MET Resistance Mechanisms and Strategies.

PRESENTED BY

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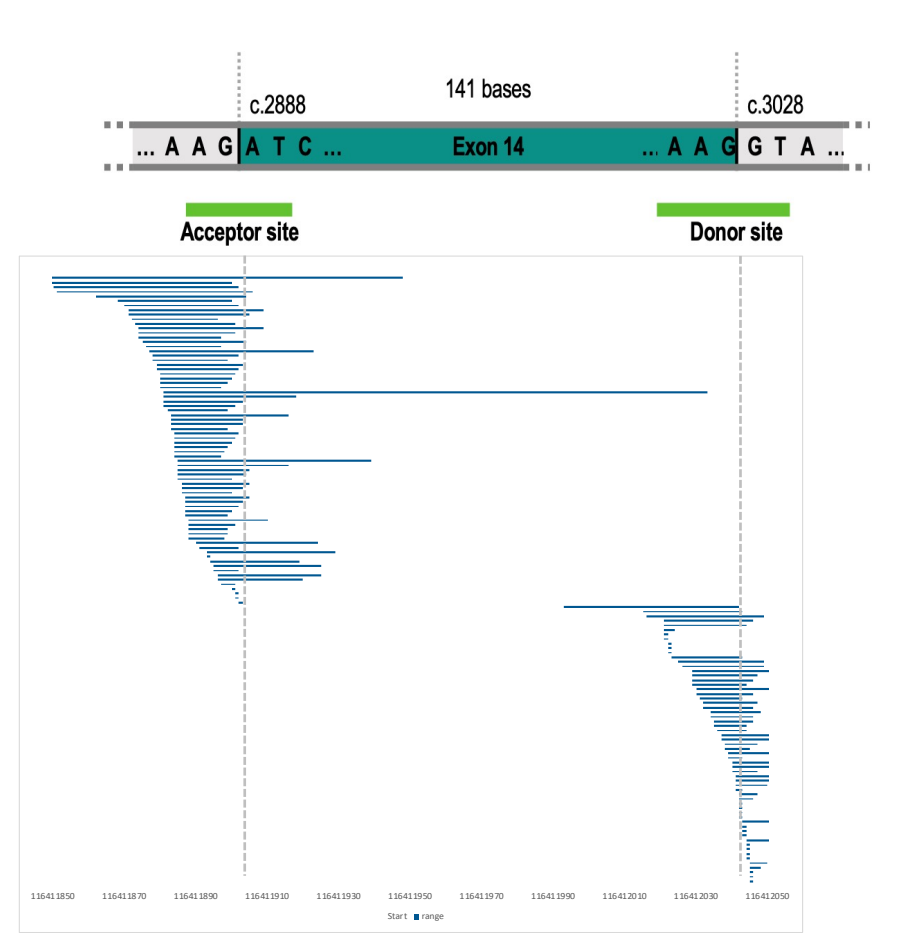
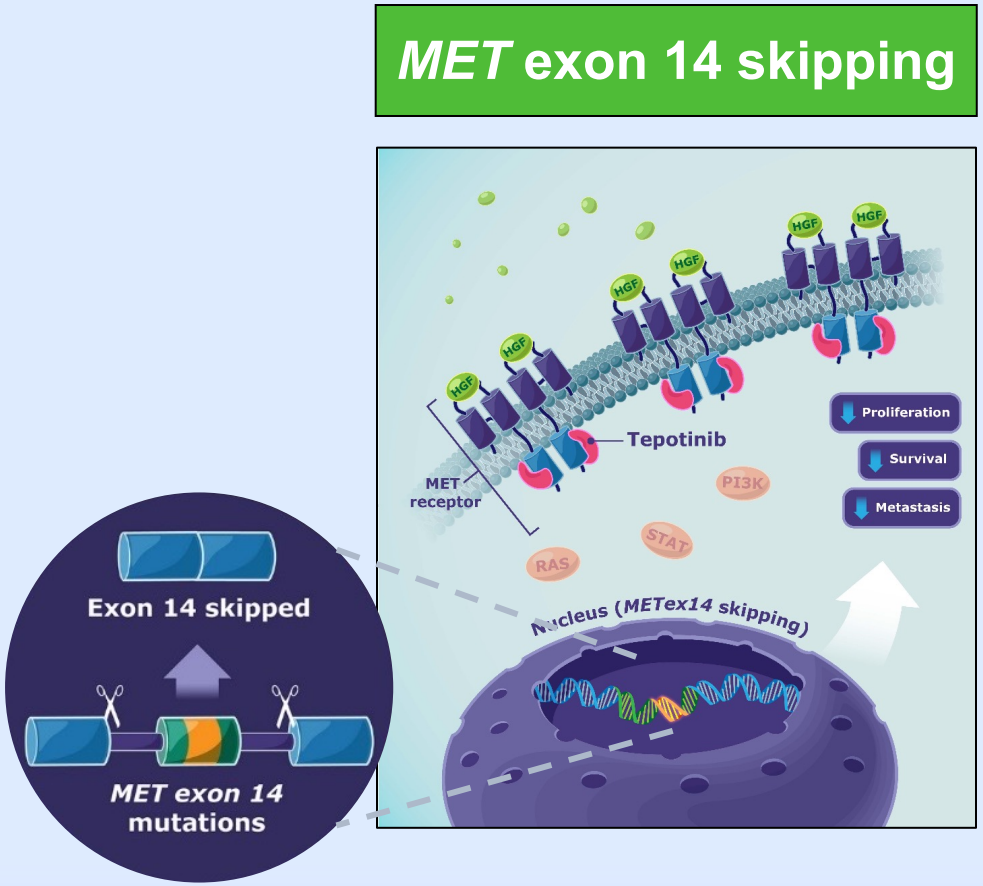
METex14 as an oncogene driver in lung cancer





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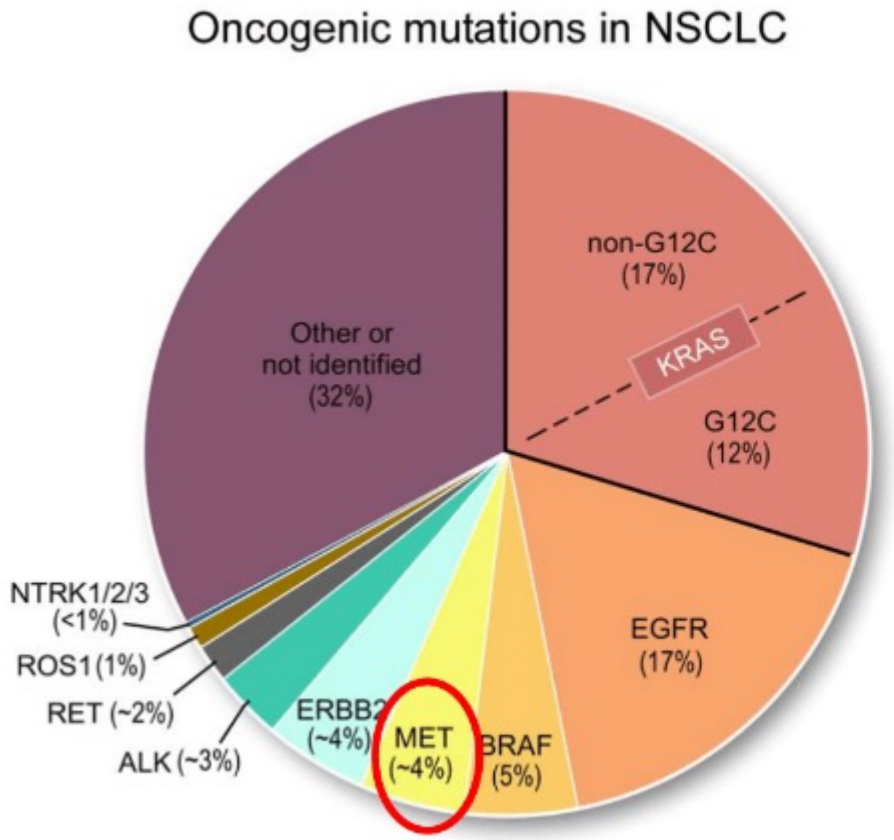
FDA approved MET therapies



May 6, 2020: FDA grants accelerated approval to capmatinib for metastatic NSCLC with METex14

February 3, 2021: FDA grants accelerated approval to tepotinib for metastatic NSCLC with METex14

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Type I MET inhibitors in MET exon 14 skipping

	Crizotinib n = 69	Capmatinib n = 28	n = 69	Tepotinib n = 69	n = 83	Savolitinib n = 28	n = 42
	Overall	1L	Previously treated	1L	Previously treated	1L	Previously treated
Median Age	72	71	71	74	73	69	
RR	32%	68%	41%	45%	45%	46%	41%
Median DOR (95% CI)	9.1 mo	12.6 mo (5.6, n.e.)	9.7 mo (5.6, 13.0)	10.8 mo (6.9, ne)	11.1 mo (9.5, 18.5)	6.8 mo (3.8, ne)	n.e. (6.9, n.e.)
Median PFS (95% CI)	7.3 mo	12.4 mo (8.2, n.e.)	5.4 mo (4.2, 7.0)	8.5 mo (6.8, 11.3)	10.9 mo (8.2, 12.7)	5.6 mo (2.8, 9.7)	13.8 (4.1, ne)

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Drilon et al Nat Med 2019; Wolf et al NEJM 2020; Paik et al WCLC 2020; Lu et al ASCO 2020

Strategies to overcome resistance

What is the reason for disease progression?

1. Is the drug getting to all sites of disease?

- For example: Isolated cancer growth in the brain, but excellent disease control in the body.

2. Did MET mutate again?

- For example: In addition to the original MET exon 14 mutation, there is now a new MET resistance mutation (e.g. D1228, Y1230, etc).

3. Has a new gene (besides MET) become abnormal?

- For example: In addition to the original MET exon 14 mutation, this is now EGFR amplification.

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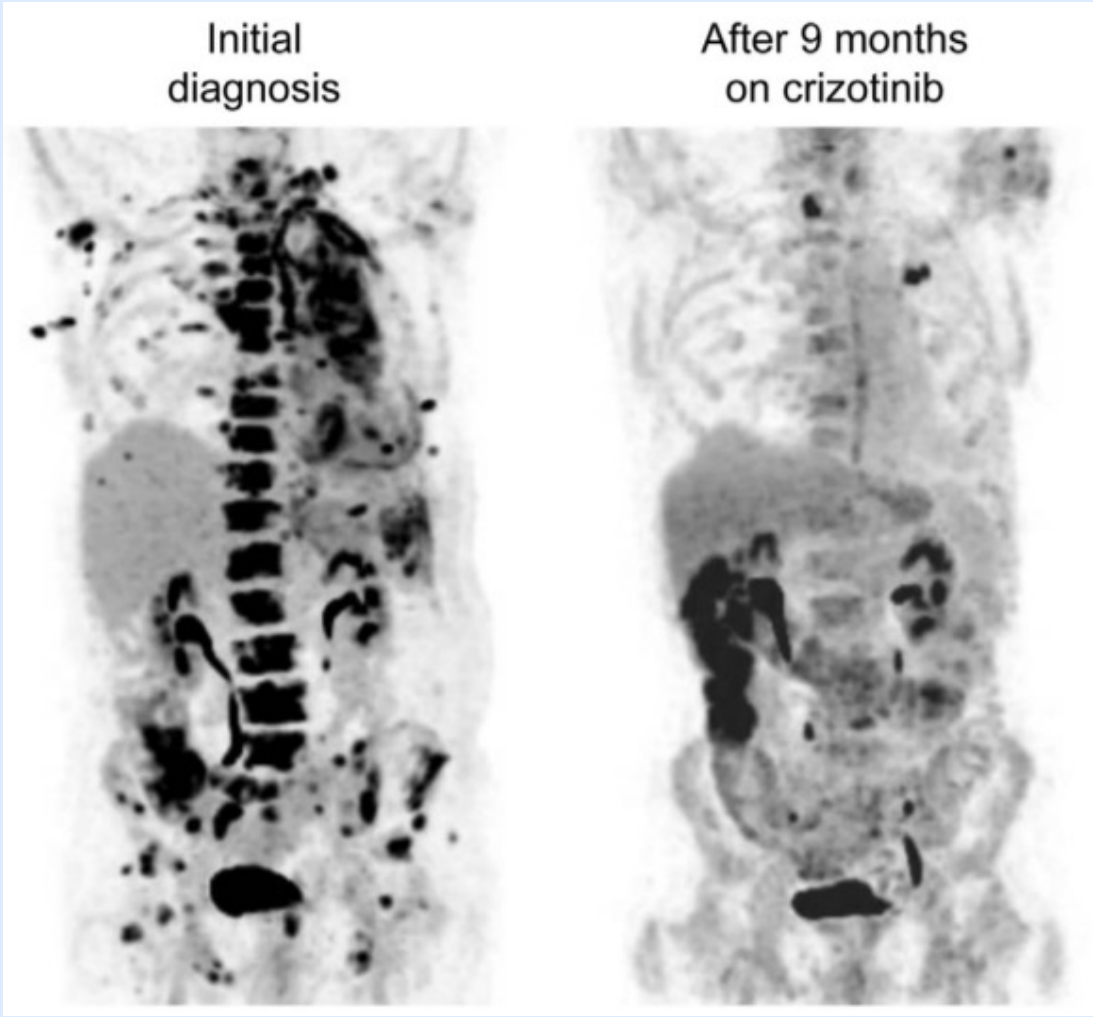
1. Is the drug getting to the central nervous system (i.e. brain, spinal cord)?



