| **Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | AZD5153 and olaparib |
| Study Code | D6520C00001 |
| Edition Number | 1.0 |
| Date | 01 Jun 2022 |
| EudraCT Number | IND 123066 |
| NCT Number | NCT03205176 |

# A Phase I, Multicenter Dose-Escalation Study to Assess the Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity of AZD5153 in Patients with Relapsed/Refractory Malignant Solid Tumors, Including Lymphomas

**Study dates:**
First subject enrolled: 30 June 2017
Last subject last visit: 19 April 2021
The analyses presented in this report are based on a clinical data lock date of 23 December 2021

**Phase of development:**
Clinical pharmacology (I)

**International Co-ordinating Investigator:**
PPD
PPD
PPD

**Sponsor's Responsible Medical Officer:**
PPD
PPD
AstraZeneca
35 Gatehouse Drive
Waltham, MA 02451

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

## Study Centers

The study was conducted at 4 centers: 3 in the US and 1 in Canada.

## Publications

Wang JS-Z, De Vita S, Karlix JL, et al. First-in-human study of AZD5153, a small molecule inhibitor of bromodomain protein 4 (BRD4), in patients (pts) with relapsed/refractory (RR) malignant solid tumor and lymphoma: Preliminary data. J. Clin. Oncol. 2019;37:3085 (ASCO 2019 Poster Presentation).

## Objectives and Criteria for Evaluation

The study objectives and criteria for evaluation are presented in Table S1.

**Table S1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To determine the safety profile, tolerability, and MTD of AZD5153 monotherapy in patients with malignant solid tumors or lymphomas.<br>• To determine safety and tolerability and establish an MTD of the combination of AZD5153 and olaparib in patients with platinum-resistant or platinum-refractory HGSO cancer, refractory TNBC, mCRPC, or PDAC. | • Incidence of DLTs, AEs, and abnormal laboratory tests (clinical chemistry, hematology, and urinalysis), physical examinations, vital signs (blood pressure and pulse), and ECGs. |
| Secondary | |
| • To characterize single- and multiple-dose plasma PK parameters of AZD5153 and its co-former for AZD5153 alone and in combination with olaparib. | • Concentration of AZD5153, its co-former, and olaparib (if applicable) in plasma and non-compartmental PK parameters (including AUC, Cmax, Tmax, t½λz, CL/F and Vd/F). |
| • To characterize the urine PK parameters of AZD5153 and its co-former. | • Assessment of urine PK parameters of AZD5153 and its co-former, if applicable. |
| • To characterize the effect of AZD5153 alone and in combination with olaparib on QTc interval. | • Assessment of QTc interval changes. |
| • To evaluate the preliminary anti-tumor activity of AZD5153 alone and in combination with olaparib. | • Disease control rate.<br>• Progression-free survival.<br>• Overall response rate.<br>• Duration of response. |

AE, adverse event; AUC, area under the curve; CL/F, apparent oral clearance; Cmax, maximum plasma concentration; DLT, dose-limiting toxicity; ECG, electrocardiogram; HGSO, high grade serous ovarian; mCRPC, metastatic castrate-resistant prostate cancer; MTD, maximum tolerated dose; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetic; QTc, corrected QT interval; t½λz, half-life; Tmax, time to maximum plasma concentration; TNBC, triple-negative breast cancer; Vd/F, volume of distribution.

## Study Design

This was a Phase I, FTIP, open-label, multicenter dose-escalation study that assessed the tolerability, PK, and anti-tumor activity of AZD5153 monotherapy or in combination with olaparib therapy in patients with relapsed/refractory malignant solid tumors, including lymphomas. Study treatment was administered in continuous cycles of 21 days. There were 4 parts planned for this study, as follows:

- AZD5153 monotherapy dose escalation in patients with advanced solid malignancies, including lymphoma, to test safety and tolerability (6 cohorts of ascending oral doses

[possible dose escalation scheme: 2 mg QD, 5 mg QD, 10 mg QD, 10 mg BID, 20 mg BID, escalate until MTD]).

