Sponsor

Novartis Pharma AG

Generic Drug Name

AUY922

Therapeutic Area of Trial

Advanced Gastric cancer (AGC)

Approved Indication

Investigational

Protocol Number

CAUY922A2205

Title

An open-label, single-arm, multi-center phase II study to evaluate the efficacy and safety of AUY922 in combination with trastuzumab standard therapy as second-line treatment in patients with HER2-positive advanced gastric cancer

Study Phase

Phase II

Study Start/End Dates

First patient first visit (FPFV): 11-Nov-2011

Early termination date: 20-Dec-2012

Last patient last visit: 13-Jun-2013

Study Design/Methodology

This was an open-label, single arm, multi-center phase II study to evaluate the efficacy of AUY922 in combination with trastuzumab standard therapy as second-line treatment in patients with HER2-positive AGC. All patients were treated with AUY922 and trastuzumab combination. In addition, the study was designed to characterize the safety, tolerability, and PK profile of this combination. Patients were to receive study treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

Each treatment cycle was of 21 days duration. All patients were to receive AUY922 in combination with trastuzumab, as follows:

- AUY922 was administered i.v. each week at a dose of 70 mg/m^2 (after the trastuzumab infusion on Day 1 of each cycle, and then independently on Days 8 and 15 of each cycle);

- Trastuzumab was administered once every 3 weeks (on Day 1 of each treatment cycle) at the standard dose of 6 mg/kg over 30 to 90 minutes (or 8 mg/kg over 90 minutes if a loading dose was necessary at Cycle 1 Day 1) in accordance with the Herceptin® Product Label for GC.

It was estimated that the study would require 48 patients to be treated with the combination specified above. However, due to lack of efficacy and slow enrollment, enrollment was stopped early in December 2012. At the time of this decision, 21 patients were enrolled and two out of 21 patients were still receiving treatment. These two patients were allowed to continue according to protocol. Last patient discontinued study treatment on 29-May-2013. This abbreviated Clinical Study Report (CSR) summarizes all available data for 21 patients enrolled in this study.

Centers

12 centers in 8 countries: Belgium (1 center), Germany (2), Spain (1), France (1), Italy (1), Japan (2), Korea (2), USA (2).

Publication

There is no publication based on this study.

Test Product (s), Dose(s), and Mode(s) of Administration

Each treatment cycle was of 21 days duration. All patients received AUY922 in combination with trastuzumab, as follows:

- AUY922 Liquid in Ampoules, individual 10 mL amber-coloured glass ampoules containing 10 mL of a 5 mg/mL active drug substance in 5% aqueous glucose solution. Diluted in 5% dextrose or glucose (500 mL); protected from light and used within 6 hours. Administered as weekly intravenous doses of 70 mg/m2 (after the trastuzumab infusion on Day 1 of each cycle, and then independently on Days 8 and 15 of each cycle). Batch numbers Y145 1110, Y105 1011, 10-1177CH, 11 3289CH, 058 0309, 11 3285CH were used.
- Trastuzumab multi-use vials containing 60, 150 or 440 mg lyophilized sterile powder; locally supplied. Administered every 3 weeks (on Day 1 of each treatment cycle) at 6 mg/kg over 30 to 90 minutes (or 8 mg/kg over 90 minutes if a loading dose was necessary at Cycle 1 Day 1) in accordance with the Herceptin® Product Label for gastric cancer.

Statistical Methods

Overall Response Rate (ORR) and Disease Control Rate (DCR) at 12 and 18 weeks and corresponding 95% confidence intervals (CIs) according to RECIST v1.1 were presented. Summary statistics from the Kaplan-Meier estimates were determined, including the median and estimated PFS rate at 16 weeks and 24 weeks, and OS rate at 32 weeks. These statistics were provided as point estimates with 95% CIs.

Pharmacokinetic parameters were estimated by non-compartmental analysis using Phoenix 6.3 (Pharsight, Mountain View, CA). Primary (AUCinf, AUClast, Cmax) and other (Tmax, t1/2, CL, Vz) PK parameters for the treatment group were reported as appropriate. AUCinf was estimated for AUY922 and its metabolite BJP762, on Day 1 of Cycle 1 only, and CL, and Vz was assessed for AUY922 on Day 1 of Cycle 1 only. Median values and ranges were given for Tmax. The ratio of geometric mean AUC and C_{max} of BJP762 to AUY922 was assessed.

