TEPOTINIB SAFETY AND MANAGEMENT

US-TEP-00584
06/2022

EMD SERONO

Important Notices

- Tepotinib is being investigated for the treatment of various diseases. Efficacy and safety of this product is still under investigation in various indications. Regulatory approval is dependent on the completion of the study programs and review by local regulatory authorities and varies from country to country. Please check with your local market authorization label for country-specific information. Clinical trial information is available at www.clinicaltrials.gov
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- EMD Serono is the healthcare business of Merck KGaA, Darmstadt, Germany, in the United States and Canada

Indication and usage

- TEPMETKO® (tepotinib) is indicated for the treatment of adult patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations
  - This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent on the verification and description of clinical benefit in confirmatory trials
- The recommended dosage of tepotinib is 450 mg (two 225 mg tablets) orally once daily with food until disease progression or unacceptable toxicity

MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Important safety information

Interstitial lung disease (ILD)/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 one patient experiencing Grade 3 or higher event; this event resulted in death

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 one patient (0.2%)
- The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Important safety information (continued)

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 one week after the final dose

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

Fatal adverse reactions:

- **Fatal adverse reactions** occurred in one patient (0.4%) due to pneumonitis, in one patient (0.4%) due to hepatic failure, and in one patient (0.4%) due to dyspnea from fluid overload

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%)

Most common adverse reactions:

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

CYP, cytochrome P450; P-gp, P-glycoprotein.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Important safety information (continued)

Clinically relevant adverse reactions:

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

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%)

Most common Grade 3-4 laboratory abnormalities

- **The most common Grade 3-4 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%)

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

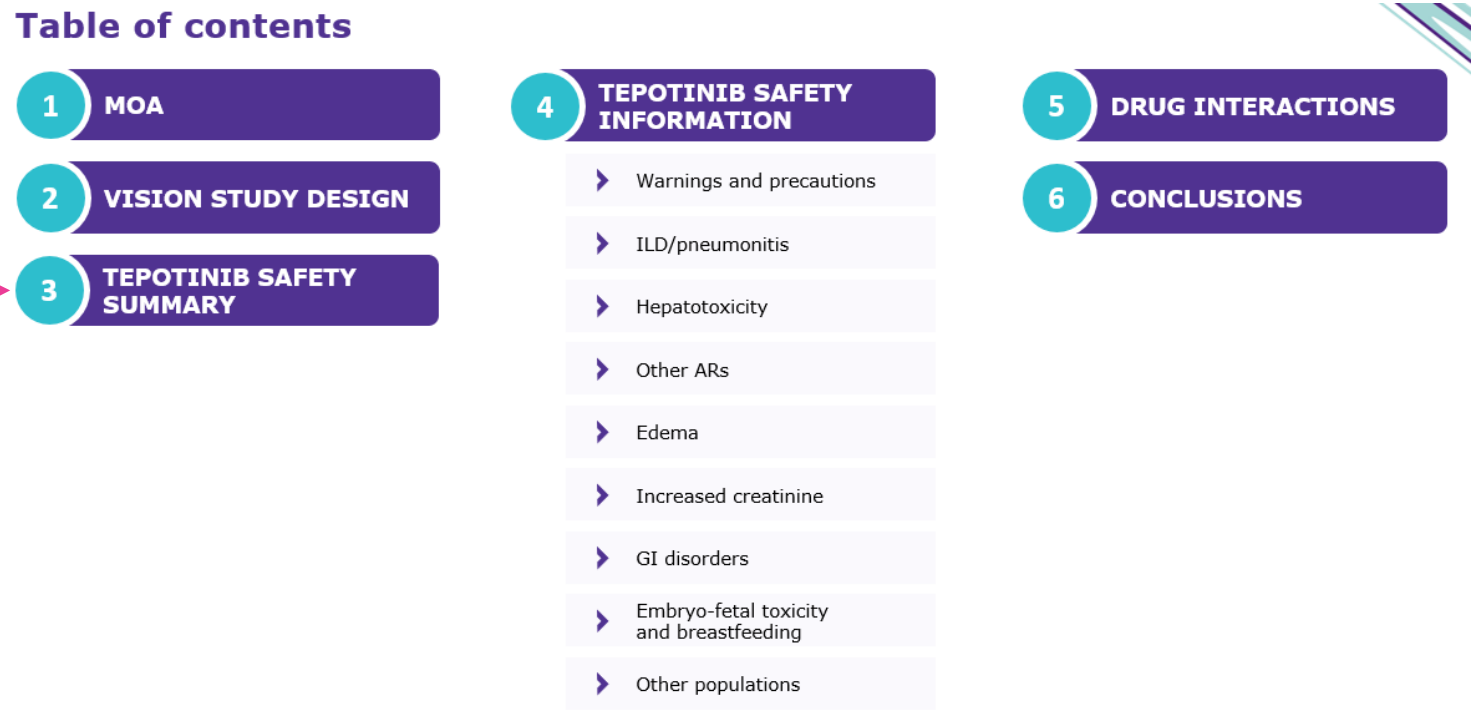
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ILD, interstitial lung disease.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Interactivity and how to use

Navigate between sections using the table of contents:

Click on a section title or subtitle to arrive at the respective page.



Icon located in the bottom left corner of the slide help you return to the table of contents.

Table of contents

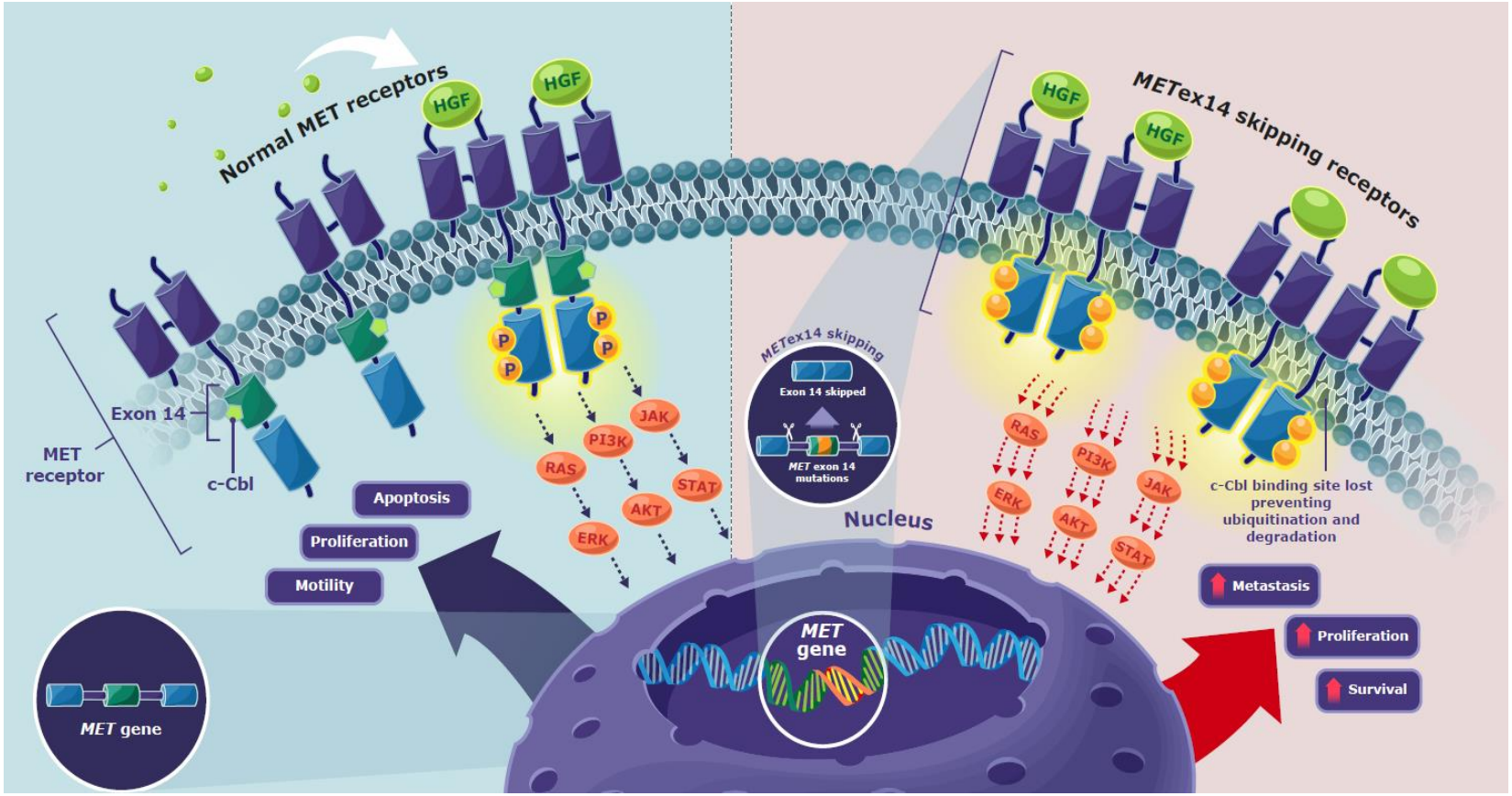
AR, adverse reaction; GI, gastrointestinal; ILD, interstitial lung disease; MOA, mechanism of action.

