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A study of the safety, pharmacokinetics, and therapeutic activity of cibisatamab in combination with atezolizumab in participants with locally advanced and/or metastatic carcinoembryonic antigen (CEA)-positive solid tumors

Submission date 23/02/2021	Recruitment status No longer recruiting	 Prospectively registered Protocol
Registration date 22/06/2021	Overall study status Completed	[_] Statistical analysis plan[X] Results
Last Edited 23/06/2021	Condition category Cancer	Individual participant data

Plain English summary of protocol

Background and study aims

This is a study to evaluate the safety, tolerability (side effects) and effectiveness of cibisatamab in combination with atezolizumab in patients with locally advanced and/or metastatic carcinoembryonic antigen (CEA)-positive solid tumors. Locally advanced cancer is cancer that has spread only to nearby tissues or lymph nodes, while metastatic cancer is cancer that has spread to other parts of the body. CEAs are substances (usually proteins) that are produced by some types of cancer.

Who can participate? Patients with locally advanced and/or metastatic CEA-positive solid tumors

What does the study involve?

Part I of the study is subdivided into parts IA and IB. In Part IA participants receive increasing doses with a starting dose of 5 mg of cibisatamab given once a week and a fixed, flat dose of 1200 mg of atezolizumab given every 3 weeks, to evaluate the safety and determine the highest tolerated dose of cibisatamab in combination with atezolizumab. Part IB is a dose/schedule finding part that will test different schedules of cibisatamab in combination with atezolizumab.

What are the possible benefits and risks of participating?

Data from previous studies suggest that cibisatamab and atezolizumab could act together in their anti-cancer properties and their combination could provide a meaningful clinical benefit in patients with cancer. Potential side effects for cibisatamab and atezolizumab include gastrointestinal (GI) side effects (diarrhea), breathing side effects (shortness of breath and lack of oxygen), and blood side effects (low white blood cell count and low red blood cell count). Where is the study run from? Hospitals in the United States, Canada, Denmark, France, Italy, Netherlands and Spain

When is the study starting and how long is it expected to run for? May 2015 to January 2020

Who is funding the study? Genentech (USA)

Who is the main contact? global-roche-genentech-trials@gene.com

Study website

https://forpatients.roche.com/en/trials/cancer/a-study-of-the-safety--pharmacokinetics--and-therapeuti-98047.html

Contact information

Type(s) Public

Contact name Miss Clinical Trials

Contact details

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Additional identifiers

EudraCT/CTIS number 2015-003771-30

IRAS number

ClinicalTrials.gov number NCT02650713

Secondary identifying numbers WP29945

Study information

Scientific Title

An open-label, multicenter, dose-escalation and expansion Phase Ib study to evaluate the safety, pharmacokinetics, and therapeutic activity of cibisatamab in combination with atezolizumab in patients with locally advanced and/or metastatic CEA-positive solid tumors

Study objectives

To evaluate the safety, tolerability and clinical activity of cibisatamab in combination with atezolizumab in patients with locally advanced and/or metastatic CEA-positive solid tumors.

Part I of the study is subdivided into parts IA and IB. Part IA is dose escalation with a starting dose of 5 mg of cibisatamab given QW (once a week) and a fixed, flat dose of 1200 mg given Q3W (every 3 weeks) of atezolizumab, to evaluate the safety and determine the MTD of cibisatamab in combination with atezolizumab. Part IB is a dose/schedule finding part that will explore different administration schedules of cibisatamab in combination with atezolizumab (1200 mg Q3W) to establish the appropriate dose/schedule of cibisatamab in combination with atezolizumab.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 15/12/2015, Ethics Committee for Clinical Investigation of Navarra (Departamento de Salud, Pabellon de Docencia, C/ Irunlarrea, 3, 31008 Pamplona, Navarra, Spain; +34 (0) 848422495; ceic@cfnavarra.es), ref: 84/15

Study design

Open-label multicenter dose-escalation and expansion Phase Ib clinical study

Primary study design Interventional

Secondary study design Non randomised study

Study setting(s) Hospital

Study type(s) Treatment

Participant information sheet No participant information sheet available

Health condition(s) or problem(s) studied Solid tumors

Interventions

Dose-Escalation (Part IA): Participants will receive cibisatamab weekly (QW) at escalating doses starting at 5 mg, in combination with a fixed dose (1200 mg) of atezolizumab every 3 weeks (Q3W). Cibisatamab dosage will not exceed the MTD if defined in the BP29541 study. Atezolizumab will be administered at a fixed dose of 1200 milligrams (mg) by intravenous (IV) infusion.

