IBTROZI THERAPY CARE GUIDE

Helping you manage your adult patients with locally advanced or metastatic ROS1+ NSCLC during their treatment experience

Visit **IBTROZIhcp.com**
for the complete IBTROZI story

NSCLC=non-small cell lung cancer; ROS1=ROS proto-oncogene 1.

INDICATION

IBTROZI™ (taletrectinib) is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

SELECT SAFETY INFORMATION

Serious adverse and sometimes fatal reactions occurred with IBTROZI treatment. Warnings and precautions include hepatotoxicity, interstitial lung disease/pneumonitis, QTc interval prolongation, hyperuricemia, myalgia with creatine phosphokinase (CPK) elevation, skeletal fractures, and embryo-fetal toxicity.

Please see complete Important Safety Information on pages 23-25 and full Prescribing Information.

IBTROZI™
taletrectinib 200 mg capsules

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This guide contains important information you will need to prepare patients for their best IBTROZI experience, including details about dosing and AR management, as well as available support through NuvationConnect™.

AR=adverse reaction.

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Introducing your patients to IBTROZI

As you prepare for clinical conversations with patients starting IBTROZI, utilize this checklist to facilitate effective discussions:

Ask about preexisting conditions	Reconfirm if patients have any preexisting liver, breathing, or heart problems, including long QT syndrome, or gout; ask about their pregnancy status.
Ask about current medications	Discuss your patients' current medications, including prescription and OTC medications, vitamins, and herbal supplements.
Ask about any symptoms	Encourage patients to describe the type of symptoms they may be experiencing, when they started, and how severe they might be.

OTC=over-the-counter.

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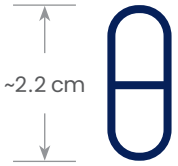
Initiating treatment[1]

Recommended dosage: 600 mg once daily



Not actual size.

IBTROZI capsules: 200 mg, immediate release, white, opaque, size 0, hard capsules filled with white to light yellow powder, imprinted with "TAL" and "200" in blue ink on the body of the capsule.

IBTROZI 600 mg should be taken orally daily and continued until disease progression or unacceptable toxicity

ONCE DAILY

Take **three 200 mg IBTROZI capsules** at approximately the **same time** each day. Swallow IBTROZI capsules whole. **Do not open, chew, crush, or dissolve** the capsules prior to swallowing

Take IBTROZI on an empty stomach (**no food intake at least 2 hours before and 2 hours after** taking IBTROZI)

Avoid food or drink containing grapefruit during treatment with IBTROZI.

Minimize sun exposure and use sun protection, including broad-spectrum sunscreen, during treatment with IBTROZI and for at least 5 days after discontinuation.

If a dose is missed, take the next dose at its scheduled time on the following day. If vomiting occurs at any time after taking a dose, take the next dose at its scheduled time on the following day.

Before initiating IBTROZI, evaluate liver function tests (including ALT, AST, and bilirubin), electrolytes, ECG, and uric acid.

Before your patients begin treatment with IBTROZI, they should know:

- How many IBTROZI capsules to take for each once-daily dose
- A good time that works consistently for their dosing (at least 2 hours before or 2 hours after eating)
- What medications to avoid when on treatment with IBTROZI, such as daily PPIs

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; PPI=proton pump inhibitor.

Please see complete Important Safety Information on pages 23-25.

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Initiating treatment[1] (cont'd)

Be aware of drug interactions

DRUG INTERACTIONS

Strong and moderate CYP3A inhibitors	Avoid concomitant use with strong or moderate CYP3A inhibitors. Taletrectinib is a CYP3A substrate. Concomitant use of IBTROZI with a strong or moderate CYP3A inhibitor increases taletrectinib exposure, which may increase the risk of IBTROZI ARs
Strong and moderate CYP3A inducers	Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of IBTROZI with a strong or moderate CYP3A inducer decreases taletrectinib exposure, which may reduce the effectiveness of IBTROZI
Gastric acid-reducing agents	Avoid concomitant use with PPIs and H2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer locally acting antacids at least 2 hours before or 2 hours after taking IBTROZI. Concomitant use of a PPI decreases taletrectinib exposure, which may reduce the effectiveness of IBTROZI
Drugs that prolong the QTc interval	Avoid concomitant use of IBTROZI with other drug(s) with a known potential to prolong the QTc interval, such as antiarrhythmic drugs. If concomitant use cannot be avoided, adjust the frequency of monitoring as recommended. Withhold IBTROZI if the QTc interval is >500 msec or the change from baseline is >60 msec. IBTROZI causes QTc interval prolongation. Concomitant use of IBTROZI with other drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation

QTc=corrected QT interval.

Please see complete Important Safety Information on pages 23-25.

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Warnings and precautions

Hepatotoxicity

IBTROZI can cause hepatotoxicity, including drug-induced liver injury and fatal adverse reactions.

- **Incidence of AST elevation was 88% and ALT elevation was 85% based on laboratory values[1]**
  - Concurrent elevations in AST or ALT ≥3 times ULN and total bilirubin ≥2 times ULN, with normal alkaline phosphatase, occurred in 2 (0.6%) patients
  - The median time to first onset of AST or ALT elevation was 15 days (range: 3 days to 20.8 months)
- **Grade ≥3 AST/ALT laboratory values[1]**
  - Increased AST: 10%
  - Increased ALT: 13%

Onset and resolution of AST/ALT elevation events[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
16.5 days (range: 6 days to 20.7 months)	**49 days** (range: 3 days to 63.9 months)

- Fatal liver outcomes occurred in 2 (0.6%) patients[1]
- The majority of liver-related events were LFT abnormalities, which were transient, and resolved with or without supportive management[2]
- **Dose modifications due to increased AST/ALT events were low[1]**
  - Interruptions: 7%
  - Reductions: 5% (AST), 9% (ALT)
  - Discontinuations: 0.3%
- **Patient counseling information[1]**
  - Advise patients of the risk of hepatotoxicity and of the need for laboratory tests to monitor liver function during treatment with IBTROZI and to immediately contact their healthcare provider if they experience symptoms of hepatotoxicity

LFT=liver function test; ULN=upper limit of normal.

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Warnings and precautions (cont'd)

ILD/pneumonitis

IBTROZI can cause severe, life-threatening, or fatal ILD or pneumonitis.

- **Incidence of ILD/pneumonitis was 2.3% with IBTROZI**[1]
- **Grade ≥3 events**[1]
  - 1.1%
  - 1 fatal case of ILD occurred in a patient who had received 400 mg once-daily dose of IBTROZI

Onset and resolution of ILD/pneumonitis[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
3.8 months (range: 12 days to 11.8 months)	**1.03 months** (range: 8 days to 4.9 months)

- **Dose modifications due to ILD/pneumonitis**[1]
  - Interruptions: 1.1%
  - Reductions: 0.6%
  - Discontinuations: 0.6%
- **Patient counseling information**[1]
  - Inform patients of the risk of ILD/pneumonitis during treatment with IBTROZI and advise them to contact their healthcare provider immediately if they experience new or worsening pulmonary symptoms indicative of ILD/pneumonitis

ILD=interstitial lung disease.

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Warnings and precautions (cont'd)

QTc interval prolongation

IBTROZI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death.

- **Incidence of QTc interval prolongation**[1]
  - Increase in QTcF of >60 msec from baseline: 13%
  - QTcF to >500 msec: 2.6%
- **Grade ≥3 events**[1]
  - 3.4%

Onset and resolution of QTc interval prolongation[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
22 days (range: 1 day to 38.7 months)	**1.41 months** (range: 1 day to 24.5 months)

- **Dose modifications due to QTc interval prolongation**[1]
  - Interruptions: 2.8%
  - Reductions: 2.8%
- **Additional information**[1]
  - Significant prolongation of the QTc interval may occur when IBTROZI is taken with food, strong and moderate CYP3A inhibitors, and/or drugs with a known potential to prolong QTc
- **Patient counseling information**[1]
  - Inform patients of the risk of QT interval prolongation during treatment with IBTROZI and advise them to contact their healthcare provider immediately if they experience any symptoms of QT interval prolongation

QTcF=QT interval corrected by Fridericia's formula.

