CLL Ireland Information Day Presentation

5 May 2018

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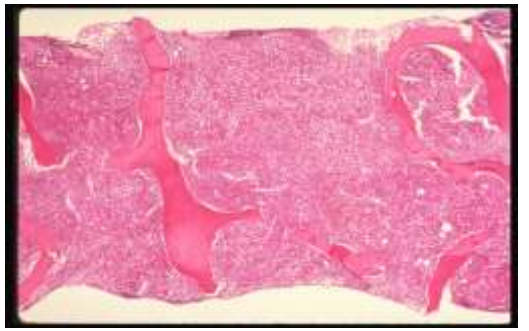
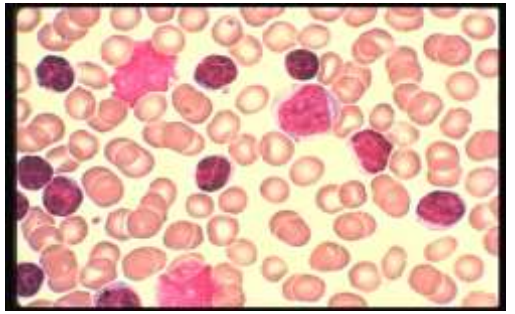
Hermitage Medical Clinic Laboratory

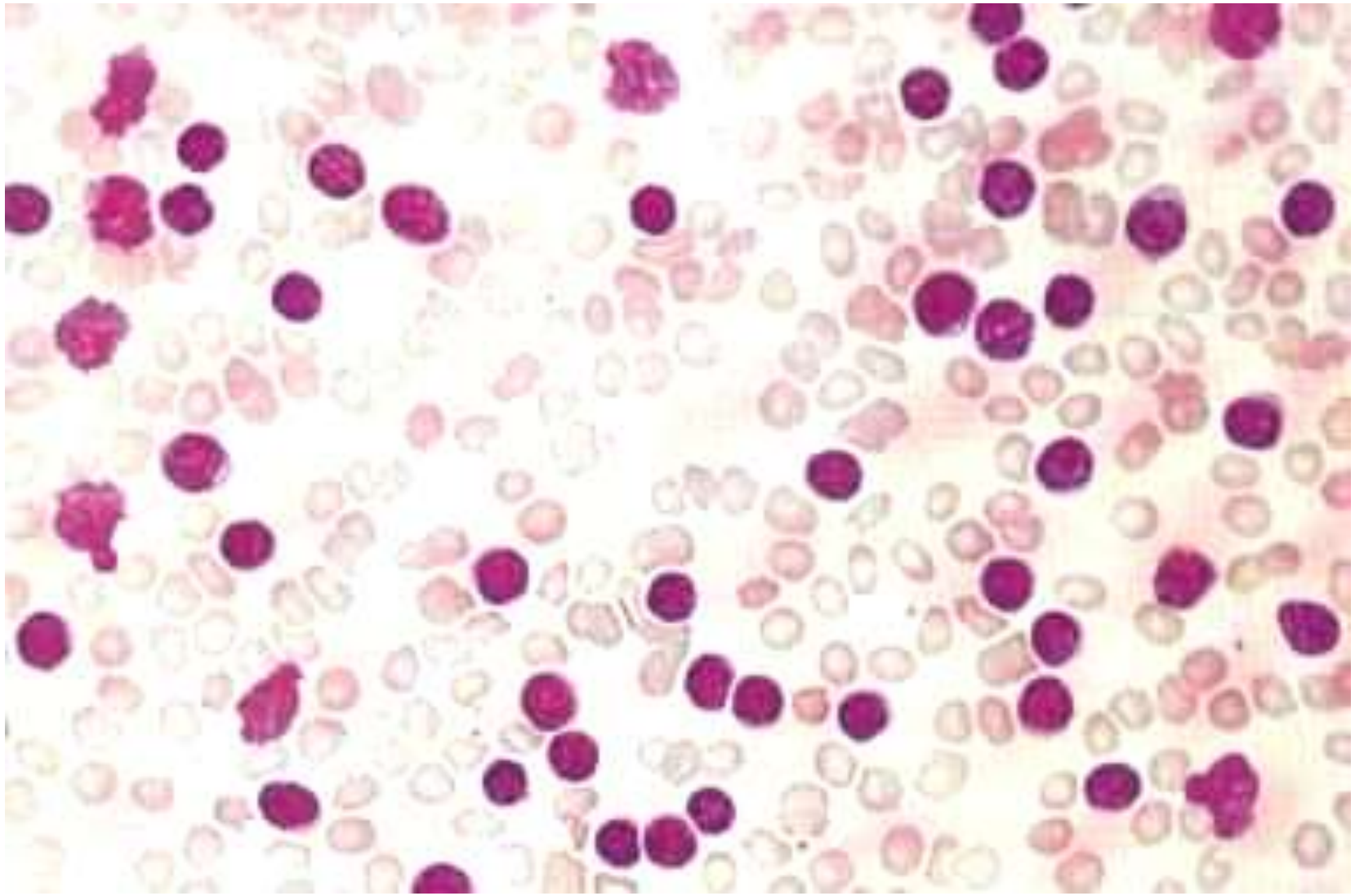
Chronic Lymphocytic Leukaemia

- Commonest leukaemia in western world
- Heterogeneous natural history
- Progression associated with increased tumour bulk and genetic complexity





CLL – Blood Film



Diagnosis of CLL

- **Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines**
- Michael Hallek1, Bruce D. Cheson2, Daniel Catovsky3, Federico Caligaris-Cappio4, Guillaume Dighiero5, Hartmut Döhner6, Peter Hillmen7, Michael J. Keating8, Emili Montserrat9, Kanti R. Rai10, and Thomas J. Kipps11

Diagnosis of CLL

(IWCLL Guidelines, 2008)

- Peripheral blood morphology
- ≥ 5,000 circulating B-lymphocytes

  (CD19+, CD20+)
- CLL immunophenotype

  (CD5+, CD23+, CD79b-/±, FMC7-/± weak staining for SmIg) – score 4-5
- No bone marrow required

Diagnosis of CLL

- B Lymphocytosis of 5X 10/9 B lymphocytes/l in peripheral blood
- Clonality confirmed by flow cytometry
- Fewer is mono clonal B lymphocytosis with a rate of transformation of 1 to 2% per year*
  - * absence of symptoms, marrow failure of lymph nodes

Investigations performed at diagnosis-staging

- Binet staging
- **Areas of involvement considered for staging**
- Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged).
- Axillae (involvement of both axillae counts as one area).
- Groins, including superficial femorals (involvement of both groins counts as one area).
- Palpable spleen.
- Palpable liver (clinically enlarged).

CLL staging system

Stage			
Value	Rai	Binet	Median survival
Lymphocytosis (>15,000/mm^3)	0	—	150 months (12.5 years)
Lymphocytosis plus nodal involvement	I	A <3 node groups	101-108 months (8.5-9 years)
Lymphocytosis plus organomegaly	II	B >3 node groups	60-71 months (5-6 years)
Anemia (RBCs)	III Hgb <11 g/dL	Hgb <10 g/dL	19-24 months (1.5-2 years)
Lymphocytosis plus thrombocytopenia (platelets)	IV PLT <100,000/mm^3	C PLT <100,000/mm^3	

Binet Staging

- ***Stage A.***
- Hb 100 g/L (10 g/dL) or more and platelets 100 × 10^9/L or more and up to 2 of the above involved.
- ***Stage B.***
- Hb 100 g/L (10 g/dL) or more and platelets 100 × 10^9/L or more and organomegaly greater than that defined for stage A (ie, 3 or more areas of nodal or organ enlargement).
- ***Stage C.***
- All patients who have Hb less than 100 g/L (10 g/dL) and/or a platelet count less than 100 × 10^9/L, irrespective of organomegaly.

Indications for treatment

(1) Progressive marrow failure

(2) Massive (i.e., > 6 cm below the left costal margin) or progressive or symptomatic

splenomegaly

(3) Massive nodes (i.e., >10 cm in longest diameter) or progressive or symptomatic lymphadenopathy

(4) Progressive lymphocytosis with an increase of >50% over a 2-month period, or lymphocyte doubling time (LDT) of less than 6 months. patients with initial blood lymphocyte counts of lessthan 30.000/µl may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

Indications for treatment

(5) Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other

standard therapy

(6) A minimum of any one of the following disease-related symptoms must be present:

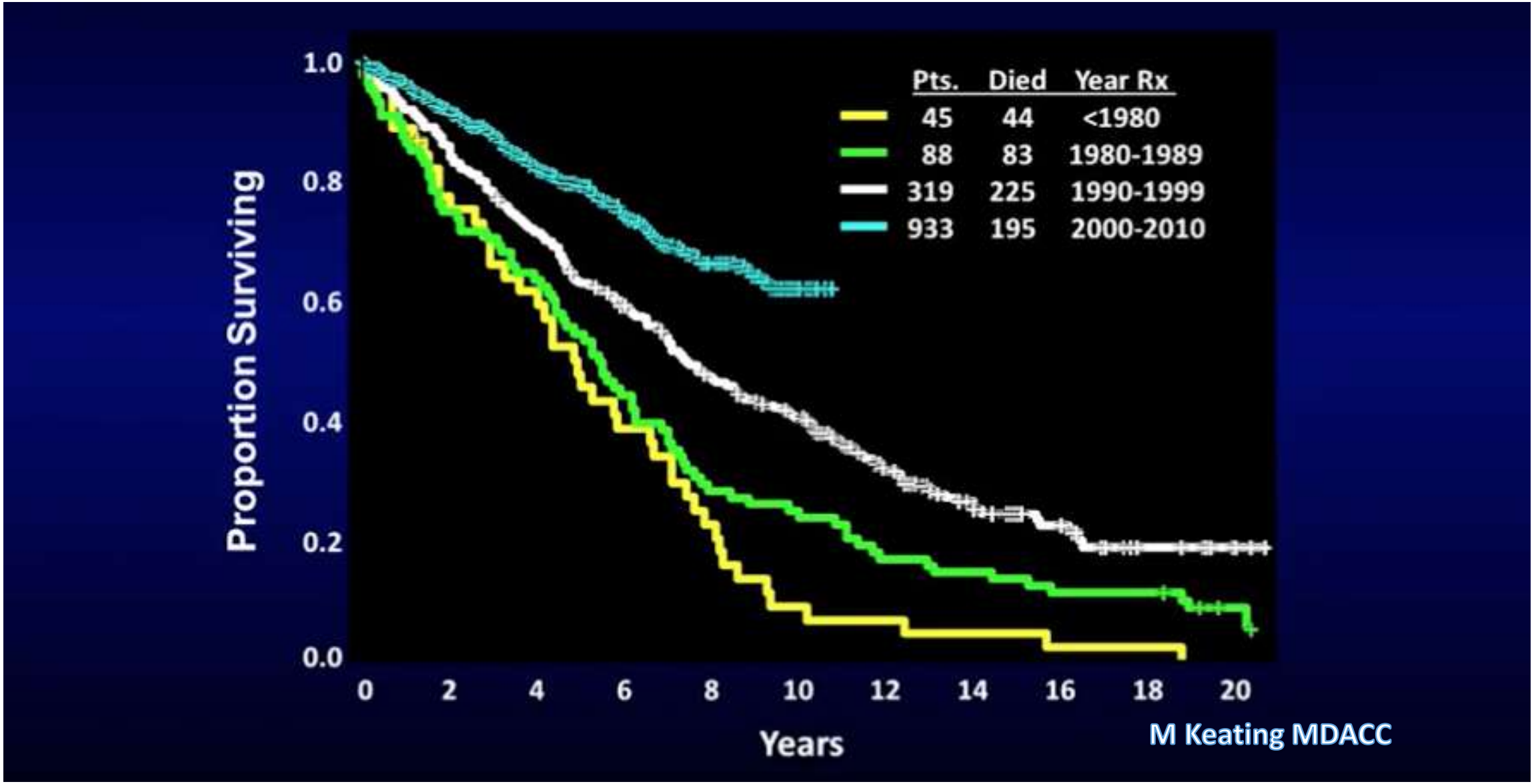
- (a) Unintentional weight loss ≥ 10% within the previous 6 months.
- (b) Significant fatigue (i.e., ECOG PS 2 or worse; cannot work or unable to perform
- usual activities).
- (c) Fevers of greater than 100.5° F or 38.0° C for 2 or more weeks without other
- evidence of infection.
- (d) Night sweats for more than 1 month without evidence of infection.

