Chronic lymphocytic leukemia

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Disclosures

- Travelling to ASH: Roche
- Consulting services: Janssen

Questions in CLL: answers in ≥ 2015?

- How to integrate new mutations?
- Should kinase inhibition become preferred R/?

  (All patients? Only unfit? Only del17p?...)
- Transplantation at the BCRi/BCL2a era in high-risk patients? (Predicting failure to new drugs)
- Side effects of new drugs?

Clinical case#1

« How to define high-risk patients »

Male 55-y, CLL diagnosed 2009, normal FISH

R/FCRx6→CR with *neg*-MRD

Nov 2014, progression requiring R/

Classical approach

- Exclude 17p deletion (FISH)
- Retreat with same regimen (FCR) or BR

Genetic landscape in CLL

mutations affecting DNA-damage response

TP53

ATM

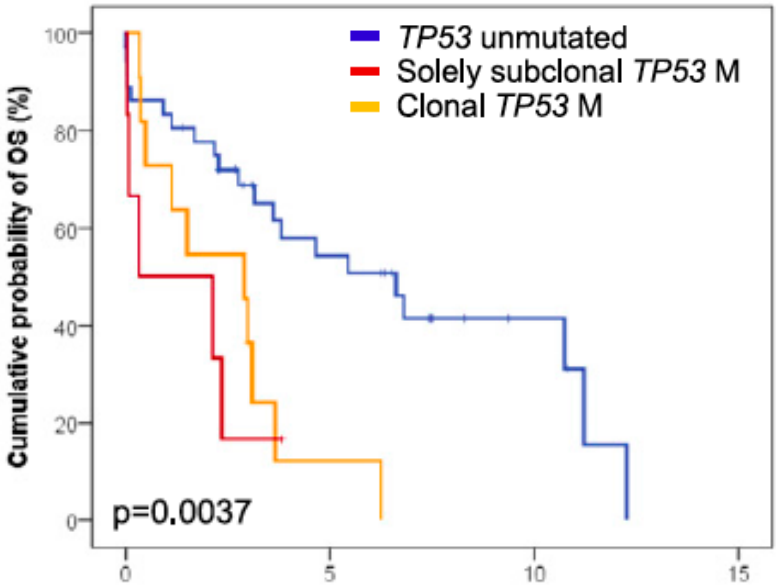
- FISH: cannot predict p53 and/or ATM dysfunction in patients with or without 17p13/11q22.3 deletions
- Sequencing *TP53* (exons 4-9) for mutations in all patients?
  - « Any detectable clone is of poor prognosis »
- Sequencing of *ATM* much more difficult

Genetic landscape in CLL

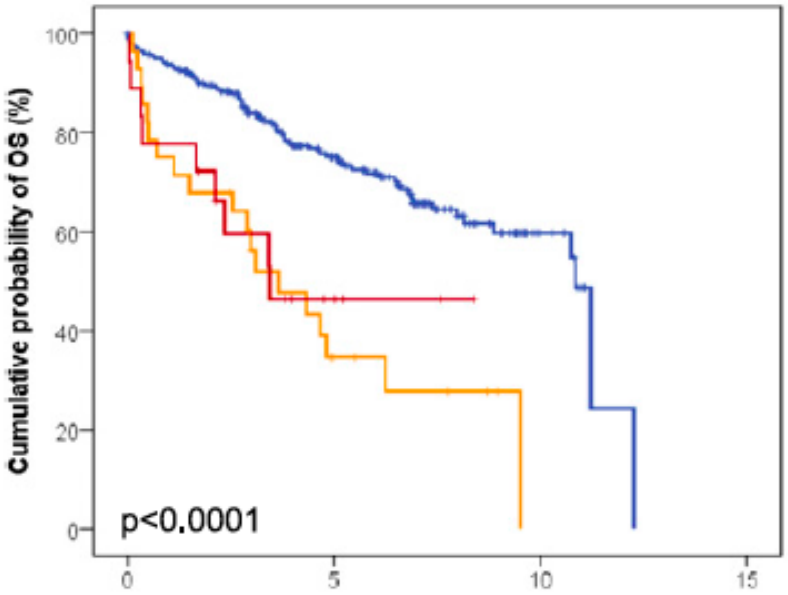
mutations affecting DNA-damage response

TP53

TP53 sequencing by ultradeep NGS: small clones (median allele frequency 2.1%) become predominant with time and anticipate chemorefractoriness