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Warnings and precautions (cont'd)

Hyperuricemia

IBTROZI can cause hyperuricemia.

- **Incidence of hyperuricemia was 14% with IBTROZI[1]**
  - Of the IBTROZI-treated patients who developed hyperuricemia, 16% required urate-lowering medication without preexisting gout or elevated uric acid at baseline
- **Grade ≥3 events[1]**
  - 0.3%

Onset and resolution of hyperuricemia[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
2.1 months (range: 7 days to 35.8 months)	**1.41 months** (range: 4 days to 45.5 months)

- **Dose modifications due to hyperuricemia[1]**
  - Interruptions: 0.3%
- **Patient counseling information[1]**
  - Advise patients of the risk of hyperuricemia during treatment with IBTROZI and to contact their healthcare provider if they experience signs or symptoms associated with hyperuricemia

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Warnings and precautions (cont'd)

Myalgia with creatine phosphokinase elevation

IBTROZI can cause myalgia with or without CPK elevation.

- **Incidence of myalgia was 10% with IBTROZI[1]**
  - Concurrent myalgia with increased CPK within a 7-day window was observed in 0.9% of patients

Onset and resolution of myalgia[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
11 days (range: 2 days to 10 months)	**12 days** (range: 1 day to 18.4 months)

- **Dose modifications due to myalgia[1]**
  - Interruptions: 1 patient (0.3%) with myalgia who also presented with concurrent CPK elevation
- **Patient counseling information[1]**
  - Advise patients of the risk of myalgia with creatine phosphokinase elevation during treatment with IBTROZI and to contact their healthcare provider if they experience unexplained muscle pain, tenderness, or weakness

CPK=creatine phosphokinase.

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Warnings and precautions (cont'd)

Skeletal fractures

IBTROZI can increase the risk of fractures. ROS1 inhibitors as a class have been associated with skeletal fractures.

- **Incidence of skeletal fractures was 3.4% with IBTROZI[1]**

  Some fractures occurred in the setting of an accidental fall or other predisposing factors such as osteoporosis, bone metastasis, and age-related degenerative diseases. Fractures involved:

  - Ribs (1.4%)
  - Spine (0.9%)
  - Femur (0.6%)
  - Humerus (0.3%)
  - Acetabulum (0.3%)

- **Grade 3 events[1]**
  - 1.4%

Onset and resolution of skeletal fractures[1,2]

MEDIAN TIME TO ONSET	MEDIAN TIME TO RESOLUTION
10.7 months (range: 26 days to 29.1 months)	**6.88 months** (range: 5 days to 18.9 months)

- **Dose modifications due to skeletal fractures[1]**
  - Interruption: 0.3%
- **Patient counseling information[1]**
  - Inform patients of the risk of bone fractures during treatment with IBTROZI and advise them to contact their healthcare provider immediately if they experience signs or symptoms of fracture

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IBTROZI safety profile

ADVERSE REACTIONS (≥15%) IN PATIENTS WITH ROS1+ NSCLC WHO RECEIVED IBTROZI IN TRUST-I AND TRUST-II[1,2]

	IBTROZI (N=337)			
ADVERSE REACTIONS*	**GRADE 1 (%)**	**GRADE 2 (%)**	**GRADE 3 OR 4 (%)**	**ALL GRADES (%)**
GASTROINTESTINAL DISORDERS				
Diarrhea†	50	11	2.1	64
Nausea	37	9	1.5	47
Vomiting	34	8	1.5	43
Constipation	18	3	0	21
NERVOUS SYSTEM DISORDERS				
Dizziness‡	20	2.1	0.3	22
Peripheral neuropathy§	13	3.6	0.3	17
Dysgeusia‖	13	2.1	0	15
SKIN AND SUBCUTANEOUS TISSUE				
Rash¶	13	8	1.8	22
GENERAL DISORDERS				
Fatigue#	15	4.5	0.9	20

*Based on NCI CTCAE version 5.0.[1]

†Includes enterocolitis.[1]

‡Includes vertigo and vertigo positional.[1]

§Includes dysesthesia, hypoesthesia, neuralgia, paresthesia, and peripheral sensory neuropathy.[1]

‖Includes ageusia.[1]

¶Includes dermatitis, dermatitis acneiform, drug eruption, eczema, eyelid rash, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, rash papular, skin exfoliation, and drug reaction with eosinophilia and systemic symptoms (DRESS).[1]

#Includes asthenia.[1]

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.

