

# 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.

<b>Submission date</b> 23/12/2014	<b>Recruitment status</b> Stopped	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 05/02/2015	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 16/09/2021	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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

### Contact name

Mrs Karen Allan

### Contact details

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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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup>, 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: C<sub>max</sub>, T<sub>max</sub> 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/m<sup>2</sup>) / 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 GCIIG 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.  $\geq 1$  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  $\leq 2$  (ECOG)
3. Estimated life expectancy  $\geq 3$  months
4. Age  $\geq 18$  years
5. Adequate haematological, renal and hepatic function as defined by:
  - 5.1 Haemoglobin (Hb)  $> 10\text{g/dl}$
  - 5.2 Neutrophil Count  $> 1.5 \times 10^9/\text{l}$
  - 5.3 Platelets  $> 100 \times 10^9/\text{l}$
  - 5.4 INR  $< 2 \times \text{ULN}$  and prothrombin time and activated partial thromboplastin time  $< 1.5 \times \text{ULN}$  in the absence of therapeutic anticoagulation
  - 5.5 Glomerular Filtration rate of  $> 50 \text{ mL/min}$  (calculated using the Wright formula or measured by EDTA clearance)
  - 5.6 Total bilirubin  $\leq 1.5 \times \text{ULN}$  and ALT and AST  $\leq 2.5 \times \text{ULN}$
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  $> \text{NYHA III}$ , severe peripheral vascular disease, clinically

significant pericardial effusion.

13. A corrected QT interval (QTc) of  $\leq 470$  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

Glasgow

United Kingdom

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