OS from diagnosis



OS from treatment

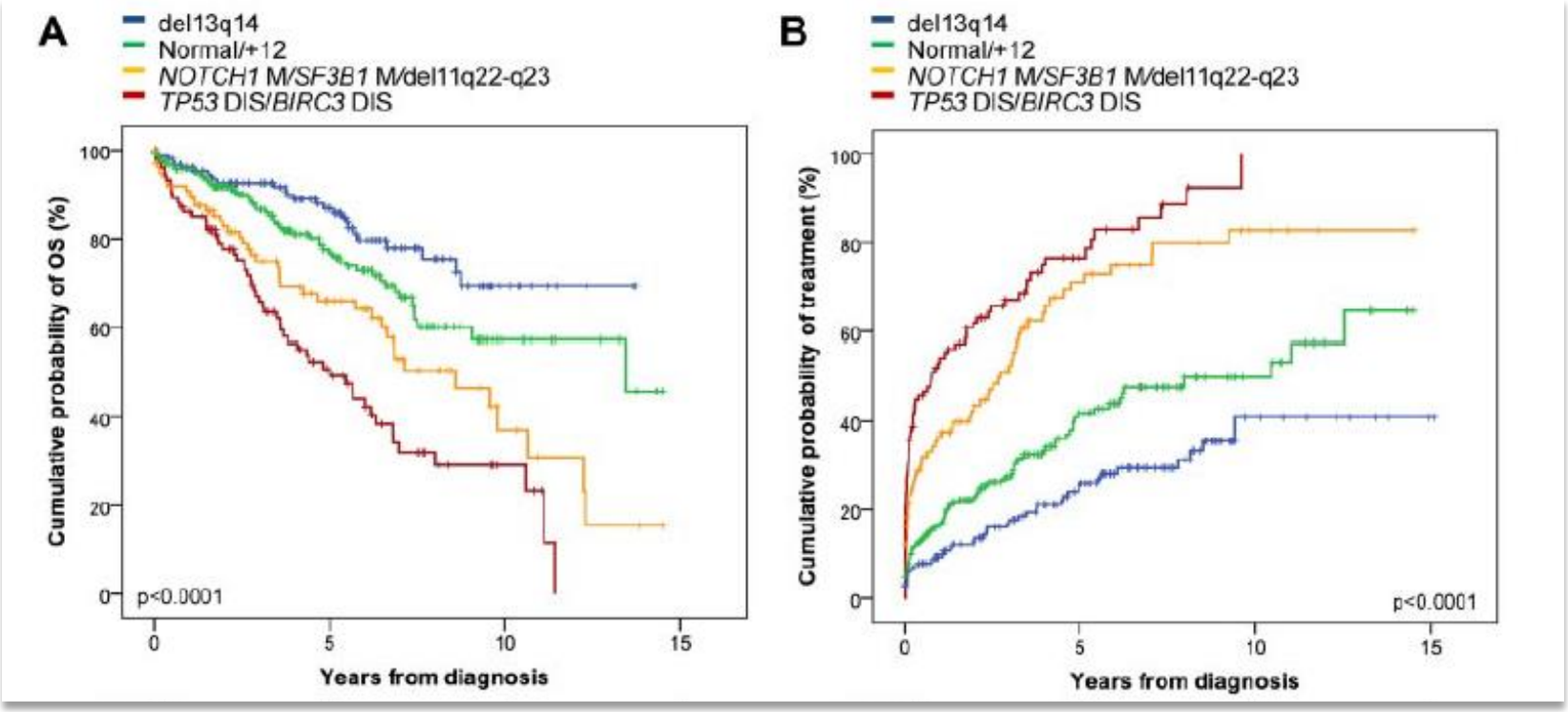
Zent *et al*, Education program 2014; Rossi *et al*, *Blood* 2014

Genetic landscape in CLL

mutations affecting signaling pathways, RNA editing

NOTCH1 *BIRC3* *SF3B1*

Independent prognostic value? How to integrate in practice?



Zent *et al*, Education program 2014; Rossi *et al*, *Blood* 2013; Foà *et* al, *Haematologica* 2013

New prognostic model integrating new molecular lesions into the backbone of FISH

Group	%	OS @ 10 years
Del13q14 single	20-25	69%
Normal or +12	40	57%
NOTCH1 and/or SF3B1 and/or del11q22-23	15-20	37%
TP53 dis and/or BIRC3 dis	15-20	29%

Four genetic groups are hierarchically classified

Survival curve comparison	Significance
Del13q14 single *vs* Normal/+12	P .0406
Normal/+12 *vs* *NOTCH1* M/*SF3B1* M/del11q22-23	P .008
NOTCH1 M/*SF3B1* M/del11q22-23 *vs* *TP53* dis/*BIRC3* dis	P .02

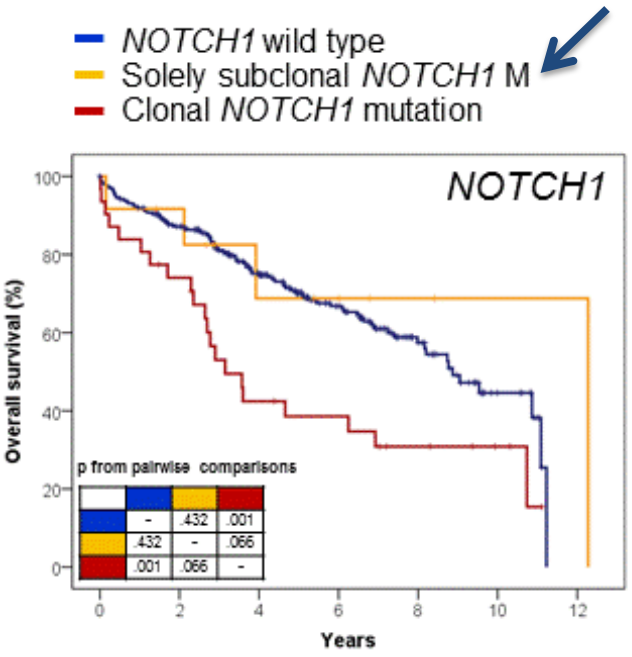
Rossi *et al*, *Blood* 2013; Foà *et* al, *Haematologica* 2013

