B-CLL

CHRONIC LYMPHOCYTIC

LEUKEMIA

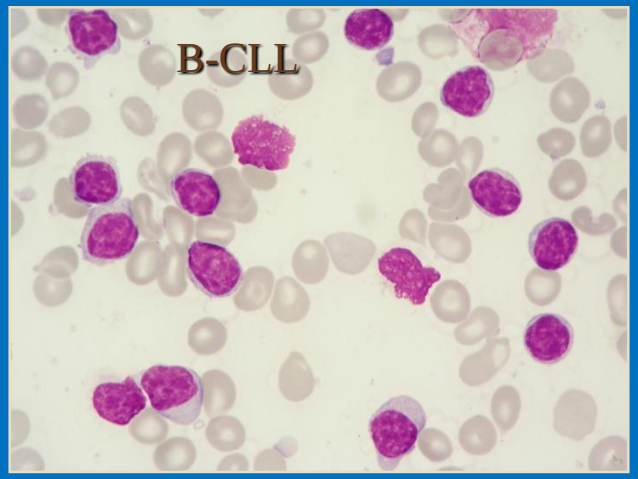
B-TYPE

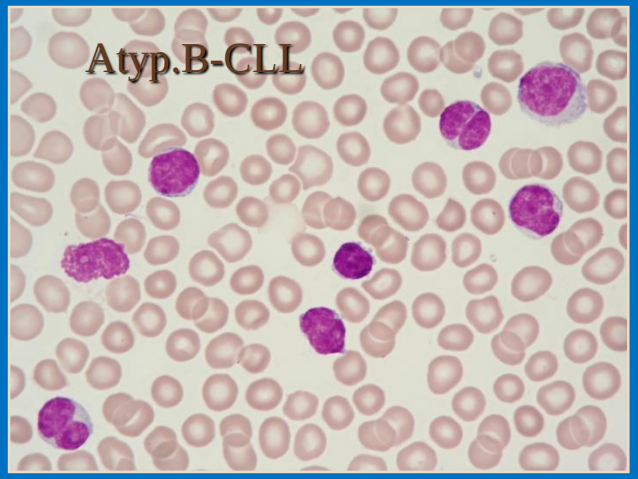
Diagnostic criteria B-CLL

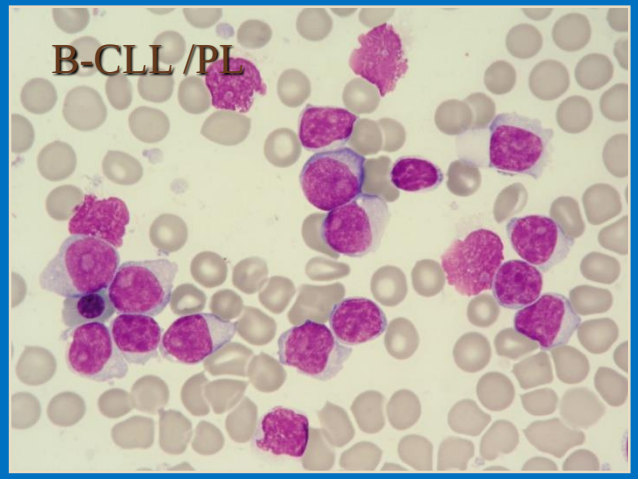
(IWCLL , NCI-WG guidelines, 2008)

- **CBC: abs. B-lymphocytosis in peripheral blood**

  $\geq 5 \times 10^9$ / l lasting at least 3 months
- **Cytologic findings: small mature lymphocytes, atypical cells + prolymphocytes < 55%.**
- **Imunophenotype: coexpress. CD5 + B markers CD19, CD20, CD23. Low expression of CD20, CD79b, sIg.**
- **<u>Bone marrow evaluation is not required for the diagnosis!</u>**







