Is this the end of chemotherapy in lymphoma?

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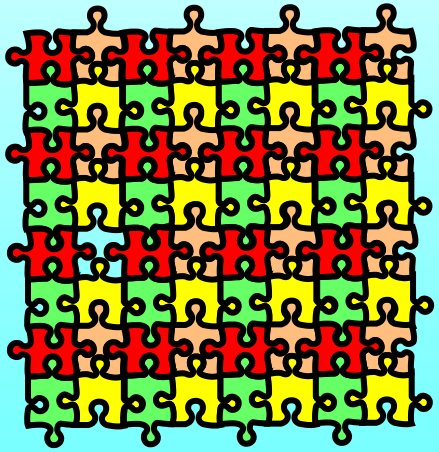
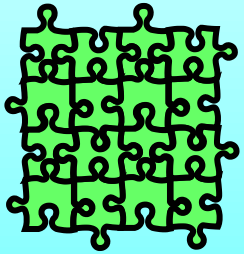
- I have no disclosures

Personalized medicine: Targeted treatment





Target present

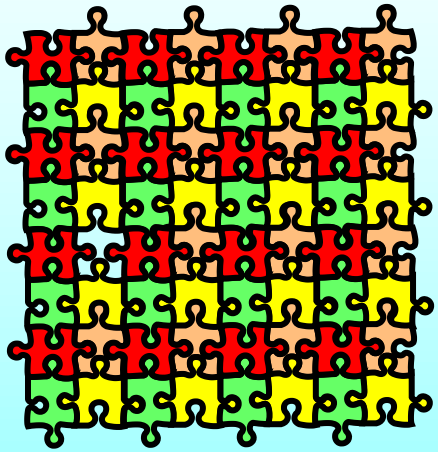
BCR Kinases
BCL2
Cyclins

Specific therapy

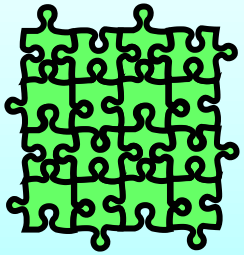
Single agent activity - Ibrutinib

DRUG	*Phase*	*ORR*	*CR*	*PFS*	*OS*	*Reference*
CLL	Ib/II (R/R patients)	71%		75% @ 26M	83% @ 26M	Byrd et al. NEJM 2013; 369: 508-46
	III (R/R patients)	63%	0 (2)%	88% @ 6M	90% @ 12M	Byrd et al. NEJM 2014; 371: 213 - 223
MCL	II (R/R patients)	68%	21%	13.9 M	58% @ 18M	Wang et al. NEJM 2013
DLCL	II (R/R patients)	40% - ABC 5% - GCB	8% - ABC 0% - GCB	2.5 M – ABC 1.2 - GCB		Wilson et al. ASH 2012, Abstract#686

Biomarkers of Response



Genetic heterogeneity between and within subtypes may account for variation in response to treatment



Target present
Biomarker test

Negative or positive

Specific therapy

Incorporating markers will facilitate drug development and ensure mechanism based therapies are effectively applied