Remember!

- 25% of patients will never require treatment and have normal life expectancy
- 46% are over 75
- The only prognostic factor that really influences treatment is p53

Watch and wait in CLL

Inc. slides c/o MD Anderson


Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
20
Years
Pts. Died Year Rx
45 44 <1980
88 83 1980-1989
319 225 1990-1999
933 195 2000-2010
M Keating MDACC

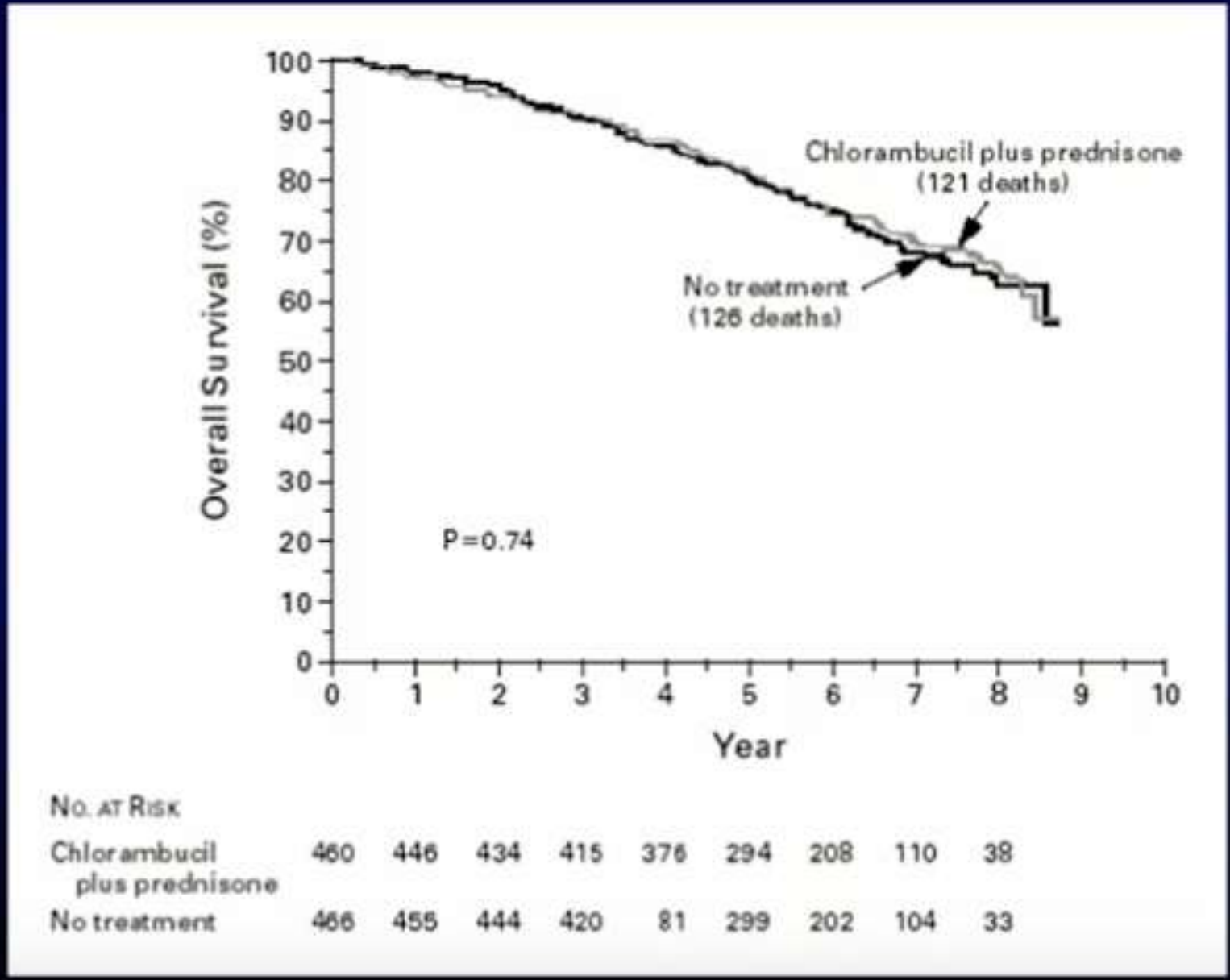
Change in Natural History

- Increase in overall survival for patients as a group
- By stage, no benefit for Binet A and B, but benefit seen for Binet stage C
- Shift to earlier stage disease at diagnosis:

Cohort	% Stage A	Survival
I (1970-1979):	26.3%	38 months
II (1980-1989):	50.3%	54 months
III (1990-1998):	72.0%	93 months

Mollica 2001

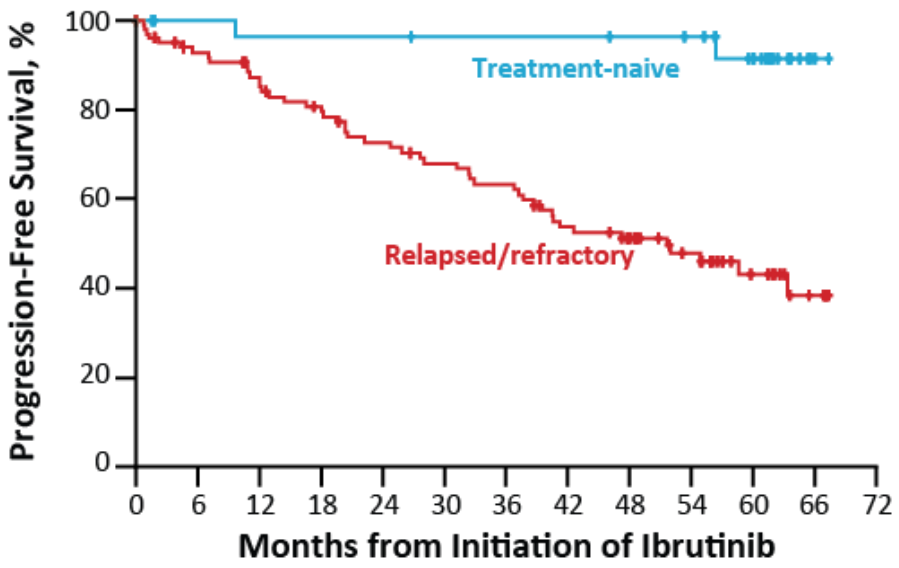
Dighiero G NEJM 1998:338:1506



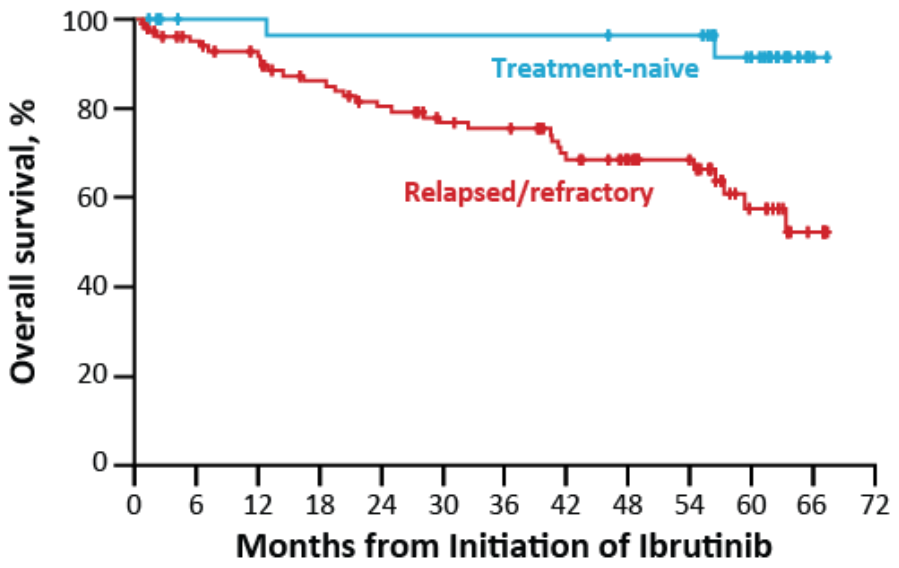
- **FCR 300:**
  - Richter's transformation = 24 (8%)
  - Hematologic malignancy = 19 (6.3%)
  - Other cancers = 63 (21%)
- **This includes 71% of deaths in first remission**
- **40% of deaths of CLL patients are associated with second solid tumors, acute leukemia/MDS or Richter's transformation**

Survival Outcomes: Overall Population

Progression-Free Survival



Overall Survival

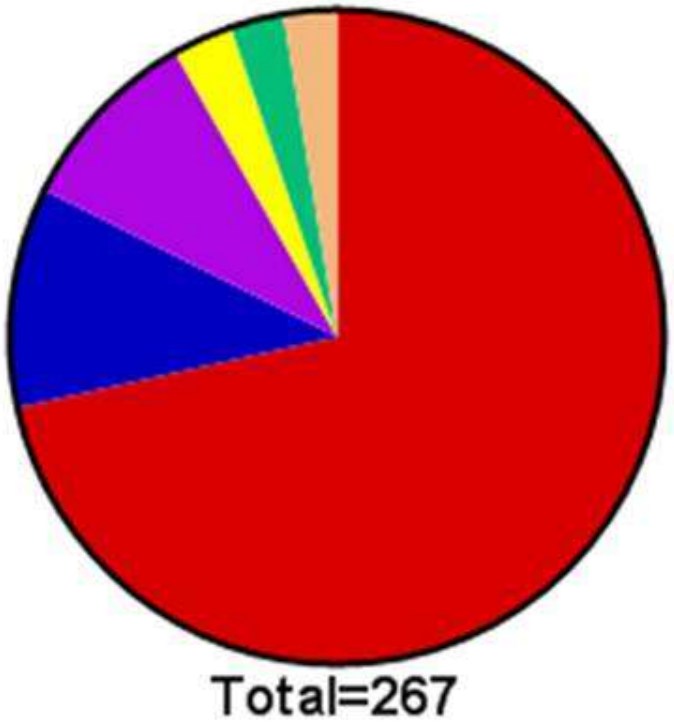


	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

NR, not reached.

