1 Tradename

Tabrecta® 150 mg and 200 mg film-coated tablets

2 Description and composition

Pharmaceutical form

Film-coated tablet

150 mg: pale orange brown, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side.

200 mg: yellow, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side.

Active substance(s)

Each 150 mg film-coated tablet contains 183.00 mg of capmatinib dihydrochloride monohydrate, which is equivalent to 150 mg of capmatinib as free base.

Each 200 mg film-coated tablet contains 244.00 mg of capmatinib dihydrochloride monohydrate, which is equivalent to 200 mg of capmatinib as free base.

Excipients

Tablet core: Cellulose microcrystalline; mannitol; crospovidone; povidone; magnesium stearate; silica colloidal anhydrous; sodium laurilsulfate.

Tablet coating:

150 mg: Hypromellose; titanium dioxide (E171); macrogol 4000; talc; iron oxide, yellow (E172); iron oxide, red (E172); iron oxide, black (E172).

200 mg: Hypromellose; titanium dioxide (E171); macrogol 4000; talc; iron oxide, yellow (E172).

3 Indications

Tabrecta is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.

4 Dosage regimen and administration

Patient selection

Patients should be selected for treatment with Tabrecta based on the presence of a MET exon 14 skipping mutation in tumor or plasma specimens using a validated test. If a MET exon 14 skipping mutation is not detected in a plasma specimen, tumor tissue should be tested if feasible.

Dosage regimen

General target population

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food (see section 11 Clinical pharmacology).

Treatment duration

Treatment should be continued based on individual safety and tolerability and as long as the patient is deriving clinical benefit from therapy.

Dose modifications for adverse drug reactions

The recommended dose reduction schedule for the management of adverse drug reactions (ADRs) based on individual safety and tolerability is listed in Table 4-1.

Table 4-1 Tabrecta dose reduction schedule

Dose level	Dose and schedule	Number and strength of tablets
Starting dose	400 mg twice daily	Two 200 mg tablets / twice daily
First-dose reduction	300 mg twice daily	Two 150 mg tablets / twice daily
Second-dose reduction	200 mg twice daily	One 200 mg tablet / twice daily

Tabrecta should be permanently discontinued in patients unable to tolerate 200 mg orally twice daily.

Recommendations for dose modifications of Tabrecta for ADRs are provided in Table 4-2.

Table 4-2 Tabrecta dose modifications for the management of adverse drug reactions

Adverse drug reaction	Severity	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Any grade treatment-related	Permanently discontinue Tabrecta.
Isolated ALT and/or AST elevations from baseline, without concurrent total bilirubin increase	Grade 3 (>5.0 to ≤20.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline ALT/AST grade.

Adverse drug reaction	Severity	Dose modification
		If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 4 (>20.0 x ULN)	Permanently discontinue Tabrecta.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	If patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN, irrespective of baseline grade	Permanently discontinue Tabrecta.
Isolated total bilirubin elevation from baseline, without concurrent ALT and/or AST increase	Grade 2 (>1.5 to ≤3.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline bilirubin grade. If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 3 (>3.0 to ≤10.0 x ULN)	Temporarily withhold Tabrecta until recovery to baseline bilirubin grade. If recovered to baseline within 7 days, then resume Tabrecta at a reduced dose as per Table 4-1, otherwise permanently discontinue Tabrecta.
	Grade 4 (>10.0 x ULN)	Permanently discontinue Tabrecta.
Other adverse drug reactions	Grade 2	Maintain dose level. If intolerable, consider temporarily withholding Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 3	Temporarily withhold Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 4	Permanently discontinue Tabrecta.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; ULN, upper limit of normal.

Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events).

Baseline = at the time of treatment initiation.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment based on population pharmacokinetic evaluations; Tabrecta has not been studied in patients with severe renal impairment (see section 11 Clinical pharmacology).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate, or severe hepatic impairment (see section 11 Clinical pharmacology).

Pediatric patients (below 18 years of age)

The safety and efficacy of Tabrecta in pediatric patients have not been established.

Geriatric patients (65 years of age or older)

No dose adjustment is necessary in patients 65 years of age or older.

Method of administration

Tabrecta should be taken orally twice daily with or without food. The tablets should be swallowed whole and should not be broken, chewed, or crushed.

If a dose of Tabrecta is missed or vomiting occurs, the patient should not make up the dose, but take the next dose at the scheduled time.

5 Contraindications

None.

6 Warnings and precautions

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta (see section 7 Adverse drug reactions). Prompt investigation should be performed in any patient with new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever). Tabrecta should be immediately withheld in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified (see section 4 Dosage regimen and administration).

Hepatic effects

Transaminase elevations have occurred in patients treated with Tabrecta (see section 7 Adverse drug reactions). Liver function tests (including ALT, AST, and total bilirubin) should be performed prior to the start of treatment, 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 transaminase or bilirubin elevations. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4 Dosage regimen and administration).

Elevations of pancreatic enzymes

Elevations in amylase and lipase levels have occurred in patients treated with Tabrecta (see section 7 Adverse drug reactions). Amylase and lipase should be monitored at baseline and regularly during treatment with Tabrecta. Based on the severity of the adverse drug reaction,

temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4 Dosage regimen and administration).

Hypersensitivity reactions

No cases of serious hypersensitivity were reported in patients treated with Tabrecta in Study GEOMETRY mono-1. In other clinical studies, cases of serious hypersensitivity were reported in patients treated with Tabrecta (see section 7 Adverse drug reactions). Clinical symptoms included pyrexia, chills, pruritus, rash, blood pressure decreased, nausea and vomiting. Based on the severity of the adverse drug reaction, temporarily withhold, or permanently discontinue Tabrecta.

Embryo-fetal toxicity

Based on findings from animal studies and its mechanism of action, Tabrecta can cause fetal harm when administered to a pregnant woman. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in fetotoxicity and teratogenicity. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta. Sexually active females of reproductive potential should use effective contraception during treatment with Tabrecta and for at least 7 days after the last dose. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Risk of photosensitivity

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta (see section 13 Non-clinical safety data). In GEOMETRY mono-1, it was recommended that patients use precautionary measures against ultraviolet exposure such as the use of sunscreen or protective clothing during treatment with Tabrecta. Patients should be advised to limit direct ultraviolet exposure during treatment with Tabrecta.