Cravero P, et al, *JTO CRR*, 2020 Vol. 1 No. 4: 1–3

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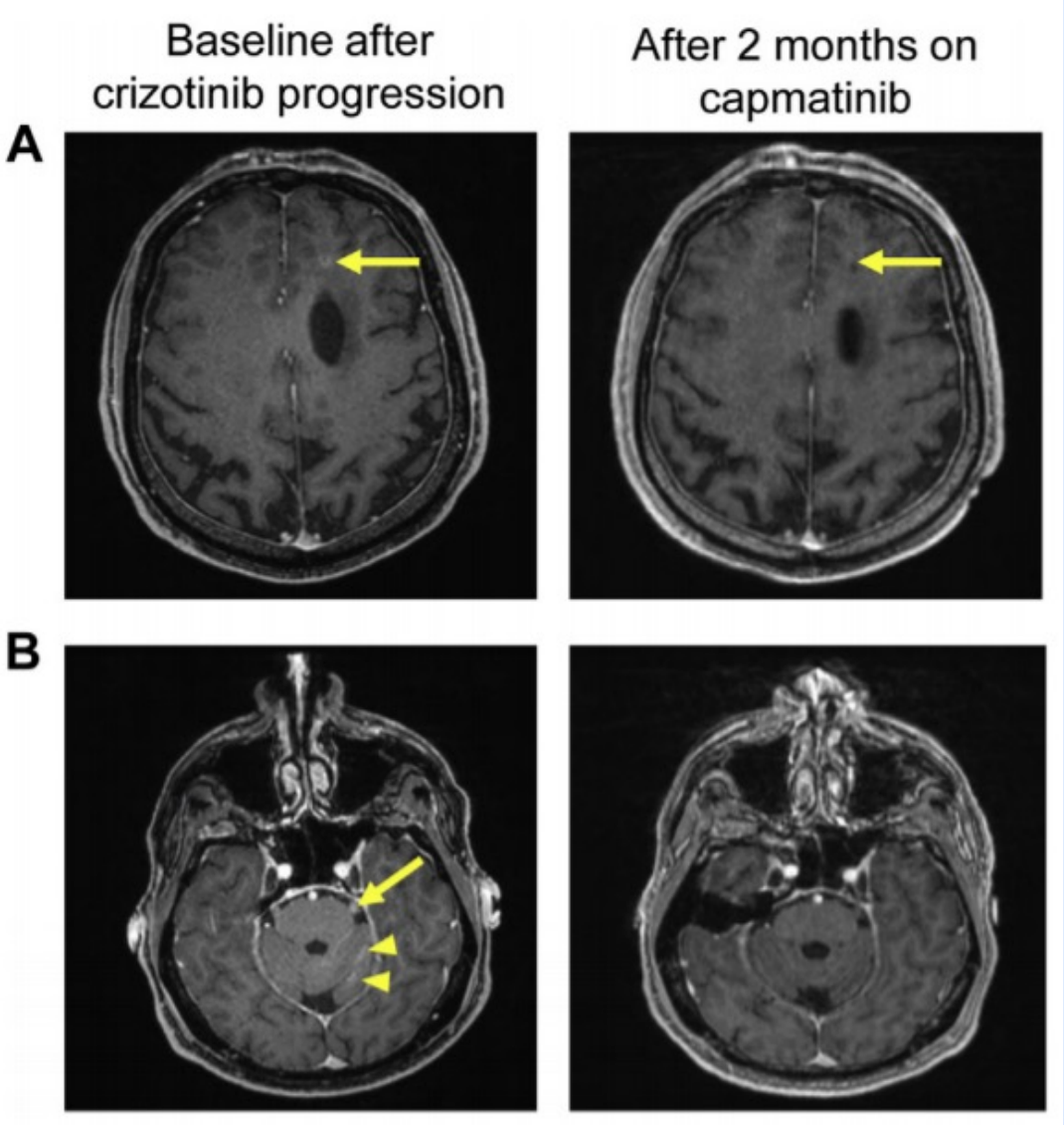
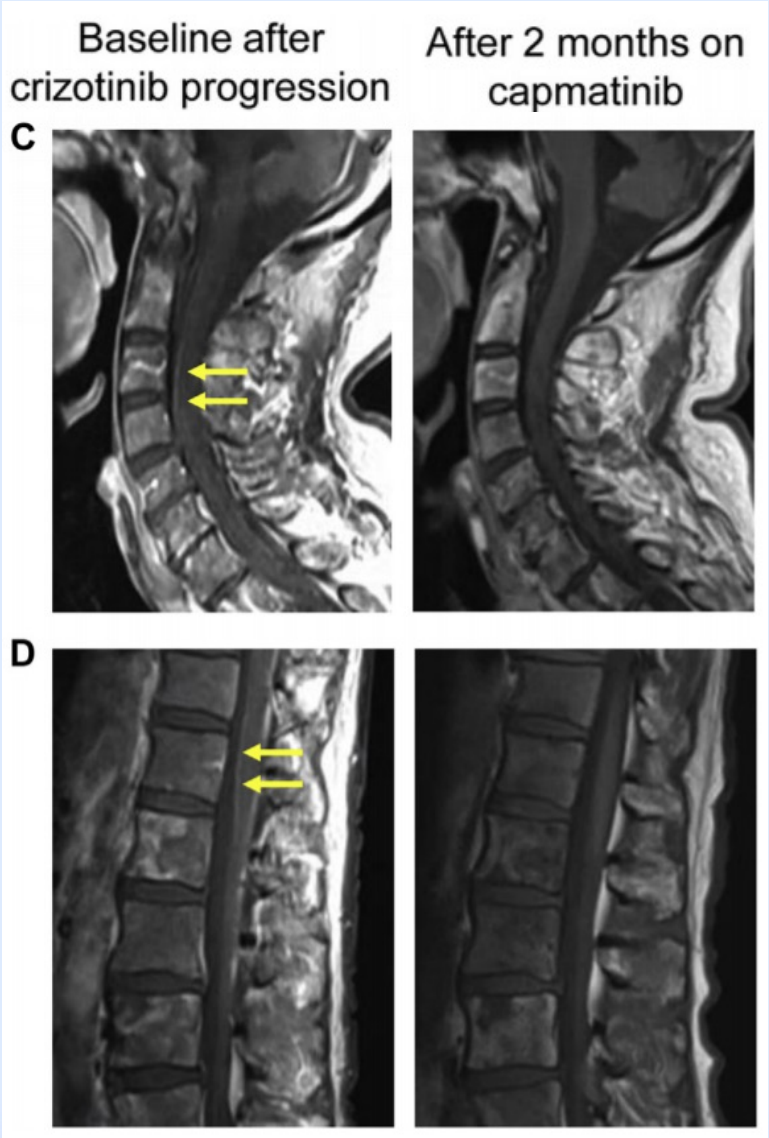
1. Is the drug getting to the central nervous system (i.e. brain, spinal cord)?





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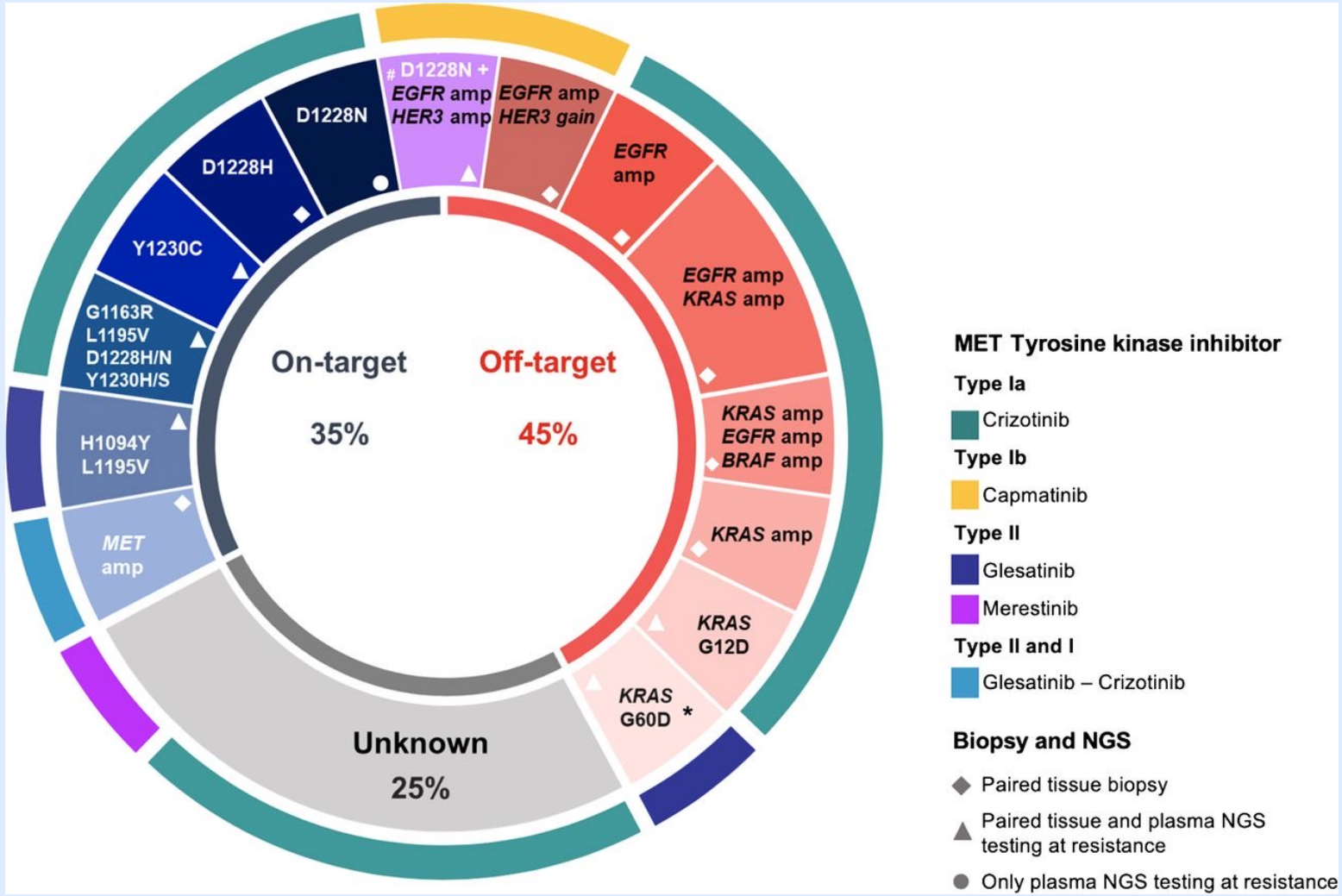
Cravero P, et al, *JTO CRR*, 2020 Vol. 1 No. 4: 1–3

2. Did the *MET* gene acquire an additional mutation?



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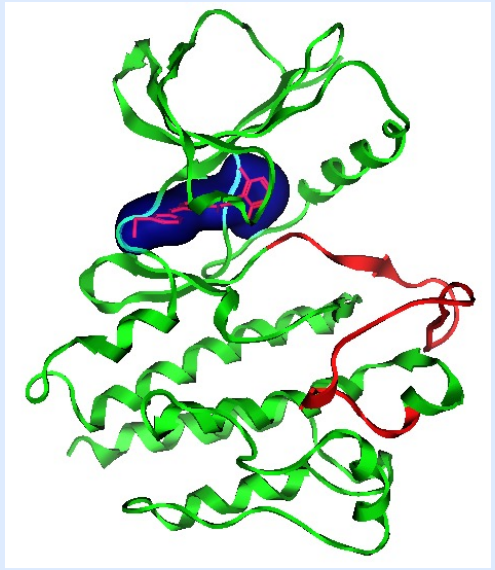
Gonzalo Recondo et al. Clin Cancer Res 2020;26:2615-2625

Different MET inhibitors have different structures

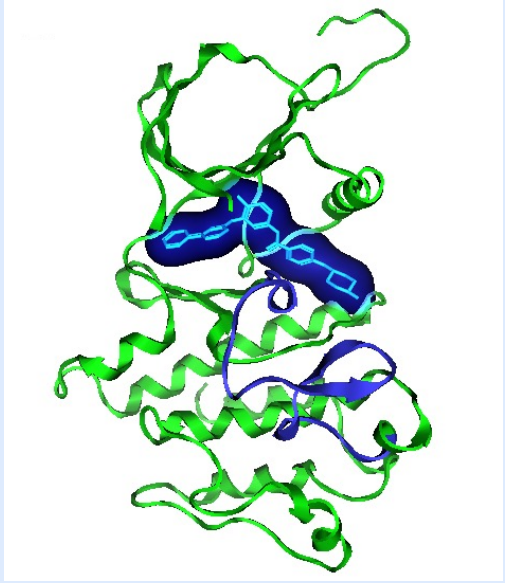
MET Kinase Inhibitors

Type I



Crizotinib
Capmatinib
Savolitinib
Tepotinib
APL-101

Type II



Cabozantinib
PF-07265807
[Merestinib]
[Glesatinib]

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Courtesy of Nathanael Gray

Certain MET resistance mutations retain sensitivity to some MET inhibitors

Mutations		Type Ia	Type Ib			Type II		
		crizotinib	capmatinib	tepotinib	savolitinib	cabozantinib	merestinib	glesatinib
Exon 14 skipping (parental)		22	0.6	3.0	2.1	7.8	8.1	21
1090	G1090A	176	7.3	145	69	0.3	0.8	1.7
	G1090S	41	3.0	42	24	0.7	1.3	6.7
1092	V1092I	292	2.8	2.6	2.9	16	13	5.7
	V1092L	223	2.5	2.3	13	1.8	10	6.5
1133	D1133V	30	0.9	2.6	7.3	88	29	62
1155	V1155M	89	3.4	23	16	17	5.6	22
1159	Y1159H	181	0.9	22	8.1	107	28	46
1163	G1163E	91	0.9	10	3.3	49	9.3	89
	G1163R	> 1000	2.5	70	8.5	62	14	66
1164	D1164G	213	7.2	74	28	25	9.7	24
1195	L1195F	23	0.3	2.6	1.8	> 1000	83	90
	L1195V	235	8.1	55	22	118	44	236
1200	F1200I	199	6.1	45	30	694	212	275
	F1200L	23	0.8	8.0	7.7	229	109	111
1211	M1211T	26	2.8	24	11	22	7.5	18

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Fujino T, et al. *J Thorac Oncol* 2019 Oct;14(10):1753-1765.