MOA

MET signaling can drive tumor growth and progression[1]

- MET is a receptor tyrosine kinase encoded by the *MET* gene[1]
- Oncogenic *MET*ex14 skipping alterations can lead to dysregulation of the MET pathway and drive tumor cell proliferation and survival[2,3]
- *MET*ex14 skipping results in a MET receptor without the c-Cbl binding site, leading to aberrant MET signaling that can drive tumorigenesis[3,4]

*MET*ex14 skipping and dysregulated MET pathway[4,5]

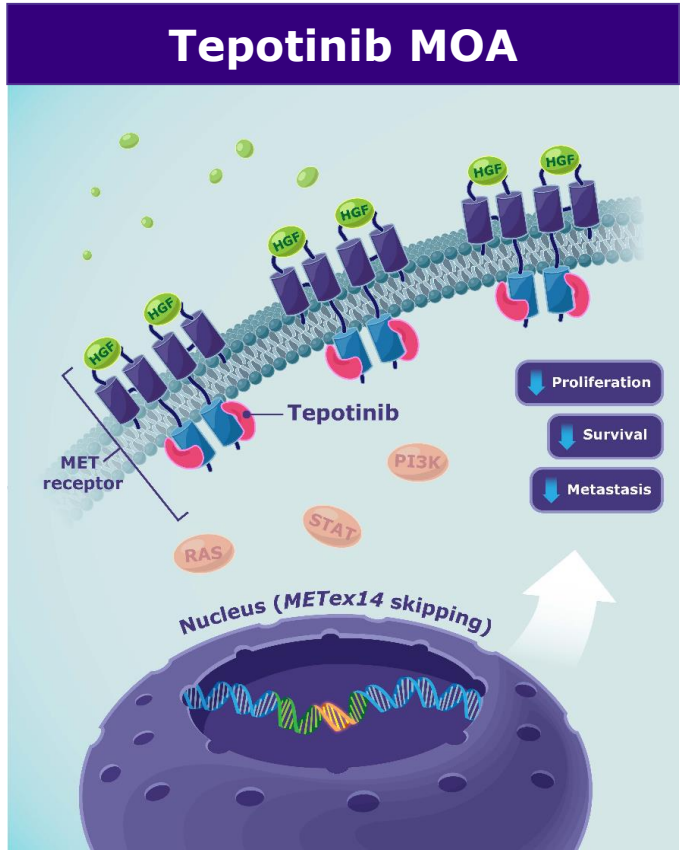


AKT, protein kinase B; ERK, extracellular regulatory kinase; c-Cbl, Casitas B-lineage lymphoma; HGF, hepatocyte growth factor; JAK, Janus kinase; MET, mesenchymal-epithelial transition; MOA, mechanism of action; *MET*ex14, *MET* exon 14; PI3K, phosphoinositide 3-kinase; RAS, RAS GTPase; STAT, signal transducer and activator of transcription.

1. Paik PK, et al. *N Engl J Med*. 2020;383(10):1–40; **2.** Tong JH, et al. *Clin Cancer Res*. 2016;22(12):3048–3056; **3.** Liang H, Wang M. *Onco Targets Ther*. 2020;13:2491–2510; **4.** Drilon A, et al. *J Thorac Oncol*. 2017;12(1):15–26; **5.** Wu YL, et al. *Cancer Treat Rev*. 2017;61:70–81.

MOA

Tepotinib is thought to bind to the MET receptor to inhibit oncogenic signaling



Based on preclinical studies, tepotinib is thought to be an ATP-competitive, reversible, type Ib MET inhibitor that binds to the MET receptor with **high selectivity**[1,2]

! By binding to the MET receptor and blocking downstream signaling, tepotinib may prevent cancer cell proliferation, survival, and metastasis[1]

ATP, adenosine triphosphate; HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; MOA, mechanism of action; PI3K, phosphoinositide 3-kinase; RAS, RAS GTPase; STAT, signal transducers and activators of transcription.

1. Bladt F, et al. *Clin Cancer Res.* 2013;19:2941–2951; **2.** Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27–37.

VISION STUDY DESIGN

VISION clinical trial overview

VISION is a single-arm, Phase II trial of the MET inhibitor tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)

Population

Eligibility:
- Patients with advanced, metastatic NSCLC harboring *MET*ex14 skipping alterations or *MET* amplification
- *EGFR*wt, *ALK*-
- ≥1 measurable lesion by RECIST v1.1
- ECOG PS 0–1
- Treatment-naïve or treatment-experienced patients

Exclusions:
- Symptomatic CNS metastases
- Clinically significant uncontrolled cardiac disease
- Prior treatment with any MET or HGF inhibitor

Cohort A: *MET*ex14 skipping alterations
Detection of alterations in plasma (DNA-based) or tissue (RNA-based)

Cohort B:* *MET* amplification
Detection of alterations in plasma (DNA-based)

Cohort C: *MET*ex14 skipping alterations
Detection of alterations in plasma or tissue

Confirmatory Part 2 of study

Tepotinib 500 mg† once daily
21-day cycles until disease progression

Endpoints

Primary endpoint:
Objective response per RECIST v1.1 by independent review committee

Secondary endpoints:
- ORR by investigator assessment
- Duration of response
- Objective disease control
- PFS
- OS
- Safety
- HRQoL

! Data shown here are based on analyses of patients with *MET*ex14 skipping NSCLC

*Enrolment into Cohort B was prematurely discontinued following the pre-planned interim analysis; †500 mg tepotinib hydrochloride hydrate (active ingredient) contains 450 mg tepotinib free-base (active moiety). ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRwt, epidermal growth factor receptor wild type; HGF, hepatocyte growth factor; HRQoL, health-related quality of life; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Paik PK, et al. *N Engl J Med*. 2020;383(10):931–943.

VISION STUDY DESIGN

Demographics and baseline disease characteristics of patients analyzed for safety in VISION*

Patients were generally **elderly,** and more likely to be **white** and have a **ECOG PS of 1**

Median treatment duration was **5.1 months** (range <0.1 to 43.2)

Treatment was **ongoing** in 101 patients (**39.6%**)

		Tepotinib (N=255)
Median age, years (range)		72 (41–94)
Female sex, n (%)		132 (51.8)
Race, n (%)†	White	171 (67.1)
	Asian	72 (28.2)
	Black or African American	3 (1.2)
ECOG PS, n (%)	0	71 (27.8)
	1	184 (72.2)
Smoking history, n (%)‡	Never smoker	124 (48.6)
	Current or former smoker	121 (47.5)
Histologic subtype, n (%)	Adenocarcinoma	207 (81.2)
	Squamous	25 (9.8)
Treatment-naïve, n (%)		125 (49.0)
Identification of *MET*ex14 skipping, n (%)§	Liquid biopsy	156 (61.2)
	Tissue biopsy	155 (60.8)

*Patients with *MET*ex14 skipping NSCLC who had received ≥1 dose of tepotinib at the data cut-off (01 Jul 2020); †Data were missing for eight patients, and one patient was classified as 'other'; ‡Data were missing for 10 patients; §Patients could have *MET*ex14 skipping detected by both methods.

ECOG PS, Eastern Cooperative Oncology Group performance status; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer.

Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

TEPOTINIB SAFETY SUMMARY

Overall safety profile of tepotinib

Summary of ARs per prescribing information[1]

- **Fatal ARs** occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to dyspnea from fluid overload
- **Serious ARs** occurred in 45% of patients who received tepotinib
  - Serious ARs 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%)
- **The most common ARs** (≥20%) in patients who received tepotinib were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea
  - The most common Grade 3–4 laboratory abnormalities (≥2%) were: decreased lymphocytes, albumin, sodium, and hemoglobin; and increased GGT, amylase, ALT, and AST

Summary of AEs per VISION study publications

AEs, n (%)	*MET*ex14 skipping (N=255)	
	All-cause[2]	TRAEs[3]
All grades	246 (96.5)	220 (86.3)
Serious AEs	115 (45.1)	31 (12.2)
Grade ≥3	135 (52.9)	64 (25.1)
Leading to dose reduction	76 (29.8)	71 (27.8)
Leading to treatment interruption	112 (43.9)	90 (35.3)
Leading to permanent discontinuation	52 (20.4)	27 (10.6)

Safety population comprised all patients from VISION Cohorts A and C who received at least one dose of tepotinib. Data cut-off: July 01, 2020. AE, adverse event; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; TRAE, treatment-related adverse event.

1. EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last Accessed 23 March 2022; **2.** Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print); **3.** Le X, et al. *Clin Cancer Res*. 2022;28(6):1117–1126.

TEPOTINIB SAFETY SUMMARY

Safety profile of TRAEs

TRAEs, n (%)		Previous treatment experience[1]		Age[1]		Prior IO* (n=66)[2]	Overall (N=255†)[1]
		Treatment-naïve (n=125)	Experienced (n=130)	<75 years (n=146)	≥75 years (n=109)		
Any grade‡		109 (87)	111 (85)	128 (88)	92 (84)	55 (83)	220 (86)
Grade ≥3		39 (31)	25 (19)	27 (18)	37 (34)	12 (18)	64 (25)
Leading to:	Dose reduction	39 (31)	32 (25)	34 (23)	37 (34)	15 (23)	71 (28)
	Treatment interruption	50 (40)	40 (31)	42 (29)	48 (44)	22 (33)	90 (35)
	Treatment discontinuation	19 (15)	8 (6)	11 (8)	16 (15)	5 (8)	27 (11)
TRAEs (any grade) occurring in ≥10% of all patients							
Peripheral edema		73 (58)	65 (50)	82 (56)	56 (51)	30 (45)	138 (54)
Nausea		30 (24)	21 (16)	29 (20)	22 (20)	8 (12)	51 (20)
Diarrhea		26 (21)	24 (18)	28 (19)	22 (20)	9 (14)	50 (20)
Blood creatinine increase		23 (18)	22 (17)	29 (20)	16 (15)	13 (20)	45 (18)
Hypoalbuminemia		21 (17)	16 (12)	18 (12)	19 (17)	9 (14)	37 (15)

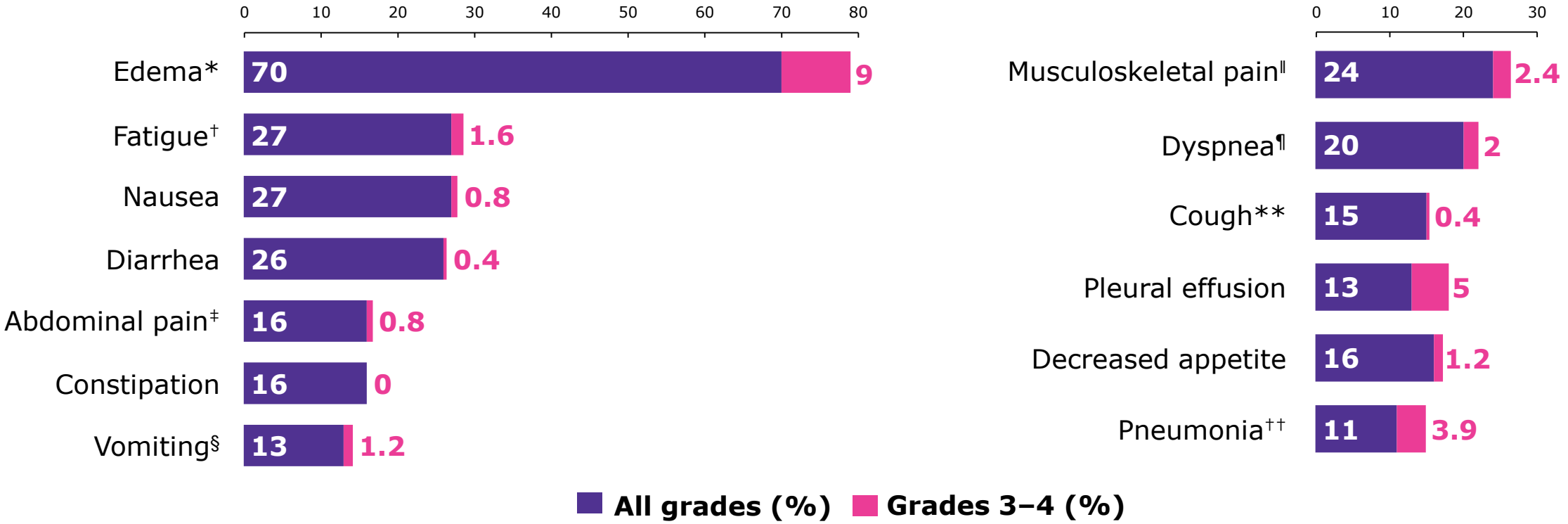
- The most common TRAE, peripheral edema, was mostly low grade (Grade ≥3: 7.5%) and rarely led to discontinuation (4%)
- The safety profile was consistent in patients who received prior IO[2]

Data cut-off: July 01, 2020. *Patients may have received IO as monotherapy or in combination with chemotherapy; †Safety population comprises VISION Cohorts A and C, all patients who received at least one dose of tepotinib; ‡Three TRAEs were fatal: acute respiratory failure secondary to interstitial lung disease, severe worsening of dyspnea with fatal outcome, and acute hepatic failure after the patient withdrew consent. AE, adverse event; IO, immunotherapy; TRAE, treatment-related adverse event.

1. Le X, et al. *Clin Cancer Res*. 2022;28(6):1117–1126; **2.** Paik P, et al. WCLC 2020. Abstract 1361.

TEPOTINIB SAFETY SUMMARY

Treatment-emergent ARs in ≥10% of patients with NSCLC with *MET*ex14 skipping alterations who received tepotinib in VISION



