Sponsor

Novartis Pharmaceutical Corporation

Generic Drug Name

AUY922

Therapeutic Area of Trial

Advanced Gastric cancer

Approved Indication

Investigational

Protocol Number

CAUY922A2202

Title

A randomized, open-label, multi-center phase II study to compare AUY922 with docetaxel or irinotecan in adult patients with advanced gastric cancer, who have progressed after one line of chemotherapy

Study Phase

Phase IIa

Study Start/End Dates

16 April 2010 to 14 May 2012

The study enrollment was put on hold in March 2011 for evaluation of the study data. Subsequently, the Steering Committee (SC) decided not to re-open the study for additional enrollment after the interim/futility analysis showed that AUY922 had no superior benefits as a single agent versus standard chemotherapy.

Study Design/Methodology

This study was a randomized, open-label, active-comparator, multi-center phase II trial. Patients with advanced gastric cancer who had progressed after one line of chemotherapy were randomized 1:1 to receive either AUY922 (AUY arm) or a comparator (docetaxel or irinotecan; comparator arm). The randomization was stratified by prior taxane use, (yes or no), and World Health Organization (WHO) performance status (0 or 1). Patients were to be treated until progression, unacceptable toxicity, or decision to discontinue the study.

After randomization, patients were treated on a 21 day schedule. Patients who were randomized to AUY922 were given weekly infusions of AUY922. Patients who were randomized to either docetaxel or irinotecan were given one infusion of study drug every three weeks.

Centers

34 Centers in 13 Countries: Australia (1), Canada (1), Switzerland (1), France (4), Great Britain (3), Italy (5), Korea (3), Russia (2), Singapore (1), Taiwan (4), USA (7), Netherlands (1), Turkey (1)

Publication

N/A

Outcome Measures

Efficacy was not powered for analysis because of the low requirement.

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

AUY922 70 mg/m^2 administered via i.v. infusion once weekly.

Docetaxel 75 mg/m^2 administered via i.v. infusion once every 3 weeks.

Irinotecan 350 mg/m2 administered via i.v. infusion once every 3 weeks.

Statistical Methods

The data were analyzed by Novartis and the statistical programming was validated by PharmaNet/i3. Statistics were analyzed using SAS Version 9.3. It was planned that the data from participating centers in this protocol would be combined, so that an adequate number of patients were available for analysis. The data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK measurements.

An interim analysis was to be performed based on all patient data up to the point that the first 39 events of disease progression or death had been observed. If the interim results satisfied the criteria to continue the study, the final analysis was to be based on all patient data up to the time that 99 events of disease progression or death had been observed. In the event, the study was terminated early following the interim analysis; an abbreviated clinical study report was to be written, using the analyses described in the remainder of the Statistical Methods section shown below.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients were eligible for inclusion if they met all of the following criteria:

- Patients with cytological or histological confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma;
- Patients with progressive disease (radiological confirmation required) after one line of chemotherapy for AGC. In addition, patients may have also received prior adjuvant therapy if recurrence occurred ≥6 months after adjuvant therapy
- Patients must have at least one measurable lesion as defined by RECIST. Irradiated lesions are only evaluable for disease progression
- Patients who meet the following criteria will be eligible* for continued PET assessments
    - *All patients will be screened at baseline
    - At least one lesion must be measurable (> 2cm);
    - To be eligible for follow-up scans, patients should have uptake of the tracer in at least one lesion where the tumor-muscle ratio is > 2;
    - Able to lie still and flat on the PET table:
- Age ≥ 18 years or age of consent in country of residence
- Able to sign Informed Consent

- WHO Performance Status of ≤ 1
- Life expectancy of ≥ 12 weeks.
- Patients must have had the following laboratory values:

Hematologic:

- Absolute Neutrophil Count (ANC) ≥1.5x10^9/L;
- Hemoglobin (Hgb) ≥ 9 g/dl;
- Platelets (plt) ≥100x10^9/L/

Biochemistry:

- Potassium within normal limits;
- Total calcium (corrected for serum albumin) and phosphorus within normal limits;
- Magnesium above LLN or correctable with supplements;
- Adequate liver function defined as:
  - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 1.5 x Upper Limit of Normal (ULN) and AP < 2.5 x ULN
  - AST/SGOT and ALT/SGPT ≤ 2.5 x ULN and AP ≤ 5.0 x ULN if liver metastases were present
  - Serum bilirubin ≤ 1.5 x ULN
  - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min;
- Negative serum pregnancy test. The serum pregnancy test must have been obtained prior to the first administration of study medication (≤ 72 hours prior to dosing) in all pre-menopausal women and women < 2 years after the onset of menopause, (cessation of menses).