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IBTROZI safety profile (cont'd)

ADVERSE REACTIONS (≥15%) IN PATIENTS WITH ROS1+ NSCLC WHO RECEIVED IBTROZI IN TRUST-I AND TRUST-II[1,2] (CONT'D)

	IBTROZI (N=337)			
ADVERSE REACTIONS*	**GRADE 1 (%)**	**GRADE 2 (%)**	**GRADE 3 OR 4 (%)**	**ALL GRADES (%)**
CARDIAC				
Electrocardiogram QT prolonged	13	2.7	3.6	19
METABOLISM AND NUTRITIONAL				
Decreased appetite	11	4.2	0.3	16
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Cough**	12	4.7	0	16

*Based on NCI CTCAE version 5.0.[1]
**Includes productive cough.[1]

Serious ARs[1]

- Serious ARs occurred in 31% of patients who received IBTROZI. Serious ARs in ≥2% of patients included pneumonia (7%), pleural effusion (4.7%), and hepatotoxicity (2.4%)
- Fatal ARs occurred in 18 (5%) patients who received IBTROZI, including pneumonia (2.4%), multiple organ dysfunction syndrome (0.6%), hepatotoxicity (0.6%), cardiac arrest (0.6%), cardiac failure (0.3%), cardiopulmonary failure (0.3%), respiratory failure (0.3%), and death not otherwise specified (0.3%)

During treatment with IBTROZI, your patients should know:

- ARs are common, but most are mild to moderate[1,2]
- Dose modifications may help manage ARs[1]
- ARs led to treatment discontinuation in 7% of patients[1]
- To report all ARs to their healthcare team, no matter how minor they perceive them to be

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IBTROZI safety profile (cont'd)

Laboratory abnormalities

LABORATORY ABNORMALITIES* (≥20%) IN PATIENTS WITH ROS1+ NSCLC WHO RECEIVED IBTROZI IN TRUST-I AND TRUST-II[1,2]

LABORATORY ABNORMALITY‡	IBTROZI†			
	GRADE 1 (%)	GRADE 2 (%)	GRADE 3 OR 4 (%)	ALL GRADES (%)
HEMATOLOGY				
Hemoglobin decreased	31	14	3.6	48
Lymphocytes decreased	14	19	4.8	38
Neutrophils decreased	11	8	5	25
CHEMISTRY				
AST increased	57	20	10	87
ALT increased	51	21	13	85
Creatine phosphokinase increased	37	11	5	53
Cholesterol increased	32	9	0	41
Triglycerides increased	30	8	2.5	41

*Laboratory abnormalities that worsened from baseline.[1]
†The denominator used to calculate the rate varied from 149 to 336 based on the number of patients with a baseline value and at least 1 post-treatment value.[1]
‡Based on NCI CTCAE version 5.0.[1]

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IBTROZI safety profile (cont'd)

Laboratory abnormalities (cont'd)

LABORATORY ABNORMALITIES* (≥20%) IN PATIENTS WITH ROS1+ NSCLC WHO RECEIVED IBTROZI IN TRUST-I AND TRUST-II[1,2] (CONT'D)

LABORATORY ABNORMALITY‡	IBTROZI†			
	GRADE 1 (%)	GRADE 2 (%)	GRADE 3 OR 4 (%)	ALL GRADES (%)
CHEMISTRY (CONT'D)				
Creatinine increased	21	18	0.3	39
Uric acid increased	38	0	0	38
Gamma glutamyl transferase increased	28	6	1.8	36
Alkaline phosphatase increased	28	2	0	30
Calcium decreased	21	5	1.8	28
Albumin decreased	19	6	0.9	25
Bilirubin increased	18	4.5	0.6	24
Potassium increased	13	7	1.2	21
Sodium increased	16	2.4	0.9	20

