AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib
Study Code	D9010C00008 AGICC-09CRC01
Edition Number	1
Date	16 July 2013

A Phase II, Open-Label, Multicenter Trial to Assess the Efficacy and Safety of the PARP inhibitor, olaparib, Alone in Previously-Treated Patients with Stage IV, Measurable Colorectal Cancer, Stratified by MSI Status

Study dates: First subject enrolled: 30 May 2009 [Intended]
Last subject last visit: 1 December 2010 [Intended]

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Eight Aptium Oncology Gastrointestinal Cancer Consortium (AGICC) Institutions and 2 AGICC Affiliates in the United States

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the response rate of olaparib in subjects with advanced colorectal cancer (CRC) who have progressed or failed to respond following standard combination therapy (or therapies) for CRC.	Response rates based on Response Evaluation Criteria in Solid Tumors (RECIST), calculated as the percentage of eligible subjects whose best confirmed response is a complete response (CR) or partial response (PR), and exact 95% confidence intervals were calculated for this estimate.
Secondary	Safety	To determine the safety, tolerability and toxicities of olaparib in subjects previously treated for advanced colorectal cancer	Adverse events (AEs), vital signs (blood pressure, pulse, and temperature), physical examinations, and safety laboratory analysis (clinical chemistry, haematology, and urinalysis).
Secondary	Efficacy	Based on the subjects enrolled in this trial, we calculated an estimate of progression free survival (PFS) for previously treated subjects with advanced CRC who were treated with olaparib on this schedule for all subjects enrolled in this trial – combined and stratified by the presence or absence of mutations in the mismatch repair genes.	Progression-free survival

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Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	Based on the subjects enrolled in this trial, we calculated an estimate of the overall survival (OS) for previously treated subjects with advanced CRC who were treated with olaparib on this schedule.	Overall survival
Exploratory	Translational	To determine whether poly (ADP-ribose) polymerases (PARP)-1 levels found in archival tissue prior to biopsy have a relationship to response and/or toxicity for subjects treated with olaparib.	Relationship of PARP-1 levels to response and/or toxicity
Exploratory	Translational	In subjects consenting to biopsy during therapy, to measure and explain drug activity levels after 7 to 10 days of therapy with olaparib.	Drug activity level
Exploratory	Translational	To determine whether pharmacogenomic parameters as determined from pre-therapy blood samples affected response or toxicity to olaparib.	Relationship of response or toxicity to pharmacogenomic parameters

Study design

This was a Phase II, open-label, multicenter trial of olaparib in the treatment of previously treated subjects with Stage IV disseminated, measurable colorectal cancer, stratified by microsatellite instability (MSI) status (MSI-H vs non-MSI-H). The target accrual was 54 patients in this Phase II trial to evaluate the single-agent anti-tumour activity of olaparib in patients with advanced, previously treated metastatic colorectal cancer. All subjects had tumour progression following standard combination front-line or second-line chemotherapy. The trial also included CRC subjects who had relapsed or recurrent disease within 6 months after completing adjuvant or neoadjuvant chemotherapy, provided all inclusion criteria had been met and none of the exclusion criteria had been met. The dosage of olaparib was 400 mg by mouth twice daily for 28-day cycles (capsule formulation). Subjects continuing to tolerate the treatment without dose-limiting toxicities were to proceed with this schedule until there was evidence of no clinical benefit (progressive disease) or until the subject withdrew consent for the study for any reason. Treatment had to be interrupted if any National Cancer Institute

Common Terminology Criteria Adverse Events (NCI-CTCAE) Grade 3 or Grade 4 adverse event occurred that the investigator considered to be related to olaparib. If this had not resolved to at least NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject had already undergone a maximum of two dose reductions already, the subject was withdrawn from the study.

Target subject population and sample size

This study was to enroll a maximum of 54 subjects; 15 in the MSI-H group and 39 in the non-MSI-H group. In the MSI-H cohort, accrual was to continue until 17 patients had been enrolled; in the non-MSI-H cohort, an interim analysis was performed after 17 patients had been enrolled, treated, and evaluated. If there was evidence that the true response rate among non-MSI-H patients was less than 10%, accrual was to be terminated early in that cohort. If accrual to the non-MSI-H cohort was terminated, then patients were to be screened for MSI-H status in order to continue accruing to the MSI-H cohort.

All subjects were to have stage IV, measurable disseminated colorectal cancer that was incurable by surgery. All subjects had tumour progression following standard combination front-line or second-line chemotherapy. The trial also included CRC subjects who had relapsed or recurrent disease within 6 months after completing adjuvant or neoadjuvant chemotherapy, provided all inclusion criteria had been met and none of the exclusion criteria had been met.

The main inclusion criteria included age 18 years or older with histologically proven stage disseminated CRC with measurable disease with at least one measurable lesion who received prior treatment with at least two regimens including a fluoropyrimidine, irinotecan, and oxaliplatin and who had progressive disease within the prior 6 months; adequate bone marrow, hepatic and renal function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and who had given written informed consent.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Olaparib 400 mg by mouth twice daily for 28 consecutive days. Unless modified for toxicity, subjects continued on the same dose of olaparib throughout a cycle. If a subject's dose was modified for toxicity, the subject was to begin the modified dose during subsequent cycles.

