A phase II open-label study with the anti-PD-L1 Atezolizumab monoclonal antibody in combination with Bevacizumab in patients with advanced chemotherapy resistant colorectal cancer and MSI-like molecular signature

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Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49178

Source
ToetsingOnline

Brief title
M16BAC - VHIO 16001 - CT3

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
bowlecancer, colorectal carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Vall D'Hebron Institute of Oncology (VHIO)
Source(s) of monetary or material Support: EU,Hoffmann-La Roche

Intervention

Keyword: Atezolizumab, Bevacizumab, colorectal cancer, MSI-like

Outcome measures

Primary outcome

The primary endpoint is overall response rate (ORR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Secondary outcome

The secondary endpoints for this study are as follows:

• Duration of RECIST response.

• Time to RECIST response.

• Immune-related (ir) response rate as measured by irRC with the use of unidimensional measurement.

• Progression free survival (PFS), defined as time from treatment initiation to progressive disease or death.

• Overall survival (OS), defined as time from treatment initiation to death.

• Safety and tolerability of atezolizumab plus bevacizumab as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

• Evaluation of predictive biomarkers correlating with response and resistance.

Study description

Background summary

Approximately 4% of patients with Stage IV CRC have tumors with deficiencies in the DNA mismatch repair system. A defining molecular feature of these tumors is high MSI. Agendia has developed a gene expression signature that identifies MSI CRC. Remarkably, this gene signature also identifies a subset of patients as MSI-like phenotypically, but these tumors are microsatellite stable (MSS) by the standard clinical diagnostic assays. Important for this application is the observation that the MSI-like tumors also have high mutation load, emphasizing the similarity between the MSI and MSI-like cancers. With the highly sensitive MSI-like signature developed by Agendia we are able to identify a population of patients with hypermutated tumors (20-25% of all CRC) more frequent than standard MSI testing.
The MSI phenotype is also associated with mutations in specific oncogenes including BRAF (Vilar and Gruber 2010). MSI tumors and other hypermutated tumors may therefore exhibit higher immunogenicity in comparison to MSS tumors. One possible correlate of higher immunogenicity MSI and other hypermutator phenotypes is the presence of high numbers of tumor-infiltrating lymphocytes (Greenson et al. 2003) and a potential role of PDL-1/PD-1 signaling in restraining a pre-existing anti-tumor immune response in the tumor microenvironment.
Anti-tumor activity, including RECIST-based responses (i.e., RECIST 1.1 responses), have been observed in patients with different tumor types, including non-small cell lung cancer, renal cell carcinoma, melanoma, gastric cancer, and colorectal cancer, treated with atezolizumab, an anti-PD-L1 antibody, in Study PCD4989g (IB). Preliminary results suggest that PD-L1 expression in tumor tissue is likely to be associated with response to atezolizumab.

Preliminary clinical data are available for 144 patients who have received at least one study treatment dose in the dose-escalating GP28328 study evaluating the safety and pharmacology of atezolizumab combined with bevacizumab, a VEGF inhibitor, or with bevacizumab plus FOLFOX. Efficacy data are available for 44 efficacy evaluable patients with colorectal cancer. (efficacy cutoff 29 Sep 2014). The treatment combinations have been generally well tolerated with the incidence of AEs in the combination arms consistent with the known safety profiles of the individual drugs. No dose limiting toxicities have been reported in this study or any other atezolizumab trial to date (IB, cutoff for safety data 10 May 2015).

Our primary hypothesis is that the addition of bevacizumab to atezolizumab will expand the efficacy of immunotherapeutics from a *real MSI* CRC population to an *MSI-like* CRC population. This potential synergistic effect of immune checkpoint inhibitors and antiangiogenic drugs is in part explained by

microenvironment changes, such as neutralization of vascular barriers preventing T-cell homing, in tumors known to have immune cell infiltration linked to a hypermutated phenotype.

Study objective

The primary objective of this study is to determine the anti-tumor activity, as measured by overall response rate (ORR) of atezolizumab in combination with bevacizumab in patients with chemotherapy resistant CRC and positivity for MSI-like molecular signature.

Study design

This is an international, open-label single arm (non-randomized), one-stage phase II trial. Patients potentially eligible for the protocol will have tumor sample pre-screened by Agendia for the MSI-like signature, among others, as part of the MoTriColor project, during first-line standard chemotherapy. If positive for the MSI-like signature, patients will be offered the trial, provided the inclusion criteria are met. The goal is to register 50 MSI-like CRC patients to complete efficacy assessment. Treatment will be administered on Day 1 of each 21 days-cycle (Figure 2) until disease progression as defined by either RECIST 1.1 or irRECIST criteria (see details later), unacceptable toxicity or withdrawal of consent.

