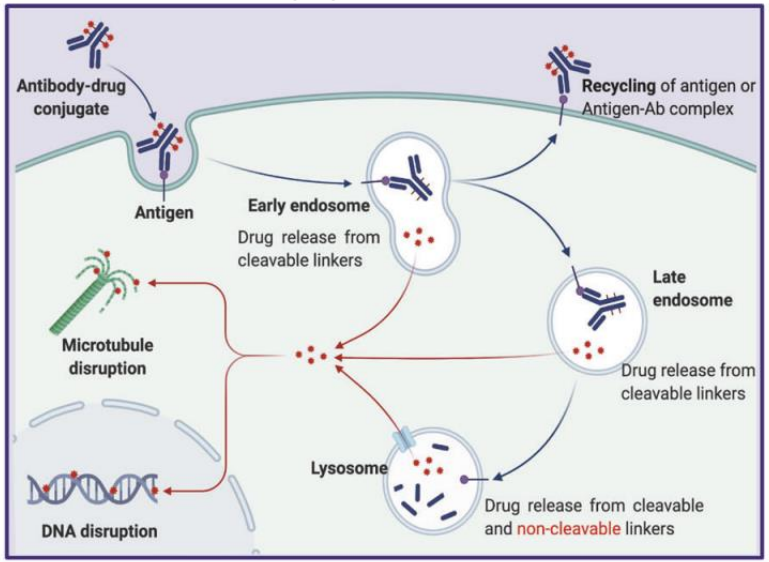


3 circulating components

Hydrophobic payloads

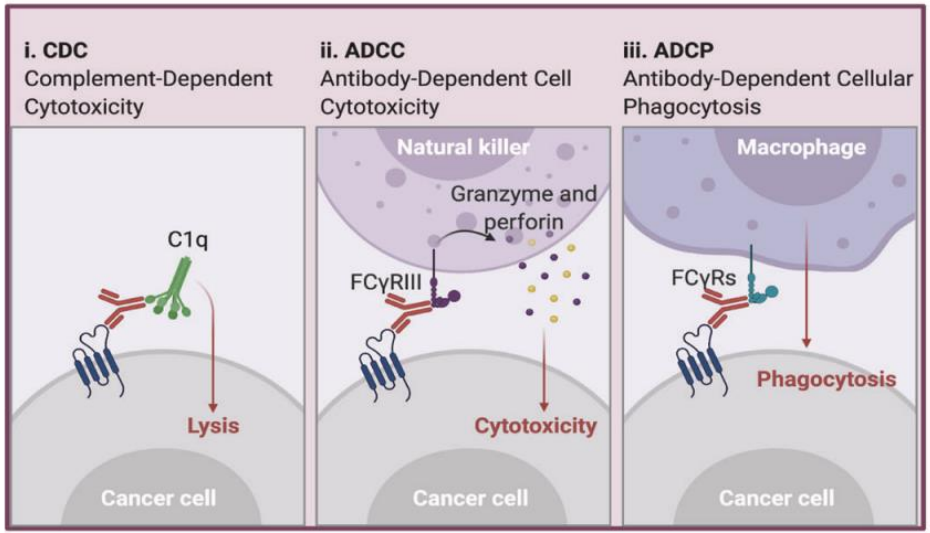
- Passive diffusion
- Heterogeneous tissue
- penetration
- Release of some payload in TME

Not all the payload reaches the tumor

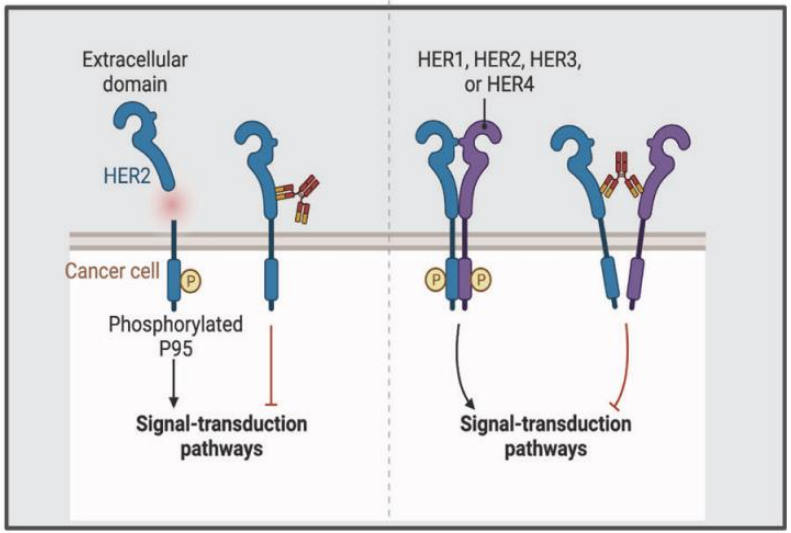


Fu et al., Signal Transduction and Targeted Therapy 2022; 7:93
Colombo, Cancer Discov. 2024 Nov

Payload independent cancer killing



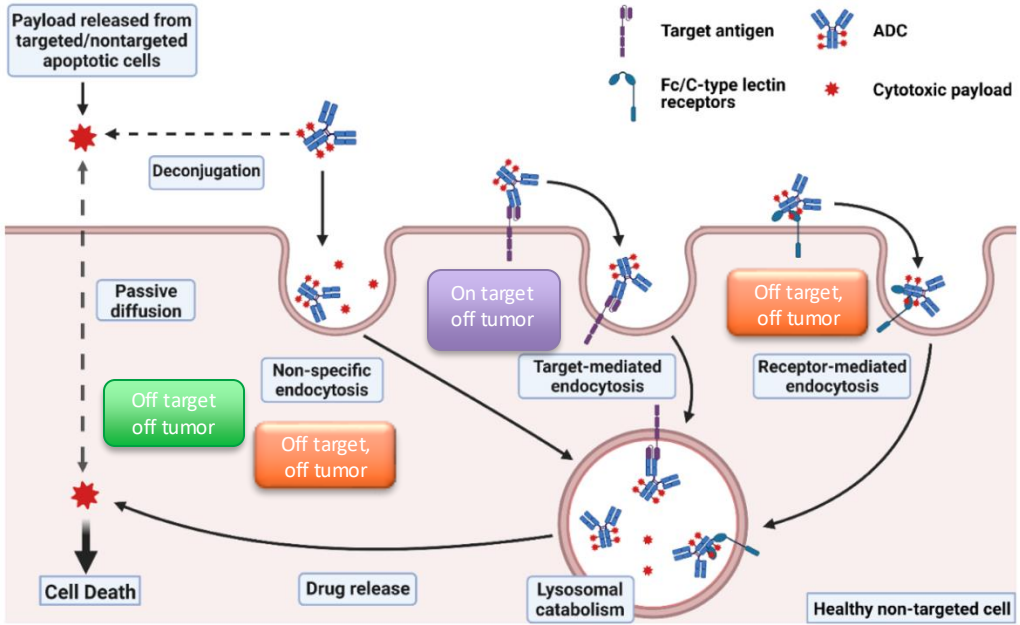
Antibody-dependent activation of immune response



Target binding disrupts function by promoting degradation or preventing dimerization

Fu et al., Signal Transduction and Targeted Therapy 2022; 7:93

Toxicity for ADCs can be difficult to predict



On target, off tumor toxicity

- Expression patterns of target Ag: ratio with tumor expression
- Not necessarily payload dependent

Off target, off tumor toxicity predominant

- Related to the payload and the linker

Target-independent ADC uptake

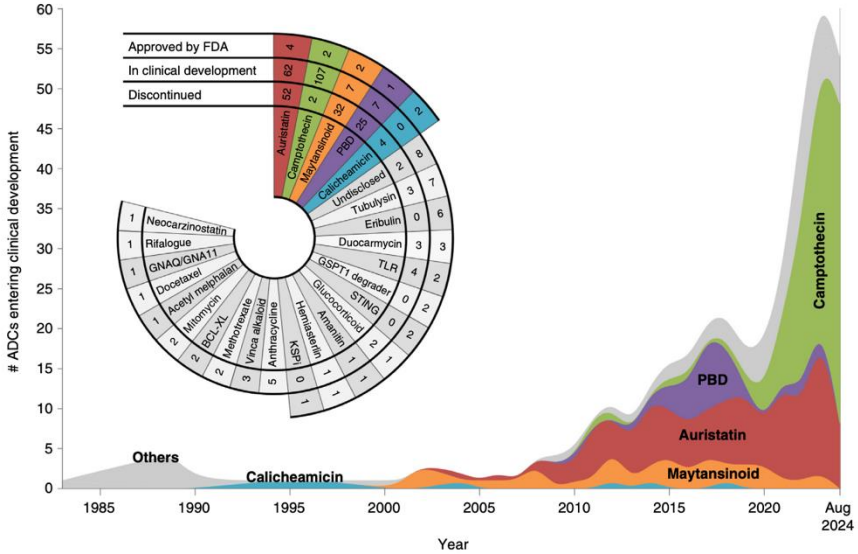
- Non-specific endocytosis
- Fc□R or C-type lectin binding: immune cells, megakaryocytes.

