Written By: Danny Nguyen, MD
Nishan Tchekmedyian, MD
André K.D. Liem, MD
City of Hope National Medical Center

Positive Quality Intervention: Mobocertinib (Exkivity™) Side Effect Management

Description: Mobocertinib (Exkivity™) is an oral EGFR tyrosine kinase inhibitor (TKI) designed to specifically target *EGFR* ex20ins mutations.[1] This PQI will discuss effective strategies for side effect management.

Background: Mobocertinib is indicated in locally advanced or metastatic non-small cell lung cancer (NSCLC). Mobocertinib demonstrated meaningful clinical benefit in 114 platinum-pretreated patients (PPP) with *EGFR* ex20ins+ NSCLC in a phase 1/2 study (NCT02716116), with confirmed objective responses by independent assessment reported in 28% of patients and median duration of response of 17.5 months.[2] The most common side effect associated with mobocertinib is diarrhea (92%), followed by rash (78%), stomatitis (46%), vomiting (40%) and nausea (37%). Mobocertinib also includes a boxed warning for QTc prolongation and Torsade's de Pointes.[4]

On October 2, 2023, Takeda announced the initiation of a voluntary withdrawal of EXKIVITY (mobocertinib) from the market in the United States. Updates available here.

PQI Process:

- Monitoring[4]
  - Monitor QTc and electrolytes (sodium, potassium, calcium, and magnesium) at baseline and periodically during treatment
  - Monitor for new or worsening pulmonary symptoms indicative of interstitial lung disease (ILD)/pneumonitis and immediately withhold in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed
  - Monitor cardiac function, including left ventricular ejection fraction (EF), at baseline and during treatment. Withhold for reduced EF, then resume at reduced dose or permanently discontinue based on severity (see PI for specific details regarding reduction in EF)
  - If patient develops diarrhea, monitor electrolytes, advise patients to start an antidiarrheal agent at first episode, and increase fluid/electrolyte intake
    - Withhold, dose reduce, or permanently discontinue based on severity
- Drug-Drug Interactions [4]
  - Mobocertinib is a CYP3A4 substrate
    - Avoid concomitant use of mobocertinib with strong or moderate CYP3A inhibitors
      - If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the mobocertinib dose by approximately 50% (eg., from 160 to 80 mg, 120 to 40 mg, or 80 to 40 mg) and monitor the QTc interval more frequently
      - After the moderate CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume at the dose taken prior to initiating CYP3A inhibitor
    - Avoid concomitant use with strong/moderate CYP3A inducers, may reduce anti-tumor activity
    - Avoid concomitant use of hormonal contraceptives, but ensure effective contraception is used
    - Avoid concomitant use of other medications known to prolong the QTc interval
      - If use is unavoidable, monitor QTc interval more frequently with ECGs

Diarrhea Severity	**Intervention**
Grade 0 or Cycle 1, Day 1	Consider prophylaxis when prescribing mobocertinib: a) Loperamide 2 mg PO daily to BID (titrate to 1-2 BM per day)
Grade 1	Loperamide 4 mg, followed by 2 mg after each loose stool (max: 16 mg/day)
Grade 2	Interventions listed in Grade 1 and: a) Hold until ≤ Grade 1, then resume at same or next lower dose b) Diphenoxylate/atropine 5 mg QID until control achieved (max: 20 mg/day) c) Consider cholestyramine 4 g orally BID (30 minute prior to meals) d) Consider budesonide 9 mg daily for 4 weeks e) Assess the need for IV hydration (saline) frequently
Grade 3	Interventions listed in Grade 1 and 2 and: a) Hold until ≤ Grade 1, then resume at same or next lower dose b) Opium tincture (morphine 10 mg/mL) 6 mg of undiluted opium tincture QID c) Octreotide 100 to 150 mcg sq TID d) Strongly consider IV hydration unless contraindicated
Grade 4	a) Hold until ≤ Grade 1, then resume at same or next lower dose b) If Grade 4 reoccurs, permanently discontinue
Rash Severity	**Intervention**
Grade 0 or Cycle 1, Day 1	Consider prophylaxis with: a) Doxycycline 100 mg PO BID or Minocycline 100 mg PO BID b) Daily moisturizing lotion, bland emollient
Grade 1	Interventions listed in Grade 0 and: a) Face: hydrocortisone 1.0% to 2.5% BID to affected area Body: triamcinolone 0.1% BID to affected area b) Derma-Smoothe* 0.01% (or similar) apply topical TID to affected area copiously
Grade 2	Interventions listed in Grade 0 and 1 and: a) Add clindamycin 1.0% cream BID to affected area
Grade 3 or 4	Interventions listed in Grade 0 and: a) Hold mobocertinib until resolution of rash to Grade ≤ 1 b) Increase clindamycin 1.0% to 2.0% cream BID to affected area c) Start on oral prednisone 5 to 10 mg PO daily. Increase by 5 to 10 mg PO weekly depending on improvement. Alternatively, can start on a Medrol DosePak
Stomatitis Severity	**Intervention**
Grade 0 or Cycle 1, Day 1	Consider prophylaxis with: a) Dexamethasone 0.5 mg/5mL oral solution: 10 mL swish and spit QID 1 hour NPO b) Biotène mouthwash Doxycycline 100 mg PO BID or minocycline 100 mg PO BID
Grade 1	Interventions listed in Grade 0
Grade 2	Interventions listed in Grade 0 and: Magic mouthwash[1]
Grade 3	Interventions listed in Grade 2 and: a) Hold mobocertinib until resolution of mucositis to Grade ≤ 1 Start on oral prednisone 5 to 10 mg PO daily. Increase by 5 to 10 mg PO weekly depending on improvement. Alternatively, can start on a Medrol DosePak

*Special consideration for folliculitis/Rash involving the scalp

Patient-Centered Activities:[3]

- Provide Oral Chemotherapy Education (OCE) Sheet
- Provide complimentary Treatment Support Kit
- Counsel patient on how to take mobocertinib and the common side effects
- Some patients may find that certain foods or may worsen diarrhea and should be avoided
- Mobocertinib is associated with a moderate or high emetic potential; administering with food may reduce nausea; standard antiemetics may be used to manage vomiting or may utilize prophylactic antiemetics if needed
- Patients should be encouraged to maintain hydration, especially if they are experiencing diarrhea
- Taking mobocertinib at different times in the day may improve symptoms; instituting a brief dose hold on mobocertinib may be required to improve symptoms, but should be minimized (impact on effectiveness)[3]
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Riely GJ, Neal JW, Camidge DR, et al. Activity and safety of mobocertinib (TAK-788) in previously treated non–small cell lung cancer with *EGFR* exon 20 insertion mutations from a phase 1/2 trial. *Cancer Discov*. 2021;11(7):1688-1699.
2. Zhou C, Ramalingam SS, Kim TM, et al. Mobocertinib in platinum-pretreated patients with *EGFR* exon 20 insertion-positive metastatic non-small cell lung cancer: phase 1/2 open-label study. *JAMA Oncol*. 2021. In press.
3. Nguyen D, Ramalingam SS, Spira AI, et al. (2021, Oct). Characterization of GI Toxicities and Their Impact on Efficacy in Patients With *EGFR* Exon 20 Insertion+ (ex20ins+) Non–Small Cell Lung Cancer (NSCLC) Treated With Mobocertinib (TAK-788) Who Previously Received Platinum Chemotherapy. European Society for Medical Oncology (Virtual).
4. EXKIVITY (mobocertinib) [prescribing information].