Certain MET resistance mutations retain sensitivity to some MET inhibitors

Mutations		Type Ia	Type Ib			Type II		
		crizotinib	capmatinib	tepotinib	savolitinib	cabozantinib	merestinib	glesatinib
1228	D1228A	> 1000	≥ 1000	> 1000	> 1000	200	89	216
	D1228E	690	137	≥ 1000	573	37	19	30
	D1228G	319	697	≥ 1000	431	72	23	46
	D1228H	665	≥ 1000	> 1000	> 1000	79	25	38
	D1228N	≥ 1000	≥ 1000	> 1000	> 1000	36	26	22
	D1228Y	≥ 1000	477	> 1000	> 1000	539	149	74
1230	Y1230C	645	≥ 1000	≥ 1000	> 1000	8.4	7.4	12
	Y1230D	698	≥ 1000	≥ 1000	> 1000	16	5.5	11
	Y1230S	811	> 1000	≥ 1000	> 1000	23	12	14
	Y1230H	216	401	≥ 1000	≥ 1000	20	8.2	19
	Y1230N	> 1000	≥ 1000	≥ 1000	≥ 1000	19	4.1	14

$IC_{50} \leqq 50nM$ | $50 < IC_{50} < 200nM$ | $IC_{50} \geqq 200nM$

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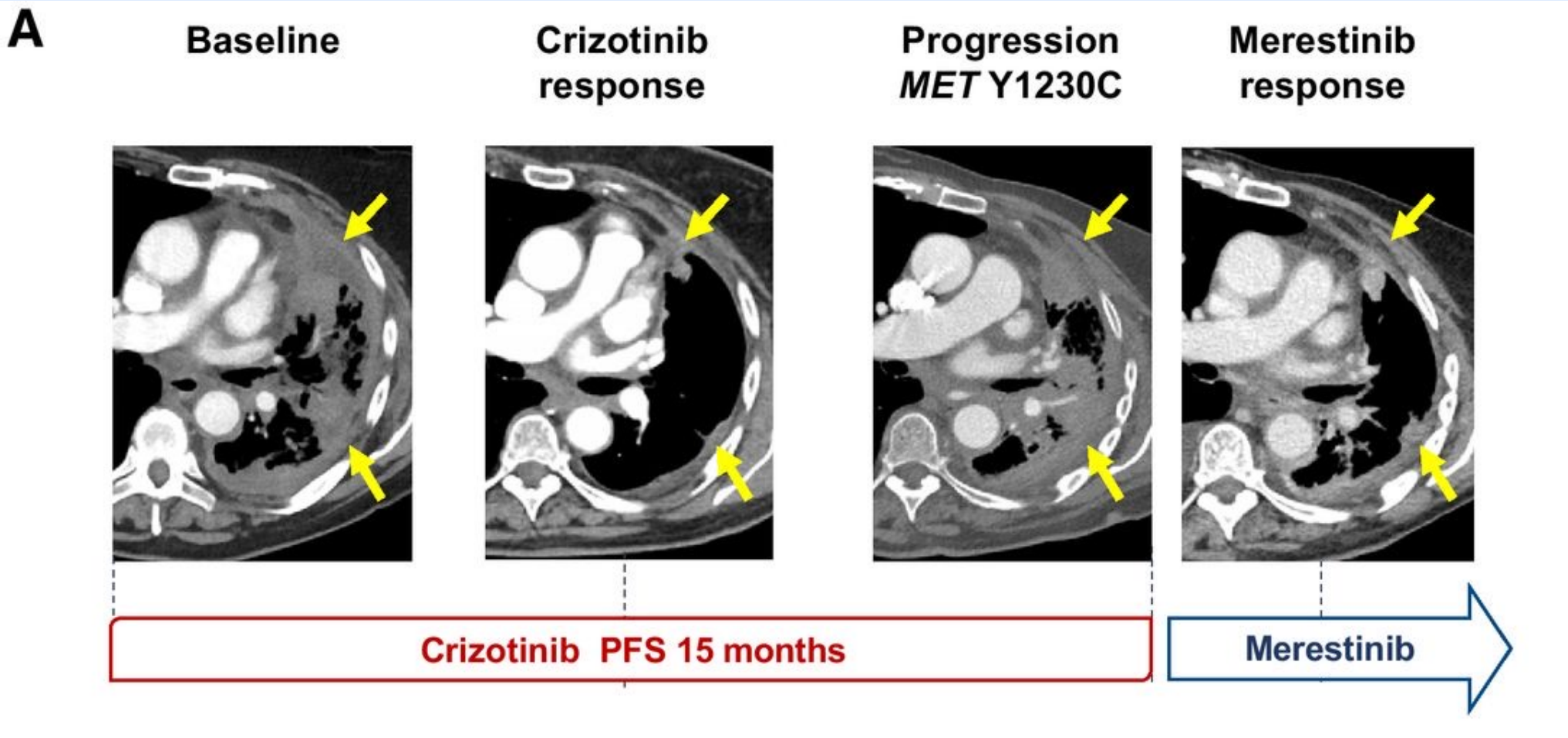
Fujino T, et al. *J Thorac Oncol* 2019 Oct;14(10):1753-1765.

Merestinib response after development of crizotinib resistance via Y1230C



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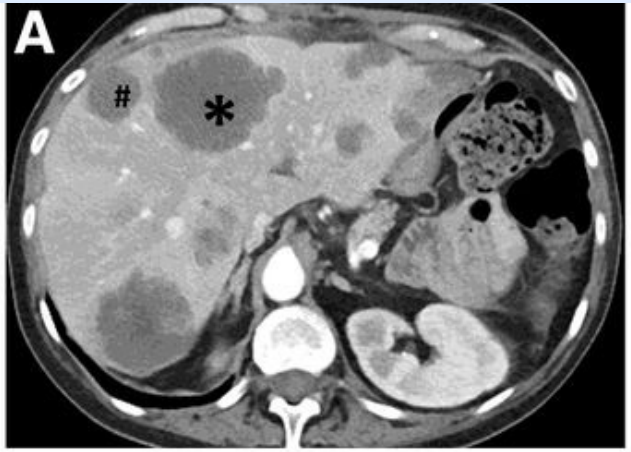
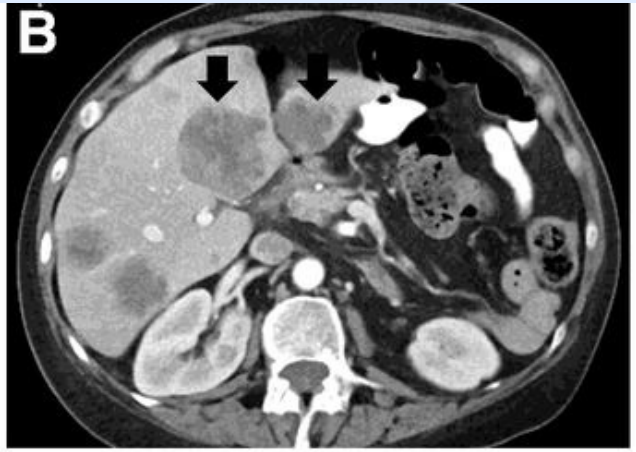
Gonzalo Recondo et al. Clin Cancer Res 2020;26:2615-2625

Some patients develop >1 resistance mutation simultaneously

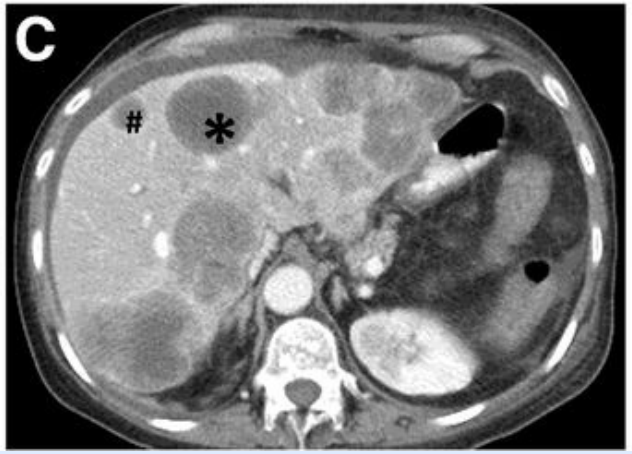
Use of glesatinib after crizotinib (liver biopsy showed Y1230H)

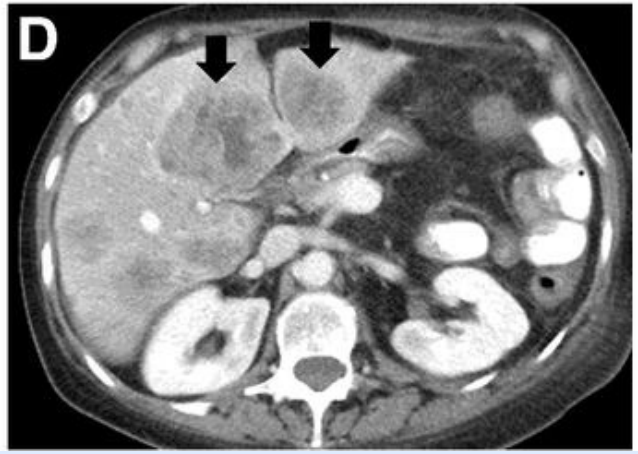
Baseline (4/19/2016)

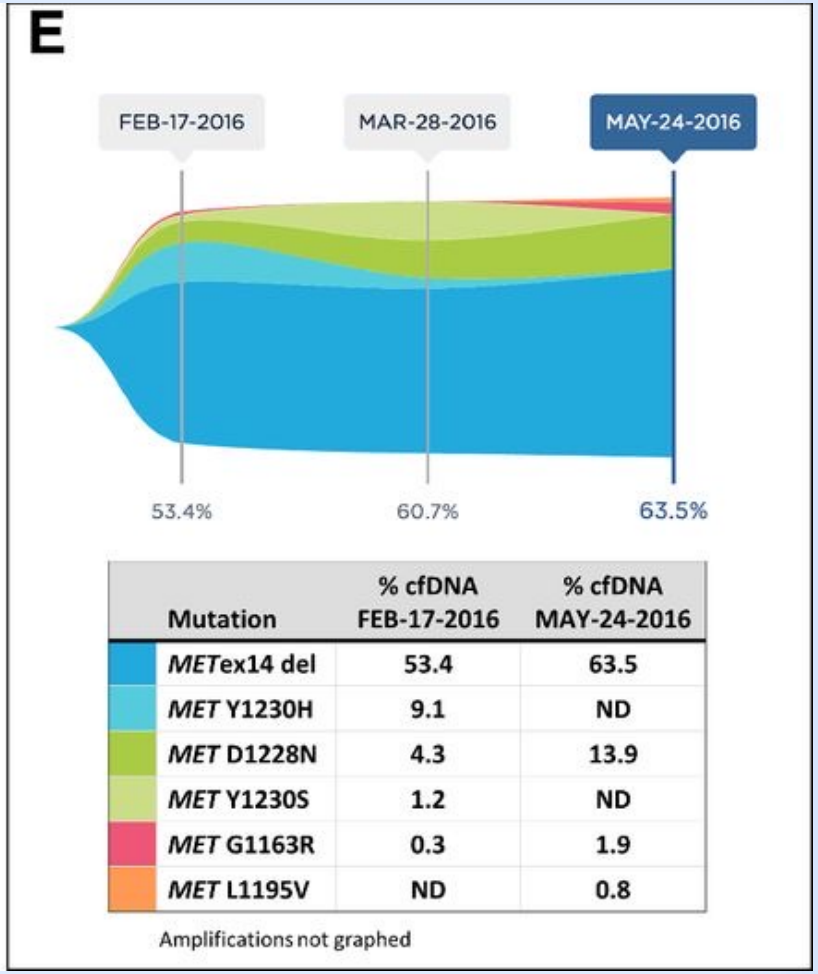




Follow-up (5/27/2016)







Mutation	% cfDNA FEB-17-2016	% cfDNA MAY-24-2016
*MET*ex14 del	53.4	63.5
MET Y1230H	9.1	ND
MET D1228N	4.3	13.9
MET Y1230S	1.2	ND
MET G1163R	0.3	1.9
MET L1195V	ND	0.8

