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A study evaluating the interaction of the body with (pharmacokinetics), clinical activity, and safety of RO6870810 and atezolizumab (PD-L1 Antibody) in participants with advanced ovarian cancer or triple-negative breast cancer

Submission date
25/11/2020

Recruitment status
No longer recruiting

Registration date
09/01/2021

Overall study status
Completed

Last Edited
05/04/2022

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
This study will investigate the dose, safety, interaction with the body (pharmacokinetics), and anti-tumor activity of the novel drug RO6870810 in combination with a fixed dose of atezolizumab in patients with advanced ovarian cancer or triple negative breast cancer with no alternative treatment options, or refusal to undergo an alternative treatment.
Patients with advanced ovarian cancer or triple negative breast cancer have a significant need for new therapies to be developed. Encouraging results have been observed for the use of atezolizumab for solid tumours. Additionally, previous studies for RO6870810 and atezolizumab suggest that atezolizumab may be effective in advanced TNBC and OC and that RO6870810 may enhance the clinical effectiveness of atezolizumab therapy.

Who can participate?
Adults and senior patients with advanced ovarian cancer or triple negative breast cancer.

What does the study involve?
The participants in the study will be divided into four groups. Group 1 will be the Dose-Escalation (DE) group and Group 2 will be the Sequential Dose Group (which will involve an initial treatment period of RO6870810 alone, followed by RO6870810 in combination with atezolizumab). For Groups 1 and 2 RO6870810 will be injected below the skin (subcutaneous) once daily for the first 14 days of a 21-day cycle. For all groups Atezolizumab will be given via the vein (intravenously) at a fixed dose on the first day of each cycle, every 3 weeks. Treatment with the study drug may occur for up to 22 months.

Participants in Group 3 and Group 4 (Expansion group) will recieve the recommended dose of RO6870810, which will have been established in Group 1, administered in combination with atezolizumab.

For each participant, mandatory (archival tissue or fresh) tumor biopsies will be collected during the study.

What are the possible benefits and risks of participating?
Previous studies for RO6870810 and atezolizumab have shown potential for positive effects on patient outcomes in advanced ovarian cancer or triple negative breast cancer . Both RO6870810 and atezolizumab have been well-tolerated as treatment when not in combination.

The most common adverse events reported with RO6870810 include tiredness, decreased appetite, digestive disorders (nausea, vomiting, diarrhea, and constipation), blood toxicities (anemia, thrombocytopenia). The most commonly reported adverse events with single-agent atezolizumab include tiredness, decreased appetite, digestive disorders (nausea, diarrhea, and constipation), and cough. Based on previous experiences with RO6870810 and atezolizumab and their respective safety profiles, there is potential for some overlapping effects. Those include fatigue, decreased appetite, and gastrointestinal toxicities.

Taking into account both the anticipated activity of the combination and the effective measures in place to manage toxicities, it is believed that the overall risk-benefit assessment for this combination is favorable and justifies its exploration in patients for whom standard treatment options are limited.

Where is the study run from?
The study will be run from Genentech, Inc (USA) and conducted across 4 countries: Australia, Canada, Denmark, United States

When is the study starting and how long is it expected to run for?
From June 2017 to February 2019

Who is funding the study?
F. Hoffmann-La Roche Ltd (USA)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2017-001147-13

IRAS number

ClinicalTrials.gov number
NCT03292172

Secondary identifying numbers
NP39487

Study information

Scientific Title
Open label, dose finding, and expansion phase IB study to evaluate the safety, pharmacokinetics, and clinical activity of RO6870810 and atezolizumab (PD-L1 antibody) in patients with advanced ovarian cancer or triple negative breast cancer

Study objectives
To evaluate the safety, pharmacokinetic, pharmacodynamic, and preliminary clinical activity in patients with triple negative breast cancer and/or ovarian cancer

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/10/2017, IntegReview IRB (3815 S. Capital of Texas Highway, Suite 320, Austin, Texas 78704, USA; +1 512 .326.3001; no email contact available)

Study design
Open label, phase IB non-randomized study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied

Advanced ovarian cancer, triple negative breast cancer

Interventions
Group 1 (Escalation Dose: RO6870810 + Atezolizumab) participants will be administered escalating doses of RO6870810 (0.3 mg/kg, 0.45 mg/kg, and 0.65 mg/kg) subcutaneously (SC) once daily (QD) during the first 14 days of each 21-day cycle and will be given a fixed dose of atezolizumab (1200 mg) intravenously (IV) on Day 1 of each 21-day cycle.

