MECHANISM OF ACTION OF TEPOTINIB

SEPTEMBER 2022 US-TEP-00616

EMD SERONO

TEPOTINIB INDICATION AND PRESCRIBING INFORMATION

INDICATION

TEPMETKO® (tepotinib) is indicated for the treatment of adult patients with metastatic NSCLC harboring *MET*ex14 skipping alterations.[1]

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

LITERATURE SEARCH

A search of the published medical literature as of August 21, 2022 has identified several articles that discuss the mechanism of action of tepotinib. A review of these articles follows.

PRESCRIBING INFORMATION

Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits HGF-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.[1]

In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET, including *MET*ex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

Please refer to the full TEPMETKO® Prescribing Information via the following link: **www.emdserono.com/TepmetkoPI**

In the event this link should not work, please access the product's approved Prescribing Information at **www.emdserono.com.**

HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer.

1. TEPMETKO® (tepotinib) [prescribing information]. EMD Serono, Inc., Rockland, MA; 2021.

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TEPOTINIB IMPORTANT SAFETY INFORMATION

INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Tepotinib can cause ILD/pneumonitis, which can be fatal.
Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever).
Immediately withhold tepotinib in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.
ILD/pneumonitis occurred in 2.2% of patients treated with tepotinib, with 1 patient experiencing Grade 3 or higher event; this event resulted in death.[1]

HEPATOTOXICITY

Tepotinib can cause hepatotoxicity, which can be fatal.
Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of tepotinib, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or total bilirubin.
Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue tepotinib.
Increased ALT/AST occurred in 13% of patients treated with tepotinib. Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients.
A fatal adverse reaction of hepatic failure occurred in 1 patient (0.2%). The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178 days).[1]

EMBRYO-FETAL TOXICITY

Tepotinib can cause embryo-fetal toxicity.
Based on findings in animal studies and its mechanism of action, tepotinib can cause fetal harm when administered to a pregnant woman.
Advise pregnant women of the potential risk to a fetus.
Advise females of reproductive potential or males with female partners of reproductive potential to use effective contraception during treatment with tepotinib and for 1 week after the final dose.[1]

DRUG INTERACTIONS

Avoid concomitant use of tepotinib with dual strong inhibitors of CYP3A and P-gp inhibitors and strong CYP3A inducers.
Avoid concomitant use of tepotinib with certain P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.[1]

ALT, alanine transaminase; AST, aspartate transaminase; CYP3A, cytochrome P450, family 3, subfamily A; ILD, interstitial lung disease; P-gp, P-glycoprotein 1.

1. TEPMETKO® (tepotinib) [prescribing information]. EMD Serono, Inc., Rockland, MA; 2021.

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TEPOTINIB IMPORTANT SAFETY INFORMATION

FATAL ADVERSE REACTIONS

Fatal adverse reactions occurred in 1 patient (0.4%) due to pneumonitis, in 1 patient (0.4%) due to hepatic failure, and in 1 patient (0.4%) due to dyspnea from fluid overload.[1]

SERIOUS ADVERSE REACTIONS

Serious adverse reactions occurred in 45% of patients who received tepotinib. Serious adverse reactions in >2% of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%).[1]

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients who received tepotinib were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.[1]

CLINICALLY RELEVANT ADVERSE REACTIONS

Clinically relevant adverse reactions in <10% of patients who received tepotinib included ILD/pneumonitis, rash, fever, dizziness, pruritis, and headache.[1]

SELECTED LABORATORY ABNORMALITIES

Selected laboratory abnormalities (≥20%) from baseline in patients receiving tepotinib in descending order were decreased albumin (76%), increased creatinine (55%), increased ALP (50%), decreased lymphocytes (48%), increased ALT (44%), increased AST (35%), decreased sodium (31%), decreased hemoglobin (27%), increased potassium (25%), increased GGT (24%), increased amylase (23%), and decreased leukocytes (23%).[1]

MOST COMMON GRADE 3 TO 4 LABORATORY ABNORMALITIES

The most common Grade 3 to 4 laboratory abnormalities (≥2%) in descending order were decreased lymphocytes (11%), decreased albumin (9%), decreased sodium (8%), increased GGT (5%), increased amylase (4.6%), increased ALT (4.1%), increased AST (2.5%), and decreased hemoglobin (2%).[1]

CLINICALLY RELEVANT LABORATORY ABNORMALITY

A clinically relevant laboratory abnormality in <20% of patients who received tepotinib was increased lipase in 18% of patients, including 3.7% Grades 3 to 4.[1]

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; ILD, interstitial lung disease; P-gp, P-glycoprotein 1.

