Retevmo®
selpercatinib capsules
40 mg • 80 mg

Retevmo

The First Precision Oncology Treatment Approved Specifically for Patients With Certain *RET*-Driven Cancers[1,2]

Retevmo was granted Accelerated Approval by the FDA[1]

RET IS ACTIONABLE WITH RETEVMO[1]

RET=rearranged during transfection.

INDICATIONS

Retevmo is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with:

- advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy
- advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION FOR RETEVMO (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

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Selective inhibition of RET marks an advancement in precision oncology

Much like what has been made possible for patients with *EGFR*, *ALK*, *ROS1*, *NTRK*, and *BRAF* alterations, Retevmo expands treatment options for patients with certain *RET*-driven cancers[1-4]

Retevmo Was Designed to Target Driver *RET* Fusions and Point Mutations, Which Promote Uncontrolled Cell Proliferation and Tumor Survival in the Following Tumor Types[1,2]:

***RET* Point Mutations[2]**

>60% sporadic MTC[2]

98% germline MTC[5]

***RET* Fusions**

10%–20% of PTC[6,7]

Different *RET* alterations drive different thyroid cancer tumor types[2]:

Point Mutations	Fusions
MTC *RET* point mutations may be present in other tumors but are believed to only drive MTC[8-10]	Thyroid cancers (other than MTC)[1,2,11] Papillary Poorly differentiated Anaplastic Hurthle cell

Retevmo may affect both healthy cells and tumor cells, which can result in side effects, some of which can be serious.[1]

RET DRIVER ALTERATIONS ARE PREDOMINANTLY MUTUALLY EXCLUSIVE FROM OTHER ONCOGENIC DRIVERS[2]

ALK=anaplastic lymphoma kinase; BRAF=v-raf murine sarcoma viral oncogene homolog B; EGFR=epidermal growth factor receptor; MTC=medullary thyroid cancer; NTRK=neurotrophic receptor tyrosine kinase; PTC=papillary thyroid cancer; ROS1=reactive oxygen species 1.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

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Retevmo was evaluated in the largest trial ever reported in patients with *RET*-driven cancer[1]

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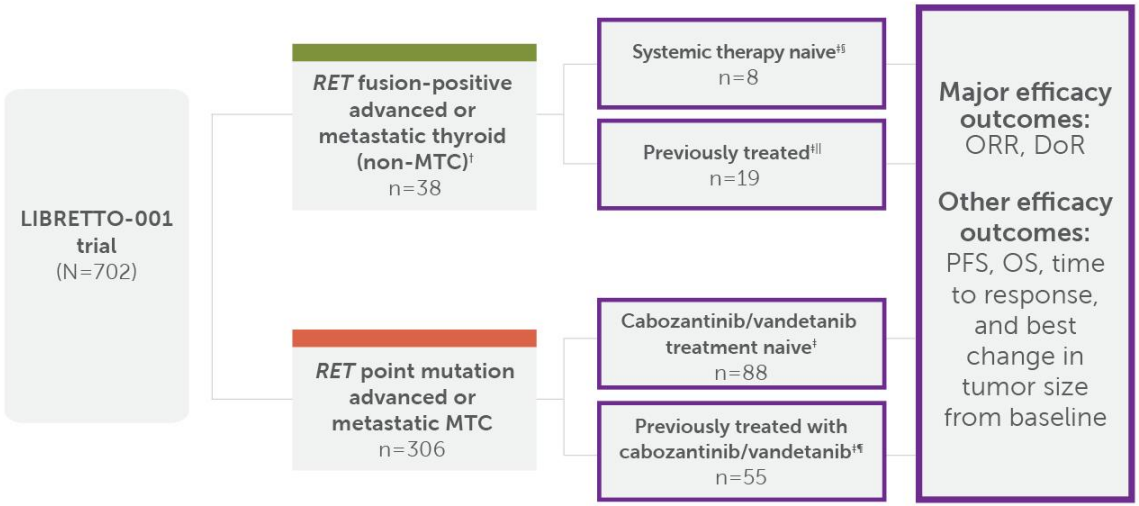
702 patients with certain *RET*-altered advanced solid tumors were included in LIBRETTO-001, an open-label, single-arm, multicenter, phase I/II, multicohort trial[1,12,13]*



Phase 1 dose escalation: Retevmo dosed at 20 mg QD–240 mg BID. Intra-patient dose escalation was allowed by protocol[14]

Phase 2 dose: Retevmo dosed at 160 mg BID[14]

See full Prescribing Information for dosing instructions.

Objective response rate (ORR) was defined as complete response (CR) + partial response (PR) and was assessed by independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[1]

*Patients with *RET*-mutant NSCLC and *RET*-mutant thyroid cancer (non-medullary thyroid cancer (non-MTC)) were not enrolled in the trial since *RET* is not the driver of tumor growth in these cancers.[1,8]

†Non-medullary thyroid cancers (non-MTC) by histology included papillary (n=31), poorly differentiated (n=4), anaplastic (n=2), and Hurthle cell (n=1).[1,13]

‡Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.[1]

§Patients in this cohort received no prior systemic therapy other than radioactive iodine (RAI).[1]

‖Patients in this cohort received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.[1]

¶The efficacy of Retevmo was evaluated in 55 patients with *RET*-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.[1]

BID=twice daily; DoR=duration of response; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; QD=once daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

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Patients in the trial reflected those seen in clinical practice[1]

The trial included treatment-naive and heavily pretreated patients[1]*

Patient Characteristics[13,15]	*RET* Point Mutation		*RET* Fusion-Positive	
	MTC (n=143)		Thyroid (Non-MTC)† (n=27)	
	Cabozantinib/ Vandetanib Naive (n=88)	Previously Treated‡ (n=55)	Systemic Therapy Naive§ (n=8)	Previously Treated‖ (n=19)
Female/Male, n	30/58	19/36	3/5	10/9
Age, Years				
Median	58	57	57	54
Range	15-82	17-84	20-72	25-88
ECOG PS, n				
0	43	11	3	5
1	42	41	4	12
2	3	3	1	2
Prior Systemic Regimens				
Median	0	2	2	4
Range	0-2	1-8¶	1-4	1-7
Brain Metastases, n	2	4	1	6

