

Phase 1/2 study to assess the safety and efficacy of Olaparib (**P**arp **I**nhibitor) in refractory **C**hronic **L**ymphocytic **L**eukaemia patients with an 11q deletion, relapsed Mantle cell Lymphoma and relapsed T-Prolymphocytic Leukaemia

**PICLLe** 

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Heart of England NHS Trust



**Leukaemia &  
Lymphoma Research**

BEATING BLOOD CANCERS

Why PARP inhibition in lymphoid malignancies with ATM mutations?

The clinical data for olaparib in solid tumours

PICCLE trial 

Why PARP inhibition in lymphoid malignancies with ATM mutations?

# Why PARP inhibition?

## Concept of synthetic lethality

Complete loss of DNA repair mechanisms is lethal for any cell

Individual deletion of one of two DNA repair pathways has no effect

Combined deletion of two DNA repair pathways is cytotoxic

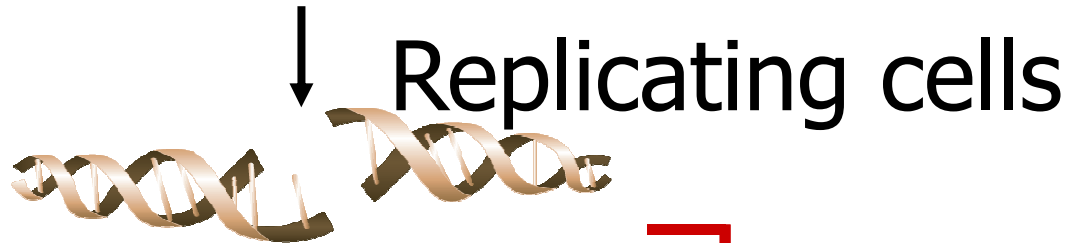
# Synthetic lethality induced by olaparib

DNA SSBs occur all the time in cells and PARP detects and repairs them



DNA damage increased by chemotherapy

During the replication process unrepaired SSBs are converted into DSBs

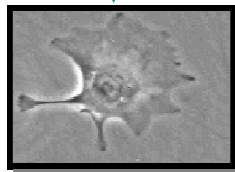


Normal cell

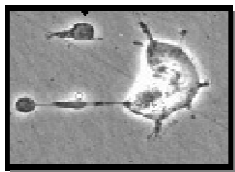
Cancer cell with defective ds DNA repair

Repair by Homologous Recombination

Survival



**Tumour specific killing by olaparib**



Cell death

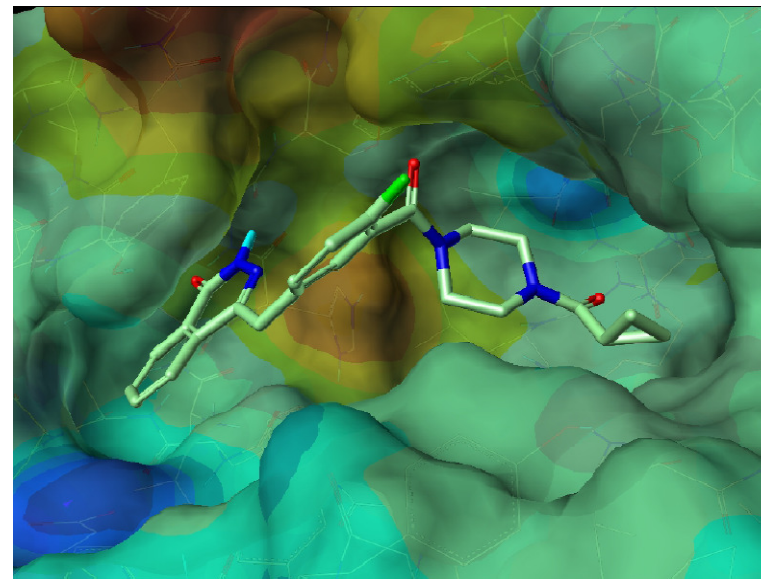
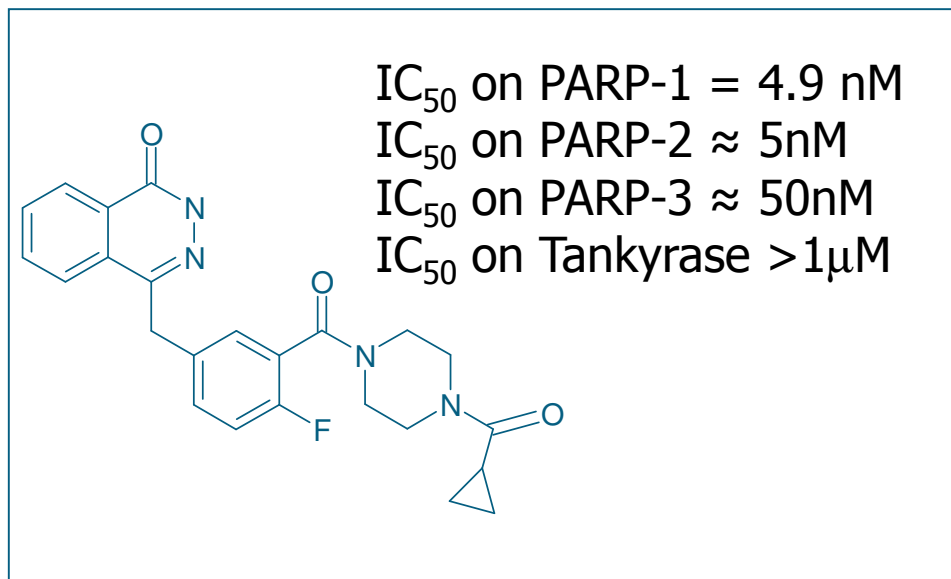
*Olaparib is an investigational drug currently in clinical development*

Bryant *et al*, Nature 2005, 434:913;  
Farmer *et al*, Nature 2005,434:917

## Tumour types exhibiting mutated/dysfunctional components of DNA ds repair pathway –targets for PARP inhibition

	% of all tumours	type of lesion
Breast	5% hereditary 11-15% sporadic	lost or mutated BRCA decreased expression
Ovarian	5-10% hereditary	lost or mutated BRCA
Prostate	5% hereditary	lost or mutated BRCA
Colon	10%	loss of MRN complex
CLL	15%	loss of ATM
Mantle cell	50%	loss of ATM
T-PLL	40%	loss of ATM
Rhabdomyosarcoma	40%	loss of ATM

