Novel Targets:
HER2, NRG1, TROP2, CEACAM5, and HER3

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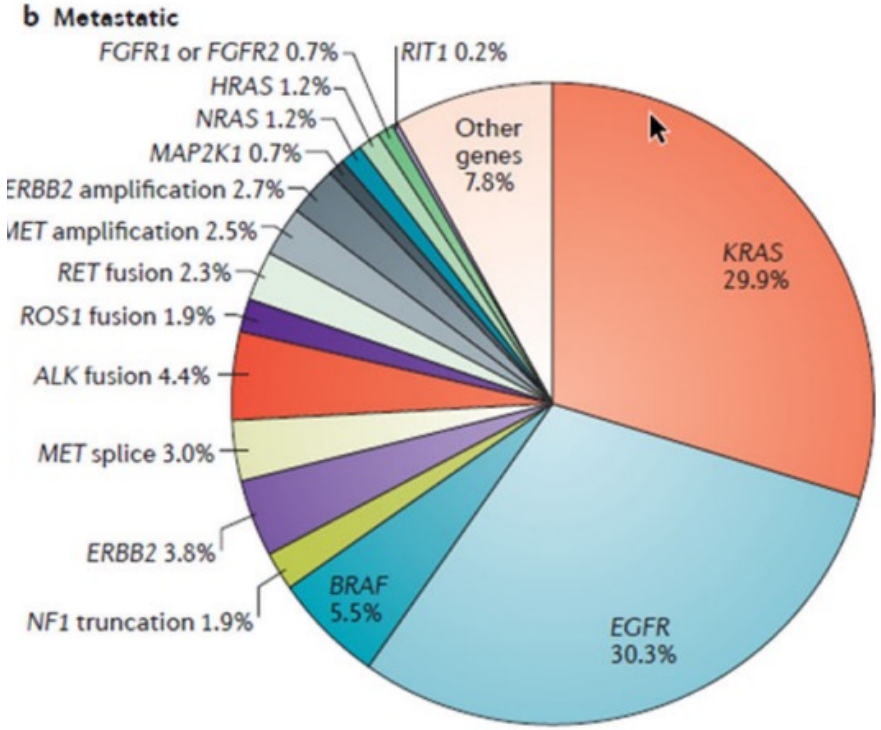
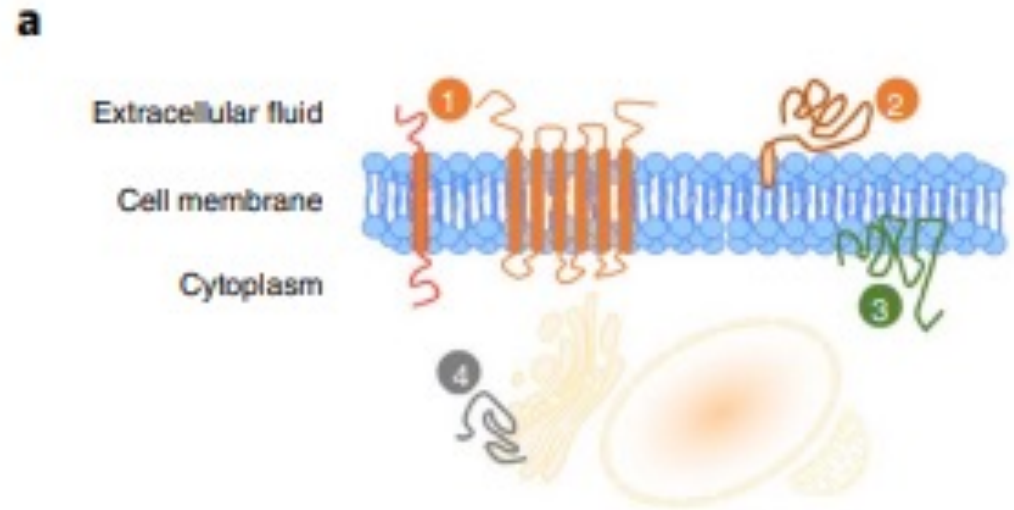
Novel Targets

Rare genomic alterations
HER2, NRG1

Cell surface proteins
TROP2, CEACAM5, HER3





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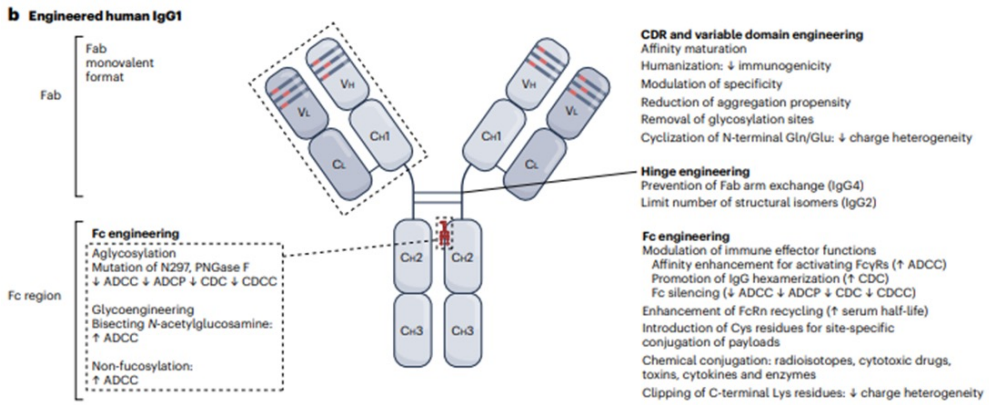
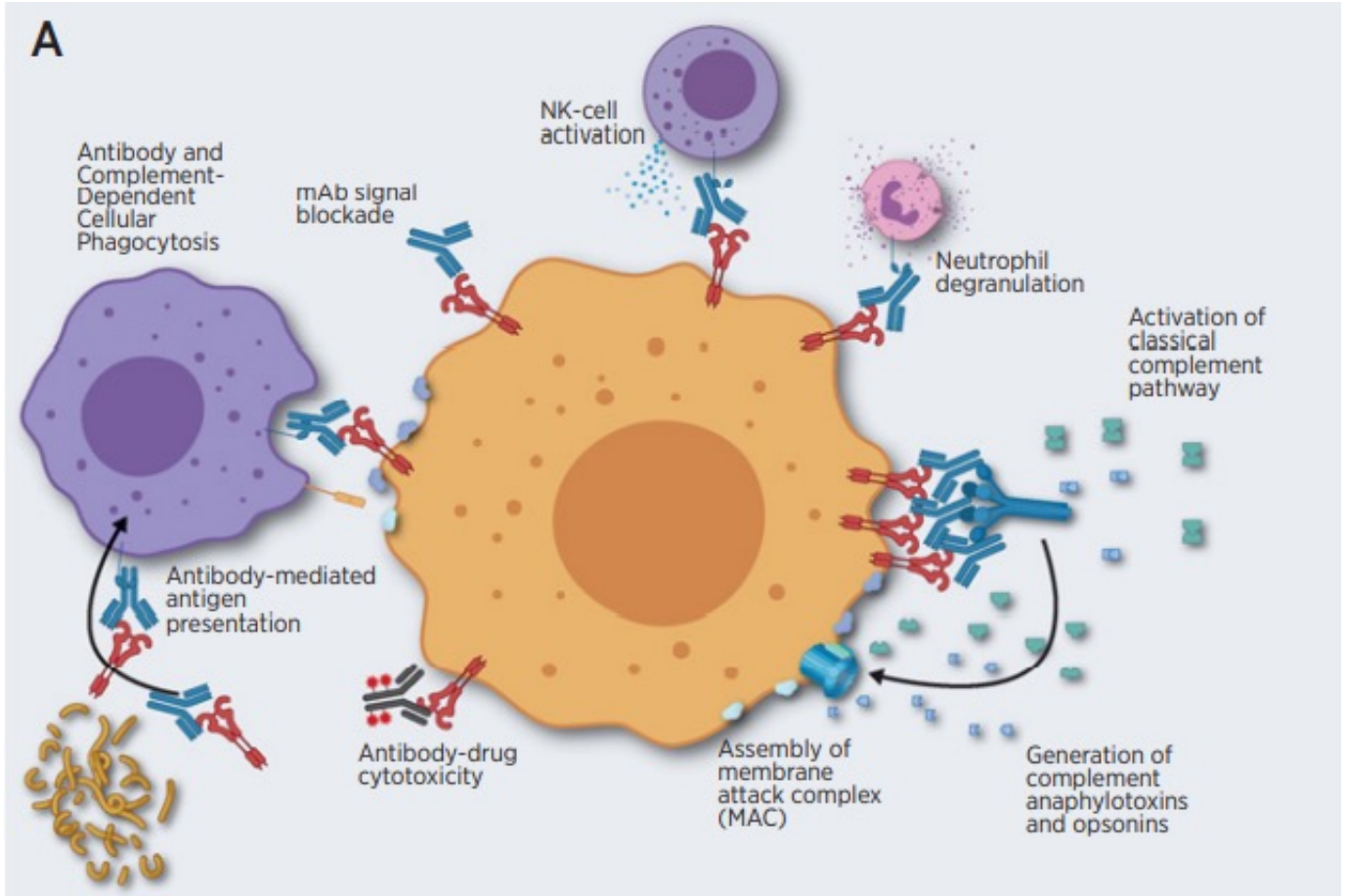
Skoulidis and Heymach, Nat Rev Cancer 2019; Hu et al Nature Cancer 2021

Mechanisms of Action of Therapeutic Monoclonal Antibodies





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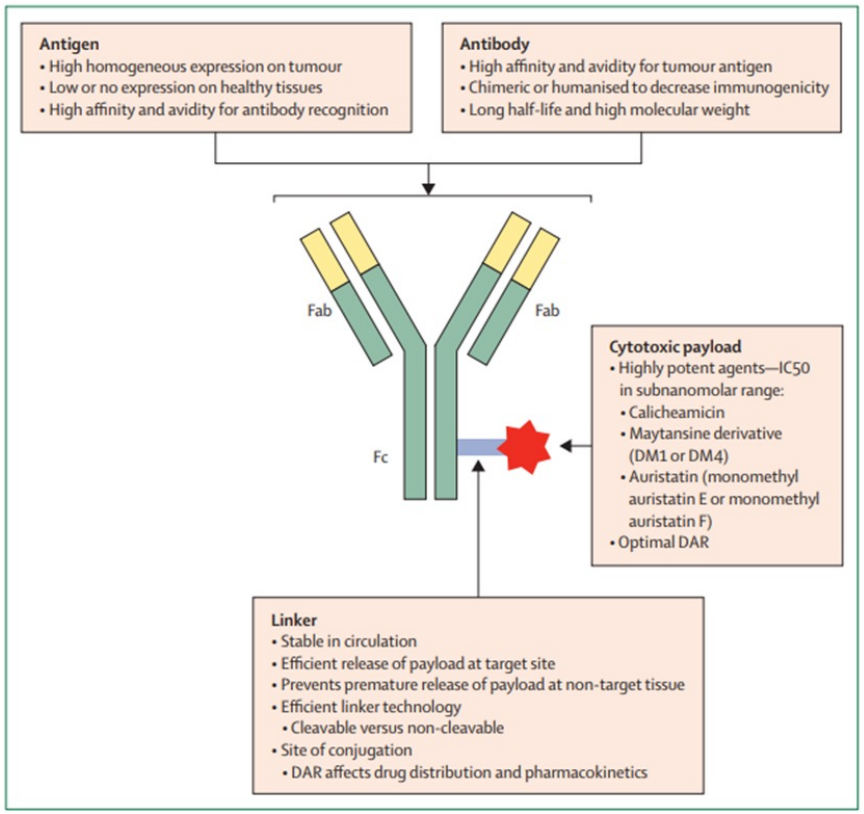
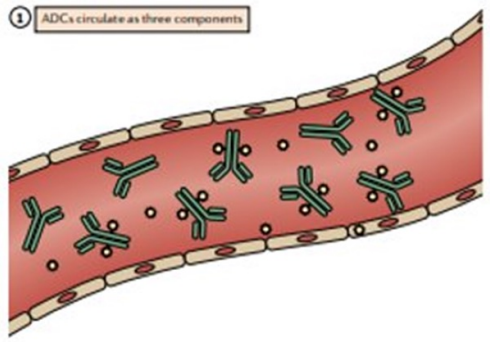
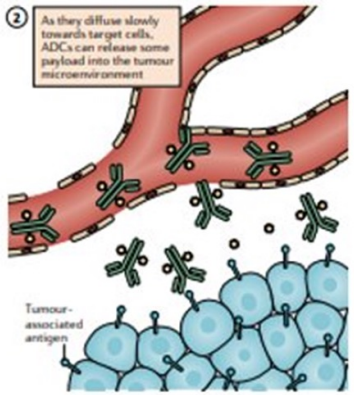
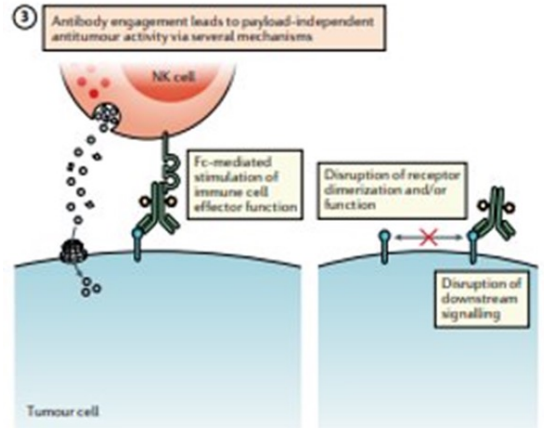
Zinn et al Nature Cancer 2023; Tsao et al Cancer Research 2021

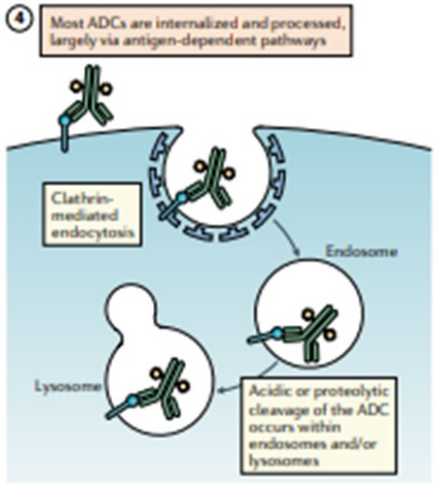
Mechanism of Action of Antibody Drug Conjugates (ADCs)

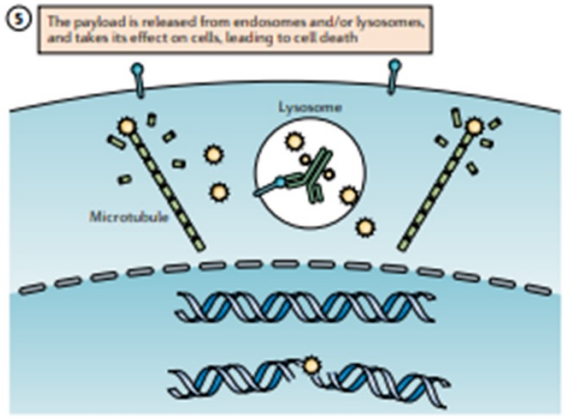


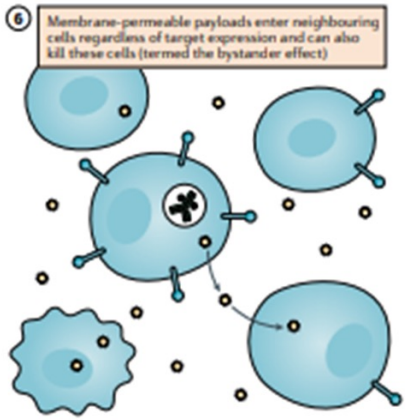












Chau et al Lancet 2019; Drago et al Nature Rev Clin Onc 2021

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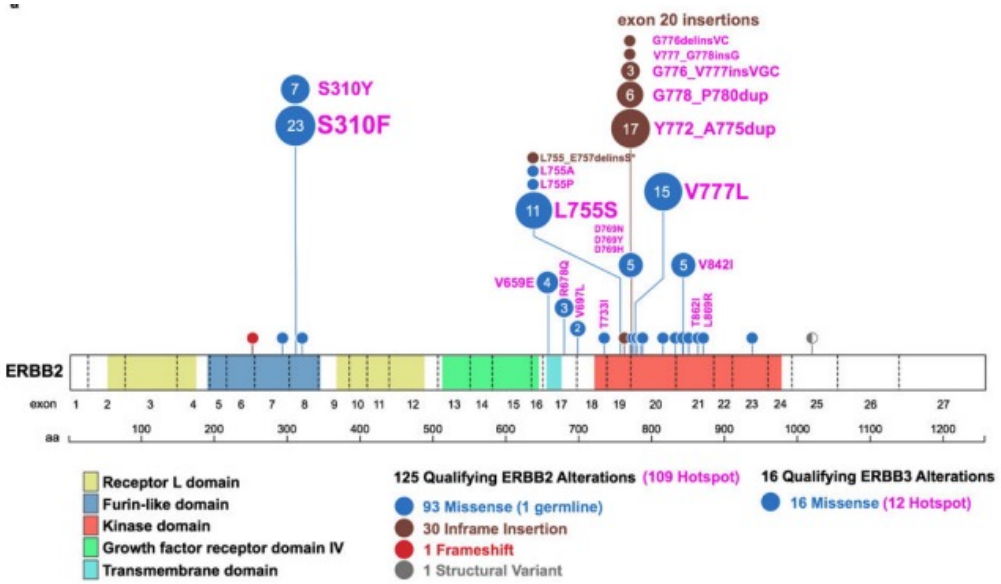
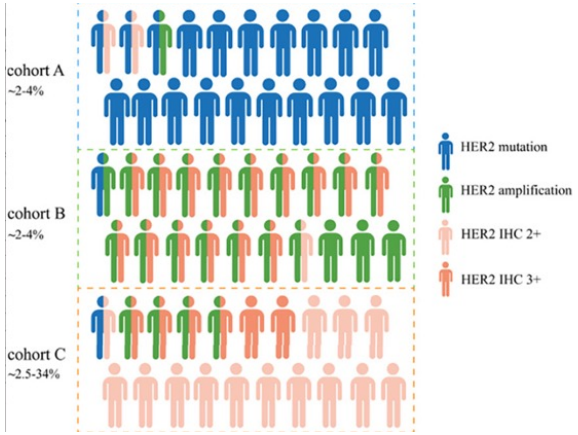
HER2 in NSCLC





HER2 mutations occur in 1-3% of NSCLC

- Exon 20 insertions (YVMA variant 85%)
- Point mutations in the tyrosine kinase, transmembrane, and extracellular domains

Little overlap with gene amplification or protein expression

Hyman et al Nature 2018; Yu et al Frontiers in Oncol 2022.