Datum a čas odběru: 12.6.2013 7:14

	Název metody			REF.MEZE	Ref.meze	Rozměr
Krevní obraz-periferní krev						
AM	Leukocyty	WBC	66,86	| | |*	4,10 - 10,20	10^9/l
AM	Erytrocyty	RBC	4,59	| |*| |	4,19 - 5,75	10^12/l
AM	Hemoglobin	HGB	130	|* | |	135 - 174	g/l
AM	Hematokrit	HCT	0,409	| |*| |	0,390 - 0,510	1
AM	Stř.obj.erytr.	MCV	89,1	| |*| |	82,6 - 98,4	fl
AM	Barvivo erytr.	MCH	28,3	| |*| |	28,0 - 34,6	pg
AM	Stř.barev.kon.	MCHC	318	|* | |	329 - 364	g/l
AM	Distr.křiv.ery	RDW	16,4	| | | *|	12,1 - 15,0	%
AM	Trombocyty	PLT	170	| |*| |	142 - 327	10^9/l
AM	Stř.obj.trombo	MPV	8,8	| |*| |	7,0 - 10,8	fl
AM	Tromb.hematokrit	PCT	0,150	| |*| |	0,127 - 0,277	1
AM	Distr.křiv.tr.	PDW	9,7	| |*| |	9,0 - 17,0	fl
Dif.stroj. relativní-periferní krev						
	Neutrofily	NE	5,2	|* | |	50,0 - 75,0	%
	Lymfocyty	LY	87,8	| | | *|	25,0 - 40,0	%
	Monocyty	MO	6,6	| |*| |	3,0 - 8,0	%
AM	Eozinofily	EO	0,3	|* | |	1,0 - 5,0	%
AM	Bazofily	BA	0,1	| |*| |	0,0 - 1,0	%
Dif.stroj. absolutní-periferní krev						
	Neutrofily abs.	NE	3,46	| |*| |	1,80 - 7,00	10^9/l
	Lymfocyty abs.	LY	58,73	| | | |*	1,00 - 4,80	10^9/l
	Monocyty abs.	MO	4,39	| | | |*	0,10 - 0,80	10^9/l
AM	Eozinofily abs.	EO	0,18	| |*| |	0,00 - 0,45	10^9/l
AM	Bazofily abs.	BA	0,10	| |*| |	0,00 - 0,20	10^9/l

Differential diagnosis of (CD5+CD23+CD19+) B-lymphocytic clone in PB

Abs. lymphocytosis ≥ $5x10^9/l$

↓

B-CLL

Abs. lymphocytosis < $5x10^9/l$

+

Lymphadenomegaly
+/- HSmegaly

↓

SLL / CLL

-

Lymphadenomegaly
HSmegaly

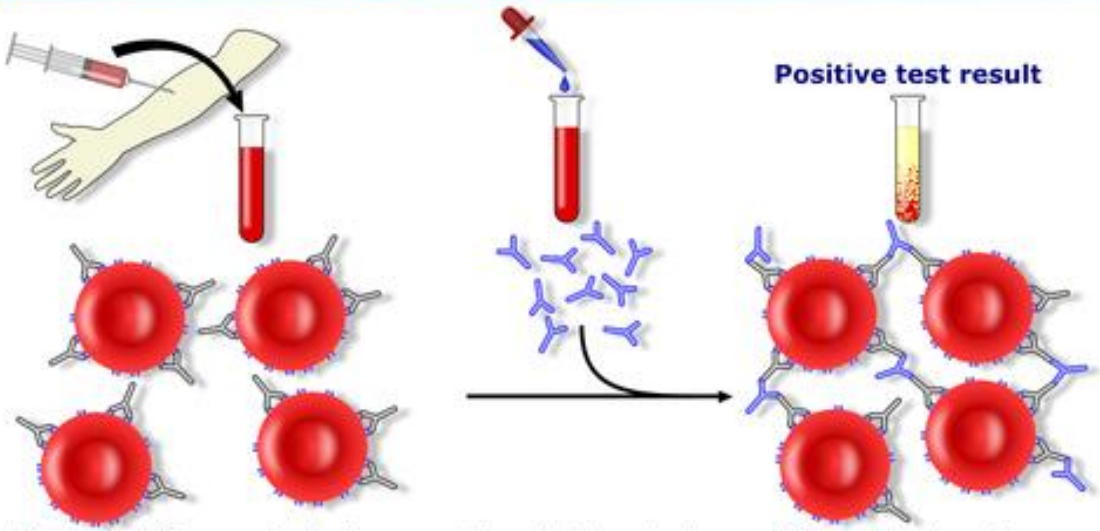
↓

Monoclonal B-lymphocytosis

Which evaluation ?