# Olaparib: an oral inhibitor of poly (ADP-ribose) polymerase (PARP)



- Inhibits PARP-1
- Favourable PK
- Good bioavailability across species
- Tumour PK: significant levels at 24 hours following single oral dose

# The clinical data for olaparib in solid tumours

# Inhibition of Poly(ADP-Ribose) Polymerase in tumours from BRCA mutation carriers.

Fong P *et al*/2009. New England Journal of Medicine

Phase I study (dose escalation; safety)

60 Multiply treated patients with solid tumours, 19 with BRCA mutations

Ovarian (21: 35%), breast (9: 15%), colorectal (8: 13%); melanoma (4: 7%)  
sarcoma (4: 7%), prostate (3: 5%) other (11: 18%)

Dose finding cohorts to find maximum tolerated dose

<100mg daily, <100mg twice daily 2/3 weeks, 100mg twice daily 2/3 weeks,  
100 mg twice daily continuously, 200mg twice daily continuously, 400 mg twice  
daily continuously, 600mg twice daily continuously

# Safety

1 x Grade 4 thrombocytopenia on 600 mg bd (patient had previously had prolonged myelosuppression with chemo)

1 x Grade 3 mood alteration and fatigue on 400mg bd

1 x Grade 3 somnolence on 600mg bd

Grade 1-2 nausea (32%), fatigue (30%), vomiting (20%)

Low incidence of myelosuppression 3% thrombocytopenia 5%  
anaemia

Maximum tolerated dose defined as 400mg bd

# Efficacy

Durable objective anti-tumour activity ONLY in patients with BRCA mutations

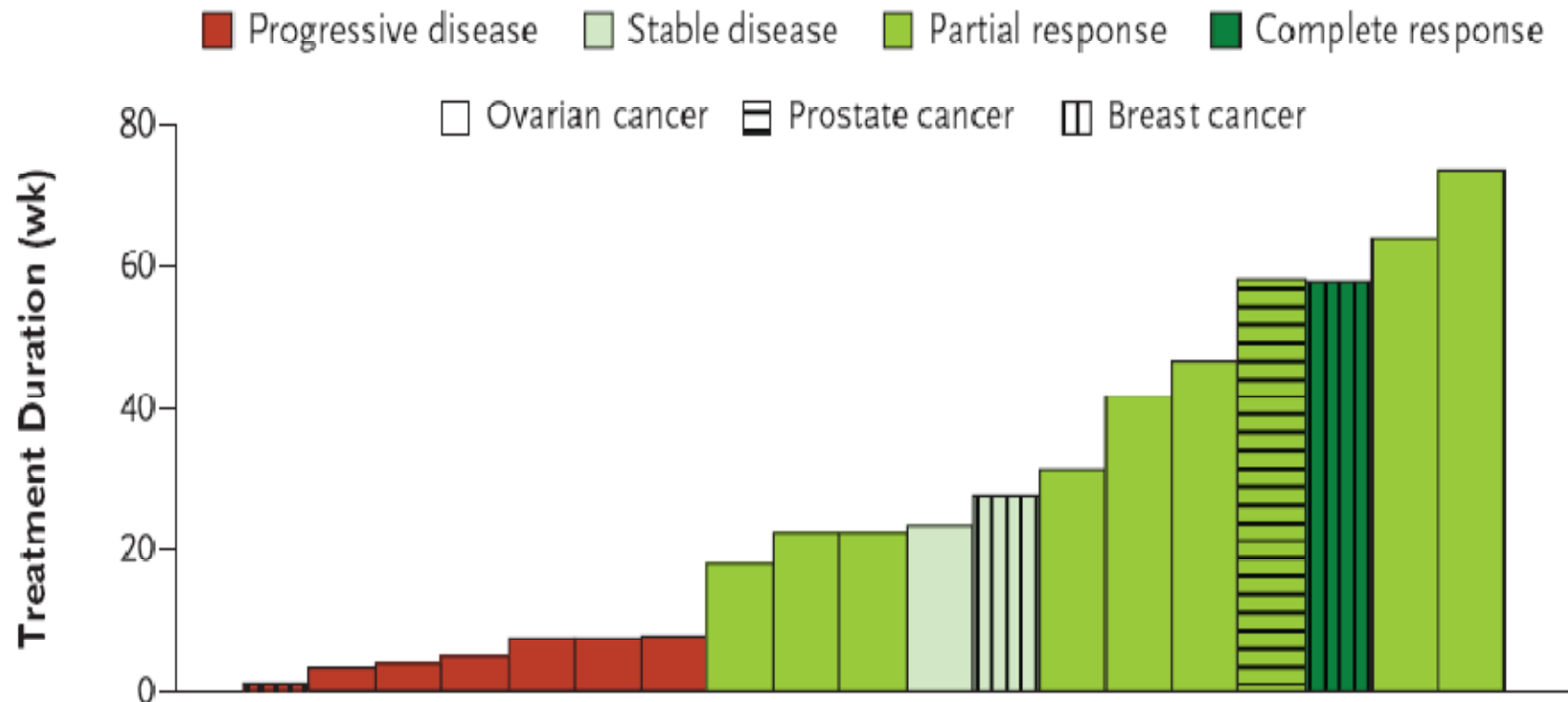
12/19 with BRCA mutations (63%) had clinical benefit from olaparib (8 Ovarian, 3 Breast, 1 prostate)

12 had radiologic or tumour marker response, 2 stable disease

However dose finding study so only 5/19 BRCA mutated cancers got 400mg bd

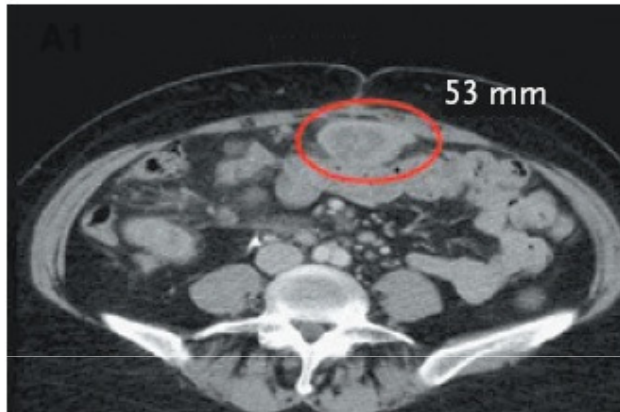
# Duration of treatment and best response

Of the 22 *BRCA* mutation carriers with ovarian, breast, or prostate cancer, data were evaluable for 19 patients

