QBGJ398-301 - The PROOF Trial (dernière mise à jour : 25/06/2020)

http://archimaid.fr/index.php?action=show&id=1167

Informations générales

Titre de l'étude : A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: The PROOF Trial

Traitement : Néoadjuvant / Métastatique ou localement avancé

Type d'étude : Hors ciblage moléculaire

Phase : III **Stade** : Localement avancé à Métastatique **Ligne(s)** : 1

Schéma : Infigratinib is an oral drug which selectively binds to fibroblast growth factor receptor (FGFR) 2 and is being developed to treat participants with FGFR2 mutated cholangiocarcinoma. The purpose of the study is to evaluate the efficacy and safety of the investigational agent oral infigratinib vs standard of care chemotherapy (gemcitabine plus cisplatin) in first-line treatment of participants with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations. Subjects will be randomized 2:1 to receive infigratinib or gemcitabine plus cisplatin.

STUDY ARMS:
- Experimental: Infigratinib (BGJ398) 125 mg
Infigratinib (BGJ398) 125 mg orally daily, 3 weeks on, 1 week off.

- Active Comparator: Gemcitabine + Cisplatin
Gemcitabine: 1000 mg/m2 IV D1 and D8 for a 21-day cycle
Cisplatin: 25 mg/m2 IV D1 and D8 for a 21-day cycle
Participants who experience disease progression while receiving gemcitabine + cisplatin will be allowed to cross over and receive infigratinib if certain criteria are met.

PRIMARY OBJECTIVE:
The primary objective is to determinate if treatment with infigratinib improves centrally assessed progression-free survival (PFS) compared to treatment with gemcitabine with cisplatin in subjects with advanced/metastatic or inoperable cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions/ translocations.

SECONDARY OBJECTIVES:
• Evaluate the efficacy of treatment with infigratinib versus gemcitabine and cisplatin in terms of overall survival (OS) for subjects with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions/translocation
• Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS
• Further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine with cisplatin by ORR best overall response (BOR), duration of response and disease control rate determined centrally and by the investigator
• Characterize the safety and tolerability of single agent infigratinib
•Evaluar la eficacia del tratamiento con infigratinib en comparación con gemcitabina y cisplatino en términos de supervivencia global (SG) en sujetos con colangiocarcinoma avanzado/metastásico o inoperable con fusiones/translocaciones del gen FGFR2.
•Evaluar la eficacia del tratamiento con infigratinib en comparación con gemcitabina y cisplatino en términos de SSP evaluada por el investigador.
•Evaluar adicionalmente la eficacia en sujetos tratados con infigratinib frente a gemcitabina y cisplatino mediante la TRG, mejor respuesta global (MRG), duración de la respuesta y tasa de control de la enfermedad determinadas de forma centralizada y por el investigador.
•Caracterizar la seguridad y la tolerabilidad de infigratinib en monoterapia.

Spécialités / Localisations

Spécialité n°1 : Organes digestifs

CIM10 - Localisation n°1 : **C22** - Tumeur maligne du foie et des voies biliaires intrahépatiques

