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First-in-human safety, pharmacokinetics, and preliminary efficacy of TPX-0022, a novel inhibitor of MET/SRC/CSF1R in patients with advanced solid tumors harboring genetic alterations in *MET* (SHIELD-1)

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Disclosures

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- TPX-0022 is investigational and not approved for the treatment of any condition in any jurisdiction

Overview of MET Landscape

MET Alterations are Known to Occur in Multiple Tumor Types

MET Exon 14: 3-4% of NSCLC[1]
Amplification: 15% of 1L EGFR TKI Resistance[2]
1-6% of NSCLC[3-5] (de novo)

Amplification: 3-5% of Gastric Cancer[6-9]

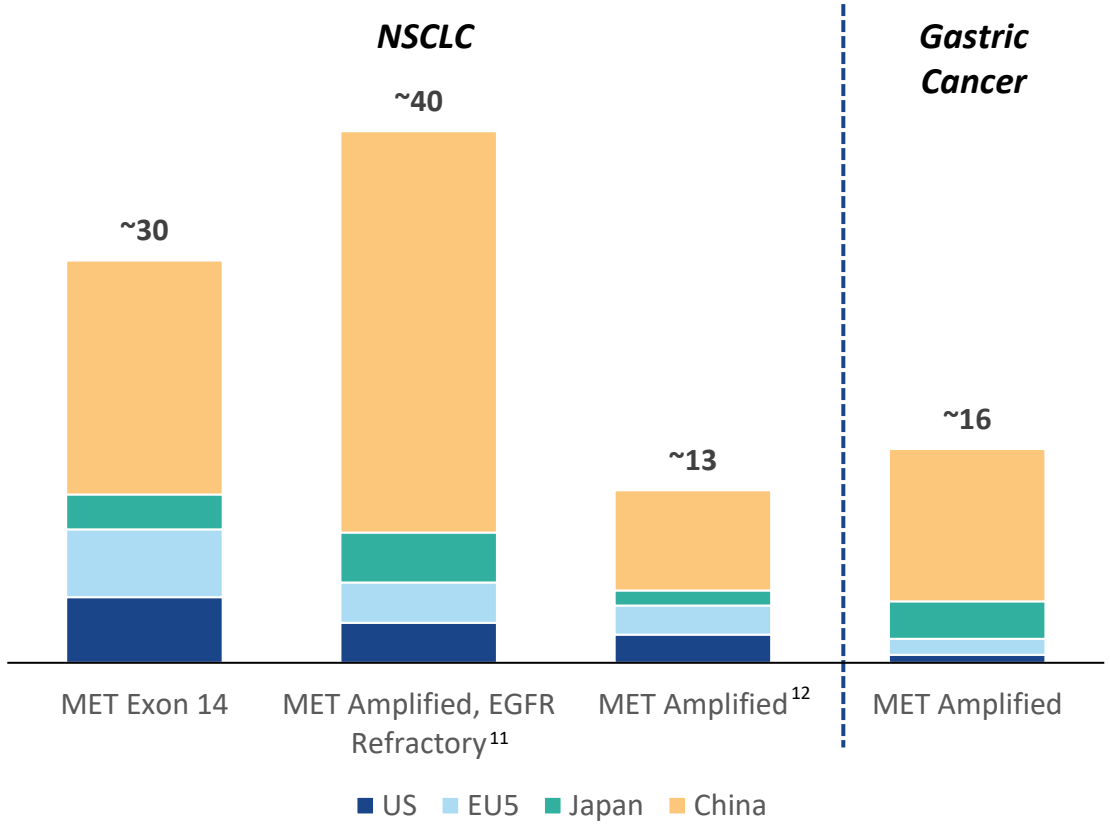
MET amplifications have also been documented across other tumor types:

- CRC, HNSCC, EC, GC, HCC, RCC, GBM

Historically, limited clinical activity observed for FIH studies of MET inhibitors

Currently only one MET inhibitor (TABRECTA) is approved in the US for NSCLC with exon 14 skipping mutations

Estimated Incidence by Region (Thousands)[10]



