New Therapies in CLL: Clinical Trials – An Overview

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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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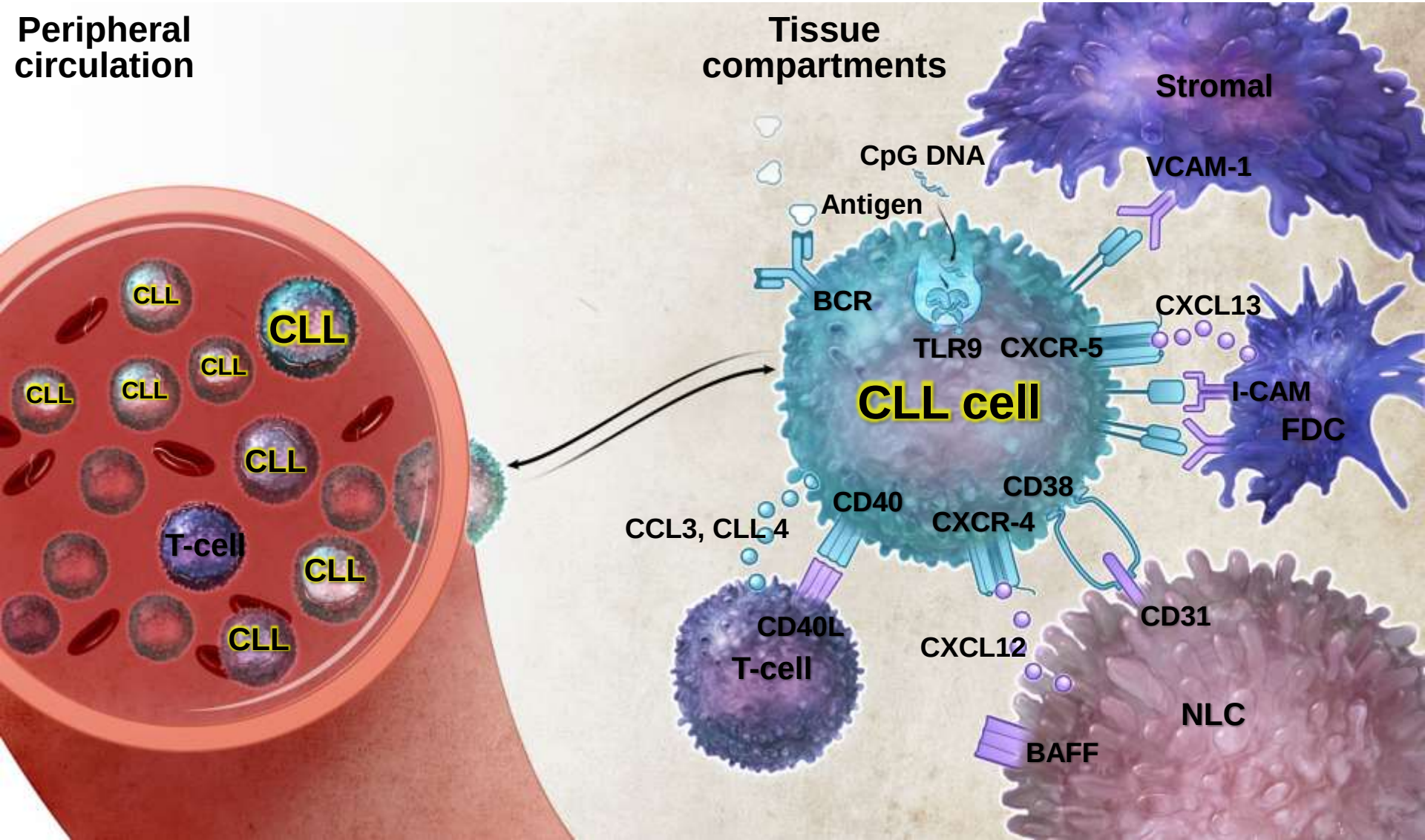
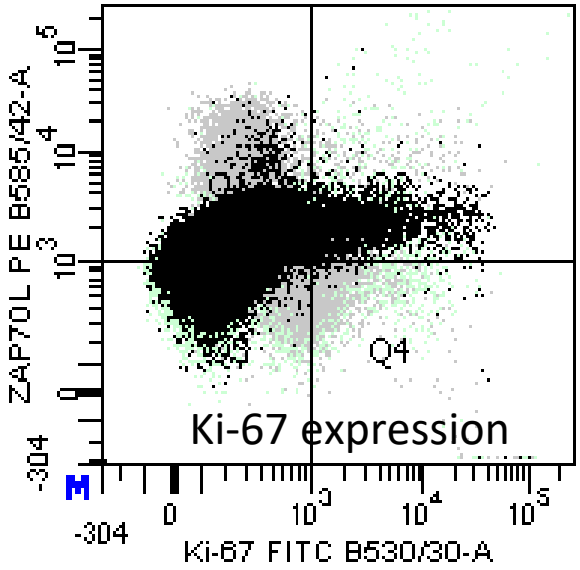
“Life Cycle”of the CLL Cell

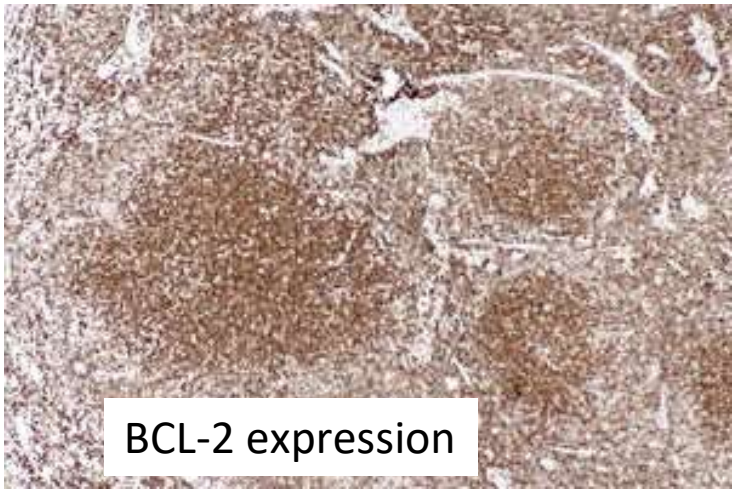


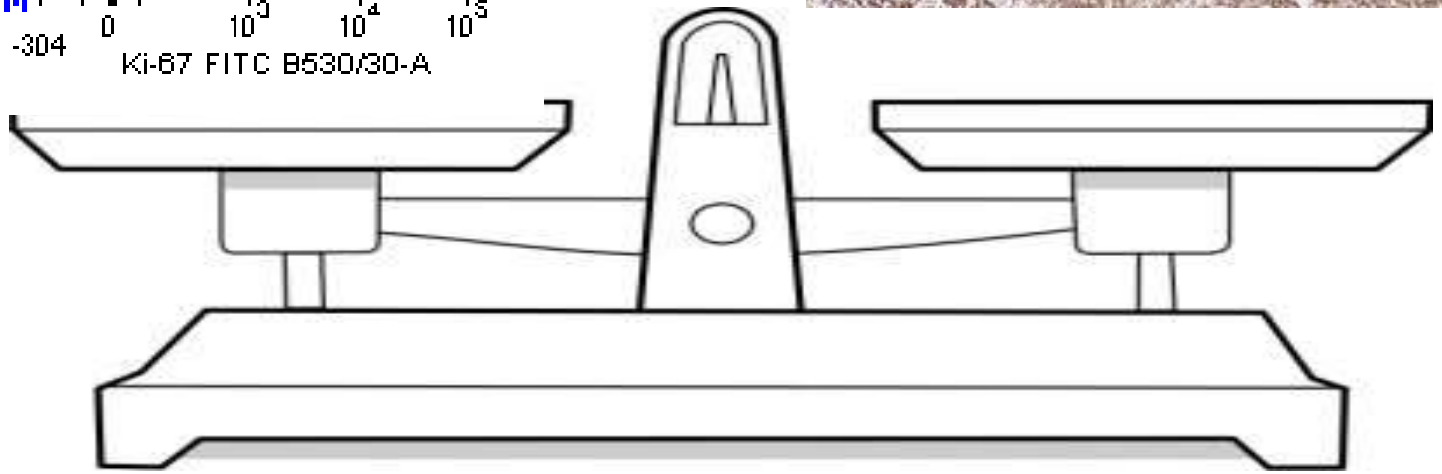
Pathophysiology of CLL: proliferation *and* apoptosis

