Placing ADCs in the lung cancer treatment algorithm

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Blueprint of an ADC

Antibody-Target

- Target - selectively expressed or over-expressed on tumor cells.
- Antibody - Human or humanized immunoglobulin.
- IgG1 most common.

Linker

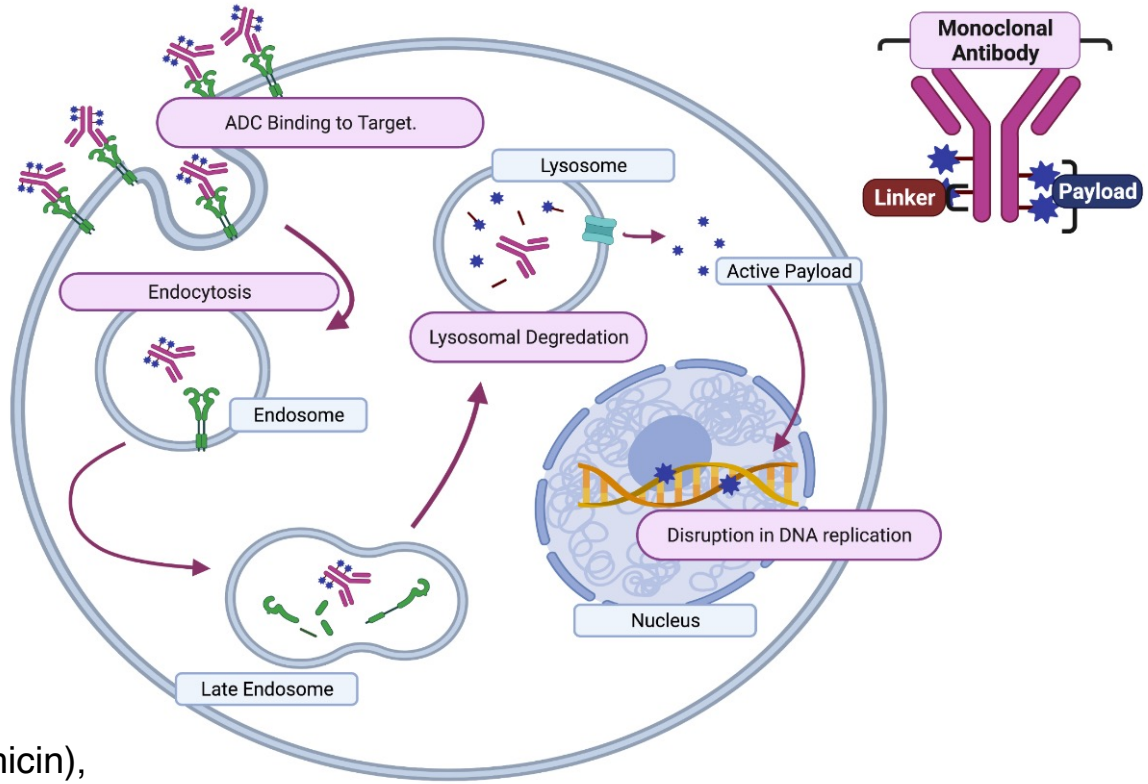
- Non-cleavable.
  - Traffic to mature lysosomes for degradation.
  - Limited “bystander effect”.
- Cleavable.
  - Cell physiology key to payload-linker uncoupling.
  - Prominent “bystander effect”.

Payload

- Highly potency cytotoxin including DNA damaging agents (PBD, calicheamicin), tubulin polymerization inhibitors (MMAE, DM1), and topoisomerase inhibitors (DXd).

Mechanism of Action

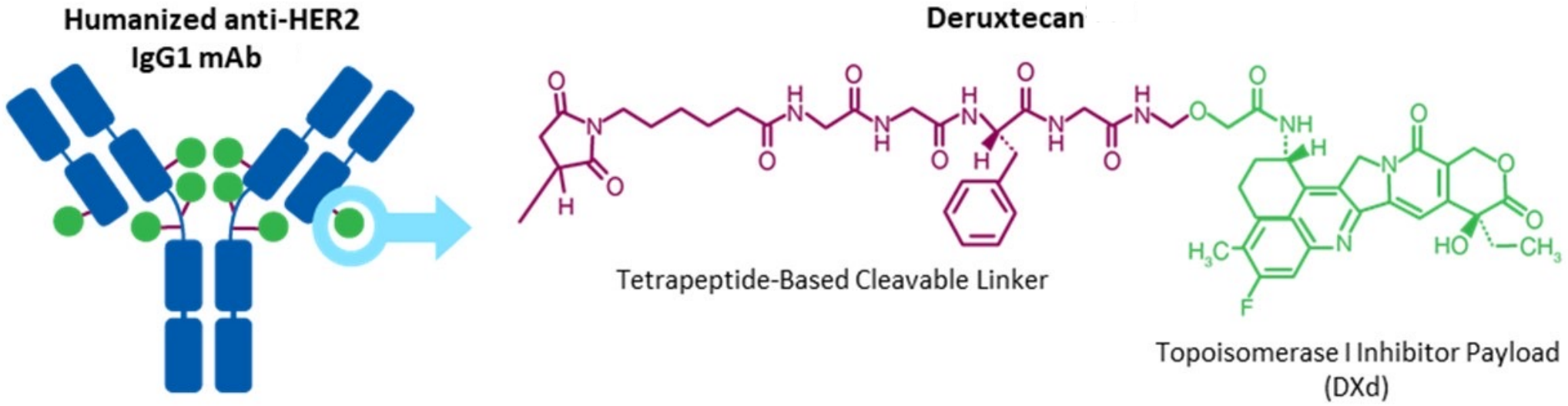
- Payload delivery, ADCC, complement-mediated cytotoxicity, inhibition of oncogenic drivers.



Marks *et al.* Curr Oncol Rep 2022

HER2 & NSCLC

Trastuzumab Deruxtecan (T-DXd)



- T-DXd: HER2-targeted ADC of trastuzumab (anti-HER2 mAb) conjugated to deruxtecan (DXd) via cleavable linker with DAR of 8.
- Elicits significant bystander effect, supporting use in tumors with heterogeneous HER2-expression.

DESTINY-Lung01

- *HER2-mutated:* ORR 55%, mOS 17.8mo, mPFS 8.2mo, mDOR 9.3mo.
- HER2 overexpression: ORR 34%, mOS 11.2mo, mPFS 6.7mo, mDOR 6.2mo.

Smith *et al.* ASCO 2020; Li *et al.* NEJM 2021; Smit *et al.* ESMO 2022

DESTINY-Lung02: Study Design

Stratified by previous use of anti–PD-1/PD-L1 therapy

Prespecified interim analysis with 80 patients (early cohort: randomized ≥4.5 mo)

Patients with metastatic *HER2*-mutated NSCLC with activating *HER2* mutations; ≥1 previous anticancer therapy, including platinum-based CT; measurable disease by BICR; ECOG PS ≤1 (N = 152)

2:1

T-DXd 5.4 mg/kg Q3W (n = 102)

T-DXd 5.4 mg/kg Q3W (n = 52)

T-DXd 6.4 mg/kg Q3W (n = 50)

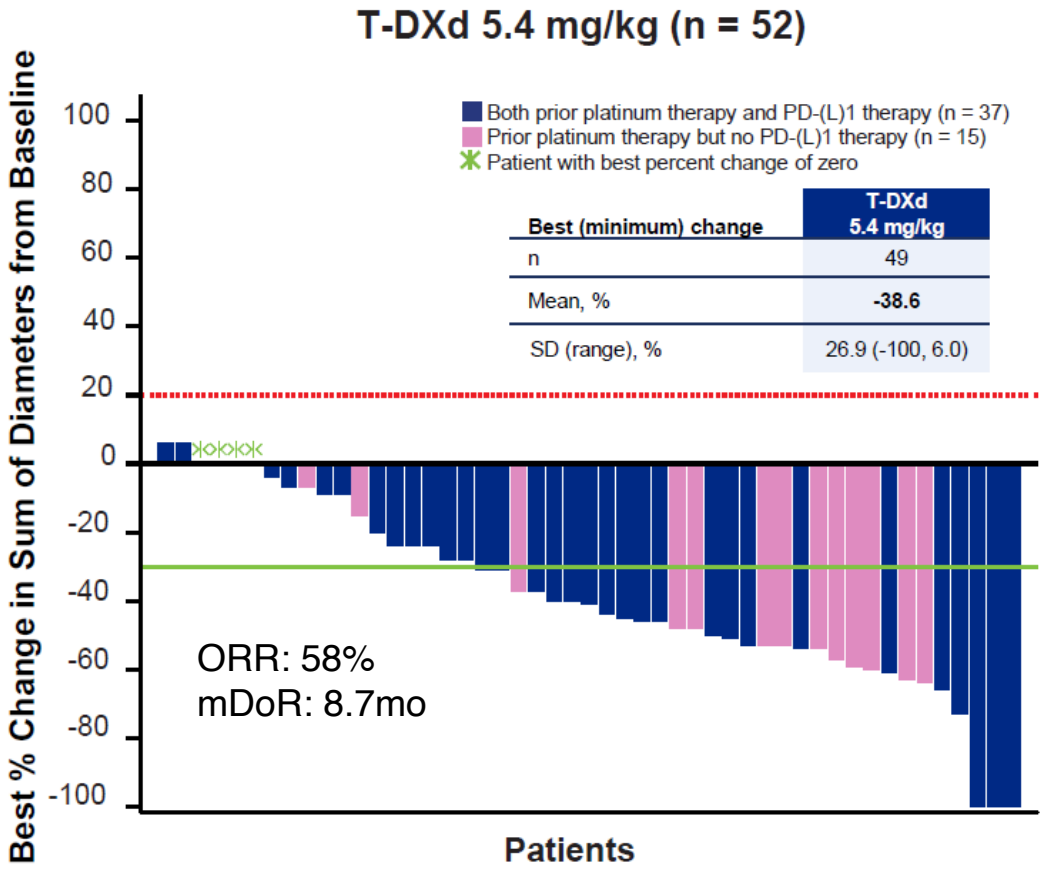
T-DXd 6.4 mg/kg Q3W (n = 28)

