ADCs in NSCLC: CEACAM5 and Teliso-V

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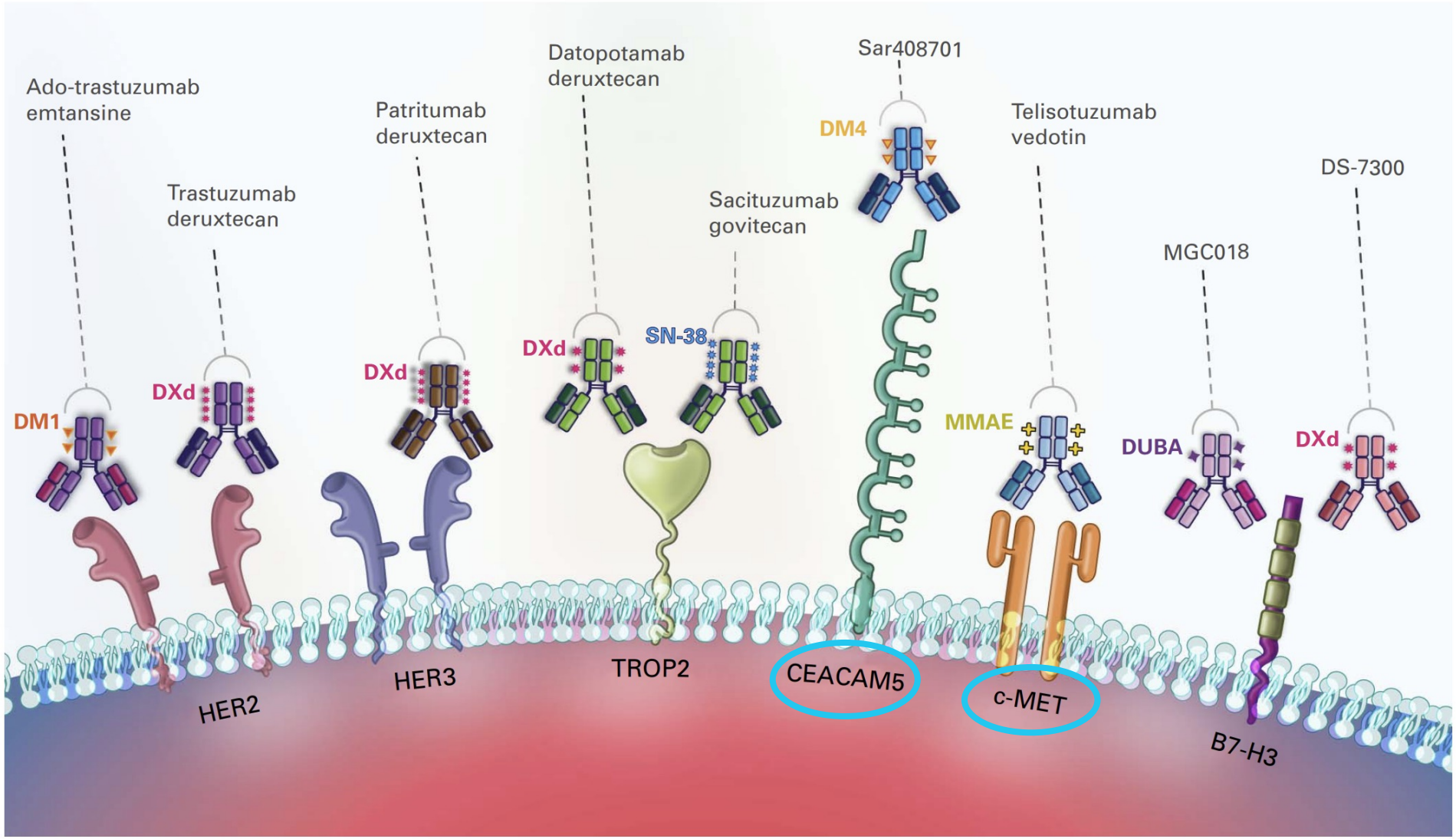
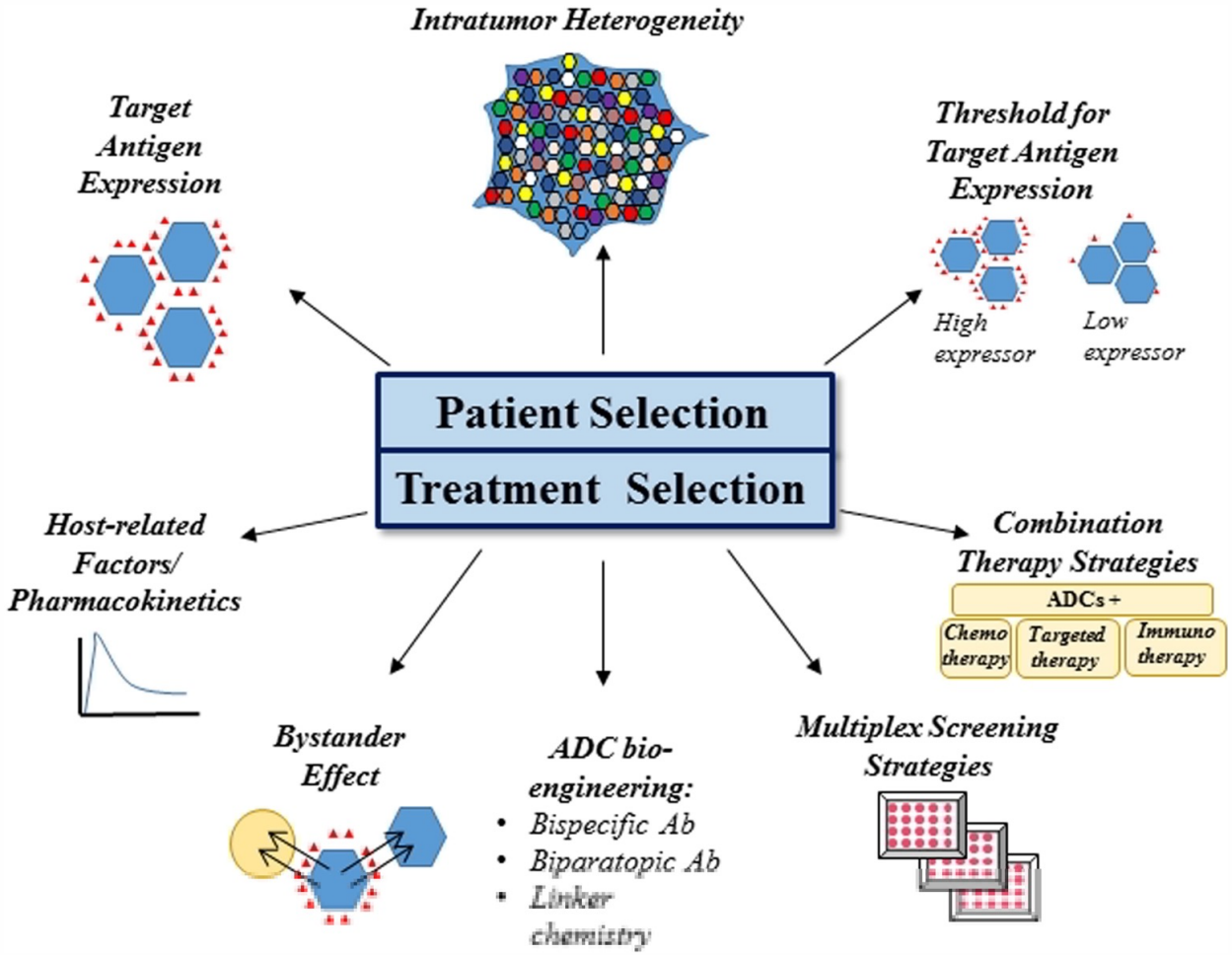
Emerging ADC Targets in NSCLC



Passaro et al. J Clin Oncol. 2023.

