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A study evaluating single-agent inavolisib and inavolisib plus atezolizumab in PIK3CA-mutated cancers

Submission date
15/03/2022

Recruitment status
No longer recruiting

Registration date
25/04/2022

Overall study status
Completed

Last Edited
04/12/2023

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cancer is a disease in which abnormal cells divide without control and can invade nearby tissues. Cancers that are known collectively as head and neck cancers usually begin in the squamous cells (a flat cell that looks like a fish scale under a microscope) that form the moist, inner lining of the head and neck (for example, those inside the mouth, throat, and voice box). The risk factors for head and neck squamous cell carcinoma (HNSCC) include tobacco use, alcohol consumption, and infection with human papillomavirus (HPV). Studies of HNSCC tumours show that there is a frequent occurrence of a mutation in the PIK3CA gene. PIK3CA is a gene that controls a message telling cells to grow and multiply. This message is often involved in cancer when cells lose the ability to turn it off. This messaging system is called the PI3K cancer pathway. Inavolisib, the drug that is being studied, is designed to block the wrong messaging from the mutated PIK3CA gene and, therefore, block the PI3K cancer pathway described above. Inavolisib is an experimental drug, which means health authorities have not approved inavolisib for the treatment of cancer. In this study, inavolisib will be tested with or without a drug called atezolizumab. Atezolizumab has been approved by health authorities for several cancers, but not for recurrent and/or metastatic HNSCC (cancer that has come back and/or spread to other organs).
The main aims of this study are:
1. To evaluate the effects, good or bad, of inavolisib alone or inavolisib plus atezolizumab in participants with PIK3CA-mutated, recurrent and/or metastatic HNSCC cancer
2. To determine how safe and tolerable inavolisib is when given alone or in combination with atezolizumab in participants with PIK3CA-mutated, recurrent and/or metastatic HNSCC cancer
3. To assess the anti-tumour activity of inavolisib when given alone or in combination with atezolizumab in participants with PIK3CA-mutated, recurrent and/or metastatic HNSCC cancer
4. To determine how the body absorbs, distributes, and eliminates inavolisib when given alone or in combination with atezolizumab

Who can participate?
People aged at least 18 years with a confirmed diagnosis of recurrent and/or metastatic HNSCC that has been previously treated with systemic therapy.

What does the study involve?
The duration of participation in the study will depend on the participant's tolerance of and response to the treatment, this could range from 1 day to more than 24 months.
The study involves three parts:
1. (Pre-)Screening (to see if the participants are eligible for the study): The participants will be asked to share a blood sample (about 1½ tablespoons) to determine whether it is positive for an eligible PIK3CA mutation. Some sites may initially test only for the presence of a PIK3CA mutation (pre-screening).
2. Treatment Phase: The participants will receive study treatment in 21-day cycles (each 21-day period is called a “cycle”). The participants will have clinic visits twice a week for the first cycle, two clinic visits during cycles 2 and 3, and then once per cycle thereafter while the participants are receiving treatment. The clinic may contact the participants by telephone mid-cycle to check their condition. Clinic visits may last 1-5 hours.
3. Follow-up (to check on the participant after treatment is finished): Following study treatment discontinuation, participants will be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the start of another anti-cancer therapy, whichever occurs first. There will be additional hyperglycaemia (high blood sugar) follow-up, if required, which will be monitored until resolution or for 90 days, whichever is sooner

Participants will be enrolled into two separate groups namely:
1. Arm A: Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily, on Days 1–21 of each cycle.
2. Arm B: Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily and atezolizumab given as an infusion (into the vein) once every 3 weeks (21 days).
The treatment will continue until the cancer worsens, the participants have medically unacceptable side effects, or if the participants decide to withdraw from the study.

