Program 16th Post-ASH meeting

Chairmen: *R. Schots (UZ Brussels) & M-Ch. Vekemans (UCL)*

13:30 **Registration**

14:00 Welcome

14:05 The best from ASH
Y. Beguin (ULg)

14:30 Myelodysplastic syndrome
M-Ch. Vekemans (UCL)

14:50 Multiple Myeloma
J. Caers (ULg)

15:10 CML/CMP
G. Verhoef (UZ KUL)

15:30 **Coffee break**

16:00 Lymphoma
A. Bosly (UCL Mt Godinne)

16:30 Thrombosis/Hemostasis
C. Van Geet (UZ KUL)

17:00 Acute leukemia
Z. Berneman (AZ Antwerpen)

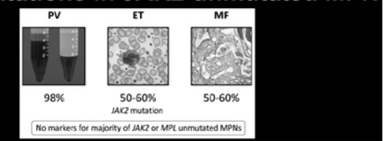
17:30 Chronic Lymphatic Leukemia
D. Mazure (UZ Gent)

17:50 **Drinks**

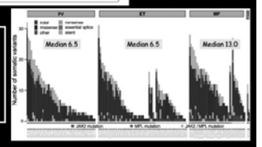
MPN

1

BEST OF ASH 2013
CALR mutations in JAK2-unmutated MPN



- Exome sequencing of 151 MPN patients (matched tumor and germline DNA)
- Follow up series of 3400 samples
- 1498 mutations in 150 patients →



NEJM 369:2391, 2013
https://ash.confex.com/ash/2013/webprogram/Paper66023.html
Nangalia et al

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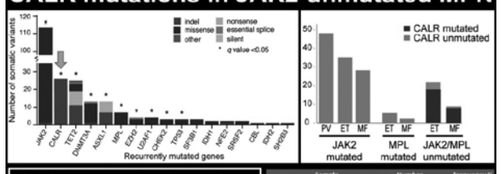
BEST OF ASH 2013
CALR mutations in JAK2-unmutated MPN



- Calreticulin mutations (19 types) in 70-84% JAK2/MPL wt patients
- Lower Hb and higher Plt, more MF
- Early events, all deletions / insertions generating novel C terminus
- Mutant CALR seen in ER, no increase within Golgi or at cell surface

Sample	Number	Frequency %
Myeloproliferative syndromes - JAK2 / MPL mutated	511	0
Myeloproliferative syndromes - JAK2 / MPL unmutated	668	69.6
Myelodysplastic syndromes	120	8.3
Other myeloid disorders	269	0.7
Lymphoid malignancy	287	0
Solid tumors	502	0
Cancer cell lines	1015	0
Controls	550	0

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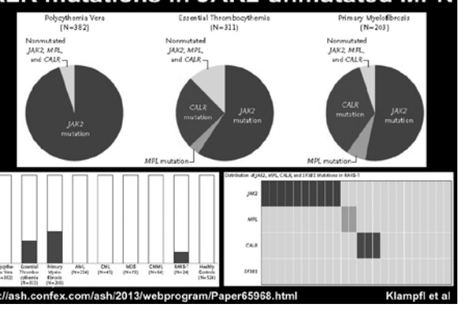
BEST OF ASH 2013
CALR mutations in JAK2-unmutated MPN



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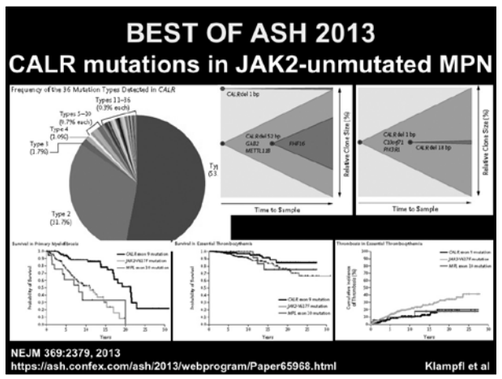
BEST OF ASH 2013
CALR mutations in JAK2-unmutated MPN



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Therapy-related AML

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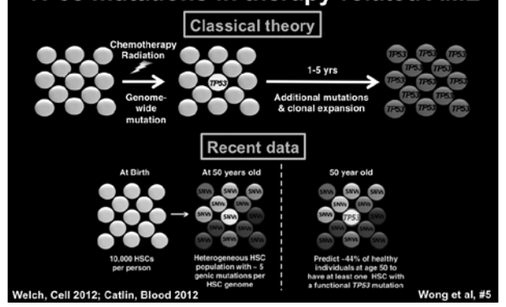
BEST OF ASH 2013
TP53 mutations in therapy-related AML



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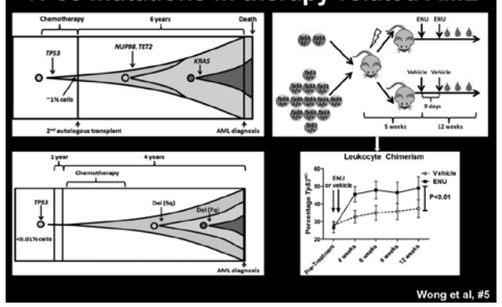
BEST OF ASH 2013
TP53 mutations in therapy-related AML



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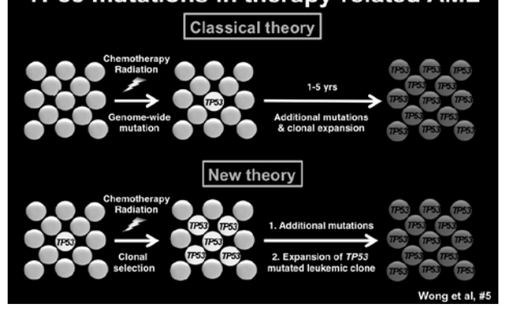
BEST OF ASH 2013
TP53 mutations in therapy-related AML



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CLL

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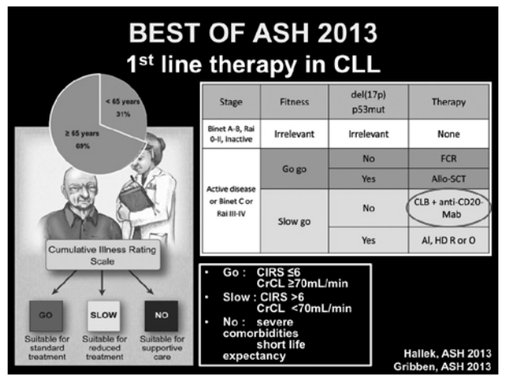
BEST OF ASH 2013
1st line therapy in CLL



Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR
		Yes	Allo-SCT
	Slow go	No	CLB + anti-CD20 Mab
		Yes	Al, HD R or O

- Go : CIRS ≤6 CrCL ≥70mL/min
- Slow : CIRS >6 CrCL <70mL/min
- No : severe comorbidities short life expectancy

Hallek, ASH 2013
Gribben, ASH 2013

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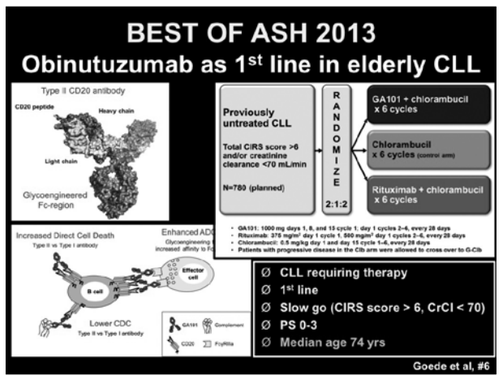
BEST OF ASH 2013
Obinutuzumab as 1st line in elderly CLL



- CLL requiring therapy
- 1st line
- Slow go (CIRS score > 6, CrCl < 70)
- PS 0-3
- Median age 74 yrs

Goede et al, #6

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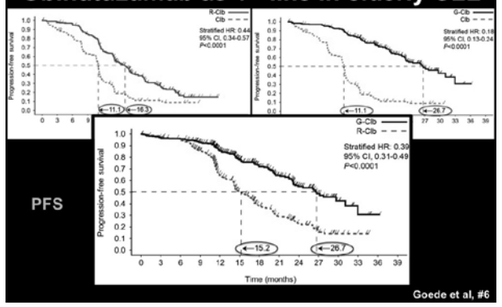
BEST OF ASH 2013
Obinutuzumab as 1st line in elderly CLL



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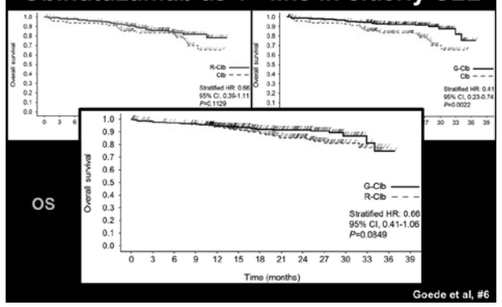
BEST OF ASH 2013
Obinutuzumab as 1st line in elderly CLL



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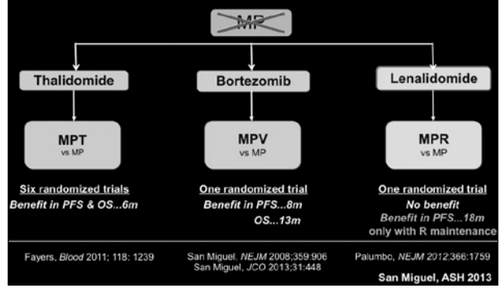
BEST OF ASH 2013
1st line therapy in elderly MM



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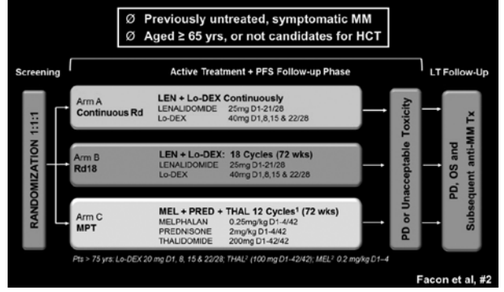
BEST OF ASH 2013
Len-Dex as 1st line therapy in elderly MM



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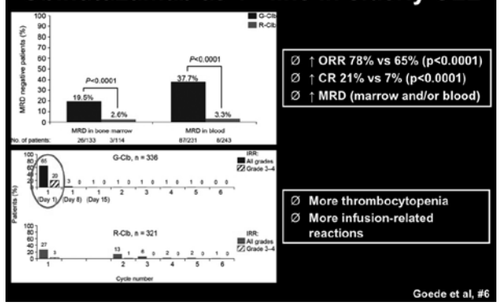
BEST OF ASH 2013
Obinutuzumab as 1st line in elderly CLL



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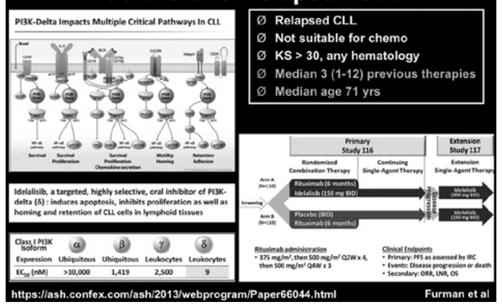
BEST OF ASH 2013
Idelalisib for relapsed CLL



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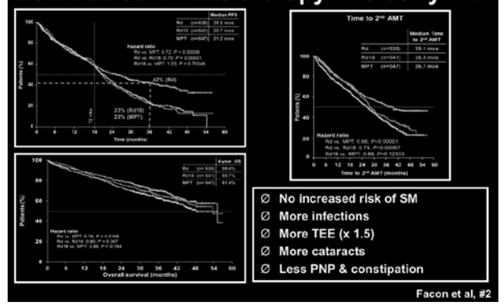
BEST OF ASH 2013
Len-Dex as 1st line therapy in elderly MM



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Cell therapy : CART

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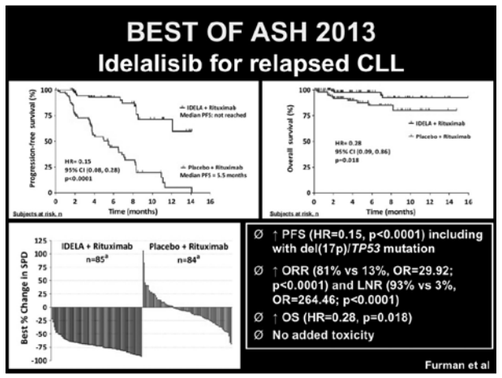
BEST OF ASH 2013
Idelalisib for relapsed CLL



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MM

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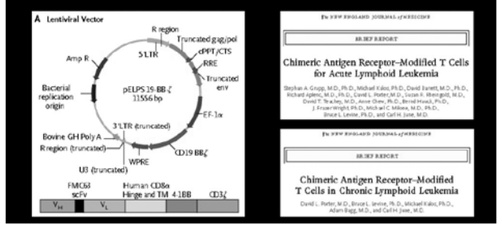
BEST OF ASH 2013
Cell therapy : CART

Chimeric antigen receptor T cells (CART)
- Single chain variable fragment (scFv) of CD19R
- Coupled to co-stimulatory molecule and TCR CD3ζ chain



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BEST OF ASH 2013
Cell therapy : CART

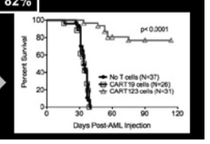
CART19 cells

Abstract	T cells	Disease	N	CR
# 67	Auto	ALL	20	82%
# 68	Auto	ALL	8	63%
# 69	Auto	ALL	13	83%
# 151	Allo	CLL-NHL	10	20%
# 152	Allo	Various	9	33%
# 874	Auto	CLL	20	82%

CART123 cells

Anti-CD123 (IL3R) CAR in NSG mice with AML

#143



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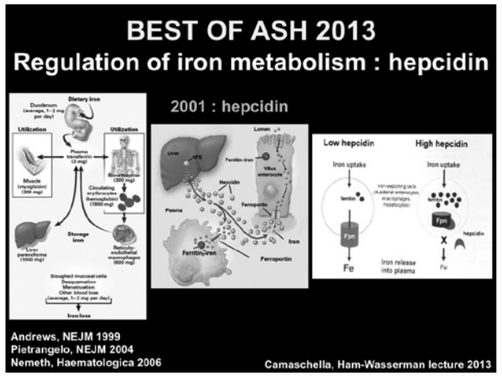