ADC Strategies:
Ubiquitous Target vs Biomarker Selected



Target Biomarker Expression Characteristics

(1) Present/Absent

(2) High/Low Expression Level

(3) Heterogeneous?

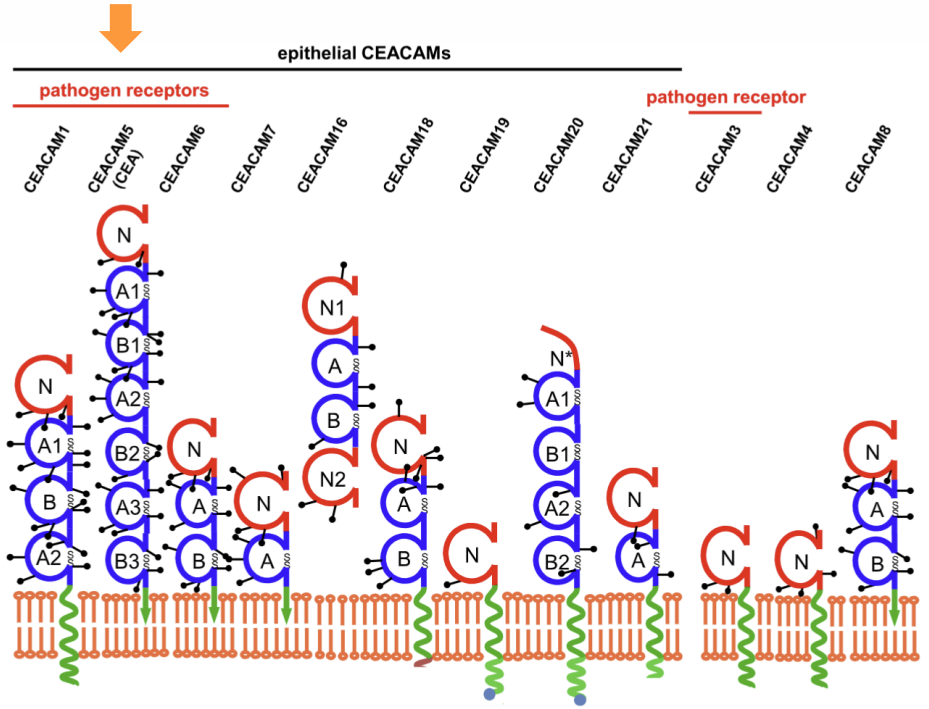
(4) Impacted by Prior Therapy?

Makawita et al ASCO Education Book. Vol 40. 2020

CEACAM5 as a potential therapeutic target in solid tumors

Type of tumor	CEA*	NCA	BGP	CGM6	CGM1	CGM2	CGM7	PSG	References
Epithelial									
Colorectal carcinoma	+	+⇑	+⇓			+⇓			[27,60,64,65] [66–72]
Gastric carcinoma	+⇑	+⇑	+⇑			+⇑			[59,71,73]
Lung adenocarcinoma	+	+	+						[64,68,71,74]
squamous cell carcinoma	–		+⇑						[70,75]
Breast carcinomas	(+)	+				–			[27,67,68] [71,74]
Pancreatic carcinoma	+								[71]
Gallbladder carcinoma	+								[71]
Urinary bladder carcinoma	+								
Mucinous ovarian carcinoma	+	+	(+)	–	–	+	–		[27]
Serous ovarian carcinoma	(+)	(+)	(+)	–	–		–		[67]
Endometrial adenocarcinoma	+	+	+	–	–		–		[67]
Hepatocellular carcinoma	–		+⇓						[71,76,77]
Thyroid carcinoma	–								[71]
Nasopharyngeal carcinoma	–								[71]
Other									
Malignant mesothelioma	–								[78]
Small cell lung carcinoma	+		–						[64,75]
Acute lymphoblastic leukemia	–	+	(+)		–		–		[79]
Melanoma	–								[71]
Different sarcoma	–								[71]
Hydatidiform mole								+	[80]
Choriocarcinoma								+	[80]

CEACAM5 (eg CEA) is a cell surface glycoprotein, overexpression in epithelial cancers relative to healthy tissues



Hammarström, Seminars in Cancer Biology, 1999; Tchoupa et al. Cell Communications and Signaling, 2014

