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Pusan National University Hospital

Therapeutic antibodies in lung cancer

- ADCs & bispecific Abs

Pusan National University

Mi-Hyun Kim

contents

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01

Introduction

Therapeutic antibodies

- Therapeutic antibodies
  - Binding to and neutralizing extracellular target molecules
  - Advantages
    - Strong and specific binding to the target antigen
    - Maximizing efficacy and safety
    - Ability to block protein-protein interaction
  - **Bispecific antibody (bsAb)** and **antibody-drug conjugate (ADC)** are the most prominent formats

Biomolecules 2020

NCCN guidelines of ADCs/BsAbs in NSCLC

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19 Deletion or Exon 21 L858R
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)[7]
  - Erlotinib + ramucirumab[8]
  - Erlotinib + bevacizumab[c] (nonsquamous)[9]
- Subsequent therapy
  - Osimertinib[10]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[11]

EGFR S768I, L861Q, and/or G719X
- First-line therapy
  - Afatinib[1,12]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,13]
- Subsequent therapy
  - Osimertinib[10]

EGFR Exon 20 Insertion Mutation
- First-line therapy
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[14]
- Subsequent therapy
  - Amivantamab-vmjw[15]

KRAS G12C Mutation[d]
- Subsequent therapy
  - Sotorasib[16]
  - Adagrasib[17]

ALK Rearrangement
- First-line therapy
  - Alectinib[18,19]
  - Brigatinib[20]
  - Ceritinib[21]
  - Crizotinib[18,22]
  - Lorlatinib[23]
- Subsequent therapy
  - Alectinib[24,25]
  - Brigatinib[26]
  - Ceritinib[27]
  - Lorlatinib[28]

ROS1 Rearrangement
- First-line therapy
  - Ceritinib[29]
  - Crizotinib[30]
  - Entrectinib[31]
  - Repotrectinib[32]
- Subsequent therapy
  - Lorlatinib[33]
  - Entrectinib[31]
  - Repotrectinib[32]

BRAF V600E Mutation
- First-line therapy
  - Dabrafenib/trametinib[34]
  - Encorafenib/binimetinib[35]
  - Dabrafenib[36]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[36,37]
  - Encorafenib/binimetinib[35]

NTRK1/2/3 Gene Fusion
- First-line/Subsequent therapy
  - Larotrectinib[38]
  - Entrectinib[39]

MET Exon 14 Skipping Mutation[d]
- First-line therapy/Subsequent therapy
  - Capmatinib[40]
  - Crizotinib[41]
  - Tepotinib[42]

RET Rearrangement[d]
- First-line therapy/Subsequent therapy
  - Selpercatinib[43]
  - Pralsetinib[44]
  - Cabozantinib[45,46]

ERBB2 (HER2) Mutation[d]
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[47]
  - Ado-trastuzumab emtansine[48]

PD-L1 ≥50% First-line Therapy

PD-L1 ≥1%–49% First-line Therapy

NCCN guideline ver1. 2024

FDA-approved ADCs/bsAbs in lung cancer

Antibody-Drug Conjugates (ADCs)

Cancer-selective delivery of potent cytotoxic payloads may eradicate target-expressing cancer cells while sparing normal healthy tissues

Bispecific antibodies (bsAbs)

Simultaneous engagement of two different targets by a single antibody-like molecule may have synergistic or emergent therapeutic effects

Biomolecules 2020

Learning objectives

- Basic structures and action mechanisms of ADCs/bsAbs
- Brief summary of representative ADCs/bsAbs in lung cancer
- Treatment-related adverse effects of ADCs/bsAbs

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02

Antibody-drug conjugates (ADCs)

ADCs research insight from the CAS Content Collection

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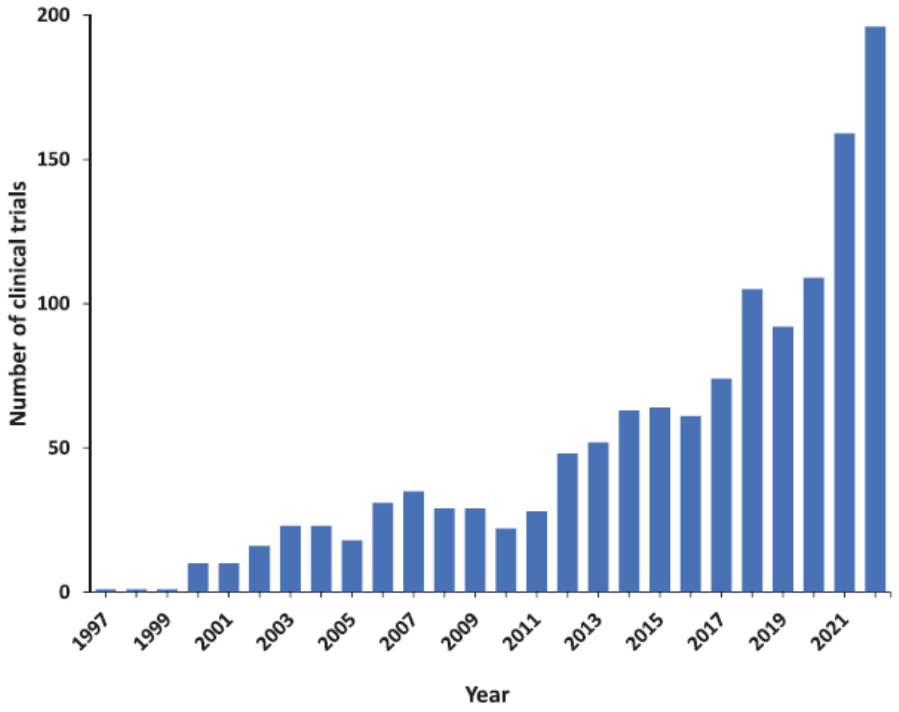
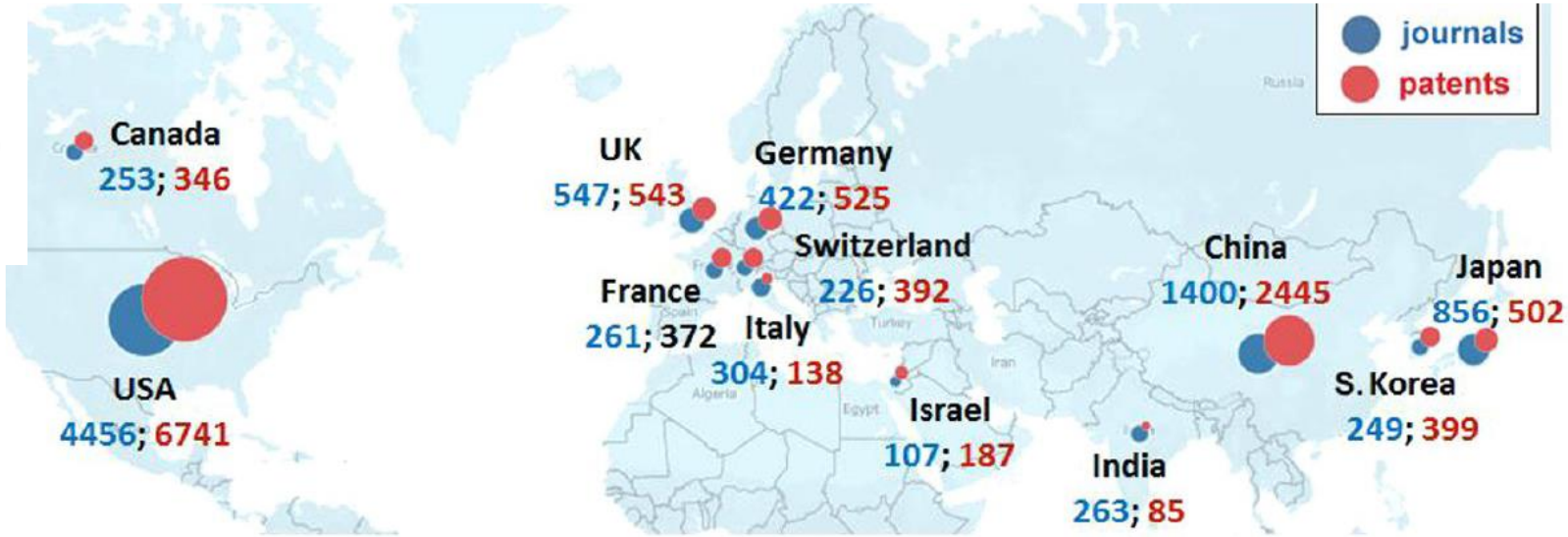
[Number of ADC clinical trials by year]

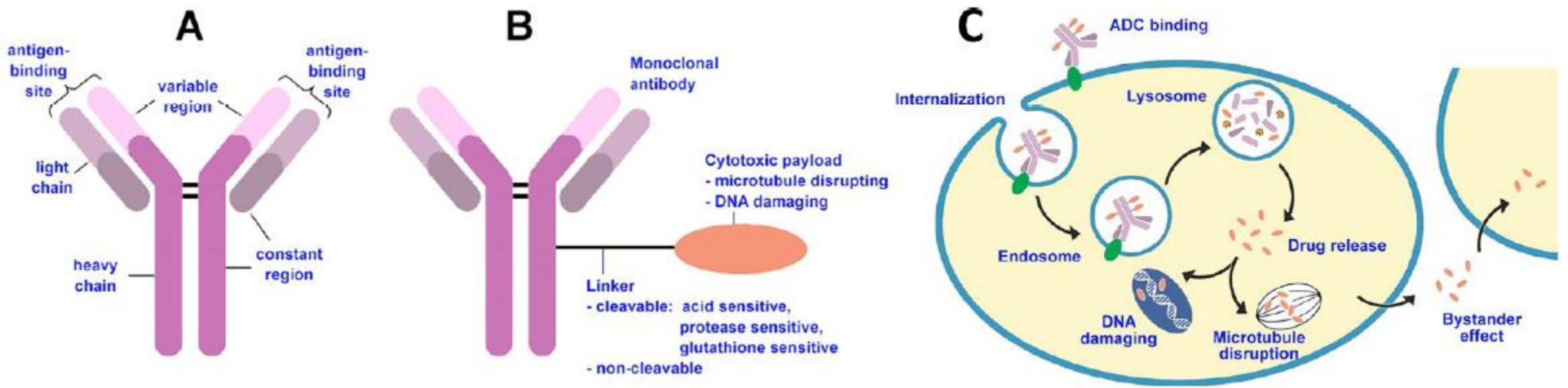


[Top countries with respect to the number of ADC-related journal articles (blue) and patents (red)]