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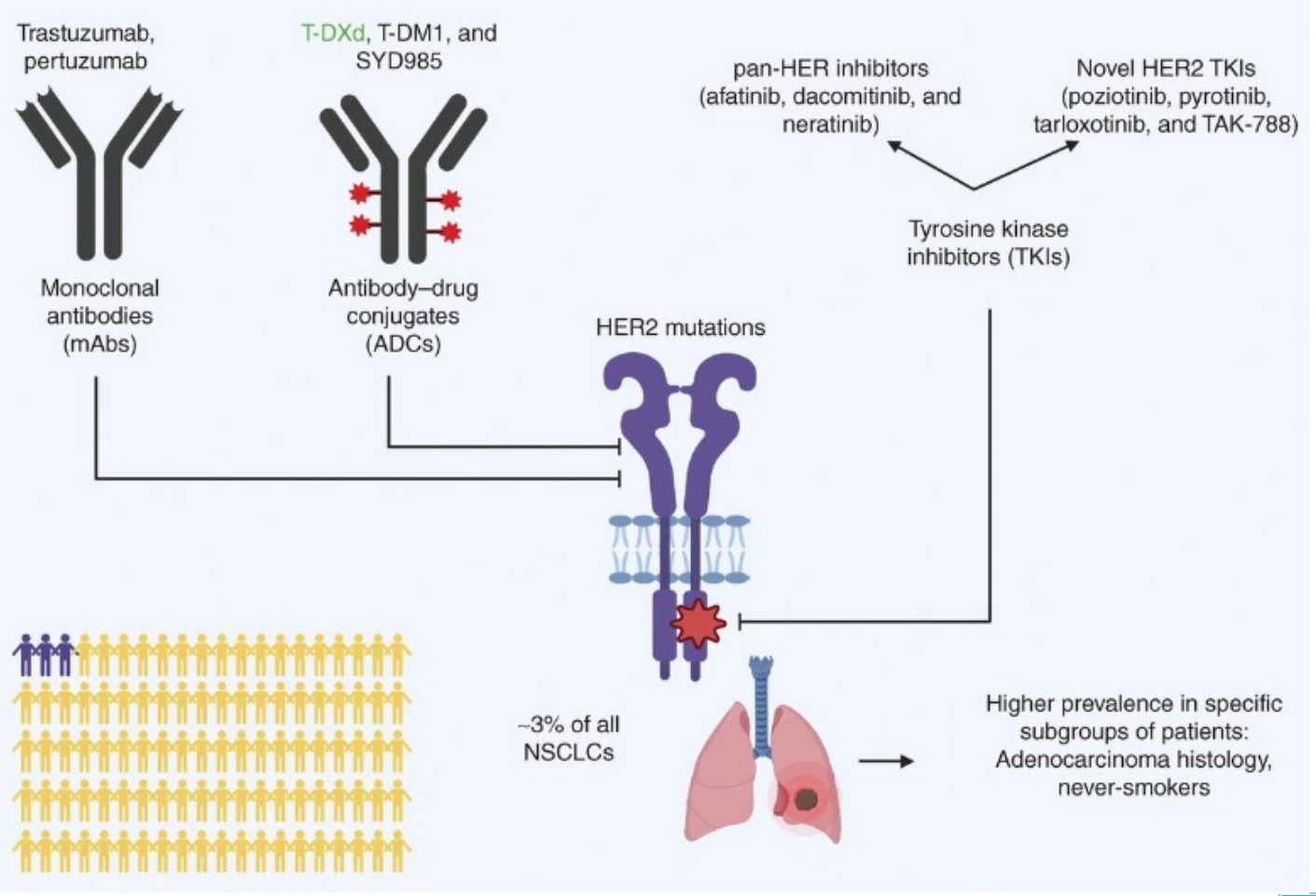
HER2: Treatment Strategies



Rolfo and Russo, Cancer Discovery 2020

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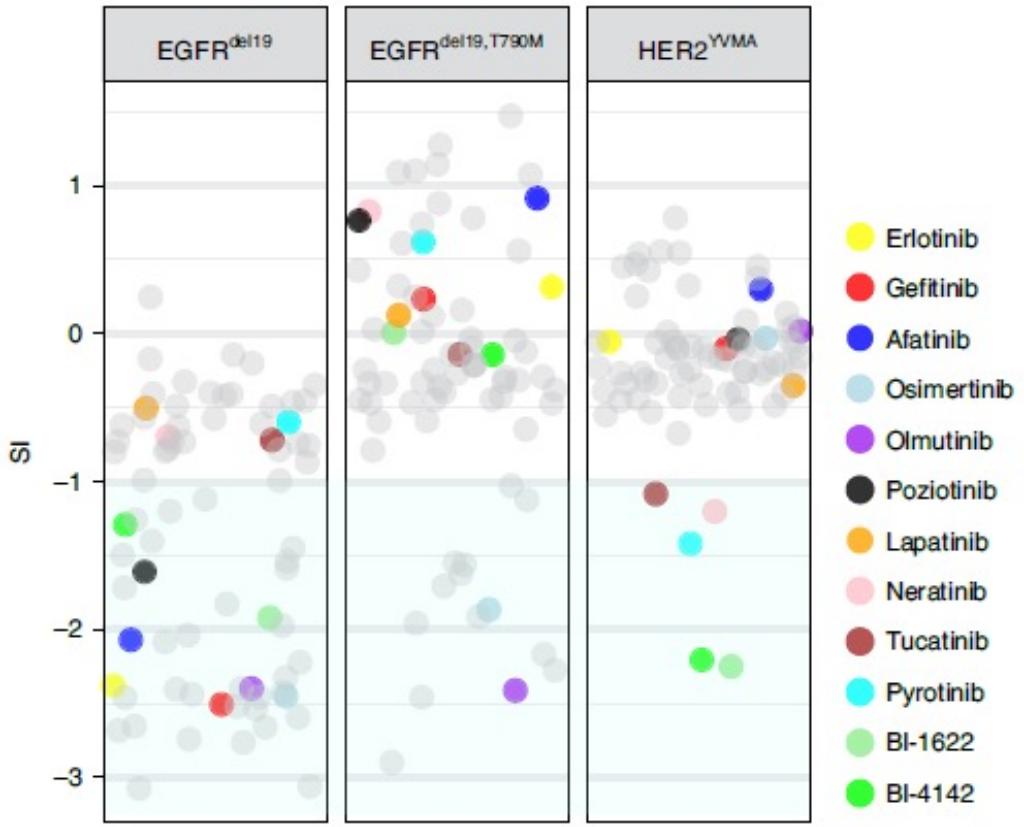
EGFR/HER2 TKIs in HER2 mutant NSCLC

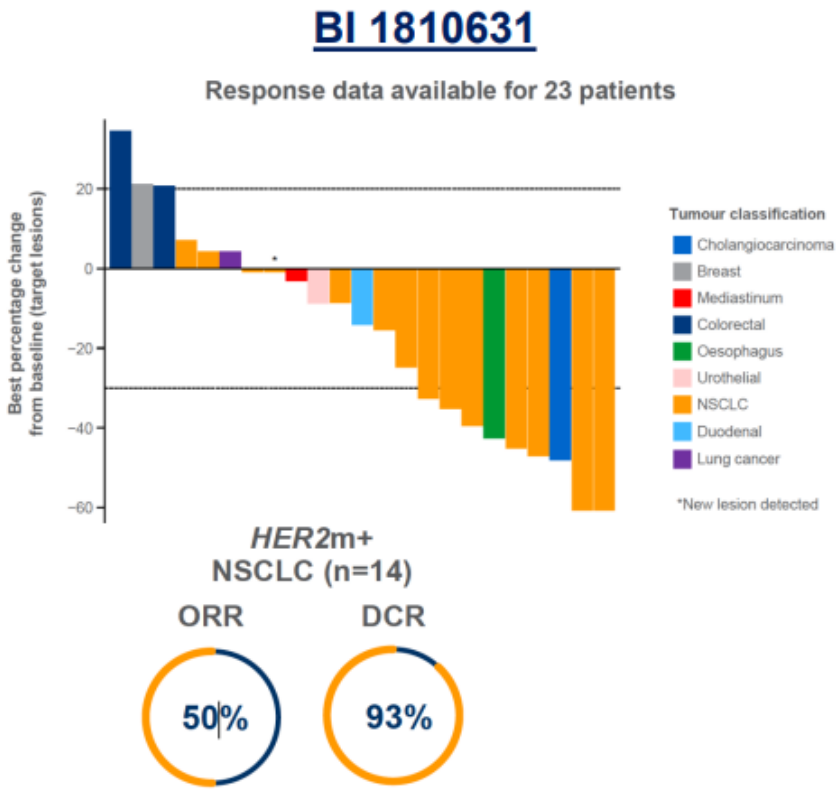
Drug	Target Pop	N	ORR	mPFS	Toxicities
Afatinib[1]	HER2^{mt}	13	8%	16 weeks	Diarrhea, vomiting, rash, paronychia, fatigue, mucositis
Afatinib[2]	HER2^{mt}	27	13%	3 mo	Diarrhea/GI toxicity, skin rash.
Neratinib[3]	HER2^{mt}	26	4%	5.5 mo	Diarrhea (74%), Nausea (43%), Vomiting (41%)
Dacomitinib[4]	HER2^{mt}	26	12%	3 mo	Diarrhea (90%), rash (73%)
Mobocertinib[5]	HER2^{mt}	5	1/5 (20%)		83% Diarrhea, 50% Anorexia
Pyrotinib[6]	HER2^{mt}	60	30%	6.9 mo	92% Diarrhea; 30% Creatinine increase
Poziotinib[7]	HER2^{mt}, Pretreated	90	28%	5.5 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea
Poziotinib[8]	HER2^{mt}, First-line	48	44%	5.6 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea

1. Dziadziuszko R, JTO 2019; 2. Lai WCV et al, European Journal of Cancer 2018; 3. Hyman DM, Nature 2018; 4. Kris MG et al. Ann Onc. 2015; 5. Zhou C et al. J Clin Oncol. 2020; 6. Neal JW et al. WCLC 2018. Abstract P1.13-44, 7. Zhou C, JCO 2020, 7. Le X, JCO 2022; 8. Cornelisson R, ESMO 2021

Slide courtesy of Z Piotrowska

Ongoing development of HER2 selective TKIs





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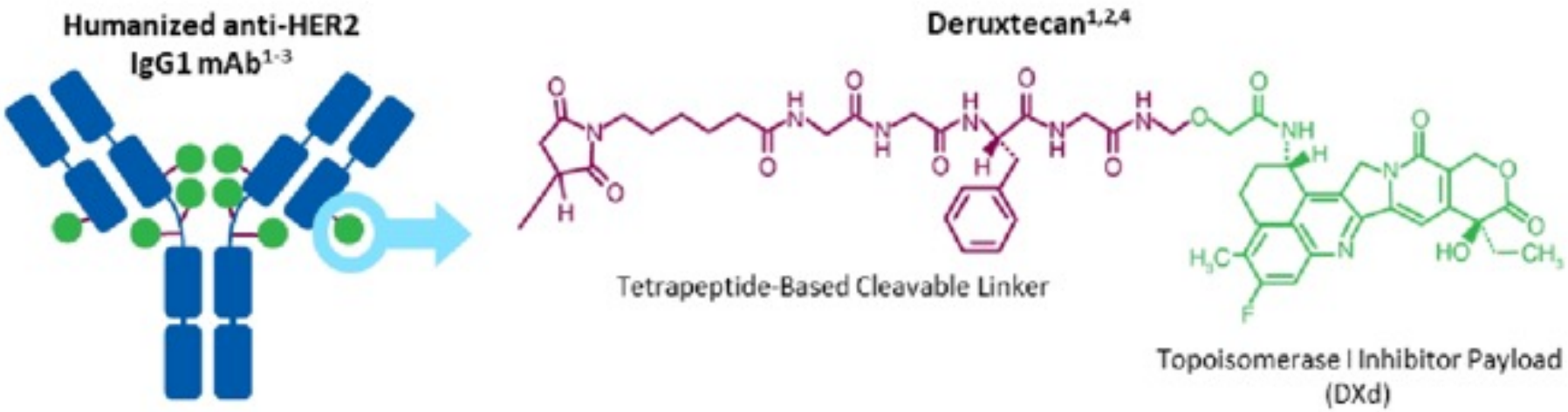
Wilding et al Nature Cancer 2022; Opdam et al AACR-NCI-EORTC 2022

HER2 ADC: Trastuzumab deruxtecan



- Humanized anti-HER2 IgG1 mAb with same amino acid sequence as trastuzumab
- Tetrapeptide based cleavable linker
- Topoisomerase I inhibitor payload, an exatecan derivative

Smit et al WCLC 2020

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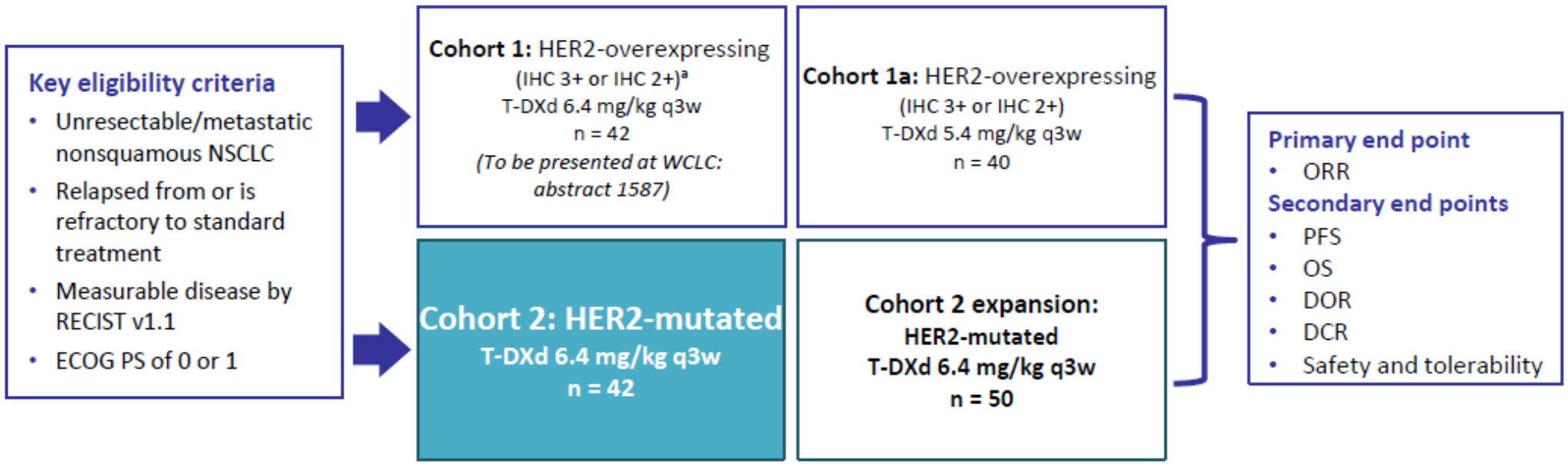
HER2 Trastuzumab Deruxtecan DESTINY Lung01 study Design



Smit et al WCLC 2020

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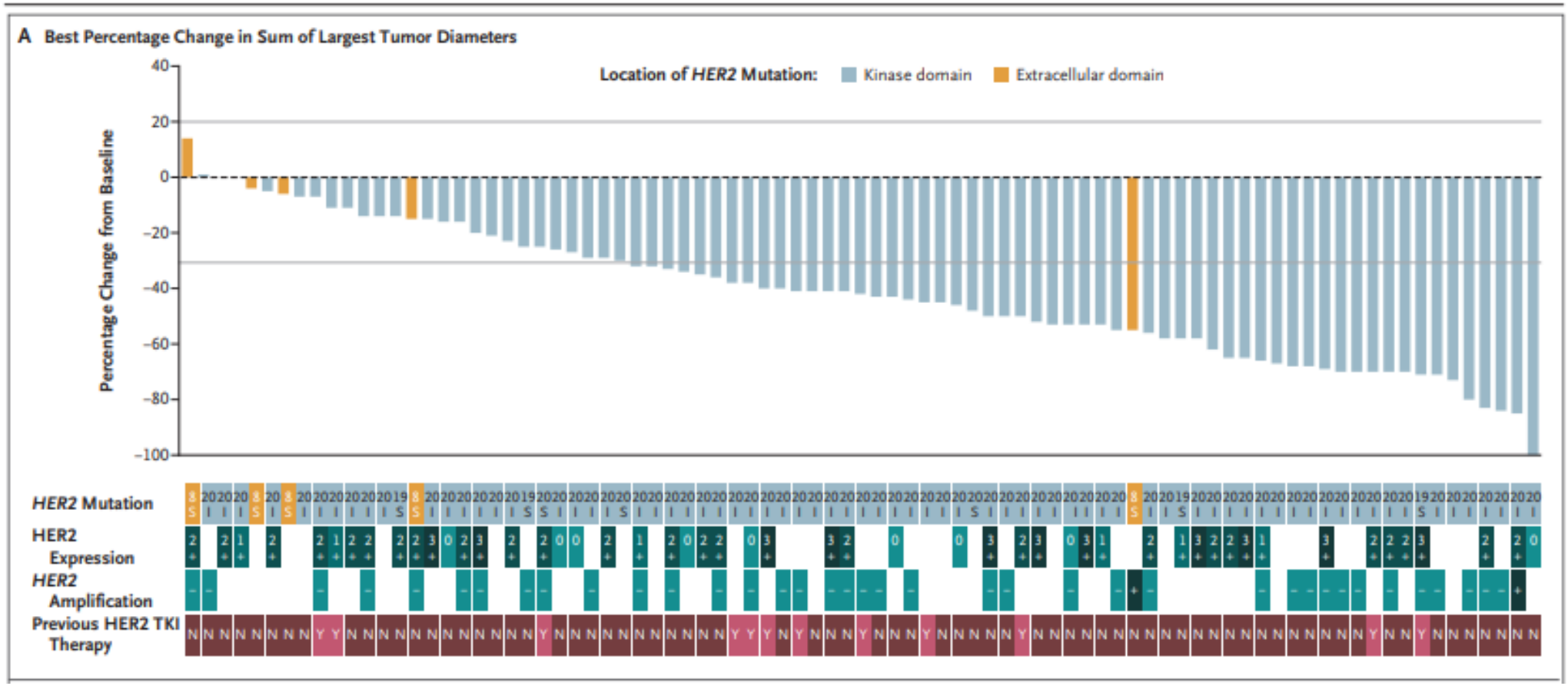
Trastuzumab Deruxtecan in HER2 mutant NSCLC (DESTINY-Lung01)



Li et al NEJM 2021

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Trastuzumab Deruxtecan Adverse Events

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

Li et al NEJM 2021

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Trastuzumab deruxtecan: what is the right dose? DESTINY-Lung02

STUDY DESIGN

N = 152

Ratio 2:1

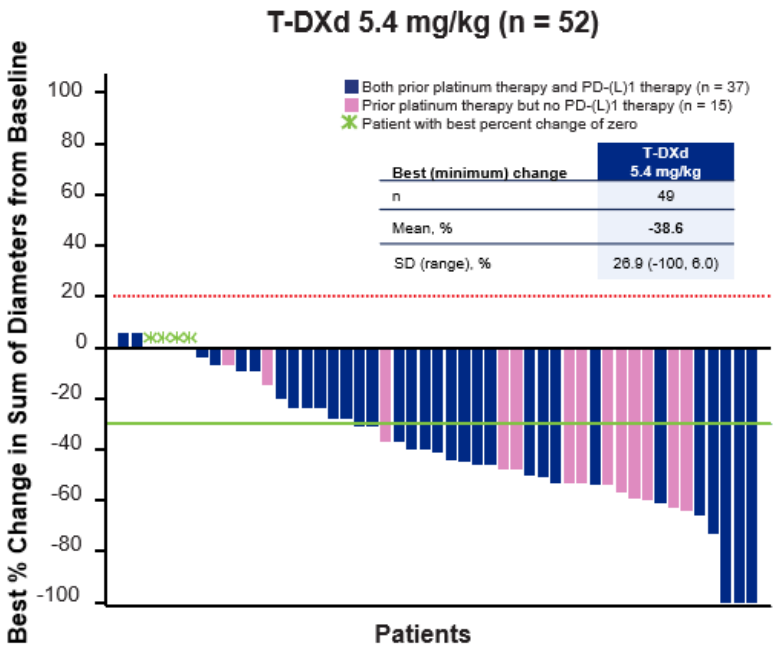
Randomization

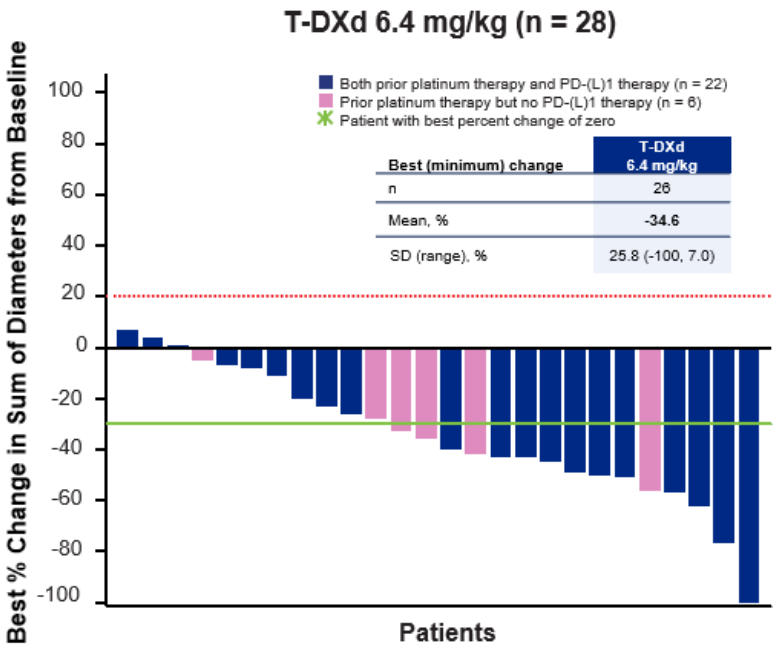
- T-DXd 5.4 mg/kg Q3W n = 102
- T-DXd 6.4 mg/kg Q3W n = 50

