Adagrasib (KRAZATI)
National Drug Monograph
May 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Adagrasib inhibits *KRAS* G12C, which is a tumor-restricted, mutant-oncogenic form of *KRAS*
- Adagrasib forms a covalent irreversible bond with the mutant cysteine in *KRAS* G12C, locking the protein in an inactive state that prevents downstream signaling; wild-type *KRAS* is not affected

Indication(s) Under Review in This Document

- 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*
  *This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

Dosage Form(s) Under Review

- Recommended dosage: 600 mg (3 x 200 mg tablets) orally twice daily
- Swallow tablets whole with or without food

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of adagrasib was evaluated in KRYSTAL-1, a phase I/II study of patients with advanced solid tumors that have a *KRAS* G12C mutation. Clinical activity has been shown in patients with solid tumors, including lung (non-small cell), colorectal, pancreatic, and biliary tract. The FDA-approval is based on results from Cohort A, a phase 2 subset of adults with *KRAS* G12C-mutated NSCLC previously treated with platinum-based chemotherapy and checkpoint inhibitor therapy, which demonstrated an objective response.
- Efficacy data from Cohort A of KRYSTAL-1 are summarized in Table 1

Table 1: Efficacy results from Cohort A of KRYSTAL-1

Design	Results
Phase II, open-label, non-randomized controlled trial **Inclusion:** Age ≥18; diagnosis of unresectable or metastatic NSCLC with *KRAS* G12C mutation and previous treatment with ≥1 platinum-	**Demographic** / **Result (N = 116)** Age, Median (Range) / 64 (25-89) Gender, % female / 56 ECOG PS 1, % / 84

containing chemotherapy regimen and checkpoint inhibitor therapy (in sequence or concurrently); ECOG PS 0-1

Exclusion: Active CNS metastases[a]; carcinomatous meningitis; receipt of systemic therapy or radiation therapy within 2 weeks before the first dose of adagrasib; previous treatment with a KRAS G12C inhibitor

Intervention: Adagrasib 600 mg PO twice daily on an empty stomach until the occurrence of disease progression (or lack of clinical benefit per judgment of the investigator), unacceptable adverse events, withdrawal of consent, or death

Primary Endpoints: ORR assessed by blinded independent central review (IRC); duration of response (DoR)

Secondary Endpoints: Disease control (complete response [CR], partial response [PR], or stable disease [SD]); time to response (TTR); PFS; OS; 1-year survival rate

Subgroup Analyses: ORR by baseline characteristics

Exploratory Analyses: Candidate biomarkers (PD-L1 status); mutational status of STK11, KEAP1, TP53, and CKDN2A

Post-hoc Analyses: Intracranial ORR; intracranial DoR; intracranial PFS

Current or former smokers, %	96
Adenocarcinoma histology, %	97
Previous platinum-based chemotherapy, %	98%
Previous platinum-based chemotherapy and checkpoint inhibitor therapy	98%
Number of previous systemic therapies, Median	2
≥4 previous systemic regimens, %	12
Baseline metastases, % Bone CNS Adrenal Liver	 40 21 19 16

Median F/U of 12.9 mo as of data cutoff for all endpoints except OS[b] and intracranial ORR[c]; median duration of treatment of 5.7 mo (range, 0.03 to 19.6)

112/116 had measurable disease at baseline according to IRC; n = 112 for all efficacy endpoints unless otherwise specified

Primary Endpoints:
ORR[d], # (%) = 48 (42.8%); CR = 1 (0.9); PR = 47 (42.0)
mDoR (n = 48): 8.5 mo (95% CI, 6.2-13.8)
Secondary Endpoints:
Disease control, # (%): 89 (79.5)
mTTR (n = 48): 1.4 mo (range, 0.9-7.2)
mPFS: 6.5 mo (95% CI, 4.7-8.4)
mOS: 12.6 mo (95% CI, 9.2-19.2)
Estimated OS at 1 yr: 50.8% (95% CI, 40.9-60.0)

Subgroup Analyses: Consistent efficacy across most prespecified subgroups except those who were current smokers and those with adrenal metastases at baseline (ORR = 9.1% and 21.7%, respectively)

Exploratory Analyses:

Mutation	N	ORR, %
PD-L1		
<1%	47	46.8
1-49%	27	44.4
≥50%	12	41.7
STK11		
Wild-type (WT)	48	47.9
Mutated	42	40.5
KEAP1		
WT	60	51.7
Mutated	21	28.6
TP53		
WT	60	41.7
Mutated	35	51.4
CDKN2A		