Nguyen, Cancers 2023, 15, 713

Toxicity often reflects payload

Payload		Mechanism of Action	Toxicity
Microtubule inhibitors	Auristatin :MMAE (vedotin), MMAF	Tubulin polymerase inhibitor	Neuropathy, myelosuppression, GI, toxicity, ocular toxicity
	Maytansine: DM1, DM4	Tubulin depolymerization	Transaminases, thrombocytopenia, GI tox
DNA damaging agents	Calicheamicin	DNA cleavage	Myelosuppression, hepatic toxicity, GI tox
	Duocarymycin	DNA alkylating agent	Myelosuppression
	Pyrrolobenzodiazepine	DNA cross-linker	Effusion, dermatitis, thrombocytopenia
Topoisomerase I inhibitor	SN38, deruxtecan, belotecan	DNA damaging agent	Myelosuppression, diarrhea, alopecia, ILD

Trends in ADC Development



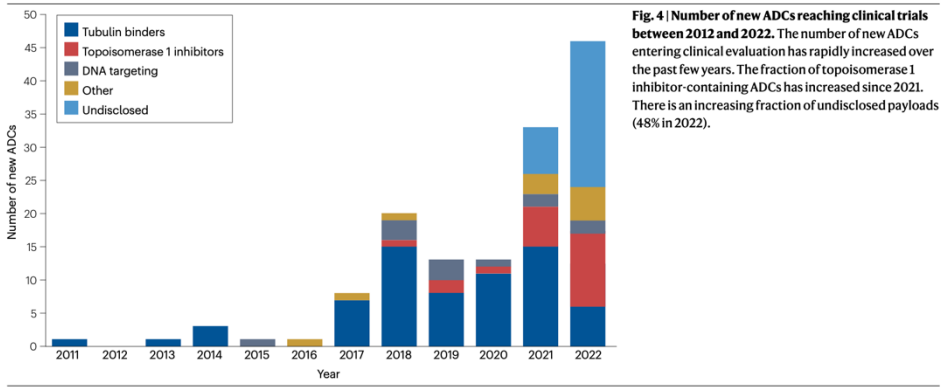
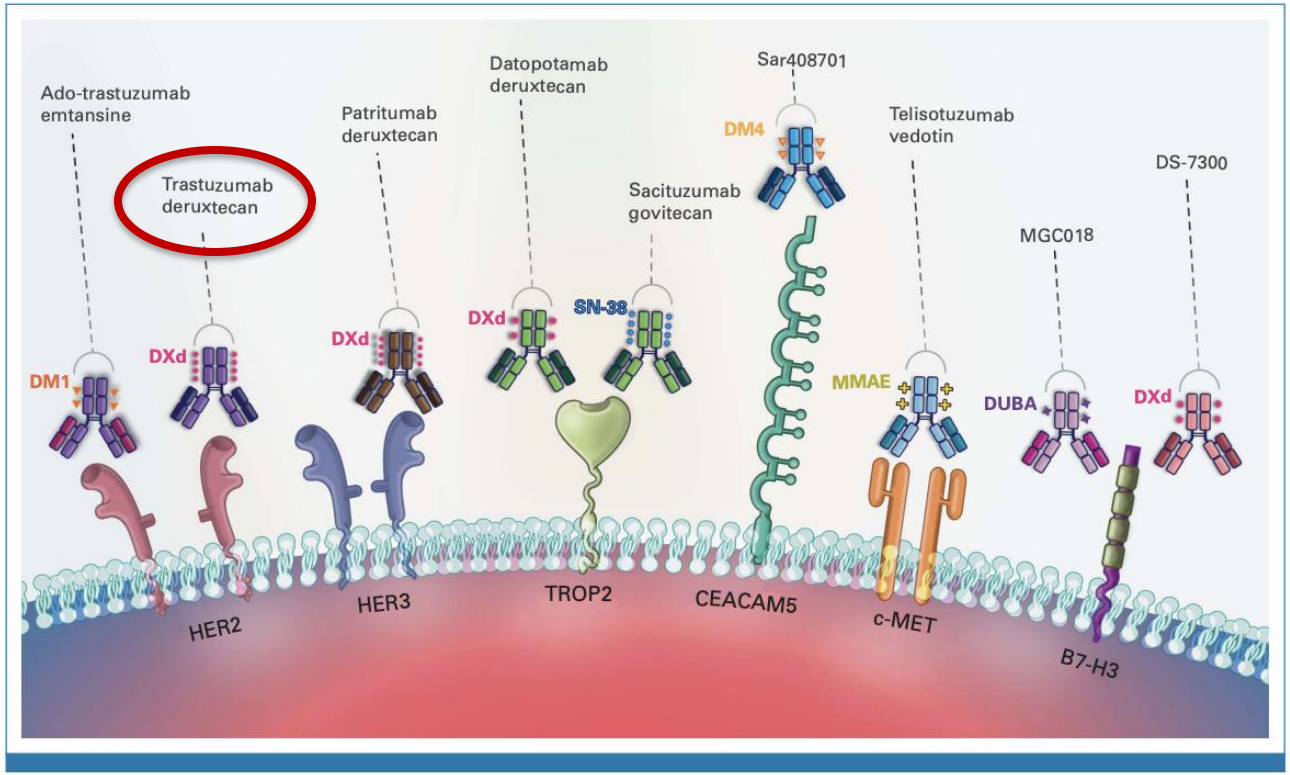


Fig. 4 | Number of new ADCs reaching clinical trials between 2012 and 2022. The number of new ADCs entering clinical evaluation has rapidly increased over the past few years. The fraction of topoisomerase 1 inhibitor-containing ADCs has increased since 2021. There is an increasing fraction of undisclosed payloads (48% in 2022).

ADCs Approved and in Development for NSCLC

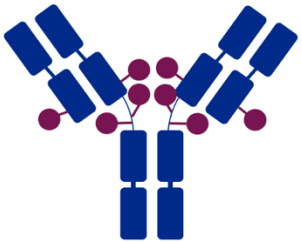


Passaro, J Clin Oncol 41:3747-3761

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

Next-generation ADCs

Trastuzumab deruxtecan (T-DXd)[1]

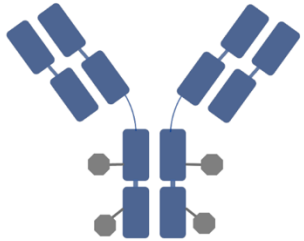


HER2-targeting ADCs with a similar mAB backbone

T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

First-generation ADCs

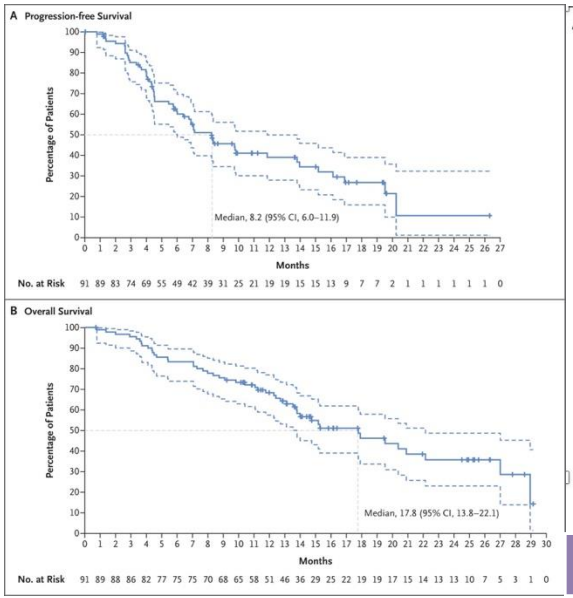
Trastuzumab emtansine (T-DM1)[5]