Reasons for Discontinuation



- Remaining on Study (N=191)
- Progressive Disease (N=29)
- Infection (N=25)
- Toxicity (N=8)
- Other (N=7)
- Transplant/Therapy Elsewhere (N=7)

BTK and PLCγ2 Mutations

- Richter's Transformation
  - Ion Torrent for BTK and PLCγ2 performed on blood in 6 patients, and transformed lymph node in 1 patient
    - Lymph node did not have either mutation; blood showed BTK mutations in 2 patients (both also had increasing WBC)
- CLL Progression
  - Ion Torrent performed on blood for 9 patients, marrow for 1
    - Previously reported 1 patient with BTK C481S, 1 with BTK C481S and PLCγ2 S707Y, L845F, R665W, 1 with PLCγ2 R665W
    - 5 additional with C481 (1C481F, 4 C481S), 1 BTK C481S and PLCγ2 D1140G, 1 PLCγ2 R665W, S707P, S707F, R742P, and L845fs

The CLL12 trial protocol: a placebo-controlled double-blind Phase III study of ibrutinib in the treatment of early-stage chronic lymphocytic leukemia patients with risk of early disease progression.

Langerbeins P[1], Bahlo J[1], Rhein C[1], Cramer P[1], Pflug N[1], Fischer K[1], Stilgenbauer S[2], Kreuzer KA[1], Wendtner CM[3], Eichhorst B[1], Hallek M[1].

Considerations before treatment- the 4 Ps

- Progression?
- Peripheral cytopenias
  - Marrow failure
  - Auto immune
- Performance status
- P53 and other prognostic markers

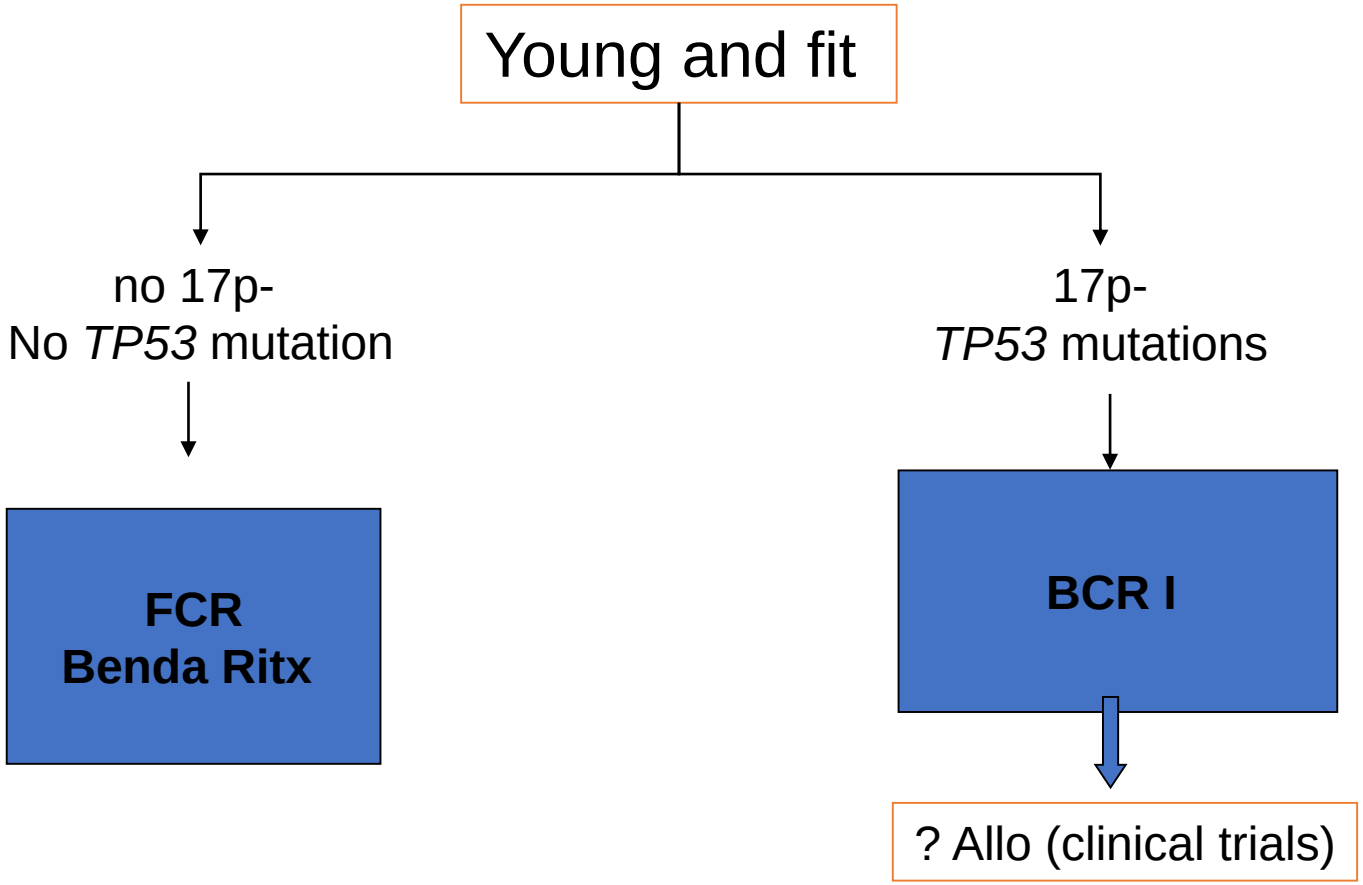
Progression

- 25% of patients will not progress and never require treatment
- More likely to be
  - Female
  - 13q deleted
  - CD38 and Zap 70 negative
  - Mutated IgVH

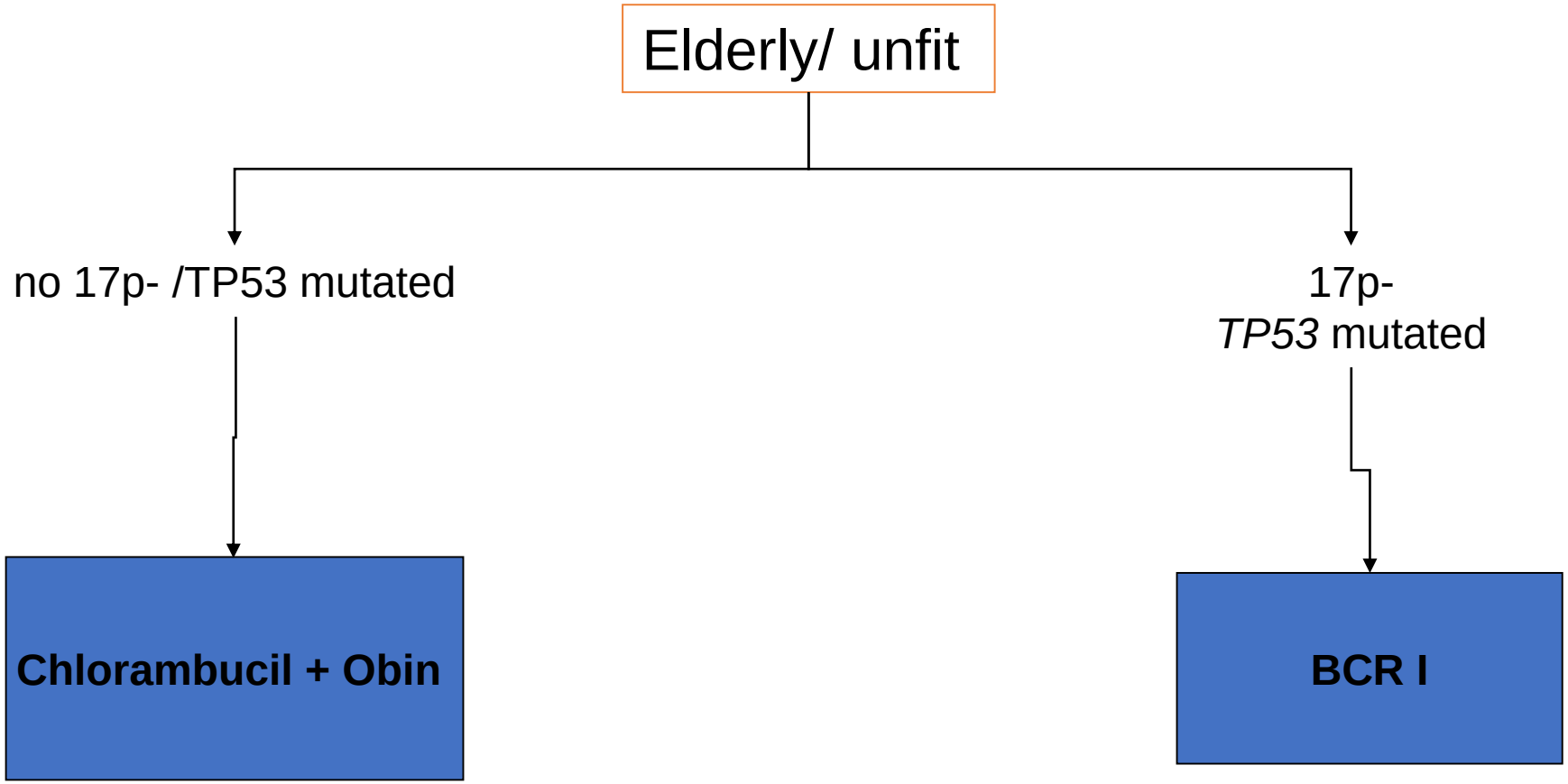
Peripheral cytopenias

- CLL patients exhibit T cell anergy and hypogammaglobulinaemia
- Increased likelihood of Auto immune haemolytic anaemia, ITP, Immune granulocytopenia
- These conditions can by severely exacerbated by purine analogue treatment