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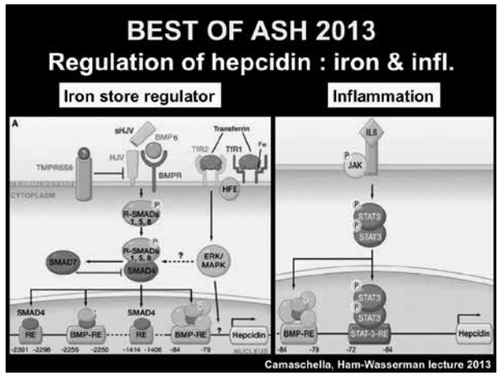

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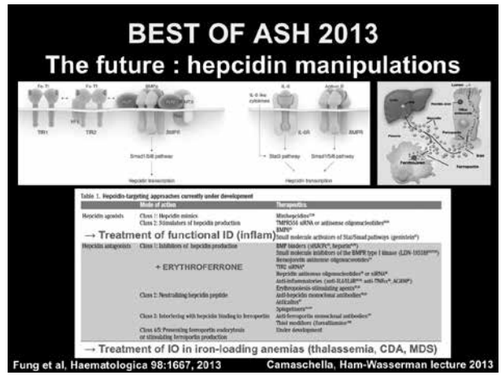

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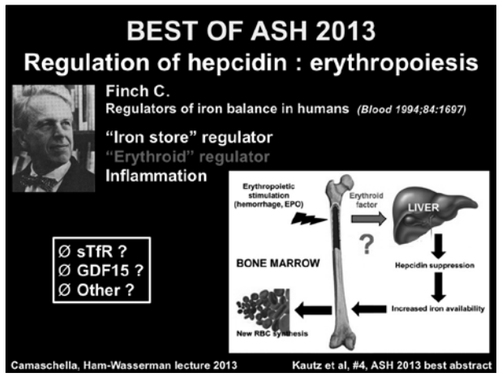

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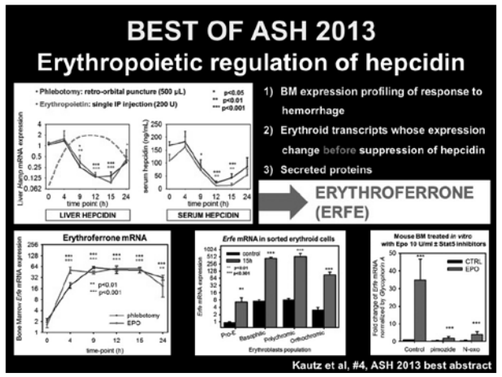

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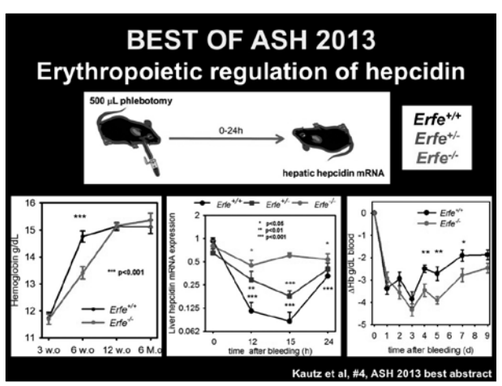

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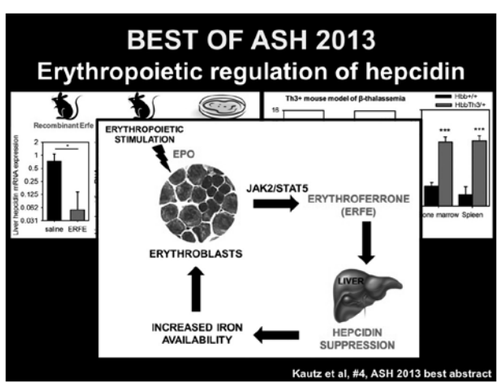

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Notes

Myelodysplastic syndromes

M.C. Vekemans
UCL, Saint-Luc

Introduction
Myelodysplastic syndromes (MDS) are a heterogeneous group of neoplastic stem cell disorders characterized by ineffective hematopoiesis with resultant cytopenias, a variable tendency to progress to acute myeloid leukemia and a common pathological phenotype characterized by 'dysplasia'.

Biology
The molecular basis of MDS has recently been elucidated by means of massive parallel sequecing studies. About 90% of MDS patients carry ≥ 1 oncogenic mutation, two thirds of them being found in individuals with normal karyotype. Recurrent mutations involve different pathways including RNA splicing, DNA methylation and chromatin modification, transcription regulation, DNA repair, signal transduction and the cohesin complex. Only a few genes are consistently mutated in ≥10% MDS patients. Mutations are powerfully associated with clinical features, 5 of them -TP53, EZH2, RUNX1, ASLX1, ETV6- being independent predictors of survival, and individual lesions are associated with specific clinical phenotypes, such as del5q in the 5q syndrome and SF3B1 in RARS.

Diagnosis
MDS are diagnosed by cytology, with consideration of the degree of dysplasia, percentage of blasts in the blood and bone marrow, and on a cytogenetic basis as recommended by the WHO classification. Chromosomal analysis is necessary for prognostication. Flow cytometry has become part of the recommended diagnostic work-up of MDS and should be part of the next WHO-classification.

Prognosis
Outcome of MDS depends on the interaction of disease-related factors and host-related factors. Among several new prognostic models, the revised International Prognosis Scoring System (IPSS-R) enables more accurate prediction of the course of the disease by dividing patients into a number of low- and high-risk groups, taking into account additional less common karyotype abnormalities, myeloblast percentage and magnitude of each lineage cytopenia. Disease–related molecular abnormalities such as somatic mutations that have prognostic value and are likely to be incorporated into newer prognostic models in the near future.

Treatment
Treatment is established on an individualized, risk-adapted basis. Aside from transfusion therapy, therapies include iron depletion for low-risk (LR) patients, lenalidomide for LR patients with del5q, and 5-azacytidine (AZA) for high-risk (HR) patients. HR patients without major co-morbidities can be offered stem cell transplantation (SCT), the cure rate ranging from 30-50%. However, in HR MDS, AZA only moderately improves survival. Prognosis after AZA failure is very poor, and patients with complex karyotype have a very poor outcome irrespective of treatment including allo-SCT. In LR MDS, some patients have a poor prognosis. Only 50% of non del5q MDS respond to ESA and 65% of del5q MDS respond to lenalidomide, for limited period of time. Efforts are made to maximize the use of available treatments, eventually in a "pick a winner approach", and develop new drugs such as HDAC inhibitors, new chemo- or immunotherapeutic agents, signal transducers and TPO receptors agonists.

Agenda

- New biological developments
- Risk assessment and pronostic factors
- New treatment options

1

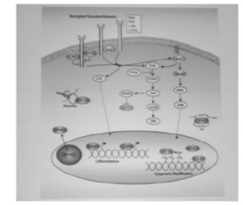
Molecular genetics

Pathogenesis of MDS involves dysfunction of many cellular pathways

RNA splicing
SF3B1, SRSF2, U2AF1, ZRSR2

DNA methylation
TET2, DNMT3a, IDH1/2

Chromatin modification
ASLX1, EZH2



Transcription regulation
RUNX1, ETV6

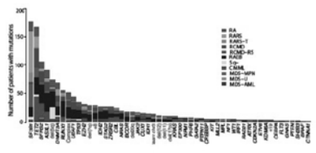
DNA repair
TP53

Signal transduction
CBL, NRAS, KRAS, JAK2

Cohesin complex
STAG2, RAD21, SMC3

2

Landscape of genetic lesions



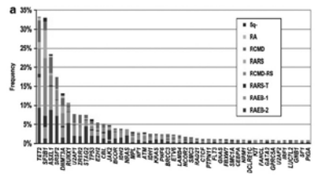
111 genes
738 MDS patients
including CMML

- 78% of MDS patients have one or more oncogenic mutations
- Over 40 genes are targets for mutation in MDS, but the vast majority are rare (<5%)
- Mutations in splicing factors are the most common, occur early, play a major role in determining the clinical features of the disease, and influence the subsequent genomic evolution of the disease

Papaemmanuil, Blood 2013

3

Landscape of genetic lesions



104 genes
944 MDS patients

- 89% MDS harbored at least one mutation (median, 3 per pt; range 0-12)
- 47 genes are significantly mutated with TET2, SF3B1, ASLX1, SRSF2, DNMT3A and RUNX1 mutated in > 10% of cases

Nagata, ASH 2013, # 521; Haferlach, Leukemia 201

4

IPSS-R

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Interm	Poor	Very poor
BM blasts (%)	≤2	-	2-5	-	5-10	>10	-
Hb (g/dl)	≥10	-	8-10	<8	-	-	-
Plt (10^3/µl)	≥100	50-100	<50	-	-	-	-
ANC (10^3/µl)	≥0.8	<0.8	-	-	-	-	-

Cytogenetic category	Cytogenetic abnormalities
Very good	Del(11q), -Y
Good	Normal, del(20q), del(5c), single and double, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any other single or double abnormality, independant clones
Poor	-7, inv(3)/t(3q)/del(3q), 2 abnormalities including -7/ del(7q), complex: 3 abnormalities
Very poor	Complex : > 3 abnormalities

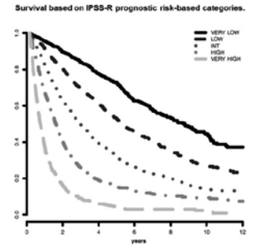
Risk category	Risk score	Median survival (y)
Very low	≤1.5	8.8
Low	1.5-3	5.3
Intermediate	3-4.5	3
High	4.5-6	1.6
Very high	>6	0.8

Greenberg, Blood

5

IPSS-R

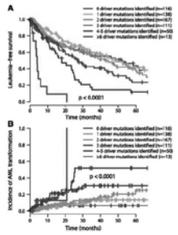
Survival based on IPSS-R prognostic risk-based categories.



Greenberg, Blood

6

Molecular markers and prognosis

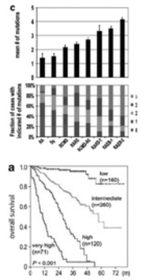


- There is a strong relationship between the number of gene mutations and outcome

Papaemmanuil, Blood 2013

7

Molecular markers and prognosis



- 27/45 genes affect survival
- Higher numbers of gene mutations observed in advanced WHO subtypes
- Hierarchy of mutations

- A set of 14 prognostic genes can be used to build a clinically relevant **prognostic score**

Nagata, ASH 2013, # 521; Haferlach, Leukemia 201

8

Future risk-based classification systems

- Add and evaluate further prognostic features in larger patients cohorts
  - Molecular : single, combinations, evolutionary
  - Cytogenetics : SNP, FISH
  - Flow cytometry
  - Microenvironment
- Integrate these features for disease classification

9

Current issues in treatment of MDS

Higher risk MDS (IPSS high or int-2)

- AZA only moderately improves survival
- Prognosis after AZA failure very poor
- Patients with complex karyotype have a very poor outcome, irrespective of treatment (including allo-SCT)

Lower risk MDS (IPSS low or int-1)

- Some low risk MDS have a poor prognosis (especially with IPSS-R and/or presence of genes mutations)
- Anemia
  - non del5q : only 50% respond to ESA, for a median of 2y
  - del5q : only 65% respond to LEN, for a median of 2.2y
- Thrombocytopenia
  - TPO receptor agonists in clinical trials

10

Maximizing the use of available treatments	New drugs in MDS

▪ Hypomethylating agents
▪ Lenalidomide
▪ Combination with other available drugs :
  ▪ ESA
  ▪ Chemotherapy (anthracyclines, AraC)
  ▪ Other (iron chelating agents)
	▪ HDAC inhibitors
	▪ Chemotherapy
	  ▪ Clofarabine
	  ▪ Sapacitabine
	▪ Immunotherapy
	  ▪ Gemtuzumab ozogamicin
	▪ Signal transduction inhibitors
	▪ TPO agonist receptors

▪ Allo-SCT	

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How to use new drugs in MDS

Higher risk MDS

- After HMA failure
  - Alone
  - As 'add on' therapy
- First line in combination with HMA

Lower risk MDS (mainly anemic patients)

- After ESA failure (non del5q) or LEN failure (del5q)
- Alone or combined to ESA or LEN

12

Current Landscape of Multiple Myeloma Management

J. Caers
CHU Liège

Multiple myeloma (MM) is a hemato-oncological disease, and in recent years, overall survival of patients has been significantly increased. Improvement of treatment results is connected not only to the introduction of autologous transplantation of hematopoietic cells into the treatment strategy for younger patients in the 90s but also to the introduction of new beneficial drugs into clinics, such as bortezomib, thalidomide and lenalidomide in the first decade of this century. These new drugs have repeatedly proven their high treatment efficacy in all age groups of patients, in primotherapy as well as refractory disease. There are also newer drugs currently under investigation, such as new proteasome inhibitors (carfilzomib, MLN9708 and other oral proteasome inhibitors) and other immunomodulatory drugs (pomalidomide) with the aim to improve or maintain treatment effects and decrease unfavorable effects. The association of these new agents with known agents such as cyclophosphamide, thalidomide or dexamethasone are currently investigated in front-line treatment, as part of maintenance strategies and at relapse. Optimization of dosage in combination with other drugs and the length of treatment have been clarified for these agents. Current dosage levels are different from recorded dosages in registration studies which in certain cases led to common or higher level of side effects than is acceptable and influencing influence the quality of life of patients after successful treatment. For elderly patients, the assessment of frailty is crucial before choosing the correct drug regimen. However, optimization of efficient drugs is a never ending process that waits for each new efficient drug, for example carfilzomib and pomalidomide in the near future.
A variety of new drugs are being tested in clinical studies at phases I/II. In MM treatment, modern target therapies are being tested, such as monoclonal antibodies against CD38 (daratumumab and SAR650984) and CD138 (Indatuximab Ravtansine), kinase inhibitors (Akt-inhibitor afuresertib, Pim Kinase Inhibitor LGH447) or inhibitors of other target molecules connected to one of the signaling pathways important for malignant cells (inhibitor of kinesin spindle protein: filanesib) and finally immunotherapies that involve vaccination (MAGE-A3, MUC1) or modification of immune cells (CAR engineered T-cells/NK-cells). Treatment results of this group of drugs and strategies are encouraging; we hope that they can ameliorate patients responses and survival in the future.

