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

General information

Drug description [1]	Indication [2]
Capmatinib (Tabrecta®, INC280) is a highly potent and selective inhibitor of the mesenchymal-epithelial transition (MET) receptor.	Capmatinib (Tabrecta®) as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Current treatment [3]

- **Current second line or further treatments for non-squamous NSCLC are**:
  - Platinum doublet chemotherapy
  - Pemetrexed with carboplatin
  - Pemetrexed maintenance
  - Docetaxel +/- nintedanib
  - Atezolizumab
  - Nivolumab
  - Pembrolizumab
- **Current second line or further treatment for squamous NSCLC are:**
  - Atezolizumab
  - Nivolumab
  - Pembrolizumab
  - Gemcitabine + carboplatin or cisplatin
  - Vinorelbine + carboplatin or cisplatin
  - Docetaxel

Regulatory status

EMA [2]

Approval status for this indication: On 22 April 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tabrecta®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 20/06/2022

<u>The full indication is:</u>

- Tabrecta® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Other indications: none

✓ **Medicine under additional monitoring**

FDA [4]

Approval status for this indication: On 6 May 2020, the FDA granted accelerated approval to capmatinib (Tabrecta®) for adult patients with metastatic NSCLC whose tumours have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test.

- ✓ This indication is approved under accelerated approval based on overall response rate and response duration.
- ✓ Orphan drug
- ✓ Breakthrough therapy designation

The FDA also approved the FoundationOne CDx assay (Foundation Medicine, Inc.) as a companion diagnostic for capmatinib.

Other indications: none

Costs

60 Tabrecta® tablets 200 mg = € 3,825.00 (ex-factory price) [5].

Warnings and precautions [6]

- **Interstitial lung disease (ILD)/pneumonitis**
  - Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis.
  - Immediately withhold Tabrecta® in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.
- **Hepatotoxicity**
  - Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of Tabrecta®, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin.
  - Withhold, dose reduce, or permanently discontinue Tabrecta® based on severity of the adverse reaction.
- **Risk of photosensitivity**
  - May cause photosensitivity reactions.
  - Advise patients to limit direct ultraviolet exposure during treatment with Tabrecta®.
- **Embryo-foetal toxicity**
  - Can cause foetal harm.
  - Advise patients of the potential risk to a foetus and to use effective contraception.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
GEOMETRY mono-1 NCT02414139	364/97[1]	capmatinib (400-mg tablet) twice daily	-	overall response (complete or partial response)[2]	**ongoing**[3], prospective, international, open-label, multiple-cohort[4], phase 2 study	METex14	Novartis Pharmaceuticals	[1]

Efficacy

The cut-off date for the efficacy analyses was 6 January, 2020[5]

<u>**Advanced NSCLC with MET Exon 14 Skipping Mutation**</u>

<u>Previously treated patients:</u>

Overall response: 41% (95% CI, 29-53)

Median duration of response: 9.7 months (95% CI, 5.6-13.0)

Patients having a tumour response at the first tumour evaluation after the initiation of capmatinib therapy: 82%

Median PFS: 5.4 months (95% CI, 4.2-7.0)

<u>Patients who had not received treatment previously:</u>

Overall response: 68% (95%CI, 48-84)

Median duration of response: 12.6 months (95% CI, 5.6-could not be estimated)

Safety (all cohorts, n=364)

Treatment-related SAEs: 48/364 (13%)

Treatment-related AEs leading to discontinuation of treatment: 39/364 (11%)

Death from causes other than advanced NSCLC during treatment: 13/364 (4%)[6]

[1] A total of 364 patients with advanced NSCLC were enrolled in the study; of these, 97 patients had a MET exon 14 skipping mutation.

[2] As assessed under blinded conditions by an independent review committee according to RECIST, version 1.1. An ad hoc blinded review (by an independent neuroradiologic review committee) involving patients with a MET exon 14 skipping mutation and brain metastases at baseline was conducted after reports of responses in the brain in some patients.

[3] The GEOMETRY mono-1 trial is currently ongoing; the estimated study completion date is 03/2023.

[4] Patients were assigned to cohorts on the basis of previous lines of therapy and MET status (MET exon 14 skipping mutation or MET amplification according to gene copy number in tumour tissue).

[5] Except in the 3 cohorts in which patients had a gene copy number of less than 10 (cohorts 1b, 2, and 3); these cohorts had been closed earlier for futility (cut-off date, 15 April, 2019). The cut-off date for the safety analyses in all the cohorts was 6 January 2020.