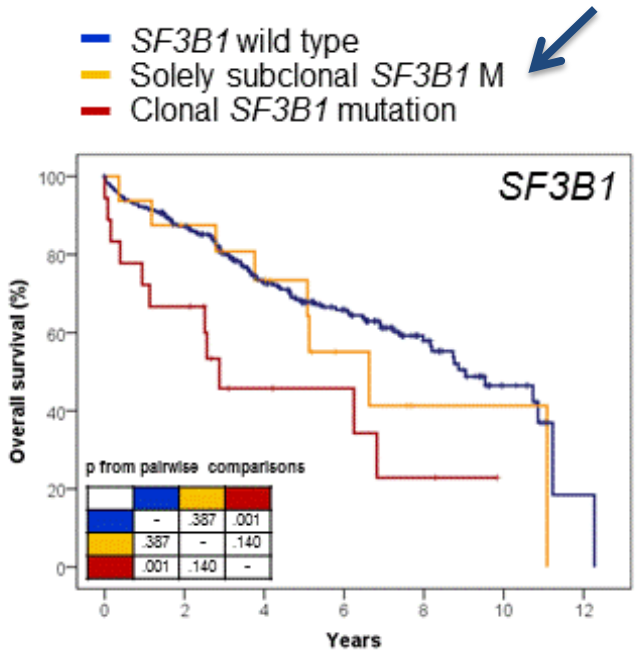
Genetic landscape in CLL

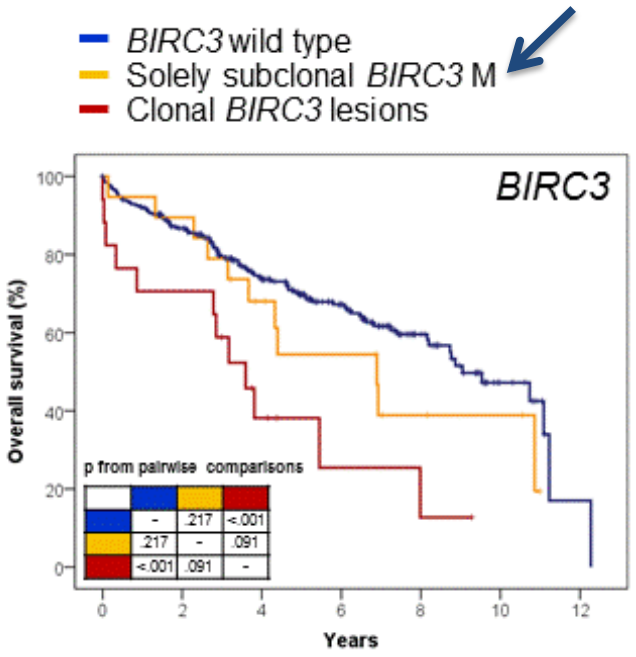
mutations affecting signaling pathways, RNA editing

NOTCH1 *BIRC3* *SF3B1*

Clinical relevancy of small subclones harboring *NOTCH1*, *SF3B1*, or *BIRC3* mutations

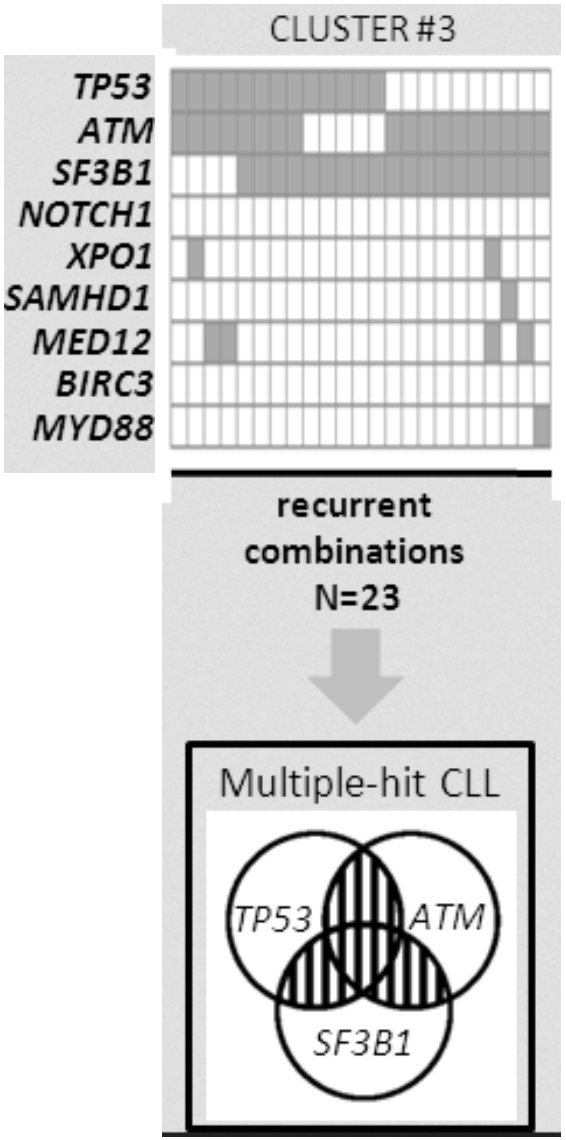






Rossi *et al*, #295

Associations of recurrent mutations



Definition of « multiple hit patients » with poor prognosis including in multivariate analysis

Robbe *et al*, #1974

New risk stratification in CLL?

Pathway		Risk
DNA Damage *17p13- TP53* mut 11q22- *ATM* mut	→	**Very High**
Cell Signaling BCR activity + *IGHV* UM Stereotypy VH3-21 ZAP70+ *NOTCH1* mut *BIRC3* mut RNA processing *SF3B1* mut	→	**High/intermediate**
None of above	→	**Low**

Zent *et al*, Education program

Cut-off values of allele frequencies!

- *TP53*: any clone
- *NOTCH1*: >25%
- *SF3B1*: >35%
- *BIRC3*: >1%

Rossi, *et* al #295;

Clinical case#1

« How to define high-risk patients »

Male 55-y, CLL diagnosed 2010 Nl FISH

R/FCRx6→CR with *neg*-MRD

Nov 2014, progression requiring R/

New approach?

