New Therapies in CLL: Clinical Trials – An Overview

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5th May 2018
Key Developments in CLL suggesting a cure is achievable

1. Understanding the biology of CLL
2. Development of MRD surrogate end-point
3. Advances in targeted therapy of CLL
4. Application of Adaptive Trial Design
   a) Novel combinations
   b) Stratifying by biological criteria
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   a) Novel combinations
   b) Stratifying by biological criteria
“Life Cycle” of the CLL Cell

Peripheral circulation

Tissue compartments

CLL cell

- BCR
- TLR9
- CXCL13
- CXCR-5
- CD38
- CD40
- CXCR-4
- CCL3, CCL4
- CD40L
- VCAM-1
- I-CAM
- FDC
- BAFF
- CXCL12
- NLC

Stromal

CpG DNA

Antigen

Peripheral circulation connected to Tissue compartments by arrows.
Pathophysiology of CLL: proliferation and apoptosis

“Proliferation” - CLL cells grow constantly

“Apoptosis” - CLL don’t die when they should
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Time to CLL progression after FCR

Minimal Residual Disease (MRD) = <1 CLL cell in 10,000 normal cells

Impact of MRD levels on long-term outcomes in CLL

Conceptual illustration.

- Before therapy
- During therapy
- Time after therapy

**Tumour load**
- MRD +ve without clinically measurable disease
- MRD –ve
- Cure
- Clinically measurable disease
- Clinical relapse
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Pathophysiology of CLL: proliferation and apoptosis

Proliferation

Apoptosis

Ibrutinib

Venetoclax

Ki-67 expression

BCL-2 expression
Development of ibrutinib

Person: Ogden Bruton (1908-2003)

Disease: Bruton’s Agammaglobulinemia, 1952

Enzyme: Bruton Tyrosine Kinase, 1993


ibrutinib
# Response to ibrutinib

<table>
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<tr>
<th>Time</th>
<th>WBC</th>
<th>Neut</th>
<th>Lymph</th>
<th>Hb</th>
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<td>Pre</td>
<td>104 x 10^9/l</td>
<td>4.4 x 10^9/l</td>
<td>98.6 x 10^9/l</td>
<td>101 g/l</td>
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<td>8 weeks</td>
<td>37.2 x 10^9/l</td>
<td>2.3 x 10^9/l</td>
<td>34.3 x 10^9/l</td>
<td>102 g/l</td>
<td>99 x 10^9/l</td>
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<td>6 months</td>
<td>5.6 x 10^9/l</td>
<td>3.3 x 10^9/l</td>
<td>1.8 x 10^9/l</td>
<td>125 g/l</td>
<td>157 x 10^9/l</td>
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Response to venetoclax

CT scan
Pre-treatment

CT scan
Week 24
Response to venetoclax Bone Marrow analysis

Orange events = CLL cells
Purple events = T-cells

Pre-venetoclax

6 months of venetoclax

No detectable CLL <0.01%!!
CLL: A rapidly changing world!

UK FRONT-LINE CLL TRIALS

**MRC CLL1**
- n=660

**MRC CLL2**
- n=640

**MRC CLL3**
- n=418

**LRF CLL4**
- n=777

**NCRI RIALTO**
- n=565

**NCRI FLAIR1**
- n=754

**NCRI FLAIR2**
- n=822

**MRC CLL1**
- 1978
- Chlorambucil
- Prednisolone

**MRC CLL2**
- 1983
- Chlorambucil
- Prednisolone

**MRC CLL3**
- 1988
- Prednisolone

**LRF CLL4**
- 1993
- Fludarabine
- Cyclophosphos

**NCRI RIALTO**
- 1998
- Chlorambucil
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**NCRI FLAIR1**
- 2003
- Fludarabine
- Cyclophosphos
- Rituximab

**NCRI FLAIR2**
- 2008
- Bendamustine
- (Rituximab)
- Venetoclax
- Obinutuzumab

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Trials in CLL: the challenges

1. Rapidly evolving standard of care
   i.e. Front-line elderly: 2010 chlorambucil monotherapy; 2013 chl+anti-CD20; 2015 ibrutinib monotherapy;

2. Rapidly evolving novel therapies
   a. Single agents and combinations
   b. Different MOA and end-points
   c. Short and long-term toxicity

3. Iterative learning from trials
UKCLL Trials: Aims

1. Effective therapy regardless of:
   a. Age or co-morbidity
   b. Disease sub-group (FISH, molecular, etc.)
   c. Front-line and relapsed or refractory CLL

2. Tolerable therapy
   a. Short-term toxicity of single agent and combinations
   b. Long-term toxicity of combinations
   c. Duration of therapy – definition of response

3. Curative therapy or disease control
   a. Do we need to cure?
   b. Do we need to eradicate disease?
   c. How do we not harm patients by stopping too soon?
Integration of Phase I/II and III trials