Primary end point: Confirmed ORR by BICR

Secondary end points:

- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- PK
- PROs
- Safety & tolerability





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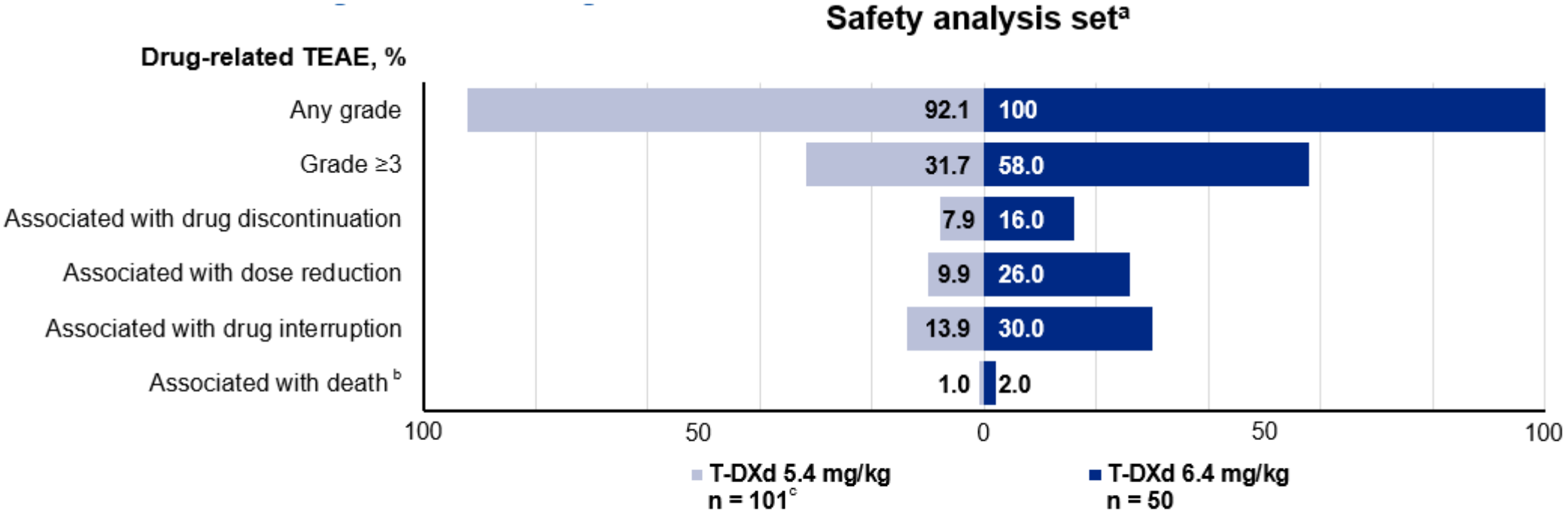
Goto et al ESMO 2022

HER2 ADC: Trastuzumab deruxtecan safety profile by dose



Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

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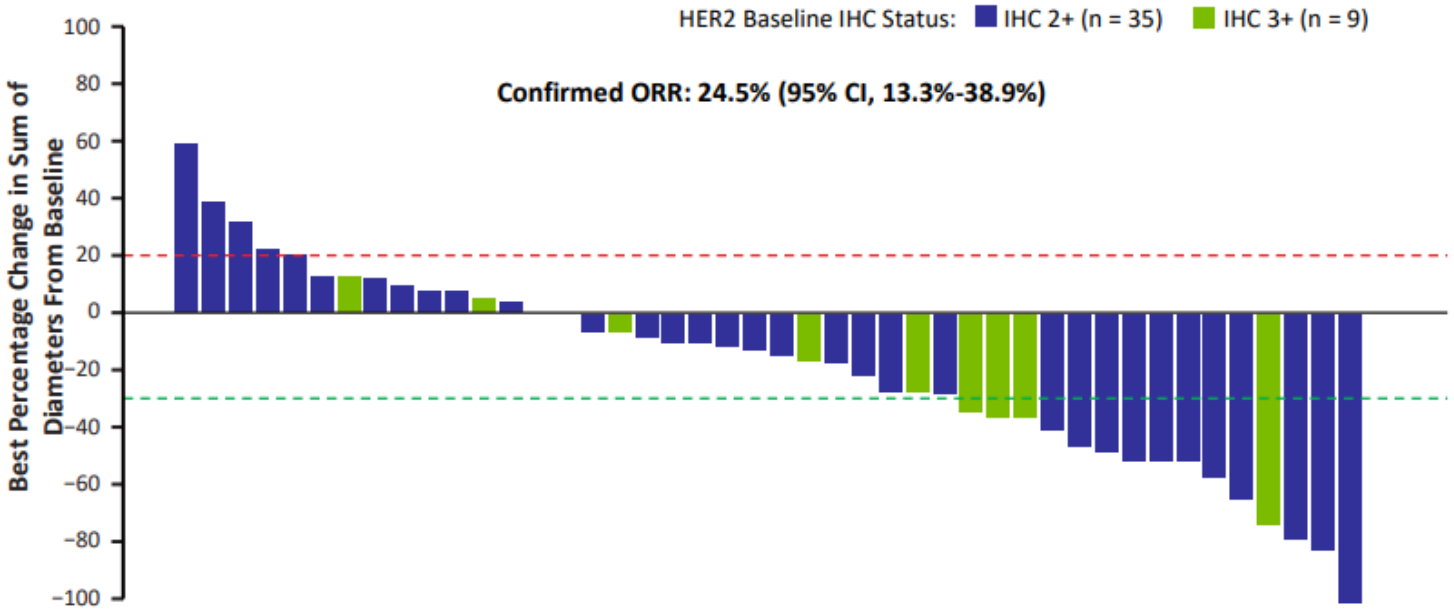
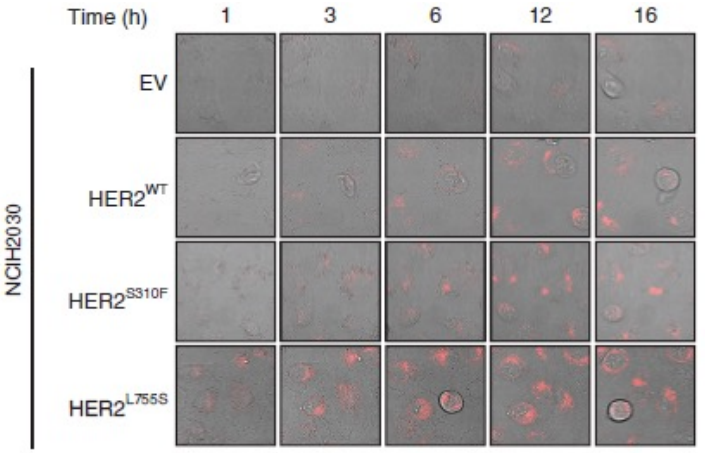
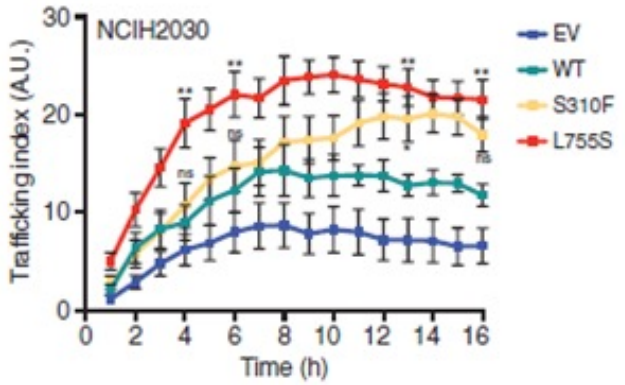
Goto et al ESMO 2022

HER2 Trastuzumab Deruxtecan in HER2 overexpressing NSCLC







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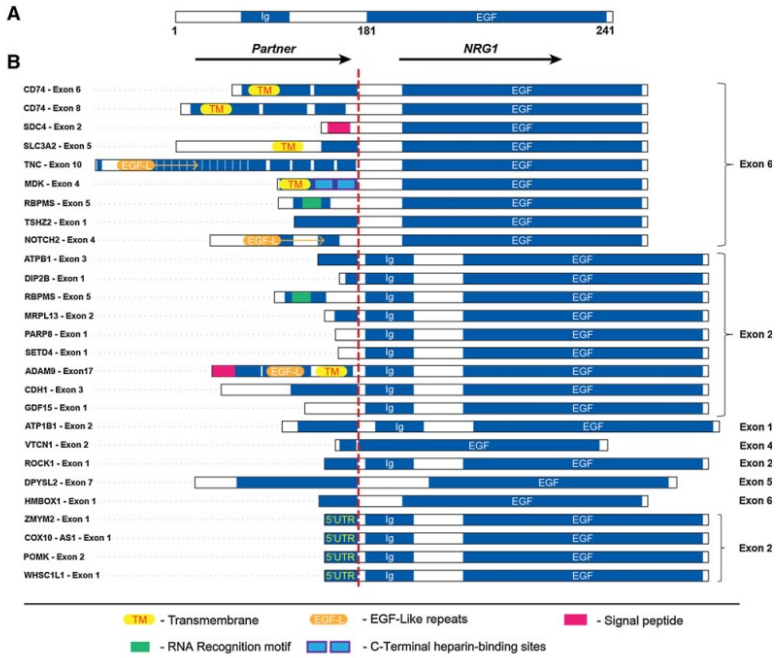
Nakagawa et al, WCLC 2020; Li et al Cancer Discovery 2020

NRG1 fusions



- Fusion of NRG1 with a partner gene
- 0.2% of all solid tumors
- Enriched in KRAS WT PDAC and invasive mucinous adenocarcinoma of lung
- NRG fusion proteins bind and activate HER3

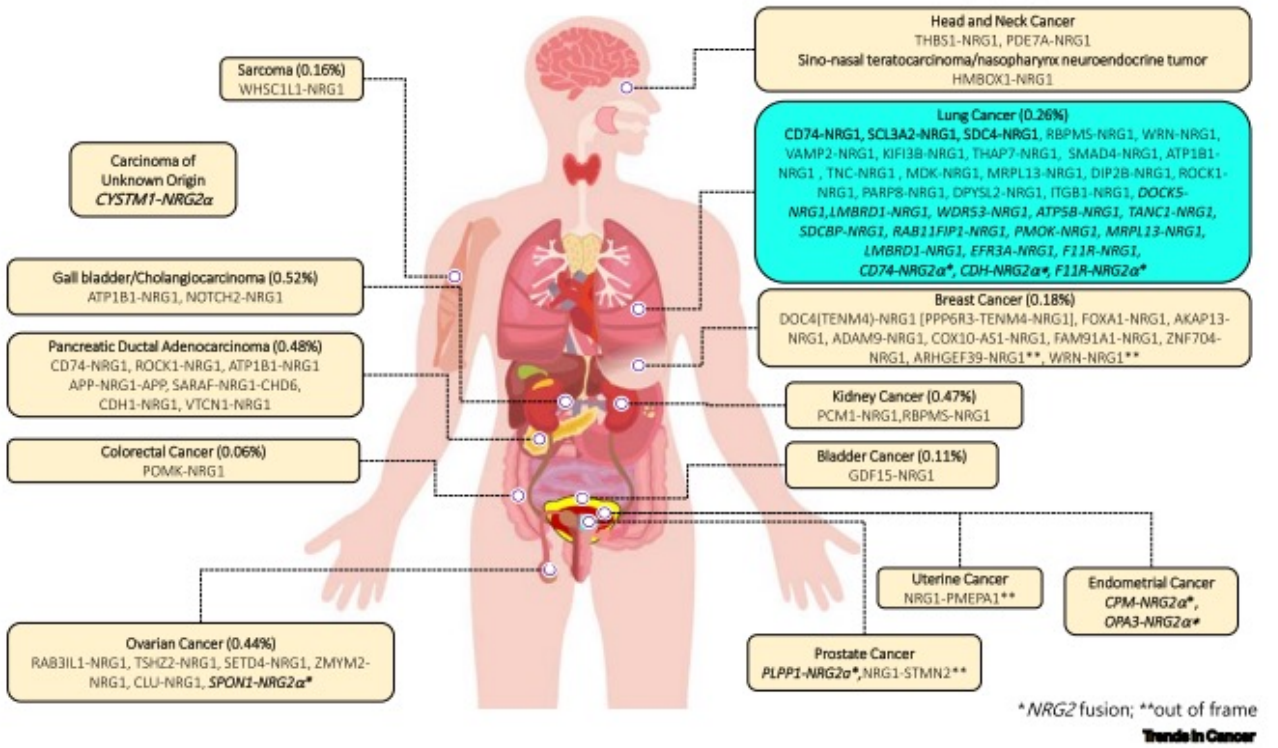


Figure 2. Distribution of *NRG1* and NRG2 fusion variants in various organs. *WHSC1L1-NRG1* is the *NRG1* fusion variant identified in a *NRG1*+ soft tissue sarcoma of the extremity/trunk. Out-of-frame (non-functional) variants are denoted by **. From references [5,9,10,36,45,48–57]. Abbreviations: NRG, neuregulin.

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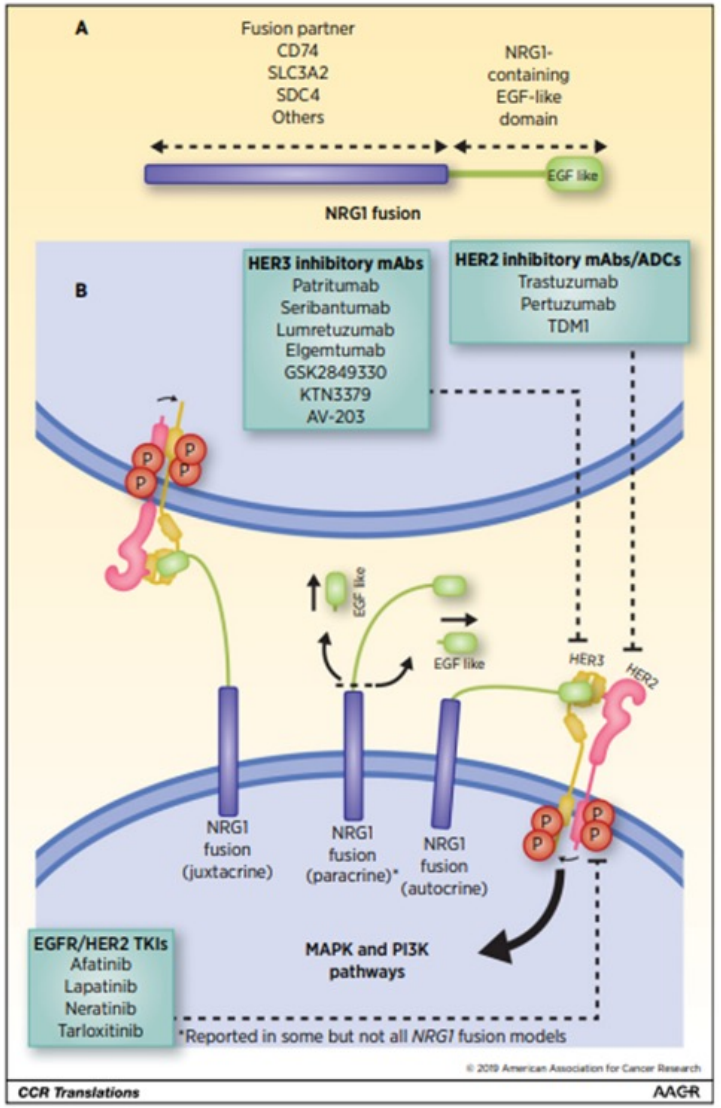
Jonna et al CCR 2019; Nagasaka and Ou Trends in Cancer 2022

NRG1: Treatment Strategies



Dimou and Camidge CCR 2019

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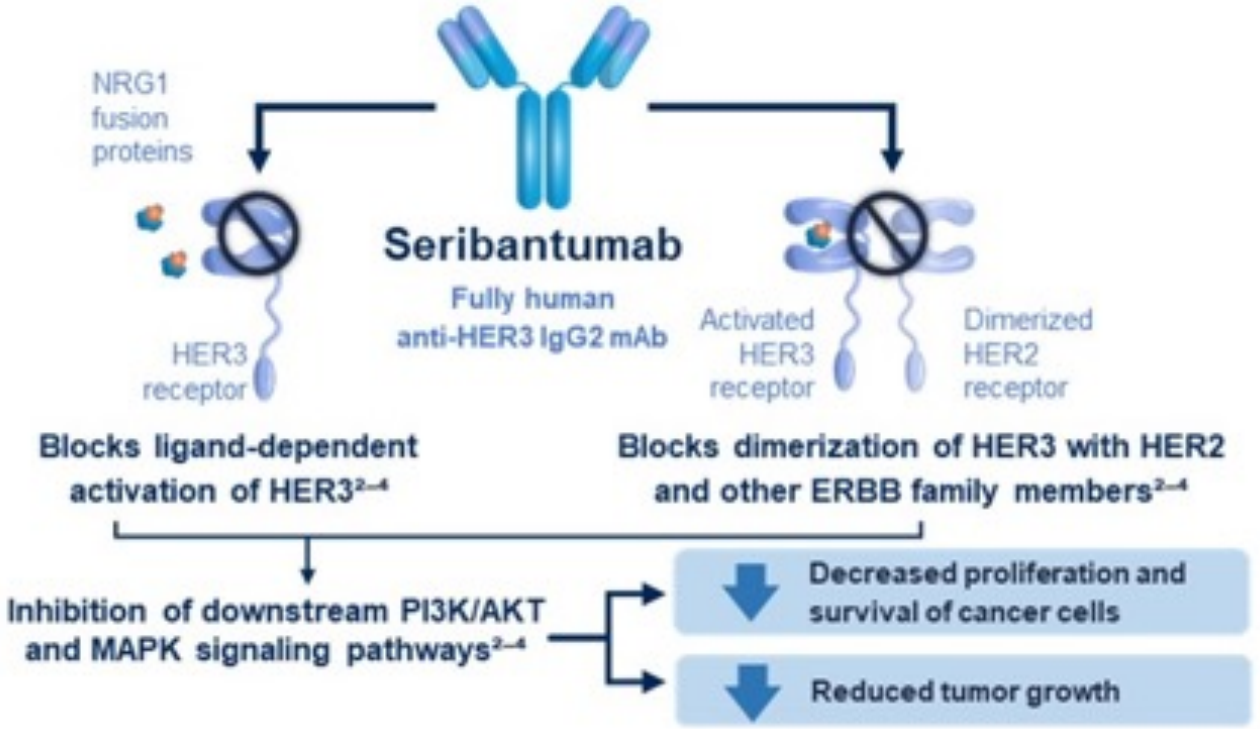
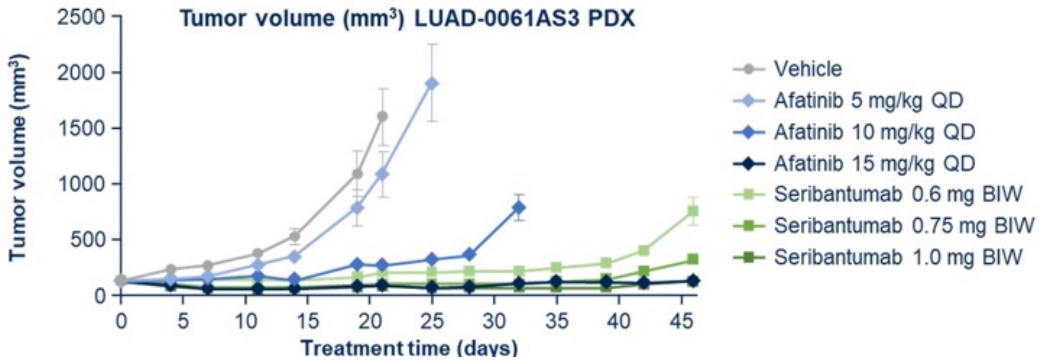
NRG1: Seribantumab





- Humanized anti-HER3 IgG2 mAb
- Competes with NRG1 to bind HER3
- Prevents dimerization and phosphorylation of HER3 with other HER2 family members