- Exclude 17p deletion (FISH)
- *TP53* exons 4-9 sequencing (any clone!)
- If no *TP53* mutation: *BIRC3*, *SF3B1*, *NOTCH1 (ATM)*
- CIT, new drugs, alloTx according to results

Clinical case#2

« BCRa/BCL2i or transplantation? »

Female 60-y, fit, **bulky**, *IgHV* **unmutated relapsed** CLL with **del17p** start R/ ibrutinib in Jul 2014 as 3rd line

RS was not formally excluded (SUV values ≈ 10)

Nov 2014: LN < 1.5 cm, hyperlymphocytosis

- continue on BCRi/BCL2a until progression

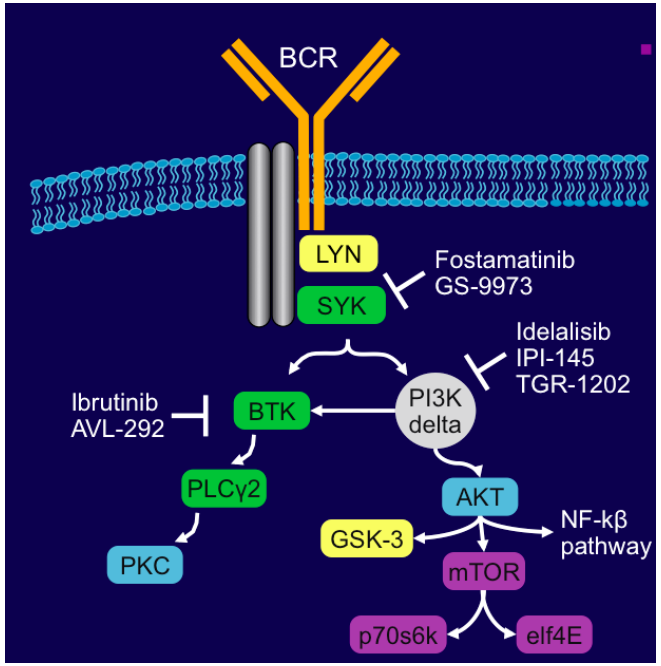
- shift to other inhibitor/combination when failure

- « deferred » allogeneic Tx

- « immediate » consolidation with allogeneic Tx

New therapeutical approaches in CLL

- BCR pathway inhibitors
  - **SYK**: fostamatinib, GS-9973
  - **BTK**: ibrutinib, CC-292…
  - **Pi3K**: idelalisib, IPI-145 (duvelisib), AMG-319
- Bcl-2 antagonists
  - ABT-199 (venetoclax) Roberts, #325



New therapeutical approaches in CLL

- **Ibrutinib**
  - Del 17p: PFS and OS @ 26 months are 57% and 70%
  - Combination studies
    - Sequence effect with mAb or lenalidomide may matter
- **Idelalisib**
  - All CLL: median PFS 32 months (≥ 150 mg dosing)
  - Active in first line ≥ 65-y old (40% PRL)
  - + rituximab: PFS 62%@12 months if del17p/*TP53*mut/del11q

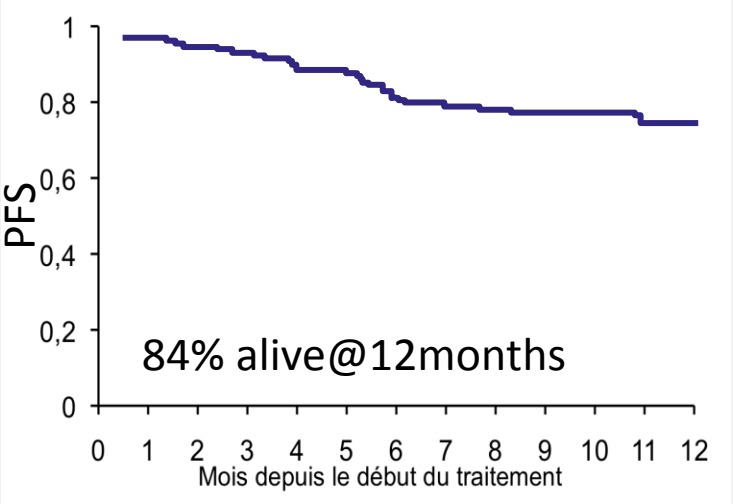
Wiestner, Education program 2014; Byrd *et al*, *NEJM* 2013; Brown *et al*, *Blood* 2014; Zelenetz *et al*, #1986; Pollyea *et al*, #1987; Sharman *et* al, #330; Jaglowski, *et al*, ASCO 2014

New therapeutical approaches in CLL R/R patients with 17p deletion

- Phase II Resonate

n:144 (FU: 13 m)

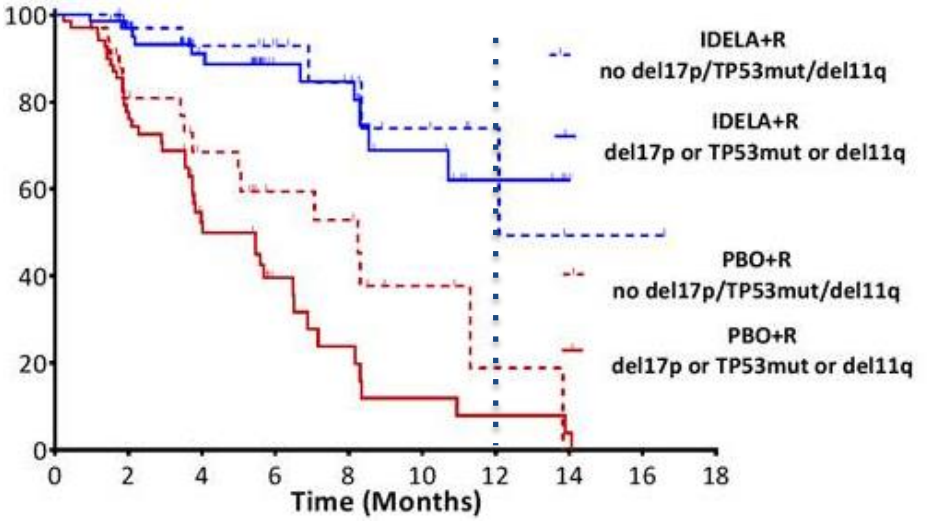
O'Brien, #327



After FCR or Alem: median PFS 11 months!

