Pralsetinib: A Drug Review

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Abstract

REarranged during Transfection (RET) is a transforming proto-oncogene that codes for the tyrosine kinase receptor. Pralsetinib is an orally bioavailable, selective inhibitor of mutant forms and fusions involving the RET proto-oncogene. Following administration, pralsetinib limits the upregulation or dysregulation of RET gene mutations. This drug review aimed to explore the pharmacokinetics, pharmacodynamics, clinical indications, contraindications, dosing regimen, dose modifications, adverse drug events, and storage and administration of pralsetinib. This review was curated after exhaustive literature screening of all existing documents available on Google Scholar, PubMed, ScienceDirect, Dimensions, and EBSCO Host, as well as by browsing the Web sites of the U.S. Food and Drug Administration (FDA), drug manuals, and conference presentations, using keywords, such as "Pralsetinib," "RET fusion," and "Gavreto." Additional supporting data were obtained from various abstracts and conference proceedings. Presently, pralsetinib has been granted FDA approval for use in non–small cell lung cancer (NSCLC), metastatic RET fusion-positive NSCLC, and metastatic RET-mutant medullary thyroid cancer.

Keywords

- pralsetinib
- Gavreto
- RET fusion
- tyrosine kinase receptor
- thyroid
- cancer

Introduction

REarranged during transfection (RET) is a transforming proto-oncogene that codes for a tyrosine kinase receptor. Tyrosine kinase RET is responsible for various aspects of fetal development; consequently, RET perturbation is a known contributor to several cancers, such as non–small cell lung cancer (NSCLC), medullary thyroid carcinoma (MTC), and papillary thyroid cancer (PTC).[1] RET fusions can be found in 1 to 2% of NSCLCs, ~20% of PTCs, and <1% of many other solid tumors, including ovarian, pancreatic, salivary, and colorectal cancers.[2] Pralsetinib is a novel RET tyrosine kinase inhibitor employed in the treatment of metastatic RET-driven cancers.[3] Previously known as BLU-667, it is an oral anticancer drug capable of selectively targeting RET mutations and displaying potent antitumor activity.[4]

Development and Approval Status

Pralsetinib was granted U.S. Food and Drug Administration (USFDA) approval on September 4, 2020, for the treatment of RET-driven NSCLC. It was approved by the USFDA for the treatment of advanced and metastatic RET-driven MTC and PTC on December 1, 2020. In addition, on November 19, 2021,

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pralsetinib was approved by the European Commission to treat RET-positive advanced NSCLC.[5] The drug was approved by the Central Drugs Standard Control Organization (CDSCO) on May 26, 2022, for RET-driven NSCLC, MTC, and PTC.[6]

Mechanism of Action

RET activation occurs via chromosomal rearrangements when the 5′ dimerizable domains fuse with the 3′ RET tyrosine kinase portion. This rearrangement leads to autophosphorylation, ultimately resulting in tumor formation and migration. CCDC6-RET is one of the most common sites of perturbed fusion. Pralsetinib is able to selectively target CCDC6-RET sites and prevent their fusion with KIF5B-RET sites. Additionally, it also inhibits other kinases, such as DDR1, TRKC, FLT3, JAK1–2, TRKA, VEGFR2, PDGFRb, and FGFR1. This prevents tumor invasion and proliferation at clinically significant concentrations.

Contraindications

Specific contraindications have not been found.[7]

Dosage

All below doses are to be administered on an empty stomach.[3]

1. MTC, advanced or metastatic, RET mutant—pediatric and adult dosing—400 mg orally once daily until disease progression or unacceptable toxicity.[3]
2. NSCLC metastatic, RET fusion-positive disease—400 mg orally once daily until disease progression or unacceptable toxicity.[3]
3. Thyroid cancer, advanced or metastatic RET fusion-positive disease, in patients who require systemic therapy and who are radioactive iodine refractory—pediatric and adult dosing—400 mg orally once daily until disease progression or unacceptable toxicity.[3]