*Systemic therapy-naive patients with advanced or metastatic *RET* fusion-positive thyroid cancer (non-MTC) received no prior systemic therapy other than RAI. Previously treated patients with advanced or metastatic *RET* fusion-positive thyroid cancer (non-MTC) had a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI. 55 of the 143 patients with advanced or metastatic *RET*-mutant MTC had previously taken cabozantinib and/or vandetanib, as well as at least 1 multikinase inhibitor (MKI).[1,15]

†Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.[1]

‡The efficacy of Retevmo was evaluated in 55 patients with *RET*-mutant advanced or metastatic MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.[1]

§Patients received no prior systemic therapy other than RAI.[1]

‖Patients received a prior systemic therapy other than RAI.[1]

¶Prior cabozantinib/vandetanib: received either, n=31; received both, n=24. Prior MKI: received 1, n=32; received ≥2, n=30.[15]

ECOG=Eastern Cooperative Oncology Group; PS=performance status.

IMPORTANT SAFETY INFORMATION (CONT'D)

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

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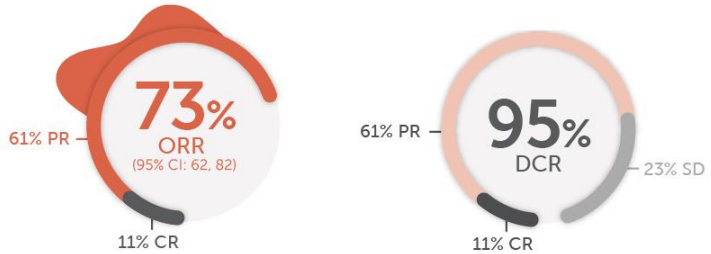
Response in patients with advanced or metastatic *RET*-mutant MTC[1]

***RET*-Mutant MTC[1,16]**

Cabozantinib/vandetanib-naive patients (n=88)



***RET*-Mutant MTC[1,16]**

Previously treated* patients (n=55)

The major efficacy outcome measures in LIBRETTO-001 were ORR and DoR. Disease control rate (DCR) was not a prespecified endpoint and is a post-hoc calculation. DCR is defined as ORR (CR + PR) + SD.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), per RECIST v1.1. In the setting of a single-arm trial without the ability to compare with a control arm provided by a randomized trial, the interpretation and clinical relevance of a best overall response of SD are not clear, and it is not possible to determine if SD is a result of natural disease progression or treatment with Retevmo.[1,17]

All results reviewed by an IRC.[16]

Due to rounding, numbers presented may not add up to the totals indicated and percentages may not reflect the absolute figures for the same reason.

*The efficacy of Retevmo was evaluated in 55 patients with *RET*-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.[1]

CI=confidence interval.

IMPORTANT SAFETY INFORMATION (CONT'D)

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

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Additional results in patients with advanced or metastatic *RET*-mutant MTC[1]

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Cabozantinib/vandetanib naive[1,18]

Median DoR: 22.0 months

(95% CI: NE, NE) (n=88) Median follow-up: 7.8 months

Previously treated[1,18]*

Median DoR not yet reached

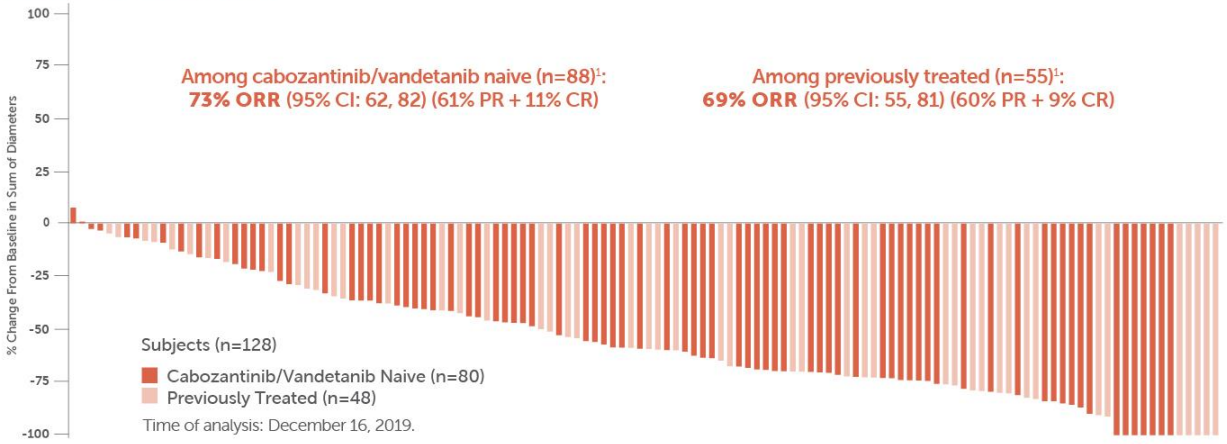
(95% CI: 19.1, NE) (n=55) Median follow-up: 14.1 months

Best Change in Tumor Size From Baseline in Cabozantinib/Vandetanib-Naive and Previously Treated* Patients (n=128†) While Receiving Retevmo[16]

The major efficacy outcome measures in LIBRETTO-001 were ORR and DoR. ORR was defined as CR (disappearance of all target lesions) + PR (≥30% decrease in the sum of target lesions) and was assessed by IRC according to RECIST v1.1. Number of cabozantinib/vandetanib-naive patients with CR, n=9; PR, n=54; SD, n=16; PD, n=1; was not evaluable, n=0. Number of previously treated patients with CR, n=2; PR, n=33; SD, n=12; PD, n=1; was not evaluable, n=0.[1,16,17]

Best change in tumor size from baseline was a prespecified secondary endpoint and was defined as the maximum decrease from baseline in the sum of longest diameters of target lesions. Clinical meaningfulness of best change in tumor size is not established. Demonstrated change in tumor size may not reflect a confirmed response (eg, CR, PR, SD, PD) and may not account for new lesions per standard response criteria. Additional criteria apply in the determination of an individual patient's overall response (per RECIST criteria), including growth of non-target lesions and the presence of new lesions.[16]

All results reviewed by an IRC.[1,16,18]



Four cabozantinib/vandetanib-naive patients and 4 previously treated patients had 100% reduction in target lesion size with an overall response of PR, each due to non-target lesions still being present.[16]

*The efficacy of Retevmo was evaluated in 55 patients with *RET*-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.[1]

†Fifteen subjects are not shown: 2 discontinued prior to any post-baseline imaging assessments, 6 subjects had non-target lesions only, 5 did not have targetable lesions at baseline, and 2 did not have post-baseline target lesion measurement.[16]

NE=not estimable.