Group 2 (Sequential Dose: RO6870810 + Atezolizumab) participants will be administered RO6870810 monotherapy (starting dose 0.30 mg/kg) during the first 14 days of a 21-day run-in period. Following the Run-in period, participants will continue to receive RO6870810 (0.30 mg /kg) subcutaneously (SC) once daily (QD) during the first 14 days of each 21-day cycle and will be given a fixed dose of atezolizumab (1200 mg) intravenously (IV) on Day 1 of each 21-day cycle.

Group 3 (Expansion in triple negative breast cancer group: RO6870810 + Atezolizumab) participants will be administered the dose of RO6870810 established in Group 1 (either 0.3 mg /kg, 0.45 mg/kg, or 0.65 mg/kg) SC QD during the first 14 days of each 21-day cycle, and a fixed dose of atezolizumab (1200 mg) IV on Day 1 of each 21-day cycle.

Group 4 (Expansion in ovarian cancer group: RO6870810 + Atezolizumab) participants will be administered the dose of RO6870810 established in Group 1 (either 0.3 mg/kg, 0.45 mg/kg, or 0.65 mg/kg) SC QD during the first 14 days of each 21-day cycle, and a fixed dose of atezolizumab (1200 mg) IV on Day 1 of each 21-day cycle.

Follow-up will continue for up to 22 months.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO6870810, atezolizumab

Primary outcome measure
1. Dose Limiting Toxicities (DLT) in group 1 participants measured using the reported safety data between baseline and 21 days (first cycle) and within the participant receives the full intended combination doses and number of administrations. No statistical analyses have been performed as this was a 3+3 design.
2. Adverse Events (AEs) in all participants graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) between baseline and 22 months
3. Change in Vital Signs, Physical Findings, Electrocardiogram (ECG) and Laboratory Parameters in all participants measured using patient and laboratory data between baseline and 22 months. No statistical analyses have been performed as this was 3+3 design.
4. Objective Response (OR) in group 3 and 4 participants as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between the first occurrence of objective response and either disease progression, death from any cause, or 22 months

Secondary outcome measures

1. Maximum concentration (Cmax) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
2. Time of maximum concentration (tmax) of RO6870810 and atezolizumabmeasured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
3. Clearance (CL) or Apparent Clearance (CL/F) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
4. Volume of Distribution (Vd) or Apparent Volume of Distribution (Vd/F) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
5. Area under the plasma concentration-time curve from time zero to end of the dosing interval (AUC0-tau) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
6. Area under the plasma concentration time curve from time zero to infinity (AUC0-inf) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
7. Half life (t1/2) of RO6870810 and atezolizumab measured using serum samples taken at pre-dose on day 1; pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 10 h on day 14; 24 and 28 h on day 15; and pre-dose on day 21 of cycle 1 and all even cycles until the end of treatment for RO6870810; and at pre-dose and end of infusion on day 1 of cycle 1; pre-dose on day 1 of all even cycles; and 22 months for atezolizumab
9. Trough concentration (Ctrough) of RO6870810 and atezolizumab measured using serum samples at pre-dose of cycle 2 and at the beginning of every subsequent even-number cycles
10. Objective Response (OR) in group 1 and 2 participants measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between the first occurrence of objective response and either disease progression, death from any cause, or 22 months
11. Objective Response (OR) measured using Immune-Modified RECIST criteria between the first occurrence of objective response and either disease progression, death from any cause, or 22 months
12. Duration of Response (DoR) measured using RECIST v1.1 and Immune-Modified RECIST criteria between the first occurrence of objective response and either disease progression, death from any cause, or 22 months
13. Progression-Free Survival (PFS) measured using RECIST v1.1 and Immune-Modified RECIST criteria between the first occurrence of objective response and either disease progression, death from any cause, or 22 months
14. Overall Survival (OS) measured between the first occurrence of objective response and

either disease progression, death from any cause, or 22 months
15. Tumor Marker Assessments measured using serum levels of CA-125, CEA, and CA15-3 at day 1 of each cycle until either disease progression, death from any cause, or 22 months
16. Changes in CD11b expression levels measurement in CD14+ monocytes from blood association with steady-state RO6870810 pharmacokinetic drug exposure from serum samples taken at 1, 8, 15, and 21 days of the run-in period of cycle 1
17. Changes in Markers measured using levels of PD-L1 and CD8/Ki 67 in tissue biopsy specimens by immunohistochemistry taken at 1, 15, and 21 days of the run-in period of cycle 1
18. Percentage of participants with transcript profiling assessment receiving combination study treatment measured using participant records pre-dose and 6 h on day 1 of cycle 1; and pre-dose on day 21 of cycle 1

