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A Phase I/Ib Trial of the Oral Hedgehog inhibitor, LY2940680, in Combination with Weekly Paclitaxel in Patients with Platinum-Resistant, Recurrent Ovarian Cancer or Recurrent, Advanced, Solid Tumours.

Submission date 23/12/2014	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol
Registration date 05/02/2015	**Overall study status** Stopped	[_] Statistical analysis plan [_] Results
Last Edited 16/09/2021	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-new-drug-called-ly2940680-and-paclitaxel-for-advanced-cancer-hiproc

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2014-004695-37

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
HIPROC_2014

Study information

Scientific Title
A Phase I/Ib Trial of the Oral Hedgehog inhibitor, LY2940680, in Combination with Weekly Paclitaxel in Patients with Platinum-Resistant, Recurrent Ovarian Cancer or Recurrent, Advanced, Solid Tumours: open-label, non-randomised, multi-centre, dose escalation trial

Acronym
HIPROC

Study objectives
The available data suggest that Hh signalling plays a role in the development and growth of ovarian cancers through multiple potential mechanisms. Activation is associated with poor prognosis and may be more frequent in ovarian cancers that persist or relapse rapidly after chemotherapy. Hh inhibitors enhance the efficacy of paclitaxel in preclinical models. LY2940860 is an orally available potent inhibitor of Hh signalling and it can be given safely at biologically effective doses.

Our hypothesis is:
1. LY2940860 can be given safely by continuous oral dosing in combination with weekly intravenous paclitaxel
2. LY2940860 will increase the activity of weekly paclitaxel in women with platinum resistant ovarian cancer.

In this trial we propose to test the first hypothesis and investigate the feasibility of combining the oral Hh inhibitor, LY2940680 with weekly paclitaxel in platinum resistant, recurrent ovarian cancer. If the combination proves feasible and data from the associated translational studies are supportive, we would plan a future randomised phase II trial to test the second hypothesis further.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland Research Ethics Service. Plan to submit in January 2015. Pending

Study design
Phase I/Ib open-label non-randomised multi-centre dose-escalation trial

Primary study design
Interventional

Secondary study design

Non randomised study

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
Ovarian cancer or recurrent, advanced, solid tumours.

Interventions
Dose Escalation Phase:
Paclitaxel 80mg/m2 IV, days 1, 8 and 15 every 28 days for up to 6 cycles
LY2940680 PO Daily Days 1-28 of a 28 day cycle. Dose cohorts as below:

Dose Level LY2940680 Dose PO
-1 50mg once daily
1 100mg once daily
2 200mg once daily
3 400mg twice daily

Interim dose levels may be added depending on data from prior cohorts.
LY2940680 will be continued as a single agent after completion of chemotherapy, until disease progression or unacceptable toxicity.

Dose Expansion Phase:
Recommended combination dose as determined in the dose escalation phase.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
LY2940680 hedgehog inhibitor Paclitaxel

Primary outcome measure
The primary outcome measure of the dose escalation phase is the maximum tolerated dose of LY2940680 when administered orally in combination with intravenous paclitaxel 80mg/m2 administered on day 1, 8 and 15 of a 28 day cycles based on clinical and laboratory toxicity which will be classified and graded according to CTCAE v 4.

The primary outcome of the dose expansion phase is the toxicity of the combination of LY2940680 at the recommended dose level and weekly paclitaxel (80mg/m2, IV days 1, 8 and 15 every 28 days) in recurrent platinum resistant ovarian cancer. The causality of each adverse event to LY2940680 and paclitaxel will be classified and graded according to CTCAE v 4.

Secondary outcome measures
The secondary outcome measures of the dose escalation phase are:
1. Pharmacokinetics: Cmax, T max and AUC of LY2940680, its metabolite LSN3185556 and paclitaxel
2. Response rate will be defined by RECIST 1.1
3. Progression free survival (PFS) defined as the time from first treatment dose to first appearance of progressive disease as defined by RECIST 1.1 or death from any cause. Patients still alive and without progression at the time of analysis will be censored at the last date known to be alive.
4. Overall survival will be measured from the date of first treatment dose to the date of death from any cause. Patients still alive at the time of analysis will be censored at the last date known to be alive.

The secondary outcome measures of the dose expansion phase are:
1. Dose intensity of paclitaxel is defined as the actual dose intensity as a percentage of the intended dose. Actual dose intensity is defined as the total dose (expressed as mg/m2) / length of treatment in weeks. The length of treatment will be defined as the time from day 1 of the first treatment to 4 weeks after the day 1 of the last treatment. The intended dose intensity is defined as what the patient should have received over the same period if there were no dose reductions, omissions or delays.
2. Response rate will be defined by RECIST 1.1 and defined by Combined GCIG criteria. To be evaluable for response a patient must receive at least two cycles of trial treatment and have an evaluable tumour response. All eligible patients will be included in the response rate calculation. The subset that will be assigned a response category are all patients who have received at least two cycles of treatment.
3. Progression free survival (PFS) defined as the time from first treatment dose to first appearance of progressive disease as defined by RECIST 1.1 or death from any cause. Patients still alive and without progression at the time of analysis will be censored at the last date known to be alive. Progression by CA125 criteria alone will not constitute progression.
4. Overall survival will be measured from the date of first treatment dose to the date of death from any cause. Patients still alive at the time of analysis will be censored at the last date known to be alive.