IMPORTANT SAFETY INFORMATION (CONT'D)

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

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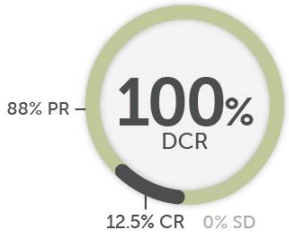
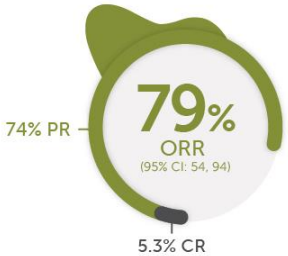
Response in patients with advanced or metastatic *RET* fusion-positive thyroid cancer (non-MTC)[1]

***RET* Fusion-Positive Thyroid Cancer (Non-MTC)[1,19]**
Systemic therapy-naive* patients (n=8)



***RET* Fusion-Positive Thyroid Cancer (Non-MTC)[1,19]**
Previously treated† patients (n=19)



The major efficacy outcome measures in LIBRETTO-001 were ORR and DoR. DCR was not a prespecified endpoint and is a post-hoc calculation. DCR is defined as ORR (CR + PR) + SD.

SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, per RECIST v1.1. In the setting of a single-arm trial without the ability to compare with a control arm provided by a randomized trial, the interpretation and clinical relevance of a best overall response of SD are not clear, and it is not possible to determine if SD is a result of natural disease progression or treatment with Retevmo.[1,17]

All results reviewed by an IRC.[19]

Due to rounding, numbers presented may not add up to the totals indicated and percentages may not reflect the absolute figures for the same reason.

RETEVMO WAS STUDIED ACROSS MULTIPLE HISTOLOGIC TYPES OF ADVANCED OR METASTATIC *RET* FUSION-POSITIVE THYROID CANCER (NON-MTC) (INCLUDING PAPILLARY, POORLY DIFFERENTIATED, HURTHLE CELL, AND ANAPLASTIC CANCERS), IN BOTH SYSTEMIC THERAPY-NAIVE* AND PREVIOUSLY TREATED† PATIENTS[1]

*Patients received no prior systemic therapy other than RAI.[1]
†Patients received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

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Additional results in patients with advanced or metastatic *RET* fusion-positive thyroid cancer (non-MTC)[1]

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Systemic therapy naive[1,18]

Median DoR not yet reached

(95% CI: NE, NE) (n=8) Median follow-up: 8.8 months

Previously treated[1,18]

Median DoR: 18.4 months

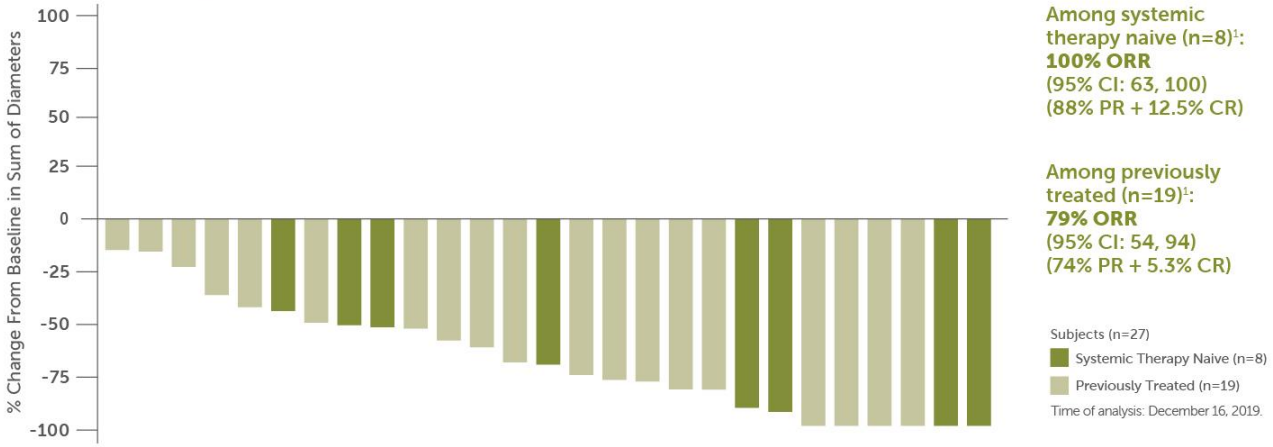
(95% CI: 7.6, NE) (n=19) Median follow-up: 17.5 months

Best Change in Tumor Size From Baseline in Systemic Therapy-Naive and Previously Treated Patients (n=27) While Receiving Retevmo[19]

The major efficacy outcome measures in LIBRETTO-001 were ORR and DoR. ORR was defined as CR (disappearance of all target lesions) + PR (≥30% decrease in the sum of target lesions) and was assessed by IRC according to RECIST v1.1. Number of systemic therapy-naive patients with CR, n=1; PR, n=7; SD, n=0; PD, n=0; was not evaluable, n=0. Number of previously treated patients with CR, n=1; PR, n=14; SD, n=4; PD, n=0; was not evaluable, n=0.[1,17,19]

Best change in tumor size from baseline was a prespecified secondary endpoint and was defined as the maximum decrease from baseline in the sum of longest diameters of target lesions. Clinical meaningfulness of best change in tumor size is not established. Demonstrated change in tumor size may not reflect a confirmed response (eg, CR, PR, SD, PD) and may not account for new lesions per standard response criteria. Additional criteria apply in the determination of an individual patient's overall response (per RECIST criteria), including growth of non-target lesions and the presence of new lesions.[19]