- Phase III Idelalisib + R *vs* placebo

Sharman, #330



Predictive factors of failure to ibrutinib

- Hyperlymphocytosis: NO (actually reduction of tumour burden!)
  - PR with lymphocytosis (PRL) can fare better than PR or even CR (Landmark analysis)
- Traditional PF (bulky, *IgHV* unmutated, del17p, del11q): NO (at least initially)
- Novel gene mutations: NO (at least initially)

Burger *et* al, #326; Murphy *et* al, #829; Woyach *et al*, *Blood* 2014

Predictive factors of response to ibrutinib

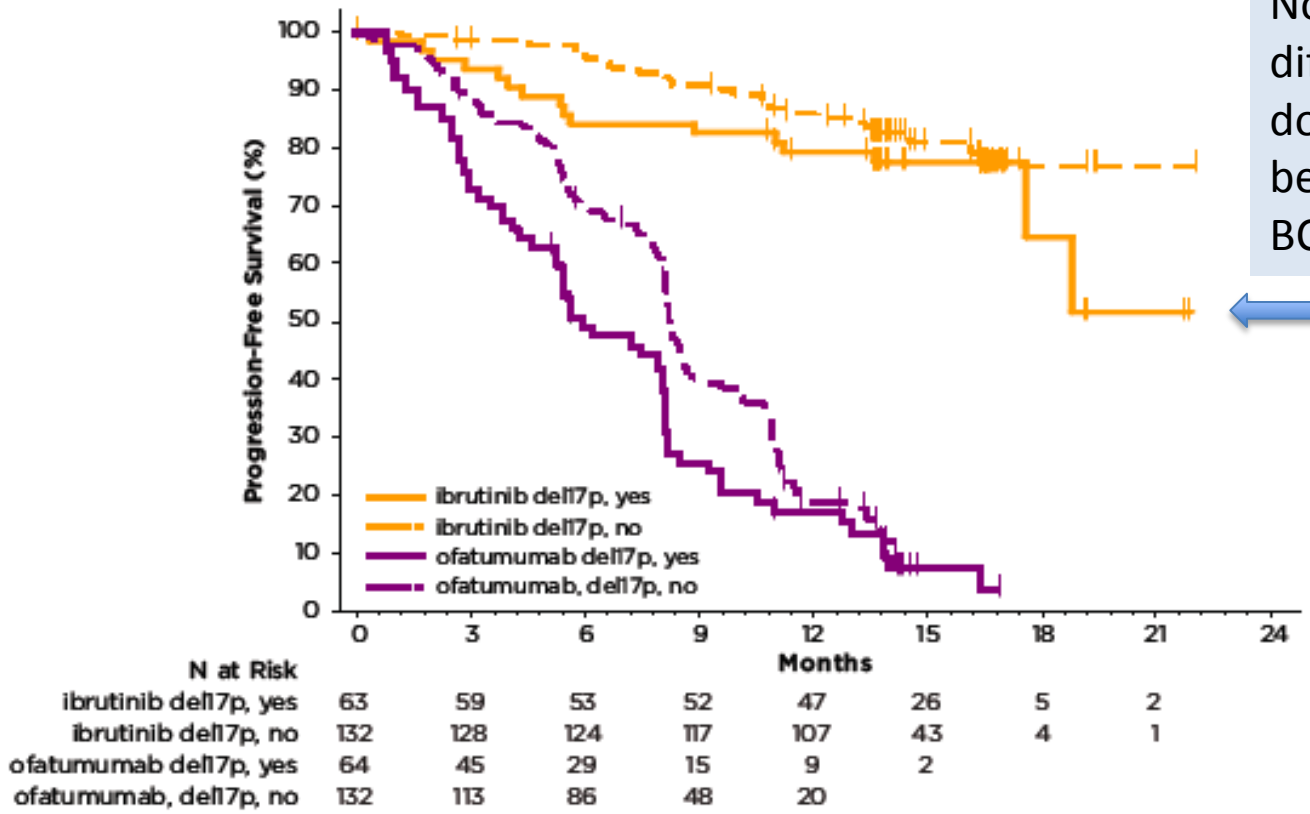
Novel gene mutations at baseline

Novel Gene Mutations	12-m PFS ibrutinib (n=121)
NOTCH1	
Mutated*	85%
Not mutated*	90.5%
SF3B1	
Mutated*	86.5%
Not mutated*	90%
TP53	
Mutated*	88%
Not mutated*	90%
MYD88	
Mutated	100%
Not mutated*	89%

Brown *et al*, #3331 (update RESONATE trial)

