Sotorasib (Lumykras®) as monotherapy for the treatment of advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation

General information

Drug description [1, 2]	Indication [1]
Sotorasib (Lumykras®) is a Kirsten rat sarcoma viral oncogene homolog (KRAS) G12C inhibitor, which covalently and irreversibly binds to the unique cysteine of KRAS G12C. Inactivation of KRAS G12C by sotorasib blocks tumour cell signalling and survival inhibits cell growth and promotes apoptosis selectively in tumours harbouring KRAS G12C, an oncogenic driver of tumorigenesis. Activating mutations in KRAS are found in 25 to 30% of non–squamous-cell NSCLCs, representing the most prevalent genomic driver event in NSCLC.	Sotorasib (Lumykras®) as monotherapy is indicated for the treatment of adults with advanced NSCLC with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.

Current treatment [3]

- ❖ There are currently no recommended treatment options for treating KRASG12C mutated, metastatic NSCLC.
- ❖ The current treatment options for second-line or greater treatment of metastatic NSCLC are often stratified by genetic mutation and can include:
  - Docetaxel
  - Pemetrexed
  - Brigatinib.

Regulatory status

EMA [1]

Approval status for this indication: On 11 November 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Lumykras®, intended for the treatment of patients with KRAS G12C mutation NSCLC.

Update: Date of issue of marketing authorisation valid throughout the European Union: 06/01/2022 [6]

The full indication is:

- ❖ Lumykras® as monotherapy is indicated for the treatment of adults with advanced NSCLC with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.

- ✓ **Additional monitoring**
- ✓ **Conditional marketing authorisation**

Other indications: none

FDA [4, 5]

Approval status for this indication: On 28 May 2021, the FDA granted accelerated approval to sotorasib (Lumakras™), a RAS GTPase family inhibitor, 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.

- ✓ This indication is approved under accelerated approval based on ORR and DOR.
- ✓ Priority review, fast-track, breakthrough therapy and orphan drug designation.

FDA also approved the QIAGEN therascreen® KRAS RGQ PCR kit (tissue) and the Guardant360® CDx (plasma) as companion diagnostics for Lumakras™. If no mutation is detected in a plasma specimen, the tumour tissue should be tested.

Other indications: none

Costs

240 Lumykras® tablets 120 mg = € 7,541.00 (ex-factory price) [7]

Warnings and precautions [5]

- ❖ **Hepatotoxicity:**

- Monitor liver function tests every 3 weeks for the first 3 months of treatment then once monthly as clinically indicated.
- Withhold, reduce dose, or permanently discontinue Lumakras™ based on the severity.

❖ **Interstitial lung disease (ILD)/pneumonitis:**

- Monitor for new or worsening pulmonary symptoms.
- Immediately withhold Lumakras™ for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

Study characteristics [2, 8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CodeBreaK100 NCT03600883	124[1]	sotorasib orally at a dose of 960 mg once daily	-	objective response (complete or partial response) according to BICR	multicenter, single-group, open-label, phase 2 trial, ongoing[2]	KRAS	Amgen and the National Institutes of Health	[2]

Efficacy (n=124)

Objective response: n=46/124 (37.1%), 95% CI, 28.6-46.2
Complete response: n=4/124 (3.2%)
Partial response: n=42/124 (33.9%)
Disease control: n=100/124 (80.6%), 95% CI, 72.6-87.2
Tumour shrinkage of any magnitude: n=102/124 patients (82.3%)
Median best percentage decrease from baseline in tumour burden[3] among all the patients who had a response: 60%
Disease progression was the best overall response in 20 patients.
Median time to response among the 46 patients with an objective response: 1.4 months (range, 1.2-10.1)
Median DOR: 11.1 months (95% CI, 6.9-could not be evaluated)
Kaplan–Meier estimate of DOR (among patients with a response): 90.5% (95% CI, 76.7-96.3) at **3 months**, 70.8% (95% CI, 54.3-82.2) at **6 months**, and 57.3% (95% CI, 40.4- 71.0) at **9 months**
The median PFS: 6.8 months (95% CI, 5.1-8.2)
Kaplan–Meier estimate of PFS: 52.2% (95% CI, 42.6-60.9) at **6 months** and 37.5% (95% CI, 28.4-46.5) at **9 months**
Median OS (among all 126 enrolled patients): 12.5 months (95% CI, 10.0-could not be evaluated)

Exploratory Biomarkers

❖ Among the 86 patients who were assessed for PD-L1 expression, objective response and tumour shrinkage were observed across the range of baseline PD-L1 expression levels, with 48% (95% CI, 32-63) of the patients in the PD-L1–negative group (tumour proportion score, <1%) having a response, as well as 42% (95% CI, 31-53) of the overall population of patients who could be evaluated.