All results reviewed by an IRC.[1,18,19]



One systemic therapy-naive patient and 3 previously treated patients had a 100% reduction in target lesion size with an overall response of PR, each due to non-target lesions still being present.[19]

IMPORTANT SAFETY INFORMATION (CONT'D)

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

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REFERENCES

Retevmo safety and tolerability evaluated in 702 patients[1]

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Adverse Reactions (ARs) Occurring in ≥15% of Patients Treated With Retevmo[1,20]

Adverse Reaction*	Retevmo (N=702)				
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grades 1-4 (%)
Gastrointestinal					
Dry Mouth	34	4.4	0	0	39
Diarrhea	25	8	3.4	0	37
Constipation	20	4.4	0.6	0	25
Nausea	18	4.3	0.6	0	23
Abdominal Pain	16	5	1.8	0	23
Vomiting	12	3.3	0.3	0	15
Vascular					
Hypertension	4	13	17	0.1	35
General					
Fatigue	21	14	1.9	0	35
Edema	34	5	0.3	0	35
Skin					
Rash	13	3.7	0.4	0	27
Nervous System					
Headache	18	3.8	1.4	0	23
Respiratory†					
Cough	15	3.5	0	0	18
Dyspnea	11	3	2	0.3	16
Investigations					
QT Prolongation	6	7	3.7	0.3	17
Blood and Lymphatic System					
Hemorrhage	14	1.9	1.3	0.1	15

5% (n=37) of patients discontinued Retevmo (N=702) due to adverse reactions; 2% (n=14) were considered treatment-related, as assessed by trial investigator. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).[1,21]

Due to rounding and potential double-counting of patients, percentages presented may not add up to the indicated totals.

*Diarrhea, abdominal pain, fatigue, edema, rash, headache, cough, dyspnea, and hemorrhage are consolidated terms. See full Prescribing Information for list of consolidated terms.

†In the LIBRETTO-001 trial, 1% of patients experienced Grade 1/2 pneumonitis/interstitial lung disease (ILD); no patients experienced Grade 3/4 or fatal pneumonitis/ILD.[20]

Laboratory Abnormalities Occurring in ≥20% of Patients Treated With Retevmo[1,20]

Laboratory Abnormality	Retevmo‡				
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grades 1-4 (%)
Chemistry					
AST Increased	37	6	7	0.7	51
ALT Increased	30	6	8	1	45
Glucose Increased	30	12	1.7	0.4	44
Albumin Decreased	30	12	0.7	0	42
Calcium Decreased	25	12	3	0.7	41
Creatinine Increased	18	19	0.6	0.4	37
Alkaline Phosphatase Increased	26	8	2.2	0.1	36
Total Cholesterol Increased	26	4.3	0	0.1	31
Sodium Decreased	20	0	7	0.7	27
Magnesium Decreased	22	1.7	0.3	0.3	24
Potassium Increased	18	4.6	0.7	0.4	24
Total Bilirubin Increased	14	7	2	0	23
Glucose Decreased	15	6	0.4	0.3	22
Hematology					
Leukocytes Decreased	27	14	1.3	0.3	43
Platelets Decreased	27	3.2	1.4	1.3	33

- Dose interruptions and dose reductions due to ARs occurred in 42% and 31% of patients who received Retevmo, respectively.[1]
- ARs requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.[1]
- ARs requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.[1]

See full Prescribing Information for dose modifications.

‡Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.[1]
ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

IMPORTANT SAFETY INFORMATION

REFERENCES

Retevmo recommended dosing and administration[1]

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Patient selection for treatment with Retevmo should be based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) or specific *RET* gene mutation (MTC) in tumor specimens or plasma. An FDA-approved test for the detection of *RET* gene fusions and *RET* mutations is not currently available for Retevmo.[1]

The recommended dosage of Retevmo is based on body weight. Patients less than 50 kg should receive 120 mg. Patients 50 kg or greater should receive 160 mg. Take Retevmo orally (PO) BID (approximately every 12 hours) until disease progression or unacceptable toxicity.[1]

Doses should be separated by approximately 12 hours.

Doses may be taken with or without food. When coadministered with a proton pump inhibitor (PPI), take with food.

Capsules should be swallowed whole. Do not crush or chew.

Do not make up a missed dose within 6 hours of the next scheduled dose.

If vomiting occurs after Retevmo administration, do not administer an additional dose, and continue to the next scheduled time for the next dose.

Recommended Retevmo Dose Reductions due to ARs[1]

Dose Reduction	Patients Weighing Less than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg PO BID	120 mg PO BID
Second	40 mg PO BID	80 mg PO BID
Third	40 mg PO QD	40 mg PO BID

Permanently discontinue Retevmo in patients unable to tolerate 3 dose reductions.[1]

See next screen for additional dose modifications.

IMPORTANT SAFETY INFORMATION (CONT'D)

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Dose modifications/reductions for ARs and concomitant use of select therapies[1]

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Adverse Reaction	Dosage Modification
Hepatotoxicity (Grade 3 or 4)	• Withhold Retevmo and monitor AST/ALT once weekly until resolution to Grade 1 or to baseline • Resume at a reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence
Hypertension (Grade 3)	• Withhold Retevmo for Grade 3 hypertension that persists despite optimal antihypertensive therapy • Resume at a reduced dose when hypertension is controlled
Hypertension (Grade 4)	• Discontinue Retevmo
QT Interval Prolongation (Grade 3)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose
QT Interval Prolongation (Grade 4)	• Discontinue Retevmo
Hemorrhagic Events (Grade 3 or 4)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Discontinue Retevmo for severe or life-threatening hemorrhagic events
Hypersensitivity Reactions (All Grades)	• Withhold Retevmo until resolution of the event. Initiate corticosteroids • Resume at a reduced dose by 3 dose levels while continuing corticosteroids • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids
Other Adverse Reactions (Grade 3 or 4)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose

Dose Management for Concomitant Use		
Strong and Moderate CYP3A Inhibitors	• Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo • If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the Retevmo dosage	• If concomitant use of strong CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 80 mg and 40 mg BID, respectively • If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 120 mg and 80 mg BID, respectively
Acid-Reducing Agents	• Avoid concomitant use of PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with Retevmo	If concomitant use cannot be avoided: - Take Retevmo with food when coadministered with a PPI - Take Retevmo 2 hours before or 10 hours after administration of an H2 receptor antagonist - Take Retevmo 2 hours before or 2 hours after administration of a locally-acting antacid

Reduce the recommended dosage of Retevmo for patients with severe hepatic impairment to 80 mg orally twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

IMPORTANT SAFETY INFORMATION

REFERENCES

Test the tumor tissue to identify *RET* alterations in thyroid cancers[2]

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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend molecular testing for *RET* fusions and *RET* point mutations for certain patients with advanced or metastatic thyroid carcinomas.[22]

RET fusions drive: 10%–20% of PTC[6,7]

Test for *RET* fusions in thyroid cancer other than MTC[2]

- NGS
- FISH
- Reverse transcription PCR

RET point mutations drive: >60% sporadic MTC[2] 98% germline MTC[5]

Test for *RET* point mutations in MTC[2,23-25]

- NGS
- Quantitative PCR (qPCR)
- Sanger sequencing

Other Thyroid Cancer Testing Considerations

- Molecular testing of tumor tissue is preferred for the detection of *RET* alterations[2,26]
  - When tissue for molecular profiling is insufficient or unavailable, consider liquid biopsy[27]
- IHC is not recommended for detecting *RET* alterations due to low sensitivity and variable specificity[4,28]

TEST THE TISSUE: ORDER MOLECULAR TESTING OF TUMOR TISSUE TO IDENTIFY *RET* ALTERATIONS[2]

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FISH=fluorescence *in situ* hybridization; IHC=immunohistochemistry; NGS=next-generation sequencing; PCR=polymerase chain reaction.

IMPORTANT SAFETY INFORMATION (CONT'D)

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

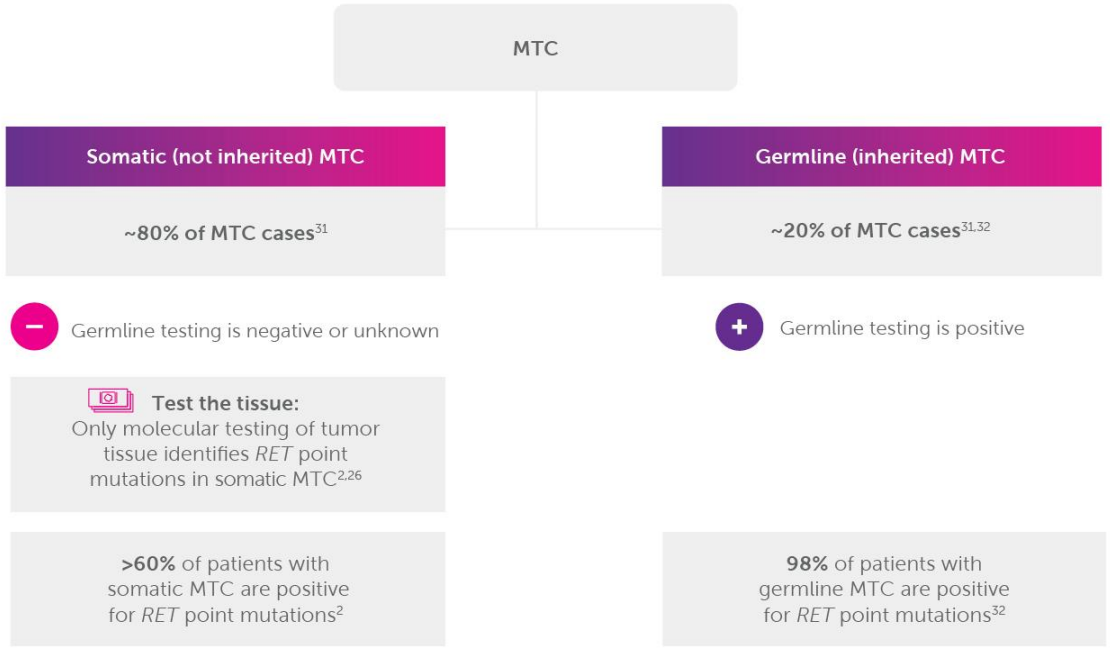
Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

IMPORTANT SAFETY INFORMATION

REFERENCES

Understanding the importance of testing tumor tissue in MTC

When germline testing is negative or unknown in MTC, the tumor should be tested for somatic *RET* point mutations[29,30]



WHILE GERMLINE TESTING IN MTC IS WELL-ESTABLISHED, THE MAJORITY OF CASES ARE NOT INHERITED, HIGHLIGHTING THE IMPORTANCE OF TESTING THE TUMOR TISSUE TO IDENTIFY SOMATIC *RET* POINT MUTATIONS[31,32]

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IMPORTANT SAFETY INFORMATION (CONT'D)

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

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Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

IMPORTANT SAFETY INFORMATION

REFERENCES

Indications & Important Safety Information

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INDICATIONS

Retevmo is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with:

- advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy
- advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

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Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

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Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

Please see full Prescribing Information for Retevmo.

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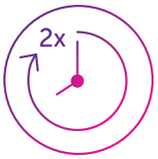
Retevmo Dosing and Support Guide

Take advantage of the first precision therapy for certain *RET*-driven cancers

Retevmo®
selpercatinib capsules
40 mg • 80 mg

Patient selection for treatment with Retevmo should be based on the presence of a *RET* gene fusion (non-small cell lung cancer (NSCLC) or thyroid cancer) or specific *RET* gene mutation (medullary thyroid cancer (MTC)) in tumor specimens or plasma. An FDA-approved test for the detection of *RET* gene fusions and *RET* mutations is not currently available for Retevmo.[1]

The recommended dosage of Retevmo is based on body weight. Patients less than 50 kg should receive 120 mg. Patients 50 kg or greater should receive 160 mg. Take Retevmo orally (PO) twice daily (BID) (approximately every 12 hours) until disease progression or unacceptable toxicity.[1]



- Doses should be separated by approximately 12 hours

- Doses may be taken with or without food. When coadministered with a proton pump inhibitor (PPI), take with food