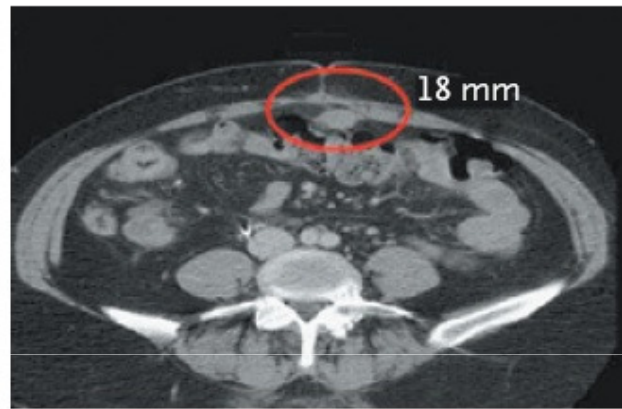


# Radiological evidence of tumour response to olaparib

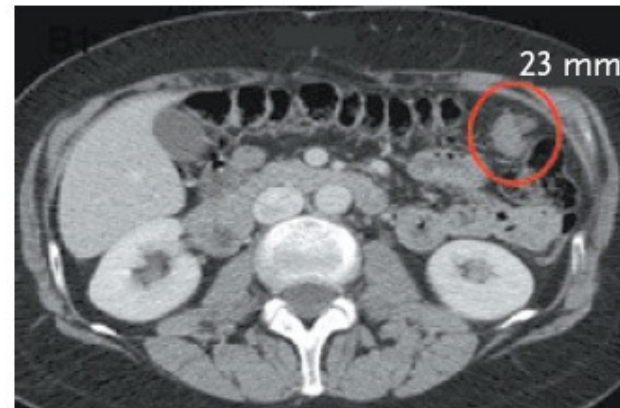
Patient 20,  
at Baseline



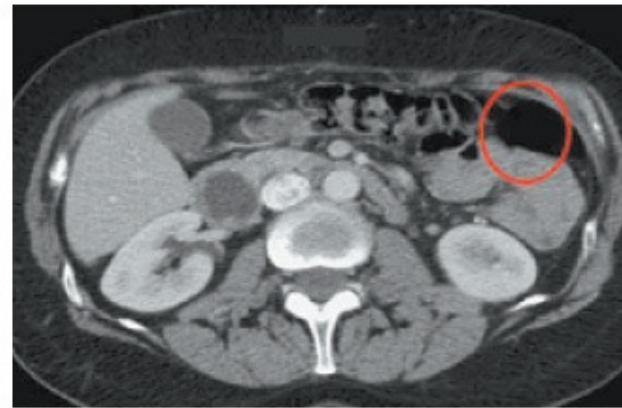
Patient 20,  
at 4 Mo



Patient 41,  
at Baseline



Patient 41,  
at 4 Mo



Pol(ADP-Ribose) polymerase inhibitors: Frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval.

Fong P *et al*/2010 Journal of Clinical Oncology

50 patients with relapsed ovarian Ca. 90% had 2 or more previous tx

All probably BRCA mutated

13 platinum sensitive, 24 platinum resistant and 13 platinum refractory

Dose escalation 8% <200mg bd, 78% 200mg bd, 14% 400mg bd

# Safety

**Table 4.** Olaparib-Related Adverse Events Reported in One or More Patients With *BRCA*-Mutated Ovarian Cancer (n = 50; all cycles)

Adverse Event	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
<b>Hematologic</b>								
Lymphopenia	0	0	0	0	3	6	1*	2
Anemia	0	0	3	6	4	8	0	0
<b>Gastrointestinal</b>								
Nausea	18	36	3	6	3	6	0	0
Vomiting	7	14	2	4	1	2	0	0
Diarrhea	2	4	1	2	1	2	0	0
Dyspepsia	3	6	5	10	0	0	0	0
Anorexia	6	12	2	4	0	0	0	0
Dysgeusia	4	8	1	2	0	0	0	0
Constipation	2	4	1	2	0	0	0	0
Dry mouth	2	4	0	0	0	0	0	0
<b>Constitutional</b>								
Fatigue	4	8	16	32	2	4	0	0
Mucosal inflammation	2	4	0	0	0	0	0	0
<b>Nervous system</b>								
Dizziness	2	4	1	2	1	2	0	0
Cognitive disorder	2	4	0	0	1	2	0	0
Anxiety	0	0	2	4	0	0	0	0
Headache	2	4	0	0	0	0	0	0
Insomnia	2	4	0	0	0	0	0	0
Paresthesia	2	4	0	0	0	0	0	0
<b>Cardiovascular system</b>								
Hypertension	1	2	2	4	0	0	0	0

NOTE. Table 4 includes the on-trial treatment-related adverse events of patient 40 (*BRCA1* fallopian tube cancer). This patient was subsequently treated outside the trial owing to an incidental brain metastasis found on day 14 of cycle 1 of olaparib. Her adverse events experienced outside the trial were grade 1 fatigue, anorexia, and weight loss.

\*No other grade 4 treatment-related adverse events were reported apart from lymphopenia. No grade 5 treatment-related adverse events were reported.