- AZD5153 + olaparib (300 mg BID) combination dose escalation in patients with platinum-resistant or platinum-refractory HGSO cancer, refractory TNBC, mCRPC, or PDAC to test safety and tolerability (4 cohorts of ascending oral doses of AZD5153 [possible dose escalation scheme: 5 mg BID, 10 mg BID, 10 mg QD (14 days on, 7 days off), and 10 mg BID (7 days on and 14 days off)]).
- AZD5153 monotherapy at MTD (monotherapy dose expansion) in patients with platinum-resistant or platinum-refractory HGSO cancer to confirm the safety and tolerability of the dose considered to be the MTD (Note: the monotherapy dose expansion was not conducted).
- AZD5153 + olaparib (300 mg BID) at AZD5153 MTD (combination dose expansion) in patients with platinum-resistant or platinum-refractory HGSO cancer, TNBC, mCRPC, and PDAC, to confirm the safety and tolerability of the dose and schedule of AZD5153 + olaparib (Note: the combination dose expansion was not conducted).

**Target Population and Sample Size**

Adult patients (aged ≥ 18 years) with a solid tumor that was refractory to, or intolerant of existing therapies known to provide clinical benefit for their clinical condition, were included in the study. Patients must have had WHO/ECOG PS of 0 or 1 and life-expectancy of ≥ 3 months. Patients with brain metastases were eligible provided they were asymptomatic, treated and stable, and off steroids for at least 4 weeks prior to study entry.

Approximately 72 eligible patients were planned to be enrolled at centers (3 in the US and 1 in Canada) across the monotherapy dose escalation cohorts, AZD5153 + olaparib combination cohorts, and expansion cohorts.

**Investigational Medicinal Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers**

**AZD5153**

AZD5153 was supplied by AstraZeneca as a dry-filled capsule containing 1 mg, 5 mg, or 20 mg of drug substance. AZD5153 was administered as an oral capsule and was provided in bottles. All doses of AZD5153 were to be taken at approximately the same time each day, in a fasted state (water to drink only for 2 hours before and 1 hour after AZD5153). Patients in cohorts where AZD5153 was dosed BID were to take the doses morning and evening, approximately 12 hours apart. Patients were instructed to take each dose with a full glass of water and to swallow the capsule(s) whole, without chewing or crushing. Two batches of AZD5153 were used in this study.

Batch numbers: CCI and CCI.

## Olaparib

Olaparib was supplied by AstraZeneca as 100 mg and 150 mg tablets. Olaparib was to be taken orally and was provided in bottles. Patients were not to eat food for at least 2 hours before or 1 hour after taking study drug treatment (AZD5153 and/or olaparib). Doses of olaparib were to be taken at the same time each day, morning and evening, approximately 12 hours apart. The tablets were to be swallowed whole and not chewed, crushed, or divided. Dosing of olaparib and AZD5153 was to occur at the same time for patients in the combination dose escalation portion of the study when applicable. Four batches of olaparib were used in this study.

Batch numbers: CCI , CCI , CCI , and CCI .

### Duration of Treatment

Dose escalation treatment with AZD5153 as a monotherapy or AZD5153 in combination with olaparib was carried out in continuous 21-day cycles except for the final combination therapy cohort who received an intermittent schedule of AZD5153 (2 weeks on, 1 week off). Patients continued on the starting dose until disease progression or other study discontinuation criteria were met. If the dose from Cohort 1 was considered safe and tolerable, dose escalation to the next planned dose was applied across cohorts. In Cohort 1, patient dosing was staggered by at least 7 days in the first 2 patients.

### Statistical Methods

The primary outcome variables which address the safety and tolerability of AZD5153 monotherapy, and AZD5153 + olaparib combination therapy, were summarized using descriptive statistics.