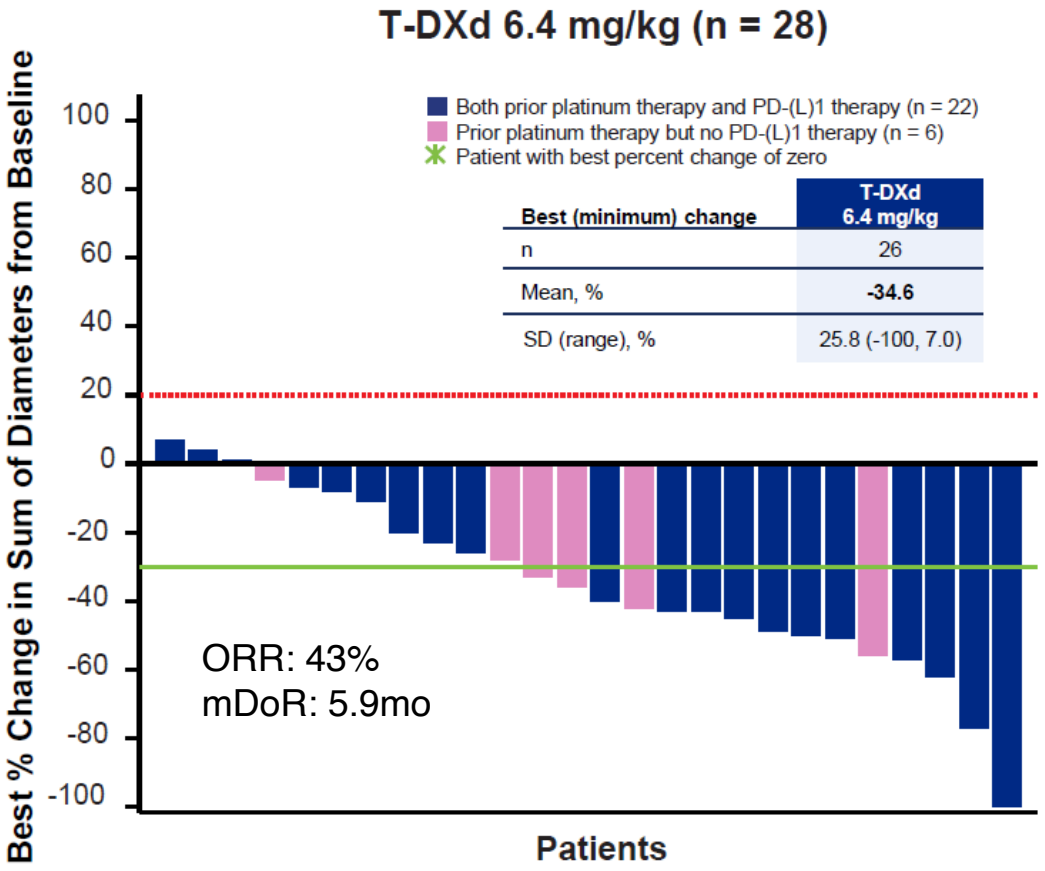
Primary Endpoint: confirmed ORR by BICR.

Secondary Endpoints: ORR by investigator, DCR, DoR, PFS, OS, PROs, Safety.

Smith *et al.* ESMO 2021; Goto *et al.* ESMO 2022

DESTINY-Lung02: Favorable efficacy & safety observed with 5.4 mg/kg dose





Goto *et al.* ESMO 2022

DESTINY-Lung02: Favorable efficacy & safety observed with 5.4 mg/kg dose

Adjudicated Drug-Related ILD

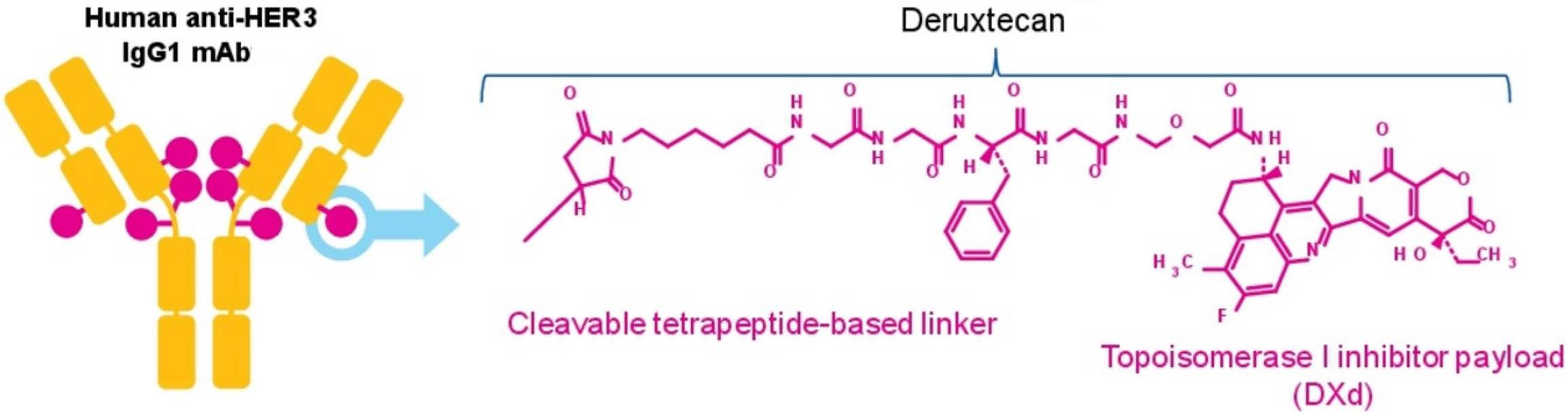
	Safety analysis set		Prespecified early cohort	
Adjudicated as drug-related ILD[a]	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50	T-DXd 5.4 mg/kg n = 51	T-DXd 6.4 mg/kg n = 28
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**	**4 (7.8)**	**5 (17.9)**
Grade 1	3 (3.0)	1 (2.0)	3 (5.9)	1 (3.6)
Grade 2	2 (2.0)	6 (12.0)	1 (2.0)	4 (14.3)
Grade 3	1 (1.0)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)	1 (25.0)	1 (20.0)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)	104.5 (40-207)	43.0 (36-208)

Other G≥3 drug-related AEs less frequent at 5.4 vs 6.4mg/kg dose: neutropenia (11.9% vs 34.0%), anemia (8.9% vs 14.0%), thrombocytopenia (4.0% vs 10.0%), fatigue (3.0% vs 10.0%).