Carrizosa et al ASCO 2022

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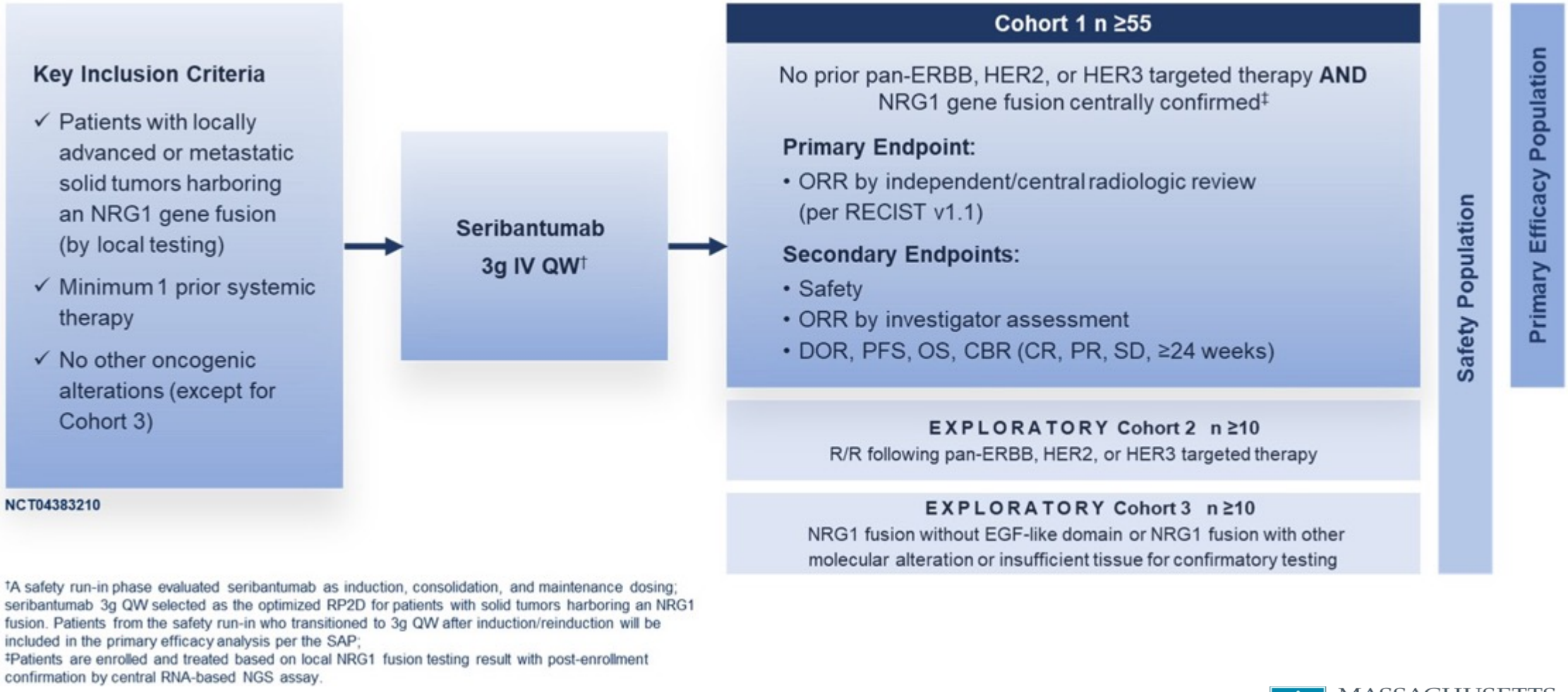
NRG1: CRESTONE Study Design



†A safety run-in phase evaluated seribantumab as induction, consolidation, and maintenance dosing; seribantumab 3g QW selected as the optimized RP2D for patients with solid tumors harboring an NRG1 fusion. Patients from the safety run-in who transitioned to 3g QW after induction/reinduction will be included in the primary efficacy analysis per the SAP;
‡Patients are enrolled and treated based on local NRG1 fusion testing result with post-enrollment confirmation by central RNA-based NGS assay.

Carrizosa et al ASCO 2022

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NRG1: CRESTONE study Seribantumab Adverse Events

Adverse events reported in ≥15% of patients

	Treatment-emergent AEs (N=35); n (%)				Treatment-related AEs (N = 35); n (%)			
Preferred Term	**Any Grade**	**Grade 1**	**Grade 2**	**Grade ≥ 3†**	**Any Grade**	**Grade 1**	**Grade 2**	**Grade ≥ 3‡**
Patients with ≥1 AE	35 (100)	8 (23)	10 (29)	17 (49)	30 (86)	17 (49)	11 (31)	2 (6)
Diarrhea	17 (49)	11 (31)	4 (11)	2 (6)	14 (40)	10 (29)	3 (9)	1 (3)
Fatigue	14 (40)	7 (20)	7 (20)	0	10 (29)	5 (14)	5 (14)	0
Rash§	11 (31)	9 (26)	2 (6)	0	9 (26)	7 (20)	2 (6)	0
Hypokalemia	10 (29)	6 (17)	3 (9)	1 (3)	3 (9)	3 (9)	0	0
Nausea	10 (29)	7 (20)	1 (3)	2 (6)	6 (17)	5 (14)	1 (3)	0
Abdominal pain¶	8 (23)	4 (11)	2 (6)	2 (6)	3 (9)	1 (3)	2 (6)	0
Decreased appetite	8 (23)	4 (11)	3 (9)	0	3 (9)	1 (3)	2 (6)	0
Headache	8 (23)	7 (20)	1 (3)	0	1 (3)	1 (3)	0	0
Hypomagnesemia	8 (23)	6 (17)	1 (3)	0	2 (6)	2 (6)	0	0
Cough	7 (20)	5 (14)	2 (6)	0	1 (3)	1 (3)	0	0
Anemia^	6 (17)	4 (11)	1 (3)	1 (3)	1 (3)	1 (3)	0	0
Dysuria	6 (17)	6 (17)	0	0	0	0	0	0

Carrizosa et al ASCO 2022

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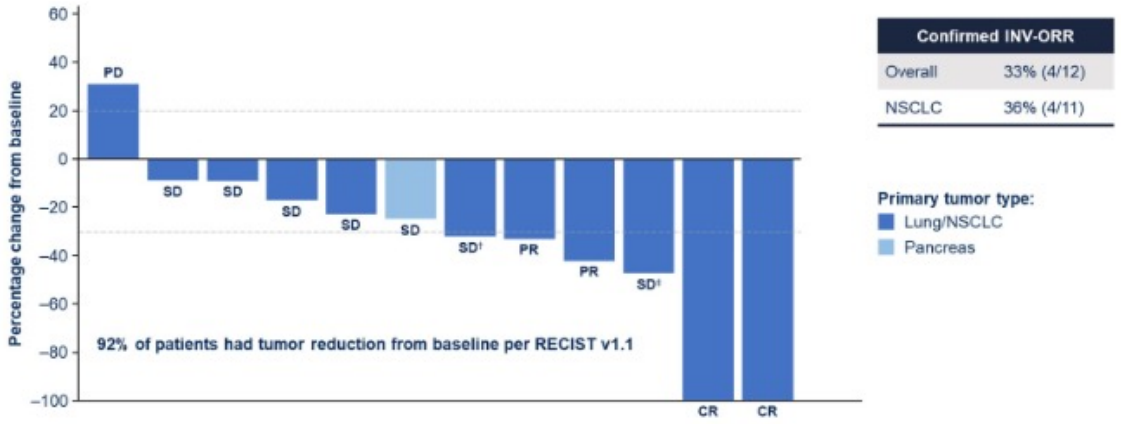
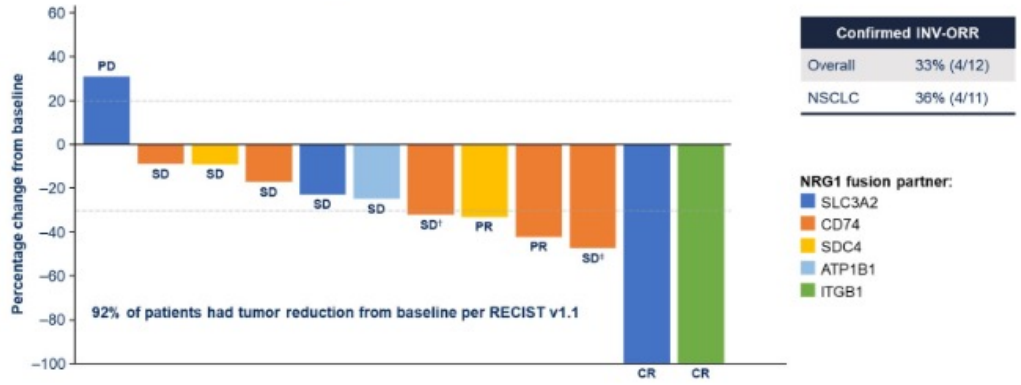
NRG1: CRESTONE study Seribantumab Efficacy

Efficacy of Seribantumab in Tumors Harboring NRG1 Fusions



†Unconfirmed PR, unable to be confirmed as subsequent scans showed patient in SD;
‡Unconfirmed PR, patient died due to lung infection (history of COVID-19 infection) before confirmatory scan was able to be completed, no evidence of clinical disease progression at time of death.
INV-ORR, investigator-assessed objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1
Visit cut-off: 18 April 2022

Efficacy of Seribantumab in Tumors Harboring NRG1 Fusions Regardless of Fusion Partner



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Visit cut-off: 18 April 2022

Carrizosa et al ASCO 2022

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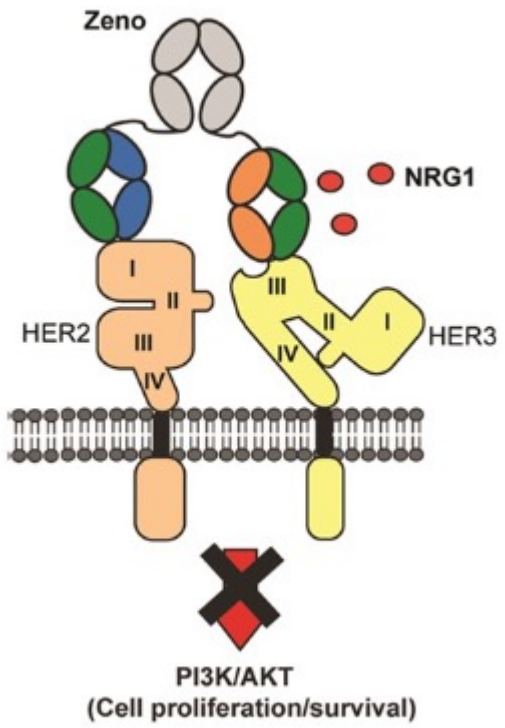
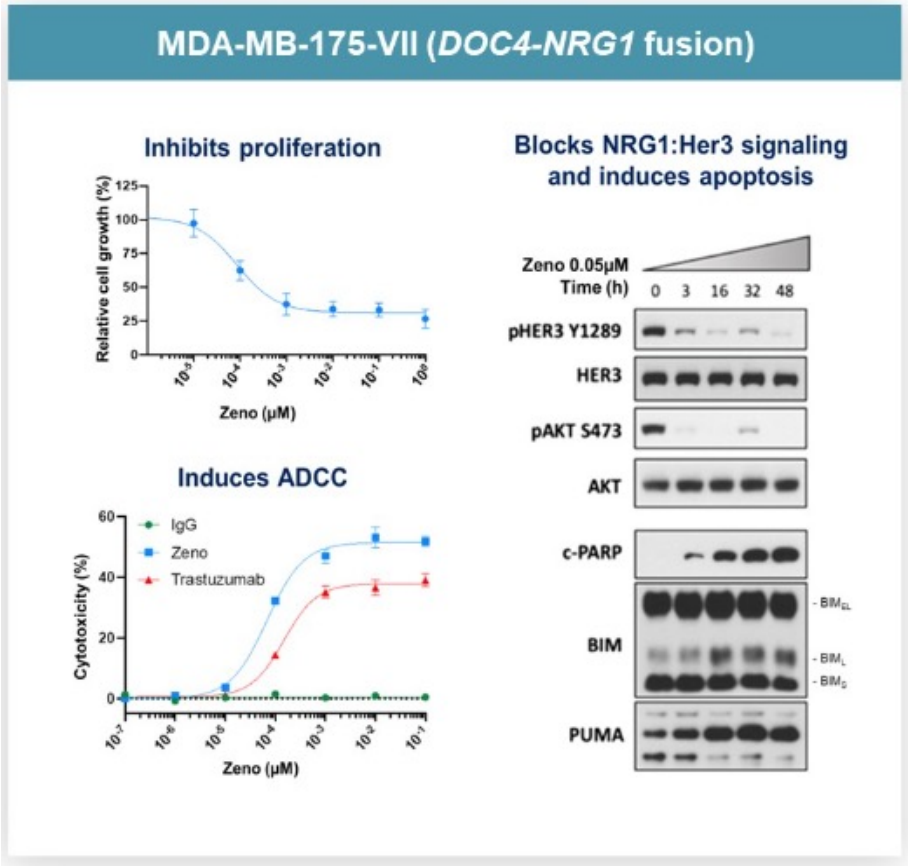
NRG1: Zenocutuzumab





- Bispecific antibody with enhanced ADCC activity
- Docks on HER2 and blocks NRG1 interaction with HER3, preventing heterodimerization

Schram et al ASCO 2022

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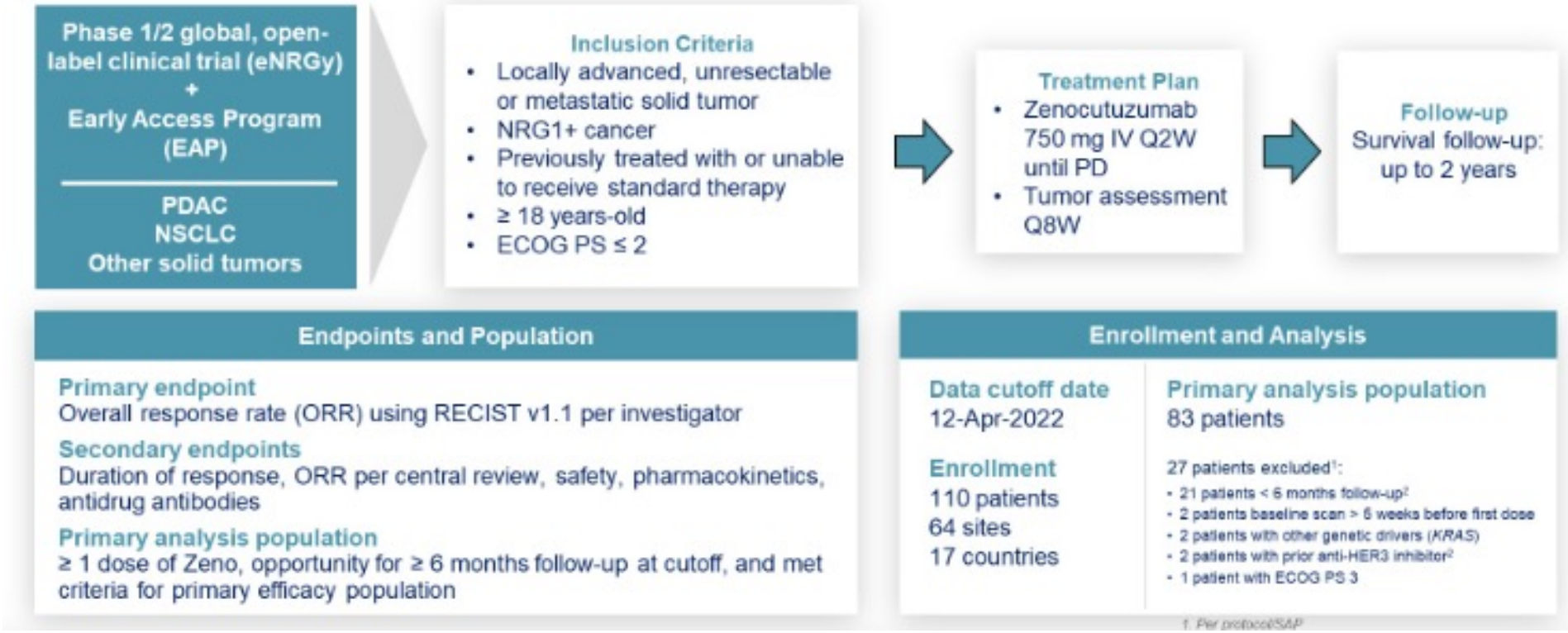
NRG1: Zenocutuzumab eNRGy and EAP trials



Schram et al ASCO 2022

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NRG1: Zenocutuzumab Adverse Events

	AEs Irrespective of Causality (>10%)			Treatment-Related AEs (>10% and all Grade 3-5)		
	ALL GRADES	GRADE 3-4	GRADE 5	ALL GRADES	GRADE 3-4[2]	GRADE 5
Patients with ≥1 AE	92%	36%	3%	61%	5%	0.5%
Diarrhea	32%	2%	-	21%	0.5%	-
Asthenia/fatigue	30%	4%	-	12%	0.5%	-
Nausea	20%	1%	-	10%	0.5%	-
Anemia	19%	3%	-	1%	-	-
Infusion-related reaction[3,4]	15%	1%	0.5%	15%	1%	0.5%[3]
Dyspnea	14%	4%	-	2%	0.5%	-
Vomiting	13%	0.5%	-	4%	-	-
Abdominal pain	12%	1%	-	2%	0.5%	-
Constipation	11%	-	-	2%	-	-
Decreased appetite	10%	0.5%	-	4%	-	-
AST increase	9%	3%	-	2%	0.5%	-
Cough	8%	0.5%	-	1%	0.5%	-
ALT increase	7%	3%	-	1%	0.5%	-
Myalgia	4%	0.5%	-	2%	0.5%	-
Neutropenia	3%	1%	-	2%	0.5%	-
Hypertension	1%	1%	-	0.5%	0.5%	-
Platelet count decrease	1%	0.5%		0.5%	0.5%	-
Hyperuricemia	0.5%	0.5%	-	0.5%	0.5%	-
Lymphadenitis	0.5%	0.5%	-	0.5%	0.5%	-
Hypoxia	0.5%	0.5%	-	0.5%	0.5%	-
Bacteremia	0.5%	0.5%	-	0.5%	0.5%	-

Schram et al ASCO 2022

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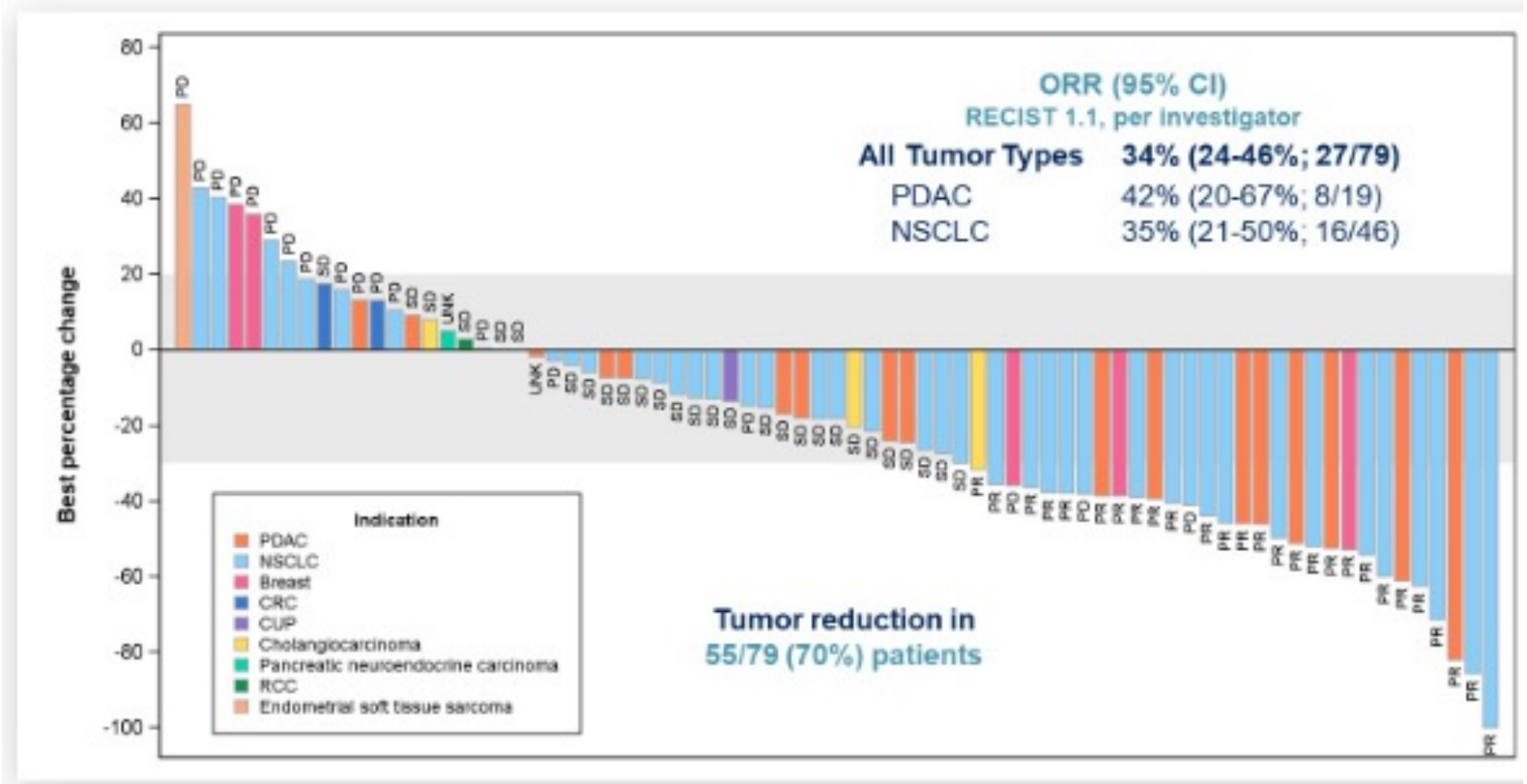
NRG1: Zenocutuzumab Efficacy