Amplifications not graphed

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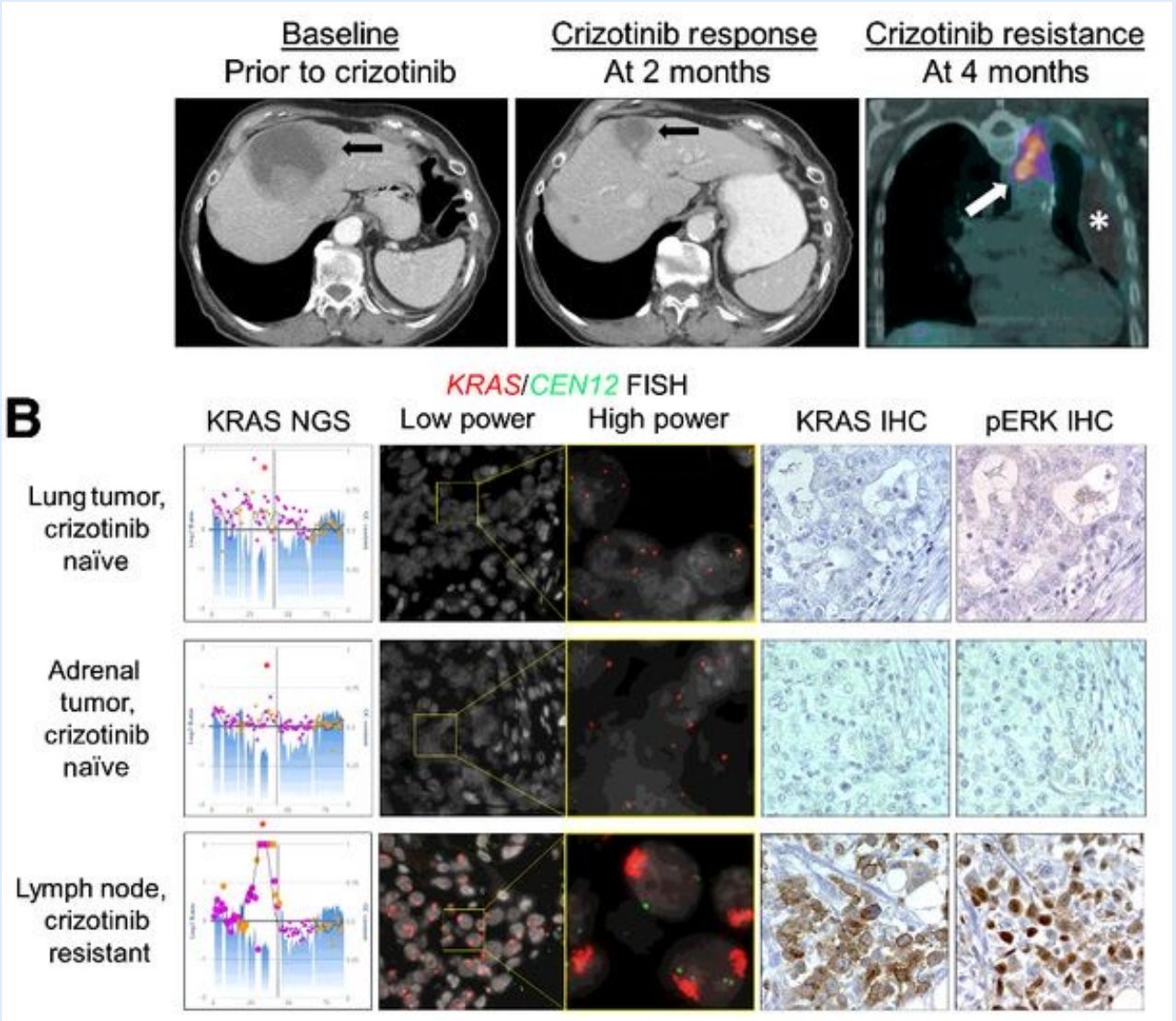
Lars D. Engstrom et al. Clin Cancer Res 2017;23:6661-6672

3. Has a new gene (besides MET) become abnormal?

***KRAS* amplification**



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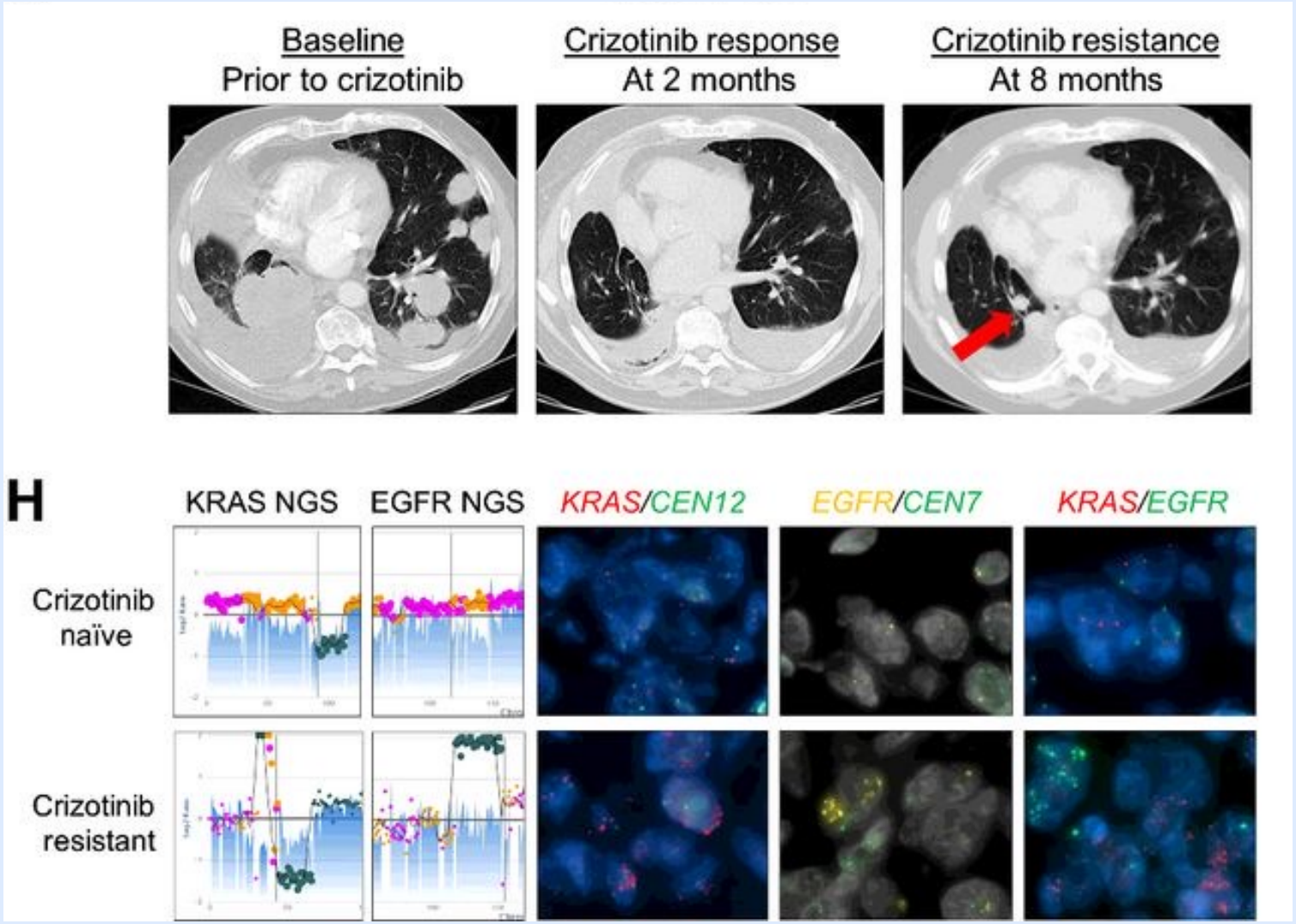
Bahcall M, et al. Clin Cancer Res 2018;24:5963-5976

3. Has a new gene (besides MET) become abnormal?

KRAS **amplification**

and

EGFR amplification



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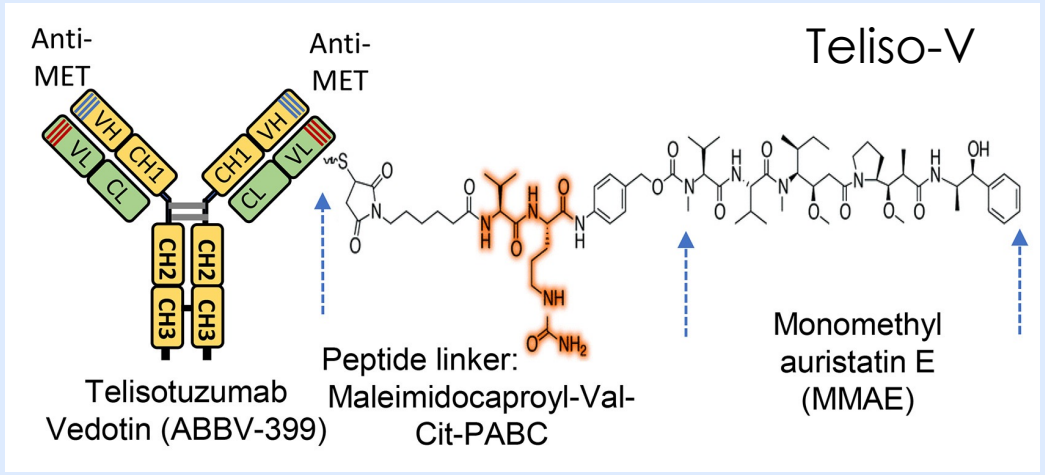
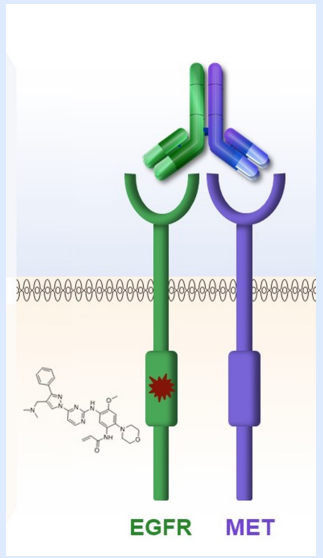
Bahcall M, et al. Clin Cancer Res 2018;24:5963-5976

Other MET targeting strategies

- **MET antibodies (e.g. REGN5093)**
- **MET antibody drug conjugates (e.g. ABBV-399 telisotuzumab vetodin)**
- **EGFR:MET bispecific antibodies (e.g. Amivantamab)**





Amivantamab

Yao H-P, et al, *Biochim Biophys Acta Rev Cancer*. 2020 Dec;1874(2):188425.
Cho BC, et al, ASCO 2021 Annual Meeting

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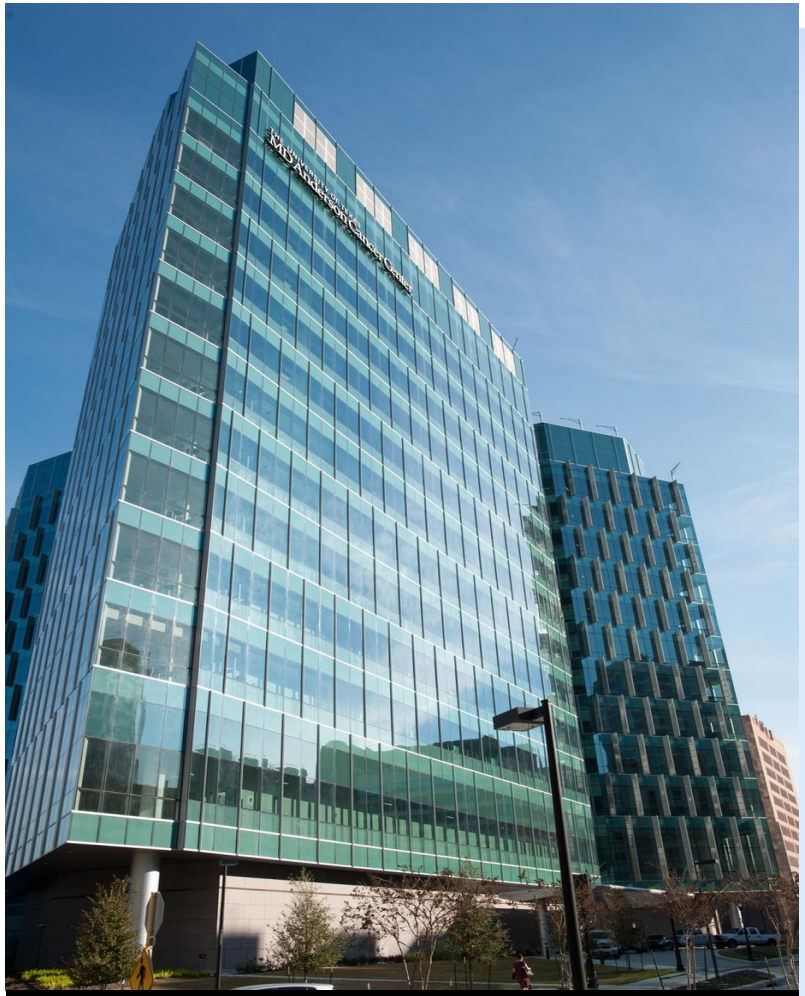

TPX-022
Telesio-V

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AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

AACR American Association for Cancer Research FINDING CURES TOGETHER
NIH NATIONAL CANCER INSTITUTE
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Poster #: P225

Preliminary interim data of elzovantinib (TPX-0022), a novel inhibitor of MET/SRC/CSF1R, in patients with advanced solid tumors harboring genetic alterations in *MET*: Update from the Phase 1 SHIELD-1 trial