"Proliferation" - CLL cells grow constantly

"Apoptosis" - CLL don't die when they should







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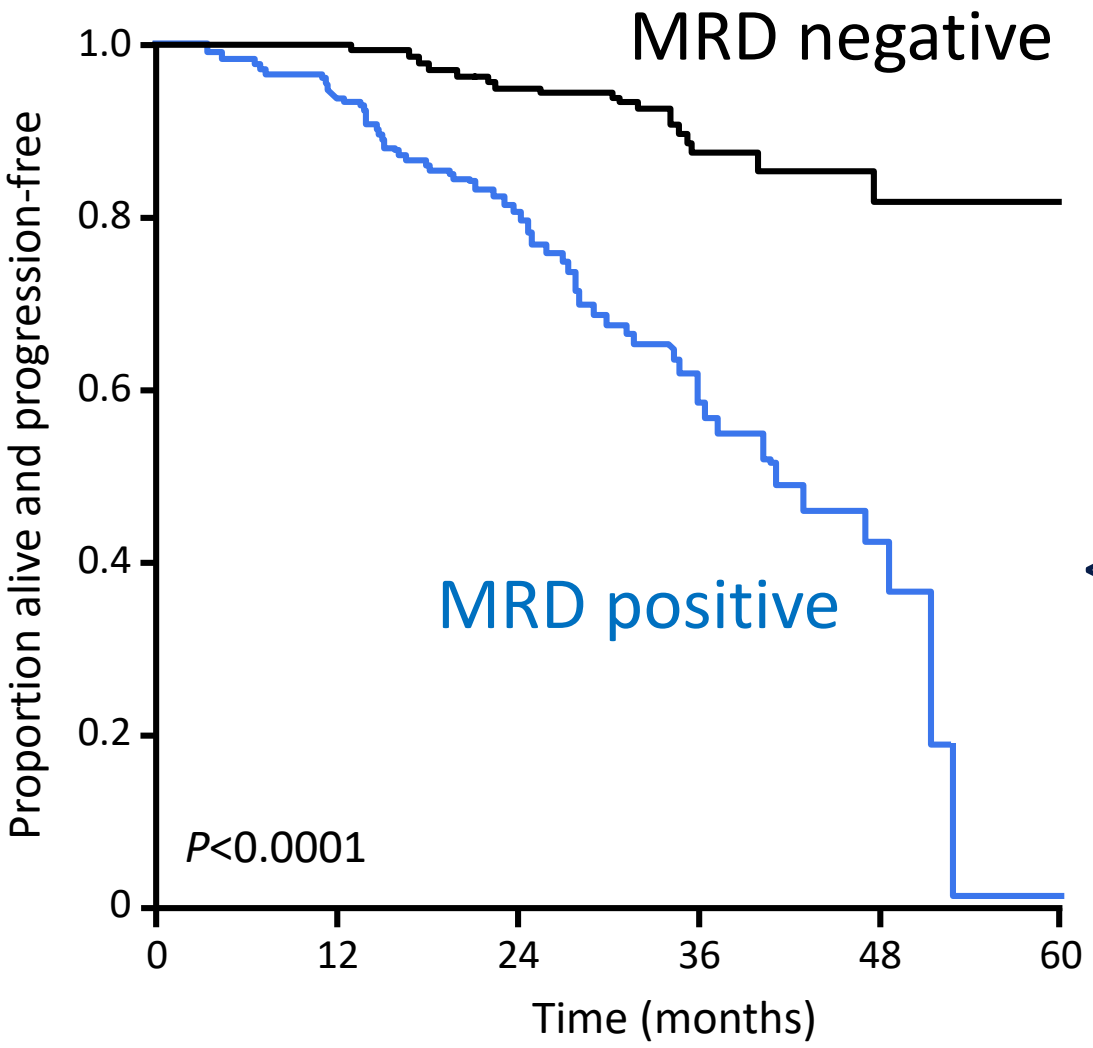
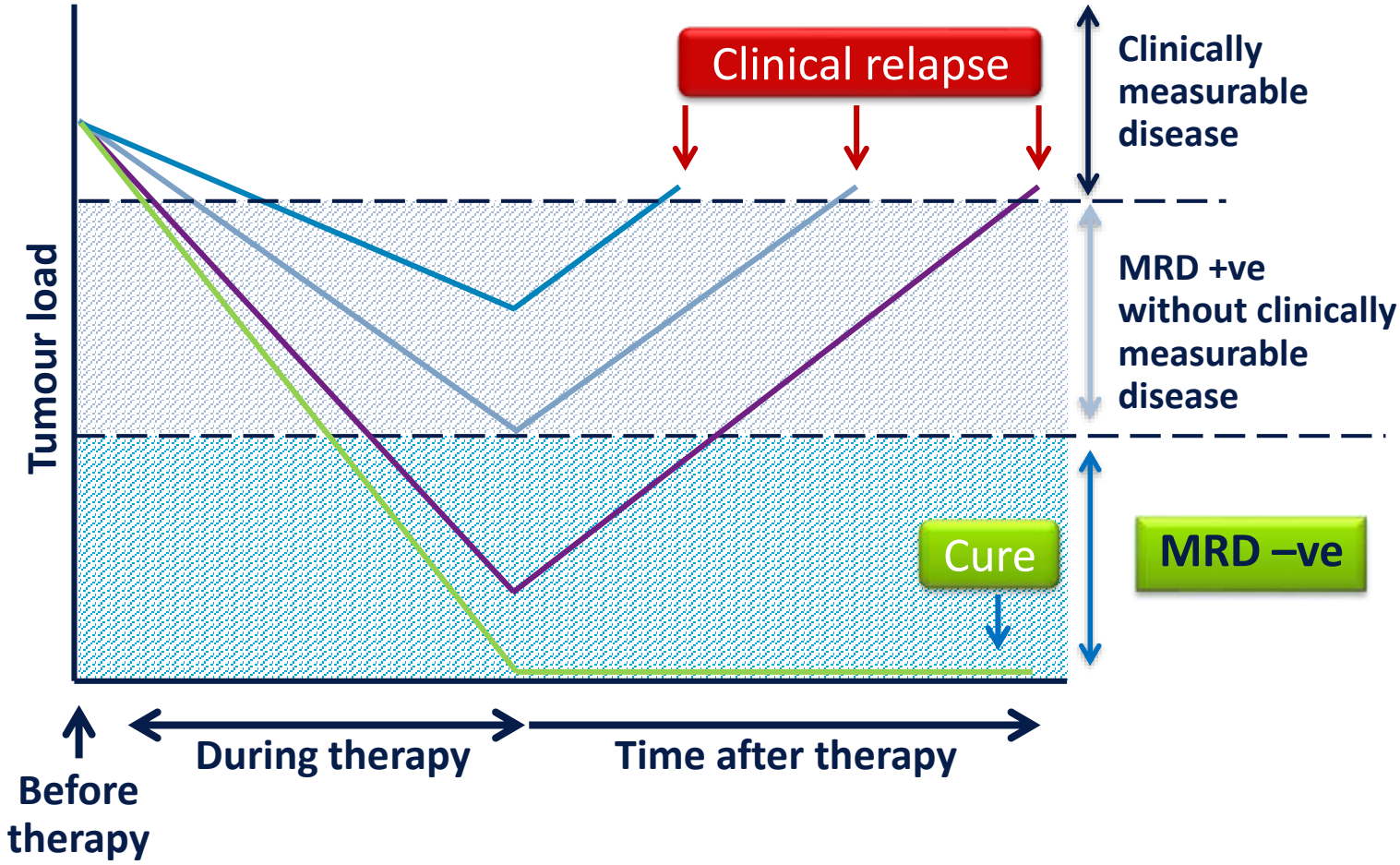
Time to CLL progression after FCR



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

Rawstron A, *et al.* EHA Annual Meeting 2015; Abstract S794.

Impact of MRD levels on long-term outcomes in CLL



Conceptual illustration.

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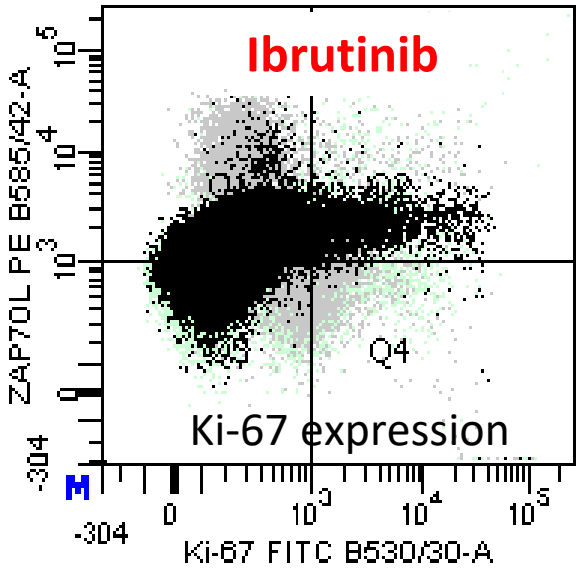
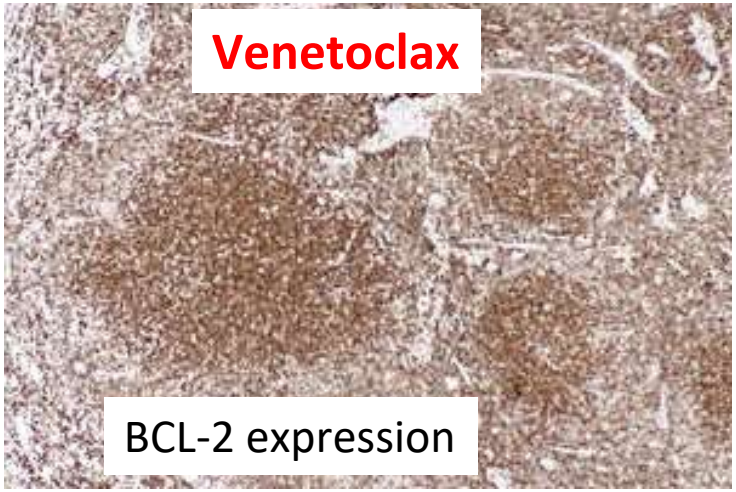
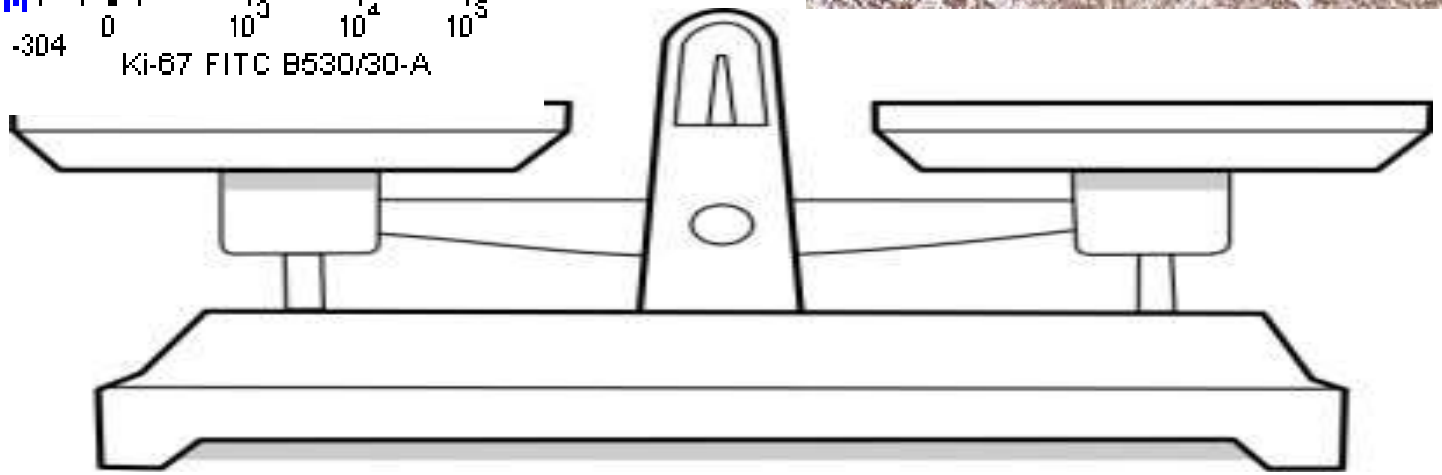
Pathophysiology of CLL: proliferation *and* apoptosis