Elderly patients

Alkylators-based induction regimens

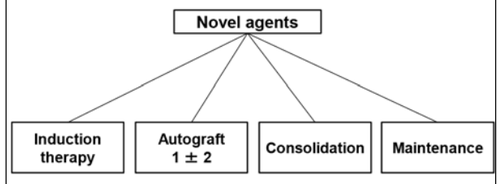
MP	MPT, MPV
Cyclo	CTDa, CyBorD
Benda	

Non Alkylators-based induction regimens

IMID	Thal/Dex, Len/Dex
Proteasome	Vel/Dex
IMID/Prot	VTD/VMP, VRD

1

Tranpslant eligible patients



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Carfilzomib

- Elderly
  - Carfilzomib, melphalan, prednisone
    #1933, P Moreau
    ORR = 91%, VGPR+ = 55% and CR = 10%
  - Carfilzomib, cyclophosphamide, dexamethasone
    #685, S Bringhen
    ORR = 90%, VGPR+ = 77% and nCR/CR/sCR = 47%
- Pre-transplant
  - Carfilzomib, thalidomide, dexamethasone
    # 538, Neha Korde
    ORR = 96%, VGPR+ = 84% and nCR/CR/sCR = 51%
  - Carfilzomib, lenalidomide, dexamethasone
    # 688, Pieter Sonneveld
    ORR = 98%, VGPR+ = 88% and nCR/CR/sCR = 67%

3

Pomalidomide

- Relapsing patients
  - Early treatment in high risk cytogenetics t(4;14) and del17p
    #689 X Leleu
  - Update from the MM03 with prolonged follow-up
    #408, M Dimopoulos
    #686, J S Miguel
- Amyloidosis (relapsing patients)
  - #288, G Palladini
  - pomalidomide 4mg/Dexamethasone
    ORR 70%, VGPR+ = 37%, CR 4%

4

New agents

- Monoclonal antibodies
  - CD38
    - Daratumumab # 1986 combined with len/dex
    - SAR650984 # 284 phase 1, ORR 31%
  - CD138
    - *Indatuximab Ravtansine* # 758 combined with len/dex
- Ixazomib (MLN9708)
  - # 535 P Richardson
    Phase 1/2 combined with len/dex
    ORR 94%, VGPR+ = 76%, CR/sCR 45%

5

Notes

Chronic myeloid leukemia and myeloproliferative neoplasms

Gregor Verhoef
Department of hematology, University Hospital Leuven

The first part will focus on **chronic Myeloid leukemia (CML)**: update of randomized studies, monitoring recommendations, discontinuation of tyrosine kinase inhibitors and best therapeutic approach for a particular patient with newly diagnosis of CML in chronic phase.

In the ENEST trial (updated data based on 5 y of follow up and presented by Saglio et al, abstract 92) patients were randomized between frontline nilotinib (400 mg, BID, 300 mg BID or imatinib (400mg).

The results confirm that nilotinib resulted in superior rates of cytogenetic and molecular remission with a lower rate of progression compared to imatinib. The lower risk of transformation had not translated in a survival advantage. A concern is the occurrence of vascular events (peripheral arterial occlusive disease, coronary artery and cerebrovascular disease, as well as hyperglycemia and hypercholesterolemia in both nilotinib arms. Most of these patients had multiple risk factors for vascular disease. See also abstract 653, Cortes et al. DASISION 4-Year Follow-up Continues to Show Superior Efficacy of Dasatinib vs Imatinib as Frontline Therapy for CML).

Preclinical and clinical in vitro studies showed that nilotinib exerts direct pro-atherogenic and anti-angiogenic effectis with multiple effects on vascular endothelial cells and other perivascular cells (abstract 257). These effects may explain the nilotinib-induced vasculopathy in CML.

One of the education programs updated the current monitoring recommendations (Oehler, Hematology, page 176) and recommended testings for disease monitoring. Most important, for an optimal response at 3 months a partial cytogenetic remission is now required and a complete cytogenetic response at 6 months. In addition RQ-PCR-IS is already introduced at 3 months (optimal response BCR-ABL-1 IS<10%) and at 6 months (optimal response BCR-ABL-1 IS<1%). European LeukemiaNet recommend not to change at 3 months in case of warning (BCR-ABL-1 IS>10%, Ph+65-95%), only in case of a failure (No CHR or Ph+>95%) but repeat all tests monthly. Patients with dose interruption/reduction of TKI in the first 3 months are less likely to obtain an optimal response at 3 months and are more likely to require a change of drug in the longer term and therefore require close observation during the first year (Apperley, abstract 93). Another interesting presentation reported on the individual reduction of BCR-ABL transcripts at 3 months (slope of the curve), allowing a more precise prediction for the individual patient at 3 months compared to the 3-months 10% BCR-ABL-IS (Hanfstein, abstract 253).

An update of the STIM1 study was presented by Mahon (abstract 255). Imatinib was discontinued in patients (n=100) with a deep molecular remission for at least 2 years Median follow up is now 50 months. 61 patients met the definition of a molecular relapse (61%). All patients were sensitive to TKI rechallenge. Among the initial 38 patients alive who are in DMR without treatment, the median follow up is 54 months. The savings within the STIM trial were estimated at 5.5 millions of Euros.

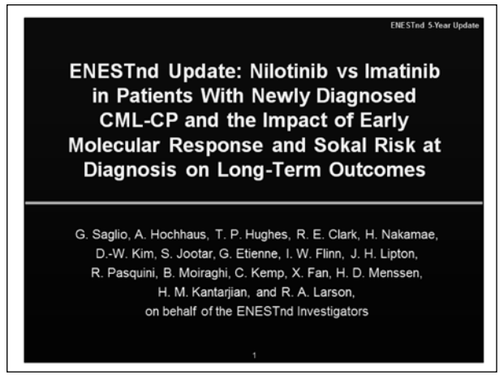
Hughes et al (Education Program, Hematology 2013, page 168) discussed the different treatment options in patients with a newly diagnosis of CML. Because none of the 3 available TKIs have shown a clear survival advantage, imatinib as well as nilotinib and dasatinib represent reasonable choices. Whatever the first choice of TKI is made, treatment failure of intolerance must be recognized early because a prompt switch to another TKI provides the best chance of achieving optimal response. However, in certain circumstances, one TKI may be a better choice. For example, in young patients maximizing the prospect of survival and improving treatment free remission is often the main goal of therapy. If a young patient or a Sokal high-risk patient had no comorbidities, nilotinib or dasatinib may be preferred, although their advantage over imatinib in this setting remains to be proven. In the case of comorbidities, imatinib may be the preferred choice with aggressive triggers (BCR-ABL-1 IS<10% in two consecutive tests at 3 months, >1% at 6 months, >0.1% at 12 months) to switch to more potent TKIs instead of increasing the dose of imatinib. Cortes et al (abstract 95) reported the results of a randomized trial that compared the effects of imatinib dose escalation with those of switching to nilotinib in patients who experience a suboptimal response to frontline imatinib. A switch to nilotinib vs imatinib dose escalation resulted higher rates of response.

Myeloproliferative neoplasms (MPN):
Many patients with BCR-ABL negative MPN carry a JAK2 mutation (V617F or exon 12). Additional mutations have been identified in patients with or without JAK2 mutation (MPL, TET2, DNMT3A). However, no specific molecular marker has been identified in the remaining 30-45% of patients. Two late-breaking abstracts now solve this puzzle and identify mutations in a specific gene in the majority of patients with MPN who have not mutated in JAK2 or MPL (Thorsten et al, paper LBA-1; Nangalia et al, paper LBA-2). They both identify recurrent mutations in the gene encoding calreticulin (CALR) using different approaches. The CALR mutations were exclusively seen in patients with essential thrombocythemia or primary myelofibrosis and were never observed in patients with polycythemia vera or in patients

with JAK2 or MPL mutations. This new mutation will potentially be used as a diagnostic test and might also guide therapeutic decision-making.

Gotlib (Education Program, Hematology 2013, page 529) discussed the different treatment options in myelofibrosis, especially the studies of JAK inhibitors. Mesa et al. (abstract 396) reported on the 3-year update from the COMFORT-1 study with Ruxolitinib in patients with myelofibrosis. After a median follow up of 149 weeks, reduction in spleen volume and improvements in symptoms and QOL measures were sustained. Overall survival favored patients originally randomized to ruxolitinib compared with those originally randomized to placebo. One of the other JAK inhibitors, Fedratinib showed promising results (Pardanani et al, abstract 393), also in patients previously treated with Ruxolitinib (Harrison et al, abstract 661). However, recently Sanofi ended all trials because of serious, unexpected cases of Wernicke's encephalopathy. One of the "on-target" effects of Ruxolitinib is anemia, because of the dependency of erythropoietin receptor or signaling via the JAK2 tyrosine kinase. Momelotinib has garnered interest because of its erythoid-remitting activity (Villeval et al, abstract 2851). Momelotinib was tested in a murine model of human PMF. It reduced the anemia associated with the development of myelofibrosis, as reported during clinical trials of patients suffering from MF. Furthermore, Momelotinib, as expected from a JAK1/2 inhibitor reduced splenomegaly, thrombocytosis and leukocytosis associated with the disease. Improvement of anemia was associated with an increase in RBC, erythroid precursor and progenitor cells suggesting that momelotinib stimulates the early stages of erythropoiesis. Further experiments are in progress to investigate whether changes in levels of cytokines known to positively or negatively effect erythropoiesis are seen. Regulation of iron metabolism, which could account for the improvement of anemia induced by momelotinib is also being investigated.

For results of other JAK inhibitors/treatment modalities: seen abstract 394,395,663,664,665 an 666).



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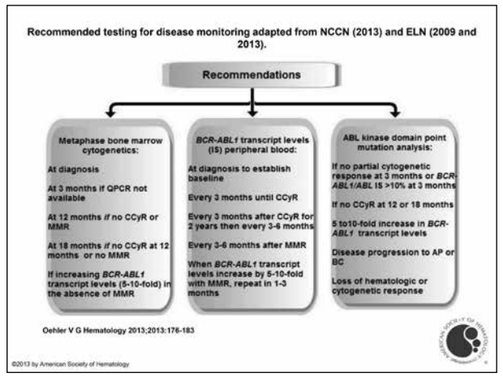

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Table 1. Comparison of the efficacy profiles (% achievement) of nilotinib,[13] dasatinib,[19] and bosutinib[45] in the 3 registration phase 3 studies compared with imatinib

End point	Nil(300)	IM	DAS	IM	BOS	IM
CCyR by 12 mo	80	65	85	73	70	68
CCyR by 24 mo	87	77	86	82	87	81
MMR by 24 mo	53	27	46	28	41	27
MMR by 24 mo	69	44	64	46	61	50
MR4.5 by 24 mo	23	10	17	8	25	17
Transformation	2.6	6.7	3.5	5.8	2	4
Death	3.7	6	6	5	2	5
Overall survival	95.1*	94*	95.3	95.2†	99‡	95‡

Nil(300) indicates nilotinib 300 mg; IM, imatinib; DAS, dasatinib; and BOS, bosutinib.
*Median follow-up was 36 months.
†Median follow-up was 24 months.
‡Median follow-up was 18 months.

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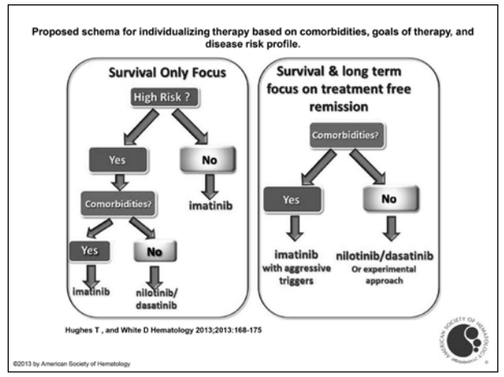

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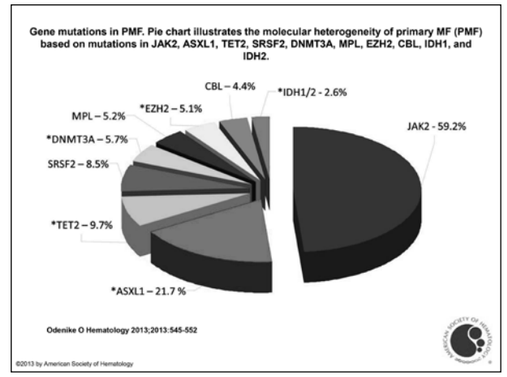

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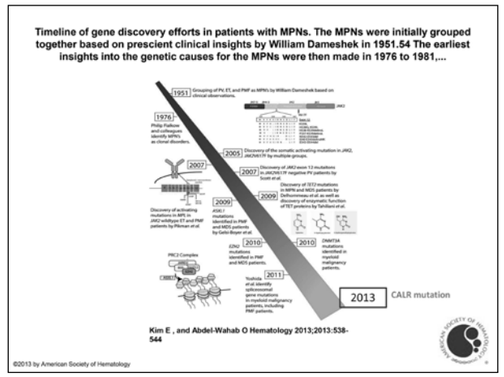

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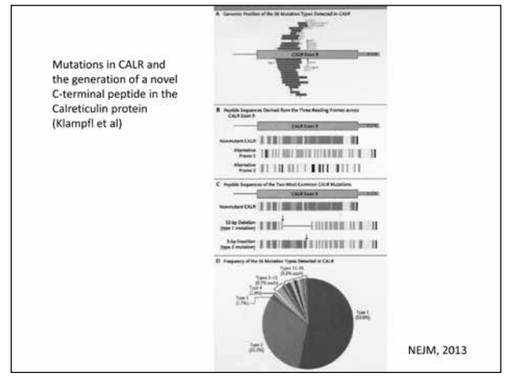

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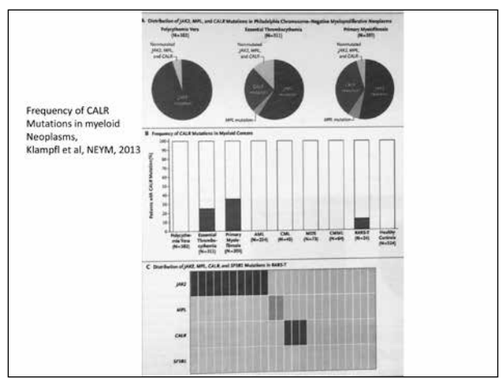

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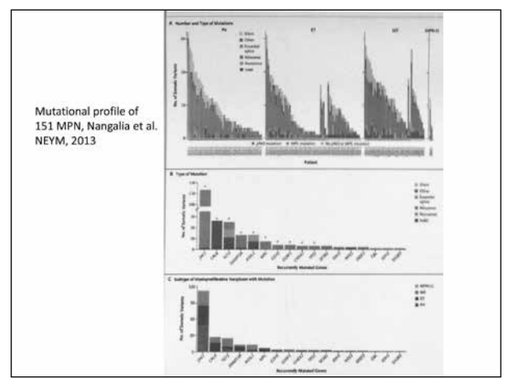