# Efficacy

50 patients

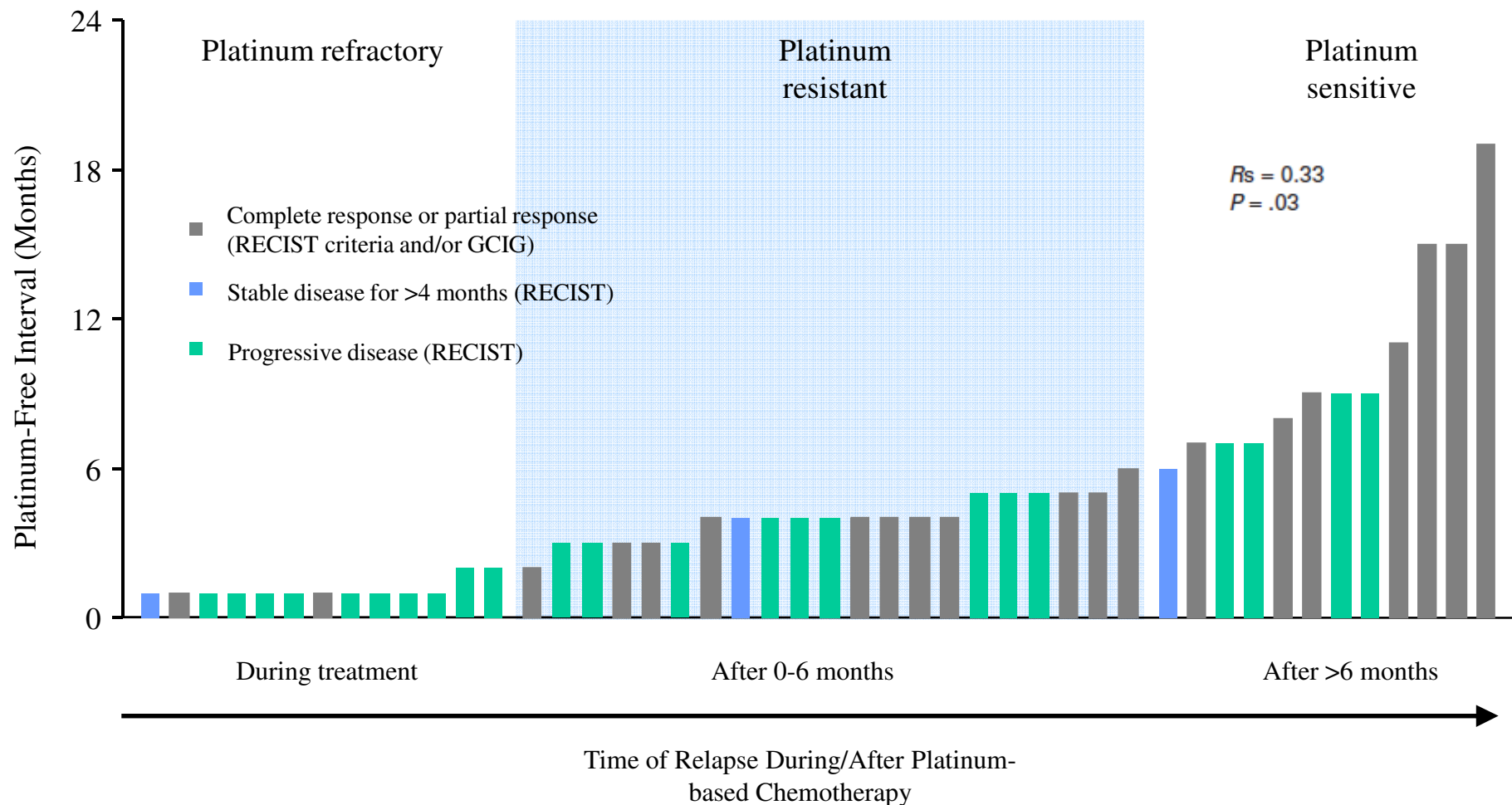
20 (40%) had complete or partial responses

3 (6%) had stable disease.

Response related to platinum status

Median duration of response was 28 weeks

# Patients with ovarian cancer who were *BRCA1* or *BRCA2* mutation carriers (n=50)



Oral poly(ADP-Ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof of concept trial.

Audeh MW et al, Lancet 2010

Confirmed *BRCA1* or *BRCA2* mutation

Advanced recurrent ovarian cancer  
after failure of  $\geq 1$  prior platinum-based chemotherapy

# Safety

	Olaparib 400 mg bid (n=33)		Olaparib 100 mg bid (n=24)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Nausea	14 (42)	2 (6)	7 (29)	2 (8)
Fatigue	10 (30)	1 (3)	9 (38)	0
Anaemia*	5 (15)	1 (3)	4 (17)	0
Diarrhoea	5 (15)	0	3 (13)	0
Vomiting	3 (9)	1 (3)	0	0
Neutropenia	0	3 (9)	0	0
Rash	3 (9)	0	2 (8)	0
Gastro-oesophageal reflux disease	3 (9)	0	0	1 (4)
Abdominal pain <sup>†</sup>	3 (9)	0	0	0
Dyspepsia	2 (6)	0	3 (13)	0
Dizziness	2 (6)	0	2 (8)	0
Headache	2 (6)	0	1 (4)	0
Asthenia	2 (6)	0	0	0
Gastritis	2 (6)	0	0	0
Peripheral neuropathy	1 (3)	0	2 (8)	0
Constipation	1 (3)	0	2 (8)	0
Haemoglobin urine	0	0	3 (13)	0

Data are number (%). \*Includes MedDRA preferred terms of reduced: \*anaemia and haemoglobin; <sup>†</sup>abdominal and low abdominal pain CTCAEs (version 3) were at least possibly, probably, and definitely related to olaparib in the investigator's opinion.