- Medical history
- Physical evaluation
- CBC, biochemistry
- Imunophenotypisation (CD 38)
- X ray L+H, abd. sono, CT
- Cytogenetics
- Mutation IgHV
- Coombs test
- *BM*

Direct Coombs test / Direct antiglobulin test

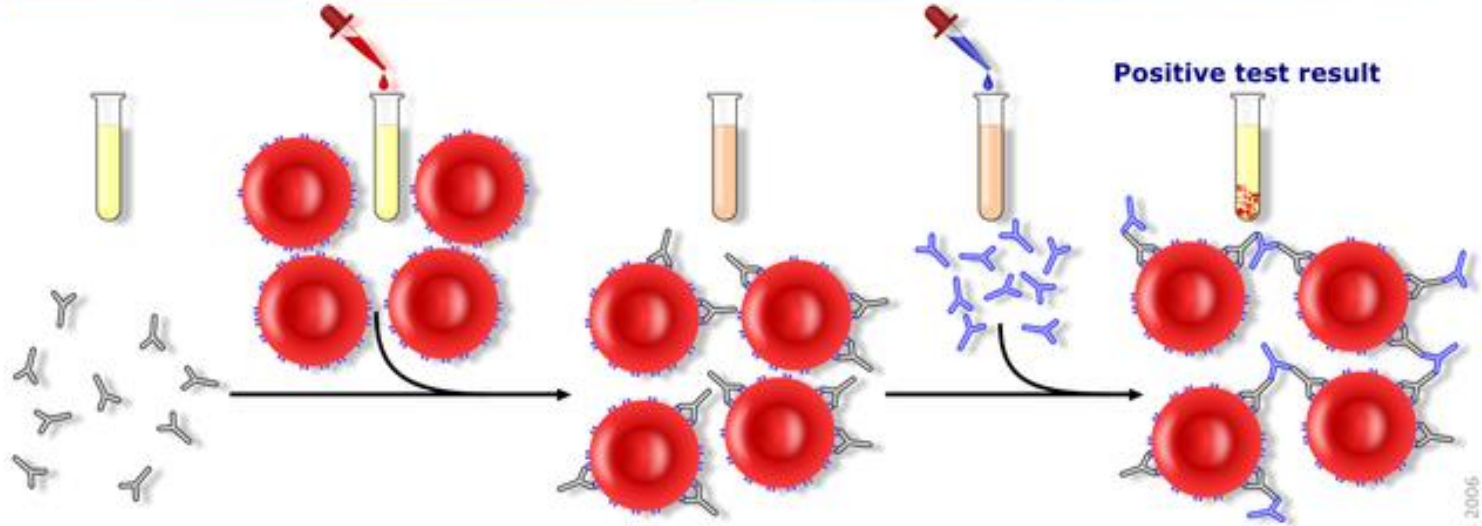


Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (*Coombs reagent*).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Indirect Coombs test / Indirect antiglobulin test



Recipient's serum is obtained, containing antibodies (Ig's).

Donor's blood sample is added to the tube with serum.

