TORMEK: A Phase Ib/IIa study of AZD2014 in combination with Selumetinib in patients with advanced cancers

Clinical Study Report (CSR)

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1 INTRODUCTION

1.1 SCIENTIFIC RATIONALE

- The PI3K/mTOR and the MAPK pathways are aberrantly activated in many tumours and interact to promote tumour growth and therapeutic resistance
- Mono-therapy has been shown to be effective in tumour types in which mutations/modulations in either the MAPK or PI3K pathway predominate. However, multiple lines of investigation suggest that activation of the PI3K/mTOR pathway can decrease the activity of inhibitors of the RAS/ MEK pathway; similarly, activation of RAS signalling can decrease the activity of PI3K/mTOR pathway inhibitors.
- Preclinical studies have demonstrated that inhibition of the PI3K/mTOR or the RAS/MAPK pathways alone results in activation of feedback loops that promote activity of the pathway upstream of the inhibition site or alternative signalling, resulting in therapeutic resistance.
- There is increasing in vitro and in vivo preclinical evidence that dual inhibition of the PI3K/mTOR and RAS/MAPK pathways can block alternative pathway reactivation and lead to increased anti-tumour effects.

1.2 SELECTION OF STUDY DRUGS AND SCHEDULES

- Selumetinib (AZD6244, ARRY-142886) is an orally available, potent, selective, non-ATP competitive inhibitor of MEK1/MEK2 kinases. Selumetinib has demonstrated clinical efficacy in pre-treated KRAS-mutant NSCLC, leading to a significantly improved progression-free survival in combination with docetaxel compared to docetaxel alone.
- AZD2014 is a dual inhibitor of both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive); compared to rapalogues, AZD2014 has a broader range of growth inhibitory activity in preclinical models based on a more profound mTORC1 inhibition and the additional inhibition of mTORC2. AZD2014 is currently in phase 2 studies in renal cell cancers and metastatic breast cancer. AZD2014 is administered in a continuous schedule twice daily. In addition, an intermittent weekly dosing schedule with 2 days of BID dosing out of 7 days is being explored, because of a potential improved dose/PK/safety and PD relationship of a short high dose exposure for around 72h with a subsequent drug holiday for 4 days.
- *In vitro* and *in vivo* preclinical studies of selumetinib and AZD2014 confirm that both agents can be combined effectively and demonstrate increased anti-tumour efficacy compared to either agent alone.
- Nonclinical and early clinical data for selumetinib and AZD2014 have identified stomatitis, diarrhoea, fatigue and rash (although the characteristics of skin changes differ for selumetinib and AZD2014 with selumetinib typically leading to an acneiform rash, whereas AZD2014 is associated with a macula-papular rash) as the main overlapping toxicities, whereas there seems to be limited overlap between selumetinib and AZD2014 with regards other toxicities.
- Both, AZD2014 and selumetinib have relatively short half-lives, enabling more flexibility for dose scheduling; continuous and intermittent schedules might therefore be explored for selumetinib and AZD2014 in order to identify a safe and feasible regimen. Pharmacodynamic assessments will help establish the optimal regimen for further development.

1.3 JUSTIFICATION OF SELECTING THE TARGET POPULATION

- Preclinical studies have demonstrated that tumours with and without aberrant activation of the PI3K/mTOR or RAS/MEK pathways may benefit from dual inhibition; the study will therefore enrol patients irrespective of their PI3K/mTOR or RAS/MEK activation status.

- Limiting recruitment in the phase I part to tumour types with frequent activation of MAPK and/or PI3K/mTOR pathways or tumours with known alteration in genes involved in the MAPK and/or PI3K/mTOR pathways (including upstream pathway activation) will enrich the study for tumours with intrinsic pathway activation; this will facilitate correlative studies aiming to better characterise the target population.
- Expansion cohorts will initially focus on Non-Small Cell Lung Cancer (NSCLC) and Triple Negative Breast Cancer (TNBC). Both PI3K/mTOR and MAPK pathways are frequently activated in NSCLC and TNBC, and preclinical studies suggest broad activity for dual pathway inhibition across all molecular phenotypes. Clinical studies have already demonstrated a benefit for selumetinib in KRAS-mutant patients with pre-treated NSCLC. Early clinical studies have furthermore shown preliminary anti-tumour activity for inhibitors of the PI3K/AKT/mTOR pathway in NSCLC (predominantly in KRAS-wild-type patients) and TNBC.
- Three distinct NSCLC subgroups have emerged with regards activation of the PI3K/mTOR and the RAS/MEK pathways (squamous cell cancers, non-squamous cell tumours with KRAS mutations, non-squamous cell tumours with KRAS wild-type); the separate expansion cohorts will enable a preliminary assessment of the activity of the regimen in distinct molecular backgrounds which will provide critical information for the development of this regimen in NSCLC
- An additional mixed tumour type cohort of uveal melanoma, colorectal cancer with RAS mutations, low grade serous ovarian cancer with KRAS mutations, HER2+ breast cancer and ER+ breast cancer will be investigated.

2 ENDPOINTS

2.1 PRIMARY ENDPOINTS

- **Phase Ib:** Dose-limiting toxicities
- **Phase IIa:** Disease Control Rate defined as complete (CR) or partial response (PR) or stable disease (SD) maintained ≥12 weeks (RECIST v1.1).

2.2 SECONDARY OBJECTIVES

Phase IIa:

- Objective Response Rate (ORR), defined as the number of patients with measurable disease at baseline with CR or PR (as assessed by the site radiologist, using RECIST 1.1) divided by the number of patients at risk
- Average change (%) in tumour size at 12 weeks compared to baseline as assessed by RECIST v1.1; tumour size is defined as the sum of the diameters of the target lesions.
- Safety and tolerability as assessed by Adverse Events (AEs) (CTCAE, v4.03).
- Progression Free Survival (PFS) defined as the time from the date of registration to the date of first documented tumour progression (RECISTv1.1) or death from any cause, whichever occurs first.
- Duration of response (DoR) defined as the time from first documentation of CR or PR to disease progression (RECIST v1.1) or death from any cause, whichever occurs first.
- Overall survival (OS) defined as the time from date of registration to the date of death due to any cause.

Pharmacokinetic and exploratory biomarker data are not included in this report.

4 MATERIALS AND METHODS

4.1 OVERALL STUDY DESIGN

This was an open-label, multicentre phase Ib/IIa study of AZD2014 in combination with Selumetinib. There were two phases to this study.

The dose escalation phase enrolled patients with treatment-refractory advanced solid tumours. This part of the study was limited to tumour types with:

- frequent activation of MAPK and/or PI3K/mTOR pathways (pancreatic, thyroid, endometrial, renal, breast or ovarian carcinoma, colorectal cancer, NSCLC, biliary tract tumours, or melanoma) OR
- tumours with known alterations in ≥1 gene involved in PI3K/AKT/mTOR or Ras/MEK pathway signalling, such as: KRAS, NRAS, BRAF, PIK3CA, PTEN, AKT, LKB1, EGFR, FGFR, HER2, MET, RET, KIT, NF1.