Predictive factors of response to ibrutinib

Presence of del17p at baseline



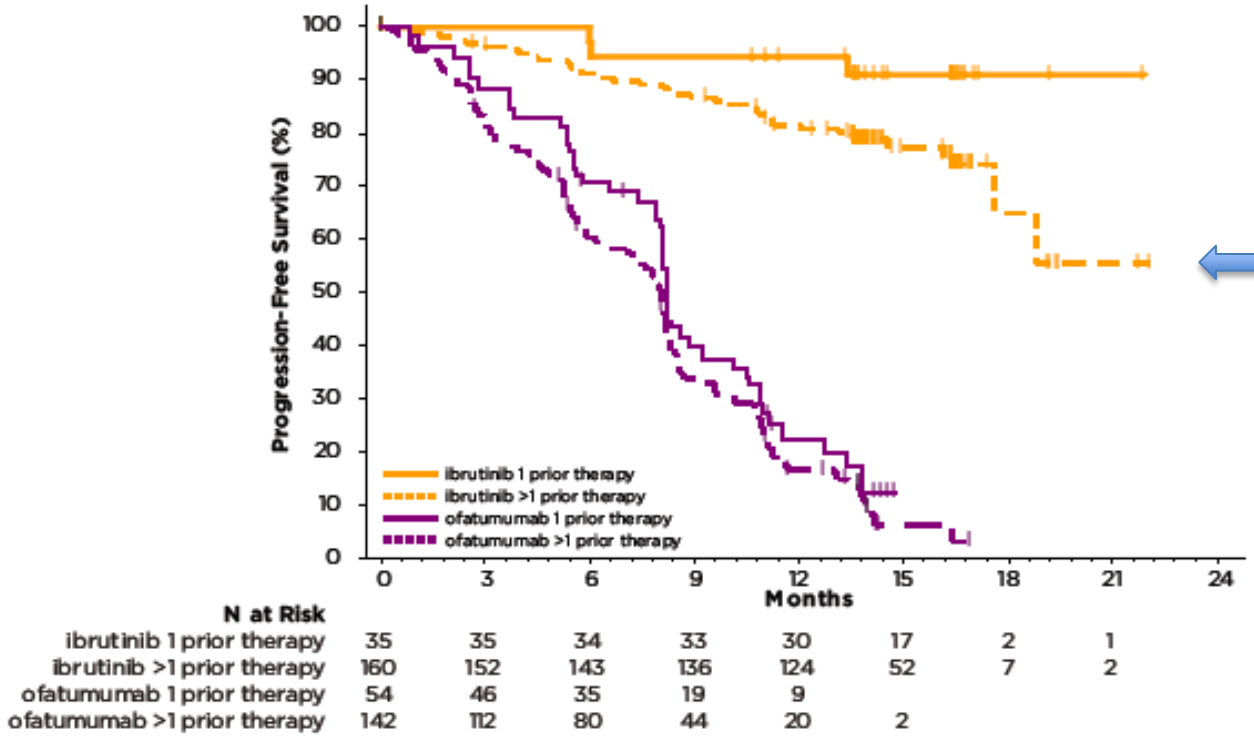
No statistical difference but doubtful that it will be abrogated by BCRi

?

Brown *et al*, #3331 (update RESONATE trial)

