A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared with Placebo Plus CAPOX as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Published: 09-10-2018
Last updated: 12-04-2024

Primary• To evaluate the efficacy of zolbetuximab plus capecitabine and oxaliplatin (CAPOX) compared with placebo plus CAPOX (as first line treatment) as measured by Progression Free Survival (PFS) in subjects with Claudin (CLDN) 18.2-positive,...

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

Summary

ID

NL-OMON52492

Source
ToetsingOnline

Brief title
GLOW

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
adenocarcinoma, colon cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: CAPOX, IMAB362, zolbetuximab

Outcome measures

Primary outcome

• PFS, defined as the time from the date of randomization until the date of

radiological PD (per IRC per RECIST 1.1) or death from any cause, whichever is

earliest

Secondary outcome

• OS, defined as the time from the date of randomization until the date of

death from any cause

* Time to confirmed deterioration (TTCD) using the PF, OG25-Pain and

GHS/QoL

scores as measured by EORTC QLQ-C30 and QLQ-OG25 plus STO22 Belching subscale.

TTCD is defined as time to first confirmed deterioration, i.e., time from

randomization to first clinically meaningful deterioration that is confirmed at

the next scheduled visit.

• ORR, defined as the proportion of subjects who have a best overall response of complete response (CR) or partial response (PR) as assessed by IRC per RECIST 1.1

• DOR, defined as the time from the date of the first response (CR/PR) until the date of PD as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest

• Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs and ECOG performance status

• HRQoL, using the additional parameters as measured by EORTC QLQ-C30, QLQ-OG25 plus STO22 Belching subscale, GP, and EQ5D-5L questionnaires

• Pharmacokinetics of zolbetuximab, Ctrough

• Immunogenicity of zolbetuximab as measured by the frequency of antidrug-antibody (ADA) positive subjects

Exploratory

• TTP, defined as the time from the date of randomization until the date of PD as assessed by IRC per RECIST 1.1.

• PFS2, defined as the time from the date of randomization until the date of PD (per investigator) following subsequent anticancer therapy, death from any cause or start of any other anticancer therapy, whichever is earliest

• DCR, defined as the proportion of subjects who have a best overall response of CR, PR or SD as assessed by IRC per RECIST 1.1

• Potential genomic and/or other exploratory biomarkers that may be related to treatment outcome of zolbetuximab

• HRU

Study description

Background summary

One hallmark of cancer is that tight junction proteins lose their organization in multimeric structures, promoting loss of cell polarity, cohesion and differentiation. Because of this, epitopes of tight junction molecules, which are shielded in the normal epithelia, might become exposed and accessible to antibodies such as zolbetuximab after malignant transformation.
Zolbetuximab is a genetically engineered antibody directed against the tight junction molecule Claudin 18.2 (CLDN18.2). CLDN18.2 is a highly cell type specific differentiation antigen that is expressed by differentiated gastric mucosa cells in the gastric glands. Moreover, CLDN18.2 is not detectable in any other normal cell type of the human body either at transcript level or as protein. This highly selective tissue distribution pattern results in CLDN18.2 expression being strictly confined to a subpopulation of gastric epithelial cells in normal tissue.
Zolbetuximab is being developed for the first-line treatment of adult subjects with locally advanced unresectable or metastatic CLDN18.2-positive, HER2-negative gastric or GEJ adenocarcinoma in combination with platinum- and fluoropyrimidine-based chemotherapy. For this study, a subject*s tumor must express CLDN18.2 in >= 75% of tumor cells demonstrating moderate to strong membranous staining as determined by immunohistochemistry testing.

Study objective

Primary
• To evaluate the efficacy of zolbetuximab plus capecitabine and oxaliplatin (CAPOX) compared with placebo plus CAPOX (as first line treatment) as measured by Progression Free Survival (PFS) in subjects with Claudin (CLDN) 18.2-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced unresectable or metastatic gastric and gastroesophageal junction (GEJ) adenocarcinoma
Secondary
• To evaluate efficacy as measured by Overall Survival (OS) as a key secondary objective
* To evaluate the physical function (PF), OG25-Pain and GHS/QoL scores as measured by
European Organization for Research and Treatment of Cancer (EORTC) as a key secondary
objective
• To evaluate efficacy as measured by Objective Response Rate (ORR)