Schram et al ASCO 2022

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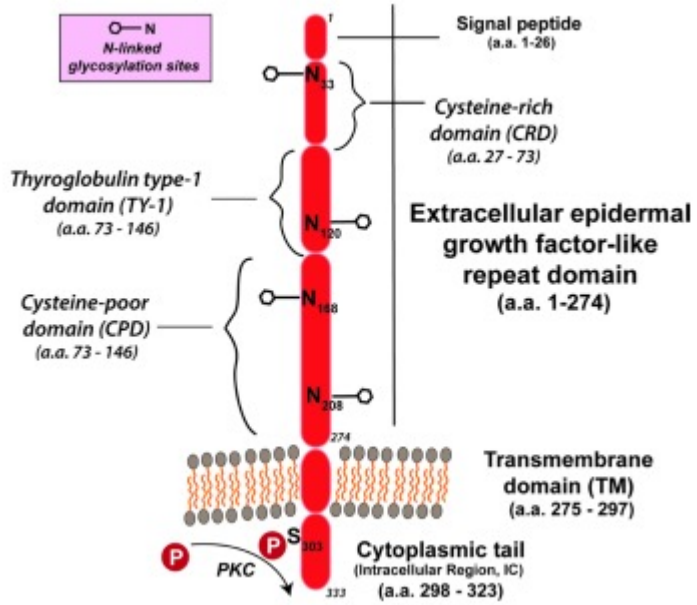
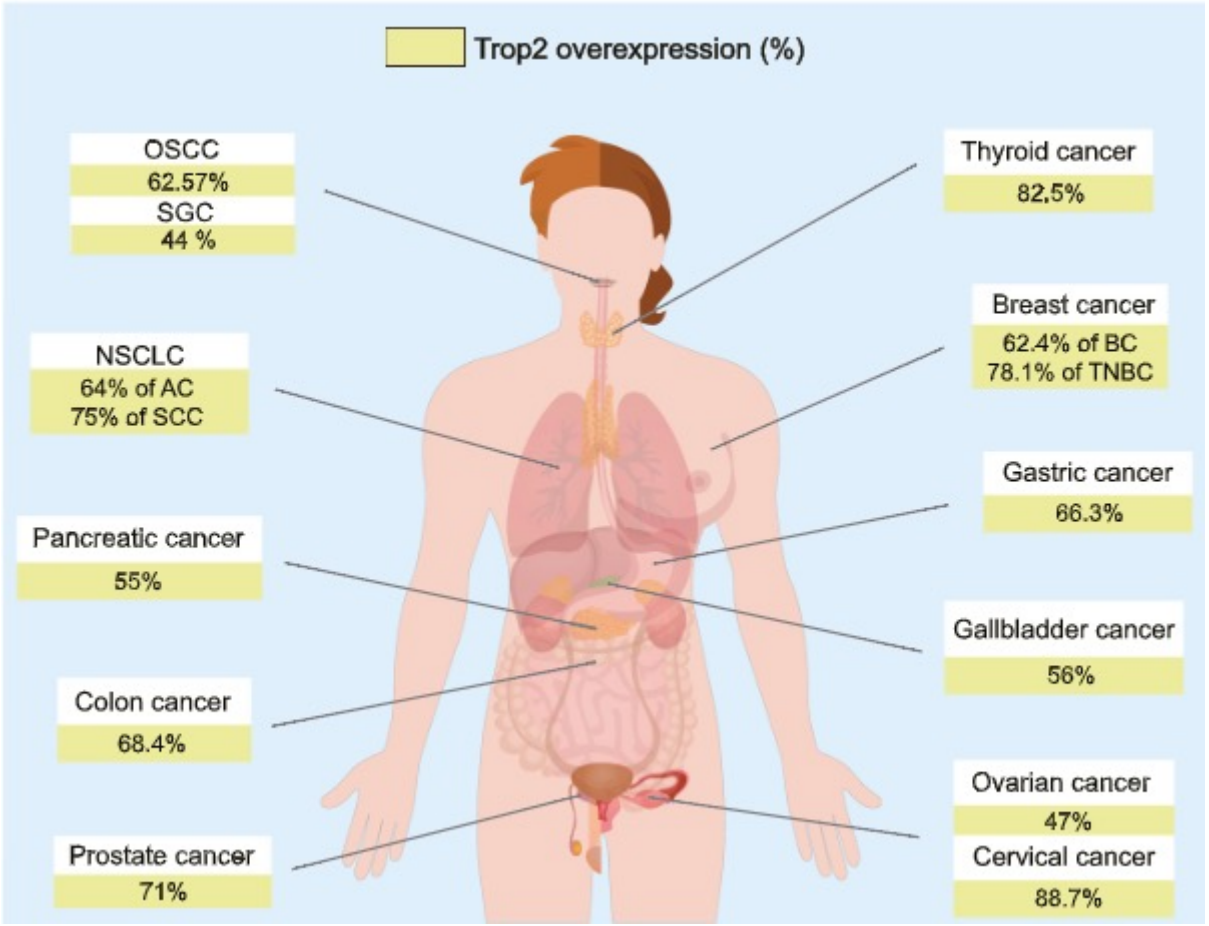
TROP2





Goldenberg et al Oncotarget 2018; Liu et al Pharmacol Therapeutics 2022

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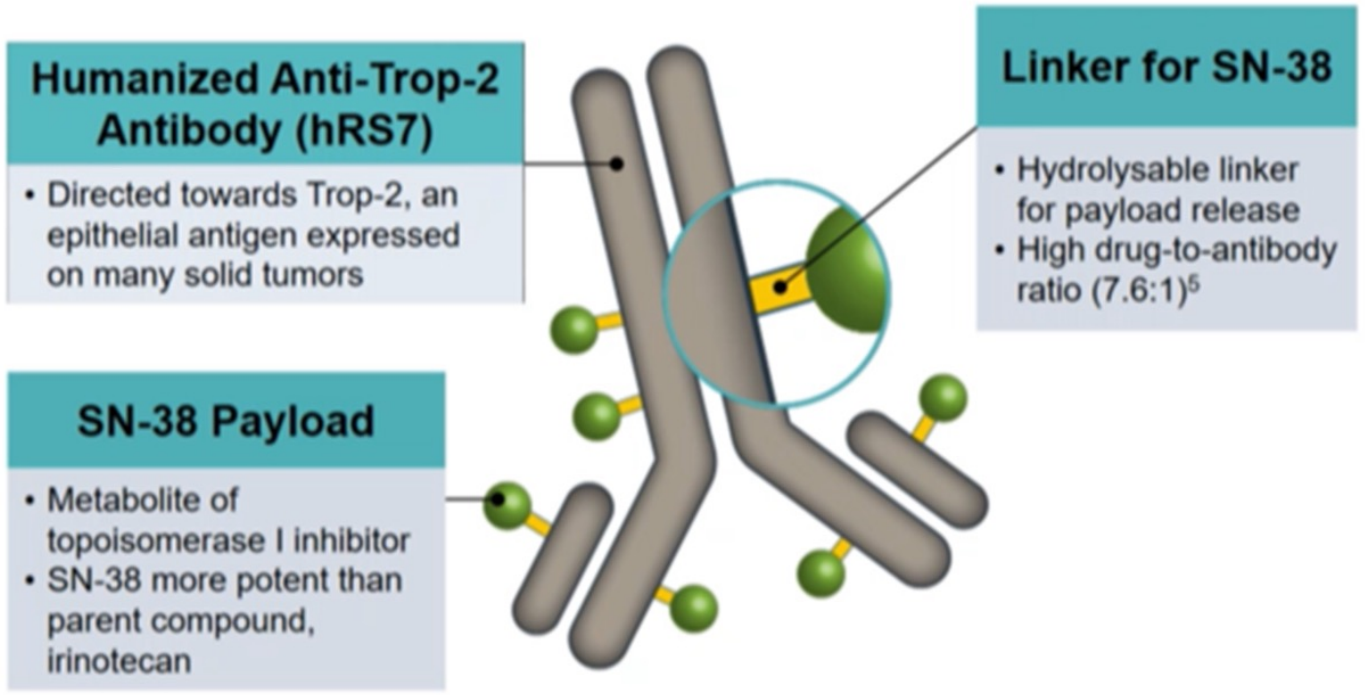
TROP2 ADCs: Sacituzumab Govitecan



Tagawa et al, ESMO 2019; Levy et al, WCLC 2021

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Sacituzumab in NSCLC

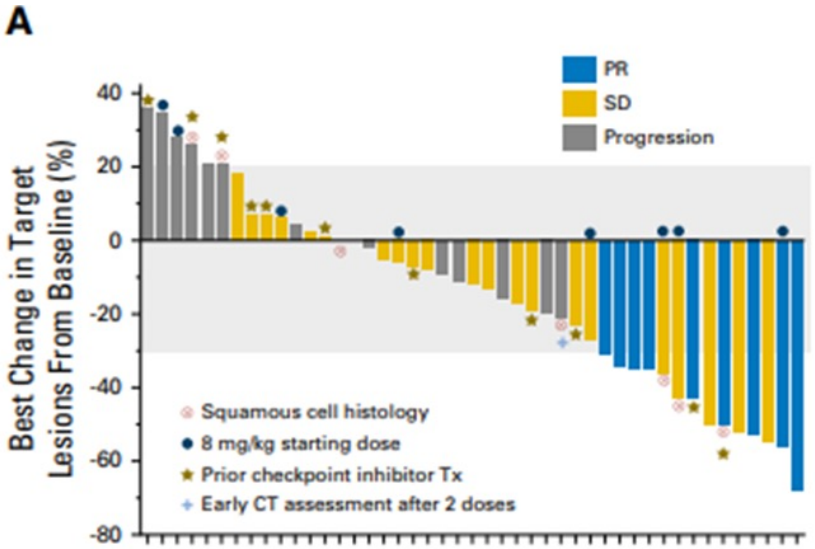

Table 2. Frequency of Adverse Events Regardless of Causality

	All Grades, No. (%)			Grade ≥ 3, No. (%)		
Adverse Event	All Patients	8 mg/kg Dose	10 mg/kg Dose	All Patients	8 mg/kg Dose	10 mg/kg Dose
No. of patients	54	8	46	54	8	46
Nausea	43 (80)	7 (88)	36 (78)	4 (7)	0 (0)	4 (9)
Diarrhea	33 (61)	5 (63)	28 (61)	4 (7)	1 (13)	3 (7)
Fatigue	25 (46)	3 (38)	22 (48)	3 (6)	0 (0)	3 (7)
Alopecia	21 (39)	3 (38)	18 (39)	NA	NA	NA
Neutropenia	20 (37)	2 (25)	18 (39)	15 (28)	1 (13)	14 (30)
Vomiting	19 (35)	4 (50)	15 (33)	2 (4)	1 (13)	1 (2)
Anemia	17 (31)	1 (13)	16 (35)	2 (4)	0 (0)	2 (4)
Constipation	17 (31)	3 (38)	14 (30)	0 (0)	0 (0)	0 (0)
Anorexia	13 (28)	0 (0)	13 (28)	1 (2)	0 (0)	1 (2)
Hypophosphatemia	12 (22)	1 (13)	11 (24)	1 (2)	0 (0)	1 (2)
Dehydration	10 (19)	0 (0)	10 (22)	2 (4)	0 (0)	2 (4)
Weight decrease	10 (19)	0 (0)	10 (22)	0 (0)	0 (0)	0 (0)
Leukopenia	10 (19)	2 (25)	8 (17)	5 (9)	1 (13)	4 (9)
Hypomagnesemia	9 (17)	0 (0)	9 (20)	0 (0)	0 (0)	0 (0)
Dyspnea	8 (15)	2 (25)	6 (13)	2 (4)	1 (13)	1 (2)
Pneumonia	7 (13)	1 (12)	6 (13)	5 (9)	0 (0)	5 (11)

Abbreviation: NA, not applicable.

- Tetrapeptide based cleavable linker

Heist et al, JCO 2017

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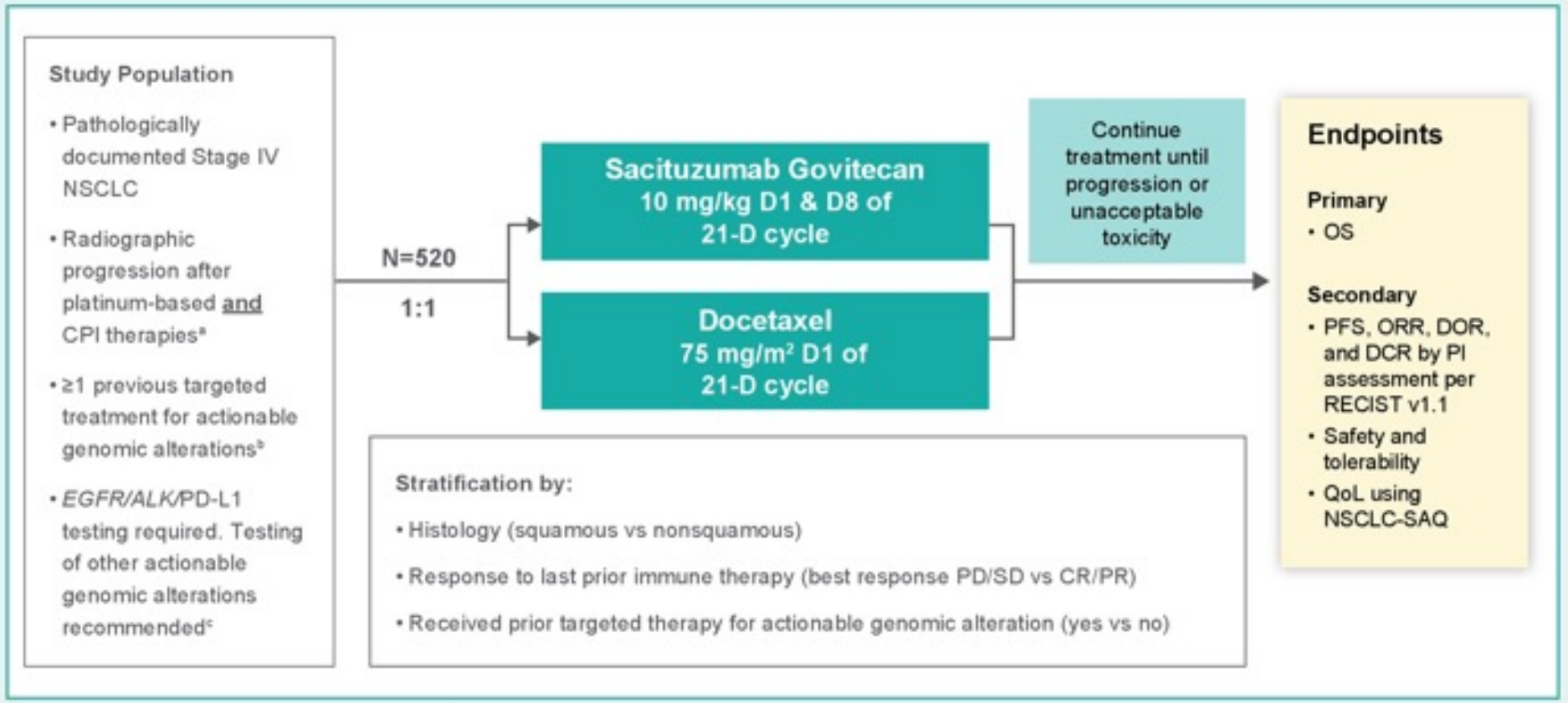
EVOKE-1

Study Design

Figure 2. EVOKE-01: An Open-Label, Global, Multicenter, Randomized, Phase 3 Study of SG Versus Docetaxel in NSCLC Progressing After Platinum-Based and CPI Therapies (NCT05089734)

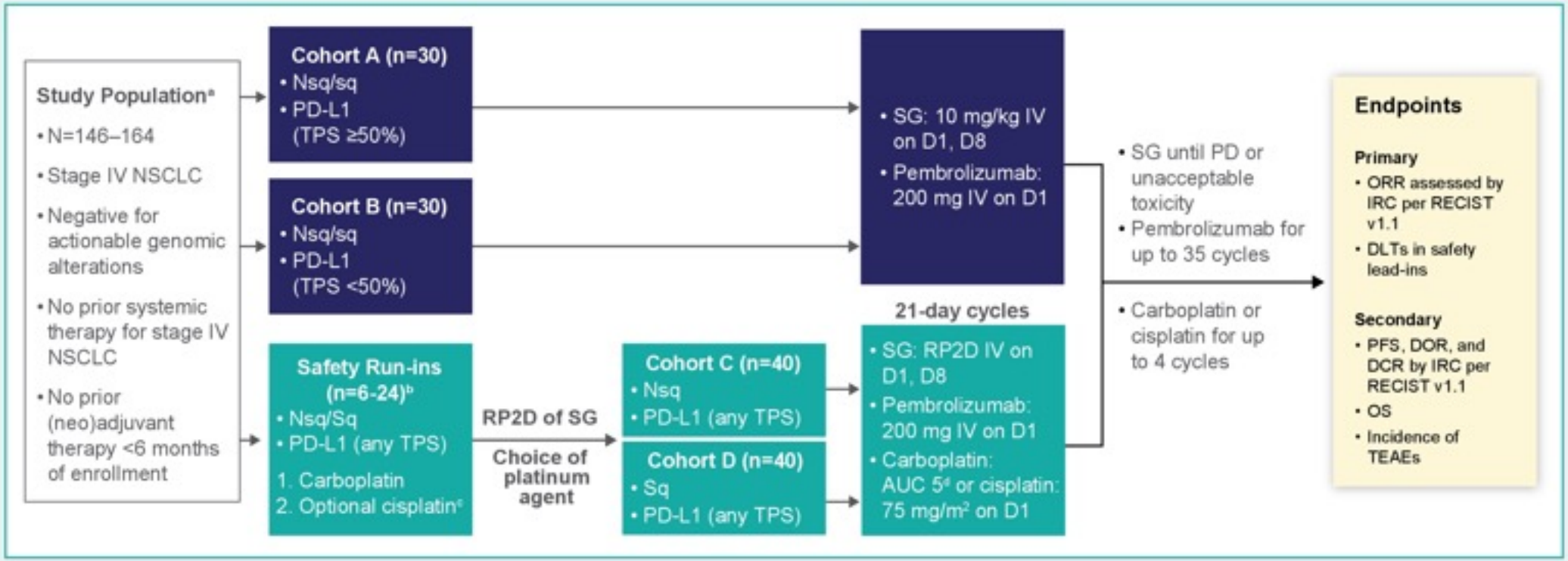


Garassino et al, ASCO 2022

EVOKE-2

Study Design

Figure 2. EVOKE-02: A Global Phase 2 Open-Label, Multicenter, Multicohort, Study of Sacituzumab Govitecan Plus Pembrolizumab +/- Platinum Chemotherapy in First-Line Metastatic NSCLC (NCT05186974)