Predictive factors of response to ibrutinib

Number of prior lines

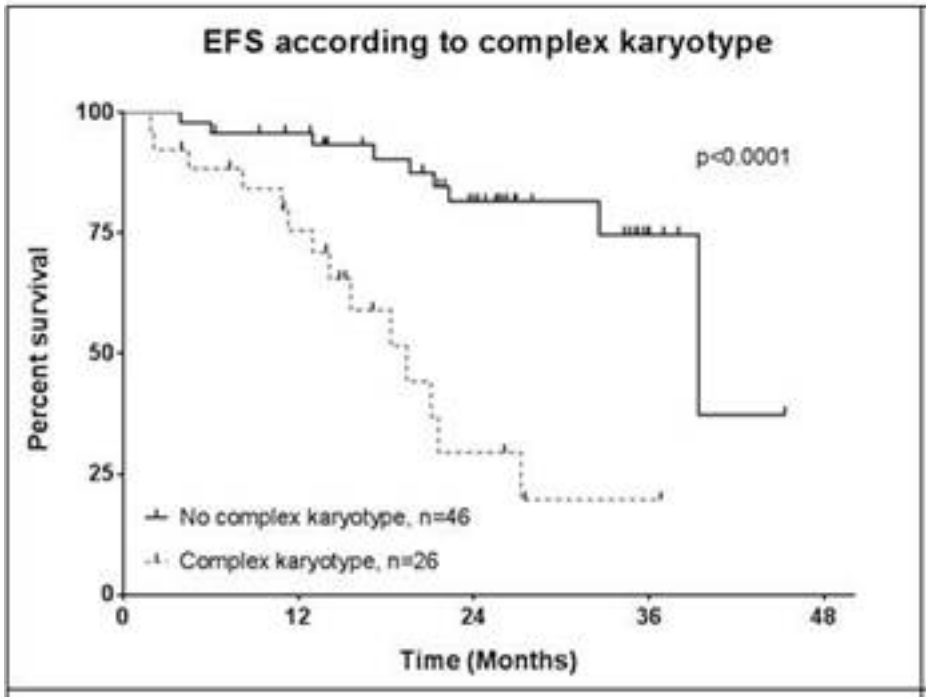


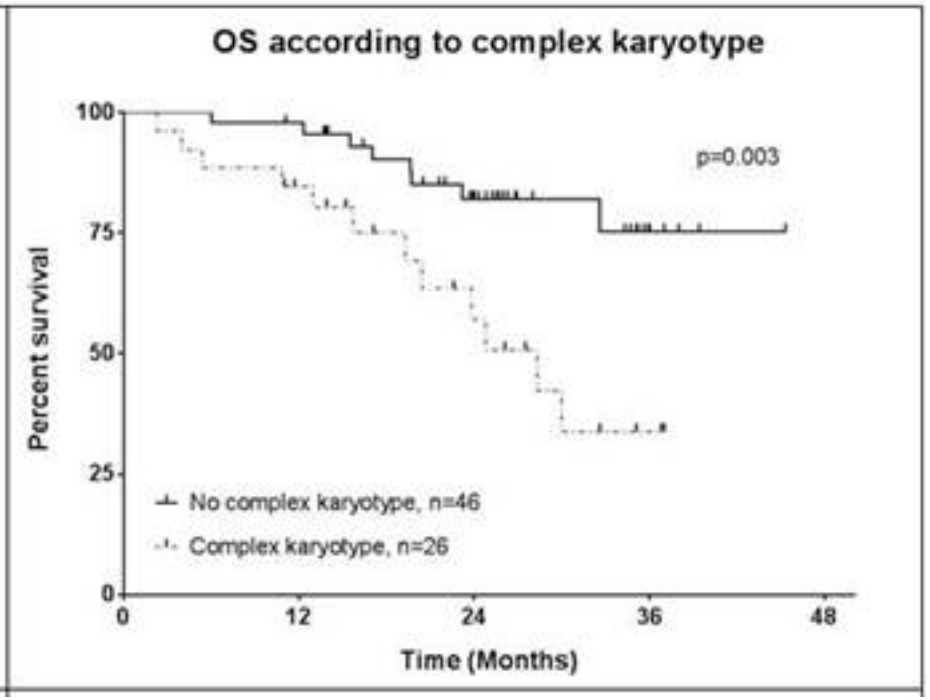
>1 prior R/

Brown *et al*, #3331 (update RESONATE trial)

Predictive factors of response to ibrutinib

Complex karyotype





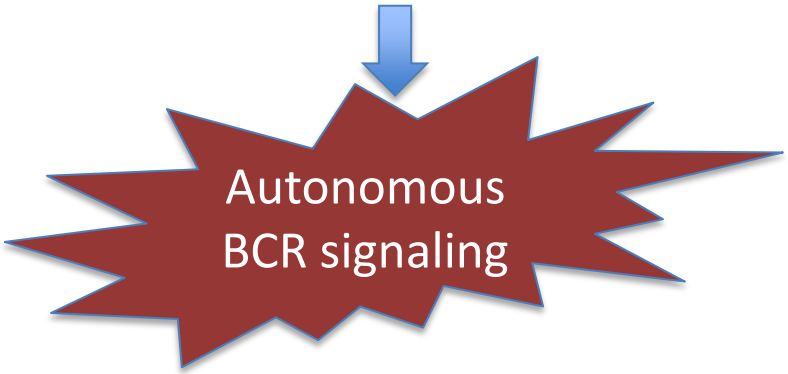
CKT independently associated with OS (CKT [HR 5.1(1.5-17.5), p=0.009])

Thompson *et al*, #22

Predictive factors of response to ibrutinib

Acquired mutations during therapy

- BTK cysteine-to-serine mutation (C481S): disrupt the covalent binding with kinase
- PLCγ2 gain-of-function mutation



- Acquired mutations in 6/246 patients (5 C481S)

Woyach *et al*, *NEJM* 2014; Furman *et al*, *NEJM* 2014; Chang, ASCO 2013

Clinical activity of Pi3K after BTK inhibition
?*Duvelisib after ibrutinib*

- pAkt pharmacodynamic response in R/R patients, even with IBR-resistance mutations in *BTK*
- **Early** evidence of clinical activity

Porcu *et al*, #3335

Risk of Richter syndrome after ibrutinib
Indication for early alloTx?

- Resonate
  - 2 RS in each arm
- NHLBI (51 pts del17p)
  - RS in 2, PLL in 2
- Resonate-17
  - RS in 11 (7.6%)

- MD Anderson
  - 63 pts with del17p
  - RS in 23% at a median 21 months (1-27)
  - Risk= complex karyotype

Might actually be less common than expected…

Byrd *et* al, *NEJM* 2014; FaroPorcu *et al*, #3335; O'Brien *et al*, #327; Strati *et al*, Haematologica 2014

Clinical case#2

« BCRi/Bcl-2a or transplantation? »

Female 60-y, fit, **bulky** *IgHV* **unmutated relapsed** CLL with **del17p** start R/ ibrutinib in Jul 2014 as 3rd line

RS was not formally excluded (high SUV values)