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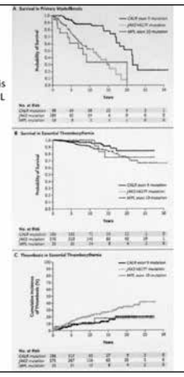
Estimated Overall survival and Cumulative incidence of thrombosis Among pts with CALR, JAK2, or MPL Mutations, Klampfl et al, NEYM, 2013



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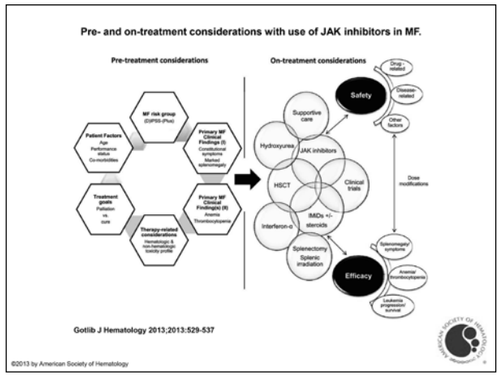

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Long-Term Outcomes of Ruxolitinib Therapy in Patients with Myelofibrosis: 3-Year Update From COMFORT-I

Srdan Verstovsek,[1] Ruben A. Mesa,[2] Jason Gotlib,[3] Richard S. Levy,[4] Vikas Gupta,[5] John F. DiPersio,[6] John V. Catalano,[7] Michael W.N. Deininger,[8*] Carole B. Miller,[9] Richard T. Silver,[10] Moshe Talpaz,[11] Elliott F. Winton,[12] Jimmie H. Harvey, Jr.,[13] Murat O. Arcasoy,[14] Elizabeth O. Hexner,[15] Roger M. Lyons,[16] Azra Raza,[17] Kris Vaddi,[4] William Sun,[4] Wei Peng,[4] Victor Sandor,[4] and Hagop Kantarjian,[1] for the COMFORT-I investigators

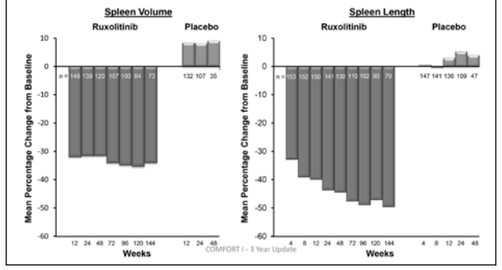
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Mayo Clinic, Scottsdale, AZ, USA; [3]Stanford Cancer Institute, Stanford, CA, USA; [4]Incyte Corporation, Wilmington, DE, USA; [5]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]Frankston Hospital and Department of Clinical Haematology, Monash University, Frankston, Australia; [8*]Oregon Health and Science University, Portland, OR, USA; [9]Saint Agnes Cancer Institute, Baltimore, MD, USA; [10]Weill Cornell Medical Center, New York, NY, USA; [11]University of Michigan, Ann Arbor, MI, USA; [12]Emory University School of Medicine, Atlanta, GA, USA; [13]Birmingham Hematology and Oncology, Birmingham, AL; [14]Duke University Health System, Durham, NC, USA; [15]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [16]Cancer Care Centers of South Texas/US Oncology, San Antonio, TX, USA; [17]Columbia Presbyterian Medical Center, New York, NY, USA

*Currently at Division of Hematology and Hematologic Malignancies and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

16

Percentage Change in Spleen Size

- Mean reductions in spleen volume and palpable spleen length with ruxolitinib were stable over time



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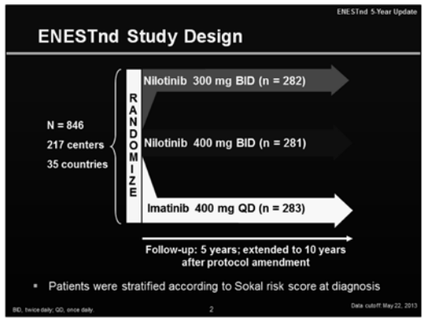

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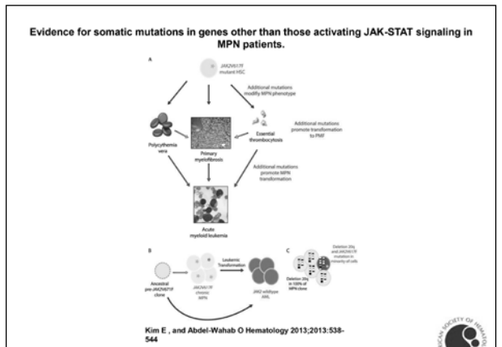

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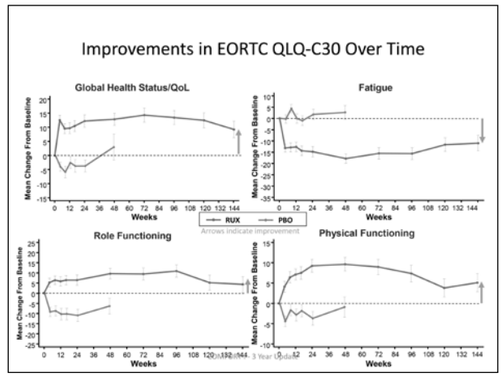

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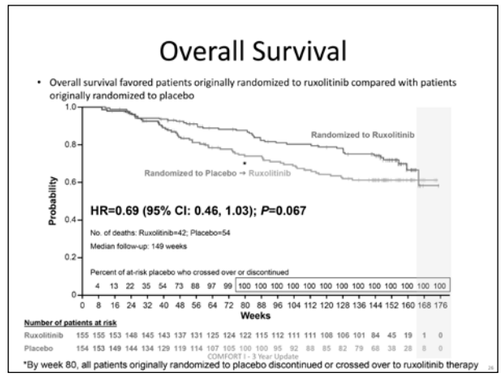

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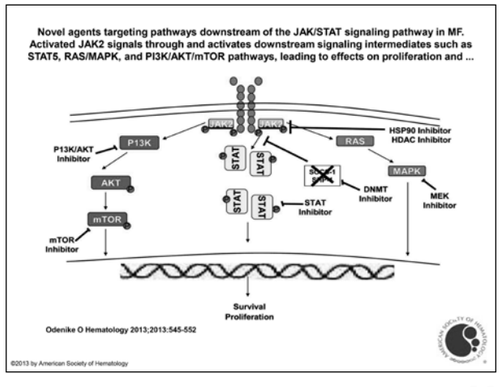

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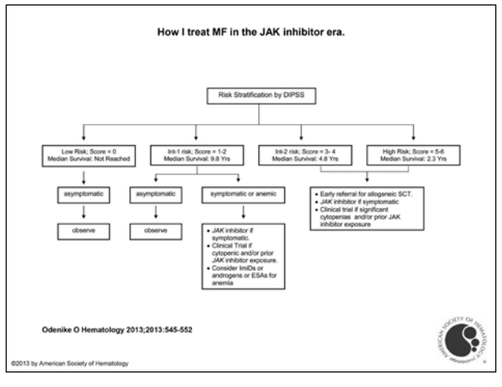

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COMFORT-I 3-Year: Conclusions

- Reductions in spleen volume and improvements in symptoms and QoL measures were sustained with longer-term therapy
- Overall survival favored patients originally randomized to ruxolitinib compared with those originally randomized to placebo
  - Results from exploratory analyses suggest cross over leads to an underestimation of the true survival difference between ruxolitinib and placebo
- The incidence of new onset grade 3 or 4 anemia and thrombocytopenia decreased with longer-term therapy
- There was no change in the rate, distribution, or severity of nonhematologic adverse events in patients originally randomized to ruxolitinib with longer-term treatment
- Collectively, these data reinforce the durable efficacy and longer-term safety of ruxolitinib in patients with myelofibrosis

COMFORT I - 3 Year Update

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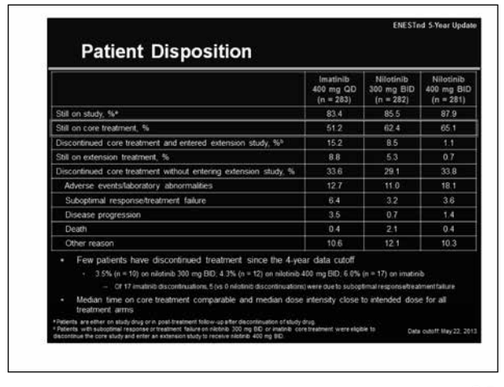

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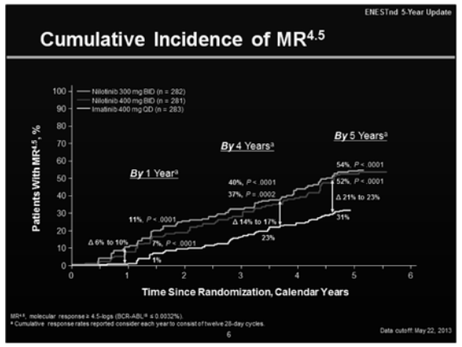

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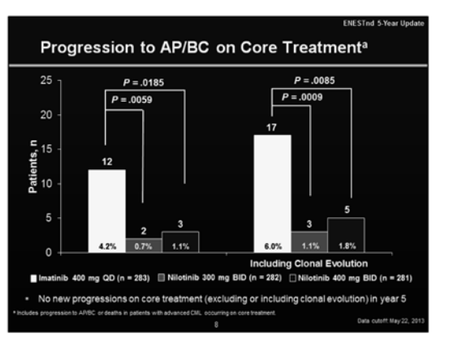

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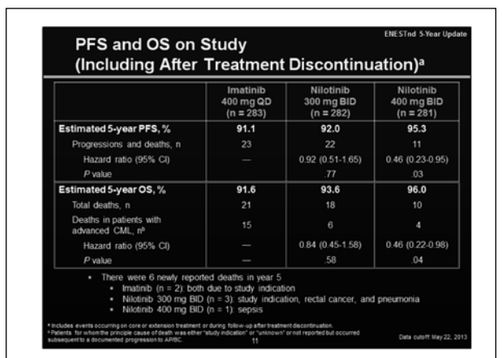

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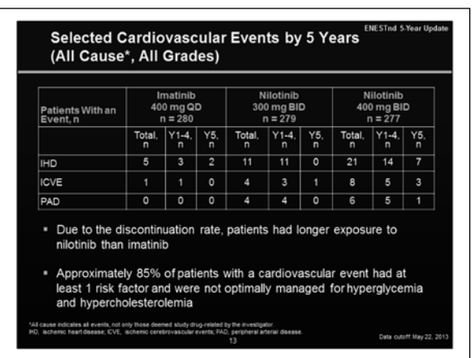

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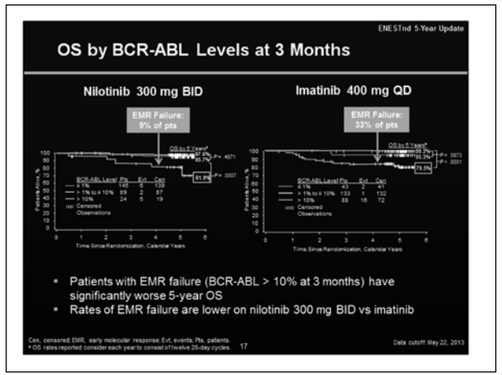

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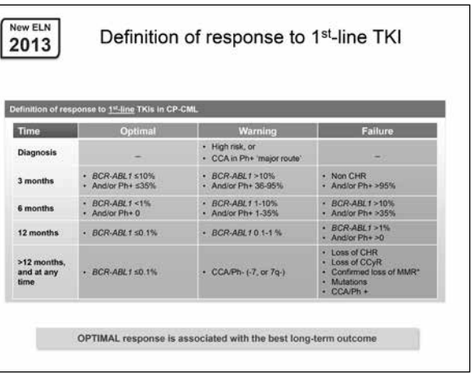

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Lymphoma

A. Bosly
CHU Dinant Godinne, UCL Namur

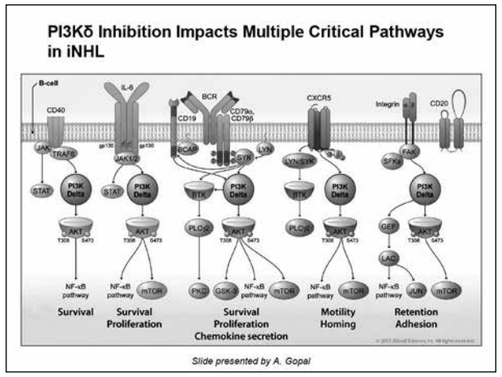
One more time, many important advances in the knowledge and the treatment of lymphoma were presented in New Orleans during 2013 ASH meeting.

Hodgkin lymphoma (HL): in localized HL, radiotherapy has still a role.
Two prospective randomized trials (EORTC/LYSA/FIL and UK) showed that omission of radiotherapy after negative early FDG-PET scan will slightly increase the rate of recurrence (~ 5 %) but probably not affect survival (Johnson Educ). Novel therapy for HL (Younes Educ.) are brentuximab vedotin, very effective in post ASCT relapse but also in first line and can eventually replace vincristine and bleomycin in BEACOPP regimen (von Tresckow # 637) and epigenetic therapy with HDAC inhibitor. Panobinostat combined with ICE chemotherapy is effective in R/R cHL (Oki # 252).

Indolent non Hodgkin Lymphoma (iNHL): targeting B cell receptor signaling is one of the most important ways of clinical research in iNHL.
Ibrutinib (BTK inh) was tested in 63 pts with Waldenström disease in at least second line : a major response rate of 57 % was obtained (Treon # 251).
Idelalisib (PI3Kinase inh) (fig 1) was tested in a phase II trial in 125 iNHL cases refractory to alkalating agents and rituximab. ORR was 57 % with 6 % CR ; 90 % had improvement in lymphadenopathy and the median DOR was 12.5 months. Diarrhea and neutropenia were the most adverse events (grade^3 3 in 13 % and 27 % respectively) (Gopal # 85).
Lenalidomide with rituximab (R2) without chemotherapy is very effective in iNHL with ORR of 74 % - 100 % and CR of 44 % - 61 % respectively in R/R or untreated pts (Yamshon #244).
R2 in mantle cell lymphoma (untreated) obtained 87 % ORR and 57 % CR (Ruan # 247).
R2 + CHOP in high burden FL, in 80 untreated pts, obtained an ORR of 94 % and a CR of 74 %. R2 CHOP appears to be better than R-CHOP but comparison with R2 trials is crucial (Tilly # 248) (fig 2).
Mature data of PRIMA study confirms benefit of 2 year rituximab maintenance in FL responding to R chemotherapy (6-y PFS : 59.2 % vs 42.7 %) (fig 3). Moreover, response to second line treatment was not affected by R maintenance (Salles # 509).
Comparison of consolidation with Zevalin (Z) versus maintenance Rituximab in 126 FL pts responding to R-CHOP showed a PFS of 77 % for R maintenance vs 63 % for Z (p = 0.02) (Lopez Guillermo # 369).