This phase planned to investigate two different dosing schedules of AZD2014: a continuous daily schedule (CC-Schedule) and an intermittent schedule of 2 days on and 5 days off treatment (IC-Schedule). A third additional schedule of combined intermittent selumetinib (3 days on and 4 days off treatment) with intermittent AZD2014 (II-Schedule) was initially planned to be considered, if escalation of the AZD2014 dose in the IC-Schedule was not feasible with the corresponding continuous selumetinib regimen. This schedule was not initiated in TORCMEK.

At the end of the dose escalation phase (phase Ib) a recommended phase 2 dose and regimen (RP2D) would be defined for further testing in expansion cohorts based on the MTD.

Dose Expansion Phase (Phase IIa): Following definition of the RP2D, expansion cohorts were planned to perform a preliminary assessment of the anti-tumour efficacy in different molecular settings and to further establish the safety profile of the selected RP2D. Expansion cohorts were selected based on their underlying distinct molecular aberrations with regards to activation of the PI3K/AKT/mTOR and RAS/MEK pathways. These were:

- Triple-negative breast cancer (TNBC).
- Squamous cell lung cancers (SCLC).
- Non-squamous cell lung cancers (NSCLC) with KRAS mutations.
- Non-squamous cell lung cancers (NSCLC) with wild-type KRAS.

In addition, a fifth mixed cohort of uveal melanoma, colorectal cancer with RAS mutations, low grade serous ovarian cancer with KRAS mutations, HER2+ breast cancer and ER+ breast cancer was investigated. This cohort followed a two-stage adaptive design whereby five patients from each of the tumour types was initially recruited. Progression to stage 2 depended on performance against pre-specified ORR criteria.

4.2 ADMINISTRATIVE STRUCTURE

The study was sponsored by Queen Mary University London. The Sponsor was responsible for the overall study management (monitoring), drug supply, data management, statistical analysis and medical writing for this clinical study report.

AZD2014 and Selumetinib was supplied by Astra Zeneca, labelled and distributed to the sites by Fisher Clinical Services.

A safety review committee (SRC) evaluated safety data acquired during the Phase Ib part of the study and made dose escalation / modification decisions. The SRC also confirmed the dose to take forward to the phase IIa part of the study. A Trial Steering Committee (TSC) monitored safety data for the duration of the study.

Following the decision by the IMP Manufacturer, AstraZeneca, to cease development of AZD2014 in June 2018, the TORCMEK TMG/TSC recommended to stop recruitment. The final patient was recruited on 10 July 2018. The trial ended on 10 January 2020 as per the protocol end of trial definition.

4.3 ETHICS AND STUDY CONDUCT

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. Investigators were trained according to the Sponsor SOPs. Approval from Ethics Committees (EC) and Competent Authorities (CA) was obtained prior to starting the study. Protocol amendments were prepared by the Sponsor and submitted to the EC and CA in accordance with local regulatory requirements. Approval was obtained from the EC and CA (as locally required) before implementation of any changes.

TORCMEK was reviewed and approved by the NRES Committee London – Chelsea, Research Ethics Committee, United Kingdom (REF: 15/LO/0404) and the MHRA (EudraCT REF: 2014-002613-31).

4.4 STUDY POPULATION

The study planned to recruit between 3 and 18 patients into its Ib phase, depending on the number of dose levels and schedules to be explored as well as the resulting toxicity experienced. 16 patients per cohort were planned for the phase IIa expansion cohorts and 30 for the mixed tumour type cohort (minimum of 5 in each tumour type).

4.4.1 *Inclusion Criteria*

Each patient had to meet **all of the following inclusion criteria** to be enrolled in the study:

1. Written informed consent prior to admission to this study
2. Age ≥18 years
3. ECOG performance status 0 or 1
4. Life expectancy ≥12 weeks
5. At least one lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements
6. Radiological or clinical evidence of disease progression
7. Formalin fixed, paraffin embedded tumour sample from the primary or recurrent cancer for central testing
8. Adequate haematologic and end organ function within 7 days prior to the first study treatment.
9. Female patients of child-bearing potential were eligible, provided they had a negative serum or urine pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible. Women of reproductive potential had to agree to use adequate contraception beginning two weeks before the first dose of investigational product and until 4 weeks after the discontinuation of treatment. Men of reproductive potential had to agree to use adequate contraception beginning two weeks before the first dose of investigational product and for 12 weeks after the discontinuation of treatment. Adequate contraception methods included: intrauterine device [IUD], birth control pills unless clinically contraindicated, or a barrier device.

Inclusion Criteria unique to the Dose Escalation Part (phase Ib part)

1. Histologically or cytologically advanced solid tumour limited to:

a. Tumour types with frequent activation of MAPK and/or PI3K pathways (pancreatic, thyroid, endometrial, renal, breast or ovarian carcinoma, colorectal cancer, NSCLC or melanoma) OR

b. Tumours with known alteration in ≥1 gene involved in PI3K/AKT/mTOR or Ras/MEK pathway signalling, such as: KRAS, NRAS, BRAF, PIK3CA, PTEN, AKT, LKB1, EGFR, FGFR, HER2, MET, RET, KIT, NF1

2. Metastatic or locally advanced disease, which is refractory to conventional treatment or for which no conventional therapy exists; locally recurrent disease had to be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible).

Inclusion Criteria unique to the lung cancer dose expansion cohorts (phase IIa part)

1. Histologically confirmed NSCLC
2. Stage III disease that was unsuitable to radio-chemotherapy or Stage IV disease or recurrent NSCLC; recurrent disease had to be amenable to resection or radical radiotherapy with curative intent.
3. Prior chemotherapy and/or, if indicated/accessible, EGFR-directed or ALK-directed therapy for advanced disease

Inclusion Criteria unique to the TNBC dose expansion cohort (Phase IIa)

1. Histologically confirmed TNCB.
2. Metastatic or locally recurrent disease; locally recurrent disease had to be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible).
3. Prior chemotherapy for advanced disease

Inclusion Criteria unique to the mixed tumour types dose expansion cohort (Phase IIa)

1. Histologically or cytologically confirmed solid tumours limited to:
   a) Uveal melanoma. Patients must must have received prior treatment with immune checkpoint inhibitor OR
   b) Colorectal cancer with RAS mutations. Patients must have experienced disease progression or be intolerant to at least two systemic chemotherapy regimens (must have included fluroropyrimidines, irinotecan, and oxaliplatin); adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease if the participant had disease recurrence within 6 months of completion; disease progression must have occurred within 3 months of the last systemic therapy administration OR
   c) Low grade serous ovarian cancer (LGSOC) with KRAS mutations. LGSOC is defined as tumours previously classified as grade 1, and most of those classified as grade 2 according to the old system cancers (LGSOCs)
   OR
   d) HER2-positive tumours with 3+ intensity on IHC staining for HER2 or amplification of the HER2 gene on ISH with at least 2 lines of HER2 directed therapy.
   e) ER+ve breast cancer resistant to endocrine therapy (previous chemotherapy treatment is not essential).