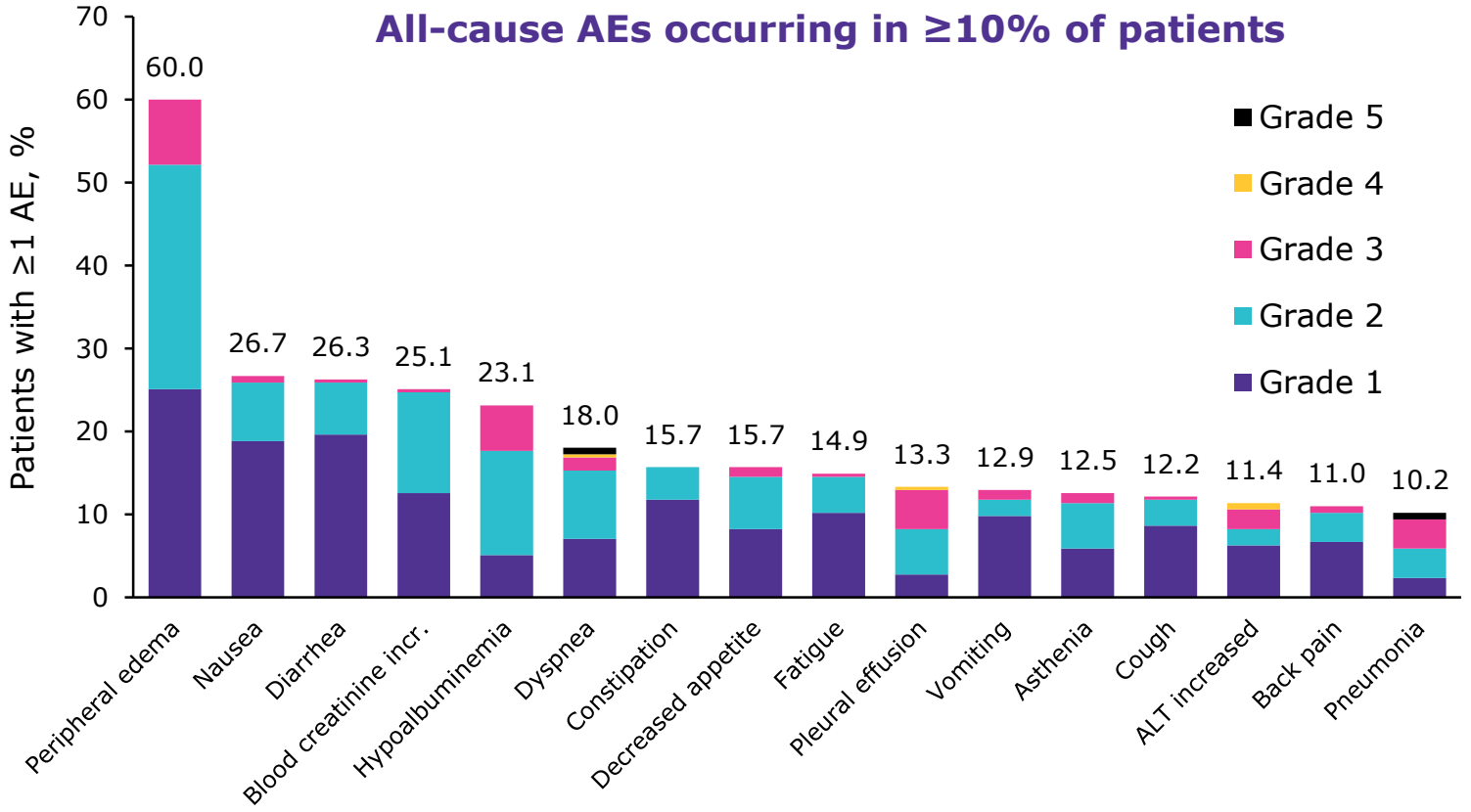
Clinically relevant adverse reactions in <10% of patients who received tepotinib included ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache

Data cut-off: July 01, 2020 (N=255). *Includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema; †Includes asthenia and fatigue; ‡Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain; §Vomiting includes retching and vomiting; ‖Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain; ¶Includes dyspnea, dyspnea at rest, and dyspnea exertional; **Includes cough, productive cough, and upper-airway cough syndrome; ††Includes pneumonia, pneumonia aspiration, and pneumonia bacterial. AR, adverse reaction; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last Accessed 23 March 2022.

TEPOTINIB SAFETY SUMMARY

All-cause AEs in ≥10% of patients with *MET*ex14 skipping NSCLC who received tepotinib in VISION[1]



All-cause AEs were reported for:
- **Any grade: 96.5%** of patients
- **Grade ≥3: 52.9%** of patients

All-cause SAEs were reported for **45.1%** of patients

Most common SAEs were:
- Pleural effusion (6.7%)
- Pneumonia (4.7%)
- Disease progression (4.7%)

11.8% of patients had fatal AEs

In three patients (1.2%), the following were considered treatment-related:[2]
- Acute respiratory failure secondary to ILD
- Severe worsening of dyspnea
- Acute hepatic failure*

! The majority of the most frequent AEs were considered treatment-related

Data cut-off: July 01, 2020. *Acute hepatic failure which led to death after the patient had withdrawn consent for study participation. AE, adverse event; ALT, alanine aminotransferase; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; SAE, serious adverse event.

1. Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print); **2.** Le X, et al. *Clin Cancer Res*. 2022;28(6):1117–1126.

TEPOTINIB SAFETY SUMMARY

Time to first onset and time to resolution of AECIs

	Patients, n	Total events, n	Events resolved, n	Time to first onset: Weeks since treatment initiation, median (range)	Time to resolution: Weeks since onset of AE, median (range)
Edema	178	337	115	7.9 weeks (0.1–58.3)	Not described due to low proportion of resolved events
Hypoalbuminemia	61	74	25	9.4 weeks (0.1–150.3)	Median not reached
Pleural effusion	34	39	15	16.6 weeks (0.1–88.9)	56.1 weeks (0.6–84.4+)
Creatinine increase	66	96	67	3.1 weeks (0.1–78.4)	12.1 weeks (0.4+ – 104.3)
Nausea	68	87	67	4.0 weeks (0.1–89.0)	5.9 weeks (0.1+ – 88.6+)
Diarrhea	67	112	102	2.4 weeks (0.1–48.0)	1.8 weeks (0.1–37.4)
Vomiting	33	47	44	5.1 weeks (0.1–61.7)	0.3 weeks (0.1–25.4)
ALT and/or AST increase	31	56	46	6.1 weeks (0.1–34.0)	5.0 weeks (0.1–31.1)

Time to first onset: 0 20 40 60 80 100 120 140 160

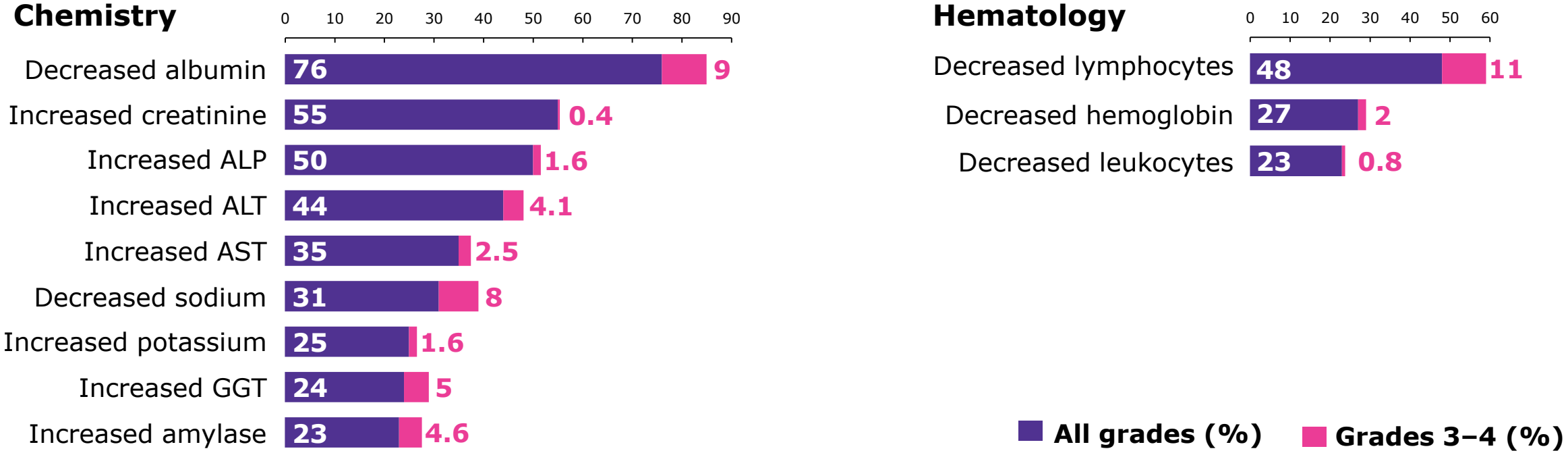
Time to resolution: 0 20 40 60 80 100 120 140 160 180 200

There was **no clear association** between edema, hypoalbuminemia, pleural effusion, and creatinine increase when analyzed irrespective of event timing

Plots indicate the median value (blue circles, size proportional to the number of patients) and range (green bars). The '+' signs denote censored values.
AE, adverse event; AECI, adverse event of clinical interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

TEPOTINIB SAFETY SUMMARY

Select laboratory abnormalities (≥20%) that worsened from baseline in patients who received tepotinib in VISION*



A clinically relevant laboratory abnormality in <20% of patients who received tepotinib was increased lipase (18%), which was Grade 3 or 4 in 3.7% of patients

Data cut-off: July 01, 2020 (N=255). *The denominator used to calculate the rate varied from 207 to 246 based on the number of patients with a baseline value and at least one post-treatment value. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