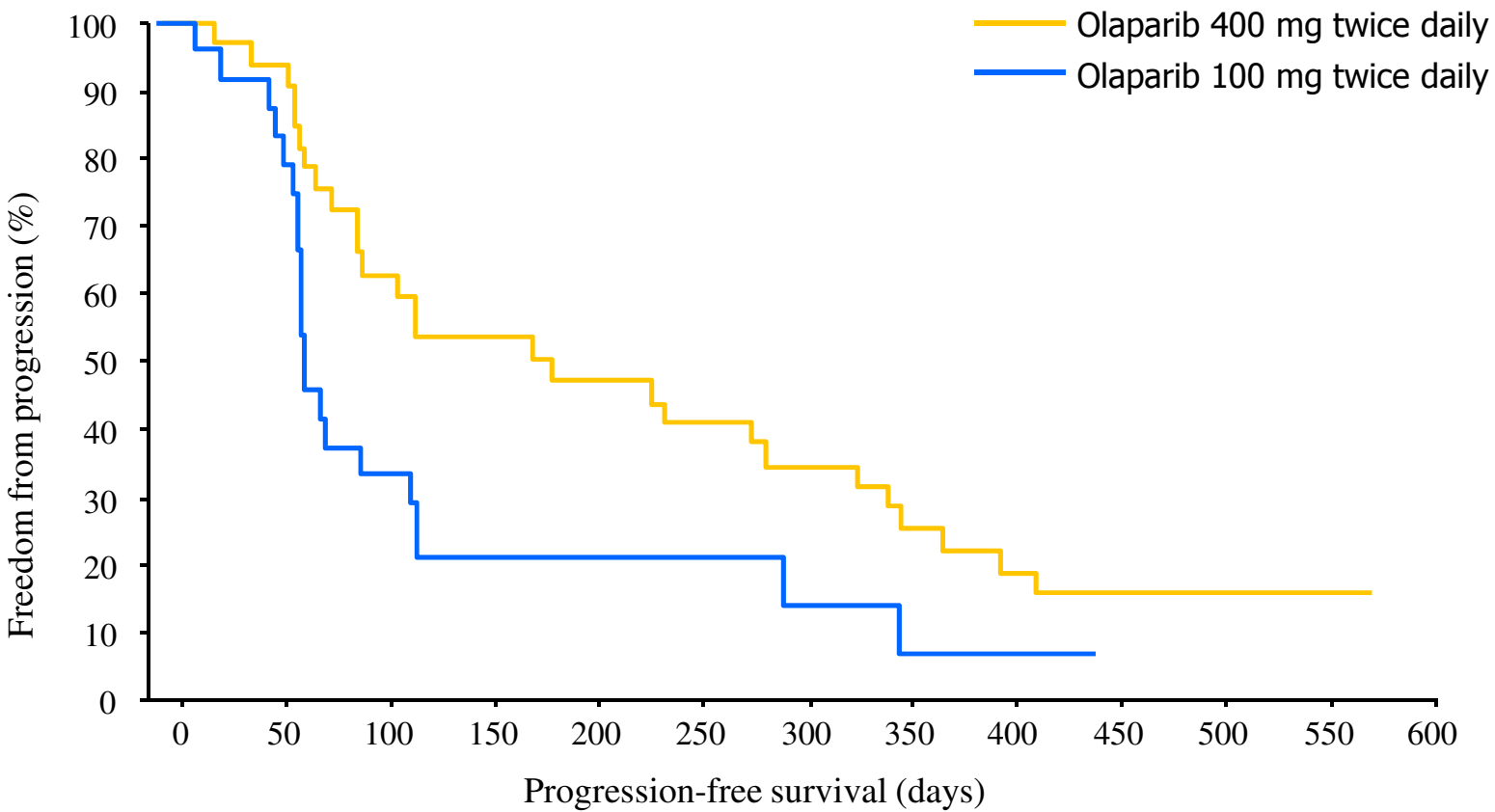
## Best overall confirmed tumour response status

	<b>Olaparib 400 mg bid (n=33)</b>	<b>Olaparib 100 mg bid (n=24)</b>
<b>Objective response</b>	11 (33%, 20–51)	3 (13%, 4–31)
<b>Complete response</b>	2 (6%, 2–20)	0
<b>Partial response</b>	9 (27%, 15–44)	3 (13%, 4–31)
<b>Stable disease</b>	12 (36%, 22–53)	7 (29%, 15–49)
<b>Progressive disease</b>	10 (30%, 17–47)	14 (58%, 39–76)
<b>Duration of response (days)</b>	290 (126–506)	269 (169–288)*

Data are number (%; 95% CI)

\*Data might be underestimated because time up to data cutoffs included for patients who responded but had not yet progressed

# Progression-free survival



Number of patients	0	50	100	150	200	250	300	350	400	450	500	550	600
Olaparib 400 mg	33	31	20	17	15	13	11	8	6	4	4	3	0
Olaparib 100 mg	24	19	8	5	4	3	2	1	1	0	0	0	0

Progression-free survival is shown for each of the two cohorts, which ran in sequence

*Olaparib is an investigational drug currently in clinical development*

Oral poly(ADP-Ribose) polymerase inhibitor  
olaparib in patients with BRCA1 or BRCA2  
mutations and advanced breast cancer: a proof  
of concept trial.

Tutt *et al*/ 2010 Lancet

54 patients with advanced breast cancer and BRCA mutations

Two dose cohorts

# Safety

	Olaparib 400 mg bid (n=27)		Olaparib 100 mg bid (n=27)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Nausea	11 (41)	4 (15)	11 (41)	0
Fatigue	11 (41)	4 (15)	7 (26)	1 (4)
Vomiting	3 (11)	3 (11)	4 (15)	0
Anaemia*	1 (4)	3 (11)	2 (7)	2 (7)
Anorexia	3 (11)	0	3 (11)	1 (4)
Diarrhoea	3 (11)	0	2 (7)	0
Constipation	2 (7)	0	4 (15)	0
Headache	2 (7)	0	3 (11)	0
Abdominal pain†	2 (7)	0	3 (11)	0
Dyspepsia	2 (7)	0	1 (4)	0
Gastro-oesophageal reflux disease	2 (7)	0	1 (4)	0
Flatulence	2 (7)	0	0	0
Arthralgia	0	0	3 (11)	0

Data are number (%). Includes MedDRA preferred terms of reduced: \*anaemia and haemoglobin; †abdominal and low abdominal pain.

