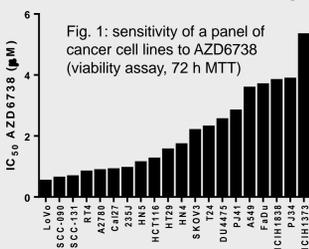
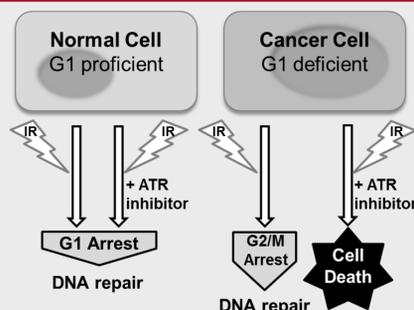


PATRIOT: A phase I study to assess the tolerability, safety and biological effects of a specific ataxia telangiectasia and Rad3-related (ATR) inhibitor (AZD6738) as a single agent and in combination with palliative radiation therapy in patients with solid tumours.

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Background

Novel strategies are required to selectively sensitize tumour cells to radiation-induced DNA damage¹. The G2 cell cycle checkpoint is an attractive target for this, as normal cells will be protected by their intact G1 checkpoint, which is lost in the majority of cancer cells. ATR is an important mediator of the G2 checkpoint. Preclinical data suggest that ATR inhibition will sensitise to DNA damaging therapies, including



RT^{2,3} (fig. 2). Single-agent activity in cancer cell lines has also been demonstrated³ (fig.1), with pre-clinical data suggesting a number of potential factors which may sensitise to ATR inhibition.

This multi-part phase 1 trial aims to assess safety and tolerability and preliminary anti-tumour activity of the ATR inhibitor AZD6738⁴ as monotherapy and in combination

with palliative RT, escalating both drug and radiation dose at a dose-fractionation relevant to radical treatment. The design aims to test a novel agent at the earliest stage of clinical development and assess safety in combination with RT, with the aim of moving to a radically-treated population if tolerated.

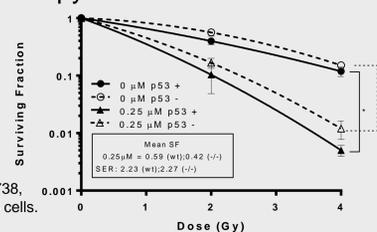


Fig. 2: radiosensitization by AZD6738, irrespective of p53 status, HCT116 cells. Clonogenic assay. * p<0.05