❖ Among the 84 patients who were assessed for tumour mutational burden, a response was seen in 42% (95% CI, 30-55) of the patients in the subgroup with a low tumour mutational burden (<10 mutations per megabase) and in 40% (95% CI, 16 to 68) of those in the subgroup with a high tumour mutational burden (≥10 mutations per megabase).

Safety (n=126)

AEs of any grade: n=125/126 (99.2%)
AEs of grade 3: n=53/126 (42.1%)
AEs of grade 4: n=4/126 (3.2%)
Treatment-related AEs of any grade: n=88/126 (69.8%)
Treatment-related AEs of grade 3: n=25/126 (19.8%)
Treatment-related AEs of grade 4: n=1/126 (0.8%)
Discontinuation due to treatment-related AEs: n=9/126 (7.1%)
Fatal AEs: n=20/126 (15.9%); no treatment-related AEs of grade 5 were reported.

[1] A total of 126 patients were enrolled; 2 patients did not have measurable lesions at baseline and were ineligible for response assessment.
[2] The CodeBreak100 is currently ongoing; estimated study completion date is 07/2026.
[3] Defined as the sum of the longest diameters of all target lesions.

- Among the 104 patients who were assessed for co-occurring genomic alterations, efficacy was seen in the subgroups with mutated STK11, KEAP1, or TP53. A response was seen in 50% (95% CI, 28-72) of the patients in the subgroup with mutated STK11 and wild-type KEAP1 and in 39% (95% CI, 30-49) of the overall population of patients who could be evaluated.
- Among patients with mutated KEAP1, a response was seen in 23% (95% CI, 5-54) of those in the subgroup with both mutated STK11 and KEAP1 and in 14% (95% CI, 0-58) of those in the subgroup with wild-type STK11 and mutated KEAP1.

PROs :

- Of 126 patients enrolled, compliance rates for each of the questionnaires were high throughout the study (>70%); data up to cycle 11 (where n>20) are presented.
- EORTC QLQ-C30 global health status/QoL and physical functioning were maintained over time (least-square mean changes ranged from -3.5-0.2 and 0.1-3.9, respectively).
- EORTC QLQ-C30 symptoms of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, and constipation were stable or improved.
- Similarly, key lung cancer-related symptoms, as measured by EORTC QLQ-LC13, remained stable or improved from baseline, with the greatest least-square mean change of -11.2 (95% CI: -16.2, -6.1) for cough, -4.9 (95% CI: -10.3, 0.4) for chest pain, and -3.4 (95% CI: -7.8, 1.0) for dyspnea.
- Most patients reported on the GP5 that they were "not at all" (54.2%-79.2%) or "a little bit" (8.3%-33.3%) bothered by side effects from sotorasib, with 0%-7.4% reporting being bothered as "quite a bit" and 0% as "very much".
- In CodeBreak100-patients, PRO measures suggested maintenance or improvement of global health status/QoL, physical functioning, and the severity of key lung cancer-related symptoms, including cough, dyspnea, and chest pain. Self-reported side effect bother was minimal.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original[4]	NC	3	-	-	-	ORR (PR+CR) ≥20-<60% AND DOR ≥9 months	3	45.3% grade 3-4 AEs	maintenance or improvement of PROs	+1/-1	3
Adapted	-	-	-	-	-	-	-	-	-	-	-

Risk of bias - study level (case series) [13]

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 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	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 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 results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes

[4] The ESMO-MCBS form 3 is only applied for single-arm studies in „orphan diseases" and for diseases with „high unmet need" when primary endpoint is PFS or ORR. There is no adapted version of form 3.

Overall risk of bias: low
First published: 11/2021 **Last updated**: 04/2011

Abbreviations: AE=adverse event, AJ=adjustment, BICR=blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DOR=duration of response, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GP5=a single item of the Functional Assessment of Cancer Therapy-General version, GTPase=guanosine triphosphatase, HR=hazard ratio, I=intervention, ILD=interstitial lung disease, Int.=intention, KRAS=Kirsten rat sarcoma viral oncogene homologue, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, ORR=overall response rate, OS=overall survival, PCR=polymerase chain reaction, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, PROs=patient-reported outcomes, QoL=quality of life, RGQ=rotor-gene Q, SAE=serious adverse event, ST=standard treatment

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