Written By: Stefanie Houseknecht, PharmD, BCOP
Institution: Johns Hopkins Hospital and Bayview Medical Center

Taletrectinib (Ibtrozi) for the Management of ROS1+ Advanced NSCLC

Description: The purpose of this document is to discuss the clinical considerations and general management of taletrectinib for the treatment of *ROS1*-positive non-small cell lung cancer (NSCLC).

Background: Taletrectinib is a CNS-penetrant tyrosine kinase inhibitor (TKI) that inhibits ROS1, including ROS1 mutations (e.g. G2032R). It also inhibits tropomyosin receptor kinases (TRKs) TRKA, TRKB, and TRKC. It is least potent against TRKB which may reduce off-target toxicity (dysgeusia, dizziness, and peripheral neuropathy) relative to other dual ROS1/TRK TKIs.[2]

- FDA-approved for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.[1]

Adverse reactions:[1]

- Most common (occurring in ≥ 20%): diarrhea, nausea, vomiting, dizziness, rash, constipation, and fatigue.
- Most common laboratory abnormalities (occurring in ≥ 30%): AST/ALT/GGT increased, creatine phosphokinase increased, hemoglobin decreased, cholesterol increased, triglycerides increased, creatinine increased, uric acid increased, lymphocytes decreased, and alkaline phosphatase increased.
- Less common, but potentially serious adverse reactions: interstitial lung disease (ILD)/pneumonitis, QT interval prolongation, and skeletal fractures.

PQI Process:

- All patients with newly diagnosed advanced NSCLC should receive molecular testing with next-generation sequencing (NGS), preferably with a platform that utilizes RNA sequencing as this enhances the ability to detect gene fusion events, such as *ROS1* fusions.[3]
    - Patients with previously identified *ROS1* fusions who are currently receiving treatment with a ROS1 TKI (such as crizotinib or entrectinib) should undergo repeat molecular testing with NGS to look for ROS1 resistance mutations that may be sensitive to taletrectinib.
    - Circulating tumor DNA (ctDNA) testing (liquid biopsy) may be used after a confirmed histologic tissue diagnosis if tissue specimen is inadequate for additional molecular testing.
- Evaluate liver function tests (LFTs) and electrolytes (comprehensive metabolic panel, CMP), ECG, uric acid, and verify pregnancy status of females of childbearing potential prior to initiating taletrectinib.[1]
- Drug-drug interactions (screen medication profile for the following interacting drugs prior to initiation and while on therapy):[1]
    - Strong and moderate CYP3A inhibitors: avoid concurrent use.
    - Strong and moderate CYP3A inducers: avoid concurrent use.
    - Gastric acid reducing drugs: avoid concurrent proton pump inhibitor (PPI) and H2 receptor antagonists. Administer locally acting antacids at least 2 hours before or 2 hours after taking taletrectinib.
    - Drugs known to prolong the QTc interval: avoid use; if use cannot be avoided, increase the frequency of ECG monitoring.

- Table 1. Dosing considerations for taletrectinib[1]

Dosage Form	200 mg capsules (in bottles of 30 capsules)
Usual Starting Dose	600 mg orally once daily on an empty stomach until disease progression or unacceptable toxicity
Dose Adjustments (for organ dysfunction)	Not specified
Dose Reductions (for toxicity)	400 mg once daily→ 200 mg once daily→ discontinue

- Monitor for:[1]
  - Signs and symptoms of rash, ILD/pneumonitis (new or worsening cough, new or worsening shortness of breath), muscle pain/tenderness/weakness, fracture (pain/changes in mobility/deformity), diarrhea/constipation, nausea/vomiting, dizziness, peripheral neuropathy, taste changes.
  - LFTs every 2 weeks for the first 2 months then monthly thereafter. Hold for Grade 3 AST or ALT (>5 – 20x ULN) or Grade 4 elevations. Permanently discontinue if ALT or AST ≥ 3x ULN with concurrent Tbili ≥ 2x ULN (in the absence of cholestasis or hemolysis).
  - CPK every 2 weeks for the first month then as clinically indicated for patients with muscle symptoms. Hold for CPK > 5x ULN.
  - ECG and electrolytes periodically as clinically indicated. Hold if QTc is > 480 msec.
  - Uric acid periodically during treatment.
  - Adherence to therapy
- Taletrectinib inhibits MATE1 and MATE2-K[1], which may increase serum creatinine without a true change in renal function. If more precise measurement of renal function is required, consider measuring cystatin C.[5]

Patient-Centered Activities:

- Once patient has a planned date for drug acquisition, ensure complete counseling on administration, proper handling/storage/disposal, missed dose management, side effect management, and reportable symptoms/side effects.
- Ensure that patient and caregiver(s) understand the goals of care and importance of adherence; provide any necessary tools to assist with adherence.
- Administer taletrectinib on an empty stomach (no food at least 2 hours before or after taletrectinib) at approximately the same time each day. Food, particularly high-fat meals, increases taletrectinib exposure and the risk of toxicity, especially hepatotoxicity. Do not open, chew, crush, or dissolve the capsule prior to swallowing.
- Avoid grapefruit and grapefruit juice.
- Inform your healthcare team of all prescription and OTC medications as well as herbal supplements prior to the start of therapy and whenever changes are made during treatment.
- If a dose is missed or vomited, take the next dose at its scheduled time the following day.
- May cause photosensitivity. Minimize sun exposure; use sun protection (including broad-spectrum sunscreen) during treatment and for at least 5 days after discontinuation.
- Ensure patient has access to sunscreen, loperamide, and antiemetics (as needed).
- Store at room temperature.
- This medication is considered hazardous; use appropriate handling precautions. If disposal of unused capsules is needed, contact your pharmacist for safe disposal options.
- Females of childbearing potential and males with partners of childbearing potential should use effective contraception during treatment and for 3 weeks after the last dose of taletrectinib.

- Do not breastfeed during treatment or for 3 weeks after the last dose of taletrectinib.
- If dose reductions must occur for toxicity, assure patient that duration of response and efficacy of taletrectinib are unlikely to be affected.[4]
- NuvationConnect™ is available for patients expressing concerns about financial toxicity (including copay assistance, bridge program for changes in insurance and insurance delays, and patient assistance program for uninsured or under-insured patients) at https://www.ibtrozi.com/patient-support/.

References:

1. Taletrectinib [package insert]. Burlington, MA: Nuvation Bio Inc.; 2025.
2. Papadopoulos KP, Borazanci E, Shaw AT, et al. U.S. phase 1 first-in-human study of taletrectinib (DS-6051b/AB-106), a ROS1/TRK inhibitor, in patients with advanced solid tumors. *Clin Cancer Res*. 2020;26(18):4785-4794.
3. National Comprehensive Cancer Network® (NCCN®). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer [v.8.2025]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed on 6 July 2025.
4. Pérol M, Li W, Pennell N, et al. Comparable efficacy and safety of taletrectinib for advanced ROS1+ non-small cell lung cancer across pivotal studies and between races and world regions. Poster presented at: American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, IL.
5. Chen MF, Harada G, Liu D, et al. Brief report: tyrosine kinase inhibitors for lung cancers that inhibit MATE-1 can lead to “false” decreases in renal function. *J Thorac Oncol*. 2024;19(1):153-159.