Exclusion criteria

Patients were to be excluded from participation if they met any of the following criteria:

- Patients with CNS metastasis which were:
  - Symptomatic or
  - Require treatment for symptom control and/or
  - Growing;
- Note: Patients without clinical signs or symptoms of CNS involvement were not required to have a CT/MRI of the brain
- Prior treatment with any HSP90 or HDAC inhibitor compounds;
- Patients who received systemic anticancer treatment prior to the first dose of study medication within the following time frames:
  - Patients must have recovered CTCAE ≤ 1 from acute toxicities of any previous therapy with the exception of alopecia.
  - Radiotherapy, conventional chemotherapy: within 4 weeks
  - Palliative radiotherapy: within 2 weeks
  - Monoclonal antibodies such as trastuzumab: within 4 weeks
  - Nitrosoureas and mitomycin: within 6 weeks

  - Any continuous dosing (i.e. daily dosing, every-other-day dosing, Monday-Wednesday-Friday dosing, weekly etc) of systemic anticancer treatment for which the recovery period is not known, or investigational drugs (i.e. targeted agents) within a duration of ≤ 5 half lives of the agent and their active metabolites (if any);
- Treatment with therapeutic doses of coumarin-type anticoagulants. (Maximum daily dose of 2 mg, for line patency permitted);
- Known sensitivity to taxanes, drugs formulated with polysorbate 80;
- Concomitant use of agents that induce, inhibit or are metabolized by CYP3A4, neuromuscular blocking agents and atazanavir sulfate;
- Unresolved diarrhea ≥ CTCAE Grade 1;
- Patients with malignant ascites that require invasive treatment;
- Patients who do not have either an archival tumor sample available or are unwilling to have a fresh tumor sample collected at baseline;
- Pregnant or lactating women;
- Fertile women of childbearing potential not using double-barrier methods of contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly, or surgically sterile);
- Patients with acute or chronic renal disease;
- Patients with active liver disease that requires 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 randomization or who have not recovered from such therapy;
- Impaired cardiac function, including any one of the following:
  - History (or family history) of long QT syndrome
  - Mean QTcF ≥ 450 msec on baseline 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] ≤ 45%) by Multi-Gated Acquisition Scan (MUGA) or echocardiogram (ECHO)
  - 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 (e.g. 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)
  - Patients who were currently receiving treatment with any medication which had a relative risk of prolonging the QTcF interval or inducing Torsades de Pointes and could not be switched or discontinued to an alternative drug prior to commencing start of treatment
  - Obligate use of a cardiac pacemaker;
- Known diagnosis of HIV infection (HIV testing is not mandatory);

- Patients with a history of another primary malignancy that was clinically significant or required active intervention;
- Patients unwilling or unable to comply with the protocol.

Participant Flow

Patient disposition by treatment group (All patients)

	AUY922 N=33	Docetaxel N=25	Irinotecan N=7	All Comparators N=32	All Patients N=65
Patients screened					99
Patients randomized					
Treated	33 (100.0%)	24 (96.0%)	7 (100.0%)	31 (96.9%)	64 (98.5%)
Untreated	0	1 (4.0%)	0	1 (3.1%)	1 (1.5%)
Patients treated					
Treatment ended	33 (100.0%)	24 (96.0%)	7 (100.0%)	31 (96.9%)	64 (98.5%)
Treatment ongoing*	0	0	0	0	0
Primary reason for end of treatment					
Disease progression	27 (81.8%)	16 (64.0%)	5 (71.4%)	21 (65.6%)	48 (73.8%)
Adverse Event (s)	4 (12.1%)	4 (16.0%)	0	4 (12.5%)	8 (12.3%)
Subject withdrew consent	2 (6.1%)	4 (16.0%)	1 (14.3%)	5 (15.6%)	7 (10.8%)
Protocol deviation	0	0	1 (14.3%)	1 (3.1%)	1 (1.5%)
Primary reason for study evaluation completion					
Death	27 (81.8%)	17 (68.0%)	5 (71.4%)	22 (68.8%)	49 (75.4%)
Administrative problems	4 (12.1%)	4 (16.0%)	1 (14.3%)	5 (15.6%)	9 (13.8%)
Subject withdrew consent	0	3 (12.0%)	0	3 (9.4%)	3 (4.6%)
Disease progression	0	1 (4.0%)	1 (14.3%)	2 (6.3%)	2 (3.1%)
Lost to follow-up	2 (6.1%)	0	0	0	2 (3.1%)