7 Adverse drug reactions

Summary of the safety profile (data cut-off: 30-Aug-2021)

The safety of Tabrecta was evaluated in patients with locally advanced or metastatic NSCLC in the pivotal, global, prospective, multi-cohort, non-randomized, open-label Phase II Study A2201 (GEOMETRY mono-1) across all cohorts (N = 373), regardless of prior treatment or MET dysregulation (mutation and/or amplification) status. The median duration of exposure to Tabrecta across all cohorts was 17.9 weeks (range: 0.4 to 281.0 weeks). Among patients who received Tabrecta, 36.7% were exposed for at least 6 months and 21.7% were exposed for at least one year.

Serious adverse events (AEs) regardless of causality were reported in 198 patients (53.1%) who received Tabrecta. Serious AEs regardless of causality in > 2% of patients included dyspnoea

(6.7%), pneumonia (5.9%), pleural effusion (4.3%), general physical health deterioration (2.9%) and vomiting (2.4%).

Fourteenpatients (3.8%) died while on treatment with Tabrecta due to causes other than the underlying malignancy. One of these deaths was confirmed as treatment-related: pneumonitis.

Permanent discontinuation of Tabrecta due to an AE regardless of causality was reported in 65 patients (17.4%). The most frequent AEs (≥0.5%) leading to permanent discontinuation of Tabrecta were peripheral oedema (2.1%), pneumonitis (1.6%), fatigue (1.3%), ALT increased (0.8%), AST increased (0.8%), blood creatinine increased (0.8%), nausea (0.8%), pneumonia (0.8%), vomiting (0.8%), blood bilirubin increased (0.5%), breast cancer (0.5%), cardiac failure (0.5%), general physical health deterioration (0.5%), ILD (0.5%), lipase increased (0.5%), organising pneumonia (0.5%), and pleural effusion (0.5%).

Dose interruptions due to an adverse event regardless of causality were reported in 211 patients (56.6%) who received Tabrecta. Adverse events regardless of causality requiring dose interruption in > 2% of patients who received Tabrecta included peripheral oedema (11.0%), blood creatinine increased (8.3%), nausea (6.2%), lipase increased (5.6%), vomiting (5.6%), ALT increased (4.8%), dyspnoea (4.6%), pneumonia (4.3%), amylase increased (3.8%), AST increased (3.2%), asthenia (2.4%) and blood bilirubin increased (2.1%).

Dose reductions due to an adverse event regardless of causality were reported in 98 patients (26.3%) who received Tabrecta. Adverse events regardless of causality requiring dose reductions in > 2% of patients who received Tabrecta included peripheral oedema (9.1%), ALT increased (3.2%) andblood creatinine increased (2.1%).

The most common ADRs reported with an incidence of ≥20% (all Grades) in patients who received Tabrecta were peripheral oedema, nausea, fatigue, vomiting, blood creatinine increased, dyspnoea, and decreased appetite. The most common Grade 3 or 4 ADRs reported with an incidence of ≥5% in patients who received Tabrecta were peripheral oedema, fatigue, dyspnoea, ALT increased and lipase increased.

At the time of the GEOMETRY mono-1 final analysis (last patient last visit: 16-May-2023), with a median duration of Tabrecta exposure of 17.9 weeks across all cohorts and with additional 20.5 months follow-up since the last data cut-off (30-Aug-2021), the safety profile remained consistent with that previously reported.

Tabulated summary of adverse drug reactions from clinical studies

Adverse drug reactions from clinical studies (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions in patients (N = 373) who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 30-Aug-2021)

Adverse drug reactions	All Grades n (%)	Frequency category	Grade 3/4 n (%)	Frequency category
Infections and infestations				
Cellulitis	11 (2.9)	Common	4 (1.1)*	Common
Metabolism and nutrition disorders				
Decreased appetite	80 (21.4)	Very common	4 (1.1)*	Common
Hypophosphataemia	24 (6.4)	Common	9 (2.4)	Common
Hyponatraemia	23 (6.2)	Common	14 (3.8)	Common
Respiratory, thoracic, and mediastinal disorders				
Dyspnoea	93 (24.9)	Very common	26 (7.0)	Common
Cough	62 (16.6)	Very common	2 (0.5)*	Uncommon
ILD / pneumonitis	17 (4.6)	Common	7 (1.9)*	Common
Gastrointestinal disorders				
Nausea	170 (45.6)	Very common	9 (2.4)*	Common
Vomiting	106 (28.4)	Very common	9 (2.4)*	Common
Constipation	70 (18.8)	Very common	3 (0.8)*	Uncommon
Diarrhoea	69 (18.5)	Very common	2 (0.5)*	Uncommon
Lipase increased	37 (9.9)	Common	25 (6.7)	Common
Amylase increased	36 (9.7)	Common	15 (4.0)	Common
Acute pancreatitis	1 (0.3)	Uncommon	1 (0.3)*	Uncommon
Hepatobiliary disorders				
Alanine aminotransferase increased	53 (14.2)	Very common	26 (7.0)	Common
Hypoalbuminaemia	47 (12.6)	Very common	5 (1.3)*	Common
Aspartate aminotransferase increased	38 (10.2)	Very common	13 (3.5)	Common
Blood bilirubin increased	14 (3.8)	Common	3 (0.8)*	Uncommon
Skin and subcutaneous tissue disorders				
Pruritus[1]	36 (9.7)	Common	1 (0.3)*	Uncommon
Rash[2]	32 (8.6)	Common	2 (0.5)*	Uncommon
Urticaria	5 (1.3)	Common	2 (0.5)*	Uncommon
Renal and urinary disorders				
Blood creatinine increased	101 (27.1)	Very common	1 (0.3)*	Uncommon
Acute kidney injury[3]	5 (1.3)	Common	1 (0.3)*	Uncommon
General disorders and administration-site conditions				
Oedema peripheral[4]	212 (56.8)	Very common	39 (10.5)*	Very common
Fatigue[5]	127 (34.0)	Very common	30 (8.0)*	Common
Back pain	63 (16.9)	Very common	3 (0.8)*	Uncommon
Non-cardiac chest pain[6]	53 (14.2)	Very common	7 (1.9)*	Common
Pyrexia[7]	53 (14.2)	Very common	3 (0.8)*	Uncommon
Weight decreased	41 (11.0)	Very common	2 (0.5)*	Uncommon

[1] Pruritus includes preferred terms (PTs) of pruritus and pruritus allergic.