Bioconjugate Chem. 2023

Structures and mechanism of action of ADCs



Bioconjugate Chem. 2023

FDA-approved ADCs available in the clinic

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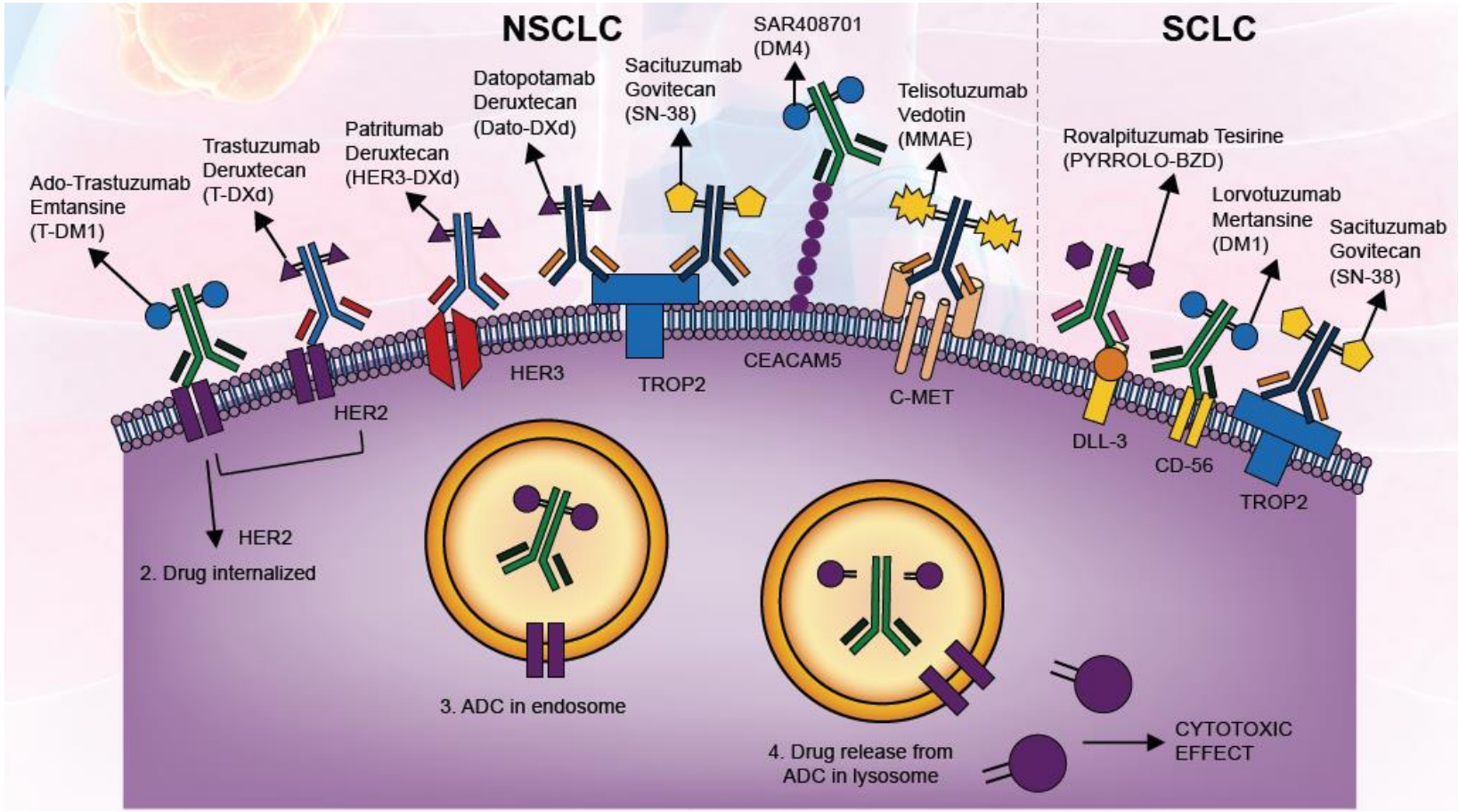
Table 1. FDA-approved antibody-drug conjugates (ADCs) available in the clinic.

ADC	Target mAb antigen isotype	Linker type	Payload	Payload class	Payload action	Disease indication	Year of Approval
Gemtuzumab ozogamicin (Mylotarg)	CD33 IgG4	Cleavable	Ozogamicin	Calicheamicin	DNA cleavage	Relapsed or refractory CD33 + AML**	2000
Brentuximab Vedotin (Adcetris)	CD30 IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	Relapsed or refractory systemic ALCL or classical HL Relapsed and/or refractory primary cutaneous ALCL or CD30 + MF (2017) classical HL, systemic ALCL or CD30 + PTCL#	2011 2018
Ado-tr… emtan… (Kadcy…							
Inotuzu… (Bespo…							
Fam-tr… deruxt… (Enhert…							
Polatuz… (Polivy)							
Sacituz… hziy (T…							
Enfortu… (Padcev)					inhibitor	progression on a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy	
Belantamab mafodotin-blmf (Blenrep)	BCMA IgG1	Non-cleavable	MMAF	Auristatin	Microtubule inhibitor	Relapsed and/or refractory multiple myeloma in the fifth-line setting or beyond	2020
Tisotumab vedotin-tftv) (Tivdak)	Tissue Factor	IgG1 Cleavable	MMAE	Auristatin	Microtubule inhibitor	Recurrent or metastatic cervical cancer, no more than two prior systemic regimens in the recurrent or metastatic setting	2021
Loncastuximab tesirine-lpyl (Zynlonta)	CD20	IgG1 Cleavable	SG3199	PBD DIMER	DNA cleavage	Relapsed and/or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma	2021
Moxetumomab pasudotox (Lumoxiti)	CD22	IgG1 Cleavable	PE38	Pseudomonas exotoxin	Immunotoxin	Relapsed and/ or refractory hairy cell leukemia	2018

Drug	Mechanism	Use	FDA approval (year)
Ado-trastuzumab emtansine	HER2-targeting	HER2-positive BC	2013 [36]
Enfortumab vedotin	Nectin-4–targeting	Advanced urothelial cancer	2019 [37]
Trastuzumab deruxtecan	HER2-targeting	HER2-positive BC	2019 [38]
		HER2-positive GC	2021 [45]
		HER2-low BC	2022 [43]
		HER2-mutant NSCLC	2022 [44]
Sacituzumab govitecan	Trop-2–targeting	Triple-negative advanced BC	2021 [39]
Tisotumab vedotin	Tissue factor	Recurrent/metastatic CV	2021 [41]
Mirvetuximab soravtansine-gynx	FRα-targeting	Epithelial ovarian, fallopian tube, or peritoneal cancer	2022 [47]

Precision Oncology.2023

Landscape of ADCs under study in Lung cancer



[Target antigen and solid tumors]

	HER2	Trop-2	Nectin-4	EGFR
breast cancer	67	9	2	22
ovarian cancer	45	13	6	37
prostate cancer	43	13	5	39
lung cancer	43	12	5	40
pancreatic cancer	38	20	7	35
cervical/uterine cancer	43	15	4	38
stomach cancer	45	13	5	37

Bioconjugate Chem. 2023
Lung cancer 2022

Summary of current key ADCs clinical data in NSCLC

- **Trastuzumab deruxtecan (T-DXd)**
  - **HER2-targeted**
  - Linker type - cleavable tetrapeptide-based linker, Antibody subclass - IgG1
  - FDA-approval - On August 11, 2022, for NSCLC patients with activating hu FDA-approved test, and who have received a prior systemic therapy
  - **Phase I DESTINY-Lung01 (NCT03505710), phase II DESTINY-Lung02 s**
  - **Ongoing phase III DESTINY-Lung04 study (first-line T-DXd vs SOC in advanced, or metastatic nonsquamous NSCLC with HER2 exon 19 or**

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

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Summary of current key ADCs clinical data in NSCLC

- **Patritumab deruxtecan (HER3-DXd)**
  - **HER3-targeted**
  - Linker type - cleavable tetrape
  - **Phase I U31402-A-U102 (loc**
    TKI and platinum-based che
    → FDA breakthrough ther
  - **Phase II HERTHENA-Lung0**
    based chemotherapy)
  - **Ongoing phase III HERTHEN**

TABLE 2. Antitumor Activity (responses by BICR per RECIST)

			All Patients by History of CNS Metastases	
Result	All Patients (n = 225)	Previous 3G EGFR TKI (n = 209)	Yes (n = 115)	No (n = 110)
Confirmed ORR, % (95% CI)	29.8 (23.9-36.2)	29.2 (23.1-35.9)	28.7 (20.6-37.9)	30.9 (22.4-40.4)
CR, No. (%)	1 (0.4)	1 (0.5)	0	1 (0.9)
Partial response, No. (%)	66 (29.3)	60 (28.7)	33 (28.7)	33 (30.0)
Stable disease/non-CR/non-PD, No. (%)	99 (44.0)	91 (43.5)	48 (41.7)	51 (46.4)
PD, No. (%)	43 (19.1)	41 (19.6)	26 (22.6)	17 (15.5)
Not evaluable, No. (%)	16 (7.1)	16 (7.7)	8 (7.0)	8 (7.3)
Disease control rate, % (95% CI)	73.8 (67.5-79.4)	72.7 (66.2-78.6)	70.4 (61.2-78.6)	77.3 (68.3-84.7)
Duration of response, months, median (95% CI)	6.4 (4.9-7.8)	6.4 (5.2-7.8)	5.5 (4.2-7.8)	6.9 (4.4-10.6)
Patients with DOR ≥6 months, %	43.3	45.9	36.4	50.0
Progression-free survival, months, median (95% CI)	5.5 (5.1-5.9)	5.5 (5.1-6.4)	4.3 (4.0-5.5)	6.2 (5.5-8.1)
Overall survival, months, median (95% CI)	11.9 (11.2-13.1)	11.9 (10.9-13.1)	11.6 (10.0-12.6)	12.9 (10.6-14.7)

NOTE. Snapshot data cutoff, May 18, 2023.

Cancer Discovery 2022 /J Clin Oncol 2023

Summary of current key ADCs clinical data in NSCLC

- **Datopotamab-deruxtecan (Dato-DXd)**
  - **TROP2-targeted**
  - Antibody subclass–IgG1, Linker type - cleavable tetrapeptide-based linker
  - **Ongoing phase III TROPION-Lung01 trial (Dato-DXd vs docetaxel in previously treated advanced/metastatic NSCLC)**

Table: LBA12

Efficacy	Dato-DXd N=299	DTX N=305	HR (95% CI)
Median PFS[a] (95% CI), mo			
FAS	4.4 (4.2-5.6)	3.7 (2.9-4.2)	0.75 (0.62-0.91); *P*=.004[b]
NSQ; *n*=*229/232*[c]	5.6 (4.4-7.0)	3.7 (2.9-4.2)	0.63 (0.51-0.78)
Confirmed ORR[a] (95% CI), %	26.4 (21.5-31.8)	12.8 (9.3-17.1)	—
Median DOR (95% CI), mo	7.1 (5.6-10.9)	5.6 (5.4-8.1)	—
Safety, n (%)	**Dato-DXd n=297[d]**	**DTX n=290[d]**	—
Related TEAEs			—
Any grade	257 (86.5)	252 (86.9)	
Grade ≥3	73 (24.6)	120 (41.4)	
Related TEAEs associated with:			
Dose reduction	58 (19.5)	85 (29.3)	
Discontinuation	23 (7.7)	34 (11.7)	
Death[e]	3 (1.0)	2 (0.7)	

[a]By BICR. [b]PFS *P* value boundary = .008. [c]No. of pts in the Dato-DXd and DTX arms. [d]No. of pts treated. [e]Per Investigator; adjudicated data will be presented.

Ann Oncol 2023/Precision Oncology 2023

Summary of current key ADCs clinical data in NSCLC

- **Telisotuzumab vedotin (Teliso-V)**
  - **MET-targeted**
  - Antibody subclass–IgG1, Linker type - cleavable dipeptide
  - **LUMINOSITY Phase II trial (Teliso-V monotherapy in patients with previously treated c-Met-overexpressing advanced NSCLC)**

    → FDA breakthrough therapy designation (BTD) in January 2022

NSCLC Group	Confirmed Responses (n/N)	ORR,% (95% CI)	Events/Responders	Median DOR, mo (95% CI)
c-Met OE NSQ *EGFR* WT	19/52	36.5 (23.6, 51.0)	8/19	6.9 (4.1, –)
c-Met high	12/23	52.2 (30.6, 73.2)	5/12	6.9 (2.4, –)
c-Met intermediate	7/29	24.1 (10.3, 43.5)	3/7	– (4.1, –)
c-Met OE NSQ *EGFR* mutant	5/43	11.6 (3.9, 25.1)	2/5	– (3.0, –)
c-Met high	5/30	16.7 (5.6, 34.7)	2/5	– (3.0, –)
c-Met intermediate	0/13	0 (–, –)	0	Not applicable
c-Met OE SQ	3/27	11.1 (2.4, 29.2)	2/3	4.4 (3.0, –)

- Ongoing phase III study TeliMET NSCLC-01 (Teliso-V vs docetaxel in previously treated patients with c-Met overexpressing, EGFR wildtype, locally advanced/metastatic nonsquamous NSCLC)

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Ongoing ADCs for NSCLC

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Table 3. Ongoing antibody-drug conjugates for NSCLC in early-phase clinical trials.