Baseline Characteristics

Demographics summary by treatment group (Full analysis set)

Demographic variable	AUY922 N=33	Docetaxel N=25	Irinotecan N=7	All comparators N=32	All patients N=65
Age (Years)					
n	33	25	7	32	65
Mean	58.09	55.36	52.29	54.69	56.42
SD	10.245	10.866	14.694	11.613	10.988
Median	56.00	57.00	57.00	57.00	57.00
Min	40.0	39.0	28.0	28.0	28.0
Max	76.0	76.0	65.0	76.0	76.0
Age group (years)					
< 65	24 (72.7%)	21 (84.0%)	5 (71.4%)	26 (81.3%)	50 (76.9%)
≥ 65	9 (27.3%)	4 (16.0%)	2 (28.6%)	6 (18.8%)	15 (23.1%)
Sex					

Demographic variable	AUY922 N=33	Docetaxel N=25	Irinotecan N=7	All comparators N=32	All patients N=65
Male	23 (69.7%)	20 (80.0%)	6 (85.7%)	26 (81.3%)	49 (75.4%)
Female	10 (30.3%)	5 (20.0%)	1 (14.3%)	6 (18.8%)	16 (24.6%)
Predominant race					
Caucasian	22 (66.7%)	11 (44.0%)	7 (100.0%)	18 (56.3%)	40 (61.5%)
Asian	11 (33.3%)	14 (56.0%)	0 (0.0%)	14 (43.8%)	25 (38.5%)
Ethnicity					
Hispanic/Latino	0 (0.0%)	3 (12.0%)	0 (0.0%)	3 (9.4%)	3 (4.6%)
Chinese	7 (21.2%)	9 (36.0%)	0 (0.0%)	9 (28.1%)	16 (24.6%)
Other	25 (75.8%)	13 (52.0%)	7 (100.0%)	20 (62.5%)	45 (69.2%)
LVEF (%) at baseline					
n	32	25	7	32	64
Mean	63.22	66.20	64.70	65.87	64.55
SD	7.149	9.119	6.637	8.562	7.938
Median	63.00	67.00	65.00	66.50	64.00
Min	51.0	46.0	53.0	46.0	46.0
Max	79.0	82.6	73.0	82.6	82.6
Weight (kg)					
n	33	25	7	32	65
Mean	65.91	66.45	77.94	68.96	67.41
SD	17.117	16.022	18.062	16.887	16.941
Median	64.30	70.00	78.50	71.65	68.20
Min	39.7	38.2	50.0	38.2	38.2
Max	108.7	93.0	97.0	97.0	108.7
WHO Performance Status					
Grade 0	15 (45.5%)	12 (48.0%)	4 (57.1%)	16 (50.0%)	31 (47.7%)
Grade 1	18 (54.5%)	13 (52.0%)	3 (42.9%)	16 (50.0%)	34 (52.3%)

Safety Results

Incidence of AEs by primary system organ class and treatment group (> 10% in any group) (Safety set)

Primary system organ class	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Patients with at least one AE	32 (97.0)	22 (91.7)	7 (100.0)	29 (93.5)	61 (95.3)
Gastrointestinal disorders	27 (81.8)	21 (87.5)	7 (100.0)	28 (90.3)	55 (85.9)
General disorders and administration site conditions	17 (51.5)	19 (79.2)	6 (85.7)	25 (80.6)	42 (65.6)
Blood and lymphatic system disorders	16 (48.5)	18 (75.0)	7 (100.0)	25 (80.6)	41 (64.1)
Metabolism and nutrition disorders	17 (51.5)	16 (66.7)	4 (57.1)	20 (64.5)	37 (57.8)