[2] Rash includes PTs of rash, rash macular, rash maculopapular, rash erythematous and rash vesicular.

[3] Acute kidney injury includes PTs of acute kidney injury and renal failure.

[4] Oedema peripheral includes PTs of peripheral swelling, oedema peripheral, and fluid overload.

Adverse drug reactions	All Grades n (%)	Frequency category	Grade 3/4 n (%)	Frequency category

[5] Fatigue includes PTs of fatigue and asthenia.

[6] Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain.

[7]Pyrexia includes PTs of pyrexia and body temperature increased.

** No Grade 4 ADRs reported in Study A2201 (GEOMETRY mono-1).*

Adverse drug reactions (ADRs) from clinical studies and post-marketing experience

Hypersensitivity has been observed in other clinical studies (frequency category: Uncommon), post-marketing experience and expanded access programs with Tabrecta.

Description of selected adverse drug reactions (data cut-off: 30-Aug-2021)

ILD/pneumonitis

Any Grade ILD/pneumonitis was reported in 17of 373 patients (4.6%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 ILD/pneumonitis was reported in 7 patients (1.9%), with a fatal event of pneumonitis reported in 1 patient (0.3%). ILD/pneumonitis occurred in 9of 173 patients (5.2%) with a history of prior radiotherapy and 8 of 200 patients (4.0%) who did not receive prior radiotherapy. Eight patients (2. 1%) discontinued Tabrecta due to ILD/pneumonitis. ILD/pneumonitis mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 7.9 weeks (range: 0.7 to 88.4weeks).

Hepatic effects

Any Grade ALT/AST elevations were reported in 55 of 373 patients (14.7%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 or 4 ALT/AST elevations were observed in 26 of 373 patients (7.0%) treated with Tabrecta. Three patients (0.8%) discontinued Tabrecta due to ALT/AST elevations. ALT/AST elevations mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of Grade 3 or higher ALT/AST elevations was 7.6 weeks (range: 2.1 to 201.6 weeks).

Elevations of pancreatic enzymes

Any Grade amylase/lipase elevations were reported in 52 of 373 patients (13.9%) treated with Tabrecta in Study A2201 (GEOMETRY mono 1). Grade 3 or 4 amylase/lipase elevations were reported in 32 of 373 patients (8.6%) treated with Tabrecta. Three patients (0.8%) discontinued Tabrecta due to amylase/lipase elevations. The median time to onset of Grade 3 or higher amylase/lipase elevations was 8.5 weeks (range: 0.1 to 135.0 weeks).

8 Interactions

Effect of other medicinal products on Tabrecta

Strong CYP3A inhibitors

In healthy subjects, coadministration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib AUCinf by 42% with no change in capmatinib Cmax compared to administration of capmatinib alone. Coadministration of Tabrecta with a strong CYP3A inhibitor may increase the incidence and severity of adverse drug reactions of Tabrecta. Patients should be closely monitored for adverse drug reactions during coadministration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole.

Strong CYP3A inducers

In healthy subjects, coadministration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib AUCinf by 67% and decreased Cmax by 56% compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumor activity. Coadministration of Tabrecta with strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort *(Hypericum perforatum)* should be avoided. An alternative medication with no or minimal potential to induce CYP3A should be considered.

Moderate CYP3A inducers

Simulations using physiologically based pharmacokinetic (PBPK) models predicted that coadministration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC0-12h and 34% decrease in Cmax at steady-state compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumor activity. Caution should be exercised during coadministration of Tabrecta with moderate CYP3A inducers.

Agents that raise gastric pH

Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Gastric acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of capmatinib and reduce its bioavailability. In healthy subjects, coadministration of a single 600 mg capmatinib dose with the proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib AUCinf by 25% and decreased Cmax by 38% compared to administration of capmatinib alone. Clinically relevant drug-drug interactions between capmatinib and gastric acid reducing agents are unlikely to occur as co-administration of rabeprazole had no clinically meaningful effect on exposure of capmatinib.

Effect of Tabrecta on other medicinal products

Substrates of CYP enzymes

In cancer patients, coadministration of caffeine (CYP1A2 probe substrate) with multiple doses of capmatinib (400 mg twice daily) increased caffeine AUCinf by 134% with no change in caffeine Cmax compared to administration of caffeine alone. Coadministration of Tabrecta with a CYP1A2 substrate may increase the incidence and severity of adverse drug reactions of these substrates. If coadministration is unavoidable between Tabrecta and CYP1A2 substrateswhere minimal concentration changes may lead to serious adverse drug reactions, including but not limited to, theophylline and tizanidine, decrease the CYP1A2 substrate dose in accordance with the approved prescribing information

In cancer patients, coadministration of midazolam (CYP3A substrate) with multiple doses of capmatinib (400 mg twice daily) did not cause any clinically significant increase in midazolam exposure (9% increase in AUCinf and 22% increase in Cmax) compared to administration of midazolam alone. Clinically relevant drug-drug interactions between capmatinib and CYP3A substrates are unlikely to occur as coadministration of capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates

In cancer patients, coadministration of digoxin (P-gp substrate) with multiple doses of capmatinib (400 mg twice daily) increased digoxin AUCinf by 47% and increased Cmax by 74% compared to administration of digoxin alone. In cancer patients, coadministration of rosuvastatin (BCRP substrate) with multiple doses of capmatinib (400 mg twice daily) increased rosuvastatin AUCinf by 108% and increased Cmax by 204% compared to administration of rosuvastatin alone. Coadministration of Tabrecta with a P-gp or BCRP substrate may increase the incidence and severity of adverse drug reactions of these substrates. If coadministration is unavoidable between Tabrecta and P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse drug reactions, decrease the P-gp or BCRP substrate dose in accordance with the approved prescribing information.