Dose Modification

1. Pralsetinib administered along with combined permeability glycoprotein (P-gp) and strong CYP3A inhibitors increased the maximum concentration of drug (C_{max}) and area under the curve infinity (AUC_{∞}) by 84 and 251%, respectively.[3] If coadministration is required, pralsetinib dosage should be reduced accordingly as suggested in ►**Table 1**.
2. Pralsetinib 400 mg dose has to be doubled prior to starting treatment if coadministered with strong CYP3A inducers. It was found that rifampin (CYP3A inducer) 600 mg once daily decreased pralsetinib C_{max} and AUC_{∞} by 30 and 68%, respectively.[3]
3. Dose reduction or discontinuation is recommended in patients with hypertension. The daily dose of pralsetinib can be reduced by one level in cases of Grade 3 hypertension. However, Grade 4 persistent hypertension requires permanent discontinuation.[8]

Table 1 Dose modification schedule for pralsetinib upon coadministration

Dose modification of pralsetinib in combination with permeability glycoprotein and strong CYP3A inhibitors	
Regular (conventional) dose	**Modified dose**
400 mg orally once daily	200 mg orally once daily
300 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily

4. In the case of interstitial lung disease (Grades 1–2), pralsetinib administration should be temporarily halted. Upon disease resolution, treatment can be resumed with reduced dosing. In cases of Grade 3 or higher, the drug should be permanently discontinued.[9]
5. Pralsetinib administration is not recommended in adolescent patients with growth plate abnormalities.[3]
6. Grade 3 or higher hepatoxicity requires dose interruption until the disease is resolved, after which treatment can be continued with dose reduction by one level.[3]
7. If adverse reactions are observed in patients with Grade 3 or 4, pralsetinib treatment is interrupted until symptoms reduce to Grade 2 or less. Treatment can be resumed at a reduced dosage if adverse reactions diminish. However, if no improvement is observed, administration should be permanently discontinued as represented in ►**Table 2**.[3]
8. Comorbidities such as renal and hepatic impairment do not lead to altered pharmacokinetics; thus, no dose modification is required in these cases. Additionally, no dose adjustment is required for geriatric patients.[3]

Administration

Pralsetinib is to be administered orally on an empty stomach. The drug should be administered 1 hour before or 2 hours postmeal. Furthermore, if a dose is vomited, no additional dose is administered, but treatment is continued as indicated. Additionally, if a dose is missed, it should be administered as soon as possible, and treatment should be resumed.[3]

Pharmacokinetics

Absorption

- Time to peak concentration (T_{max}) was found to be 2 to 4 hours for oral route of administration.[3]

Table 2 Dose modification of pralsetinib in an instance of adverse reactions

Dose modifications for adverse reactions	
Dose reduction schedule	**Modified dose**
First reduction	300 mg orally once daily
Second reduction	200 mg orally once daily
Third reduction	100 mg orally once daily

- Effect of food—C_{max} increased by 104%, AUC_{∞} increased by 122%, and T_{max} decreased by 4.5 hours.[3]

Distribution

- Protein binding of pralsetinib was found to be 97.1%.[3]
- Volume of distribution was found to be 228 L.[3]

Metabolism

Pralsetinib is metabolized in the liver primarily by enzyme CYP3A4, and to a lesser extent by CYP2D6 and CYP1A2. It is also a substrate of P-gp and breast cancer resistance protein (BCRP).[3]

- Pralsetinib induces microsomal enzymes CYP2C8, CYP2C9, CYP3A4, and CYP3A5.[3]
- It inhibits enzymes CYP3A4, CYP3A5, CYP2C8, CYP2C9, and P-gp.[3]
- Further, it also inhibits BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP transporters.[3]

Excretion

- Renal excretion was found to be 6%, 4.8% was unchanged.[3]
- Fecal excretion was found to be 73%, 66% was unchanged.[3]
- Rate of total body clearance was found to be 9.1 L/h.[3]

Elimination Half-Life

It was found to be 22.2 hours.[3]

Adverse Drug Effects

1. Common adverse effects[10]
   - Cardiovascular effects—edema (20–29%).
   - Gastrointestinal effects—diarrhea (24–34%) and constipation (35–41%).
   - Hepatic effects—pralsetinib administration displayed increased aspartate aminotransferase (AST) (34%), increased alanine aminotransferase (ALT) (23%).
   - Musculoskeletal pain was also observed (32–42%).
   - Respiratory effects—cough (23–27%) and pneumonia (17%).
   - Other common adverse effects include dry mouth (16%), pyrexia (20%), fatigue (35% for Grades 1–4 and 2.3% for Grades 3–4) and decreased lymphocytes (52 and 20%).
2. Serious adverse effects[10]
   - Cardiovascular—hypertension (28–40%), including 14% with Grade 3.
   - Dermatologic—wound healing impairment.
   - Hematologic—hemorrhage, Grade 3 or higher (2.5%).
   - Hepatic—hepatotoxicity (2.1%) may be observed. Increased AST (69%), including Grade 3 or 4 in 5.4% and increased ALT (46%), including Grades 3 and 4 in 6%.
   - Immunologic—şepsis.
   - Respiratory—pneumonitis (10%), including 2.7% incidence with Grades 3 and 4.