	WT Mutated	49 12	44.9 58.3
	***STK11*- and *KEAP1*-mutated**	14	35.7
	***STK11*-mutated and *KEAP1*-WT**	25	44.0
	***STK11*-WT and *KEAP1*-mutated**	7	14.3
	***STK11*- and *KEAP1*-WT**	34	55.9

Post-hoc Analyses (n = 35 unless otherwise specified)
Intracranial ORR: 33.3% (95% CI, 18.0-51.8)
Intracranial DoR: 11.2 mo (95% CI, 2.99-NE)
Intracranial mPFS (n = 42): 5.4 mo (95% CI, 3.3-11.6)

[a] Patients were eligible if CNS metastases were adequately treated and neurologically stable
[b] OS data based on median F/U of 15.6 mo
[c] Intracranial response data based on median F/U of 15.4 mo
[d] 17 patients (15.2%) could not be evaluated; ORR in the 95 clinically evaluable patients was 50.5%
Definitions: ORR = percent of patients documented to have a confirmed CR or PR; DoR = time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of objective progression of disease (PD) or death due to any cause; disease control = percent of patients documented to have an objective response (CR or PR) plus percent of patients documented to have stable disease; mTTR = time from date of first study treatment to first CR or PR; PFS = time from date of first study treatment to first PD or to death due to any cause; OS = time from date of first study treatment to death due to any cause

- In this phase 2 cohort, treatment led to durable clinical benefit in patients with previously treated, advanced KRAS G12C-mutated NSCLC
- Treatment with adagrasib led to a confirmed ORR of 42.9%, a median DoR of 8.5 mo, a mPFS of 6.5 mo, and a median OS of 12.6 mo
- Adagrasib showed evidence of clinical efficacy across most subgroups defined according to baseline characteristics, including in patients with CNS metastases, and across most co-occurring mutations

Safety Considerations

Safety Results from Clinical Trials:

- The safety of adagrasib was evaluated in KRYSTAL-1, a phase I/II study of patients with advanced solid tumors
- 85 patients (73.3%) had discontinued adagrasib at the time of data cutoff, with the most common reasons being disease progression (in 31 patients [26.7%]) and adverse events (in 16 patients [13.8%])
- Treatment-related adverse events led to dose reduction in 60 patients (51.7%) and dose interruption in 71 patients (61.2%), with the most common reasons being gastrointestinal-related events, hepatic events (increased ALT and AST levels), and fatigue
- Safety data from Cohort A of KRYSTAL-1 are summarized in Table 2

Table 2: Safety results from Cohort A of KRYSTAL-1

Event	Regardless of Attribution, # (%)	Treatment-Related, # (%)
Any	116 (100)	113 (97.4)
Any Grade ≥3	95 (81.9)	52 (44.8)
Adverse event leading to:		
Dose reduction	--	60 (51.7)
Dose interruption	--	71 (61.2)
Either	96 (82.8)	--
Adverse event leading to discontinuation	18 (15.5)	8 (6.9)
Common (≥20%)		
Diarrhea	82 (70.7)	73 (62.9)
Nausea	81 (69.8)	72 (62.1)
Fatigue	69 (59.5)	47 (40.5)
Vomiting	66 (56.9)	55 (47.4)
Anemia	42 (36.2)	21 (18.1)
Dyspnea	41 (35.3)	--
Increased blood creatinine	40 (34.5)	30 (25.9)
Decreased appetite	37 (31.9)	28 (24.1)
Increased ALT	33 (28.4)	32 (27.6)
Peripheral edema	33 (28.4)	12 (10.3)
Increased AST	31 (26.7)	29 (25.0)
Constipation	27 (23.3)	--
Hyponatremia	27 (23.3)	12 (10.3)
Cough	24 (20.7)	--
Dizziness	24 (20.7)	--
Grade ≥3 (≥5%)		
Anemia	14.7	6 (5.2)
Pneumonia	12.1	--
Dyspnea	10.3	--
Hyponatremia	8.6	5 (4.3)
Hypoxia	7.8	--
Increased lipase	7.8	7 (6.0)
Fatigue	6.9	5 (4.3)
Acute kidney injury	6.9	2 (1.7)
Malignant neoplasm progression	6.9	--
Lung infection	6.9	--
Decreased lymphocyte count	6.0	2 (1.7)
ECG QT prolonged	6.0	5 (4.3)
Increased ALT	5.2	4 (3.4)
Increased AST	5.2	4 (3.4)
Sepsis	5.2	--