Drug-food/drink interactions

Tabrecta can be administered with or without food (see section 4 Dosage regimen and administration and section 11 Clinical pharmacology).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Based on findings from animal studies and its mechanism of action, Tabrecta can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in fetotoxicity and teratogenicity. Reduced fetal weights and increased incidences of fetal malformations were observed in rats and rabbits following prenatal exposure to capmatinib at or below the exposure in humans at the maximum recommended human dose (MRHD) of

400 mg twice daily based on area under the curve (AUC) (see Data). Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta.

Data

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of capmatinib up to 30 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis. At 30 mg/kg/day in rats and 60 mg/kg/day in rabbits, the maternal systemic exposure (AUC) was approximately 1.4 and 1.5 times, respectively, the exposure in humans at the MRHD of 400 mg twice daily.

In rats, maternal toxicity (reduced body weight gain and food consumption) was observed at the dose of 30 mg/kg/day. Fetal effects included reduced fetal weights, irregular/incomplete ossification, and increased incidences of fetal malformations (e.g., abnormal flexure/inward malrotation of hindpaws/forepaws, thinness of forelimbs, lack of/reduced flexion at the humerus/ulna joints, narrowed or small tongue) at doses of ≥10 mg/kg/day (with maternal systemic exposure at 0.56 times the exposure in humans at the MRHD of 400 mg twice daily).

In rabbits, no maternal effects were detected at doses up to 60 mg/kg/day. Fetal effects included small lung lobe at ≥5 mg/kg/day (with systemic exposure at 0.016 times the exposure in humans at the MRHD of 400 mg twice daily), and reduced fetal weights, irregular/incomplete ossification and increased incidences of fetal malformations (e.g. abnormal flexure/malrotation of hindpaws/forepaws, thinness of forelimbs/hindlimbs, lack of/reduced flexion at the humerus/ulna joints, small lung lobes, narrowed or small tongue) at the dose of 60 mg/kg/day (with systemic exposure at 1.5 times the exposure in humans at the MRHD of 400 mg twice daily).

9.2 Lactation

Risk summary

It is not known if capmatinib is transferred into human milk after administration of Tabrecta. There are no data on the effects of capmatinib on the breastfed child or on milk production. Because of the potential for serious adverse drug reactions in breast-fed children, breastfeeding is not recommended during treatment with Tabrecta and for at least 7 days after the last dose.

9.3 Females and males of reproductive potential

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Tabrecta.

Contraception

Females

Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Tabrecta and for at least 7 days after the last dose.

Males

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose.

Infertility

There are no data on the effect of capmatinib on human fertility. Fertility studies with capmatinib were not conducted in animals.

10 Overdosage

There is limited experience with overdose in clinical studies with Tabrecta. Patients should be closely monitored for signs or symptoms of adverse drug reactions, and general supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX17.

Mechanism of action (MOA)

Capmatinib is a highly selective and potent inhibitor of the MET receptor tyrosine kinase. High MET selectivity of capmatinib was demonstrated in two different screening panels, indicating a selectivity factor of approximately 1000 times or greater when compared to more than 400 other kinases or mutant kinase variants. At tolerated doses, capmatinib treatment results in regression of tumor xenograft models derived from lung cancer with MET exon 14 skipping mutations or MET amplification, among others. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET-mediated phosphorylation of downstream signaling proteins, as well as proliferation and survival of MET-dependent cancer cells.

Pharmacodynamics (PD)

Pharmacodynamic properties

Capmatinib induced regression in multiple cancer xenograft models including a lung cancer xenograft model that expressed a mutant MET variant lacking exon 14. The relationship between pharmacodynamics and efficacy was studied in the S114 mouse tumor model, where deep regression was associated with more than 90% inhibition of MET phosphorylation during most of the dosing interval.

Cardiac electrophysiology

Capmatinib did not prolong the QT interval to any clinically relevant extent following administration of Tabrecta at the recommended dose. Following a dose of 400 mg twice daily in clinical studies, no patient had a new post-baseline QTcF interval value greater than 500 msec. A concentration-QT analysis showed that the estimated mean QTcF increase from baseline was 1.33 msec with upper bound 90% confidence interval (CI) of 2.58 msec at the mean steady-state Cmax following 400 mg twice daily dosing.

Pharmacokinetics (PK)

Capmatinib exhibited dose-proportional increases in systemic exposure (AUCinf and Cmax) across the dose range tested (200 to 400 mg twice daily). Steady state is expected to be achieved after approximately 3 days after oral dosing of capmatinib 400 mg twice daily, with a geometric mean accumulation ratio of 1.39 (coefficient of variation (CV): 42.9%).

Absorption

In humans, absorption is rapid after oral administration of capmatinib. Peak plasma levels of capmatinib (Cmax) were reached approximately 1 to 2 hours (Tmax) after an oral 400 mg dose of capmatinib tablets in cancer patients. The absorption of capmatinib tablets after oral administration is estimated to be greater than 70%.

Food effect:

Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food (see section 4 Dosage regimen and administration).

When capmatinib was administered with food in healthy subjects, oral administration of a single 600 mg dose with a high-fat meal increased capmatinib AUCinf by 46% and Cmax by 15% compared to when capmatinib was administered under fasted conditions. A low-fat meal increased AUCinf by 20% and Cmax by 11%.

When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC0-12h) was similar after administration of capmatinib with food and under fasted conditions.

Distribution

Capmatinib is 96% bound to human plasma proteins, independent of concentration. The apparent mean volume of distribution at steady state (Vss/F) is 164 L in cancer patients.

The blood-to-plasma ratio was 1.5 (concentration range of 10 to 1000 ng/mL) but decreased at higher concentrations to 0.9 (concentration 10000 ng/mL), indicating a saturation of distribution into red blood cells.

Capmatinib crossed the blood-brain barrier in rats with a brain-to-blood exposure (AUCinf) ratio of approximately 9%.

Metabolism

In vitro and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 and aldehyde oxidase. The biotransformation of

capmatinib occurs essentially by Phase I metabolic reactions including *C*-hydroxylation, lactam formation, *N*-oxidation, *N*-dealkylation, carboxylic acid formation, and combinations thereof. Phase II reactions involve glucuronidation of oxygenated metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity AUC0-12h). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC0-12h.