Intervention

Treatment with atezolizumab in combination with bevacizumab

Study burden and risks

- Blood will be drawn for pharmacokinetic, pharmacodynamic and pharmacogenetic research

Contacts

Public
Vall D'Hebron Institute of Oncology (VHIO)

Pg Vall Hebron 119-129
Barcelona 08035
ES
Scientific
Vall D'Hebron Institute of Oncology (VHIO)

Pg Vall Hebron 119-129
Barcelona 08035
ES

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Written informed consent must be given according to ICH/GCP and national/local regulations.
-Histological or cytological proof of metastatic CRC.
- Disease progression or relapse after at least one line of treatment for advanced CRC with a fluoropyrimidine containing chemotherapy as single agent or in combination (combinations with oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab are allowed).
-Written documentation of positivity for MSI-like gene signature as determined by Agendia test.
-Unresectable disease, with at least one measurable lesion according to RECIST 1.1.
-Age >= 18 years.
-WHO performance status of 0-1.
-Ability and capacity to comply with study and follow-up procedures.
-Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 calendar days prior to the first study treatment:
* ANC > 1.5 x 109/L (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
*WBC counts > 2500/µL
*Platelet count > 100,000/ µL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
*Hemoglobin > 9.0 g/dL
*AST, ALT, and alkaline phosphatase < 2.5 x ULN, with the following

exceptions:
i Patients with documented liver metastases: AST and ALT < 5 x ULN
ii Patients with documented liver or bone metastases: alkaline phosphatase < 5 x ULN
*Bilirubin <1.5 x ULN. Patients with known Gilbert disease who have serum bilirubin level < 3 x ULN may be enrolled.
*PT and PTT <1.5 x ULN, unless on a stable dose of warfarin
*Serum albumin > 2.5 g/dL
*Creatinine clearance > 30 mL/min (Cockcroft-Gault formula or based on 24-hour urine collection)
*Protein < 2+ on dipstick urinalysis or <= 1.0 g in a 24-hour urine collection. All patients with >=2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.
-Women of child bearing potential (WOCBP) must have a negative serum pregnancy test before registration.
-Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 6 months after the last bevacizumab treatment (for women and men) and 5 months after the last atezolizumab treatment (for women) . A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
-Female subjects who are breast feeding should discontinue nursing before trial registration and until 6 months after the last bevacizumab treatment and 5 months after the last atezolizumab treatment.

Exclusion criteria

· Any treatment with investigational drugs within 28 d prior to Cycle 1, Day 1.· Previous cytotoxic agent within 14 d of planed treatment initiation.· Active or untreated CNS metastases as determined by computed CT or MRI· Radiotherapy within 14 d prior to Cycle 1, Day 1.· Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures.· Previous (within the last 5 y) or concurrent malignancies, with the exception of those treated with expected curative outcome as cone-biopsied in situ carcinoma of the cervix, basal cell carcinoma of the skin, localized prostate cancer or ductal carcinoma in situ of thebreast.· Life expectancy of < 12 w.· History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.· Positive test for HIV.· Active hepatitis B or hepatitis C.· Active tuberculosis.· Severe infections within 4 w prior to Cycle 1, Day 1.· Infection within 2 w prior to Cycle 1, Day 1.· Received therapeutic oral or IV antibiotics within 2 w prior to Cycle 1, Day 1.· Significant cardiovascular or cerebrovascular disease· Major surgical procedure within 28 d prior to cycle 1, day 1, or planned procedure or surgery during the study.· Prior allogeneic stem cell or solid

organ transplant.· Any other diseases, 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 or that may affect the interpretation of the results or render the patient at high risk from treatment complications.· Prior treatment with CD137 agonists, anti*CTLA-4, anti*PD-1, or anti*PD-L1 therapeutic antibody or immune-related pathway-targeting agents.· Current or recent use of dipyridamole, ticlopidine, clopidogrel, or cilostazol .· Unstable dose in the last 2 w prior to the first study treatment of prophylactic or therapeutic low molecular*weight heparin, direct thrombin inhibitors, or warfarin. Stable dose is permitted where appropriate anticoagulation indices are stable.· Inadequately controlled hypertension.· Prior history of hypertensive crisis or hypertensive encephalopathy.· Significant vascular disease within 6 m prior to Cycle 1, Day 1.· Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the bevacizumab or atezolizumab formulation.· Evidence of bleeding diathesis or clinically significant coagulopathy.· Patients with history of pulmonary hemorrhage/hemoptysis within 6 m prior to Cycle 1, Day 1.· Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab.· History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 m prior to Cycle 1, Day 1.· Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.· Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.· Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture.· History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome,Wegener*s granulomatosis, Sjögren*s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis:· Prior allogeneic bone marrow transplantation or prior solid organ transplantation.· History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.· Administration of a live, attenuated vaccine within 4 w before Cycle 1, day 1· Treatment with systemic immunostimulatory agents within 4 w or five half-lives of the drug, whichever is longer, prior to study treatment.· Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 w prior to start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial. The use of inhaled corticosteroids and mineralocorticoids is allowed.· If receiving a RANKL inhibitor, unwilling to adopt alternativetreatment such as bisphosphonates, while receiving atezolizumab.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-03-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Atezolizumab
Generic name:	Atezolizumab
Product type:	Medicine
Brand name:	Avastin
Generic name:	bevacizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-07-2017
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	14-09-2017
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2021
Application type:	Amendment

Review commission: METC NedMec

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	EUCTR2016-002001-19-NL
ClinicalTrials.gov	NCT02982694
CCMO	NL59204.031.17

Study results

Date completed: 01-06-2023

Results posted: 23-01-2025

Actual enrolment: 5

First publication
17-05-2024