Descriptive statistics were also used for all other variables, as appropriate. Continuous variables were summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles (as applicable), minimum, and maximum. For log-transformed data, geometric mean, coefficient of variation (CV%), median, minimum and maximum were presented. Categorical variables were summarized by frequency counts and percentages for each category. SAS® version 9.4 was used for all analyses.

### Study Population

A total of 49 patients were enrolled in this study at 4 centers (3 in the US and 1 in Canada). All 49 patients were included in the safety population. All 49 patients discontinued study treatment. The most common reason for study treatment discontinuation was progressive disease (36 [73.5%] patients).

Across the AZD5153 monotherapy cohorts, all 34 patients discontinued AZD5153 treatment due to either progressive disease (27 [79.4%] patients), physician decision (3 [8.8%] patients), adverse events (3 [8.8%] patients), or withdrawal by patient (1 [2.9%] patient). Across the AZD5153 + olaparib combination therapy cohorts, all 15 patients discontinued AZD5153 and olaparib treatment due to either progressive disease (9 [60.0%] patients), withdrawal by patient (3 [20.0%] patients), physician decision (2 [13.3%] patients), or lost to follow-up (1 [6.7%] patient).

Overall, 3 (8.8%) AZD5153 monotherapy patients and 4 (26.7%) AZD5153 + olaparib combination therapy patients had 1 important protocol deviation each in this study. Of the 7 important protocol deviations recorded, 3 (6.1%) were related to protocol implementation, 2 (4.1%) were related to safety, and 2 (4.1%) were related to informed consent.

In the AZD5153 monotherapy cohorts there were more females (26 [76.5%] patients) than males (8 [23.5%] patients). Most patients were White (28 [82.4%]). The mean (SD) age of patients at baseline was 65.9 (11.03) years and mean (SD) body mass index was 29.5 (9.5) kg/m$^2$. Most AZD5153 monotherapy patients (23 [67.6%]) had a baseline ECOG PS of 1; the remainder had a baseline ECOG PS of 0 (11 [32.4%] patients). The most common AJCC stage at baseline was Stage IV (12 [35.3%] patients).

In the AZD5153 + olaparib combination therapy cohorts there were more females (13 [86.7%] patients) than males (2 [13.3%] patients). Most patients were White (14 [93.3%]). The mean (SD) age of patients at baseline was 63.7 (9.48) years and mean (SD) body mass index was 27.7 (5.6) kg/m$^2$. Most AZD5153 + olaparib combination therapy patients (11 [73.3%]) had a baseline ECOG PS of 1; the remainder had a baseline ECOG PS of 0 (4 [26.7%] patients). The most common AJCC stage at baseline was Stage IV (8 [53.3%] patients).

**Summary of Efficacy Results**

Evaluation of the anti-tumor activity of AZD5153 alone and in combination with olaparib was a secondary objective in this study, and interpretation of the preliminary data are limited by the small patient numbers in each dose level cohort (n = 3–7).

The DCR for monotherapy patients at 6 weeks was 48.5% overall, with small numbers of patients in each AZD5153 monotherapy dose cohort achieving disease control and no dose-related trend evident. The DCR for combination patients at 6 weeks was 26.7% overall, with only patients in the 5 mg BID + olaparib 300 mg BID cohort (2 [40%] patients) and 10 mg QD (2WK on/1WK off) + olaparib 300 mg BID cohort (2 [28.6%] patients) contributing to the total.

One patient with a primary diagnosis of PDAC (Cohort 11: AZD5153 10 mg QD [2WK on/1WK off] + olaparib 300 mg BID) achieved a PR, with a DoR of 4.2 months; no other patients achieved CR or PR during the study. Another patient with PDAC in the same cohort,

who was classed as PD on Day 37 and Day 79 after starting AZD5153 + olaparib combination therapy, subsequently had a 4% reduction from baseline in target lesion diameter on Day 205 and Day 252.