1. TEPMETKO® (tepotinib) [prescribing information]. EMD Serono, Inc., Rockland, MA; 2021.

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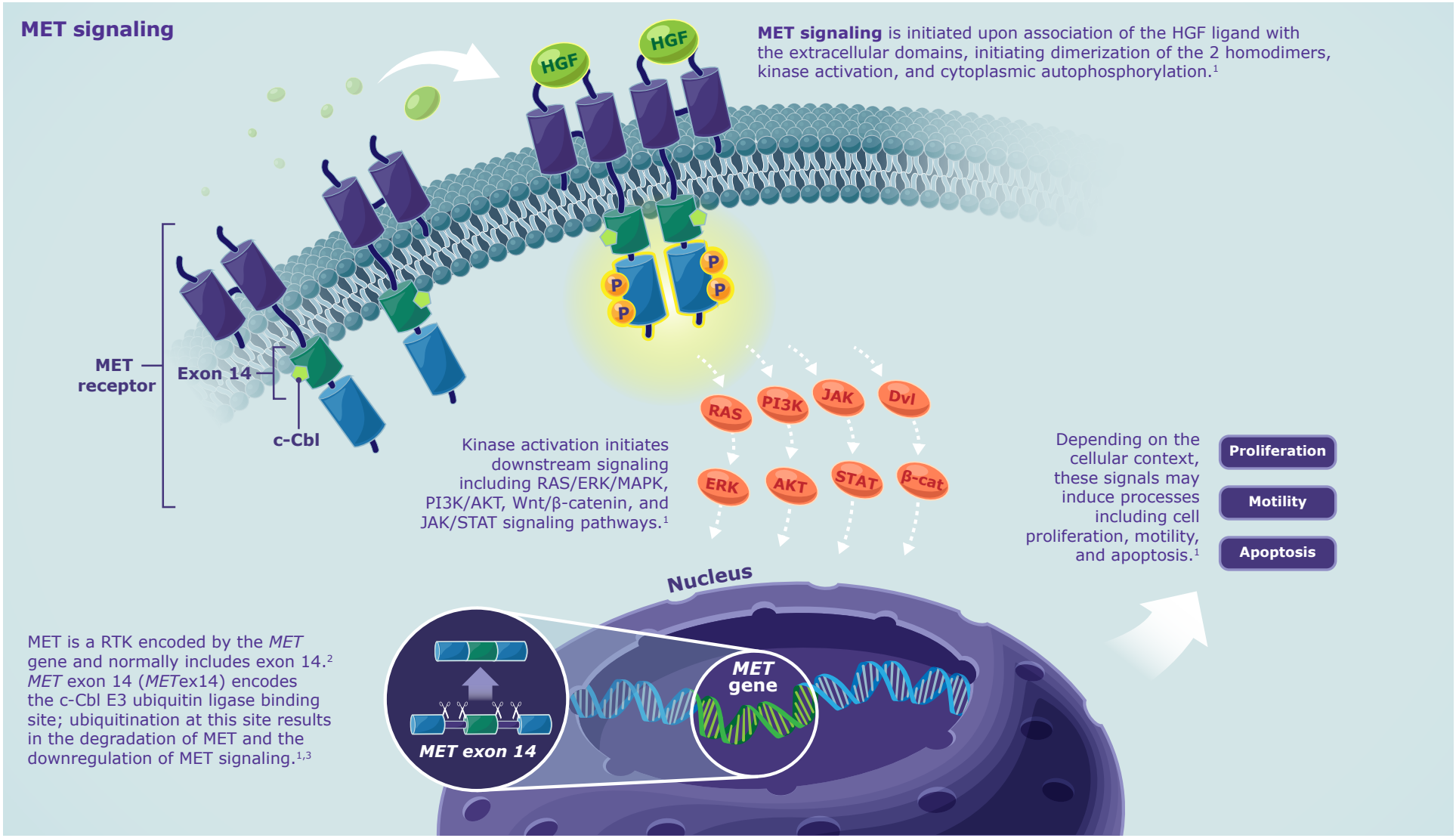
THE MET SIGNALING PATHWAY AND REGULATION

MET signaling is known to drive numerous cellular processes and plays a critical role during embryonic development; organ development; and in adult wound healing, tissue repair, and liver regeneration.[1]



AKT, protein kinase B; β-cat, β-catenin; c-Cbl, Casitas B-lineage lymphoma; Dvl, dishevelled; ERK, extracellular signal-regulated kinase; HGF, hepatocyte growth factor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; PI3K, phosphoinositide 3-kinase; RAS, RAS GTPase; RTK, receptor tyrosine kinase; STAT, signal transducers and activators of transcription; Wnt, *wingless* and *integrated-1*.

1. Drilon A, Cappuzzo F, Ou SHI, et al. *J Thor Oncol.* 2017;12(1):15-26; 2. Drilon A. *Clin Can Res*. 2016;22(12):2832-2834; 3. Wu YL, Soo RA, Locatelli G, et al. *Cancer Treat Rev*. 2017;61:70-81.