Diffuse large B cell lymphoma (DLBCL)
Epigenetic mechanism of lymphomagenesis involves EZH2 histone methyl transferase and BCL-6. EZH2 is highly upregulated in germinal center (GC) B cells and is highly expressed in DLBCL. EZH2 gain of function by somatic mutation occurs in 30 % DLBCL (GCB type). BCL-6 is required for GC formation and is involved in B-cell lymphomagenesis. Inhibition of EZH2-BCL-6 combinatorial therapy synergistically suppresses DLBCL and it could be a new target for therapy (Béguelin # 1 plenary session).
PKC inhibitor (enzastaurin) was tested in high IPI DLBCL in 758 pts in CR after initial therapy. No improvement of DFS, EFS or OS was observed (Crump # 371).
What works in DLBCL ? (Wilson Educ). DA-EPOCH-R may improve outcome of GCB DLBCL (fig 4) and may overcome the adverse prognosis of MYC and BCL-2 expression.
Ibrutinib may modulate ABC DLBCL. Ibrutinib + R-CHOP in a phase IB trial had an acceptable toxicity and was very effective : ORR 100 %, CR 64 % (Younes # 852).
Phase II Lenalidomide + R-CHOP in 49 elderly DLBCL pts showed an ORR of 92 % and a CR of 86 % ; 2-y OS : 92 % and 2-y PFS : 80 %. No difference according to subtype (ABC vs GCB) was noted (Chiapella # 850).

Impact of monoclonal antibodies (brentuximab vedotin, rituximab, GA101), B cell receptor inhibitors (ibrutinib, Idedalisib) and immunomodulators (lenolidamide) in the treatment of lymphoma were highlighted during ASH meeting.



Slide presented by A. Gopal

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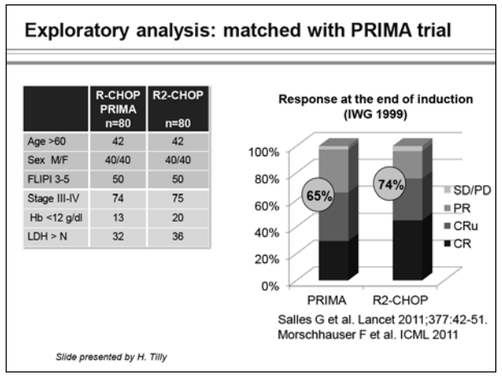

Slide presented by H. Tilly

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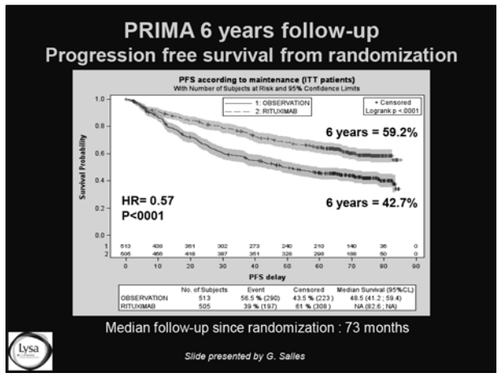

Slide presented by G. Salles

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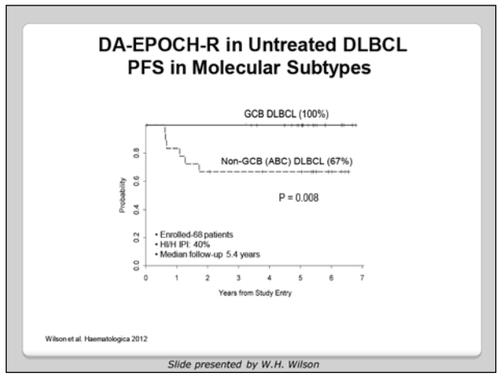


Slide presented by W.H. Wilson

4

Notes

Hemostasis and Thrombosis at the ASH meeting – New Orleans - 2013

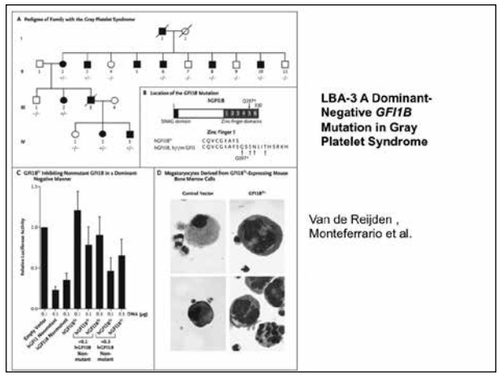
C. Van Geet
UZ KUL

Hemostasis

Due to improvement in diagnostic tools, some new and exciting etiologies for bleeding disorders were presented. Genome-wide linkage analysis combined with whole genome sequencing resulted in the discovery of the cause of autosomal dominant familial immune thrombocytopenia (ITP). NOS3 is the disease causing gene and compatible with the well-known role of NO in autoimmunity and oxidative stress. The co-segregation of the NOS3 variant with the phenotype of ITP in this family was validated via Sanger sequencing. Finally, an in vitro study demonstrated reduced NO production by mutant NOS3 protein compared to wild type NOS3 protein. (Zhang et al, abstr 565).
Two research groups (Ward et al, abstr 566 and Van der Reijden et al LBA-3) have discovered independently the same genetic cause of an autosomal dominant hereditary thrombocytopenia. The responsible gene for this disorder is GFI-Ib. In both described families a similar autosomal dominant thrombocytopenia with a phenotype of gray platelet syndrome, was presented. Further studies are ongoing to unravel the mechanisms of action of this genetic defect.
In bleeding disorders due to clotting factor deficiencies major advances are made in the development of synthetic clotting factors with prolonged half life (Educational session, Kaufman and Powell, Shapiro, Ragni and Buchbinder). Indeed this strategy would lead to major advantages in the treatment of severe hemophilia, by improving not only the quality of life (less frequent injections) but also by better protection of severe hemophilia patients against spontaneous hemorrhages and bleedings after minor trauma. Different strategies are under development, whereby the pegylation of clotting factors or the production of fusion proteins have been widely studied. Several clinical trials with modified actor VIII are ongoing. This strategy is also very promising for factor IX. One of these fase III trials has already been completed and many of the patients with severe hemophilia B are well protected with only one injection every 14 days. Also for bypassing agents this approach is currently under investigation with recombinant factor VII.

Thrombosis

Regarding venous thromboembolism, the clinical probability scores for PE and DVT have been elaborated with a diagnostic algorithm in patients with suspected DVT and in patients with suspected PE respectively (Educational session, Wells and Anderson). One study (LBA-4) by Righini et al, used the D-dimer age adjusted normal values to refine the negative diagnostic value of the D-dimers in this diagnostic algorithm for pulmonary PE. By using this D-dimer age-adjusted cut-off (patient's age x 10 in µg/L in patients > 50 years), in combination with the clinical probability score, a lot more elderly patients could be safely excluded for further imaging tests.
In the approach of VTE disease also treatment has been re-assessed and the use of the novel oral anti-coagulants, targeting directly thrombin or FXa (Educational session, Bauer) has been evaluated as they have major pharmacologic advantages over the classical vitamin K antagonists. However, some precautions are needed as e.g. no monitoring is possible in most centers en no specific antidotes are available. Moreover there still exists some uncertainty about dosing in some patient populations.
Finally, platelet transcription profiling has revealed molecules that are very promising as biomarkers for atherosclerotic thrombosis (SCI54). As platelets participate in events that immediately precede acute myocardial infarction, platelet mRNA from patients with acute ST-segment–elevation myocardial infarction (STEMI, n=16) or stable coronary artery disease (n=44) was profiled. A new pathway of inflammation and thrombosis involving MRP-14 was identified, and this was confirmed in mice.



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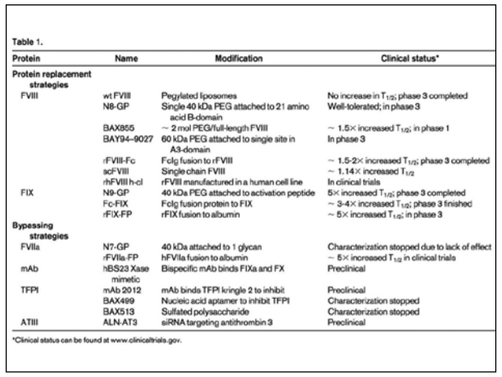

Table 1.

Protein	Name	Modification	Clinical status*
Protein replacement strategies			
FVIII	wt FVIII	Pegylated liposomes	No increase in $T_{1/2}$; phase 3 completed
	N8-GP	Single 40 kDa PEG attached to 21 amino acid B-domain	Well-tolerated; in phase 3
	BAX855	~ 2 mol PEG/full-length FVIII	~ 1.5× increased $T_{1/2}$; in phase 1
	BAY94–9027	60 kDa PEG attached to single site in A3-domain	In phase 3
	rFVIII-Fc	Fc/g fusion to rFVIII	~ 1.5-2× increased $T_{1/2}$; phase 3 completed
	scFVIII	Single chain FVIII	~ 1.14× increased $T_{1/2}$
	rhFVIII h-cl	rFVIII manufactured in a human cell line	In clinical trials
FIX	N9-GP	40 kDa PEG attached to activation peptide	5× increased $T_{1/2}$; phase 3 completed
	Fc-FIX	Fc/g fusion protein to FIX	~ 3-4× increased $T_{1/2}$; phase 3 finished
	rFIX-FP	rFIX fusion to albumin	~ 5× increased $T_{1/2}$; in phase 3
Bypassing strategies			
FVIIa	N7-GP	40 kDa attached to 1 glycan	Characterization stopped due to lack of effect
	rFVIIa-FP	hFVIIa fusion to albumin	~ 6× increased $T_{1/2}$ in clinical trials
mAb	hBS23 Xase mimetic	Biapecific mAb binds FIXa and FX	Preclinical
TFPI	mAb 2012	mAb binds TFPI kringle 2 to inhibit	Preclinical
	BAX499	Nucleic acid aptamer to inhibit TFPI	Characterization stopped
	BAX513	Sulfated polysaccharide	Characterization stopped
ATIII	ALN-AT3	siRNA targeting antithrombin 3	Preclinical

*Clinical status can be found at www.clinicaltrials.gov.

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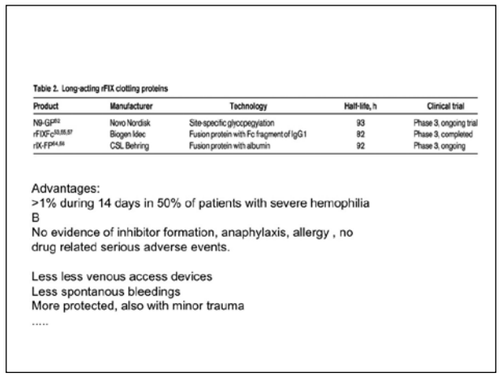

Table 2. Long-acting rFIX clotting proteins

Product	Manufacturer	Technology	Half-life, h	Clinical trial
N9-GP[62]	Novo Nordisk	Site-specific glycopegylation	93	Phase 3, ongoing trial
rFXFc[63,65,67]	Biogen Idec	Fusion protein with Fc fragment of IgG1	82	Phase 3, completed
rIX-FP[64,66]	CSL Behring	Fusion protein with albumin	92	Phase 3, ongoing

Advantages:
>1% during 14 days in 50% of patients with severe hemophilia B
No evidence of inhibitor formation, anaphylaxis, allergy , no drug related serious adverse events.

Less less venous access devices
Less spontanous bleedings
More protected, also with minor trauma
.....

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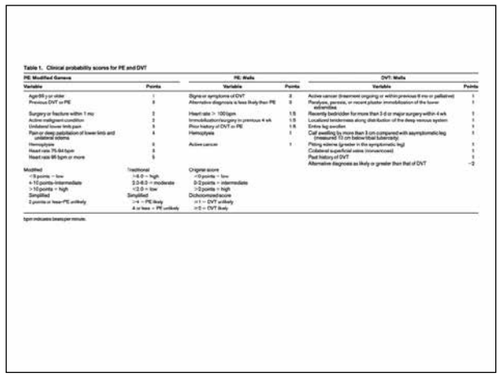

Table 1. Clinical probability scores for PE and DVT

PE: Modified Geneva		PE: Wells		DVT: Wells	
Variable	Points	Variable	Points	Variable	Points
Age>65 y or older	1	Signs or symptoms of DVT	3	Active cancer (treatment ongoing or within previous 6 mo or palliative)	1
Previous DVT or PE	3	Alternative diagnosis is less likely than PE	3	Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Surgery or fracture within 1 mo	2	Heart rate > 100/pm	1.5	Recently bedridden for more than 3 d or major surgery within 4 wk	1
Active malignant condition	1	Immobilization/surgery in previous 4 wk	1.5	Localized tenderness along distribution of the deep venous system	1
Unilateral lower limb pain	3	Prior history of DVT or PE	1.5	Entire leg swollen	1
Pain or deep palpitation of lower limb and unilateral edema	4	Hemoptysis	1	Calf swelling by more than 3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Hemoptysis	2	Active cancer	1	Pitting edema (greater in the symptomatic leg)	1
Heart rate 75-94/pm	3			Collateral superficial veins (nonvaricose)	1
Heart rate ≥95 bpm or more	5			Past history of DVT	1
				Alternative diagnosis as likely or greater than that of DVT	−2
Modified	Traditional	Original score			
<3 points = low	<4.0 = high	<2 points = low			
4-10 points = intermediate	2.0-6.0 = moderate	2-3 points = intermediate			
>10 points = high	>2.0 = low	>3 points = high			
Simplified	Simplified	Dichotomized score			
2 points or fewer PE unlikely	>4 = PE likely	<1 = DVT unlikely			
	4 or less = PE unlikely	>1 = DVT likely			

bpm indicates beats per minute.