Elimination

The effective elimination half-life (calculated based on geometric mean accumulation ratio) of capmatinib is 6.54 hours. The geometric mean steady-state apparent oral clearance (CLss/F) of capmatinib was 19.8 L/hr.

Excretion

Capmatinib is eliminated mainly through metabolism, and subsequent fecal excretion. Following a single oral administration of [14C]-capmatinib to healthy subjects, 78% of the total radioactivity was recovered in the feces and 22% in the urine. Excretion of unchanged capmatinib in urine is negligible.

In vitro evaluation of drug interaction potential

Interactions between enzymes and Tabrecta

In vitro studies showed that capmatinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19. Capmatinib also showed weak induction of CYP2B6 and CYP2C9 in cultured human hepatocytes. Simulations using PBPK models predicted that capmatinib given at a dose of 400 mg twice daily is unlikely to cause clinically relevant interaction via CYP2B6, CYP2C8, CYP2C9 or CYP2C19.

Interactions between transporters and Tabrecta

Based on *in vitro* data, capmatinib showed reversible inhibition of hepatic uptake transporters OATP1B1, OATP1B3, and OCT1. However, capmatinib is not expected to cause clinically relevant inhibition of OATP1B1, OATP1B3, and OCT1 uptake transporters based on the concentration achieved at the therapeutic dose. Capmatinib is not a multidrug resistance-associated protein (MRP2) inhibitor *in vitro*.

Based on *in vitro* data, capmatinib is not an inhibitor of renal transporters OAT1 or OAT3, but capmatinib and its major metabolite CMN288 showed reversible inhibition of renal transporters MATE1 and MATE2K. Capmatinib may inhibit MATE1 and MATE2K at clinically relevant concentrations.

Based on *in vitro* data, capmatinib is a P-gp substrate, but not a BCRP or MRP2 substrate. Capmatinib is not a substrate of transporters involved in active hepatic uptake in primary human hepatocytes.

Special populations

Geriatric patients

In Study A2201 (GEOMETRY mono-1), 61% of the 373 patients were 65 years of age or older, and 18% were 75 years of age or older. No overall differences in the safety or effectiveness were observed between these and younger patients.

Age/Gender/Race/Body weight

Population pharmacokinetic analysis showed that there is no clinically relevant effect of age/gender/race/body weight on the systemic exposure of capmatinib.

Renal impairment

Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (creatinine clearance [CLcr] ≥90 mL/min), 200 patients with mild renal impairment (CLcr 60 to 89 mL/min), and 94 patients with moderate renal impairment (CLcr 30 to 59 mL/min), mild or moderate renal impairment had no clinically significant effect on the exposure of capmatinib. Tabrecta has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) (see section 4 Dosage regimen and administration).

Hepatic impairment

A study was conducted in non-cancer subjects with various degrees of hepatic impairment based on Child-Pugh classification using a 200 mg single-dose of capmatinib. The geometric mean systemic exposure (AUCinf) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (N = 6) and moderate (N = 8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (N = 6) hepatic impairment compared to subjects with normal (N = 9) hepatic function. Cmax was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while Cmax was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4 Dosage regimen and administration). Mild, moderate, or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib.

12 Clinical studies

Locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation (treatment-naïve and previously treated)

The efficacy of Tabrecta for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation was demonstrated in the pivotal, global, prospective, multi-cohort, non-randomized, open-label Phase II Study A2201 (GEOMETRY mono-1).). Patients (N = 373) were enrolled into study cohorts based on their prior treatment and MET dysregulation (mutation and/or amplification) status. Patients with MET mutations (N = 160) were enrolled into the MET-mutated cohorts regardless of MET amplification. Patients without MET mutations were enrolled into the MET-amplified cohorts based on their level of MET amplification.

In the MET-mutated cohorts, eligible patients were required to have Epidermal Growth Factor Receptor (EGFR) wild-type (for exon 19 deletions and exon 21 L858R substitution mutations) and Anaplastic Lymphoma Kinase (ALK) negativestatus, and MET-mutated NSCLC with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, along with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within the prior 2 weeks to manage CNS symptoms, patients with clinically significant uncontrolled cardiac disease, or patients pre-treated with any MET or HGF inhibitor were not eligible for the study.

Patients continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The primary endpoint of the study was overall response rate (ORR) as determined by a Blinded Independent Review Committee (BIRC) according to RECIST 1.1. The key secondary endpoint was duration of response (DOR) by BIRC. Additional secondary endpoints were time-to-response (TTR), progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). The efficacy data for treatment-naïve and previously treated patients were analyzed independently.

Efficacy analysis (data cut-off: 15-Apr-2019)

In the MET-mutated cohorts, a total of 97 adult patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation as determined using an RNA-based clinical trial assay at a central laboratory were enrolled and treated with Tabrecta. The treatment-naïve cohort (Cohort 5b) enrolled 28 patients. The previously treated cohort (Cohort 4) enrolled 69 patients who had been treated with 1 or 2 prior lines of systemic therapy for advanced disease.

The demographic characteristics of the MET-mutated study population were 60% female, median age 71 years (range: 49 to 90 years), 82% aged 65 years of age or older, 75% white, 24% Asian, 0% black, 60% never smoked, 80% had adenocarcinoma, 24% had ECOG PS0, 75% had ECOG PS1, and 12% had CNS metastases. In the previously treated cohort (N = 69), 94% had prior chemotherapy, 88% had prior platinum-based chemotherapy, 28% had prior immunotherapy, and 23% had received 2 prior systemic therapies.

Efficacy results from Study A2201 (GEOMETRY mono-1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarized in Tables 12-1 and 12-2. The primary endpoint of ORR as assessed by BIRC was met irrespective of the line of treatment and thus demonstrated that Tabrecta is efficacious in both treatment-naïve and previously treated MET-mutated NSCLC patients. The responses in treatment-naïve MET-mutated NSCLC patients were durable with 68.4% of patients having responses of 6 months or longer and 47.4% of patients having responses of 12 months or longer (median DOR of 12.58 months (95% CI: 5.55, 25.33 by BIRC assessment. The responses in previously treated MET-mutated NSCLC patients were also durable with 64.3% of patients having responses of 6 months or longer and 32.1% of patients having responses of 12 months or longer (median DOR of 9.72 months (95% CI: 5.55, 12.98)) by BIRC assessment. In both MET-mutated cohorts, the onset of response occurred within 7 weeks of treatment in the majority of patients (68.4% of treatment-naïve patients and 82.1% of previously treated patients) as assessed by BIRC. The analyses by investigator assessment were similar to the analyses by BIRC assessment.