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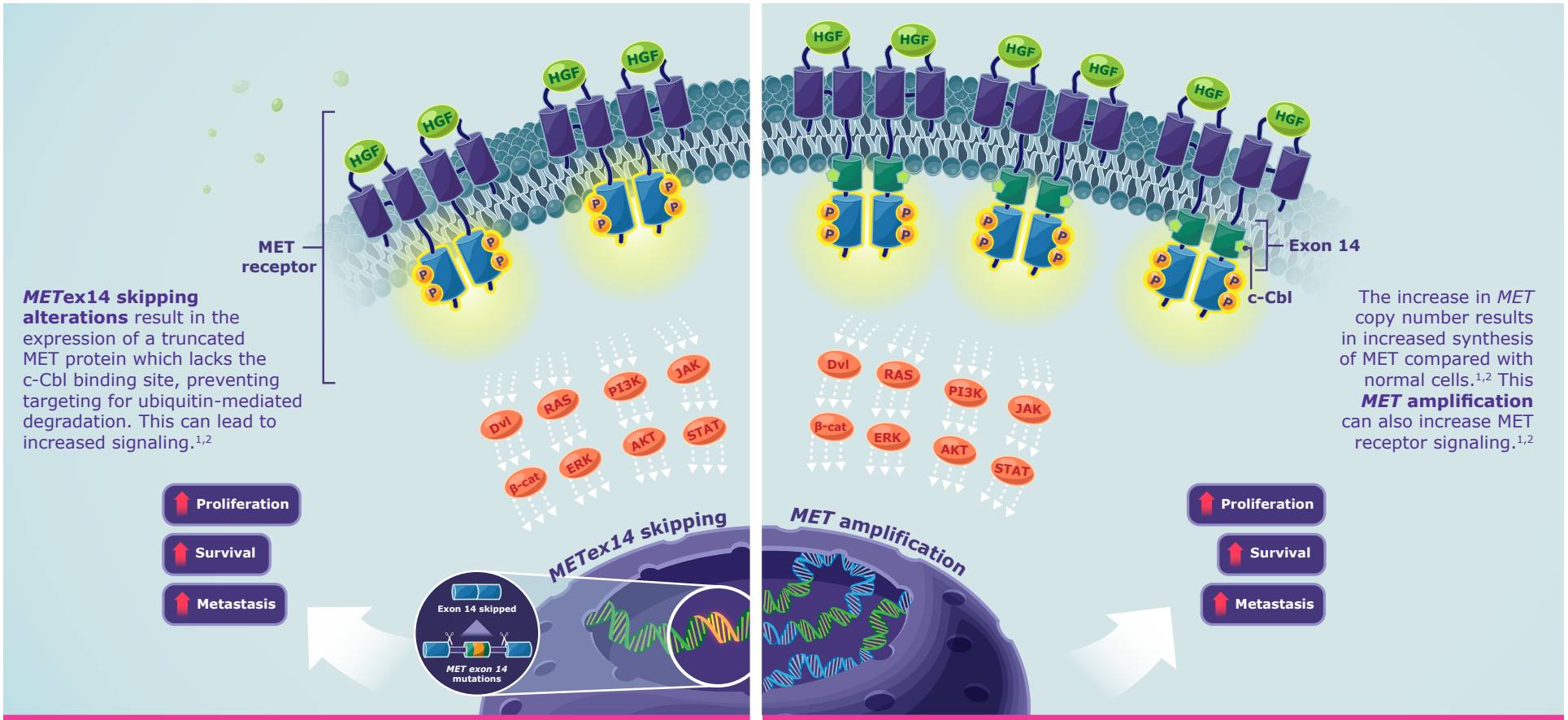
ABERRANT MET SIGNALING

MET signaling can be dysregulated through many mechanisms including *MET*ex14 skipping, amplification, rearrangement, fusion, activating mutations in the kinase domain, MET receptor overexpression and increased expression of HGF.[1]

Oncogenic alterations in the MET pathway and dependency on MET signaling drives tumor growth through increased cell proliferation, survival, invasion, and metastasis and also confers resistance to other cancer therapies.[1]



In NSCLC, *MET*ex14 skipping is associated with poorer OS compared with patients without *MET* alterations (HR=2.156; 95% CI, 1.096–4.242; P=0.026).[3]

***MET*ex14 skipping in NSCLC** is a primary oncogenic driver in approximately 3–4% of adenocarcinomas, 2% of squamous cell carcinomas and 8–30% of sarcomatoid carcinomas.[2,4,5]

In NSCLC, high-level *MET* amplification is associated with poorer OS compared with patients without *MET* alterations (HR=3.444; 95% CI, 1.398–8.482; P=0.007).[3]

***MET* amplification** is the primary oncogenic driver in ~1–5% of NSCLCs.[2]

AKT, protein kinase B; β-cat, β-catenin; c-Cbl, Casitas B-lineage lymphoma; CI, confidence interval; Dvl, dishevelled; ERK, extracellular signal-regulated kinase; HGF, hepatocyte growth factor; HR, hazard ratio; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; OS, overall survival; PI3K, phosphoinositide 3-kinase; RAS, RAS GTPase; STAT, signal transducers and activators of transcription; Wnt, *wingless* and *integrated-1*.

1. Wu YL, Soo RA, Locatelli G, et al. *Cancer Treat Rev*. 2017;61:70-81; 2. Drilon A, Cappuzzo F, Ou SHI, et al. *J Thor Oncol*. 2017;12(1):15-26; 3. Tong JH, Yeung SF, Chan AWH, et al. *Clin Cancer Res*. 2016;22(12):3048-3056; 4. Frampton GM, Ali SM, Rosenzweig M, et al. *Cancer Discov*. 2015;5(8):850-859; 5. Schrock AB, Frampton GM, Suh J, et al. *J Thorac Oncol*. 2016;11(9):1493-1502.

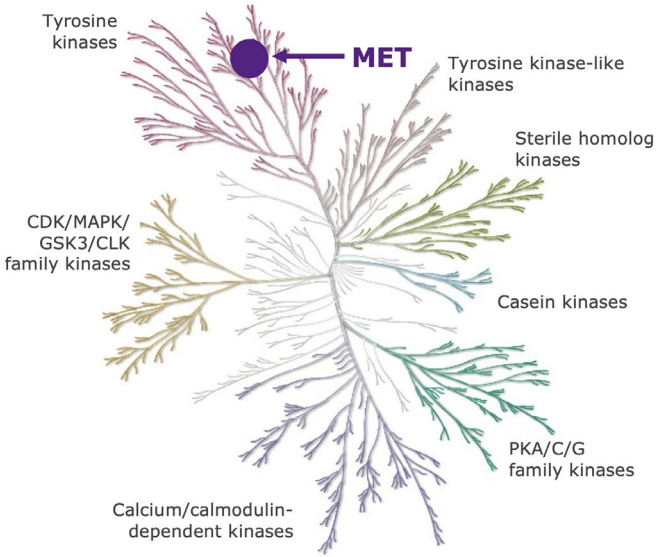
TEPOTINIB MECHANISM OF ACTION

Based on preclinical studies, tepotinib is thought to be a highly selective, potent, ATP-competitive, type-Ib MET inhibitor that inhibits ligand-dependent and -independent MET signaling.[1,2] The IC_{50} of MET was determined as 1.7 nmol/L, and screening against >400 kinases showed high selectivity of tepotinib for MET.[1,3,4]