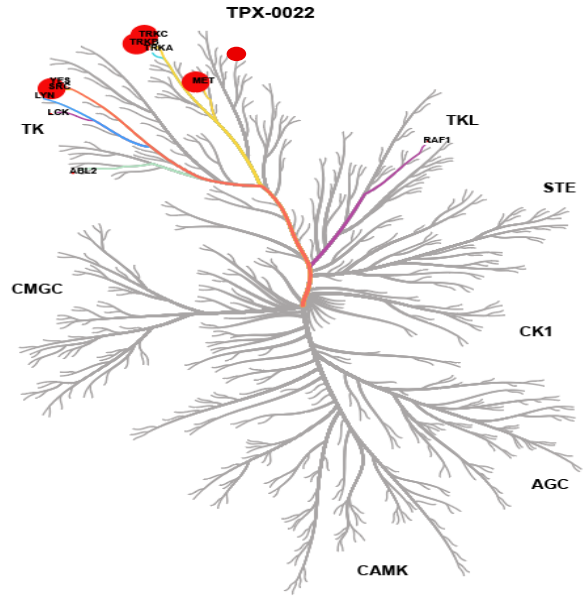
FIH: First in human CRC: colorectal cancer HSNCC: Head and Neck Squamous Cell Carcinoma, EC: Esophageal Cancer, GC: Gastric Cancer, RCC: Renal Cell Carcinoma, GBM: Glioblastoma Multiforme
Sources: TABRECTA (USPI); Falchook, G. S. et al. Clin Cancer Res 26, 1237–1246 (2020); Gan, H. K. et al. clincanres.1189.2018 (2019); American Cancer Society, SEER, GLOBOCAN
[1] Drilon A, et al: J Thorac Oncol. 2017. [2] Ramalingam SS, et al: Annals of Oncology 2018. [3] Onozato R, et al: J Thorac Oncol. 2009. [4] Okuda K, et al: Cancer Sci. 2008. [5] Overbeck TR, et al: Translational lung cancer research 2020; 1-2% of NSCLC estimated at gene copy number of 10 or greater. [6] Loberg RD et al: Journal of Clinical Oncology 2014. [7] Yang Y, et al: Gastric Cancer 2016. [8] Inokuchi M, et al: World J Gastrointest Oncol. 2015. [9] Lennerz JK, et al: J Clin Oncol. 2011. [10] Includes only locally advanced and metastatic disease based on SEER staging (regional and distant), and applies frequency based on the midpoint of the range shown. [11] Assumes EGFR frequency of 15% in US and EU5 (Hirsch FR, et al: Lancet 2017), 35% in Japan and 40% in China (Zhang YL, et al: Oncotarget 2016). [12] Based on gene copy number of 10 or greater (1-2% of NSCLC).

TPX-0022 Is a Potent Inhibitor of MET, SRC, and CSF1R Tyrosine Kinases

- TPX-0022 is a potent MET inhibitor in both biochemical and cellular assays

	Biochemical IC_{50} (nM)	Cell Proliferation IC_{50} (nM)	
Inhibitor	**MET**	**SNU-5**	**MKN-45**
TPX-0022	**0.14**	**<0.2**	**<0.2**
Capmatinib	0.20	<0.2	<0.2
Crizotinib	4.0	2.8	10.5
Savolitinib	4.0	1.1	4.9

- TPX-0022 is highly selective for MET/SRC/CSF1R in a screen of 373 kinases



- Targeting of SRC and CSF1R can potentially improve clinical efficacy
  - SRC is a downstream MET effector involved in malignant transformation, tumor metastasis, and drug resistance
  - CSF1R plays an important role in regulation of tumor associated macrophages that can promote tumor progression and angiogenesis

CSF1R, colony-stimulating factor 1 receptor; SRC, proto-oncogene tyrosine-protein kinase Src; MET, mesenchymal-epithelial transition factor

Phase 1 Study of TPX-0022 in Patients With Advanced Solid Tumors Harboring Genetic Alterations in MET

Population

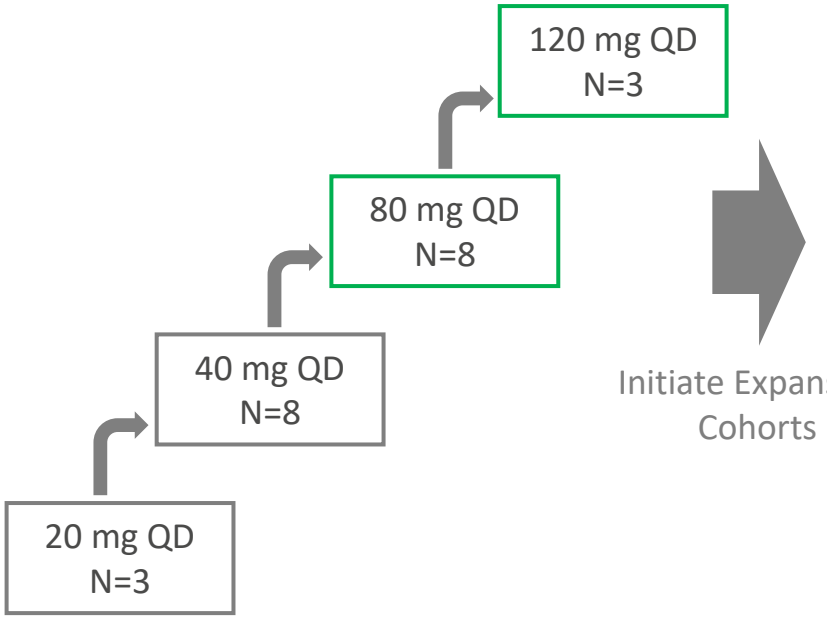
- Adults with advanced solid tumors
- MET genetic alterations assessed by local testing (exon 14 deletion, amplification, fusion, or oncogenic kinase domain mutation)
- Asymptomatic CNS disease allowed