- Capsules should be swallowed whole. Do not crush or chew

- Do not make up a missed dose within 6 hours of the next scheduled dose

- If vomiting occurs after Retevmo administration, do not administer an additional dose, and continue to the next scheduled time for the next dose

Recommended Retevmo Dose Reductions for Adverse Reactions (ARs)[1]

Dose Reduction	Patients Less than 50 kg	Patients 50 kg or Greater
First	80 mg PO BID	120 mg PO BID
Second	40 mg PO BID	80 mg PO BID
Third	40 mg PO QD	40 mg PO BID

Permanently discontinue Retevmo in patients unable to tolerate 3 dose reductions.[1]

INDICATIONS

Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

QD=once daily; RET=rearranged during transfection.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

Dose modifications/reductions for ARs and concomitant use of select therapies[1]

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Adverse Reaction	Dosage Modification
Hepatotoxicity (Grade 3 or 4)	• Withhold Retevmo and monitor AST/ALT once weekly until resolution to Grade 1 or to baseline • Resume at a reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence
Hypertension (Grade 3)	• Withhold Retevmo for Grade 3 hypertension that persists despite optimal antihypertensive therapy • Resume at a reduced dose when hypertension is controlled
Hypertension (Grade 4)	• Discontinue Retevmo
QT Interval Prolongation (Grade 3)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose
QT Interval Prolongation (Grade 4)	• Discontinue Retevmo
Hemorrhagic Events (Grade 3 or 4)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Discontinue Retevmo for severe or life-threatening hemorrhagic events
Hypersensitivity Reactions (All Grades)	• Withhold Retevmo until resolution of the event. Initiate corticosteroids • Resume at a reduced dose by 3 dose levels while continuing corticosteroids • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids
Other Adverse Reactions (Grade 3 or 4)	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose

Dose Management for Concomitant Use		
Strong and Moderate CYP3A Inhibitors	• Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo • If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the Retevmo dosage	• If concomitant use of strong CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 80 mg and 40 mg BID, respectively • If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 120 mg and 80 mg BID, respectively
Acid-Reducing Agents	• Avoid concomitant use of PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with Retevmo	• If concomitant use cannot be avoided: - Take Retevmo with food when coadministered with a PPI - Take Retevmo 2 hours before or 10 hours after administration of an H2 receptor antagonist - Take Retevmo 2 hours before or 2 hours after administration of a locally-acting antacid

Reduce the recommended dosage of Retevmo for patients with severe hepatic impairment to 80 mg PO BID.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

Monitoring patient response to Retevmo

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selpercatinib capsules
40 mg • 80 mg

Monitoring	
Clinical Assessment	Laboratory and other clinical tests may be ordered more frequently at the discretion of the provider or according to institutional standards. • **Hepatotoxicity:** Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. • **Hypertension:** Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. • **QT interval prolongation:** - Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. - Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. • **Assess patients for the following:** - **Hemorrhagic events** - **Hypersensitivity reactions** - **Risk of impaired wound healing** - **Embryo-fetal toxicity** • **Potential consideration:** Consider alternative markers of renal function if persistent elevations in serum creatinine are observed. Serum creatinine increased 18% after 10 days in healthy volunteers given Retevmo 160 mg BID.
Treatment Parameters	Labs and clinical assessments should be monitored to evaluate treatment, toxicity and for dose modifications at the discretion of the treating provider. • **Hepatotoxicity:** Withhold, reduce dose, or permanently discontinue Retevmo based on the severity of ALT/AST increase. • **Hypertension:** Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity. • **QT interval prolongation:** Withhold and dose reduce or permanently discontinue Retevmo based on the severity. • **Hemorrhagic events:** Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage. • **Hypersensitivity:** If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity [see Dosage and Administration (2.5)]. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity. • **Risk of impaired wound healing:** Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established. • **Embryo-fetal toxicity:** Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose.

IMPORTANT SAFETY INFORMATION (CONT'D)

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

Retevmo capsule strength and dosing regimen: 30 day supply

Retevmo®
selpercatinib capsules
40 mg • 80 mg

Available as 80-mg and 40-mg capsules

Target Dose	Dosage Modification: Patient Weight 50 kg or Greater	Dosage Modification: Patient Weight Less than 50 kg	How Dispensed	How Supplied (NDC #)
160 mg PO BID	Standard Dose	-	Two (2) 80-mg capsules BID	0002-2980-26*
120 mg PO BID	First Dose Reduction	Standard Dose	Three (3) 40-mg capsules BID	0002-3977-60†
80 mg PO BID	Second Dose Reduction	First Dose Reduction	One (1) 80-mg capsule BID	0002-2980-60
40 mg PO BID	Third Dose Reduction	Second Dose Reduction	One (1) 40-mg capsule BID	0002-3977-60
40 mg PO QD	-	Third Dose Reduction	One (1) 40-mg capsule QD	0002-3977-60‡

*For 160-mg oral BID dosing, dispensing one (1) 80-mg #120 count bottle will provide a 30 day supply.
†For 120-mg oral BID dosing, dispensing three (3) 40-mg #60 count bottles will provide a 30 day supply.
‡For 40-mg capsule QD dosing, dispensing a 40-mg #60 count bottle will provide a 60 day supply.

NDC=National Drug Code.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

MyRightDose: Helping your patients continue their Retevmo treatment journey without delays or additional co-pays

Retevmo®
selpercatinib capsules
40 mg • 80 mg

Eligibility Requirements

To be eligible for the MyRightDose program, a patient must:

- Return unused pills in the provided pre-addressed envelope and according to the instructions provided by MyRightDose
- Be 18 years of age or older
- Be a resident of the United States or Puerto Rico
- Be prescribed Retevmo for an FDA-approved indication

Please note: To provide their dose at no charge, this program is dispensed by Sonexus rather than your in-office dispensary or the specialty pharmacy that is currently dispensing your patient's prescription. Retevmo can be shipped to the patient as early as 48 hours after the receipt of this form. We will contact your office as soon as the patient has received their new dose so you can begin the process of starting the next month's script.