Tusamitamab ravtansine: A CEACAM5 ADC

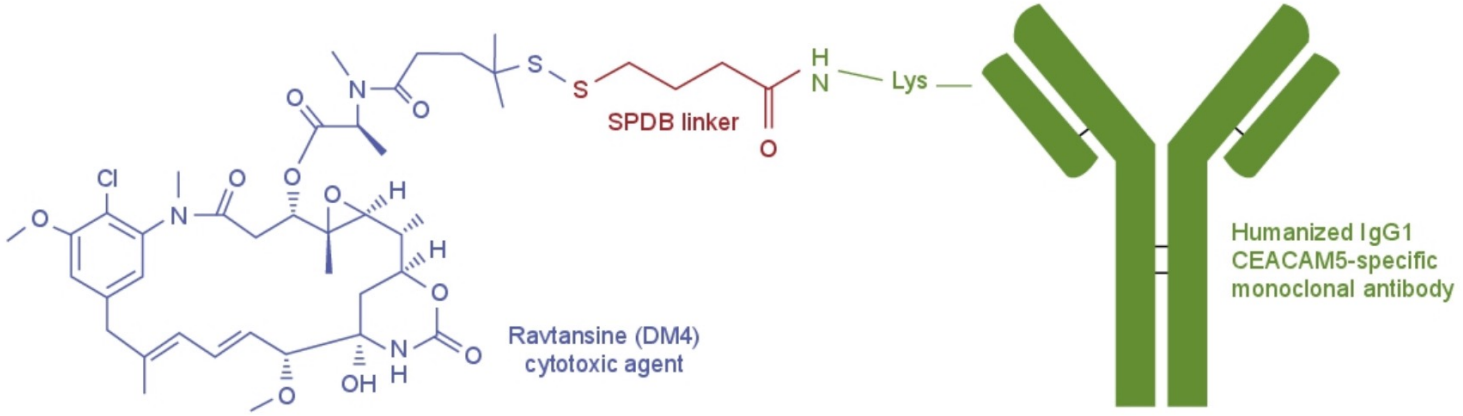
Humanized CEACAM5 Antibody

+

Cleavable Linker

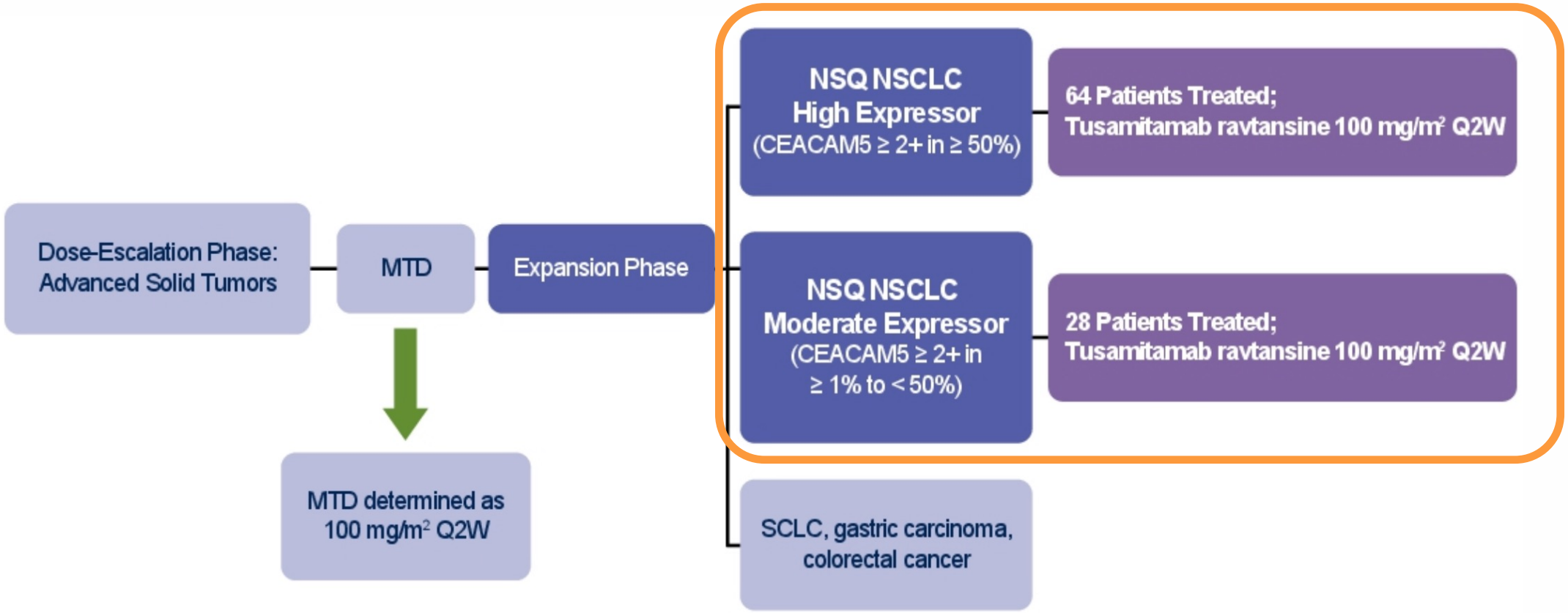
+

Ravtansine (DM4) Payload (tubule polymerization inhibitor



Ricordel et al ASCO 2022

Tusamitamab ravtansine for CEACAM5+ Nonsquamous NSCLC NCT02187848, a Phase I/2 Study



Ricordel et al ASCO 2022

Baseline Patient Characteristics

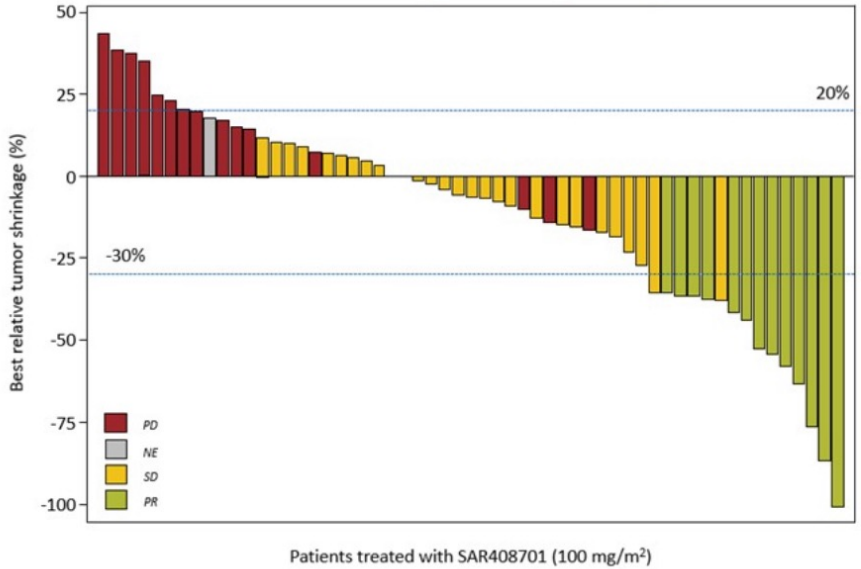
Characteristic	High expressors (n = 64)	Moderate expressors (n = 28)	Total (n = 92)
Age, years			
Median (range)	61.5 (41-91)	64.5 (31-73)	62.5 (31-91)
Race, n (%)			
White	52 (81.3%)	25 (89.3%)	77 (83.7%)
Asian	12 (18.8%)	3 (10.7%)	15 (16.3%)
Sex, n (%)			
Male	37 (57.8%)	10 (35.7%)	47 (51.1%)
Female	27 (42.2%)	18 (64.3%)	45 (48.9%)
ECOG PS, n (%)*			
0	19 (29.7%)	7 (25.0%)	26 (28.3%)
1	45 (70.3%)	20 (71.4%)	65 (70.7%)
Number of organs involved, n (%)			
≥3	38 (59.4%)	14 (50%)	52 (56.5%)
Number of prior regimens for advanced disease			
Median (range)	3.0 (1-10)	3.0 (1-7)	3.0 (1-10)
Prior treatment, n (%)			
Anti-tubulin	39 (60.9%)	17 (60.7%)	56 (60.9%)
Anti-PD-1/PD-L1	45 (70.3%)	24 (85.7%)	69 (75.0%)

A total of 91 patients had adenocarcinoma; *One patient in the moderate expressor cohort had an ECOG PS of 3.

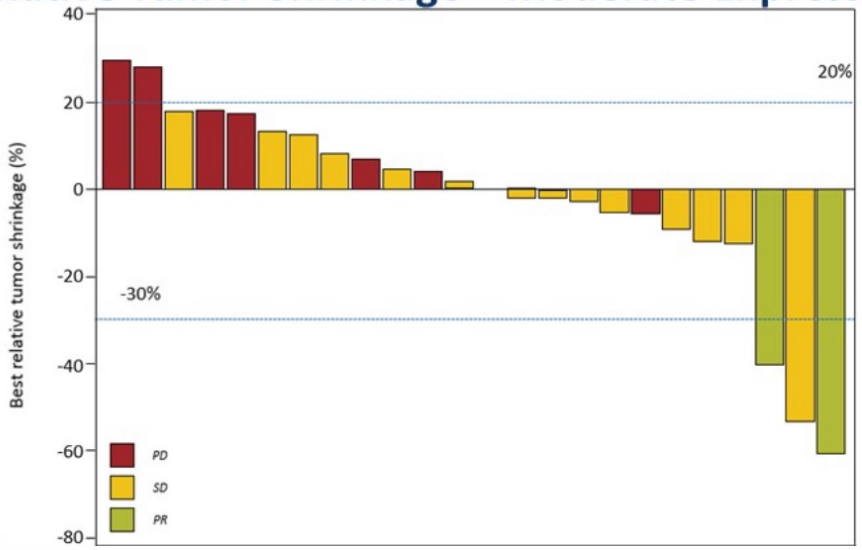
PRESENTED BY: Anas Gazzah, MD

Gazzah et al J Clin Oncol 2020 38(15 suppl):Abs. 9505.