Design

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

Dose Escalation (n=22)

Doses evaluated from 18 Sep 2019 to 15 Oct 2020
Dose evaluation ongoing at 80 and 120 mg QD cohorts



Dose Expansion

- NSCLC exon 14 deletion TKI-Naïve
- NSCLC exon 14 deletion TKI-Pretreated
- NSCLC MET amplified TKI-Naive
- GI (GC/GEJ, CRC, HCC) MET amplified TKI-Naive
- Solid tumors with MET fusions or oncogenic KD mutations TKI-Naive

Primary Objectives:
Evaluate safety/tolerability and determine maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)

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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

Enrolled Patients

N=22
13 NSCLC, 4 CRC, 4 Gastric, 1 Glioblastoma

Evaluable Patients[a]

N=15

TKI-Naïve (N=10)
3 NSCLC, 4 CRC,
3 Gastric

TKI-Pretreated (N=5)
5 NSCLC

Non-Evaluable Patients

Awaiting
1st Scan[b]
N=4

Off Treatment Prior
to 1st Scan
N=2[c]

No Baseline
Measurable Disease
N=1

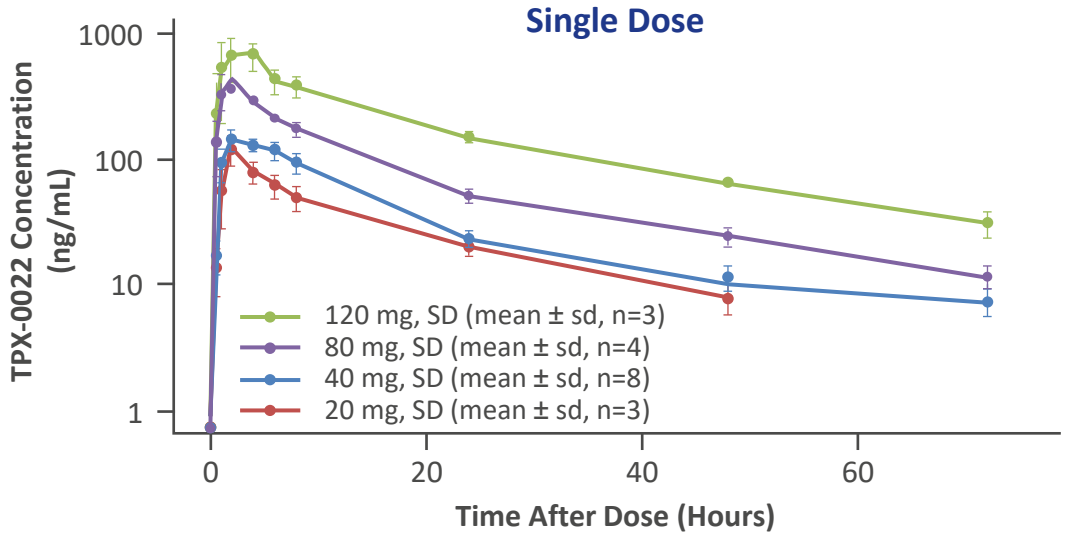
[a] Patients with baseline measurable disease and at least one post-baseline scan
[b] Patients on treatment but with no post-baseline scan as of data cut-off date
[c] One patient due to unrelated pneumonia; one patient due to DLT (Grade 2 dizziness)
Data Cutoff Date: October 15, 2020