Study Design

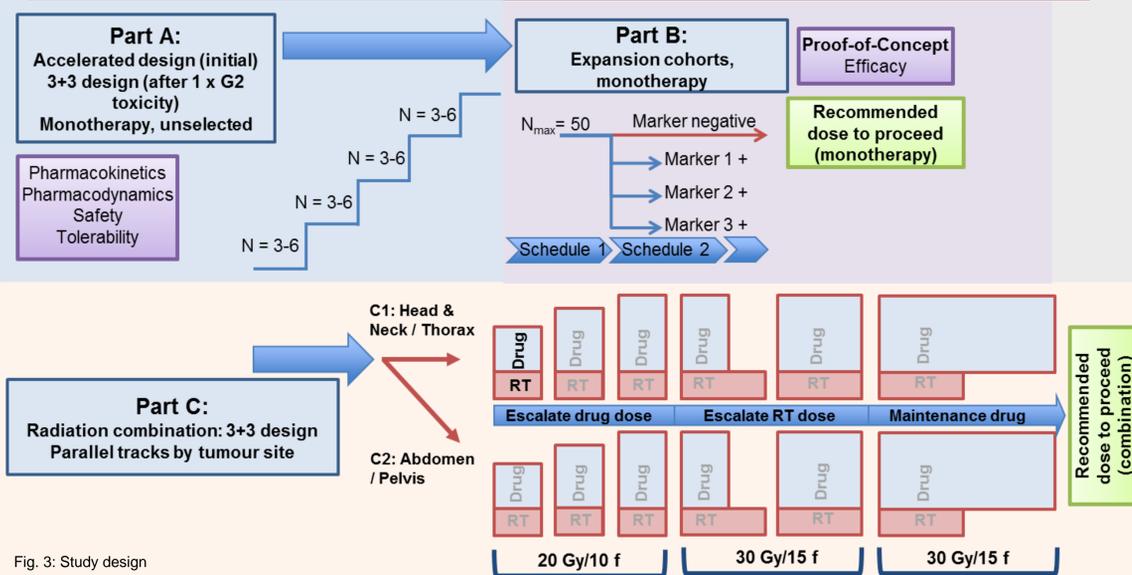


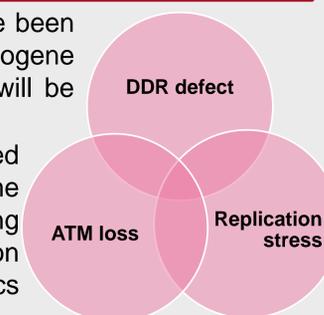
Fig. 3: Study design

The study comprises three parts (fig. 3): parts A and B will assess AZD6738 as a single agent in dose escalation to MTD (part A), followed by expansion cohorts enriched for defective DNA damage response (part B). Part C will assess AZD6738 in combination with palliative RT in which participants will receive 20 Gy in 10 fractions, with per cohort escalation of drug dose to monotherapy MTD if tolerated. At the highest tolerated combination dose, the RT dose will be escalated to 30 Gy in 15 fractions. Maintenance AZD6738 post-RT will be tested at the highest tolerated combination dose.

Enrichment for expansion cohorts

Numerous potential predictive biomarkers for ATR inhibitors have been suggested, including loss of DDR components, loss of ATM, oncogene activation, and high levels of replication stress. Fresh biopsy will be mandatory for participants entering the expansion phase.

Patients will be stratified according to the presence of impaired DNA damage response (DDR), assessed using whole-exome sequencing; high levels of replication stress, measured using immunohistochemical (IHC) markers; and loss of ATM expression on IHC. A group of participants without any of these characteristics will also be assessed.



Objectives

Primary objectives

Feasibility and safety of administration of single-agent AZD6738 in patients with solid tumours and in combination with radiotherapy in patients with solid tumours during different schedules of fractionated palliative radiotherapy.

Secondary objectives

Guide dose and schedule selection for subsequent studies of AZD6738 as a single-agent or with palliative or radical radiotherapy. Preliminary anti-tumour activity.

Key Inclusion and Exclusion Criteria

Key Inclusion criteria	Key Exclusion criteria
1. Advanced solid tumour	1. Therapy with any other investigational medical product concurrently or within 28 days
2. Documented disease progression prior to study entry and measurable disease (Part B only)	2. Investigational medicinal products, endocrine therapy, immunotherapy or chemotherapy during the previous four weeks before treatment.
3. Presence of putative markers of sensitivity to AZD6738 defined on analysis of tumour material (part B only).	3. Receiving, or having received, concomitant medications, herbal supplements and/or foods that significantly modulate CYP3A4 or P-gp activity
4. Age must be 18 years or over	4. Pregnant or breast-feeding women.
5. All acute toxic effects of any prior chemotherapy or surgical procedures must have resolved to CTCAE4 Grade ≤1. Surgery must have occurred at least 14 days prior to study enrolment.	5. Male patients with partners of child-bearing potential (unless they agree to use highly effective contraception during the trial and for six months afterwards).
6. ECOG performance status 0-1 (part A); 0-2 (parts B and C)	6. Ability to become pregnant (or already pregnant or lactating)
7. Life expectancy of at least 3 months.	7. Clinically significant cardiac disease
8. Normal organ and bone marrow function measured within 7 days prior to administration of study treatment	8. Known HIV positive or active hepatitis B or C infection
9. Signed informed consent	9. Uncontrolled active infection
10. Part B only: tumour site amenable to fresh biopsy (clinical or radiologically-guided)	10. Symptomatic and progressive or steroid-requiring brain metastases or leptomeningeal disease involvement.
11. Symptomatic disease or disease that is likely to cause symptoms within a short period of time such that palliative radiotherapy is indicated or justified (Part C only).	11. Relative hypotension (<100/60mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20mmHg
	12. Prior radiotherapy to the treatment site (Part C only).

Study Status

The study opened in August 2014. The study is dose escalating in part A and part C has opened and treated its first patient. Part B will open when dose escalation has completed.

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