What are the possible benefits and risks of participating?
Participants may not receive any direct medical benefit from participating in this study, but the information collected will help other people who have a similar medical condition in the future.
Participants may have side effects from the drugs or procedures used in this study; these may range from mild to severe and even life-threatening, and they can vary from person to person.
The side effects associated with inavolisib, based on human and laboratory studies or knowledge of similar drugs, are listed below. There may be side effects that are not known at this time.
Known side effects:
1. Hyperglycaemia (increased blood sugar levels)
2. Diarrhoea (loose stools)
3. Decreased appetite
4. Vomiting
5. Nausea
6. Decreased weight
7. Constipation
8. Flatulence (gas)
9. Rash
10. Mucosal inflammation/stomatitis (inflammation of the lining of the mouth or ulcers of the lip or mouth)

Potential side effects:
1. Eye disorder (eye pain or sensitivity to light, blurred vision, cataract which may cause cloudiness of the eye)

2. Colitis (inflammation [swelling and redness] of the large bowel [colon])
3. Possible harm to a developing foetus, including birth defects and/or miscarriage
4. Pneumonitis (inflammation of the lungs that may cause difficulty breathing and can be life-threatening)
5. Depressed immune function (low levels of white blood cells that may lead to increased risk of infections, low levels of platelets)
6. In males, reduced fertility or permanent sterility

Among the side effects known to be associated with atezolizumab, the following would require more attention:
1. Inflammation of the intestines (colitis), thyroid gland, adrenal glands, pituitary gland, liver, brain and surrounding membranes, lungs (pneumonitis), pancreas (pancreatitis), kidneys, blood vessels (vasculitis), muscles, eye, or heart muscle (myocarditis)
2. Nerve damage
3. Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
4. Condition of high levels of sugar in the blood
5. Severe skin or mucosal reactions
6. Development of special antibodies to atezolizumab by the immune system
7. Potential to cause harm to a developing foetus
8. Breakdown of red blood cells (autoimmune haemolytic anaemia)
9. Allergic reactions may occur with atezolizumab and typically occur while it is being given into the vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability.
10. In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection

There may be some risks associated with the procedures performed during the study:
1. The tumour tissue sample (biopsy) can cause pain, redness, swelling, excessive bleeding, bruising, or draining at the needle site. Abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site can also occur
2. The screening test for PIK3CA mutations in a blood sample to establish eligibility for the study can rarely produce an incorrect test result. If the enrolment in the study is based on an incorrect test result (“false positive”), the participant may be less likely to respond to the study treatment
3. For blood samples, drawing blood can cause pain, bruising, or infection where the needle is inserted. The participants may experience dizziness, fainting, or upset stomach when their blood is drawn
4. Tumour assessments involving a computed tomography (CT) scan, a magnetic resonance imaging (MRI) scan, or a bone scan may have the following risks:
4.1. The participant may have an allergic reaction to a tracer or contrast agent
4.2. Oral and rectal contrast agents may cause nausea, constipation, diarrhoea, and abdominal bloating
4.3. Injected contrast agents may cause nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. There may be pain, bruising, or infection at the injection site
4.4. CT and MRI scanners may cause some anxiety and claustrophobia (fear of being in small places)
4.5. Although there are no known long-term harmful effects from the radiation of a single scan, the risk of harmful effects from multiple scans over a period is not known
4.6. Reports indicate that deposits of gadolinium-based contrast agents may remain in the brain

long after MRI scan completion in some participants undergoing four or more scans. The implications of this are unknown.
There may be a risk in exposing an unborn child to the study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to the study drug. Participants who are pregnant, become pregnant or are currently breastfeeding cannot take part in this study.

Where is the study run from?
F. Hoffmann-La Roche Ltd (USA)

When is the study starting and how long is it expected to run for?
December 2021 to April 2025

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

Contact name
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Additional identifiers

Protocol serial number
CO43909

Study information

Scientific Title
A Phase I/Ib study evaluating single-agent inavolisib and inavolisib plus atezolizumab in PIK3CA-mutated cancers

Study objectives

The purpose of the study is to assess the safety and efficacy of inavolisib as a single-agent and in combination with atezolizumab in participants with phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA)-mutated cancers, including previously treated head and neck squamous cell carcinoma (HNSCC).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/02/2022, US Food and Drug Administration (Silver Spring, MD 20993, USA; +1 (0) 240 402 4558; opeyemi.udoka@fda.hhs.gov), ref: 4944076, IND 160141

Primary study design
Interventional

Study design
Phase I/Ib open-label multi-centre parallel study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
PIK3CA-mutated solid cancers including previously treated recurrent or metastatic HNSCC

Interventions
This is a non-randomized study and treatment assignment will be conducted with an interactive voice or Web-based response system (IxRS).