Goto *et al.* ESMO 2022

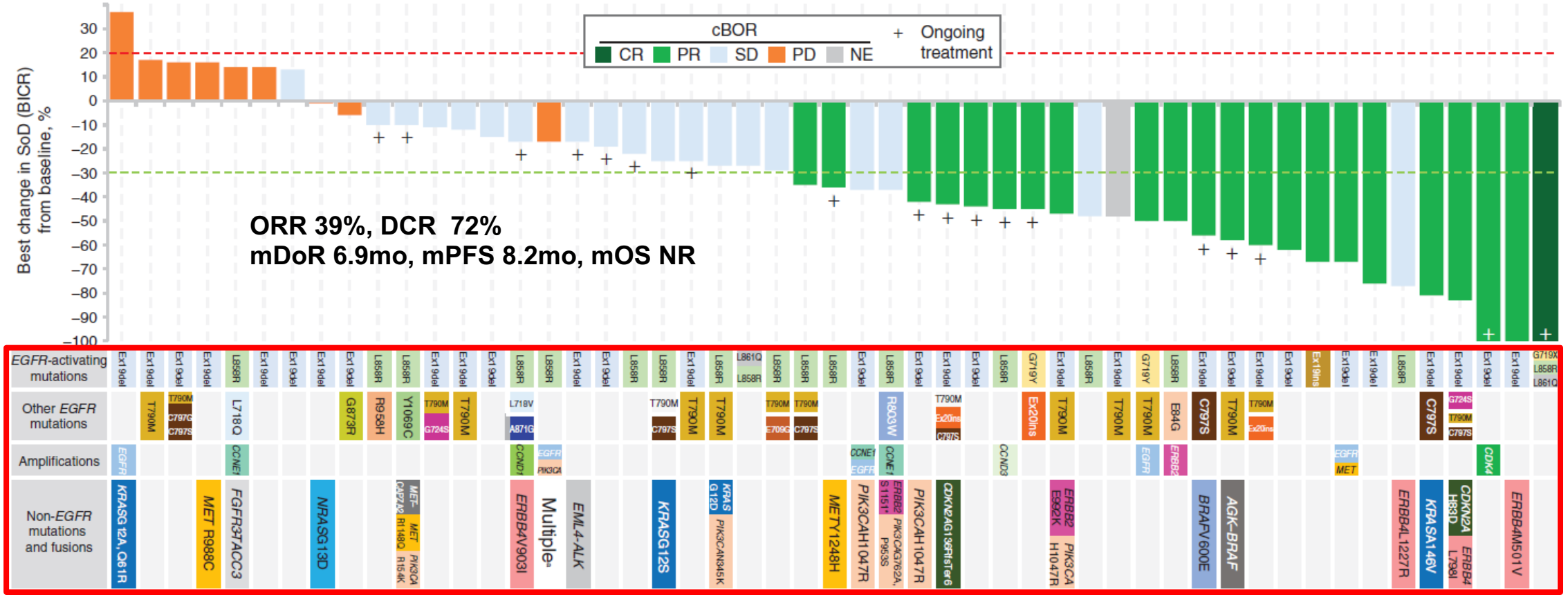
Patritumab Deruxtecan (HER3-DXd)

- HER3 is a partner with HER2 hetero-dimerization and subsequent PI3K/AKT signalling.
- Expressed in ~83% NSCLC, associated with poor prognosis.
- Upregulated expression observed in *EGFR*-mutated NSCLC.
- HER3-DXd: anti-HER3 mAb conjugated to DXd via cleavable linker with DAR 8.



Jänne *et al.* ASCO 2021

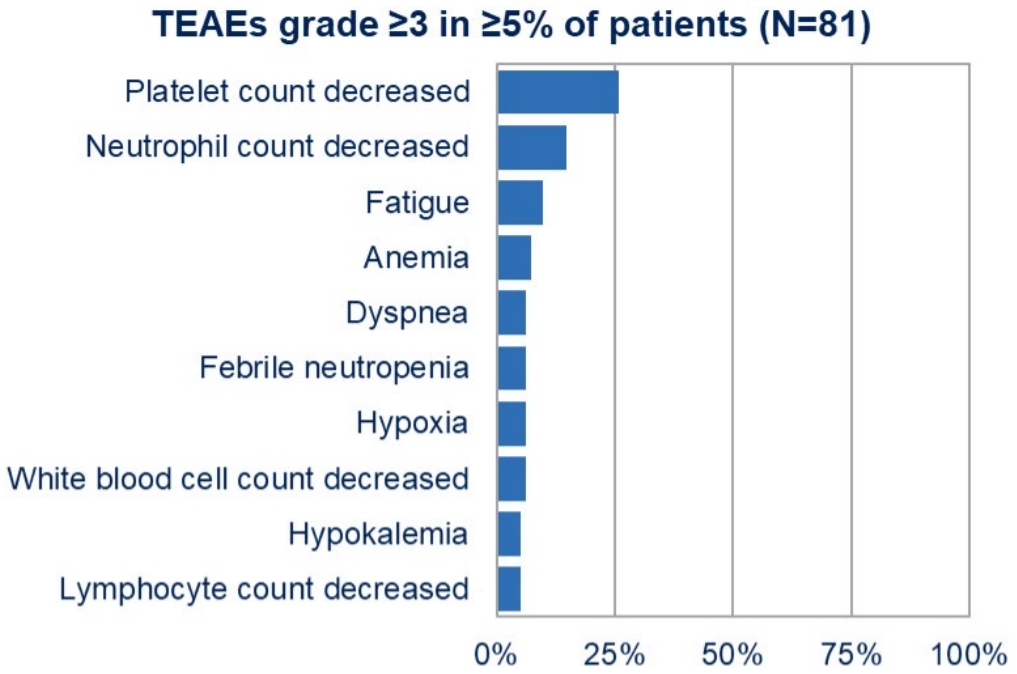
Phase 1 U31402-A-U102 Study – promising efficacy in *EGFR*m NSCLC with progression on prior targeted therapy



Jänne *et al.* ASCO 2021; Jänne *et al.* Cancer Discov 2021

Phase 1 U31402-A-U102 Study – promising efficacy in EGFRm NSCLC with progression on prior targeted therapy

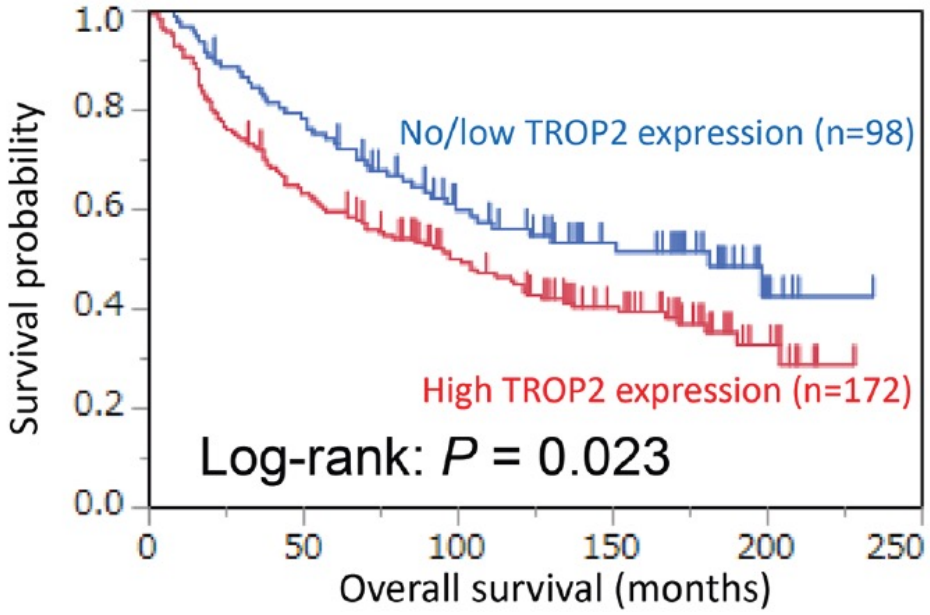
TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death	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	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

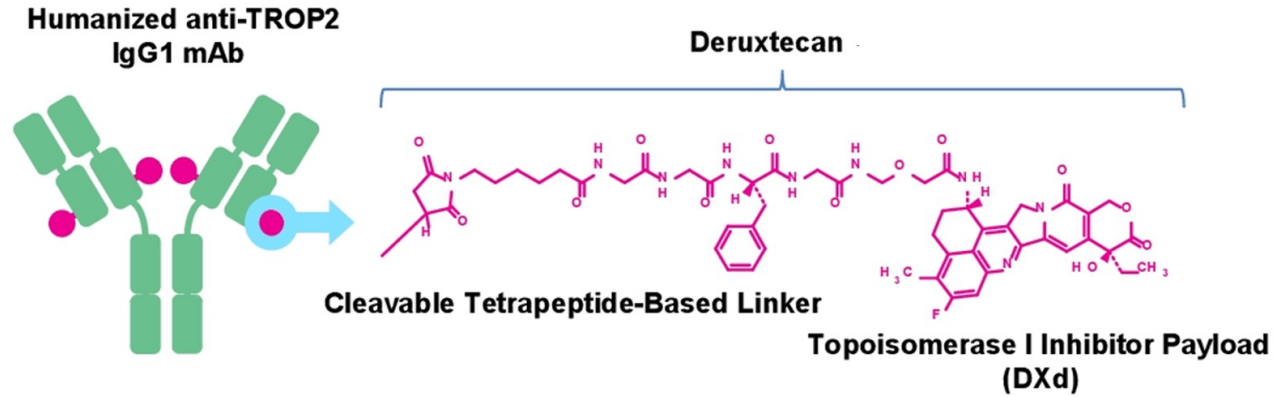


Jänne *et al.* ASCO 2021; Jänne *et al.* Cancer Discov 2021

TROP2 & NSCLC

- Cell surface signal transducer expressed in >90% NSCLC.
- Associated with poor prognosis in multiple tumor types, including NSCLC.
- Multiple drugs in development: Datopotomab deruxtecan (Dato-DXd), sacitizumab govitecan, SKB-264, STI-3258, JS-108.





