CT084: A Phase I dose-escalation study of ATR inhibitor monotherapy with AZD6738 in advanced solid tumors (PATRIOT Part A)

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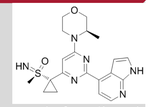
Introduction

AZD6738[1] is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related (ATR), a serine-threonine kinase which is critical in the response to DNA replication stress[2].



Many cancers have high levels of replication stress and a poorly functional G1/S DNA damage checkpoint[3]. This may render them more susceptible than normal tissues to inhibition of ATR. Pre-clinical studies have identified oncogene activation[4], hypoxia[5], ATM loss[6] and DNA damage response defects[7,8,9] as potential sensitizers to ATR inhibition, as well as sensitization to ionizing radiation[10].

We report the results of the monotherapy dose-escalation phase of the PATRIOT study of AZD6738, an orally active ATR inhibitor in patients with advanced solid tumors, the endpoints of which were MTD, safety, tolerability, pharmacokinetics (PK) and preliminary efficacy.

Objectives

Primary

- To determine the feasibility and safety of administration of single-agent AZD6738 in patients with solid tumours

Secondary

- To guide dose and schedule selection for subsequent studies of AZD6738 as a single-agent
- To assess preliminary anti-tumour activity (by RECIST response) of AZD6738

Exploratory

- To conduct pharmacodynamic studies on tumour and normal tissue.
- To assess the value of putative predictive biomarkers for response to AZD6738.

Methods

Key Inclusion Criteria

- Histologically or cytologically documented solid tumor refractory to, or for which there is no existing, conventional therapy
- Measurable disease by RECIST 1.1
- ECOG performance status of 0 or 1
- Age 18 years or over
- Adequate organ function

Key Exclusion Criteria

- Concomitant investigational medical product, or other anti-cancer therapy
- Concomitant therapy with significant modulators of CYP3A4
- Pregnant, breastfeeding or of childbearing potential
- Symptomatic CNS metastases

Table1: baseline characteristics

Demographics		Tumor Types	
Median (range) age	59 (41-80)	SCCHN	6 (23%)
Median (range) prior systemic therapy	2 (1-4)	Colorectal	6 (23%)
% Female	31	Naso-pharyngeal	2 (8%)
ECOG PS 0		Other*	12 (46%)

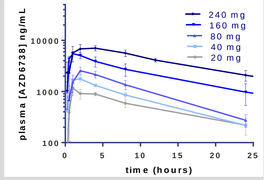
*** Adrenal cortical carcinoma, peritoneal carcinoma, mesothelioma, small bowel adenocarcinoma, unknown primary, external auditory adenocarcinoma, eccrine adenocarcinoma, esophageal SCC (all n=1)**

Results

26 patients were enrolled between July 2014 and July 2016 in a 3+3 design. Baseline characteristics are shown in table 1.

Patients received continuous twice daily (BD) dosing.

Figure 1: AZD6738 concentration-time profiles



Preliminary PK analysis

AZD6738 is rapidly orally absorbed (median t_{max} 1-5 h), with mean terminal elimination half-life 6.1-12.1 h. Following single dosing, AZD6738 exposure increased approximately proportionally with dose between 80 – 240 mg. The increase between 20 mg and 40 mg appeared to be slightly more than dose proportional (fig. 1).

Table 2: dose escalation

Dose Level (mg BD)	Evaluable (total treated)	DLTs (N)	G3-4 AEs
20	3 (3)	0	elevation GGT (1, G3)
40	3 (3)	0	nil
80	6 (7)	1	Thrombocytopenia with epistaxis (1, G3)
160	6 (6)	0	Anaemia (1, G3)
240	6 (7)	4	Thrombocytopenia (2, G4), pancytopenia (1, G4), elevated amylase (1, G3), photosensitivity (1, G3), mucositis (1, G3), anemia (1, G3)

Table 3: Treatment-related AEs affecting ≥2 participants (probable or definite)

Adverse Event	Number (%) G1-4	Number (%) G3-4
Fatigue	9 (35%)	0
Anemia	7 (23%)	3 (12%)
Nausea	4 (15%)	0
Thrombocytopenia	5 (19%)	4 (16%)
Anorexia	3 (12%)	0
Dysgeusia	3 (12%)	0
Vomiting	2 (8%)	0
Rash	2 (8%)	0

N=1 AEs: dyspnoea G1, nail changes, insomnia G2, tinnitus G1, stomatitis G2

The maximum tolerated dose was 160 mg BD.

