ISRCTN16358704 https://doi.org/10.1186/ISRCTN16358704

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

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

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 Step-up 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 bi-functional PK assay at baseline up to 60 months
3. PK: maximum serum concentration (Cmax) of cibisatamab measured using a validated bi-functional 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.
8. 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.
9. 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