MaTOS™
Masters in Thoracic Oncology Summit
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Updates in Bispecific Antibodies in NSCLC (bsAB)

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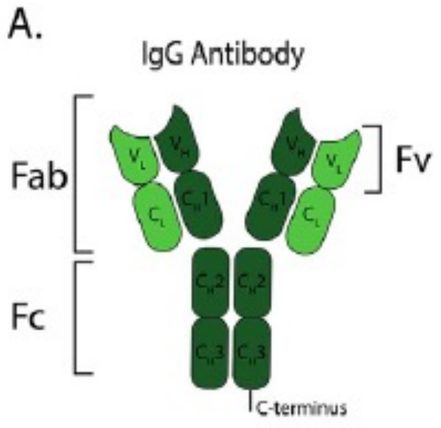
Human Antibody refresher

- Standard human antibodies are monospecific and bivalent. Both binding sites are directed against the same target and each antibody has two binding sites.



- The antibody exists of two heavy chains (V_H and C_H) and two light chains (V_L and C_L).
- Each heavy chain has four domains, and each light chain has two domains.
- These chains can be subdivided by variable (V_H and V_L) and constant domains (C_H and C_L).
- Fab Region
  - The binding part of the Fab region is called the single chain variable fragment (scFv).
- Fc Region
  - mediates the effector functions that lead to immune-mediated target-cell killing
- Two parts connect at hinge region
  - variability in those connections gives rise to IgG antibody subtypes

Suurs et al, Pharmacology and therapeutics 2019

Historical perspective

- The first monoclonal antibody Muromonab-CD3 was approved in 1986 for prophylactic use in cardiac transplantation.
- Multiple monoclonal antibodies for cancer followed
  - thoracic oncology: bevacizumab, cetuximab first to be approved
- Acquired resistance to monoclonal antibodies is common.
  - altered antigen expression or binding
  - impaired complement-mediated cytotoxicity (CMC) or antibody-dependent cellular cytotoxicity (ADCC)
  - altered intracellular signaling effects
  - inhibition of direct induction of cell death.
- Bispecific antibodies were initially developed to overcome resistance.
  - the binding sites are directed to different targets
- In thoracic oncology amivantamab is the only bsAb approved by FDA

Torka et al Current Hematologic Malignancy Reports (2019) 14:426–438

Factors influencing effects of bsAb constructs

Biological rationale

- Biological targets and its modes of action (TAA, TSA, immune cell binding)
- Target binding properties (affinity)

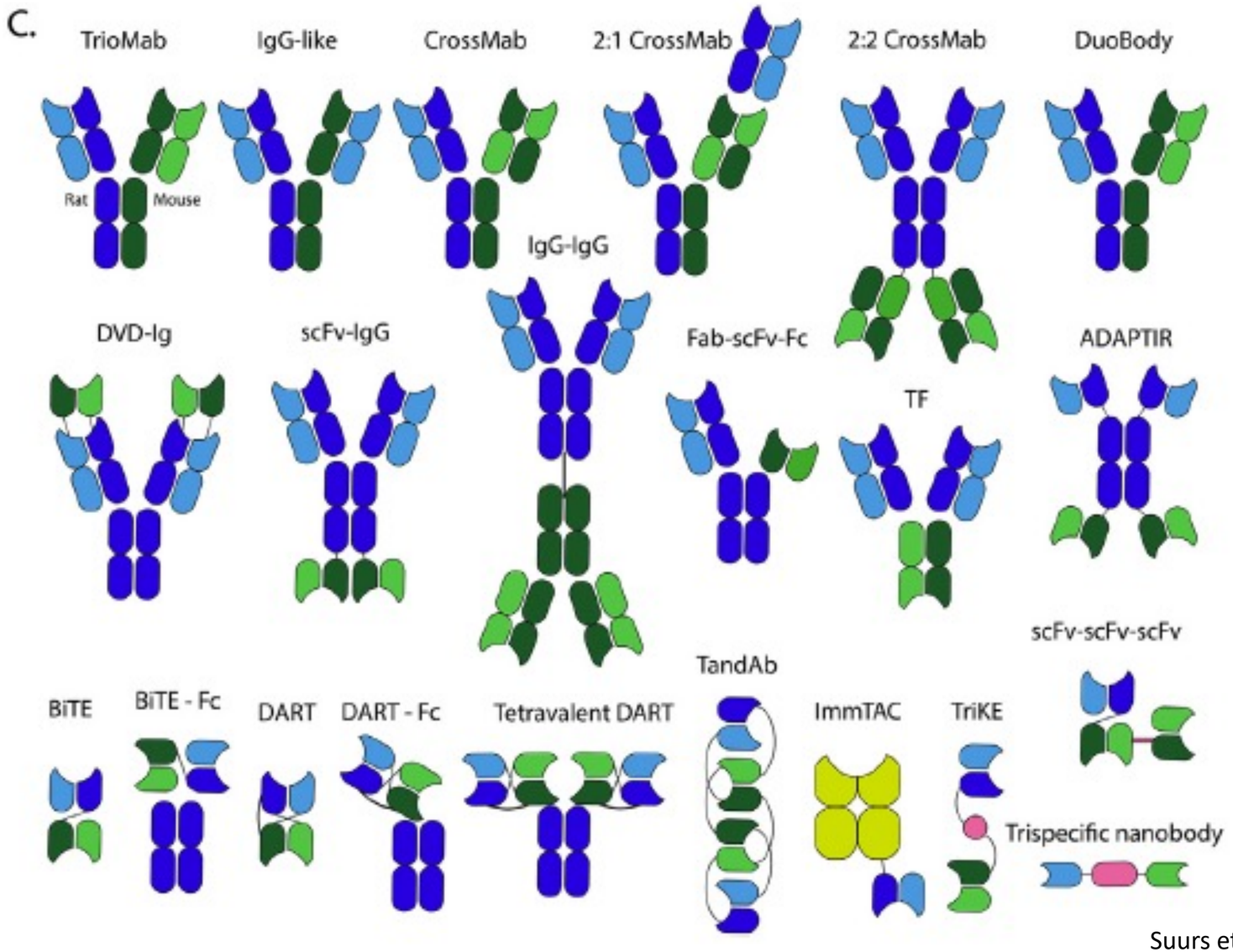
Bispecific format

- Size, binding valency
- Manufacturability

Fc domain (IgG based antibodies)