• To evaluate efficacy as measured by Duration of Response (DOR)
• To evaluate safety and tolerability of zolbetuximab
• To further evaluate other health related quality of life (HRQoL) using additional parameters as measured by EORTC, QLQ-C30 and QLQ OG25 plus STO22 Belching subscale, Global Pain (GP) and the EuroQOL Five Dimensions Questionnaire 5L (EQ5D 5L) questionnaires
• To evaluate the pharmacokinetics of zolbetuximab
• To evaluate the immunogenicity profile of zolbetuximab
Exploratory
• To evaluate efficacy as measured by Time to Progression (TTP)
• To evaluate PFS following subsequent anticancer treatment (PFS2)
• To evaluate Disease Control Rate (DCR)
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome to zolbetuximab and CAPOX.
• To evaluate Health Resource Utilization (HRU)

Study design

This global, multicenter, double-blind, 1:1 randomized, phase 3 study will evaluate efficacy of zolbetuximab plus CAPOX versus placebo plus CAPOX as first-line treatment in subjects with CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma.
PFS as assessed by the Independent Review Committee (IRC) is the primary outcome. Secondary outcomes include OS, ORR, DOR, safety and tolerability, HRQoL, pharmacokinetics and the immunogenicity profile of zolbetuximab. Exploratory outcomes include TTP, PFS2, DCR, biomarkers, and HRU.
Approximately 500 subjects will be randomized 1:1 into 1 of 2 treatment arms:
• Arm A (zolbetuximab in combination with CAPOX chemotherapy)
• Arm B (placebo in combination with CAPOX chemotherapy)
Randomization of subjects will be stratified by the following factors:
• Region (Asia vs Non-Asia)
• Number of Organs with Metastatic Sites (0 to 2 vs >= 3)
• Prior Gastrectomy (Yes or No)

Intervention

Subjects will be treated with either zolbetuximab (Arm A) or placebo (Arm B) on Day 1 of each cycle until the subject meets study treatment discontinuation criteria. For all study treatments, a cycle is defined as 21 days.

Study burden and risks

In general, study participants can experience physical or psychological discomfort through examination tests, examination procedures and questionnaires. In addition, subjects can experience side effects from the study medication.

The study load consists of:
- Visits to the research location
- Physical examination
- Measuring vital functions / weight
- Rardiologic assesments
- ECG
- Blood collection
- Urine collection
- Receive CAPOX
- If applicable, collect a tumor sample

Contacts

Public
Astellas Pharma

Astellas Way 1
Northbrook IL60062
US
Scientific
Astellas Pharma

Astellas Way 1
Northbrook IL60062
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Waivers to the inclusion criteria will NOT be allowed.
General Criteria:
1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject or legally authorized representative (if applicable) prior to any study-related procedures.
2. Subject is considered an adult (e.g., >= 18 years of age in the US) according to local regulation at the time of signing the informed consent.
3. A female subject is eligible to participate if she is not pregnant (negative serum pregnancy test at screening; female subjects with elevated serum beta human chorionic gonadotropin (βhCG) and a demonstrated non-pregnant status through additional testing are eligible) and at least 1 of the following conditions applies:
• Not a woman of childbearing potential (WOCBP) as defined in [protocol appendix 12.3 Contraception Requirements]
OR
• WOCBP who agrees to follow the contraceptive guidance as defined in [protocol appendix 12.3 Contraception Requirements] throughout the treatment period and for
9 months after the final administration of oxaliplatin and 6 months after the final
administration of all other study drugs.
4. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 6 months after the final study treatment administration.
5. Female subject must not donate ova starting at screening and throughout the study period, and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.
6. A male subject with female partner(s) of childbearing potential:
• must agree to use contraception as detailed in [Appendix 12.3 Contraception Requirements] during the treatment period and for 6 months after the final study treatment administration.
7. A male subject must not donate sperm during the treatment period and for 6 months after the final study treatment administration.
8. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 6 months after the final study treatment administration.
9. Subject agrees not to participate in another interventional study while receiving study drug in present study.
Disease Specific Criteria:
10. Subject has histologically confirmed diagnosis of Gastric or GEJ adenocarcinoma.