Adverse events were listed and summarized in hierarchical tables using Medical Dictionary for Regulatory Activities coding, by system organ class (SOC), preferred term (PT), treatment group and, in some cases, maximum grade, suspected to be related or regardless of causality. All deaths were listed, with separate summaries for on-study deaths. For events within the SOC of Eye disorders, time to onset of the first event from first dose of study drug, and time to resolution were summarized.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients with HER2+ cytologically or histologically confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma
- Patients with progressive disease (radiological confirmation required according to Response Evaluation Criteria In Solid Tumors [RECIST]) after first line of trastuzumab in combination with chemotherapy for advanced gastric cancer
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- HER2-overexpressing positive gastric tumor by immunohistochemistry (IHC)3+ or IHC2+ with positive *in situ* hybridization
- Measurable disease according to RECIST 1.1
- Laboratory values within protocol specified limits (absolute neutrophil count $\geq 1.5 \times 10^9$/L; hemoglobin ≥ 9 g/dL; platelets $\geq 100 \times 10^9$/L; serum total bilirubin ≤ 1.5 x upper limit of normal (ULN); serum albumin > 2.5 g/dL; serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≤ 50 mL/min; aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 2.5 x ULN or ≤ 5.0 x ULN if liver metastases were present)
- Negative serum pregnancy test ≤ 72 hours prior to dosing (in all pre-menopausal women and for women < 2 years after the onset of menopause).
- ≥ 18 years or age of consent in country of residence and gave written informed consent prior to any screening procedures.

Exclusion criteria

- Evidence of spinal cord compression or current evidence of central nervous system metastases (computed tomography [CT]/magnetic resonance imaging of the brain was mandatory within 3 weeks before study start in case of clinical suspicion or evidence of brain metastases)

- Patients < 4 weeks since last chemotherapy or treatment with another systemic anti-cancer agent and /or had not recovered (CTC ≤ 1) from acute toxicities of any previous therapy (with the exception of alopecia)
- Prior treatment with an agent that acts via HER2/c-erbB2 targeting other than first line trastuzumab, including (but not limited to) lapatinib and pertuzumab
- Treatment with therapeutic doses of coumarin-type anticoagulants (maximum daily dose of 2 mg for line patency permitted); malignant ascites requiring invasive treatment; acute or chronic renal disease and active and chronic liver disease requiring intervention
- Other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromise compliance with the protocol
- Major surgery ≤ 2 weeks prior to enrollment or who had not recovered from such therapy
- Impaired cardiac function (including history/family history of long QT syndrome; mean QTc ≥ 450 msec on baseline electrocardiogram (ECG); history of clinically manifested ischemic heart disease ≤ 6 months prior to study start; history of heart failure or left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 50%) by multigated acquisition or echocardiogram
- Clinically significant ECG abnormalities; history or presence of atrial fibrillation, atrial flutter or ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes; other clinically significant heart disease such as congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen; clinically significant resting bradycardia [< 50 beats per minute]; current treatment with any medication with relative risk of prolonging the QTcF interval or inducing Torsades de Pointes; obligate use of a cardiac pacemaker)
- Concurrent malignancies or invasive cancers diagnosed within the previous 5 years (except adequately treated basal cell cancer of the skin or in situ cancer of the cervix)
- Chronic or high dose corticosteroid therapy (except inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant)
- Patient unwilling or unable to comply with the protocol
- HIV positive patients
- Known hypersensitivity to study drugs or their excipients
- Participation in another clinical study within 30 days before first study treatment
- Pregnant/lactating women
- Women of childbearing potential not using adequate contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) during the study and for 5 half-lives after stopping treatment.
- Patients could have received prior radiotherapy for management of local disease providing that disease progression was documented, all toxicities had resolved (common toxicity criteria [CTC] ≤ 1) (with the exception of alopecia), and the last fraction of radiotherapy was completed at least 4 weeks prior to the study.

Participant Flow

Patient disposition (Full analysis set)

	AUY922 + Trastuzumab N=21 n (%)
Study evaluations	
Completed	21 (100.0)
Primary reason for end of study evaluations	
Follow up phase completed as per protocol	11 (52.4)
Patient withdrew consent	6 (28.6)
Disease progression	2 (9.5)
Lost to follow-up	1 (4.8)
Death	1 (4.8)
Adverse event(s)	0 (0.0)
Administrative problems	0 (0.0)
New cancer therapy	0 (0.0)
Protocol deviation	0 (0.0)
Patients treated	
Treatment discontinued	21 (100.0)
Primary reason for end of treatment	
Disease progression	17 (81.0)
Adverse event(s)	2 (9.5)
Patient withdrew consent	2 (9.5)
Lost to follow-up	0 (0.0)
Administrative problems	0 (0.0)
Death	0 (0.0)
Protocol deviation	0 (0.0)