David S. Hong[1], Daniel Catenacci[2], Lyudmila Bazhenova[3], Byoung Chul Cho[4], Mariano Ponz-Sarvise[5], Rebecca Heist[6], Victor Moreno[7], Gerald Falchook[8], Viola W. Zhu[9], Aurélie Swalduz[10], Benjamin Besse[11], Dong-Wan Kim[12], Shinkyo Yoon[13], Xiuning Le[1], Tingting Zhao[14], Justine Lam[14], Zachary Zimmerman[14], Jeeyun Lee[15]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]University of Chicago Medical Center, Chicago, IL, USA; [3]UC San Diego Moores Cancer Center, San Diego, CA, USA; [4]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Clinica Universidad de Navarra, Pamplona, Spain; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Fundación Jiménez Díaz - START Madrid, Madrid, Spain; [8]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [9]University of California Irvine, Orange, CA, USA; [10]Centre de Lutte Contre le Cancer - Centre Leon Berard, Lyon, France; [11]Institut Gustave Roussy, Villejuif Cedex, France; [12]Seoul National University Hospital, Seoul, Republic of Korea; [13]Asan Medical Center, Seoul, Republic of Korea; [14]Turning Point Therapeutics, Inc., San Diego, CA, USA; [15]Samsung Medical Center, Seoul, Republic of Korea

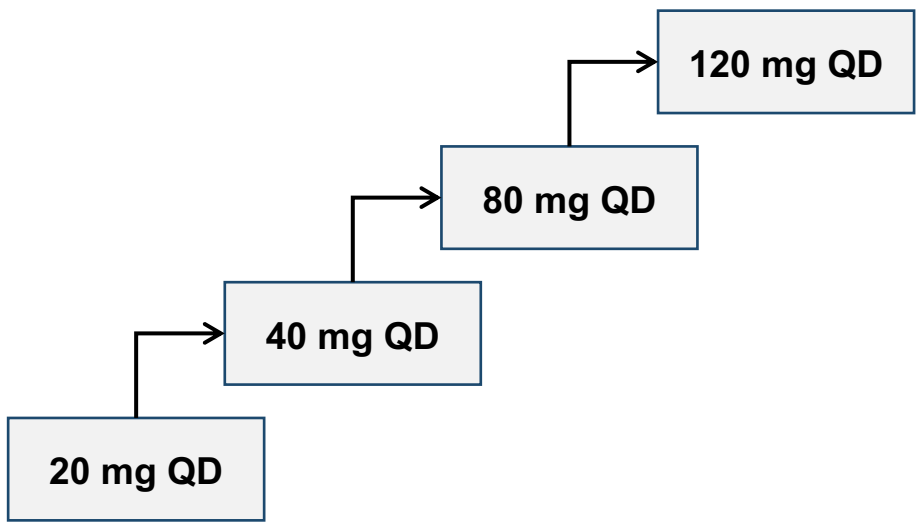
Phase 1 SHIELD-1 Study Design

Population
- Adults with advanced solid tumors
- MET genetic alterations assessed by local testing (exon 14 deletion, amplification, fusion, or oncogenic kinase domain mutation)
- Asymptomatic CNS disease allowed

Design
- 3+3 with expansion allowed at doses where clinical activity is observed
- Response evaluation by RECIST v1.1

Primary Objectives
- Evaluate safety/tolerability and determine MTD and RP2D

Dose Finding – Enrollment Complete



Titration Schedules:
- **80 mg QD (14 days) → 120 mg QD**
- **40 mg QD (14 days) → 40 mg BID**
- **40 mg QD (14 days) → 80 mg QD**

Dose Expansion – Enrolling

Expansion Cohorts

- **NSCLC Exon 14 Deletion** *TKI-Naive*
- **NSCLC Exon 14 Deletion** *TKI-Pretreated*
- **NSCLC *MET* Amplified (GCN ≥ 10)** *TKI-Naive*
- **GI (GC/GEJ, CRC, HCC) *MET* Amplified (GCN ≥ 10)** *TKI-Naive*
- **NSCLC or GI (GC/GEJ, CRC, HCC) *MET* Amplified (GCN 5-9)** *TKI-Naive*
- **Other*** *TKI-Naive*

Proposed RP2D of 40 mg QD → 40 mg BID determined and enrollment into Dose Expansion cohorts initiated

*Solid Tumors with MET Fusions or Oncogenic KD Mutations OR MET-amplified other than GI/NSCLC OR otherwise eligible for Cohorts I, III, or IV and >2 lines prior systemic therapy.
BID, twice daily; CNS, central nervous system; CRC, colorectal cancer; GC, gastric cancer; GEJ, gastroesophageal junction; GI, gastrointestinal; HCC, hepatocellular carcinoma; KD, kinase domain; MET, mesenchymal-epithelial transition factor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; QD, once daily; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; RP2D, recommended phase 2 dose.

Subject Disposition

Phase 1 Dose Finding
All Treated Patients

N=54
31 NSCLC, 9 GC/GEJ, 5 CRC, 9 Other*

Evaluable Patients†

N=46

TKI-Naïve (N=32)
11 NSCLC, 9 GC/GEJ, 5 CRC, 7 Other‡

TKI-Naïve NSCLC and GC/GEJ (n=20)

TKI-Pretreated (N=14)
13 NSCLC, 1 Liver

Non-Evaluable Patients

Off Treatment Prior to 1st Evaluable Scan
N=7

No Baseline Measurable Disease
N=1

Data cut-off date August 23, 2021
*Includes 2 liver cancers, 2 melanoma, 1 esophageal cancer, 1 glioblastoma multiforme, 1 ovarian/fallopian tube/peritoneal cancer, 1 pancreatic cancer, 1 uterine cancer.
†Patients with baseline measurable disease and at least one post-baseline evaluable scan. ‡Includes 1 esophageal cancer, 1 glioblastoma multiforme, 1 liver cancer, 2 melanoma, 1 pancreatic cancer, 1 uterine cancer.
CRC, colorectal cancer; GC/GEJ, gastric cancer/gastroesophageal junction; NSCLC, non-small cell lung cancer
Note: CRC includes colorectal adenocarcinoma and rectal neuroendocrine tumor.

Demographics and Baseline Characteristics

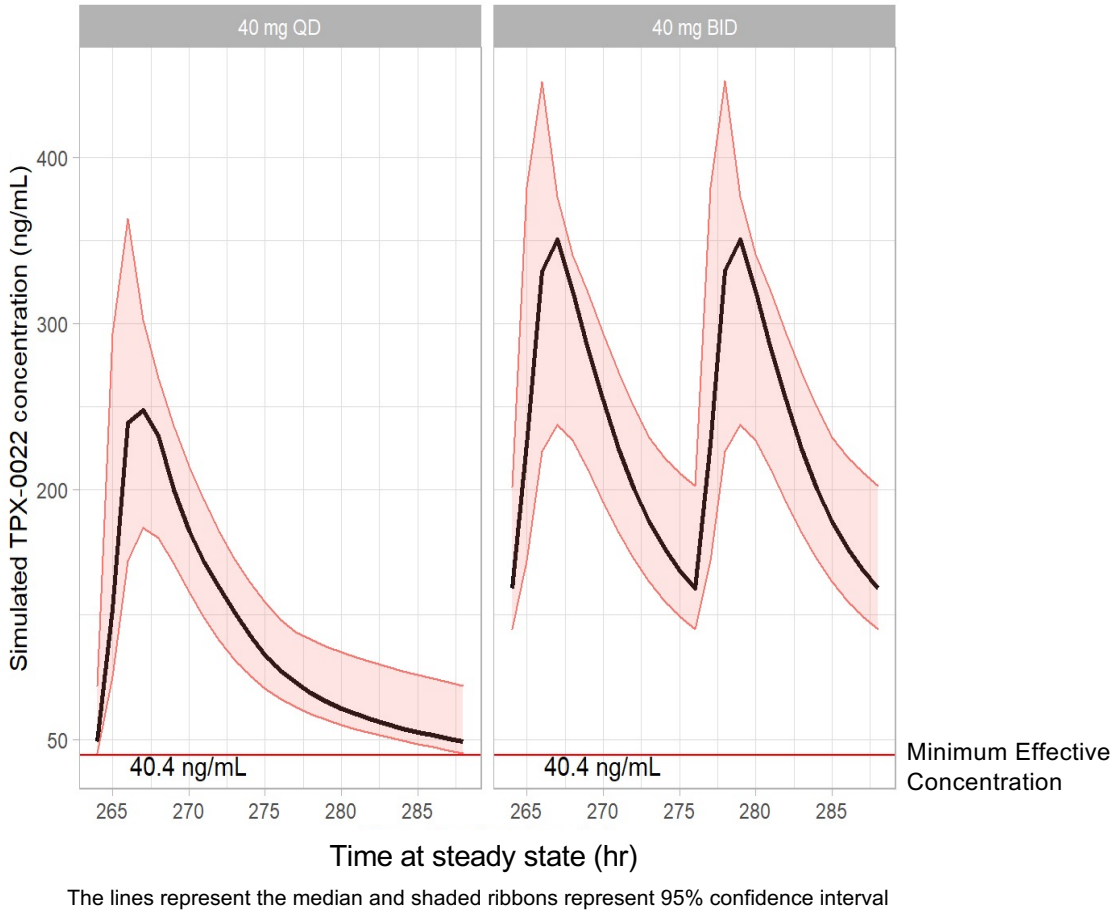
	All Treated Patients (N=54)
Age (years)	
Median (range)	63 (33–84)
Sex, n (%)	
Female	27 (50.0)
ECOG Performance Status, n (%)	
0	15 (27.8)
1	39 (72.2)
Baseline Brain Metastasis, n (%)	
Yes	9 (16.7)
Number of Prior Regimens, n (%)	
0	3 (5.6)
1	9 (16.7)
2	19 (35.2)
≥3	23 (42.6)
Median (range)	2 (0–6)
Prior MET TKI Treatment, n (%)	
Yes	18 (33.3)
Type of Cancer, n (%)	
NSCLC	31 (57.4)
GC/GEJ Cancer	9 (16.7)
CRC*	5 (9.3)
Other†	9 (16.7)

Data cut-off date August 23, 2021

CRC, colorectal cancer; GC/GEJ, gastric cancer/gastroesophageal junction; NSCLC, non-small cell lung cancer. *CRC includes colorectal adenocarcinoma and rectal neuroendocrine tumor.

†Other includes 2 liver cancers, 2 melanoma, 1 esophageal cancer, 1 glioblastoma multiforme, 1 ovarian/fallopian tube/peritoneal cancer, 1 pancreatic cancer, 1 uterine cancer.

PK Coverage at Proposed RP2D



The lines represent the median and shaded ribbons represent 95% confidence interval

Dose (mg)	Median $C_{trough,ss}$ (ng/mL)	Fold Coverage over MEC	% of Subjects with $C_{trough,ss}$ above MEC
20 QD	28.9	0.71	25.0
40 QD	58.4	1.45	73.1
40 BID	144	3.56	94.2
80 QD	119	2.95	92.3
120 QD	181	4.48	94.2

- 40 mg QD dose is predicted to result in trough concentration that is 1.45-fold above the minimum effective concentration (MEC) at steady state
- 40 mg BID dose is predicted to result in trough concentration that is 3.56-fold above the MEC at steady state

Preliminary Safety Summary

Adverse Events	All Treated Patients (N=54) TEAEs (≥15% of patients) All Grades n (%)	Grades≥3 n (%)	TRAEs All Grades n (%)	Grades≥3^ n (%)
Dizziness	35 (64.8)	2 (3.7)	31 (57.4)	1 (1.9)
Constipation	18 (33.3)	1 (1.9)	3 (5.6)	-
Fatigue	17 (31.5)	3 (5.6)	12 (22.2)	2 (3.7)
Lipase increased	17 (31.5)	3 (5.6)	17 (31.5)	2 (3.7)
Anaemia	16 (29.6)	5 (9.3)	2 (3.7)	-
Amylase increased	15 (27.8)	1 (1.9)	13 (24.1)	1 (1.9)
Nausea	12 (22.2)	1 (1.9)	7 (13.0)	-
Vomiting	12 (22.2)	3 (5.6)	4 (7.4)	-
Oedema peripheral	11 (20.4)	-	9 (16.7)	-
Abdominal pain	10 (18.5)	2 (3.7)	1 (1.9)	-

- TPX-0022 was generally well tolerated
- Most common TEAE was dizziness, likely due to off target TRK inhibition
  - All Grade dizziness at proposed RP2D (40 mg QD → 40 mg BID) in 46.7% of patients (no Grade ≥ 3 event)
- Dose modifications due to TEAE
  - 21 (38.9%) patients with TEAEs leading to dose reduction
  - 3 (5.6%) patients with TEAEs leading to drug discontinuation
- 2 DLTs at 120 mg QD*
- All Grade peripheral edema in 11 (20.4%) patients (no Grade ≥ 3 event)
- No related Grade ≥ 3 ALT/AST elevation
- No ILD/pneumonitis of any Grade

Data cut-off date August 23, 2021.
^ Other reported Grade 3 TRAEs are: asthenia, blood creatine phosphokinase increased, delirium, vertigo, vestibular disorder. No Grade 4 or 5 TRAEs.
* Grade 3 vertigo and Grade 2 dizziness.
ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; DLT, dose-limiting toxicity; ILD, interstitial lung disease; QD, once daily; TEAE, treatment emergent adverse event; TRAE, treatment related adverse event.