Drug	Target	Payload	ClinicalTrials.gov (Study Name)	Other solid tumors treated in early-phase clinical trials
Trastuzumab Emtansine (TDM1)	HER2	Emtansine (DM1)	NCT02289833	Breast
Trastuzumab Deruxtecan (DS-8201)	HER2	Deruxtecan (DXd)	NCT04644227 (DESTINY-LUNG02)	Breast, gastric, gastro-esophageal, osteosarcoma, biliary tract, cervical, endometrial, ovarian, pancreas
ARX788HE	HER2	Monomethyl Auristatin F (MMAF)	NCT03255070 (ACE-Pan Tumor 01)	Breast, gastric
Patritumab Deruxtecan	HER3	Deruxtecan (DXd)	NCT04619004 (HERTHENA- Lung01)	Breast, colon, head & neck cancer
Enapotamab-Vedotin (HuMax-AXL-ADC)	AXL	Vedotin (MMAE)	NCT02988817	Ovarian, cervical, endometrial, thyroid, melanoma, sarcoma
CAB-AXL-ADC (BA3011)	AXL	Vedotin (MMAE)	NCT04681131	Pancreas, melanoma, sarcoma
CX2029	CD71	Vedotin (MMAE)	NCT03543813 (PROCLAIM-CX-2029)	Head & neck, diffuse large b-cell lymphoma, esophageal
Tusamitanib-Ravtansine (SAR408701)	CEACAM5	Ravtansine (DM4)	NCT04154956 (CARMEN-LC03) NCT04524689 (CARMEN-LC05)	Breast, pancreas
Mirvetuximab-Soravtansine (MIRV)	FRα	Soravtansine (DM4)	NCT01609556	Ovarian, endometrial, fallopian tube, primary peritoneal, breast
ELU-001 (FA-CDC)	FRα	C'Dot-Drug-Conjugate (CDC)	NCT05001282	Ovarian, endometrial, peritoneal, colorectal, gastric, esophageal, breast, cholangiocarcinoma, biliary duct
Datopotamab-Deruxtecan (DS-1062)	HER2	Deruxtecan (DXd)	NCT04656652 (TROPION- Lung01) NCT04484142 (TROPION-Lung05) NCT03401385 (TROPION-PanTumor01)	Breast (triple-negative, hormone receptor positive/HER2-negative breast cancer), urothelial, gastric, esophageal
RG7841 (DLYE5953A)	Ly6E	Vedotin (MMAE)	NCT02092792	Breast, pancreas, ovarian
Anetumab-ravtansine (BAY94-9343)	Mesothelin	Ravtansine (DM4)	NCT03102320	Mesothelioma, ovarian, pancreas, breast
Telisotuzumab vedotin (ABBV-399)	c-MET	Vedotin (MMAE)	NCT03539536	Solid tumors
Lifastuzumab-vedotin (RG- 7599, DNIB0600A)	NaPi2b	Vedotin (MMAE)	NCT01363947 NCT01995188	Ovarian
Upifitamab-Rilsodotin (XMT-1536)	NaPi2b	Rilsodotin (AF- HPA)	NCT03319628 (UPLIFT)	Ovarian
Enfortumab-vedotin (ASG- 22CE)	Nectin-4	Vedotin (MMAE)	NCT04225117	Urothelial, breast, head & neck, gastric, gastro-esophageal, esophageal, prostate, ovarian
Tisotumab vedotin (HuMax- TF-ADC)	Tissue Factor (TF)	Vedotin (MMAE)	NCT03245736 NCT01631552	Cervical, ovarian, endometrial, bladder, prostate, esophageal
Sacituzumab govitecan (IMMU-132, hRS7-SN-38)	Trop2	Govitecan (SN-38)	NCT03964727 (TROPiC S-03) NCT03337698 (Morpheus Lung)	Breast, head & neck, endometrial, gastric, esophageal, hepatocellular, ovarian, prostate, bladder, renal cell, cervical, pancreas, GBM
Naptumomab-estafentanox (NAP, ABR-217620, Anyara)	Staphlococcal enterotoxin A and 5 T4 (TPBG)	Immune-conjugate	NCT04880863 (NT-NAP-102–1)	Renal cell, pancreas
Cofetuzumab-pelidotin (ABBV-647, PF- 06647020)	PTK7	Pelidotin (Aur0101)	NCT04189614	Breast, ovarian
Trastuzumab-duocarmazine (SYD985)	HER2	Duocarmazine	NCT04235101	Breast, ovarian, endometrial
MORAb-202 (Farletuzumab Linked to Eribulin Mesylate)	Folate Receptor-α	Eribulin	NCT03386942	Solid tumors

Precision Oncology 2023

Adverse events of ADCs

Treatment-related adverse events of antibody–drug conjugates in clinical trials: A systematic review and meta-analysis

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Funding information
The Clinical Research Project of Xiangya Hospital, Grant/Award Number: 2016L06

Abstract

Background: Antibody–drug conjugates (ADCs) have complex molecular structures and have been tested in numerous clinical trials. Therefore, understanding the mechanisms of their toxicity when applied in medical practice is of high importance.

Methods: In a systematic review and meta-analysis of data gathered from different scientific databases (PubMed, Embase, Cochrane, and Web of Science) between January 1, 2000, and June 7, 2022, the authors applied a random-effects model with logit transformation and evaluated the heterogeneity between studies using I^2 statistics. The primary outcome was the incidence and 95% confidence interval (CI) for all-grade and grade ≥3 treatment-related adverse events and differences between different drugs, molecular structures, and cancer types.

Results: In total, 2511 records were identified that included 169 clinical trials involving 22,492 patients. The overall incidence of treatment-related adverse events was 91.2% (95% CI, 90.7%–91.7%; I^2 = 95.9%) for all-grade adverse events and 46.1% (95% CI, 45.2%–47.0%; I^2 = 96.3%) for grade ≥3 adverse events. The most common all-grade adverse events were lymphopenia (53.0%; 95% CI, 48.7%–57.3%), nausea (44.1%; 95% CI, 43.2%–44.9%), neutropenia (43.7%; 95% CI, 42.6%–44.9%), blurred vision (40.5%; 95% CI, 37.4%–43.6%), and peripheral neuropathy (39.6%; 95% CI, 38.2%–41.1%); and the most common grade ≥3 adverse events were neutropenia (31.2%; 95% CI, 30.2%–32.3%), hypoesthesia (23.3%; 95% CI, 10.6%–35.9%), thrombocytopenia (22.6%; 95% CI, 21.3%–23.9%), febrile neutropenia (21.2%; 95% CI, 19.3%–23.1%), and lymphopenia (21.0%; 95% CI, 18.2%–23.7%).

Conclusions: Different ADCs appear to affect various treatment-related adverse events and provide comprehensive data on treatment-related adverse events for ADCs. The current results provide an important reference for clinicians and patients on how to care for toxicities from ADCs in clinical practice.

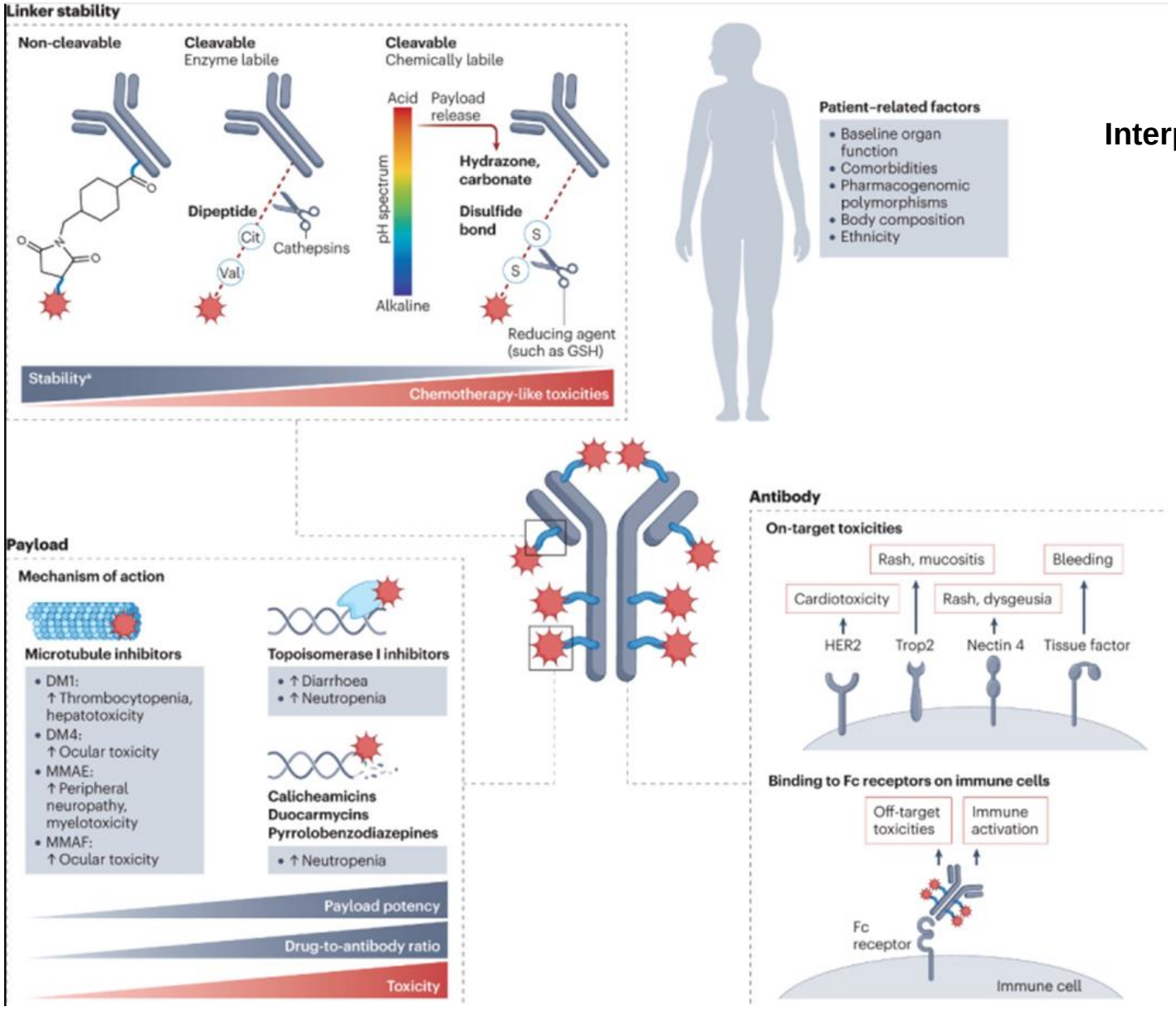
- Meta-analysis of 169 clinical trials involving 22,492 patients
  - All-grade adverse events: 91.2%
    - lymphopenia(53.0%), nausea(44.1%), neutropenia(43.7%), blurred vision (40.5%), peripheral neuropathy(39.6%)
  - Grade ≥3 events: 46.1%
    - neutropenia(31.2%), hypoesthesia(23.3%), thrombocytopenia(22.6%), febrile neutropenia(21.2%), lymphopenia(21.0%)