Options for first line treatment in CLL



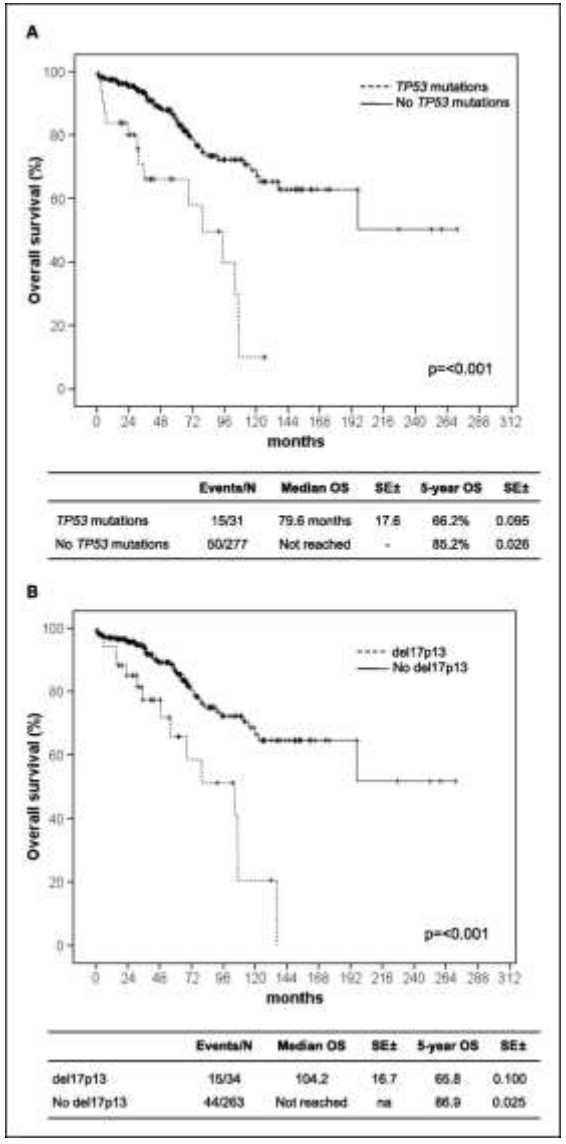
Options for first line treatment in CLL



P53

- Median survival less than 2 years
- Purine analogues unlikely to achieve durable if any remission

TP53 mutations and poor outcome in CLL

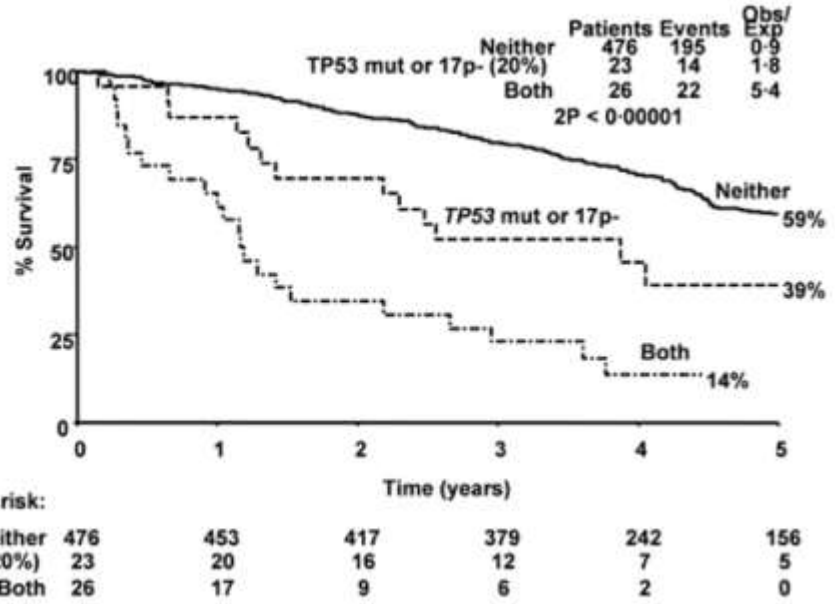


	Events/N	Median OS	SE±	5-year OS	SE±
TP53 mutations	15/31	79.6 months	17.6	66.2%	0.095
No TP53 mutations	50/277	Not reached	-	85.2%	0.026

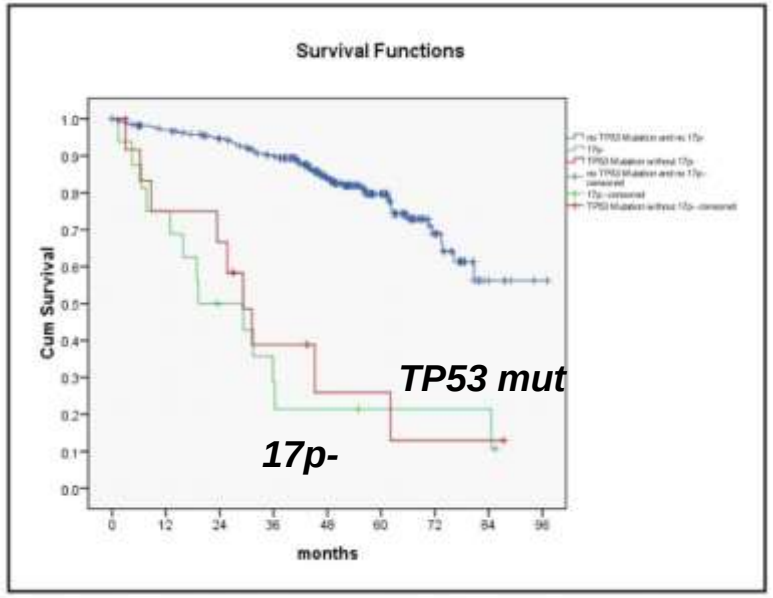
	Events/N	Median OS	SE±	5-year OS	SE±
del17p13	15/34	104.2	16.7	65.8	0.100
No del17p13	44/263	Not reached	na	86.9	0.025

Rossi, D. et al.
Clin Cancer Res 2009;15:995-1004

Gonzalez et al, UKCLL4; abs 784, ash, 2008



Stilgenbauer et al
ASH 2008 112: Abstract 2089



P53

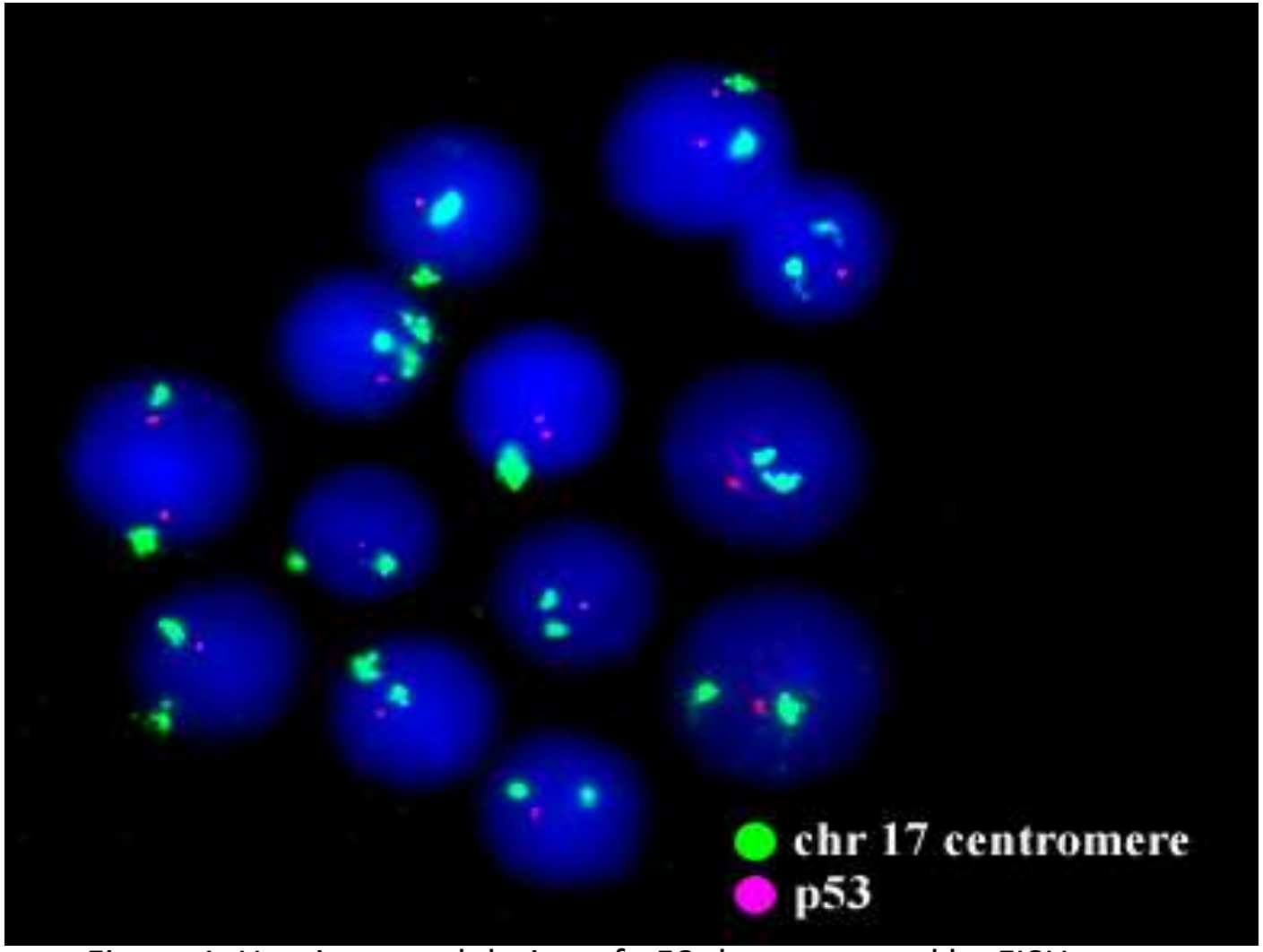
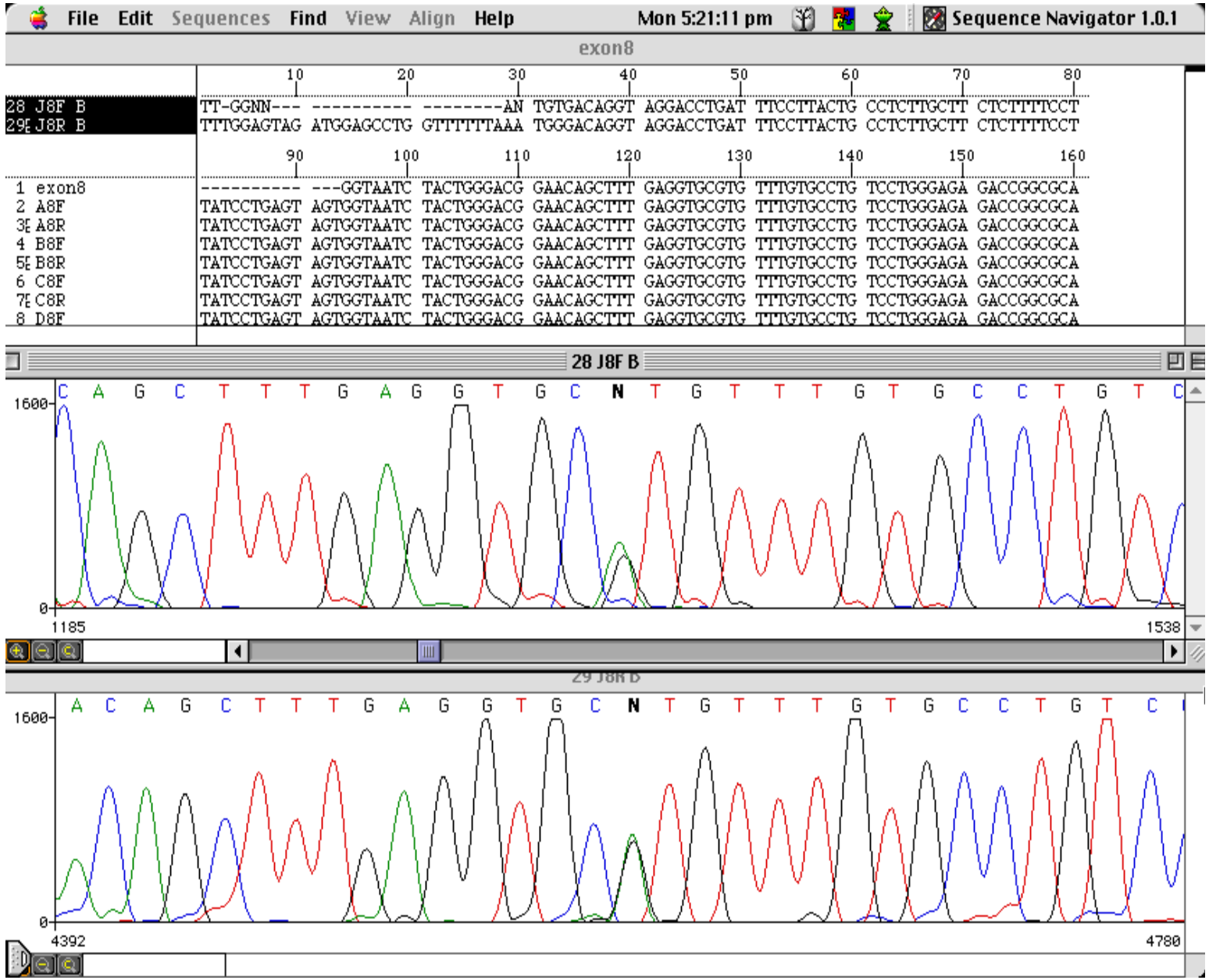