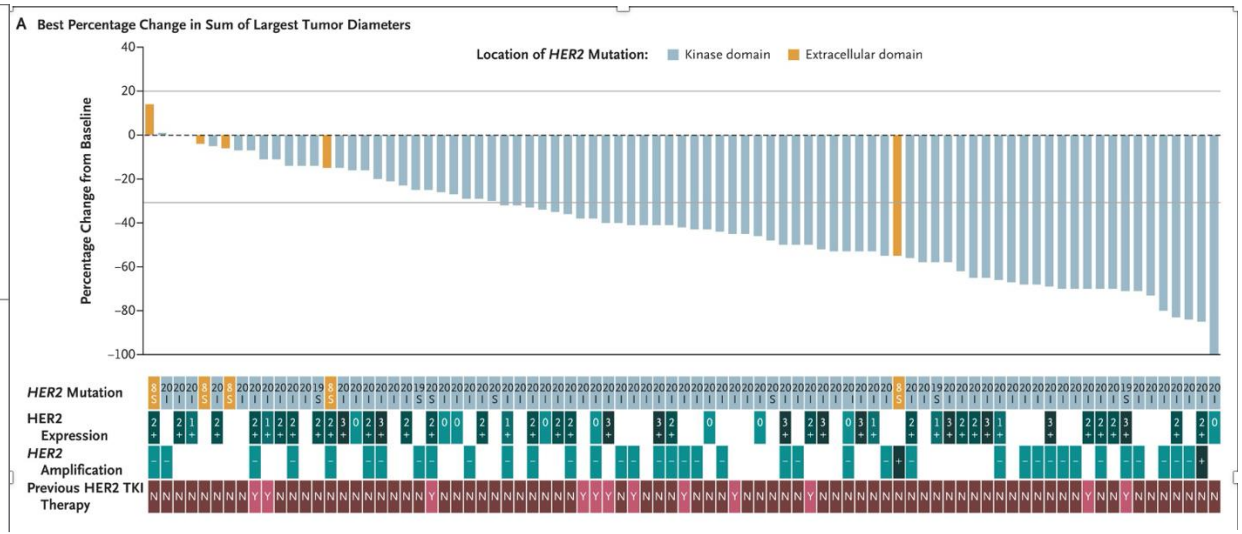


1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85; 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108; 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42; 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

T-DXd in NSCLC with *HER2* mutations

Destiny-Lung01 Phase II Trial



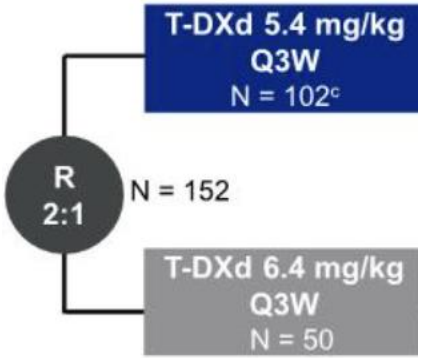


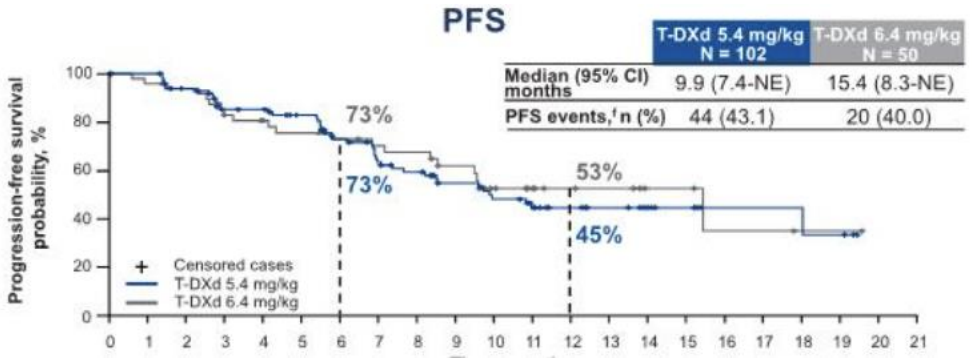
ILD	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
N (%)	3 (3.3)	15 (16.5)	4 (4.4)	0	24 (26.4)

Gr 3 neutropenia 18.7%, Gr 2 Alopecia 46.2%

Destiny-Lung02:Dose optimization of T-Dxd

- HER2+ NSCLC
- >2nd line
- PS 0-1





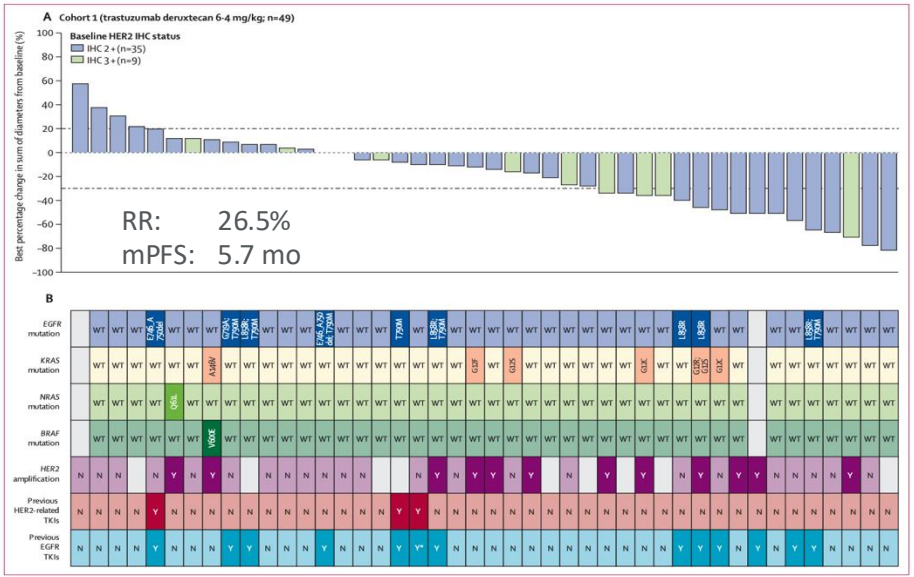
	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	9.9 (7.4-NE)	15.4 (8.3-NE)
PFS events,f n (%)	44 (43.1)	20 (40.0)

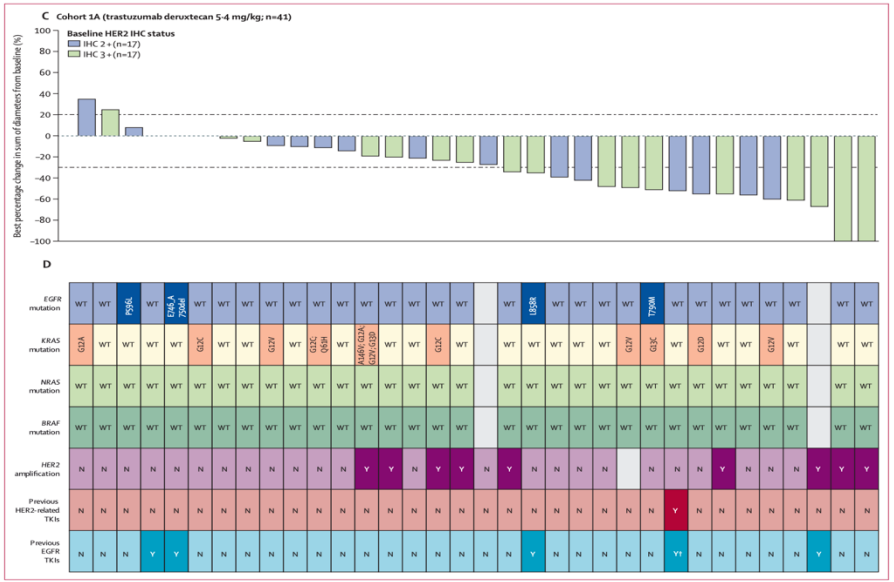
Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,a n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluableb	3 (2.9)	2 (4.0)
DCR,c n (%) [95% CI]	95 (93.1) [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)

More any grade ILD (5.9 vs 14%) in 6.4 vs. 5.4, so 5.4 mg/kg is approved dose for patients with previously treated HER2+ NSCLC