4.4.2 *Exclusion Criteria*

Patients meeting **any of the following exclusion criteria** were not enrolled in the study.

1. Symptomatic CNS involvement or CNS involvement requiring steroid therapy; patients with treated brain metastases that are asymptomatic and have been clinically stable for 1 month will be eligible for protocol participation
2. Prior chemotherapy, biological therapy, radiation therapy, immunotherapy and, other anticancer agents and within 21 days of starting study treatment (not including palliative radiotherapy at focal sites)
3. Any unresolved toxicity > CTCAE Grade 1 from previous anti-cancer therapy, with the exception of alopecia
4. Current refractory nausea and vomiting, chronic gastrointestinal disease or inability to swallow the

formulated product or previous significant bowel resection that would preclude adequate absorption of the study medication

5. Significant cardiovascular disease
6. QTc prolongation defined as a QTc interval >470 msecs
7. Concomitant medications known to prolong QT interval
8. Patients receiving concomitant immunosuppressive agents or chronic systemic corticosteroids (≥10 mg prednisolone or an equivalent dose of other anti-inflammatory corticosteroids) use for ≥28 days at the time of study entry except in cases outlined below: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed. Patients on stable low dose (<10 mg prednisolone or an equivalent dose of other anti-inflammatory corticosteroids) of corticosteroids for at least two weeks before registration are allowed
9. Evidence of interstitial fibrotic lung disease (bilateral, diffuse, parenchymal lung disease)
10. Clinically significant abnormalities of glucose metabolism.
11. Ophthalmological conditions as follows:
    a. Intra-ocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intra-ocular pressure)
    b. Current or past history of central serous retinopathy or retinal vein occlusion
12. Exposure to potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) BCRP if taken within the stated washout periods before the first dose of study treatment
13. Exposure to sensitive or narrow therapeutic range substrates of the drug metabolising enzymes CYP2C9, CYP2C19, CYP2D6 or the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K within the appropriate wash-out period before the first dose of study treatment and until 2 weeks after the last dose of treatment.
14. Active second malignancy (except non-melanomatous skin cancer): active secondary malignancy is defined as a current need for cancer therapy or a high possibility (>30%) of recurrence during the study.
15. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV)
16. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
17. Psychological, familial, sociological or geographical conditions that do not permit compliance with the study protocol.
18. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug ≤30 days prior to study entry depending on the half-life of the investigational drug and/or guidance issued by the TORCMEK IMP manufacturer. Please contact the TORCMEK Coordinating team for further information.

Exclusion Criteria unique to the dose expansion cohorts (phase IIa part)

1. Prior treatment with PI3K inhibitors, AKT inhibitors, mTOR inhibitors (prior mTOR inhibitor treatment allowed for ER+ve breast cancer patients only) or MEK, Ras or Raf inhibitors.
2. Prior radiotherapy to the indicator lesion(s); Newly arising lesions in previously irradiated areas are accepted

4.5 STUDY TREATMENTS

4.5.1 *Investigational Product(s)*

AZD2014 and Selumetinib were the IMPs in this study. Both AZD2014 and Selumetinib are tablets administered orally.

4.5.2 *Dosage and Administration*

Phase Ib investigated two different dosing schedules of AZD2014: a continuous daily schedule (CC-Schedule) and an intermittent schedule of 2 days on and 5 days off treatment (IC-Schedule). The dose of selumetinib remained unchanged in both schedules. Dose escalation did not exceed the maximum tolerated doses (MTDs) which have been established for each drug at the selected schedules (Table 1).

Table 1: Dose escalation schedules

	Continuous/Continuous Schedule (CC)			**Intermittent/Continuous Schedule (IC)**		
	Cohort Name	**AZD2014** Continuous daily [mg BD]	**Selumetinib** Continuous daily [mg BD]	**Cohort Name**	**AZD2014** 2 days on/5 days off [mg BD]	**Selumetinib** Continuous daily [mg BD]
1st Dose level	C1C (to be started after I1C has been completed)	25	75	I1C	50	75
2nd Dose level	C2C	35	75	I2C	100	75
3rd Dose level	C3C	50	75	I3C	125	75

A third additional schedule of combined intermittent selumetinib (3 days on and 4 days off treatment) with intermittent AZD2014 (II-Schedule) was initially included to be considered if escalation of the AZD2014 dose in the IC-Schedule is not feasible with the corresponding continuous selumetinib regimen. This schedule was not initiated.

4.5.3 *Method of Treatment Assignment*

Phase Ib followed a standard 3+3 design. Treatment schedule and doses were assigned at registration according to the dose escalation scheme. Doses were not escalated intra-individually. Dose escalation and determination of the MTD was based on the occurrence of DLTs during the first 21 days of treatment.

DLTs were defined as:

- Any grade ≥3 non-haematological toxicity (excluding nausea, vomiting, or diarrhoea)
- Grade 3 nausea, vomiting or diarrhoea lasting ≥48 hours despite supportive care or any Grade 4 nausea, vomiting or diarrhoea
- Grade 4 neutropenia lasting ≥5 days or febrile neutropenia
- Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia
- Inability to receive at least 75% of the planned doses due to unresolved toxicity, or
- Any treatment delays for ≥14 days due to unresolved toxicity

Phase IIa patients were assigned to the relevant tumour cohort based on their tumour type, as per the eligibility criteria.

4.5.4 *Blinding*

This was not a blinded study.

5 RESULTS: STUDY POPULATION

5.1 DISPOSITION OF PATIENTS

From July 2015 to July 2018, 80 patients were screened for this trial (30 for Phase Ib and 50 for Phase IIa). Of these, 61 patients were recruited into the study from 4 sites in the United Kingdom, 25 into phase Ib and 36 into phase IIa.

5.2 OVERVIEW OF ANALYSIS POPULATIONS

Evaluable Population: This population included all patients enrolled into the trial who completed the first 2 cycles of treatment or progressed within the first 2 cycles of treatment, regardless of whether they were later found to be ineligible or a protocol violator. Efficacy analyses were performed on the evaluable population.

Maximum Tolerated Dose (MTD) Population: This population included all patients enrolled into the trial who completed the first 21 days of treatment without dose modification (delays, dose reductions) or experienced a DLT during the first 21 days of treatment.

Safety Set (SS) Population: This population included all patients enrolled into the trial who received at least one dose of study treatment. All safety analyses were performed on the SS population.