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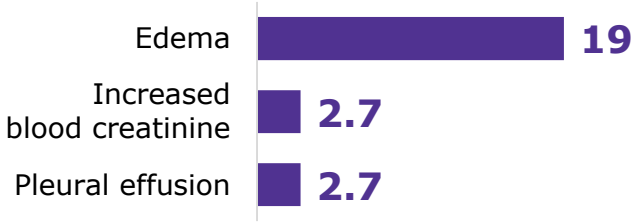
TEPOTINIB SAFETY SUMMARY

Permanent discontinuations, dosage interruptions, dose reductions, and dose modifications for ARs

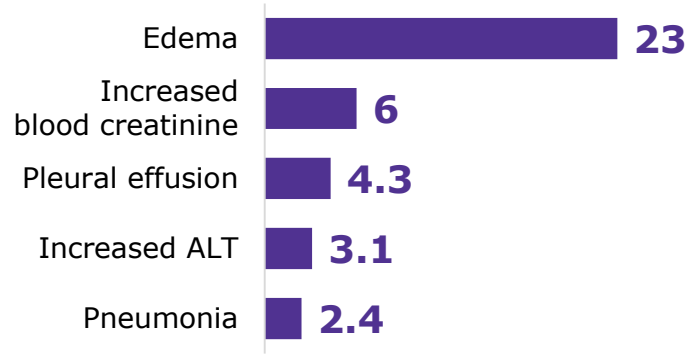
Dose reductions (Overall 30%)

ARs that required dose reductions in >2% of patients who received tepotinib (%)



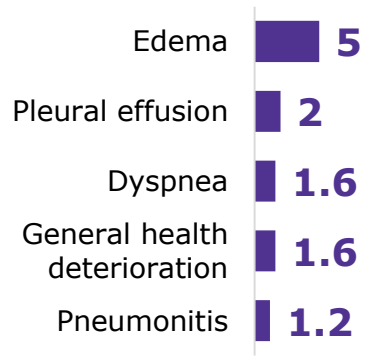
Dosage interruptions (Overall 44%)

ARs that required dosage interruption in >2% of patients who received tepotinib (%)



Permanent discontinuation (Overall 20%)

Most frequent ARs (>1%) leading to permanent discontinuation of tepotinib (%)



Dose modifications for ARs

- The recommended dose reduction of tepotinib for the management of ARs is 225 mg orally once daily
- Permanently discontinue tepotinib in patients who are unable to tolerate the 225 mg dose
- Management of some ARs may require temporary interruption or permanent discontinuation
- See the full prescribing information for recommended dosage modifications of tepotinib

Data cut-off: July 01, 2020 (N=255).

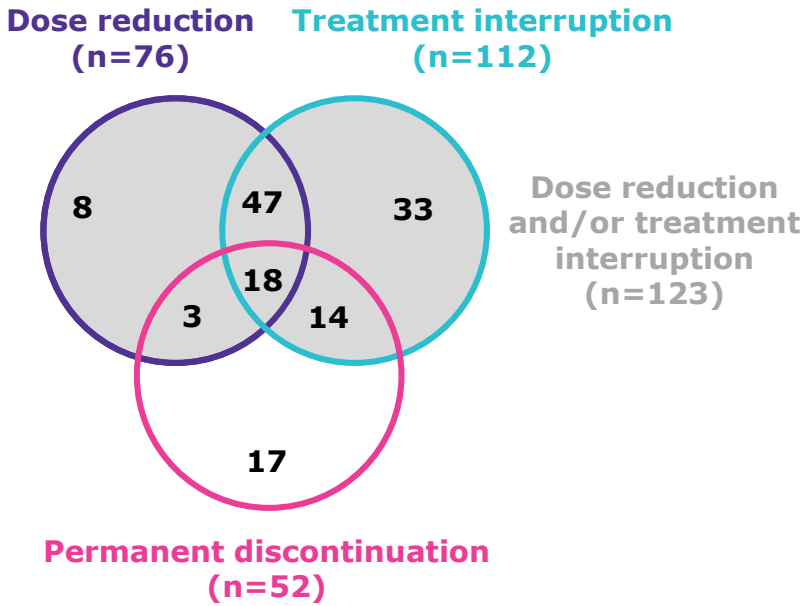
AR, adverse reaction; ALT, alanine aminotransferase.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last Accessed 23 March 2022.

TEPOTINIB SAFETY SUMMARY

Overall safety profile: All-cause AEs leading to dose modifications or discontinuations

Patients with all-cause AEs leading to dose reduction, treatment interruption, and/or permanent discontinuation (n=140)



All-cause AEs leading to permanent discontinuation*

Patients, n (%)	Tepotinib (N=255)
Peripheral edema	9 (3.5)
Pleural effusion	5 (2.0)
Disease progression	4 (1.6)
Dyspnea	4 (1.6)
General physical health deterioration	4 (1.6)
Genital edema	3 (1.2)
Pneumonitis	3 (1.2)
Blood creatinine increased	2 (0.8)
Pneumonia	2 (0.8)
Spinal fracture	2 (0.8)

Response at time of discontinuation (n=21)†

- Partial response: n=7
- Stable disease: n=10
- Disease progression: n=4

Disease control‡ after discontinuation:

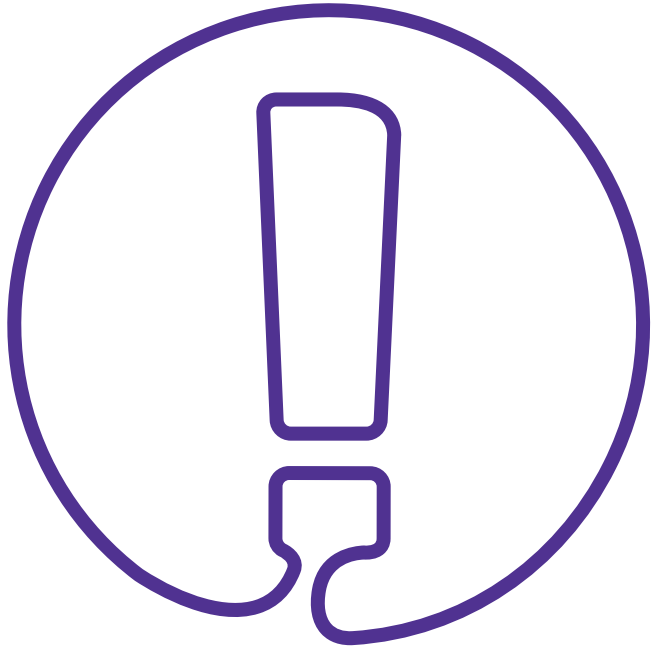
- 7 out of 10 patients at ≥6 weeks
- 4 out of 5 patients at ≥12 weeks
- 3 out of 3 patients at ≥18 weeks

*The following all-cause AEs each led to treatment discontinuation in one patient (0.4%): abdominal pain; acute myocardial infarction; acute respiratory failure; cardiac failure; cardiac tamponade; cardio-respiratory arrest; death; diarrhea; dysphagia; edema; electrolyte imbalance; embolism; face edema; headache; interstitial lung disease; localized edema; lung disorder; mental status changes; mucosal inflammation; nausea; neoplasm progression; pneumothorax; pulmonary embolism; pulmonary hemorrhage; respiratory tract infection; scrotal edema; spinal cord compression; and subdural hematoma; †Investigator-assessed response in patients with ≥1 tumor assessment; ‡Disease control defined as stable disease or better. AE, adverse event.

Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

TEPOTINIB SAFETY INFORMATION

Tepotinib warnings and precautions



- The pooled safety population described in the ‘warnings and precautions’ reflect **exposure to tepotinib in 448 patients with solid tumors** enrolled in five open-label, single-arm studies receiving single-agent tepotinib at a dosage of 450 mg once daily
- **This included 255 patients with NSCLC positive for *MET*ex14 skipping alterations who received tepotinib in VISION**
- Among 448 patients who received tepotinib, 32% were exposed for 6 months or longer and 12% were exposed for greater than 1 year

Warnings and precautions: Interstitial lung disease/pneumonitis, hepatotoxicity, and embryo-fetal toxicity.

MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last Accessed 23 March 2022. Please see Important Safety Information at www.TEPMETKO.com.