Trastuzumab-Dxd in HER2-overexpressing NSCLC

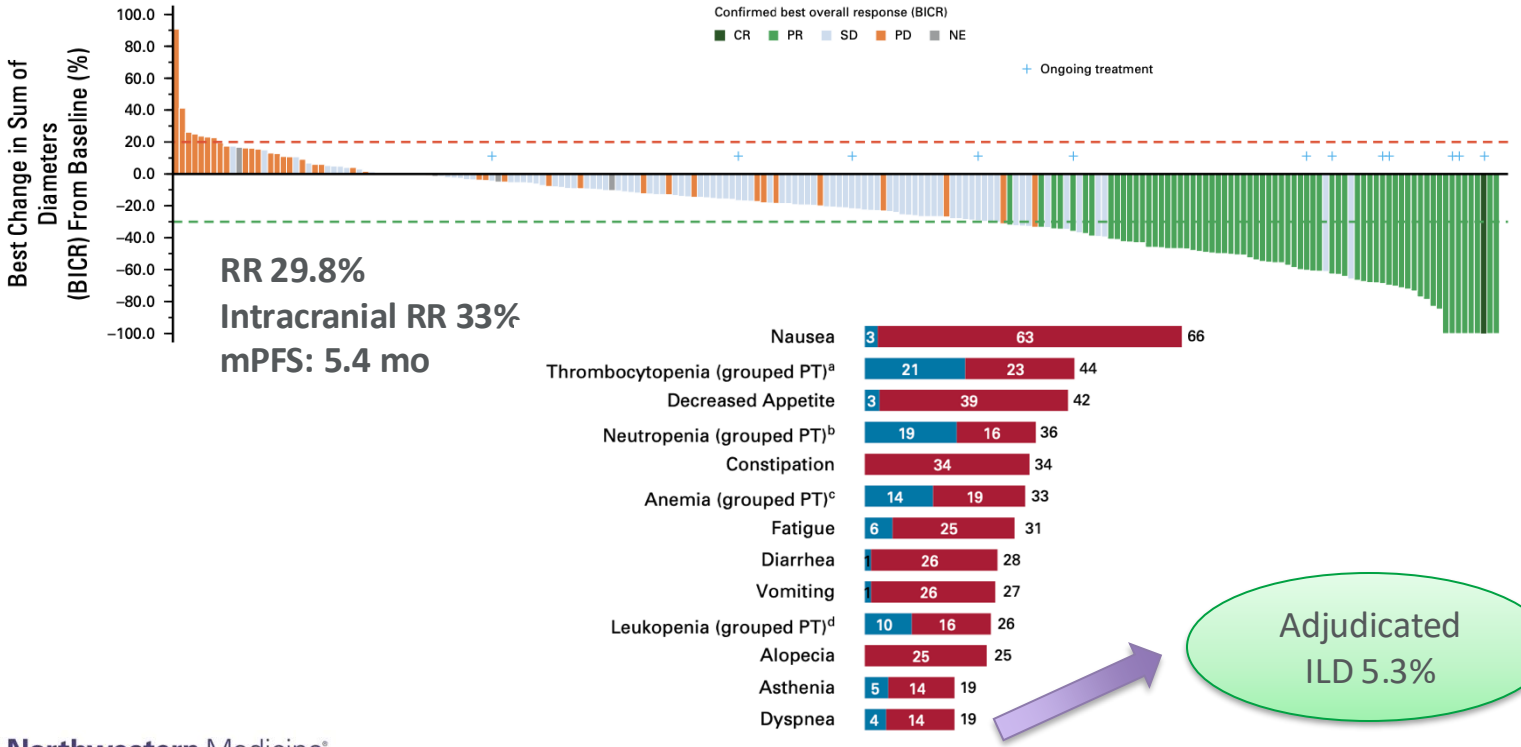
Destiny-01, HER3 IHC 2 or 3+





Patritumab deruxtecan in EGFR+ NSCLC Post EGFR TKI and Chemo

HERTHENA-Lung01



Patritumab deruxtecan in EGFR+ NSCLC Post EGFR TKI

HERTHENA-Lung02

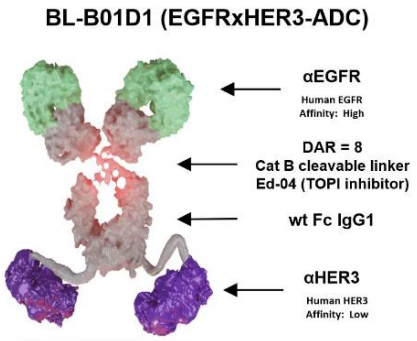
NEWS RELEASE

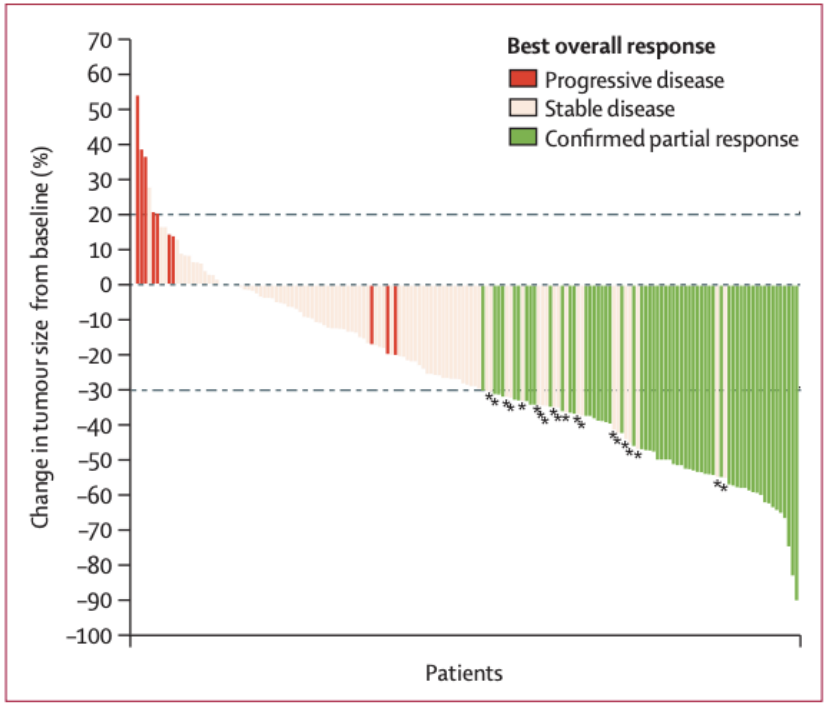
Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

2024-09-17

Daiichi Sankyo and Merck's patritumab deruxtecan demonstrates a statistically significant progression-free survival improvement in this EGFR-mutated non-small cell lung cancer population with high unmet need following prior EGFR TKI treatment

BL-B01D1: EGFRxHER3 bispecific ADC

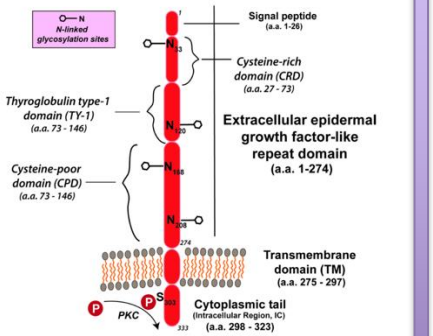




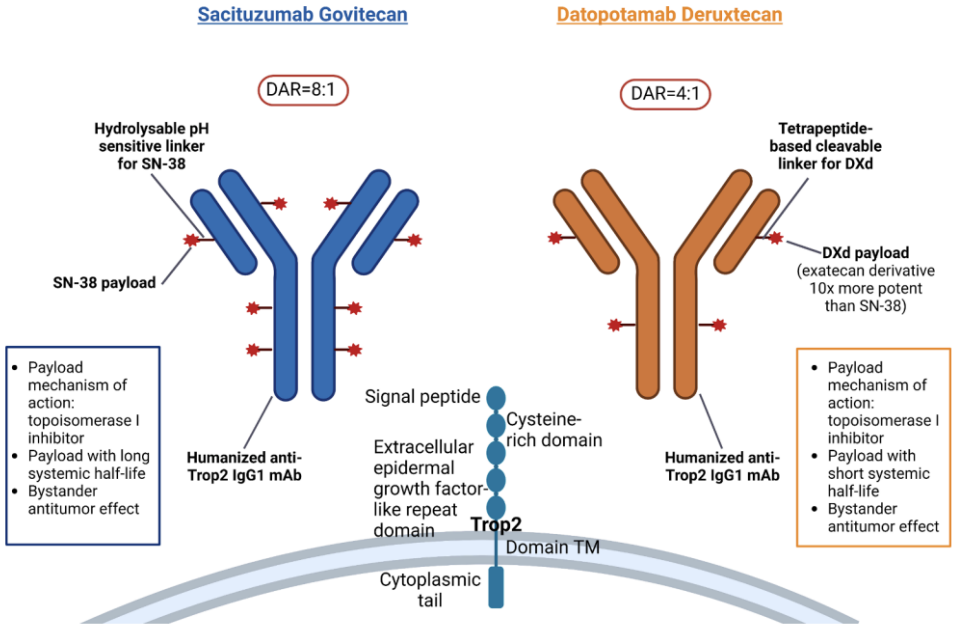
EGFRwt (N=40)
RR 67.5%
EGFRmut (N=62)
RR 40.3%

Grade 3+ TRAE 57%

Trophoblast cell-surface antigen (TROP2)-ADCs



TROP2:overexpressed in epithelial cancers



MK2870
Humanized IgG1
Belotecan (topo1 inh)
Hydrolyzable linker/conjugated cysteine residues
DAR 7.4

Goldenberg, Oncotarget 2018;Parisi, Cancer Treatment Reviews, 2023

TROPION-Lung01

Key Eligibility Criteria

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

Without actionable genomic alterations[a]

