Pralsetinib (Gavreto®) as monotherapy for the treatment of patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]	Indication [2]
Pralsetinib is a highly potent, oral, selective RET inhibitor.	Pralsetinib is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

Current treatment [3]

- At the advanced stage (III and IV), NSCLC treatment aims to control cancer for as long as possible and help with symptoms.
- Treatment generally includes chemotherapy, targeted drugs, radiotherapy and symptom control treatment.
- There are specific treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations but not for RET fusions/mutations.
- Patients with NSCLC (with no gene mutation or fusion protein that has a specific treatment pathway) who progress after platinum-based therapy receive:
  - Immunotherapy treatment with pembrolizumab, nivolumab or without PD-L1 expression; atezolizumab.
  - Docetaxel with or without the multikinase inhibitor nintedanib.

Regulatory status

EMA	FDA [5, 6]
Approval status for this indication: On 16 September 2021, CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Gavreto®. The full indication is: ❖ Gavreto® is indicated as monotherapy for the treatment of adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 18/11/2021 **Other indications**: none ✓ Medicine under additional monitoring ✓ Medicine received a conditional marketing authorisation[1]	**Approval status for this indication**: On 4 September 2020, the FDA granted accelerated approval to pralsetinib (Gavreto®) for adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test. **Other indications**: Gavreto® is indicated for the treatment of: ❖ Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy. This indication is approved under accelerated approval based on the overall response rate and duration of response. ❖ Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on the overall response rate and duration of response.

Costs [7]

120 Gavreto® hard capsules 100 mg = 8,200.20 (ex-factory price)

Warnings and precautions

- **Interstitial Lung Disease (ILD)/Pneumonitis:**
  - Withhold Gavreto® for Grade 1 or 2 reactions until resolution and then resume at a reduced dose.
  - Permanently discontinue for recurrent ILD/pneumonitis.
  - Permanently discontinue for Grade 3 or 4 reactions.
- **Hypertension:**

[1] 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.

- Do not initiate Gavreto® in patients with uncontrolled hypertension.
- Optimise blood pressure prior to initiating Gavreto®.
- Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated.
- Withhold, reduce dose, or permanently discontinue Gavreto® based on severity.

❖ **Hepatotoxicity:**
- Monitor ALT and AST prior to initiating Gavreto®, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated.
- Withhold, reduce dose, or permanently discontinue Gavreto® based on severity.

❖ **Hemorrhagic Events:**
- Permanently discontinue Gavreto® in patients with severe or life-threatening haemorrhage.

❖ **Tumour Lysis Syndrome:**
- Closely monitor patients at risk and treat as clinically indicated.

❖ **Risk of Impaired Wound Healing:**
- Withhold Gavreto® for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.
- The safety of resumption of Gavreto® after resolution of wound healing complications has not been established.

❖ **Embryo-Foetal Toxicity:**
- Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective non-hormonal contraception.

❖ **QT prolongation:**
- Prolongation of the QT interval has been observed in patients who received Gavreto® in clinical trials. Therefore, before starting Gavreto® treatment, patients should have a QTc interval ≤470 ms and serum electrolytes within normal range.
- Hypokalaemia, hypomagnesaemia, and hypocalcaemia should be corrected both prior and during Gavreto® treatment.
- Electrocardiograms and serum electrolytes should be monitored at the end of the first week and of the first month of Gavreto® treatment, then periodically, as clinically indicated, depending also on presence of other risk factors (e.g. intercurrent diarrhoea, vomiting, nausea, concomitant medications).
- Pralsetinib should be used with caution in patients with medical history of cardiac arrhythmias or QT interval prolongation, as well as in patients on strong CYP 3A4 inhibitors or on medicinal products known to be associated with QT/QTc prolongation.
- Gavreto® may require interruption, dose modification, or discontinuation.

Study characteristics [1, 9, 10]

Trial name	*n*	Intervention	Comparator	PE	Characteristics	Biomarker	Funding	Publication(s)
ARROW, BLU-667-1101 NCT03037385	233	400 mg oral pralsetinib once daily	-	**Phase 2 PEs:** **overall response rate** (according to RECIST version1.1 and assessed by BICR) and **safety**	**ongoing,** multi-cohort, open-label, phase 1/2 study	RET	Blueprint Medicines	[1]

Efficacy[2]

Patients who previously received platinum-based chemotherapy (n=87)
Response rate: n=53/87 (61%); 95% CI 50–71 (including two responses that were pending confirmation at the time of the data cutoff and were subsequently confirmed)
Complete responses: n=5/87 (6%)
Patients who continued treatment at the time of the data cut off (among the 51 patients with confirmed responses): n=34/51 (67%)

Safety (n=233)[3]

Treatment-related AEs: n=216/233 (93%)
Grade ≥3 treatment-related AEs: n=111/233 (48%)
Serious treatment-related AEs: n=55/233 (24%)
Discontinuation[4]: n=14/233 (6%)
Deaths considered related to pralsetinib: n=0:

[2] Interim analysis data; ARROW trial is ongoing until 02/2024.
[3] Interim analysis data; ARROW trial is ongoing until 02/2024.
[4] Discontinuation due to a treatment-related AE

Median time to first response: 1.8 months (IQR 1.7–1.9; measured as part of the duration of response analyses) **Median duration of response**: not reached (95% CI 15.2–not estimable) at a median follow-up from the first response of 12.9 months (11.1–16.7) **Tumour shrinkage**: n=79/83 (95%; 88–99) **Median PFS**: 17.1 months (95% CI 8.3–22.1) at a median follow-up of 14.7 months (IQR 12.7–18.4) **Patients who had progression events or died**: 46% **Median OS**: not reached at a median follow-up of 17.1 months (IQR 14.6–20.3); 25 (27%) patients died **<u>Patients who were systemic treatment-naive (n=27):</u>** **Confirmed response**: n=19/27 (70%); 95% CI 50–86; including n=3/27 (11%) complete responses **Median duration of response in all responders**: 9.0 months (95% CI 6.3–not estimable) at a median duration of follow-up of 10.2 months (IQR 7.8–11.8) **Tumour shrinkage**: 100% **Median PFS**: 9.1 months (95% CI 6.1–13.0) at a median follow-up of 11.6 months (IQR 11.0–17.3) **Patients who had progression events or died**: 59% **OS**: not reached at a median follow-up of 13.6 months (IQR 13.0–17.6) with five deaths (17%)	**Patients with RET fusion positive NSCLC who had died by the data cutoff**: n=40/233 (17%)[5]

ESMO-MCBS version 1.1 [11]											
Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS is not applicable since no statistically significant endpoints were reported in the analyses.											

Risk of bias - study level (case series) [12]								
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	yes	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	no	yes	yes	yes	partial
Overall risk of bias: low risk								

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, AST=aspartate aminotransferase, BICR=blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EGFR-TK=epidermal growth factor receptor tyrosine kinase, 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, HR=hazard ratio, I=intervention, ILD=Interstitial Lung Disease, Int.=intention, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, ORR=overall response

[5] 24 (10%) deaths occurred during the treatment-emergent period (during or after administration of first pralsetinib dose until 30 days after last pralsetinib dose), of which ten (4%) were due to disease progression and 14 (6%) were due to other adverse events, and 16 (7%) occurred after the treatment-emergent period, of which 13 (6%) were due to disease progression, one (<1%) to strong reduced general condition, and two (1%) for unknown reasons.

rate, OS=overall survival, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, ST=standard treatment

References:

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