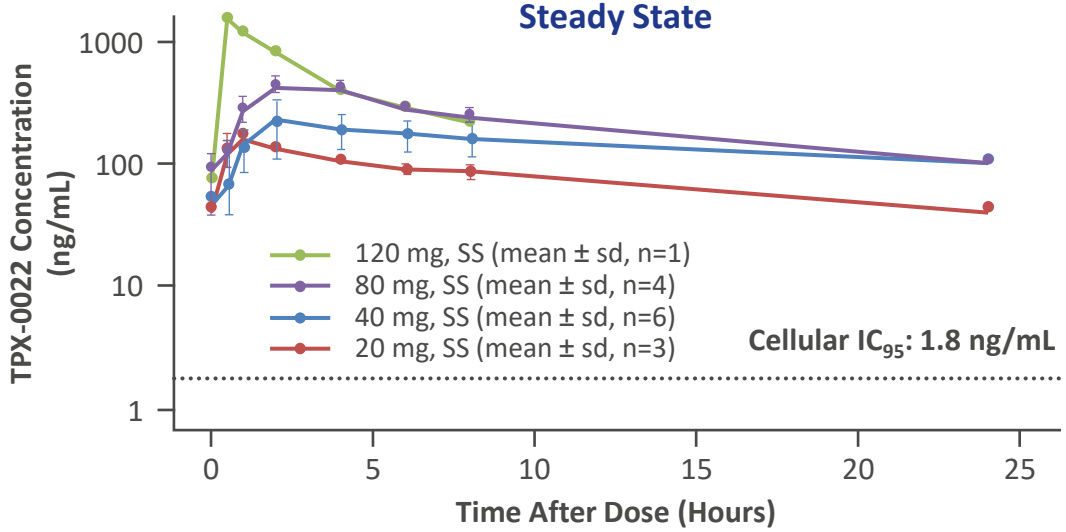
Demographics and Baseline Characteristics

	(N=22)
Age (years)	
Median (range)	63 (44–84)
Sex, n (%)	
Female	10 (45.5)
ECOG Performance Status, n (%)	
0	7 (31.8)
1	15 (68.2)
Baseline Brain Metastasis, n (%)	
Yes	5 (22.7)
Number of Prior Regimens, n(%)	
1	4 (18.2)
2	6 (27.3)
≥3	12 (54.5)
Median (range)	3 (1–6)
Prior MET TKI Treatment, n (%)	
Yes	8 (36.4) ^
Type of Cancer, n (%)#	
NSCLC	13 (59.1)
Colorectal Cancer	4 (18.2)
Gastric/GEJ Cancer	4 (18.2)
Glioblastoma	1 (4.5)

^All 8 are NSCLC patients including 5 MET EXON14 skipping, and 3 MET amplification
#GEJ, gastroesophageal junction; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor
Data Cutoff Date: October 15, 2020

TPX-0022 Preliminary PK Summary





Single Dose	20 mg (n=3)	40 mg (n=8)	80 mg (n=4)	120 mg (n=3)
C_{max} (ng/mL)	139	203	462	1056
AUC_{inf} (h*ng/mL)	1551	2501	5483	12550
$T_{1/2}$ (h)	12.6	20.1	25.2	21.2
Steady State	**20 mg (n=3)**	**40 mg (n=6)**	**80 mg (n=4)**	**120 mg (n=1)**
C_{max} (ng/mL)	176	286.8	510.7	1540
AUC_{24} (h*ng/mL)	1880	3231	5023	NC
C_{trough} (ng/mL)	38.6	89	97.6	NC

- TPX-0022 systemic PK exposure increased in a dose-dependent manner
- The steady state C_{trough} at all doses were above the cellular IC_{95} (1.8 ng/mL) for inhibition of MET phosphorylation, suggesting sustained target inhibition throughout the dosing interval

AUC_{inf}, the area under the plasma concentration-time curve from zero to infinity; AUC_{24}, the area under the plasma concentration-time curve from 0 to 24 h; C_{max}, maximum concentration; C_{trough}, trough concentration; IC_{95}, 95% inhibitory concentration; NC, not calculated; PK, pharmacokinetic; SD, single dose; sd, standard deviation; $T_{½}$, half-life

TPX-0022 Preliminary Safety Summary

	All Treated Patients (n=22)			
	TEAEs (≥20% of patients)		TRAEs	
Adverse Events	All Grades	Grades≥3	All Grades	Grades≥3
	n (%)	n (%)	n (%)	n (%)
Dizziness	12 (54.5)	-	10 (45.5)	-
Lipase increased	7 (31.8)	-	5 (22.7)	-
Fatigue	7 (31.8)	-	3 (13.6)	-
Amylase increased	6 (27.3)	-	4 (18.2)	-
Nausea	6 (27.3)	1 (4.5)	3 (13.6)	-
Vomiting	6 (27.3)	2 (9.1)	3 (13.6)	-
Constipation	5 (22.7)	1 (4.5)	-	-
Anemia	5 (22.7)	1 (4.5)	2 (9.1)	-

- TPX-0022 has been generally well tolerated
- Most AEs were Grade 1 or 2
- Most common TEAE was dizziness, likely due to off target TRK inhibition
- Infrequent dose modifications due to TEAE
  - 5 (23%) patients with TEAEs that led to dose reduction
  - 2 (9%) patients with TEAEs that led to drug discontinuation
- MTD not reached; 1 DLT at 120 mg QD*
- All Grade peripheral edema reported in 9.1% of patients (no Grade 3 or higher event)
- No related Grade ≥ 3 ALT/AST elevation
- No ILD/pneumonitis of any Grade