Proliferation



Apoptosis



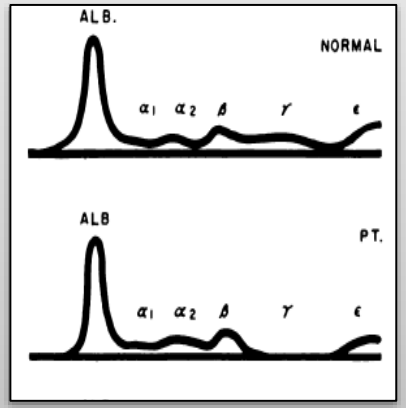


Development of ibrutinib

Person

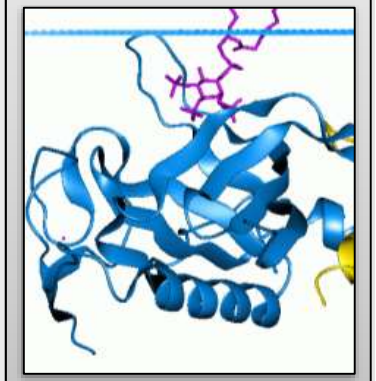
Ogden *Bruton*
(1908-2003)

Disease



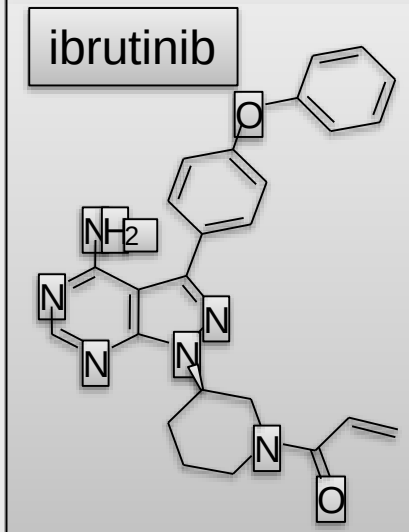
Bruton's
Agammaglobulinemia,
1952

Enzyme



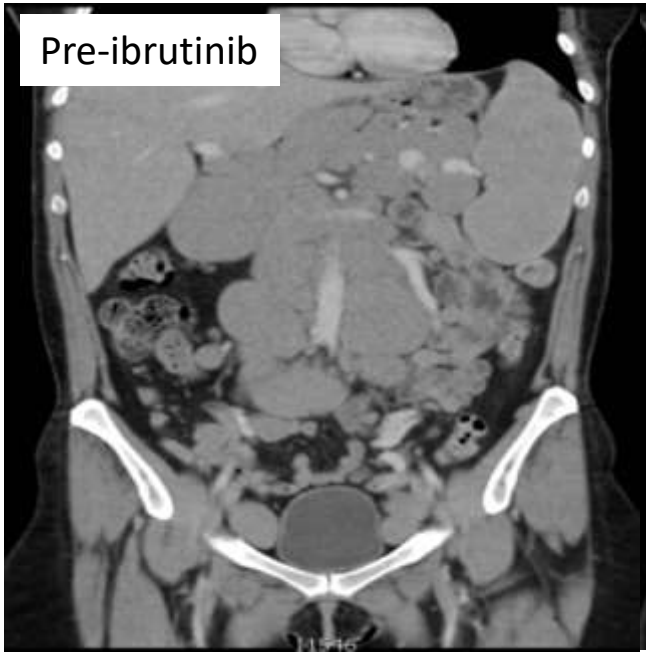
Bruton
Tyrosine
Kinase, 1993

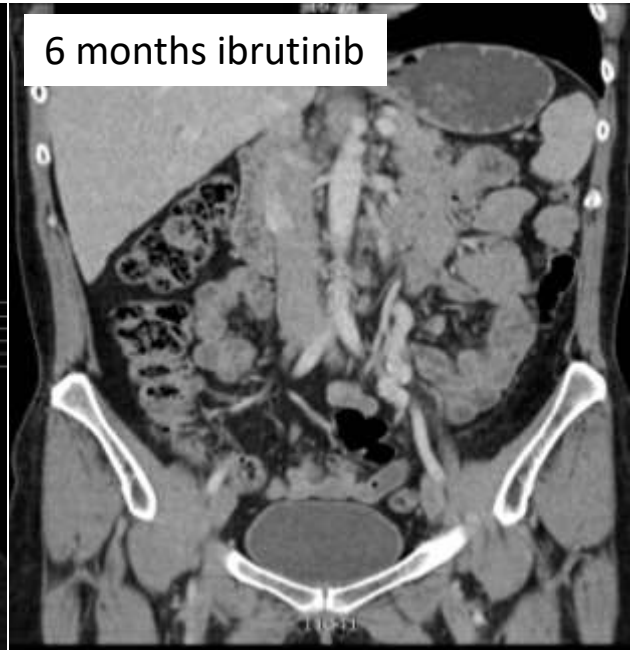
Drug



Synthesized 2005
First in human 2009
1st approval 2013

Response to ibrutinib



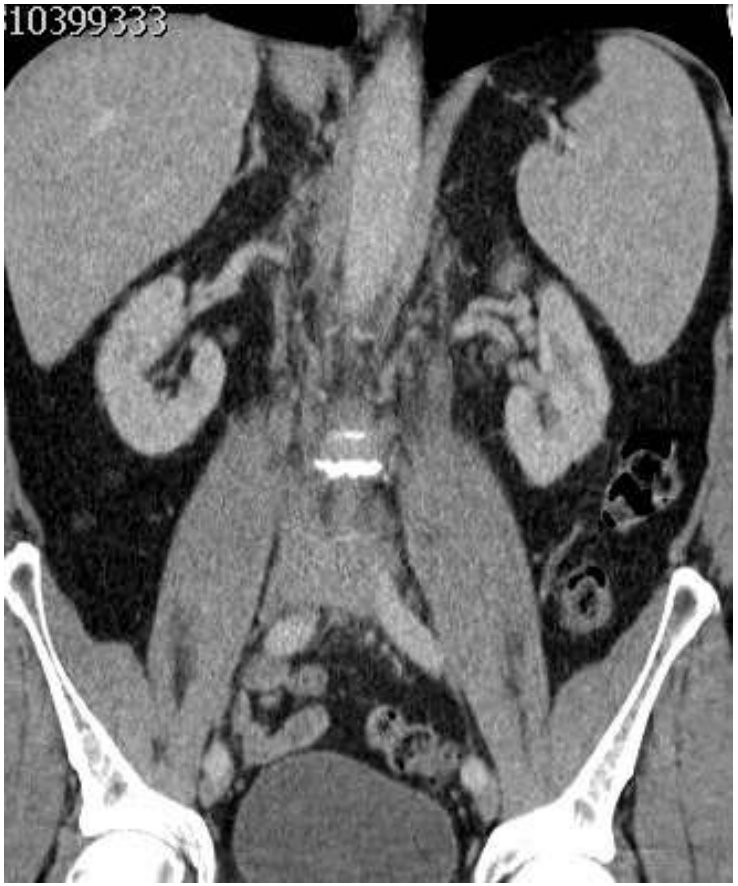


WBC	104 x 10^9/l	WBC	37.2 x 10^9/l	WBC	5.6 x 10^9/l
Neut	4.4 x 10^9/l	Neut	2.3 x 10^9/l	Neut	3.3 x 10^9/l
Lymph	98.6 x 10^9/l	Lymph	34.3 x 10^9/l	Lymph	1.8 x 10^9/l
Hb	101 g/l	Hb	102 g/l	Hb	125 g/l
Plt	72 x 10^9/l	Plt	99 x 10^9/l	Plt	157 x 10^9/l