Figure 1. Hemizygous deletion of p53 demonstrated by FISH


File Edit Sequences Find View Align Help
Mon 5:21:11 pm
Sequence Navigator 1.0.1
exon8
28 J8F B
29 J8R B
1 exon8
2 A8F
3 A8R
4 B8F
5 B8R
6 C8F
7 C8R
8 D8F
28 J8F B
29 J8R B
1600
0
1185
1538
4392
4780

Current Guidelines

- BCSH revised CLL Guidelines 2015-

Pre-treatment assessment of disease status and biology (eg. role of bone marrow assessment, CT scans, TP53 disruption) remains as per current guideline. Note that CLL with lost TP53 function either by 17p deletion, assessed by FISH, or TP53 mutation, assessed by sequencing, does not respond well to genotoxic therapies. These will be referred to as cases with TP53 disruption throughout this document.

- ESMO Guidelines (Eichhorst et al 2015, Annals of Oncology)

Table 1. Diagnostic and staging work-up

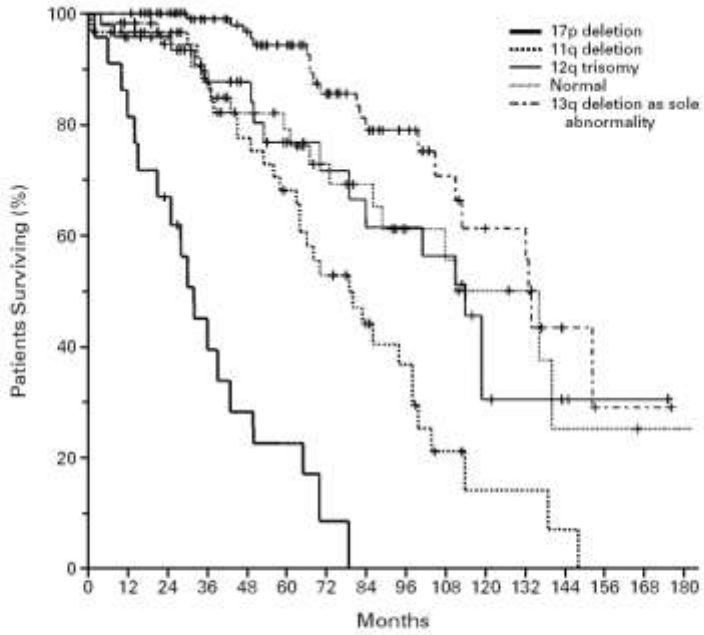
	Pretreatment evaluation	Response evaluation
History, physical examination and performance status	+	+
Complete blood count and differential	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+
Cytogenetics (FISH) for del (17p)/ molecular genetics for *TP53* mutation	+	–

Investigations performed before treatment prognostic

- FISH
  - P53, 11q23, 13q, 12+,
- CD38 / Zap 70
- B2microglobulin
  - IgVH mutation ? NOTCH ?BIRC ?SFB3

Genomic aberrations: Dohner 2000 NEJM

GENOMIC ABERRATIONS AND SURVIVAL IN CHRONIC LYMPHOCYTIC LEUKEMIA



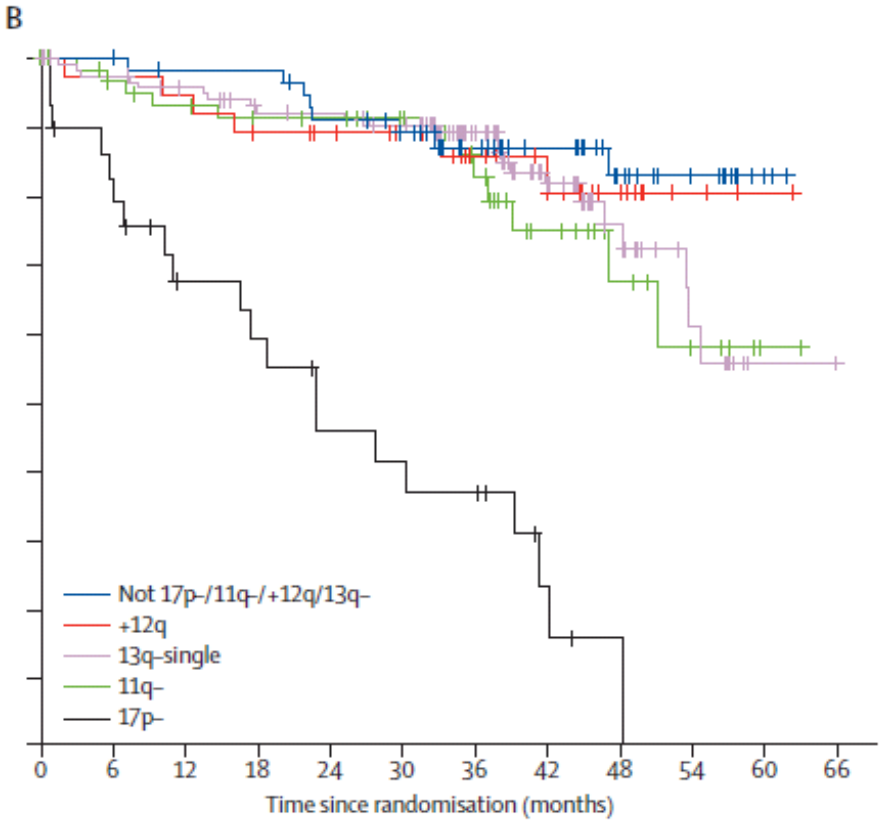
No. at Risk																
17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

Figure 1. Probability of Survival from the Date of Diagnosis among the Patients in the Five Genetic Categories.
The median survival times for the groups with 17p deletion, 11q deletion, 12q trisomy, normal karyotype, and 13q deletion as the sole abnormality were 32, 79, 114, 111, and 133 months, respectively. Twenty-five patients with various other chromosomal abnormalities are not included in the analysis.

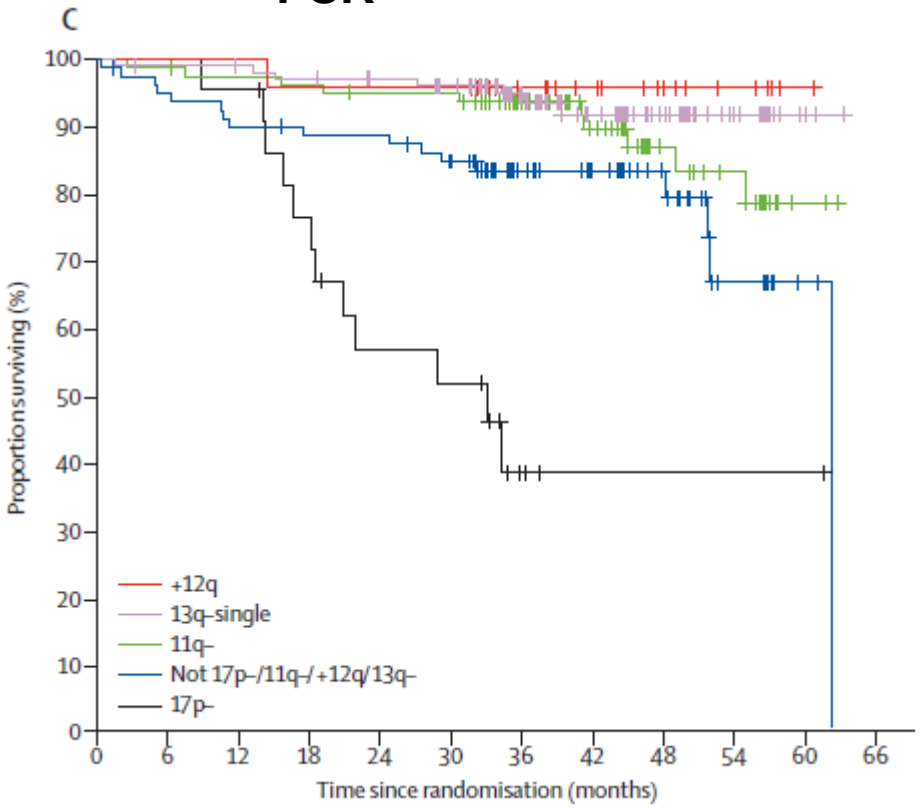
Addition of rituximab to fluda and CTX in CLL: a randomised, open-label, phase 3 trial

