Adagrasib (Krazati®) as monotherapy for the treatment of advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]

The active substance of Krazati® is adagrasib (MRTX849), a KRAS G12C (Kirsten rat sarcoma viral oncogene homologue) inhibitor which covalently and irreversibly binds to the unique cysteine of KRAS G12C. Inactivation of KRAS G12C by adagrasib blocks tumour cell signalling and survival inhibits cell growth and promotes apoptosis selectively in tumours harbouring KRAS G12C, an oncogenic driver of tumorigenesis.

Indication [1]

Adagrasib (Krazati®) as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy.

Incidence [2]

In Austria, in 2020, the age-standardized[1] incidence rate of carcinomas of the lung, bronchia and trachea was 67.4/100,000 in men and 41.1/100,000 in women.

Current treatment [3]

For the treatment of stage IV NSCLC with KRAS mutations, Onkopedia recommends the following:

- Oncogenic KRAS mutations occur in approximately 30% of cases in NSCLC, especially in adenocarcinomas, depending also on ethnicity and smoking status.
- The most common, oncogenic KRAS variants in NSCLC are G12C ~53%, G12V ~27%, G12D~6%, G12A ~6%, G12S ~4%, others ~4%.
- In the phase II CodeBreak 100 trial, 124 patients with second-line KRASG12C mutations were given sotorasib 960 mg/day after platinum-containing chemotherapy or immunochemotherapy. The response rate was 37.1% and the median PFS was 6.3 months. The 2-year survival rate was 32.5%.
- Sotorasib is approved for KRASG12C-mutated NSCLC patients after failure of standard first-line therapy. There are no approvals for the other mutated KRAS alleles.
- In a recent analysis of the randomized phase III CodeBreak 200 trial comparing sotorasib vs. docetaxel in patients with KRASG12C-mutated NSCLC patients, sotorasib led to prolongation of PFS (median 1.1 months; HR 0.66; p=0.002), but not in OS. Comparison of toxicity showed advantages for sotorasib in alopecia, anaemia, fatigue and stomatitis, and disadvantages for diarrhoea and elevated transaminases.
- Other, KRASG12C-specific TKIs are in clinical development. This also includes combination therapies.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On 9 November 2023, the CHMP, following a **re-examination** procedure, adopted a positive opinion recommending the granting of a conditional marketing authorisation for Krazati®. The full indication is: ❖ Krazati® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy. Adagrasib (Krazati®) will be available as 200 mg film-coated tablets. **Other indications**: none ✓ **Medicine received a conditional marketing authorisation[2]**	**Approval status for this indication**: not approved **Other indications:** On 12 December 2022, the FDA granted accelerated approval to adagrasib (Krazati®), for adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. FDA also approved the QIAGEN therascreen KRAS RGQ PCR kit (tissue) and the Agilent Resolution ctDx FIRST Assay (plasma) as companion diagnostics for Krazati®. If no mutation is detected in a plasma specimen, the tumour tissue should be tested.

Manufacturer

Krazati® is manufactured by Mirati Therapeutics B.V.

[1] European Standard Population 2013.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks, and the applicant should be in a position to provide the comprehensive clinical data in the future.

Costs

Currently, there is no cost information available.

Study characteristics [5-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
KRYSTAL-1 NCT03785249	116	adagrasib 600 mg orally twice daily	-	objective response assessed by BICR	12.9 months	**ongoing**[3], single-arm, registrational phase 2 cohort trial	KRAS	Mirati Therapeutics	KRYSTAL-1 [7]

Inclusion criteria[4]

- ≥18 years with a histologically confirmed diagnosis of a solid tumour malignancy with KRAS G12C mutation.
- Unresectable or metastatic disease.
- Available and prior therapy:
  - no available treatment with curative intent,
  - no available standard-of-care treatment or the patient is ineligible or declines treatment, except
  - in Phase 2 NSCLC cohorts, patients must have previously received treatment with at least a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy.
- Presence of tumour lesions is to be evaluated per RECIST 1.1.
- Life expectancy of at least 3 months.
- Most recent prior systemic therapy and radiation therapy were discontinued at least 2 weeks before the first dose date.
- Recovery from the adverse effects of prior therapy at the time of enrolment to ≤ Grade 1 (excluding alopecia).
- ECOG PS 0 or 1.
- Laboratory values within the screening period:
  - Absolute neutrophil count ≥ 1,000/mm^3 (≥ 1.0 x 10^9/L)
  - Platelet count ≥ 100,000/mm^3 (≥ 100 x 10^9/L)
  - Haemoglobin ≥ 9 g/dL, in the absence of transfusions for at least 2 weeks
  - Total bilirubin ≤1.5 x ULN (if associated with liver metastases or Gilbert's disease, ≤3 x ULN)
  - AST and ALT ≤3.0 x ULN (if associated with liver metastases, ≤5 x ULN)
  - Calculated creatinine clearance ≥60 mL/min by the Cockcroft-Gault equation.

