NCCN Guidelines: Systemic Therapy for Patients with *KRAS* G12C Mutated Advanced NSCLC

First line (PS 0-1)

Preferred	Other recommended	Useful in certain circumstances
Pembrolizumab + chemotherapy as appropriate for histology*	Additional combination regimens involving: • Atezolizumab**, • Nivolumab/ipilimumab, • Cemiplimab-rwlc, or • Tremelimumab-actl/durvalumab, as appropriate for histology*	Contraindications to PD-1/PD-L1 inhibitors • Chemotherapy as appropriate for histology* • Bevacizumab + chemotherapy for adenocarcinoma*

*Bevacizumab and pemetrexed not recommended for SCC
**Atezolizumab not recommended for first line treatment of SCC

Subsequent therapy

Second line	Later lines	
After at least 1 previous line of therapy: • **Adagrasib** • **Sotorasib**	If no previous G12C targeted therapy: • **Adagrasib** • **Sotorasib** Adagrasib and sotorasib have a similar MoAs and it is not recommended to switch between these agents at time of progression.	Or other systemic therapy: Preferred (no previous IO) • Nivolumab • Pembrolizumab • Atezolizumab Other (no previous or previous IO) • Chemotherapy as appropriate for histology

See guidelines for full recommendations. PS, performance status; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; MoAs, mechanisms of action; IO, immunotherapy. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023. Updated April 13, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450.

Adagrasib in *KRAS* G12C Mutated Advanced NSCLC

Efficacy Results

KRYSTAL-1

Phase 1/2 multicohort, open label trial

- Solid tumors with *KRAS* G12C mutation
- Unresectable or metastatic disease
- Treated or stable brain metastases
- **Cohort A (NSCLC):** Progression on or following treatment with a PD-1 or PD-L1 inhibitor in combination with or following platinum-based chemotherapy (results shown here)

	Cohort A (N = 112)
Objective response, n, %, (95% CI)	48, 42.9% (33.5–52.6)
Disease control, n (%)	89, 79.5% (70.8–86.5)
Median duration of response, mo (95% CI)	8.5 (6.2–13.8)
Median PFS, mo (95% CI)	6.5 (4.7–8.4)
Median OS, mo (95% CI)*	12.6 (9.2–19.2)

Data cutoff date for efficacy end points: October 15, 2021 (median follow-up, 12.9 months) except mOS

*Updated data cutoff date for mOS: January 15, 2022 (median follow-up, 15.6 months)

FDA approved Dec. 2022 for patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy

PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; CI, confidence interval; PFS, median progression-free survival; mOS, median overall survival; mo, months.

Jänne PA et al. *N Engl J Med*. 2022;387:120-131; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Adagrasib in *KRAS* G12C Mutated Advanced NSCLC

Safety Results

KRYSTAL-1

Cohort A (NSCLC)
Safety population (N = 116)

	n (%)
Any adverse event	Any grade: 116 (100) Grade ≥3: 95 (81.9)
Adverse event leading to dose reduction or interruption	96 (82.8)
Adverse event leading to discontinuation of therapy	18 (15.5)

TRAEs in >20% of patients	Any grade, n (%)	Grade ≥3, n (%)
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	42 (36.2)	17 (14.7)
Dyspnea	41 (35.3)	12 (10.3)
Blood creatinine increased	40 (34.5)	1 (0.9)
Decreased appetite	37 (31.9)	5 (4.3)
ALT increased	33 (28.4)	6 (5.2)
Edema peripheral	33 (28.4)	0
AST increased	31 (26.7)	6 (5.2)
Constipation	27 (23.3)	0
Hyponatremia	27 (23.3)	10 (8.6)
Cough	24 (20.7)	1 (0.9)
Dizziness	24 (20.7)	1 (0.9)

TRAEs, treatment-related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Jänne PA et al. *N Engl J Med*. 2022;387:120-131.

Sotorasib in *KRAS* G12C Mutated Advanced NSCLC

Efficacy Results

CodeBreaK 100

Phase 1/2 multicenter, open label trial

- Locally advanced or metastatic NSCLC
- *KRAS* G12C mutation
- Progressed on prior standard therapies
- Stable brain metastases allowed

Registrational data	N = 124
Objective response, % (95% CI)	37.1 (28.6–46.2)
Disease control, % (95% CI)	80.6 (72.6–87.2)
Median duration of response, mo (95% CI)	11.1 (6.9–NE)

Data cutoff date: March 15, 2021 (median follow-up, 15.3 mo)

Updated 2-year analysis	N = 174
Objective response, % (95% CI)	41 (33.3–48.4)
mDOR, mo (95% CI)	12.3 (7.1–15.0)
DCR, % (95% CI)	84 (77.3–88.9
mPFS, mo (95% CI)	6.3 (5.3–8.2)
mOS, mo (95% CI)	12.5 (10.0–17.8)

Data cutoff date: February 22, 2022 (median follow-up, 24.9 mo)

FDA approved May 2021 for patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy

CI, confidence interval; mDOR, median duration of response; DCR, disease control rate; mo, months; mPFS, median progression-free survival; mOS, median overall survival; NE, not evaluable.

Skoulides F et al. *New Engl J Med*. 2021;384:2371-2381; Dy GK et al. *J Clin Oncol*. 2023:Jco2202524; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Sotorasib in *KRAS* G12C Mutated Advanced NSCLC

Safety Results

CodeBreak 100

Phase 1/2 multicenter, open label trial
Safety population (N = 126)

	n (%)
Any adverse event	Any grade: 125 (99.2) Grade ≥3: 95 (81.9)
Treatment-related adverse event (TRAE)	96 (82.8)
TRAE leading to discontinuation of therapy	18 (15.5)

TRAEs in >5% of patients	Any grade, n (%)	Grade ≥3, n (%)
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
ALT increase	19 (15.1)	8 (6.3)
AST increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)
Maculopapular rash	7 (5.6)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Skoulides F et al. *New Engl J Med*. 2021;384:2371-2381.