Primary system organ class	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Skin and subcutaneous tissue disorders	7 (21.2)	16 (66.7)	2 (28.6)	18 (58.1)	25 (39.1)
Eye disorders	22 (66.7)	1 (4.2)	1 (14.3)	2 (6.5)	24 (37.5)
Musculoskeletal and connective tissue disorders	11 (33.3)	13 (54.2)	0 (0.0)	13 (41.9)	24 (37.5)
Nervous system disorders	13 (39.4)	9 (37.5)	2 (28.6)	11 (35.5)	24 (37.5)
Investigations	11 (33.3)	8 (33.3)	3 (42.9)	11 (35.5)	22 (34.4)
Infections and infestations	7 (21.2)	11 (45.8)	1 (14.3)	12 (38.7)	19 (29.7)
Psychiatric disorders	12 (36.4)	6 (25.0)	0 (0.0)	6 (19.4)	18 (28.1)
Respiratory, thoracic and mediastinal disorders	7 (21.2)	9 (37.5)	1 (14.3)	10 (32.3)	17 (26.6)
Vascular disorders	7 (21.2)	6 (25.0)	1 (14.3)	7 (22.6)	14 (21.9)
Cardiac disorders	6 (18.2)	3 (12.5)	1 (14.3)	4 (12.9)	10 (15.6)
Renal and urinary disorders	5 (15.2)	4 (16.7)	0 (0.0)	4 (12.9)	9 (14.1)
Hepatobiliary disorders	5 (15.2)	0 (0.0)	3 (42.9)	3 (9.7)	8 (12.5)
Injury, poisoning and procedural complications	4 (12.1)	3 (12.5)	0 (0.0)	3 (9.7)	7 (10.9)
Immune system disorders	2 (6.1)	1 (4.2)	1 (14.3)	2 (6.5)	4 (6.3)

Incidence of AEs by preferred term and treatment group (at least 10% incidence in any group) (Safety set)

Preferred term	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Patients with at least one AE	32 (97.0)	22 (91.7)	7 (100.0)	29 (93.5)	61 (95.3)
Diarrhoea	19 (57.6)	9 (37.5)	6 (85.7)	15 (48.4)	34 (53.1)
Nausea	17 (51.5)	11 (45.8)	6 (85.7)	17 (54.8)	34 (53.1)
Decreased appetite	13 (39.4)	13 (54.2)	0 (0.0)	13 (41.9)	26 (40.6)
Anaemia	14 (42.4)	6 (25.0)	5 (71.4)	11 (35.5)	25 (39.1)
Fatigue	9 (27.3)	15 (62.5)	0 (0.0)	15 (48.4)	24 (37.5)
Neutropenia	0 (0.0)	16 (66.7)	5 (71.4)	21 (67.7)	21 (32.8)
Abdominal pain	12 (36.4)	4 (16.7)	4 (57.1)	8 (25.8)	20 (31.3)
Vomiting	11 (33.3)	4 (16.7)	4 (57.1)	8 (25.8)	19 (29.7)
Alopecia	1 (3.0)	14 (58.3)	1 (14.3)	15 (48.4)	16 (25.0)
Constipation	10 (30.3)	5 (20.8)	1 (14.3)	6 (19.4)	16 (25.0)
Asthenia	6 (18.2)	5 (20.8)	2 (28.6)	7 (22.6)	13 (20.3)
Pyrexia	5 (15.2)	5 (20.8)	2 (28.6)	7 (22.6)	12 (18.8)
Back pain	6 (18.2)	5 (20.8)	0 (0.0)	5 (16.1)	11 (17.2)
Insomnia	9 (27.3)	2 (8.3)	0 (0.0)	2 (6.5)	11 (17.2)
Abdominal pain upper	3 (9.1)	4 (16.7)	3 (42.9)	7 (22.6)	10 (15.6)
Stomatitis	3 (9.1)	6 (25.0)	1 (14.3)	7 (22.6)	10 (15.6)
Dyspnoea	5 (15.2)	3 (12.5)	1 (14.3)	4 (12.9)	9 (14.1)
Headache	6 (18.2)	3 (12.5)	0 (0.0)	3 (9.7)	9 (14.1)
Vision blurred	8 (24.2)	0 (0.0)	0 (0.0)	0 (0.0)	8 (12.5)