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**:
    - **GI toxicity:** Adagrasib may cause severe GI adverse reactions and may result in dose reduction or discontinuation. GI bleeding and GI obstruction have been reported, including grade 3 and 4 events; colitis, ileus, and stenosis have also occurred. Nausea, diarrhea, or vomiting was reported in the majority of patients, including grade 3 events. Supportive care should be provided as needed

- **Hepatotoxicity:** Adagrasib may cause hepatotoxicity, which may result in drug-induced liver injury and hepatitis. In a clinical trial, increased ALT and/or AST were observed, including grade 3 and 4 events in 5.2% of patients. The median time to first onset of elevated ALT and/or AST was 3 weeks (range: 0.1 to 48 weeks). Monitor liver function laboratory tests prior to starting
  - Inclusion criteria in the KRYSTAL-1 trial included baseline total bilirubin ≤1.5 times the upper limit of normal (ULN) [or ≤3 times the ULN if associated with liver metastases or Gilbert's disease) and AST and ALT ≤3 times the ULN (or ≤5 times the ULN if associated with liver metastases)
- **Pulmonary toxicity:** Interstitial lung disease (ILD)/pneumonitis may occur and could be fatal. In a clinical trial, ILD/pneumonitis was reported; grade 3 or higher cases were observed in 2.6% of cases, including one fatality. The median time to first onset of ILD/pneumonitis was 12 weeks (range: 5 to 31 weeks)
- **QTc interval prolongation:** Adagrasib may cause QTc interval prolongation, which may increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death. In a clinical trial, grade 3 or higher QTc prolongation occurred in 6.0% of patients. In patients who had at least one postbaseline ECG in a clinical study, an average QTc ≥501 msec was observed in a small percent of patients, and some patients had an increase from baseline of QTc >60 msec. Adagrasib causes concentration-dependent QTc interval increases. Avoid adagrasib in patients with congenital long QT syndrome and in those with concurrent QTc prolongation, as well as in patients taking other medications known to prolong the QTc interval. Monitor EKG and electrolytes prior to starting
  - Exclusion criteria in the KRYSTAL-1 trial included baseline QTc >480 milliseconds or family history of long QT syndrome

- **Adverse reactions:**
  - **Common (≥20%)**: Nausea, fatigue, vomiting, anemia, dyspnea, increased blood creatinine level, and decreased appetite
  - **Serious adverse events / Deaths / Discontinuation:**
    - The most common grade 3 or higher treatment-related adverse events were fatigue, nausea, and increased transaminases
    - Two grade 5 fatal events were reported, one cardiac failure in a patient with a medical history of pericardial effusion and one pulmonary hemorrhage
    - Treatment-related adverse events led to dose reduction in 60 patients (51.7%), dose interruption in 71 patients (61.2%), and discontinuation in 8 patients (6.9%); the most common reasons were gastrointestinal-related events, increased transaminases, and fatigue

Other Considerations

- **Appropriate use:** Select patients for treatment of locally advanced or metastatic non–small cell lung cancer based on the presence of KRAS G12C mutation in tumor or plasma specimens; if no mutation is detected in a plasma specimen, test tumor tissue. Information on approved tests for the detection of KRAS G12C mutations is available at http://www.fda.gov/CompanionDiagnostics
- **Pregnancy considerations:** In animal reproduction studies, adverse embryo-fetal events in the presence of maternal toxicity were observed using doses near the recommended human dose
- **Breastfeeding considerations:** It is not known if adagrasib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 1 week after the last adagrasib dose
- **Dosage adjustment for concomitant therapy:**
  - Strong CYP3A4 inducers: Avoid concomitant use
  - Strong CYP3A4 inhibitors: Avoid concomitant use until adagrasib concentrations have reached steady state
  - Sensitive CYP3A4, CYP2C9, CYP2D6, or P-gp substrates: Avoid concomitant use as minimal concentration changes may lead to serious adverse reactions
  - Drugs that prolong QT interval: Avoid concomitant use

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:**
  - **ORR: 42.8%**
  - **mDoR: 8.5 mo**
  - mPFS: 6.5 mo
  - mOS: 12.6 mo
- **Effect Size:**
  - **ORR: 95% CI, 33.5-52.6**
  - **mDoR: 95% CI, 6.2-13.8**
  - mPS: 95% CI, 4.7-8.4
  - mOS: 95% CI, 9.2-19.2
- **Potential Harms:** Moderate
- **Net Clinical Benefit:** N/A (accelerated approval)

Other Therapeutic Options

Supporting efficacy and safety data for other KRAS G12C inhibitors and chemotherapy options in the second-line and beyond settings (following platinum-based therapy and immune checkpoint inhibitors, if eligible) are summarized in Table 3.

