ISRCTN66171897 https://doi.org/10.1186/ISRCTN66171897

A trial of AZD4547 in combination with cisplatin and capecitabine

Submission date 14/12/2011	**Recruitment status** Stopped	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/03/2012	**Overall study status** Stopped	
Last Edited 24/11/2015	**Condition category** Cancer	

Plain English summary of protocol
http://cancerhelp.cancerresearchuk.org/trials/a-trial-of-azd4547-with-cisplatin-and-capecitabine-for-advanced-cancer

Study website
http://www.crukctuglasgow.org/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
AZD4547-2011

Study information

Scientific Title
A Phase I/II trial of AZD4547 in combination with cisplatin and capecitabine

Acronym
FACING

Study objectives
Stage 1:
1. To identify a recommended dose of AZD4547 when administered in combination with Cisplatin and Capecitabine (CX)
2. To identify the DLT (Dose-Limiting Toxicity) of AZD4547 when administered in combination with Cisplatin and Capecitabine
2.1. To explore the safety and tolerability of AZD4547 when administered in combination with Cisplatin and Capecitabine
2.2. To determine the pharmacokinetic profile of AZD4547 when administered in combination with Cisplatin and Capecitabine
3. To investigate the use of biomarkers of predictive and pharmacodynamic effects of AZD4547 when administered in combination with Cisplatin and Capecitabine
3.1. To explore the anti-tumour efficacy of the combination of AZD4547 administered with Cisplatin and Capecitabine

Stage 2:
1. To determine the effect of AZD4547 in combination with Cisplatin and Capecitabine (AZD4547-CX) compared with Cisplatin and Capecitabine (CX) and placebo on progression-free survival (PFS) when administered to patients with locally advanced or metastatic gastro-oesophageal adenocarcinoma and with FGFR2 polysomy or amplification (FISH > 4)
2. To compare the mean change in tumour size assessments from baseline after 9 weeks of treatment between the study arms
2.1. To compare objective overall (complete and partial) response rates in these patients treated with either AZD4547-CX or CX-placebo
2.2. To compare overall survival in these patients treated with either AZD4547-CX or CX-placebo
2.3. To compare PFS in the FISH 6 and FISH 4/5 sub-groups
2.4. To compare the effect of AZD4547 between the FISH 6 and the FISH 4/5 sub-groups
2.5. To further describe the safety and toxicity profiles of AZD4547-CX and CX-placebo in this patient population
3. To investigate the use of biomarkers of predictive and pharmacodynamic effects of AZD4547-CX and CX-placebo in these patients
3.1. To determine the incidence of FGFR2 polysomy or amplification in the UK population with locally advanced or metastatic gastro-oesophageal adenocarcinoma
3.2. To determine the association between changes in tumour size after 9 weeks of treatment and progression-free survival
3.3 To explore sparse population pharmacokinetics in a subset of patients

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland Research Ethics Committee, 18 October 2011, ref: 11/WS/0039

Study design
Multi-centre two stage trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Cancer

Interventions
Stage 1
AZD4547 will be administered orally twice daily in equally divided doses at 12-hourly intervals in a days 1-14 3-weekly administration schedule.
The starting dose of AZD4547 will be 40mgs at 12 hourly intervals in a day 1-14 3-weekly scheduled based upon emerging safety and tolerability data, and it will be administered in combination with cisplatin and capecitabine. Cisplatin will be administered at a dose of 80 mg /m2 intravenously 3-weekly, and capecitabine will be administered orally twice daily in equally divided doses (1000 mg/m2 bid) on days 1 C 14 of each 3-weekly cycle. The number of tablets of capecitabine to be administered based on body surface area (BSA).

Stage 2
Patients who are recruited into the Stage 2 part of the study will receive either AZD4547-CX, consisting of AZD4547 orally at the recommended dose (as determined in the Phase I part of the study) in combination with cisplatin (80 mg/m2 intravenously 3-weekly) and capecitabine (1000 mg/m2 bid orally days 1 C 14 of each 3-weekly cycle) or CX, consisting of cisplatin (80 mg/m2 intravenously 3-weekly) and capecitabine (1000 mg/m2 bid orally days 1 ¨C 14 of each 3-weekly cycle) plus placebo at 12 hourly intervals in a days 1-14 3-weekly schedule.

Intervention Type
Other

Phase
Phase I/II

Primary outcome measure
Stage 1:
Toxicity, with determination of the safety, toxicity, dose-limiting toxicity and the recommended dose of AZD4547 when administered orally in a twice daily days 1-14 3-weekly schedule in combination with Cisplatin and Capecitabine, administered three-weekly, based on clinical and laboratory toxicity.

Stage 2: T
Progression-free survival.

Secondary outcome measures
Stage 1:
The pharmacokinetic profile of AZD4547 when administered in this combination and tertiary (exploratory) endpoints which include anti-tumour activity of the combination and the use of biomarkers for prediction and pharmacodynamic effects of AZD4547 when administered in this combination.

Stage 2:
Mean tumour size assessments after 9 weeks of therapy, objective response, safety and tolerability of the treatment regimens, differential effect of AZD4547 in FISH 4/5 and FISH6 subgroups, progression free survival in the FISH6 subgroup and overall survival. The tertiary (exploratory) endpoints will include the use of biomarkers for predictive and pharmacodynamic effects of AZD4547 in these patients, the incidence of FGFR2 polysomy or amplification in the UK population of patients with gastro-oesophageal adenocarcinoma, and sparse population pharmacokinetics.