Preferred term	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Weight decreased	5 (15.2)	2 (8.3)	1 (14.3)	3 (9.7)	8 (12.5)
Abdominal distension	4 (12.1)	3 (12.5)	0 (0.0)	3 (9.7)	7 (10.9)
Ascites	3 (9.1)	4 (16.7)	0 (0.0)	4 (12.9)	7 (10.9)
Blood alkaline phosphatase increased	4 (12.1)	3 (12.5)	0 (0.0)	3 (9.7)	7 (10.9)
Hypotension	3 (9.1)	4 (16.7)	0 (0.0)	4 (12.9)	7 (10.9)
Leukopenia	1 (3.0)	3 (12.5)	3 (42.9)	6 (19.4)	7 (10.9)
Oedema peripheral	1 (3.0)	6 (25.0)	0 (0.0)	6 (19.4)	7 (10.9)
Photopsia	7 (21.2)	0 (0.0)	0 (0.0)	0 (0.0)	7 (10.9)
Rash	1 (3.0)	6 (25.0)	0 (0.0)	6 (19.4)	7 (10.9)
Alanine aminotransferase increased	5 (15.2)	1 (4.2)	0 (0.0)	1 (3.2)	6 (9.4)
Aspartate aminotransferase increased	5 (15.2)	1 (4.2)	0 (0.0)	1 (3.2)	6 (9.4)
Cough	1 (3.0)	4 (16.7)	1 (14.3)	5 (16.1)	6 (9.4)
Dyspepsia	3 (9.1)	3 (12.5)	0 (0.0)	3 (9.7)	6 (9.4)
Thrombocytopenia	2 (6.1)	3 (12.5)	1 (14.3)	4 (12.9)	6 (9.4)
Depression	2 (6.1)	3 (12.5)	0 (0.0)	3 (9.7)	5 (7.8)
Dizziness	2 (6.1)	3 (12.5)	0 (0.0)	3 (9.7)	5 (7.8)
Febrile neutropenia	0 (0.0)	3 (12.5)	2 (28.6)	5 (16.1)	5 (7.8)
Myalgia	1 (3.0)	4 (16.7)	0 (0.0)	4 (12.9)	5 (7.8)
Oropharyngeal pain	0 (0.0)	5 (20.8)	0 (0.0)	5 (16.1)	5 (7.8)
Visual impairment	5 (15.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.8)
Hyperbilirubinaemia	3 (9.1)	0 (0.0)	1 (14.3)	1 (3.2)	4 (6.3)
Hypoaesthesia	0 (0.0)	4 (16.7)	0 (0.0)	4 (12.9)	4 (6.3)
Hypoalbuminaemia	1 (3.0)	3 (12.5)	0 (0.0)	3 (9.7)	4 (6.3)
Hypocalcaemia	0 (0.0)	3 (12.5)	1 (14.3)	4 (12.9)	4 (6.3)
Hypokalaemia	1 (3.0)	2 (8.3)	1 (14.3)	3 (9.7)	4 (6.3)
Hypophosphataemia	2 (6.1)	1 (4.2)	1 (14.3)	2 (6.5)	4 (6.3)
Neutropenic sepsis	0 (0.0)	4 (16.7)	0 (0.0)	4 (12.9)	4 (6.3)
Pain	0 (0.0)	2 (8.3)	2 (28.6)	4 (12.9)	4 (6.3)
Haemorrhoids	0 (0.0)	1 (4.2)	2 (28.6)	3 (9.7)	3 (4.7)
Hypersensitivity	2 (6.1)	0 (0.0)	1 (14.3)	1 (3.2)	3 (4.7)
Hyponatraemia	1 (3.0)	1 (4.2)	1 (14.3)	2 (6.5)	3 (4.7)
Musculoskeletal pain	0 (0.0)	3 (12.5)	0 (0.0)	3 (9.7)	3 (4.7)
Nail disorder	0 (0.0)	3 (12.5)	0 (0.0)	3 (9.7)	3 (4.7)
Proctalgia	0 (0.0)	3 (12.5)	0 (0.0)	3 (9.7)	3 (4.7)
Chest pain	0 (0.0)	1 (4.2)	1 (14.3)	2 (6.5)	2 (3.1)
Chills	0 (0.0)	1 (4.2)	1 (14.3)	2 (6.5)	2 (3.1)
Hyperkalaemia	0 (0.0)	1 (4.2)	1 (14.3)	2 (6.5)	2 (3.1)
Peripheral sensory neuropathy	0 (0.0)	1 (4.2)	1 (14.3)	2 (6.5)	2 (3.1)
Adverse drug reaction	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Blood sodium decreased	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Bundle branch block right	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)

Preferred term	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Diabetes mellitus	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Dry eye	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Gallbladder enlargement	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
General physical health deterioration	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Hot flush	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Hyperaesthesia	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Hyperhidrosis	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Small intestinal obstruction	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Splenic vein thrombosis	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Streptococcal infection	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)

Deaths, other serious or clinically significant adverse events or related discontinuations (Safety Set)