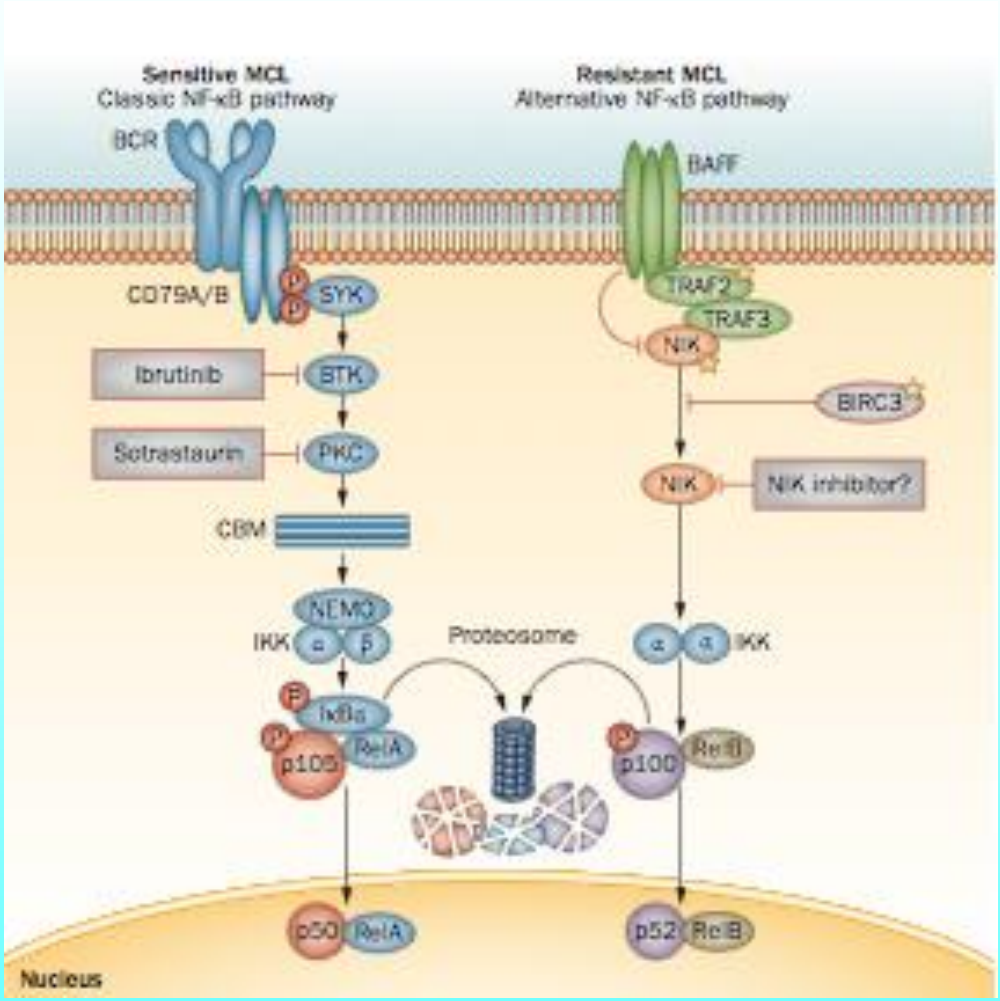
Intlekofer and Younes, Nature Reviews Clinical Oncology 2014

Biomarkers of response

Rahal *et al* described a possible mechanism of resistance to Ibrutinib in MCL

Depends which NFkB pathway MCL signals through

Activation of the alternate NFkB pathway can occur via mutation in BIRC3, TRAF2, INK



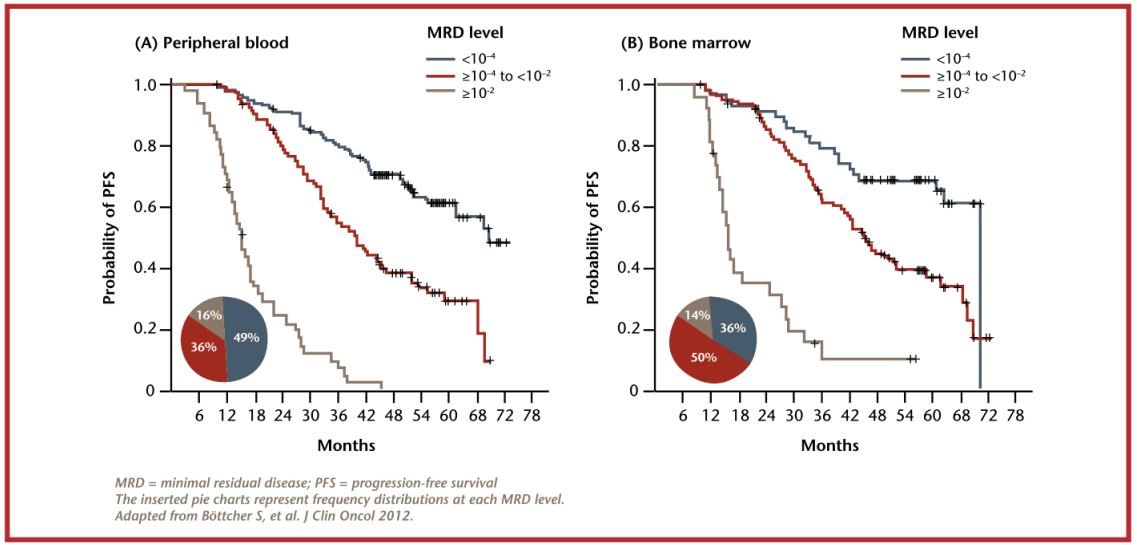
Rahal et al Nature Medicine 2014
Intlekofer and Younes, Nature Reviews Clinical Oncology 2014