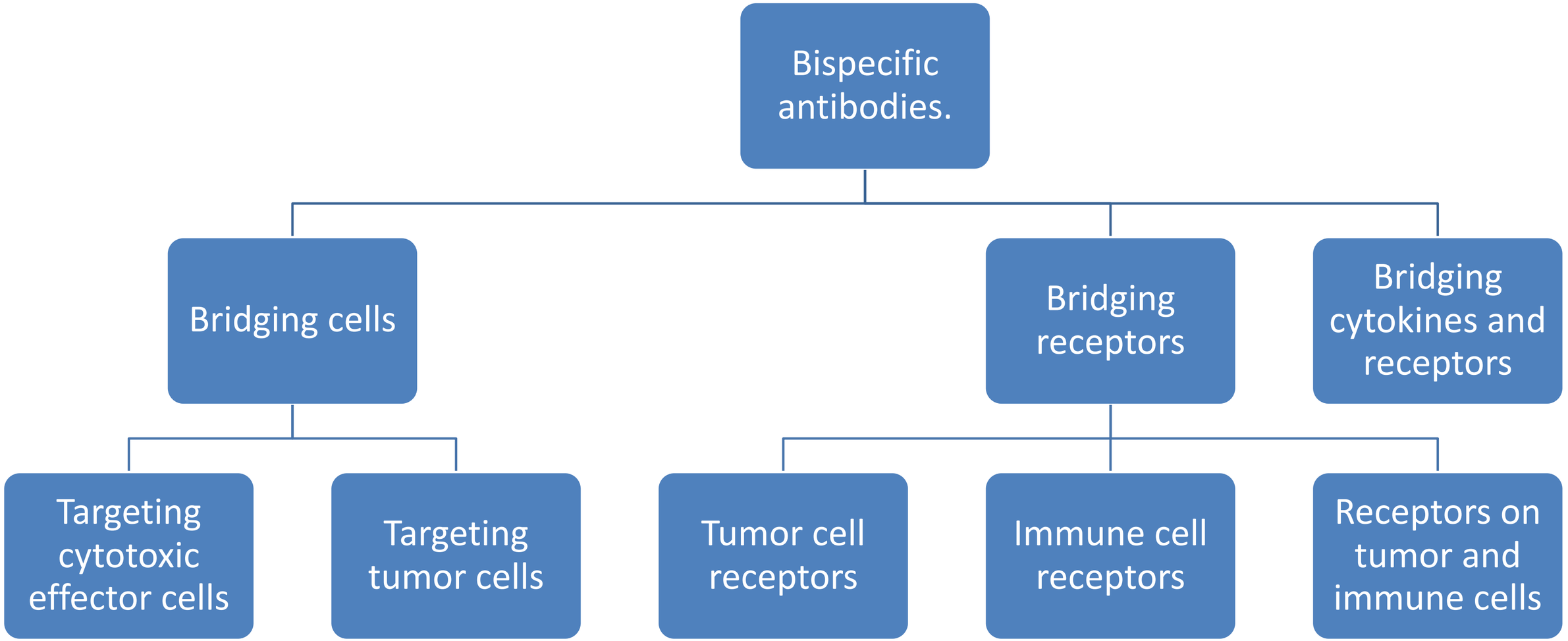
- Sustained circulation half life
- Added effector functions (ADCC, CDC)
- Poor tumor penetration
- High cost
- Chain association issue