*Laboratory abnormalities that worsened from baseline.[1]
†The denominator used to calculate the rate varied from 149 to 336 based on the number of patients with a baseline value and at least one post-treatment value.[1]
‡Based on NCI CTCAE version 5.0.[1]

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Additional safety information

Most GI events were mild to moderate and resolved quickly[1,2]

- **Incidence of GI events with IBTROZI was 88% (310/352)[2]**
  - The most frequently (≥10%) reported GI events were diarrhea, nausea, vomiting, and constipation, and most were mild to moderate[1,2]
- **Grade ≥3 events[2]**
  - 6%

Onset and resolution of GI events (any grade)[2]

MEDIAN TIME TO ONSET	MEDIAN EVENT DURATION
1 day (range: 1 day to 35.4 months)	**2 days** (range: 1 day to 55.9 months)

- 92.3% of GI events recovered* (79.9% without and 12.4% with treatment)[2]

In TRUST-II, standard antiemetics, such as prochlorperazine, were used for treatment of vomiting. Use of prophylactic antiemetics was also permitted. Loperamide as well as other medications and supportive care according to institution protocol were used to treat diarrhea. Constipation was treated with laxatives, and prophylactic treatment of constipation was permitted. In TRUST-I, supportive care was permitted, and utilization of antiemetics or antidiarrheals was not prohibited.[3,4]

- **Dose modifications due to GI events were low[2]**
  - Interruptions: 7%
  - Reductions: 4.3%
  - Discontinuations: 0.6%

**Recovered* means the GI event recovered to normal or baseline range.[2]*

GI=gastrointestinal.

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Additional safety information (cont'd)

The majority of CNS events were mild to moderate and transient[1,2]

- **Incidence of CNS events with IBTROZI was 48.9% (172/352)[2]**
  - The most frequently (≥5%) reported CNS events were dizziness, dysgeusia, headache, hypoesthesia, and muscular weakness
- **Grade ≥3 events[2]**
  - 5%

Onset and resolution of CNS events (any grade)[2]

MEDIAN TIME TO ONSET	MEDIAN EVENT DURATION
13.5 days (range: 1 day to 30.9 months)	**8 days** (range: 1 day to 59.4 months)

- **Dose modifications due to CNS events were low[2]**
  - Interruptions: 2.8%
  - Reductions: 2.0%
  - Discontinuations: 0.6%

CNS=central nervous system.

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Optimizing outcomes for your patients

MONITORING FOR ADVERSE REACTIONS[1]

TEST	PRIOR TO INITIATION/ AT BASELINE	MONITORING
Liver function tests	Monitor AST, ALT, and bilirubin prior to administration of IBTROZI	Evaluate every 2 weeks during the first 2 months of treatment, and then monthly as clinically indicated, with more frequent testing in patients who develop transaminase elevations
Pulmonary function tests	No initial evaluation needed	Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis
Electrocardiogram	Monitor ECGs and electrolytes prior to administration of IBTROZI	Monitor periodically thereafter as clinically indicated during treatment with IBTROZI. Adjust the frequency of monitoring based on risk factors such as known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure, and concomitant medications associated with QTc interval prolongation
Uric acid	Monitor serum uric acid levels prior to administration of IBTROZI	Monitor periodically during treatment as clinically indicated. Initiate treatment with urate-lowering medications as clinically indicated
Creatine phosphokinase	No initial evaluation needed	Monitor serum CPK levels during IBTROZI treatment every 2 weeks during the first month of treatment and then as clinically indicated in patients reporting unexplained muscle pain, tenderness, or weakness

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Optimizing outcomes for your patients (cont'd)

RECOMMENDED DOSE REDUCTIONS FOR ARs[1]

DOSAGE REDUCTION	RECOMMENDED DOSAGE
First dose reduction	400 mg once daily
Second dose reduction	200 mg once daily
Permanently discontinue IBTROZI capsules in patients unable to tolerate 200 mg once daily	

IBTROZI has specific dose modifications for hepatotoxicity, ILD/pneumonitis, QTc interval prolongation, hyperuricemia, creatine phosphokinase elevation, and other ARs. See dose modifications for more information.

