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Positive Quality Intervention: Sotorasib (Lumakras®) Companion Diagnostics (QIAGEN therascreen® KRAS RGQ PCR Kit and Guardant360® CDx)

Description: Sotorasib (Lumakras®) is a first-in-class oral medication FDA-approved 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. In order to be assessed for drug eligibility, a patient's *KRAS* G12C positive status must first be determined by an FDA-approved companion diagnostics test including QIAGEN therascreen® KRAS RGQ PCR Kit or Guardant360® CDx prior to therapy initiation.[1,2]

Background: Sotorasib is the first FDA-approved, once-daily, oral, highly selective *KRAS* inhibitor proven to successfully target *KRAS* G12C, a once deemed undruggable target. The *KRAS* protein functions as an on/off switch to the body's cell growth regulator. When the *KRAS* protein becomes mutated, the cellular on/off switch becomes fixed in the "on" position thereby leading to tumor formation caused by continuous and uncontrollable cell growth. *KRAS* G12C is documented as one of the most common oncogenic driver mutations seen in NSCLC, whereby 1 in 8 NSCLC patients possess this biomarker.[3] *KRAS* mutations are most often found in smokers; however they can occur regardless of clinical or demographic characteristics.[2] Proven to have reduced responsiveness to *EGFR* tyrosine kinase inhibitors, this actionable driver mutation now highlights a gene-drug match with sotorasib (Lumakras®) as a targeted treatment option for eligible patients.[4] Such personalized treatment regimens are planned and tailored with the clinical application of pharmacogenomic test results from FDA-approved tissue and/or liquid companion diagnostics utilizing Next Generation Sequencing (NGS), real-time polymerase chain reaction (PCR), and Sanger sequencing methods. *KRAS* G12C testing via a comprehensive broad molecular panel or single-gene biomarker testing should be considered for all NSCLC at diagnosis as this mutation is considered to be truncal (clonal) in nature - typically arising early on and remaining stable during disease progression.[2]

PQI Process:

- Upon consideration of treatment with sotorasib (Lumakras®), ensure *KRAS* G12C-mutation and patient has received at least one prior systemic therapy
    - Clinical practice guidelines including NCCN, ASCO, and CAP/IASLC/AMP recommend testing for actionable biomarkers such as *KRAS* in all eligible patients with advanced NSCLC utilizing either a comprehensive panel or targeted testing[2]
    - The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and testing techniques, but do not endorse any specific commercially available biomarker assays or commercial laboratories[4]

- Companion Diagnostics Test Selection
    - FDA-approved tissue and liquid companion diagnostics are available to test for *KRAS* G12C using well-validated common molecular testing methods[2]
    - Physicians should use their own medical judgment in determining which test is most appropriate for their patients
    - Treatment is indicated based on the presence of the *KRAS* G12C mutation in either tumor or plasma/liquid biopsy specimens. Liquid biopsy has high degrees of concordance with tissue-based testing, with 93% concordance for *KRAS* mutations in patients with mNSCLC.[2] However, if no mutation is detected in a plasma specimen, tumor tissue should be tested for confirmation.
    - Tissue PCR: QIAGEN therascreen® *KRAS* RGQ PCR Kit[5,6]
        - First and only FDA-approved tissue diagnostic for *KRAS* G12C to help guide the

treatment of NSCLC
        - Detection of 7 somatic mutations in *KRAS* gene (codons 12/13 including *KRAS* G12C)
        - Available as a ready-to-use kit and reagents
    - Liquid NGS: Guardant360 ® CDx[7,8]
        - The first FDA-approved liquid biopsy test that utilizes NGS
        - Designed to detect 55 gene mutations found in circulating cell-free DNA (cfDNA) within the patient's blood
        - A liquid biopsy is useful to replace or complement tissue analysis, depending on the clinical scenario (ex. if the patient is unable to repeat a tissue biopsy or if there is insufficient tissue sample remaining from their original tissue biopsy to allow for testing)
- Clinical Practice Recommendations:
    - Information on the aforementioned FDA-approved companion diagnostics tests can be found at www.qiagen.com/KRAS and www.guardant360cdx.com
    - Assess a patient's archival tissue to determine its eligibility based on limited quantity or deemed insufficient for NGS
    - When comparing broad molecular profiling versus single-gene biomarker testing, it has been noted that comprehensive panel testing conserves tissue and is cost-effective while avoiding the added cost and risk of a repeat biopsy
    - *KRAS* mutations are reported at the variant level, thus the provider should be aware of the various nomenclatures for interpretation by which the specific variant may be notated (ex. *KRAS* G12C, *KRAS Gly12Cys* or *KRAS 12Cys*)[2]
    - For eligible patients, retrospective data mining is recommended for past reports of *KRAS* G12C identified as a variant of unknown/uncertain significance (VUS) prior to the approval of sotorasib (Lumakras®)
    - Consider formulating a plan to maintain records of test results for all actionable biomarkers for future reference[2]

Patient-Centered Activities:

- Testing for actionable biomarkers is recommended at diagnosis via a broad, panel-based approach[2]
- All eligible patients with NSCLC should consider seeking testing for *KRAS* G12C
- *KRAS* G12C testing can be performed via a biopsy either using tissue from the tumor (tissue biopsy) or a blood test (liquid biopsy)
- Patients are encouraged to share any prior pathology, germline (genetic testing), and/or somatic (NGS, PCR, etc.) reports with their current healthcare team in order to provide full access to the patient's identified predictive and prognostic biomarkers for the best informed treatment decisions based on precision medicine
- A patient's out-of-pocket (OOP) cost will vary depending on their insurance; the average patient OOP cost is $0 for original Medicare and $65 for commercially insured patients[2]
    - Financial assistance is also offered through many of the commercially available biomarker assays or laboratories

References:

1. Lumakras® (sotorasib) [package insert]. Thousand Oaks, CA: Amgen, Inc.
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4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer v.5.2022.
5. QIAGEN therascreen® KRAS RGQ PCR Kit CDx test Flashcard.
6. U.S. Food and Drug Administration. therascreen KRAS RGQ PCR Kit - P110027/S012.
7. Guardant360® CDx test Flashcard.
8. U.S. Food and Drug Administration. Guardant360 CDx - P200010/S002.