Overall survival

FC



FCR



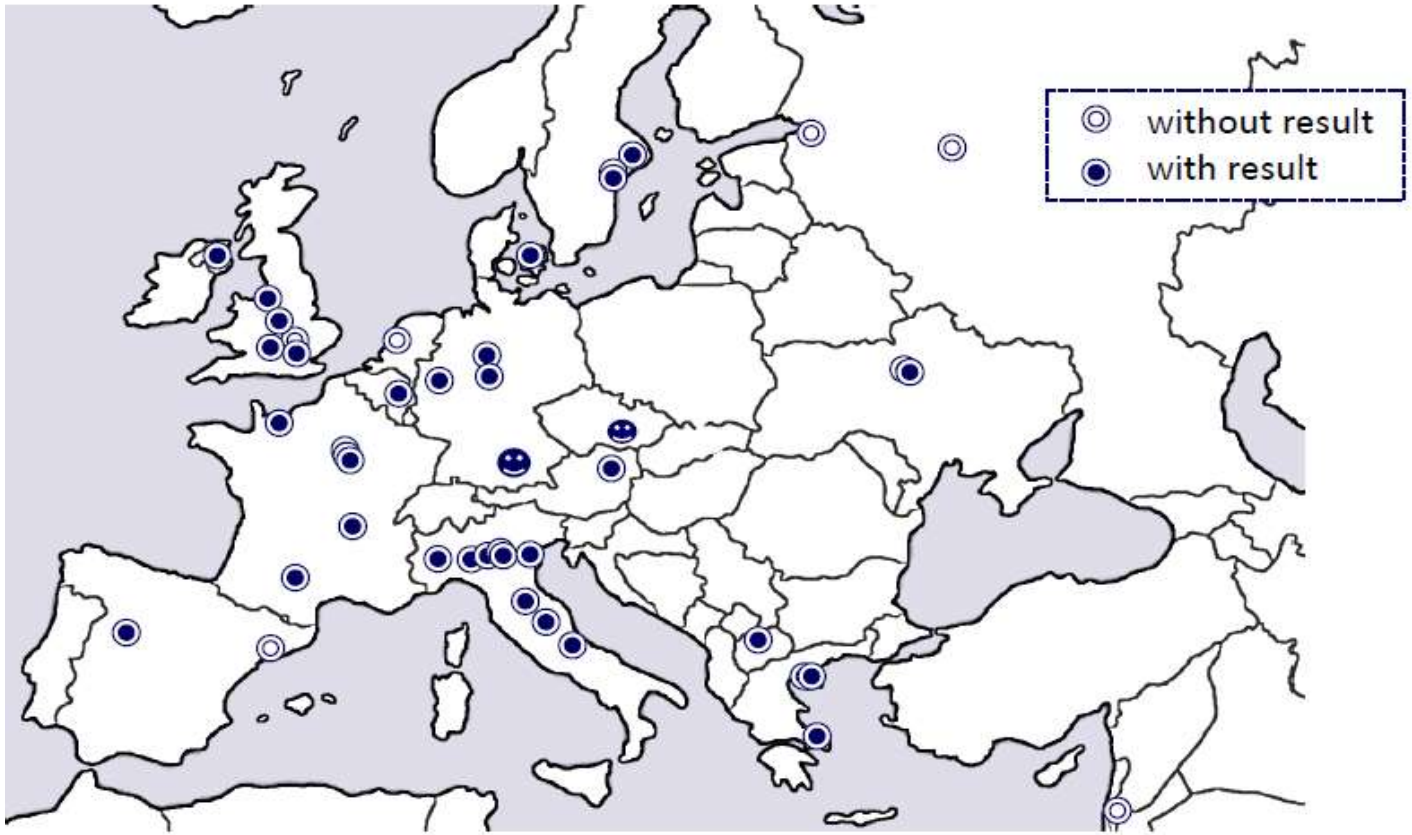
M Hallek et al Lancet 2010; 376: 1164–74

Participating Labs

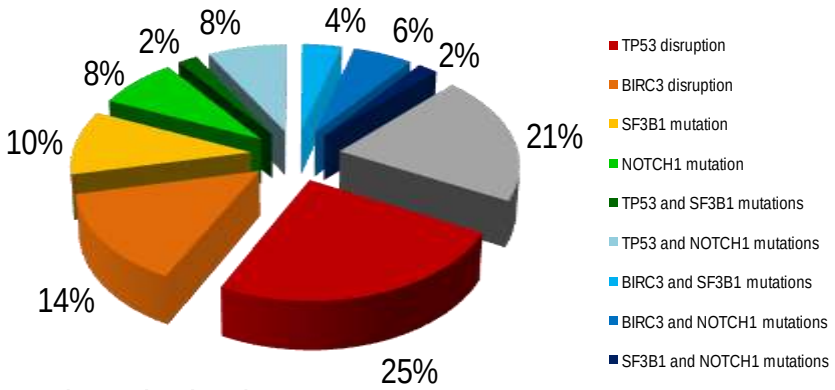
- 49 centers participated in the study and asked for samples

european research initiative on CLL
TP53 Certified Center

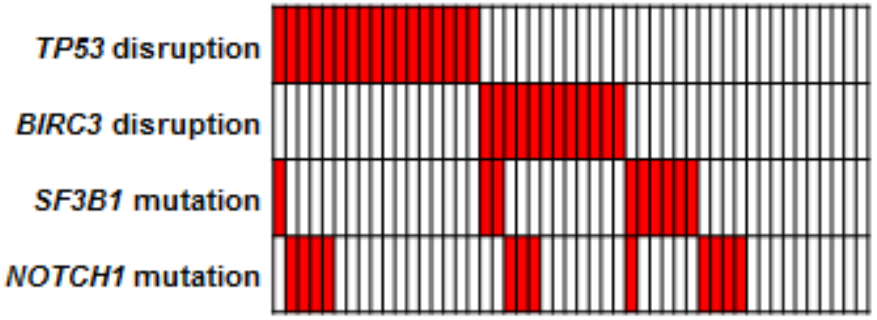
Belfast: ERIC TP53 Network Reference Centre



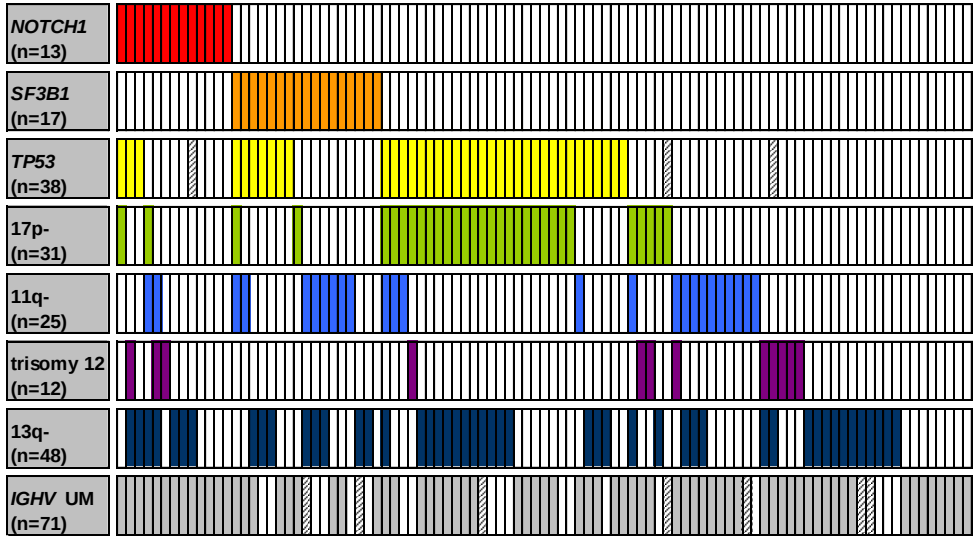
Molecular basis of fludarabine-refractory CLL



Rossi, et al. Blood 2012



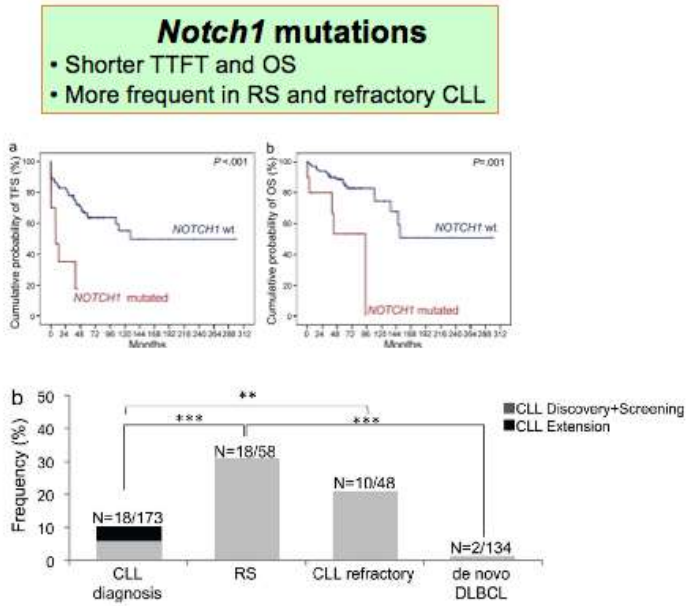
Fludarabine-refractory CLL (n=49)



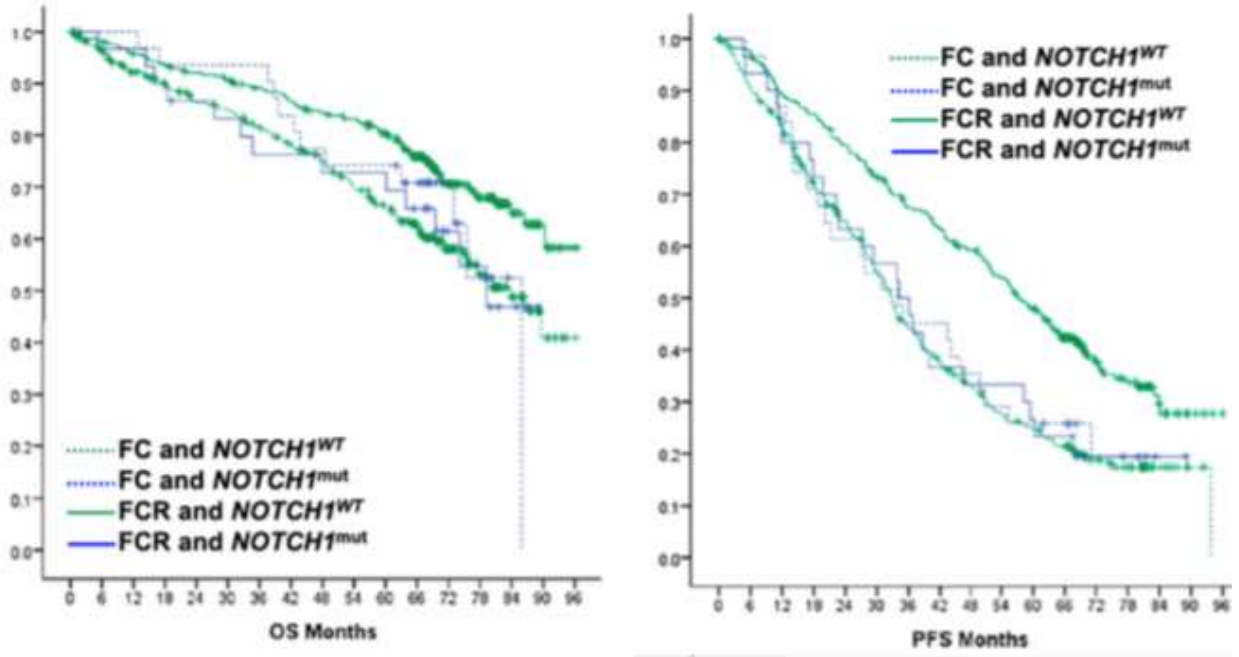
CLL2H
Alemtuzumab treatment in Fludarabine-refractory CLL (n=97)