Baseline Characteristics

Demographic summary (Full analysis set)

Demographics Variable	AUY922 + Trastuzumab N=21
Age (years)	
n	21
Mean (SD)	61.9 (9.23)
Median (Min-Max)	63.0 (41-74)
Age group (years) - n (%)	
<65	13 (61.9)
>=65	8 (38.1)
Gender - n (%)	
Male	19 (90.5)
Female	2 (9.5)
Predominant race - n (%)	
Caucasian	11 (52.4)
Black	0 (0.0)
Asian	10 (47.6)
Native American	0 (0.0)
Pacific Islander	0 (0.0)
Other	0 (0.0)
BSA (m^2)	
n	21
Mean (SD)	1.760 (0.1591)
Median (Min-Max)	1.762 (1.51-2.04)
LVEF (%) at baseline	
n	20
Mean (SD)	62.3 (5.40)
Median (Min-Max)	64.0 (52-75)
ECOG performance status - n (%)	
Grade 0	7 (33.3)
Grade 1	14 (66.7)

ECOG Performance Status Scale:

Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work; Grade 2: Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 3: Capable of only limited self care, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

- BSA (m^2) = ([Height(cm) x Weight(kg)] / 3600)1/2.
- LVEF = Left Ventricular Ejection Fraction.

Outcome Measures

Primary Outcome Result(s)

Best overall response as per RECIST using investigator assessed radiological review (Full analysis set)

	AUY922 + Trastuzumab N=21
Best overall response - n (%)	
Complete response	0 (0.0)
Partial response	0 (0.0)
Stable disease	12 (57.1)
Progressive disease	8 (38.1)
Unknown	0 (0.0)
Not assessed	1 (4.8)
Overall response rate (ORR) (CR or PR) - n (%)	0 (0.0)
95% confidence interval*	[0.0,16.1]
Disease control rate (DCR) (CR, PR or SD) - n (%)	
12 weeks (95% confidence interval*)	12 (57.1) [34.0,78.2]
18 weeks (95% confidence interval*)	12 (57.1) [34.0,78.2]

* Exact binomial confidence intervals.

Secondary Outcome Result(s)

Progression Free Survival

Progression free survival (PFS) as per investigator radiological review (Full analysis set)

	AUY922 + Trastuzumab N=21
Number of PFS events - n (%)	19 (90.5)
Progression	18 (85.7)
Death	1 (4.8)
Number censored	2 (9.5)
Kaplan-Meier estimates (%)	
PFS rate [95% CI] at:	
16 weeks	29.2 [8.5,49.9]
24 weeks	11.7 [0.0,26.7]
25th percentile for PFS in months [95% CI]	1.2 [1.0,1.9]
Median for PFS in months [95% CI]	2.6 [1.2,2.8]
75th percentile for PFS in months [95% CI]	3.9 [2.8,6.1]

Overall survival

Overall survival (OS) (Full analysis set)

	AUY922 + Trastuzumab N=21
Number of events - n (%)	
Death	9 (42.9)
Number censored	12 (57.1)
Kaplan-Meier estimates (%)	
OS rate [95% CI] at:	
32 weeks	68.7 [45.5,91.9]
25th percentile for OS in months [95% CI]	7.4 [5.8,8.5]
Median for OS in months [95% CI]	8.5 [7.4,13.5]
75th percentile for OS in months [95% CI]	13.5 [8.5,13.5]

Safety Results

Adverse Events by regardless of study treatment relationship, by System Organ Class (Safety analysis set)

	AUY922 + Trastuzumab N=21 n (%)
Patients with at least one AE	21 (100.0)
Adverse events by primary system organ class	
Gastrointestinal disorders	20 (95.2)
Eye disorders	19 (90.5)
General disorders and administration site conditions	16 (76.2)
Blood and lymphatic system disorders	10 (47.6)
Metabolism and nutrition disorders	10 (47.6)
Nervous system disorders	9 (42.9)
Investigations	8 (38.1)
Musculoskeletal and connective tissue disorders	5 (23.8)
Vascular disorders	5 (23.8)
Respiratory, thoracic and mediastinal disorders	4 (19.0)
Skin and subcutaneous tissue disorders	4 (19.0)
Infections and infestations	3 (14.3)
Psychiatric disorders	3 (14.3)
Cardiac disorders	2 (9.5)
Hepatobiliary disorders	1 (4.8)
Injury, poisoning and procedural complications	1 (4.8)

Primary system organ classes are sorted in descending frequency.