No grade 5 AEs were reported at the time of this analysis

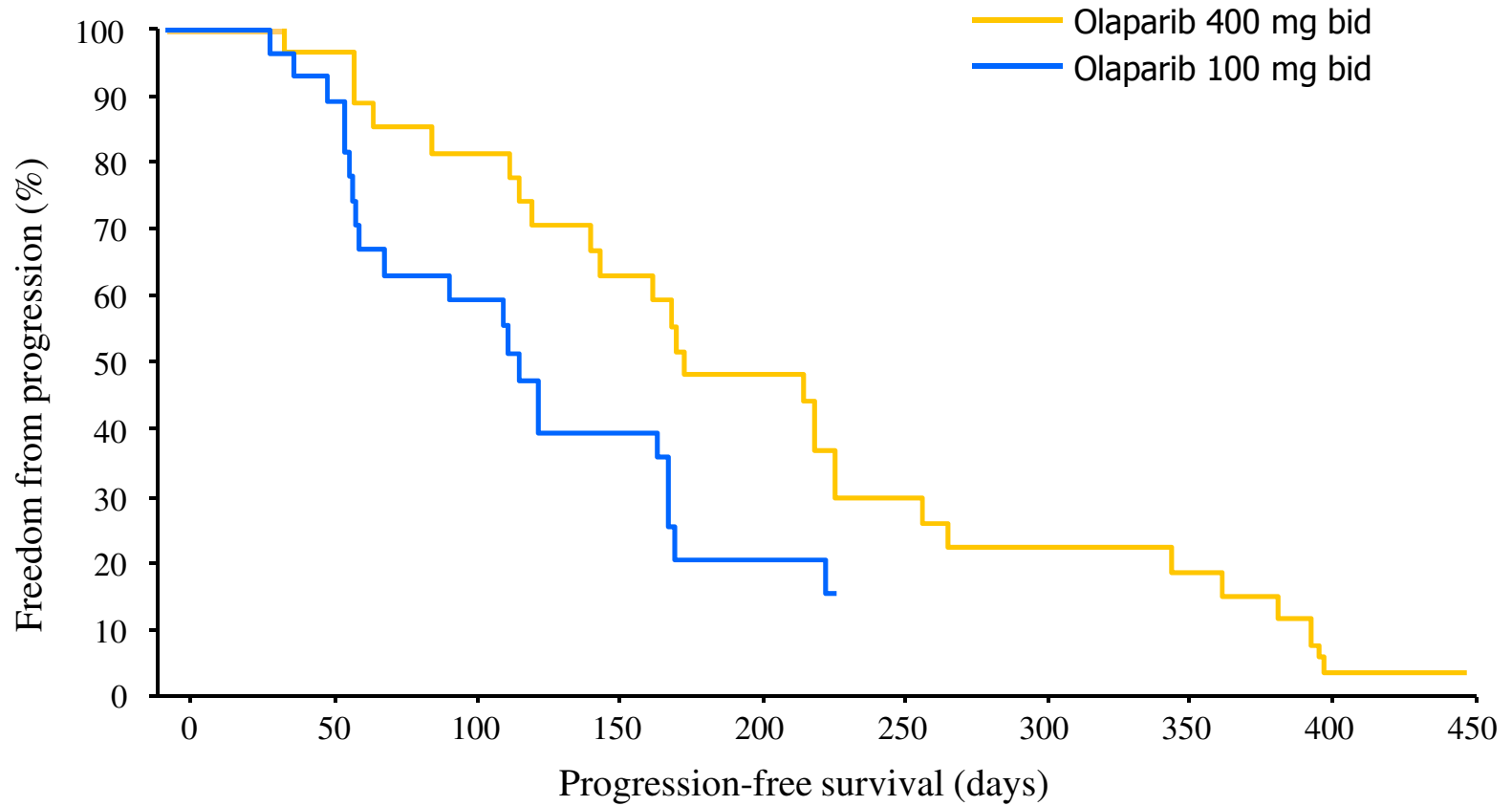
# Efficacy

	<b>Olaparib 400 mg bid (n=27)</b>	<b>Olaparib 100 mg bid (n=27)</b>
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI)

## Median duration of response 144 days

# Progression-free survival



Number of patients

Olaparib 400 mg bid	27	26	22	17	13	8	6	5	1	0
Olaparib 100 mg bid	27	24	16	10	4	0	0	0	0	0

# Combination studies

Olaparib + paclitaxel in Breast Ca (all BRCA neg)

Olaparib + cisplatin in Breast Ca (all BRCA neg)

Olaparib + gemcitabine in advanced pancreatic cancer

Olaparib + topotecan in advanced solid tumours

Olaparib + bevacizumab in advanced solid tumours

Olaparib + irinotecan in advanced colorectal ca

Olaparib + carboplatin in breast/ovarian Ca (BRCA neg)

Olaparib + cisplatin + gemcitabine in advanced solid tumours

Olaparib + liposomal doxorubicin in advanced solid tumours

# Summary of data in relapsed solid tumours

Olaparib is safe and well tolerated

Side effects mainly grade I-II gastrointestinal upset and fatigue

Mild anaemia, thrombocytopenia uncommon with olaparib alone

Myelosuppression more common in combination studies

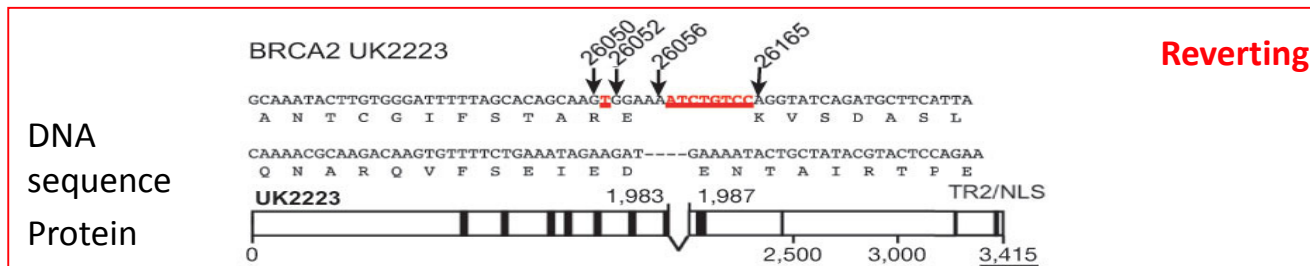
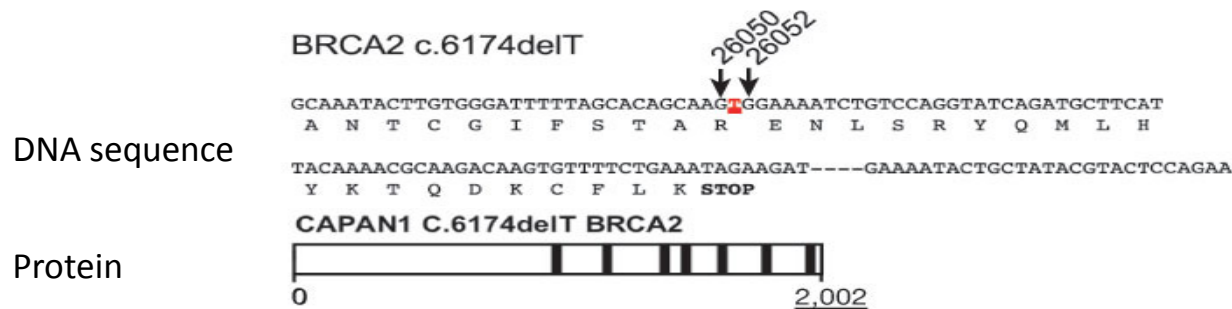
Efficacy in relapsed BRCA mutated solid tumours of around 40% CR+PR and also 6-40% stable disease.

Median duration of response 144-290 days.