Overall, 5 (15.2%) of patients in AZD5153 monotherapy cohorts had measurable reductions in target lesion size, with 1 patient in the 30 mg QD cohort (stable disease to Day 583) and 1 patient in the 40 mg QD cohort (stable disease to Day 134) each achieving a best reduction in target lesion size > 10%. Measurable reductions in target lesion size were observed for 5 (33.3%) patients across the AZD5153 + olaparib combination therapy cohorts, with 1 patient in the 5 mg BID + olaparib 300 mg BID cohort (stable disease to Day 154) and 2 patients in the 10 mg QD (2WK on/1WK off) + olaparib 300 mg BID cohort (stable disease to Day 84 for both, followed by PR from Day 125 to Day 252 for 1 patient) each achieving a best reduction in target lesion size > 10%.

**Summary of Pharmacokinetic Results**

AZD5153 PK was characterized following single and multiple doses, along with its co-former, AZ10196812, following oral administration alone or repeat administration in the presence of olaparib.

AZD5153 was rapidly absorbed, with median Tmax in the range of 0.5 to 3 hours post-dose. Mean exposure generally increased over the dose range of 2 to 40 mg QD and 10 to 20 mg BID, with exceptions between some dose pairs, potentially due to small sample size and relatively high inter-patient variability. The increase in exposure was less than proportional over the range of 2 to 40 mg QD, in terms of Cmax and AUC. From 10 to 20 mg BID, a 2-fold increase in dose resulted in 1.6- to 3.2-fold increases in AUC and Cmax.

Estimates of mean t½λz ranged from approximately 1 to 9 hours, with mean MRTinf estimates in the range of 3 to 6 hours following single or multiple doses of AZD5153 as monotherapy. There was no notable evidence of AZD5153 accumulation for any dose regimen evaluated.

Renal excretion of unchanged AZD5153 was not a primary route of elimination; less than 2% of the dose was excreted in collection intervals of up to 24 hours.

AZ10196812 was rapidly absorbed, with median Tmax in the range of 0.5 to 1 hour post-dose. Mean t½λz estimates ranged from approximately 1 to 5 hours, with no consistent evidence of notable accumulation following repeat daily or twice daily administration.

AZD5153 PK was characterized in the presence of olaparib for a limited number of patients; at 5 mg BID, mean exposure was 2- to 3-fold higher under combination therapy with olaparib compared to single-dose exposure. This trend was not evaluable for AZ10196812, due to the limited data available.

**Summary of Safety Results**

The median total duration of exposure to AZD5153 in the AZD5153 monotherapy cohorts was 1.38 months (range: 0.3 to 18.0). The median total duration of exposure to AZD5153 in the AZD5153 + olaparib combination therapy cohorts was 1.41 months (range: 0.1 to 8.7). The median total duration of exposure to olaparib in the AZD5153 + olaparib combination therapy was 1.38 months (range: 0.0 to 8.7).

The median relative dose intensity of AZD5153 in the monotherapy cohorts was 99.05%, and in the AZD5153 + olaparib combination therapy cohorts was 81.58%. The median relative dose intensity of olaparib in the AZD5153 + olaparib combination therapy cohorts was 79.07%.

In the AZD5153 monotherapy cohorts, the most commonly reported TEAEs by preferred term were fatigue (13 [38.2%] patients), thrombocytopenia (11 [32.4%] patients), and diarrhoea (11 [32.4%] patients); no obvious dose-related trends were observed for fatigue or thrombocytopenia, but reports of diarrhoea tended to occur more frequently in the higher dose cohorts. In the AZD5153 + olaparib combination therapy cohorts they were nausea (10 [66.7%] patients), fatigue (8 [53.3%] patients), dysgeusia (6 [40.0%] patients), vomiting (6 [40.0%] patients), thrombocytopenia (5 [33.3%] patients), and platelet count decreased (5 [33.3%] patients), with no obvious dose-related trends observed for any of these events.