The MET inhibitory activity and antitumor effects of tepotinib were investigated *in vitro* and *in vivo*, using human cancer cell lines and mouse xenograft models.[3]

Tepotinib selectivity

Tepotinib effects on human kinome[1]



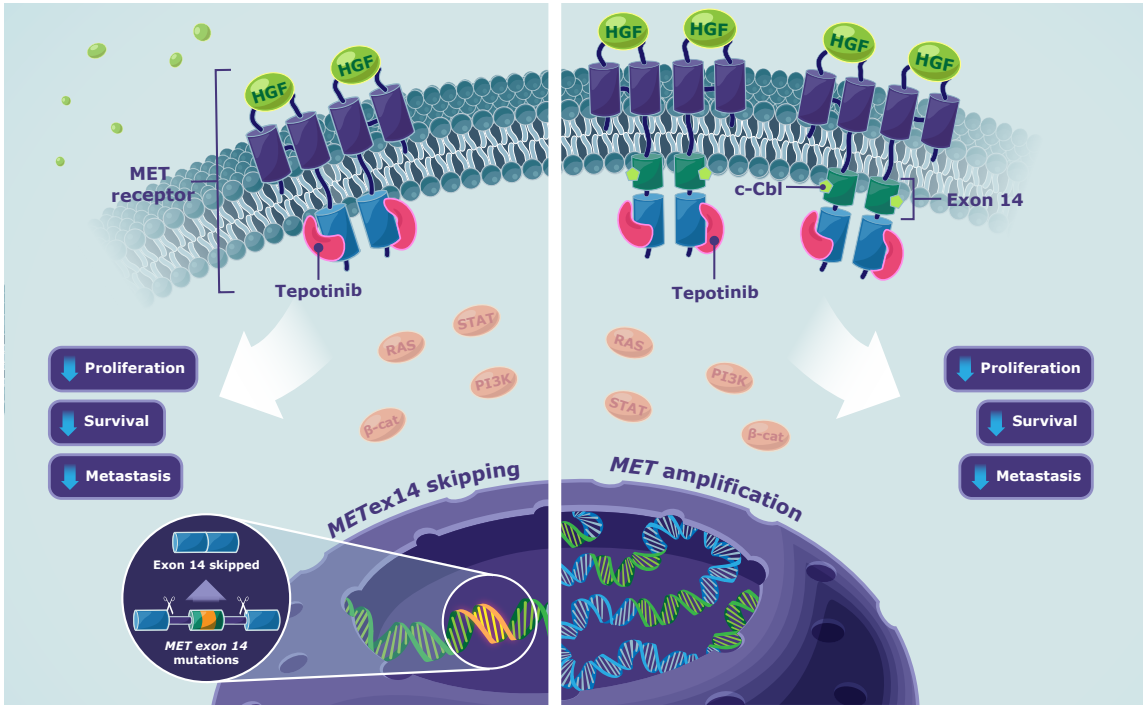
The purple circle represents kinases that are >90% inhibited by 100 nM tepotinib, showing the selective binding of tepotinib to MET.[1]

At 10 µM (1,000X > tepotinib IC_{90}), only 5 kinases were inhibited by more than 50%. The IC_{50} for these kinases makes it unlikely that tepotinib will achieve pharmacologically relevant inhibition of these kinases *in vivo*.[1]

Tepotinib alters MET signaling in preclinical models

By binding to the MET receptor and blocking downstream signaling, tepotinib may inhibit cancer cell proliferation, survival, and metastasis.[3]

Tumor cells with *MET* alterations



***MET*ex14 skipping alterations** protect MET receptors from degradation, increasing signaling.[5,6]

***MET* amplification** can also increase MET receptor signaling.[5,6]

ATP, adenosine triphosphate; β-cat, β-catenin; c-Cbl, Casitas B-lineage lymphoma; CDK, cyclin-dependent kinase; CLK, cdc2-like kinase; HGF, hepatocyte growth factor; GSK, glycogen synthase kinase; IC_{50}, 50% inhibitory concentration; IC_{90}, 90% inhibitory concentration; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; PI3K, phosphoinositide 3-kinase; PK, protein kinase; RAS, RAS GTPase; STAT, signal transducers and activators of transcription.

1. Schadt O, Blaukat A. 8.08 - Tepotinib. Comprehensive Medicinal Chemistry III. Chackalamannil S, Rotella D, Ward SE. 2017;178-203; 2. Dorsch D, Schadt O, Stieber F, et al. *Bioorg Med Chem Lett*. 2015;25(7):1597-1602; 3. Bladt F, Faden B,Friese-Hamim M, et al. *Clin Cancer Res*. 2013;19(11):2941-2951; 4. Falchook GS, Kurzrock R, Amin HM, et al. *Clin Cancer Res*. 2020;26(6):1237-1246; 5. Drilon A, Cappuzzo F, Ou SHI, et al. *J Thor Oncol*. 2017;12(1):15-26; 6. Wu YL, Soo RA, Locatelli G, et al. *Cancer Treat Rev*. 2017;61:70-81.