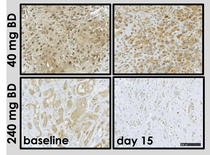
Dose-limiting toxicities were thrombocytopenia, pancytopenia and elevated amylase (table 2). All resolved on interruption of AZD6738.

Other adverse events related to AZD6738 (defined as definitely or probably related by the investigator) are shown in table 3.

Median duration taking AZD6738 was 101 days, range 30-281 days (evaluable patients only).

One patient remains on treatment, three patients discontinued due to treatment-related toxicities.

Figure 2: p[S345]Chk1 IHC



Preliminary evidence of target engagement

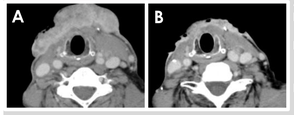
Paired biopsies were taken in a limited number of patients. Fig. 2 shows reduction in Chk1 phosphorylation at Ser-345 indicative of reduced ATR activity at 40 and 240 mg BD.

Figure 3 ATR activates Chk1

Summary of preliminary anti-tumor responses

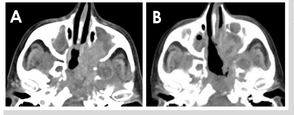
Two RECIST partial responses were observed in patients with SCCHN (fig. 4 A, B) and nasopharyngeal carcinoma (fig. 5 A, B), one confirmed.

Figure 4: Recurrent SCC head and neck



62 year old female, recurrent SCC oral cavity.
AZD6738 40 mg BD
Prior treatment: cisplatin-5FU (best response: SD); nivolumab (best response: SD).
Biomarker: Wee1 mutation with predicted functional impact. 40% Ki67 positivity
Response: PR in target lesions, new lesion on confirmation CT

Figure 5: Recurrent nasopharyngeal carcinoma



40 year-old male, recurrent undifferentiated nasopharyngeal carcinoma
AZD6738 240 mg BD
Prior treatment: cisplatin-5FU (best response: SD); vaccination study: durvalumab (best response: SD)
Biomarker: NRAS oncogenic mutation, 90% Ki67 positivity
Response: confirmed PR

Figure 6: best responses

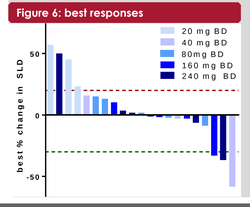
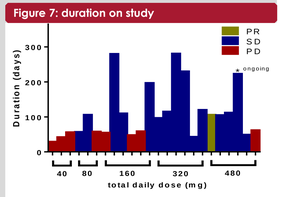


Figure 7: duration on study



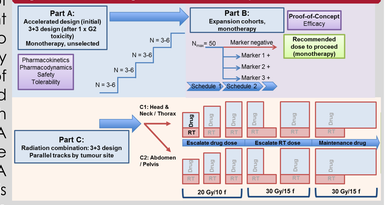
Conclusions

- AZD6738 is tolerated at 160 mg BD as continuous monotherapy.
- AZD6738 pharmacokinetics are approximately dose-proportional.
- Preliminary evidence of target engagement has been observed.
- Preliminary data suggest that monotherapy ATR inhibition may be associated with objective responses or disease stabilisation. Expansion cohorts will further examine these observations:
  - Tumor responses in patients with defective DNA damage response;
  - Tumor responses in lesions with high Ki67.

Further development

Expansion cohorts have been initiated at 160mg BD, exploring a number of alternative treatment schedules designed to offset cumulative toxicity and test efficacy of AZD6738 monotherapy and the presence of high replication stress, DNA damage response deficiencies or ATM loss. A parallel part of the study is investigating AZD6738 in combination with palliative radiotherapy.

Figure 8: overall design of the PATRIOT study



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Author Disclosures

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