Table 12-1 Treatment-naïve (Cohort 5b) MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 15-Apr-2019)

Efficacy Parameters	Tabrecta by BIRC N = 28	Tabrecta by Investigator N = 28
Overall Response Rate[a] (95% CI)[b]	67.9% (47.6, 84.1)	60.7% (40.6, 78.5)
Complete Response, n (%)	1 (3.6)	0 (0.0)
Partial Response, n (%)	18 (64.3)	17 (60.7)
Duration of Response[a, †]		
Number of responders, n	19	17
Median, months (95% CI)[c]	12.58 (5.55, 25.33)	13.83 (4.27, 25.33)
Patients with DOR ≥6 months	68.4%	76.5%
Patients with DOR ≥12 months	47.4%	52.9%
Disease Control Rate[a] (95% CI)[b]	96.4% (81.7, 99.9)	96.4% (81.7, 99.9)
Progression-Free Survival[a]		
Number of events, n (%)	17 (60.7)	17 (60.7)
Progressive Disease , n (%)	14 (50.0)	16 (57.1)
Deaths, n (%)	3 (10.7)	1 (3.6)
Median, months (95% CI)[c]	9.69 (5.52, 13.86)	11.14 (5.52, 15.24)
Overall Survival		
Number of events, n (%)	13 (46.4)	
Median, months (95% CI)[c]	15.24 (12.22, NE)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DOR, Duration of Response; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]*Determined by RECIST v1.1.*

[b]*Clopper and Pearson exact binomial 95% CI.*

[c]*Based on Kaplan-Meier estimate.*

† Updated based on data cut off date 28-Oct-2019

Table 12-2 Previously treated (Cohort 4) MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 15-Apr-2019)

Efficacy Parameters	Tabrecta by BIRC N = 69	Tabrecta by Investigator N = 69
Overall Response Rate[a] (95% CI)[b]	40.6% (28.9, 53.1)	42.0% (30.2, 54.5)
Complete Response, n (%)	0 (0.0)	1 (1.4)
Partial Response, n (%)	28 (40.6)	28 (40.6)
Duration of Response[a,†]		
Number of responders, n	28	30
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	8.31 (5.45, 12.06)
Patients with DOR ≥6 months	64.3%	60.0%
Patients with DOR ≥12 months	32.1%	30.0%
Disease Control Rate[a] (95% CI)[b]	78.3% (66.7, 87.3)	76.8% (65.1, 86.1)
Progression-Free Survival[a]		

Efficacy Parameters	Tabrecta by BIRC N = 69	Tabrecta by Investigator N = 69
Number of events, n (%)	55 (79.7)	57 (82.6)
Progressive Disease, n (%)	49 (71.0)	49 (71.0)
Deaths, n (%)	6 (8.7)	8 (11.6)
Median, months (95% CI)[c]	5.42 (4.17, 6.97)	4.80 (4.11, 7.75)
Overall Survival		
Number of events, n (%)	44 (63.8)	
Median, months (95% CI)[c]	13.57 (8.61, 21.19)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DOR, Duration of Response; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NSCLC, Non-Small Cell Lung Cancer; PD, ORR, Overall Response Rate; Progressive Disease; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]Determined by RECIST v1.1.

[b]Clopper and Pearson exact binomial 95% CI.

[c]Based on Kaplan-Meier estimate.

† Updated based on data cut off date 28-Oct-2019

Efficacy analysis (data cut-off: 30-Aug-2021)

This efficacy analysis is based on data from 60 treatment-naïve patients with MET-mutated NSCLC enrolled in Cohort 5b (28 patients) supplemented by Cohort 7 (32 patients), and from 100 previously treated patients with MET-mutated NSCLC enrolled in Cohort 4 (69 in 2nd/ 3rd line) supplemented by Cohort 6 (31 patients in 2nd line). Patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation as determined using an RNA based clinical trial assay at a central laboratory were enrolled and treated with Tabrecta.

The demographic characteristics of the MET-mutated study population, including Cohorts 6 and 7, were 61% female, median age 71 years (range: 48 to 90 years), 85% aged 65 years or older, 77% white, 19% Asian, 1.3% black, 61% never smoked, 83% had adenocarcinoma, 25% had ECOG PS 0, 74% had ECOG PS 1, and 16% had CNS metastases. In the previously treated cohorts (Cohorts 4 and 6) (N=100), 91% had received prior chemotherapy, 86% had prior platinum-based chemotherapy, 32% had prior immunotherapy, and 16% had received 2 prior systemic therapies.

Efficacy results from Study A2201 (GEOMETRY mono-1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarized in Tables 12-3 and 12-4. In all MET-mutated cohorts, the onset of response occurred within 2 months of treatment in the majority of patients (65.9% of treatment-naïve patients and 75.0% of previously treated patients) as assessed by BIRC. The analyses by investigator assessment were similar to the analyses by BIRC assessment.