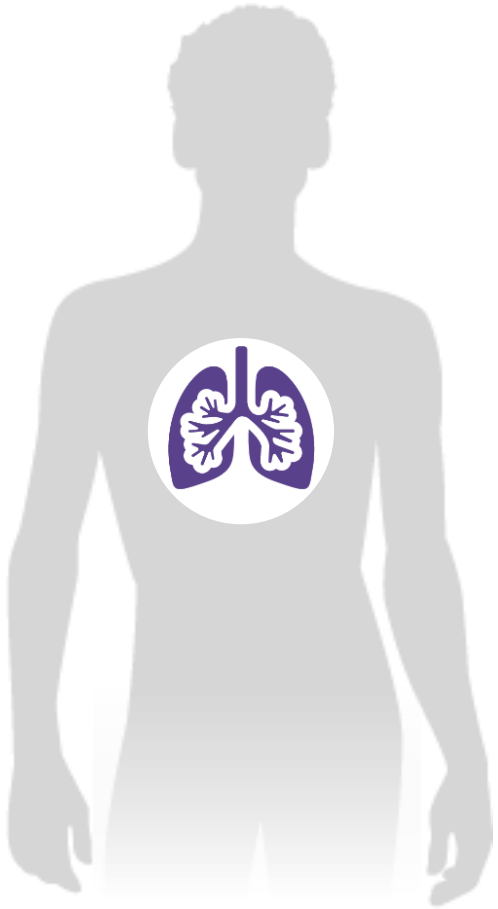
TEPOTINIB SAFETY INFORMATION

Interstitial lung disease/pneumonitis

ILD/pneumonitis, which can be fatal, occurred in patients treated with tepotinib

ILD/pneumonitis	
All grades	2.2%
Grade ≥3	1 case; this event resulted in death
Discontinuation of tepotinib due to ILD/pneumonitis	0.9% (n=4)

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever)



Recommended dose modifications for ILD/pneumonitis (any grade)

Immediately withhold tepotinib in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified

ILD, interstitial lung disease.

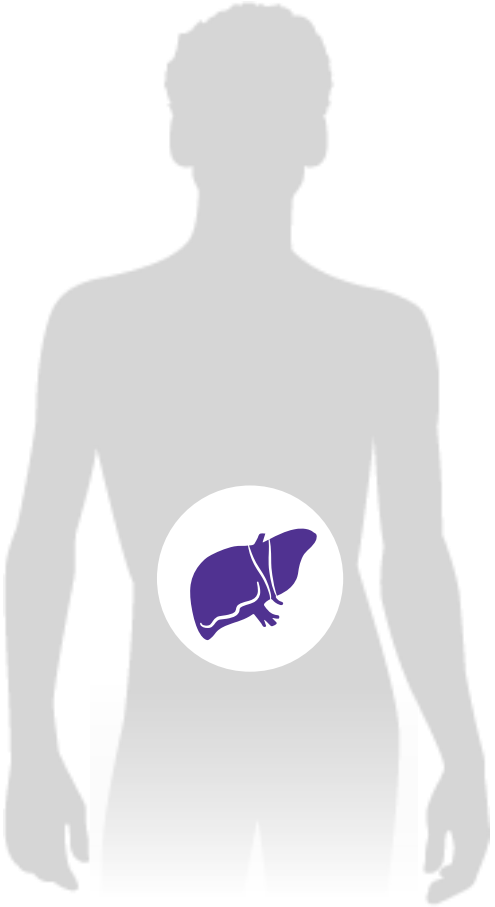
EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

TEPOTINIB SAFETY INFORMATION

Hepatotoxicity

Hepatotoxicity occurred in patients treated with tepotinib	
Increased ALT/AST All grades Grade 3 or 4	 13% 4.2%
Fatal adverse reaction of hepatic failure	0.2% (n=1)
Discontinuation of tepotinib due to increased ALT/AST	0.7% (n=3)
Median time to onset of Grade ≥3 increased ALT/AST	30 days (range 1–178)

Monitor liver function tests (including ALT, AST, and total bilirubin) before 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 bilirubin



Recommended dose modifications for hepatotoxicity

Based on the severity of the adverse reaction, withhold, reduce, or permanently discontinue tepotinib

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

TEPOTINIB SAFETY INFORMATION

Hepatotoxicity (continued)

Increased ALT and/or AST without increased total bilirubin

Grade 3

Increased total bilirubin without concurrent increased ALT and/or AST

Grade 3

Withhold tepotinib until recovery to baseline ALT/AST/bilirubin

If recovered to baseline within 7 days, then resume tepotinib at the same dose; otherwise resume tepotinib at a reduced dose

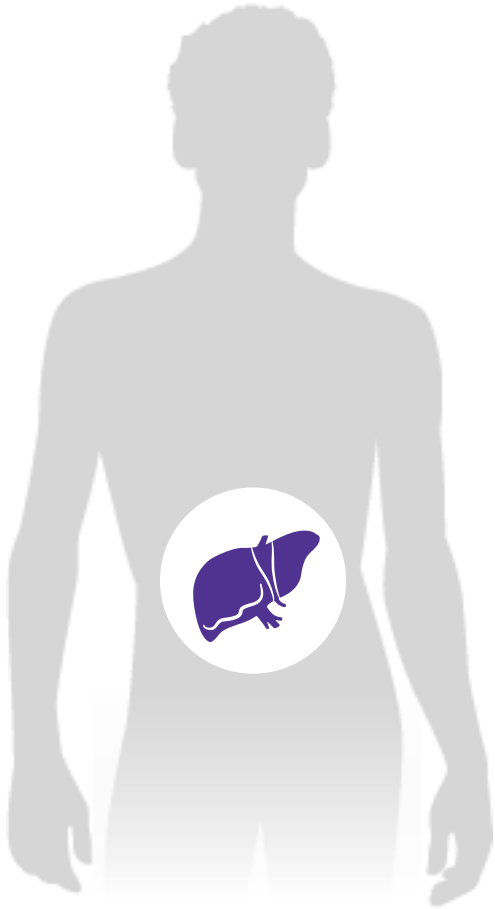
Grade 4

Grade 4

Permanently discontinue tepotinib

Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis

ALT and/or AST >3× ULN with total bilirubin >2× ULN



ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

TEPOTINIB SAFETY INFORMATION

Dose modifications for other adverse reactions

Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 4	Permanently discontinue tepotinib

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

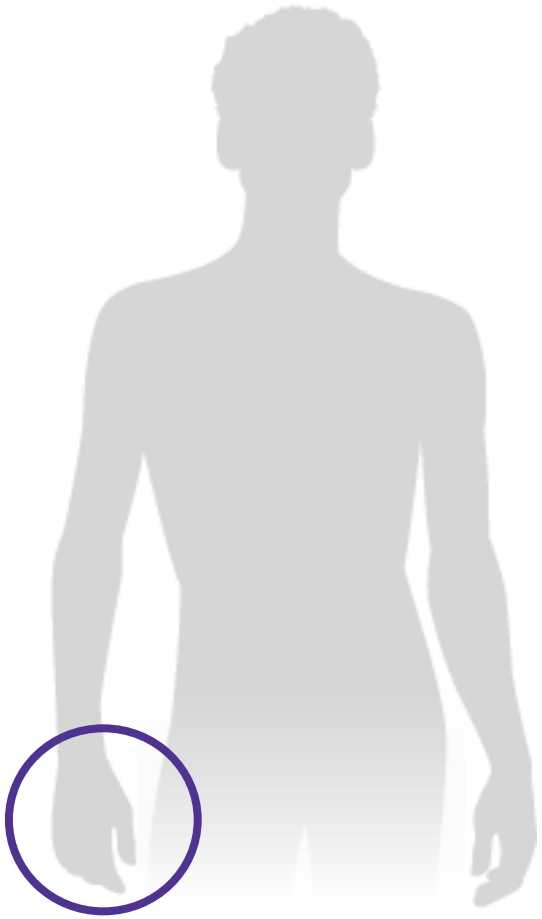
TEPOTINIB SAFETY INFORMATION

Edema

Edema (composite term)* was one of the most common ARs that occurred in patients treated with tepotinib