11. Subject has radiologically confirmed locally advanced unresectable or metastatic disease within 28 days prior to randomization.
12. Subject has radiologically evaluable disease (measurable and/or non-measurable) according to RECIST 1.1, per local assessment, <= 28 days prior to randomization. For subjects with only 1 evaluable lesion and prior radiotherapy <= 3 months before randomization, the lesion must either be outside the field of prior radiotherapy or have documented progression following radiation therapy.
13. Subject*s tumor expresses CLDN18.2 in >= 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central IHC testing.
14. Subject has a HER2-negative tumor as determined by local or central testing on a gastric or GEJ tumor specimen.
Physical or Laboratory Findings:
15. Subject has ECOG performance status 0 or 1.
16. Subject has predicted life expectancy >= 12 weeks in the opinion of the investigator.
17. Subject must meet all of the following criteria based on the centrally or locally analyzed laboratory tests collected within 14 days prior to randomization. In the sample collection within this period, the most recent sample collection with available results should be used to determine eligibility.
a. Hemoglobin (Hb) >= 9 g/dl. Subjects requiring transfusions are eligible if they have post-transfusion Hgb >= 9 g/dL.
b. Absolute Neutrophil Count (ANC) >= 1.5x109/L
c. Platelets >= 100x109/L
d. Albumin >= 2.5 g/dL
e. Total Bilirubin <= 1.5 x upper limit of normal (ULN) without liver metastases (or < 3.0 x ULN if liver metastases are present)
f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 x ULN without liver metastases (or <= 5 x ULN if liver metastases are present)
g. Estimated creatinine clearance >= 30 mL/min
h. Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) <= 1.5 x ULN (except for subjects receiving anticoagulation therapy)

Exclusion criteria

Waivers to the exclusion criteria will NOT be allowed.
Subject who meets any of the following exclusion criteria prior to enrollment is not eligible for enrollment:
Prohibited Treatment or Therapies:
1. Subject has received prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. However, subject may have received either neo-adjuvant or adjuvant chemotherapy , immunotherapy or other systemic anticancer therapies as long as it was completed at least 6

months prior randomization.
2. Subject has received radiotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma <= 14 days prior to randomization and has not recovered from any related toxicity.
3. Subject has received treatment with herbal medications or other treatments that have known antitumor activity within 28 days prior to randomization.
4. Subject has received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to randomization. Subject using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) receiving a single dose of systemic corticosteroids, or receiving systemic corticosteroids as premedication for radiologic imaging contrast use is eligible.
5. Subject has received other investigational agents or devices within 28 days prior to randomization.
Medical History or Concurrent Disease:
6. Subject has prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanized or chimeric antibodies.
7. Subject has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
8. Subject has prior severe allergic reaction or intolerance to any component of CAPOX.
9. Subject has known dihydropyrimidine dehydrogenase (DPD) deficiency. (NOTE: Screening for DPD deficiency should be conducted per local requirements.)
10. Subject has a complete gastric outlet syndrome or partial gastric outlet syndrome with persistent/recurrent vomiting.
11. Per investigator judgement, subject has significant gastric bleeding and/or untreated gastric ulcers that exclude the subject from participation.
12. Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B (positive HBs Ag) or C infection. NOTE: Screening for these infections should be conducted per local requirements.
a. For subjects who are negative for HBs Ag, but HBc Ab positive, an HB DNA test will be performed and if positive, the subject will be excluded.
b. Subjects with positive hepatitis C virus (HCV) serology but negative HCV RNA test results are eligible.
c. Subjects treated for HCV with undetectable viral load results are eligible.
13. Subject has an active autoimmune disease that has required systemic treatment within the past 3 months prior to randomization.
14. Subject has active infection requiring systemic therapy that has not completely resolved within 7 days prior to randomization.
15. Subject has significant cardiovascular disease, including any of the following:
a. Congestive heart failure (defined as New York Heart Association [NYHA] Class III or IV), myocardial infarction, unstable angina, coronary angioplasty, coronary stenting, coronary artery bypass graft, cerebrovascular accident

(CVA), or hypertensive crisis within 6 months prior to randomization;
b. History of clinically significant ventricular arrhythmias (i.e., sustained ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes);
c. QTc interval > 450 msec for male subjects; QTc interval > 470 msec for female subjects;
d. History or family history of congenital long QT syndrome
e. Cardiac arrhythmias requiring anti-arrhythmic medications (Subjects with rate controlled atrial fibrillation for > 1 month prior to randomization are eligible.)
16. Subject has a history of central nervous system (CNS) metastases and/or carcinomatous meningitis from gastric/GEJ cancer.
17. Subject has known peripheral sensory neuropathy > grade 1 unless the absence of deep tendon reflexes is the sole neurological abnormality.
18. Subject has had a major surgical procedure <= 28 days prior to randomization.
a. Subject is without complete recovery from a major surgical procedure <= 14 days prior to randomization.
19. Subject has psychiatric illness or social situations that would preclude study compliance, per investigator judgement.
20. Subject has another malignancy for which treatment is required per investigator*s clinical judgment
21. Subject has any concurrent disease, infection, or co-morbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	28-10-2020
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	zolbetuximab
Generic name:	zolbetuximab

Ethics review

Approved WMO Date:	09-10-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-05-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	28-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-000519-26-NL
ClinicalTrials.gov	NCT03653507
CCMO	NL67148.091.18