5.3 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

Table 2: Patient demographics and disease characteristics at baseline, by phase (Safety Set Population)

	Phase Ib [a] (N=25)	Phase IIa [b] (N=36)
Age (years), median (range)	55 (35 – 76)	64 (40 – 73)
Age category (years), n (%)		
18 to 64	20 (80)	20 (56)
65 to 84	5 (20)	16 (44)
Gender, n (%)		
Female	15 (60)	25 (69)
Male	10 (40)	11 (31)
Number of previous anti-tumour treatments, n (%)		
1	1 (4)	1 (3)
2	3 (12)	6 (17)
3 or more	21 (84)	29 (81)
Tumour grade, n (%)		
G1	1 (4)	0
G2	4 (16)	1 (3)
G3	17 (68)	21 (58)
Not known	3 (14)	14 (39)
Tumour lymph node status, n (%)		
N0	8 (32)	12 (33)
N1	9 (36)	8 (22)
N2	5 (20)	8 (22)
N3	2 (8)	3 (8)
N4	1 (4)	1 (3)
Not known	0	4 (11)
ECOG, n (%)		
0 - Fully Active	10 (40)	8 (22)
1 - Ambulatory, capable of light work	15 (60)	28 (78)

ECOG = Eastern cooperative oncology group. RP2D = Recommended phase 2 dose.
[a] These patients received either one of the following: I1C, I2C, I3C, C1C, C2C and C3C. [b] These patients receive the RP2D of I3C. N= Number of patients in the SS population for the specified population.

6 RESULTS: DOSE LIMITING TOXICITIES

DLTs presented for all patients in phase Ib of the study who completed the first 21 days of treatment without dose modifications (delays, dose reductions) or who experienced DLT during the first 21 days of treatment. Table 3 presents all AEs that were deemed to be DLTs at study safety review committee meetings.

Table 3: Phase Ib DLT, listed by patient (MTD population).

Dose Level	CTCAE v4.03 PT	Grade	Is it related to study medication?	Is this an SAE?
C2C	Mucositis	3	Yes	No
C2C	Dizziness	3	No	No
C2C	Rash	3	Yes	No
C3C	Mucositis	3	Yes	No
C3C	Aspartate aminotransferase increased	3	Yes	No

CTCAE = Common toxicity criteria for adverse events. DLT = Dose limiting toxicities. MTD = Maximum tolerated dose. PT = Preferred term. SAE = Serious adverse event.

Table has been sorted by dose level and then by patient. Each event corresponds to an individual patient.

7 RESULTS: EFFICACY

7.1 PRIMARY EFFICACY ENDPOINT

Disease Control (DC) was defined as the number of patients with at least one confirmed response of complete response (CR) or partial response (PR) or maintained stable disease (SD) for at least 12 weeks. DCR was defined as the number of patients with a DC divided by the number of patients analysed. DCR analyses was carried out on the evaluable population. An estimate of the DCR and 95% CIs were calculated. Table 4 presents the results of this analysis.

Table 4: Disease Control Rate (DCR), by dose expansion cohort and for all RP2D patients (evaluable population).

	TNBC Patients [a] (N=4)	SCLC Patients [a] (N=5)	NSCLC with KRAS mutations Patients [a] (N=3)	NSCLC with wild-type KRAS Patients [a] (N=7)	Mixed tumour types Patients [a, b] (N=6)	All Phase IIa Patients [a] (N=25)	RP2D Patients [c] (N=28)
Patients with DC [d], n (%)	0	3 (60)	2 (67)	1 (14)	1 (17)	5 (20)	9 (32)
DCR % (95% CI)	-	21.9 (14.7–94.7)	66.7 (9.4 – 99.2)	14.3 (0.4 – 57.9)	16.7 (0.4 – 64.1)	20.0 (6.8 – 40.7)	32.1 (15.9–52.4)

CI = Confidence interval. DC = Disease control. DCR = Disease control rate. FAS = Full analysis set. NSCLC = Non-squamous cell lung cancer. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.
[a] These patients receive the RP2D of I3C.
[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.
[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).
[d] RECIST version 1.1 disease control is based on overall visit response, and thus not programmatically derived from Target, Non Target and New Lesions.
N = Number of patients in the evaluable population for the specified population.

7.2 SECONDARY EFFICACY ENDPOINTS

7.2.1 *Objective Response Rate*

Confirmed response was defined as the number of patients with at least one confirmed response of CR or PR. Unconfirmed response was defined as the number of patients with at least one response of CR or PR that was not confirmed. ORR was defined as the number of patients with a confirmed response divided by the number of patients with measurable disease at baseline. ORR analyses were performed on the evaluable population and are presented in Table 5.

Table 5: ORR by dose expansion cohort and for all recommended phase 2 dose (RP2D) patients (Evaluable Population)

	TNBC [a] (N=4)	SCLC [a] (N=5)	NSCLC with KRAS mutations [a] (N=3)	NSCLC with wild-type KRAS [a] (N=7)	Mixed tumour types [a, b] (N=6)	All Phase IIa [a] (N=25)	RP2D patients [c] (N=28)
Patients with confirmed response, n (%)	0	0	1 (33)	1 (14)	0	2 (8)	2 (7)
Patients with no confirmed but an unconfirmed response, n (%)	0	0	0	0	0	0	0
Patients with unconfirmed response due to missing subsequent scans, n (%)	0	0	0	0	0	0	0
Patients with unconfirmed response due to subsequent scans not confirming, n (%)	0	0	0	0	0	0	0
Patients with no confirmed and no unconfirmed response, n (%)	4 (100)	5 (100)	2 (67)	6 (86)	6 (100)	23 (92)	26 (93)
ORR, % (95% CI)	-	-	33.3 (0.8 – 90.6)	14.3 (0.4 – 57.9)	-	8.0 (1.0 – 26.0)	7.1 (0.9 – 23.5)

CI = Confidence interval. CR = Complete response. NSCLC = Non-squamous cell lung cancer. ORR = Objective response rate. PR = Partial response. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.
[a] These patients receive the RP2D of I3C.
[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.
[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).
[d] RECIST version 1.1 response is based on overall visit response, and thus not programmatically derived from Target, Non Target and New Lesions.
N = Number of patients in the evaluable population for the specified population with measurable disease at baseline.

7.2.2 *Progression Free Survival*

PFS was calculated using the Kaplan-Meier technique and was defined as the time from the date of registration to the date of first documented disease progression (using RECIST v1.1) or death from any cause, whichever occurs first. For patients who had not died or experienced disease progression at the time of analysis, PFS was censored on the last date the patient was known to be progression-free. PFS analyses was carried out on the evaluable population and are presented in Table 6.