Edema	
Grades 1–4	70%
Grades 3–4	9%
Serious ARs in >2% of patients included edema	3.9%
Permanent discontinuation due to edema	5%
Dose interruption due to edema	23%
Dose reduction due to edema	19%

Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 4	Permanently discontinue tepotinib



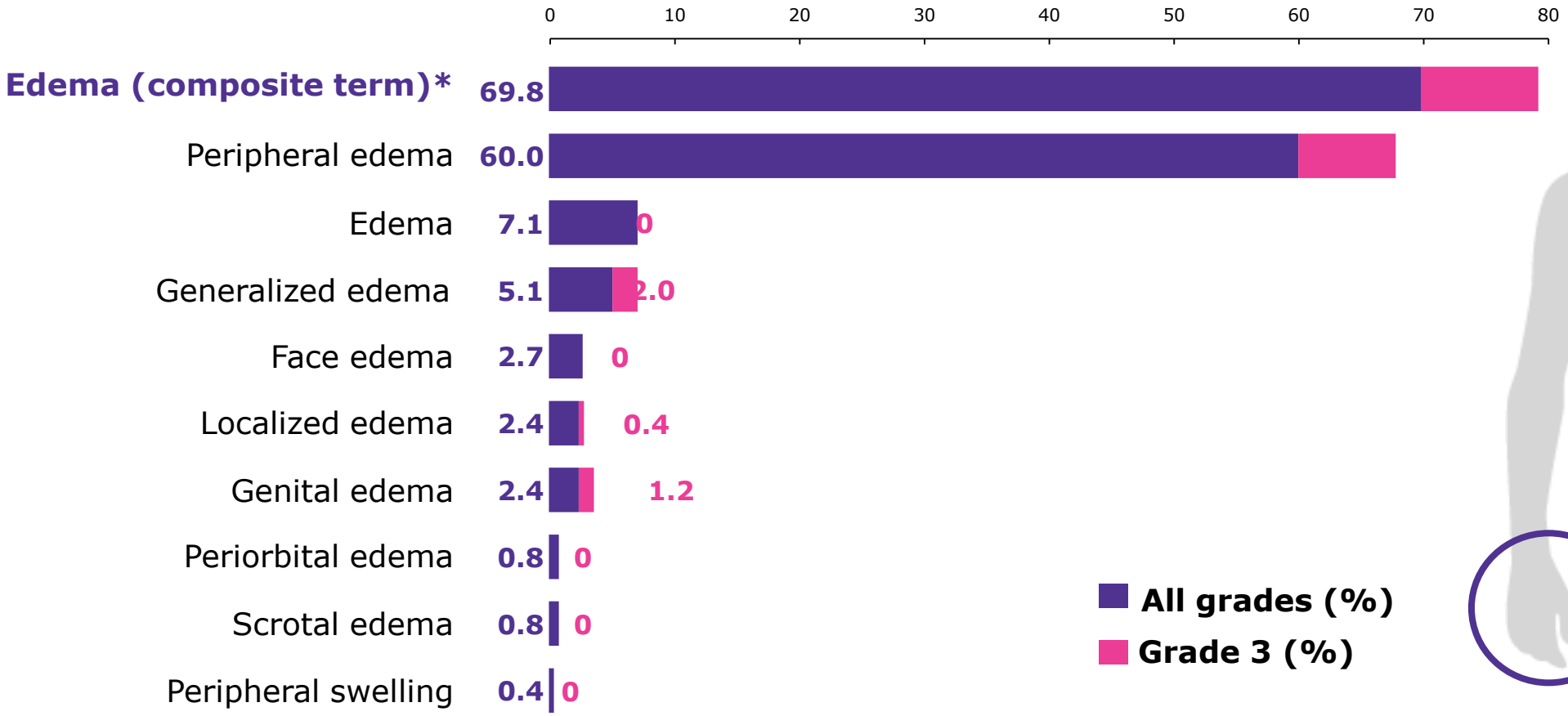
Data cut-off: July 01, 2020. *Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema. AR, adverse reaction.

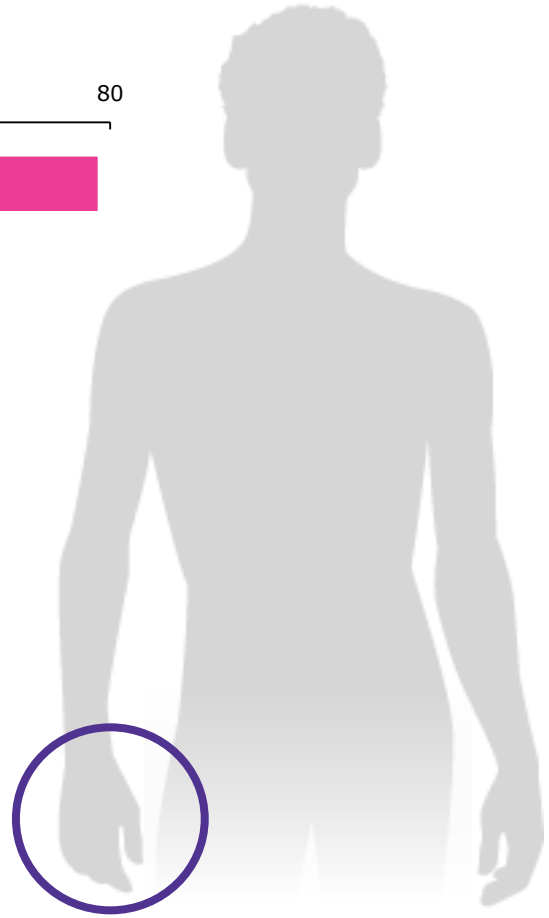
EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

TEPOTINIB SAFETY INFORMATION

Edema (continued)

All-cause incidence of edema





Data cut-off: July 01, 2020. No Grade 4 or 5 all-cause edema events (composite term) occurred. *Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema.

Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

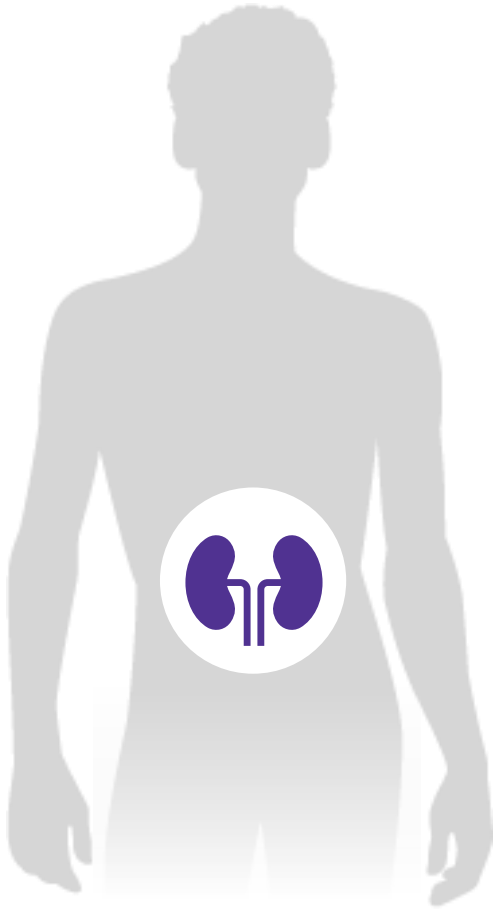
TEPOTINIB SAFETY INFORMATION

Increased creatinine[1]

A median increase in serum creatinine was reversible upon treatment completion*

Increased creatinine	
Grades 1–4	55%
Grades 3–4	0.4%
Hypercreatininemia[2]	
Grades 1–4	0.8%
Grades 3–4	0%
Permanent discontinuation of tepotinib due to increased blood creatinine[2]	0.8%
Dose interruption of tepotinib due to increased blood creatinine	6%
Dose reduction of tepotinib due to increased blood creatinine	2.7%

Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 4	Permanently discontinue tepotinib