Overall study start date
30/06/2017

Completion date
26/02/2019

Eligibility

Key inclusion criteria
Groups 1 and 2:
1. Histologically confirmed advanced ovarian cancer or triple negative breast cancer who in the opinion of the Investigator are appropriate for this study
2. Received prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies, provided the following requirements are met:
2.1. Minimum of 5 months from the last dose of anti-PD-1, anti-CTLA-4, anti-PD- L1, or CD137 agonist treatment
2.2. No history of severe immune-related adverse effects from CD137 agonist, anti-CTLA-4, anti-PD-1, or anti-PD-L1 (NCI CTCAE Grade 3 and 4). Any toxicity related to the therapy must have resolved completely, no residual toxicity as assessed by NCI CTCAE (v4.03)
2.3. Agree to use protocol defined methods of contraception For all participants, the reliability of sexual abstinence must be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception

Group 3:
1. Histologically confirmed triple negative breast cancer
2. Received either one or 2 prior systemic treatments for metastatic breast cancer
3. Documented disease progression on or after the most recent treatment

Group 4:
1. Recurrent ovarian cancer
2. Received no more than two prior lines of platinum therapy in the recurrent setting and have progressed within 9 months from the last platinum containing regimen

All participants:
1. Measurable disease by RECIST criteria version 1.1 prior to study drug administration
2. Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale

3. Life expectancy, in the opinion of the Investigator, of at least 3 months
4. Disease-free of active second/secondary or prior malignancies for ≥2 years with the exception of squamous cell carcinoma of the skin, or carcinoma in situ of the cervix or breast
5. Willing to provide the protocol specified tumor biopsies
6. Acceptable hematologic status, liver and renal function

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Targeted 80, Actual 36

Total final enrolment
36

Key exclusion criteria
1. History of prior malignancy except solid tumor treated curatively more than 3 years ago without evidence of recurrence
2. Asymptomatic or symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
3. History of leptomeningeal disease
4. Uncontrolled tumor-related pain
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. Participants with indwelling catheters are allowed.
6. Uncontrolled or symptomatic hypercalcemia
7. New York Heart Association Class III or IV cardiac disease, pericarditis, myocardial infarction within the past 6 months, unstable arrhythmia
8. Fredericia-corrected QT interval (QTcF) >470 msec (female) or >450 msec (male), or history of congenital long QT syndrome. Any electrocardiogram (ECG) abnormality, including pericarditis, which in the opinion of the investigator would preclude safe participation in the study.
9. Active, uncontrolled bacterial, viral, or fungal infections within 7 days of study entry requiring systemic therapy. Participants with active TB infection are excluded from the study.
10.Known clinically important respiratory impairment
11. History of major organ transplant
12. History of an autologous or allogeneic bone marrow transplant
13. Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor
14. Pregnant or nursing women
15. Any systemic anticancer therapy within 3 weeks prior to Cycle 1 Day 1
16. Any radiation treatment to metastatic site within ≤14 days of Cycle 1 Day 1
17. Major surgical procedure, open biopsy, or significant traumatic injury within 30 days prior to Cycle 1 Day 1 or anticipation of the need for major surgical procedure during the course of the study
18. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human or humanized antibodies or fusion proteins

19. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
20. Active or history of autoimmune disease
21. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
22. Positive test for Human immunodeficiency virus (HIV)
23. Active hepatitis B or hepatitis C
24. Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study
25. Treatment with an investigational therapy within 28 days prior to initiation of study treatment
26. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
27. Consumption of agents which strongly inhibit CYP3A4 enzyme, within 7 days prior to the first dose of study treatment and during the study
28. Consumption of agents which strongly induce CYP3A4 enzyme, within 14 days prior to the first dose of study treatment and during the study
29. Treatment with systemic immuno-stimulatory agents within 4 weeks or five half-lives of the drug (whichever is shorter) prior to the first dose of study treatment
30. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to the first dose of study treatment, or anticipated requirement for systemic immunosuppressive medications during the trial
31. Unwillingness or inability to comply with procedures required in this protocol

Date of first enrolment
08/11/2017

Date of final enrolment
18/12/2018

Locations

Countries of recruitment
Australia

Canada

Denmark

England

Scotland

United Kingdom

United States of America

Study participating centre

Dana Farber Cancer Institute
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Study participating centre
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Sponsor type
Industry

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

Funder(s)

Funder type
Industry

Funder Name
Genentech, Inc

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal , anticipated for the first half of 2021.

Intention to publish date
30/06/2021

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v8	17/08/2018	04/02/2021	No	Yes
Basic results		21/01/2020	05/04/2022	No	No