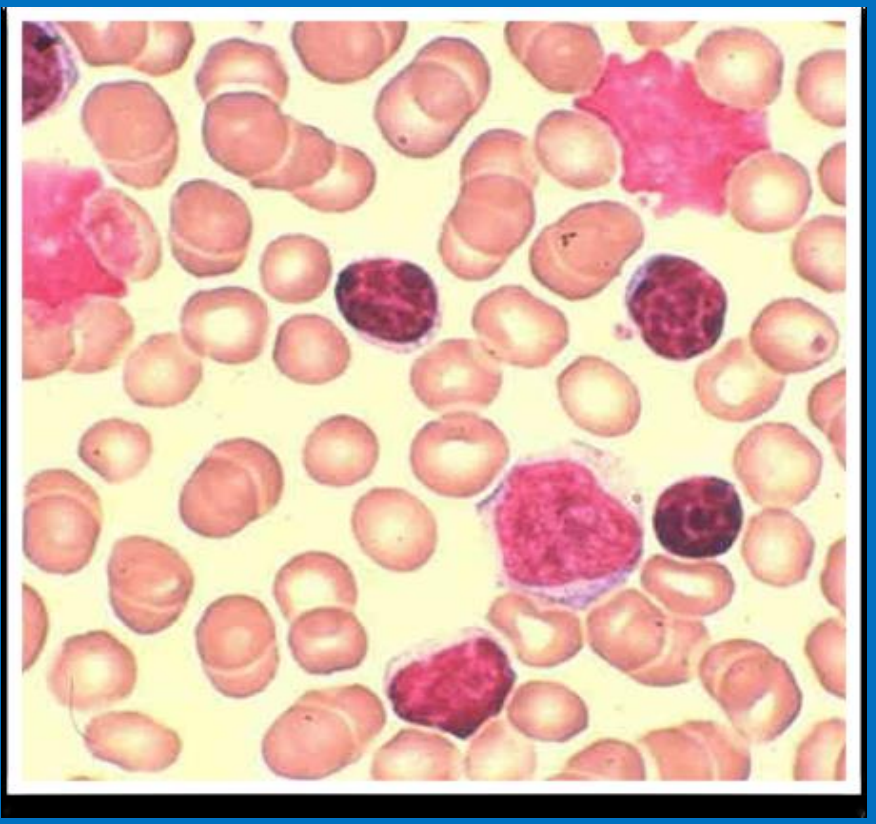
Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (*Coombs antibodies*) are added to the solution.

Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.

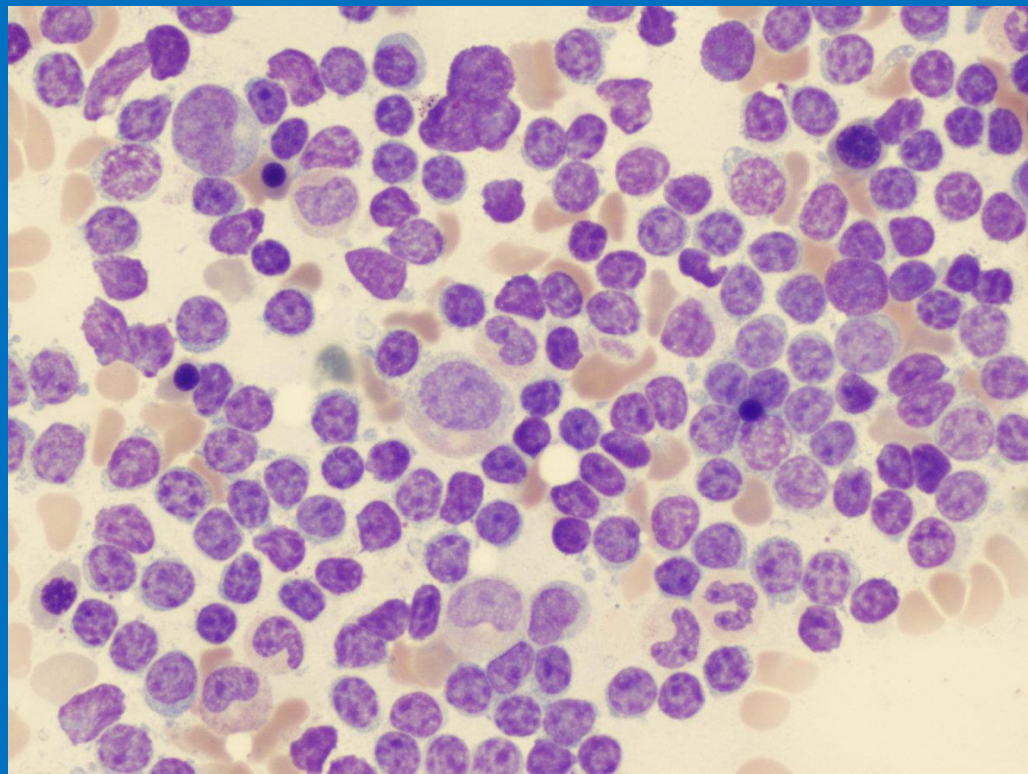
Patient before the dg.