End of Chemo - only targeted agents? Key questions moving forward

- Is achieving a complete response important response?
- What are the expectations of the patient?
- The role of inherent resistance and clonal evolution?
- The role of acquired resistance - complex signaling pathways and microenvironment?

1. Importance of complete response

Figure 2. CLL8 trial: PFS in patients grouped by MRD levels assessed in (A) peripheral blood and (B) bone marrow at final restaging



MRD = minimal residual disease; PFS = progression-free survival
The inserted pie charts represent frequency distributions at each MRD level.
Adapted from Böttcher S, et al. J Clin Oncol 2012.

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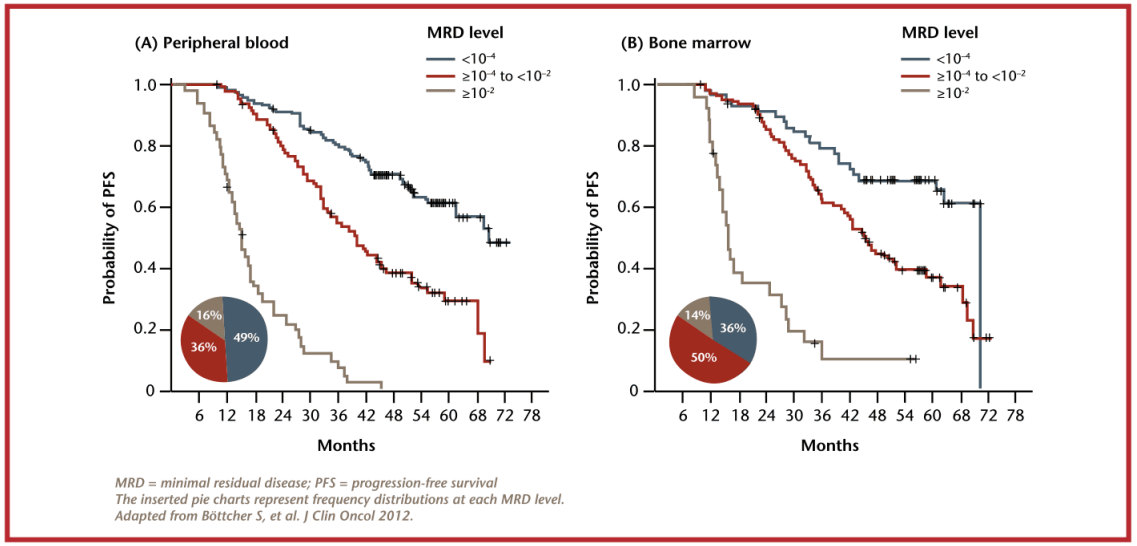

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Ibrutinib	III (R/R patients)	63%	0 (2)%	88% @ 6M	90% @ 12M	Byrd et al. NEJM 2014; 371: 213 - 223