Please see complete Important Safety Information on pages 23-25.

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Optimizing outcomes for your patients (cont'd)

DOSE MODIFICATIONS FOR ADVERSE REACTIONS[1]

ADVERSE REACTION	SEVERITY*	DOSAGE MODIFICATION
Hepatotoxicity (elevation of ALT or AST)	**Grade 3** (>5-20 × ULN)	Withhold IBTROZI until recovery to grade ≤1 or baseline • If resolved within 6 weeks, resume IBTROZI at a reduced dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI Recurrence: • If resolved within 6 weeks, resume IBTROZI at a reduced dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI
	Grade 4 (>20 × ULN)	Withhold IBTROZI until recovery to grade ≤1 or baseline • If resolved within 6 weeks, resume IBTROZI at a reduced dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI Recurrence: • Permanently discontinue IBTROZI
	ALT or AST ≥3 × ULN with concurrent total bilirubin ≥2 × ULN (in the absence of cholestasis or hemolysis)	• Permanently discontinue IBTROZI
ILD/pneumonitis	**Grade 1**	Withhold IBTROZI if ILD/pneumonitis occurs or is suspected until recovery to grade 0 or baseline • If resolved within 6 weeks, resume IBTROZI at the same dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI Recurrence: • Permanently discontinue IBTROZI

*Graded per NCI CTCAE version 5.0.

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Optimizing outcomes for your patients (cont'd)

DOSE MODIFICATIONS FOR ADVERSE REACTIONS[1] (CONT'D)

ADVERSE REACTION	SEVERITY*	DOSAGE MODIFICATION
ILD/pneumonitis	**Grade 2**	Withhold IBTROZI if ILD/pneumonitis occurs or is suspected until recovery to grade 0 or baseline • If resolved within 6 weeks, resume IBTROZI at a reduced dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI Recurrence: • Permanently discontinue IBTROZI
	Grade 3 or 4	Permanently discontinue IBTROZI
QTc interval prolongation	**Grade 2** (QTc interval 481-500 msec)	Withhold IBTROZI until recovery to grade ≤1 or baseline • Correct electrolytes and/or change concomitant medications • Resume IBTROZI at same dose
	Grade 3 (QTc interval ≥501 msec or QTc interval increase of >60 msec from baseline)	Withhold IBTROZI until recovery to grade ≤1 or baseline • Correct electrolytes and/or change concomitant medications • Resume IBTROZI at a reduced dose
	Grade 4 (Torsades de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Permanently discontinue IBTROZI

*Graded per NCI CTCAE version 5.0.

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Optimizing outcomes for your patients (cont'd)

DOSE MODIFICATIONS FOR ADVERSE REACTIONS[1] (CONT'D)

ADVERSE REACTION	SEVERITY*	DOSAGE MODIFICATION
Hyperuricemia	**Grade 3 or 4**	Withhold IBTROZI until improvement of signs or symptoms • Resume IBTROZI at same or reduced dose level, or permanently discontinue
Creatine phosphokinase elevation	**CPK elevation >5 times ULN**	Withhold until recovery to baseline or ≤2.5 times ULN, then resume at same dose
	CPK elevation >10 times ULN or second occurrence of CPK elevation of >5 times ULN	Withhold until recovery to baseline or ≤2.5 times ULN, then resume at reduced dose
Other ARs	**Grade 3**	Withhold IBTROZI until recovery to grade ≤1 or baseline • If resolved within 6 weeks, resume IBTROZI at a reduced dose level • If unresolved after 6 weeks, permanently discontinue IBTROZI Recurrence: • Resume treatment at reduced dose or permanently discontinue IBTROZI
	Grade 4	Withhold IBTROZI until recovery to grade ≤1 or baseline. Resume IBTROZI at reduced dose or permanently discontinue as clinically indicated Recurrence: • Permanently discontinue IBTROZI

*Graded per NCI CTCAE version 5.0.