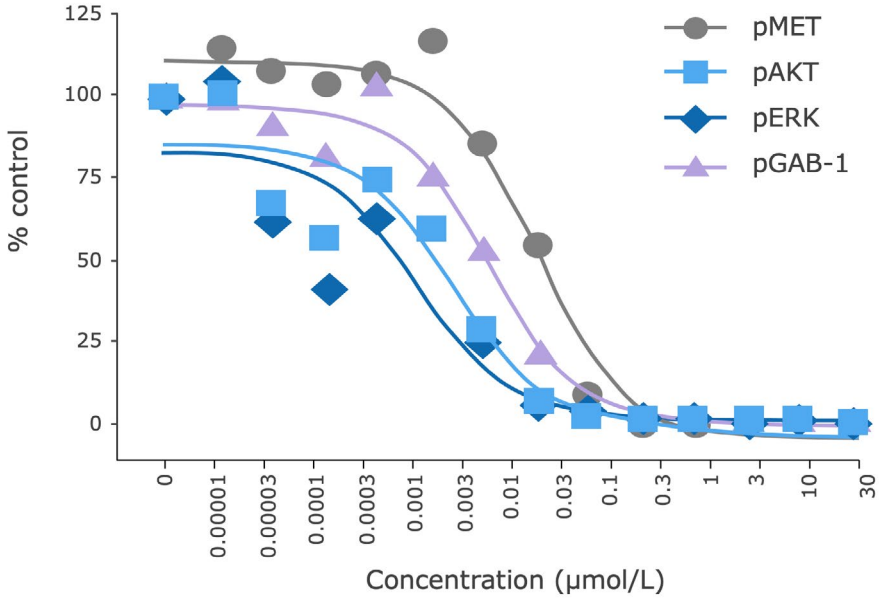
TEPOTINIB INHIBITS MET ACTIVATION AND DOWNSTREAM SIGNALING *IN VITRO*

Tepotinib inhibits MET signaling *in vitro* by blocking MET tyrosine kinase phosphorylation and resulting activation of the PI3K/AKT and MAPK/ERK pathways.[1]

MET kinase activity

Reduced MET phosphorylation in EBC-1 lung cancer cells

Inhibition of MET phosphorylation with concentrations of tepotinib[1]



Tepotinib induced a marked reduction in MET autophosphorylation and downstream signaling in a dose-dependent fashion in a ligand-dependent lung carcinoma cell model (A549; HGF binding).[1]

In the liposarcoma cell line model (Lipo246) in which the MET receptor is constitutively active because of autocrine signaling, tepotinib effectively inhibited MET signaling and the phosphorylation of downstream AKT, PI3K, and MAPK.[2]

In ligand-independent NSCLC and gastric cancer cell line models (EBC-1, MKN-45, and Hs746T) in which MET signaling is aberrant because of *MET* amplification or *MET*ex14 skipping, tepotinib treatment effectively blocked phosphorylation of major downstream effectors of the MET signaling pathway, GAB-1, AKT, and ERK1/2.[1]

The inhibition of MET phosphorylation lasted for more than 14 hours.[1] These data show cellular retention of tepotinib and sustained MET inhibition.[1]

AKT, protein kinase B; ERK, extracellular signal-related kinase; GAB, growth factor receptor-bound 2 (Grb2)-associated binder; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinase; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; pAKT, phosphorylated AKT; pERK, phosphorylated ERK; pGAB, phosphorylated GAB; PI3K, phosphoinositide 3-kinase; pMET, phosphorylated MET.

1. Bladt F, Faden B, Friese-Hamim M, et al. *Clin Cancer Res*. 2013;19(11):2941-2951; 2. Bill KL, Garnett J, Ma X, et al. *Lab Invest*. 2015;95(8):951-961.

TEPOTINIB INHIBITS MET-MEDIATED CELL VIABILITY, PROLIFERATION AND MIGRATION *IN VITRO*

Tepotinib decreased tumor cell viability, proliferation, and migration of MET-dependent cell lines *in vitro*.[1]

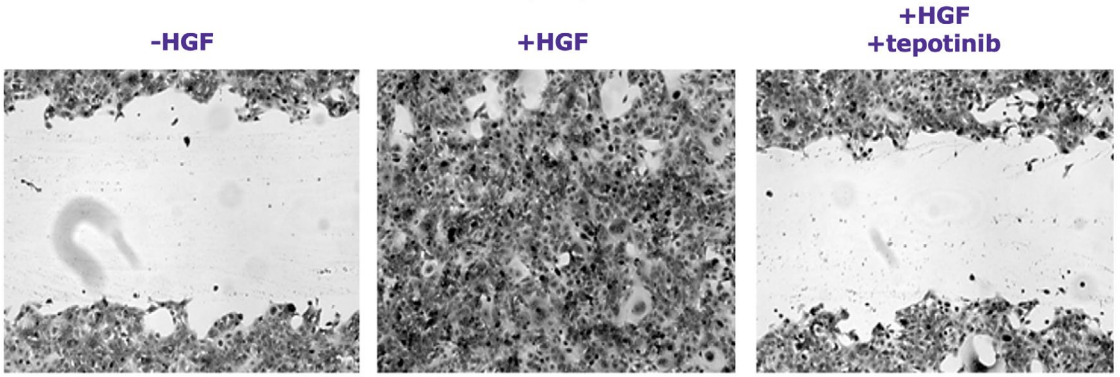
Cell viability and migration assays

Inhibition of cell proliferation observed in MET-addicted and non-MET-addicted cell lines[1]