2. Expectations of the patient

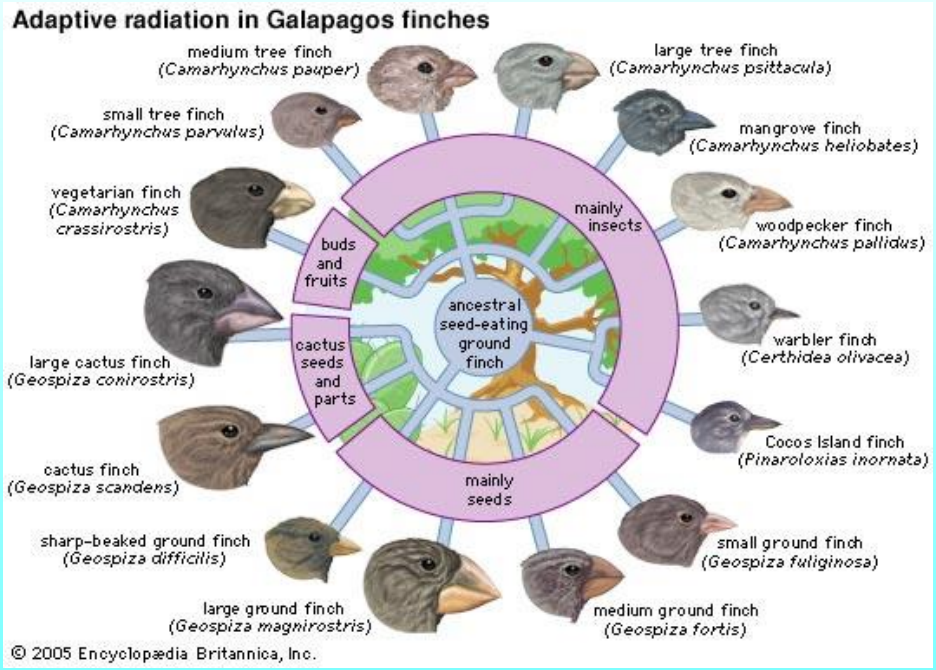
- Depends on your life circumstances, co-morbidities etc
  - Cure (?only with chemo) vs long term disease control
  - Complete response vs partial response
  - Side effect profile
  - Chemo free regimen

3. Inherent resistance - Clonal Evolution

“Nothing in biology makes sense

except in the light of evolution”