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

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

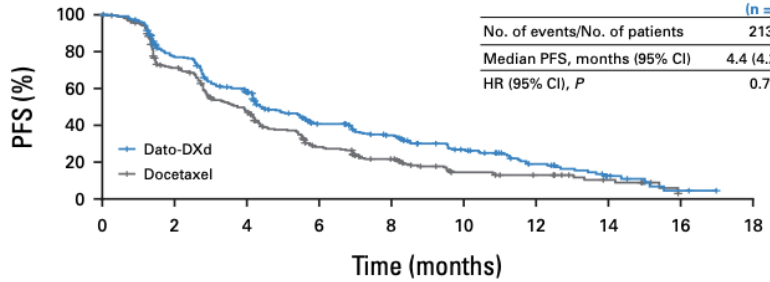
R 1:1

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

Dual Primary Endpoints: PFS and OS

Most common G3+ toxicities: with Dato-DXd mucositis (7%) & pneumonitis/ILD (4%), with docetaxel –neutropenia (23%) & leukopenia (13%)

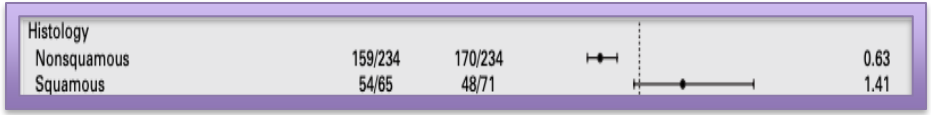
A



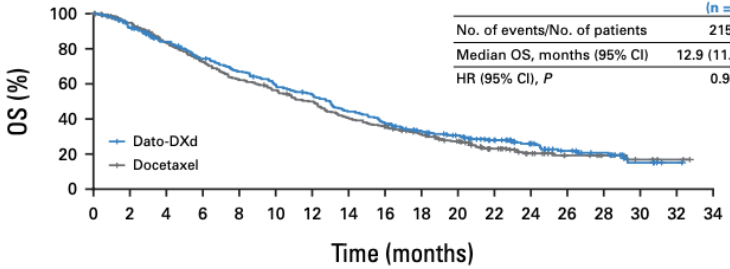
	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	213/299	218/305
Median PFS, months (95% CI)	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)
HR (95% CI), *P*	0.75 (0.62 to 0.91), *P* = .004	

Number 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



A



	Dato-DXd (n = 299)	Docetaxel (n = 305)
No. of events/No. of patients	215/299	218/305
Median OS, months (95% CI)	12.9 (11.0 to 13.9)	11.8 (10.0 to 12.8)
HR (95% CI), *P*	0.94 (0.78 to 1.14), *P* = .530	

Number at risk

Dato-DXd	299	272	242	213	190	168	151	124	106	84	71	51	35	22	16	5	1	0
Docetaxel	305	273	239	205	175	157	138	112	98	81	63	41	26	15	11	4	2	0

TROPION-Lung05

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

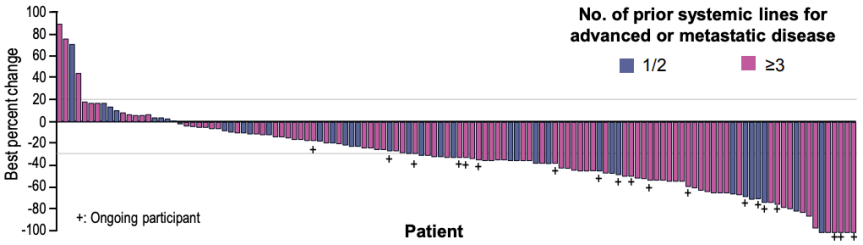
Dato-DXd
6 mg/kg
Q3W

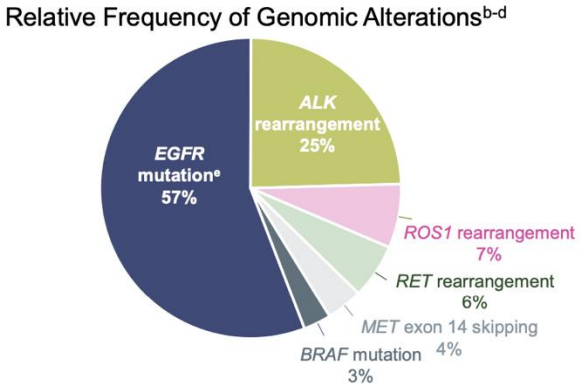
Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

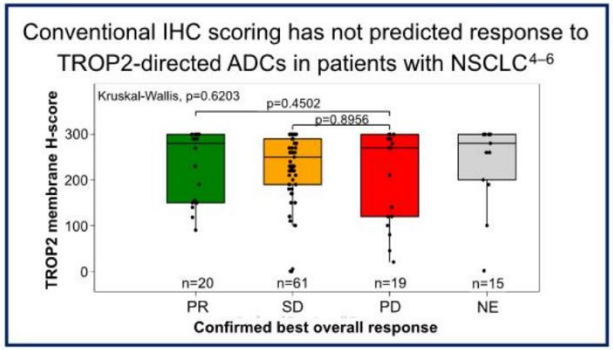


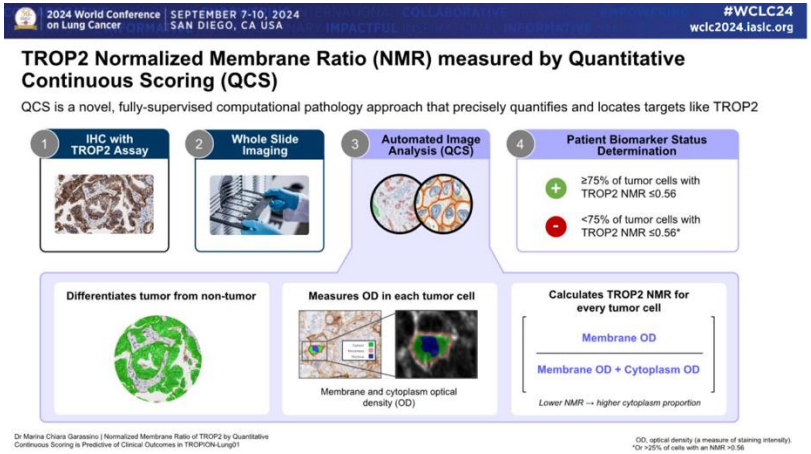


Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, 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)

A Better Biomarker?

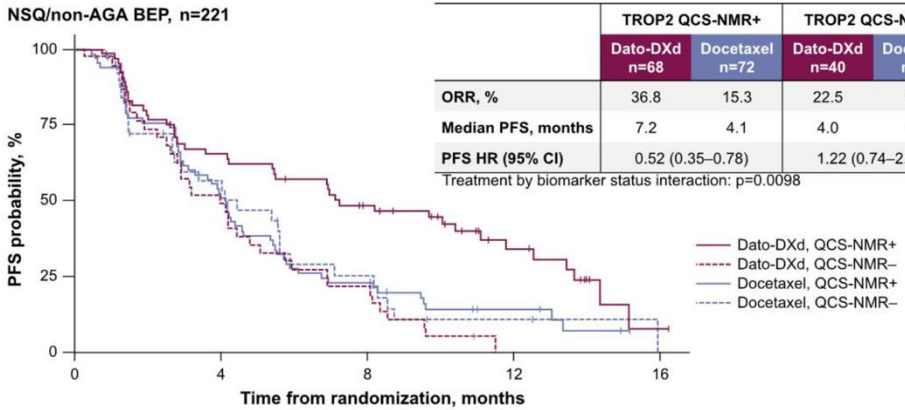
Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring





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

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



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

Treatment by biomarker status interaction: p=0.0098

Dato-Dxd: New Filing

Datopotamab deruxtecan new BLA submitted for accelerated approval in the US for patients with previously treated advanced EGFR-mutated non-small cell lung cancer

PUBLISHED
12 November 2024

AstraZeneca and Daiichi Sankyo's new application is based on the TROPION-Lung05 Phase II trial and supported by data from additional trials including TROPION-Lung01

Previously submitted BLA based on TROPION-Lung01 Phase III trial for patients with nonsquamous NSCLC has been voluntarily withdrawn

EVOKE-01: Sacituzumab govitecan vs Docetaxel

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]

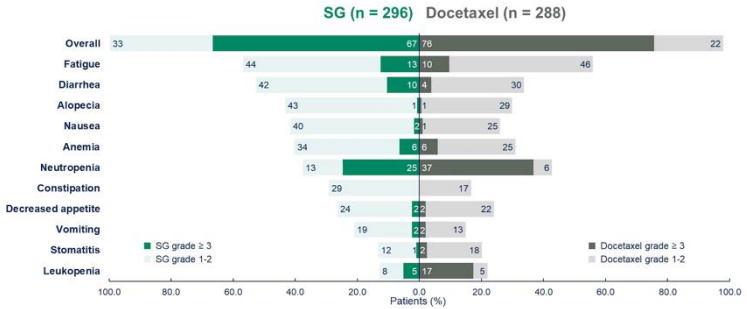
Docetaxel
75 mg/m² on Day 1 of 21-day cycles[d]

