An Open Label Phase 1, First-In-Human Study of TRAIL Receptor Agonist ABBV-621 in Subjects with Previously-Treated Solid Tumors and Hematologic Malignancies

Published: 28-03-2017
Last updated: 13-04-2024

The primary objectives are to determine the maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of ABBV-621 and to evaluate pharmacokinetics (PK) of (A) single agent ABBV-621; and (B) the combination of ABBV-621 and venetoclax in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON49604

Source
ToetsingOnline

Brief title
M15-913

Condition

- Leukaemias
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, Solid tumors and hematologic malignancies

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: ABBV-621, Hematologic malignancies, Sold tumors, TRAIL receptor

Outcome measures

Primary outcome

The primary objectives are to determine the maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of ABBV-621 and to evaluate pharmacokinetics (PK) of (A) single agent ABBV-621; and (B) the combination of ABBV-621 and venetoclax in patients with AML or DLBCL (C) ABBV-621 with FOLFIRI plus bevacizumab in patients with KRASmutant colorectal cancer (CRC) who have failed one prior line of systemic therapy and (D) ABBV-621 with FOLFIRI in patients with RAS-mutant colorectal cancer (CRC) who have failed on prior line of systemic therapy

Secondary outcome

Safety and tolerability and DLT.

Study description

Background summary

Study M15-913 is a clinical study of ABBV-621 for subjects with previously-treated malignancies. ABBV-621 is a tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor agonist that targets death receptor 4 and 5 (DR4 and DR5, respectively). Pre-clinical data support the investigation of ABBV-621 for the treatment of cancer in humans.
In addition, there is evidence from preclinical data that the anti-tumor activity of the combination of ABBV-621 and venetoclax exceeds that of either

agent alone. Furthermore, pre-clinical models also suggest that the anti-tumor activity of ABBV-621 in combination with chemotherapy agents exceeds that of either agent alone.

Study objective

The primary objectives are to determine the maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of ABBV-621 and to evaluate pharmacokinetics (PK) of (A) single agent ABBV-621; and (B) the combination of ABBV-621 and venetoclax in patients with AML or DLBCL (C) ABBV-621 with FOLFIRI plus bevacizumab in patients with KRASmutant colorectal cancer (CRC) who have failed one prior line of systemic therapy and (D) ABBV-621 with FOLFIRI in patients with RAS-mutant colorectal cancer (CRC) who have failed on prior line of systemic therapy

Study design

Open-label phase 1 dose escalation study.

Intervention

Subjects will receive doses of ABBV-621 intraveneously as monotherapy or in combination with venetoclax or chemotherapy.

Study burden and risks

GLP toxicology studies indicate virtually no systemic or target organ toxicity. In general, the most common toxicities observed in clinical trials involving TRAIL receptor agonists have been constitutional symptoms and liver toxicity. Venetoclax has been evaluated as a single agent and in combination with standard or investigational therapies in multiple hematological malignancies: cytopenias and mild gastrointestinal toxicities are the known risks of venetoclax.
This is the first trial investigating the combination of FOLFIRI, bevacizumab and ABBV-621; therefore safety risk of the combination is unknown. However, the known clinical profile of this chemotherapy in the patient population and emerging safety profile of ABBV-621 do not suggest an overlap of expected severe toxicities.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Subject must have a diagnosis of a solid tumor, AML or non-Hodgkin lymphoma (NHL). Subjects in the dose-optimization cohorts must have either colorectal cancer with documented KRAS mutations (as determined by local testing), or pancreatic cancer (irrespective of mutational status). NHL may be of any subtype for dose escalation but is limited to DLBCL for those enrolled to the cohort evaluating the combination of ABBV-621 and venetoclax.Subjects in the chemotherapy combination cohorts must have metastatic or advanced unresectable colorectal cancer with documented RAS mutation (as determined by local testing).
2. Subject in dose escalation or dose optimization cohort must have received at least one prior systemic therapy, and must have relapsed or progressed after, or failed to respond to any/all available effective therapy or therapies. Any subject with AML must a. have disease that has either persisted or progressed following allogeneic stem cell transplantation (SCT); b. be ineligible for allogeneic SCT (for any reason, including age and/or inability to achieve adequate response); or c. have declined allogeneic SCT. Subject in chemotherapy cohorts with CRC must have progressed after or failed to respond to initial systemic therapy consisting of an oxaliplatin and luoropyrimidine-based regimen without irinotecan (e.g., FOLFOX or CAPOX), CRC subjects enrolled in ABBV-621