Theodosius Dobzhansky, 1973



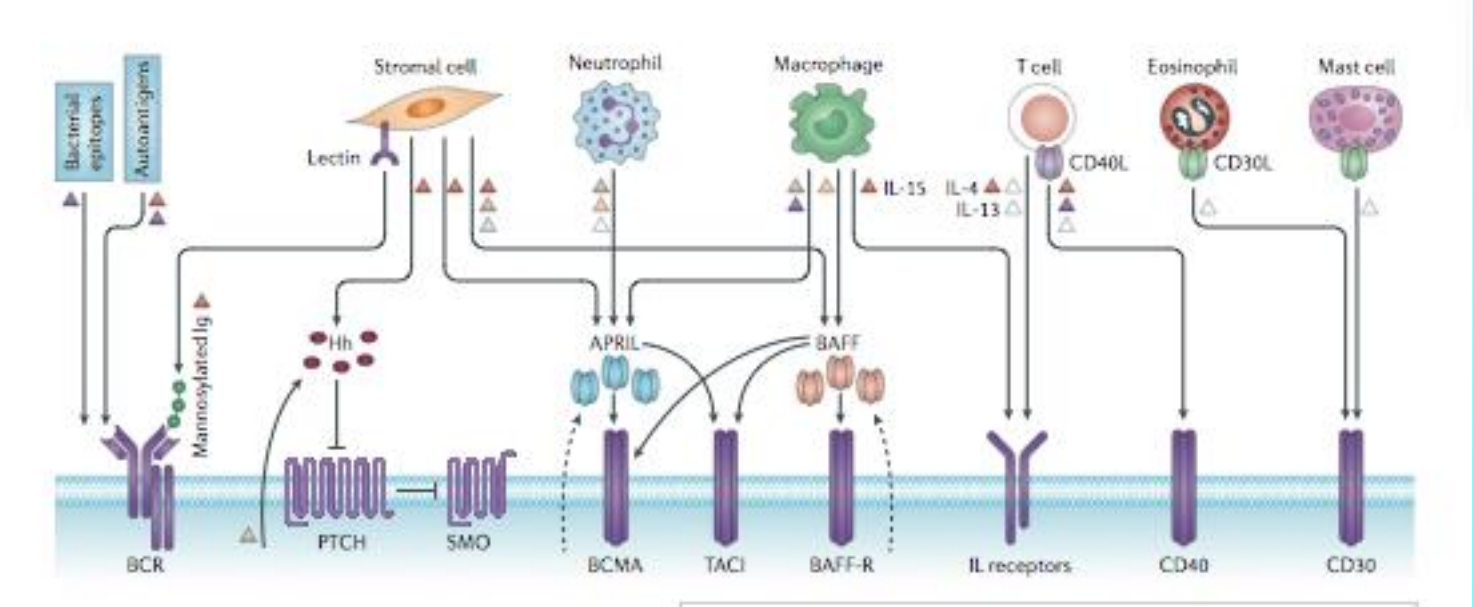
Adaption and survival of the fittest – Darwin

Present at diagnosis and throught disease course

Treatment acts as a selection pressure and alters the clonal equilibrium

4. Acquired resistance

- Mutation and classical drug resistance mechanisms
- Complex signaling pathways
  - Up regulation of parallel pathways
- Microenvironment



Survival and proliferation signals from the tumour microenvironment

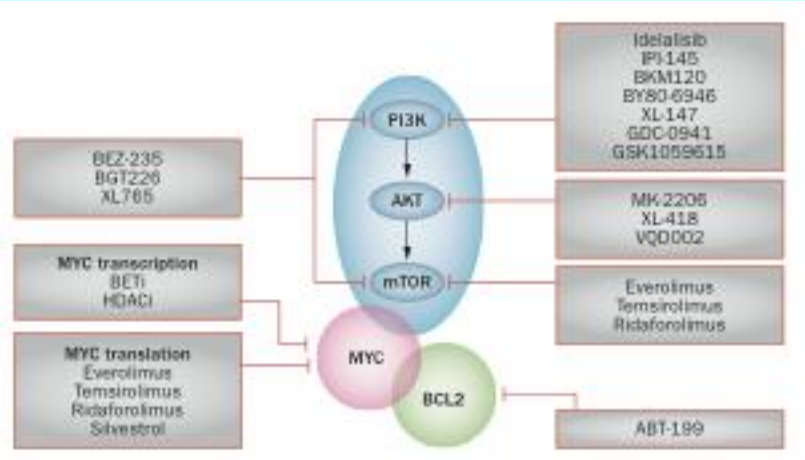
Scott and Gascoyne, Nature Cancer Reviews 2014

? Better Together

bettertogether
A stronger Scotland, a United Kingdom

? Better in combination

- In combination with what?
  - Two biologic treatments together or one biologic with chemotherapy
  - Biology
    - different pathways
    - Sensitizers/primers



Venn diagram showing biological interactions between MYC, BCL2, PI3k in DLBCL and potential therapies

Intlekofer and Younes, Nature Reviews Clinical Oncology 2014

The future?

Progressed made – the hard part may have been done
- subgroups, biology, targets and novel therapeutics

Work to do – predictive biomarkers to guide therapy, treatment combination trials, Biological agent combination and biological/chemotherapy combinations

Is this the end of chemotherapy in lymphoma?

'Extinct! Good gracious no... you're thinking of the WHITE rhino'