Response to venetoclax

CT scan
Pre- treatment

CT scan
Week 24

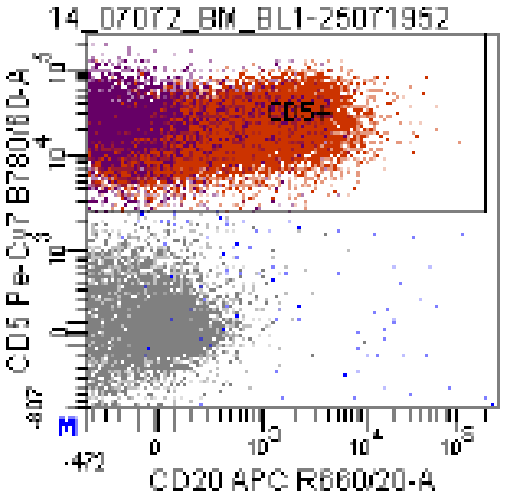


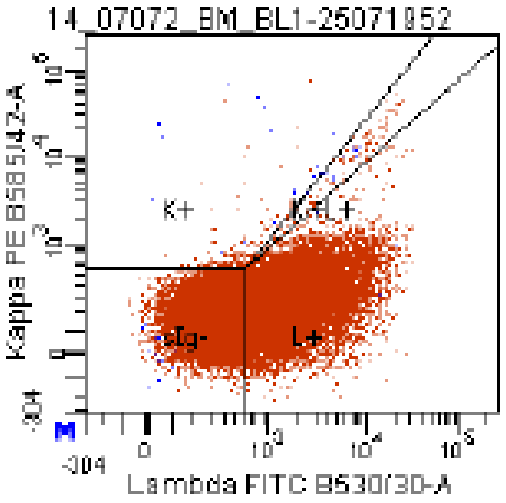
Response to venetoclax
Bone Marrow analysis

Orange events
= CLL cells

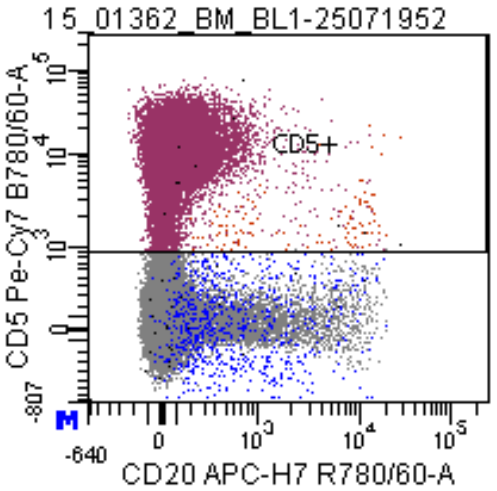
Purple events
= T-cells

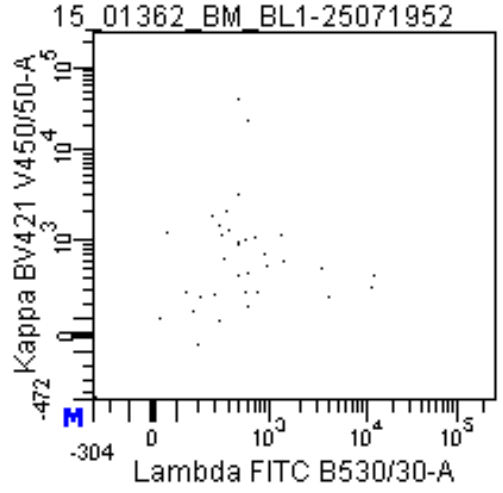
Pre-venetoclax





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 ADM/ARC n=565

NCRI RIALTO n=565

NCRI FLAIR1 n=754

NCRI FLAIR2 n=822

1978 1983 1988 1993 1998 2003 2008 2014 2018

Chlorambucil

Chlorambucil Prednisolone

Fludarabine

Fludarabine Cyclophos

Campath

Fludarabine Cyclophos Rituximab

Ofatumumab

Chlorambucil Obinutuzumab

Ibrutinib

Venetoclax Obinutuzumab

Bendamustine (Rituximab)

Chlorambucil Ofatumumab

Idelalisib Rituximab

Acalabrutinib

Venetoclax Ibrutinib Obinutuzumab

Acalabrutinib ±obinutuzumab

Zanbrutinib

Venetoclax

SNS-62

AZD6738

Ibrutinib + TGR-1202

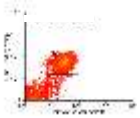
Venetoclax

Tirabrutinib

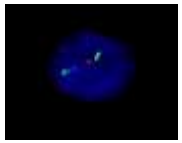
CAR-T

Morphology

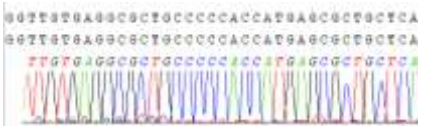
Flow



FISH



Sanger



NGS WGS

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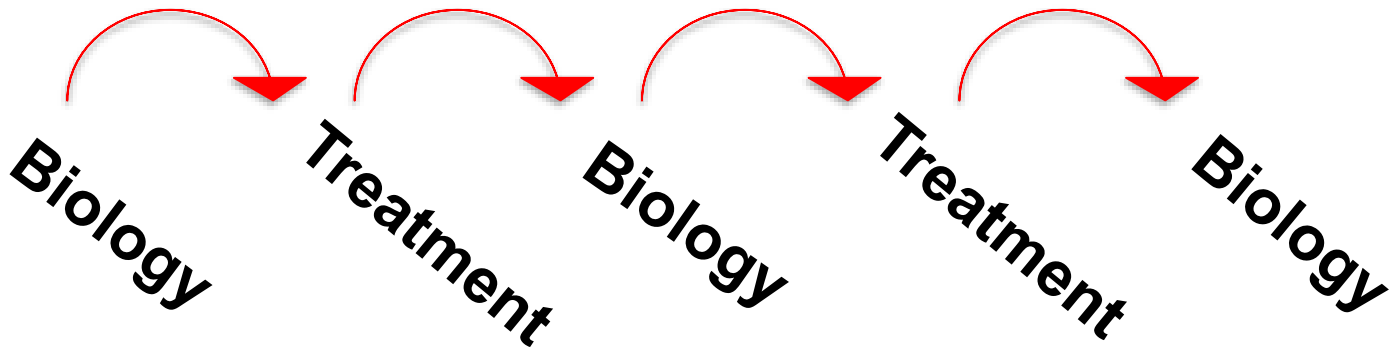
Trials in CLL: the challenges

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

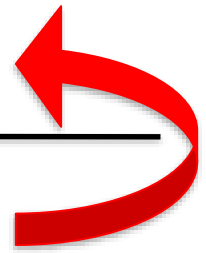
2. **Tolerable therapy**
   a. Short-term toxicity of single agent and combinations
   b. Long-term toxicity of combinations
   c. Duration of therapy – definition of response

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

Front-line

Relapsed/ refractory

NCRI National Cancer Research Institute

TAP Bloodwise
Beating blood cancer since 1960

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)

Bloodwise
Beating blood cancer since 1960

Trial	Recruited	Time point	No Patients
AdMire	215	Baseline	168
		Response	97
		Progression	41
ARCTIC	200	Baseline	172
		Response	95
		Progression	40
RESPECT	5	Baseline	5
CHOP-OR	34	Baseline	31
		Progression	2
CLEAR	78	Baseline	67
		Follow up	51
FLAIR	805	Baseline	531
		Follow up	257
		Progression	17
GALACTIC	26	Baseline	24
		Response	8
		Progression	2

Trial	Recruited	Time point	No Patients
RIAltO	430	Baseline	479
		Follow-up	910
		Progression	92
CLL210	64	Baseline	69
		Sequential samples	455
		Progression	15
COSMIC	61	Baseline	52
		Response	31
		Progression	18
IcICLLe	40	Baseline	21
		1 month	19
		6 months	11
CyCLLe	5	Baseline	5

Total (March '18):
1,624 patients; 3,785 samples

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Assessment of the Mechanism of Action of Ibrutinib (PCI-32765) in B-cell Receptor Pathway Inhibition in CLL

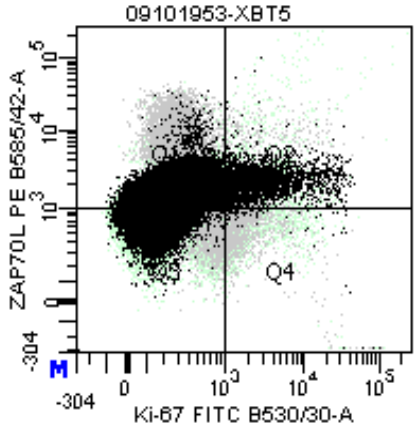
Feasibility study is to confirm the mechanism of action of ibrutinib. Results from this trial will then inform the design of a randomized phase II/III trial using response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity in these cohorts of patients.