Cell line	Tumor cell viability, nM (IC_{50})
MET-addicted	
Gastric carcinoma (Hs746T)	0.41
NSCLC (EBC-1)	0.57
Gastric cancer (MKN-45)	3.03
Non-MET-addicted	
Colorectal adenocarcinoma (HT29)	3620
Lung carcinoma (A549)	5840

Tepotinib inhibited the viability of MET-addicted gastric cancer cells (Hs746T, MKN-45) and lung carcinoma cells (EBC-1) with IC_{50} values <5 nM.[1] Reduced viability was also observed in non–MET-addicted colorectal adenocarcinoma cells (HT29) and lung carcinoma cells (A549) at higher concentrations (IC_{50} <6 µL).[1]

Inhibition of HGF-mediated migration with 1 µM tepotinib[1]



In *in vitro* wound-healing assays, tepotinib (as low as 0.1 nmol/L) inhibited HGF-induced cell migration, and concentrations of 100 nmol/L to 1 µmol/L almost completely prevented it.[1]

HGF, hepatocyte growth factor; IC_{50}, 50% inhibitory concentration; MET, mesenchymal–epithelial transition proto-oncogene receptor tyrosine kinase; NSCLC, non-small cell lung cancer.

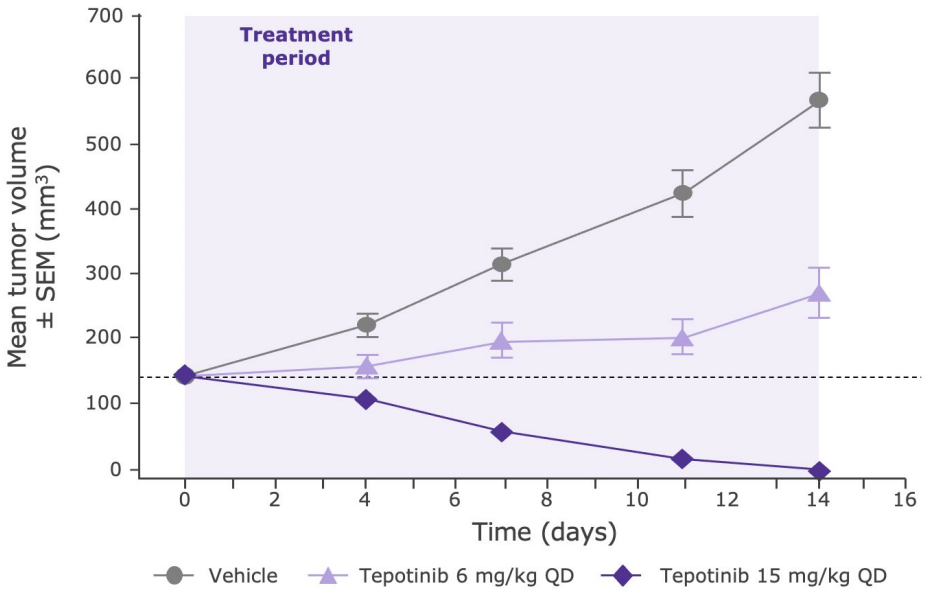
1. Bladt F, Faden B, Friese-Hamim M, et al. *Clin Cancer Res*. 2013;19(11):2941-2951.

TEPOTINIB INHIBITS TUMOR GROWTH AND PROMOTES REGRESSION *IN VIVO*

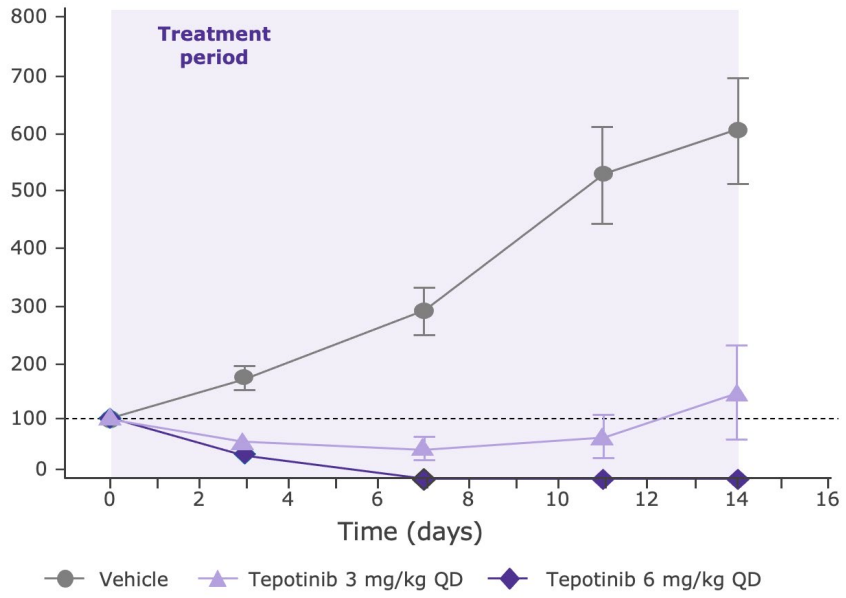
In murine xenograft models with HGF ligand-independent MET signaling, tepotinib has been shown to induce dose-dependent inhibition and regression of tumor growth.[1]

Assessment of tumor growth and regression

***MET* amplification**
NSCLC EBC-1[1]



***MET* amplification/*MET*ex14 skipping**
Gastric cancer Hs746T[1]



Tumor regression in gastric cancer Hs746T and NSCLC EBC-1 xenograft models with ligand-independent activation of MET signaling through *MET* amplification and MET overexpression.[1]

In the *MET*-amplified NSCLC EBC-1 xenograft model, tepotinib treatment at a dose of 15 mg/kg led to statistically significant antitumor activity ($P < 0.001$), resulting in complete tumor regression in 8/8 mice.[2]

HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; QD, once daily; SEM, standard error of the mean.