Best Relative Tumor Shrinkage – High Expressor Cohort



Best Relative Tumor Shrinkage – Moderate Expressor Cohort



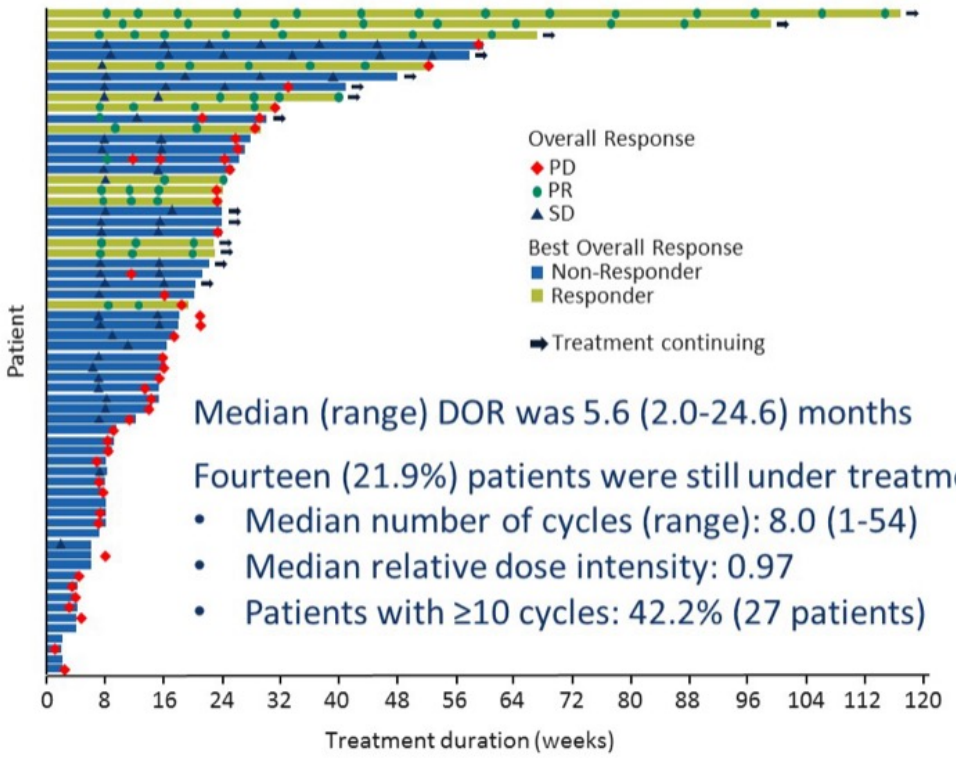
Tusamitamab Ravtansine: Radiographic Response Rates

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 J Clin Oncol 2020 38(15 suppl):Abs. 9505.

Dose Intensity and Duration of Treatment

High expressors

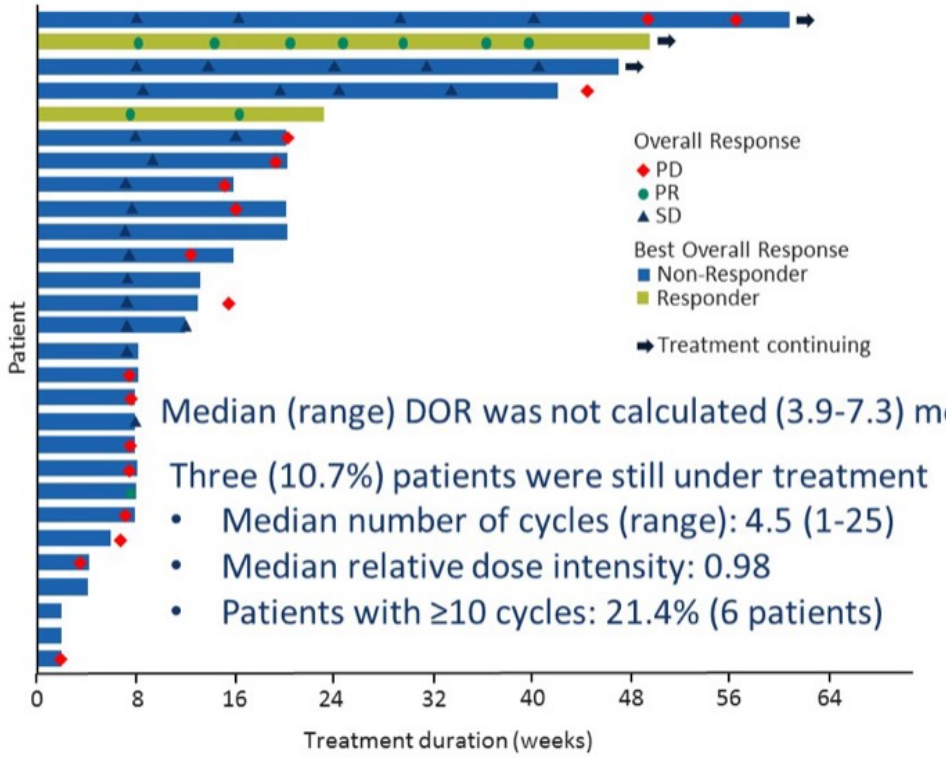


Median (range) DOR was 5.6 (2.0-24.6) months

Fourteen (21.9%) patients were still under treatment

- Median number of cycles (range): 8.0 (1-54)
- Median relative dose intensity: 0.97
- Patients with ≥10 cycles: 42.2% (27 patients)

Moderate expressors



Median (range) DOR was not calculated (3.9-7.3) months

Three (10.7%) patients were still under treatment

- Median number of cycles (range): 4.5 (1-25)
- Median relative dose intensity: 0.98
- Patients with ≥10 cycles: 21.4% (6 patients)

Gazzah et al J Clin Oncol 2020 38(15 suppl):Abs. 9505.

Treatment Emergent 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
Hematological toxicity		
Neutropenia	4 (4.4%)	0
Anemia	69 (75.8%)	2 (2.2%)
Thrombocytopenia	11 (12.2%)	0

Microcystic corneal dystrophy

- Non-inflammatory corneal deposits
- Most commonly occurs in the 1st 4 cycles of treatment
- Treatment with dose modification and topical steroids
- Only 1.1% require permanent treatment continuation

Gazzah et al J Clin Oncol 2020 38(15 suppl):Abs. 9505.

Safety in Longer-Term (12 months+) Treated Patients

Table 3. Most common TEAEs (≥ 20% of patients) in patients treated for ≥ 12 months

	Treated ≥ 12 mo (n = 11)	
n (%)	All Grades	Grade ≥ 3
Any TEAE	11 (100)	8 (72.7)
Any eye disorder	10 (90.9)	5 (45.5)
Keratitis	6 (54.5)	4 (36.4)
Keratopathy	6 (54.5)	2 (18.2)
Cataract	5 (45.5)	2 (18.2)
Any TEAE in other system organ classes		
Asthenia	5 (45.5)	0
Decreased appetite	4 (36.4)	1 (9.1)
Bronchitis	4 (36.4)	0
Peripheral sensory neuropathy	4 (36.4)	0
Cough	4 (36.4)	0
Pruritis	4 (36.4)	0
Arthralgia	4 (36.4)	0
Diarrhea	3 (27.3)	0
Peripheral edema	3 (27.3)	0

Safety Outcomes, Longer-Term Treated Patients (n=11)

72.7% had keratitis or keratopathy (36.4% Grade 3+)

7 of 11 patients had dose modification due to this AE, no patients require treatment discontinuation