Table 12-3 Treatment-naïve MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 30-Aug-2021)

Efficacy Parameters	Cohort 5b N=28		Cohort 7 N=32	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Overall Response Rate[a] (95% CI)[b]	67.9% (47.6, 84.1)	60.7% (40.6, 78.5)	68.8% (50.0, 83.9)	56.3% (37.7, 73.6)
Complete Response, n (%)	2 (7.1)	0 (0.0)	1 (3.1)	1 (3.1)
Partial Response, n (%)	17 (60.7)	17 (60.7)	21 (65.6)	17 (53.1)
Duration of Response[a]				
Number of responders, n	19	17	22	18
Median, months (95% CI)[c]	12.58 (5.55, NE)	13.83 (4.27, 25.33)	16.59 (8.34, NE)	15.21 (6.77, NE)
Patients with DOR ≥6 months	68.4%	76.5%	72.7%	77.8%
Patients with DOR ≥12 months	47.4%	52.9%	50.0%	61.1%
Disease Control Rate[a] (95% CI)[b]	96.4% (81.7,99.9)	96.4% (81.7, 99.9)	100.0% (89.1, 100.0)	96.9% (83.8, 99.9)
Progression-Free Survival[a]				
Number of events, n (%)	18 (64.3)	23 (82.1)	19 (59.4)	22 (68.8)
Progressive Disease, n (%)	15 (53.6)	22 (78.6)	15 (46.9)	18 (56.3)
Deaths, n (%)	3 (10.7)	1 (3.6)	4 (12.5)	4 (12.5)
Median, months (95% CI)[c]	12.42 (8.21, 23.39)	11.99 (5.52, 16.92)	12.45 (6.87, 20.50)	9.79 (5.75, 16.36)
Overall Survival				
Number of events, n (%)	17 (60.7)		13 (40.6)	
Median, months (95% CI)[c]	20.76 (12.42, NE)		NE (12.85, NE)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DOR, Duration of response; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]Determined by RECIST v1.1.

[b]Clopper and Pearson exact binomial 95% CI.

[c]Based on Kaplan-Meier estimate.

Table 12-4 Previously treated MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 30-Aug-2021)

Efficacy Parameters	Cohort 4 (2/3L) N = 69		Cohort 6 (2L) N = 31	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Overall Response Rate[a] (95% CI)[b]	40.6% (28.9, 53.1)	43.5% (31.6, 56.0)	51.6% (33.1, 69.8)	45.2% (27.3, 64.0)
Complete Response, n (%)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Partial Response, n (%)	27 (39.1)	29 (42.0)	16 (51.6)	14 (45.2)
Duration of Response[a]				
Number of responders, n	28	30	16	14
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	8.31 (5.45, 12.06)	9.05 (4.17, NE)	15.75 (4.17, 27.60)

Efficacy Parameters	Cohort 4 (2/3L) N = 69		Cohort 6 (2L) N = 31	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Patients with DOR ≥6 months	64.3%	60.0%	62.5%	64.3%
Patients with DOR ≥12 months	32.1%	33.3%	43.8%	50.0%
Disease Control Rate[a] (95% CI)[b]	78.3% (66.7, 87.3)	76.8% (65.1, 86.1)	90.3% (74.2, 98.0)	90.3% (74.2, 98.0)
Progression-Free Survival[a]				
Number of events, n (%)	60 (87.0)	63 (91.3)	23 (74.2)	23 (74.2)
Progressive Disease, n (%)	54 (78.3)	55 (79.7)	21 (67.7)	21 (67.7)
Deaths, n (%)	6 (8.7)	8 (11.6)	2 (6.5)	2 (6.5)
Median, months (95% CI)[c]	5.42 (4.17, 6.97)	4.80 (4.11, 7.75)	6.93 (4.17, 13.34)	6.90 (5.55, 17.31)
Overall Survival				
Number of events, n (%)	53 (76.8)		17 (54.8)	
Median, months (95% CI)[c]	13.57 (8.61, 22.24)		24.28 (13.54, NE)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; ORR, Overall Response Rate; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]*Determined by RECIST v1.1.*

[b]*Clopper and Pearson exact binomial 95% CI.*

[c]*Based on Kaplan-Meier estimate.*

Final analysis (last patient last visit: 16-May-2023)

At the time of GEOMETRY mono-1 final analysis (LPLV: 16-May-2023), the median duration of exposure to Tabrecta across MET-mutated cohorts was 34.9 weeks (1L patients: 43.9 weeks and 2/3L patients: 27.9 weeks).

Updated efficacy results from Study A2201 (GEOMETRY mono-1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarized in Tables 12-5 and 12-6. The analyses by investigator assessment were similar to the analyses by BIRC assessment.

Table 12-5 Treatment-naïve MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Last patient last visit: 16-May-2023)

Efficacy Parameters	Cohort 5b N=28		Cohort 7 N=32	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Overall Response Rate[a] (95% CI)[b]	67.9% (47.6, 84.1)	60.7% (40.6, 78.5)	68.8% (50.0, 83.9)	56.3% (37.7, 73.6)
Complete Response, n (%)	2 (7.1)	0 (0.0)	1 (3.1)	1 (3.1)
Partial Response, n (%)	17 (60.7)	17 (60.7)	21 (65.6)	17 (53.1)
Duration of Response[a]				
Number of responders, n	19	17	22	18

Efficacy Parameters	Cohort 5b N=28		Cohort 7 N=32	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Median, months (95% CI)[c]	12.58 (5.55, 38.67)	13.83 (4.27, 25.33)	16.59 (8.34, NE)	15.21 (6.77, 31.77)
Patients with DOR ≥6 months	68.4%	76.5%	72.7%	77.8%
Patients with DOR ≥12 months	47.4%	52.9%	50.0%	61.1%
Disease Control Rate[a] (95% CI)[b]	96.4% (81.7, 99.9)	96.4% (81.7, 99.9)	100.0% (89.1, 100.0)	96.9% (83.8, 99.9)
Progression-Free Survival[a]				
Number of events, n (%)	20 (71.4)	23 (82.1)	21 (65.6)	25 (78.1)
Progressive Disease, n (%)	17 (60.7)	22 (78.6)	16 (50.0)	20 (62.5)
Deaths, n (%)	3 (10.7)	1 (3.6)	5 (15.6)	5 (15.6)
Median, months (95% CI)[c]	12.42 (8.21, 23.39)	11.99 (5.52, 16.92)	12.45 (6.87, 22.05)	9.79 (5.75, 16.36)
Overall Survival				
Number of events, n (%)	18 (64.3)		21 (65.6)	
Median, months (95% CI)[c]	20.76 (12.42, 43.93)		21.36 (12.85, 34.76)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DOR, Duration of response; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]Determined by RECIST v1.1.

[b]Clopper and Pearson exact binomial 95% CI.

[c]Based on Kaplan-Meier estimate.