bsAb constructs currently approved or in clinical trials

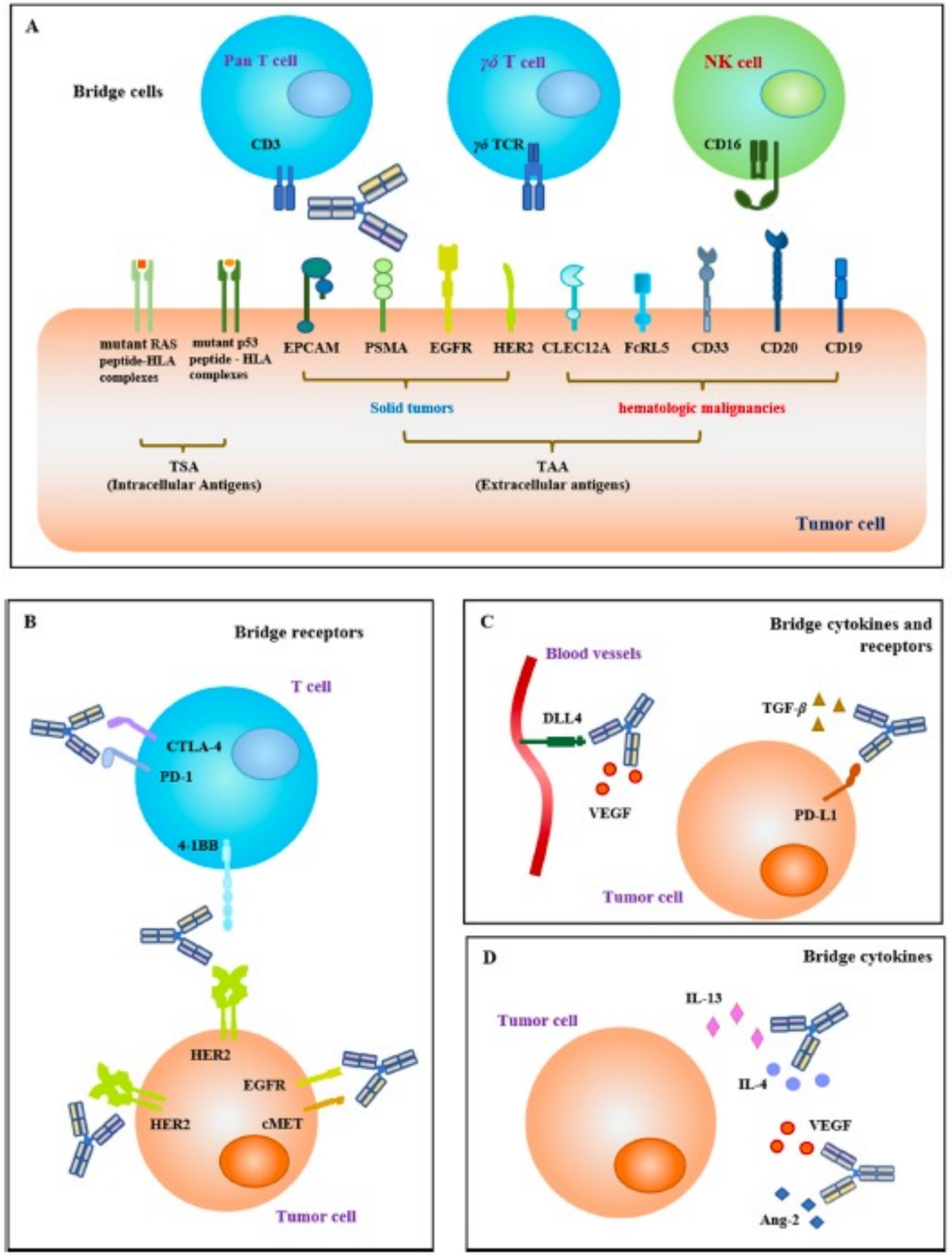


Suurs et al, Pharmacology and therapeutics 2019

Types of bsAb



bsAb classification



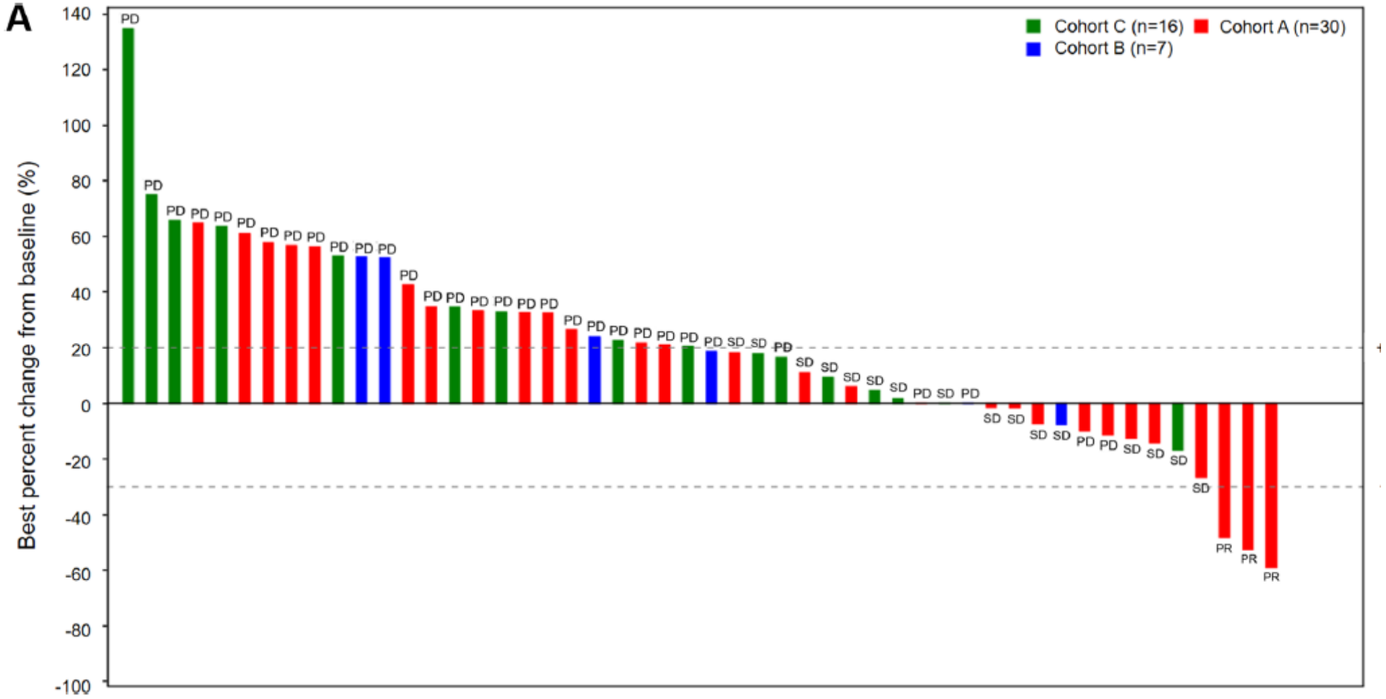
sun et al *Acta Pharmaceutica Sinica B 2023;13(9):3583e3597*

Bispecific Ab in Thoracic Oncology

Classification		Name	FDA approval	Proposed indication	Clinical trial
Bridging receptors on tumor cells	EGFR + MET	amivantamab	EGFR ex 20 insertion	EGFR sensitizing mutation	
Bridging receptors on tumor cells	HER2 + HER3	zenocutuzimab		NRG1 fusion positive	NCT02912949
Bridging cytokines and receptors	VEGF+ PD-L1	Ivonescimab		Advances NSCLC	*NCT04900363*
Bridging immune cells and tumor cells	DLL3 + Cd3	Tarlatamab (AMG 757)		ED SCLC	NCT05060016
Bridging receptors in immune cells	PD-L1 + TIGIT	Rilvegostomic (AZD 2936)		Advanced NSCLC	NCT04995523
Bridging receptors on Immune cells	PD-L1 + CTLA3	Cadonilimab		Advanced NSCLC	NCT04172454

Cadonilimab (AK104) PD-L1/CTLA4) bispecific antibody

- Bispecific IgG-single-chain Fv fragment (ScFv) antibody that binds to PD-1 and CTLA-4.
- Phase 1b/II trial. China. 2L+ post platinum doublet.
  - Cohort A IO naïve
  - Cohort B primary IO resistance (terminated due to lack of efficacy)
  - Cohort C quired IO resistance (terminated due to lack of efficacy)