Exclusion criteria

- Active brain metastases.
- Patients with carcinomatous meningitis.
- History of significant haemoptysis or haemorrhage within 4 weeks of the first dose date.
- Undergone major surgery within 4 weeks of first dose date.
- History of intestinal disease or major gastric surgery likely to alter the absorption of study treatment or inability to swallow oral medications.
- Any of the following cardiac abnormalities within the last 6 months:
  - Unstable angina pectoris.
  - Congestive heart failure ≥ NYHA Class 3.
  - QTc > 480 milliseconds or family history of Long QT Syndrome.
- History of stroke or transient ischemic attack within the previous 6 months.
- Ongoing need for a medication with a known risk of Torsades de Pointes that cannot be switched to alternative treatment prior to study entry.
- Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.
- Known HIV seropositivity or active Hepatitis B or C. Patients treated for hepatitis C with no detectable viral load are permitted.
- Pregnancy.
- Breast-feeding or planning to breastfeed during the study or within 6 months after study treatment.
- Any serious illness, uncontrolled inter-current illness, psychiatric illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the

Patient characteristics at baseline (n=116)

- Median age: 64 years (range, 25-89)
- Female sex: 56.0%
- Race or ethnic group:
  - White: 83.6%
  - Black: 7.8%
  - Asian: 4.3%
  - American Indian or Alaskan Native: 0.9%
  - Other: 3.4%
- ECOG PS score
  - 0: 15.5%
  - 1: 83.6%
  - Data missing: 0.9%
- Smoking history
  - Never smoked: 4.3%
  - Current smoker: 9.5%
  - Former smoker: 86.2%
- Histologic type
  - Adenocarcinoma: 97.4%
  - Squamous: 2.6%
- Disease stage
  - Locally advanced: 11.2%
  - Metastatic: 88.8%
- Previous lines of systemic therapy
  - 1: 43.1%
  - 2: 34.5%
  - 3: 0.3%
  - ≥4: 12.1%
- Previous platinum-based therapy or checkpoint inhibitor therapy
  - Previous platinum-based therapy only: 1.7%
  - Both therapies: 98.3%
- Baseline metastases burden

[3] KRYSTAL-1 trial is currently ongoing; the estimated study completion date is 09/2024.
[4] For detailed in- and exclusion criteria, please see Study Protocol.

❖ Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agree to use contraception while participating in this study and for a period of 6 months following termination of study treatment. ❖ Completed informed consent process. ❖ Willing to comply with clinical trial instructions and requirements.	patient's participation in the study, or with the interpretation of the results. ❖ Exclusion criterion specific to Phase 2 cohorts: • Prior treatment with a therapy targeting KRAS G12C mutation.	• Bone: 39.7% • CNS: 20.7% • Adrenal: 19.0% • Liver: 16.4% ❖ PD-L1 tumour proportion score • PD-L1 <1%: 40.5% • PD-L1 1 to 49%: 23.3% • PD-L1 ≥50%: 10.3% • Data not available: 25.9%

Efficacy (n=112[5])	**Safety** (n=116)
Data cutoff date: 15 October 2021 **Confirmed ORR**: 42.9% (95% CI, 33.5-52.6) **Tumour shrinkage of any magnitude**: 79.5% **CR:** 0.9% **PR**: 42.0% **Stable disease for a minimum of 6 weeks:** 36.6% **Progressive disease was the best overall response**: 5.4% **ORR among the 95 patients who were clinically evaluable and had an on-treatment scan obtained at the specified time**: 50.5%. **Patients who received adagrasib beyond investigator-assessed progression**: 76.9% **The median duration of treatment beyond progression**: 6.6 weeks **Median time to response among 48 patients with a response**: 1.4 months (range, 0.9-7.2); median duration of response: 8.5 months (95% CI, 6.2-13.8) **Patients with a response still receiving treatment at the data cutoff date**: 33.3% **Kaplan–Meier estimate of the duration of response among patients with a response at 9 months**: 48.4% (95% CI, 32.5-2.6) **Median PFS**: 6.5 months (95% CI, 4.7-8.4) **Median OS:** 11.7 months (95% CI, 9.2-NE) **Updated data cutoff date 15 January 2022 (median follow-up of 15.6 months)** **Median OS**: 12.6 months (95% CI, 9.2-19.2) **Estimated OS at 1 year:** 50.8% (95% CI, 40.9-60.0) **Post hoc evaluation for intracranial response; median follow-up 15.4 months:** **Intracranial confirmed ORR as assessed by the independent committee**: 33.3% (95% CI, 18.0-51.8) **Median duration of intracranial response**: 11.2 months (95% CI, 2.99-NE) **Median intracranial PFS in 42 patients with CNS metastases at baseline**: 5.4 months (95% CI, 3.3-11.6) **Exploratory Biomarker Analyses** ❖ Confirmed ORR in patients with co-occurring alterations in STK11, KEAP1, TP53, and CDKN2A: 40.5%, 28.6%, 51.4%, and 58.3%, respectively.	**Any AE of any grade**: 100% **Any AE of grade ≥3**: 81.9% **AEs leading to dose reduction or interruption**: 82.8% **AEs leading to discontinuation of therapy**: 15.5% **AEs attributed by the investigators to the treatment**: 97.4% **Grade ≥3 or higher treatment-related AEs**: 44.8% **Grade 5 fatal events**: 1.7%[6] **Discontinuation of adagrasib due to TRAEs**: 6.9%

[5] 4 patients had measurable disease at baseline according to investigator assessment but not according to the independent committee.
[6] 1 cardiac failure in a patient with a medical history of pericardial effusion and 1 pulmonary haemorrhage.