Designed With 7 Key Attributes:

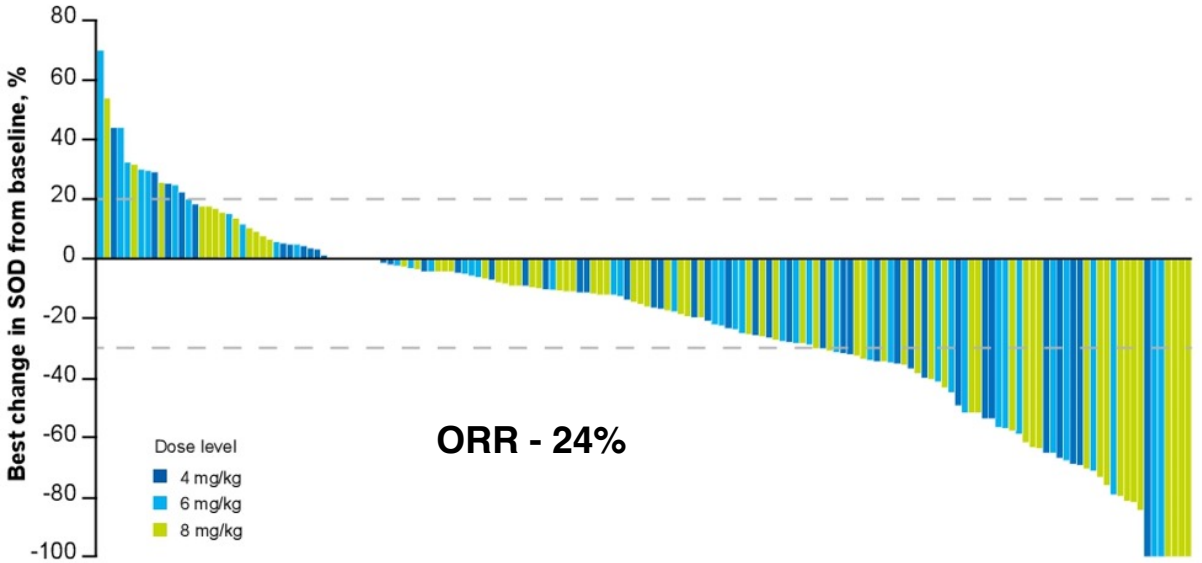
- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- Optimized DAR ≈4
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

Inamura *et al.* Oncotarget 2017; Meric-Bernstein *et al.* ASCO 2021

TROPION-PanTumor01 Trial – Early efficacy in NSCLC

Patients[a]	Dato-DXd Dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)	12 (24)	13 (26)	19 (24)
CR/PR	10 (20)	11 (22)	19 (24)
CR/PR (too early to be confirmed)	2 (4)	2 (4)	0
DCR, n (%)	38 (76)	35 (70)	64 (80)
PD, n (%)	7 (14)	10 (20)	7 (9)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (4.1-NE)	9.0 (5.8-NE)
PFS, median (95% CI), mo[b]	4.3 (3.5-8.4)	6.9 (2.7-8.8)	5.2 (4.1-7.1)

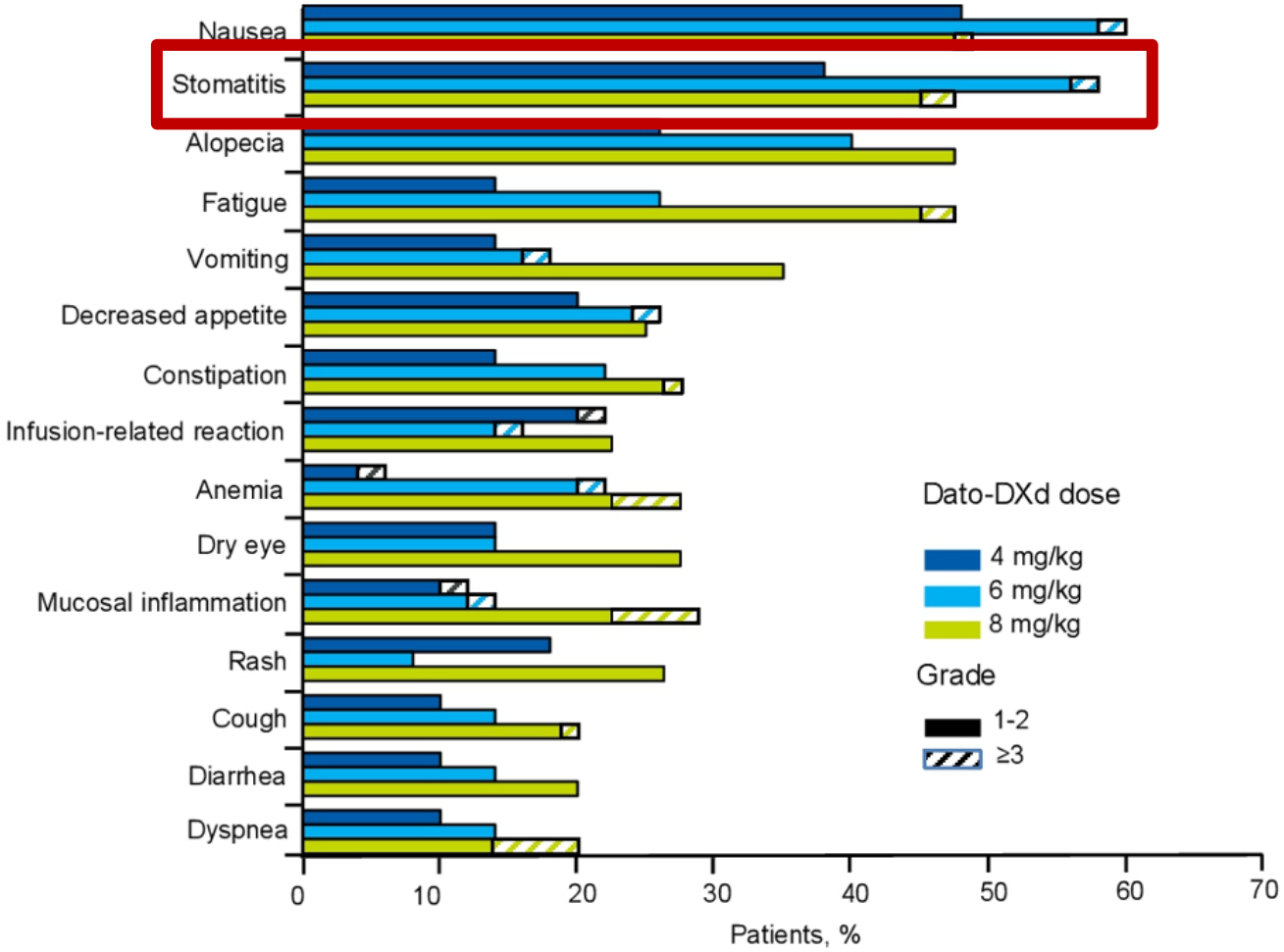
BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] Median PFS was limited by immature duration of follow-up in the 4- and 6-mg/kg dosing cohorts.