Cancer 2023

Determinants of the toxicities of ADCs

Linker
The type, incidence and severity of these toxicities are also a function of the stability of the linker

Payload
Major implications for the expected toxicity profile of ADCs

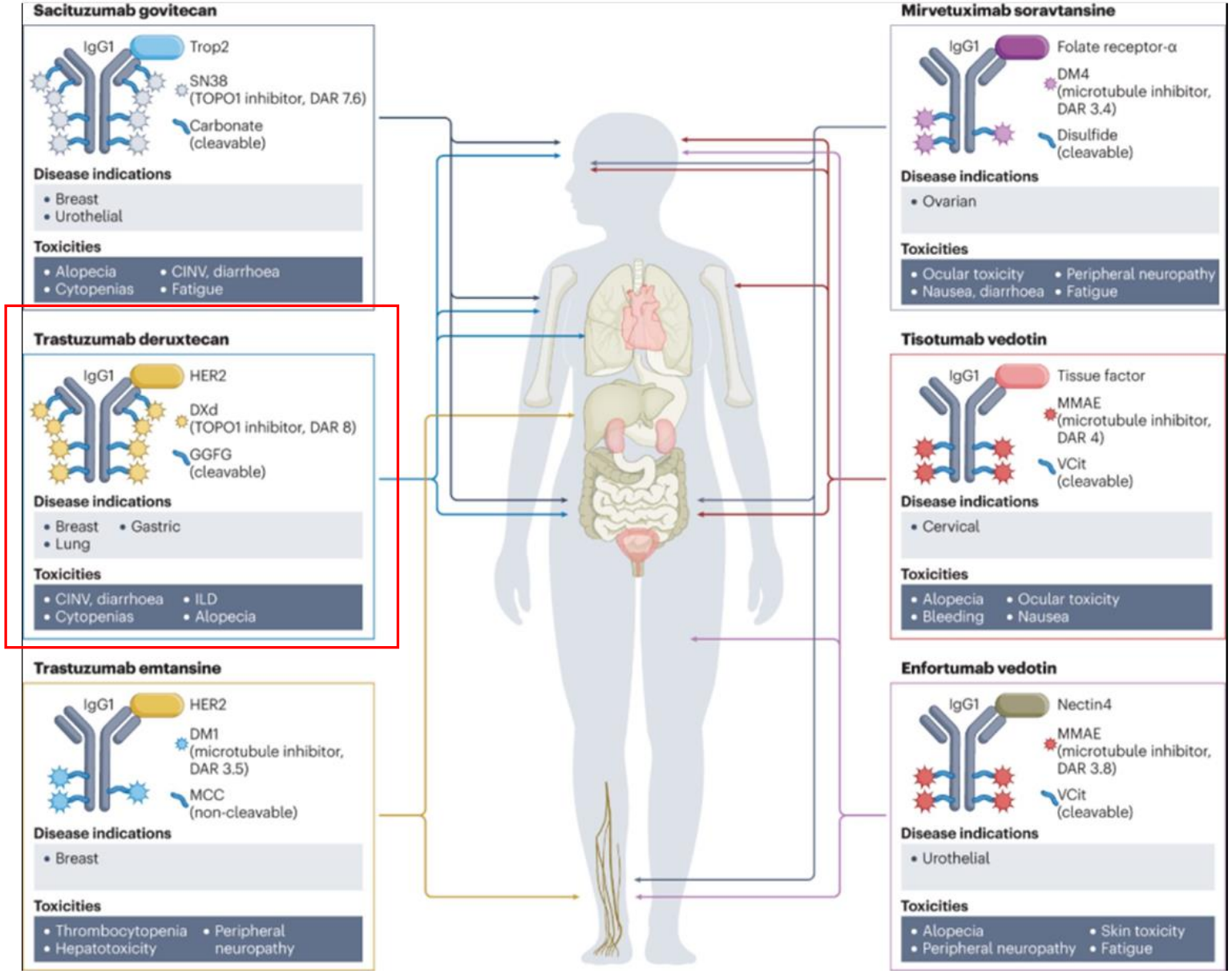


Interpatient variability

Antibody
On-target, off-tumor toxicities as well as via engagement of Fc receptors on immune cells

Nat Rev Clin Oncol. 2023

Main toxicities of ADCs currently approved for solid tumors



Nat Rev Clin Oncol. 2023

ILD events based on trial data

Drug	Grade toxicities events, n (%)			Median time to onset of ILD
	Grade 1–2	Grades 3–4	Grade 5	
Ado-trastuzumab emtansine				
Dieras *et al* [17]	7 (0.7)	2 (0.2)	1 (0.1)	-
Montemurro *et al* [19]	-	9 (0.4)	4 (0.2)	-
Enfortumab vedotin [50]	-	-	1 (0.8)	-
Mirvetuximab soravtansine [46]	-	5(1)	-	-
Trastuzumab deruxtecan				
Saura *et al.* [22]*	23 (12.5)	6 (3.2)	5 (2.7)	-
Cortés *et al.* [56]*	25 (9.7)	2 (0.8)	0 (0)	168 days
Tamura *et al.* [21]*†	17 (15)	1 (1)	2 (2)	187 days‡
Van Cutsem E *et al.* [23]†	5 (6.3)	1 (1.3)	1 (1.3)	68.5 days
Yamaguchi *et al.* [58]†	13 (10.4)	3 (2.4)	0 (0)	-
Li *et al.* [59]†	18 (20)	4 (4)	2 (2)	141 days
Goto *et al.* [60]*	5 (5)	1 (1)	0 (0)	67.5 days
Goto *et al.* [60]†	7 (14)	0 (0)	0 (0)	41 days
Modi *et al.* [57]*	37 (10)	5 (1.3)	3 (0.8)	129 days

*Trastuzumab deruxtecan dose: 5.4 mg/kg; †Trastuzumab deruxtecan dose: 6.4 mg/kg; ‡Median time to onset for pneumonitis was 251.5 days [21].

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY 2022

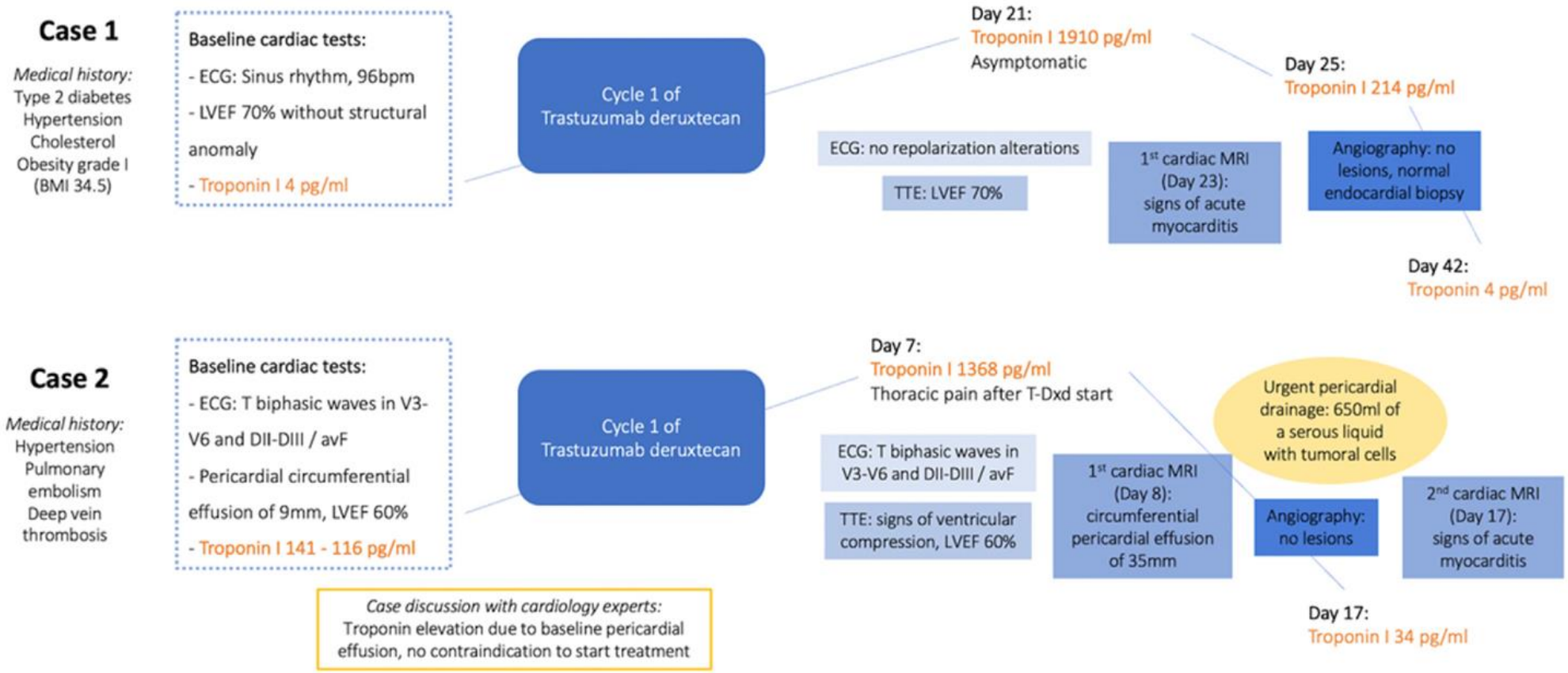
Recommended management of ILD/Pneumonitis

Severity	Treatment Modification
Asymptomatic ILD/pneumonitis (grade 1)	Interrupt trastuzumab deruxtecan until resolved to grade 0, then: • If resolved in ≤28 days from date of onset, maintain dose • If resolved in >28 days from date of onset, reduce dose one level • Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected
Symptomatic ILD/pneumonitis (grade ≥2)	• Permanently discontinue trastuzumab deruxtecan • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected

Recommended starting dose	5.4 mg/kg
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

Modified from PeerView.com/FVE910

Case report: Unexpected cardiotoxicity



- ✓ Routine troponin monitoring
- ✓ Cardiac MRI

JTO Clin Res Rep. 2022;12:100432

부산대학교병원
Pusan National University Hospital

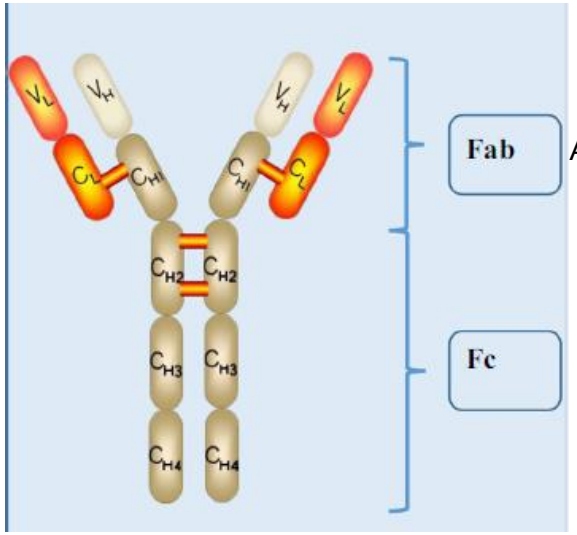
03

Bispecific Antibodies (BsAbs)

Structures of Bispecific antibody (bsAbs)