Cibisatamab is administered by IV infusion weekly (QW) on days 1,8 and 15 of each 21-day cycle. Step up dose cohorts: cibisatamab starting dose will be 40 mg and increase with each administration up to the MTD or 1200 mg, whichever is lower.

Tocilizumab will be administered as an IV infusion as necessary to treat adverse events.

Dose/Schedule Finding (Part IB):

Part IB will explore different cibisatamab administration schedules in combination with atezolizumab:

Cohort A: will compare the QW vs Q3W dosing schedules at a flat dose of cibisatamab. Step up dosing schedules: cibisatamab dose will start at 40 mg and increase with each administration up to the MTD or 1200 mg, whichever occurs first.

Atezolizumab will be administered at a fixed dose of 1200 milligrams (mg) by intravenous (IV) infusion.

Cibisatamab is administered by IV infusion weekly (QW) or every 3 weeks (Q3W). Cohort A: cibisatamab starting dose will be 100 mg either QW or Q3W.

Step up dose cohorts: cibisatamab starting dose will be 40 mg and increase with each administration up to the MTD or 1200 mg whichever is lower.

Tocilizumab will be administered as an IV infusion as necessary to treat adverse events.

Intervention Type

Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)

Cibisatamab, atezolizumab, tocilizumab

Primary outcome measure

1. Number of participants with adverse events (AEs) measured using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 (NCI CTCAE v5 was used for CRS) at baseline up to 60 months

2. Percentage of participants with dose-limiting toxicities (DLTs) measured using NCI CTCAE v4. 03 (NCI CTCAE v5 was used for CRS) at Day 1 up to Day 21

3. Maximum-tolerated dose (MTD) of cibisatamab in combination with atezolizumab measured using NCI CTCAE v4.03 (NCI CTCAE v5 was used for CRS) Part IA: Day 1 up to Day 21; Part IB Stepup Cohorts: Day 1 up to Day 7 after each dose escalation

4. Recommended Phase II Dose (RP2D) of cibisatamab in combination with atezolizumab measured using NCI CTCAE v4.03 (NCI CTCAE v5 was used for CRS) at Day 1 up to 60 months

Secondary outcome measures

1. Pharmacokinetics (PK): area under the concentration-time curve (AUC) of cibisatamab measured using a validated bi-functional PK assay at baseline up to 60 months

2. PK: volume of distribution at steady state (Vss) of cibisatamab measured using a validated bifunctional PK assay at baseline up to 60 months

3. PK: maximum serum concentration (Cmax) of cibisatamab measured using a validated bifunctional PK assay at baseline up to 60 months

4. PK: clearance (CL) of cibisatamab measured using a validated bi-functional PK assay at baseline up to 60 months

5. Pharmacodynamics: immune cell numbers measured using immunohistochemistry (IHC), gene expression and fluorescence-activated cell sorting (FACS) at pre-infusion (1 hour before infusion start) on Day 1 of Cycles 1, 2, 3, 6; Cycle 1 Days 2 and 8 (cycle length = 21 days)

6. Percentage of participants with objective response (partial response [PR] or complete response [CR] measured using Response Evaluation Criteria in Solid Tumors [RECIST]) at baseline up to 60 months. Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or treatment discontinuation.

7. Percentage of participants with disease control (PR, CR or stable disease [SD]) measured using RECIST at baseline up to 60 months. Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or treatment discontinuation.

 Percentage of participants with stable disease (SD) measured using RECIST at baseline up to 60 months. Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or treatment discontinuation.
 Duration of response (DOR) measured using RECIST from initial objective response (PR or CR to the first disease progression or death from any cause (up to 60 months). Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks

thereafter until disease progression or treatment discontinuation. 10. Progression-free survival (PFS) measured using RECIST V1.1 from first study treatment to the first occurrence of objective disease progression or death from any cause (up to 60 months).

Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or treatment discontinuation.

11. Overall survival (OS) measured using the date of death from first study treatment to death from any cause (up to 60 months)

12. Best overall response (BOR) measured using RECIST v1.1 at baseline up to 60 months. Assessed at screening and after the start of treatment every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or treatment discontinuation.

Overall study start date

27/05/2015

Completion date

13/01/2020

Eligibility

Key inclusion criteria

1. Confirmed locally advanced and/or metastatic solid tumor, with at least one tumor lesion of accessible non-critical location to biopsy, in participants who have progressed on a standard therapy, are intolerant to standard therapy, and/or are non-amenable to standard therapy 2. Radiologically measurable and clinically evaluable disease (as per RECIST v1.1)

3. Life expectancy (in the opinion of the investigator) of at least 12 weeks and lactate dehydrogenase (LDH) levels </= 2.5 ULN (upper limit of normal)

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1

5. All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade </= 1 or returned to baseline except alopecia (any grade) and Grade 2 peripheral neuropathy

6. Adequate hematological, liver, and renal function

7. Negative serum pregnancy test within 7 days prior to study treatment in premenopausal women and women </= 2 years after start of menopause (menopause is defined as amenorrhea

for more than 2 years)

8. Participants must agree to remain abstinent or be willing to use effective methods of contraception as defined in the protocol

9. Participants with non-colorectal cancer should have confirmed CEA expression in tumor tissue. For colorectal cancer (CRC), the CEA assessment should be performed but the result is not required for participant selection

Participant type(s)

Patient

Age group

Mixed

Sex Both

Target number of participants
228

Total final enrolment 228

Key exclusion criteria

1. Active or untreated central nervous system (CNS) metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments

2. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for at least 2 weeks prior to enrollment

3. Leptomeningeal disease

4. Participants with paraspinal, paratracheal, and mediastinal pathological lesions larger than 2 cm unless they are previously irradiated

5. Malignancies within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome

6. Significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results

7. Uncontrolled hypertension, unstable angina, congestive heart failure (CHF), serious cardiac arrhythmia requiring treatment history of myocardial infarction within 6 months of enrollment 8. Administration of a live, attenuated vaccine within 28 days before Cycle 1 Day 1 or anticipation that such a live attenuated vaccine will be required during the study

9. Human Immunodeficiency Virus (HIV), active Hepatitis B or Hepatitis C (HCV)

10. Severe infections within 28 days prior to Cycle 1 Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia or active tuberculosis

11. Received oral or intravenous (IV) antibiotics within 14 days prior to Day 1 12. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug

13. Major surgery or significant traumatic injury less than 28 days prior to Cycle 1 Day 1 (excluding biopsies) or anticipation of the need for major surgery during study treatment 14. Known history of autoimmune disease as defined in the protocol 15. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis (including drug induced) on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted

16. Participants with bilateral lung lesions and dyspnea and/or oxygen saturation level (SaO2) less than 92% (at rest, room air and exertion) or participants with lobectomy or pneumonectomy with lung metastases in the remaining lung and either dyspnea or SaO2 less than 92% (at rest, room air and exertion) at baseline

17. Pregnant or breastfeeding

18. Known hypersensitivity to any of the components of cibisatamab and atezolizumab; hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies 19. Investigational therapy (defined as treatment for which there is no regulatory authority approved indication) or last dose of prior immunotherapies within 28 days prior to Cycle 1 Day 1. Participants previously treated with anti-programmed death-ligand 1 (PD-L1), or anti-PD-1 are excluded

20. Last dose of any approved anti-cancer therapy within 28 days prior to the first cibisatamab infusion

21. Prior systemic corticosteroids greater than 10mg prednisone (or equivalent) within 14 days of Cycle 1 Day 1. Inhaled and/or topical steroids are permitted

22. Expected need for regular immunosuppressive therapy

23. Radiotherapy within the last 28 days before Cycle 1 Day 1 with the exception of limited-field palliative radiotherapy