Table 6: PFS by dose expansion cohort and for all recommended phase 2 dose (RP2D) patients (Evaluable Population)

	TNBC Patients [a] (N=4)	SCLC Patients [a] (N=5)	NSCLC with KRAS mutations Patients [a] (N=3)	NSCLC with wild-type KRAS Patients [a] (N=7)	Mixed tumour types Patients [a, b] (N=6)	All Phase IIa Patients [a] (N=25)	RP2D Patients [c] (N=28)
Total events, n (%)	3 (75)	3 (60)	2 (33)	5 (71)	6 (100)	19 (76)	22 (79)
RECIST progression [d], n (%)	3 (100)	1 (33)	2 (100)	3 (60)	5 (83)	14 (74)	17 (77)
Death in the absence of progression, n (%)	0	2 (67)	0	2 (40)	1 (17)	5 (26)	5 (23)
Censored patients, n (%)	1 (25)	2 (40)	1 (67)	2 (29)	0	6 (24)	6 (21)
PFS (months), median (95% CI)	1.8 (1.7–NR)	5.3 (3.9 – NR)	9.7 (3.0 – NR)	3.0 (1.4–NR)	2.8 (1.2–NR)	3.5 (2.8–5.3)	3.5 (2.8–5.3)

CI = Confidence interval. NR = Not reached. NSCLC = Non-squamous cell lung cancer. PFS = Progression-free survival. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.
[a] These patients receive the RP2D of I3C.
[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.
[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).
[d] RECIST version 1.1 progression is based on overall visit response, and thus not programmatically derived from Target, Non Target and New Lesions.
N = Number of patients in the evaluable population for the specified population.

7.2.3 *Duration of Response*

Duration of Response (DoR) was calculated using the Kaplan-Meier technique. For patients with an OR, DoR was defined as the time from the date of first documented confirmed CR or confirmed PR to the date of first documented disease progression (using RECIST v1.1) or death from any cause, whichever occurs first. For patients with an OR who had not died or experienced disease progression at the time of analysis, DoR was censored on the last date the patient was known to be progression-free. Analyses were carried out on the evaluable population and presented in Table 7.

Table 7: Duration of response (DoR), by dose expansion cohort and for all recommended phase 2 dose (RP2D) patients (Evaluable Population)

	TNBC [a] (N=0)	SCLC [a] (N=0)	NSCLC with KRAS mutations [a] (N=1)	NSCLC with wild-type KRAS [a] (N=1)	Mixed tumour types [a, b] (N=0)	All Phase IIa [a] (N=2)	RP2D [c] (N=2)
Total events, n (%)	-	-	0	0	-	0	0
RECIST progression [d], n (%)	-	-	0	0	-	0	0
Death in the absence of progression, n (%)	-	-	0	0	-	0	0
Censored patients, n (%)	-	-	1 (100)	1 (100)	-	2 (100)	2 (100)
Duration of response (months), median (95% CI)	-	-	NR (NR – NR)	NR (NR – NR)	-	NR (NR – NR)	NR (NR – NR)

CI = Confidence interval. CR = Complete response. DoR = Duration of response. NR = Not reached. NSCLC = Non-squamous cell lung cancer. OR = Objective response. PR = Partial response. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.

[a] These patients receive the RP2D of I3C.

[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.

[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).

[d] RECIST version 1.1 progression is based on overall visit response, and thus not programmatically derived from Target, Non Target and New Lesions.

N = Number of patients in the evaluable population for the specified population with an OR.

7.2.4 *Duration of Disease Control*

Duration of disease Control (DoDC) was calculated using the Kaplan-Meier technique. For patients with DC, DoDC was defined as the time from registration to disease progression or death from any cause whichever occurs first. Analyses was performed on the evaluable population and presented in Table 8.

Table 8: Duration of disease control (DoDC), by dose expansion cohort and for all recommended phase 2 dose (RP2D) patients (Evaluable Population)

	TNBC [a] (N=0)	SCLC [a] (N=3)	NSCLC with KRAS mutations [a] (N=2)	NSCLC with wild-type KRAS [a] (N=1)	Mixed tumour types [a, b] (N=1)	All Phase IIa [a] (N=7)	RP2D [c] (N=9)
Total events, n (%)	-	2 (67)	1 (50)	0	1 (100)	4 (57)	6 (67)
RECIST progression [d], n (%)	-	1 (50)	1 (100)	0	1 (100)	3 (75)	5 (83)
Death in the absence of progression, n (%)	-	1 (50)	0	0	0	1 (25)	1 (17)
Censored patients, n (%)	-	1 (33)	1 (50)	1 (100)	0	3 (43)	3 (33)
Duration of disease control (months), median (95% CI)	-	5.3 (5.3 – NR)	9.7 (NR – NR)	NR (NR – NR)	NR (NR – NR)	8.5 (5.3 – NR)	8.1 (5.3 – NR)

CI = Confidence interval. DC = Disease control. DoDC = Duration of disease control. NR = Not reached. NSCLC = Non-squamous cell lung cancer. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.

[a] These patients receive the RP2D of I3C.

[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.

[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).

[d] RECIST version 1.1 progression is based on overall visit response, and thus not programmatically derived from Target, Non Target and New Lesions.

N = Number of patients in the evaluable population for the specified population with DC.

7.2.5 *Overall Survival*

Overall survival (OS) was calculated using the Kaplan-Meier technique and was defined as the time from the date of registration to the date of death due to any cause. For patients who had not died at the time of analysis, OS was censored at the date of last contact. OS analyses was carried out on the evaluable population and presented in Table 9.

Table 9: OS by dose expansion cohort and for all RP2D patients (evaluable population).

	TNBC Patients [a] (N=4)	SCLC Patients [a] (N=5)	NSCLC with KRAS mutations Patients [a] (N=3)	NSCLC with wild-type KRAS Patients [a] (N=7)	Mixed tumour types Patients [a, b] (N=6)	All Phase IIa Patients [a] (N=25)	RP2D Patients [c] (N=28)
Total deaths, n (%)	4 (100)	5 (100)	3 (100)	7 (100)	6 (100)	25 (100)	28 (100)
Censored patients, n (%)	0	0	0	0	0	0	0
OS (months), median (95% CI)	5.6 (4.3 – NR)	8.5 (3.9 – NR)	23.2 (3.5 – NR)	8.0 (3.7 – 22.8)	6.5 (1.4 – NR)	8.4 (5.6 – 11.8)	8.5 (6.5 – 12.1)

CI = Confidence interval. NR = Not reached. NSCLC = Non-squamous cell lung cancer. OS = Overall survival. RP2D = Recommended phase 2 dose. SCLC = Squamous cell lung cancer. TNBC = Triple negative breast cancer.
[a] These patients receive the RP2D of I3C.
[b] Mixed tumour types consists of uveal melanoma, colorectal cancer, low grade serious ovarian cancer, HER2+ and ER+ breast cancer.
[c] RP2D patients consists of all patients treated at the RP2D (regardless of whether they are within phase Ib or IIa).
N = Number of patients in the evaluable population for the specified population.

8 RESULTS: SAFETY

AEs were collected from the time of consent to the safety visit (28 days ± 3 days from last IMP administration). Analyses presented in section 8 is based on the Safety Set population.