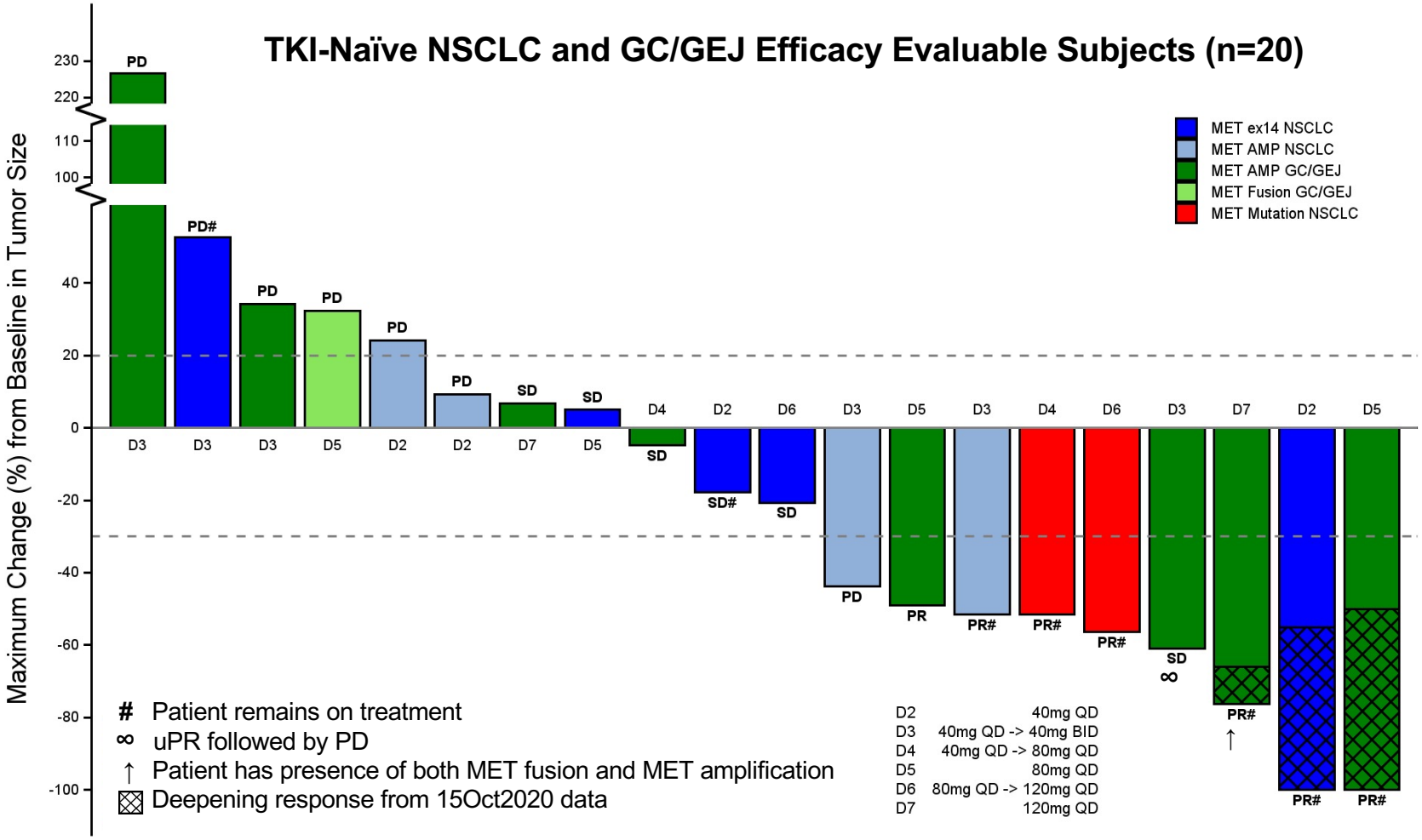
Preliminary Efficacy by Investigator Assessment

TKI-Naïve Efficacy Evaluable Patients (N=32)			
Efficacy Outcomes	**NSCLC (N=11)**	**GC/GEJ (N=9)**	**Other Tumor Types (N=12)**
Best Overall Response			
PR – n (%)	4 (36)	3 (33)	1 (8)
SD – n (%)	3 (27)	3 (33)	7 (58)
PD – n (%)	4 (36)	3 (33)	4 (33)
cORR	**36%**	**33%**	**8%**
CBR	64%	67%	67%

TKI Pre-treated Efficacy Evaluable (N=14)
Among 14 TKI-pretreated efficacy evaluable patients (13 NSCLC and 1 liver cancer), 36% received at least 5 lines of prior therapy (median: 3; range: 1-6), 7 NSCLC patients achieved SD as best overall response.

Data cut-off date August 23, 2021
CBR, clinical benefit rate; cORR, confirmed objective response rate; GC/GEJ, gastric cancer/gastroesophageal junction; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.
CBR = PR + SD

Preliminary Efficacy by Investigator Assessment

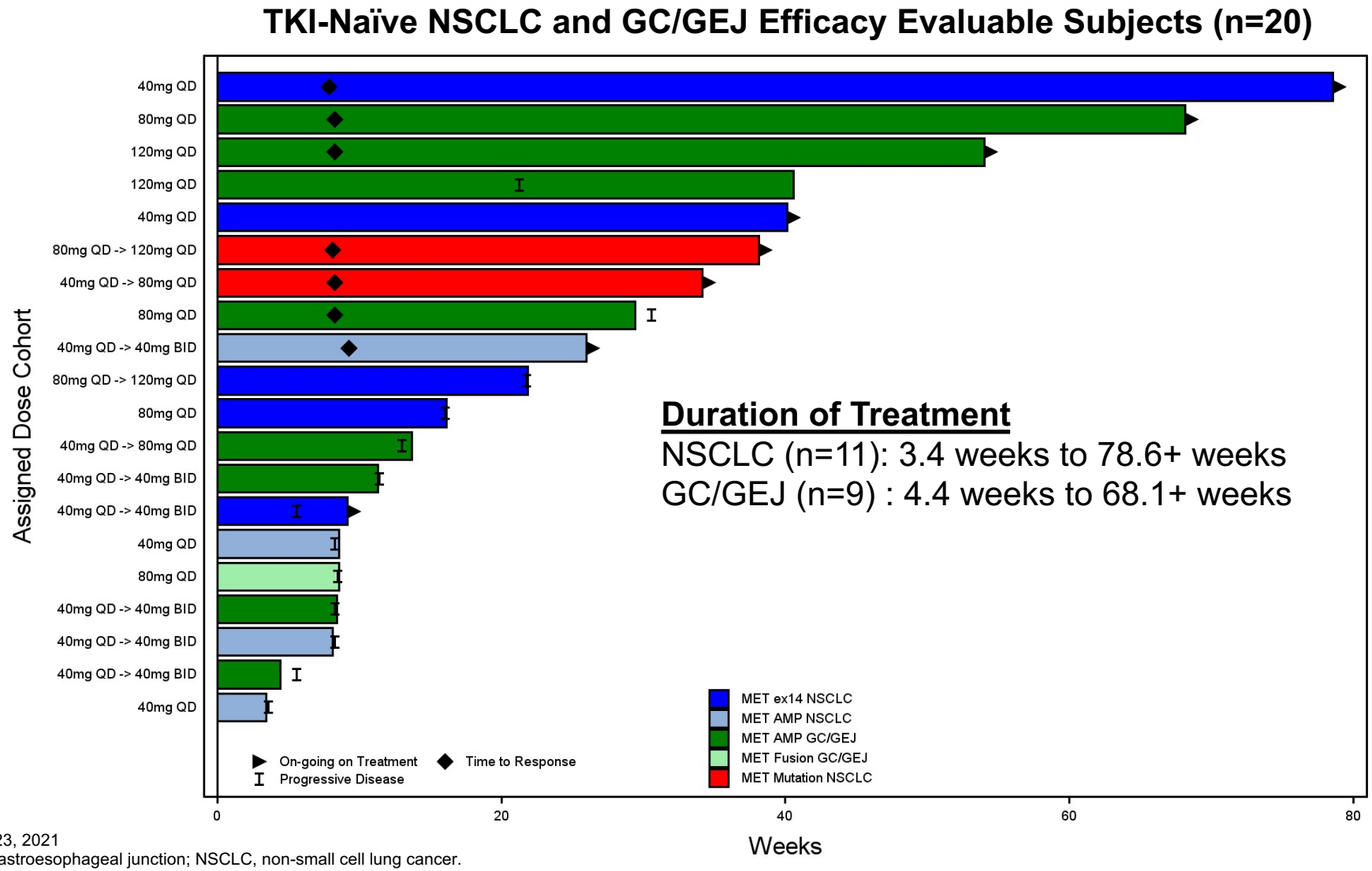


Preliminary Efficacy	TKI-Naïve Efficacy Evaluable	
	NSCLC	GC/GEJ
All Dose Levels, N	**11**	**9**
cORR (95% CI)	**36% (11 - 69)**	**33% (7 - 70)**
CBR (95% CI)	64% (31 - 89)	67% (30 - 93)
RP2D & Above, N	**7**	**9**
cORR (95% CI)	**43% (10 - 82)**	**33% (7 - 70)**
CBR (95% CI)	71% (29 - 96)	67% (30 - 93)

Note:
- 95% patients received prior Chemo/IO therapy
- DOR for 7 PRs were 15+, 12.9+, 9.2+, 5.6+, 5.6+, 5.2, and 1.8+ months.
- MET amplification: 4 PRs (GCN: 7, 12, 14, and 25); 8 non-responders (GCN: n=6 had <10; n=1 had ≥6; n=1 had >13)

Data cut-off date August 23, 2021
CBR, clinical benefit rate; cORR, confirmed objective response rate; DOR, duration of response; GC/GEJ, gastric cancer/gastroesophageal junction adenocarcinoma; GCN, gene copy number; IO, immunotherapy; NSCLC, non-small cell lung cancer; PD, progressive disease; RP2D, recommended phase 2 dose.

Duration of Treatment



Data cut-off date August 23, 2021
GC/GEJ, gastric cancer/gastroesophageal junction; NSCLC, non-small cell lung cancer.

Conclusions

- TPX-0022 was generally well tolerated
- SHIELD-1 dose expansion is ongoing at the proposed RP2D of 40 mg QD → 40 mg BID
- Responses in MET TKI-naïve NSCLC and GC/GEJ cancers
  - 95% patients received prior Chemo/IO therapy
  - NSCLC: cORR 36% (all dose levels); cORR 43% (proposed RP2D & above)
  - GC/GEJ Cancer: cORR 33% (all dose levels and proposed RP2D & above)
- Limited activity in MET TKI-pretreated patients (36% with ≥5 lines of prior therapy)
- Subject to FDA feedback, including agreement on the proposed RP2D, the company plans to revise the study into a Phase 1/2 trial and proceed to multi-cohort Phase 2

#214
Session:
OA15.04

Telisotuzumab vedotin (teliso-v) monotherapy in patients with previously treated c-Met+ advanced non-small cell lung cancer

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Background and Objective

c-Met, a receptor tyrosine kinase and receptor for hepatocyte growth factor (HGF), is encoded by the *MET* proto oncogene, and aberrant activation has been associated with multiple aspects of cancer behavior[3]

c-Met is widely expressed on different cancerous cell types with overexpression observed in 35-72% of NSCLC tumors in various studies[4]

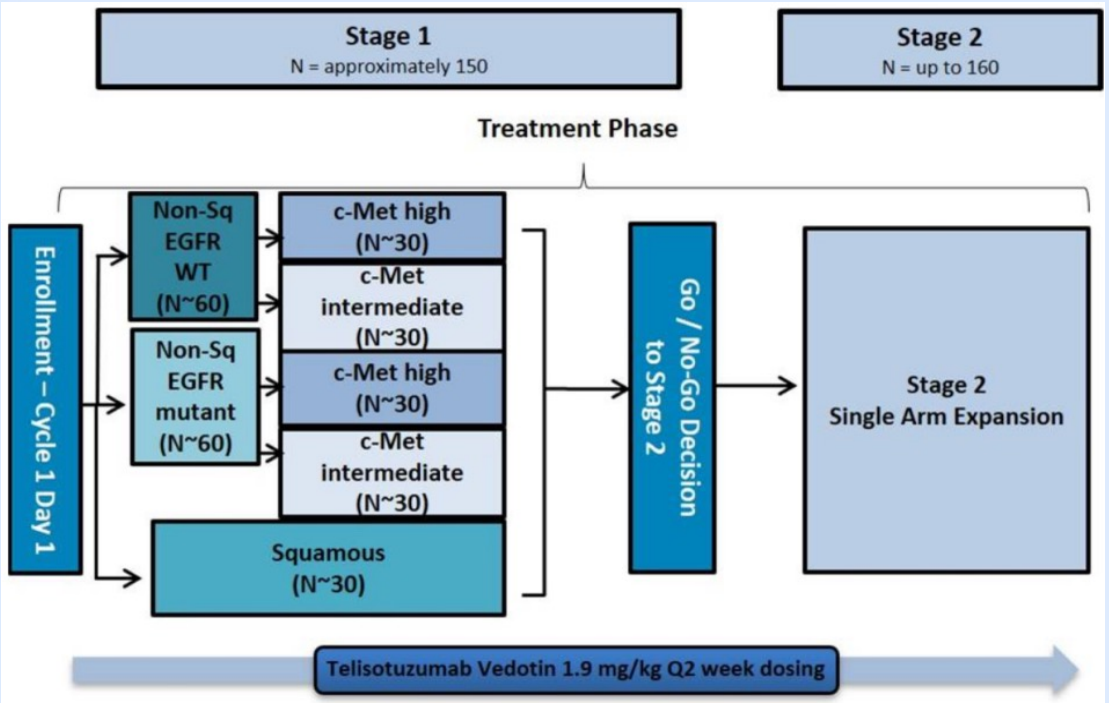
Teliso-v is a first-in-class anti-c-MET antibody-drug conjugate (ADC) composed of the humanized recombinant IgG1κ antibody ABT-700 (telisotuzumab) conjugated to the microtubule inhibitor and cytotoxin monomethyl auristatin E (MMAE) via a valine-citrulline linker

- Teliso-V binds to c-Met-expressing tumor cells and is internalized. Upon internalization, the linker is cleaved resulting in the release of MMAE inside the cell. MMAE inhibits cell division by blocking tubulin polymerization leading to the inhibition of cell division and subsequent tumor cell death[7]

Preliminary data from a phase 1/1b study (NCT02099058) suggest that teliso-v monotherapy has anti-tumor activity and a tolerable safety profile that warrants further study in this ongoing phase 2 study (NCT03539536)[8,9]

OBJECTIVE: Evaluate the safety and efficacy of telisotuzumab vedotin (teliso-V; formerly ABBV-399) in cohorts (based on histopathology and epidermal growth factor receptor [EGFR] mutation) and subgroups (based on c-Met expression) of patients with previously treated, locally advanced or metastatic non-small cell lung cancer (NSCLC) and c-Met protein overexpression (c-Met^{+})

Study Design



- Phase 2 multicenter, non-randomized, single-arm, 2-stage, adaptive study in patients with c-Met+ locally advanced or metastatic NSCLC (NCT03539536)
  - Stage 1: Assess efficacy of teliso-v monotherapy (1.9 mg/kg, once every 2 weeks) in 3 NSCLC cohorts (based on histopathology and EGFR mutation status) and adaptively enrich into 5 groups (based on intermediate vs high c-Met expression levels) to identify those with the highest ORR to be included in Stage 2
  - Stage 2: Expand and further evaluate efficacy of teliso-v in specific group(s) that demonstrated the most promising results in Stage 1 according to prespecified criteria

EGFR, epidermal growth factor receptor; Non-Sq, non-squamous; Q2, once every 2 weeks; WT, wild type.