Arm A: Participants will receive inavolisib, 9 mg, orally, once daily (QD) on Days 1-21 of each 21-day cycle until unequivocal disease progression as assessed by the investigator, unacceptable toxicity, participant withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Arm B: Participants will receive inavolisib, 9 mg, orally, once daily (QD), on Days 1-21 of each 21-day cycle until unequivocal disease progression as assessed by the investigator, unacceptable toxicity, participant withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Participants will also receive atezolizumab, 1200 mg, as intravenous (IV) infusion once every 3 weeks (Q3W) on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, participant withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)

1. Percentage of participants with select treatment-related toxicities (TRT) in Arm B as assessed by the investigator from Day 1 of Cycle 1 to Day 3 of Cycle 2
2. Percentage of participants with adverse events (AEs) and serious adverse events (SAEs) as assessed by the investigator from start of treatment until 30 days after the final dose of inavolisib or atezolizumab, or until initiation of another anti-cancer therapy, whichever occurs first (approximately up to 3 years)
3. Percentage of participants with adverse events of special interest (AESIs) as assessed by the investigator from start of treatment until 30 days after the final dose of inavolisib or atezolizumab, or until initiation of another anti-cancer therapy, whichever occurs first (approximately up to 3 years)
4. Severity of AEs, SAEs and AESIs as assessed by the investigator per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE V5.0) from screening until up to 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first (approximately up to 3 years)
5. Change from baseline in targeted vital signs measured using weight, respiratory rate, pulse rate, blood oxygenation (pulse oximetry), systolic and diastolic blood pressure, and temperature at screening, Days 1, 4, 8, and 15 of Cycle 1, Days 1 and 10 of Cycles 2 and 3, and Day 1 of subsequent cycles and treatment discontinuation (approximately up to 3 years)
6. Change from baseline in targeted clinical laboratory tests (including ECGs) assessed using blood and urine samples and 12-lead ECG recordings at multiple timepoints from screening to end of each cycle up to treatment discontinuation (approximately up to 3 years)

Key secondary outcome(s)

1. Overall response rate (ORR) as determined by the investigator using Response Evaluation Criteria for Solid Tumours version 1.1 (RECIST v1.1) every 9 weeks from Day 1 of Cycle 1 during the first 2 years, and every 12 weeks thereafter until disease progression or initiation of another anti-cancer therapy whichever occurs first (approximately up to 3 years)
2. Best overall response rate (BOR) as determined by the investigator using RECIST v1.1 every 9 weeks from Day 1 of Cycle 1 during the first 2 years, and every 12 weeks thereafter until disease progression or initiation of another anti-cancer therapy whichever occurs first (approximately up to 3 years)
3. Duration of response (DOR) as determined by the investigator using RECIST v1.1, or death, whichever occurs first every 9 weeks from Day 1 of Cycle 1 during the first 2 years, and every 12 weeks thereafter until disease progression or initiation of another anti-cancer therapy whichever occurs first (approximately up to 3 years)
4. Clinical benefit rate (CBR) as determined by the investigator using RECIST v1.1 every 9 weeks from Day 1 of Cycle 1 during the first 2 years, and every 12 weeks thereafter until disease progression or initiation of another anti-cancer therapy whichever occurs first (approximately up to 3 years)
5. Progression-free survival (PFS) as determined by the investigator using RECIST v1.1, or death, whichever occurs first every 9 weeks from Day 1 of Cycle 1 During the first 2 years, and every 12 weeks thereafter until disease progression or initiation of another anti-cancer therapy whichever occurs first (approximately up to 3 years)
6. Plasma concentration of inavolisib in Arm A measured using plasma samples at predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and at Predose on Day 1 of Cycle 3
7. Area under the concentration-time curve (AUC) of inavolisib in Arm A measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and at Predose on Day 1 of Cycle 3
8. Maximum plasma concentration (Cmax) of inavolisib in Arm A measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and at Predose on Day 1 of Cycle 3

9. Minimum plasma concentration (Cmin) of inavolisib in Arm A measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and at Predose on Day 1 of Cycle 3
10. Plasma concentration of inavolisib in Arm B measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and Predose on Day 1 of Cycle 3
11. AUC of inavolisib in Arm B measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and Predose on Day 1 of Cycle 3
12. Cmax of inavolisib in Arm B measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and Predose on Day 1 of Cycle 3
13. Cmin of inavolisib in Arm B measured using plasma samples at Predose and 3 hours post-dose on Day 1 of Cycle 1 and 2 and Predose on Day 1 of Cycle 3