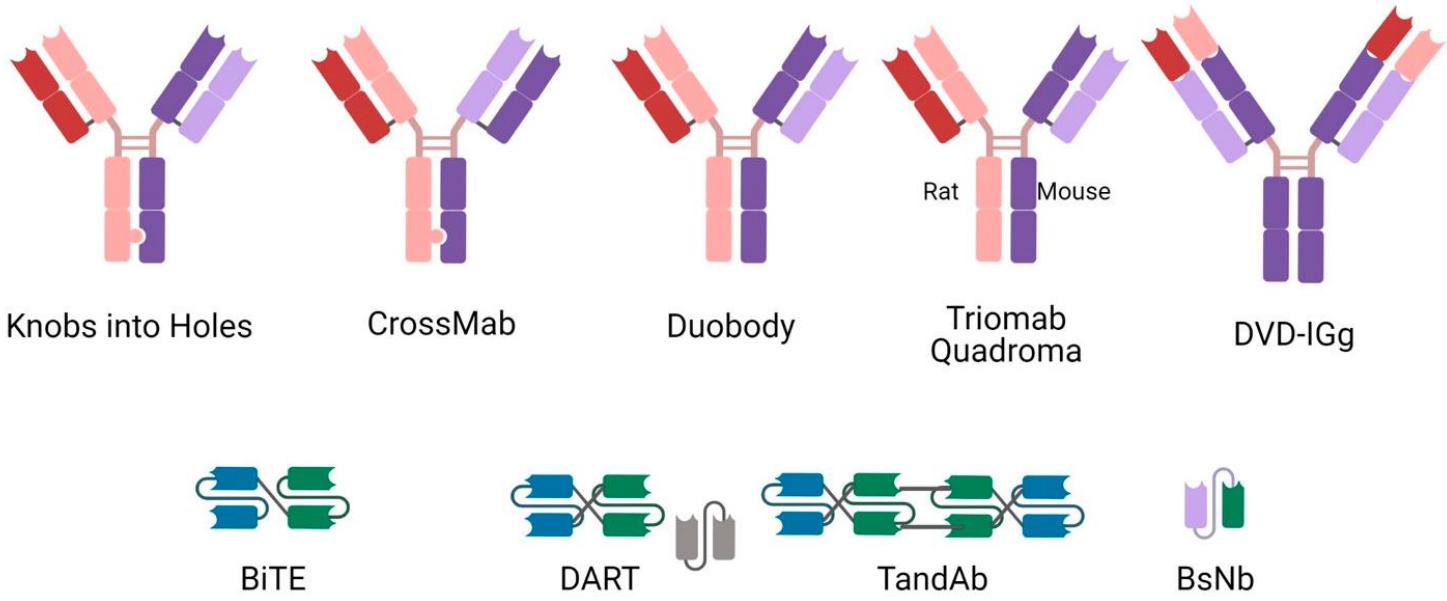
- IgG-like subtypes vs. non-IgG-like subtypes

[Structure of nature IgG molecule]



Antigen-binding fragments (Fab)

Constant region (Fc)



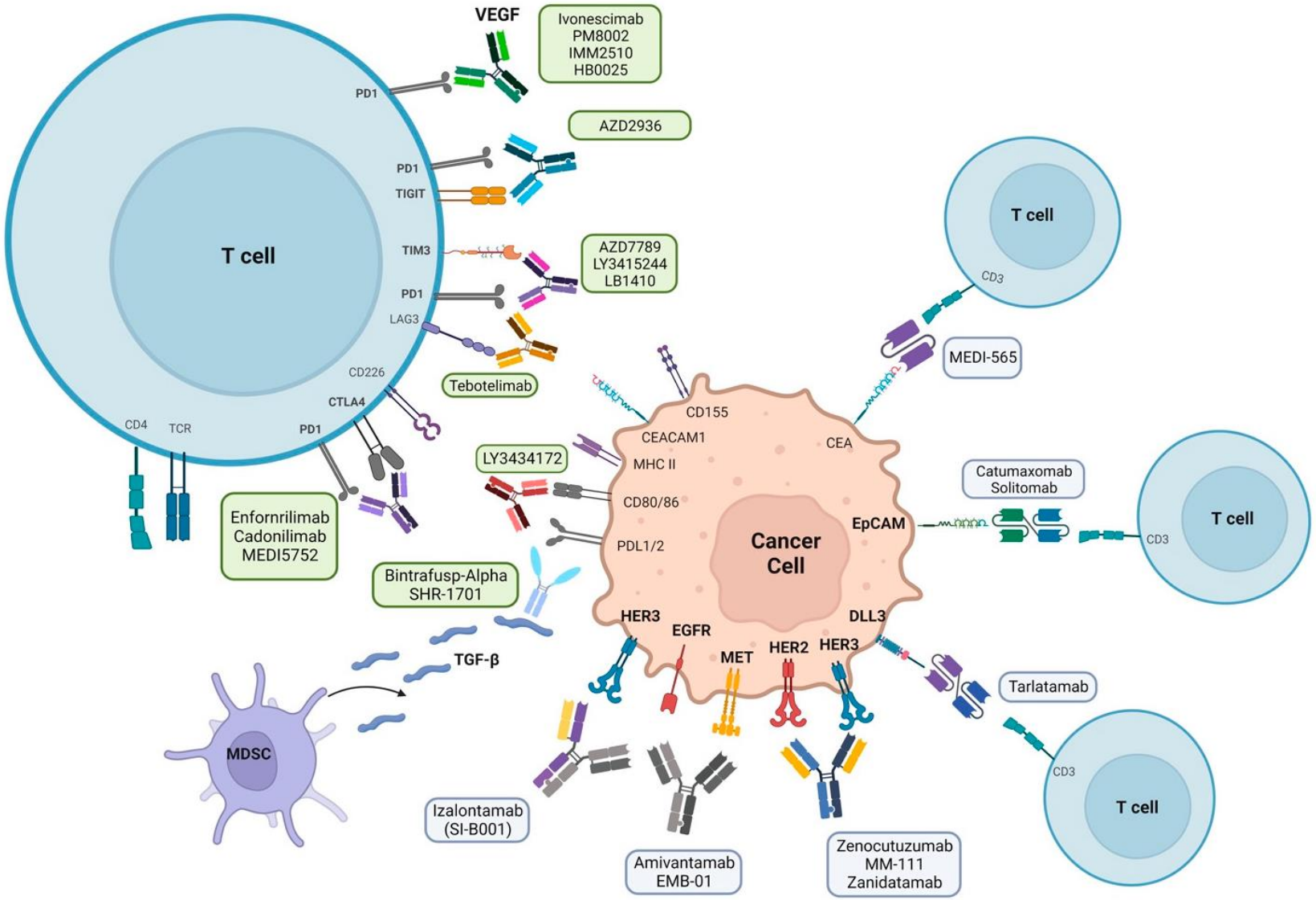
Exp Hematol Oncol. 2021/Pharmaceuticals 2023

Approved bsAbs in oncology

S No.	NCT	N	Phase	Target	Therapy	Trade Name	Indication	Approval Date	Approved by
1	NCT00836654	24	I/II	CD3/EpCAM	Catumaxomab	Removab	Malignant Ascites	April 2009	EMA
2	NCT01209286	36	II	CD3/CD19	Blinatumomab	Blincyto	Relapsed/Refractory B-cell ALL	December 2014	FDA
3	NCT02609776	362	I	MET/EGFR	Amivantamab	Rybrevant	EGFR Exon20ins NSCLC	May 2021	FDA
4	NCT03070392	378	II	CD3/TCR	Tebentafusp-tebn	Kimmtrak	Metastatic uveal melanoma	January 2022	FDA
5	NCT02500407	238	I/II	CD20/CD3	Mosunetuzumab	Lunsumio	Relapsed/Refractory B-cell lymphoma	June 2022	FDA
6	NCT04868708	45	I	PD-1/CTLA-4	Candonilimab		Recurrent/Metastatic cervical cancer	June 2022	NMPA
7	NCT03145181 NCT04557098	165	I/II	CD3/BCMA	Teclistamab-cqyv	Tecvayli	Relapsed/Refractory Multiple Myeloma	October 2022	FDA
8	NCT03625037	148	I/II	CD3/CD20	Epcoritamab-bysp	Epkinly	Relapsed/Refractory DLBCL	May 2023	FDA
9	NCT03075696	132	I/II	CD3/CD20	Glofitamab-gxbm	Columvi	Relapsed/Refractory DLBCL or large B-cell lymphoma	June 2023	FDA
10	NCT04649359	97	II	CD3/BCMA	Elranatamab-bcmm	Elrexfio	Relapsed/Refractory Multiple Myeloma	August 2023	FDA

Pharmaceuticals 2023

bsAbs and their target sites in lung cancer



Pharmaceuticals 2023

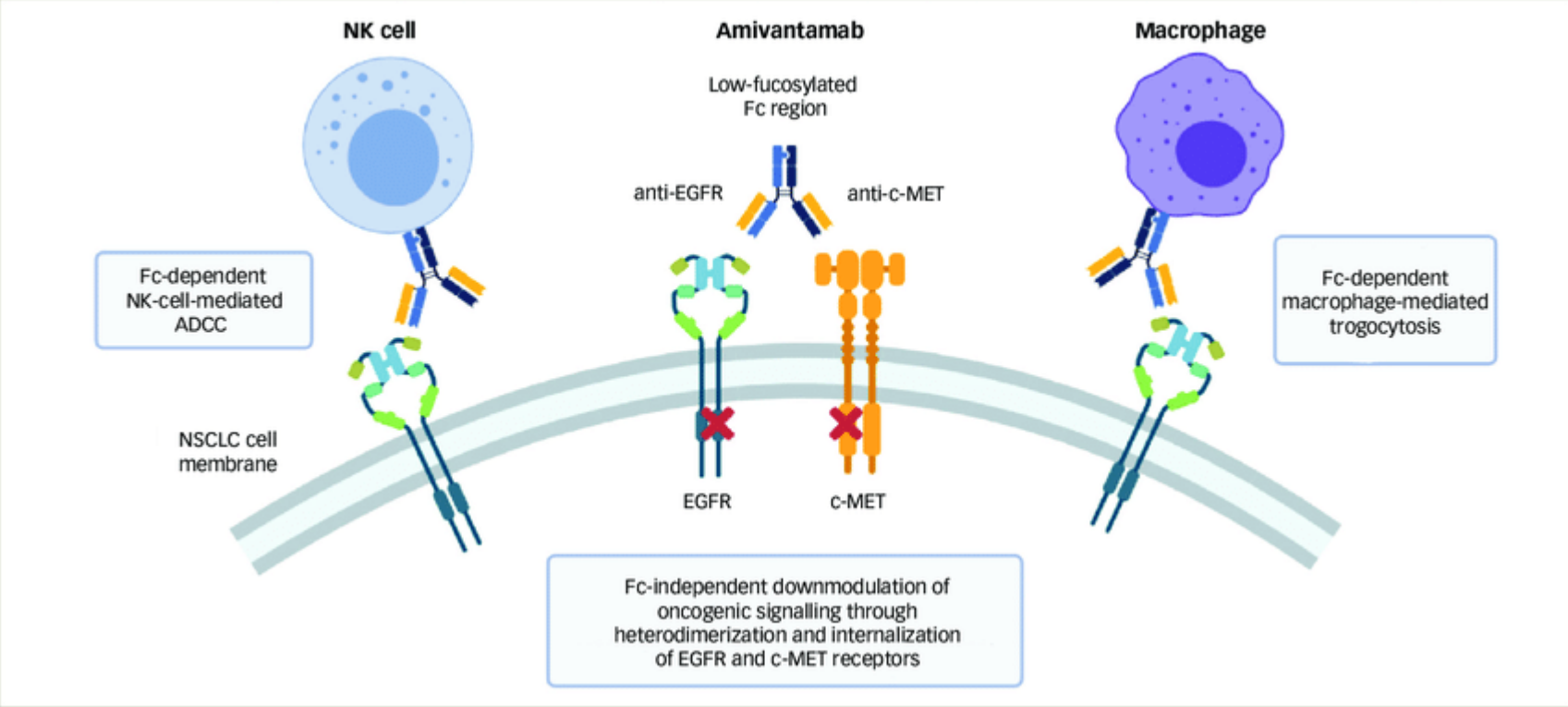
Clinical trials utilizing bsAbs in lung cancer