Table 3 Treatment Alternatives

Drug/Regimen	Formulary Status	Clinical Guidance	Other Considerations
Adagrasib	TBD	**FDA-approved indication (accelerated approval): For 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** VHA Clinical Pathway for NSCLC: No current recommendation for adagrasib **Efficacy:** **KRYSTAL-1** Phase 2 study of patients with previously treated, locally-advanced and unresectable or metastatic NSCLC with KRAS G12C mutation **ORR** = 42.8% (95% CI, 33.5-52.6) **mPFS:** 6.5 mo (95% CI, 4.7-8.4) **mOS:** 12.6 mo (95% CI, 9.2-19.2) **Estimated OS at 1 yr:** 50.8% (95% CI, 40.9-60.0) ~21% of patients included had previously treated, asymptomatic brain metastases; **intracranial ORR:** 33.3% (95% CI, 18.0-51.8); **intracranial**	**Dosing:** 600 mg PO twice daily until disease progression or unacceptable toxicity; no clinically significant differences in PK for CrCL 15-90 mL/min or in mild to severe hepatic impairment **PK:** Half-life = 23 hr; metabolism = hepatic via CY3A4; inhibits its own CYP3A4 metabolism at steady state, which allows CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2D6 to contribute to metabolism **Drug-drug interactions:** Strong CYP3A4 inducers or inhibitors; sensitive CYP3A4, CYP2C9, CYP2D6, or P-gp substrates; drugs that prolong QT interval **Warnings and precautions:** Gastrointestinal adverse reactions; QTc interval prolongation; hepatoxicity; interstitial lung disease (ILD)/pneumonitis **Safety:** **Event** | **# (%)** **Any** | 116 (100)

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<td>mPFS (n = 42): 5.4 mo (95% CI, 3.3-11.6)

ORRs with respect to co-mutations:
<table>
<tr><th>Mutation</th><th>ORR, %</th></tr>
<tr><td>PD-L1</td><td></td></tr>
<tr><td><1%</td><td>46.8</td></tr>
<tr><td>1-49%</td><td>44.4</td></tr>
<tr><td>≥50%</td><td>41.7</td></tr>
<tr><td>STK11</td><td></td></tr>
<tr><td>Wild-type (WT)</td><td>47.9</td></tr>
<tr><td>Mutated</td><td>40.5</td></tr>
<tr><td>KEAP1</td><td></td></tr>
<tr><td>WT</td><td>51.7</td></tr>
<tr><td>Mutated</td><td>28.6</td></tr>
<tr><td>TP53</td><td></td></tr>
<tr><td>WT</td><td>41.7</td></tr>
<tr><td>Mutated</td><td>51.4</td></tr>
<tr><td>CDKN2A</td><td></td></tr>
<tr><td>WT</td><td>44.9</td></tr>
<tr><td>Mutated</td><td>58.3</td></tr>
<tr><td>STK11- and KEAP1-mutated</td><td>35.7</td></tr>
<tr><td>STK11-mutated and KEAP1-WT</td><td>44.0</td></tr>
<tr><td>STK11-WT and KEAP1-mutated</td><td>14.3</td></tr>
<tr><td>STK11- and KEAP1-WT</td><td>55.9</td></tr>
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<table>
<tr><td>Any Grade ≥3</td><td>95 (81.9)</td></tr>
<tr><td>Common (≥20%)</td><td></td></tr>
<tr><td>Diarrhea</td><td>82 (70.7)</td></tr>
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<tr><td>Vomiting</td><td>66 (56.9)</td></tr>
<tr><td>Anemia</td><td>42 (36.2)</td></tr>
<tr><td>Dyspnea</td><td>41 (35.3)</td></tr>
<tr><td>Increased SCr</td><td>40 (34.5)</td></tr>
<tr><td>Decreased appetite</td><td>37 (31.9)</td></tr>
<tr><td>Increased ALT</td><td>33 (28.4)</td></tr>
<tr><td>Peripheral edema</td><td>33 (28.4)</td></tr>
<tr><td>Increased AST</td><td>31 (26.7)</td></tr>
<tr><td>Constipation</td><td>27 (23.3)</td></tr>
<tr><td>Hyponatremia</td><td>27 (23.3)</td></tr>
<tr><td>Cough</td><td>24 (20.7)</td></tr>
<tr><td>Dizziness</td><td>24 (20.7)</td></tr>
<tr><td>Grade ≥3 (≥5%)</td><td></td></tr>
<tr><td>Anemia</td><td>14.7</td></tr>
<tr><td>Pneumonia</td><td>12.1</td></tr>
<tr><td>Dyspnea</td><td>10.3</td></tr>
<tr><td>Hyponatremia</td><td>8.6</td></tr>
<tr><td>Hypoxia</td><td>7.8</td></tr>
<tr><td>Increased lipase</td><td>7.8</td></tr>
<tr><td>Fatigue</td><td>6.9</td></tr>
<tr><td>Acute kidney injury</td><td>6.9</td></tr>
<tr><td>Disease progression</td><td>6.9</td></tr>
<tr><td>Lung infection</td><td>6.9</td></tr>
<tr><td>Decreased lymphocytes</td><td>6.0</td></tr>
<tr><td>ECG QT prolonged</td><td>6.0</td></tr>
<tr><td>Increased ALT</td><td>5.2</td></tr>
<tr><td>Increased AST</td><td>5.2</td></tr>
<tr><td>Sepsis</td><td>5.2</td></tr>
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Emetic risk: Moderate to high (≥30%)
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<td>Sotorasib</td>
<td>NF</td>
<td><u>FDA-approved indication (accelerated approval): For the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy</u>