Table 12-6 Previously treated MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Last patient last visit: 16-May-2023)

Efficacy Parameters	Cohort 4 (2/3L) N = 69		Cohort 6 (2L) N = 31	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Overall Response Rate[a] (95% CI)[b]	40.6% (28.9, 53.1)	43.5% (31.6, 56.0)	51.6% (33.1, 69.8)	45.2% (27.3, 64.0)
Complete Response, n (%)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Partial Response, n (%)	27 (39.1)	29 (42.0)	16 (51.6)	14 (45.2)
Duration of Response[a]				
Number of responders, n	28	30	16	14
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	8.31 (5.45, 12.06)	9.05 (4.17, 27.60)	14.57 (4.17, 27.60)
Patients with DOR ≥6 months	64.3%	60.0%	62.5%	64.3%
Patients with DOR ≥12 months	32.1%	33.3%	43.8%	50.0%

Efficacy Parameters	Cohort 4 (2/3L) N = 69		Cohort 6 (2L) N = 31	
	Tabrecta by BIRC	Tabrecta by Investigator	Tabrecta by BIRC	Tabrecta by Investigator
Disease Control Rate[a] (95% CI)[b]	78.3% (66.7, 87.3)	76.8% (65.1, 86.1)	90.3% (74.2, 98.0)	90.3% (74.2, 98.0)
Progression-Free Survival[a]				
Number of events, n (%)	62 (89.9)	65 (94.2)	24 (77.4)	24 (77.4)
Progressive Disease, n (%)	55 (79.7)	56 (81.2)	22 (71.0)	22 (71.0)
Deaths, n (%)	7 (10.1)	9 (13.0)	2 (6.5)	2 (6.5)
Median, months (95% CI)[c]	5.42 (4.17, 6.97)	4.80 (4.11, 7.75)	6.93 (4.17, 13.34)	6.90 (5.55, 17.31)
Overall Survival				
Number of events, n (%)	58 (84.1)		22 (71.0)	
Median, months (95% CI)[c]	13.57 (8.61, 22.24)		25.95 (13.54, 43.40)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; ORR, Overall Response Rate; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

[a]*Determined by RECIST v1.1.*

[b]*Clopper and Pearson exact binomial 95% CI.*

[c]*Based on Kaplan-Meier estimate.*

13 Non-clinical safety data

Repeat-dose toxicity

Repeat-dose toxicity studies conducted in rats and cynomolgus monkeys revealed the following target organs or systems: pancreas, brain/central nervous system (CNS), liver, and potentially the kidney.

Reversible findings in the pancreas were observed in rats and monkeys in 28-day and 13-week studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation, occasionally accompanied by increased amylase or lipase. In rats, the doses of 60 mg/kg/day or higher in males and 30 mg/kg/day or higher in females showed reversible low-grade pancreatic changes in 28-day and/or 13-week studies. In monkeys, pancreatic findings included reversible low-grade acinar cell apoptosis in all groups with higher serum amylase at the high dose of 150 mg/kg/day in the 28-day study and increases in amylase and lipase in a small number of animals at 75 mg/kg/day in the 13-week study.

Signs indicative of CNS toxicity (such as tremors and/or convulsions), and histopathological findings of white matter vacuolation in the thalamus were observed in rats at a dose of 60 mg/kg/day for females and 120 mg/kg/day for males in a 28-day toxicity study (at doses $\geq$ 2.2 times the human exposure based on AUC at the 400 mg twice daily clinical dose). Additionally, results from a 13-week rat toxicity study reproduced the CNS effects and histopathological findings in the brain, and also demonstrated that the CNS effects and brain

lesions were reversible. No signs of CNS toxicity or brain abnormalities were observed in cynomolgus monkey studies.

Slight changes in serum liver enzymes (ALT, AST, and/or SDH) were observed in several different studies in rats and monkeys. These changes were restricted to highly variable, minimal-to-mild elevations lacking a clear dose response. These liver enzyme elevations were mostly observed in the absence of any histological correlate within the liver, with the exception of a 13-week monkey study, which showed a reversible, minimal-to-mild subcapsular neutrophilic infiltration associated with single cell necrosis in males at 75 mg/kg/day.

Histopathologic changes were observed in the kidneys in a 28-day monkey study where mild-to-moderate deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen were present at a dose of 75 mg/kg/day and higher. However, in a 13-week monkey study, renal precipitates or kidney toxicity was not observed at any doses tested (up to 75 mg/kg/day). Follow-up investigations on the identity of the crystalline-like material indicated that the material is not capmatinib or its metabolites, but rather calcium phosphate precipitates.

No effects on male and female reproductive organs occurred in general toxicology studies conducted in rats and monkeys at doses resulting in exposures of up to approximately 3.6 times the human exposure based on AUC at the 400 mg twice daily clinical dose.

Safety pharmacology

Safety pharmacology studies with capmatinib indicated no significant effects on CNS and respiratory functions in rats, and no effects on cardiovascular function in monkeys. Capmatinib inhibited hERG potassium current by 50% at 18.7 microM.

Carcinogenicity and mutagenicity

Carcinogenicity studies with capmatinib have not been conducted.

Capmatinib was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and did not cause chromosomal aberrations in the *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Capmatinib was not clastogenic in the *in vivo* bone marrow micronucleus test in rats.

Photosensitivity

In vitro and *in vivo* photosensitization assays with capmatinib suggested that capmatinib has the potential for photosensitization. The no-observed-adverse-effect-level (NOAEL) for *in vivo* photosensitization was 30 mg/kg/day (Cmax of 14000 ng/mL), about 2.9 times the human Cmax at the 400 mg twice daily clinical dose.

Reproductive toxicity

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Store in the original package to protect from moisture.

See folding box. Do not store above 30ºC.

Store in the original package. Protect from moisture.

Tabrecta must be kept out of the reach and sight of children.

Instructions for use and handling

In-use period (for HDPE bottle only): Discard any unused Tabrecta remaining after 6 weeks of first opening the bottle.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Presentation

For both 150 mg and 200 mg strengths: Tablets are packed in PCTFE/PVC-Alu or PVC/PE/PVDC-Alu blister, in a box of 60 tablets.

Not all presentations may be available locally.

Novartis Pharma AG, Basel, Switzerland