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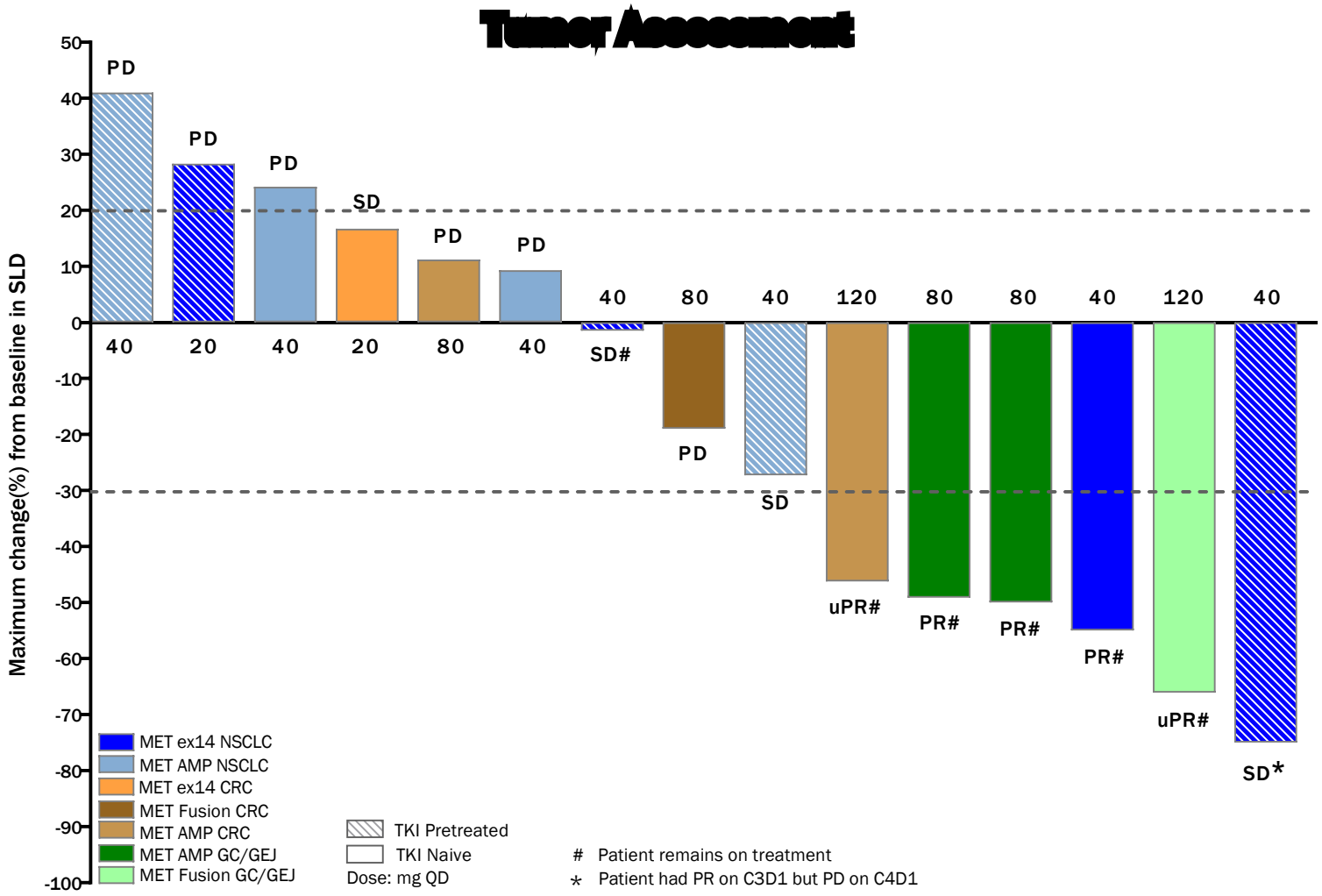
* DLT was reported as Grade 2 dizziness
TEAE: treatment emergent adverse event; TRAE : treatment related adverse event
Data Cutoff Date: October 15, 2020