Cohort A N=30
PD-L < 1% 17 (56.7)
PD-L1 1-49 9 (30.0)
PD-L1 > 50 4 (13.3)

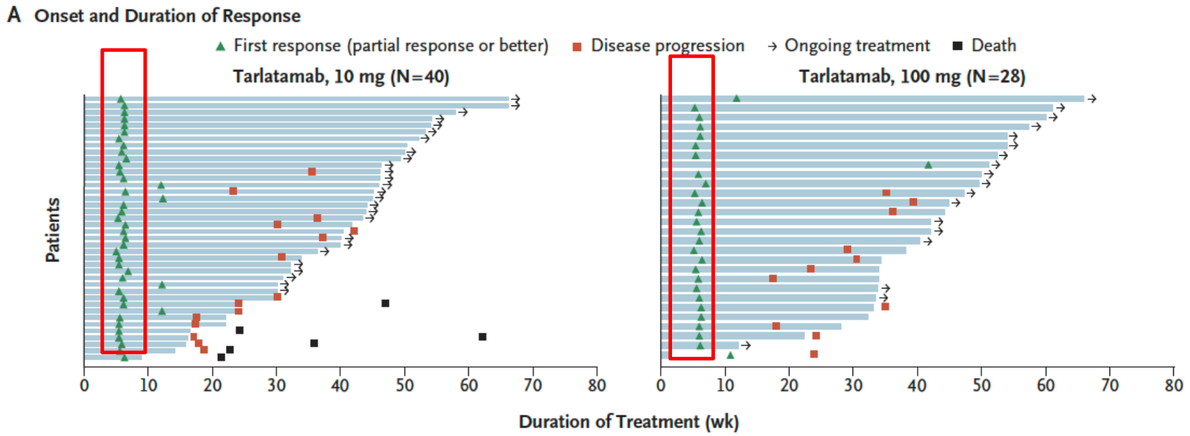
ORR 10.0% (95% CI 2.1–26.5)
mOS 19.6 months (95% CI 11.3-not reached)
mPFS 1.9 months (95% CI 1.84–3.65),

No unexpected toxicities.
study did not meet it's primary end point
.

Zhao et al *Lung Cancer 184 (2023) 107355*

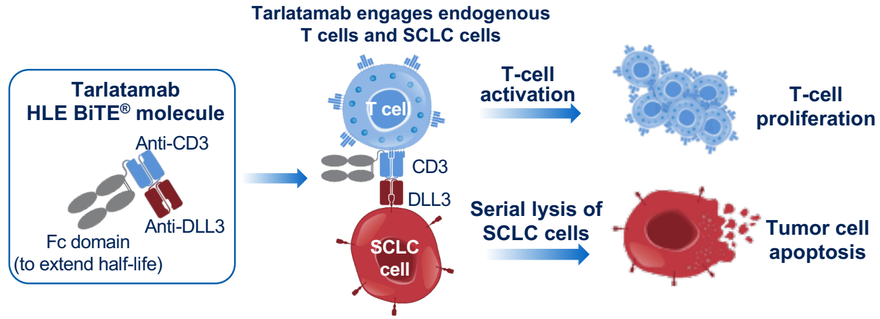
Tarlatamab (AMG 737). Phase II DeLLphi-301 NCT05060016

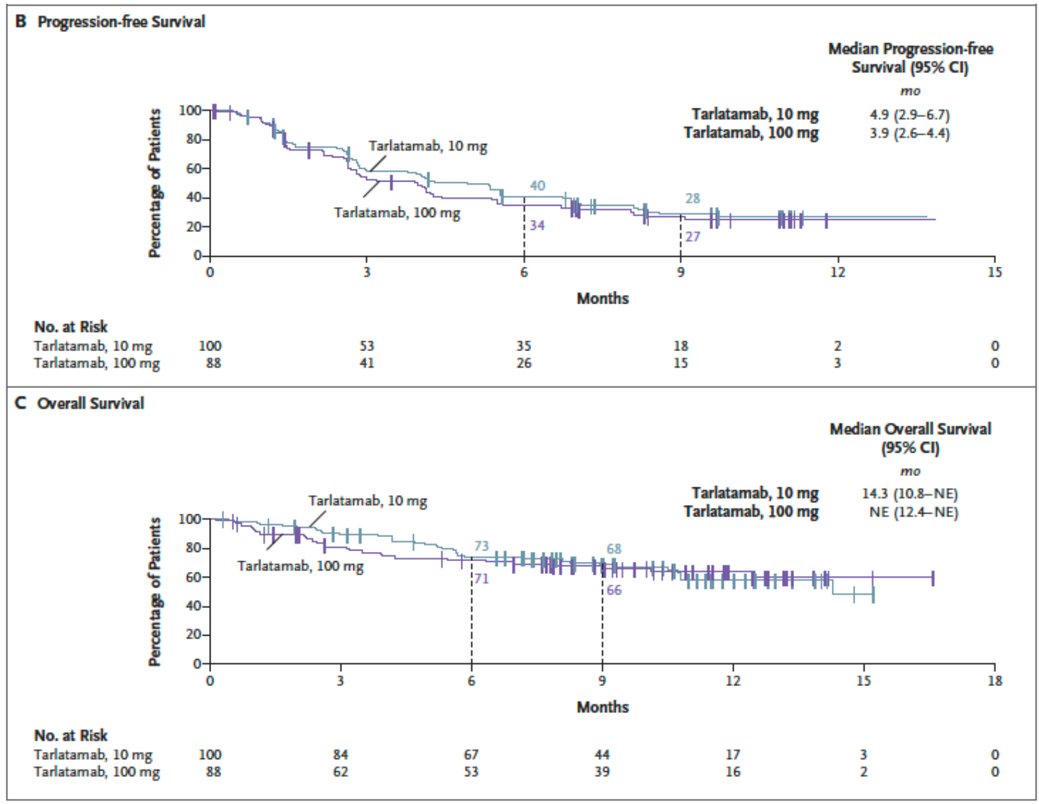
- Tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3 and CD3
- Directs the patient's T cells to cancer cells expressing delta-like ligand 3 (DLL3), independent of major histocompatibility complex (MHC) class I leading to T-cell–mediated lysis of cancer cells.
  - DLL3 is expressed in 85 to 94% of patients with small-cell lung cancer
- Phase II trial in previously treated SCLC. Two or more lines of therapy. Two doses 10 mg and 100 mg. N 220
  - 73 and 82% PD-L1 pretreated
  - 33 and 36% 3 or more lines of therapy