Batch numbers: 09-005247AZ, 09-001890AZ, 09-005248AZ, 09-002627AZ, 09-001890A2, 10-003289AZ, WK970547.001

Duration of treatment

Treatment continued until the subject had progressive disease or withdrew consent.

Statistical methods

The primary efficacy variable was tumor response as assessed by RECIST version 1.0. Response rates were calculated as the percentage of eligible patients whose best confirmed

response was CR or PR, and Clopper-Pearson exact 95% confidence intervals was calculated for this estimate.

Progression-free survival (PFS) was calculated from date of start of treatment until first evidence of disease progression or until death from any cause – which ever occurred first. Patients who were still alive and had not yet progressed at their last follow-up were censored at the date that the patient was last documented to be alive and free of progression. Overall survival was calculated from date of start of treatment until death from any cause. Patients who were still alive at their last follow-up were censored at the date that the patient was last documented to be alive. Kaplan-Meier plots for PFS and overall survival were presented.

Adverse events reported during the study were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 15.0 and summarized using descriptive statistics. All laboratory data were summarised at each scheduled assessment time and by treatment using descriptive statistics.

Subject population

A total of 33 subjects were enrolled into the trial. The 2 treatment groups were well-balanced for gender, median weight and height, and median BMI. The Median age was higher in the non-MSI-H group (61 years) than in the MSI-H group (51 years). Microsatellite instability (MSI-H) is a hallmark feature of Lynch syndrome and is a disorder caused by germline mutation in a mismatch repair (MMR) gene (Poynter et al 20008, Pawlik et al 20004) A substantial number of sporadic cases of MSI-H colorectal cancer may be the result of hypermethylation of the *MLH1* promoter and may tend to occur in patients who are older than those with inherited mutations of a MMR gene. The average age of onset of colon cancer in Lynch syndrome is estimated to be 42 to 61 (Gryfe et al 2000) compared to 71 in the general population. (http://www.fightlynch.org/physician.php). In general, however, the role of age in the comparisons of populations of patients with MSI-H versus non-MSI-H colorectal cancer has been inconclusive (Benatti et el 2005)

There were only two patients with a diagnosis of Lynch Syndrome reported in the current study, and both were in the MSI-H group (207021 and 2070024). They were age 50 and 42, respectively, at the time of diagnosis. There were no other reports of a hereditary basis of colorectal cancer in either patient group, thus it is difficult to draw firm conclusions about the difference in age between the two groups, MSI-H and non-MSI-H.

Only 33 patients were enrolled into the trial instead of the planned 54 patients due to scarcity of patient population.

All subjects were representative of previously treated stage IV colorectal cancer. Seventeen (51.5%) of the subjects had moderately differentiated tumours. Twelve subjects (36.4%) had poorly differentiated tumours, with slightly more subjects in the non-MSI-H group (40%) than in the MSI-H group (30.8%). All subjects had received previous chemotherapy, and 3 subjects (23.1%) in the MSI-H group and 6 subjects (30.0%) in the non-MSI-H group had prior radiotherapy.

The majority of subjects discontinued due to disease progression (27 out 33 subjects). Five of the subjects also had AEs requiring discontinuation of olaparib treatment due to the subject's worsening condition. Four subjects terminated due to adverse events and one subject discontinued due to a laboratory abnormality.

Summary of efficacy results

The primary objective was to determine a response rate of olaparib in previously treated patients with advanced CRC. A response rate of 12 to 15% in the MSI-H and 8 to 10% in the non-MSI-H arm would indicate sufficient activity to warrant further study. The results indicated that no subjects in either group achieved a CR or PR. Five subjects (15.2%) subjects had SD for $\geq$ 4 weeks; 3 (23.2%) in the MSI-H group and 2 (10.0%) subjects in the non-MSI-H group. With neither group achieving sufficient levels of response, no further investigation was pursued.

The secondary objectives for the study included calculating estimates progression free survival (PFS) and overall survival (OS) for previously treated patients with advanced CRC who are treated on this schedule for all patients enrolled in this trial. The median PFS in the MSI-H group was 61 days with a 95% confidence interval (52.0, 360.0) and 55 days in the non-MSI-H group (49.0, 56.0).

The median OS was longer in the non-MSI-H group (290.5 days; 95%: 157.0, 429.0) than in the MSI-H group (248.0 days; 95% CI: 121.0, 554.0).

Summary of pharmacogenetic results

Pharmacogenetic results will be presented in a separate report.

Summary of safety results

The majority of subjects treated in the study experienced at least 1 AE (32 subjects, 97%). Of the adverse events reported, 76.9% of the events in the MSI-H arm and 80% of the events in the non-MSI-H arm were considered to be causally related to the treatment. Adverse events of CTCAE grade 3 or higher, were experienced in 46.2% of subjects in the MSI-H arm and 50% of subjects in the non-MSI-H arm and most were considered to be related to treatment.

There were 9 (27.3%) subjects who had SAEs during the study; including 2 (6.1%) subjects who had SAEs that were causally-related to study treatment. One subject had an adverse event with an outcome of death. A total of 9 (27.3%) subjects discontinued study treatment due to an AE, 6 (18.2%) subjects discontinued due to AEs that were considered by the investigator to be causally related to study treatment. Three (9.1%) of the nine subjects discontinued study treatment due to an SAE, none of whom had SAEs that were considered by the investigator to be treatment-related.