 Please see complete Important Safety Information on pages 23-25.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Hepatotoxicity, including drug-induced liver injury and fatal adverse reactions, can occur. 88% of patients experienced increased AST, including 10% Grade 3/4. 85% of patients experienced increased ALT, including 13% Grade 3/4. Fatal liver events occurred in 0.6% of patients. Median time to first onset of AST or ALT elevation was 15 days (range: 3 days to 20.8 months).

Increased AST or ALT each led to dose interruption in 7% of patients and dose reduction in 5% and 9% of patients, respectively. Permanent discontinuation was caused by increased AST, ALT, or bilirubin each in 0.3% and by hepatotoxicity in 0.6% of patients.

Concurrent elevations in AST or ALT ≥3 times the ULN and total bilirubin ≥2 times the ULN, with normal alkaline phosphatase, occurred in 0.6% of patients.

Monitor liver function tests (AST, ALT, and bilirubin) prior to treatment, every 2 weeks during the first 2 months, and then monthly thereafter as clinically indicated. Test more frequently if transaminase elevations occur. Advise patients to immediately report symptoms of hepatotoxicity. Based on severity and resolution, withhold, then resume at a reduced dose or permanently discontinue.

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, or fatal ILD or pneumonitis can occur. ILD/pneumonitis occurred in 2.3% of patients, including 1.1% Grade 3/4. One fatal ILD case occurred at the 400 mg daily dose. Median time to first onset of ILD/pneumonitis was 3.8 months (range: 12 days to 11.8 months).

ILD/pneumonitis led to dose interruption in 1.1% of patients, dose reduction in 0.6% of patients, and permanent discontinuation in 0.6% of patients.

Monitor patients for new or worsening pulmonary symptoms. Advise patients to report symptoms. If ILD/pneumonitis is suspected, immediately withhold; based on severity and resolution, resume at same or reduced dose, or permanently discontinue.

QTc Interval Prolongation: QTc interval prolongation can occur, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death. IBTROZI prolongs the QTc interval in a concentration-dependent manner.

In patients who received IBTROZI and underwent at least one post baseline ECG, QTcF increase of >60 msec compared to baseline and QTcF >500 msec occurred in 13% and 2.6% of patients, respectively. 3.4% of patients experienced Grade ≥3. Median time from first dose of IBTROZI to onset of ECG QT prolongation was 22 days (range: 1 day to 38.7 months). Dose interruption and dose reduction each occurred in 2.8% of patients.

Monitor ECGs and electrolytes prior to start of therapy, and then periodically thereafter as clinically indicated. Adjust frequency based on risk factors such as known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure, and concomitant medications.

Please see additional Important Safety Information on pages 24-25 and accompanying full Prescribing Information.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

QTc Interval Prolongation (cont'd)**:** Significant QTc interval prolongation may occur when IBTROZI is taken with food, strong and moderate CYP3A inhibitors, and/or drugs with a known potential to prolong QTc. Administer IBTROZI on an empty stomach. Avoid concomitant use with strong and moderate CYP3A inhibitors and/or drugs with a known potential to prolong QTc.

Advise patients to immediately report any symptoms of QT interval prolongation. Based on severity and resolution, withhold, then resume at same or reduced dose, or permanently discontinue.

Hyperuricemia: Hyperuricemia can occur and was reported in 14% of patients, with 16% of these requiring urate-lowering medication without pre-existing gout or hyperuricemia. 0.3% of patients experienced Grade ≥3. Median time to first onset was 2.1 months (range: 7 days to 35.8 months). Dose interruption occurred in 0.3% of patients.

Monitor serum uric acid levels prior to initiating and periodically during treatment. Initiate urate-lowering medications as clinically indicated. Advise patients to report symptoms. Based upon severity and resolution, withhold, then resume at same or reduced dose, or permanently discontinue.