Meric-Bernstein *et al.* ASCO 2021

TROPION-PanTumor01 Trial – Safety profile in NSCLC

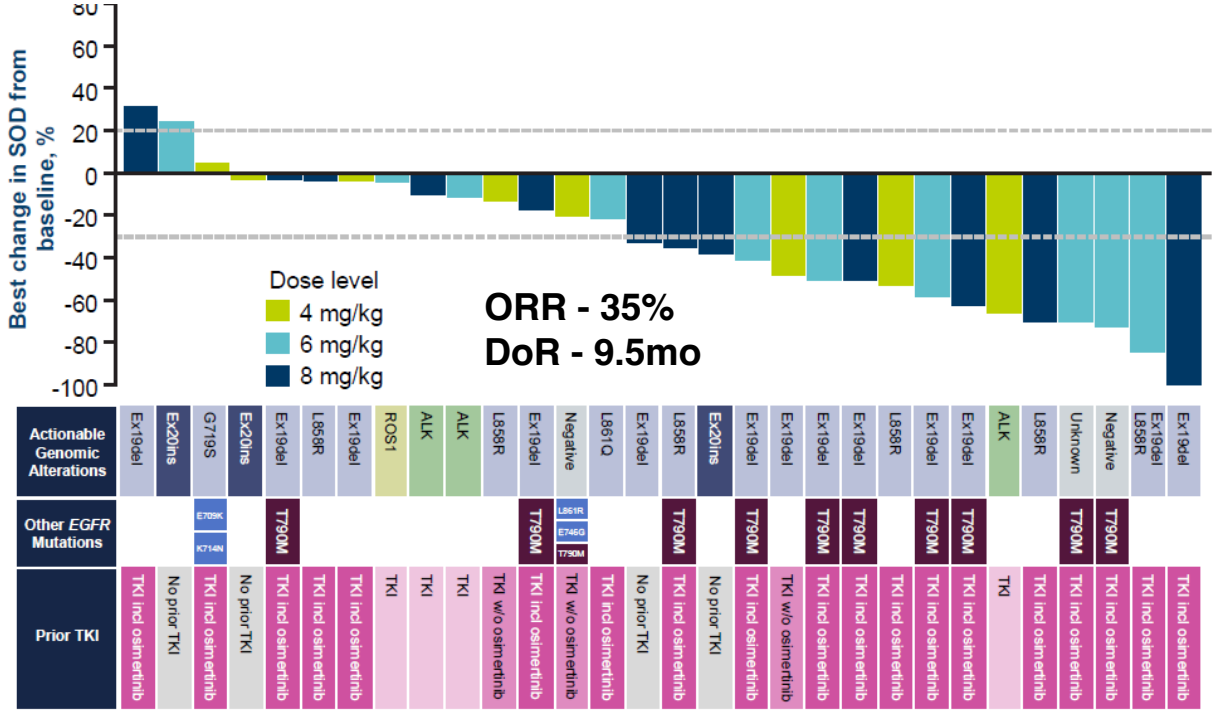
- ≥G3 treatment-related adverse events occurred in 14%, 16%, and 18% of patients treated at 4, 6, and 8 mg/kg respectively.
- Drug-related ILD occurred in ~10% of patients, majority low grade and at 8 mg/kg dose.



Meric-Bernstein *et al.* ASCO 2021

Dato-DXd – encouraging efficacy in other populations

TROPION-PanTumor01: Efficacy in pts with genomic driver mutations



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

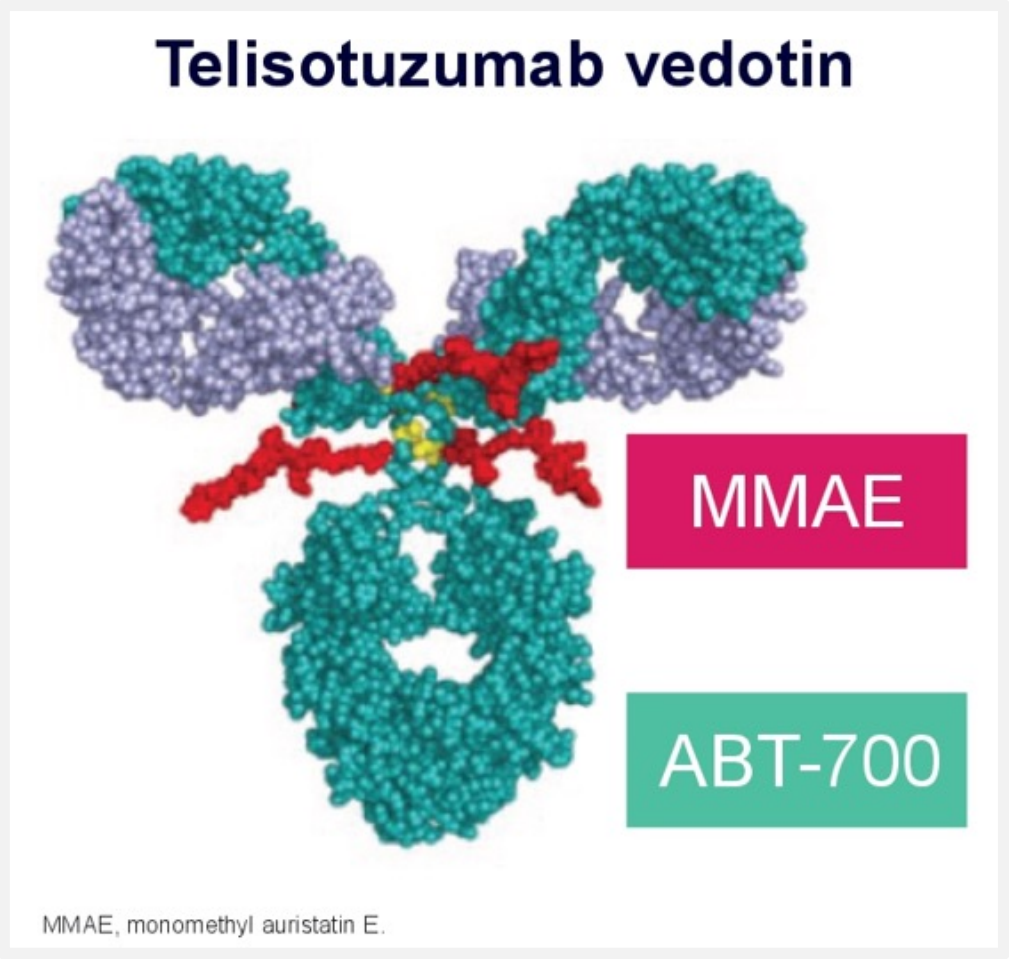
BOR With 1L Therapy For Advanced NSCLC

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%)

Garon *et al.* ESMO 2021; Levy *et al.* WCLC 2022

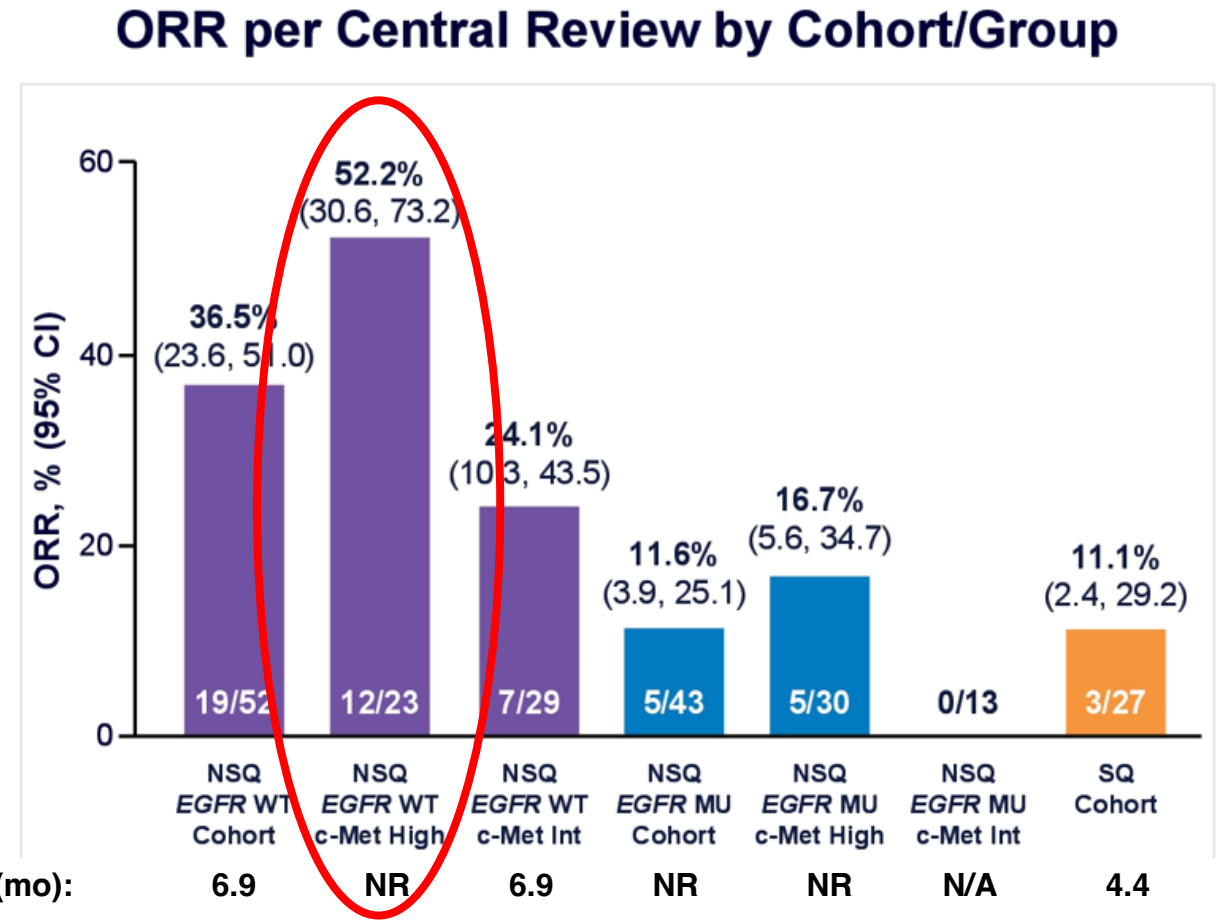
MET & NSCLC

- *MET* activating genomic alterations (exon 14 skipping mutations), *MET* amplification and MET overexpression are observed in NSCLC.
  - Tepotinib, Capmatinib approved for *METex14*
  - Amivantamab (MET/EGFR bispecific antibody)
- MET alterations commonly observed as mechanisms of acquired resistance in other driver+ NSCLC (EGFR, ALK, ROS1, KRAS, etc).
- Telisotuzumab Vedotin (Teliso-V): ADC composed of anti-cMET mAb conjugated to MMAE via cleavable linker with DAR ~3.1.