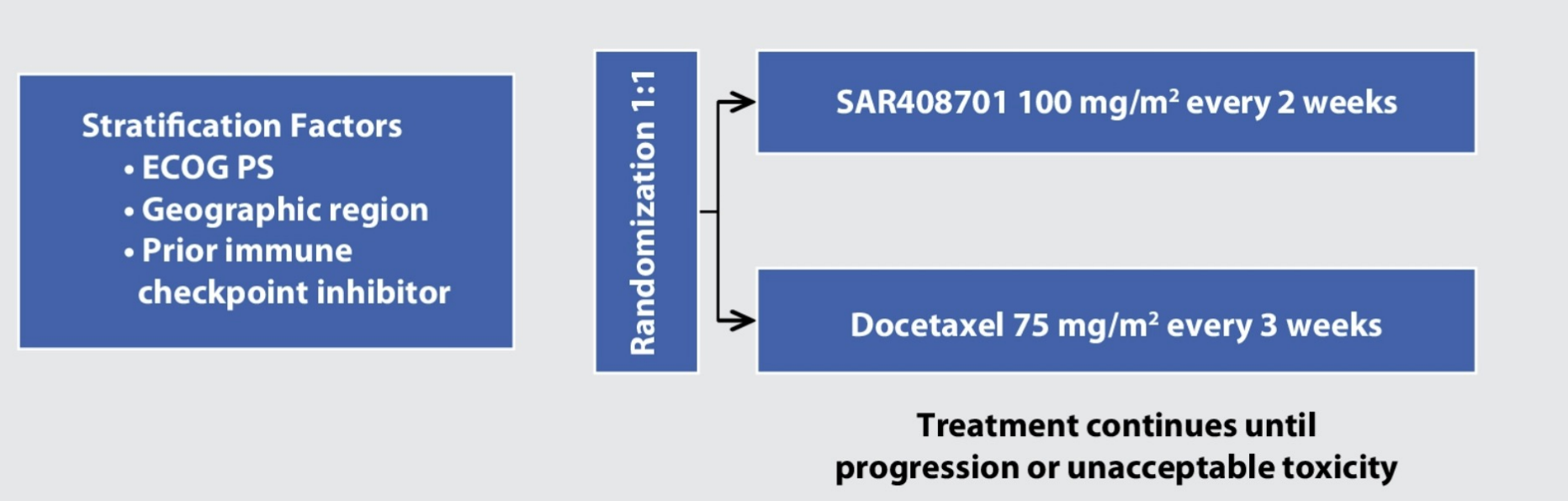
Efficacy Outcomes, Longer-Term Treated Patients

For patients with NSQ NSCLC with a confirmed PR (n=15), 47% had maintained PR at 1 year treatment

Ricordel et al ASCO 2022

CARMEN-LC03, A phase 3 study of tusamitamab ravtansine vs docetaxel

CEACAM5+ Nonsquamous NSCLC, prior platinum-based chemotherapy and ICI therapy
(CEACAM5+ defined as 2+ in ≥50% of tumor cell population)

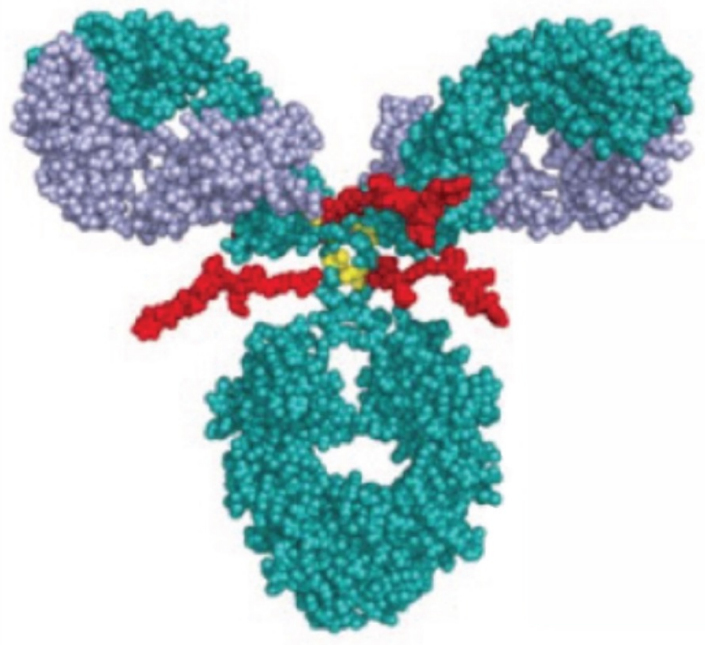


Primary Endpoints: PFS (IRC) and OS
Secondary Endpoints: ORR (IRC), AEs, duration response, time to deterioration in symptoms/function

Johnson et al. ASCO 2020 TPS9625

Teliso-V:
MET-ADC Therapy in NSCLC

Telisotuzumab vedotin



Humanized c MET Antibody

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Cleavable Linker

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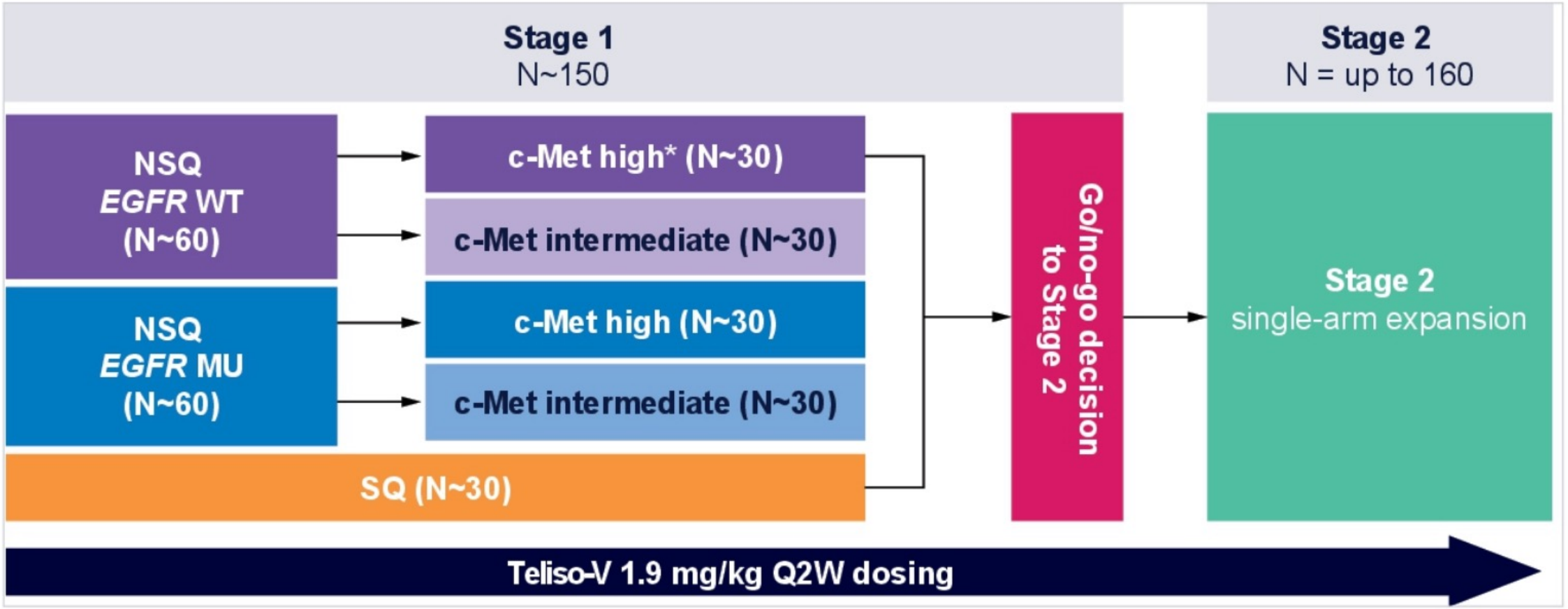
MMAE Payload