ORR (IRC)

- 40% (97.5% CI, 29 to 52) in the 10-mg group
- 32% (97.5% CI, 21 to 44) in the 100-mg group
- mDOR NE





Owonikoko TK et al. ASCO 2021, Abstract 8510
M.-J. Ahn, et al NEJM 2023

Toxicity

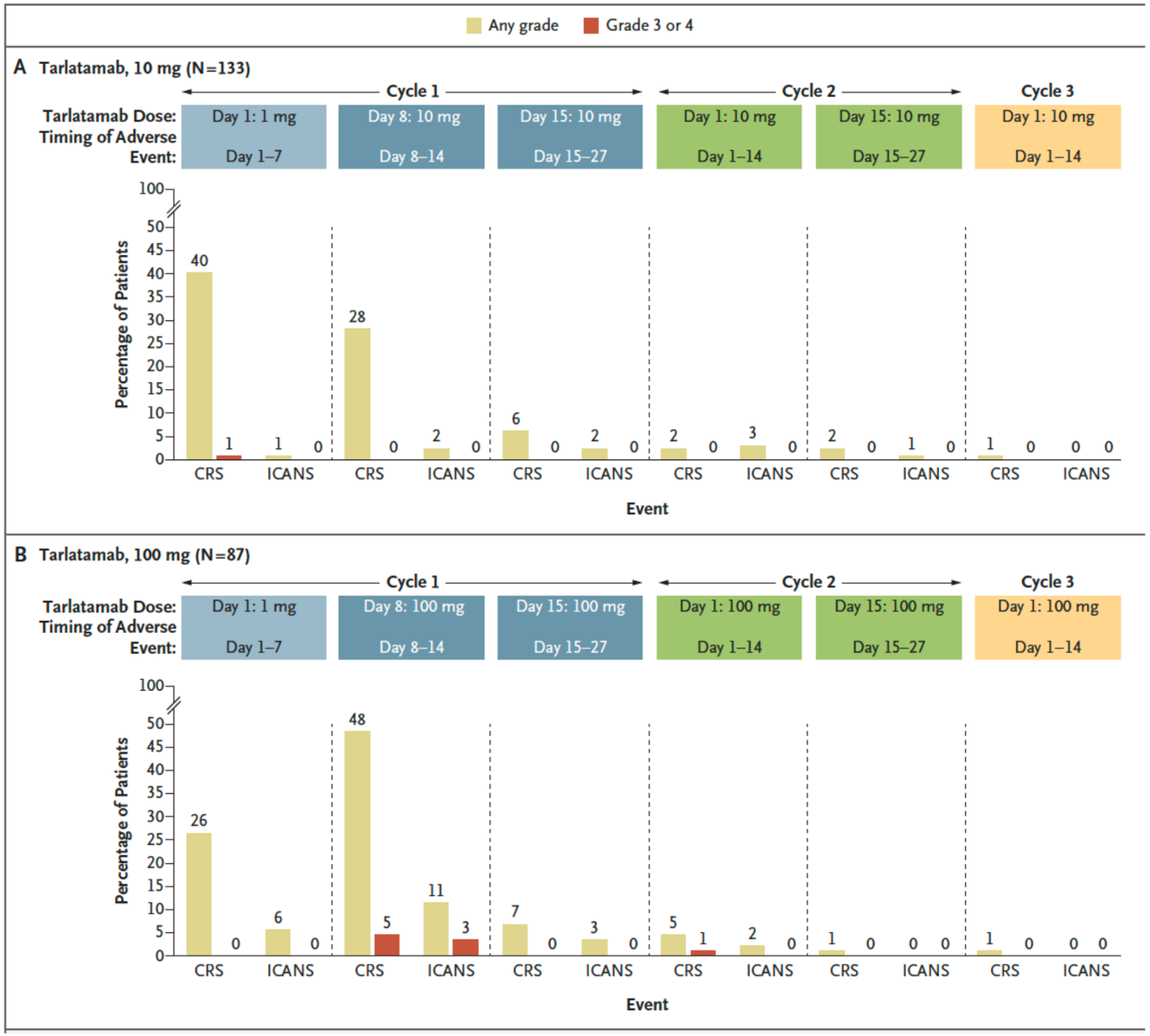


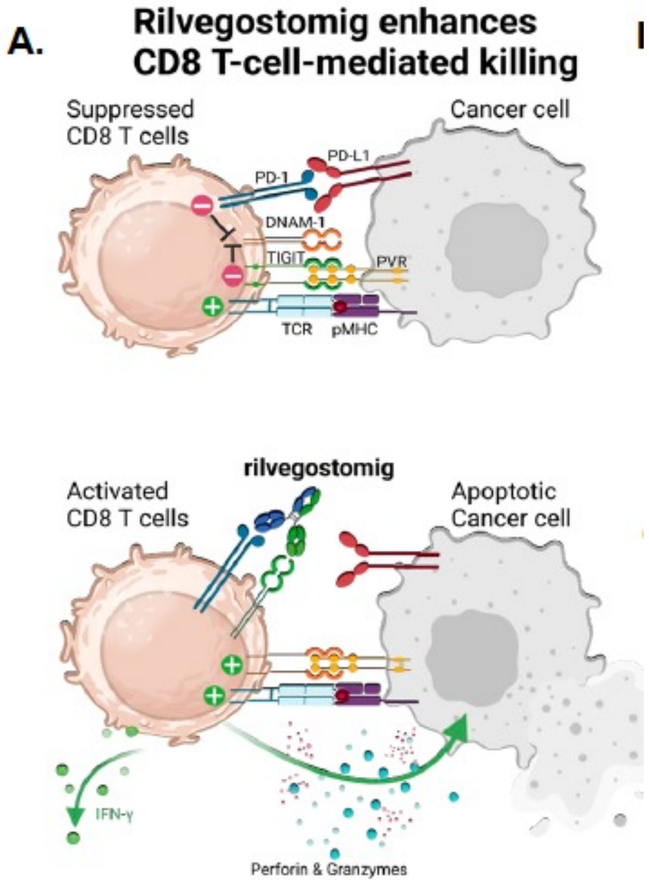
Table 3. Adverse Events (Safety Analysis Population).*