1. Bladt F, Faden B, Friese-Hamim M, et al. *Clin Cancer Res*. 2013;19(11):2941-2951. 2. Dorsch D, Schadt O, Stieber F, et al. *Bioorg Med Chem Lett*. 2015;25(7):1597-1602;

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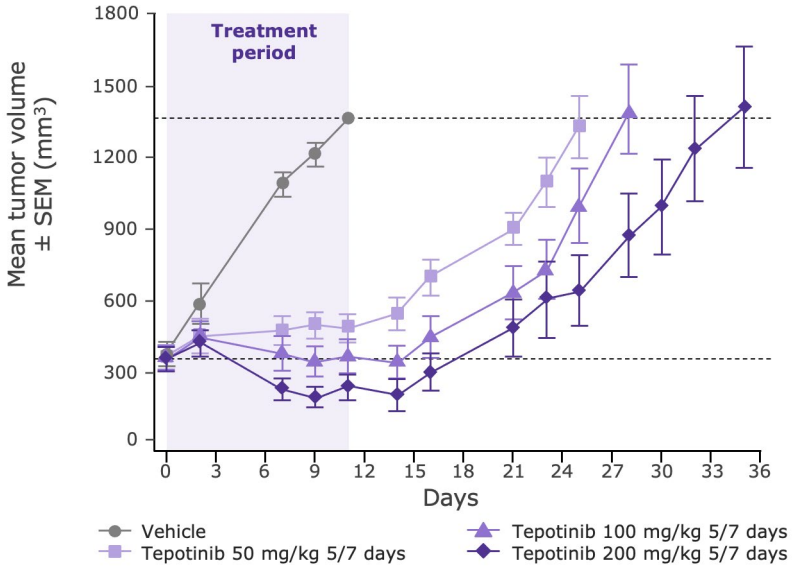
In murine xenograft models with HGF ligand-dependent MET signaling, tepotinib has been shown to induce dose-dependent inhibition and regression of tumor growth.[1]

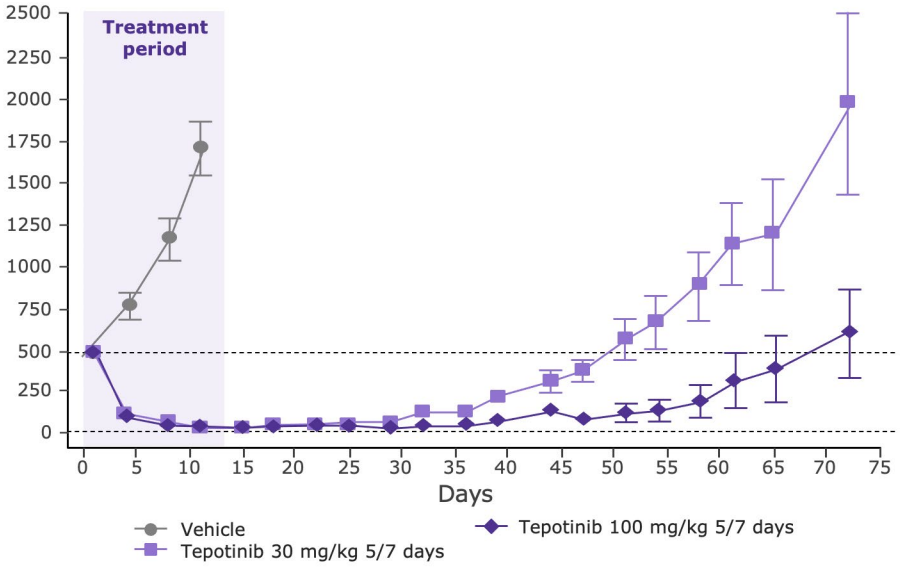
Assessment of tumor growth and regression

Increased synthesis of HGF
Glioblastoma U87MG[1]



Tumor regression in a glioblastoma U87MG xenograft model with ligand-dependent MET activation from co-expression of HGF.[1]

Increased synthesis of HGF and *MET* amplification
HCC MHCC97H[2]



Tumor regression in HCC MHCC97H xenograft models with ligand-dependent MET activation from MET overexpression.[2]

Primary liver explant models with strong MET/HGF activation showed increased responsiveness to tepotinib, with tepotinib showing similar or superior activity to sorafenib.[2] Tumors characterized by low MET expression were less sensitive to tepotinib.[2]

HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; SEM, standard error of the mean.