Warnings and Precautions

- *Cardiovascular system*: Grade 3 hypertension has been documented and treatment is not recommended for

Table 3 Key clinical trials and their recent results

Name of study	Phase	Condition(s)	Sample size	Overall response rate	Disease control rate	Median duration of response (12 mo)	Clinical benefit rate
ARROW—NSCLC—NCT03037385[4]	Multicohort, open-label, phase 1/2	Previously treated with platinum	$n = 87$	53 (61%; 50–71)	79 (91%; 83–96)	74%; 61–87	69% (58–79)
		No previous systemic treatment	$n = 27$	19 (70%; 50–86)	23 (85%; 66–96)	26%; 0–52	70% (50–86)
ARROW—MTC NCT03037385[2]	Multicohort, open-label, phase 1/2	Previously treated with cabozantinib or vandetanib or both	$n = 55$	33 (60%; 46–73)	51 (93%); (82–98)	92% (82–100)	80% (67–90)
		No previous systemic treatment	$n = 21$	15 (71%; 48–89)	51 (93%); (82–98)	84% (63–100)	100% (84–100)
ARROW—RET fusion-positive thyroid cancer—NCT03037385[11]	Multicohort, open-label, phase 1/2	Previously treated RET fusion-positive thyroid cancer	$n = 9$	8 (89%; 52–100)	9 (100%); (66–100)	86% (60–100)	89% (52–100
ARROW—RET fusion-positive solid tumors—NCT03037385[11]	Multi-cohort, open-label, phase 1/2	RET fusion-positive solid tumors	$n = 23$	13 (57%; 35–77)	19 (83%); (61–95)	11.7 (5.5–19)	70% (47–87)

Abbreviations: MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; RET, RErarranged during transfection.
Note: Data are *n* (%), % (95% confidence interval), or median (interquartile range).

patients with uncontrolled hypertension. Blood pressure levels should be optimized before the commencement of therapy. Furthermore, continuous monitoring followed by dose modification or permanent discontinuation should be implemented as required.[3]

- *Hematological effects*: Trials have reported serious, even fatal, hemorrhagic episodes among patients. In such cases, immediate cessation of therapy is recommended.[3]
- *Hepatic system*: Studies have shown increased AST and ALT levels in patients. In cases of serious hepatic adverse reactions, rigorous monitoring is advised, followed by dose adjustment or discontinuation of therapy if necessary.[3]
- *Reproductive system*: Pralsetinib is contraindicated in pregnancy due to embryo–fetal toxicity (10). Further, females of reproductive potential are advised to use nonhormonal contraception throughout the duration of treatment and for 2 weeks following the final dose.[3]
- *Respiratory system*: Trials have reported life-threatening, fatal pneumonitis/interstitial lung disease in patients. In such cases, rigorous monitoring is advised, followed by dose adjustment or discontinuation of therapy if necessary.[3]
- *Tumor lysis syndrome (TLS)*: TLS was observed in patients with medullary thyroid cancer. Patients with preexisting renal dysfunction, dehydration, rapidly growing tumors, and high tumor burden are at high risk for TLS. In such cases, rigorous monitoring along with prophylactic treatment is recommended.[3]
- *Wound healing*: Pralsetinib administration may impair wound healing by inhibiting the vascular endothelial growth factor signaling pathway. In the case of elective surgeries, treatment is halted for at least 5 days in advance. In the case of major surgeries, drug administration is halted for 2 weeks following surgery or until complete wound healing occurs.[3]

Significant Clinical Studies

The recent significant clinical trials[4] and their studies are tabulated in ►**Table 3**.

Storage

Pralsetinib is to be stored at 20 to 25°C (68–77°F); excursions are permitted from 15 to 30°C (59–86°F). It should be protected from moisture.[10]

Applicability to India

The cost for pralsetinib (Gavreto) in India for 60 capsules of 100 mg is approximated Indian Rupee (INR) 250,000.

Funding
None.

Conflict of Interest
None declared.

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