S No.	NCT	Study Name	Estimated Number	Phase	Target	Therapy [Platform]	Start Date	Completion Date
1	NCT02609776	CHRYSALIS	780	I	MET/EGFR	Amivantamab [Duobody]	May 2016	January 2024
2	NCT04606381	PALOMA	196	Ib	MET/EGFR	Amivantamab	November 2020	October 2024
3	NCT04077463	Chrysalis-2	460	I/Ib	MET/EGFR	Amivantamab + Lazertinib	September 2019	March 2026
4	NCT04538664	PAPILLON	308	III	MET/EGFR	Amivantamab + Carboplatin + Pemetrexed	October 2020	January 2025
5	NCT04487080	MARIPOSA	1074	III	MET/EGFR	Amivantamab + Lazertinib	September 2020	November 2025
6	NCT04521179	-	30	II	HER2	KN026 [Charge Repulsion Induced Bispecific]	December 2020	October 2023
7	NCT02912949	eNRGy	250	I/II	HER2/HER3	Zenocutuzumab (MCLA-128) [Biclonics]	January 2015	December 2024
8	NCT03821233	-	174	I	HER2	ZW49 [Azymetric]	April 2019	August 2025
9	NCT02892123	-	279	I	HER2	ZW25 (Zanidatamab) [Azymetric]	September 2016	August 2023
10	NCT03261011	-	153	1a/1b	PD-1/CTLA-4	Cadonilimab (AK104) [Tetrabody]	October 2017	September 2020
11	NCT04647344	-	60	Ib/II	PD-1/CTLA-4	Cadonilimab (AK104)	November 2020	April 2023
12	NCT04646330	-	114	Ib/II	PD-1/CTLA-4	Cadonilimab (AK104) + Anlotinib	November 2020	December 2023
13	NCT04544644	-	30	II	PD-1/CTLA-4	Cadonilimab (AK104) + Anlotinib	September 2020	September 2023
14	NCT03819465	MAGELLAN	258	Ib	PD-1/CTLA-4	MEDI5752 [Duetmab]	December 2018	March 2026
15	NCT03838848	-	120	II	PD-1/CTLA-4	KN046 [single-domain antibody]	May 2019	Terminated
16	NCT04054531	-	50	II	PD-1/CTLA-4	KN046 + Platinum chemotherapy	September 2019	June 2021
17	NCT04474119	ENREACH-L-01	482	III	PD-1/CTLA-4	KN046 + Paclitaxel + Carboplatin	September 2020	August 2023
18	NCT04900363	-	108	Ib/II	PD-1/VEGF	AK112 [Tetrabody]	May 2021	May 2024
19	NCT04995523	ARTEMIDE-01	192	I/II	PD-1/TIGIT	AZD2936	September 2021	July 2025
20	NCT04931654	-	81	I/IIa	PD-1/TIM-3	AZD7789	September 2021	July 2025
21	NCT02324257	-	149	I	CD3/CEA	RO6958688 [CrossMab]	December 2014	September 2019
22	NCT02650713	-	228	Ib	CD3/CEA	RO6958688 + Atezolizumab	January 2016	January 2020
23	NCT03337698	Morpheus Lung	435	Ib/II	CD3/CEA	RO6958688	January 2018	August 2025
24	NCT01221675	-	18	I/II	HSG/CEA	TF2 (IMP288)	June 2011	April 2016
25	NCT04822298	-	3	I	CD3/PSMA	Acapatamab (AMG160) [BiTE]	August 2021	January 2022
26	NCT04496674	-	86	I	CD3/PSMA	CC-1	February 2022	September 2025
27	NCT04750239	-	3	I/II	CD3/GD2	Nivatrotamab	August2021	April 2022

- Target sites in lung cancer
  - MET-targeted
  - DLL3-targeted
  - EpCAM
  - HER2/HER3
  - CEA
  - Immune-checkpoint
  - VEGF

Pharmaceuticals 2023

Amivantamab

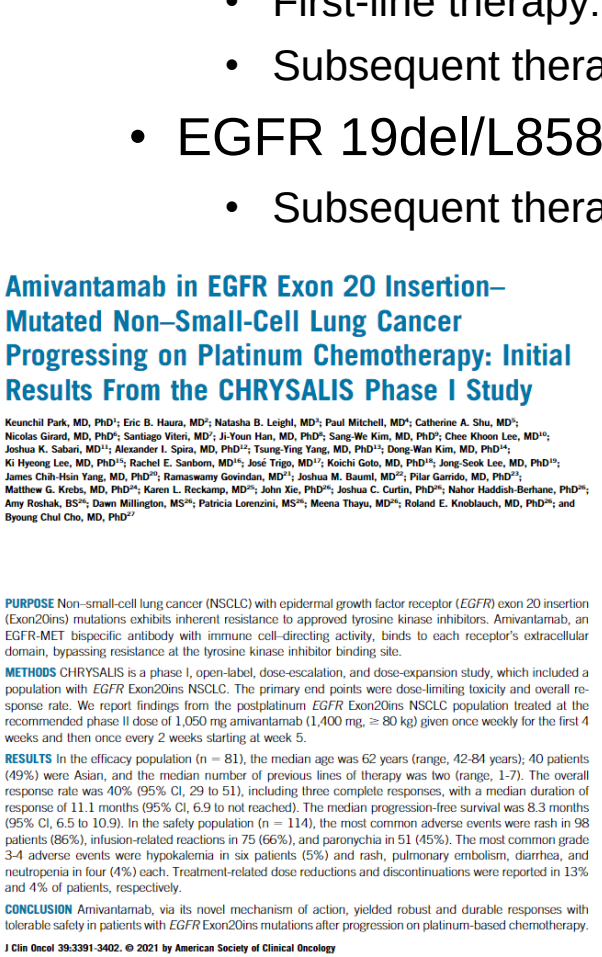


J Clin Oncol 2021

Amivantamab

부산대학교병원 Pusan National University Hospital

- NSCLC Ix
  - EGFR exon 20 insertion mutation
    - First-line therapy: Amivantamab+Carboplatin+Pemetraxed (nonsquamous) (Phase III PAPILLON study)
    - Subsequent therapy (Phase I CHRYSALIS study)
  - EGFR 19del/L858R mutation
    - Subsequent therapy: Amivantamab+Carboplatin+Pemetraxed (nonsquamous) (Phase III MARIPOSA-2 study)



Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Keunchil Park, MD, PhD[1]; Eric B. Haura, MD[2]; Natasha B. Leighl, MD[3]; Paul Mitchell, MD[4]; Catherine A. Shu, MD[5]; Nicolas Girard, MD, PhD[6]; Santiago Viteri, MD[7]; Ji-Youn Han, MD, PhD[8]; Sang-We Kim, MD, PhD[9]; Chee Khoon Lee, MD[10]; Joshua K. Sabari, MD[11]; Alexander I. Spira, MD, PhD[12]; Tsung-Ying Yang, MD, PhD[13]; Dong-Wan Kim, MD, PhD[14]; Ki Hyeong Lee, MD, PhD[15]; Rachel E. Sanborn, MD[16]; José Trigo, MD[17]; Koichi Goto, MD, PhD[18]; Jong-Seok Lee, MD, PhD[19]; James Chih-Hsin Yang, MD, PhD[20]; Ramaswamy Govindan, MD[21]; Joshua M. Bauml, MD[22]; Pilar Garrido, MD, PhD[23]; Matthew G. Krebs, MD, PhD[24]; Karen L. Reckamp, MD[25]; John Xie, PhD[26]; Joshua C. Curtin, PhD[26]; Nahor Haddish-Berhane, PhD[26]; Amy Roshak, BS[26]; Dawn Millington, MS[26]; Patricia Lorenzini, MS[26]; Meena Thayu, MD[26]; Roland E. Knoblauch, MD, PhD[26]; and Byoung Chul Cho, MD, PhD[27]

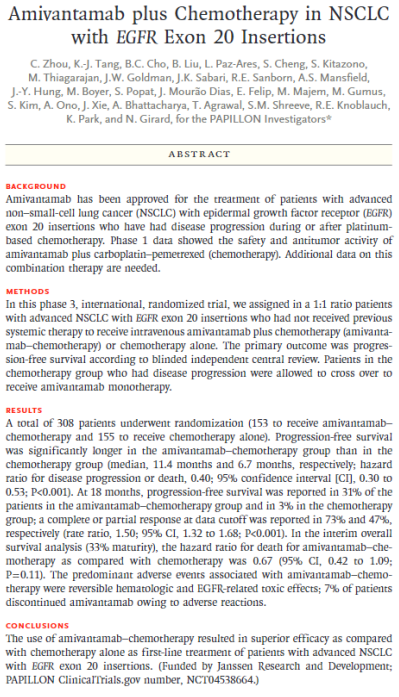
PURPOSE Non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertion (Exon20ins) mutations exhibits inherent resistance to approved tyrosine kinase inhibitors. Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, binds to each receptor's extracellular domain, bypassing resistance at the tyrosine kinase inhibitor binding site.

METHODS CHRYSALIS is a phase I, open-label, dose-escalation, and dose-expansion study, which included a population with *EGFR* Exon20ins NSCLC. The primary end points were dose-limiting toxicity and overall response rate. We report findings from the postplatinum *EGFR* Exon20ins NSCLC population treated at the recommended phase II dose of 1,050 mg amivantamab (1,400 mg, ≥ 80 kg) given once weekly for the first 4 weeks and then once every 2 weeks starting at week 5.

RESULTS In the efficacy population (n = 81), the median age was 62 years (range, 42-84 years); 40 patients (49%) were Asian, and the median number of previous lines of therapy was two (range, 1-7). The overall response rate was 40% (95% CI, 29 to 51), including three complete responses, with a median duration of response of 11.1 months (95% CI, 6.9 to not reached). The median progression-free survival was 8.3 months (95% CI, 6.5 to 10.9). In the safety population (n = 114), the most common adverse events were rash in 98 patients (86%), infusion-related reactions in 75 (66%), and paronychia in 51 (45%). The most common grade 3-4 adverse events were hypokalemia in six patients (5%) and rash, pulmonary embolism, diarrhea, and neutropenia in four (4%) each. Treatment-related dose reductions and discontinuations were reported in 13% and 4% of patients, respectively.

CONCLUSION Amivantamab, via its novel mechanism of action, yielded robust and durable responses with tolerable safety in patients with *EGFR* Exon20ins mutations after progression on platinum-based chemotherapy.