Terms and Conditions

- The MyRightDose Program is available at no charge to a patient prescribed Retevmo for an FDA-approved indication for up to three separate dose exchanges in a 12-month period. The quantity to be exchanged should be between 5 and 30 days per exchange
- Neither the prescriber, prescriber's institution, pharmacy, pharmacist, or any other person, including the patient, may seek payment or accept reimbursement from any patient, any third-party payer, including any state or federal entity or any private or other insurance plan, or from any other person or entity, for Retevmo supplied under this program, regardless of whether the payer subsequently determines it will cover the product
- Product provided pursuant to this program may not be sold, traded, or distributed for sale
- If a patient is enrolled in a Medicare Part D plan, the prescriber must notify the patient that they must not attempt to have this prescription or any costs associated with it counted as any portion of true out-of-pocket ("TrOOP") cost for prescription drug calculations
- No purchase contingency or other obligation accompanies program participation
- Lilly reserves the right to change or end the program at any time without notice. Benefits provided under the program are not transferable

IMPORTANT SAFETY INFORMATION (CONT'D)

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

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Reference: 1. Retevmo (selpercatinib) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2021.

Savings & Support

Support tailored to your eligible patient's Retevmo treatment journey*

Retevmo®
selpercatinib capsules
40 mg • 80 mg

Savings Card

Eligible commercially insured covered patients pay as little as $0 a month*

Digital cards can be downloaded online. You and your patients can get a savings card by visiting Retevmo.com.*†

Interim Access Program

The Retevmo Interim Access Program may provide a temporary supply of Retevmo at no cost to insured, eligible patients who have been prescribed Retevmo for the first time and are experiencing a delay in their insurance coverage decision‡

Insurance and Coverage Assistance*

May help eligible patients minimize co-pay or out-of-pocket costs by providing:

- A benefits investigation
- Guidance through the specialty pharmacy process
- Identification of savings opportunities

Ongoing Support*

Dedicated support staff: patients speak to the same person every time

The Companion in Care™ can help eligible patients by:

- Providing emotional support when patients need it
- Reiterating treatment information when taking Retevmo

The Companion in Care™ does not replace a trained healthcare provider; when medical questions arise, your patients will always be directed back to your office.

To enroll your eligible patients in all or any of these support offerings,* please visit **Retevmo.com**, or call the Lilly Oncology Support Center at **1-866-472-8663**, Monday-Friday, 8 AM-10 PM ET.

*Retevmo Support programs and offerings are not a guarantee of coverage. Terms and conditions apply for all programs. See enrollment form for details.

Terms and Conditions: †Offer good for up to 12 months until 12/31/2020. Patients must have coverage for Retevmo through their commercial drug insurance to pay as little as $0 for a 30-day supply of Retevmo, subject to a monthly cap of wholesale acquisition cost plus usual and customary pharmacy charges and a separate $25,000 maximum annual cap. Participation in the program requires a valid patient HIPAA authorization. Patient is responsible for any applicable taxes, fees, or amounts exceeding monthly or annual caps. **This offer is invalid for patients without commercial drug insurance or those whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program, including, without limitation, Medicaid, Medicare, Medicare Part D, Medigap, DoD, VA, TRICARE®/CHAMPUS, or any state patient or pharmaceutical assistance program.** Offer void where prohibited by law and subject to change or discontinue without notice. Card activation is required. Subject to additional terms and conditions, which can be found at Retevmo.com.

‡The Retevmo Interim Access Program (or "Program") provides a 15-day supply of Retevmo at no charge for eligible, insured patients who are: 1) prescribed Retevmo for the first time after testing positive for a *RET* alteration, 2) experiencing a minimum 5-business-day delay in insurance coverage determination, 3) prescribed Retevmo for an FDA-approved indication or an indication medically supported by CMS-recognized compendia, 4) enrolled in the Lilly Oncology Support Center, and 5) residents of the United States or Puerto Rico. May not be combined with any other offer. Not available to patients whose insurers have made a final determination to deny the patient coverage for Retevmo. If a denial is received after the initial 5 business days have passed and appeal rights are being pursued, or if there is a persistent coverage delay, the patient, under appropriate circumstances, may be eligible for up to 3 additional 15-day supplies of Retevmo. Product provided through the Program is only available through the Program non-commercial specialty pharmacy. Product is provided free of charge and may not be sold, bartered, or returned for credit. Reimbursement cannot be sought from any third party for product provided under the program. Patients enrolled in Medicare Part D are prohibited from counting any portion of the cost of the product provided under the Program towards true out-of-pocket ("TrOOP") costs for prescription drug calculations. No purchase contingency or other obligation accompanies program participation. This Program is not health insurance and does not guarantee coverage. Lilly reserves the right to change or end the program at any time. Benefits under the program are not transferable.

Please see Important Safety Information throughout and full Prescribing Information for Retevmo.

Retevmo is available through contracted specialty pharmacies. For a full list of specialty pharmacies, please visit Retevmo.com. Retevmo can be purchased through authorized specialty distributors, which can be found at lillytrade.com.

RET testing in germline is well established[16]

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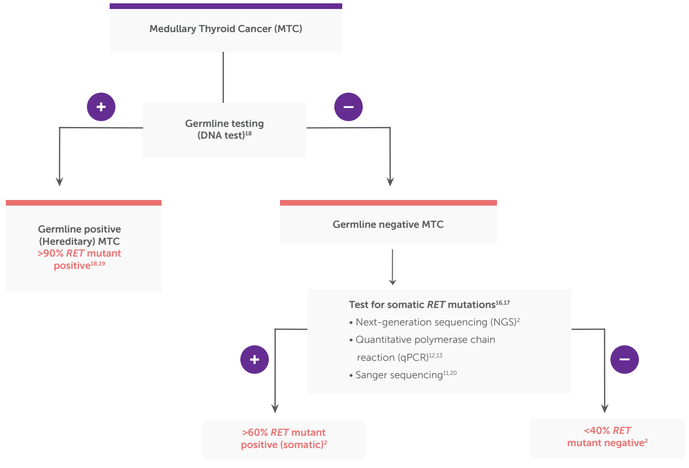
When germline testing is negative or unknown in MTC, the tumor should be tested for somatic *RET* point mutations[16,17]



CONSULT YOUR PATHOLOGIST OR LAB TO HELP IDENTIFY PATIENTS WHO MAY BE ELIGIBLE TO RECEIVE RETEVMO

IMPORTANT SAFETY INFORMATION (CONT'D)

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Please see Important Safety Information throughout, and accompanying full Prescribing Information for Retevmo located in the pocket.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

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Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

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Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

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Please see accompanying full Prescribing Information for Retevmo in pocket.