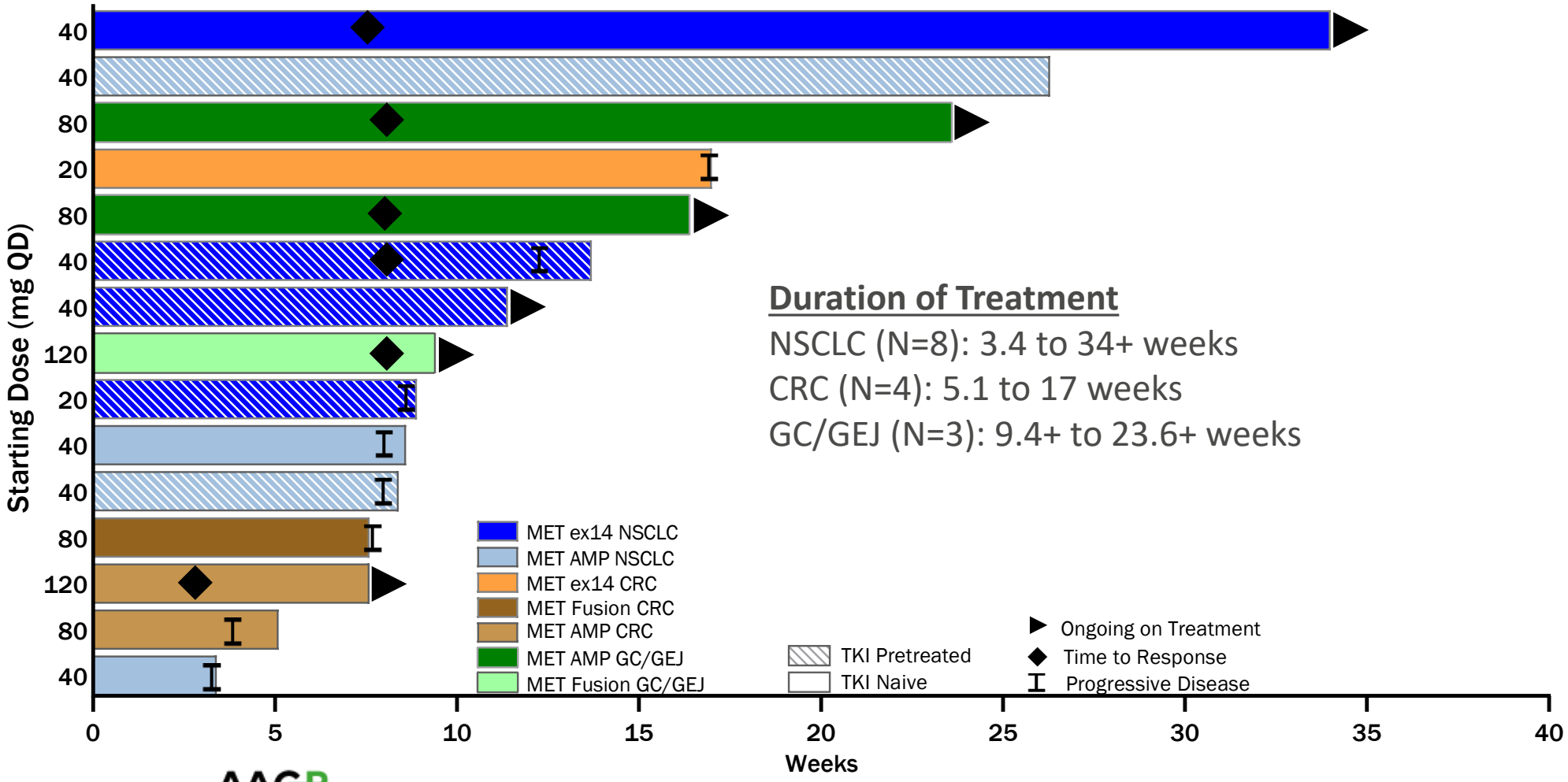
TPX-0022 Preliminary Efficacy by Investigator Assessment



- Of 10 MET TKI-Naïve patients, 5 have achieved PRs
  - 3 gastric/GE junction, 1 CRC, and 1 NSCLC
    - 3 cPRs are ongoing with DOR range 1.0+ to 3.9+ months
    - 2 uPR on treatment pending confirmation
- Of the 5 MET TKI-Pretreated NSCLC patients, 3 had stable disease
  - All 5 patients were treated at 20 or 40 mg QD dose levels
- Clinical benefit rate for all patients is 9/15

uPR, unconfirmed PR patient remains on treatment and awaits confirmatory scan
Data Cutoff Date: October 15, 2020