A patient with multiple adverse events within a primary system organ class is counted only once in each row.

Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Adverse events occurring in at least two patients, regardless of study treatment relationship, by preferred term (Safety analysis set)

	AUY922 + Trastuzumab N=21 n (%)
Patients with at least one AE	21 (100.0)
Adverse events by preferred term	
Diarrhoea	15 (71.4)
Anaemia	10 (47.6)
Fatigue	8 (38.1)
Vision blurred	7 (33.3)
Abdominal pain	6 (28.6)
Asthenia	6 (28.6)
Nausea	6 (28.6)
Decreased appetite	5 (23.8)
Hypertension	5 (23.8)
Weight decreased	5 (23.8)
Alanine aminotransferase increased	4 (19.0)
Visual acuity reduced	4 (19.0)
Visual field defect	4 (19.0)
Blood alkaline phosphatase increased	3 (14.3)
Dysphagia	3 (14.3)
Headache	3 (14.3)
Night blindness	3 (14.3)
Photophobia	3 (14.3)
Photopsia	3 (14.3)
Visual impairment	3 (14.3)
Vomiting	3 (14.3)
Aspartate aminotransferase increased	2 (9.5)
Back pain	2 (9.5)
Constipation	2 (9.5)
Dyspnoea	2 (9.5)
Hypokalaemia	2 (9.5)
Musculoskeletal pain	2 (9.5)
Oedema peripheral	2 (9.5)
Platelet count decreased	2 (9.5)
Pyrexia	2 (9.5)

White blood cell count decreased	2 (9.5)

A patient with multiple occurrences of an AE is counted only once in the AE category.

A patient with multiple adverse events is counted only once in the total row.

Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Serious Adverse Events and Deaths

Serious adverse events regardless of study treatment relationship by primary system organ class, preferred term (Safety analysis set)

Primary system organ class Preferred term	AUY922 + Trastuzumab N=21 n (%)
Any primary system organ class	8 (38.1)
Blood and lymphatic system disorders	1 (4.8)
Anaemia	1 (4.8)
Gastrointestinal disorders	5 (23.8)
Abdominal pain	3 (14.3)
Diarrhoea	1 (4.8)
Gastric haemorrhage	1 (4.8)
Upper gastrointestinal haemorrhage	1 (4.8)
General disorders and administration site conditions	1 (4.8)
Pyrexia	1 (4.8)
Injury, poisoning and procedural complications	1 (4.8)
Joint dislocation	1 (4.8)
Metabolism and nutrition disorders	1 (4.8)
Hypoglycaemia	1 (4.8)
Musculoskeletal and connective tissue disorders	1 (4.8)
Back pain	1 (4.8)
Nervous system disorders	1 (4.8)
Convulsion	1 (4.8)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency.

A patient with multiple occurrences of an AE is counted only once for that AE.

A patient with multiple events within a primary system organ class is counted only once in the total row.

Includes all AEs on study and up to 30 days after last dose.

Number of patients who dies or experienced other serious or clinically significant adverse event (Safety analysis set)

Patients with serious or significant AEs	AUY922 + Trastuzumab N=21 n (%)
Death on study[1]	
On-treatment deaths	1 (4.8)
Due to study indication	8 (38.1)
Due to other reasons	1 (4.8)[2]
SAEs	
Study drug related SAEs	1 (4.8)
Discontinued due to SAEs[3]	1 (4.8)
AEs	
Study drug related AEs	20 (95.2)
Discontinued due to AEs[3]	1 (4.8)
Grade 3 or 4 AEs	15 (71.4)
AEs of special interest	20 (95.2)

Patients discontinuing due to SAEs are not also counted in the category of discontinuing due to AEs.

On-treatment deaths: Deaths occurring during treatment or within 30 days of the last study medication.

AEs of special interest: Ocular, cardiac, GI and Asthenia/Fatigue events.

[1] There were a total of nine deaths. One death (due to study indication) occurred within 30 days of last dose of study treatment. A further eight patients died >30 days after last dose (seven due to study indication, and one due to other reason [disease progression])

[2] Death due to disease progression

[3] Two patients discontinued due to AEs, one of them was a serious adverse event.

Other Relevant Findings

None

Date of Clinical Trial Report

11-Dec-2013

Date Inclusion on Novartis Clinical Trial Results Database

21-Feb-2013

Date of Latest Update