Key Inclusion Criteria

- ✓ Adults ≥18, c-Met+ NSCLC assessed by a designated immunohistochemistry (IHC) laboratory and available archival/fresh tumor material for determination of c-Met expression levels prior to first dose of teliso-v
- ✓ Histologically documented non-squamous cell NSCLC with known EGFR status (wild type or mutant) or squamous cell NSCLC
- ✓ Locally advanced or metastatic NSCLC with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- ✓ Received ≤2 prior lines of systemic therapy, including cytotoxic chemotherapy (≤1 line), immunotherapy in the locally advanced or metastatic setting, and therapy targeting driver gene alterations
- ✓ Eastern Cooperative Oncology Group Performance Status (ECOG) of 0–1 and adequate bone marrow, renal and hepatic function

Key Exclusion Criteria

- ✗ Adenosquamous histology
- ✗ Prior c-Met targeted antibody therapies or history of a major immunologic reaction to any IgG-containing agent
- ✗ Unresolved clinically significant adverse events (AEs) grade ≥2 resulting from prior anticancer therapy, except anemia or alopecia
- ✗ Major surgery within 21 days prior to the first dose of teliso-v
- ✗ Anticancer therapy within 28 days or herbal therapy/strong cytochrome P450 3A4 inhibitors within 7 days prior to the first dose of teliso-v
- ✗ History of interstitial lung disease or pneumonitis requiring systemic steroid treatment
- ✗ Uncontrolled central nervous system metastases unless patient has received definitive therapy, is asymptomatic, and is off systemic steroids and anticonvulsants at least 2 weeks prior to the first dose of teliso-vg

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Assessments

- ✓ c-Met expression was determined by IHC staining using the SP44 antibody (Ventana; Tucson, AZ) and the ultraView Universal DAB Detection Kit (Ventana) on archival or fresh tissue.
  - Non-squamous: c-Met membrane staining on ≥25% of tumor cells at 3+ intensity
    - c-Met intermediate: ≥25% to <50% membrane staining at 3+ intensity
    - c-Met high: ≥50% membrane staining at 3+ intensity
  - Squamous: c-Met membrane staining on ≥75% of tumor cells at 1+ intensity[1]

- ✓ ORR, DoR, and DCR were assessed by an ICR per RECIST v1.1 criteria; investigator-assessed ORR and DoR were also documented
  - This interim analyses was conducted using a Bayesian hierarchical model to assess the ORR for each group, with the threshold for advancement to stage 2 being a posterior probability of at least 70% that the true ORR is >25%
  - Patients who experienced clinical progression or death prior to the first post-baseline tumor assessment were considered non-responders

- ✓ Tumor assessments were performed at baseline and every 6 weeks according to RECIST v1.1

- ✓ AE severity was graded according to the NCI Common Terminology Criteria for Adverse Events v4.03. Treatment emergent AEs (TEAEs) were those that occurred during treatment or up to 30 days after teliso-v discontinuation

- ✓ Safety analyses included all patients who received ≥1 dose of teliso-v. Efficacy analyses included patients enrolled ≥12 weeks prior to the data cutoff date who received ≥1 dose of teliso-v and ≥1 post-baseline tumor assessment (or had clinical evidence of progression or died prior to post-baseline assessment)

1. The cut-offs for c-Met staining were chosen by correlating objective responses with different cut-offs in the phase 1 study, and then applied prospectively to enrollment of the phase 2 study, for both NSQ and SQ

Demographics and Baseline Characteristics

- As of December 2020, 841 patients were screened with evaluable c-Met IHC data
  - > C-Met^{+} rates were generally lower in the *EGFR* WT (25%) vs *EGFR* MU (37%) non-squamous cohorts
  - > 39% of patients in the squamous cohort had c-Met^{+} tumors

Screening Rates for c-Met Expression by Cohort

	Patients	Percentage C-Met^{+a}	Percentage c-Met high	Percentage c-Met Int	Percentage of c-Met high within c-Met^{+}
Non-Sq *EGFR* WT NSCLC	446	25	12	13	48
Non-Sq *EGFR* MU NSCLC	245	37	22	15	59
Sq NSCLC	150	39	-	-	

[a]The cutoff for c-Met^{+} is lower for the squamous cohort than the non-squamous cohorts
EGFR, epidermal growth factor receptor; int, intermediate; MU, mutant; Non-Sq, non-squamous; NSCLC, non-small cell lung cancer; Sq, squamous; WT, wild type.

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Demographics and Baseline Characteristics

Characteristic	NSQ EGFR WT NSCLC (N=37)	NSQ EGFR MU NSCLC (N=31)	SQ NSCLC (N=22)
Age, median [range]	66 [33, 81]	58 [36, 80]	67 [45, 76]
Gender, n (%)			
Male	26 (70)	15 (48)	12 (55)
Female	11 (31)	16 (52)	10 (45)
ECOG performance status, n (%)			
0	7 (19)	10 (32)	3 (14)
1	29 (78)	21 (68)	19 (86)
EGFR mutation status, n (%)			
WT	37 (100)	0	9 (41)
Unknown/unspecified	0	0	0
DEL19	0	12 (39)	0
L858R	0	10 (32)	0
T790M	0	6 (19)	0
Other rare mutations[a]	0	3 (10)	0
Missing	0	0	13 (59)
c-MET status			
H-score, median [range]	225 [120, 300]	265 [200, 300]	164 [100, 285]
c-Met expression, n (%)			
High	13 (35)	22 (71)	–
Intermediate	24 (65)	9 (29)	–

Characteristic	NSQ EGFR WT NSCLC (N=37)	NSQ EGFR MU NSCLC (N=31)	SQ NSCLC (N=22)
Number of prior systemic cancer therapies, median [range]	2 [1-4]	2[1-4]	2[1-4]
Prior systemic cancer therapies, n (%)	27 (73)	4 (13)	20 (91)
Immune checkpoint inhibitors	35 (95)	26 (84)	21 (95)
Platinum-based therapies	4 (11)	0	1 (5)
Docetaxel-based	3 (8)	0	0
c-Met inhibitor			
EGFR TKI	0	27 (87)	1 (5)
1st/2nd generation	0	12 (39)	1 (5)
3rd generation			
Time from initial diagnosis to study entry, weeks, median [range]	60 [17–216]	113 [33–483]	77 [36–466]

**Central analyses for MET amplification and Exon 14 skipping mutations are ongoing*

- 113 patients with c-Met+ NSCLC were enrolled in Stage 1; 90 patients met efficacy-evaluable criteria and had ≥ 12 weeks of follow-up
  - c-Met expression, based on H-score, was generally lower in squamous vs non-squamous cohorts
  - In the non-squamous cohorts, a greater frequency of patients with wild type EGFR had intermediate c-Met expression, while a greater frequency of patients with mutated EGFR had high c-Met expression
- Patients in the non-squamous EGFR mutant cohort had a longer median duration of prior systemic cancer therapy than the other two cohorts
- Prior treatment with platinum-based therapies was most common in all cohorts (>80%)
  - The majority of patients in the non-squamous EGFR wild type and squamous cohorts (73% and 91%, respectively) received prior therapy with immune checkpoint inhibitors; all patients in the non-squamous EGFR mutant cohort received prior therapy with an EGFR TKI

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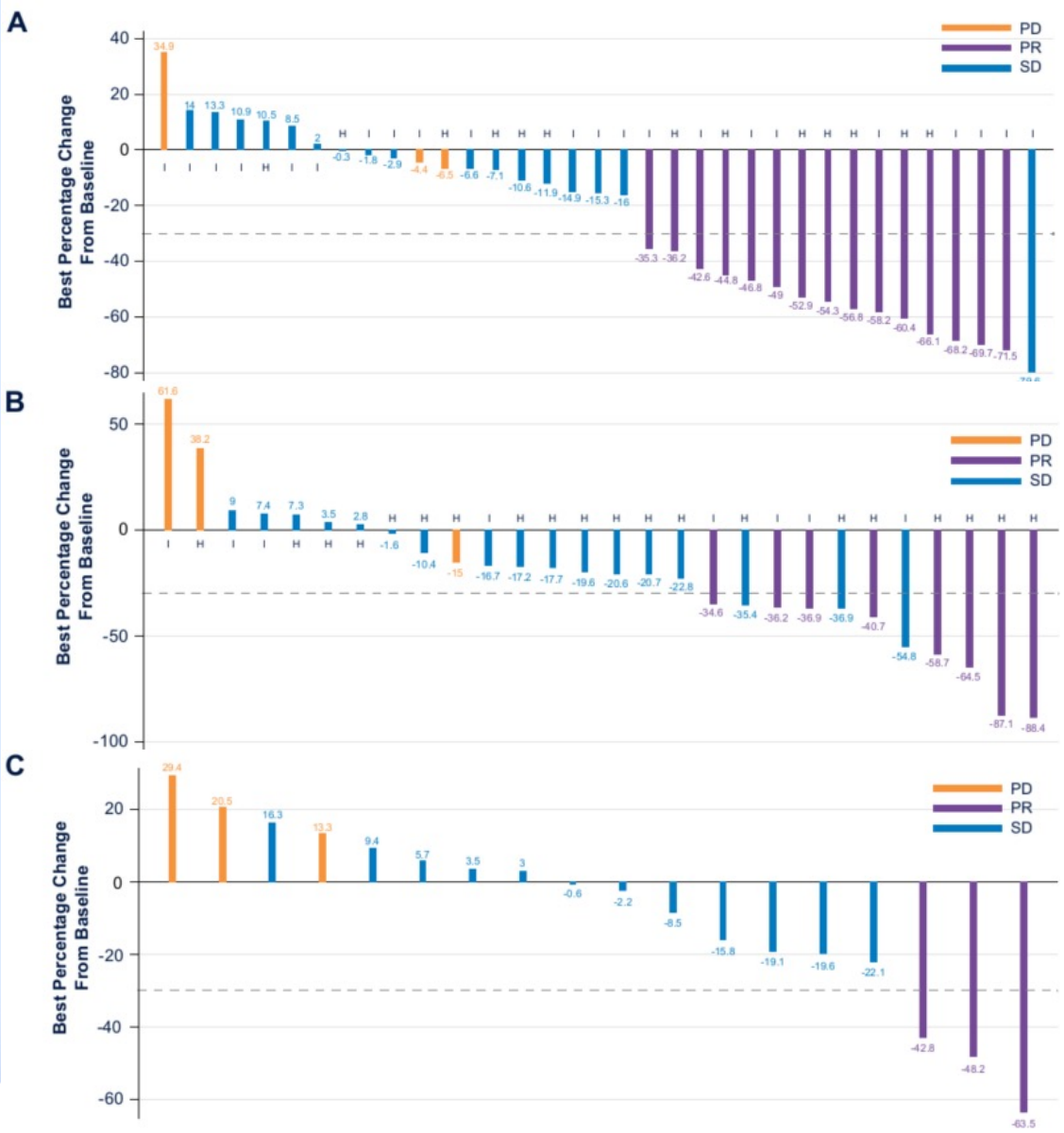
Efficacy Endpoints

Efficacy endpoints by NSCLC group

NSCLC Group	ORR (CR+PR)[a] by ICR, n/N (%) [95% CI]	ORR (CR+PR) by INV, n/N (%) [95% CI]	mDoR by ICR[b], months [95% CI]	mDoR by INV[c], months [95% CI]
NSQ EGFR WT	13/37 (35.1) [20.2, 52.5]	13/36 (36.1) [20.8, 53.8]	6.9 [3.8, -]	5.5 [4.2, 9.6]
c-Met high	7/13 (53.8) [25.1, 80.8]	6/12 (50.0) [21.1, 78.9]	---	---
c-Met int	6/24 (25.0) [9.8, 46.7]	7/24 (29.2) [12.6, 51.1]	---	---
NSQ EGFR MU	4/30 (13.3) [3.8, 30.7]	8/31 (25.8) [11.9, 44.6]	NA	5.9 [2.6, -]
c-Met high	4/22 (18.2) [5.2, 40.3]	8/22 (36.4) [17.2, 59.3]	---	---
c-Met int	0/8 (0) [-, -]	0/9 (0) [-, -]	---	---
SQ	3/21 (14.3) [3.0, 36.3]	1/22 (4.5) [0.1, 22.8]	4.4 [3.0, -]	4.4 [-, -]