VHA Clinical Pathway for NSCLC – Non-Squamous Relapse: For patients with KRAS G12C-mutated, metastatic NSCLC as second-line therapy following progression after chemotherapy plus or minus immunotherapy or immunotherapy alone (either used in combination or sequentially, respectively)</td>
<td>Dosing: 960 mg PO once daily until disease progression or unacceptable toxicity; has not been studied when eGFR <30 mL/min or in moderate to severe hepatic impairment

PK: Half-life = 5 hr; metabolism = nonenzymatic conjugation and oxidative metabolism via CYP3As; bioavailability = absorption increased when administered with a high-fat, high-calorie meal

Drug-drug interactions: Acid-reducing agents; strong CYP3A4 inducers; CYP3A4 substrates; P-gp substrates</td>
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Efficacy

CodeBreaK100:

Phase 2 study of patients with previously treated, locally-advanced and unresectable or metastatic NSCLC with KRAS G12C mutation

ORR: 46/126 patients (37.1%), with CR in 4 (3.2%) and PR in 42 (33.9%)

mPFS: 6.8 mo (95% CI, 72.6-87.2)

mOS: 12.5 mo (95% CI, 10.0-NE)

~20% of patients included had previously treated, asymptomatic brain metastases; **intracranial response not studied**

ORRs with respect to co-mutations:

Mutation	N	ORR, %
PD-L1		
<1%	44	48
1-49%	33	39
≥50%	9	22
STK11		
WT	69	39
Mutated	35	40
KEAP1		
WT	84	44
Mutated	20	20
TP53		
WT	20	40
Mutated	84	39
STK11**- and *KEAP1*-mutated**	13	23
STK11**-mutated and *KEAP1*-WT**	22	50
STK11**-WT and *KEAP1*-mutated**	7	14
STK11**- and *KEAP1*-WT**	62	42

CodeBreaK200:

Phase 3 comparing sotorasib vs. docetaxel in patients with previously treated, locally-advanced and unresectable or metastatic NSCLC with KRAS G12C mutation

mPFS: 5.6 mo vs. 4.5 mo (HR, 0.66; 95% CI, 0.51-0.89)

mOS: 10.6 mo vs. 11.3 mo (HR, 1.01; 95% CI 0.77-1.33)

Warnings and precautions:

Hepatoxicity; ILD

Safety:

Common ADRs per package labeling: Diarrhea; MSK pain; nausea; fatigue; hepatoxicity; cough; decreased lymphocytes; decreased hemoglobin; increased ALT/AST; decreased calcium; increased Alk Phos; increased urine protein; decreased sodium

Emetic risk: Minimal to low (<30%)