Overall study start date
15/01/2012

Completion date
15/12/2015

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Male or female and over 25 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status 0, or 1
3. Written informed consent
4. No chemotherapy, hormonal therapy, immunotherapy, targeted systemic cancer therapy, or investigational therapy within 4 weeks of study entry (6 weeks for mitomycin C and nitrosureas)
5. No radiotherapy within 4 weeks of study entry.
6. Adequate haematological function, as follows:
6.1. Haemoglobin > 10g/dl
6.2. Neutrophils > 1.5 x 109/l
6.3. Platelets > 100 x 109/l
7. Adequate biochemical function, as follows:
7.1. Bilirubin < 1.5 x ULN (Upper Limit of Normal)
7.2. ALT or AST < 2.5 x ULN

7.3. Alkaline Phosphatase < 2.5 x ULN
7.4. Serum Phosphate < ULN
7.5. Serum Calcium < ULN
7.6. Serum Magnesium < ULN
8. Adequate renal function with creatinine clearance / glomerular filtration rate > 60 mls/min. If the creatinine clearance / glomerular filtration rate is less than 60 mls/min as calculated by the Cockroft-Gault formula, then the creatinine clearance / glomerular filtration rate should be measured by either a radio-isotope technique or by 24-hour urine collection
9. Life expectancy >12 weeks
10. Able to reliably tolerate and comply with oral medication

Additional stage 1 inclusion criteria:
1. Histologically or cytologically proven advanced solid tumour that is refractory to standard therapies, or for whom no standard therapies exist, or for whom cisplatin and capecitabine is an acceptable treatment option
2. No concomitant use of another anti-cancer therapy with the exception of patients with prostate cancer who are on a LHRH analogue who can continue this during the study
3. Disease which is either measurable (RECIST 1.1) or evaluable

Additional stage 2 inclusion criteria:
1. Histologically or cytologically proven adenocarcinoma or undifferentiated carcinoma of the oesophagus, gastro-oesophageal junction, or stomach
2. Locally advanced (inoperable) disease (that is not suitable for a combined chemo-radiation approach for tumours confined to the lower oesophagus) or metastatic disease
3. Tumours with FGFR2 polysomy or amplification (FISH 4/5 or FISH 6)
4. No prior neo-adjuvant or adjuvant chemotherapy, and no prior chemotherapy for advanced disease
5. No concomitant use of another anti-cancer therapy during the study
6. At least one bi-dimensional measurable lesion as defined by RECIST 1.1

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
18 patients in Stage 1 and 140 patients in Stage 2

Key exclusion criteria
1. History of physical or psychiatric disorder that would prevent informed consent and compliance
2. Pregnant or lactating women
3. Fertile woman of childbearing potential not willing to use adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards. It is not known whether AZD4547 can induce hepatic enzymes. If oral contraception is used, it is recommended that this is used in combination with a barrier method as well. Fertile men who

are not willing to use a barrier method of contraception (condoms with spermicidal jelly). Fertile men should also refrain from donating sperm from the start of dosing until 16 weeks after discontinuing study treatment. Male patients wishing to subsequently father children should attend for freezing of sperm samples prior to dosing.
4. Evidence of uncontrolled infection (defined as infection that cannot be resolved readily with antibiotics prior to patient entry into the trial)
5. Major surgery within 28 days prior to study entry or anticipated to occur while on study
6. Prolonged QTc (corrected) interval of > 470ms on ECG or a family history of long QT syndrome
7. History of active or treated brain metastases (with the exception of patients with resected brain metastases and no evidence of recurrence on CT or MRI of the brain)
8. CNS disease (uncontrolled seizures or cerebrovascular accident/transient ischaemic attack /subarachnoid haemorrhage within 6 months)
9. Any unresolved toxicity CTC Grade 1 from previous systemic anti-cancer therapy except alopecia
10. Pre-existing sensory or motor neuropathy ¡Ý grade 1
11. Known hypersensitivity to cisplatin
12. Known DPD deficiency or hypersensitivity to capecitabine
13. Known hypersensitivity to AZD4547
14. History of significant cardiac disease including myocardial infarction within the previous 6 months, uncontrolled ischaemic heart disease, second or third degree heart block, any other persistent or intermittent cardiac arrhythmia requiring medication, congestive cardiac failure > NYHA Grade 2 (Appendix 3), or left ventricular ejection fraction of < 50%
15. Patients with a lack of physical integrity of the GI tract leading to a malabsorption syndrome or intestinal obstruction
16. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications
17. Patients with significant hearing loss such that Cisplatin is contra-indicated
18. Patients taking CYP3A4 and CYP2D6 inducers or inhibitors
19. Current evidence or previous history of retinal pigmented epithelium detachment (RPED)
20. Previous laser treatment or intra-ocular injection for treatment of macular degeneration
21. Current evidence or previous history of dry or wet age-related macular degeneration
22. Current evidence or previous history of retinal vein occlusion (RVO)
23. Current evidence or previous history of retinal degenerative diseases (e.g. hereditary)
24. Current evidence or previous history of any other clinically relevant chorioretinal defect

Additional Stage 2 exclusion criteria:
History of prior malignancy within the last 5 years other than patients with basal cell carcinoma of the skin or in situ neoplasia of the cervix uteri who have undergone potentially curative treatment

Date of first enrolment
15/01/2012

Date of final enrolment
15/12/2015

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
The Beastson West of Scotland Cancer Centre
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Sponsor information

Organisation
NHS Greater Glasgow and Clyde (UK)

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Sponsor type
Hospital/treatment centre

Website
http://www.nhsggc.org.uk/

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name

Cancer Research (UK) ref: C2193/A12946

Funder Name
AstraZeneca (UK) ref: D2610C00010

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No