Myalgia with Creatine Phosphokinase (CPK) Elevation: Myalgia with or without CPK elevation can occur. Myalgia occurred in 10% of patients. Median time to first onset was 11 days (range: 2 days to 10 months).

Concurrent myalgia with increased CPK within a 7-day time period occurred in 0.9% of patients. Dose interruption occurred in 0.3% of patients with myalgia and concurrent CPK elevation.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor serum CPK levels during treatment every 2 weeks during the first month, and then as clinically indicated. Based on severity, withhold, then resume at same or reduced dose upon improvement.

Skeletal Fractures: IBTROZI can increase the risk of fractures. ROS1 inhibitors as a class have been associated with skeletal fractures. 3.4% of patients experienced fractures, including 1.4% Grade 3. Some fractures occurred in the setting of a fall or other predisposing factors such as osteoporosis, bone metastasis, and age-related degenerative conditions. Median time to first onset of fracture was 10.7 months (range: 26 days to 29.1 months). Dose interruption occurred in 0.3% of patients.

Advise patients to immediately report symptoms. Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures.

There are no data on the effects of IBTROZI on healing of known fractures and risk of future fractures.

Please see additional Important Safety Information on pages 23 and 25 and accompanying full Prescribing Information.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Embryo-Fetal Toxicity: Based on literature, animal studies, and its mechanism of action, IBTROZI can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating IBTROZI. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 weeks following the last dose.

ADVERSE REACTIONS

Among patients who received IBTROZI, the most frequently reported adverse reactions (≥20%) were diarrhea (64%), nausea (47%), vomiting (43%), dizziness (22%), rash (22%), constipation (21%), and fatigue (20%).

The most frequently reported Grade 3/4 laboratory abnormalities (≥5%) were increased ALT (13%), increased AST (10%), decreased neutrophils (5%), and increased creatine phosphokinase (5%).

DRUG INTERACTIONS

- **Strong and Moderate CYP3A Inhibitors:** Avoid concomitant use.
- **Strong and Moderate CYP3A Inducers:** Avoid concomitant use.
- **Gastric Acid Reducing Agents:** Avoid concomitant use with PPIs and H2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer locally acting antacids at least 2 hours before or 2 hours after taking IBTROZI.
- **Drugs that Prolong the QTc Interval:** Avoid concomitant use. If concomitant use cannot be avoided, adjust the frequency of monitoring as recommended. Withhold IBTROZI if the QTc interval is >500 msec or the change from baseline is >60 msec.

OTHER CONSIDERATIONS

- **Pregnancy:** Please see important information in Warnings and Precautions under Embryo-Fetal Toxicity.
- **Lactation:** Advise women not to breastfeed during treatment and for 3 weeks after the last dose.
- **Effect on Fertility:** Based on findings in animals, IBTROZI may impair fertility in males and females. The effects on animal fertility were reversible.
- **Pediatric Use:** The safety and effectiveness of IBTROZI in pediatric patients has not been established.
- **Photosensitivity:** IBTROZI can cause photosensitivity. Advise patients to minimize sun exposure and to use sun protection, including broad-spectrum sunscreen, during treatment and for at least 5 days after discontinuation.

Please see accompanying full Prescribing Information.

References: 1. IBTROZI™ (taletrectinib). Prescribing Prescribing Information. Nuvation Bio Inc.; 2025. **2.** Data on file. Nuvation Bio Inc. **3.** AnHeart Therapeutics. Study protocol AB-106-C203. *J Clin Oncol*. Updated June 6, 2022. Accessed April 22, 2025. https://ascopubs.org/action/downloadSupplement?doi=10.1200%2FJCO-25-00275&file=protocol+1_JCO-25-00275.pdf **4.** AnHeart Therapeutics. Study protocol AB-106-G208. *J Clin Oncol*. Updated June 6, 2022. Accessed April 22, 2025. https://ascopubs.org/action/downloadSupplement?doi=10.1200%2FJCO-25-00275&file=protocol+2_JCO-25-00275.pdf

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