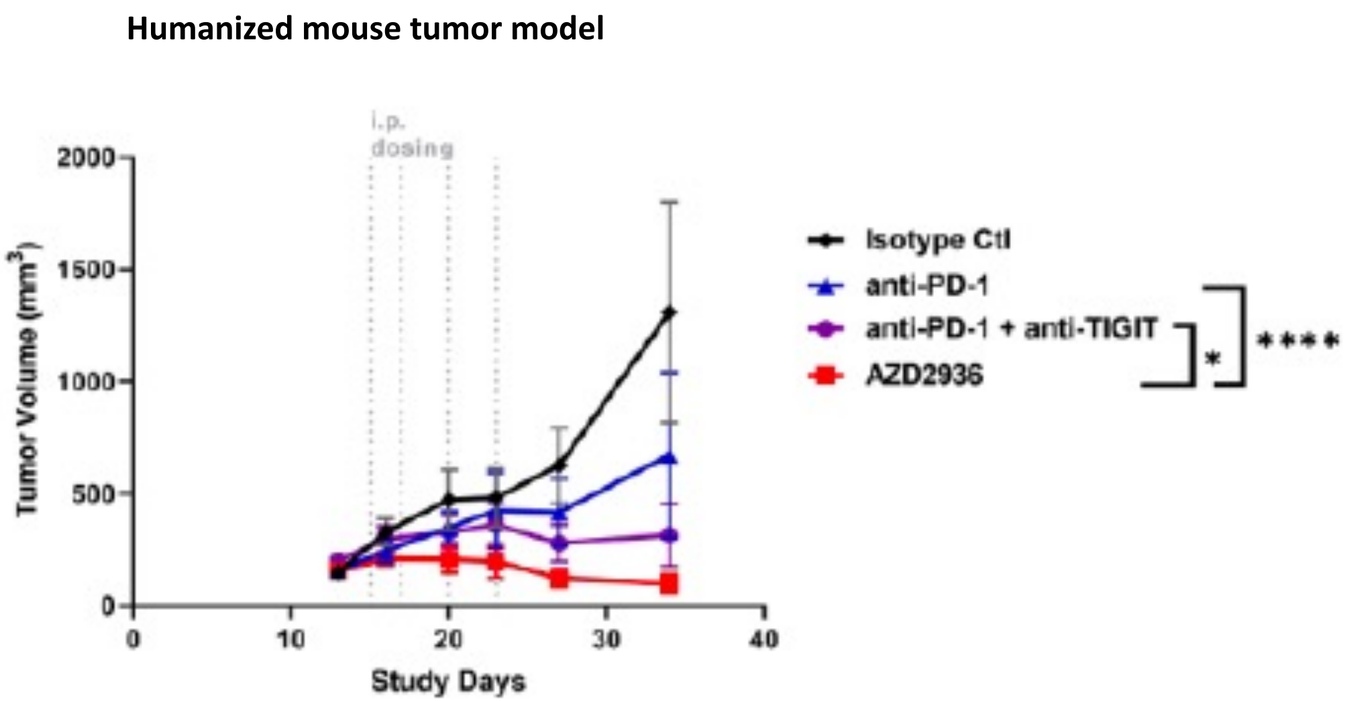
Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0
Events related to treatment			
According to severity			
Any grade	89 (90)	29 (85)	81 (93)
Grade ≥2	69 (70)	23 (68)	66 (76)
Grade ≥3	29 (29)	5 (15)	29 (33)
Grade ≥4	5 (5)	2 (6)	3 (3)
Fatal	0	1 (3)	0
Serious	37 (37)	7 (21)	46 (53)

M.-J. Ahn, et al NEJM 2023

ARTEMIDE-01 (NCT04995523)

Rilvegostomig (AZD2936) is a monovalent, bispecific, humanised IgG1 antibody targeting PD-1 and TIGIT. It is constructed on the backbone of the DuetMab molecule





brandao et al ESMO 2023 1446P

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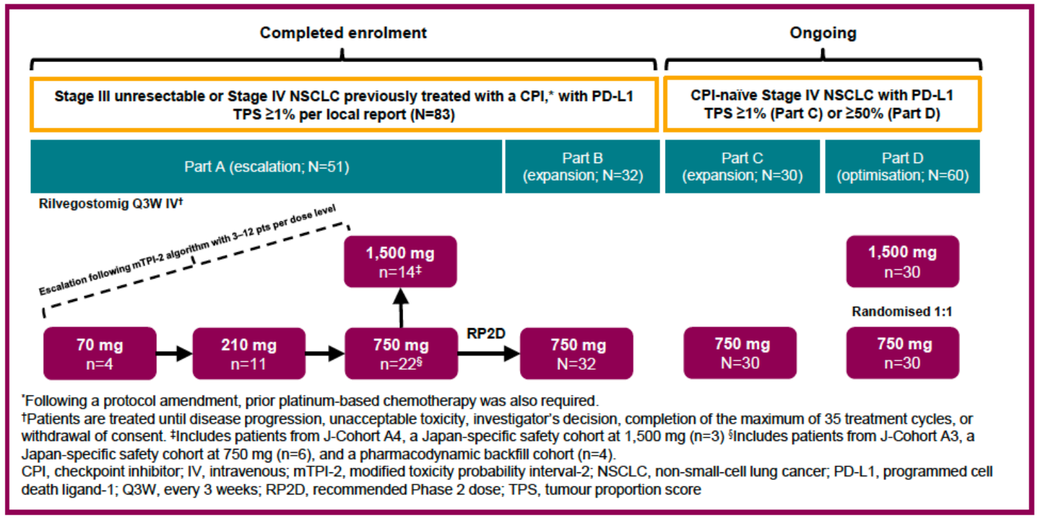