More than half of patients in the AZD5153 monotherapy cohorts (19 [55.9%] patients) and in the AZD5153 + olaparib combination therapy cohorts (10 [66.7%] patients) experienced an AE of CTCAE Grade ≥ 3. In the AZD5153 monotherapy cohorts, the most commonly reported CTCAE Grade ≥ 3 event by preferred term was thrombocytopenia (5 [14.7%] patients), with no obvious relationship between dose and event frequency observed. In the AZD5153 + olaparib combination therapy cohorts the most commonly reported CTCAE Grade ≥ 3 events were thrombocytopenia (4 [26.7%] patients), hyponatraemia (3 [20.0%] patients), fatigue (2 [13.3%] patients), and nausea (2 [13.3%] patients), with the highest frequency of thrombocytopenia, hyponatraemia and nausea observed in the AZD5153 10 mg BID + olaparib 300 mg BID cohort.

Approximately 15% of AZD5153 monotherapy and AZD5153 + olaparib combination therapy patients experienced AEs leading to AZD5153 dose reductions, while 22 (64.7%) AZD5153 monotherapy patients and 11 (73.3%) AZD5153 + olaparib combination therapy patients experienced AEs leading to AZD5153 interruptions. Thrombocytopenia was the most common AE leading to AZD5153 dose reductions and interruptions in the AZD5153 monotherapy cohorts (4 [11.8%] and 8 [23.5%] patients, respectively) and AZD5153 + olaparib interruptions in the combination therapy cohorts (5 [33.3%] patients).

Dose-limiting toxicities were experienced by 2/6 patients in the AZD5153 20 mg BID monotherapy cohort (Grade 4 thrombocytopenia and Grade 3 diarrhoea), with no DLTs observed in prior or subsequent monotherapy cohorts. Dose-limiting toxicities were experienced by 3/3 patients in the AZD5153 10 mg BID + olaparib 300 mg BID cohort (all thrombocytopenia: Grade 3 [1 patient] or Grade 4 [2 patients]) and 2/7 patients in the AZD5153 10 mg QD (2WK on/1WK off) + olaparib 300 mg BID cohort (Grade 2 or Grade 3 platelet count decreased resulting in < 75% of olaparib dosing during Cycle 1).

Overall, 4 (8.2%) patients had an AESI, all of whom were treated with AZD5153 monotherapy; 3 patients had herpes zoster (1 each in the 10 mg BID, 20 mg BID, and 40 mg QD cohorts) and 1 patient had herpes dermatitis (in the 20 mg BID cohort).

Overall, 3 (6.1%) patients had an OAE, all of whom were treated with AZD5153 monotherapy; 1 patient each in the 5 mg QD cohort (syncope), 10 mg BID cohort (sinus tachycardia and electrocardiogram QT prolonged), and 40 mg QD cohort (tachycardia).

Overall, 7 (20.6%) AZD5153 monotherapy patients and 3 (20.0%) AZD5153 + olaparib combination therapy patients experienced an SAE during the study. In the AZD5153 monotherapy cohorts, the most commonly reported SAE by preferred term was pleural effusion (2 [5.9%] patients); all other SAE preferred terms were each reported for a single patient. In the AZD5153 + olaparib combination therapy cohorts, all SAEs (by system organ class and preferred term) affected only a single patient. No relationship between dose and SAE frequency was observed in the AZD5153 monotherapy or AZD5153 + olaparib combination therapy cohorts.

No SAEs were considered by the Investigator to be causally related to AZD5153 treatment. A single patient taking AZD5153 10 mg BID + olaparib 300 mg BID had a Grade 3 SAE of nausea on Day 8 that was considered by the Investigator to be causally related to olaparib with or without AZD5153; the patient's AZD5153 and olaparib doses were not changed and the patient recovered.

Overall, 3 (6.1%) patients had an AE that led to discontinuation of AZD5153 treatment, all of whom were in AZD5153 monotherapy cohorts; 2 patients in the 20 mg BID cohort (1 patient with a Grade 1 autoantibody test and 1 patient with a Grade 3 hip fracture [which was also an SAE, and which resolved]) and 1 patient in the 40 mg QD cohort who had a Grade 2 AE of fatigue.