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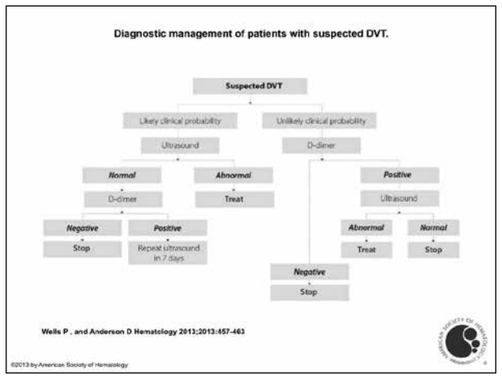

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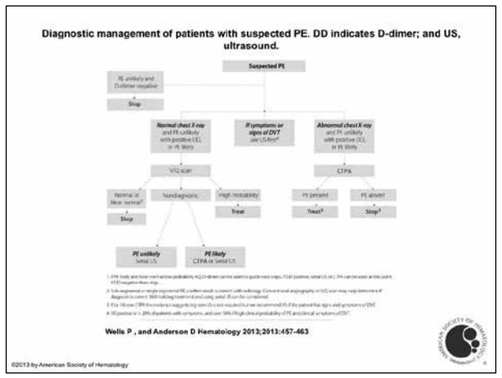

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Acute leukemia

Z.N. Berneman
University of Antwerp and Antwerp University Hospital

Acute myeloid leukemia (AML), especially the substantial group of high-risk cases, still has a dismal prognosis and no major improvement has been reproducibly made with regard to overall survival, except with allogeneic hematopoietic stem cell transplantation (allo-HSCT). It is recommended to enroll patients with high-risk AML in clinical trials with new investigational agents acting on the key molecular events associated with the leukemia (eg. tyrosine kinase inhibitors acting on FLT3). Patients with core-binding factor (CBF) AML have a good prognosis, that is adversely impacted by concomitant KIT or FLT3 mutations. But at present, it is not generally recommended to perform allo-HSCT in first-line complete remission of those cases. Tyrosine kinase inhibitors (TKI) targeting the products of these genes have started to be used in clinical trials. Some patients with FLT3/ITD AML have a worse prognosis, except in acute promyelocytic leukemia; it is still unclear whether this mutation impacts the already bad prognosis of AML arising from MDS or in patients older than 65. The disease seems to be worse if patients disclosing a high allelic ratio of mutated vs. wild-type FLT3. Available data support performing a sib allo-HST once complete remission (CR) has been reached in FLT3/ITD AML. The FLT3 inhibitor quizartinib has disclosed a high level of activity in patients with relapsed/refractory disease (51% CR rate), allowing a sizable part of them to go on to receive an allo-HSCT.

In the field of **acute lymphoblastic leukemia (ALL)**, major conceptual and practical progress is being made using immune strategies, some new, some old, to treat the disease. This progress is necessary, in view of the poor prognosis of the disease in adults. Pre-B ALL constitutes the majority of ALL cases and much attention has been paid in trying to improve treatment outcome with monoclonal antibodies targeting B-cell antigens. Encouraging results have been obtained in phase II studies with the monoclonal antibodies rituximab (against CD20), epratuzumab (against CD22) and its ozogamicin conjugate inotuzumab. Conceptually more novel approaches have shown spectacular results, often in patients with resistant disease. These approaches include the use of: 1) blinatumomab, a bispecific T cell engager (BiTE) antibody, reacting with CD19 on the ALL cells and with CD3 on T cells, which are thereby recruited to attack the ALL cells; and 2) (autologous) T cells, transduced with a chimeric antigen receptor (CAR), that binds CD19 on the ALL cells, but also has been constructed in such a way that it can stimulate the T lymphocytes that bind CD19 to unleash their lytic potential on the ALL cells.

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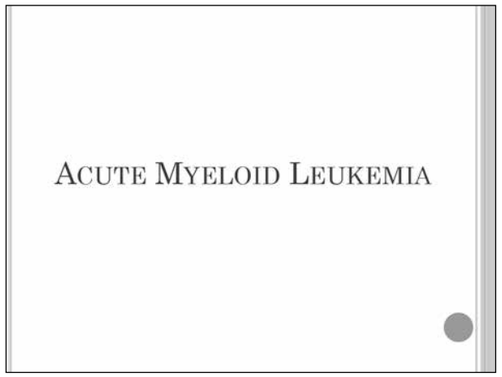

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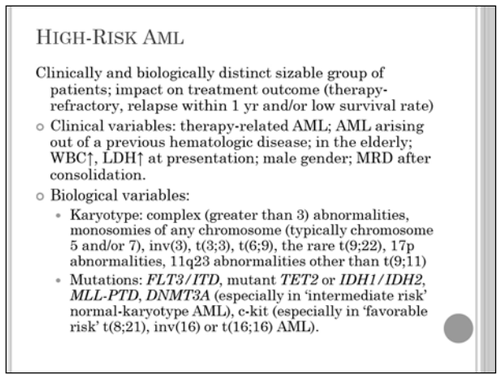


3

Routine Evaluation of AML for Risk Stratification
(Gary Schiller, UCLA)

Standard

- Morphology
- Flow cytometry/immunohistochemistry
- FISH for common abnormalities: t(8;21) *RUNX1-RUNX1T1*; inv(16) or t(16;16) *CBFB-MYH11*; t(15;17) *PML-RARα*; t(9;11) *MLLT3-MLL*; inv(3) or t(3;3) *RPN1-EVI1*
- Karyotype
- Molecular studies for mutations in *FLT3*, *NPM-1*, *Kit*, *CEBPa*

Potentially useful

- Molecular studies for mutations in *DNMT3*, *TET2*, *MLL*, IDH1, and/or *IDH2*

4

Progress in the Therapy of High-Risk AML?

- No established or confirmed improvement in overall survival (OS) when adding different agents (eg. clofarabine, gemtuzumab, higher dose of chemotherapy).
- FLT3 TKI midostaurin, lestaurtinib, quizartinib, and sorafenib: single-agent activity in the relapsed setting; quizartinib most promising for relapsed disease, but may select for mutations that confer resistance.
- Allo-HSCT: at present only (post-consolidation) treatment that seems to work, especially for patients with intermediate-risk cytogenetics and patients with *FLT3/ITD* or adverse cytogenetics AML (retrospective studies), not for patients with advanced disease.

5

Core-Binding Factor (CBF) AML (1)

- AML with t(8;21) or inv(16) or t(16;16): good prognosis (90% CR, 50% cure with chemotherapy, especially high dose Ara-C in consolidation).
- Genetic heterogeneity of CBF AML: *RAS, KIT , FLT3* mutations.
- KIT or FLT3 TKI: already in trials in combination with conventional chemotherapy; use of TKIs as an adjunct to chemotherapy in CBF AML only within clinical trials.
- Allo-HSCT not be generally offered as frontline treatment to CBF AML.
- Unclear whether patients with CBF AML and *KIT* or *FLT3* mutations benefit from allo-HSCT in CR1; to be investigated in clinical trials.

6

Core-Binding Factor (CBF) AML (2)

- No influence on current patient management → no routine *KIT* mutation screening at diagnosis of CBF AML. But: data on *KIT* and *FLT3* mutations needed within clinical trials, especially if TKI used.
- MRD in CBF AML recommended at baseline, after each treatment cycle and every 3 months during follow-up. Impending relapse: close monitoring and availability of a HLA-compatible donor. Not enough evidence for preemptive therapeutic interventions in CBF-AML based on MRD follow-up
- Allo-HSCT as a salvage option for relapsing CBF AML (Robert Paschka, University Hospital of Ulm).

7

FLT3/ITD AML

- Adverse effect of *FLT3/ITD* on prognosis of AML, except in M3 AML/t(15;17); unclear effect on MDS/AML and on AML in patients older than 65.
- Impact of the length of *ITD* on clinical outcome: longer mutations are usually (but not always) associated with reduced remission rate and/or worse overall survival.
- Allelic ratio: ratio of *ITD*-mutated to wild type alleles
  - Higher allelic ratio predictive of worse outcomes, with loss of the wild-type allele being the worst
  - But limited sensitivity of *FLT3/ITD* assay:
    - PCR primers used to amplify the mutant allele also amplify the wild-type allele (increasing the number of PCR cycles will not increase the sensitivity)
    - Competitive advantage of the shorter wild-type allele; the longer the ITD, the greater the PCR bias; bias can be minimized by decreasing the number of PCR cycles, but this can decrease sensitivity when there is a low burden of leukemia cells in the sample.

8

FLT3/ITD Assay

- Allelic ratio: ratio of ITD-mutated to wild type alleles is influenced by:
  - the amount of malignant vs. nonmalignant cells
  - percentages of cells with 0, 1, or 2 mutated alleles
    - At diagnosis: polyclonal at presentation with, in most cases, dominant clone heterozygous for the mutation; subpopulations can lack the mutation; other can be biallelic; other be hemizygous for the mutant allele, by loss of the chromosome 13 containing the wild-type allele or through a smaller deletion of the wild-type.
    - At relapse/progression: dominant clone emerges and the allelic ratio generally increases; in most cases: mutation originally detected at diagnosis also present at relapse. Occasionally, ITD undetectable at relapse (typically seen in cases with low allelic ratio (eg. 5%-15%) at diagnosis) → FLT3/ITD mutations have been regarded as unsuitable for use as a MRD marker.

9

FLT3 Inhibitors

- Midostaurin, lestaurtinib, sorafenib, quizartinib, ponatinib, PLX3397.
- Quizartinib: so far, most potent, most selective and most tolerable FLT3 inhibitor at doses that completely inhibit FLT3 *in vivo*.
- Phase II trial: 191 relapsed/refractory *FLT3/ITD* AML patients, 2 cohorts treated with quizartinib as single-agent therapy (1st cohort: 92 older patients (median age 69 yr), relapsed/refractory to a single line of therapy; 2nd cohort: 99 younger patients (median age 55 yr) relapsed/refractory after 2 lines of therapy. CR (CR + Cri) 51%. Responses associated with rapid apoptosis of circulating blasts coupled with the induction of terminal differentiation of BM blasts over the course of a few weeks; no systemic toxicity. This allowed 47/136 patients (35%) of cohort 2 to undergo allo-HSCT with a significant number of long-term survivors from this very poor-risk group.
- Patients with response to quizartinib: often resistance, usually at D835 and less frequently at F691 → development of new TKI with activity against these new mutants.

10

Allo-HSCT for *FLT3/ITD* AML

- No prospective studies regarding the place of allo-HSCT in *FLT3/ITD* AML.
- Most (retrospective) studies: *FLT3/ITD*+AML patients who undergo allo-HSCT in CR1 have a better outcome than those treated with conventional consolidation chemotherapy only, but still relapse at a higher rate than transplanted *FLT3/ITD*- AML patients. Thus: *FLT3/ITD AML* patient in CR1 should be offered a sib allo-HSCT as consolidation. Also, start MUD search, as soon as diagnosis of a *FLT3/ITD* AML; maybe: if no sib donor, decide on a MUD allo-HSCT, depending on *FLT3/ITD* allelic ratio and on concomitant NPM1 mutation (Mark Levis, Johns Hopkins University, Baltimore). No reliable data comparing myeloablative vs. reduced-intensity conditioning.
- Treatment paradigm: add FLT3 inhibitors to induction chemotherapy of *FLT3/ITD* AML to increase the remission rate and to maintain CR, so the patient can be taken to allo-HSCT; after transplantation, the TKI could be used as maintenance therapy (cfr. TKI inhibitors in the succesful treatment of Phi+ ALL).

11

Acute Lymphoblastic Leukemia

12

ALL and Monoclonal Antibodies

- Pediatric ALL: 90% cure; adult ALL: overall survival (OS) at 3 yr 41% (< 30 yr 57%; 30-59 yr 38%; >60 yr 12%) → need for new approaches
- 80% of ALL: pre-B ALL → targeting by monoclonal antibodies (Mab) recognizing B-cell antigens
  - CD20: rituximab, ofatumumab
  - CD22: epratuzumab, inotuzumab ozogamicin
  - CD52: alemtuzumab
  - CD19: blinatumomab (bispecific T cell engager (BiTE) antibody); chimeric antigen receptor (CAR) transduced in (autologous) T cells

13

Rituximab in ALL

- CD20 less commonly expressed than CD19 in pre-B ALL
- CD20+ ALL worse prognosis than CD20- ALL
- CD20 upregulated in pre-B ALL during induction treatment
- MD Anderson: modified hyper-CVAD + rituximab for 204 Ph- ALL, CD20+ on >20% blasts; non-randomized study in patients <60 yr: improvement of CR rate and OS.
- Randomized trial ongoing
- Other CD20 Mab : eg. ofatumumab (may be more effective in killing ALL cells by ADCC).

14

CD22 Mab in ALL

- CD22 attractive target: expressed on >90% of B-cell malignancies, not shed in extracellular environment, not internalized (→ good candidate for immunoconjugates and immunotoxins).
- Epratuzumab (humanized naked Mab) in ALL:
  - MRD↓, DFS↑, OS↑
  - SWOG: clofarabine + Ara-C + epratuzumab in refractory ALL: CR/Cri 52% (cfr. 17% in prior trial with clofarabine + Ara-C.
- Inotuzumab (ozogamicin immunoconjugate): CR/Cri 57% (of those 63% complete molecular response), but grade 3-4 myelosuppression and non-hematological adverse events.

15

Blinatumomab in ALL

- BiTE antibody, targeting CD19
- Phase II study in ALL patients, in molecular failure or relapse after chemotherapy: complete molecular response (primary endpoint) was reached in 80% of cases; responses were rapid, all occurring within the first cycle, including patients with high-risk disease (eg. t(4;11)) and patients who did not go on to allo-HSCT.
- Phase III trial: chemotherapy +/- blinatumomab in newly diagnosed BCR/ABL-negative B-ALL in adults (40-70 yr).

16

CD19-CAR for ALL (published cases)

- Brentjens et al. *Sci Transl Med* 2013 (CD19.z.28): 5 adults with B-ALL (2 chemo-refractory, 2 MRD+, 1 MRD-); all MRD- after CAR; 4/5 allo-SCT; 1/5 relapse after 90 days.
- Grupp et al. *NEJM* 2013 (CD19.z.BB): 2 children with B-ALL; 1 prolonged CR, 1 transient response with $CD19^-$ relapse; severe cytokine release syndrome, successfully treated with anti-IL-6R (tocilizumab)+ anti-TNFα (etanercept).
- Cruz et al. *Blood* 2013 (virus-specific T cells 19.z.28): 8 patients with B-ALL 3 mo – 13 yr post HSCT; antitumor activity in 2/6 patients with relapse.