Garon et al, ASCO 2022

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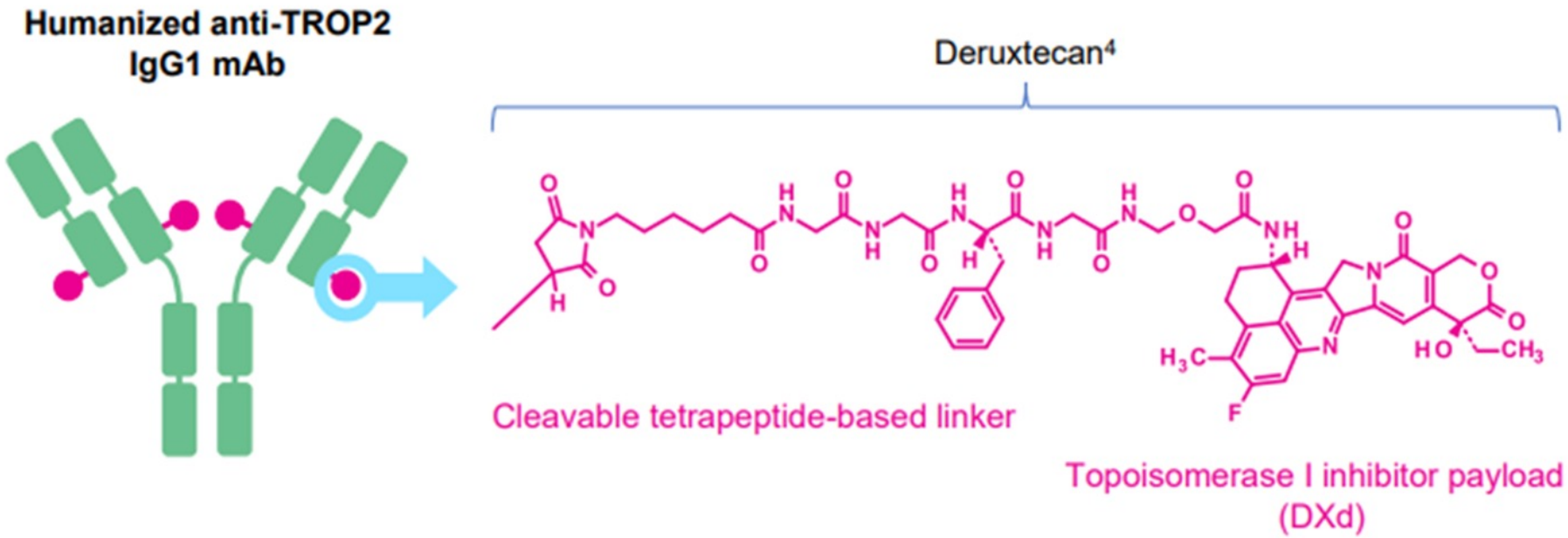
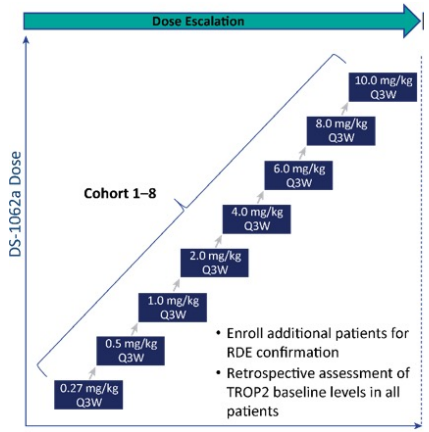
TROP2 ADCs: Datopotamab Deruxtecan



- Humanized anti-TROP2 IgG1 mAb
- Tetrapeptide based cleavable linker
- Topoisomerase I inhibitor payload, an exatecan derivative

Levy et al, WCLC 2021

Datopotamab deruxtecan: TROPION PanTumor01 Study Design



Key Inclusion Criteria

- Relapsed/refractory advanced/metastatic NSCLC
- Unselected for TROP2 expression[c]
- Age ≥18 (US) or ≥20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST version 1.1
- Stable, treated brain metastases allowed

Dose Escalation

Dato-DXd 0.27 to 10 mg/kg Q3W[d]

MTD established: 8 mg/kg Q3W

Dose Expansion[b]

NSCLC cohort

- 50 patients at 4 mg/kg
- 50 patients at 6 mg/kg
- 80 patients at 8 mg/kg

TNBC, HR+/HER2−, and other tumor types

Primary objectives

- Establish MTD; safety, tolerability

Secondary objectives[e]

- Efficacy,[f] PK, ADAs

6-mg/kg dose chosen for further development[6,7]

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Heist et al WCLC 2019; Meric-Bernstam et al ASCO 2021; Garon et al, WCLC 2021

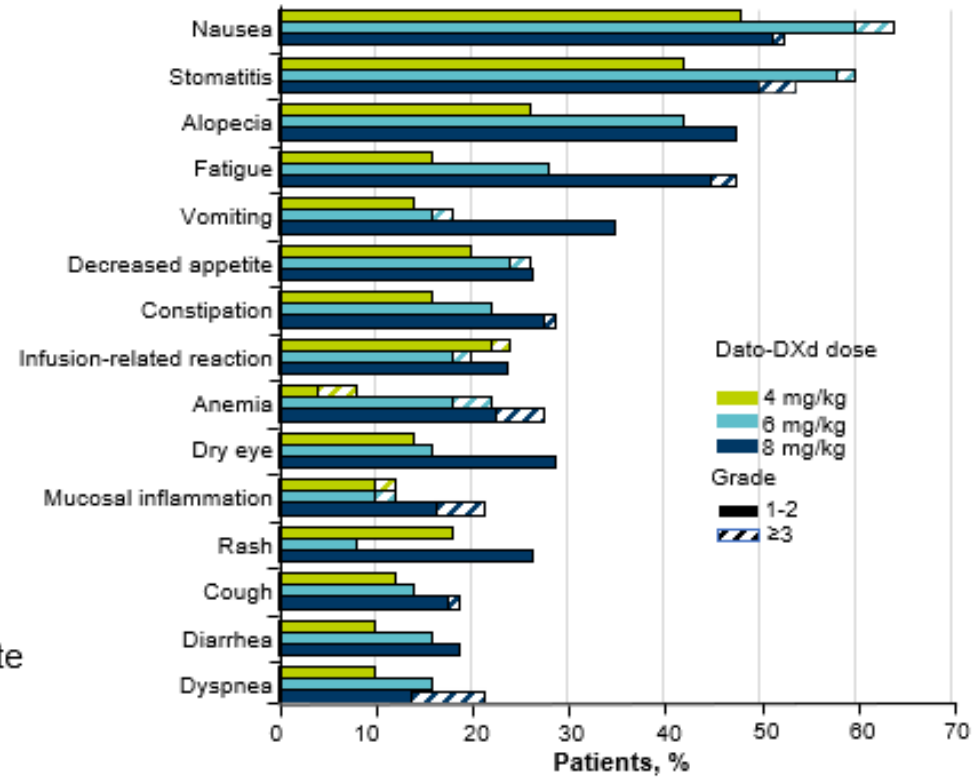
TROP2: Datopotamab deruxtecan Adverse Events

Overall Safety Summary

Patients, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grades 3-4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)

- The safety profile was manageable with mainly mild/moderate toxicity; TEAEs were primarily nonhematologic

TEAEs in ≥15% of Patients[b]



Data cutoff: April 6, 2021.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] Cases of ILD adjudicated as drug related comprised 5 patients in the 4-mg/kg cohort (1 grade 1, 3 grade 2, 1 grade 3), 3 patients in the 6-mg/kg cohort (2 grade 2, 1 grade 4), and 11 patients in the 8-mg/kg cohort (2 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). [b] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).

Garon et al, WCLC 2021

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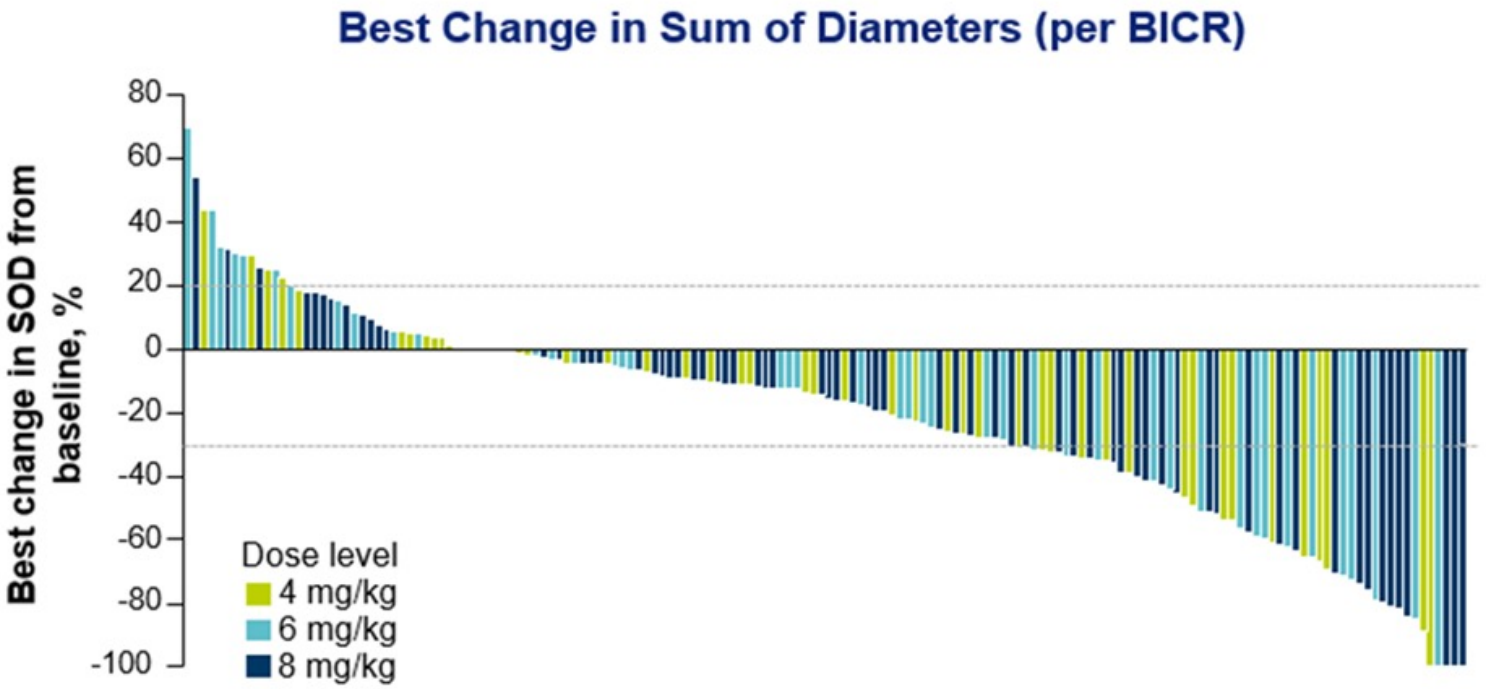
TROP2: Datopotamab deruxtecan TROPION PanTumor01 Efficacy in NSCLC



Best Overall Response (BICR)

Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

Garon et al, WCLC 2021

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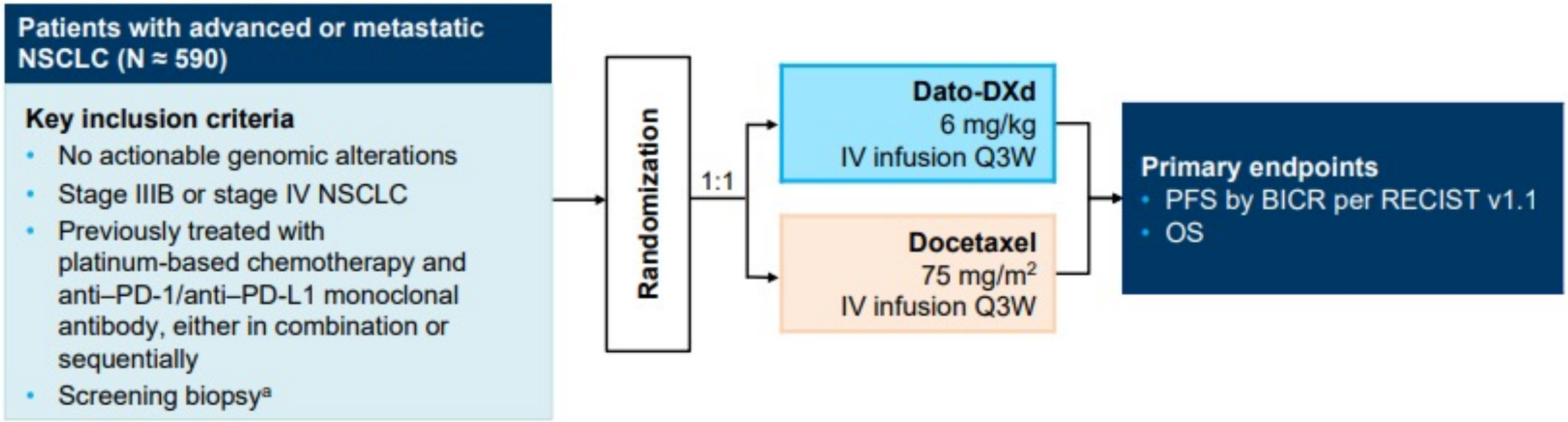
TROPION-Lung01



Yoh et al, ASCO 2021

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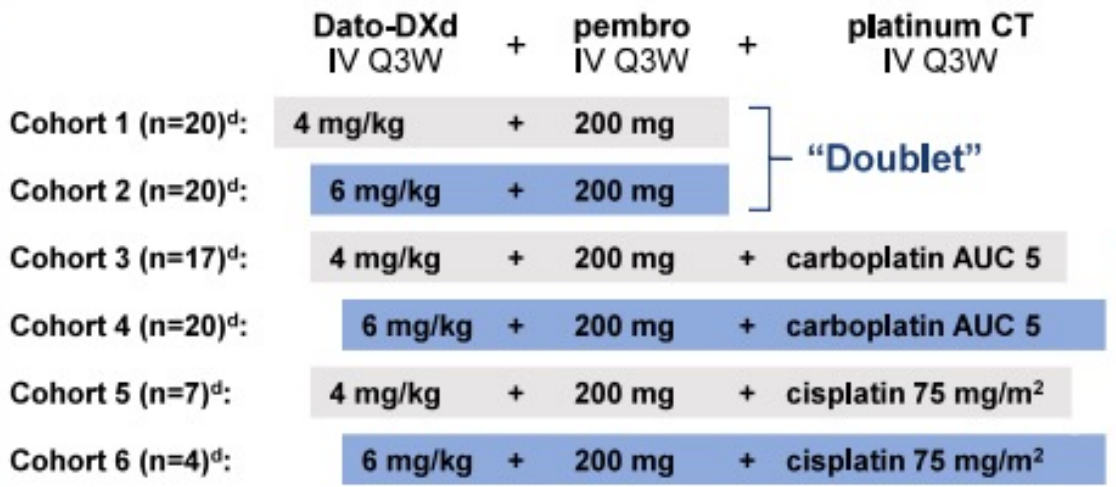
TROPION-Lung02

Key eligibility

- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and anti-drug antibodies

Levy et al, WCLC 2022

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TROPION-Lung02 Pt Characteristics

Characteristic		Doublet (n=40)	Triplet (n=48)
Age, median (range), years		68 (44-77)	64 (33-84)
Male, n (%)		28 (70%)	33 (69%)
Histology, n (%)[a]	Non-squamous	28 (70%)	41 (85%)
	Squamous	11 (28%)	7 (15%)
History of brain metastases, n (%)		8 (20%)	10 (21%)
PD-L1 expression, n (%)[b]	<1%	13 (33%)	21 (44%)
	1-49%	13 (33%)	14 (29%)
	≥50%	12 (30%)	11 (23%)
Prior lines of therapy, median[c]		1	0
Previous systemic treatment, n (%)	Immunotherapy	12 (30%)	18 (38%)
	Platinum CT	24 (60%)	17 (35%)
Dato-DXd combination line of therapy, n (%)	1L	13 (33%)[d]	30 (63%)[d]
	2L+	27 (68%)[d]	18 (38%)[d]

At the time of data cutoff for doublet and triplet therapy, respectively:

- Study treatment was ongoing in 53% and 77% of patients
- Median treatment duration was 4.1 months and 3.0 months
- Median follow-up was 6.5 months and 4.4 months

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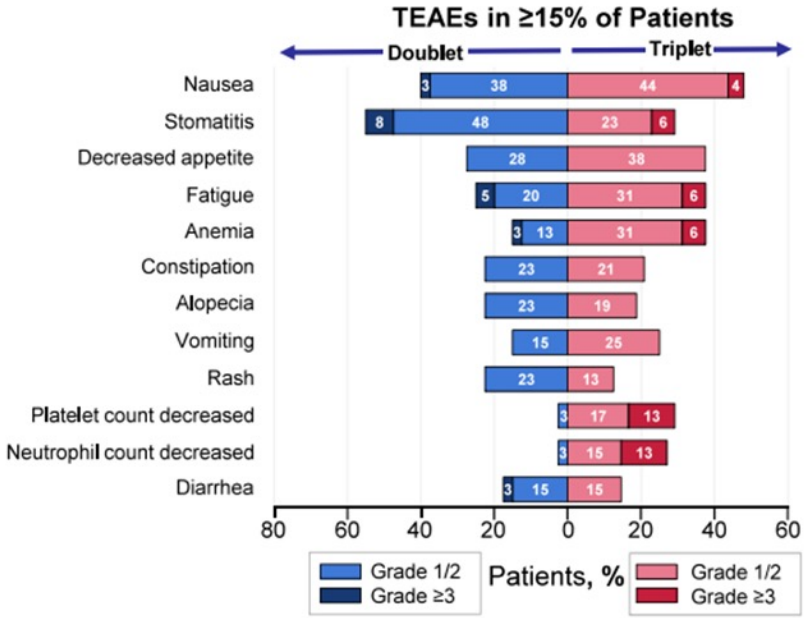
TROPION-Lung02 Safety and Efficacy – Preliminary Data



Events, n (%)	Doublet (n=40)	Triplet (n=48)
TEAEs	37 (93%)	47 (98%)
Study treatment-related[a]	33 (83%)	46 (96%)
Grade ≥3 TEAEs	16 (40%)	29 (60%)
Study treatment-related[a]	14 (35%)	26 (54%)
Serious TEAEs	9 (23%)	13 (27%)
Study treatment-related	4 (10%)	7 (15%)
TEAEs associated with		
Death[b]	2 (5%)	1 (2%)
Discontinuation due to any drug	9 (22%)	9 (19%)
Discontinuation due to Dato-DXd	6 (15%)	5 (10%)
ILD adjudicated as drug related[c]		
Grade 1/2	2 (5%)	0
Grade 3	1 (3%)	1 (2%)

BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

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Levy et al, WCLC 2022

Ongoing trials of Sacituzumab govitecan and Datopotamab deruxtecan

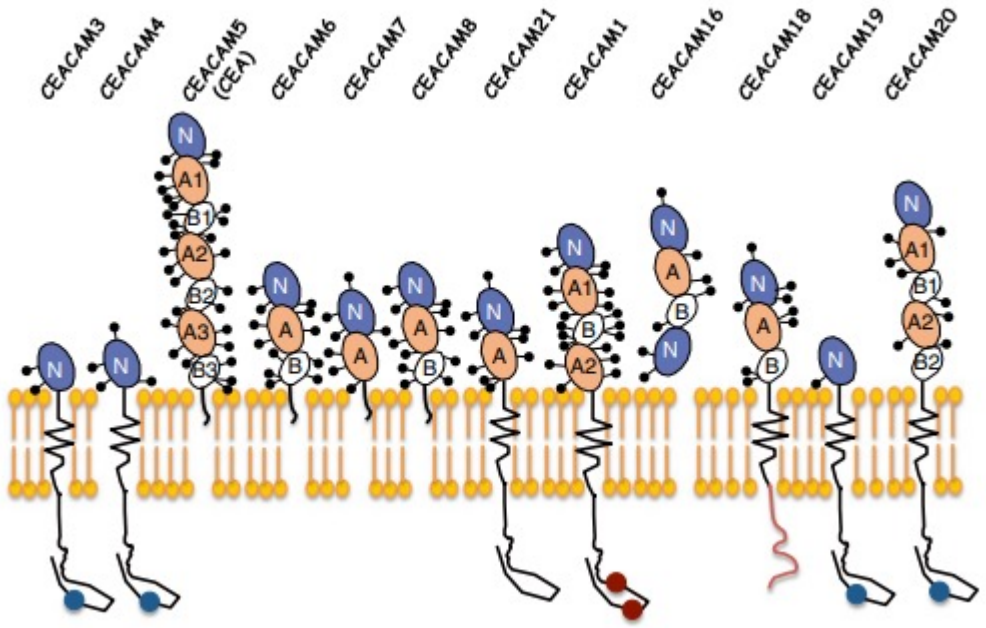
TROPION-Lung01	III	Dato-DxD Docetaxel	2L/3L	NCT04656652
TROPION-Lung02	IB	Dato-DxD + pembro + pembro + platinum	1L/2L	NCT04526691
TROPION-Lung04	IB	Dato-DxD + durva + durva + platinum	1L/2L	NCT04612751
TROPION-Lung05	II	Dato-DxD	Genomic alterations	NCT04484142
TROPION-Lung07	III	Dato-DXd + pembro + platinum Dato-Dxd + pembro Pembro + pemetrexed + platinum	1L PDL1 < 50%	NCT05555732
TROPION-Lung08	III	Dato-Dxd + pembro Pembro	1L PDL1 $\geq$ 50%	NCT05215340
EVOKE-1	III	Sacituzumab Docetaxel	2L/3L	NCT05089734
EVOKE-2	II	Sacituzumab + pembro Sacituzumab + pembro + platinum	1L	NCT05186974