Goldman *et al.* ASCO 2022

Promising efficacy of Teliso-V in *EGFR* wt NSCLC w/ high c-MET expression

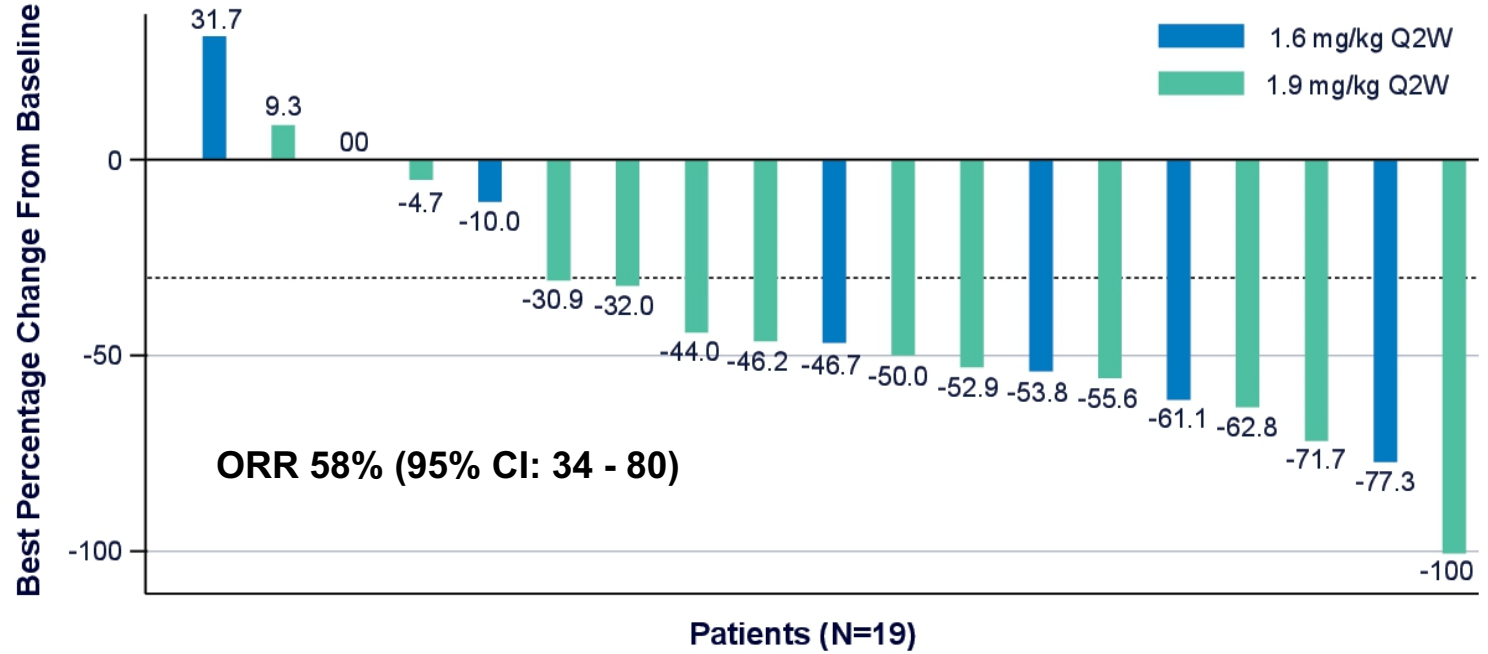


≥G3 TEAEs: Peripheral neuropathy (4%), fatigue (4%), dyspnea (3%), pneumonitis (3%)

Camidge *et al.* ASCO 2022

Encouraging efficacy of Teliso-V + osimertinib in setting of osimertinib failure with c-MET overexpression

Best Percentage Change From Baseline in Target Lesion



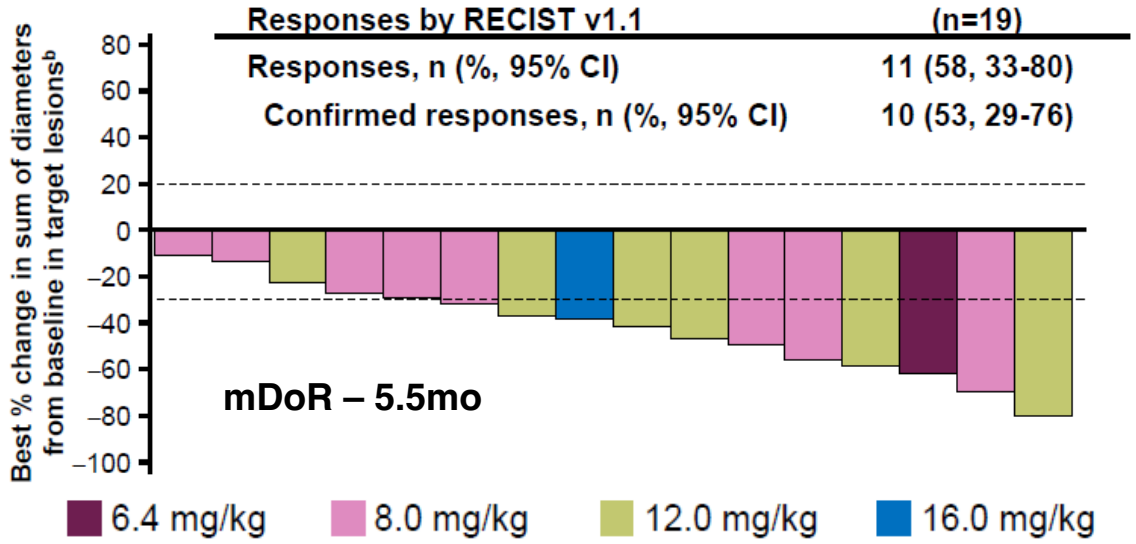
Response	PD	SD	SD	PD	PD	PR	PR	SD	PR	PR	SD	PR	PR	PR	PR	PR	PR	PD	PR
c-Met Scores	I	I	H	H	I	H	I	H	I	H	H	H	H	I	I	L	I	H	H