CCI [redacted]

There were no notable trends observed with respect to dose for hematology and clinical chemistry assessments. One patient in Cohort 6 (AZD5153 15 mg BID monotherapy) experienced ALT ≥ 3 × ULN or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN concurrently over 3 consecutive visits (Day 66 through Day 80, inclusive). These findings were first observed 25 days after the last dose of AZD5153 in a patient with known liver metastases. There were no confirmed Hy's Law cases in the study.

There were no notable trends observed with respect to dose for ECG, vital signs, or physical findings in the AZD5153 monotherapy or AZD5153 + olaparib combination therapy cohorts during the study.

**Conclusion(s)**

- Formal MTDs were not declared for AZD5153 as either monotherapy or in combination with olaparib 300 mg BID; however, the SRC recommended AZD5153 30 mg daily (30 mg QD or 15 mg BID) as the monotherapy dose and AZD5153 10 mg QD (2WK on/1 WK off) in combination with olaparib 300 mg BID (continuous) be considered in future studies, since they anticipated an increased risk of thrombocytopenia with AZD5153 monotherapy doses higher than 30 mg daily, and continuous AZD5153 dosing at 10 mg QD (or above) when combined with continuous olaparib dosing.
- Treatment with AZD5153 as monotherapy and in combination with olaparib demonstrated a manageable safety and tolerability profile. The most common AEs with AZD5153 monotherapy were fatigue, thrombocytopenia, and diarrhoea. The most common AEs with AZD5153 combined with olaparib were nausea, fatigue, dysgeusia, vomiting, and thrombocytopenia, and platelet count decreased. There were no obvious safety signals detected from the review of the AEs and no ADRs were identified.
- Due to the small number of patients in each treatment cohort, limited inferences can be drawn for individual dose levels in the efficacy analyses. One patient in Cohort 11 (AZD5153 10 mg QD [2WK on/1WK off] + olaparib 300 mg BID) with a primary diagnosis of PDAC achieved a PR (DoR of 4.2 months); no other patients achieved CR or PR during the study. Another patient with PDAC, in the same cohort, who was classed as PD shortly after starting treatment, had a 4% reduction from baseline in target lesion diameter approximately 6.5 months after starting treatment. These observations may be an early indication that AZD5153 10 mg QD (2WK on/1WK off) combined with olaparib 300 mg BID (continuous) could be considered for further exploration in PDAC.
- AZD5153 was rapidly absorbed, with median Tmax in the range of 0.5 to 3 hours post-dose. Mean exposure generally increased over the dose range of 2 to 40 mg QD and 10 to 20 mg BID, with some exceptions. The increase in exposure was less than proportional over the range of 2 to 40 mg QD, in terms of Cmax and AUC; from 10 to 20 mg BID, a 2-fold increase in dose resulted in 1.6- to 3.2-fold increases in AUC and Cmax.
- Estimates of mean t½λz ranged from approximately 1 to 9 hours, with mean MRTinf estimates in the range of 3 to 6 hours following single or multiple doses of AZD5153 as

monotherapy. There was no notable evidence of AZD5153 accumulation for any dose regimen evaluated.

- Renal excretion of unchanged AZD5153 was not a primary route of elimination, as < 2% of the dose was excreted in collection intervals of up to 24 hours.
- AZ10196812 was rapidly absorbed, with median Tmax in the range of 0.5 to 1 hour post-dose. Mean t½λz estimates ranged from approximately 1 to 5 hours, with no consistent evidence of notable accumulation following repeat administration QD or BID.
- AZD5153 PK was characterized in the presence of olaparib for limited number of patients in a single cohort, where mean exposure was 2- to 3-fold higher under combination therapy with olaparib compared to single-dose administration of AZD5153 alone.