As yet no evidence for effect in BRCA wild type tumours

Toxicity similar irrespective of BRCA status

# Acquired resistance to PARPi in HRR deficient *BRCA2* mutant tumours has been observed by secondary *BRCA2* mutations



# **Potential mechanisms of resistance to PARPi in *ATM* mutant tumours**

**Up-regulation of P-glycoprotein efflux pumps (described in *Brca1* null mice treated with olaparib)**

## **PARP related resistance**

- a) Mutations in the inhibitor binding site
- b) Upregulation of PARP1,2
- c) Upregulation of PARP related proteins: PARP3, PARP4, Tankyrase 1 and 2

## **Secondary mutations in HRR pathway to correct repair defect**

Expression of Rad51, Rad52, XRCC2, XRCC4, BRCA1/2

Loss of 53BP1

## **Other mechanisms**

## **Strategies to counteract potential resistance to Olaparib in patients with ATM deficient lymphoid tumours**

Combination with DSB inducing agents or chromatin modifying compounds

P-glycoprotein inhibition

New generation of PARP inhibitors

**Can targeting/loss of other proteins in DNA repair pathways or related pathways enhance sensitivity of ATM null tumours to PARP inhibition?**

Phase 1/2 study to assess the safety and efficacy of Olaparib (**P**arp **I**nhibitor) in refractory **C**hronic **L**ymphocytic **L**eukaemia patients with an 11q deletion, relapsed Mantle cell Lymphoma and relapsed T-Prolymphocytic Leukaemia

**PICLLe** 

Dr Guy Pratt  
School of Cancer Sciences, University of Birmingham  
Heart of England NHS Trust

# Trial Design

- Single arm, multi-centre phase I/II study of Olaparib
- Administered daily continuously until disease progression/poor tolerability
  - Chronic Lymphocytic Leukaemia  
(Phase I –any CLL, Phase 2 only CLL with an ATM mutation / 11q deletion)
  - Mantle Cell Lymphoma
  - T-Prolymphocytic Leukaemia
- Planned Recruitment:
  - Phase I: 18 patients (maximum)
  - Phase II: 60 patients

# Trial Objectives

## Primary Objective:

- **Phase I:** To identify the maximum tolerated dose (MTD) of olaparib in haematological tumours
  - MTD in solid tumours is 400mg bd ?the same
- **Phase II:** To assess the efficacy of olaparib in patients with ATM deficient, CLL

## Exploratory Objectives (phase 2):

- Develop biomarkers for the activity of this agent

# Trial outcome measures

## Primary outcome measures:

- Demonstrate sufficient efficacy of olaparib in CLL, ATM<sup>-</sup> patients to warrant Phase III investigation
  - Defined as:  $\geq 20\%$  of patients with CR/PR following 16 weeks treatment
  - CR/PR defined by:
    - CLL & T-PLL: International Workshop on Chronic Lymphocytic Leukaemia
    - MCL: International Workshop to Standardize Response Criteria for non-Hodgkins Lymphoma

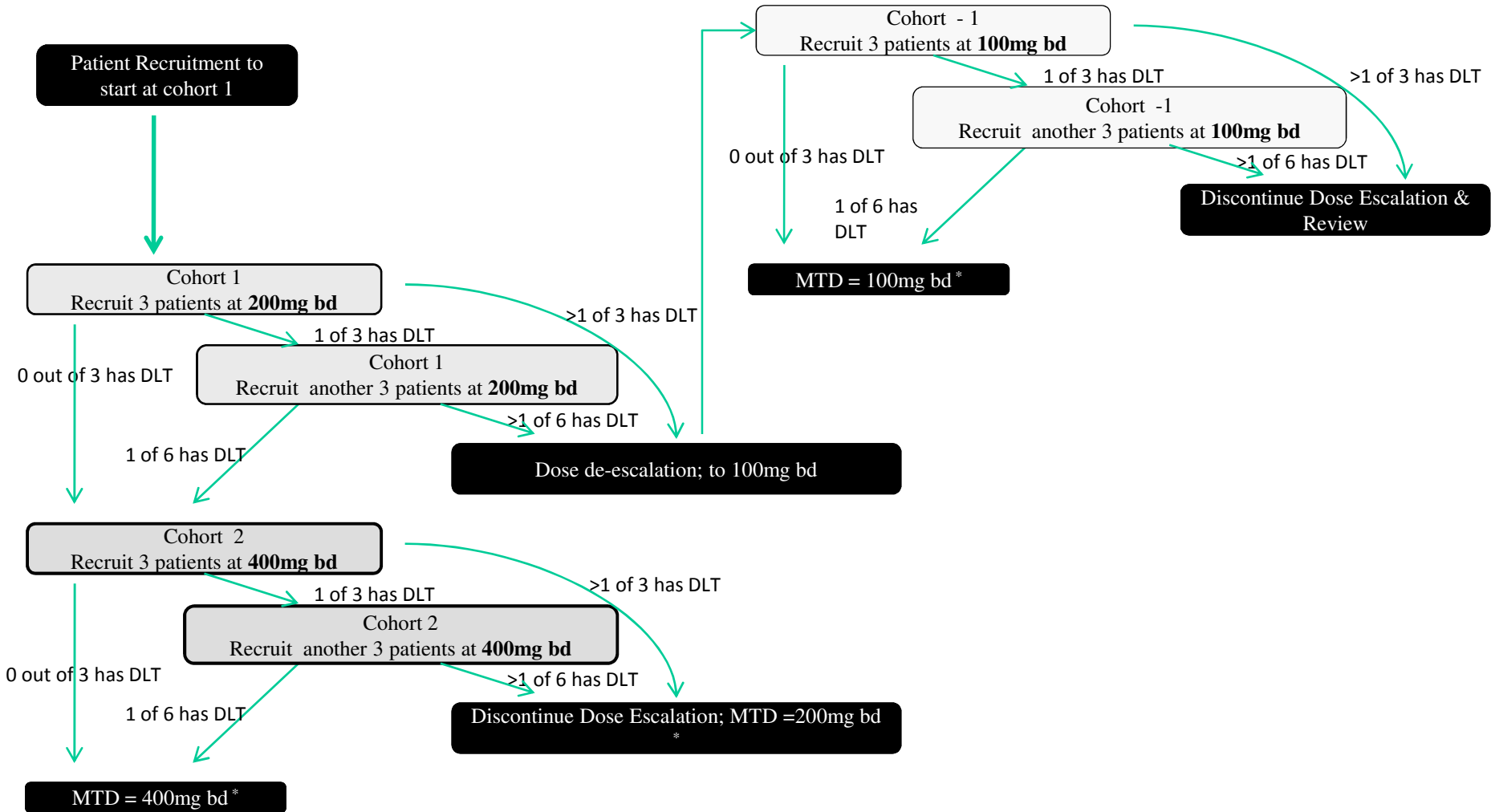
## Secondary outcome measures:

- Evidence of efficacy within CLL, MCL, T-PLL patients dependent on ATM status of remaining ATM allele
- Measure PFS and OS of patients treated with Olaparib
- Determine safety, tolerability and toxicity of olaparib treatment

# Phase I

## Dose escalation study

## Cumulative 3+3 design



\* An extra 3 patients will be recruited (if necessary) so that 6 patients will be treated at the proposed MTD.