Stilgenbauer et al ASH

Notch Mutations in CLL



Fabbri G et al. J Exp Med. 2011;208(7):1389-401



JEM

Figure 2.4.1 Kaplan-Meier curves for Overall Survival and Progression Free Survival from the CL

NOTCH1-mut patients seem not to benefit from the addition of rituximab to the protocol. Adapte

Stilgenbauer et al.[133]

CLL treatment options (in Ireland)

- Supportive :(Growth factors, Immunoglobulin replacement, transfusion)
- Chlorambucil
- Cyclophosphamide
- Fludarabine
- *Bendamustine*
- Monoclonal antibodies
  - CD 20
- Combination therapy
- *B Cell Receptor pathway inhibitors*
- Bone marrow transplantation
- *BCL-2 inhibitors*
- CAR –T cells

CLL 13

DEUTSCHE
STUDIENGRUPPE
Kontakt | Sitemap | Impressum | Login
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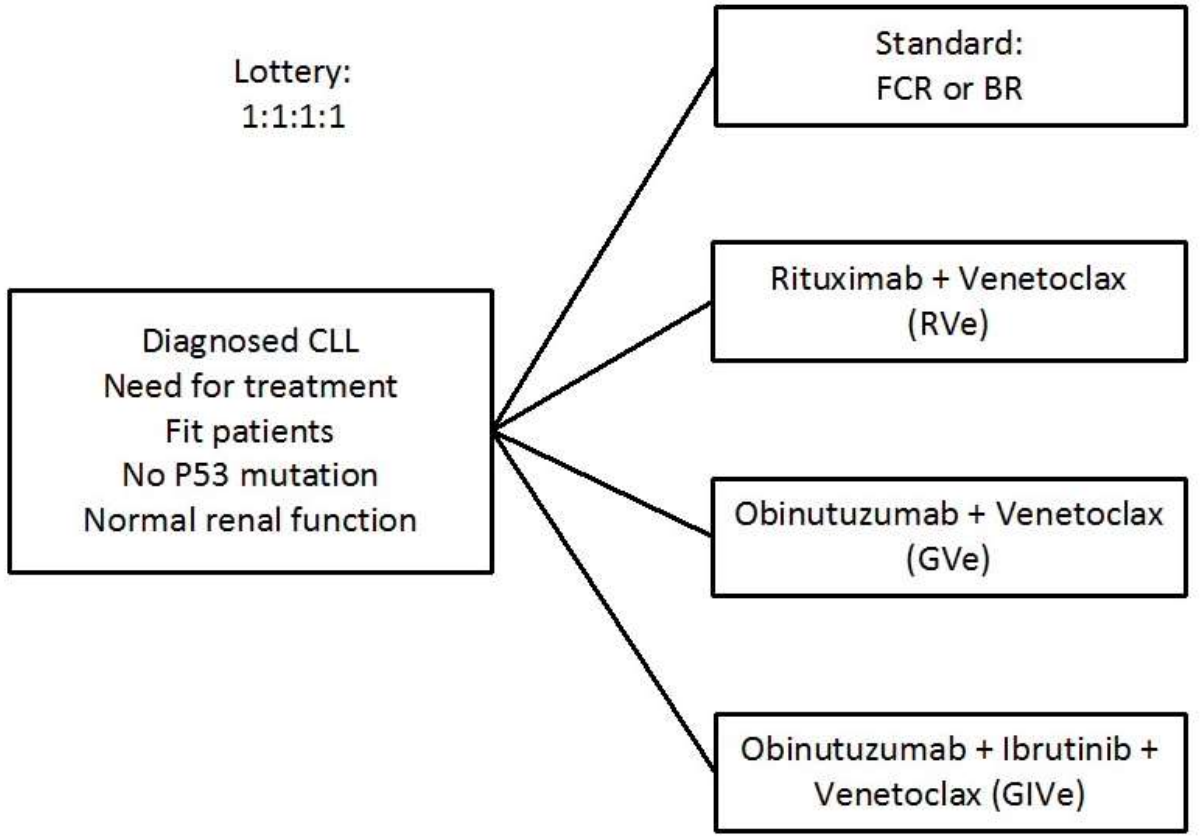
DCLLSG
Home
Aktuelles
Über uns
CLL Information
Studien
Patienten
Publikationen
Deutsch
CLL13 Trial
Title
A phase 3 multicenter, randomized, prospective, open-label trial of standard chemoimmunotherapy (FCR/BR) versus rituximab plus venetoclax (RVe) versus obinutuzumab (GA101) plus venetoclax (GVe) versus obinutuzumab plus ibrutinib plus venetoclax (GIVe) in fit patients with previously untreated chronic lymphocytic leukemia (CLL) without del(17p) or TP53 mutation

DCLLSG

CLL13

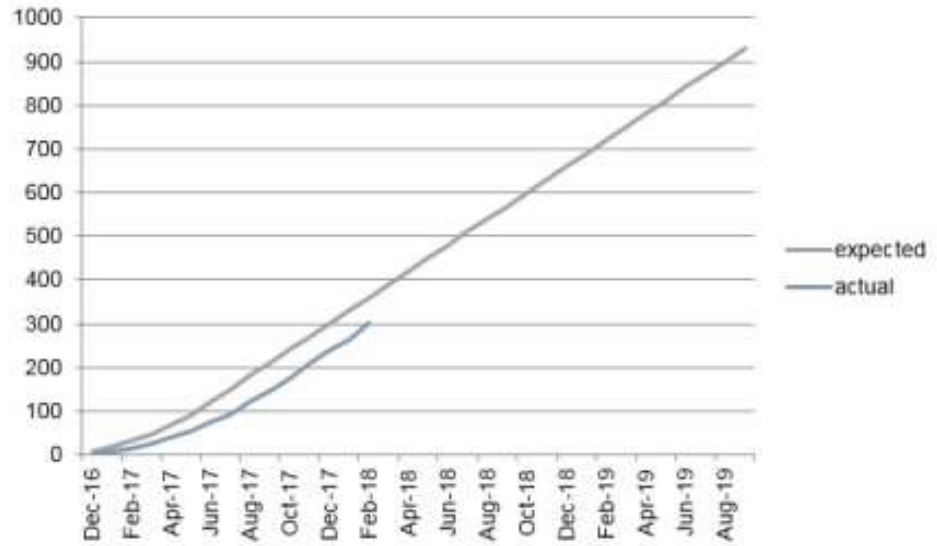


CLL13

Study Status (as of 1st March 2018)

Enrolment Status

Randomized patients (expected vs actual)



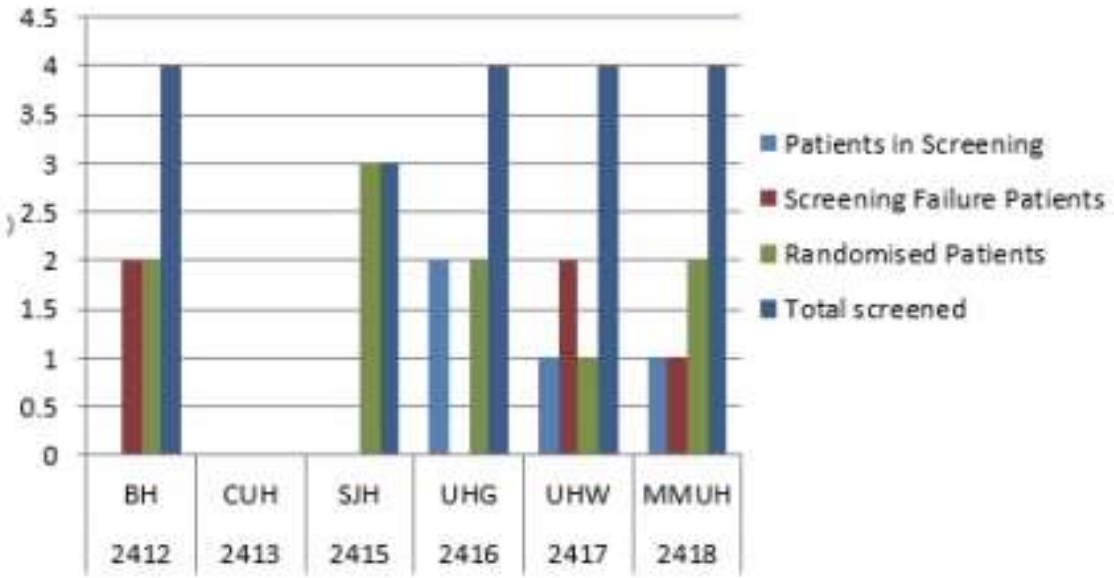
Site Activation and Enrolment

Global

Open Sites	138	
Ireland	6	
Denmark	9	
Germany	58	
Sweden	9	
Netherlands	28	
Belgium	5	
Austria	3	
Finland	5	
Switzerland	15	
Patients registered		389
Patients randomised		301
Screening Failures		57
End of Therapy		21
End of Study		6