Patients with serious or significant AEs	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Death on study					
All deaths	2 (6.1)	2 (8.3)	1 (14.3)	3 (9.7)	5 (7.8)
Due to progression	1 (3.0)	0 (0.0)	1 (14.3)	1 (3.2)	2 (3.1)
Others	1 (3.0)	2 (8.3)	0 (0.0)	2 (6.5)	3 (4.7)
SAEs	16 (48.5)	14 (58.3)	4 (57.1)	18 (58.1)	34 (53.1)
Discontinued due to AEs	4 (12.1)	1 (4.2)	0 (0.0)	1(3.2)	5 (7.8)
Discontinued due to SAEs	0 (0.0)	3 (12.5)	0 (0.0)	3 (9.7)	3 (4.7)

Serious adverse events, regardless of study drug relationship by preferred term and treatment group (Safety set)

Preferred term	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Patients with at least one SAE	16 (48.5)	14 (58.3)	4 (57.1)	18 (58.1)	34 (53.1)
Febrile neutropenia	0 (0.0)	3 (12.5)	2 (28.6)	5 (16.1)	5 (7.8)
Neutropenia	0 (0.0)	4 (16.7)	0 (0.0)	4 (12.9)	4 (6.3)
Neutropenic sepsis	0 (0.0)	4 (16.7)	0 (0.0)	4 (12.9)	4 (6.3)
Anaemia	2 (6.1)	1 (4.2)	0 (0.0)	1 (3.2)	3 (4.7)
Decreased appetite	1 (3.0)	2 (8.3)	0 (0.0)	2 (6.5)	3 (4.7)
Back pain	1 (3.0)	1 (4.2)	0 (0.0)	1 (3.2)	2 (3.1)
Bile duct obstruction	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.1)
Hydronephrosis	1 (3.0)	1 (4.2)	0 (0.0)	1 (3.2)	2 (3.1)
Infection	0 (0.0)	2 (8.3)	0 (0.0)	2 (6.5)	2 (3.1)

Preferred term	AUY922 N=33 n (%)	Docetaxel N=24 n (%)	Irinotecan N=7 n (%)	All comparators N=31 n (%)	All patients N=64 n (%)
Pneumonia	0 (0.0)	2 (8.3)	0 (0.0)	2 (6.5)	2 (3.1)
Urinary tract infection	1 (3.0)	1 (4.2)	0 (0.0)	1 (3.2)	2 (3.1)
Abdominal pain	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Abdominal pain upper	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Ascites	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Aspartate aminotransferase increased	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Blood lactate dehydrogenase increased	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Cardiac arrest	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Catheter site infection	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Chest pain	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Compression fracture	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Diarrhoea	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Diverticulitis	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dizziness	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Dyspnoea	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Fatigue	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Feeding tube complication	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Flank pain	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Gastric stenosis	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
General physical health deterioration	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Herpes zoster	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Intestinal obstruction	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Liver disorder	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Mediastinitis	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Obstruction gastric	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Pneumonitis	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Pyrexia	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Rectal haemorrhage	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Septic shock	0 (0.0)	1 (4.2)	0 (0.0)	1 (3.2)	1 (1.6)
Small intestinal obstruction	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.2)	1 (1.6)
Thrombocytopenia	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Toothache	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Other Relevant Findings

Duration of exposure by treatment group (Safety set)

	AUY922 N=33	Docetaxel N=24	Irinotecan N=7	All comparators N=31	All patients N=64
Duration of exposure (weeks)					
n	33	24	7	31	64

	AUY922 N=33	Docetaxel N=24	Irinotecan N=7	All comparators N=31	All patients N=64
Mean	8.2	14.6	21.4	16.2	12.1
SD	8.74	10.92	14.12	11.82	11.01
Median	6.0	12.0	15.0	15.0	6.0
Min	1	3	6	3	1
Max	41	48	48	48	48
Exposure (weeks)					
1-4	10 (30.3%)	2 (8.3%)	0 (0.0%)	2 (6.5%)	12 (18.8%)
5-8	14 (42.4%)	8 (33.3%)	1 (14.3%)	9 (29.0%)	23 (35.9%)
9-12	5 (15.2%)	3 (12.5%)	1 (14.3%)	4 (12.9%)	9 (14.1%)
13-16	1 (3.0%)	1 (4.2%)	2 (28.6%)	3 (9.7%)	4 (6.3%)
> 16	3 (9.1%)	10 (41.7%)	3 (42.9%)	13 (41.9%)	16 (25.0%)

Date of Clinical Trial Report

13-Mar-2013

Date Inclusion on Novartis Clinical Trial Results Database

2-May-2013

Date of Latest Update