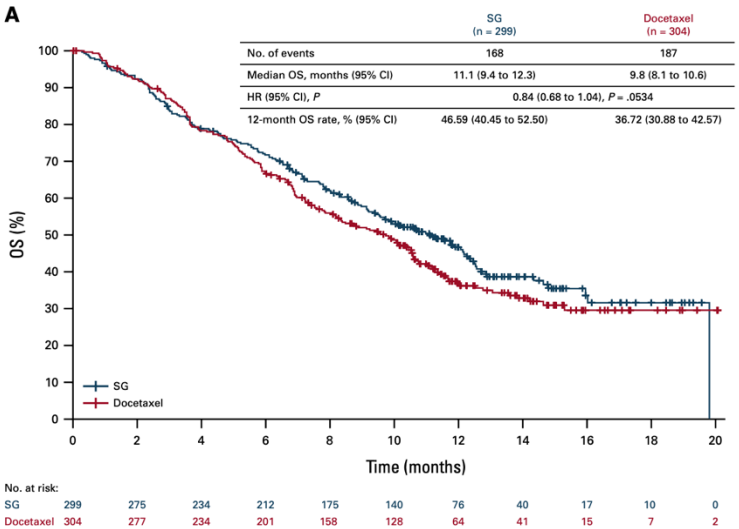
End points

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)



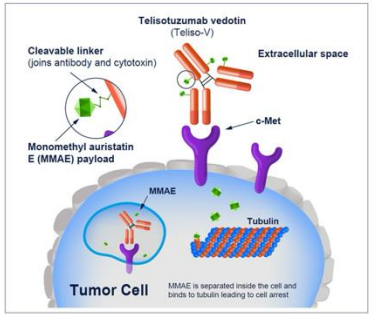


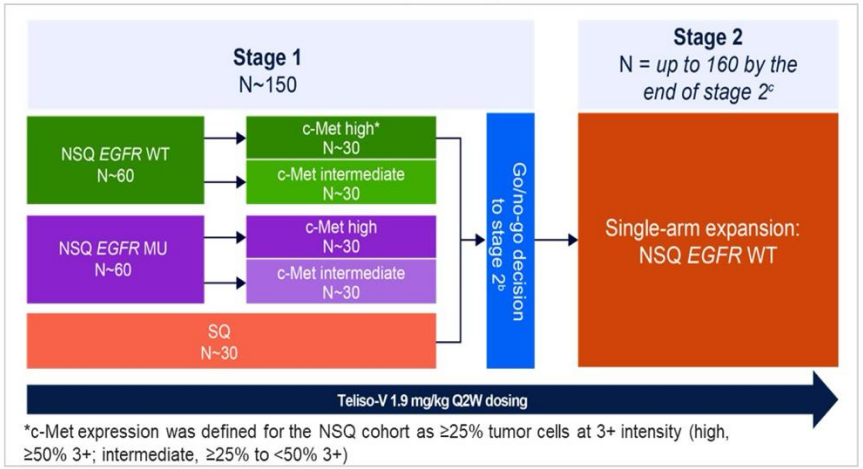
TROP-2 ADCs: ongoing trials in frontline advanced NSCLC

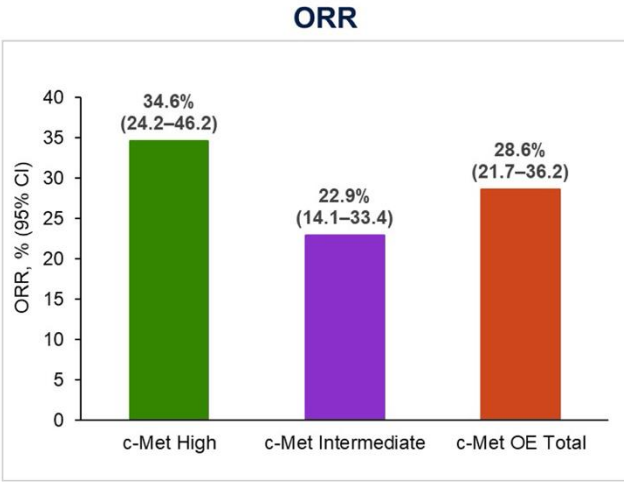
Trial	Phase	Setting	N	Treatment arms	Primary endpoint
TROPION-Lung07	III	Non-squamous, PD-L1<50%, no AGA, 1L PS 0-1	975	Dato-DXd + pembrolizumab + cisP/carboP Dato-DXD + pembrolizumab Pembrolizumab + cisP/carboP-pemetrexed	PFS OS
TROPION-Lung08	III	NSCLC, PD-L1≥50%, no AGA, 1L PS 0-1	740	Dato-DXd + pembrolizumab Pembrolizumab	PFS OS
AVANZAR	III	NSCLC, all PD-L1, no AGA, 1L PS 0-1	1000	Dato-DXd + durvalumab + carboplatin Pembrolizumab + chemotherapy	PFS in TROP2+ OS in TROP2+
EVOKE-03/KND46	III	NSCLC, PD-L1≥50%, no AGA, 1L PS 0-1	614	Sacituzumab-govitecan + pembrolizumab Pembrolizumab	PFS OS

Targeting c-MET overexpression in NSCLC

Telisotuzumab vedotin in pretreated NSCLC

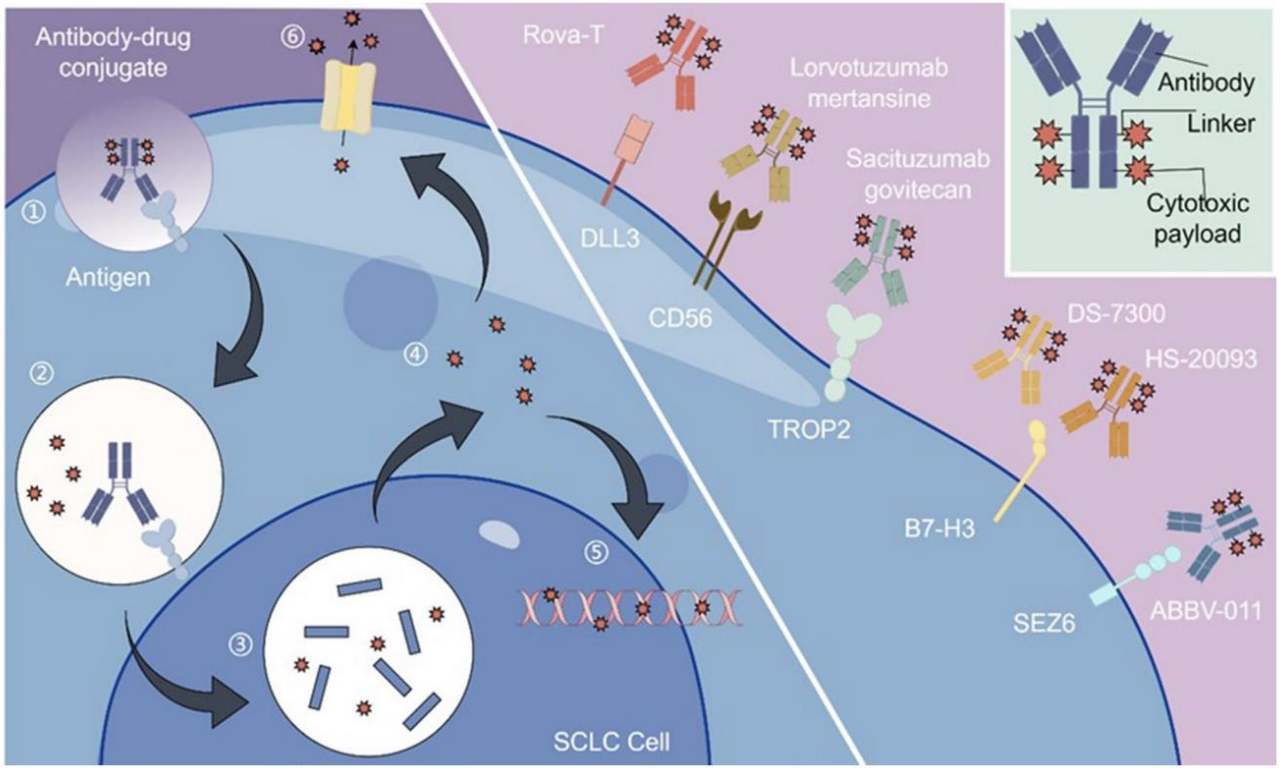






- 21.5% of patients discontinued treatment due to TRAEs, most commonly (>1 patient) due to peripheral neuropathy SMQ and ILD SMQ events

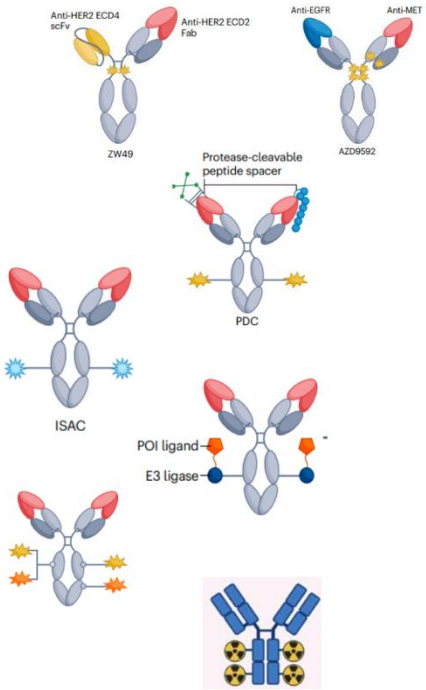
ADCs in SCLC


Antibody-drug conjugate
⑥
①
Antigen
②
④
③
⑤
SCLC Cell
Rova-T
Lorvotuzumab mertansine
Sacituzumab govitecan
DLL3
CD56
TROP2
DS-7300
HS-20093
B7-H3
SEZ6
ABBV-011
Antibody
Linker
Cytotoxic payload

Next generation ADCs

Conjugate the conjugates!