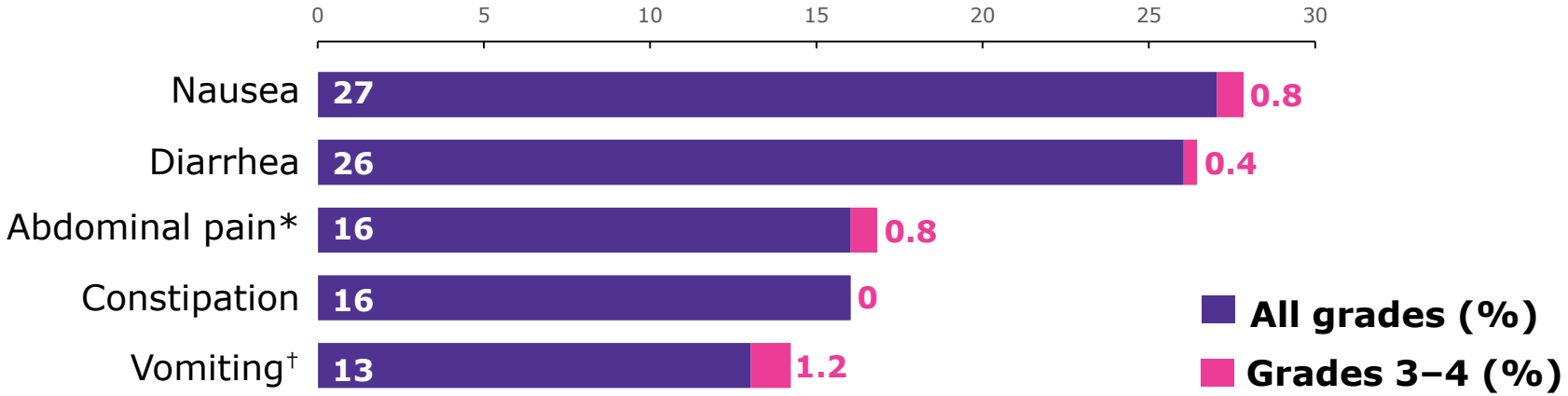
Data cut-off: July 01, 2020. *A median increase in serum creatinine of 31% was observed 21 days after tepotinib initiation. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion.

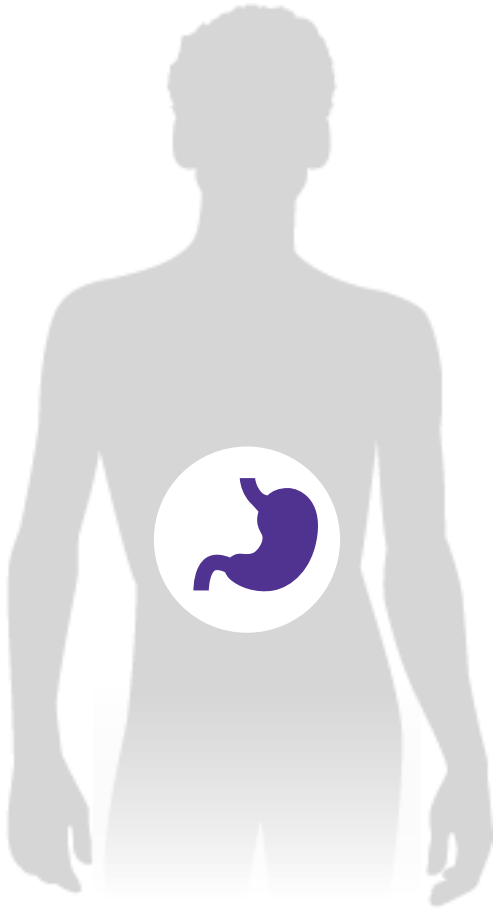
1. EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022; **2.** Veillon R, et al. *Lung Cancer.* 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

TEPOTINIB SAFETY INFORMATION

Gastrointestinal disorders

All-cause incidence of gastrointestinal adverse events





Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose
Grade 4	Permanently discontinue tepotinib

Data cut-off: July 01, 2020. *Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain; †Vomiting includes retching and vomiting.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Embryo-fetal toxicity and breastfeeding

- Based on findings from animal studies and its mechanism of action, tepotinib can cause fetal harm when administered to pregnant women
- Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at exposures less than the human exposure based on AUC at the 450 mg daily clinical dose
- 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

Additional information on use in specific populations

- Verify pregnancy status in females of reproductive potential before initiating tepotinib
- There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breastfed infants or on milk production
- Advise women not to breastfeed during treatment with tepotinib and for 1 week after the final dose

AUC, area under the curve.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Other populations

Population	Safety recommendation
Pediatric patients	The safety and efficacy of tepotinib in pediatric patients have not been established
Geriatric patients	Of 255 patients with *MET*ex14 skipping alterations in VISION who received 450 mg tepotinib once daily: • 79% were 65 years or older • 43% were 75 years or older No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients
Patients with renal impairment	No dosage modification is recommended in patients with mild or moderate renal impairment (CLcr 30–89 mL/min, estimated by Cockcroft–Gault) The recommended dosage has not been established for patients with severe renal impairment (CLcr <30 mL/min)
Patients with hepatic impairment	No dosage modification is recommended in patients with mild (Child–Pugh Class A) or moderate (Child–Pugh Class B) hepatic impairment The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child–Pugh Class C) have not been studied

CLcr, creatinine clearance; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

Tepotinib drug–drug interactions

Effects of other drugs on tepotinib:

- Avoid concomitant use of tepotinib with dual strong inhibitors of CYP3A and P-gp inhibitors
- Avoid concomitant use of tepotinib with strong CYP3A inducers

Effects of tepotinib on other drugs:

- 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

CYP, cytochrome P450; P-gp, P-glycoprotein.

EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022.

TEPOTINIB SAFETY INFORMATION

Conclusions

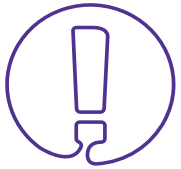
In VISION, comprising the largest population of patients with *MET*ex14 skipping NSCLC (N=255):

Most common AEs (≥20%) were **edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea**[1]

Consistent with previously reported results for tepotinib monotherapy,[2] **peripheral edema** was the most common TRAE, followed by **nausea, diarrhea, and blood creatinine increase**[3]

AEs of clinical interest included **edema, nausea, diarrhea, vomiting, and increased creatinine**[3]

Notable warnings and precautions for toxicities, and AR management guidance, from the prescribing information include:



The warnings and precautions for tepotinib include **ILD/pneumonitis, hepatotoxicity, and embryo-fetal toxicity**[1]

The recommended dose reduction of tepotinib for the management of ARs is **225 mg orally** once daily

- Management of some ARs may require temporary interruption or permanent discontinuation[1]

AE, adverse event; AR, adverse reaction; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; TRAE, treatment related adverse event.

1. EMD Serono. TEPMETKO® (tepotinib) Prescribing Information. Revised Feb 2021. Available at: https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf. Last accessed 23 March 2022; **2.** Paik PK, et al. *N Engl J Med*. 2020;383(10):931–943; **3.** Veillon R, et al. *Lung Cancer*. 2022; doi: 10.1016/j.cllc.2022.03.002 (epub ahead of print).

Glossary

AE = adverse event

AECI = adverse event of clinical interest

AKT = protein kinase B

ALK = anaplastic lymphoma kinase

ALT = alanine aminotransferase

ALP = alkaline phosphatase

AR = adverse reaction

AST = aspartate aminotransferase

ATP = adenosine triphosphate

AUC = area under the concentration-time curve

c-Cbl = Casitas B-lineage lymphoma

CLCr = creatinine clearance

CNS = central nervous system

CYP = cytochrome P450

ECOG = Eastern Cooperative Oncology Group

EGFR = epidermal growth factor receptor

ERK = extracellular regulatory kinase

GGT = gamma glutamyl transferase

GI = gastrointestinal

HGF = hepatocyte growth factor

HRQoL = health-related quality of life

ILD = interstitial lung disease

IO = immunotherapy

JAK = Janus kinase

MET = mesenchymal-epithelial transition

***MET*ex14** = *MET* exon 14

MOA = mechanism of action

NSCLC = non-small cell lung cancer

ORR = objective response rate

OS = overall survival

P-gp = P-glycoprotein

PI3K = phosphoinositide 3-kinase

PFS = progression-free survival

PS = performance status

RAS = RAS GTPase

RECIST = Response Evaluation Criteria in Solid Tumors

STAT = signal transducer and activator of transcription

SAE = serious adverse event

TRAE = treatment-related adverse event

ULN = upper limit of normal

wt = wild type