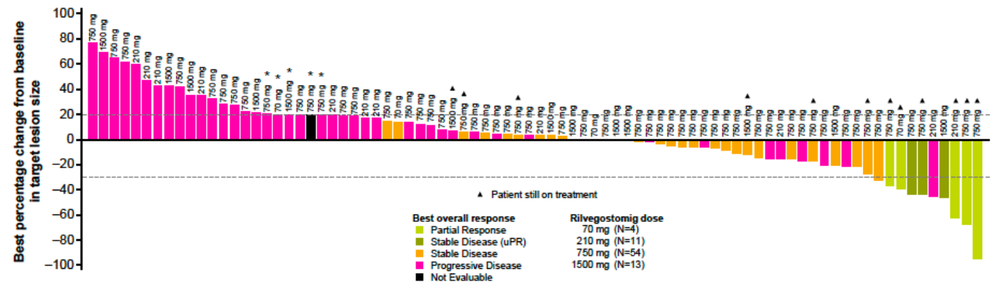
*Following a protocol amendment, prior platinum-based chemotherapy was also required.
†Patients are treated until disease progression, unacceptable toxicity, investigator's decision, completion of the maximum of 35 treatment cycles, or withdrawal of consent. ‡Includes patients from J-Cohort A4, a Japan-specific safety cohort at 1,500 mg (n=3) §Includes patients from J-Cohort A3, a Japan-specific safety cohort at 750 mg (n=6), and a pharmacodynamic backfill cohort (n=4).
CPI, checkpoint inhibitor; IV, intravenous; mTPI-2, modified toxicity probability interval-2; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; RP2D, recommended Phase 2 dose; TPS, tumour proportion score

Table 1. Patient demographics and disease characteristics

	Dose escalation (Part A)	Dose expansion (Part B)
	70–1500 mg Q3W (N=51)	750 mg Q3W (N=32)
Median age (range), years	65.0 (39–83)	63.0 (41–85)
Male / Female, n (%)	30 (58.8) / 21 (41.2)	23 (71.9) / 9 (28.1)
White / Asian / other, n (%)	27 (52.9) / 22 (43.1) / 2 (3.9)	20 (62.5) / 12 (37.5) / 0
ECOG PS 0 / 1, n (%)	20 (39.2) / 31 (60.8)	6 (18.8) / 26 (81.3)
Histology, n (%)		
Adenocarcinoma	34 (66.7)	26 (81.3)
Squamous	13 (25.5)	6 (18.8)
PD-L1 TPS 1–49% / ≥50%, n (%)	28 (54.9) / 23 (45.1)	16 (50.0) / 16 (50.0)
Current or former smoker / never smoker, n (%)	41 (80.4) / 10 (19.6)	26 (81.3) / 6 (18.8)
Primary / secondary resistance* to prior CPI treatment, n (%)	19 (37.3) / 32 (62.7)	12 (37.5) / 20 (62.5)
Liver metastasis / brain metastases, n (%)	4 (7.8) / 5 (9.8)	6 (18.8) / 13 (40.6)

*Primary resistance is defined as resistance with exposure to CPI therapy <6 months; secondary resistance is defined as resistance with exposure to CPI therapy ≥6 months.
CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed cell-death ligand 1; Q3W, every three weeks; TPS, tumour proportion score

Figure 4. Best percentage change from baseline in target lesion size, all doses (N=82)



RECIST version 1.1.
*Imputed data: If best percentage change cannot be calculated due to missing data (including if the patient has no TLs at baseline), a value of +20% is imputed in the following situations: if a patient has no post-baseline assessment and has died, if a patient has new lesions or progression of NTLs or TLs, or if a patient has withdrawn due to PD and has no evaluable TL data before or at PD.
NTL, non-target lesion; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; TL, target lesion; uPR, unconfirmed partial response

Table 3. Antitumour activity in patients with CPI-resistant NSCLC

	Dose escalation (Part A)	Dose expansion (Part B)	Total (Parts A and B)	
	70–1500 mg (n=51)	750 mg (n=32)	750 mg (n=54)	70–1500 mg (N=83)
ORR, % (95% CI)	7.8 (2.2, 18.9)	3.1 (0.1, 16.2)	5.6 (1.2, 15.4)	6.0 (2.0, 13.5)
Complete response, n (%)	0	0	0	0
Partial response, n (%)	4 (7.8)	1 (3.1)	3 (5.6)	5 (6.0)
Median DoR (range), months*	14.5 (4.8–14.5)	4.1 (NC)	14.5 (4.1–14.5)	14.5 (4.1–14.5)
Durable response at 6 months, n (%)	3 (5.9)	0	2 (3.7)	3 (3.6)
Stable disease, n (%)	21 (41.2)	12 (37.5)	24 (44.4)	33 (39.8)
Unconfirmed complete or partial response, n (%)	2 (3.9)	1 (3.1)	2 (3.7)	3 (3.6)
Disease control rate, % (95% CI)†	31.4 (19.1–45.9)	28.1 (13.8–46.8)	31.5 (19.5–45.6)	30.1 (20.5–41.2)
Median PFS (95% CI), months	3.1 (2.0, 4.1)	2.1 (2.0, 5.2)	3.8 (2.0, 4.2)	2.1 (2.0, 4.0)
Median duration of follow-up (range), months	9.1 (0.4–21.3)	10.1 (1.6–13.7)	9.9 (0.8–17.9)	9.7 (0.4–21.3)

*DoR was calculated based on the Kaplan-Meier technique
†Disease control = complete response + partial response + stable disease at or after 182 days
CI, confidence interval; DoR, duration of response; NC, not calculable; ORR, objective response rate; PFS, progression-free survival