17

Notes

CLL: a new treatment era is born

Post-ASH January 10th, 2014
D. Mazure
Hematology – UZ Gent

1

CLL 10: R-FC vs R-Benda

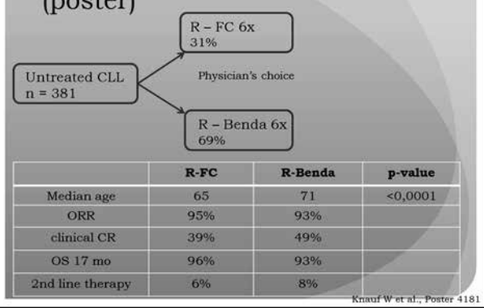
	R-FC	R-Benda	p-value
Median age	61	62,1	0,131
Age ≥70 years	13,8%	21,5%	0,020
IgHV unmutated	55%	68%	0,003
ORR	97,8%	97,8%	1
CR (MRD neg)	47,4% (71,7%)	38,1% (66,7%)	0,031 (0,448)
2 year PFS	85%	78,2%	0,041
Med PFS <65 years	not reached	36,5 mo	0,016
Med PFS >65 years	45,6 mo	not reached	0,757
2 year OS	94,2%	95,8%	0,593
CTC grade 3-5	90,8%	78,5%	<0,001

Eichhorst et al., ASH 2013

-> trade-off between efficacy and toxicity

2

Prospective observational trial (poster)



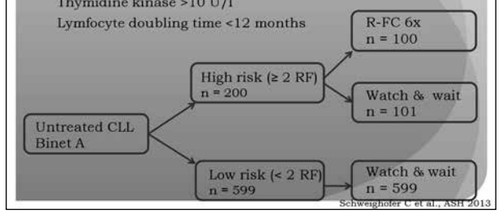
	R-FC	R-Benda	p-value
Median age	65	71	<0,0001
ORR	95%	93%	
clinical CR	39%	49%	
OS 17 mo	96%	93%	
2nd line therapy	6%	8%	

Knauf W et al., Poster 4181

3

Watch and wait?: **CLL 7**

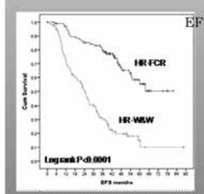
Risk factors:
- Unfavorable cytogenetics (17p-, 11q-, tri12)
- IgHV unmutated
- Thymidine kinase >10 U/l
- Lymfocyte doubling time <12 months



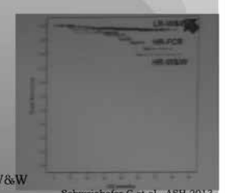
Schweighofer C et al., ASH 2013

4

Watch and wait?: CLL 7



EFS: R-FC (not reached) >> W&W (24,5 mo)



OS: R-FC = W&W

Schweighofer C et al., ASH 2013

Identification of high risk group possible:
5j PFS low risk 78,6% vs high risk 57,5 (R-FC) and 23,7% (W&W)

5

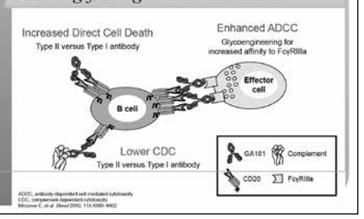
New players – monoclonal antibodies

6

Monoclonal antibodies

- **Obinutuzumab** = GA101

Type 2 humanized glycoengineered antiCD20 antibody



7

Monoclonal antibodies

- **Ofatumumab**

Type 1 humanized antiCD20 antibody

8

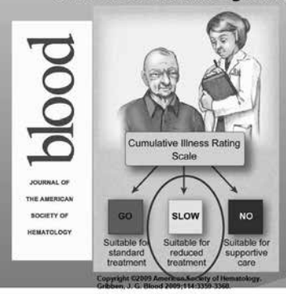
Monoclonal antibodies

	Type 1	Type 2
Lipid rafts	+	-
CDC	high	low
ADCC	+	++
Direct Cytotoxicity	weak	strong
Homotypic aggregation	weak	strong

9

Fitness-adapted therapy of CLL

Cumulative Illness Rating Scale (CIRS)*



10

The slow go

- Treatment?
  Yes, because life expectancy is not so short and CLL does impact on life expectancy
  At 70 years: life expectancy = >15 years
- Criteria?
  Age – performance status – organ function – comorbidity – functional assessment
  → IWCLL working group
- Goal: prolong life but balance efficacy and tolerability

11

Content

- The fit
- The new part 1
- The slow go
- The new part 2
- The immunotherapy
- The strategy
- The pipeline

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CLL 11

GA101: C1: 100 mg d1, 900 mg d2, 1000 mg d8+15 - C2-6: 1000 mg d1

Untreated CLL n = 781

2 : 1 : 2

- G – Clb 6x n = 333
- Clb 6x
- R – Clb 6x n= 330

CIRS >6 and/or creat clear <70 ml/min

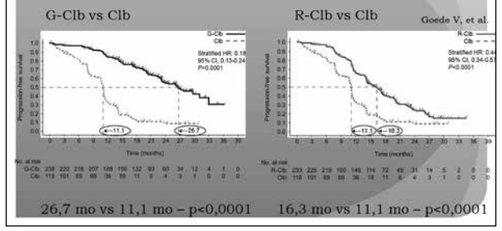
Rituximab: C1: 375 mg/m², C2-6: 500 mg/m²

Chlorambucil: 0,5 mg/kg d1 and d15 – cycle = 28 days

13

CLL 11 update: G-Clb vs Clb and R-Clb vs Clb

Progression-free survival

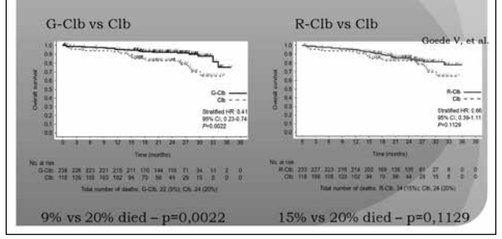


26,7 mo vs 11,1 mo – p<0,0001 16,3 mo vs 11,1 mo – p<0,0001

14

CLL 11 update: G-Clb vs Clb and R-Clb vs Clb

Overall survival



9% vs 20% died – p=0,0022 15% vs 20% died – p=0,1129

15

CLL 11: G-Clb vs R-Clb

Well balanced groups:
- med age: 73 years
- med CIRS 8
- med CrCl 62,5 ml/min
- equally distributed adverse prognostic factors

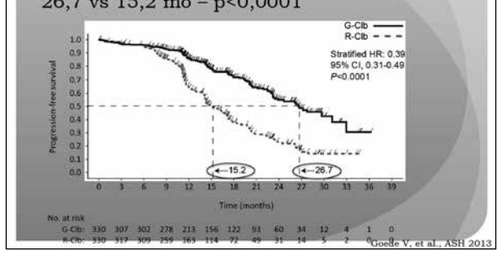
	G-Clb	R-Clb
ORR (CR)	78% (21%)	65% (7%)
MRD negativity	29,4% (63/214)	2,5% (6/243)
PFS	26,7 mo	15,2 mo
OS	NR	NR
Adverse events gr 3-5	66%	47%
Infusion reactions	20%	4%

Goede V et al., ASH 2013

16

CLL 11: G-Clb vs R-Clb

Progression-free survival
26,7 vs 15,2 mo – p<0,0001

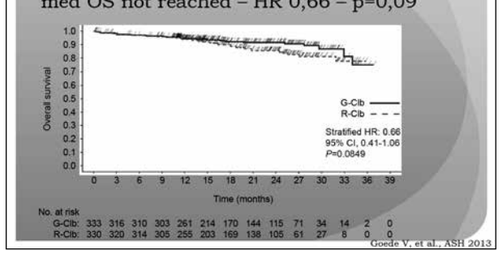


Goede V, et al., ASH 2013

17

CLL 11: G-Clb vs R-Clb

Overall survival
med OS not reached – HR 0,66 – p=0,09



Goede V, et al., ASH 2013

18

CLL 11: G-Clb vs R-Clb

Conclusion:

G-Clb =
- acceptable safety profile,
- prolongation of progression-free and overall survival
- superior to R-Clb

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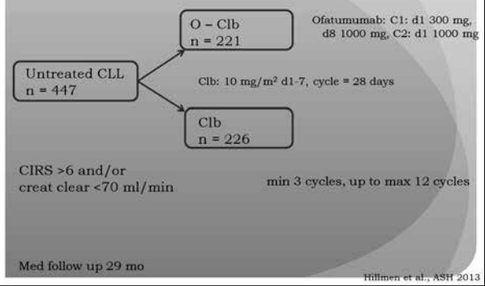
Complement 1



20

Complement 1: O-Clb vs Clb

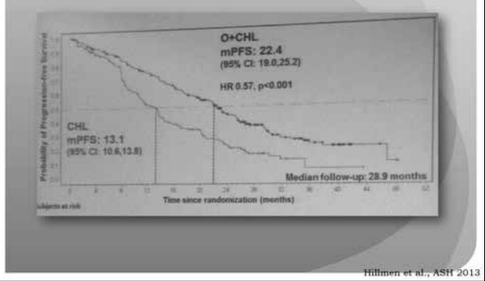
Well balanced groups:
- med age: 69 years
- equally distributed adverse prognostic factors

	O-Clb	Clb	p
ORR (CR)	82% (12%)	69% (1%)	p=0,001
MRD negativity	37% of CR	0% of CR	
PFS	22,4 mo	13,1 mo	p<0,001
OS	NR	NR	
Adverse events >gr 3	50%	43%	
Infusion reactions	10%		

Hillmen et al., ASH 2013

21

Complement 1: O-Clb vs Clb

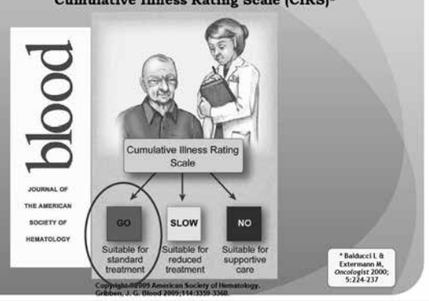


Hillmen et al., ASH 2013

22

Fitness-adapted therapy of CLL

Cumulative Illness Rating Scale (CIRS)*



23

Complement 1: O-Clb vs Clb

Conclusion:

O-Clb demonstrates clinically important improvements with a manageable side effect profile

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The slow go

First choice:
immunochemotherapy as well?

GA101 (Obinutuzumab) the better choice amongst the antiCD20 Ab's?

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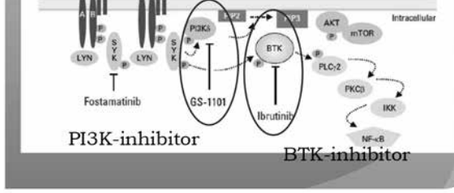
New players – small molecules

26

B-cell receptor signaling targeting agents



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BTK-inhibitor (**Ibrutinib**)

Bruton's tyrosine kinase inhibitor

Orally available
420 mg once daily

AE:
- diarrhea (CTC gr1-2 and self-limiting)
- redistribution lymphocytosis

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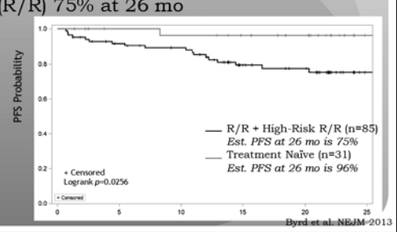
PCYC1102-trial: Ibrutinib monotherapy

ORR: 81 – 89% (incl nodal responses)

PFS (R/R) 75% at 26 mo

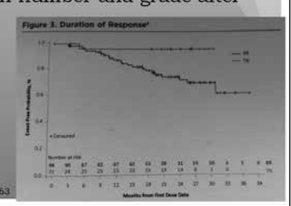


Byrd et al. NEJM 2013

29

Open-label extension study

- >1 year on therapy: safe, tolerable and durable respons
- AE decreased in number and grade after 1 year



O' Brien et al. Poster 4163

30

Ibrutinib single agent equally active in 17p-

med age 66 years – prior treatments possible

response at 6 months:

	no 17p-	17p-
PR	81%	53%
PR with lymphocytosis	9%	43%

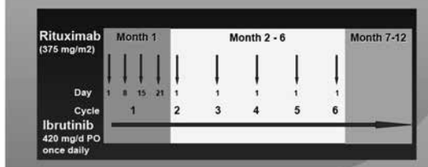
Farooqui M et al., ASH 2013

31

Ibrutinib + Rituximab (iR) in high-risk CLL

high-risk disease (17p-, p53 mutation, 11q-, rapid relapse)

med age 65 years – med prior therapies 2



Burger J et al., ASH 2013

32

Ibrutinib + Rituximab (iR) in high- risk CLL

at med follow up 14 months:

32 of 40 patients on treatment in remission

discontinuation because of toxicity 2, progression 1

	All (n=39)	17p-/p53 mut (n=20)
ORR	95%	90%
PR	87%	80%
CR	8% (n=3, 1 MRD neg)	10%

improved quality of life after 6 months

more rapid resolution of redistribution lymphocytosis

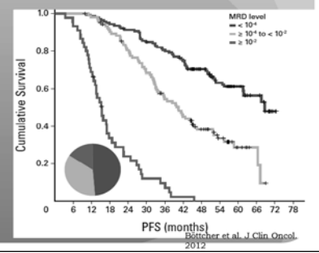
Burger J et al., ASH 2013

33

First line treatment for the fit

= CIRS <6 and creat clearance >60-70 ml/min

Goal:
MRD-negativity



Bottcher et al. J Clin Oncol. 2012

34

Ibrutinib + R-Benda in R/R CLL

Ibrutinib 420 mg OD
Rituximab C1 375 mg/m², C2-6 500 mg/m²
Bendamustine 70 mg/m² on d1-2

med age 62 years – med prior therapies 2

including 17p- (23%)

Brown J et al., ASH 2013

35

Ibrutinib + R-Benda in R/R CLL

med treatment duration 16 months

ORR 93% (CR 5 out of 28 pt)

estimated 1 year PFS 90%

AE = no more than expected with the compounds:

- diarrhea (70%)
- nausea (66%)
- neutropenia (40%)
- redistribution lymphocytosis less pronounced

Brown J et al., ASH 2013

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PI3K-inhibitors

PI3-kinases: different subtypes

PI3 kinase family	Cellular expression	Primary role
alpha	many cell types	insulin signaling, angiogenesis
beta	many cell types	platelet function
gamma	leucocytes	neutrophil & T-cell function
delta	leucocytes	B-cell development, signaling & survival