- Bispecific ADCs
  - Biparatopic ADCs targeting 2 epitopes on the same antigen
  - Bispecific ADCs targeting 2 different antigens
- Probody drug-conjugates
- Immune-stimulating antibodies conjugates (ISAC)
- Antibodies-based protein degraders (PROTACs)
- Dual-drug ADCs
- Radionuclide ADCs



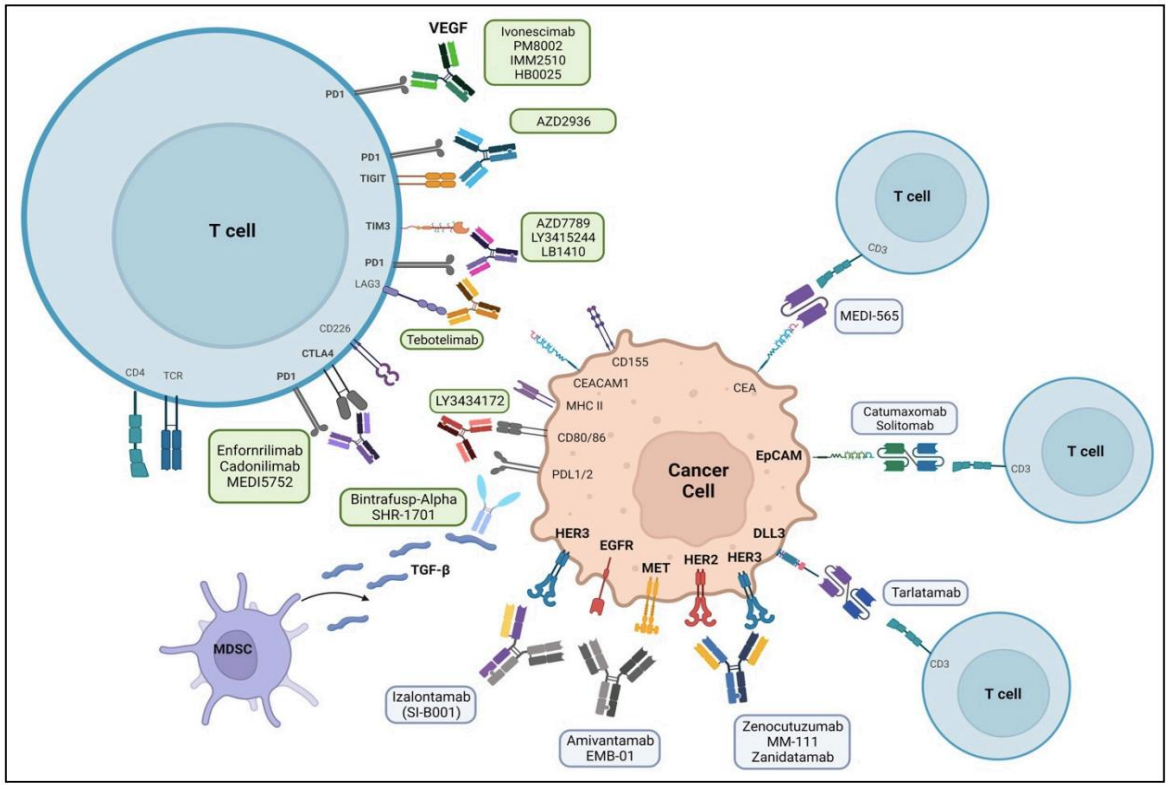
ADCs in NSCLC (2024)

- One of the fastest growing therapeutic class in solid tumor oncology: complex, imperfectly understood drugs

- 2nd generation ADCs
  - Outlier: trastuzumab-DXd in biomarker-selected patients (HER2 mutation)
  - Patritumab-DXd in EGFR+ patients: active in 3rd line, await vs. chemo
  - TROP2 ADCS: activity in AGA pts, need to under outcome with ICI and in 1st line
  - anti-MET Teliso-V in MET IHC+ NSCLC RR 25-35%

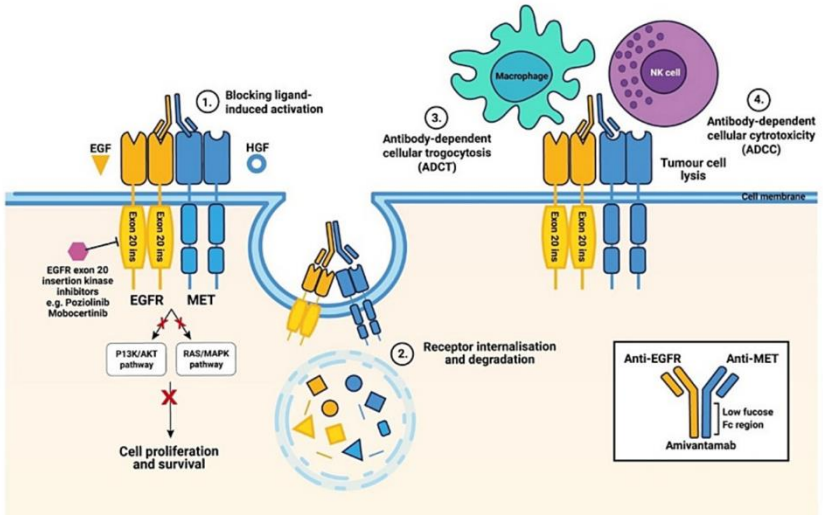
- Most ADCs still confer frequent and sometimes life-threatening toxicities: key for expanding their spectrum to earlier stages and combinations