# Eligibility – Inclusion Criteria

- Relapsed/Refractory CLL, MCL or T-PLL not considered for further conventional treatment
- For CLL patients, Phase II only:
  - Confirmation of chromosome 11q deletion by FISH, or
  - Confirmation of ATM mutation
- ECOG performance status  $\leq 2$
- $\geq 18$  years, with written informed consent
- No known HIV Ab, Hep B surface antigen, or Hep C Ab
- Estimated life expectancy  $> 16$  weeks

# Eligibility – Exclusion Criteria

- ✍ Receiving treatment for CLL, MCL, T-PLL 4 weeks prior to study entry
- ✍ Receiving corticosteroid treatment
- ✍ Previous PARP-inhibitor treatment
- ✍ Known hypersensitivity to Olaparib or any component of the product
- ✍ Treatment with any IMP within 28 days of registration
- ✍ Receiving CYP3A4 inhibitors:
  - Azole antifungals; Macrolide antibiotics; Protease Inhibitors

## CYP3A4 inducers/inhibitors

Phenytoin

Rifampicin

Carbamzepine

Modafinil

Ketoconazole

Itraconazole

Clarithromycin

# Eligibility – Exclusion Criteria

- ✎ Impaired hepatic/renal function
  - ALT/AST  $>2.5 \times$  ULN, Bilirubin  $>2 \times$  ULN, Serum Creatinine  $>2 \times$  ULN
- ✎ Persisting severe pancytopenia from previous therapy
- ✎ CNS involvement with CLL
- ✎ Cardiac Dysfunction
- ✎ Other malignancies active/treated within past 3 years
- ✎ Inability to swallow medications

# Eligibility – Exclusion Criteria

- ✍ Uncontrolled seizures
- ✍ Active infection requiring antibiotic/antiviral/antifungal drugs
- ✍ Concurrent severe and/or controlled medical or psychiatric condition
- ✍ Pregnant/lactating women
- ✍ Women/partners of women with child bearing potential unwilling to use contraception.

# Baseline Tests (pre treatment)

## Physical Exam

- Spleen, Liver and Lymph

- Height and weight

- Ongoing Medical Conditions

## Haematology and Biochemistry

- Amylase (if conducted locally)

## Peripheral Blood Sample for exploratory analysis

## Bone Marrow (not mandatory for phase I)

## CT Scan (not mandatory for phase I)

## Complete CRFs: (Initial Disease Assessment Form, Medical Screening Form & Concomitant Medication Form)

# Trial Treatment



- White, size 0, gelucire capsules (50mg)
- Taken whole (not chewed/crushed/dissolved/divided)
- same time everyday, 1 hour after food twice daily
- Refrain from eating for further 2 hours

## Phase I:

- Take olaparib @ allocated dose for cohort
- Dose = BD
- No dose delays/reductions allowed

Cohort	Dose (Twice Daily)	Number of tablets (Twice Daily)
Cohort 1	200mg	4
Cohort 2	400 mg	8
Cohort -1	100 mg	2

## Phase II:

- Take olaparib at MTD established from phase I

# Trial Treatment Phase I

- Initially 8 weeks of treatment to assess safety. If three patients get to week 8 without DLT then next cohort can start.
- First cohort= three patients at 200mg bd
- Second cohort = three patients at 400mg bd
- Patients may continue to receive olaparib at allocated dose as long as clinical benefit
  - At discretion of Investigator
  - Progressive disease or unacceptable toxicity indication to stop

# Trial Treatment Phase II

- ✍ Dose determined from phase I
- ✍ Patients may continue to receive olaparib at allocated dose as long as clinical benefit
  - ✍ At discretion of Investigator
  - ✍ Progressive disease or unacceptable toxicity indication to stop

# Patient Schedule

- Weeks 1-8 -seen weekly
  - Weeks 8-16 seen fortnightly
  - Week 16 disease assessment (CT and bone marrow)
  - Monthly thereafter
- 
- Investigations
    - Physical Exam (inc ECOG, weight, Spleen, Liver and Lymph)
    - Haematology and Biochemistry
- 
- Safety
    - Record ALL adverse events
- 
- Compliance

# Sample Collection

## Phase I

- 20ml peripheral blood (in lithium heparin) at baseline

## Phase II

- 20ml peripheral blood (in lithium heparin) at baseline
- Fresh bone marrow biopsy and lymph node biopsy (where possible) at baseline and 16 weeks

## Send using safeboxes provided by PICLLe Trial Office

- Central Laboratory Labels provided

## Immediately, at ambient temperature

## Complete Pre-Treatment Sample Form

- Fax Form immediately to Trial Office

# Dose Limiting Toxicities

A Dose Limiting Toxicity (DLT) is defined as a drug-related:

- **Grade  $\geq 3$  non-haematological toxicity**

- excluding nausea and vomiting or diarrhoea unless not resolved by symptom-directed therapy

- **All Grade 4 haematological toxicities**


- Thrombocytopenia with platelets  $< 10 \times 10^9/L$  despite transfusion support  $\geq 7$  days

- Grade 4 neutropenia for  $\geq 7$  days

## UK Centres

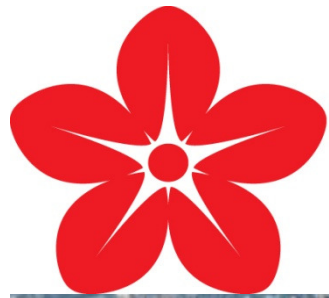
-  Heartlands, Birmingham
-  Queen Elizabeth, Birmingham
-  Addenbrookes
-  Bournemouth
-  Cardiff
-  Christie
-  Hull
-  Kings
-  Leeds
-  Leicester
-  Liverpool
-  Marsden
-  Plymouth

# Contact Details

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**Leukaemia &  
Lymphoma Research**  
BEATING BLOOD CANCERS



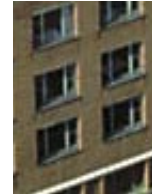
Thanks to...  
Tanja Stankovic  
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Belinda Austen  
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Anna Skowronska  
Azra Alvi  
Judy Powell  
Malcolm Taylor

*lora* Nicola Fenwick  
*lora* Andrea Liggett  
*lora* Chris Parry



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