Complex karyotype

Nov 2014: LN < 1.5 cm, hyperlymphocytosis

Familial donor, low HCT-CI

Data on switch to other BCRi/BCL2a not mature

→Allogeneic Tx

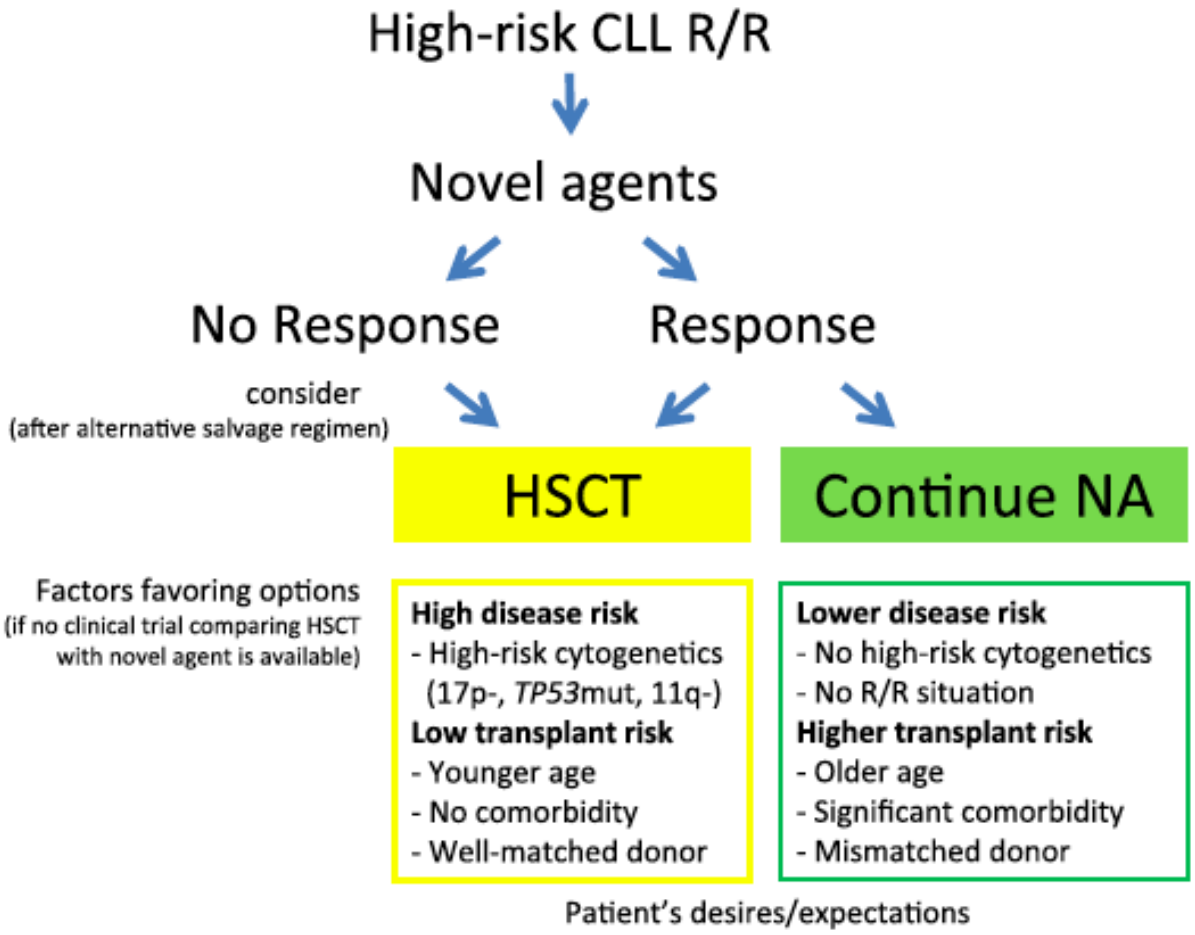
Managing high-risk CLL

Stem cell transplantation or novel agent?

- Potential indications for allogeneic HSCT in CLL
- Standard definition of HR-CLL (Dreger, *Leukemia* 2007)
  - Refractory to PA
  - Relapse < 2 years after PA
  - Del17p/*TP53* mutations

Managing high-risk CLL

Stem cell transplantation or novel agent?



Dreger *et* al, *Blood* 2014 (ERIC and EBMT recommendations)

Ibrutinib after stem cell transplantation?

- Hints for sustained disease response and promising donor immune modulation
- Potential resolution of chronic GVH?
- Limited +++ number of patients
- But…*in vitro* ibrutinib can promote a Th-1 skewed T-cell response (Dubovski *et al*, *Blood* 2013)

Ryan *et al*, #1186; Coutre *et al*, #4697; Dubovski *et al*, *Blood* 2013

Clinical case#3

Side effects of BCR signaling inhibitors

Male 71-y, relapsed CLL with del17p. Taking **Asaflow** 80mg/day (Stemi). Start R/ ibrutinib in Jun 2014

Jul 2014: atrial fibrillation

Cardiac surgery (aorto-coronary bypass) R/**Xarelto**

Ibritunib-Asaflow-Xarelto « impossible » (bleedings)

Ibrutinib-Asaflow-fraxiparine

Use of AC and/or AP agents with Ib

- Pattern of AC/AP use (PCYC-1102/Resonate):
  - 54% of patients with AC (11%) and/or AP (43%)
  - Few patients with AC/AP/Ib
  - 2% major bleedings (confoundant factors!)

  (Jones *et al*, #1990)
- Prediction of bleeding risk using aggregometry? Discordant results!

  (Ysebaert *et al*, #3296)

Ibrutinib: side effects/practical aspects

- Does not trigger AIHA/ITP and can facilitate tapering of chronic AIC treatments (Rogers *et al*, #1997)

Ibrutinib or idelalisib/rituximab in CLL?

- For patients with history of inflammatory bowel disease, colitis, pneumonitis (?)

→Rather ibrutinib?

- For patients requiring AC, with histories of atrial fibrillation

→Rather idelalisib?

Rogers *et al*, #1997; full prescribing information of both drugs

Miscellaneous

- *Notch1* mutations may confer lack of benefit of anti-CD20 therapy (Del Poeta, EHA#102; Pozzo, #296)
- New mutations involving Ikβ (Mansouri, Sutton, #297)
- Anti-CD20 maintenance (Greil, #20; van Oers, #21)
- MRD (Kovacs, #23)
- CLL10 (FCR vs BR) (Eichhorst, #19)
- CLL11 (GA101-Clb *vs* RTX-Clb) (Goede, #642; *NEJM* 2014)
- GA-101 (Green study) (Bosch, #3345)
- SC vs IV rituximab (Assouline, #1995)
- CAR-engineered T cells (Porter, #1982)

Conclusions

- Time to start mutational screening in selected indications?
- A proportion of patients (1/3?, mainly good-risk) could be CURED by FCR. Thus remains standard. Role of novel agents needs to be demonstrated in this subgroup of patients
- Novel agents: life-saving options in patients in greatest need BUT continuous decline of the PFS curve with all BCRi/BCL2a