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Retevmo was designed to target *RET*, the primary driver of certain *RET*-driven cancers[1,2]

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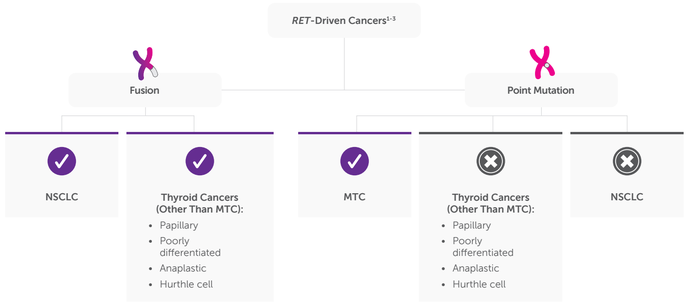

Retevmo may affect both healthy cells and tumor cells, which can result in side effects, some of which can be serious.[1]

RET POINT MUTATIONS MAY BE PRESENT IN OTHER TUMORS BUT ARE BELIEVED TO ONLY DRIVE MTC[4-6]

MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; RET=rearranged during transfection.

INDICATIONS

Retevmo is a kinase inhibitor indicated for the treatment of:

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These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

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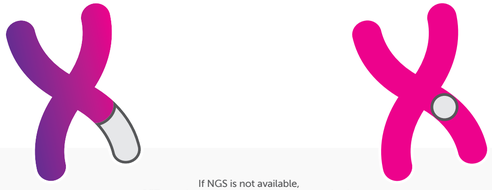
Test for *RET*: an actionable biomarker with Retevmo[1]

NGS can be an accurate and tissue-efficient method to test for actionable genomic alterations[7-10]*

SELECT AN NGS TEST THAT CAN DETECT BOTH *RET* FUSIONS AND POINT MUTATIONS*



If NGS is not available,
RET can also be detected using other methods:

RET fusions in metastatic NSCLC and advanced thyroid cancers (other than MTC)[2]:

- Fluorescence *in situ* hybridization (FISH)
- Reverse transcription polymerase chain reaction (PCR)

RET point mutations in MTC can be detected via germline or tumor tissue testing[11-13]:

- Sanger sequencing
- Quantitative polymerase chain reaction (qPCR)

- Immunohistochemistry (IHC) is not preferred for detecting *RET* alterations due to low sensitivity and variable specificity[14,15]

An FDA-approved test for the detection of *RET* gene fusions and *RET* gene mutations is not currently available for Retevmo.

SELECT TESTING THAT CAN DETECT DRIVER *RET* FUSIONS AND POINT MUTATIONS IN THE APPROPRIATE TUMORS

*Through design and validation, the test has established high sensitivity, specificity, and reproducibility for the detection of genomic alterations.
NGS=next-generation sequencing.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Consult your pathologist to ensure your test methods can detect driver *RET* fusions and point mutations in the appropriate tumors

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This list is not all-inclusive and does not represent all laboratories and tests. This list is intended for informational purposes and your consideration only, and is based on publicly available information for these organizations. Eli Lilly and Company (Lilly) makes no representations regarding the clinical or analytical validity, manufacturing quality, or design of the testing offered by the laboratories included on this list. Inclusion on this list does not represent an endorsement, referral, or recommendation by Lilly. Contact the laboratory for more information.

Laboratory	Test	*RET* Gene Detection	
		Point mutations	Fusions
Caris Life Sciences®	Molecular Intelligence® Comprehensive Tumor Profiling[1]	✓	✓
	Molecular Intelligence® Tumor Seek™[2]	✓	✓
Foundation Medicine	FoundationOne® CDx[3]	✓	✓
Integrated Oncology (LabCorp)/OmniSeq®	OmniSeq Advance℠ Assay[4]	✓	✓
	OmniSeq Comprehensive® Profiling Assay[5]	✓	✓
Mayo Clinic Laboratories	Solid Tumor-Targeted Cancer Gene Panel[6]	✓	x
	Lung Cancer-Targeted Gene Panel[7]	✓	✓
NeoGenomics Laboratories	NeoTYPE® Discovery Profile for Solid Tumors[8]	✓	✓*
	Lung NGS Fusion Profile[9]	✓	✓
	NeoTYPE® Lung Tumor Profile[10]	x	✓*
	NTRK & RET NGS Fusion Profile[11]	✓	✓
	NeoTYPE® Thyroid Tumor Profile[12]	✓	✓*
Paradigm Diagnostics	Paradigm Cancer Diagnostic (PCDx™)[13]	✓	✓
PathGroup	SmartGenomics™ Complete[14]	✓	✓
	SmartGenomics™ Lung Profile[15]	✓	✓*
	SmartGenomics™ Thyroid Profile[16]	✓	✓
Quest Diagnostics/ Med Fusion	IBM Watson™ Genomics from Quest Diagnostics®, Core[17]	✓	x
	Thyroid Cancer Mutation Panel[18]	x	✓
	RET/*PTC* Rearrangement, Thyroid Cancer[19]	x	✓
	50SEQ® With FISH[20]	✓	✓*
	LUNGSEQ With FISH®[21]	✓	✓*
Tempus	Tempus xT Gene Panel[22]	✓	✓
Turnaround times range from 5 to 22 days			

CHOOSE TESTING THAT ACCURATELY† DETECTS *RET* GENE FUSIONS AND *RET* POINT MUTATIONS

*FISH performed for fusion detection.
†Through design and validation, the test has established high sensitivity, specificity, and reproducibility for the detection of genomic alterations.
CDx=companion diagnostic; FISH=fluorescence *in situ* hybridization; NGS=next-generation sequencing; RET=rearranged during transfection.

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Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

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Ensure your testing methods include *RET*

Consider NGS for your patients

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