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Positive Quality Intervention: Sotorasib (Lumakras®) for *KRAS* G12C-mutated Non-Small Cell Lung Cancer (NSCLC)

Description: The purpose of this PQI is to review Sotorasib treatment in KRAS G12C mutated NSCLC including management of adverse effects.

Background: Sotorasib (Lumakras®) is a first-in-class oral medication indicated for the treatment of adult patients with locally advanced or metastatic *KRAS* G12C-mutated non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy. A patient's *KRAS* G12C positive status must be determined by an FDA-approved test prior to therapy initiation.[1] Sotorasib is a second-line treatment administered orally once daily at a dose of 960 mg (eight 120 mg tablets) until disease progression or unacceptable toxicity. Lower dosing is currently under investigation making it important to know that dose adjustments may be common due to tolerability. It is the first FDA-approved highly selective *KRAS* inhibitor proven to successfully target *KRAS* G12C, once deemed an undruggable target. The efficacy of sotorasib was demonstrated through patient enrollment in Amgen's CodeBreaK 100, a single-arm, open-label, multicenter clinical trial (n= 357; 124 patients with *KRAS* G12C confirmed NSCLC in the phase 2 cohort).[2] The most common adverse reactions (≥ 20%) reported were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. Sotorasib can cause hepatotoxicity (1.7% all grades; 1.4% Grade 3) which may lead to drug-induced liver injury and hepatitis. Additionally, interstitial lung disease (ILD)/pneumonitis occurred in 0.8% of patients. All cases of ILD were Grade 3 or 4 at onset, and 1 case was fatal. Dosage modifications can be made for adverse reactions, with a maximum of two dose reductions permitted. In certain instances, sotorasib will need to be held or permanently discontinued *(*see Supplemental Information*)*.[1-3] Also of note, at the one year read out of CodeBreak 200, sotorasib demonstrated a progression free survival of 25% as compared to 10% for docetaxel. Providing guidance on priority placement over docetaxel in the initial readout.

PQI Process:[1,3] Upon receipt of an order for sotorasib (Lumakras®)

- Ensure the patient is *KRAS* G12C-mutated and has received at least one prior systemic therapy
  - Largely these patients have progressed on immunotherapy and chemotherapy
  - Refer to Sotorasib (Lumakras®) Companion Diagnostics (QIAGEN therascreen® KRAS RGQ PCR Kit and Guardant360® CDx) PQI for further information on *KRAS* G12C testing
- Discuss potential risks of sotorasib therapy (see Supplemental Information)
  - Hepatotoxicity
    - Monitor liver function tests (ALT, AST, and total bilirubin) at baseline, every 3 weeks for 3 months, then monthly or more frequently if elevated
    - Withhold, reduce dose, or permanently discontinue medication based on severity
  - ILD/Pneumonitis
    - Monitor for new or worsening pulmonary symptoms
    - Immediately withhold medication for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified
    - Consider use of ILD/Pneumonitis Assessment Tool
- Alternative administration for patients who have difficulty swallowing solids
  - Disperse tablets in 120 mL (4 ounces) of non-carbonated, room-temperature water without crushing *No other liquids should be used*
  - Stir until tablets are dispersed into small pieces (the tablets will not completely dissolve) and drink within 2 hours
    - The appearance of the mixture may range from pale yellow to bright yellow

        - Patient should be counseled to avoid chewing pieces of the tablet
    - Rinse the container with an additional 120 mL (4 ounces) of water and drink
    - If the mixture is not consumed immediately, stir again to ensure that tablets are dispersed
- Dosage modifications (review Supplemental Information)
    - If adverse reactions occur, a maximum of two dose reductions are permitted; discontinue sotorasib if patients are unable to tolerate the minimum dose of 240 mg once daily
- Drug-Drug interactions
    - Avoid coadministration with proton pump inhibitors (PPIs) and H2 receptor antagonists. Administer sotorasib 4 hours before or 10 hours after antacid therapy if therapy is necessary
    - Avoid co-administration with strong CYP3A4 inducers, CYP3A4 substrates, and P-gp substrates
    - Pharmacists should thoroughly review all concomitant medications, including prescription medications, over-the-counter medications, vitamins, dietary and herbal products

Patient-Centered Activities:[1,3,4]

- Provide Oral Chemotherapy Education Sheet
- Instruct the patient to swallow whole (do not cut/crush/chew) with or without food at approximately the same time each day
- Advise patients to inform their healthcare provider of all concomitant medications, including prescription and over-the-counter medications, vitamins, dietary and herbal products
- Inform patients to avoid co-administration with PPIs and H2 receptor antagonists; recommend to take sotorasib 4 hours before or 10 hours after antacid
- If the patient misses a dose of sotorasib by more than 6 hours, instruct them to take the next dose as prescribed the next day; do not take 2 doses at the same time to make up for the missed dose
- If vomiting occurs after taking sotorasib, the patient should not take an additional dose; the next dose should be taken the next day as prescribed
- Encourage patients to immediately contact their healthcare provider to report any signs and symptoms of liver dysfunction and/or new or worsening respiratory symptoms
- Inform the patient to avoid breastfeeding during treatment and for 1 week after discontinuation

Supplemental Information:

Table 1. Recommended LUMAKRAS Dose Reduction Levels for Adverse Reactions[1]

Dose Reduction Level	Dose
Initial dose	960 mg (8; 120 mg tablets or 3; 320 mg tablets) once daily
First dose reduction	480 mg (4 tablets) once daily
Second dose reduction	240 mg (2 tablets) once daily

Table 2. Recommended LUMAKRAS Dosage Modifications for Adverse Reactions[1]

Adverse Reaction	Severity[a]	Dosage Modification
Hepatotoxicity	Grade 2 AST or ALT with symptoms or Grade 3 to 4 AST or ALT	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	• Permanently discontinue LUMAKRAS.

Interstitial Lung Disease (ILD)/ pneumonitis	Any Grade	• Withhold LUMAKRAS if ILD/pneumonitis is suspected. • Permanently discontinue LUMAKRAS if ILD/pneumonitis is confirmed.
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy)	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Other adverse reactions	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[a] Grading defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

References:

1. Lumakras® (sotorasib) [package insert]. Thousand Oaks, CA: Amgen, Inc.
2. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *New England Journal of Medicine*. 2021;384(25):2371-2381. doi:10.1056/nejmoa2103695.
3. Lumakras® (sotorasib) [prescribing information]. Thousand Oaks, CA: Amgen, Inc.
4. Lumakras® (sotorasib) [patient information]. Thousand Oaks, CA: Amgen, Inc.