- Symptomeless
- Adenomegaly, hepatosplenomegaly
  - Weight loss
  - Febriles
  - Itching
  - Sweating
  - Dyspnoea
- Icterus



Gumprecht (nuclear) shadows

BM - chronic lymphocytic leukemia

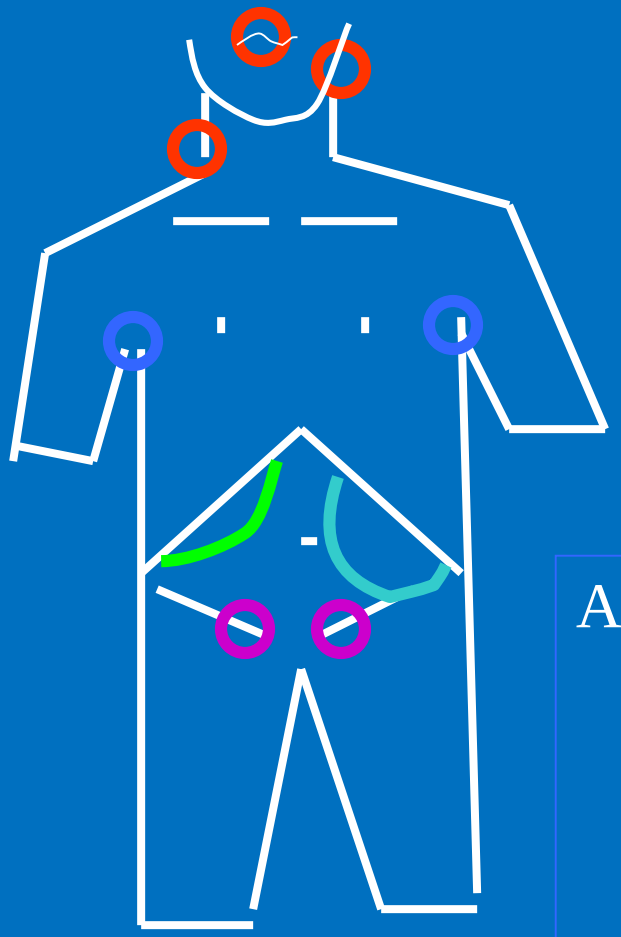


Staging B-CLL - Rai (Rai,1975)

Stage	Physical and laboratory parameters	Median survival
„Low risk“		
0	Lymphocytosis $\geq 5 \times 10^9 / l$ PB	12-15 years
„Intermediate risk“		
I	Lymphocytosis and lymphadenomegaly	9 years
II	Lymphocytosis ± LM + hepatomegaly and/or splenomegaly	5 years
„High risk“		
III	Lymphocytosis ± LM ± HS + anaemia (Hgb < 110)	1-2 years
IV	Lymphocytosis ± LM ± HS ± A + thrombocytopenia (Plt < 100)	<1-2 years

Staging B-CLL Binet (Binet,1981)

Affected areas	Medián přežití
Stadge **A**: < 3 areas	>10y
Stadge **B**: ≥ 3 areas	5y
Bone marrow failure	
Stadge **C**: Hb <100 g/l Tr <100 G/l	1,5-3y



CT is not necessary for this staging!

Indication to start the therapy at B-CLL

- Progressive disease !
  - Clinical stage III and IV Rai (C Binet)
  - B symptoms
  - LDT < 6 month
  - Bulky disease, extrem splenomegaly
  - Refractery autoimunne cytopenia
  - Richter syndrom

Indication to start therapy

Patients in early stages of CLL without clinical signs of the disease or the progression should be monitored and the treatment should be reserved for the advanced stages or symptomatic or progressive cases. (Halek et al,Blood 2008, 111, 5446-5456)

Leucocytosis (not fast progressing) is not the indication for the treatment !!!

Biologic prognostic features should NOT to be used as a criterion for the treatment initiation outside of clinical trials.