TPX-0022 Duration of Treatment



Duration of Treatment

NSCLC (N=8): 3.4 to 34+ weeks

CRC (N=4): 5.1 to 17 weeks

GC/GEJ (N=3): 9.4+ to 23.6+ weeks

Data Cutoff Date: October 15, 2020

Patient Case: NSCLC Exon 14 Deletion

Demographics

- 84-year old man with metastatic NSCLC

Molecular Characteristics

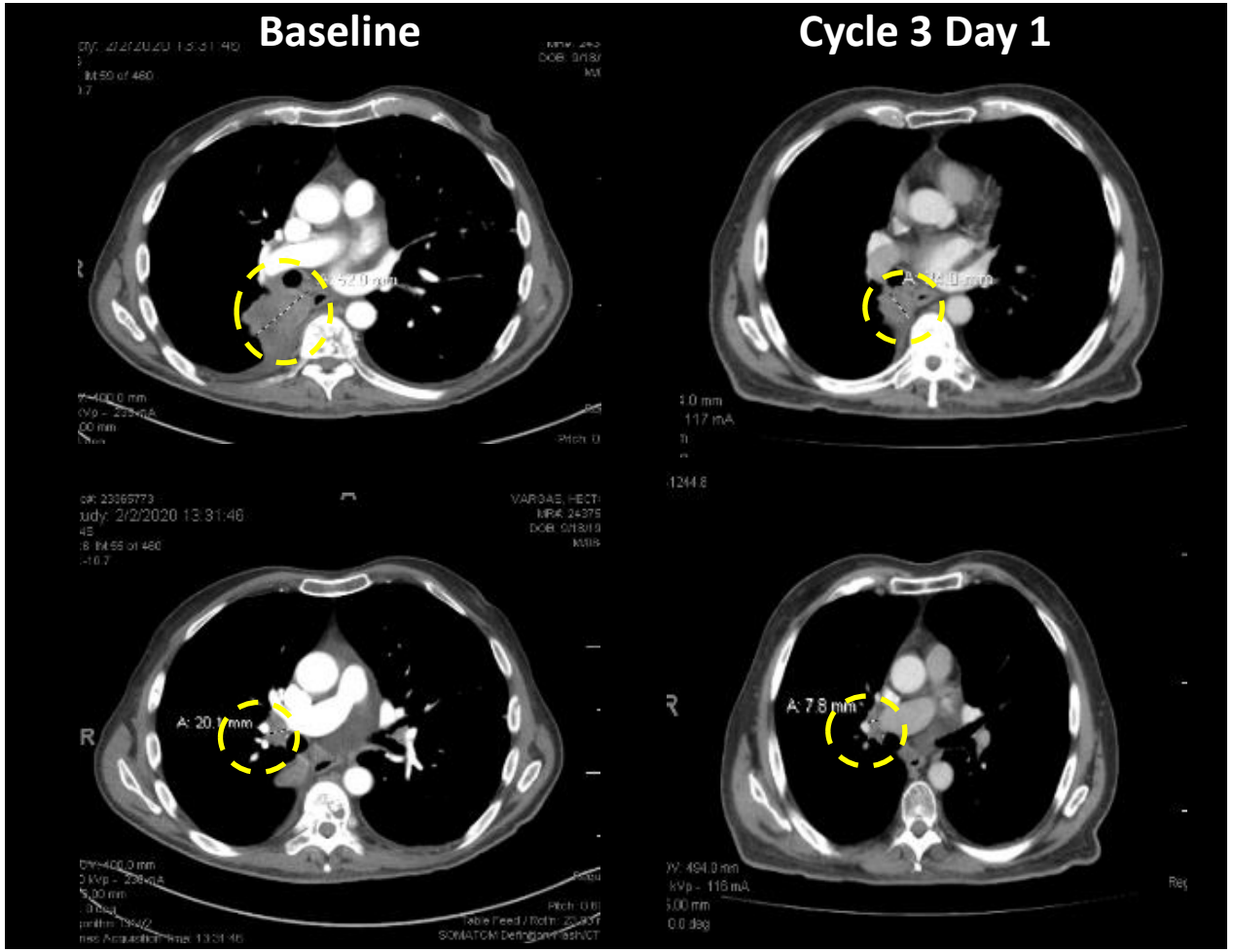
- Exon 14 deletion by NGS

Prior Treatment History

- Received gamma knife to brain metastasis
- 3 cycles of pembrolizumab → PD

TPX-0022 Treatment Course

- Received TPX-0022 at 40 mg QD
- Best response: PR (−55% SLD); subject remains on TPX-0022 in Cycle 8 in response



NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PR, partial response; PD, progressive disease; QD, once daily; SLD, sum of longest diameter