J Clin Oncol 39:3391-3402. © 2021 by American Society of Clinical Oncology



Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions

C. Zhou, K.-J. Tang, B.C. Cho, B. Liu, L. Paz-Ares, S. Cheng, S. Kitazono, M. Thiagarajan, J.W. Goldman, J.K. Sabari, R.E. Sanborn, A.S. Mansfield, J.-Y. Hung, M. Boyer, S. Popat, J. Mourão Dias, E. Felip, M. Majem, M. Gumus, S. Kim, A. Ono, J. Xie, A. Bhattacharya, T. Agrawal, S.M. Shreeve, R.E. Knoblauch, K. Park, and N. Girard, for the PAPILLON Investigators*

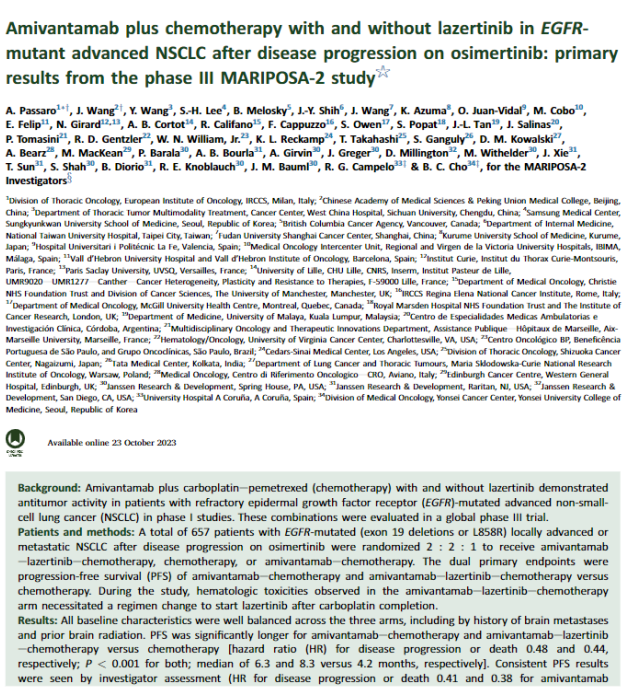
ABSTRACT

BACKGROUND
Amivantamab has been approved for the treatment of patients with advanced non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertions who have had disease progression during or after platinum-based chemotherapy. Phase 1 data showed the safety and antitumor activity of amivantamab plus carboplatin–pemetrexed (chemotherapy). Additional data on this combination therapy are needed.

METHODS
In this phase 3, international, randomized trial, we assigned in a 1:1 ratio patients with advanced NSCLC with *EGFR* exon 20 insertions who had not received previous systemic therapy to receive intravenous amivantamab plus chemotherapy (amivantamab–chemotherapy) or chemotherapy alone. The primary outcome was progression-free survival according to blinded independent central review. Patients in the chemotherapy group who had disease progression were allowed to cross over to receive amivantamab monotherapy.

RESULTS
A total of 308 patients underwent randomization (153 to receive amivantamab–chemotherapy and 155 to receive chemotherapy alone). Progression-free survival was significantly longer in the amivantamab–chemotherapy group than in the chemotherapy group (median, 11.4 months and 6.7 months, respectively; hazard ratio for disease progression or death, 0.40; 95% confidence interval [CI], 0.30 to 0.53; P<0.001). At 18 months, progression-free survival was reported in 31% of the patients in the amivantamab–chemotherapy group and in 3% in the chemotherapy group; a complete or partial response at data cutoff was reported in 73% and 47%, respectively (rate ratio, 1.50; 95% CI, 1.32 to 1.68; P<0.001). In the interim overall survival analysis (33% maturity), the hazard ratio for death for amivantamab–chemotherapy as compared with chemotherapy was 0.67 (95% CI, 0.42 to 1.09; P=0.11). The predominant adverse events associated with amivantamab–chemotherapy were reversible hematologic and EGFR-related toxic effects; 7% of patients discontinued amivantamab owing to adverse reactions.

CONCLUSIONS
The use of amivantamab–chemotherapy resulted in superior efficacy as compared with chemotherapy alone as first-line treatment of patients with advanced NSCLC with *EGFR* exon 20 insertions. (Funded by Janssen Research and Development; PAPILLON ClinicalTrials.gov number, NCT04538664.)



Amivantamab plus chemotherapy with and without lazertinib in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study☆

A. Passaro[1,*], J. Wang[2], Y. Wang[3], S.-H. Lee[4], B. Melosky[5], J.-Y. Shih[6], J. Wang[7], K. Azuma[8], O. Juan-Vidal[9], M. Cobo[10], E. Felip[11], N. Girard[12,13], A. B. Cortot[14], R. Califano[15], F. Cappuzzo[16], S. Owen[17], S. Popat[18], J.-L. Tan[19], J. Salinas[20], P. Tomasini[21], R. D. Gentzler[22], W. N. William, Jr.[23], K. L. Reckamp[24], T. Takahashi[25], S. Ganguly[26], D. M. Kowalski[27], A. Bearz[28], M. MacKean[29], P. Barala[30], A. B. Bourla[31], A. Girvin[30], J. Greger[30], D. Millington[32], M. Withelder[30], J. Xie[31], T. Sun[31], S. Shah[30], B. Diorio[31], R. E. Knoblauch[30], J. M. Bauml[33], R. G. Campelo[33] & B. C. Cho[34], for the MARIPOSA-2 Investigators[3]

[1]Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [2]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [3]Department of Thoracic Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]British Columbia Cancer Agency, Vancouver, Canada; [6]Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan; [7]Fudan University Shanghai Cancer Center, Shanghai, China; [8]Kurume University School of Medicine, Kurume, Japan; [9]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [11]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France; [13]Paris Saclay University, UVSQ, Versailles, France; [14]University of Lille, CHU Lille, CNRS, Inserm, Institut Pasteur de Lille, UMR9020 – UMR1277 – Canther – Cancer Heterogeneity, Plasticity and Resistance to Therapies, F-59000 Lille, France; [15]Department of Medical Oncology, Christie NHS Foundation Trust and Division of Cancer Sciences, The University of Manchester, Manchester, UK; [16]IRCCS Regina Elena National Cancer Institute, Rome, Italy; [17]Department of Medical Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [18]Royal Marsden Hospital NHS Foundation Trust and The Institute of Cancer Research, London, UK; [19]Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [20]Centro de Especialidades Medicas Ambulatorias e Investigación Clínica, Córdoba, Argentina; [21]Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique – Hôpitaux de Marseille, Aix-Marseille University, Marseille, France; [22]Hematology/Oncology, University of Virginia Cancer Center, Charlottesville, VA, USA; [23]Centro Oncológico BP, Beneficência Portuguesa de São Paulo, and Grupo Oncoclínicas, São Paulo, Brazil; [24]Cedars-Sinai Medical Center, Los Angeles, USA; [25]Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi, Japan; [26]Tata Medical Center, Kolkata, India; [27]Department of Lung Cancer and Thoracic Tumours, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [28]Medical Oncology, Centro di Riferimento Oncologico – CRO, Aviano, Italy; [29]Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK; [30]Janssen Research & Development, Spring House, PA, USA; [31]Janssen Research & Development, Raritan, NJ, USA; [32]Janssen Research & Development, San Diego, CA, USA; [33]University Hospital A Coruña, A Coruña, Spain; [34]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

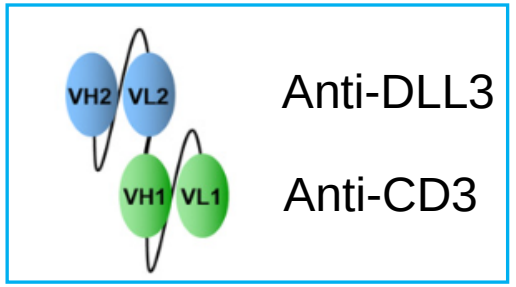
Available online 23 October 2023

Background: Amivantamab plus carboplatin–pemetrexed (chemotherapy) with and without lazertinib demonstrated antitumor activity in patients with refractory epidermal growth factor receptor (*EGFR*)-mutated advanced non-small-cell lung cancer (NSCLC) in phase I studies. These combinations were evaluated in a global phase III trial.
Patients and methods: A total of 657 patients with *EGFR*-mutated (exon 19 deletions or L858R) locally advanced or metastatic NSCLC after disease progression on osimertinib were randomized 2 : 2 : 1 to receive amivantamab –lazertinib–chemotherapy, chemotherapy, or amivantamab–chemotherapy. The dual primary endpoints were progression-free survival (PFS) of amivantamab–chemotherapy and amivantamab–lazertinib–chemotherapy versus chemotherapy. During the study, hematologic toxicities observed in the amivantamab–lazertinib–chemotherapy arm necessitated a regimen change to start lazertinib after carboplatin completion.
Results: All baseline characteristics were well balanced across the three arms, including by history of brain metastases and prior brain radiation. PFS was significantly longer for amivantamab–chemotherapy and amivantamab–lazertinib –chemotherapy versus chemotherapy [hazard ratio (HR) for disease progression or death 0.48 and 0.44, respectively; $P < 0.001$ for both; median of 6.3 and 8.3 versus 4.2 months, respectively]. Consistent PFS results were seen by investigator assessment (HR for disease progression or death 0.41 and 0.38 for amivantamab

Ann Oncol 2023;S0923-7534:04281-04283.
N Engl J Med 2023;389:2039-2051.
J Clin Oncol 2021;39:3391-3402.

Tarlatamab

- bispecific T-cell engager(HLE BiTE) molecule
  - binds both DLL3 on cancer cells and CD3 on T cells → T-cell–mediated tumor lysis
  - Phase 1 DeLLphi-300, phase 2 DeLLphi-301, phase 3 DeLLphi-304 study



Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study

Luis Paz-Ares, MD, PhD[1]; Stephane Champiat, MD, PhD[2]; W. Victoria Lai, MD[3]; Hiroki Izumi, MD, PhD[4]; Ramaswamy Govindan, MD[5]; Michael Boyer, MB, BS, PhD[6]; Horst-Dieter Hummel, MD[7]; Hossein Borghaei, DO[8]; Melissa L. Johnson, MD[9]; Neeltje Steeghs, MD, PhD[10]; Fiona Blackhall, MD, PhD[11]; Afshin Dowlati, MD[12]; Noemi Reguart, MD, PhD[13]; Tatsuya Yoshida, MD, PhD[14]; Kai He, MD, PhD[15]; Shirish M. Gadgeel, MD[16]; Enriqueta Felip, MD, PhD[17]; Yiran Zhang, PhD[18]; Amrita Pati, PhD[18]; Mukul Minocha, PhD[18]; Sujoy Mukherjee, MD[18]; Amanda Goldrick, MD[18]; Dirk Nagorsen, MD, PhD[18]; Nooshin Hashemi Sadraei, MD[18]; and Taofeek K. Owonikoko, MD, PhD[19]

PURPOSE Small-cell lung cancer (SCLC) is an aggressive malignancy with limited treatments. Delta-like ligand 3 (DLL3) is aberrantly expressed in most SCLC. Tarlatamab (AMG 757), a bispecific T-cell engager molecule, binds both DLL3 and CD3 leading to T-cell–mediated tumor lysis. Herein, we report phase I results of tarlatamab in patients with SCLC.

PATIENTS AND METHODS This study evaluated tarlatamab in patients with relapsed/refractory SCLC. The primary end point was safety. Secondary end points included antitumor activity by modified RECIST 1.1, overall survival, and pharmacokinetics.

RESULTS By July 19, 2022, 107 patients received tarlatamab in dose exploration (0.003 to 100 mg; n = 73) and expansion (100 mg; n = 34) cohorts. Median prior lines of anticancer therapy were 2 (range, 1-6); 49.5% received antiprogrammed death-1/programmed death ligand-1 therapy. Any-grade treatment-related adverse events occurred in 97 patients (90.7%) and grade ≥ 3 in 33 patients (30.8%). One patient (1%) had grade 5 pneumonitis. Cytokine release syndrome was the most common treatment-related adverse event, occurring in 56 patients (52%) including grade 3 in one patient (1%). Maximum tolerated dose was not reached. Objective response rate was 23.4% (95% CI, 15.7 to 32.5) including two complete and 23 partial responses. The median duration of response was 12.3 months (95% CI, 6.6 to 14.9). The disease control rate was 51.4% (95% CI, 41.5 to 61.2). The median progression-free survival and overall survival were 3.7 months (95% CI, 2.1 to 5.4) and 13.2 months (95% CI, 10.5 to not reached), respectively. Exploratory analysis suggests that selecting for increased DLL3 expression can result in increased clinical benefit.