Table 10: AE summary by phase (Safety Set Population)

	Phase Ib [a] (N=25)	Phase IIa [b] (N=36)
AEs reported, n	444	600
Patients with at least one AE, n	25	36
AEs per patient [c], median (range)	11 (5 – 52)	13 (1 – 50)
≥ Grade 3 AEs reported, n	40	59
Patients with at least one ≥ Grade 3 AE, n	14	25
≥ Grade 3 AEs per patient [c], median (range)	2 (1 – 8)	2 (1 – 5)
AEs related to study medication, n	239	356
Patients with at least one AE related to study medication, n	24	34
AEs related to study medication per patient [c], median (range)	7 (1 – 36)	9 (1 – 37)
SAEs reported, n	22	30
Patients with at least one SAE, n	12	17
SAEs per patient [c], median (range)	1 (1 – 5)	1 (1 – 4)
Non-serious AEs reported, n	422	570
Patients with at least one non-serious AE, n	25	36
Non-serious AEs per patient [c], median (range)	11 (5 – 50)	12 (1 – 48)

AE = Adverse events. RP2D = Recommended phase 2 dose. SAE = Serious adverse event.
[a] These patients receive either one of the following: I1C, I2C, I3C, C1C, C2C and C3C.
[b] These patients receive the RP2D of I3C.
[c] This counts each instance once e.g. if a patient has the same term three times this is counted as 3 instances.
Related to study medication means related to either AZD2014 or Selumetinib.
N = Number of patients in the Safety Set population for the specified population.

8.1 SERIOUS ADVERSE EVENTS

8.1.1 *Phase Ib SAEs*

Tables 11 and 12 below present all SAEs and those SAEs related to study treatment respectively. SAEs have been grouped by preferred term and the worst toxicity for each patient of each SAE preferred term has been presented. Related SAEs include those classified by the PI as likely or possibly related to IMP.

Table 11: Phase Ib SAEs by preferred term (Safety Population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=25)
Infection	0	1	2	0	1	4
Gastrointestinal haemorrhage	0	0	2	0	0	2
Vomiting	0	0	2	0	0	2
Hyponatraemia	0	0	0	1	0	1
Anaemia	0	0	1	0	0	1
Diarrhoea	0	0	1	0	0	1
Drug Hypersensitivity	0	0	1	0	0	1
Nervous system disorder	0	0	1	0	0	1
Tumour thrombosis	0	0	1	0	0	1
Cardiac failure congestive	0	1	0	0	0	1
Dehydration	0	1	0	0	0	1
Hypoalbuminemia	0	1	0	0	0	1
Oedema	0	1	0	0	0	1
Dizziness	1	0	0	0	0	1
Urinary tract disorder	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term. SAE = Serious adverse event.
[a] These patients receive either one of the following: I1C, I2C, I3C, C1C, C2C and C3C.
N = Number of patients in the Safety Set population for the specified population.

Table 12: Phase Ib SAE occurrences related to study medication by preferred term (Safety Set Population).

CTCAE v4.03 PT	Total (N=25) [a]
Cardiac failure congestive	1
Dehydration	1
Diarrhoea	1
Dizziness	1
Drug Hypersensitivity	1
Hypoalbuminemia	1
Hyponatraemia	1
Infection	1
Oedema	1
Urinary tract disorder	1
Vomiting	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. G = Grade. PT = Preferred term. SAE = Serious adverse event.
[a]These patients receive either one of the following: I1C, I2C, I3C, C1C, C2C and C3C.
All occurrences of each SAE related to treatment PT have been reported i.e. this may include multiple counts per patient of the same SAE related to treatment PT.
N = Number of patients in the Safety Set population for the specified population.

8.1.2 *Phase IIa SAEs*

Tables 13 and 14 below present all SAEs and those SAEs related to study treatment respectively. SAEs have been grouped by preferred term. Related SAEs include those classified by the PI as likely or possibly related to IMP.

Table 13: Phase IIa SAEs by preferred term (Safety Population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36) [a]
Infection	0	1	7	0	1	9
Pyrexia	0	1	2	0	0	3
Vomiting	0	1	1	0	0	2
Embolism	0	0	0	1	0	1
Acute coronary syndrome	0	0	1	0	0	1
Anaemia	0	0	1	0	0	1
Arrhythmia	0	0	1	0	0	1
Confusional state	0	0	1	0	0	1
Dehydration	0	0	1	0	0	1
Dysphagia	0	0	1	0	0	1
Mental disorder	0	0	1	0	0	1
Mucositis	0	0	1	0	0	1
Rash	0	0	1	0	0	1
Fall	1	0	0	0	0	1
Troponin T increased	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term. RP2D = Recommended phase 2 dose. SAE = Serious adverse event.
[a] These patients received the RP2D of I3C.
The worst toxicity for each patient of each SAE PT has been reported.
N = Number of patients in the Safety Set population for the specified population.

Table 14: Phase IIa SAE occurrences related to IMP by preferred term (Safety Population)

CTCAE v4.03 PT	Total (N=36) [a]
Pyrexia	3
Acute coronary syndrome	1
Anaemia	1
Arrhythmia	1
Infection	1
Mucositis	1
Rash	1
Troponin T increased	1
Vomiting	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. G = Grade. PT = Preferred term. RP2D = Recommended phase 2 dose. SAE = Serious adverse event.
[a] These patients receive the RP2D of I3C.
All occurrences of each SAE related to treatment PT have been reported i.e. this may include multiple counts per patient of the same SAE related to treatment PT.
Related is defined as likely or possibly related.
N = Number of patients in the Safety Set population for the specified population.

8.2 NON-SERIOUS ADVERSE EVENTS

Tables 15 and 16 below present all AEs and those AEs related to study treatment respectively. AEs have been grouped by preferred term. Related AEs include those classified by the PI as likely or possibly related either AZD2014 or selumetinib.

8.2.1 *Phase Ib AEs*

Table 15: Phase Ib AEs by preferred term (safety set population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=25)[a]
Rash	8	10	3	0	0	21
Fatigue	11	7	2	0	0	20
Nausea	9	8	0	0	0	17
Diarrhoea	10	3	2	0	0	15
Decreased appetite	11	2	0	0	0	13
Mucositis	7	3	2	0	0	12
Infection	0	7	2	0	1	10
Vomiting	6	2	2	0	0	10
Musculoskeletal pain	5	4	0	0	0	9
Dyspnoea	5	3	0	0	0	8
Blood creatine phosphokinase increased	3	2	1	1	0	7
Abdominal pain	6	1	0	0	0	7
Oedema	6	1	0	0	0	7
Pruritus	5	1	0	0	0	6
Urinary tract disorder	6	0	0	0	0	6
Constipation	4	1	0	0	0	5
Sleep disorder	4	1	0	0	0	5
Cough	5	0	0	0	0	5
Dyspepsia	5	0	0	0	0	5
Aspartate aminotransferase increased	1	1	2	0	0	4
Skin injury	2	2	0	0	0	4
Pain	3	1	0	0	0	4
Pyrexia	3	1	0	0	0	4
Dry mouth	4	0	0	0	0	4
Gastrointestinal disorder	2	0	0	1	0	3
Dizziness	1	1	1	0	0	3
Alopecia	2	1	0	0	0	3
Dry skin	2	1	0	0	0	3
Eye disorder	2	1	0	0	0	3
Dysgeusia	3	0	0	0	0	3
Flu like symptoms	3	0	0	0	0	3
Paraesthesia	3	0	0	0	0	3
Visual impairment	3	0	0	0	0	3
Gastrointestinal haemorrhage	0	0	2	0	0	2
Anaemia	0	1	1	0	0	2
Blood alkaline phosphatase increased	0	1	1	0	0	2
Alanine aminotransferase increased	1	0	1	0	0	2
Arthralgia	1	1	0	0	0	2
Chills	1	1	0	0	0	2
Hypertension	1	1	0	0	0	2
Neuralgia	1	1	0	0	0	2
Headache	2	0	0	0	0	2
Lymphoedema	2	0	0	0	0	2
Mental Disorder	2	0	0	0	0	2
Neuropathy peripheral	2	0	0	0	0	2
Hyponatraemia	0	0	0	1	0	1
Blood creatinine increased	0	0	1	0	0	1
Drug Hypersensitivity	0	0	1	0	0	1
Nervous system disorder	0	0	1	0	0	1