[6] The reported causes were atrial fibrillation, hepatitis, pneumonia, organising pneumonia, bacterial pneumonia, pneumonitis, respiratory distress, sepsis, septic shock, sudden death, and assisted suicide (in 1 patient each) and cardiac arrest (in 2 patients). Only **one death** (from pneumonitis) **was suspected to be related to capmatinib** according to review by the investigator and according to medical review by the sponsor.

Patients having a tumour response at the first tumour evaluation after the initiation of capmatinib therapy: 68%
Median PFS: 12.4 months (95%CI, 8.2-could not be estimated)

Advanced NSCLC with MET amplification
Overall response observed in:
- 12% of those (95% CI, 4-26) who had tumour tissue with a gene copy number of 6 to 9
- 9% of those (95% CI, 3-20) who had tumour tissue with a gene copy number of 4 or 5
- 7% of those (95% CI, 1-22) who had tumour tissue with a gene copy number of less than 4

Median PFS:
- 2.7 (95% CI, 1.4-3.1) months among patients who had tumour tissue with a gene copy number of 6 to 9
- 2.7 (95% CI, 1.4-4.1) months among those who had tumour tissue with a gene copy number of 4 or 5
- 3.6 (95% CI, 2.2-4.2) months among those who had tumour tissue with a gene copy number of less than 4

Previously treated patients:
Overall response: 29% (95% CI, 19-41)
Median duration of response: 8.3 months (95% CI, 4.2-15.4)
Median PFS: 4.1 months (95% CI, 2.9-4.8)
Patients who had not received treatment previously:
Overall response: 40% (95% CI, 16-68)
Median duration of response: 7.5 months (95% CI, 2.6-14.3)
Median PFS: 4.2 months (95% CI, 1.4-6.9)

UPDATE: Efficacy results by BIRC in previously-treated NSCLC patients with a METex14 skipping mutation (data cut-off: 30 August, 2021) [10]:
Overall previously treated population (n=100)
Overall response rate: 44.0% (95%CI, 34.1-54.3)
Complete response: 1.0%
Partial response: 43.0%
Median duration of response: 9.72 months
Cohort 4 (n=69)
Overall response rate: 40.6% (95% CI, 28.8-53.1)
Complete response: 1.4%
Partial response: 39.1%
Median duration of response: 9.72 months
Cohort 6 (n=31)
Overall response rate: 51.6% (95% CI, 33.1-69.8)
Complete response: 0%
Partial response: 51.6%
Median duration of response: 9.05 months

ESMO-MCBS version 1.1 [11]											
Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

Original	NC	3	-	ORR: 41% DOR: 9.7 months	-	ORR (PR+CR) ≥20-<60% AND DOR ≥9 months	3	-	-	-	3
The adapted version is not applicable for single-arm studies.											
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	unclear	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	no	no	yes	yes	unclear	yes			
Overall risk of bias: moderate											
First published: 05/2022 **Last updated**: 10/2022											

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BIRC=Blinded Independent Review Committee, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, 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, MET=mesenchymal-epithelial transition, METex14=mesenchymal epithelial transition factor gene exon 14, MG=median gain, n=number of patients, NSCLC=non small-cell lung cancer, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

1. Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14–Mutated or MET-Amplified Non–Small-Cell Lung Cancer. N Engl J Med 2020;383:944-57. . [Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2002787].
2. European Medicines Agency (EMA). Medicines. Tabrecta. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/tabrecta].
3. National Institute for Health Research (NIHR). Capmatinib for advanced non-small cell lung cancer. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/7920-Capmatinib-for-NSCLC-v1.0.-APR21-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to capmatinib for metastatic non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-capmatinib-metastatic-non-small-cell-lung-cancer].

5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online [Available from: https://www.ema.europa.eu/en/documents/product-information/tabrecta-epar-product-information_en.pdf].
6. U.S. Food and Drug Administration (FDA). Tabrecta. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213591s004lbl.pdf].
7. Supplement to: Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET exon 14–mutated or MET-amplified non–smallcell lung cancer. N Engl J Med 2020;383:944-57.
8. Protocol for: Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET exon 14–mutated or MET-amplified non–small-cell lung cancer. N Engl J Med 2020;383:944-57.
9. U.S. National Library of Medicine, ClinicalTrials.gov. Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer (Geometry Mono-1). [Available from: https://www.clinicaltrials.gov/ct2/show/NCT02414139].
10. European Medicines Agency (EMA). Tabrecta: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/tabrecta-epar-product-information_en.pdf].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].