and FOLFIRI cohort must have had bevacizumab in the prior line; maintenance therapy is considered part of first-line therapy. Prior adjuvant therapy is allowed for CRC.
3. Subject must have measurable disease (by RECIST 1.1 for those with solid tumors; by Lugano classification for those with NHL), except those with AML, who must have histologically confirmed relapsed or refractory disease (central review not required).
4. Subject must consent to provide the following biomarker analyses:
· All subjects: archived tumor tissue (if available)
· Dose optimization subjects(excluding AML): pre and on treatment paired fresh tissue biopsies. If it is determined that tumor biopsies are not appropriate for a given subject, the subject may still be enrolled following investigator consultation with AbbVie. Subjects with DLBCL: Pre and on-treatment paired fresh biopsies are required from at least six subjects with DLBCL. Note: Pre- and on-treatment paired fresh tissue biopsies will be optional for subjects with solid tumor or NHL in Dose Escalation and will be collected so long as consent is provided.
· All subjects with AML: pre and on-treatment bone marrow aspirates (BMA)
· For subjects on chemotherapy combination cohorts, subjects must provide a fresh biopsy if an archival biopsy is not available.
5. Subject in chemotherapy cohorts with CRC must have confirmed RAS mutation
6.Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 - 2; subjects in chemotherapy combination cohorts must have ECOG Performance Score of 0-1.
7.Subject must have adequate hematologic, renal and hepatic function

Exclusion criteria

1. Subjects has a history of brain metastases who have not shown clinical and radiographic stable disease for at least 28 days after definitive therapy. In addition, any AML patient identified, through CSF analysis, as having active CNS disease, will be excluded from enrollment.
2. Presence of primary hepatobiliary malignancy, including cholangiocarcinoma or hepatocellular carcinoma, gallbladder carcinoma, cancer of ampulla of Vater
3. Receipt of any systemic anti-cancer agent, including investigational anti-cancer products, within 21 days prior to study drug administration or 3 half-lives, whichever is longer
4. Prior receipt, at any time, of TRAIL or TRAIL-like agonist(s) for the treatment of the malignancy under study.
5. Subjects with history of cirrhosis or other indication of significant possible hepatic dysfunction
6. Subjects with a positive diagnosis of hepatitis A, B or C
7. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Prior receipt, at any time, of a BCL-2 inhibitor.

8. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Subject has received strong or moderate CYP3A inducers within 7 days prior to initiation of study treatment or strong or medium CYP3A inhibitors within 3 days prior to the initiation of study treatment.
9. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within 3 days prior to the initiation of study treatment.
10. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
11. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Subject has Richter Transformation with or without concurrent chronic lymphocytic leukemia (subjects with DLBCL transformed from follicular lymphoma or from other indolent lymphomas are permitted to enroll).
12. Venetoclax + ABBV-621 Combination Therapy Subjects Only: Subject has acute promyelocytic leukemia (M3).
13. CRC chemotherapy cohort only: Participant with minor surgical procedures, such as fine needle aspirations or core biopsies, within 7 days prior to first dose of study drug are excluded.
14. Participants in CRC chemotherapy combination cohort only: cardiomyopathy, coronary/peripheral artery bypass graft, aneurysm or aneurysm repair, angioplasty, pulmonary hypertension, cerebrovascular accident or transient ischemic attack, within 1 year of first dose of study drug.
15. Chemotherapy combination CRC participants only: Disease progression within 3-months of initiating first line therapy.
16. Chemotherapy combination CRC participants only: Prior receipt of an irinotecan-based chemotherapy.
17. Chemotherapy combination CRC participants only: history of Gilbert's syndrome or UG1T1A1 genotypes.
18. Chemotherapy Combination CRC Participants Only: Clinically significant conditions that may place the participant at higher risk with anti-angiogenic therapy.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-08-2017
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane
Generic name:	nab-paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Venetoclax 100 mg
Generic name:	Venetoclax 100 mg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Venetoclax 50 mg
Generic name:	Venetoclax 50 mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2017

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	13-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	26-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003887-37-NL
ClinicalTrials.gov	NCT02573324
CCMO	NL60490.078.17

Study results

Results posted: 06-04-2023

First publication
01-01-1900