Phase III Trials
- Adaptive trial design – changing standard of care
- Adaptive – changing end-points of therapy and trial
- Adaptive – by biology

Phase I/II Trials
- Acceleration and streamlined
- Biological correlative studies and biobanking
- Combinations that are informative for Phase III
UK CLL Trials Biobank

Manager: Dr Melanie Oates
melly@liverpool.ac.uk

Samples stored in the UK CLL Trials Biobank

- Samples collected in GLP facility
  - Viable mononuclear cells
  - Serum/plasma
  - Germline DNA (saliva)
- Pre-treatment and sequential (depending on trial)
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<td>11</td>
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<td>CyCLLe</td>
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<td>Baseline</td>
<td>5</td>
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**Total (March ‘18):**

1,624 patients; 3,785 samples
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Feasibility study is to confirm the mechanism of action of ibrutinib. Results from this trial will then inform the design of a randomized phase II/III trial using response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity in these cohorts of patients.

- Cohort A (Treatment naïve): 20 patients
- Cohort B (Relapsed/Refractory): 20 patients
Translational Research

Ibrutinib Extension Study

**N=40**

**Frequent Samples:**
- **PB:** -14d, 0, 4, 24, 7d, 14d, 28d, 56d, 6mo
- **BM:** -14d, 28d, 6mo

**Immunophenotyping**

**PhosPho Flow (signaling)**

**Calcium flux (functional)**

**Epigenetics**

**Genetics**

**Resistance mechanisms**

- **EGR1 coding region**
- **In vitro Kinase assay**
40 patients with relapsed/refractory CLL

Cohort A: 20 patients roll-over from IcIcICLLe
Cohort B: 20 ibrutinib naïve patients

Assessment of the Mechanism of Action of Ibrutinib plus obinutuzumab in CLL

• MRD response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity

• Results will inform a potential modification of Flair
50 patients with relapsed/refractory CLL who are ibrutinib naïve
Using TAP trials to inform Phase III

FLAIR

FCR  n=377

Ibrutinib+R  n=377

R

Front-line

Relapsed/refractory

IcICLLe
(Ibr mono)  IcICLLe amendment
(I+Obinutuzumab)
Using TAP trials to inform Phase III

FLAIR

FCR  n=377

Ibrutinib+R  n=377

Front-line

Relapsed/refractory

IcICLle (Ibr mono)

IcICLle amendment (I+Obinutuzumab)

CLARITY (I+venetoclax)
Using TAP trials to inform Phase III

FLAIR amended

- FCR
  - n=566

- Ibrutinib+R
  - n=377

- Ibrutinib+R (ibr mono)
  - n=377

- IcICLLe amendment (I+Obinutuzumab)
- CLARITY (I+Venetoclax)
- LLR TAP4 (I+X+Y)
- LLR TAP5 (I+X+Z)

Front-line
Refractory
Relapsed/refractory
Using TAP trials to inform Phase III

**FLAIR amended**
- Ibrutinib+R (n=377)

**FLAIR 2**
- Ibr+venet (n=377)
- FCR (n=566)

**Front-line**
- Ibrutinib (Ibr mono)
- IcICLLe amendment (I+Obinutuzumab)
- CLARITY (I+venetoclax)

**Relapsed/refractory**
- LLR TAP4 (I+X+Y)
- LLR TAP5 (I+X+Z)
Initial Results of Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL (Bloodwise TAP CLARITY Study): High Rates of Overall Response, Complete Remission and MRD Eradication after 6 Months of Combination Therapy

Peter Hillmen, Talha Munir, Andy Rawstron, Kristian Brock, Samuel Muñoz-Vicente, Francesca Yates, Rebecca Bishop, Christopher Fegan, Donald MacDonald, Alison McCaig, Anna Schuh, Andrew Pettitt, John G. Gribben, Stephen Devereux, Adrian Bloor, Christopher P. Fox, Francesco Forconi

Abstract: 428
Sunday, December 10, 2017: 12:15 PM
Venetoclax (400mg/day)
Ibrutinib (420mg/day)

Bone marrow
CT-scan

- VEN and IBR stop at 14 months if 8 month BM is MRD negative
- VEN and IBR stop at 26 months if 14 month BM is MRD negative
- IBR alone continues if 26 month BM is MRD positive

Hillmen et al. ASH 2017; Abst 428
Patient Recruitment

- 4 patients stopped ibrutinib before adding venetoclax due to toxicity
- 50 patients recruited to combination part of trial
- 49 patients successfully passed through venetoclax escalation phase

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<th>TNO</th>
<th>Toxicity category/event</th>
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<td>Infections and infestations</td>
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<td>25</td>
<td>Brain abscess</td>
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<td>34</td>
<td>Vascular disorder</td>
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<td>50</td>
<td>Gastrointestinal disorder, renal disorder, general disorder, injury</td>
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</table>