Critères

Critères d'inclusion : 1. Have histologically or cytologically confirmed non-resectable, recurrent, or metastatic cholangiocarcinoma. Subjects with gallbladder cancer or ampulla of Vater carcinoma are not eligible.
2. Have written documentation of local or central laboratory determination of FGFR2 gene fusions/translocations. Note: Central confirmation is not required prior to enrollment in study.
3. Have a representative tumor sample available for central FGFR2 fusion/translocation molecular testing. An archival tumor sample and associated pathology report may be submitted. However, if not available, a newly obtained tumor biopsy may be submitted instead.Note: If available FGFR2 fusion/translocation written documentation is from the central laboratory being used in the study, a tumor sample does not need to be submitted for central FGFR2 fusion/translocation molecular testing.
4. Have full recovery from the following permitted prior treatments (as applicable) such that the subject is reasonably expected to tolerate study treatment (gemcitabine/cisplatin or infigratinib) according to the investigator's assessment:
a. A non-curative operation (ie., R2 resection [with macroscopic residual disease] or palliative bypass surgery only)
b. Curative surgery with evidence of non-resectable disease relapse requiring systemic chemotherapy
c. Adjuvant radiotherapy (with or without radio-sensitizing low-dose chemotherapy) for localized disease provided there has been clear evidence of disease progression before inclusion in this study
d. Adjuvant chemotherapy, provided the treatment was completed > 6 months before trial entry
e. Photodynamic treatment provided there is clear evidence of disease progression at the local site or at a new metastatic site.
5. Are >= 18 years of age of either gender.
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status <= 1.
7. Have a life expectancy > 3 months.
8. Are able to read and/or understand the details of the study and provide written evidence of informed consent as approved by Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
9. Have recovered from AEs of previous systemic anti-cancer therapies to baseline or Grade 1, except for alopecia.
10. Are able to swallow and retain oral medication.
11. Are willing and able to comply with scheduled visits, treatment plan and laboratory tests.
12. If a woman of childbearing potential (WOCBP), must have a negative pregnancy test within 7 days of the first dose of study drug. A woman is not of childbearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months, with an appropriate clinical profile, and there is no other cause of amenorrhea (eg., hormonal therapy, prior chemotherapy).

Critères de non-inclusion : 1. Have received treatment with any systemic anti-cancer therapy for unresectable, recurrent, or metastatic cholangiocarcinoma. Prior neoadjuvant or adjuvant therapy is permitted if completed > 6 months prior to first dose of study drug.
2. Have history of a liver transplant.
3. Have received prior or current treatment with a MEK or selective FGFR inhibitor.
4. Have neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Note: Steroid use for management of central nervous system tumors is allowed but must be at a stable dose for at least 2 weeks preceding study entry.
5. Have a history of another primary malignancy within 3 years except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated malignancy that is not expected to require treatment for recurrence during the course of the study.
6. Have any other medical condition that would, in the investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
7. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.

8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.
9. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, eg., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.
11. Are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
12. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug.
13. Have used medications known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose of study drug.
14. Have used amiodarone within 90 days prior to first dose of study drug.
15. Are currently using therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants or using direct thrombin inhibitors (e.g., argatroban) or Factor Xa inhibitors (e.g., rivaroxaban) that are primarily metabolized by CYP3A4.
16. Have insufficient bone marrow function.
17. Have insufficient hepatic and renal function.
18. Have amylase or lipase >2.0 × ULN
19. Have abnormal calcium-phosphate homeostasis:
a. Inorganic phosphorus outside of local normal limits
b. Total corrected serum calcium outside of local normal limits
20. Have clinically significant cardiac disease.
21. Have had a recent (<= 3 months prior to first does of study drug) transient ischemic attack or stroke.
22. CTCAE (v4.0 or later) Grade >= 2 hearing loss.
23. CTCAE (v4.0 or later) Grade >= 2 neuropathy.
24. If female, is pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
25. Have known microsatellite instability-high (MSI-H) disease and the decision is made by the treating investigator that an alternative, non-study therapy is warranted according to standard of care.

Informations promoteur

Nom du promoteur : QED Therapeutics, Inc.

Type de promoteur : Industriel

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Informations centre investigateur n°1

Nom du centre : Centre Hospitalier Universitaire de Lille

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Investigateur : Docteur Anthony TURPIN

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Statut de l'essai : OUVERT

Liens utiles

ClinicalTrials (anglais) : https://clinicaltrials.gov/ct2/show/record/NCT03773302?term=proof+trial%3B+qed&draw=2&rank=1

EU clinical trial register (anglais) : https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004004-19/ES

QED : https://www.qedprooftrial.com/pdfs/PROOF-HCP-Factsheet-Jan2020.pdf