Goldman *et al.* ASCO 2022

Other promising ADC targets in lung cancer

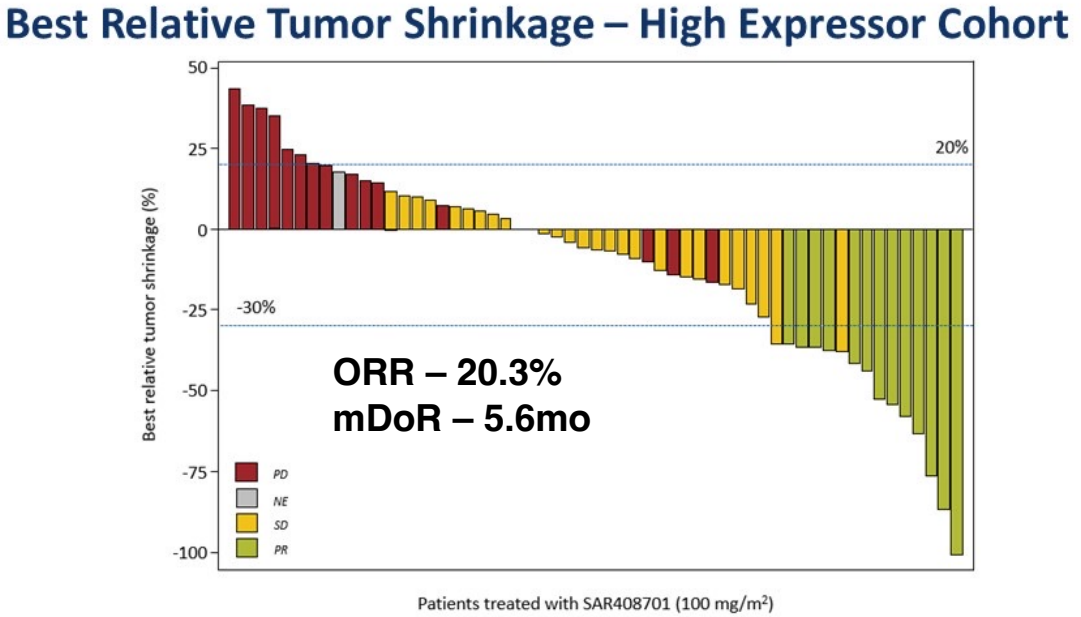
B7-H3

Ifinatamab deruxtecan (I-DXd) in ES-SCLC



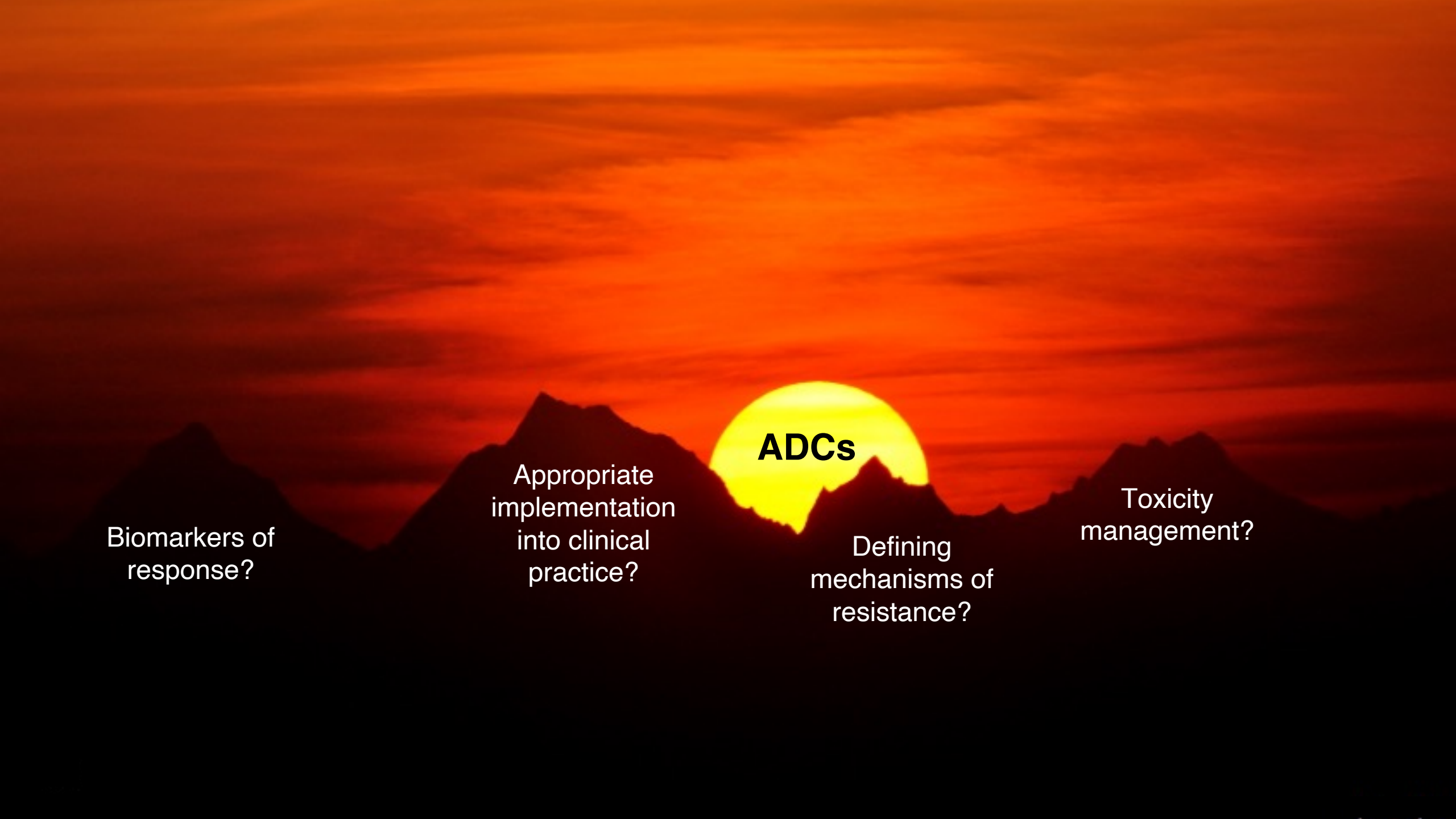
CEACAM5

Tusamitamab ravtansine (TUSA) in advanced NSCLC



- Other targets: NaPi2b, PTK7, mesothelin, tissue factor, nectin 4, folate receptor alpha

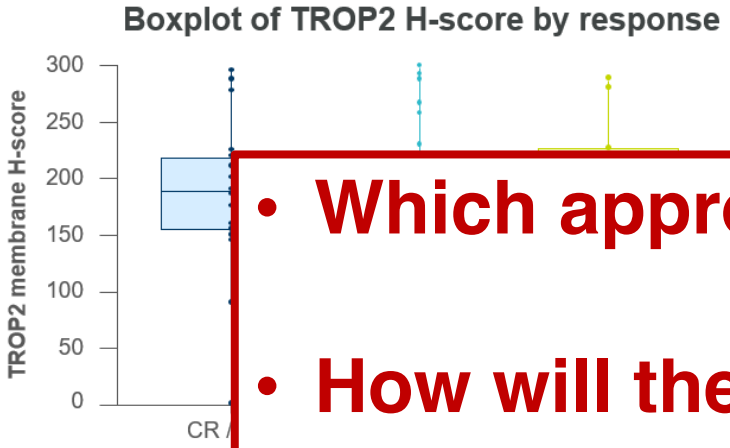
Doi *et al.* ESMO 2022; Gazzah ASCO 2020


ADCs
Biomarkers of response?
Appropriate implementation into clinical practice?
Defining mechanisms of resistance?
Toxicity management?

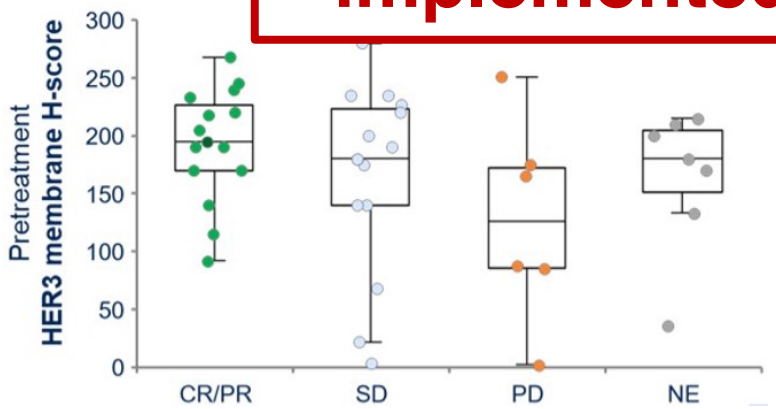
Defining appropriate predictive biomarkers for ADCs in NSCLC - where are we going?