CONCLUSION In patients with heavily pretreated SCLC, tarlatamab demonstrated manageable safety with encouraging response durability. Further evaluation of this promising molecule is ongoing.

J Clin Oncol 41:2893-2903. © 2023 by American Society of Clinical Oncology

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND
Tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3 and CD3, showed promising antitumor activity in a phase 1 trial in patients with previously treated small-cell lung cancer.

METHODS
In this phase 2 trial, we evaluated the antitumor activity and safety of tarlatamab, administered intravenously every 2 weeks at a dose of 10 mg or 100 mg, in patients with previously treated small-cell lung cancer. The primary end point was objective response (complete or partial response), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

RESULTS
Overall, 220 patients received tarlatamab; patients had previously received a median of two lines of treatment. Among patients evaluated for antitumor activity and survival, the median follow-up was 10.6 months in the 10-mg group and 10.3 months in the 100-mg group. An objective response occurred in 40% (97.5% confidence interval [CI], 29 to 52) of the patients in the 10-mg group and in 32% (97.5% CI, 21 to 44) of those in the 100-mg group. Among patients with an objective response, the duration of response was at least 6 months in 59% (40 of 68 patients). Objective responses at the time of data cutoff were ongoing in 22 of 40 patients (55%) in the 10-mg group and in 16 of 28 patients (57%) in the 100-mg group. The median progression-free survival was 4.9 months (95% CI, 2.9 to 6.7) in the 10-mg group and 3.9 months (95% CI, 2.6 to 4.4) in the 100-mg group; the estimates of overall survival at 9 months were 68% and 66% of patients, respectively. The most common adverse events were cytokine-release syndrome (in 51% of the patients in the 10-mg group and in 61% of those in the 100-mg group), decreased appetite (in 29% and 44%, respectively), and pyrexia (in 35% and 33%). Cytokine-release syndrome occurred primarily during treatment cycle 1, and events in most of the patients were grade 1 or 2 in severity. Grade 3 cytokine-release syndrome occurred less frequently in the 10-mg group (in 1% of the patients) than in the 100-mg group (in 6%). A low percentage of patients (3%) discontinued tarlatamab because of treatment-related adverse events.

CONCLUSIONS
Tarlatamab, administered as a 10-mg dose every 2 weeks, showed antitumor activity with durable objective responses and promising survival outcomes in patients with previously treated small-cell lung cancer. No new safety signals were identified. (Funded by Amgen; DeLLphi-301 ClinicalTrials.gov number, NCT05060016.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Paz-Ares can be contacted at lpazaresr@seom.org or at Hospital Universitario 12 de Octubre, CNIO-H12o Lung Cancer Unit, Complutense University and Ciberonc, Av de Andalucia s/n, 28041 Madrid, Spain.

*A list of the DeLLphi-301 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 20, 2023, at NEJM.org.

N Engl J Med 2023;389:2063-75.
DOI: 10.1056/NEJMoa2307980

Randomized phase 3 study of tarlatamab, a DLL3-targeting bispecific T-cell engager (BiTE), compared to standard of care in patients with relapsed small cell lung cancer (DeLLphi-304).

J Clin Oncol 2023;41:2893-903..
N Engl J Med 2023; 389:2063-2075.

Adverse effects of bsAbs

- Most frequent AEs

  : fever, fatigue, nausea, abdominal pain, elevated liver enzyme, leukopenia

- AEs commonly associated with T-cell immunotherapies

  : cytokine-release syndrome (CRS), immune-cell associated neurotoxicity syndrome (ICANS)

Experimental Hematology & Oncology 2021
Frontiers in immunology 2021

Adverse effects of bsAbs (CRS)

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- **Cytokine release syndrome (CRS)**
  - Caused by massive cytokine levels and T cell expansion
  - Overshooting systemic inflammatory response with a wild range of symptoms

    : mild, flu-like symptoms ~ severe anaphylactic shock with a life-threatening presentation

    : cytopenia, elevated liver enzymes, dysregulation of coagulation parameters and elevated ferritin
  - Most efficient approach for controlling CRS

    : Dose escalation + Pretreatment with corticosteroid
  - Anti-IL6 receptor antagonist

Experimental Hematology & Oncology 2021
Frontiers in immunology 2021

Adverse effects of bsAbs (ICANS)

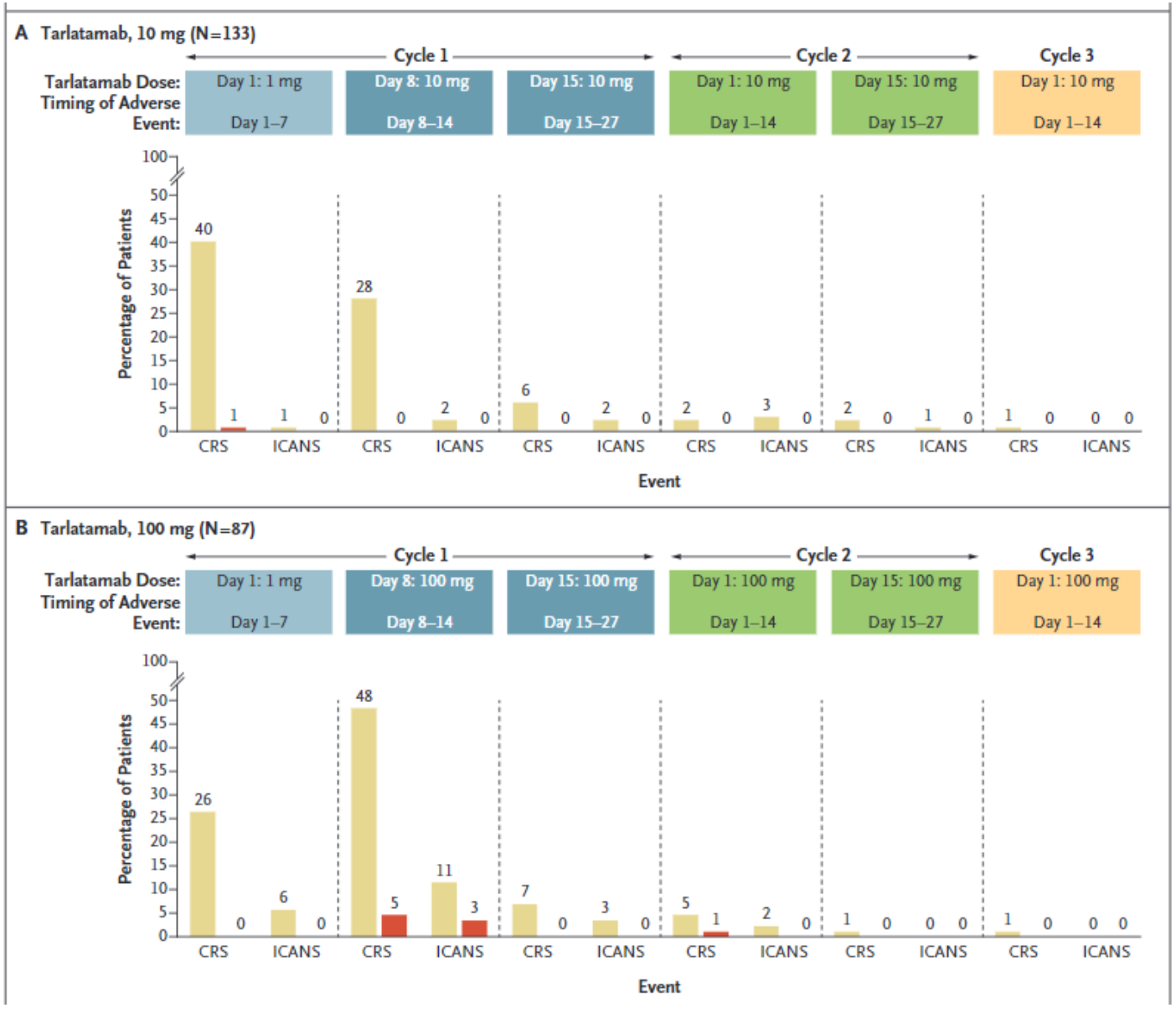
부산대학교병원 Pusan National University Hospital

- **Immune-cell associated neurotoxicity syndrome (ICANS)**

ICANS Grade	Management
Grade 1	Consider levetiracetam seizure prophylaxis (750 mg BD) Avoid medications that cause central nervous system depression Seek neurology specialist consultation Supportive care Fundoscopic examination to assess for papilloedema Brain MRI with contrast (brain CT if brain MRI is not feasible) Consider diagnostic lumbar puncture with measurement of opening pressure where possible, sending samples for culture and sensitivity, cytology, biochemistry, and virology as a minimum Consider spine MRI if the patient has focal peripheral neurological deficits Consider electroencephalogram (EEG) Consider tocilizumab 8 mg/kg but only if concurrent CRS Twice daily neurocognitive assessment using the ICE score and ICANS grading
Grade 2	Investigations and supportive care as per grade 1 Consider dexamethasone at a high dose with rapid weaning Consider transferring the patient to the intensive care unit (ICU)
Grade 3	Investigations and supportive care as per grade 1 Administer dexamethasone 10–20 mg IV every 6 h or methylprednisolone equivalent until improvement to grade 1 and then taper Management of seizures with lorazepam 0.5 mg IV or other benzodiazepines as needed, followed by loading with levetiracetam or other anticonvulsants as required If fundoscopy reveals stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure > 20 mmHg, seek urgent advice from neurologist Consider repeat neuroimaging (CT or MRI) every 2–3 days if the patient has persistent grade ≥ 3 ICANS
Grade 4	Investigations and supportive care as per grade 1 Transfer patient to intensive care unit (ICU); consider mechanical ventilation for airway protection Seizure management as per grade 3 For convulsive status epilepticus, seek urgent advice from neurologist Administer methylprednisolone 1000 mg/day for 3 days, then taper at 250 mg every 12 hrs for 2 days, then 125 mg every 12 hrs for 2 days, then 60 mg every 12 hrs for 2 days For management of raised intracranial pressure, consider acetazolamide 1000 mg IV, followed by 250–1000 mg IV every 12 h; elevating the head of the bed; hyperventilation; and hyperosmolar therapy with mannitol

Front Immunol 2022

CRS and ICANS from clinical study



N Engl J Med 2023; 389:2063-2075.

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04

Summary

Summary (1)

- Antibody-drug conjugate (ADC) and Bispecific antibody (bsAb) are the most prominent formats of therapeutic antibodies
- FDA-approved ADCs/BsAbs in lung cancer
  - Trastuzumab deruxtecan (T-DXd)
  - Patritumab deruxtecan (HER3-Dxd), telisotuzumab vedotin (Teliso-V): FDA Breakthrough Therapy Designation and are currently under evaluation
  - Amivantamab is the only bispecific antibody approved by the FDA
- Hundreds of ADCs/BsAbs in preclinical and clinical development across tumor types

Summary (2)

- Challenges
  - Off-target binding, manufacturing difficulties, low efficacy, immunogenicity, cost, resistance mechanisms, AEs
- Treatment-related AEs
  - Despite their ideally targeted mechanism of action, most therapeutic antibodies still confer frequent and sometimes life-threatening toxicities
  - AEs commonly associated with T-cell immunotherapies (bsABs)

  : CRS, ICANS

  → Awareness of these adverse events and their management is crucial

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Thank you for your attention

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