50 patients recruited in 15 months – 9 months ahead of target.
PB & BM MRD level by time-point (up to 6 months I+V)

Peripheral Blood CLL Level

- Venetoclax
- Ibrutinib

 Bone Marrow CLL Level

- Venetoclax
- Ibrutinib

Percentage of patients

- MRD5 (<0.001%)
- MRD4 (0.001% - 0.01%)
- 0.01 - 0.1%
- 0.1 - 1%
- 1 - 10%
- >10%

PRE (n=42)
WK8 (n=42)
M4 (n=42)
M5 (n=40)
M8 (n=40)

PRE (n=42)
WK8 (n=42)
M8 (n=40)

Hillmen et al. ASH 2017; Abst 428
Using TAP trials to inform Phase III trials

- **Flair**
  - **Front-line**
  - **Relapsed/refractory**

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<thead>
<tr>
<th>Years</th>
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- **Ibrutinib + rituximab**
  - **Ibrutinib + venetoclax**
  - **Ibrutinib (Ibr mono)**
  - **Ibrutinib + Obinutuzumab (I+Obinutuzumab)**
  - **CLARITY (IBR + VEN)**

- TAP Bloodwise: Beating blood cancer since 1960
- NCRI National Cancer Research Institute: Partners in cancer research
- ctru University of Leeds
- CRCTU Cancer Research UK Clinical Trials Unit
NCRI Flair (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab

As of 9\textsuperscript{th} April 2018

823 patients randomised in total
(728 patients randomised to FCR / IR (97\% of 754))

Monthly recruitment targets
7 per month Sept ‘14 – Feb ‘15 (6 months)
22 per month Jul ‘17 – Apr ‘18 (10 months)
17 per month Mar ‘15 – Jun ‘17 (2.5 years)
30 per month May ‘18 – Jan ‘20 (2 years)

Centres open: 98
Chronic Lymphocytic Leukaemia: 2018

Advances in the therapy of CLL
• Targeting BCR signaling or apoptosis are extremely effective in CLL
• Linking together Phase I/II and Phase III programmes allows rapid acceleration of combination therapies into front-line CLL
• Biobanking & translational research critical to improving outcomes
• Detailed health economic analysis in large NCRI trials

Challenges/opportunities
• Current therapies for CLL lead to long remissions therefore we need to design trials large enough and using early end-points to move forward quickly
• We need to ensure patients are followed up for the long-term
• We need to collect “real-world” information to ensure patients unable to enter trials are also benefitting
Acknowledgements

NCRI CLL Trials Sub-group

Peter Hillmen (Chair)
David Allsup
Garry Bisshopp
Adrian Bloor
Daniel Catovsky
Claire Dearden
Caroline Duncan
Martin Dyer
Chris Fegan
George Follows

Francesco Forconi
Chris Fox
John Gribben
S Hewamana
Anna Hockaday
Dena Howard
Claire Hutchinson
Ben Kennedy
Scott Marshall
Alison McCaig

Helen McCarthy
Mel Oates
Piers Patten
Andy Pettitt
Chris Pocock
Guy Pratt
Anna Schuh
Jon Strefford
Renata Walewska
Nick York

UKCLL Trials

Biobank,
Melanie Oates
Melanie Goss
Emily Cass
Andy Pettitt

HMDS, Leeds
Andy Rawstron
Talha Munir
Ruth de Tute
Nicola Webster
Jane Shingles
Cathy Burton

University of Leeds
Katie Holmes
Charlotte Evans
Pascal LeFevre

Surita Dalal
Alasdair Dewar
Darren Newton

University of Leeds

Patients with CLL and their families

Hospitals and trials teams

Abbvie Janssen Novartis Acerta/AZ
Napp Pharmacyclics Gilead Roche

Leeds CTRU

Anna Hockaday
Jamie Oughton
Lucy Williams
Claire Dimbleby
David Philips
Seren Langley
James Baglin
Julia Brown

Dena Howard
Fabrizio Messina
Lucy McParland
David Stones
Chris Linsey
David Cairns
Walter Gregory

Bloodwise TAP Programme
Rebecca Bishop
Kristian Brock
Tina McLeod
Yolande Jefferson-Hulme
Shamyla Siddique
Francesca Yates
Samuel Muñoz-Vicente
Sonia fox
Sophie Cramp
Charles Craddock

Liverpool CTU
Matthew Bickerstaff
James Dodd
Lucy Read
Chantelle Murphy
Zelicia Gerald
Jo Goulding
Frances Sweeney
Zviona Gore
Kate Culshaw
Bernadette O’Donnell

The Leeds Teaching Hospitals
The Royal Liverpool and Broadgreen University Hospitals

Cancer Research UK

University of Oxford

Bloodwise
Beating blood cancer since 1960