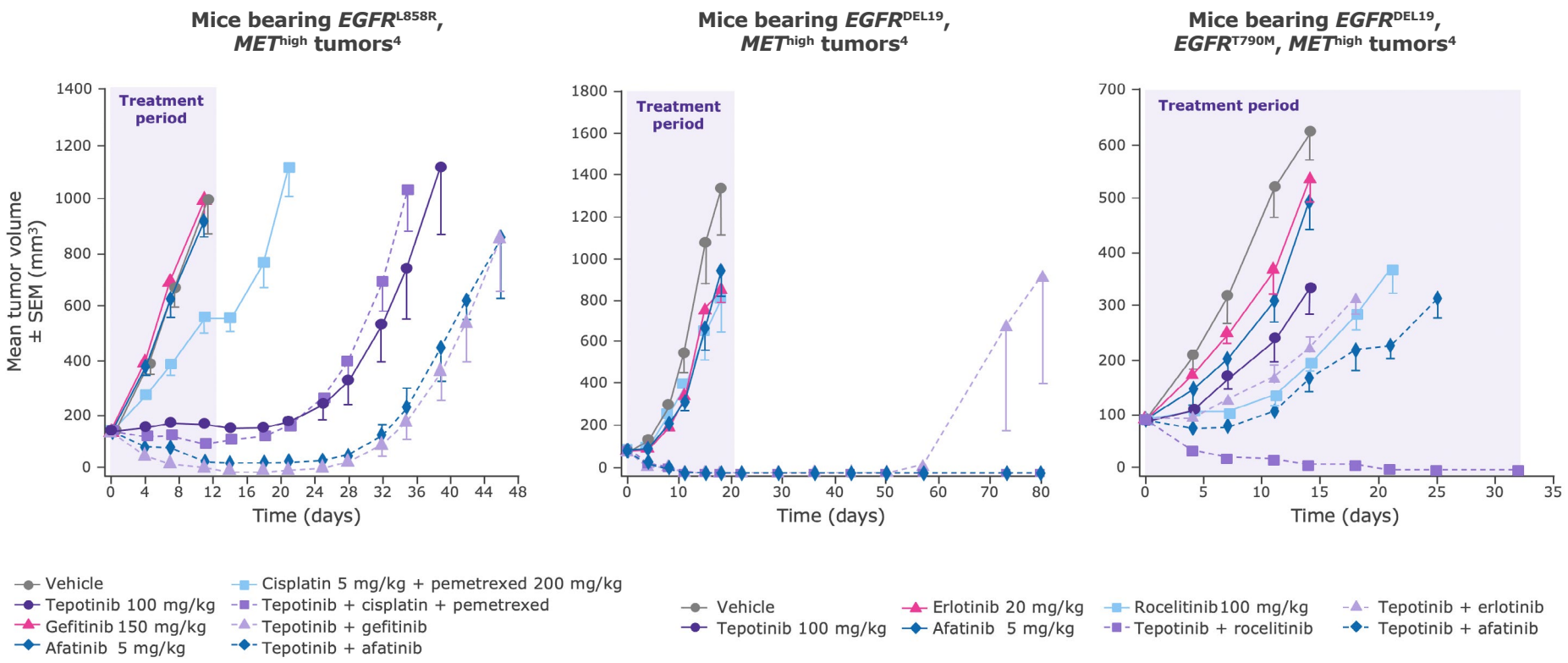
1. Bladt F, Faden B, Friese-Hamim M, et al. *Clin Cancer Res*. 2013;19(11):2941-2951; 2. Bladt F, Friese-Hamim M, Ihling C, et al. *Cancers*. 2014;6(3):1736-1752.

TEPOTINIB HAS BEEN SHOWN TO OVERCOME EGFR TKI RESISTANCE IN EGFR-MUTANT NSCLC *IN VIVO*

In NSCLC, ***MET* amplification** is a secondary or co-driver in acquired **EGFR TKI** resistance (5%) and acquired **osimertinib** resistance (15–19%).[1-3]

Tepotinib can overcome EGFR-TKI resistance in xenograft models of *EGFR*-mutant NSCLC with aberrant MET signaling due to *MET* amplification.[4]

Assessment of tumor growth and regression



del, deletion; EGFR, epidermal growth factor receptor; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; NSCLC, non-small cell lung cancer; SEM, standard error of the mean; TKI, tyrosine kinase inhibitor.

1. Drilon A, Cappuzzo F, Ou SHI, et al. *J Thor Onco*l. 2017;12(1):15-26; 2. Ramalingam S, Cheng Y, Zhou C, et al. Abstract presented at: ESMO 2018. LBA50; 3. Papadimitrakopoulou V, Wu Y, Han J, et al. ESMO 2018. Abstract 5121; 4. Friese-Hamim M, Bladt F, Locatelli G, et al. *Am J Cancer Res*. 2017; 7(4):962-972.

TEPOTINIB HAS BEEN SHOWN TO OVERCOME EGFR TKI RESISTANCE IN EGFR-MUTANT NSCLC *IN VIVO*

Tepotinib can overcome EGFR-TKI resistance in xenograft models of *EGFR*-mutant NSCLC with aberrant MET signaling due to *MET* amplification, where tumors with low MET expression are insensitive to tepotinib.[1]

Xenograft	EGFR TKIs	Tepotinib + EGFR TKIs	Tepotinib alone
EGFR exon 19 deletion (del19) activating mutation and low MET expression[1]	Caused tumors to shrink, but growth resumed upon treatment cessation (afatinib, gefitinib, erlotinib)	Delayed tumor regrowth	No effect on tumor growth
EGFRdel19 mutations and high levels of MET and HGF expression[1]	No effect on tumor growth	Complete tumor regression	Tumor stasis
EGFRdel19 mutation and *MET* amplification[1]	Ineffective	–	Complete tumor regression
EGFRdel19-positive, *EGFR T790M*-positive, and *MET* amplification-positive[1]	• Erlotinib and afatinib showed no significant antitumor activity • Rociletinib (3rd-generation EGFR TKI) slowed tumor growth	Tepotinib + rociletinib induced complete tumor regression	–

del, deletion; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition proto-oncogene; MET, MET receptor tyrosine kinase; NSCLC, non-small cell lung carcinoma; TKI, tyrosine kinase inhibitor.

1. Friese-Hamim M, Bladt F, Locatelli G, et al. *Am J Cancer Res*. 2017;7(4):962-972.