- **Cohort A (Treatment naïve)**: 20 patients
- **Cohort B (Relapsed/Refratory)**: 20 patients

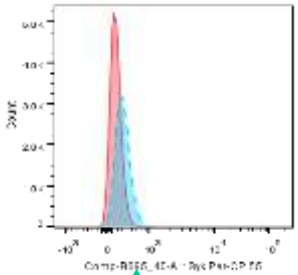
TAP
Bloodwise
Beating blood cancer since 1960

Translational Research

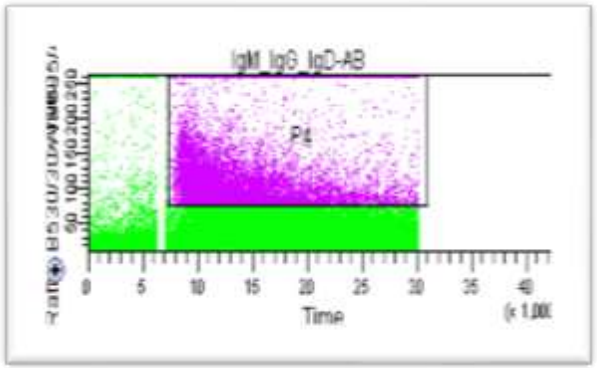
Immunophenotyping



PhosPho Flow (signaling)



Calcium flux (functional)



Ibrutinib

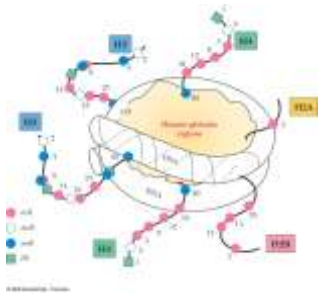
N=40 → Extension study

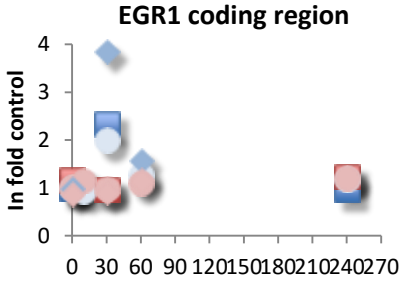
Frequent Samples:

PB: -14d, 0, 4, 24, 7d, 14d, 28d, 56d, 6mo

BM: -14d, 28d, 6mo

Epigenetics

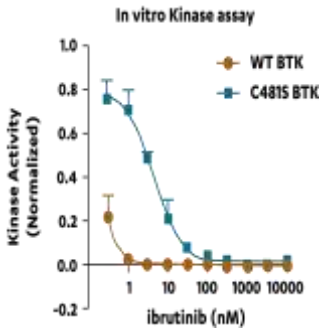




Genetics

Genomics england

Resistance mechanisms



AMENDMENT

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

TAP
From Leukaemia & Lymphoma Research

- MRD response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity
- Results will inform a potential modification of Flair

40 patients with relapsed/refractory CLL

Cohort A: 20 patients roll-over from IcICLLe

Cohort B: 20 ibrutinib naïve patients

CLARITY

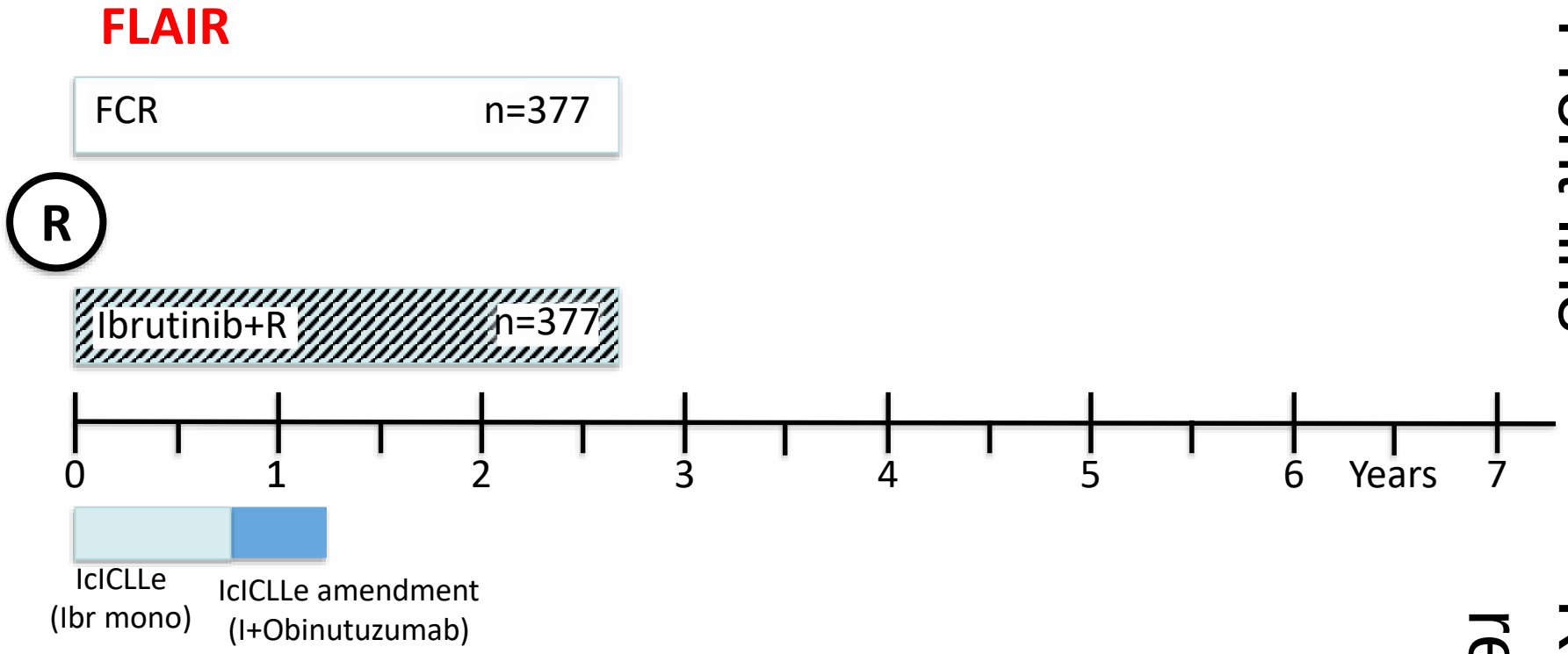
TAP
From Leukaemia & Lymphoma Research

Assessment of venetoCLAx in combination with ibRutInib plus ABT-199 in relapsed/refracTory chronic lymphocYtic leukaemia

- Feasibility study to investigate the combination of ibrutinib and ABT-199 in relapsed refractory CLL.
- MRD response as the primary outcome measure to determine whether ibrutinib + ABT-199 shows sufficient evidence of activity and safety.
- Results from this trial will inform a potential modification of Flair

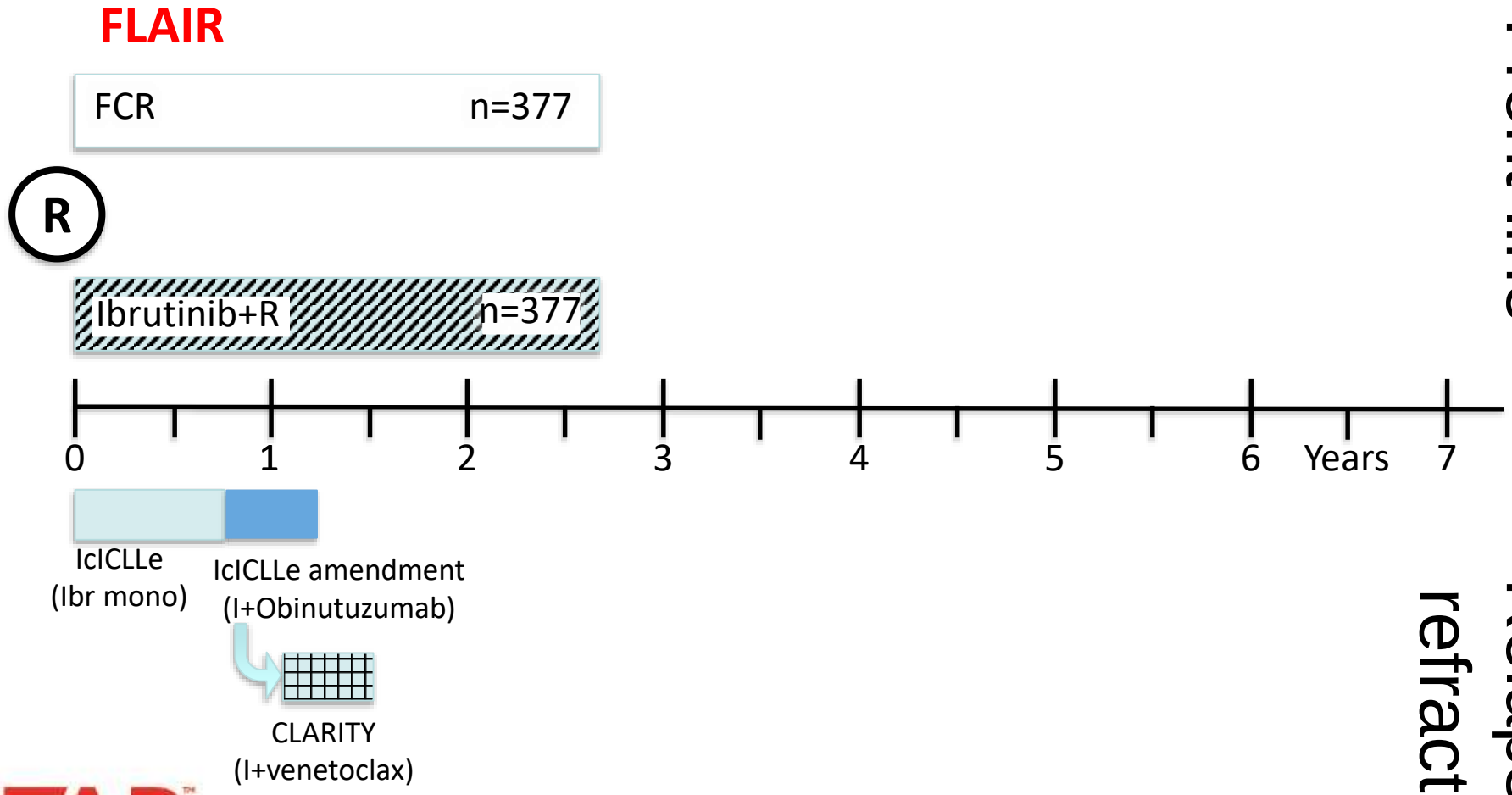
50 patients with relapsed/refractory CLL who are ibrutinib naïve

Using TAP trials to inform Phase III



TAP™
From Leukaemia & Lymphoma Research

Using TAP trials to inform Phase III



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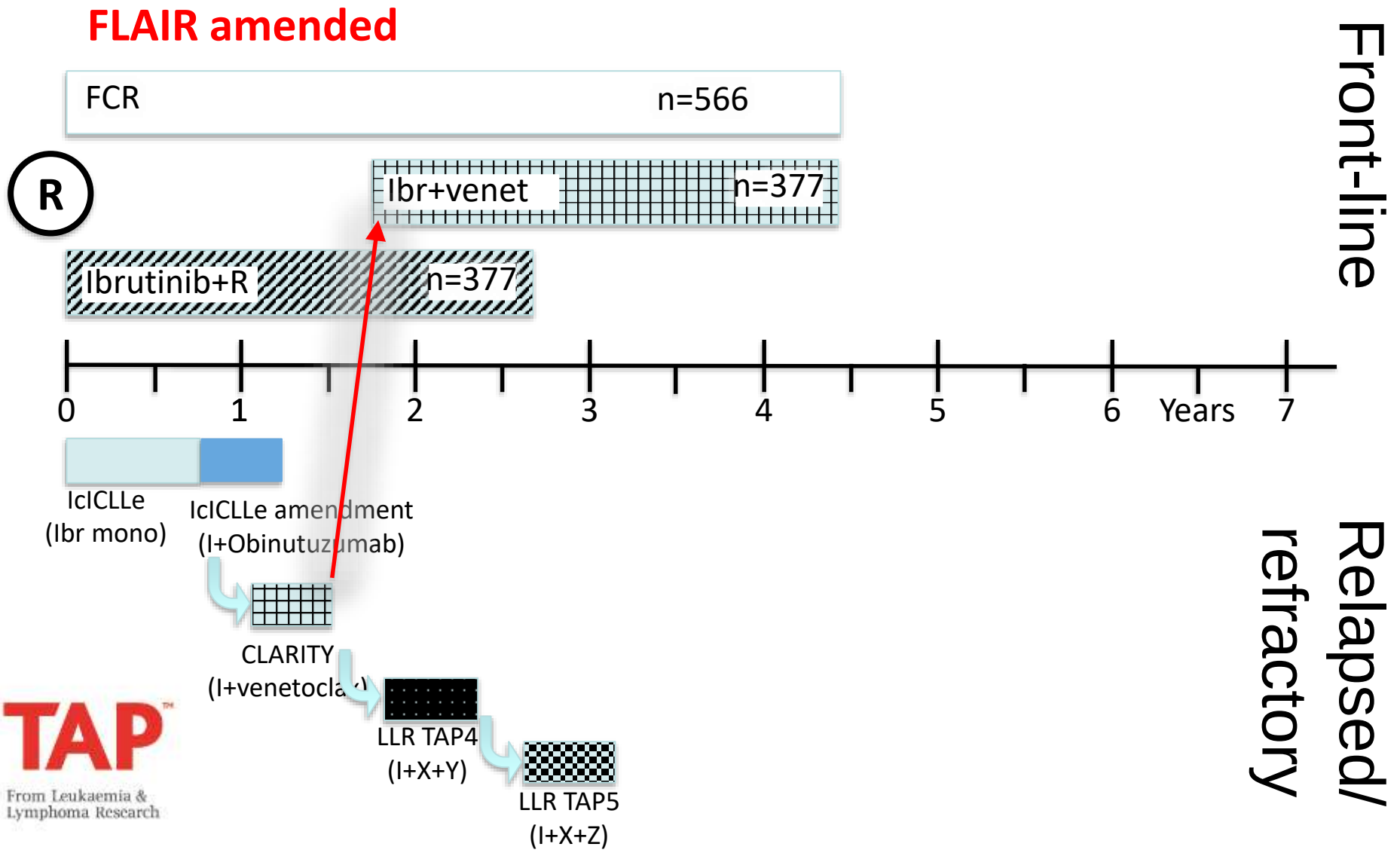
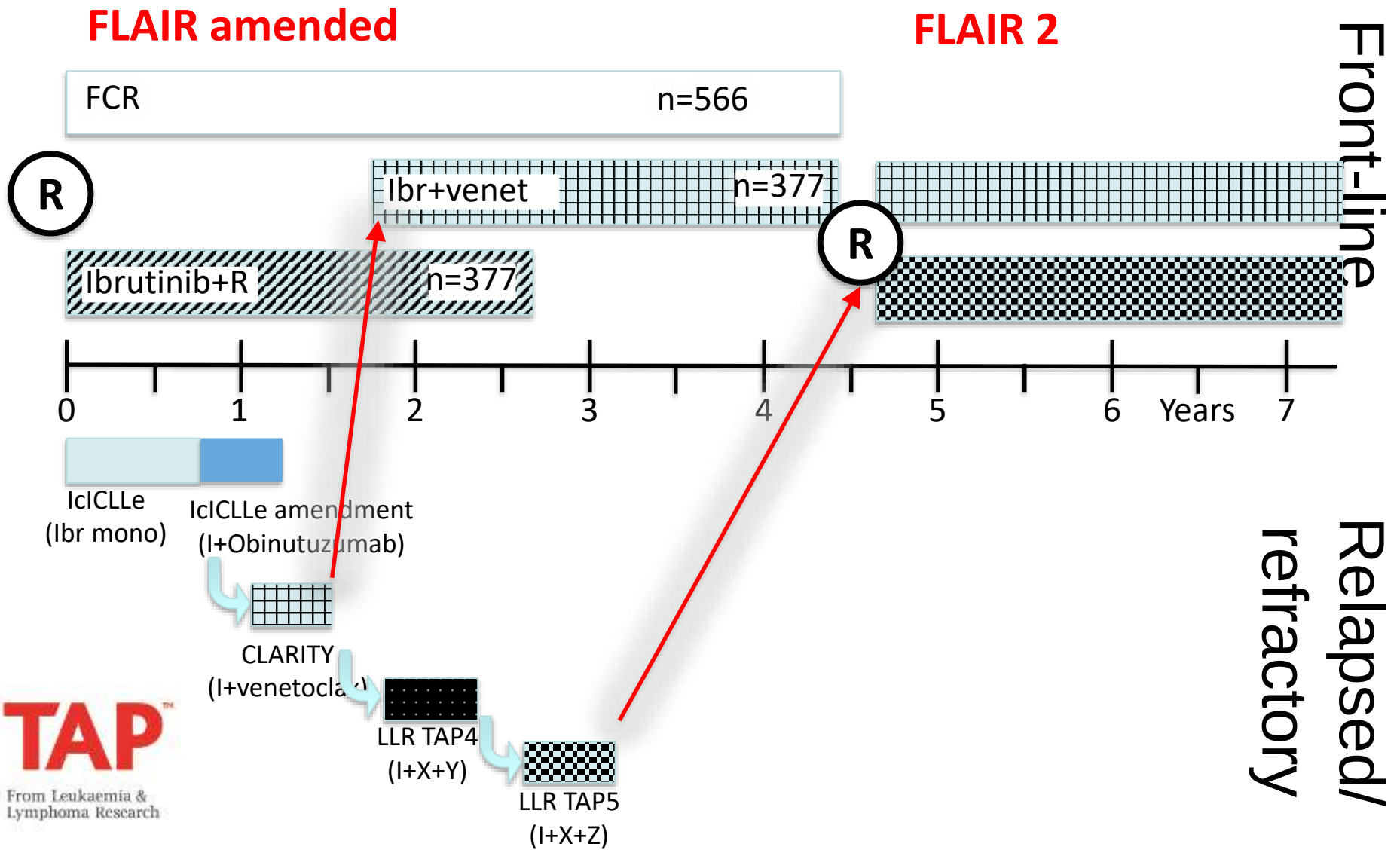
Using TAP trials to inform Phase III