Biomarker UNSELECTED

Dato-DXd

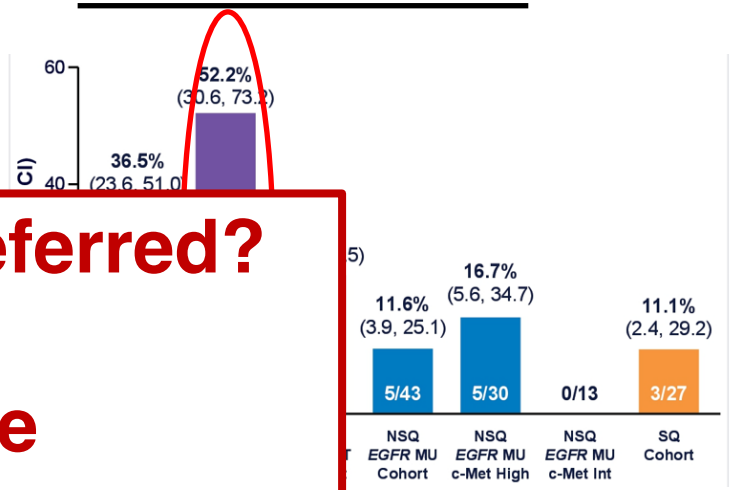


HER3-DXd

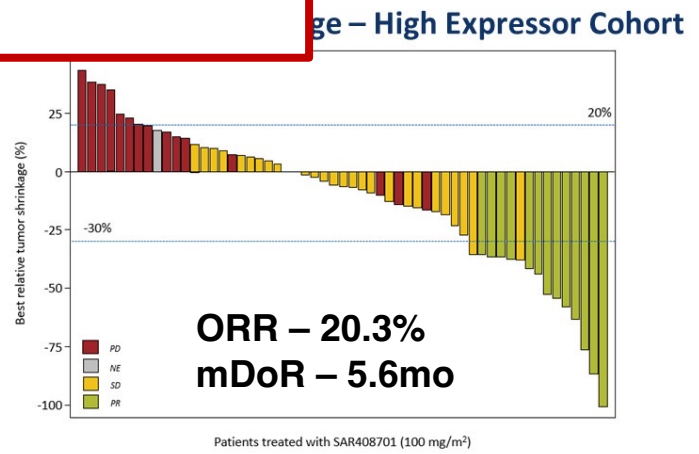


Biomarker SELECTED

Teliso-V

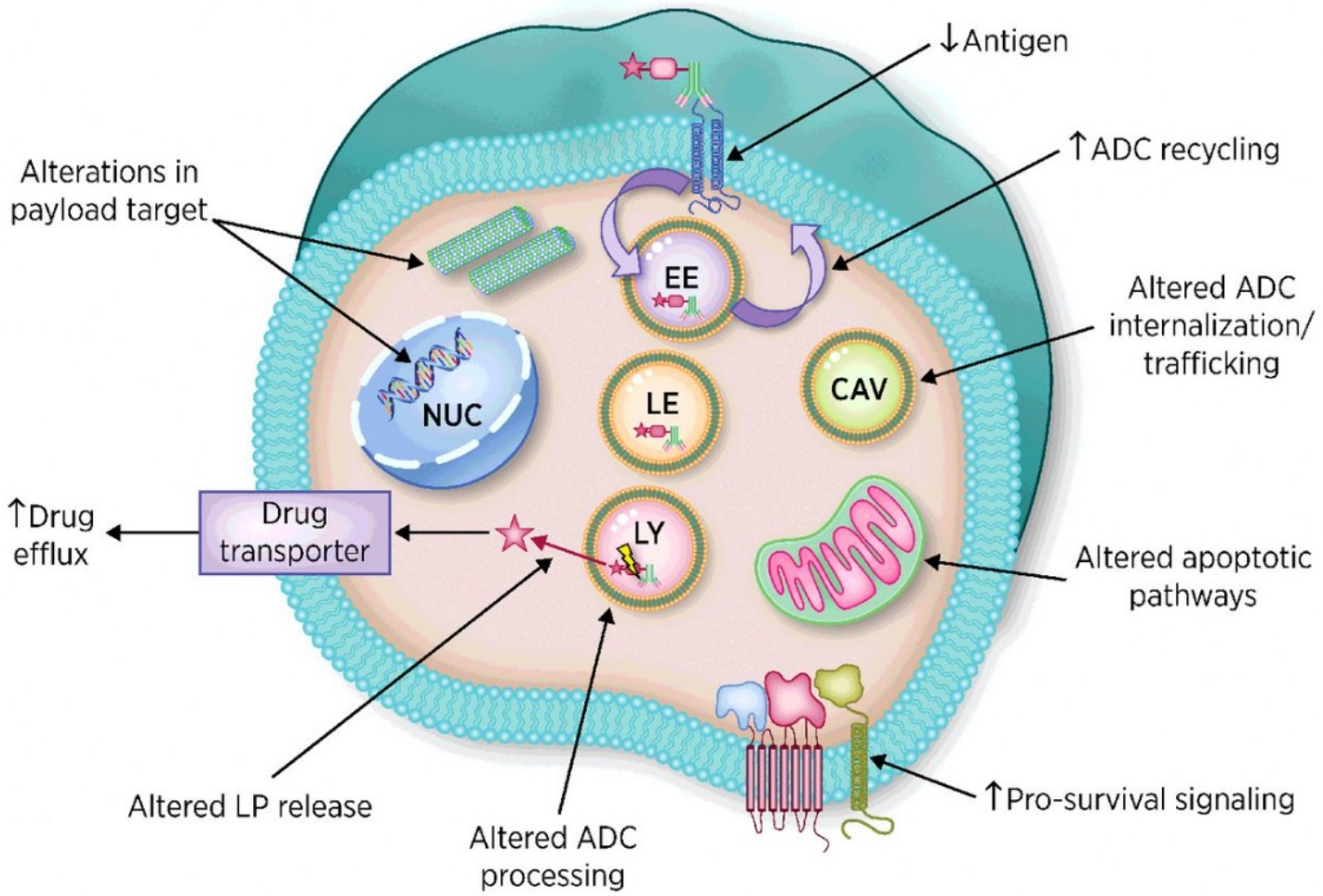


- **Which approach will be preferred?**
- **How will these strategies be implemented in the clinic?**



Lisberg *et al.* ASCO 2020; Jänne *et al.* ASCO 2021; Camidge *et al.* ASCO 2022; Gazzah *et al.* ASCO 2020

Defining mechanisms of resistance to ADCs in NSCLC



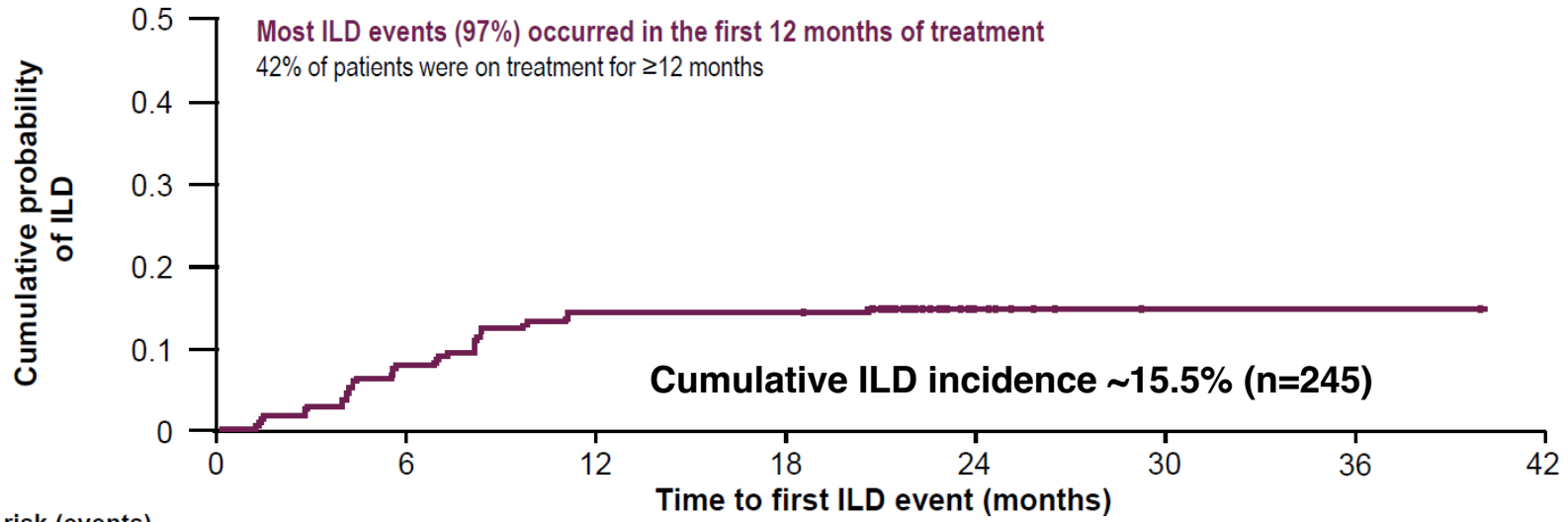
Loganzo *et al.* Mol Cancer Ther 2016

Implementing effective management strategies for unique ADC-related adverse events

- Majority of cases identified by investigators ***after*** being found by independent adjudication committee.
- 43 of 44 cases occurred prior to implementation of updated toxicity management guidelines.

KAPLAN-MEIER ANALYSIS OF TIME TO FIRST ILD EVENT

The risk of all-grade ILD decreased after 12 months, as the cumulative probability of adjudicated drug-related ILD began to plateau at this point. Median time to first ILD event, 5.6 months (range, 1.1–20.8 months)



No. at risk (events)								
HER2+ BC	245 (0)	178 (20)	100 (37)	72 (37)	17 (38)	3 (38)	2 (38)	0 (38)
ILD rate	0	8.2%	15.1%	15.1%	15.5%	15.5%	15.5%	15.5%

Powell *et al.* ESMO Breast 2021

Concluding Remarks

- ADCs are an emerging class of anti-cancer therapeutic in the treatment of advanced lung cancer, with T-DXd carrying an accelerated approval for subsequent line therapy in advanced *HER2*-mutated NSCLC.

- Several agents carry FDA breakthrough designation, among which multiple phase 3 registrational studies are ongoing.

- Many questions remain: Appropriate biomarker selection, optimal sequencing, proper clinical implementation, toxicity management.

THANK YOU!