- ORR was 13/37 (35.1%) in the non-squamous EGFR wild type cohort (7/13 (53.8%) in c-Met high group and 6/24 (25.0%) in c-Met intermediate group, but was modest in the non-squamous EGFR mutant and squamous cohorts
- At the time of this interim analysis, no patients had achieved a complete response, 26/88 (30%) had achieved a partial response, and 9/88 (10%) experienced disease progression

Best percentage change in size of target lesion from baseline in patients with ≥1 post-baseline tumor assessment in non-squamous *EGFR* wild type (A), non-squamous *EGFR* mutant (B), and squamous (C) cohorts



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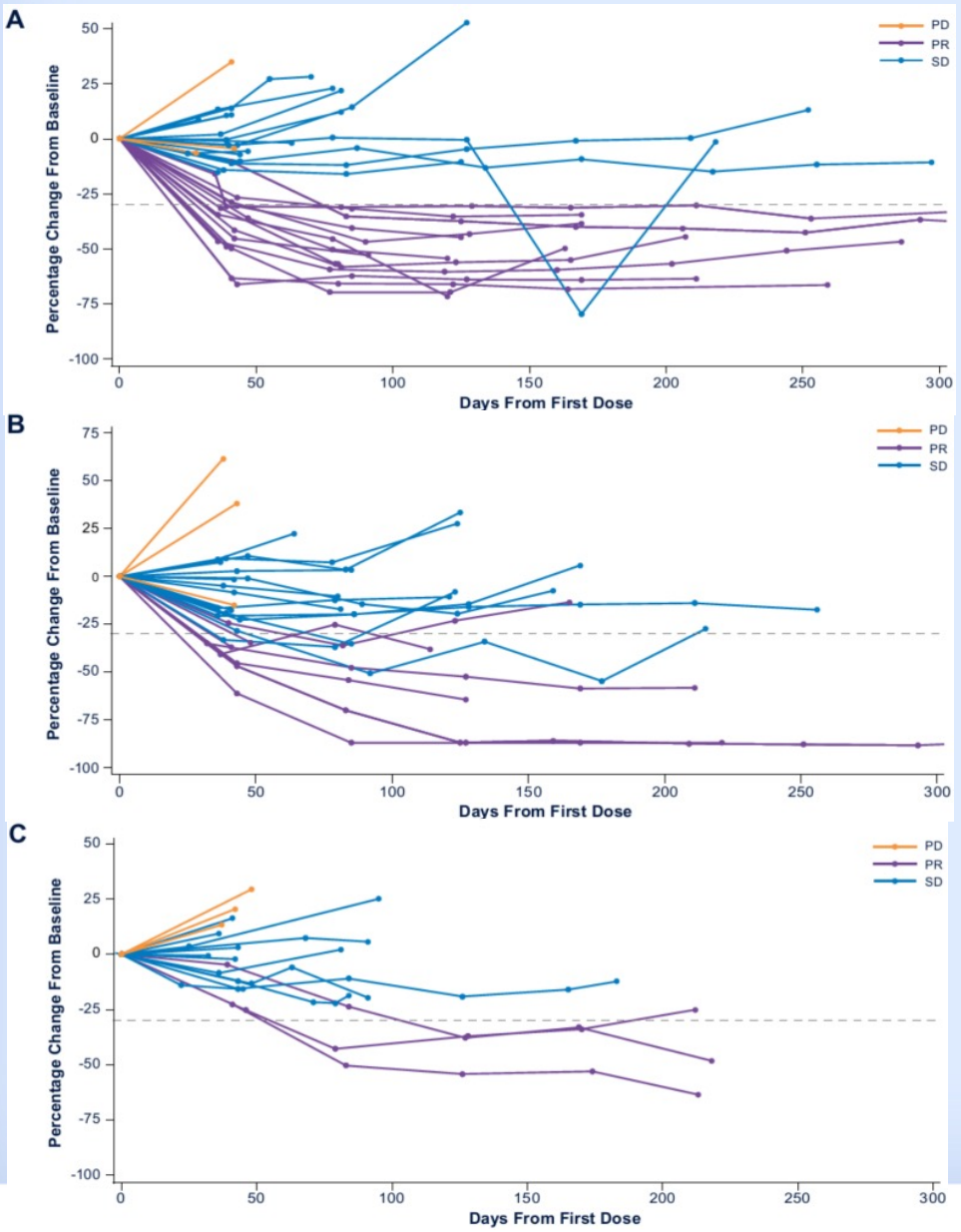
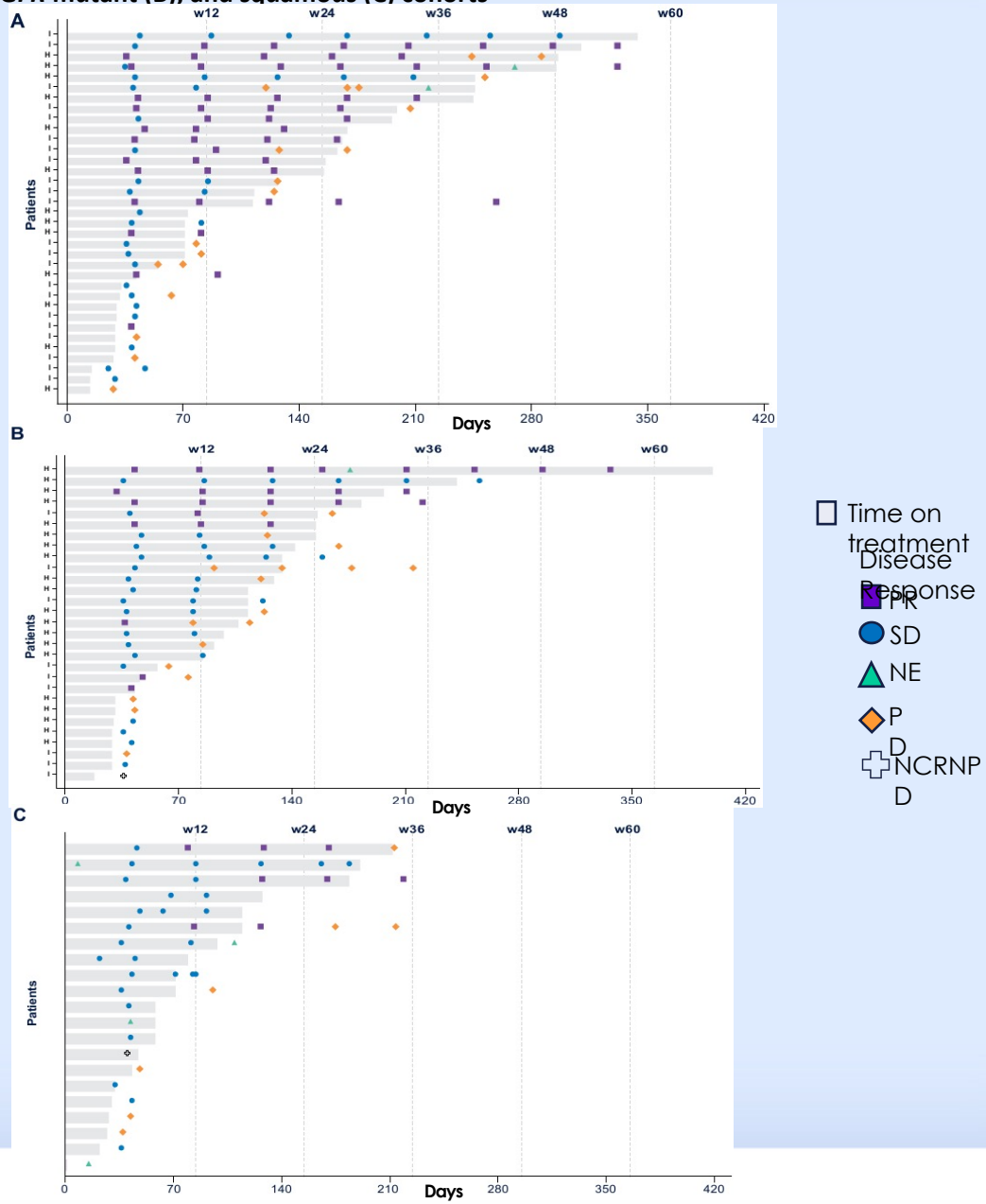
Efficacy Endpoints

Percentage reduction in size of target lesion in non-squamous *EGFR* wild type (A), non-squamous *EGFR* mutant (B), and squamous (C) cohorts



Time on treatment and best response by patient in non-squamous *EGFR* wild type (A), non-squamous *EGFR* mutant (B), and squamous (C) cohorts



Safety

- In total, 96% of patients experienced a treatment-emergent adverse event (TEAE), and 72% experienced a TEAE related to teliso-v as assessed by investigators
  - TEAEs (any grade) occurring in ≥10% of total patients are summarized
- Grade ≥3 TEAEs occurred in 50 (44%) patients
  - The most frequent was malignant neoplasm progression occurring in 6% of patients
- The most common serious TEAEs were pneumonia (n=6, 5%), malignant neoplasm progression (n=4, 4%), and pneumonitis (n=4, 4%)
- Three patients died as a result of a TEAE considered possibly related to teliso-V by investigators (sudden death, dyspnea, pneumonitis, n=1 each)

Safety

Summary of treatment-emergent adverse events by cohort

TEAEs, n (%)	NSQ EGFR WT NSCLC (N=47)	NSQ EGFR MU NSCLC (N=38)	SQ NSCLC (N=28)
Any	44 (94)	37 (97)	27 (96)
Related to study drug per INV	32 (68)	33 (87)	16 (57)
Grade ≥3	24 (51)	13 (34)	13 (46)
Serious	19 (40)	8 (21)	7 (25)
Leading to teliso-v discontinuation	16 (34)	8 (21)	10 (36)
Leading to death possibly related to teliso-v per INV	1 (2)	0	2 (7)
Any-grade AEs (≥10% of patients), n (%)			
Nausea	10 (21)	11 (29)	5 (18)
Hypoalbuminemia	12 (26)	5 (13)	5 (18)
Decreased appetite	9 (19)	9 (24)	2 (7)
Peripheral edema	10 (21)	7 (18)	3 (11)
Peripheral sensory neuropathy	10 (21)	8 (21)	2 (7)
Vision blurred	7 (15)	7 (18)	3 (11)
Asthenia	6 (13)	7 (18)	3 (11)
Gamma-glutamyltransferase increased	6 (13)	4 (11)	6 (21)
Keratitis	4 (9)	10 (26)	2 (7)
Constipation	5 (11)	8 (21)	2 (7)
Fatigue	4 (9)	7 (18)	4 (14)

TEAEs, n (%)	NSQ EGFR WT NSCLC (N=47)	NSQ EGFR MU NSCLC (N=38)	SQ NSCLC (N=28)
Any-grade AEs (≥10% of patients), n (%)			
Anemia	7 (15)	4 (11)	3 (11)
Alanine aminotransferase increased	4 (9)	5 (13)	3 (11)
Diarrhea	3 (6)	6 (16)	3 (11)
Dizziness	4 (9)	5 (13)	3 (11)
Dyspnoea	6 (13)	3 (8)	3 (11)
Grade ≥3 AEs (≥3 patients), n (%)			
Malignant neoplasm progression	3 (6)	3 (8)	1 (4)
Pneumonia	3 (6)	2 (5)	1 (4)
Hyponatremia	0	1 (3)	4 (14)
Anemia	2 (4)	1 (3)	0
Dyspnoea	1 (2)	1 (3)	1 (4)
Fatigue	1 (2)	0	2 (7)
Gamma-glutamyltransferase increased	0	2 (5)	1 (4)
Peripheral sensory neuropathy	2 (4)	0	1 (4)
Pneumonitis	1 (2)	1 (3)	1 (4)

- In total, 96% of patients experienced a treatment-emergent adverse event (TEAE), and 72% experienced a TEAE related to teliso-v as assessed by investigators
  - TEAEs (any grade) occurring in ≥10% of total patients are summarized
- Grade ≥3 TEAEs occurred in 50 (44%) patients
  - The most frequent was malignant neoplasm progression occurring in 6% of patients

- The most common serious TEAEs were pneumonia (n=6, 5%), malignant neoplasm progression (n=4, 4%), and pneumonitis (n=4, 4%)
- Three patients died as a result of a TEAE considered possibly related to teliso-V by investigators (sudden death, dyspnea, pneumonitis, n=1 each)

TAKE HOME MESSAGE

- Teliso-V at a dose of 1.9 mg/kg every two weeks demonstrated a promising ORR and tolerable safety profile in the non-squamous EGFR WT NSCLC cohort
  - > Based on pre-specified criteria, this cohort has expanded into Stage 2 enrollment
  - > ORR was highest in the c-Met high group, though also clinically meaningful in the c-Met intermediate group
- Based on prespecified criteria, enrollment in the squamous cohort was discontinued while enrollment in the EGFR MU cohort will continue until the next interim analysis.
- Comparison with the ongoing EGFR MU Osimertinib + Teliso-V trial will provide insights into tolerability and efficacy of continuing TKI with ADCs

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For further questions please contact: dshong@mdanderson.org

Conflict of Interest

Dr. Xiuning Le receives consulting/advisory fees from EMD Serono (Merck KGaA), AstraZeneca, Spectrum Pharmaceutics, Novartis, Hengrui, Eli Lilly, Daiichi Sankyo, Boehringer Ingelheim, and Bristol-Myers Squibb, and Research Funding from Eli Lilly and Boehringer Ingelheim.

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Disclosures (last 36 months)

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