Using TAP trials to inform Phase III



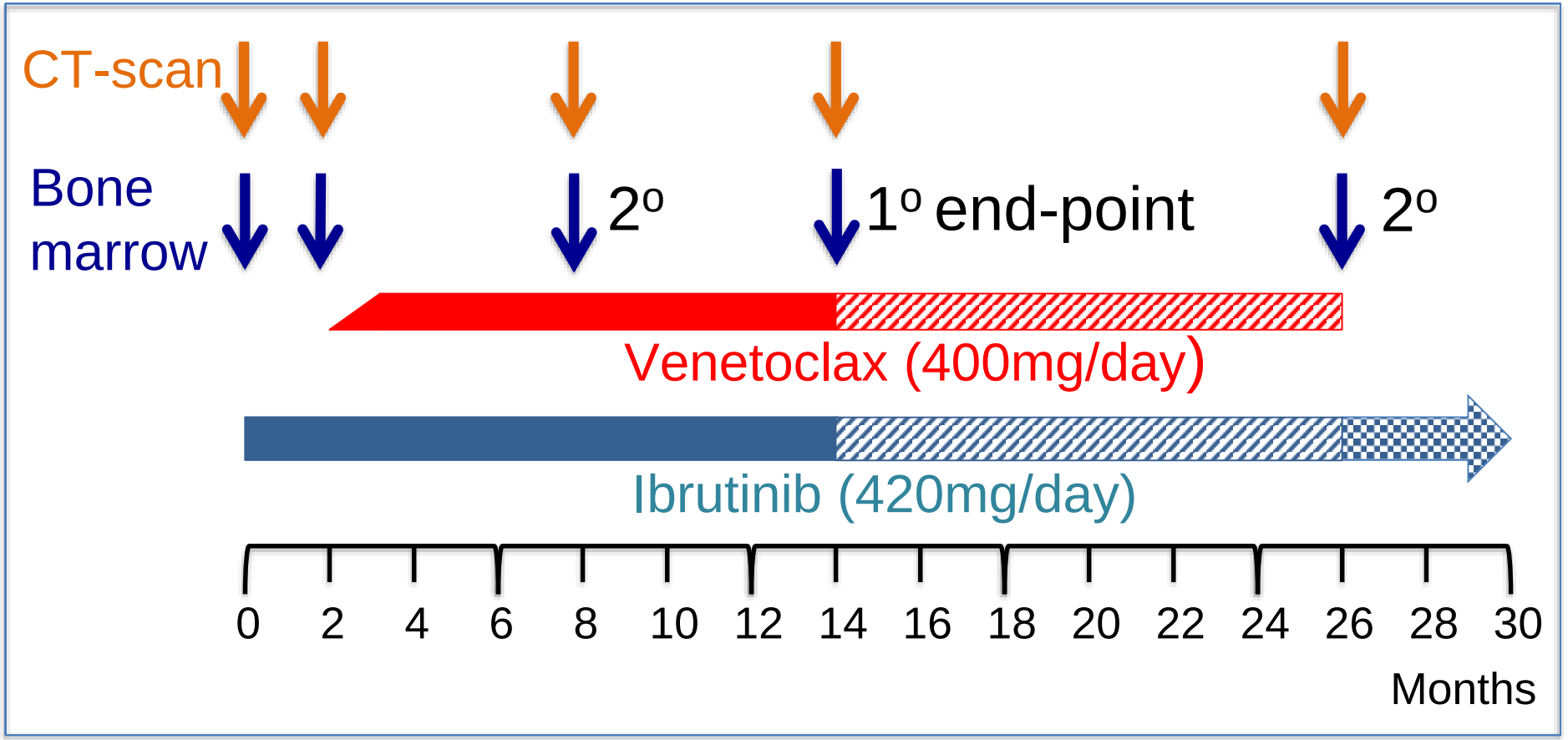
Initial Results of Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL (Bloodwise TAP CLARITY Study): High Rates of Overall Response, Complete Remission and MRD Eradication after 6 Months of Combination Therapy

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

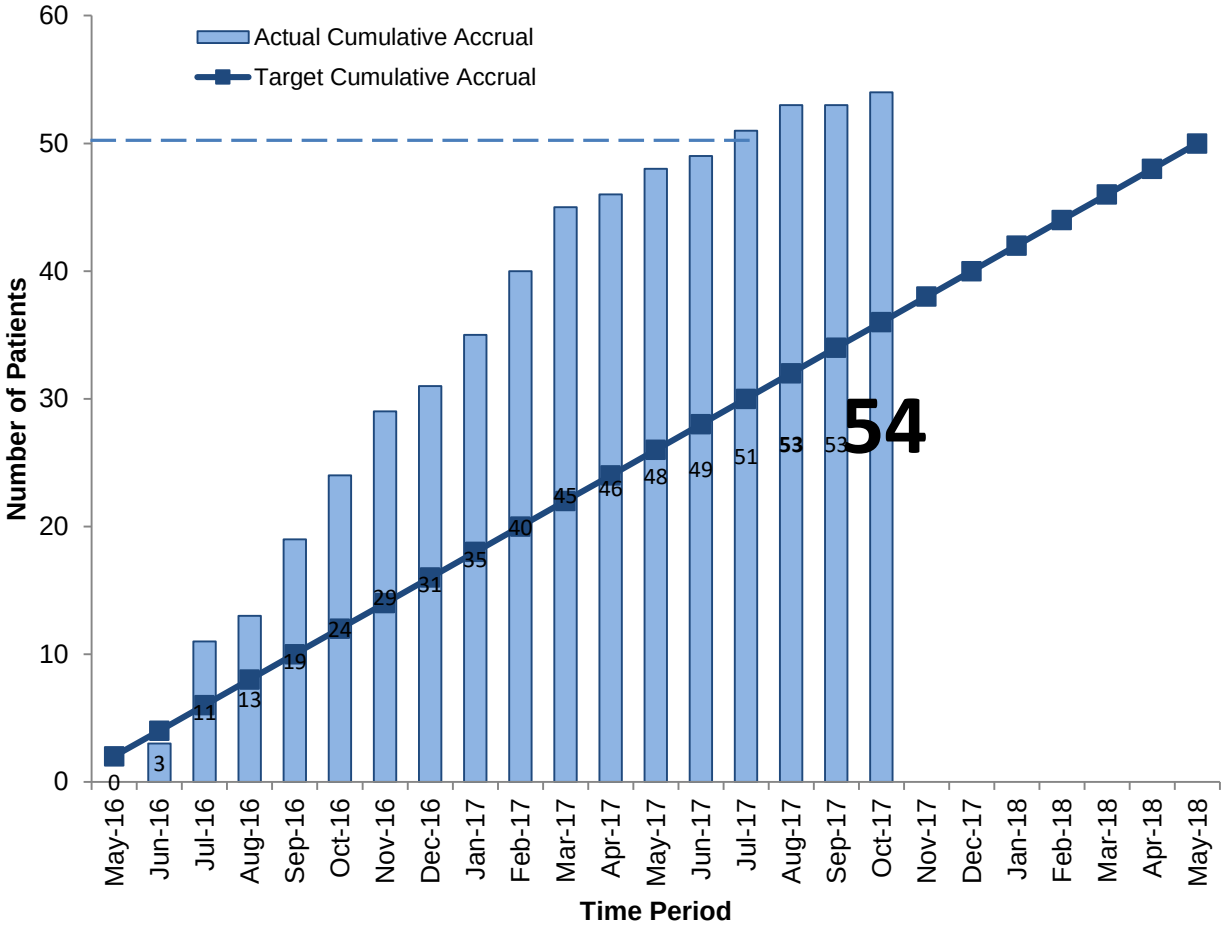
Treatment Schedule



- 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



50 patients recruited in 15 months – 9 months ahead of target.

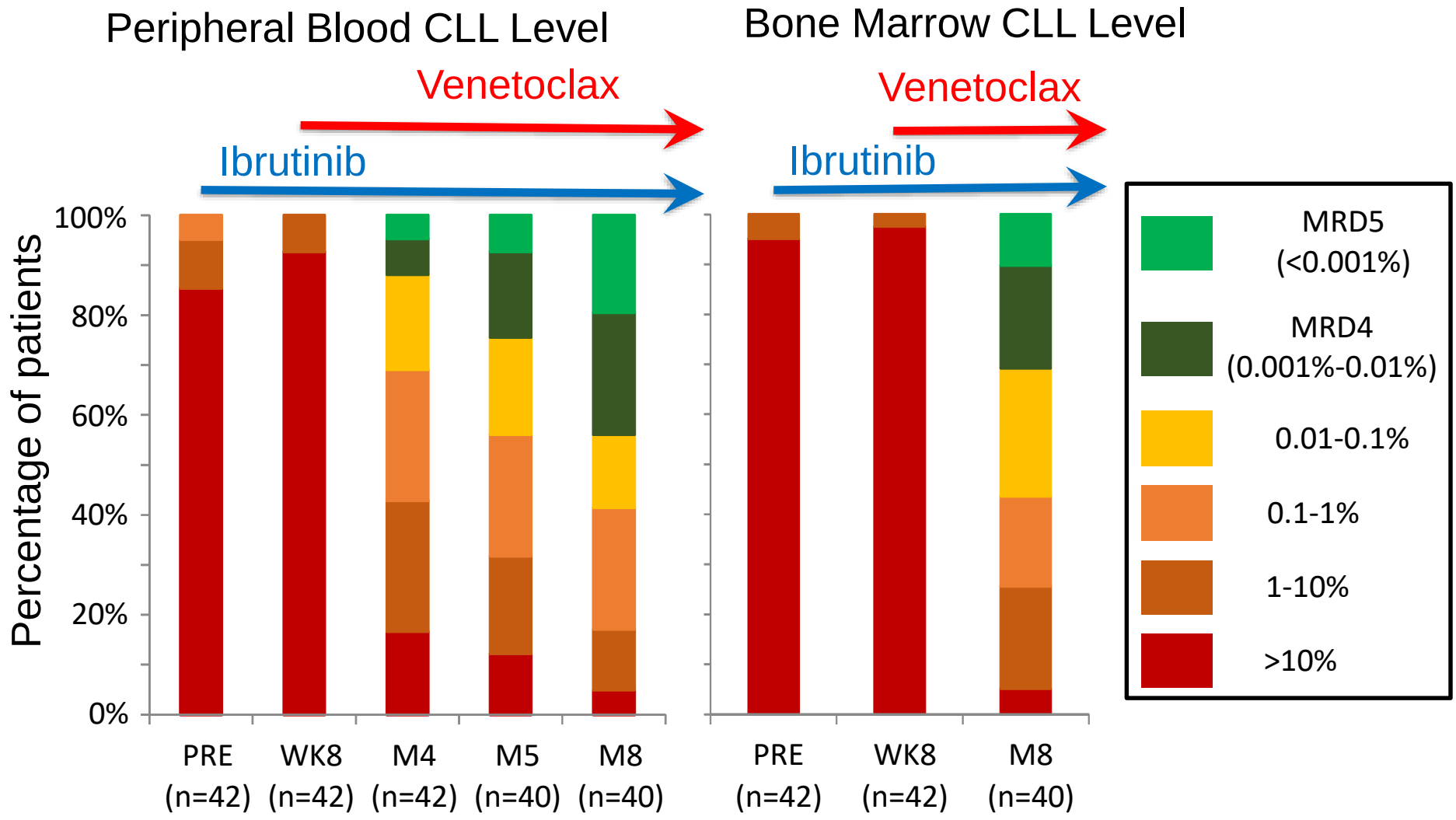
- 4 patients stopped ibrutinib before adding venetoclax due to toxicity

