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

Positive Quality Intervention: Adagrasib (Krazati™)

Description: On December 12, 2022, the U.S. Food and Drug Administration (FDA) granted accelerated approval to adagrasib for the treatment of adult patients with KRAS^{G12C} mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA approved test, who have received at least one prior systemic therapy.[1]

Background: Adagrasib is the second KRAS^{G12C} inhibitor to be granted accelerated approval by the FDA, now joining sotorasib (Lumakras®; FDA-approved 5/28/21), for the management of patients with advanced NSCLC harboring a KRAS^{G12C} mutation. KRAS is the most frequently mutated oncogene in human cancers.[2] KRAS is a GTPase that cycles between an inactive GDP-bound state and an active GTP-bound state; the active state leads to a conformational change in the protein that promotes downstream signaling. Both the MAP kinase pathway and the PI3K-AKT-mTOR pathways are downstream of KRAS and these pathways regulate cell cycle/cellular proliferation and cell survival/resistance to apoptosis, respectively. In NSCLC, KRAS mutations are typically found in patients with adenocarcinoma histology and a smoking history. The most common KRAS mutation is G12C in which the normal glycine residue is replaced by cysteine at codon 12, found in 14% of lung adenocarcinomas.[3] Adagrasib is an orally available small molecule inhibitor of KRAS^{G12C} that covalently binds to the cysteine residue and locks the protein in the inactive GDP-bound state, preventing downstream signaling. The efficacy and safety of adagrasib was studied in the KRYSTAL-1 phase 1-2 study.[2] A phase 2 registrational cohort included patients with KRAS^{G12C} NSCLC who had previously received platinum chemotherapy and checkpoint inhibitor therapy. Patients received adagrasib in capsule form in the fasted state at a dose of 600 mg by mouth twice daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Of 116 patients treated, 112 were evaluable for response, and the ORR was 42.9%. The median duration of response was 8.5 months, and the median overall survival was 12.6 months. Treatment-related adverse events occurred in most patients with 44.8% experiencing Grade 3 or higher toxicity. Most common Grade ≥ 3 being lab abnormalities, cardiac disorders, infections, fatigue, musculoskeletal pain, nausea, and decreased appetite. The most common adverse events were diarrhea, nausea, vomiting, fatigue, increased ALT/AST, and increased Scr. These side effects were managed with dose holds, dose reductions, and supportive care interventions. Only 6.9% of patients had to discontinue drug due to toxicity. The FDA approved adagrasib in a tablet formulation based on this surrogate endpoint of ORR and duration of response.[4] A phase 3 confirmatory trial, KRYSTAL-12 (NCT04685135), comparing adagrasib to docetaxel in the second-line setting is ongoing.

PQI Process:

- All patients with metastatic lung adenocarcinoma, large cell carcinoma, or NSCLC NOS should undergo broad molecular profiling, preferably with next-generation sequencing (NGS), to identify patients with KRAS^{G12C} mutations; testing should be considered for patients with squamous histology[5]
    - FDA-approved tests for the detection of KRAS^{G12C} are QIAGEN therascreen KRAS RGQ PCR kit (tissue), Agilent Resolution ctDx FIRST Assay (plasma), and Guardant360 CDx (plasma)[6]
- Physicians and advanced practice providers should identify patients who are candidates for adagrasib therapy by confirmation of KRAS^{G12C} and documented progression of disease after receipt of prior chemotherapy and/or immunotherapy
- Adagrasib will be available through a limited distribution network (Biologics and Onco360) or through medically integrated pharmacies/dispensaries
- Review all existing patient prescriptions for any necessary dose adjustments or alternative therapy
    - Avoid use with CYP3A, CYP2C9, CYP2D6, and P-gp substrates

    - Avoid with QTc prolonging medications
    - There are no interaction with PPI, H2 Blockers, or antacids
- Once medication access is secured and an estimated start date is known, schedule patient for medication education session, if not already completed; ensure that patient understands rationale for treatment, expected benefit, how to take medication, common and rare but serious side effects, and when to call the healthcare team
- Table 1. Dosing considerations for adagrasib

Dosage form	200 mg tablets
Usual starting dose	600 mg (3 tablets) twice daily orally ± food
Dose adjustments (renal/hepatic)	None reported
Dose reductions for toxicity	400 mg twice daily → 600 mg daily → discontinue

- Monitoring parameters[1,4]
    - Liver function tests at baseline; monthly for 3 months and as clinically indicated
    - Blood creatinine levels at baseline; monthly for 3 months and as clinically indicated
    - Complete blood count with differential at baseline and periodically while on treatment
    - ECG and electrolytes (for QT interval prolongation) at baseline and as clinically indicated
    - Signs/symptoms of interstitial lung disease/pneumonitis (new or worsening cough or shortness of breath)

Patient Centered Activities:[1]

- Provide Oral Chemotherapy Education (OCE) Sheet
- Adagrasib is associated with a moderate or high emetic potential; antiemetics may be recommended to prevent nausea and vomiting
- Counseling pearls
    - Swallow tablet whole; do not crush, chew, or split
    - If vomiting occurs do not take an additional dose; resume dosing at next scheduled time
    - Gastrointestinal toxicity: take with food and consider prophylactic or PRN antiemetics as well as counsel patient on the use of OTC anti-diarrheals (loperamide)
    - Potential for significant drug interactions: notify care team about any new medications prescribed by other doctors or OTC or herbal supplements
    - May cause infertility: encourage patients of child-bearing potential to discuss fertility preservation with the care team prior to treatment start

References:

1. *Krazati™ (adagrasib)*. United States Package Insert.
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3. Parikh, K., Banna G., Liu S. V., Friedlander A., Desai A., Subbiah V., & Addeo A. (2022). Drugging KRAS: current perspectives and state-of-art review. *Journal of Hematology & Oncology*, *15*(152). https://doi.org/10.1186/s13045-022-01375-4.
4. Zhang, J. et. al. (2023). Practical Guidance for the Management of Adverse Events in Patients with KRASG12C-Mutated Non-Small Cell Lung Cancer Receiving Adagrasib. The Oncolgist. https://doi.org/https://doi.org/10.1093/oncolo/oyad05.
5. National Comprehensive Cancer Network. *Non-small cell lung cancer*. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
6. U.S. Food and Drug Administration. (2022, Dec 2). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#CDx_Table.