Other TROP2 ADCs in clinical development

Study	Drug	Phase	Payload
NCT04152499	SKB264	I-II	belotecan-derived payload
NCT04601285	JS108	I	Tub196
NCT05174637	FDA018-ADC	I	undisclosed

From clinicaltrials.gov

CEACAM5



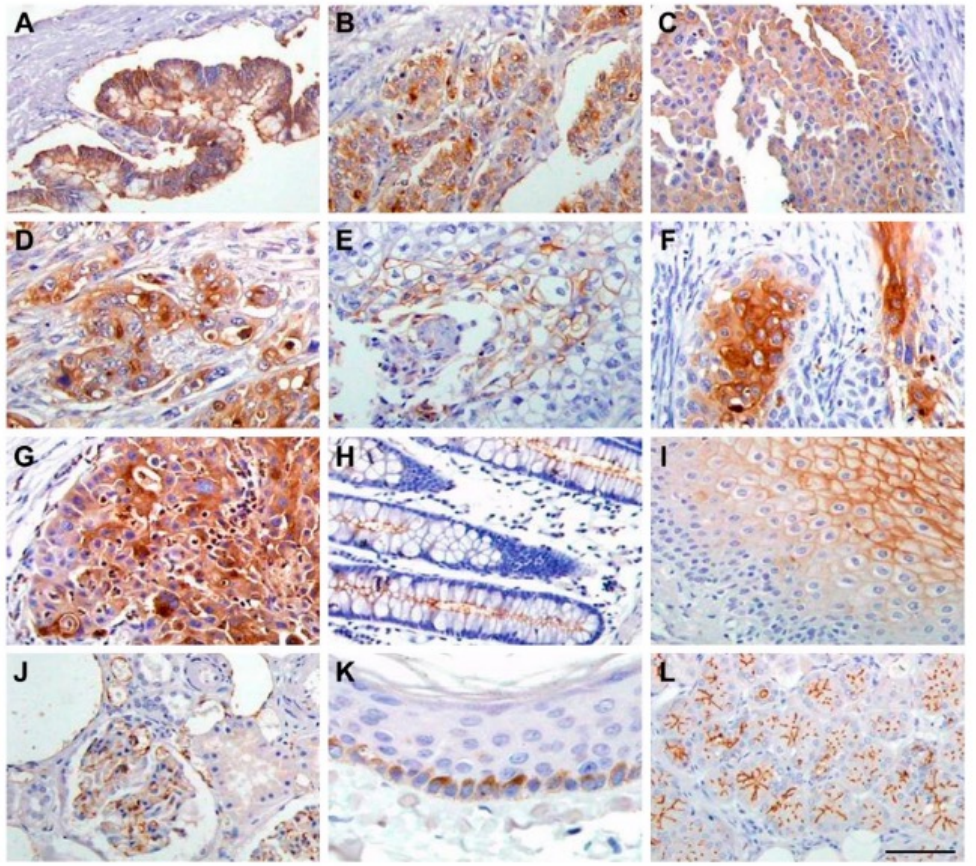
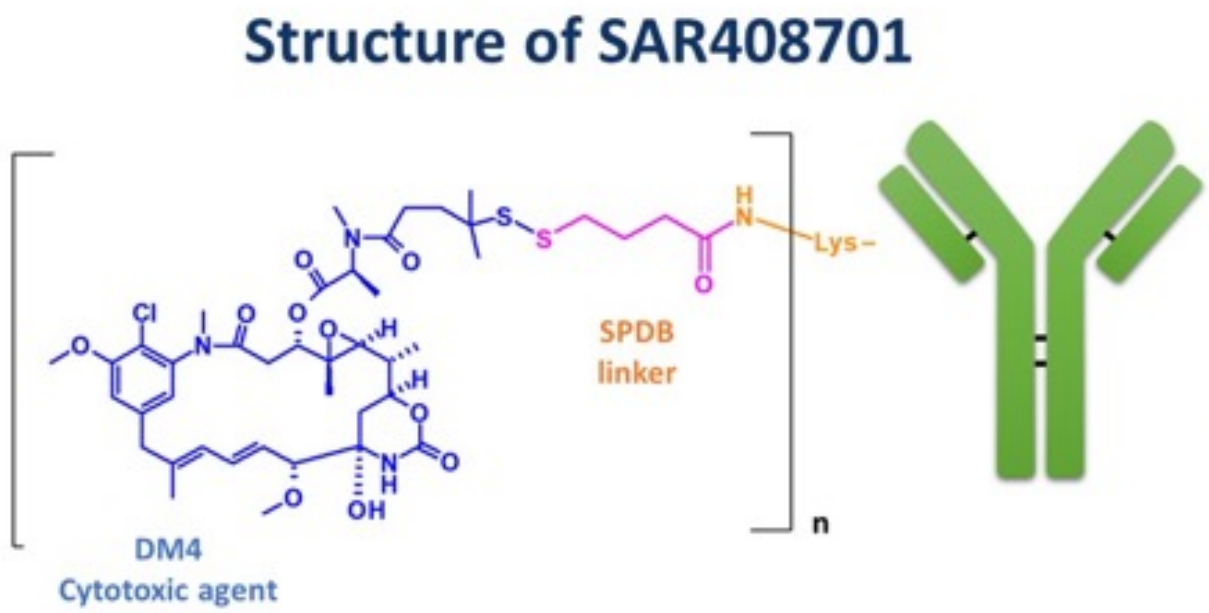


Figure 3. CEACAM5 immunostaining in different tumor tissues and normal tissues. (A) gastric carcinoma; (B) adenocarcinoma of colon; (C) epithelial cancer of bladder; (D) adenocarcinoma of rectum; (E) squamous cell carcinoma of lung; (F) squamous cell carcinoma of cervix; (G) pancreatic adenocarcinoma; (H) colon; (I) esophagus; (J) kidney; (K) skin; (L) sublingual gland. Scale, 200 μm.

Beauchemin and Arabzadeh Cancer Metastasis Rev 2013; Zhou et al, J Histochem Cytochem 2015

CEACAM5 ADC: SAR408701



Humanized antibody: Specific for **CEACAM5**

Cytotoxic agent: Maytansinoid **DM4** (inhibits tubulin polymerization)

SPDB linker: Cleavable inside cells

Gazzah et al ASCO 2020

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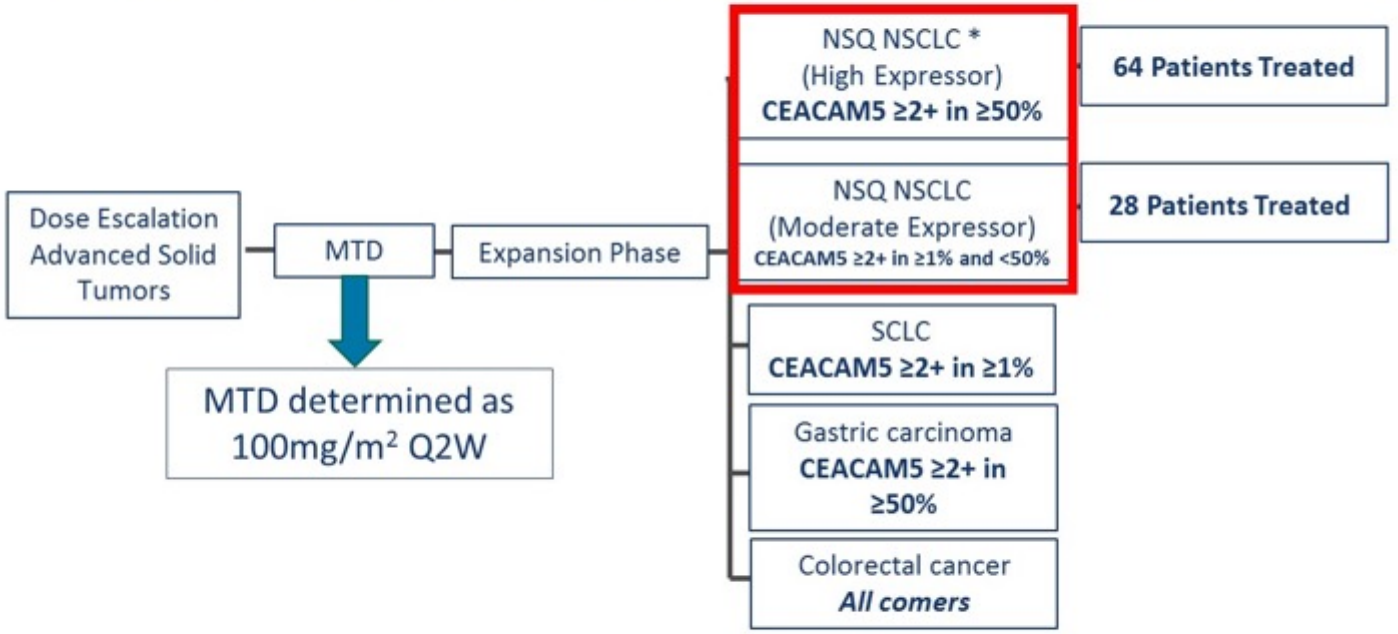
CEACAM5 ADC Study Design: SAR408701

A first-in-human study for the evaluation of the safety, PK and antitumor activity of SAR408701 in patients with advanced solid tumors (NCT02187848)



Primary endpoints: DLT (escalation phase), overall response rate (ORR; expansion phase)
Secondary endpoints: Safety, recommended Phase 2 dose identification, duration of response (DOR)
*High Expressor NSCLC – 2 interim analyses (at first 15 treated patients and at first 30 treated patients)

Expansion Phase in NSCLC

Inclusion restricted with CEACAM5 expression, via IHC testing in most recent archival tissue sample

- **High expressor cohort: CEACAM5 at ≥50% at ≥2+ intensity**
  - **20% of NSQ NSCLC**
- **Moderate expressor cohort: CEACAM5 between ≥1% and <50% at ≥2+ intensity**
  - **24% of NSQ NSCLC**

- Tumor assessments - every 4 cycles (8 weeks)

Gazzah et al ASCO 2020

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CEACAM5 ADC: SAR408701 Adverse Events

Preferred Term	SAR408701 100 mg/m² Q2W (n=92)	
	All Grades, n (%)	Grade ≥3, n (%)
Any class, TEAEs ≥ 10%	92 (100%)	47 (51.1%)
Corneal AE (Keratopathy/Keratitis)	35 (38.0%)	10 (10.9%)
Asthenia	34 (37.0%)	4 (4.3%)
Peripheral neuropathy (SMQ*)	25 (27.2%)	1 (1.1%)
Diarrhea	21 (22.8%)	1 (1.1%)
Dyspnea	20 (21.7%)	10 (10.9%)
Decreased appetite	19 (20.7%)	0
Cough	14 (15.2%)	0
Nausea	12 (13.0%)	1 (1.1%)
Arthralgia	10 (10.9%)	0
Constipation	10 (10.9%)	0

Laboratory Abnormalities	SAR408701 100 mg/m² Q2W (n=92)	
	All Grades, n (%)	Grade ≥3, n (%)
Hematological toxicity		
Neutropenia	4 (4.4%)	0
Anemia	69 (75.8%)	2 (2.2%)
Thrombocytopenia	11 (12.2%)	0

Dyspnea was the most frequent serious TEAE, reported in 5 (5.4%) patients, all as a symptom of progressive disease.

*Standardized MedDRA Queries (SMQ): "peripheral neuropathy" (broad + narrow)

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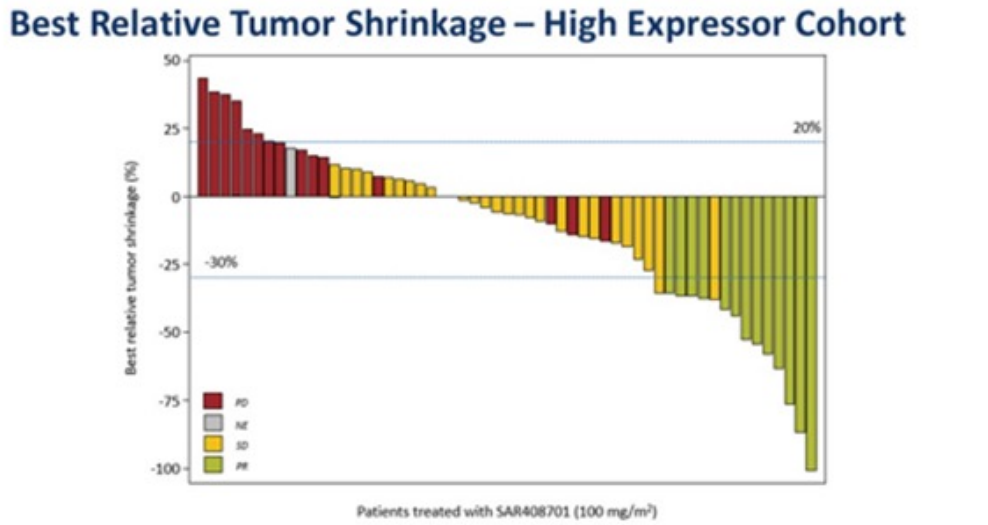
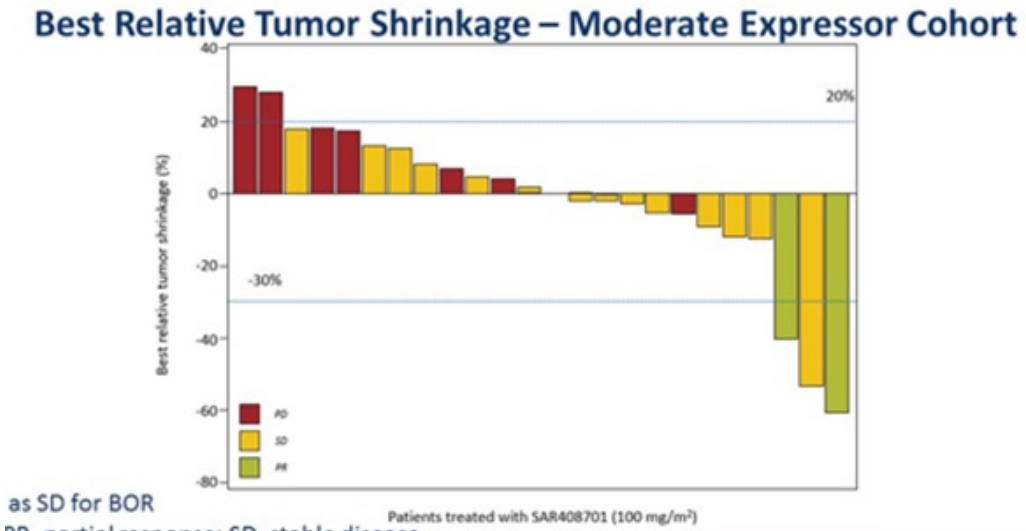
CEACAM5 ADC: SAR408701 Efficacy





as SD for BOR

PR, partial response; SD, stable disease.

Response, n (%)	High expressors (n = 64)	Moderate expressors (n = 28)
ORR [95% CI]	13 (20.3%) [12.27-31.71]	2 (7.1%) [1.98-22.65]
Confirmed PR	13 (20.3%)	2 (7.1%)
SD	28 (43.8%)	15 (53.6%)
DCR	41 (64.1%)	17 (60.7%)
PD	21 (32.8%)	10 (35.7%)
NE	2 (3.1%)	1 (3.6%)

Gazzah et al ASCO 2020

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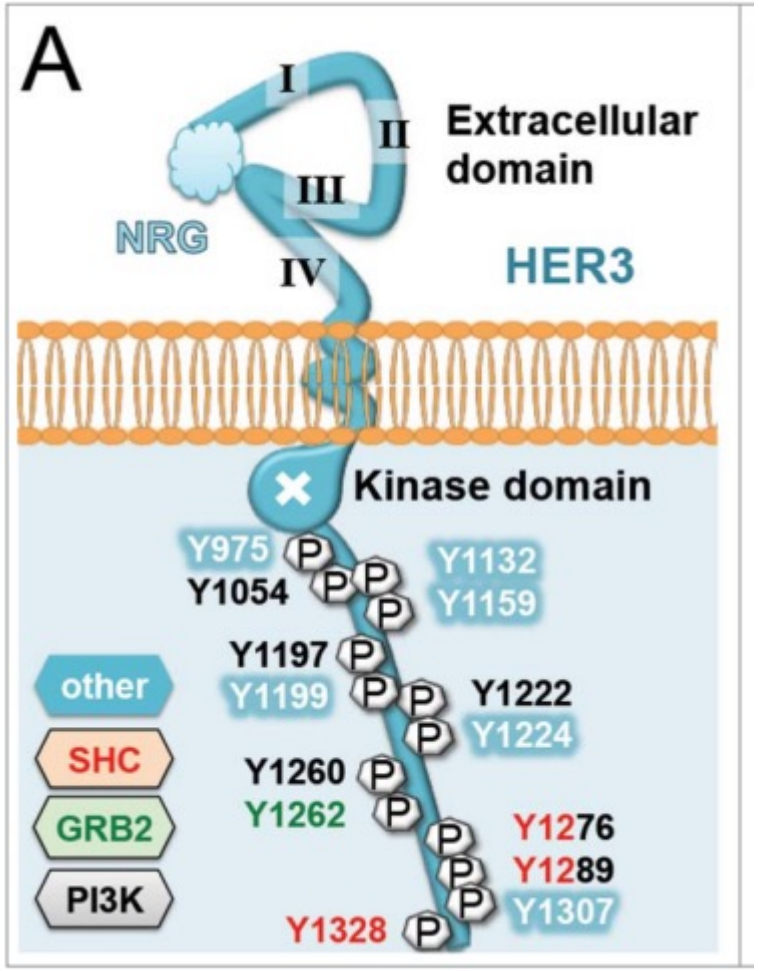
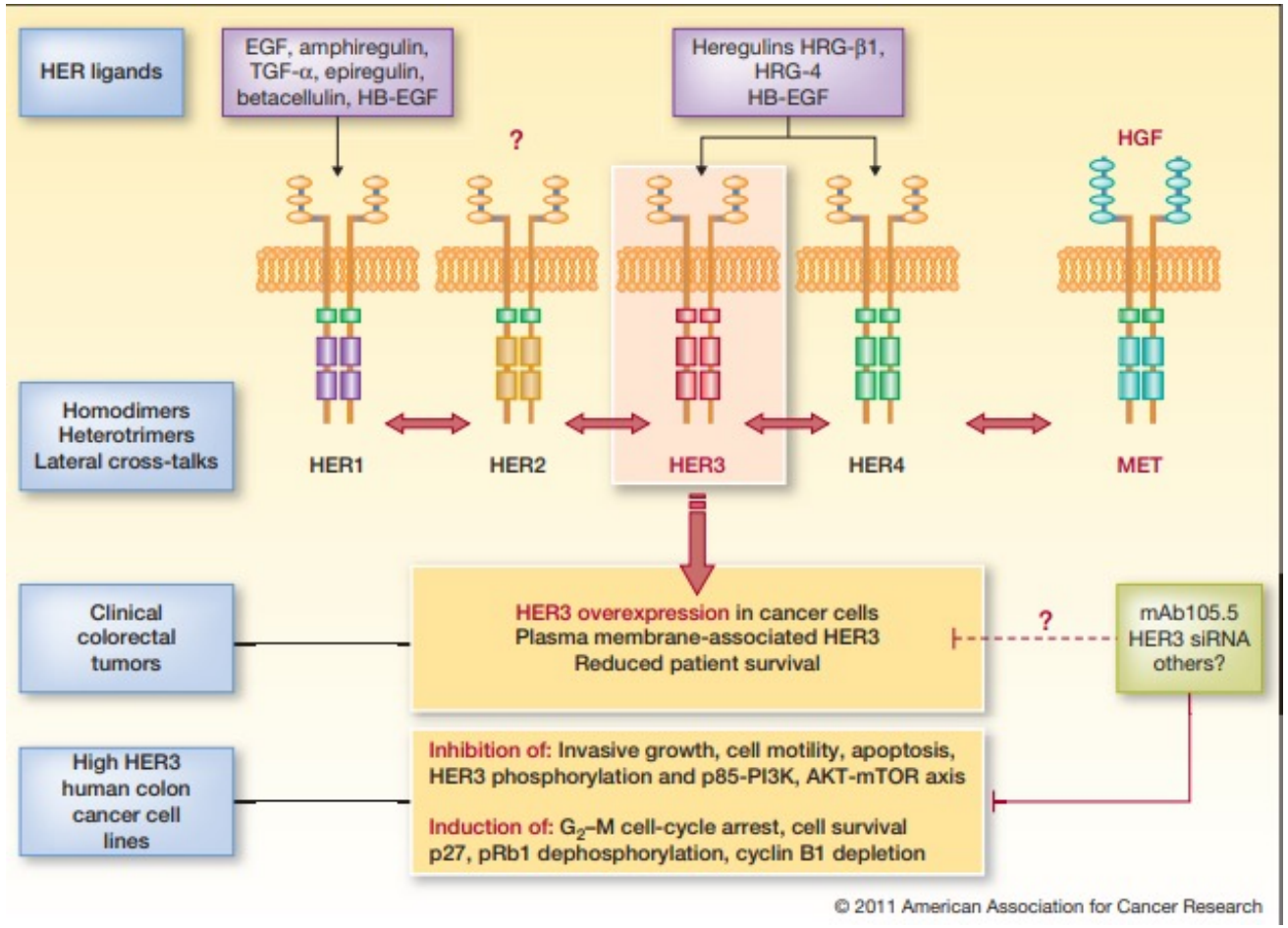
HER3