Completion date
01/04/2025

Eligibility

Key inclusion criteria
1. Participants must be at least 18 years of age
2. Histologically or cytologically confirmed recurrent and/or metastatic HNSCC that has been previously treated with systemic therapy in the recurrent and/or metastatic setting
3. Documented positive or negative human papillomavirus (HPV) status as determined locally by p16 immunohistochemistry (IHC; preferred), in situ hybridization, and/or by polymerase chain reaction-based assay. Participants with either HPV-positive or HPV-negative status are eligible ("unknown" HPV status is not eligible)
4. Eligible participants must not be suitable for treatment with surgery and/or radiation
5. Confirmation of biomarker eligibility: Valid results from either central testing of blood or local testing of blood or tumour tissue documenting PIK3CA-mutated tumour status
6. Consent to provide fresh (preferred) or archival tumour tissue specimen
7. Negative hepatitis B surface antigen (HBsAg) and total hepatitis B core antibody (HBcAb) test or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA at screening
8. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
9. Measurable disease per RECIST v1.1
10. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
11. Life expectancy of ≥12 weeks

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria

1. Prior treatment with any phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or mammalian target of rapamycin (mTOR) inhibitor, or any agent whose mechanism of action is to inhibit the PI3K/AKT/mTOR pathway
2. Appropriate for treatment with surgery and/or radiation at the time of entry into the study, as per national or local treatment guidelines
3. Type II diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type I diabetes
4. Malabsorption syndrome or other condition that would interfere with enteral absorption
5. Known and untreated, or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Participants with a history of treated CNS metastases are eligible provided they meet specified criteria
6. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures twice per week or more frequently
7. Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1
8. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of the need for such a vaccine during study treatment
9. Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
10. Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
11. Requirement for daily supplemental oxygen
12. Symptomatic active lung disease, including pneumonitis
13. History of or active inflammatory bowel disease (e.g., Crohn’s disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)
14. Known Human Immunodeficiency Virus (HIV) infection
15. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the participant at high risk from treatment complications
16. Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before enrolment
17. Investigational drug(s) within 4 weeks before enrolment
18. Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade ≤ 2 peripheral neuropathy
19. History of other malignancy within 5 years prior to screening, with specified exceptions
20. History of or active clinically significant cardiovascular dysfunction
21. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the participant's safe participation in and completion of the study)
22. Chronic corticosteroid therapy of ≥10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
23. Allergy or hypersensitivity to components of the inavolisib formulation
24. Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or five drug-elimination half-lives, whichever is longer, prior to initiation of study treatment

25. Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1; or anticipation of the need for major surgery during study treatment
26. Minor surgical procedures <7 days prior to the first dose of study treatment

Exclusion criteria specific to arms utilizing atezolizumab:
27. Prior serious immune-mediated toxicities resulting from treatment with any checkpoint inhibitor including, but not limited to, atezolizumab, pembrolizumab, or nivolumab
28. Treatment with any checkpoint inhibitor within 5 half-lives of Day 1 of Cycle 1
29. Uncontrolled or symptomatic hypercalcemia
30. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with specified exceptions
31. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan; a history of radiation pneumonitis in the radiation field (fibrosis) is permitted
32. Active tuberculosis
33. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia
34. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment; participants receiving prophylactic antibiotics may be eligible for the study
35. Prior allogeneic stem cell or solid organ transplantation
36. Current treatment with anti-viral therapy for HBV
37. Treatment with systemic immunostimulatory agents within 4 weeks or five drug-elimination half-lives of the drug (whichever is longer)
38. Treatment with systemic immunosuppressive medication within 2 weeks prior to initiation of study treatment, or anticipation of the need for systemic immunosuppressive medication during study treatment, with specified exceptions
39. Poor peripheral venous access that would preclude repeated IV infusions
40. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
41. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

Date of first enrolment
31/05/2022

Date of final enrolment
01/04/2025

Locations

Countries of recruitment
United Kingdom

Canada

France

Spain

United States of America

Study participating centre
To be confirmed
United States of America
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Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

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.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes