Hope for the Future

CLL- Research and clinical trials

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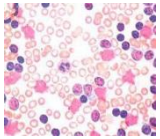
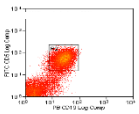
CLL: A rapidly changing world!

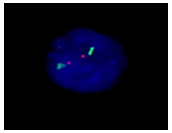
- Different/long-term side-effects: chemo-related side-effects, secondary malignancy, infusion reactions, immuno-suppression, bleeding, arrythmia, TLS, colitis/pneumonitis etc etc
- Practicalities: iv, oral, long-term until PD, requiring hospital admission
- Cost: only cure (or death) is cheap
- Last not least: Different biology

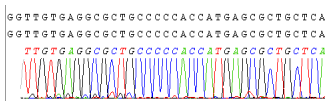
	1970	2000	2010	2011	2012	2013	2014	2015	2016
1st line	Chlorambucil Prednisolone	Fludarabine Cyclophos	Fludarabine Cyclophos Rituximab		Bendamustine (Rituximab)		Chlorambucil Obinutuzumab Chlorambucil Ofatumumab	Ibrutinib	
R/R			Campath		Ofatumumab		Ibrutinib Idelalisib Rituximab		Venetoclax Acalabrutinib

Morphology Flow FISH Sanger NGS WGS









“Novel” treatments in CLL in 2017

Btk inhibitors
Ibrutinib
***ONO-4059**
***ACP-196**
***BGB-3111**

PI3K inhibitors
Idelalisib
***Duvelisib**
***TGR1202**

Other BCR inhibitors
Fostamatinib
GS-9973
Dasatinib
AZD5363

Pro-apoptotic
***Venetoclax**

Monoclonal antibodies
Ofatumumab
Obinutuzumab
Blinatumomab

iMID’s
Lenalidomide
Pomalidomide
CC-122

Checkpoint inhibitors
***PD-1**
PD-L1
CTLA-4

Chemotherapy
FCR
Bendamustine

Immunotherapy
CART
ROR-1
RIC-AlloSCT

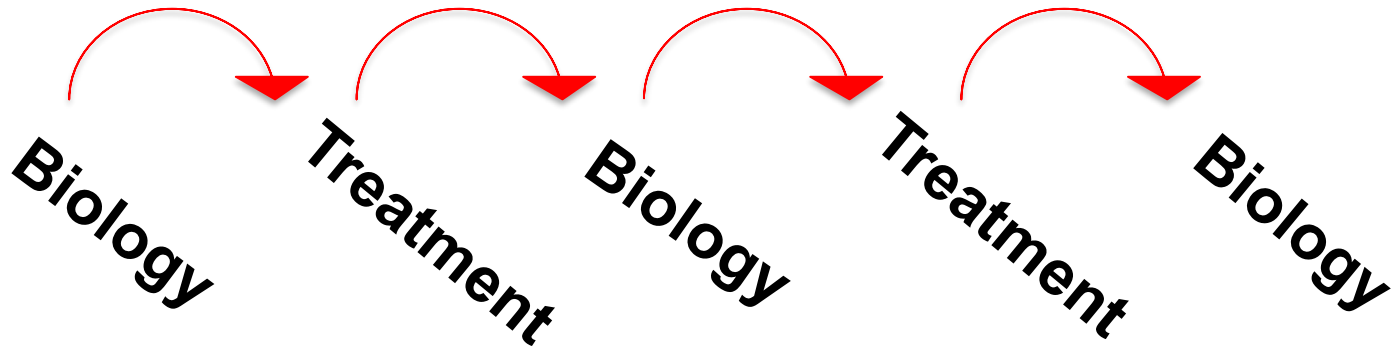
The question is how to test them?

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

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

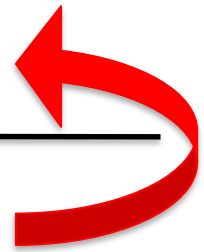
2. **Tolerable therapy**
   a. Short-term toxicity of single agent and combinations
   b. Long-term toxicity of combinations
   c. Duration of therapy – definition of response

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

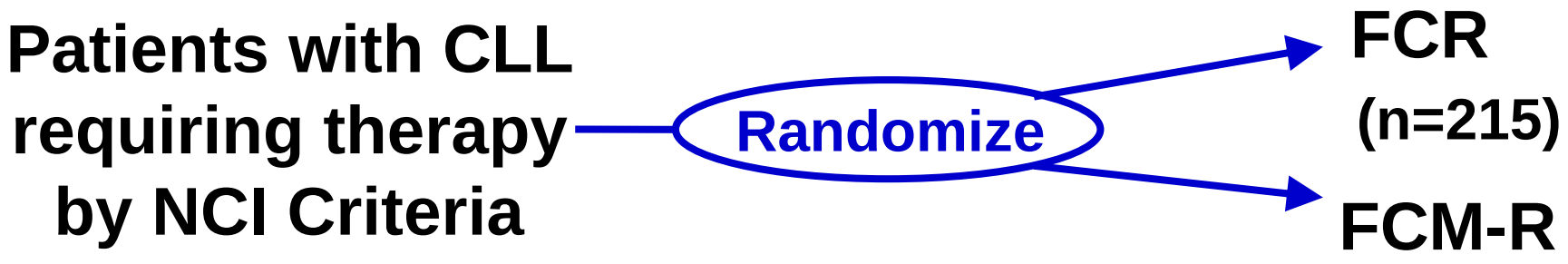
Relapsed/ refractory

TAP Bloodwise
Beating blood cancer since 1960

Recent NCRI trials for fit patients with CLL

NCRI ADMIRE (randomised Phase II) Trial

Does the Addition of Mitoxantrone Improve Response to FCR chemotherapy in patients with CLL



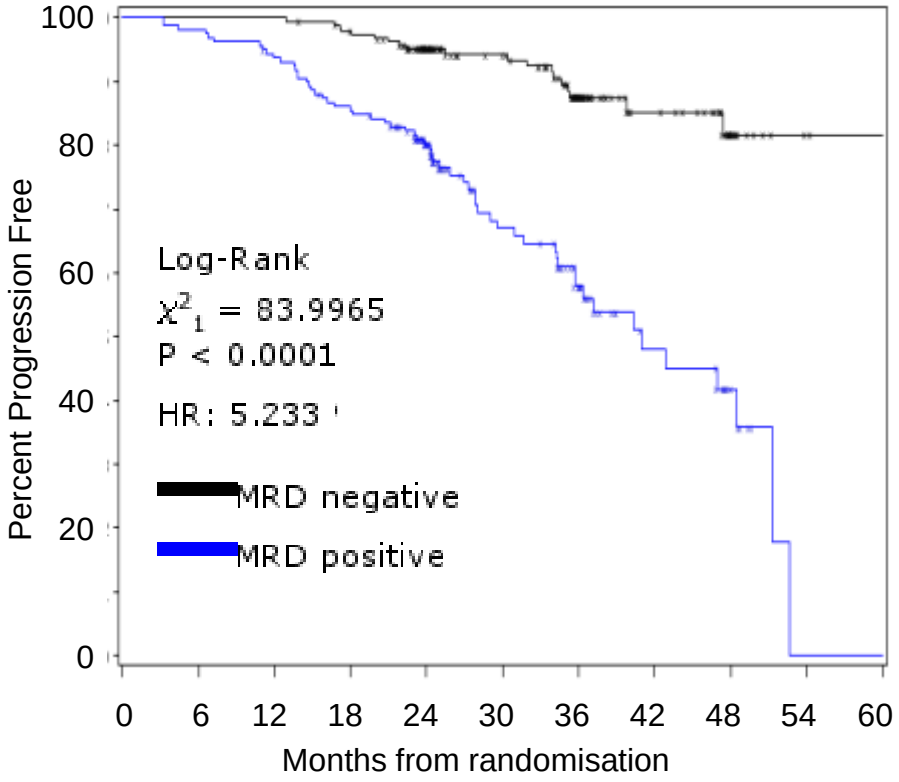
NCRI ARCTIC (randomised Phase II) Trial

Attenuated dose Rituximab with ChemoTherapy In CLL

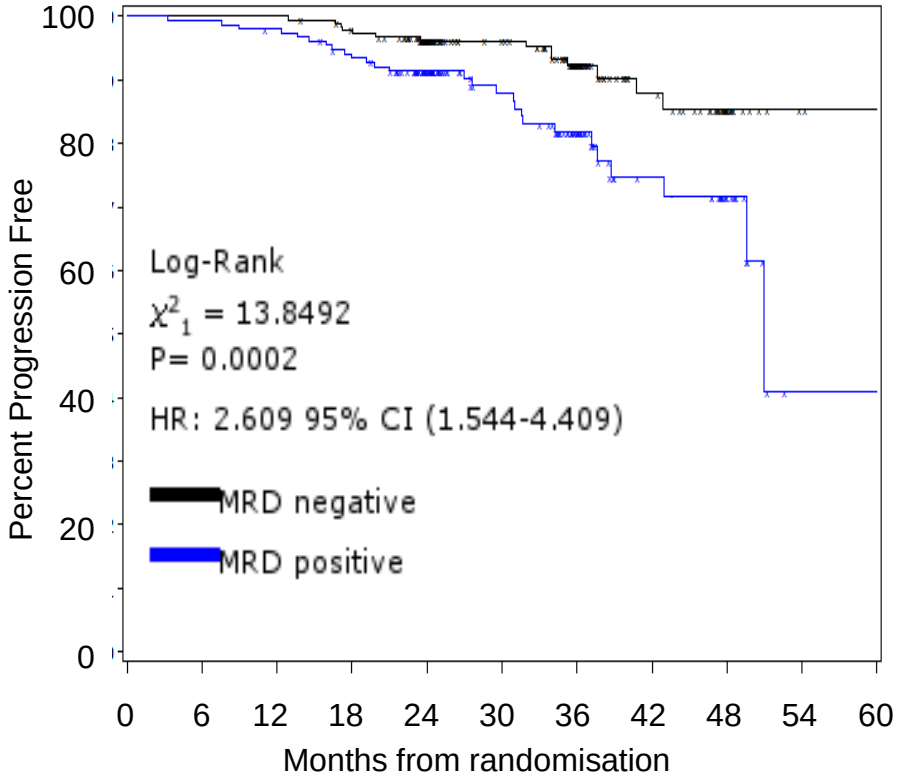
ADMIRE EHA 2013 & BSH 2014; ARCTIC ASH 2013 & BSH 2014; Combined EHA 2014

ADMIRE and ARCTIC (n=345): Time to Progression and Overall Survival – MRD in marrow at 3 months post-FCR(±M)

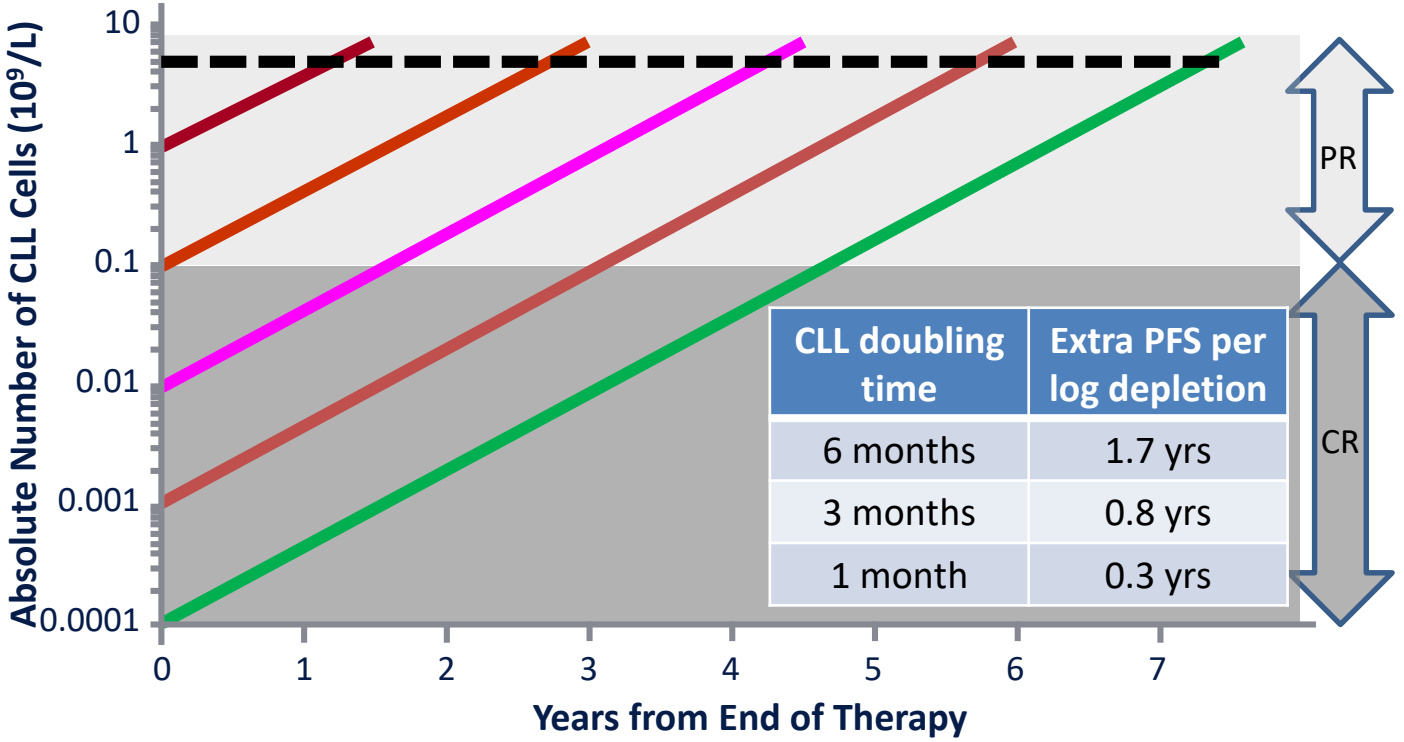
Progression-free survival



Overall survival



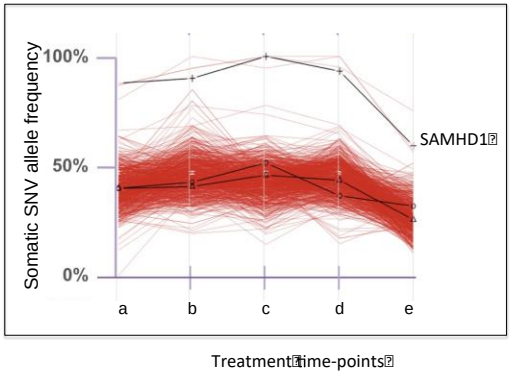
Assuming Exponential Growth at the MRD Level → Linear Increase in PFS per Log Tumour Depletion



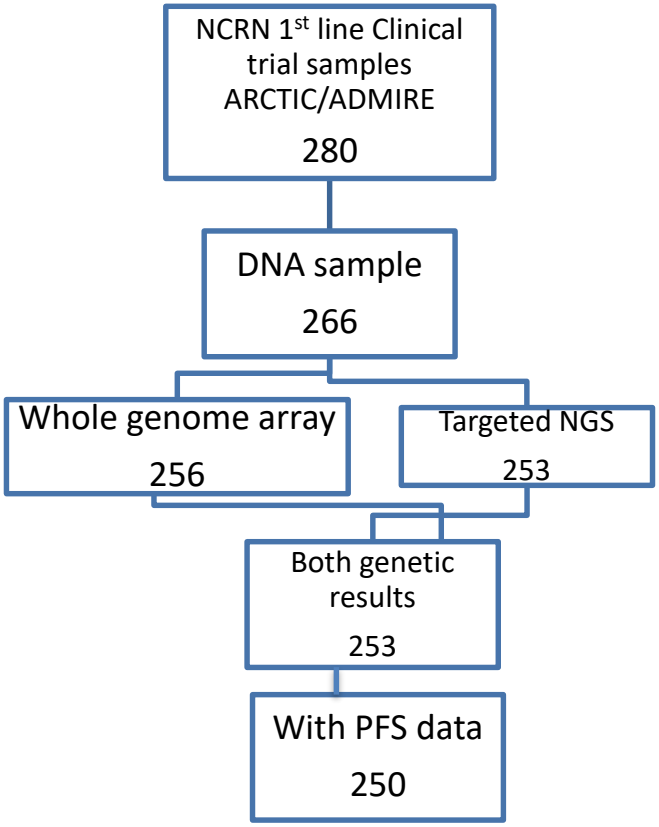
CR, complete remission; PR, partial remission.

Integrated analysis of NCRI CLL Frontline FCR Trials in the UK

Gene	Target
ATM	All exons
BIRC3	All exons
MED12	All exons
MYD88	Exon 5
NOTCH1	Exon 34
SAMHD1	All exons
SF3B1	Exons 14, 15, 16 & 18
TP53	All exons
XPO1	All exons



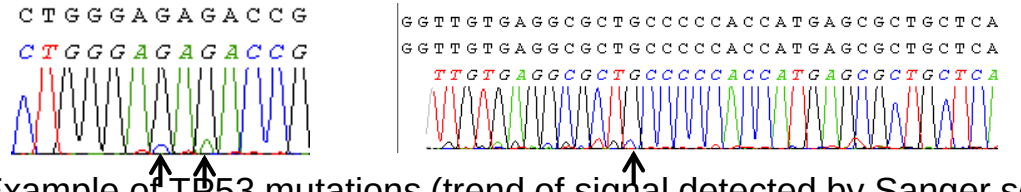
Schuh A, *et al*. *Blood* 2012;120:4191–4196



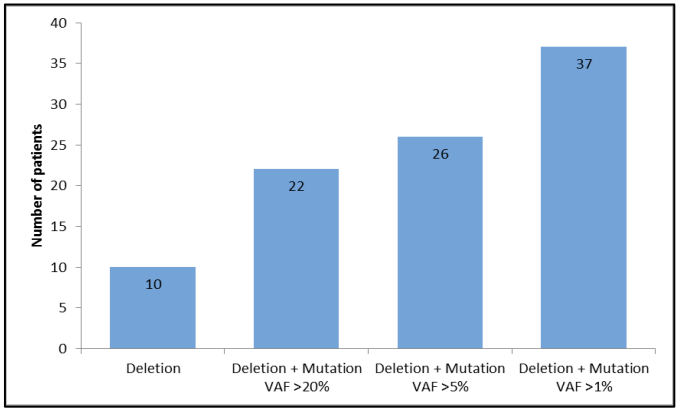
Average sequencing depth: 2032X

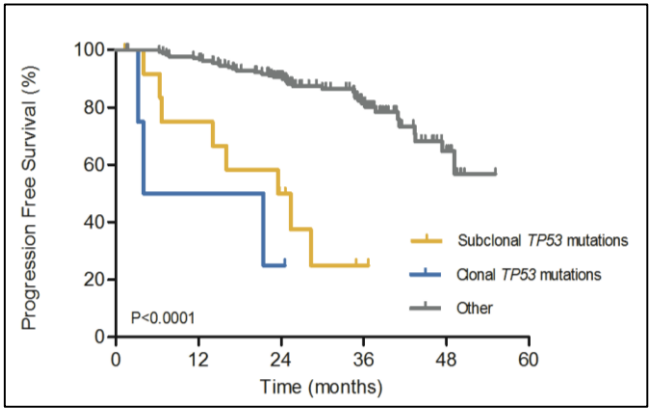
Using the validated NGS method,TP53 mutations can be detected to 1% Variant allele Frequency (VAF)

samples	Gene.refGene	ExonicFunc.refGene	AAChange.refGene	AAChange.refGene2	VF
TRO-Mic	TP53	nonsynonymous	SNV	TP53:NM_001126115:exon4:c.G443C:p.R148T	0.0541
TRO-Mic	TP53	nonsynonymous	SNV	TP53:NM_001126115:exon4:c.G445A:p.D149N	0.0645
GRUMar	TP53	frameshift	insertion	TP53:NM_001126115:exon1:c.136dupC:p.H46fs	0.0736



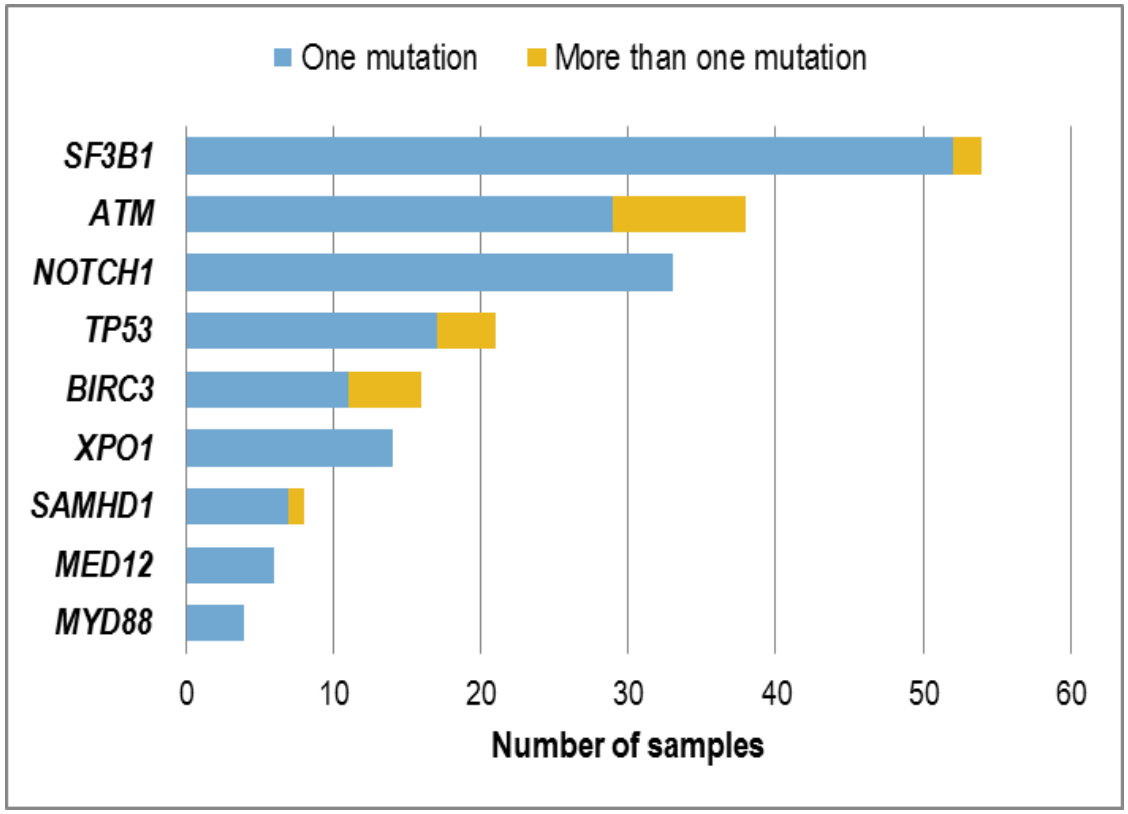
Example of TP53 mutations (trend of signal detected by Sanger sequencing)





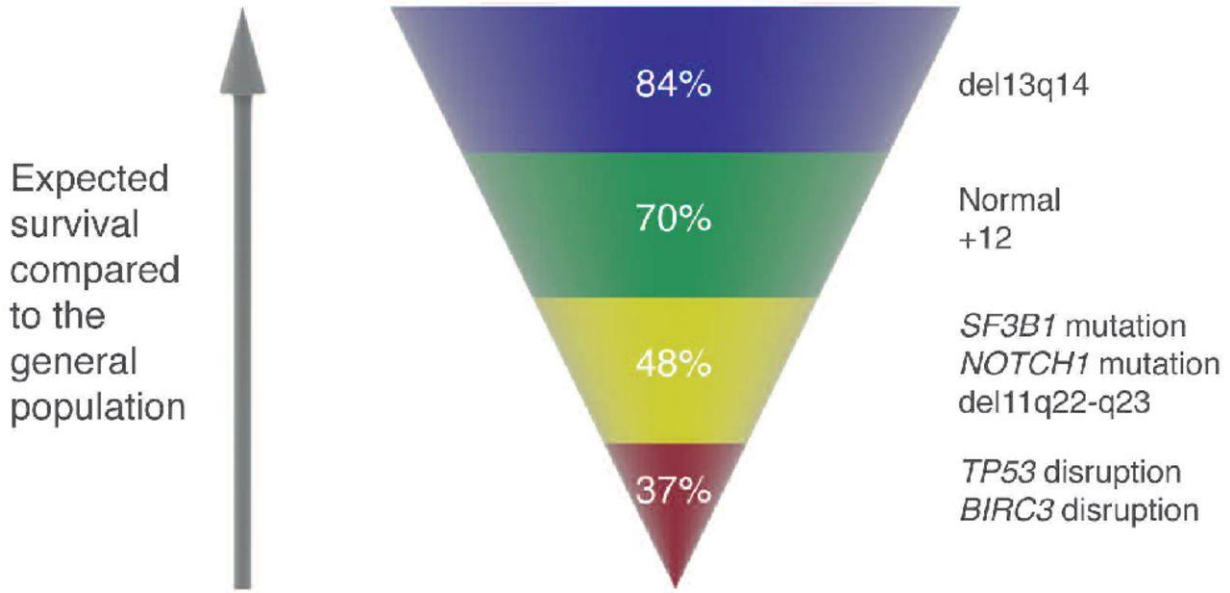
Clifford *et al.,* Manuscript submitted. 2016

Integrated analysis of NCRI CLL Frontline FCR Trials in the UK: Common mutated genes

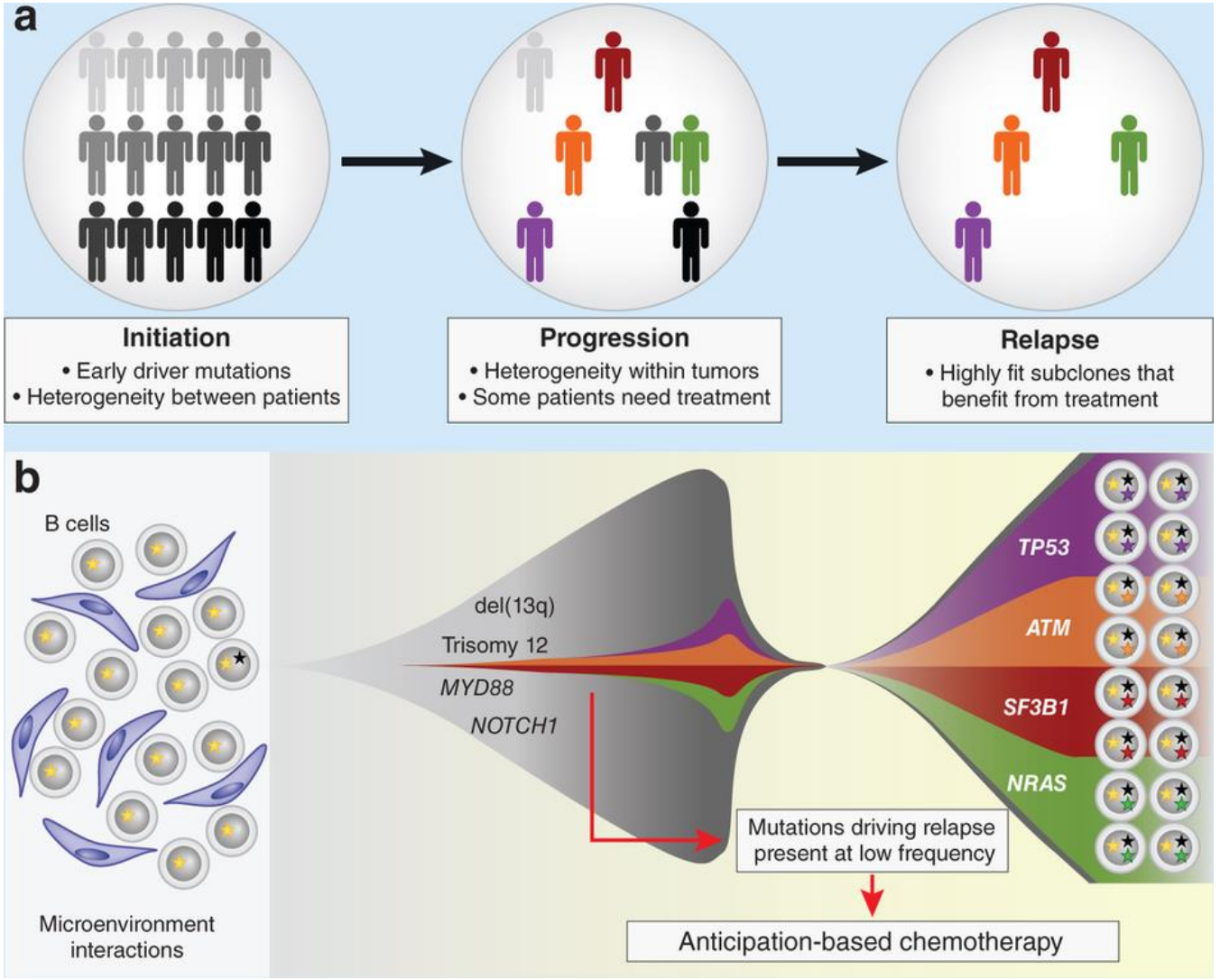


Clifford *et al.,* Manuscript submitted. 2016

Expected survival of CLL patients stratified according to the integrated mutational and cytogenetic model and compared to the matched general population.

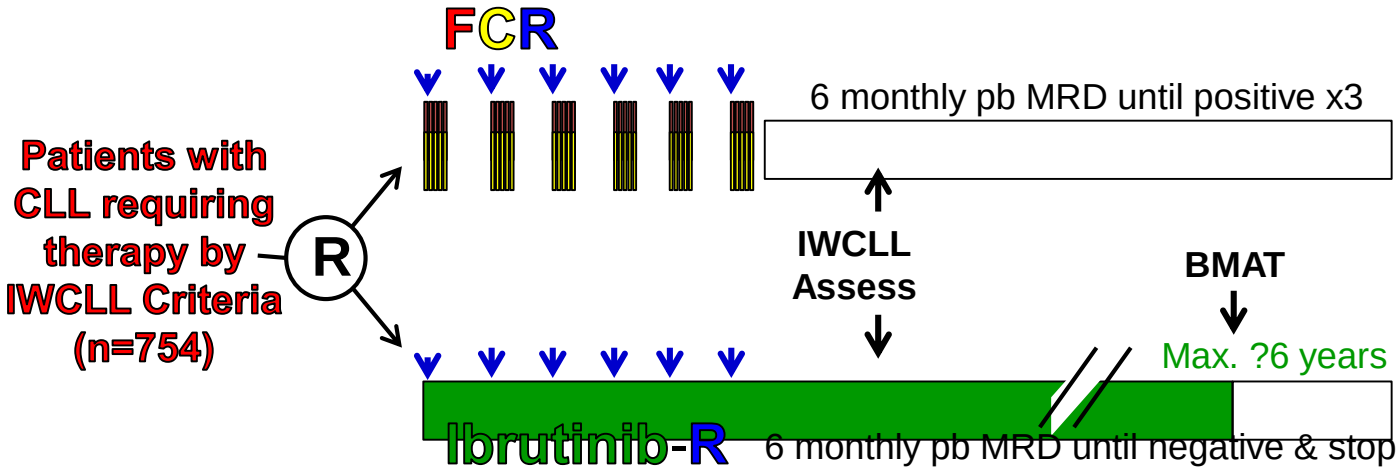


Robin Foà et al. Haematologica 2013;98:675-685


a
Initiation
• Early driver mutations
• Heterogeneity between patients
Progression
• Heterogeneity within tumors
• Some patients need treatment
Relapse
• Highly fit subclones that benefit from treatment
b
B cells
Microenvironment interactions
del(13q)
Trisomy 12
MYD88
NOTCH1
TP53
ATM
SF3B1
NRAS
Mutations driving relapse present at low frequency
Anticipation-based chemotherapy

Next front-line trial for patients fit for FCR:
NCRI *Flair* (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



NCRI Flair (CLL10) Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab

Treatment:

Ibrutinib – 6 monthly PB MRD → stop if MRD negative or 6 yrs

FCR – oral FC as in ADMIRE and ARCTIC

End-points:

Primary – Progression Free Survival

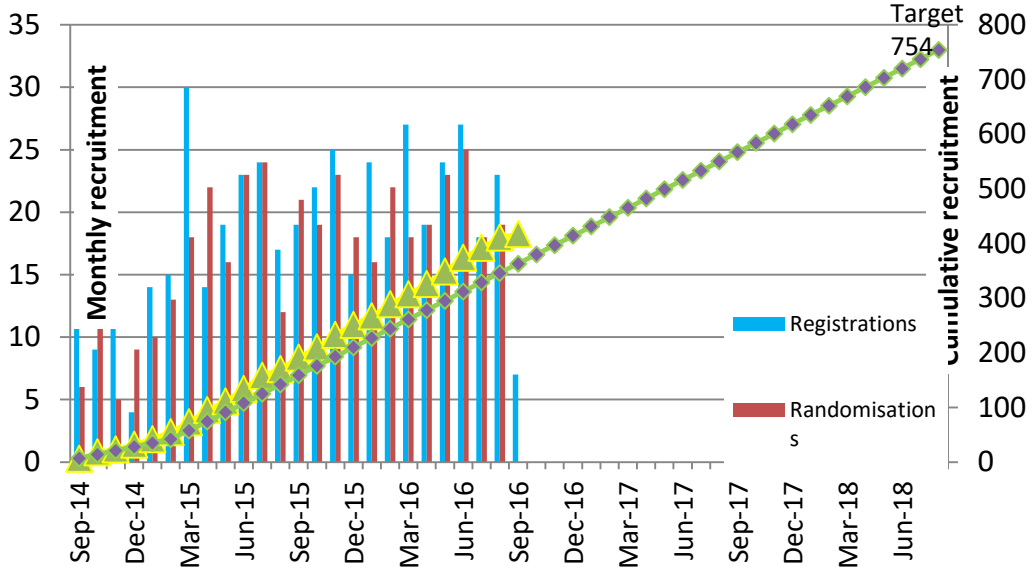
Secondary – Overall Survival, MRD, IWCLL response, safety, QoL, cost effectiveness

Statistics:

Assumptions: Med PFS – FCR 4.5 yrs; IR 6 yrs (HR 0.75)

Statistics: 80% power at the 5% significance level

Flair Recruitment (as 8th Sept 2016)

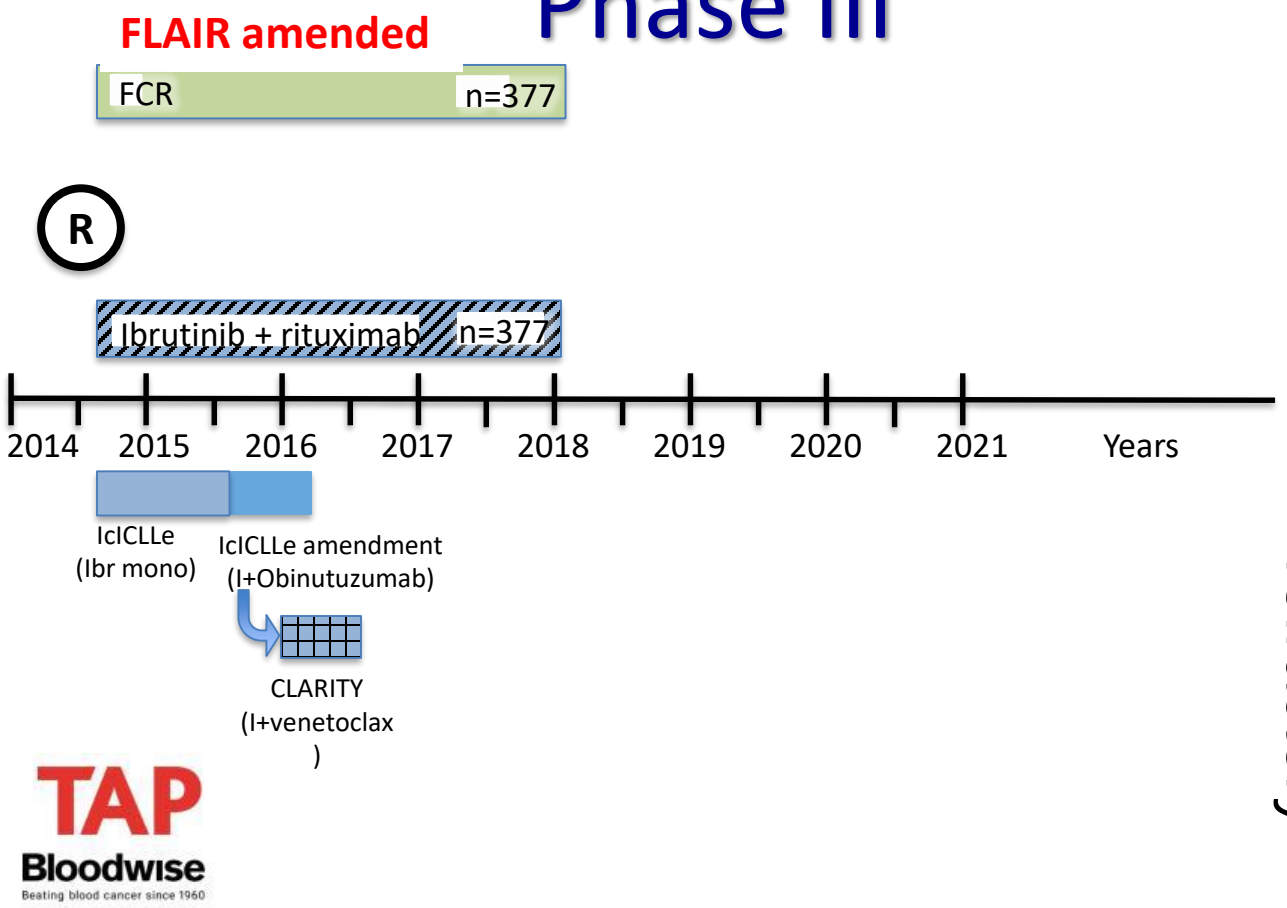


As of 8th Sept 2016
Centres open: 95

As of 8th September 2016
Number of patients registered: 463
Number of patients randomised: 418
Target (end of Sept): 363 randomisations

<u>Monthly recruitment targets (70 centres)</u>
7 per month Sept '14 – Feb '15 (6 months)
17 per month Mar '15 – Aug '18 (3.5 years)

Using TAP trials to inform Phase III



TAP
Bloodwise
Beating blood cancer since 1960

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

Amendment

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

40 patients with relapsed/refractory CLL

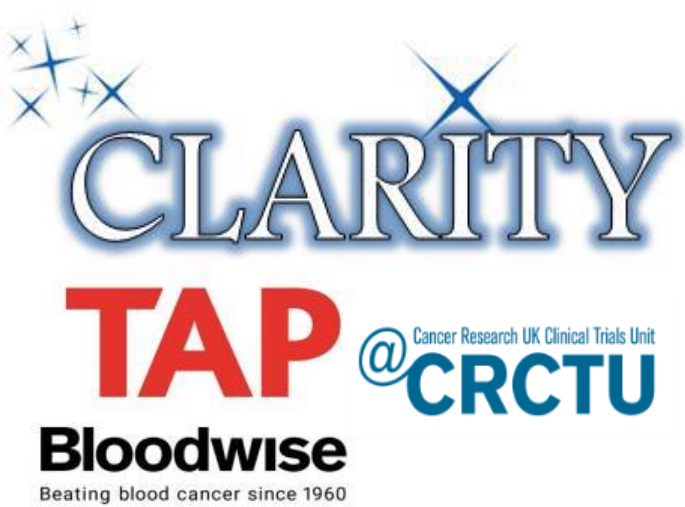
Cohort A: 20 patients roll-over from IcICLLe

Cohort B: 20 ibrutinib naïve patients

TAP

Bloodwise

Beating blood cancer since 1960



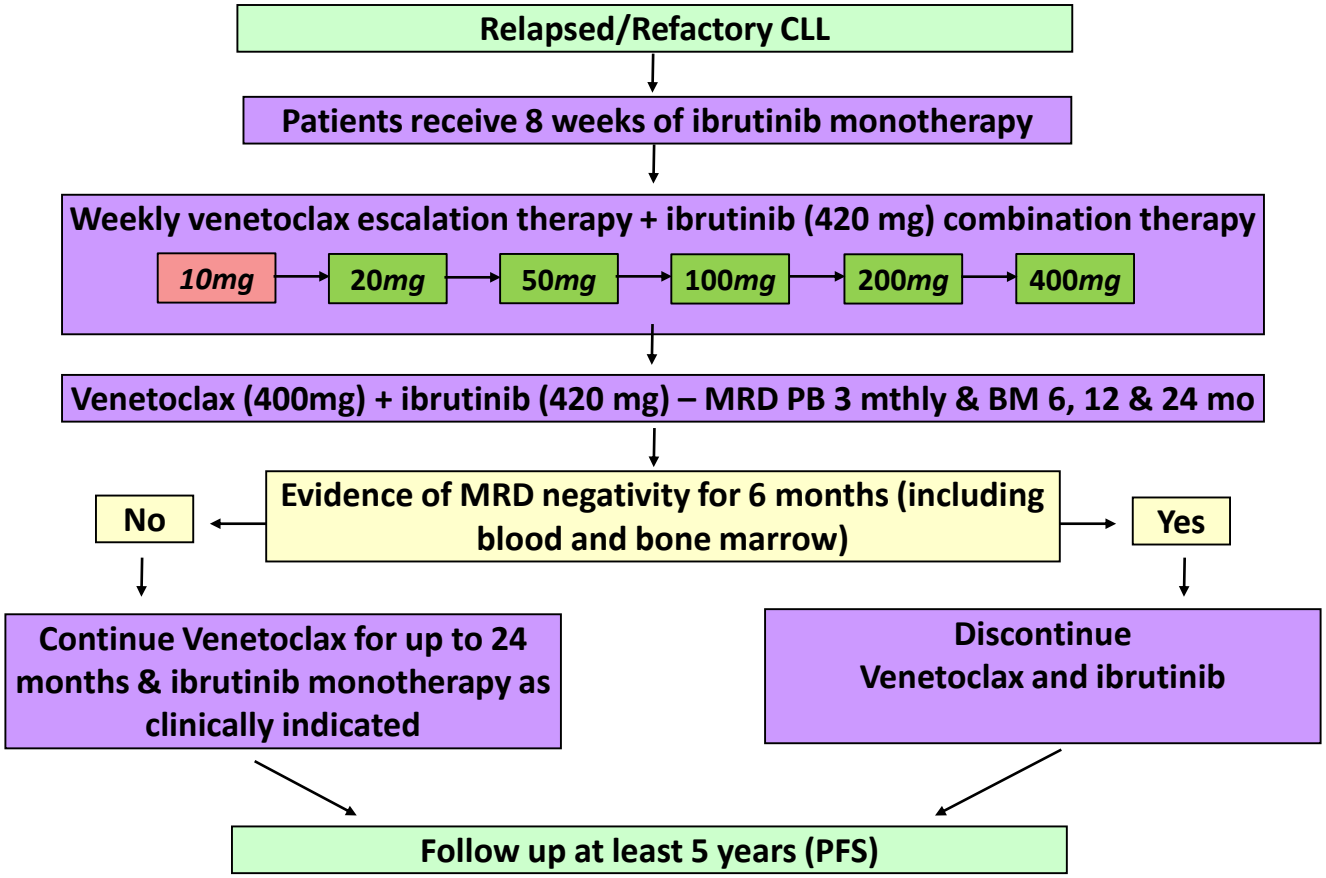
Assessment of venetoCLAx in combination with ibRutInib plus ABT-199 in relapsed/refracTory chronic lymphocYtic leukaemia

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

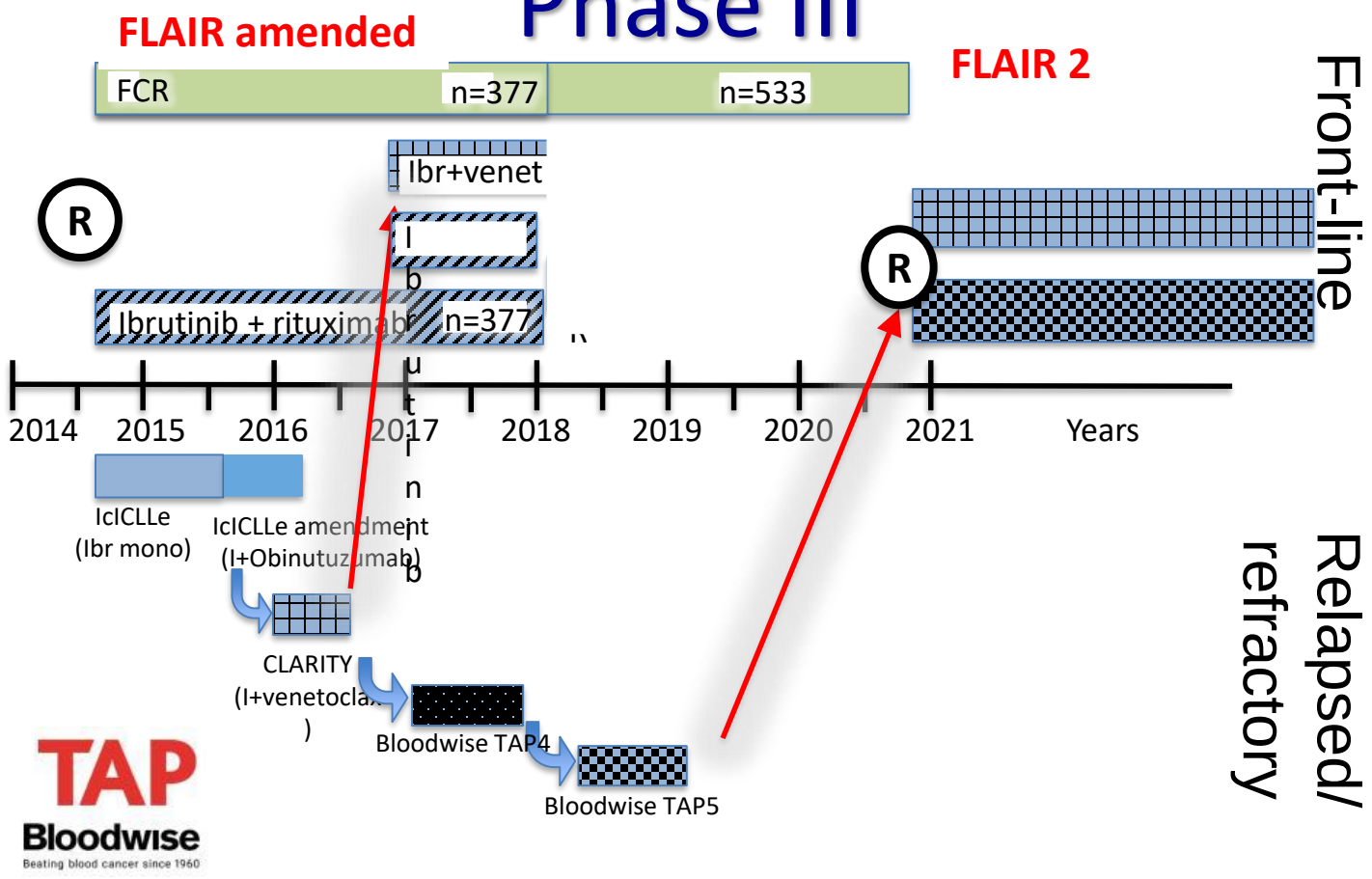
50 patients with relapsed/refractory CLL who are ibrutinib naïve

TAP CLARITY Trial

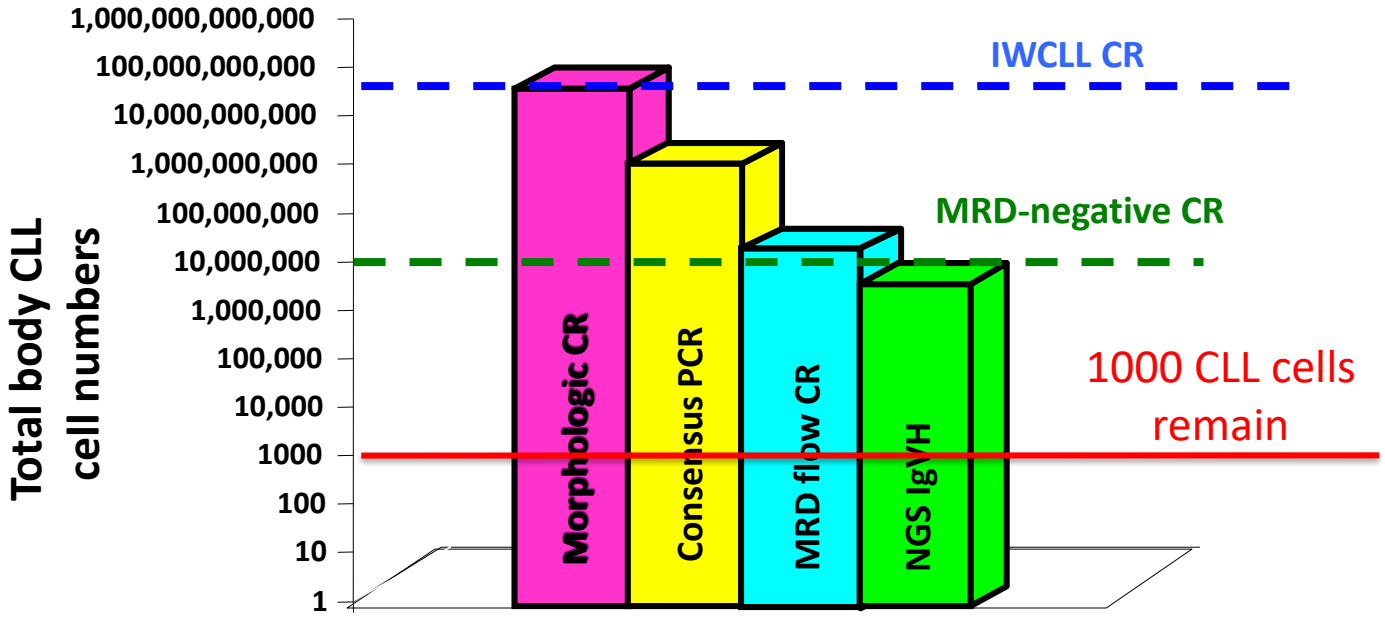
Bloodwise
Beating blood cancer since 1960



Using TAP trials to inform Phase III

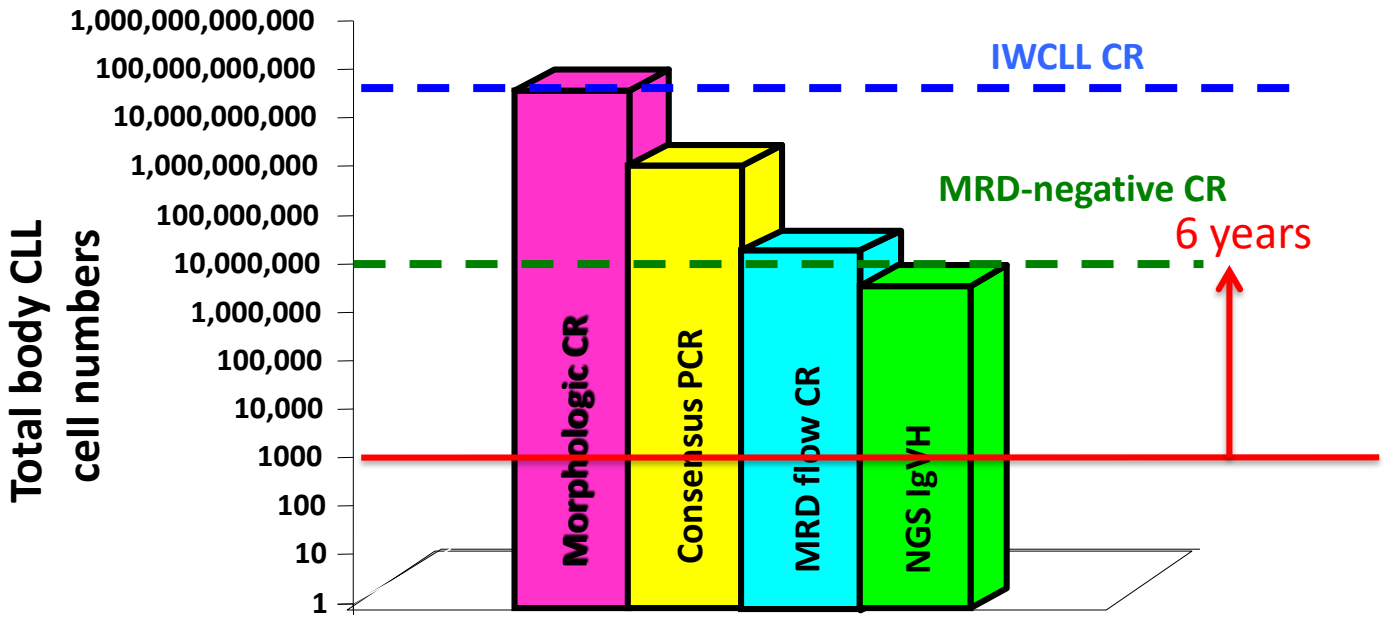


Patient with a CLL doubling time of 6 months - MRD negative remission with 1000 residual CLL cells