ARTEMIDE-01 (NCT04995523)

Table 2. Safety summary

Event, n (%)	Dose Escalation (Part A)					Dose Expansion (Part B)	Total (Parts A and B)	
	70 mg (n=4)	210 mg (n=11)	750 mg (n=22)	1500 mg (n=14)	70–1500 mg (n=51)	750 mg (n=32)	750 mg (n=54)	70–1500 mg (N=83)
Any TEAE	3 (75.0)	9 (81.8)	20 (90.9)	12 (85.7)	44 (86.3)	31 (96.9)	51 (94.4)	75 (90.4)
Any TRAE*	1 (25.0)	4 (36.4)	14 (63.6)	7 (50.0)	26 (51.0)	18 (56.3)	32 (59.3)	44 (53.0)
Any Grade ≥3 TEAE	1 (25.0)	3 (27.3)	6 (27.3)	7 (50.0)	17 (33.3)	11 (34.4)	17 (31.5)	28 (33.7)
Any Grade ≥3 TRAE*	0	0	2 (9.1)	2 (14.3)	4 (7.8)	3 (9.4)	5 (9.3)	7 (8.4)
Any treatment-emergent SAE	1 (25.0)	3 (27.3)	7 (27.3)	6 (42.9)	17 (33.3)	11 (34.4)	18 (33.3)	28 (33.7)
Any treatment-related SAE*	0	0	1 (4.5)	2 (14.3)	3 (5.9)	3 (9.4)	4 (7.4)	6 (7.2)
Any treatment-emergent SAE leading to death	1 (25.0)	0	1 (4.5)	2 (14.3)	4 (7.8)	0	1 (1.9)	4 (4.8)
Any treatment-related SAE leading to death*	0	0	0	0	0	0	0	0
Any TEAE leading to discontinuation	0	0	1 (4.5)	0	1 (2.0)	2 (6.3)	3 (5.6)	3 (3.6)
Any imAE†	1 (25.0)	2 (18.2)	3 (13.6)	3 (21.4)	9 (17.6)	5 (15.6)	8 (14.8)	14 (16.9)

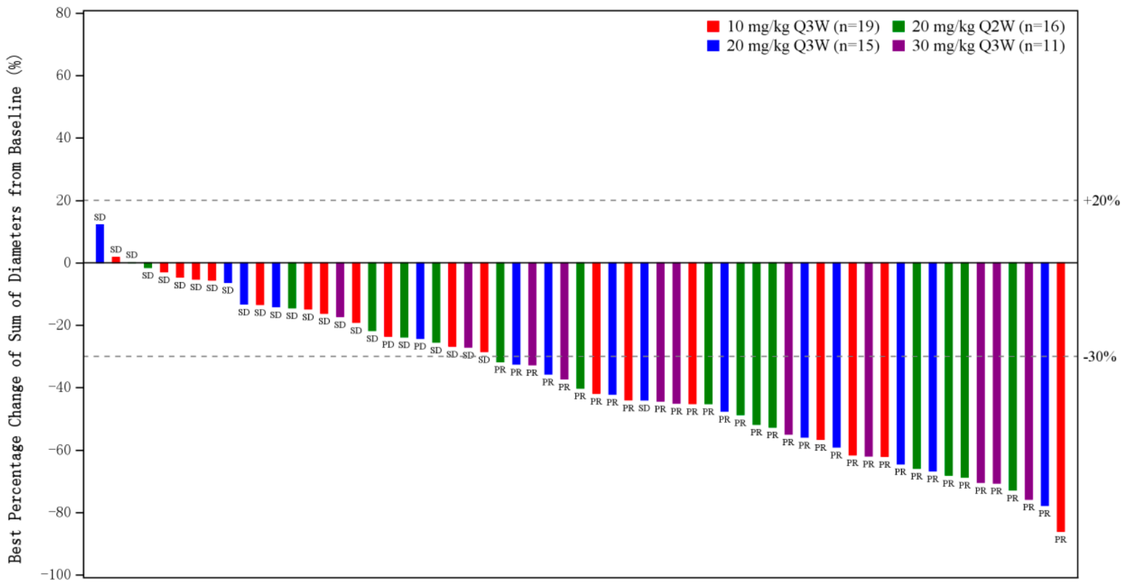
*Possibly related to rilvegostomig as assessed by the investigator. †Immune-mediated as assessed by the investigator.
AE, adverse event; AESI, adverse event of special interest; imAE, immune-mediated adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Currently being tested in CPI naïve NSCLC patients

Ivonescimab (*AK112/SMT112*) (PD-1 and VEGF humanized bispecific antibody)

- Anti-VEGF inhibits angiogenesis and also leads to an immune responsive environment by
  - increasing immune effector cell trafficking and infiltration into the tumor microenvironment
  - modulating T-regulatory cells and myeloid-derived suppressor cells
- Phase Ib China. Monotherapy, NSCLC, all histologies, IO naïve, not selected by PD-L1 expression, EGFR and ALK wt. N = 108
  - 86% treatment naïve, 51% SCC
  - standard distribution of PD-L1 expression

PD-L1 ≥ 1



	ORR %	PFS m	9mPFS	OS m	9mOS
All patients	39.8	NR		NR	
treatment naïve PD-L1 ≥ 1 All doses	52.2	NR		NR	
Treatment naïve PD-L1 ≥ 1 20 mg/kg and above	61	NR	54	NR	84
Treatment naïve PD-L1 1-49 20 mg/kg and above	52	NR		NR	
Treatment naïve PD-L1 ≥ 1 > 50 20 mg/kg and above	74	NR		NR	

Toxicities as expected from PD-L1 and VEGF Mab

Lei Wang et all JTO 2023

Summary

- Bispecific antibodies represent a new modality for treatment of lung cancer
  - –Amivantamab FDA approved for EGFR ex 20 ins mutation.
- There are multiple clinical trials with bsAb in clinical development.
- For some of the drugs. CRS and neurologic toxicities will require administration in specialized units