KURZPROTOKOLL
Cosmic

Öffentlicher Titel	Phase III Studie zu Cabozantinib bei Schilddrüsenkrebs nach Radioiod- und VEGFR-gerichteter Therapie
Wissenschaftl. Titel	A Phase 3, Randomized, Double-Blind, PlaceboControlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy
Kurztitel	Cosmic
Studienart	prospektiv, Therapiestudie, randomisiert, doppelblind, zweiarmig
Studienphase	Phase III
Erkrankung	Drüsen/Hormone/Stoffwechsel: Schilddrüsenkrebs: Zweitlinie oder höher
Einschlusskriterien	- Histologically or cytologically confirmed diagnosis of DTC, including the following subtypes (Note: results of a previous biopsy will be accepted): a. PTC including histological variants of PTC such as follicular variant, tall cell, columnar cell, cribriform -morular, solid, oxyphil, arthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated b. FTC including histological variants of FTC such as Hürthle cell, clear cell, insular, and poorly differentiated - Measurable disease according to RECIST 1.1 on CT/MRI performed within 28 days prior to randomization - Must have been previously treated with or deemed ineligible for treatment with Iodine -131 for DTC - Must have been previously treated with at least one of the following VEGFR-targeting TKI agents for DTC: lenvatinib or sorafenib. (Note: Up to two prior VEGFR-targeting TKI agents are allowed including (but not limited to) lenvatinib and sorafenib.) - Must have experienced documented radiographic progression per RECIST 1.1 per Investigator during or following treatment with a VEGFR-targeting TKI prior to starting the next anticancer therapy (which may be treatment in this study) - Recovery to baseline or <= Grade 1 (Common Terminology Criteria for Adverse Events Version 5 [CTCAE v5]) from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy - Age >=18 years old on the day of consent - Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 - Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 10 days before randomization: a. Absolute neutrophil count >= 1500/mm3 (>=1.5 GI/L) without receipt of granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection b. Platelets >=100,000/mm3 (100 GI/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection c. Hemoglobin >=9 g/dL (>=90 g/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection d. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) <=3 × upper limit of normal (ULN). ALP <=5 × ULN if the subject has documented bone metastases e. Bilirubin <= 1.5 × the ULN. For subjects with known Gilbert's disease <= 3 × ULN f. Serum creatinine <= 2.0 × ULN or calculated creatinine clearance >= 30 mL/min (>= 0.5 mL/sec) using the Cockcroft-Gault (see Table 5-2 for Cockcroft-Gault formula). g. Urine protein/creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol) - Must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 IU/mL), whichever is lower, within 28 days before randomization. (Note: If hormone replacement therapy is tolerated a TSH level of <= 0.1 mIU/L should be targeted.) - Capable of understanding and complying with the protocol requirements and signed informed consent

- Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and for 4 months after the last dose of study treatment. For females, such methods include combined hormonal contraception (oral, intravaginal, dermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable hormonal contraception, implantable hormonal contraception), placement of an intrauterine device, or placement of an intrauterine hormone-releasing system. A barrier contraceptive method (eg. condom) is also required because hormonal contraception may not be reliably effective enough. Males must agree to use a barrier method unless they have had a vasectomy. Female partners of male subjects in the study are to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 4 months after the last dose of treatment in the male participant. Male subjects must refrain from donating sperm for the duration of the study treatment and until 4 months after the last dose of study treatment
- Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause)

Ausschlusskriterien

- Prior treatment with any of the following: a. Cabozantinib b. Selective small-molecule BRAF kinase inhibitor (eg, vemurafenib, dabrafenib) c. More than 2 VEGFR-targeting TKI agents (eg, lenvatinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib) d. More than 1 immune checkpoint inhibitor therapy (eg, PD-1 or PD-L1 targeting agent) e. More than 1 systemic chemotherapy regimen (given as single agent or in combination with another chemotherapy agent)
- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before randomization
- Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization
- Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (eg, radiation esophagitis or other inflammation of the viscera)
- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization
- Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants: • Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH) • Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before randomization and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor

	- The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions: a. Cardiovascular disorders: i. Congestive heart failure class 3 or 4 as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis [DVT], pulmonary embolism) within 6 months before randomization. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before randomization. b. Gastrointestinal disorders (GI; eg, malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation: i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before randomization Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red blood or history of other significant bleeding within 3 months before randomization d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation e. Lesions invading major pulmonary blood vessels f. Other clinically significant disorders such as: • Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or chronic hepatitis B or C infection • Serious non-healing wound/ulcer/bone fracture • Malabsorption syndrome • Moderate to severe hepatic impairment (Child-Pugh B or C) • Requirement for hemodialysis or peritoneal dialysis • Uncontrolled diabetes mellitus • History of solid organ transplantation - Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Complete wound healing from major surgery must have occurred 4 weeks before randomization and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible
Alter	18 Jahre und älter
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Sponsor	Exelixis
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03690388 (primäres Register) EudraCT 2018-001771-21