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=25)[a]
Syncope	0	0	1	0	0	1
Tumour thrombosis	0	0	1	0	0	1
Cardiac failure congestive	0	1	0	0	0	1
Dehydration	0	1	0	0	0	1
Diabetes mellitus	0	1	0	0	0	1
Dysphagia	0	1	0	0	0	1
Embolism	0	1	0	0	0	1
Hypoalbuminemia	0	1	0	0	0	1
Inferior vena caval occlusion	0	1	0	0	0	1
Nail disorder	0	1	0	0	0	1
Pleural effusion	0	1	0	0	0	1
Weight decreased	0	1	0	0	0	1
Abdominal distension	1	0	0	0	0	1
Chest discomfort	1	0	0	0	0	1
Cold sweat	1	0	0	0	0	1
Confusional state	1	0	0	0	0	1
Dysphonia	1	0	0	0	0	1
Ejection fraction decreased	1	0	0	0	0	1
Epistaxis	1	0	0	0	0	1
Haemorrhoids	1	0	0	0	0	1
Hepatomegaly	1	0	0	0	0	1
Mental disorder	1	0	0	0	0	1
Oropharyngeal Pain	1	0	0	0	0	1
Palpitations	1	0	0	0	0	1
Tinnitus	1	0	0	0	0	1
Vaginal discharge	1	0	0	0	0	1
Wound	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term.
[a] These patients receive either one of the following: I1C, I2C, I3C, C1C, C2C and C3C.
The worst toxicity for each patient of each AE PT has been reported.
AEs have been grouped by PT.
N = Number of patients in the Safety Set population for the specified population.

Table 16: Phase Ib AEs related to study medication by preferred term (Safety set population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=25) [a]
Rash	7	10	3	0	0	20
Diarrhoea	8	3	2	0	0	13
Nausea	8	5	0	0	0	13
Fatigue	7	4	1	0	0	12
Mucositis	5	3	2	0	0	10
Vomiting	6	0	1	0	0	7
Blood creatine phosphokinase increased	1	2	1	1	0	5
Decreased appetite	5	0	0	0	0	5
Pruritus	3	1	0	0	0	4
Aspartate aminotransferase increased	1	0	2	0	0	3
Infection	0	2	1	0	0	3
Skin injury	2	1	0	0	0	3
Dry mouth	3	0	0	0	0	3
Alanine aminotransferase increased	1	0	1	0	0	2
Dizziness	1	1	0	0	0	2
Dry skin	1	1	0	0	0	2
Dyspnoea	1	1	0	0	0	2
Eye disorder	1	1	0	0	0	2
Pyrexia	1	1	0	0	0	2
Constipation	2	0	0	0	0	2
Dysgeusia	2	0	0	0	0	2

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=25) [a]
Dyspepsia	2	0	0	0	0	2
Paraesthesia	2	0	0	0	0	2
Urinary tract disorder	2	0	0	0	0	2
Visual impairment	2	0	0	0	0	2
Hyponatraemia	0	0	0	1	0	1
Blood alkaline phosphatase increased	0	0	1	0	0	1
Drug Hypersensitivity	0	0	1	0	0	1
Alopecia	0	1	0	0	0	1
Anaemia	0	1	0	0	0	1
Arthralgia	0	1	0	0	0	1
Cardiac failure congestive	0	1	0	0	0	1
Dehydration	0	1	0	0	0	1
Dysphagia	0	1	0	0	0	1
Embolism	0	1	0	0	0	1
Hypoalbuminemia	0	1	0	0	0	1
Nail disorder	0	1	0	0	0	1
Oedema	0	1	0	0	0	1
Pain	0	1	0	0	0	1
Weight decreased	0	1	0	0	0	1
Abdominal pain	1	0	0	0	0	1
Confusional state	1	0	0	0	0	1
Dysphonia	1	0	0	0	0	1
Ejection fraction decreased	1	0	0	0	0	1
Flu like symptoms	1	0	0	0	0	1
Gastrointestinal disorder	1	0	0	0	0	1
Neuropathy peripheral	1	0	0	0	0	1
Palpitations	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term.
[a] These patients receive either one of the following: I1C, I2C, I3C, C1C, C2C and C3C.
Related to study medication means related to either AZD2014 or Selumetinib.
The worst toxicity for each patient of each AE related to study medication PT has been reported.
N = Number of patients in the Safety Set population for the specified population.

8.2.2 *Phase IIa AEs*

Table 17: Phase IIa AE by preferred term (safety set population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36)[a]
Rash	7	12	8	0	0	27
Fatigue	10	10	6	0	0	26
Nausea	7	12	0	0	0	19
Mucositis	7	5	5	0	0	17
Diarrhoea	11	4	2	0	0	17
Decreased appetite	8	9	0	0	0	17
Infection	2	6	7	0	1	16
Vomiting	6	7	3	0	0	16
Dyspnoea	10	2	1	0	0	13
Constipation	8	4	0	0	0	12
Cough	9	2	0	0	0	11
Pruritis	3	5	2	0	0	10
Musculoskeletal pain	6	3	1	0	0	10
Pain	5	5	0	0	0	10
Headache	7	3	0	0	0	10
Oedema	6	3	0	0	0	9
Dyspepsia	7	2	0	0	0	9
Blood creatine phosphokinase increased	6	1	1	0	0	8
Chills	5	2	0	0	0	7
Pyrexia	2	2	2	0	0	6