Watch and wait

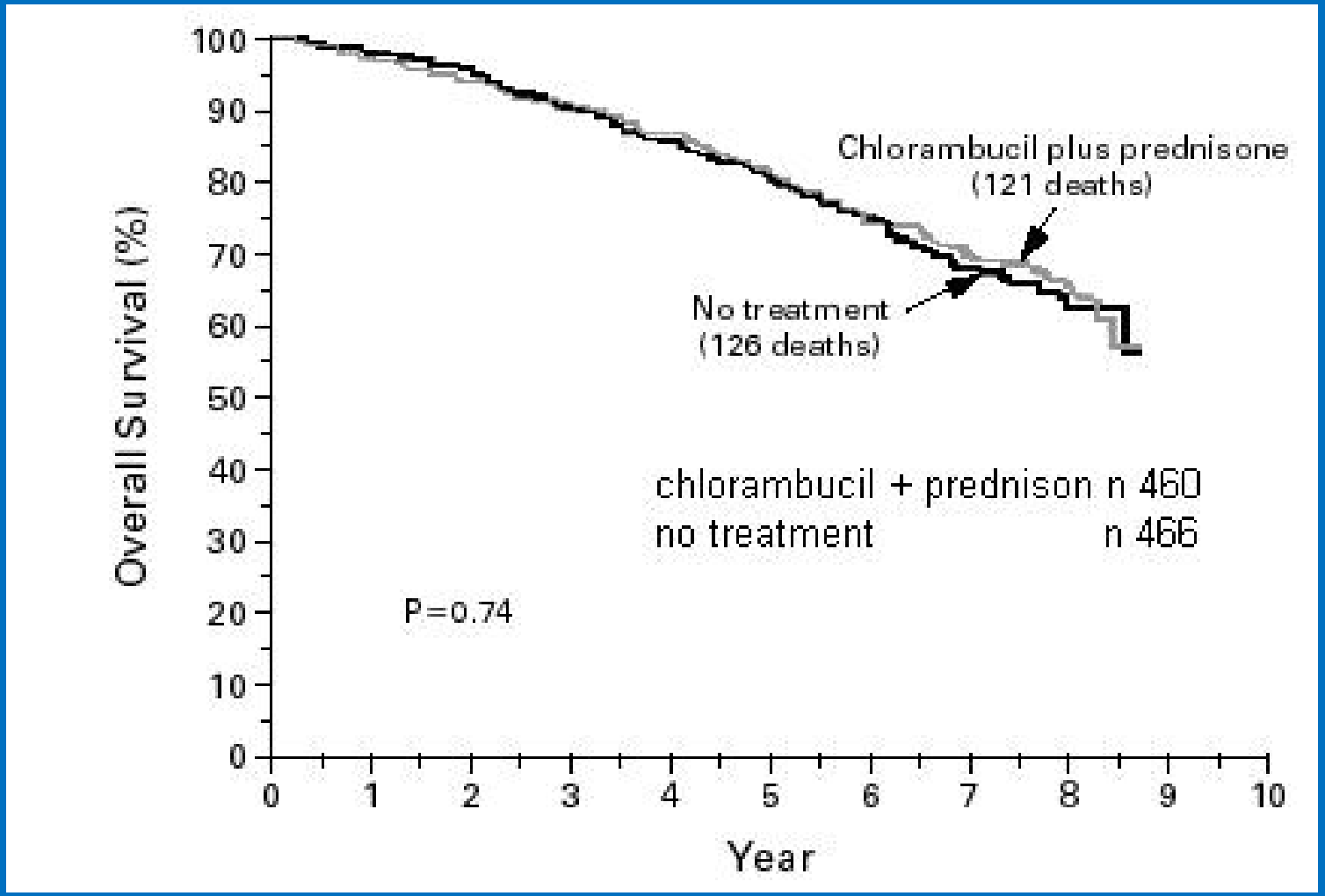
No survival benefit from early (immediate) treatment

Assessed retrospectively - chlorambucil and anthracycline based regimens, novel agents