Overall study start date
30/06/2015

Completion date
31/03/2018

Eligibility

Key inclusion criteria
Inclusion criteria of the dose escalation phase:
Histologically or cytologically confirmed advanced solid tumours refractory to standard therapy or for whom weekly paclitaxel is considered, by the investigator, to be an appropriate therapy.

Inclusion criteria of the dose expansion phase:
1. Histologically confirmed high grade serous or G3 endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer with progressive or recurrent disease (patients with carcinosarcoma are eligible but mucinous, clear cell carcinoma and grade 1 or 2 tumours are not eligible). Progression may be defined radiologically by RECIST 1.1 or by CA125 criteria in combination with clinical symptoms or signs indicative of progression. Asymptomatic rise of CA125 alone will not be defined as progressive disease. Progression of disease must have occurred within 6 months of the last dose of platinum chemotherapy.
2. ≥ 1 previous platinum based chemotherapy. This may have been given in the adjuvant setting.
3. No previous treatment with single agent weekly paclitaxel for relapsed disease. Weekly paclitaxel may have been given in the first line setting if given in combination with platinum chemotherapy.
4. No contra-indication to an image guided biopsy and tumour amenable to image guided biopsy.
5. Measurable or non-measurable disease.
6. Patients must have archival formalin-fixed paraffin-embedded tissue from their original diagnosis available for the purposes of translational research.
7. Patients with synchronous tumours e.g. ovarian and endometrial or history of prior malignancy are eligible provided that there is biopsy evidence that the disease measurable on CT and/or MRI is ovarian in origin

The following inclusion criteria will be required for all patients:
1. Written informed consent
2. Performance status ≤2 (ECOG)
3. Estimated life expectancy ≥ 3 months
4. Age ≥ 18 years
5. Adequate haematological, renal and hepatic function as defined by:
5.1 Haemoglobin (Hb)> 10g/dl
5.2 Neutrophil Count> 1.5 x 109/l
5.3 Platelets> 100 x 109/l
5.4 INR <2 x ULN and prothrombin time and activated partial thromboplastin time < 1.5 x ULN in the absence of therapeutic anticoagulation
5.5 Glomerular Filtration rate of > 50 mL/ min (calculated using the Wright formula or measured by EDTA clearance)
5.6 Total bilirubin ≤1.5 x ULN and ALT and AST ≤ 2.5 x ULN
6. No history of grade 2 peripheral neuropathy at any time during prior treatment and no greater than grade 1 residual peripheral neuropathy.
7. No use within the last 7 days of or requirement to continue medications that are strong inhibitors of CYP3A4.
8. No prior treatment with LY2940680 or other Hedgehog pathway inhibitor.
9. Female patients with reproductive potential must have a negative serum pregnancy test within 7 days of trial enrolment and agree to use an effective double barrier method of contraception during and for 6 months after last dose of treatment. Male patients of childbearing potential and their female partner must also agree to use an effective double barrier method of contraception during and for 6 months after treatment.
10. No symptoms or signs of gastrointestinal obstruction requiring parenteral nutrition or hydration or any other gastro-intestinal disorders or abnormalities, including difficulty swallowing, that would interfere with drug absorption, including ileostomies.
11. Ability to swallow capsules.
12. No significant cardiovascular diseases, including uncontrolled hypertension, clinically relevant cardiac arrhythmia, unstable angina or myocardial infarction within 6 months prior to randomisation, congestive heart failure > NYHA III, severe peripheral vascular disease, clinically

significant pericardial effusion.
13. A corrected QT interval (QTc) of ≤470 msec on screening electrocardiogram (ECG).
14. No treatment within 28 days prior to randomisation with any investigational drug, radiotherapy, immunotherapy, chemotherapy, hormonal therapy (excluding HRT) or biological therapy. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases, provided that the radiotherapy does not affect target lesions.
15. No serious infections in particular if requiring systemic antibiotic (antimicrobial, antifungal) or antiviral therapy, including known hepatitis B and/or C infection and HIV-infection.
16. No symptomatic CNS metastasis or leptomeningeal carcinomatosis.
17. No other severe concurrent disease, which may increase the risk associated with trial participation or trial drug administration and, in the judgement of the investigator, would make the patient inappropriate for entry into this trial, including significant neurologic, psychiatric, infectious, hepatic, renal, or gastrointestinal diseases or laboratory abnormality.
18. No known, uncontrolled hypersensitivity to the investigational drugs or their excipients.
19. No psychological, familial, sociological or geographical consideration potentially hampering compliance with the trial protocol and follow up schedule.
20. No known SIADH or adrenal insufficiency.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Phase I – 9-18 patients and Phase Ib – 12 patients

Total final enrolment
16

Key exclusion criteria
The exclusion criteria are covered by the negative inclusion criteria

Date of first enrolment
30/06/2015

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
The Beatson West of Scotland Cancer Centre
United Kingdom
G12 0YN

Study participating centre
Imperial College Healthcare NHS Trust - Hammersmith Hospital
United Kingdom
W12 0HS

Study participating centre
Bart's Health NHS Trust - St Bartholomew's Hospital
United Kingdom
EC1A 7BE

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

Sponsor details
Research and Development Management Office
The Tennent Institute, 1st Floor
Western Infirmary General
38 Church Street
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G11 6NT

Sponsor type
Government

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Industry

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Lilly

Results and Publications

Publication and dissemination plan
We would present the findings at national or international meetings and publish them in peer-reviewed journals as well as on the Cancer Research UK website.

Updated 22/03/2019:
The researchers are currently data cleaning and hope to have a final report available by July 2019.

Intention to publish date
01/07/2019

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request