Date of first enrolment

07/01/2016

Date of final enrolment

14/05/2018

Locations

Countries of recruitment Canada

Denmark

France

Italy

Netherlands

Spain

United States of America

Study participating centre UCLA Cancer Center 10945 Le Conte Ave, Suite 3360

Los Angeles United States of America 90095

Study participating centre Princess Margaret Cancer Center 700 University Avenue 7th Floor, Room 7723 Toronto Canada M5G 1Z6

Study participating centre Rigshospitalet; Onkologisk Klinik Blegdamsvej 9 København Denmark 2100

Study participating centre Institut Gustave Roussy 114 Rue Edouard Vaillant, Cedex Villejuif France 94805

Study participating centre Centre Leon Berard Departement Oncologie Medicale 28 Rue Laennec, CEDEX 08 Lyon France 69373

Study participating centre Azienda Ospedaliera Universitaria Senese, U.O.C. Immunoterapia Oncologica Viale Bracci 16 Siena Italy 53100

Study participating centre IRCCS IST. Tumori Fondaz. Pascale S.C. Oncologia Medica, Melanoma, Immunoterapia E Terapie Innovative Via Mariano Sammola, 3 Napoli Italy 80131

Study participating centre Antoni van Leeuwenhoek Ziekenhuis Gastro-Enterologie Plesmanlaan 121 Amsterdam Netherlands 1066 CX

Study participating centre Clinica Universitaria De Navarra Servicio de Oncologia Avenida Pio Xii N0. 36 Pamplona Spain 31008

Study participating centre Hospital Univ Vall d'Hebron Servicio de Oncologia Passeig De La Vall D'hebron 119-129 Barcelona Spain 08035

Study participating centre Hospital Universitario 12 de Octubre Servicio de Oncologia Avenida Cordoba Km 5.4 Madrid Spain 28041 **Study participating centre Hospital del Mar** Servicio de Oncologia Passeig Maritim 25-29, Planta Baja Barcelona Spain 08003

Study participating centre START Madrid

Centro Integral Oncologico Clara Campal (CIOCC) Oña, 10 Madrid Spain 28050

Study participating centre START Madrid-FJD, Hospital Fundacion Jimenez Diaz Avenida Reyes Catolicos 2, Floor 1 Madrid Spain 28040

Study participating centre Memorial Sloan Kettering Cancer Center 300 E 66th Street New York United States of America 10065

Study participating centre Smilow Cancer Hospital at Yale 25 York Street New Haven United States of America CT, 06510

Study participating centre Duke Cancer Center Morris Cancer Clinic 15110 Morris Building Trent Drive Durham United States of America NC, 27710

Study participating centre Stanford Comprehensive Cancer Center 875 Blake Wilbur Dr. Palo Alto United States of America CA, 94305

Study participating centre Medical University of South Carolina 86 Jonathan Lucas St, Rm 380 MSC 955 Charleston United States of America SC, 29425

Study participating centre Columbia University Medical Center

161 Fort Washington Ave, 9th Floor New York United States of America NY, 10032

Study participating centre University Of Colorado

12801 E. 17th Ave, Rm L18-8126 Mail Stop 8117 Aurora United States of America CO, 80045

Study participating centre MD Anderson Cancer Center 1515 Holcombe Boulevard, Unit 426

Houston United States of America TX, 77030

Study participating centre Sarah Cannon Cancer Center 250 25th Avenue North, Suite 110 Germantown United States of America TN, 38138

Sponsor information

Organisation

Genentech, Inc

Sponsor details

1 DNA Way South San Francisco United States of America 94080 +1 (0)888 662 6728 global-roche-genentech-trials@gene.com

Sponsor type

Industry

Website https://www.roche.com/about_roche/roche_worldwide.htm

Funder(s)

Funder type Industry

Funder Name Genentech

Alternative Name(s) Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type

Private sector organisation

Funding Body Subtype

For-profit companies (industry)

Location United States of America

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal. No protocol or other study documents are available.

Intention to publish date

30/11/2021

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement for Phase I studies.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		19/01/2021	23/06/2021	No	No