Docetaxel	F	**FDA-approved indication: As a single agent for locally advanced or metastatic NSCLC after platinum therapy failure** VHA Clinical Pathway for NSCLC – Non-Squamous Relapse: For patients with metastatic NSCLC (without *KRAS* G12C, *EGFR* exon 20 insertion, or *HER2/*ERBB2) as second- or third-line therapy following progression with immunotherapy and chemotherapy (either used in combination or sequentially, respectively) VHA Clinical Pathway for NSCLC – Squamous Relapse: For patients with metastatic NSCLC as third-line following progression (defined as >4 sites not amenable to radiation) on chemotherapy with or without immunotherapy ***J Clin Oncol. 2000 Jun;18(12):2354-62:*** Phase 3 comparing docetaxel 100 mg/m2 (D100) or 75 mg/m2 (D75) vs. control (vinorelbine or ifosfamide [V/I]) **ORR:** 10.8% with D100 vs. 6.7% with D75 vs. 0.8% with V/I (D[100+75] vs. V/I: p = 0.002) **PFS at 26 weeks:** 19 weeks with D100 vs. 17 weeks with D75 vs. 8 weeks with V/I (D[100+75] vs. V/I: p = 0.005) **OS:** 5.5 mo with D100 vs. 5.7 mo with D75 with 5.6 mo with V/I (D[100+75] vs. V/I: p = NS) **1-yr survival:** 21% with D100 vs. 32% with 19% (D[100+75] vs. V/I: p = 0.025)	**Dosing:** 75 mg/m2 IV every 3 weeks until disease progression or unacceptable toxicity; no renal dose adjustments needed; hepatic dose adjustments required **PK:** Half-life = 11 hr; metabolism = hepatic oxidation via CYP3A4 to metabolites **Drug-drug interactions:** CYP3A4 inducers, inhibitors, or substrates **Black box warnings:** Increased mortality; hepatic function impairment; neutropenia; hypersensitivity; fluid retention **Warnings and precautions:** Second primary malignancies; cutaneous reactions; neurologic reactions; eye disorders; asthenia; embryo-fetal toxicity; alcohol content; tumor lysis syndrome **Safety:** Common ADRs per package labeling: Infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia **Emetic risk:** Low (10-30%) **Pre-medications:** Corticosteroids for 3 days, beginning 1 day prior to docetaxel administration for prevention of fluid retention and hypersensitivity reactions

Projected Place in Therapy

- Lung cancer is the third most common type of cancer in the United States, with approximately 80% to 85% of cases being NSCLC. Lung cancer is consistently one of the top two cancers diagnosed in the VHA.
- Mutations in *KRAS* G12C occur in approximately 14% of adenocarcinomas and in 0.5% to 4% of squamous NSCLCs

- First-line treatment of NSCLC in the metastatic setting, regardless of *KRAS* G12C mutation status, is well-established and consists of immunotherapy alone or in combination with platinum-based chemotherapy
- For patients with a *KRAS* G12C mutation, guidelines suggest sotorasib or adagrasib as subsequent therapy following progression on or after first-line. Single-agent or combination chemotherapy is recommended for third-line and beyond
- The CodeBreaK100 trial evaluated sotorasib in patients with previously treated, locally-advanced and unresectable metastatic NSCLC with *KRAS* G12C mutation. The objective response rate was approximately 37%, with a median progression free survival of 6.8 months and a median overall survival of 12.5 months
    - The confirmatory phase 3 trial, CodeBreaK200, did not show a significant difference in overall survival compared with docetaxel
- Similarly, the KRYSTAL-1 trial evaluated adagrasib in patients with previously treated, locally-advanced and unresectable metastatic NSCLC with *KRAS* G12C mutation. The objective response rate was approximately 43%, with a median progression free survival of 6.5 months and a median overall survival of 12.6 months
    - The KRYSTAL-12 trial is a confirmatory phase 3 trial designed to compare adagrasib vs. docetaxel. The trial is currently enrolling patients and results are not yet available
- While caution should be used interpreting cross-trial comparisons, current data suggests adagrasib may have increased intracranial activity and enhanced activity in patients with co-occurring mutations compared with sotorasib, at the potential cost of increased toxicity, QTc prolongation, and additional drug-drug interactions
- In the VA, adagrasib should be reserved for 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. Patients who have previously received another KRAS G12C inhibitor such as sotorasib should not receive adagrasib

References

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information