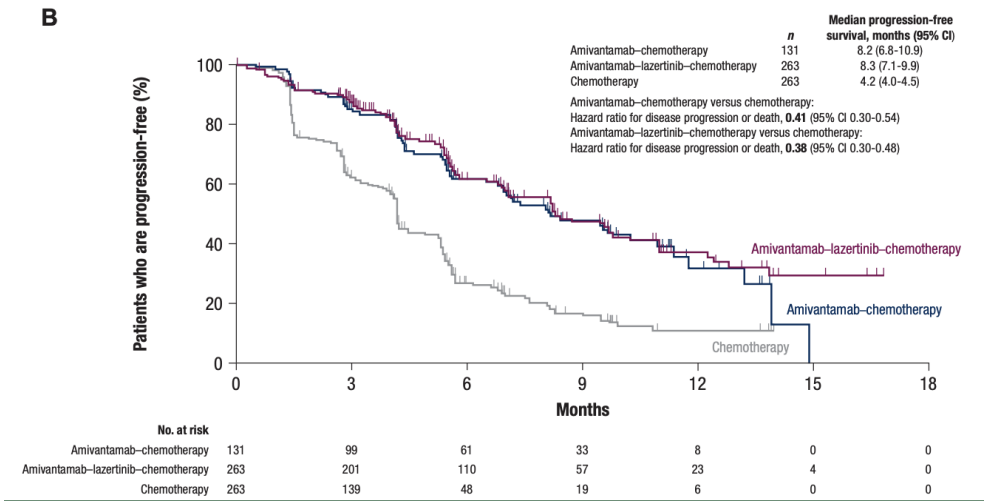
Bispecifics Come of Age in Lung Cancer



Khosla, Pharmaceuticals 2023, 16, 1461

Amivantamab

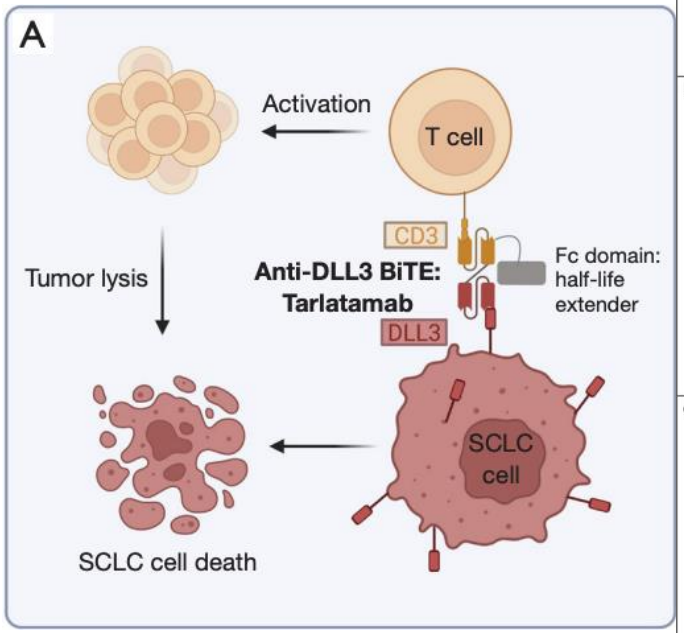


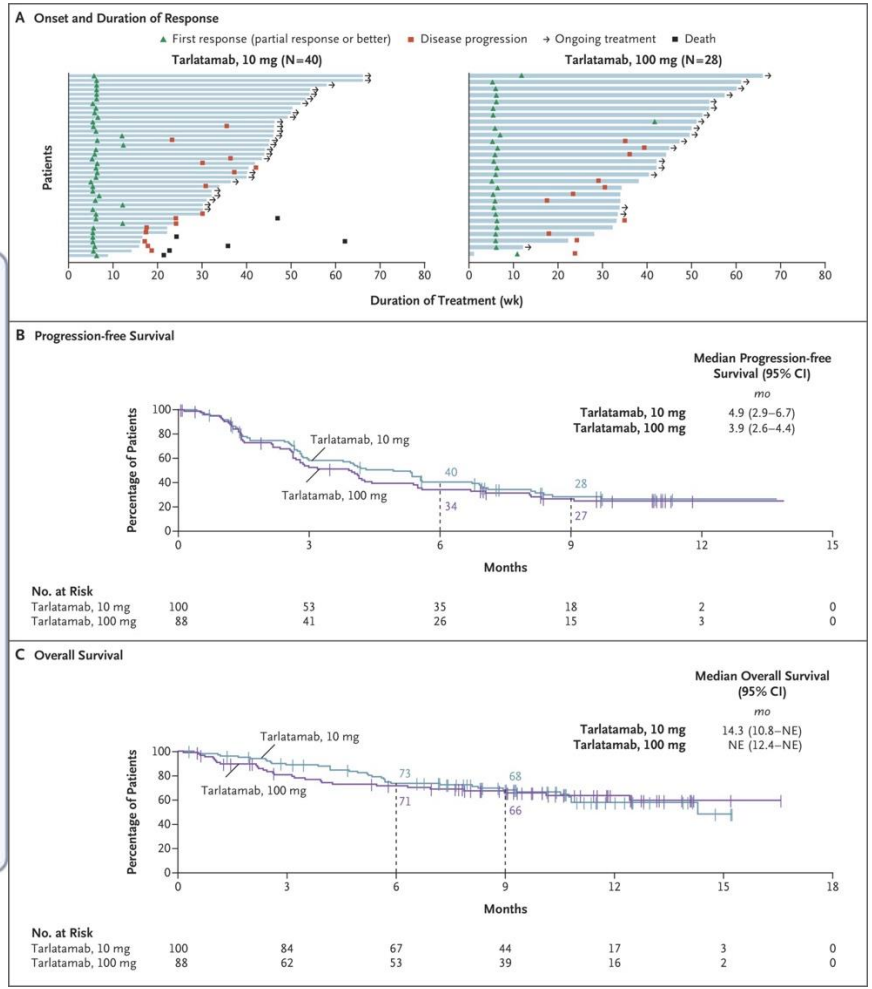


Zavaleta-Monestel, Cureus, 2023; Passaro, Annals of Onc, 2023

Tarlatamab in SCLC

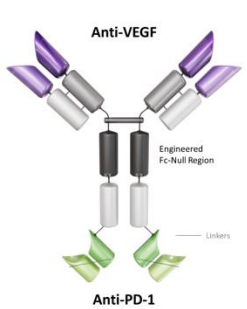
DLL3/CD3

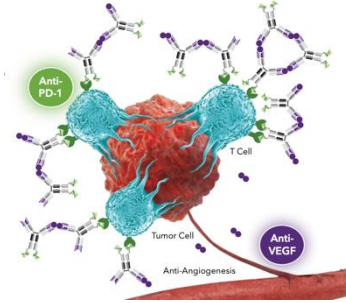




Ivonescimab

Bispecific VEGF/PD-1





HARMONi-2 (AK112-303) Study Design

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

Patient Population

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

R 1:1

N=398

Ivonescimab 20 mg/kg Q3W (N=198)

Pembrolizumab 200 mg Q3W (N=200)

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

Stratification

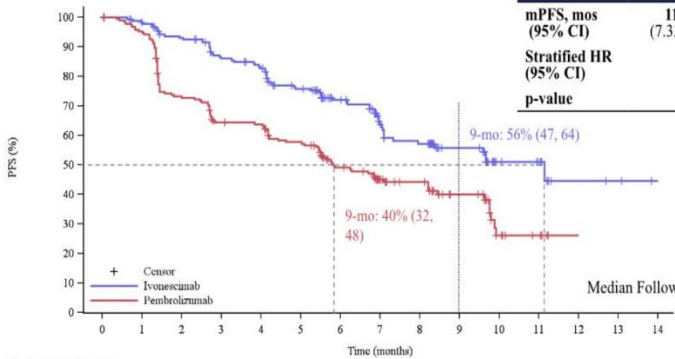
- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

Endpoints

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

Primary endpoint: PFS per IRRC

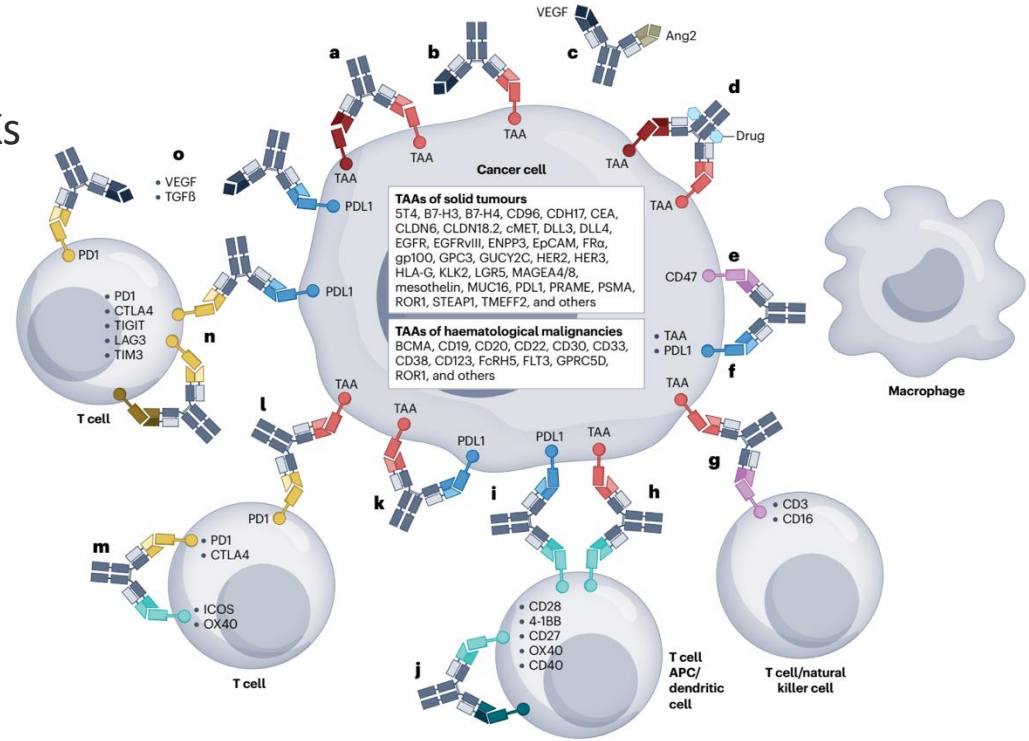
	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	11.14 (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	0.51 (0.38, 0.69)	
p-value	<0.0001	



Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

Bispecific Abs: A New Era

- BsAbs targeting tumor-associated RTKs for tumors with defined dependencies
- BsADCs for targeting tumors with increased selectivity
- Bispecific PROTACs for the targeted degradation of cell surface proteins applicable to various pathways
- Multi-specific antibodies for cancer immunotherapy



Klein C, Nature Reviews Drug Discovery,April 2024

Thank you!

- Northwestern Thoracic Oncology
  - Bilal Anouti
  - Young Chae
  - Divya Gupta
  - Jacobi Hines
  - Nisha Mohindra