Patient Case: Gastric Cancer MET Amplification

Demographics

- 44-year-old woman with gastric cancer

Molecular Characteristics

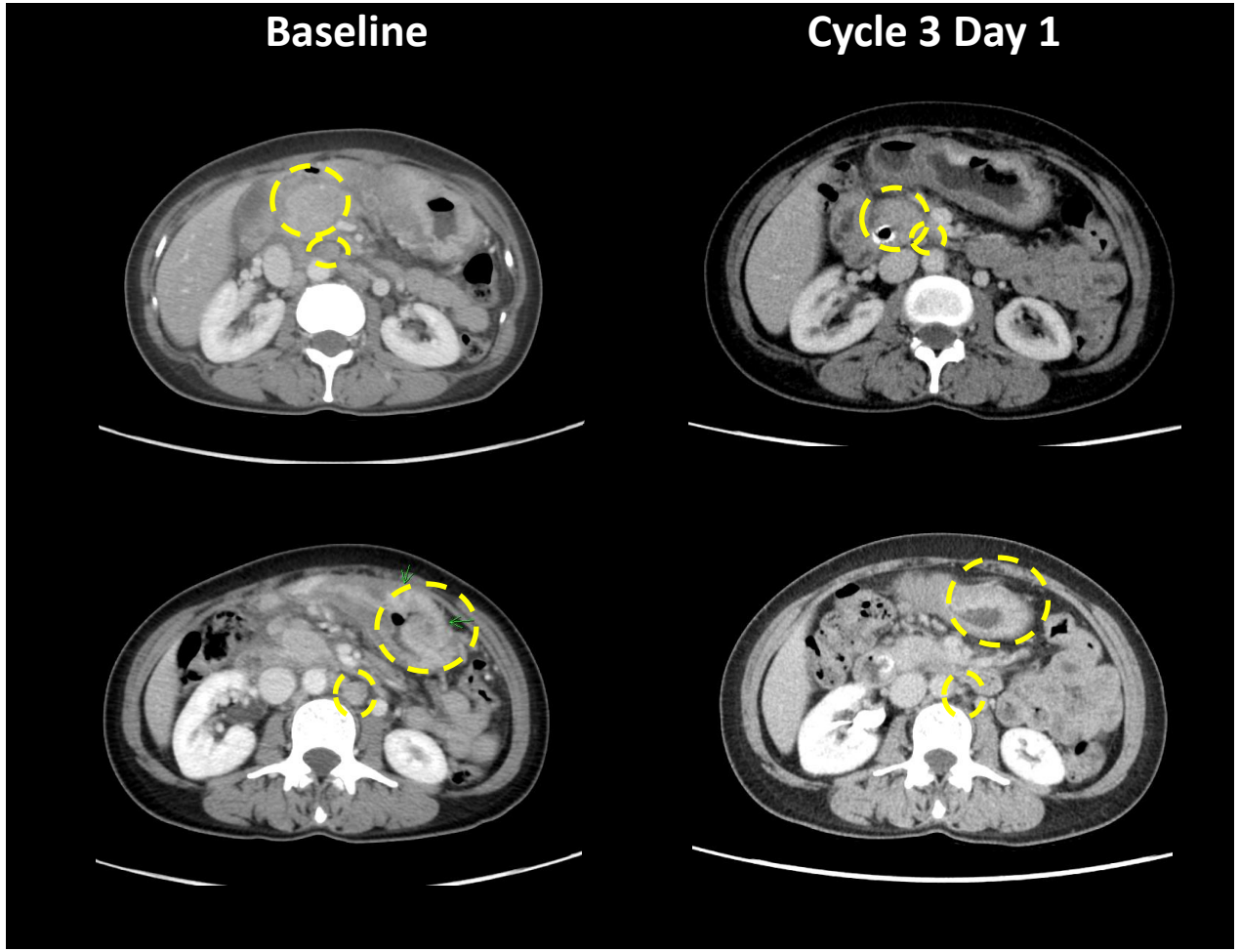
- MET amplification, GCN=10

Prior Treatment History

- Oxaliplatin + capecitabine + pembrolizumab

TPX-0022 Treatment Course

- Received TPX-0022 at 80 mg QD
- Best response: PR (–49% SLD); subject remains on TPX-0022 in Cycle 5 in response



GCN, gene copy number; MET, mesenchymal-epithelial transition factor; PR, partial response; QD, once daily; SLD, sum of longest diameter

Conclusions

- Oncogenic alterations in MET occur in many tumor types*
- TPX-0022 is a potent MET/SRC/CSF1R inhibitor
- PK exposure increased in a dose-dependent manner and steady state trough concentrations were above the IC_{95} for inhibition of MET phosphorylation
- TPX-0022 was generally well tolerated among 22 treated patients with 1 DLT at 120 mg QD^
- Preliminary Phase 1 data suggest pan-tumor potential
  - Responses observed in exon 14 deletion NSCLC and MET amplified gastric and colorectal cancers
- Phase 1 evaluation is ongoing with 80 and 120 mg QD
- Sponsor to modify SHIELD-1 Study to include potential registrational Phase 2

*exon 14 deletion, amplifications, fusions, and activating KD mutations

^ As of data cut-off, 1 reported DLT of Grade 2 dizziness

CSF1R, colony-stimulating factor 1 receptor; EGFRm+, modified epidermal growth factor receptor-positive; FDA, Food and Drug Administration; IC_{95}, 95% inhibitory concentration; KD, kinase domain; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor

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For further questions please contact:
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