Camidge et al. ASCO 2022 #9016

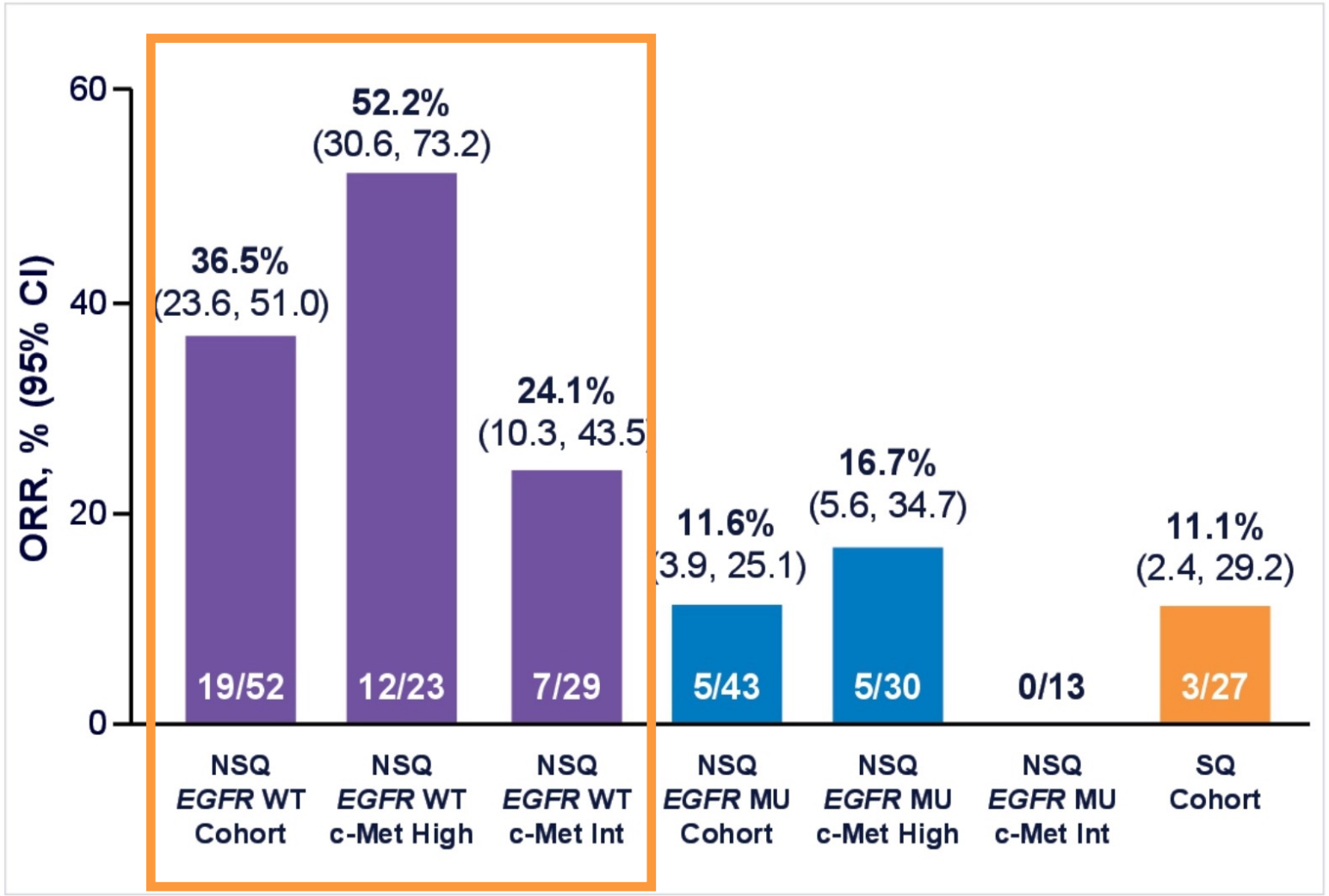
LUMINOSITY: Teliso-V Monotherapy



*c-Met overexpression was defined for the NSQ cohort as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to <50% 3+), and for the SQ cohort as ≥75% of tumor cells at 1+ intensity. *EGFR*, epidermal growth factor receptor; MU, mutant; NSQ, non-squamous; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin; WT, wild-type

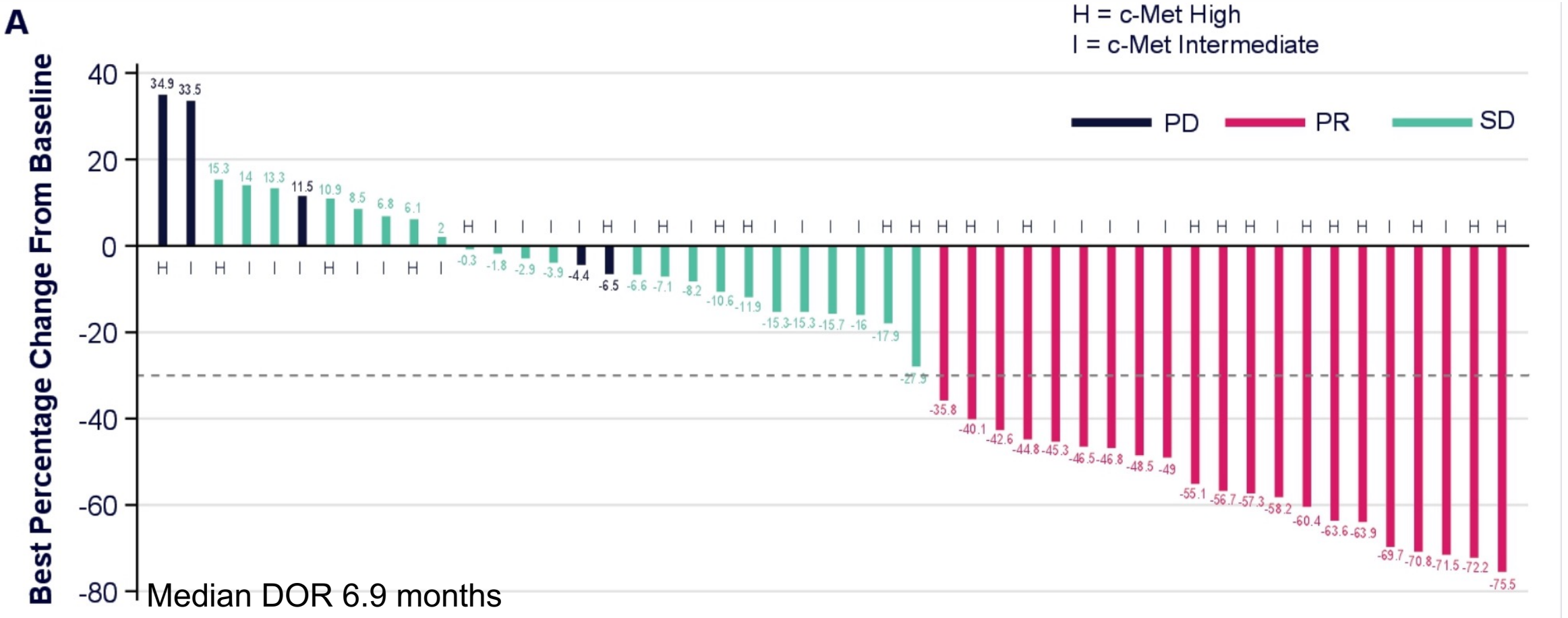
Camidge et al. ASCO 2022 #9016

LUMINOSITY: Teliso-V Monotherapy



Camidge et al. ASCO 2022 #9016

LUMINOSITY: Teliso-V Monotherapy
Nonsquamous, EGFR wild-type cohort



Median DOR 6.9 months

Camidge et al. ASCO 2022 #9016

Teliso-V Monotherapy Adverse Events

TEAEs, n (%)	Total N=136	
	Any Grade	Grade ≥3
Any TEAE	131 (96)	65 (48)
Most common any-grade TEAEs (≥10%)		
Peripheral sensory neuropathy	34 (25)	6 (4)
Nausea	30 (22)	1 (1)
Hypoalbuminemia	28 (21)	1 (1)
Peripheral edema	25 (18)	0
Blurred vision	25 (18)	1 (1)
Decreased appetite	24 (18)	0
Fatigue	22 (16)	5 (4)
Anemia	19 (14)	3 (2)
Dyspnea	19 (14)	4 (3)
Asthenia	18 (13)	3 (2)
Increased gamma-glutamyl transferase	18 (13)	3 (2)
Keratitis	18 (13)	0
Constipation	16 (12)	1 (1)
Cough	14 (10)	0
Diarrhea	14 (10)	0
Dizziness	14 (10)	0
Malignant neoplasm progression	14 (10)	11 (8)
Vomiting	14 (10)	1 (1)