Gaboriet et al Hum Vacc Immuno 2015; Gespach CCR 2011

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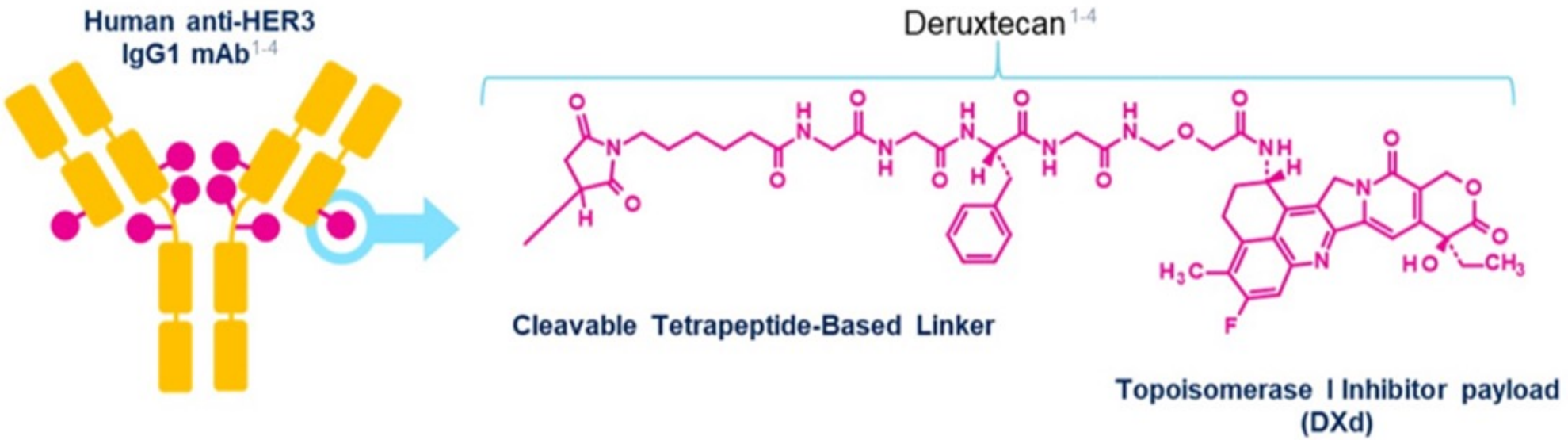
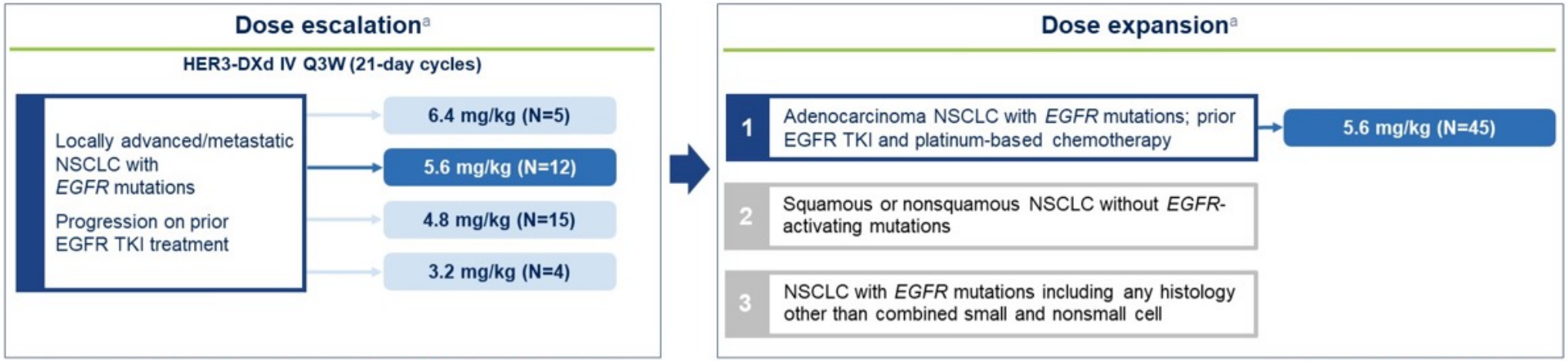
HER3 ADC: Patritumab Deruxtecan



- Humanized HER3 IgG1 mAb
- Tetrapeptide based cleavable linker
- Topoisomerase I inhibitor payload, an exatecan derivative

Janne et al ASCO 2021

HER3 ADC: U31402-A-U102 Patritumab Deruxtecan Study Design



57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

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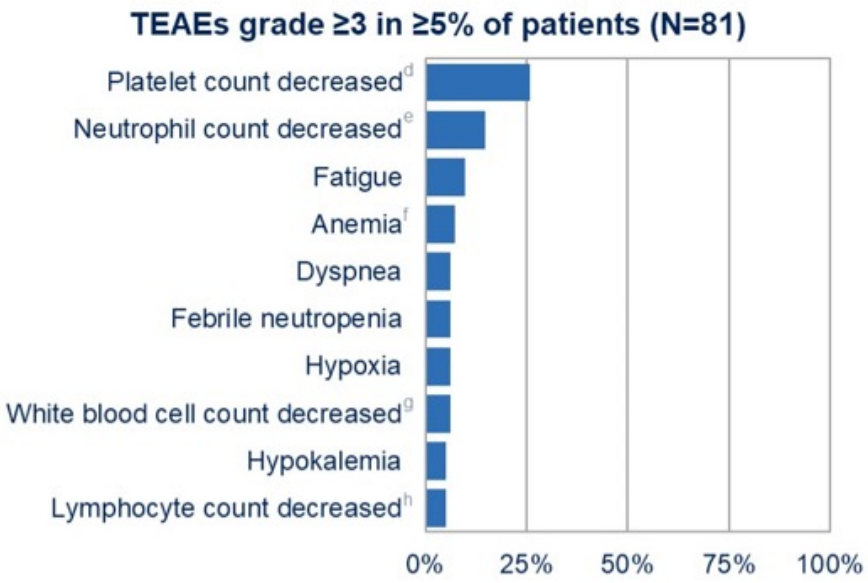
HER3 ADC: Patritumab Deruxtecan Adverse Events

TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[c]	4 (7)	4 (5)
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0



- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5
- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

Data cutoff: September 24, 2020.
[a]TEAEs associated with treatment discontinuation were fatigue (2), nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b]TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c]One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d]Includes thrombocytopenia. [e]Includes neutropenia. [f]Includes hemoglobin decreased. [g]Includes leukopenia. [h]Includes lymphopenia.

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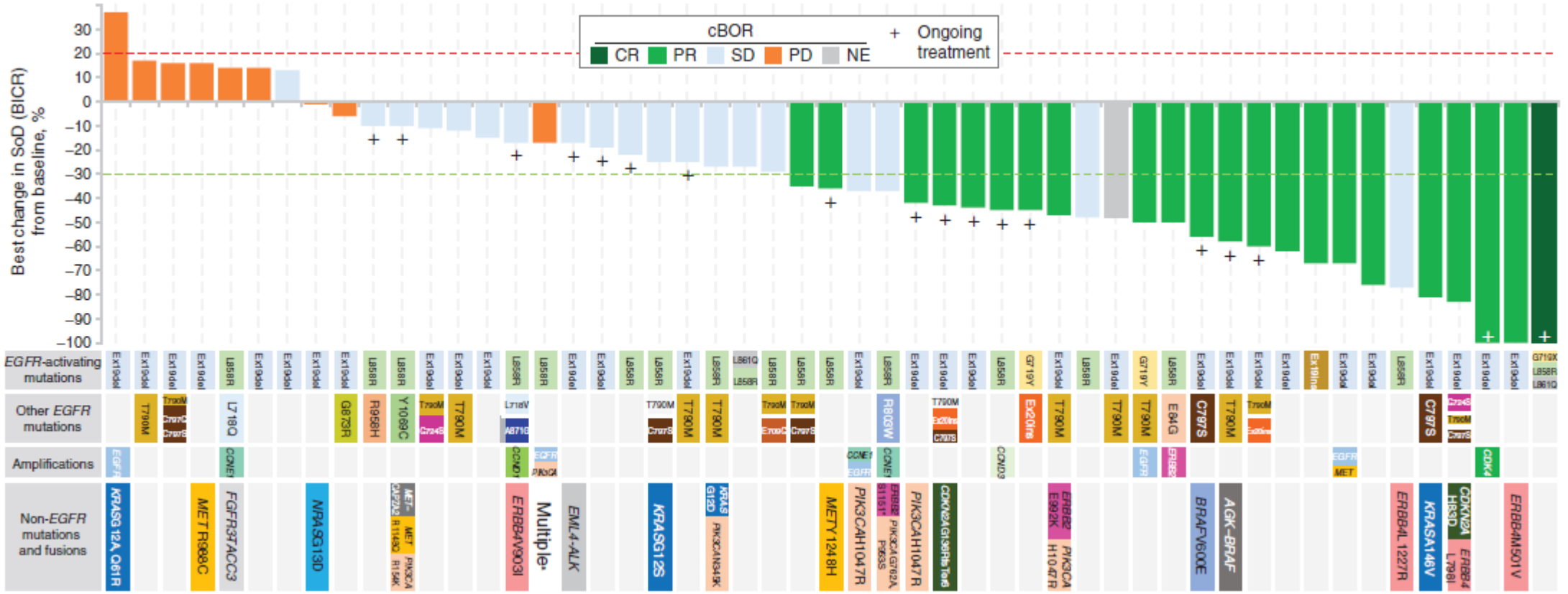
HER3 ADC: Patritumab Deruxtecan Efficacy



Janne et al Cancer Discovery 2022

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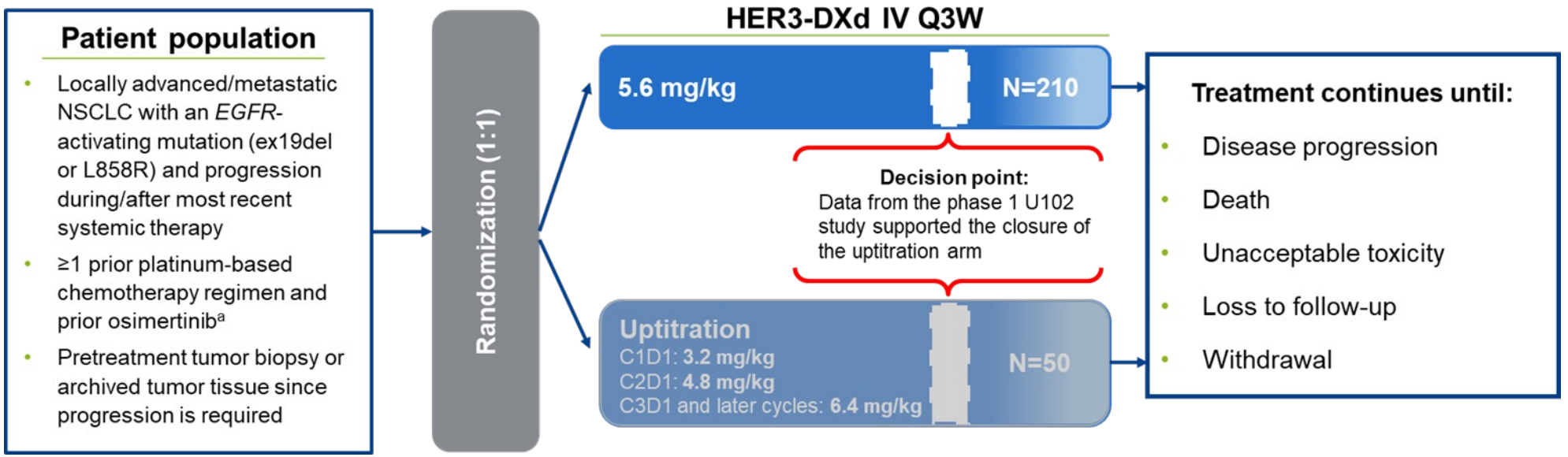
HERTHENA Lung 01 (NCT04619004)



Primary endpoint: ORR by BICR per RECIST 1.1
Secondary endpoints: DOR, PFS, ORR, DCR, OS, safety, time to response

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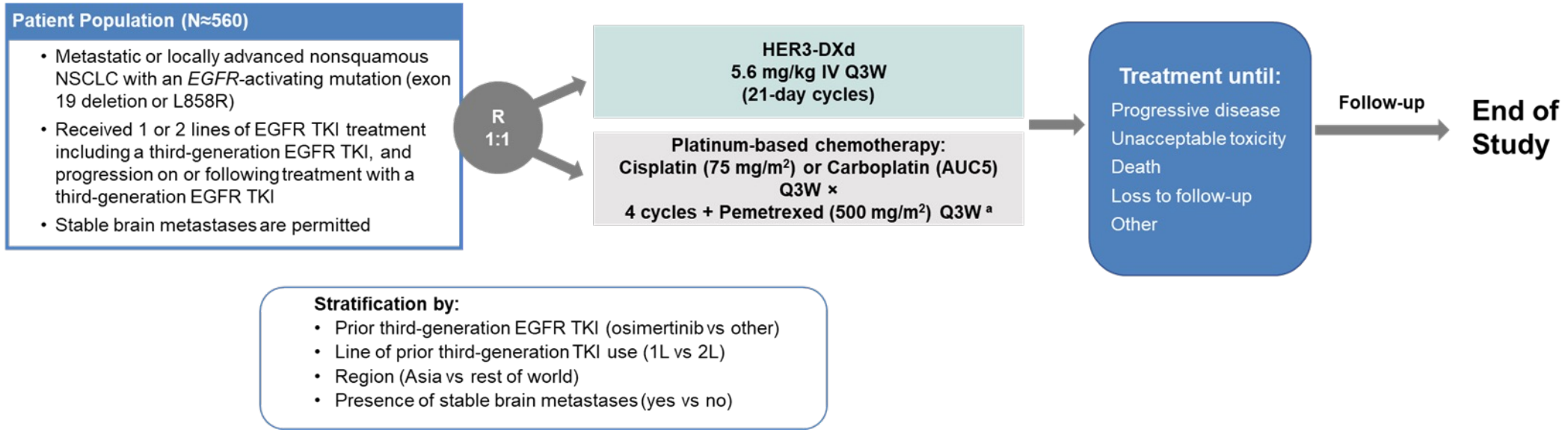
HERTHENA Lung 02 (NCT05338970)



Primary endpoint: PFS by BICR per RECIST 1.1
Secondary endpoints: PFS by inv, ORR, DOR, DCR, time to response, safety

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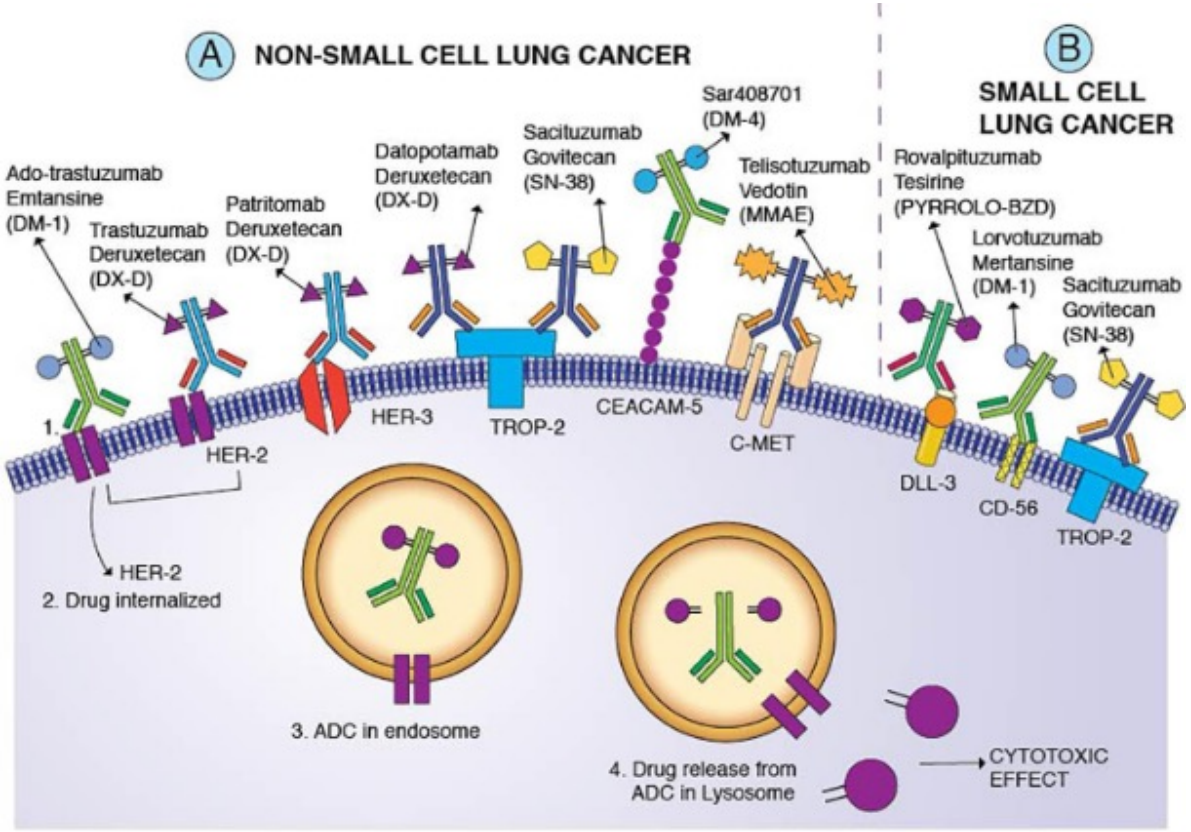
Selected Antibody and ADC Treatment Strategies for Novel Targets



HER2	Trastuzumab deruxtecan
HER3	Patritumab deruxtecan
NRG1	Seribanumab Zenocutuzumab
TROP2	Sacituzumab govitecan Datopotamab deruxtecan
CEACAM5	SAR408701

Desai et al Lung Cancer 2021

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