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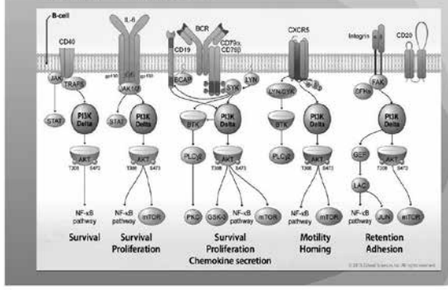
PI3K-inhibitor



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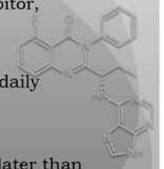
PI3Kδ-inhibitor (**Idelalisib** = CAL101)

Phosphoinositide 3-kinase inhibitor, selective for PI3K-δ



Orally available - 150 mg twice daily

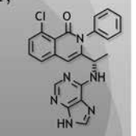
AE:

- diarrhea, more profound and later than with Ibrutinib – pyrexia – transaminitis – neutropenia
- redistribution lymphocytosis

39

PI3Kγ,δ-inhibitor (**IPI-145**)

Phosphoinositide 3-kinase inhibitor, selective for PI3K-γ,δ



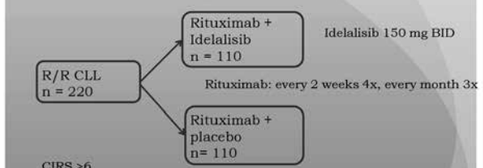
Orally available

AE:

- diarrhea, more profound and later than with Ibrutinib – pyrexia – transaminitis – neutropenia
- redistribution lymphocytosis

40

Idelalisib + Rituximab in R/R CLL in unfit patients



CIRS >6
CrCl <60 ml/min
cytopenia

Observation time 24 months

Furman et al., ASH 2013

41

Idelalisib + Rituximab in R/R CLL in unfit patients

med age 71 years – med prior therapies 3

including 17p- (45%) and unmutated IgHV (>80%)

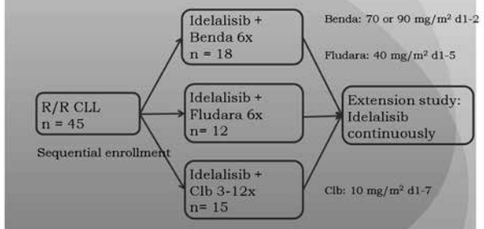
	Idel + R	R	p-value
ORR	81%	13%	<0,0001
PFS	NR	5,5 mo	<0,0001
OS			0,018
>50% reduction lnn	93%	4%	
AE: gr 3 neutropenia	34%	22%	

PFS better in all subgroups, including 17p-
Infusion reactions less in Idelalisib-group

Furman et al., ASH 2013

42

Idelalisib + Benda, Fludara or Chlorambucil in R/R CLL



De Vos et al., Poster 2878

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Idelalisib + Benda, Fludara or Chlorambucil in R/R CLL

med age 65 years – med prior therapies 3

including 17p- (42%), unmutated IgHV (84%)

	Idel + B n = 18	Idel + F n = 12	Idel + Clb n = 15	all
med idel exposure	10,6 mo	13,1 mo	11,1 mo	
ORR (CR)	78% (0%)	92% (8%)	73% (13%)	80% (7%)
PFS	19,9 mo	NR	NR	28,5 mo
Any AE	89%	75%	60%	76%
Neutropenia ≥gr 3	67%	58%	73%	67%

Feasible combinations with good respons in heavily pretreated CLL

De Vos et al., Poster 2878

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Idelalisib + antiCD20-Ab in R/R CLL

med age 66 years – med prior therapies 2

including 17p-/p53 (28%), unmutated IgHV (75%)

	all	17p-/p53
med idel exposure	18 mo	
ORR (CR)	83% (8%)	73%
PFS	20 mo	19 mo
Any AE	75%	
Neutropenia ≥gr 3	30%	
Diarrhea	53%	

Idelalisib + antiCD20 non-cytotoxic with good activity

Furman R et al., Poster 4180

49

Preliminary safety and efficacy of IPI-145

44 pt R/R CLL – med age 67 year

MTD 75 mg BID – biol active dose 25 mg BID

ORR 52% and some PR with lymphocytosis

Rapid redistribution lymphocytosis and nodal respons (79% after 2 cycles)

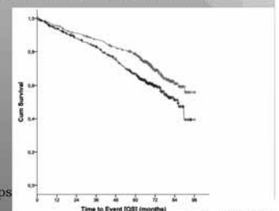
AE: neutropenia gr 3: 20%

50

First line treatment for the fit

R-FC = gold standard (cfr. CLL 8 trial):

ORR 92,8% (CR 44,5%); med OS at 7 years not reached



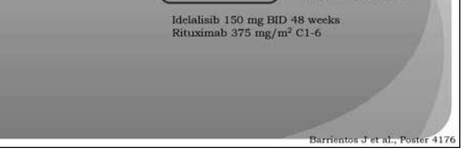
Problems:

- No cure
- Unfavorable subgroups

Fischer K, ASH 2012

45

Idelalisib + R-Benda or R-Clb in R/R CLL



Barrientos J et al., Poster 4176

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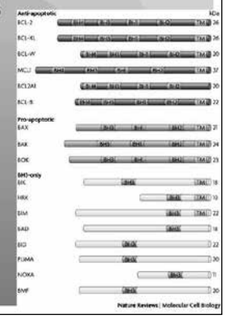
Bcl-2 antagonists

Bcl-2 family:

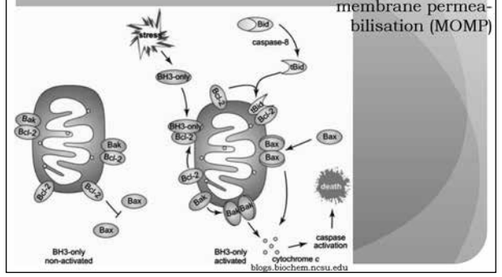
- Anti-apoptotic eg. Bcl-2
- Pro-apoptotic eg. BAX
- Regulatory BH3 only domain eg. BID



51

Bcl-2 antagonists

Bcl-2 family proteins regulate commitment to cell death by controlling mitochondrial outer membrane permeabilisation (MOMP)



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Idelalisib + R-Benda or R-Clb in R/R CLL

med age 64 years – med prior therapies 3

including 17p-/p53 (10%), unmutated IgHV (79%)

	Idel + R-B n = 15	Idel + R-Clb n = 14	all
med idel exposure	18,4 mo	7,7 mo	
ORR (CR)	87% (13%)	93% (14%)	90% (14%)
PFS	NR	NR	23 mo
Any AE	53%	71%	62%
Neutropenia ≥gr 3	60%	43%	52%

Tolerable and active combinations in heavily pretreated CLL

Barrientos J et al., Poster 4176

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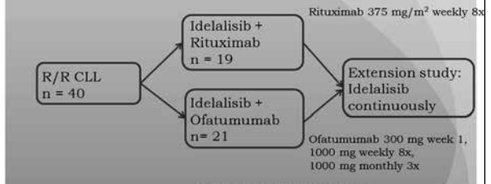
Idelalisib + antiCD20-Ab in R/R CLL



Furman R et al., Poster 4180

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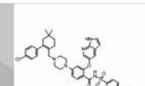
Bcl-2 antagonists



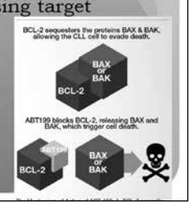
CLL shows high levels of Bcl-2 expression and CLL is Bcl-2 dependent

→Bcl-2 inhibition is promising target

ABT-199

Selective Bcl-2 inhibitor

Orally available



53

ABT-199 in high-risk R/R CLL

Dose-finding study, dose 150-1200 mg OD

Dose limiting toxicity 7 of which 5 tumor lysis syndrome

ORR 84% (CR 21% and some MRD-), including 17p-

AE: diarrhea 46% - neutropenia 43% - fatigue 34% - tumor lysis

Seymour J et al., ASH 2013

54

Immunotherapy

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Benda or FC?

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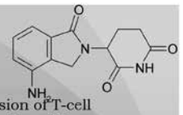
Lenalidomide



Mechanism: downregulates expression of T-cell inhibitory molecules, enhances T-cell motility

Problem of tumor flare

Monotherapy in R/R – Bühler A et al, poster 1638:
- ORR 44% (p53 mut 36% - 17p- 22%)
- PFS 45 we (p53 mut 47,6 we – 17p- 21,4 we)
- OS 151,6 we (p53 mut 151,6 we – 17p- 80,9 we)
- → Promising respons in heavily pretreated CLL, with no influence of p53 mutations

57

Lenalidomide

Len-Rituximab (R^2) maintenance after Len-FR induction in 1st line – Egle A et al., poster 4164
- 45 pts – med age 66 years – including 17p-
- CR 67%, PR 29% - PR to CR after maintenance: 25%
- med fu 35 mo with PFS 89% - med PFS 46 mo
- ≥ grade 3 neutropenia 45%

Len-Rituximab (R^2) in 1st line – Strati P et al., poster 4183
- 35 pts – med age 68 years – including 17p-
- ORR 85% with CR 10%
- med fu 9 mo – med PFS/OS NR
- ≥ grade 3 neutropenia 36%

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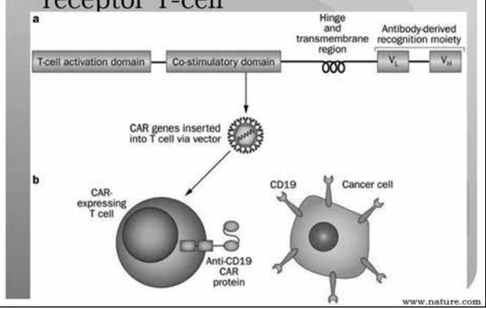
CART: Chimeric antigen receptor T-cell



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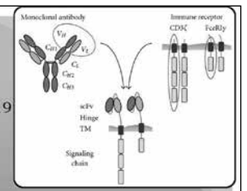
CAR T-cells



Target antigen? Mostly CD19

Pre-infusion therapy?
- Lymphodepleting chemo?

Toxicity?
- B-cell aplasia
- Cytokine release syndrome – correlates with respons – IL6 important driver, R/ Tocilizumab
- Neurotoxicity: selflimiting

Potential?
- Consolidate MRD
- Bridge to SCT
- Reinduce remission

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CAR T-cells

Promising results:

Porter et al., poster 4162 – CAR against CD19:
- 14 pts – med age 66 years – med prior therapies 4
- Cytokine release syndrome in all responding pts
- ORR 57% (CR 28,5%)
- med fu 12 mo (20 mo for responders) – no relapse in CR pts

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Allogeneic stem cell transplantation

- Up until now: only curative option
- Conditioning: reduced intensity – trials with new combinations
- 5j OS: 50-60% but problem of GVHD (50% extensive chronic GVHD)
- Indications:
  - Del17p or p53 mutated needing treatment, frontline
  - Fludarabine-refractory
  - Relapse within 2 years after purine-analogue based therapy
- Same indications applicable in era of new molecules?

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Treatment strategies

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Treatment algorithm for CLL patients in frontline indications

A

Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR
		Yes	Allo-SCT
	Slow go	No	CLB + anti-CD20-Mab
		Yes	Al, HD R or O

Hallek M Blood 2013;122:3723-3734

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Treatment algorithm for CLL patients in second-line indications

B

Response to First-Line Therapy	Fitness	Therapy	
		Standard	Alternatives (trials)
Refractory or progress within 2 years	Go go	Al-Dex, FA, FCR→Allo SCT	Lenalidomide, BR, BR^2 Combination with kinase inhibitors
	Slow go	Change therapy (if possible, include in trial)	Al for del(17p), FCRlite, BR, bendamustine, lenalidomide, ofatumumab, HD rituximab, kinase inhibitors
Progress after 2 years	All	Repeat first-line therapy	

Hallek M Blood 2013;122:3723-3734

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New molecules monotherapy: the solution?

Very promising response rates but...

Very few MRD negativity

Durable remission?

The solution? No! →

"You'll never walk alone"

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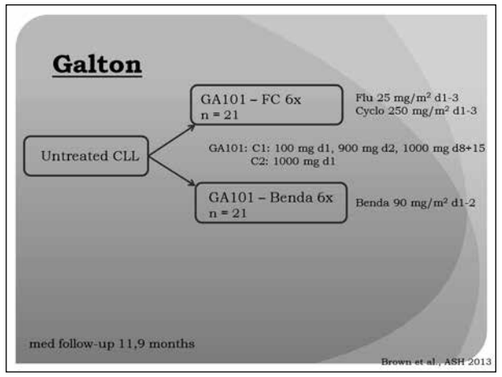

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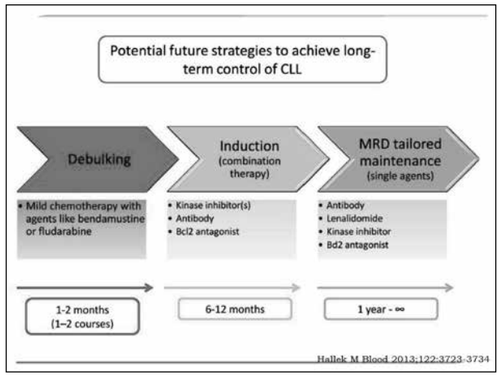

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The pipeline

- Second generation BTK-inhibitor
- Anti-CXCL-4
- CDK-inhibitor
- Anti-ROR-1
- Syk-kinase inhibitor
- Akt-inhibitor
- CLL-trial 12, 13 and 14
- ...

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Take home messages

Fit?
FC vs Benda: efficacy vs toxicity

AntiCD20?
For fit and slow go
GA101 probably the winner

New molecules?
Promising
Results of phase 3 trials to be expected in the next years

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Galton: G-FC vs G-Benda

	G-FC	G-Benda
Median age	58	62
Discontinuation of therapy	33%	15%
ORR (CR)	62% (10%)	90% (20%)

Conclusion:
Number of patients too small to draw conclusions
Large proportion of patients didn't complete treatment

Brown et al., ASH 2013

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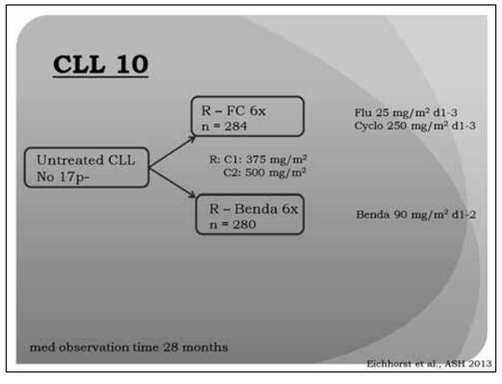

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Notes

Notes