- ❖ Further analysis of patients with co-occurring alterations in STK11, KEAP1, or both indicated that responses were observed across genomically defined populations (35.7-55.9%) but were lower for those who had STK11 wildtype with a KEAP1 co-mutation (14.3%).
- ❖ Of 86 patients assessed for PD-L1 expression, confirmed ORR were similar across PD-L1 expression subgroups (41.7-46.8%).

Patient-reported outcomes

The evaluation of patient-reported outcomes is not provided in this trial.

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 42.9%	-	ORR ≥40-<60	2	>30% grade 3-4 toxicities	-	-1[7]	1

Due to the low level of evidence (single-arm study design) the adapted scale was not applied.

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at a similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly, described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[8]	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by the results?	Were both competing interests and sources of support for the study reported?
yes	yes	yes	yes	no	yes	yes	partial[9]	yes

Overall risk of bias: Moderate

Ongoing trials [11]

NCT number/trial name	Description	Estimated study completion date
NCT03785249 / KRYSTAL-1	Please see above.	09/2024
NCT04613596 / KRYSTAL-7	A phase 2 trial of MRTX849 monotherapy in combination with pembrolizumab and a phase 3 trial of adagrasib in combination with pembrolizumab vs. pembrolizumab in patients with advanced NSCLC with KRAS G12C mutation.	10/2029
NCT04685135 / KRYSTAL-12	Phase 3 study of MRTX849 vs. docetaxel in patients with advanced NSCLC with KRAS G12C mutation.	12/2024

Available assessments

- ❖ In May 2023, NIHR published a Health Technology Briefing „Adagrasib for previously treated KRAS G12C mutated advanced non-small-cell lung cancer" [12].
- ❖ No assessments were identified via NICE, CADTH, G-BA and ICER.

Other aspects and conclusions

- ❖ In November 2023, the **CHMP,** following a re-examination procedure, **adopted a positive opinion** recommending the granting of a conditional marketing authorisation for Krazati®. Krazati® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy. In December 2022, the **FDA** granted accelerated approval to Krazati® for adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy.
- ❖ **KRYSTAL-1** (NCT03785249) is an **ongoing, single-arm,** registrational **phase 2** cohort trial, evaluating adagrasib in patients with KRASG12C-mutated NSCLC previously treated with platinum-based chemotherapy and anti–PD-1 or PD-L1 therapy. Eligible patients were ≥18 years old with a histologically confirmed diagnosis of unresectable or metastatic NSCLC with KRASG12C

[7] Toxicity adjustment -1.
[8] Characteristics at baseline were heterogenous (e.g. ECOG, number of previous therapies, metastases burden).
[9] KRYSTAL-1 1 is currently ongoing and final analysis data is not available.

mutation who had previously received treatment with at least one platinum-containing chemotherapy regimen and checkpoint inhibitor therapy, who had measurable tumour lesions according to the RECIST, version 1.1; and who had an ECOG PS score of 0 or 1. Exclusion criteria were active CNS metastases, carcinomatous meningitis, receipt of systemic therapy or radiation therapy within 2 weeks before the first dose of adagrasib, and previous treatment with a KRASG12C inhibitor.

- The primary endpoint was the **objective response** assessed **by BICR**. After a median follow-up of 12.9 months, **42.9%** of patients achieved a confirmed objective response.
- The evaluation of **patient-reported outcomes is not provided** in the KRYSTAL-1 trial.
- The **original ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit **grade of 1**. Due to the low level of evidence (single-arm study design) the adapted scale was not applied.
- The **risk of bias** was considered **moderate**. It is **increased** by the single-arm trial design, heterogenous patient characteristics at baseline and its ongoing status.
- Besides the KRYSTAL-1 trial, two ongoing trials, assessing the efficacy and safety of adagrasib in patients with advanced NSCLC, were identified.
- Final analysis data of the KRYSTAL-1 trial is required, as well as robust **phase 3 data** from further trials. In particular, evaluation of **patient-reported outcomes** is essential.

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Abbreviations: AE=adverse event, AJ=adjustment, BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, KRAS=Kirsten rat sarcoma viral oncogene homologue, MG=median gain, n=number of patients, NE=not evaluable, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, NSCLC=non-small cell lung cancer, NYHA=New York Heart Association, ORR=objective response rate, OS=overall survival, PD-1=programmed death 1, PD-L1= programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse event, ULN=upper limit of normal, WOCBP=woman of childbearing potential

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