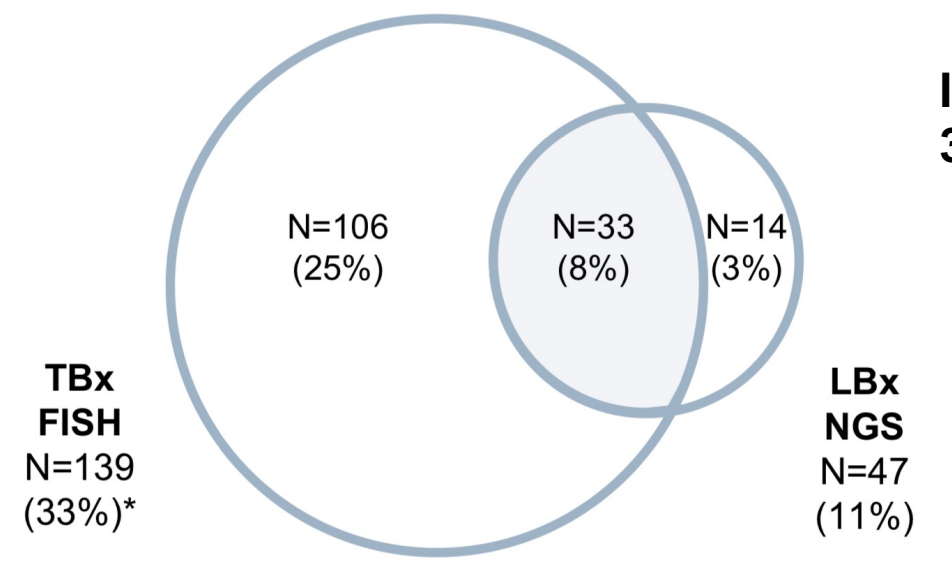
Treatment discontinuation rate for adverse events: 33%

6.6% Pneumonitis

- 2.2% Grade 3+
- One case of fatal pneumonitis

Camidge et al. ASCO 2022 #9016

How to Define “MET Positive”?



INSIGHT 2: Osimertinib + Tepotinib Screening Data
35% amplified (FISH or NGS defined)

Teliso-V Prescreening
25-37% MET overexpression

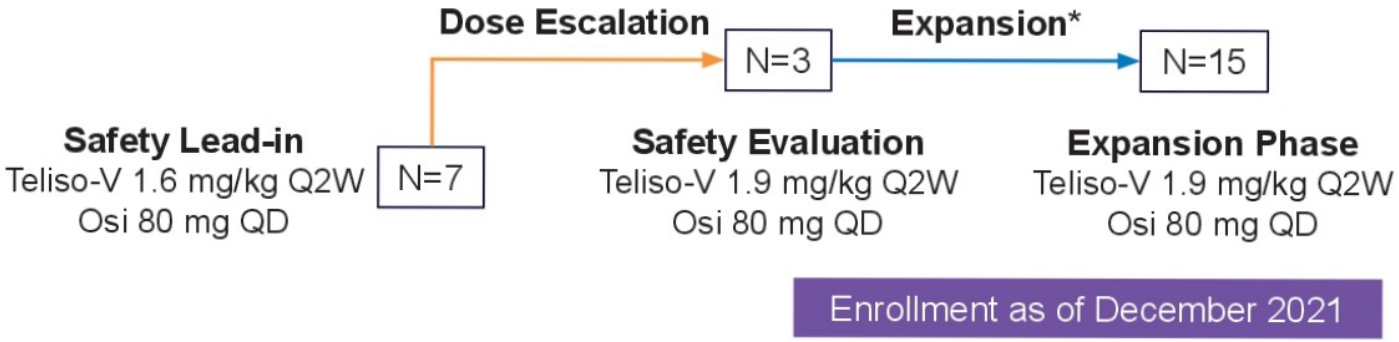
	Patients	c-Met Positive, %[a] (n)
NSQ *EGFR* MU	245	37 (90)
NSQ *EGFR* WT	446	25 (122)
Squamous	150	39 (58)

Mazieres et al ESMO 2022 LBA52; Motwani et al JTO 2021

Teliso-V + Osimertinib for MET+ Osimertinib REsistance

Arm E: Phase 1/1b Multicenter, Open-Label Study Design (NCT02099058)

- Patients (≥18 years of age) with metastatic nSQ NSCLC who had progressed on prior Osi
- Documented L858R or del19 *EGFR* mutation(s)
- c-Met overexpressing (by central IHC)
  - c-Met overexpression: ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to 49% 3+)



- Tumor assessments were performed Q8W according to RECIST v1.1
- Efficacy analyses included all evaluable dosed patients
- Safety analyses included all patients who received ≥1 dose of Teliso-V (AE severity by NCI CTCAE v4.03)
- PK were assessed throughout the study
- Patients received study treatment until disease progression, unacceptable toxicity, or for up to 24 months

*Two or fewer prior lines of systemic therapy; 1 must have contained Osi, and no more than 1 may have contained chemotherapy (ie, second- and third-line patients).
AE, adverse event; EGFR, epidermal growth factor receptor; IHC immunohistochemistry; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; nSQ, non-squamous; Osi, osimertinib; PK, pharmacokinetics; Q2W, every 2 weeks; Q8W, every 8 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; Teliso-V, telisotuzumab vedotin; v, version.