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36)[a]
Dysgeusia	4	2	0	0	0	6
Dry mouth	5	1	0	0	0	6
Abdominal pain	4	0	1	0	0	5
Visual impairment	4	1	0	0	0	5
Embolism	0	0	2	1	1	4
Eye disorder	3	1	0	0	0	4
Skin injury	3	1	0	0	0	4
Urinary tract disorder	3	1	0	0	0	4
Ear disorder	4	0	0	0	0	4
Epistaxis	4	0	0	0	0	4
Arrhythmia	1	1	1	0	0	3
Mental disorder	2	0	1	0	0	3
Nail disorder	0	3	0	0	0	3
Oropharyngeal Pain	1	2	0	0	0	3
Dry skin	2	1	0	0	0	3
Alopecia	3	0	0	0	0	3
Arthralgia	3	0	0	0	0	3
Dizziness	3	0	0	0	0	3
Gastrointestinal haemorrhage	3	0	0	0	0	3
Muscle disorder	3	0	0	0	0	3
Pruritus	3	0	0	0	0	3
Dysphagia	0	1	1	0	0	2
Pleural effusion	0	1	1	0	0	2
Transaminase increased	1	0	1	0	0	2
Haemorrhoids	0	2	0	0	0	2
Weight decreased	0	2	0	0	0	2
Abdominal distension	1	1	0	0	0	2
Blood creatinine increased	1	1	0	0	0	2
Flu like symptoms	1	1	0	0	0	2
Gastrointestinal disorder	1	1	0	0	0	2
Aspartate aminotransferase increased	2	0	0	0	0	2
Sleep disorder	2	0	0	0	0	2
Thrombocytopenia	2	0	0	0	0	2
Acute coronary syndrome	0	0	1	0	0	1
Anaemia	0	0	1	0	0	1
Ascites	0	0	1	0	0	1
Confusional state	0	0	1	0	0	1
Dehydration	0	0	1	0	0	1
Fracture	0	0	1	0	0	1
Amylase increased	0	1	0	0	0	1
Ejection fraction decreased	0	1	0	0	0	1
Genital ulceration	0	1	0	0	0	1
Hypertension	0	1	0	0	0	1
Hypocalcemia	0	1	0	0	0	1
Lymphoedema	0	1	0	0	0	1
Nervous system disorder	0	1	0	0	0	1
Wound	0	1	0	0	0	1
Axillary mass	1	0	0	0	0	1
Dysphonia	1	0	0	0	0	1
Fall	1	0	0	0	0	1
Gingival bleeding	1	0	0	0	0	1
Haemoptysis	1	0	0	0	0	1
Hot flush	1	0	0	0	0	1
Hypokalaemia	1	0	0	0	0	1
Musculoskeletal Pain	1	0	0	0	0	1
Neuropathy peripheral	1	0	0	0	0	1
Palpitations	1	0	0	0	0	1
Peripheral coldness	1	0	0	0	0	1
Pleural rub	1	0	0	0	0	1

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36)[a]
Raynaud's phenomenon	1	0	0	0	0	1
Tinnitus	1	0	0	0	0	1
Troponin T increased	1	0	0	0	0	1
Tumor haemorrhage	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term. RP2D = Recommended phase 2 dose.
[a] These patients receive the RP2D of I3C.
The worst toxicity for each patient of each AE PT has been reported.
Table has been sorted in descending order by Total then by Grade 5, Grade 4, Grade 3, Grade 2, Grade 1 then alphabetically by PT.
AEs have been grouped by PT.
N = Number of patients in the Safety Set population for the specified population.
Safety Set population is defined as all patients enrolled into the trial who received at least one dose of study treatment.

Table 17: Phase IIa AEs related to study medication by preferred term (safety set population)

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36) [a]
Rash	7	12	8	0	0	27
Nausea	8	10	0	0	0	18
Fatigue	4	7	6	0	0	17
Mucositis	7	5	5	0	0	17
Vomiting	6	7	2	0	0	15
Diarrhoea	9	3	1	0	0	13
Decreased appetite	4	9	0	0	0	13
Pruritis	3	5	2	0	0	10
Blood creatine phosphokinase increased	6	1	0	0	0	7
Dry mouth	5	1	0	0	0	6
Infection	2	3	0	0	0	5
Oedema	3	2	0	0	0	5
Dysgeusia	4	1	0	0	0	5
Pyrexia	1	1	2	0	0	4
Dyspepsia	3	1	0	0	0	4
Visual impairment	3	1	0	0	0	4
Nail disorder	0	3	0	0	0	3
Dry skin	2	1	0	0	0	3
Eye disorder	2	1	0	0	0	3
Skin injury	2	1	0	0	0	3
Abdominal pain	3	0	0	0	0	3
Alopecia	3	0	0	0	0	3
Epistaxis	3	0	0	0	0	3
Arrhythmia	1	0	1	0	0	2
Transaminase increased	1	0	1	0	0	2
Oropharyngeal Pain	0	2	0	0	0	2
Pain	0	2	0	0	0	2
Blood creatinine increased	1	1	0	0	0	2
Chills	1	1	0	0	0	2
Constipation	1	1	0	0	0	2
Headache	2	0	0	0	0	2
Pruritus	2	0	0	0	0	2
Thrombocytopenia	2	0	0	0	0	2
Acute coronary syndrome	0	0	1	0	0	1
Anaemia	0	0	1	0	0	1
Dyspnoea	0	0	1	0	0	1
Amylase increased	0	1	0	0	0	1
Ejection fraction decreased	0	1	0	0	0	1
Genital ulceration	0	1	0	0	0	1
Haemorrhoids	0	1	0	0	0	1

CTCAE v4.03 PT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N=36) [a]
Hypocalcemia	0	1	0	0	0	1
Weight decreased	0	1	0	0	0	1
Wound	0	1	0	0	0	1
Arthralgia	1	0	0	0	0	1
Axillary mass	1	0	0	0	0	1
Dizziness	1	0	0	0	0	1
Dysphagia	1	0	0	0	0	1
Gastrointestinal disorder	1	0	0	0	0	1
Gastrointestinal haemorrhage	1	0	0	0	0	1
Gingival bleeding	1	0	0	0	0	1
Hypokalaemia	1	0	0	0	0	1
Muscle disorder	1	0	0	0	0	1
Peripheral coldness	1	0	0	0	0	1
Raynaud's phenomenon	1	0	0	0	0	1
Troponin T increased	1	0	0	0	0	1
Tumor haemorrhage	1	0	0	0	0	1
Urinary tract disorder	1	0	0	0	0	1

AE = Adverse event. CTCAE = Common terminology criteria for adverse events. PT = Preferred term. RP2D = Recommended phase 2 dose.
[a] These patients receive the RP2D of I3C.
The worst toxicity for each patient of each AE related to study medication PT has been reported.
AEs have been grouped by PT.
N = Number of patients in the Safety Set population for the specified population.

9 CONCLUSIONS

- The TORCMEK safety review committee agreed that the I3C schedule (125mg BD AZD2014 2 days on/ 5 days and 75mg BD selumetinib continuous daily) was the best option to take forward to the Phase IIa part of the study.
- There were overall no concerns about taking C2C (35mg BD AZD2014 continuous daily plus 75mg BD continuous daily) into a confirmatory safety Phase II study in other protocols.
- Following the decision by the IMP Manufacturer, AstraZeneca, to cease development of AZD2014, recruitment into the study stopped prematurely when only 36 patients out of 94 were recruited. Efficacy data has been presented in this report, but drawing meaningful conclusions per disease cohort was difficult.