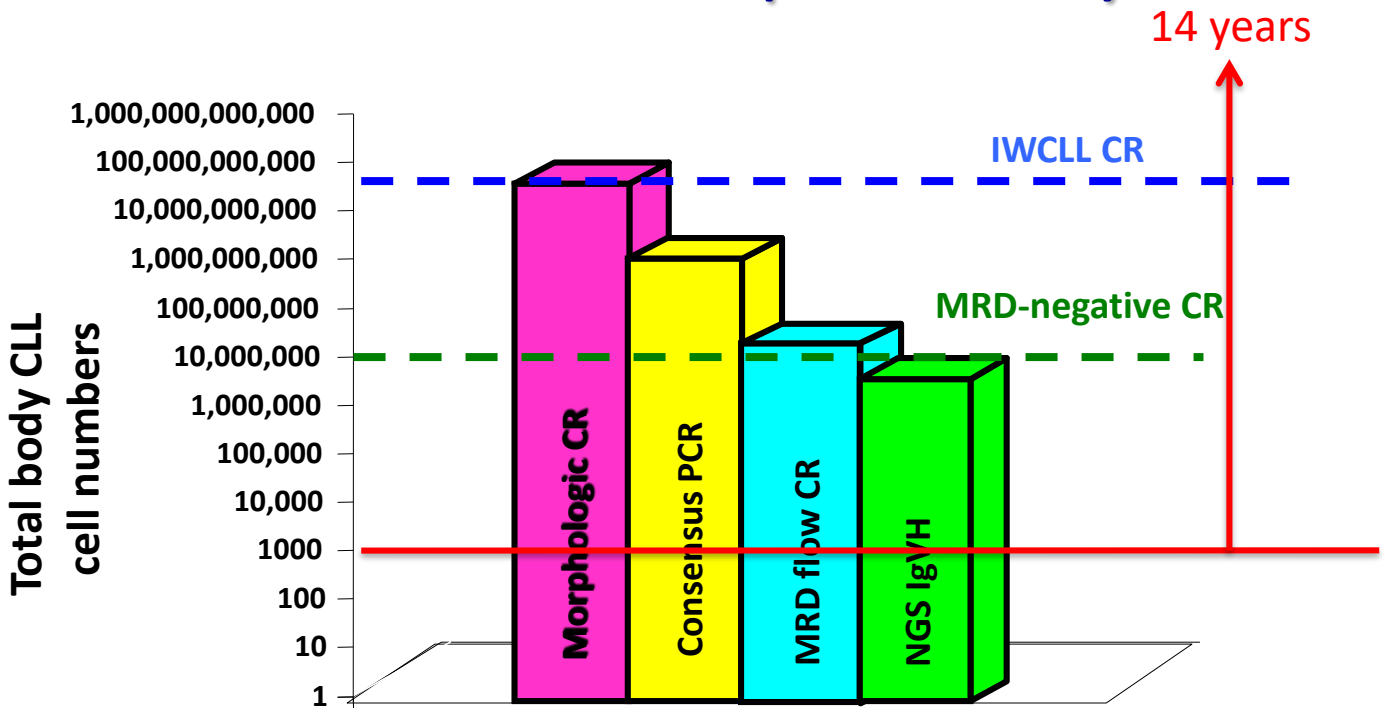
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - MRD positive at 6 years



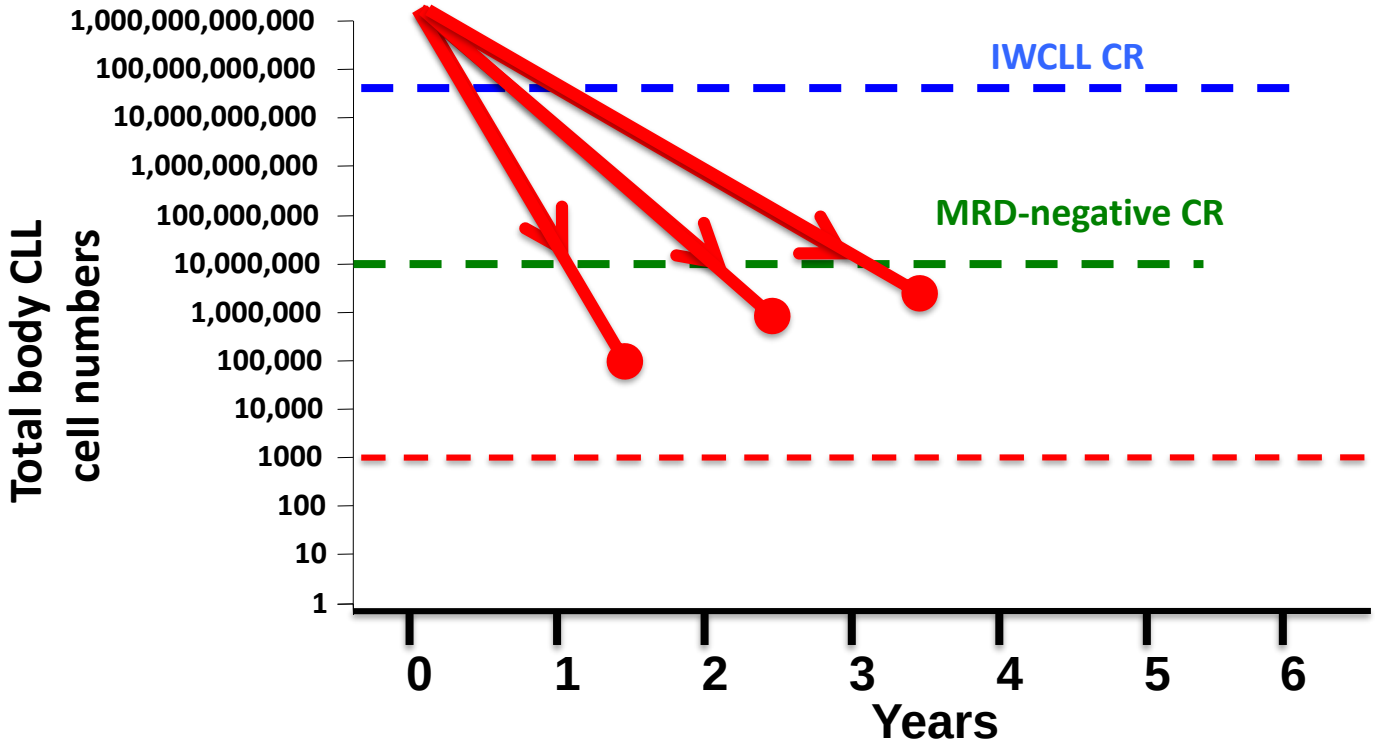
3 CLL doubling times = 8-fold increase in MRD

Patient with a CLL doubling time of 6 months - clinical relapse at 14 years

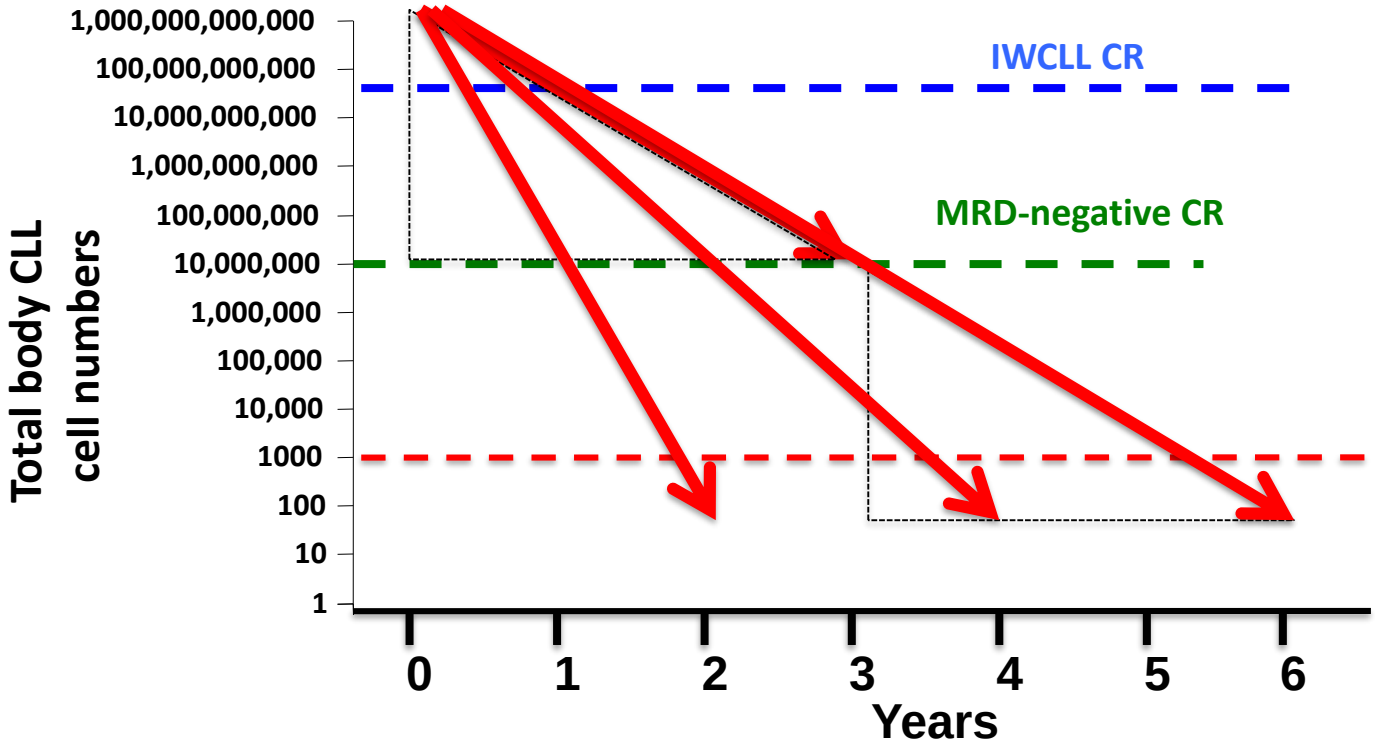


3 CLL doubling times = 8-fold increase in MRD

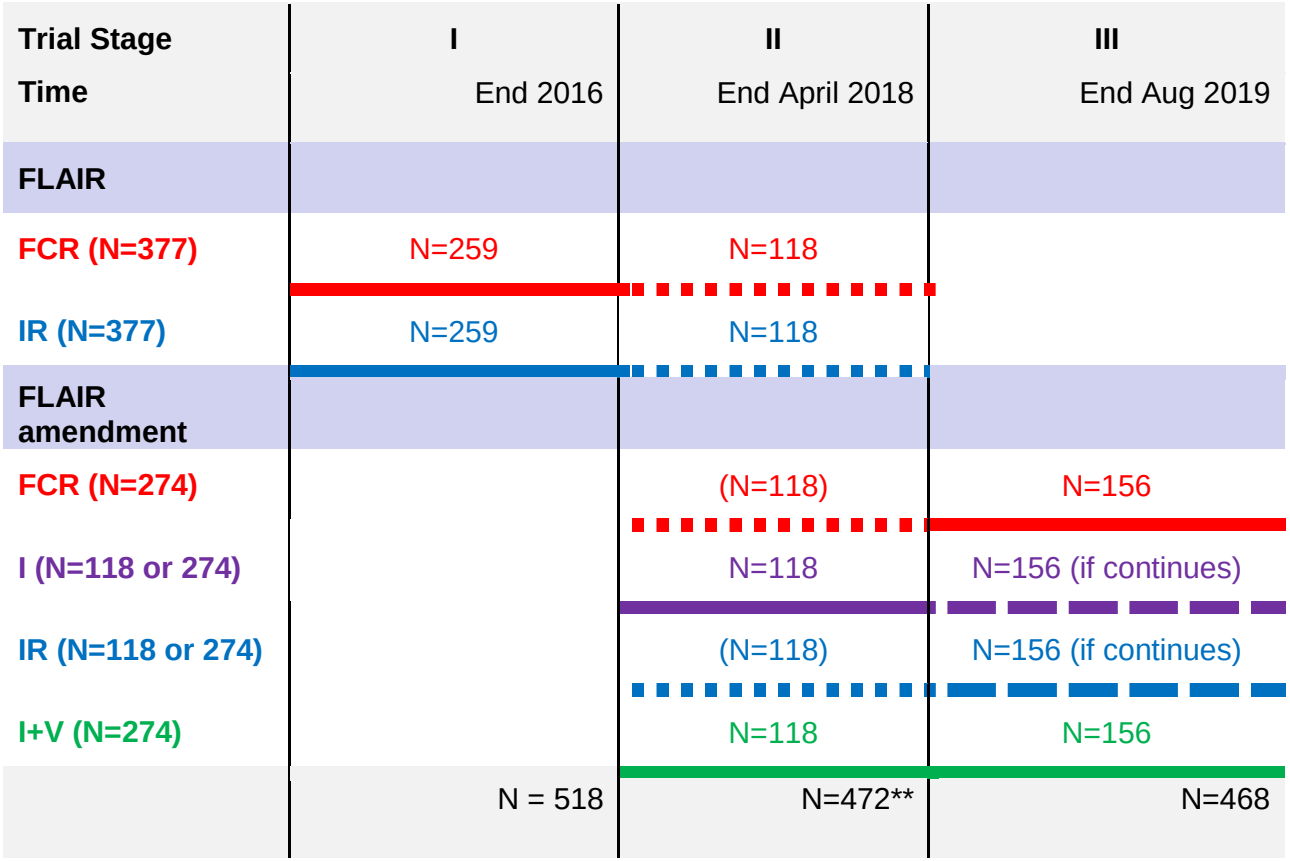
Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



Modified treatment stopping rule in FLAIR - duration of therapy defined by speed of response



Modification of NCRI FLAIR (CLLFlair include ibrutinib + venetoclax



Next steps in the treatment of CLL: "Targetable" molecular lesions

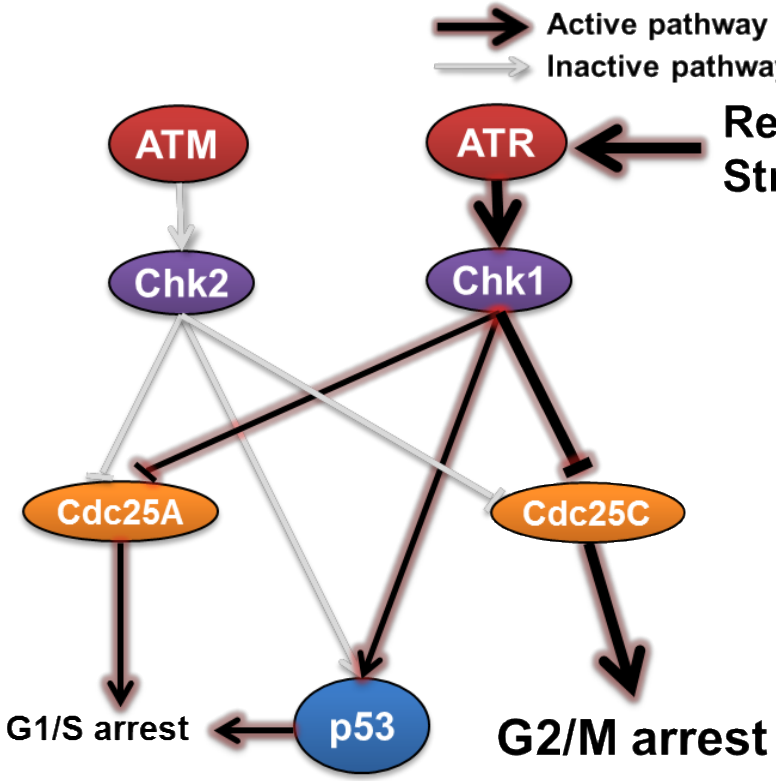
ATR inhibition induces synthetic lethality and overcomes chemoresistance in *TP53* or *ATM* defective chronic lymphocytic leukemia cells

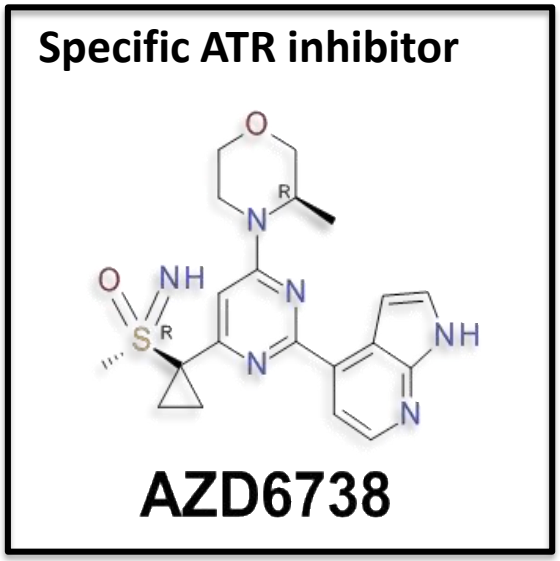
Marwan Kwok,[1,2*] Nicholas Davies,[1*] Angelo Agathaggelou,[1] Edward Smith,[1] Ceri Oldreive,[1] Eva Petermann,[1] Grant Stewart,[1] Jeff Brown,[3] Alan Lau,[4] Guy Pratt,[1,5] Helen Parry,[1,2] Malcolm Taylor,[1] Paul Moss,[1,2] Peter Hillmen,[6] Tatjana Stankovic[1,2]

[1]School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom; [2]Centre for Clinical Haematology, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom, [3]Oncology iMed, AstraZeneca Pharmaceuticals, Waltham, MA, [4]R&D Oncology iMed, AstraZeneca Pharmaceuticals, Alderley Park, United Kingdom; [5]Birmingham Heartlands Hospital, Birmingham, United Kingdom; [6]Section of Experimental Haematology, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, United Kingdom

Kwok *et al., Blood* , 2016, in press

ATR kinase – resolves replication stress and maintains genome integrity





Kwok *et al., Blood*, 2016, in press

CONCLUSIONS

- Future for CLL looks very promising
- We may be able to use the word ‘cure’ in coming years
- The boundaries between go go/slow go/no go are becoming blurred
- Personalized treatment will be the ultimate goal

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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
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Emily Cass
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Talha Munir
Abraham Varghese
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Andrew Jack
Ruth de Tute

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Pharmacyclics
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Bloodwise
Beating blood cancer since 1960