Goldman et al. ASCO 2022 #9013

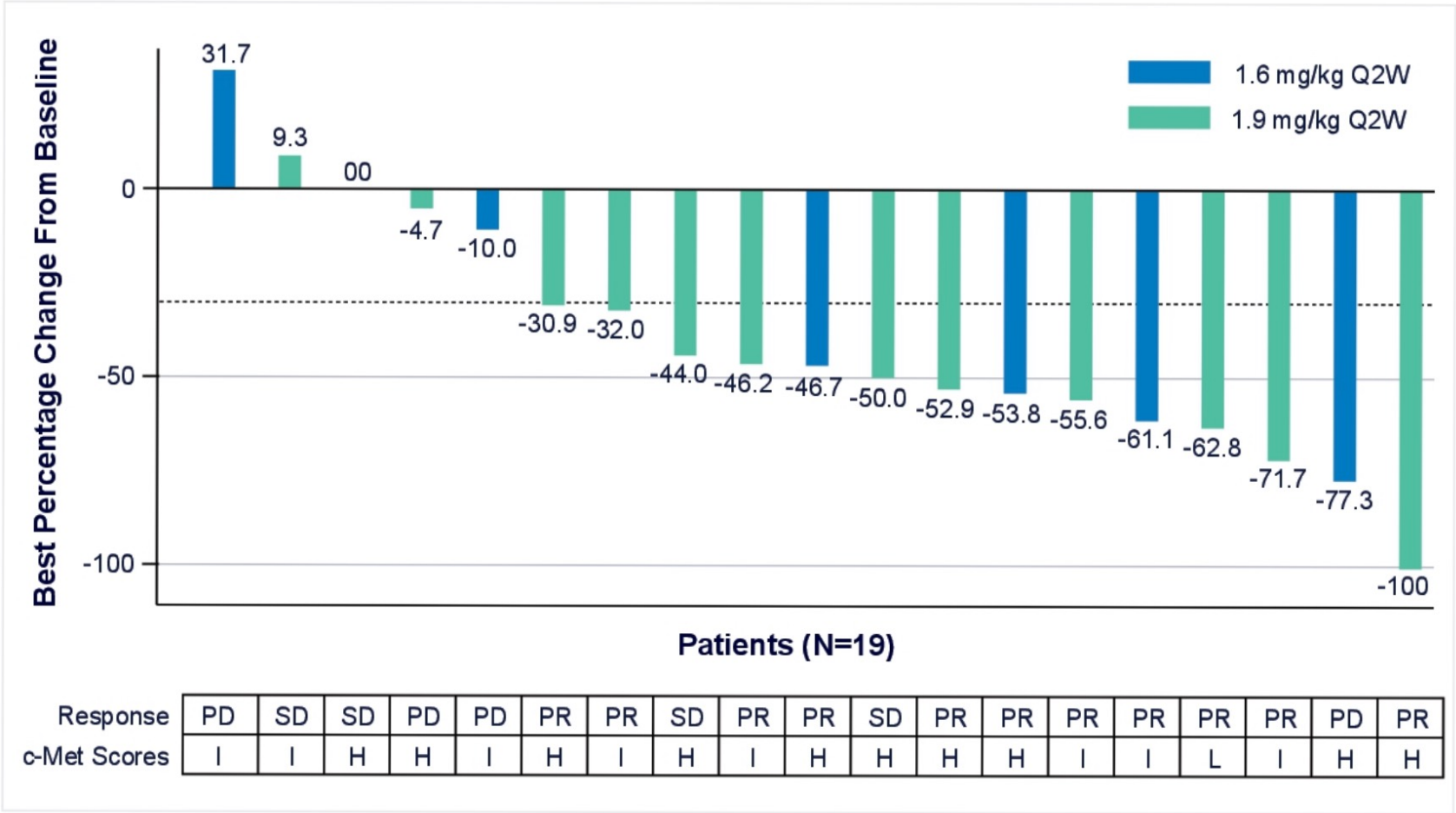
Teliso-V + Osimertinib for MET+ Osimertinib Resistance

By eligibility criteria, all with fairly high level cMET expression

23% had > 6 months since prior osimertinib treatment

Patient Characteristics	Teliso-V (1.6 mg/kg) + Osi n=7	Teliso-V (1.9 mg/kg) + Osi n=18	Total N=25
Sex, n (%)			
Female	4 (57)	13 (72)	17 (68)
Male	3 (43)	5 (28)	8 (32)
Median age (range), years	61 (40–73)	59 (41–79)	60 (40–79)
Age ≥65 years, n (%)	2 (29)	5 (28)	7 (28)
EGFR mutations, n (%)			
Exon 19 deletions	3 (43)	7 (39)	10 (40)
L858R	3 (43)	11 (61)	14 (56)
G719S	1 (14)	0	1 (4)
c-Met level, n (%)			
Int (25–49%, 3+ staining)	3 (43)	8 (44)	11 (44)
High (≥50%, 3+ staining)	4 (57)	9 (50)	13 (52)
Other	0	1 (6)	1 (4)
Number of prior lines [metastatic], n (%)			
1	1 (14)	7 (39)	8 (32)
2	2 (29)	10 (56)	12 (48)
>2	4 (57)	1 (6)	5 (20)
Prior platinum-based regimen, n (%)			
Yes	6 (86)	9 (50)	15 (60)
No	1 (14)	9 (50)	10 (40)
Duration of prior Osi treatment, n (%)			
0 to <6 months	2 (29)	4 (24)	6 (25)
6 to 12 months	2 (29)	2 (12)	4 (17)
>12 months	3 (43)	11 (65)	14 (58)
Missing	0	1	1
Time since end of prior Osi treatment to first dose of study drug, n (%)			
<1 month	2 (33)	8 (50)	10 (45)
1–6 months	2 (33)	5 (31)	7 (32)
>6 months	2 (33)	3 (19)	5 (23)
Missing	1	2	3

Teliso-V + Osimertinib for MET+ Osimertinib Resistance



ORR 58%

MET High ORR 50%
MET Int ORR 63%

Osimertinib in immediate prior regimen?

Yes: ORR 50%
No: ORR 64%

Goldman et al. ASCO 2022 #9013

Adverse Events, Teliso-V + Osimertinib

Overview of Interim Treatment-Emergent Adverse Events

MedDRA 24.1 Preferred Term	Teliso-V (1.6 mg/kg) + Osi n=7	Teliso-V (1.9 mg/kg) + Osi n=18	Total N=25
Any-grade TEAE [≥15% total], n (%)	7 (100)	18 (100)	25 (100)
Peripheral sensory neuropathy	3 (43)	6 (33)	9 (36)
Peripheral edema	2 (29)	4 (22)	6 (24)
Anemia	2 (29)	3 (17)	5 (20)
Fatigue	2 (29)	3 (17)	5 (20)
Nausea	0	5 (28)	5 (20)
Cough	2 (29)	2 (11)	4 (16)
Diarrhea	1 (14)	3 (17)	4 (16)
Dizziness	1 (14)	3 (17)	4 (16)
Dyspnea	0	4 (22)	4 (16)
Paresthesia	2 (29)	2 (11)	4 (16)
Pulmonary embolism	0	4 (22)	4 (16)
Blurred vision	1 (14)	3 (17)	4 (16)
Grade ≥3 TEAE [≥10% total], n (%)	3 (43)	8 (44)	11 (44)
Anemia	1 (14)	2 (11)	3 (12)
Pulmonary embolism	0	3 (17)	3 (12)
Serious TEAE [>1 patient], n (%)	1 (14)	5 (28)	6 (24)
Malignant neoplasm progression	0	2 (11)	2 (8)
Pneumonia	1 (14)	1 (6)	2 (8)
Pulmonary embolism	0	2 (11)	2 (8)

MedDRA, Medical Dictionary for Regulatory Activities; Osi, osimertinib; TEAE, treatment-emergent adverse event; Teliso-V, telisotuzumab vedotin

Goldman et al. ASCO 2022 #9013

Targeting MET at EGFR TKI Resistance

MET-ADC Therapy

Teliso-V + Osimertinib
Biomarker: MET IHC High
Response Rate in Biomarker “Positive”: ORR 58%, n = 19

MET TKIs

Tepotinib, Capmatinib, or Savolitinib + Osimertinib
Biomarker (INSIGHT 2): NGS or FISH status
Response Rate in Biomarker “Positive”: 50-54.5%, n = 16-22

EGFR-MET Bispecfics

Amivantamab + Lazertinib
Biomarker: MET IHC High
Response Rate in Biomarker “Positive”: ORR 61%, n = 28

Mazieres et al ESMO 2022 LBA52; Goldman et al ASCO 2022 #9013; Besse et al ASCO 2023 #9013

Take Aways

- Novel ADC targets continue to demonstrate activity in advanced/metastatic NSCLC
- CEACAM5 and MET-targeted ADCs are active in biomarker-selected populations
- Optimal strategies to screen patients in clinical practice for ADC-targets are needed