TNO	Toxicity category/event
11	Infections and infestations
25	Brain abscess
34	Vascular disorder
50	Gastrointestinal disorder, renal disorder, general disorder, injury

- 50 patients recruited to combination part of trial
- 49 patients successfully passed through venetoclax escalation phase

Munir, BSH 2018

PB & BM MRD level by time-point (up to 6 months I+V)



Hillmen *et al.* ASH 2017; Abst 428

Using TAP trials to inform Phase III trials

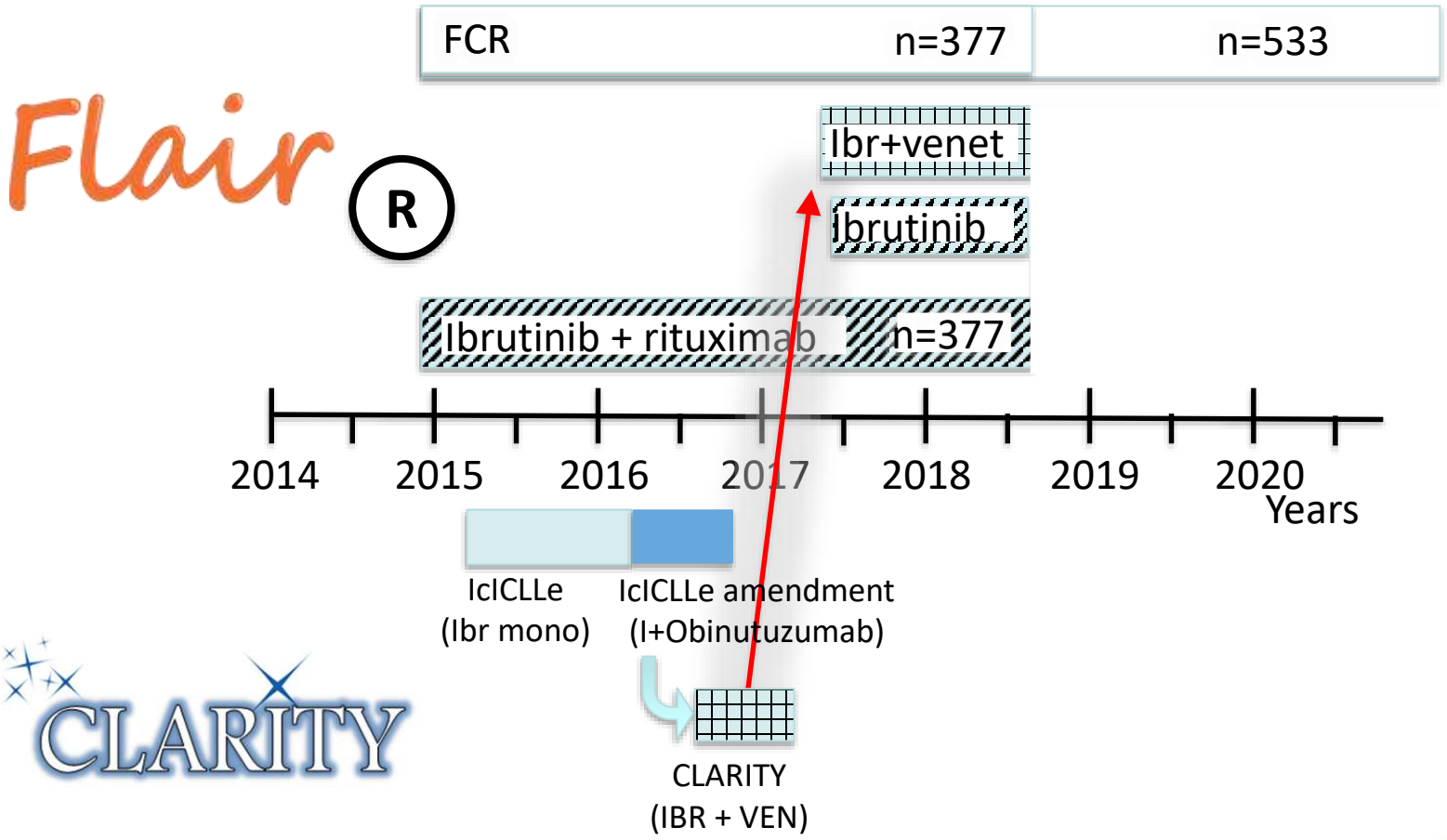
TAP Bloodwise
Beating blood cancer since 1960

NCRI National Cancer Research Institute
Partners in cancer research

ctru University of Leeds

Front-line

Relapsed/ refractory

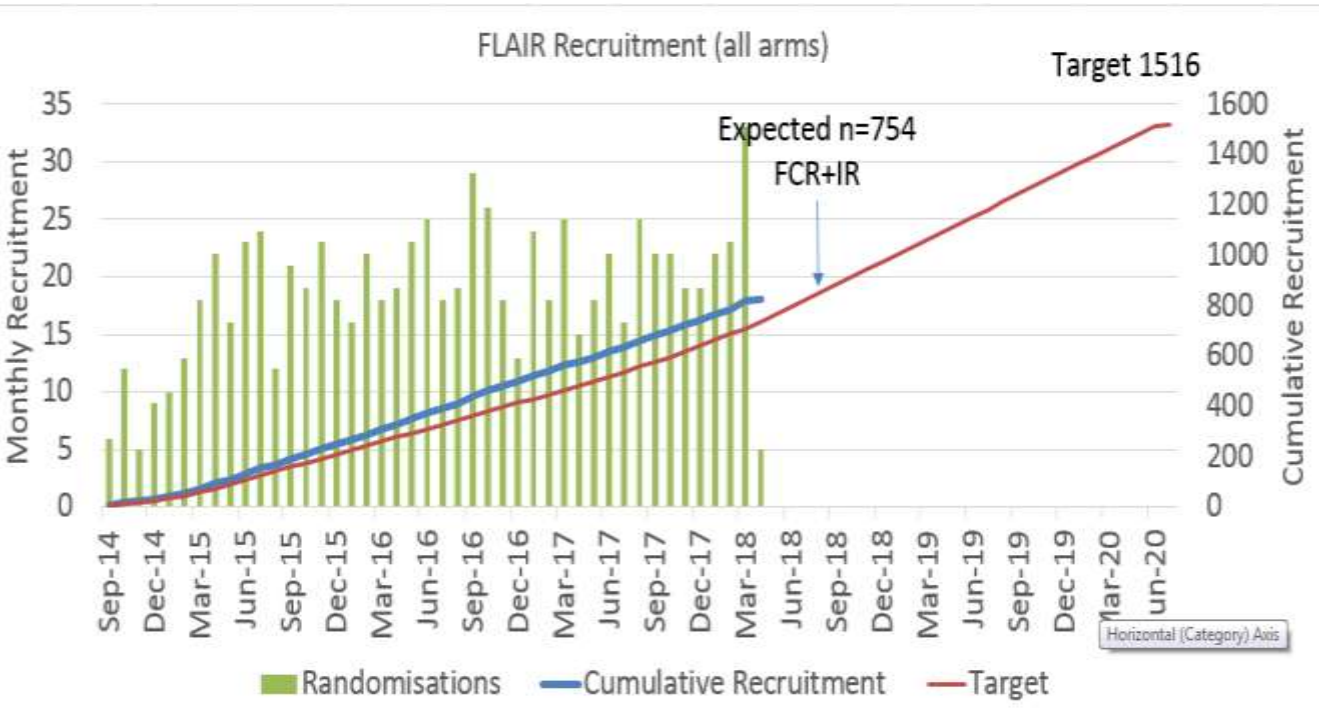


CLARITY

@CRCTU Cancer Research UK Clinical Trials Unit

NCRI Flair (CLL10) Trial

Front **L**ine therapy in CLL: **A**ssessment of **I**brutinib plus **R**ituximab



As of 9th April 2018
823 patients randomised in total
(728 patients randomised to FCR / IR (97% of 754))

As of 9th April 2018
Centres open: 98

<u>Monthly recruitment targets</u>

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)

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

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NCRI CLL Trials Sub-group

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Patients with CLL and their families

University of Leeds

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Charlotte Evans
Pascal LeFevre
Surita Dalal
Alasdair Dewar
Darren Newton

UNIVERSITY OF LEEDS

Hospitals and trials teams

Abbvie Janssen Novartis Acerta/AZ Napp Pharmacyclics Gilead Roche

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UNIVERSITY OF OXFORD

Bloodwise
Beating blood cancer since 1960