CLL13

Patient Status per Site



Site Activation and Enrolment

Ireland

Open Sites	6
Total Screened	19
In Screening	4
Screened failed	5
Randomised	10

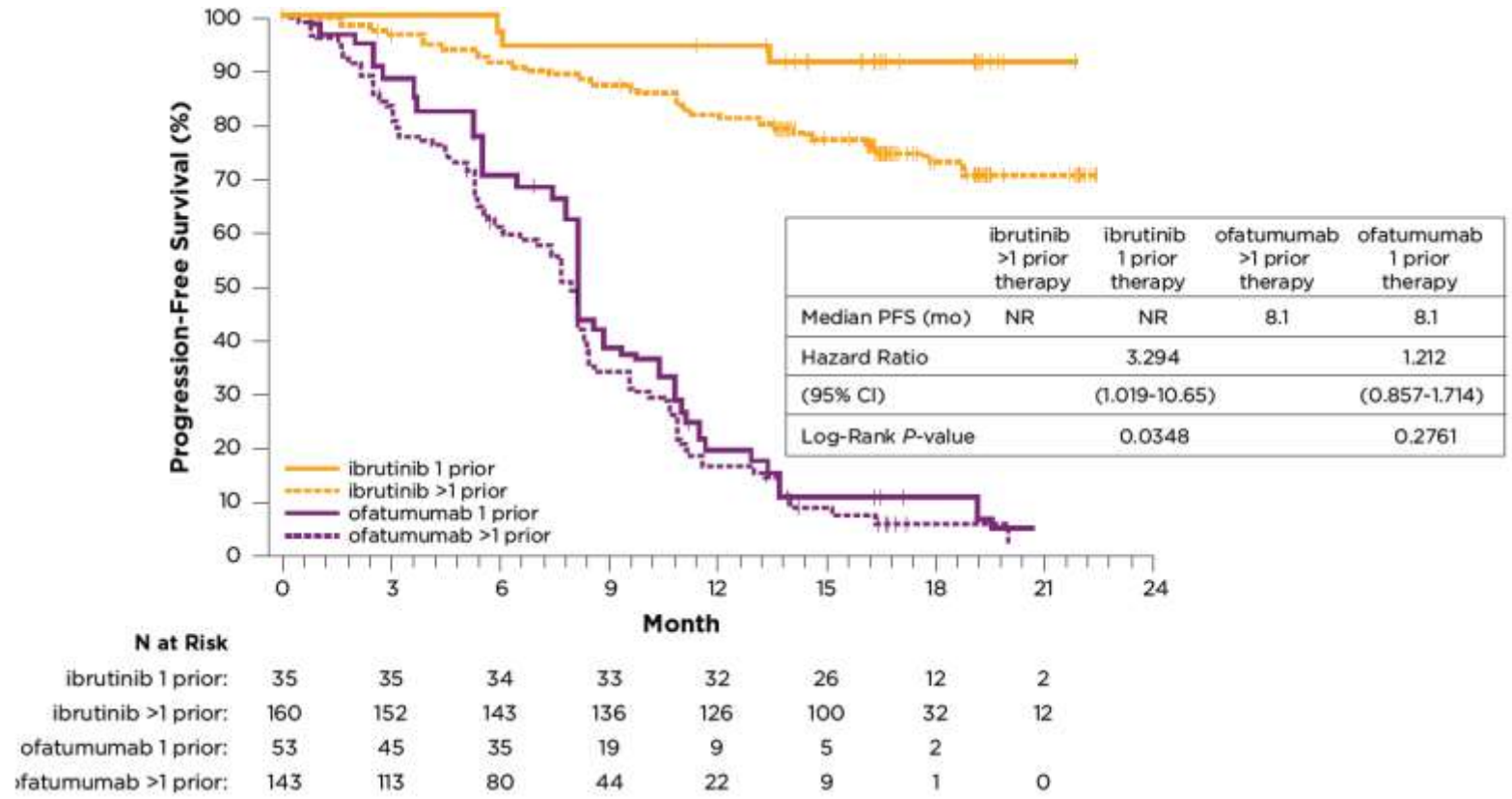
Cork University Hospital has been activated on 7th February 2018. Congratulations to Dr Derville O'Shea and all the CUH research team!

CTRIAL-IE 16-60 CLL13 / GAIA Study Newsletter Vol. 4 Mar 2018

Managing Relapse

Options in Ireland

PFS with Ibrutinib by Number of Prior Therapies



	ibrutinib >1 prior therapy	ibrutinib 1 prior therapy	ofatumumab >1 prior therapy	ofatumumab 1 prior therapy
Median PFS (mo)	NR	NR	8.1	8.1
Hazard Ratio		3.294		1.212
(95% CI)		(1.019-10.65)		(0.857-1.714)
Log-Rank *P*-value		0.0348		0.2761

N at Risk								
ibrutinib 1 prior:	35	35	34	33	32	26	12	2
ibrutinib >1 prior:	160	152	143	136	126	100	32	12
ofatumumab 1 prior:	53	45	35	19	9	5	2	
ofatumumab >1 prior:	143	113	80	44	22	9	1	0

- PFS was statistically significantly better for patients treated with ibrutinib in second-line vs later lines of therapy (p = 0.0348)

Brown JR, et al. ASH Meeting on Lymphoma Biology 2016; Abstract 7520 (Poster Presentation).

Venetoclax Plus Rituximab is Superior to Bendamustine Plus Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia – Results from Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study

Adapted from the Seymour presentation at ASH on December 12, 201

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The American Society of Hematology – 59th Annual Meeting and Exposition
Atlanta, Georgia ● December 9–12, 2017

MURANO Study Design

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region

R 1:1

C1D1

VEN 5-week ramp-up

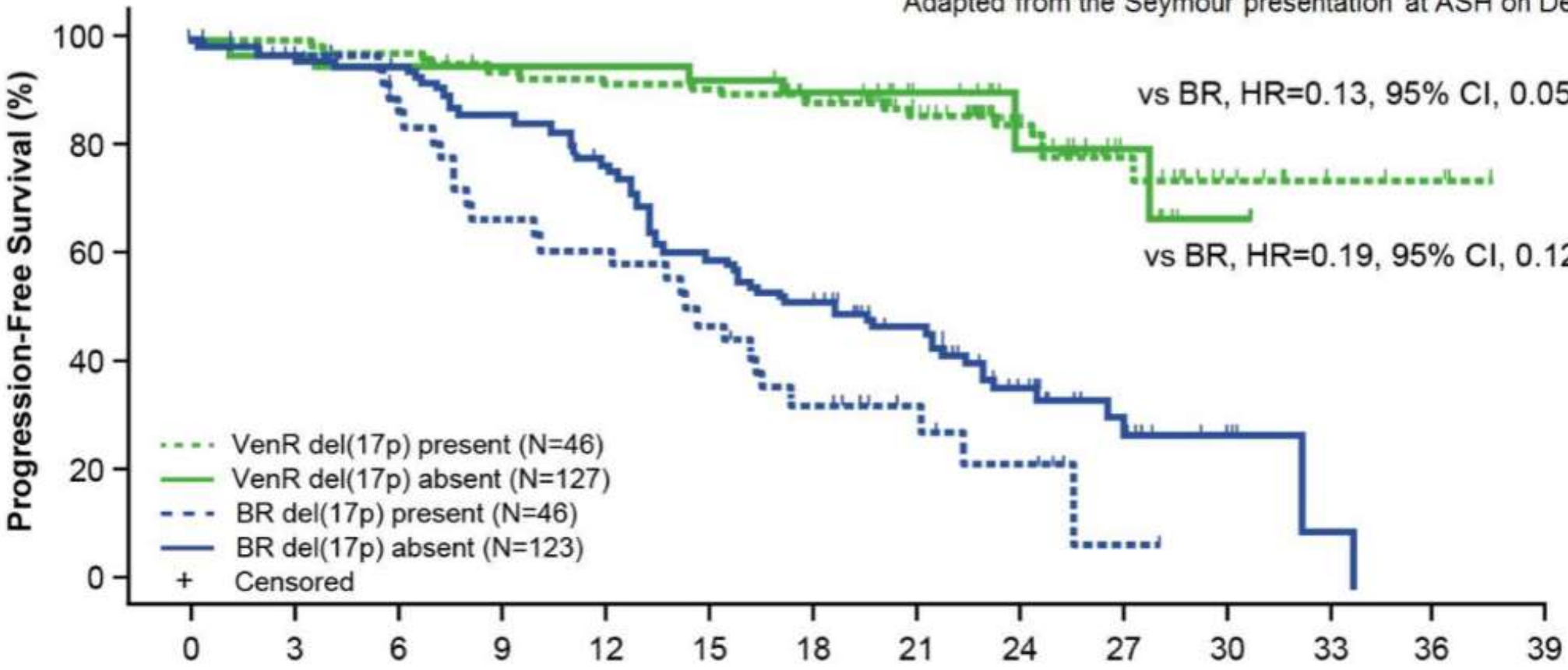
Venetoclax 400 mg orally once daily to PD, cessation for toxicity, or max. 2 years from Cycle1 Day1

Rituximab
375 mg/m² Day 1, Cycle 1;
500 mg/m² Day 1 Cycles 2–6

Bendamustine
70 mg/m² Days 1 and 2 Cycles 1–6
+
Rituximab

Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)

Adapted from the Seymour presentation at ASH on December 12, 2017



No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Venice -1

M15-550 Study March 2017 update! AKA VENICE 1

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) Including Those with the 17p Deletion or TP53 Mutation OR Those Who Have Received Prior Treatment with a B-Cell Receptor Inhibitor

ear Investigators and study teams,
don't know about you, but I am in shock that I need to be getting into Easter mode! This year is flying by at a rate of knots and as the sunny weather tentatively peeps its head around the corner I am writing to give you a study pdate on what happened in the UK and Ireland in March. Thank you all so much for your hard work in identifying patients, setting up your sites and in data entry. In particular I would like to acknowledge the following 2 Investigators nd teams.

Dr. Patrick Thornton **and team at Beaumont hospital, Dublin who enrolled their second patient**

Dr. Francesco Forconi **and team in Southampton who screened their 3rd patient.**

hat's 6 enrolled and 1 in screening.

PI	Date opened	In screening	Enrolled	CRA
Dr. Marian Macheta	15 Nov 16	0	0	Elena Townson
Dr. Abraham Jacob	5 Dec 16	0	1	Lucinda Driscoll
Dr. Francesco Forconi	6 Dec 16	1	2	Elena Townson
Prof Elisabeth Vandenberghe	7 Dec 16	0	1	Christine Murphy
Dr. Patrick Thornton	27 Jan 17	0	2	Christine Murphy

Allogeneic SCT

- non myeloablative transplant in CLL up to the age of 65 achieve a 75% overall survival (OS) and 70% relapse free survival (RFS) at 3 years.
- The transplant related mortality was 7%, 7% suffered severe GVHD and 50% chronic GVHD.
- In prospective studies there are no significant outcome differences in choice of donor whether it is sibling or alternative donor
- The adverse prognostic outcome of 17p deletions is not observed following allogeneic SCT

Summary of Indications for Allo-HCT in High-Risk CLL at Time of Transplant Evaluation

	Clinical Scenarios	Strength of Recommendation
High-risk CLL at time of transplant evaluation	The panel **does not recommend** offering an allogeneic HCT in the front-line consolidation setting	Strong
	The panel **does not recommend** offering an allogeneic HCT for patients who relapse after front-line therapy and demonstrate sensitive disease after second line therapy (not BCR inhibitors)	Weak
	The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line (not BCR inhibitors), but show an objective response to BCR inhibitors or to a clinical trial	Strong
	The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line therapy including BCR inhibitors (not BCL-2 inhibitors), but show an objective response to BCL-2 inhibitors, namely venetoclax, or to a clinical trial	Strong
	The panel **recommends** allogeneic HCT when there is lack of response or there is progression after BCL-2 inhibitors, namely venetoclax	Strong
Richter transformation	The panel **recommends** allogeneic HCT for patients with Richter transformation after achieving an objective response to anthracycline-based chemotherapy	Strong
Purine analogue relapsed and/or refractory disease	The panel **considers** purine analogue relapsed and/or refractory disease high-risk disease but **not** an indication for immediate allogeneic HCT	Strong

High-risk is defined as the presence of Del17p and/or *TP53* mutations and/or complex karyotype.

Thank you