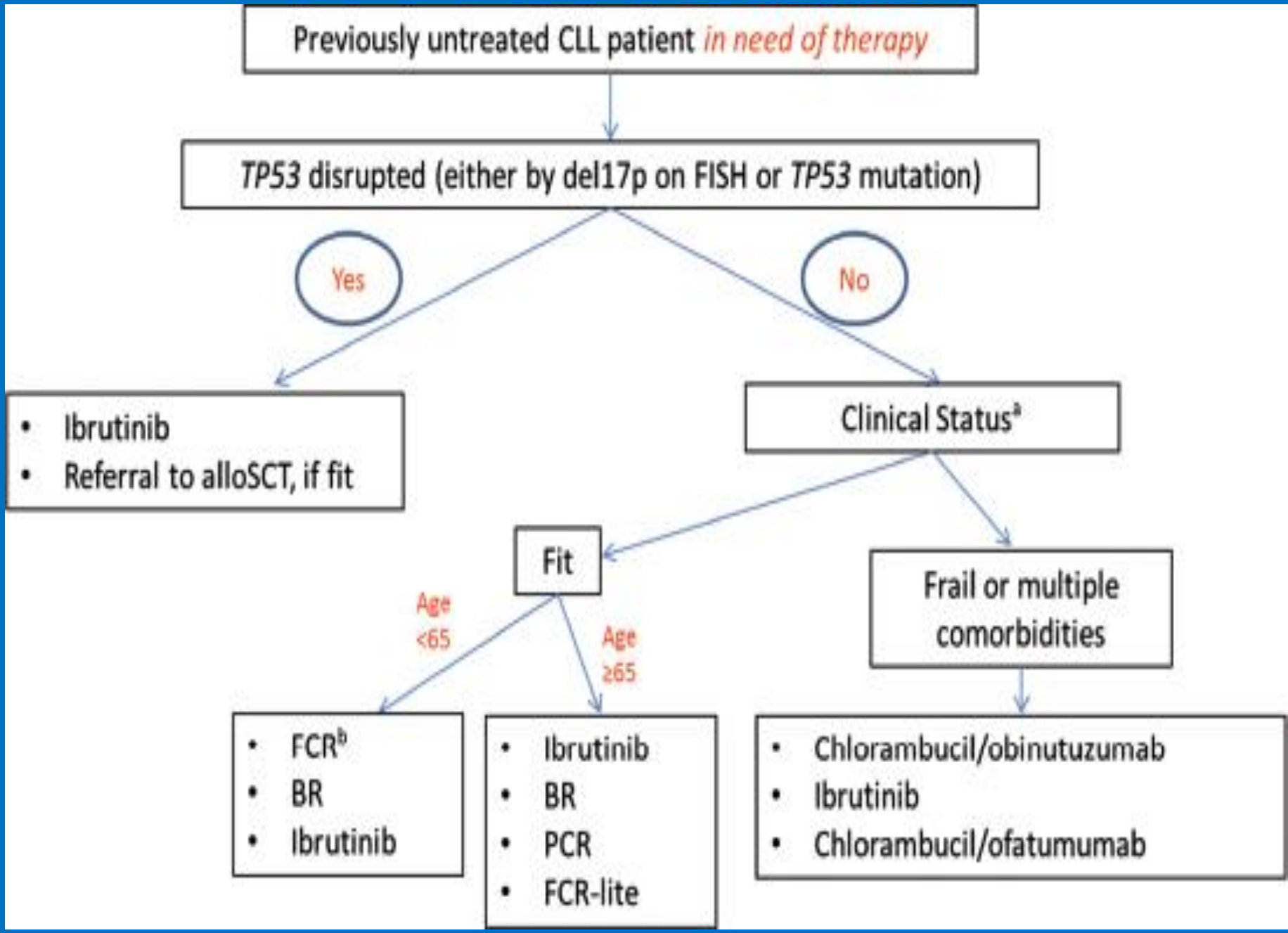
Pro: no treatment complications (risk of neutropenia and infection, genom instability, secondary malignities, quality of life)

Con: patient anxiety

Binet – stadium A – immediate vs delayed Tx



Dighieri et al, NEJM 1998



Winthrobe, 2019

- Good status
- No comorbidities
- Normal survival proposed

- Partialy worse

- Handicaped
- More comorbidities
- Shortend survival proposed

‘Go go’

Intensive therapy: FC, R-FC, Tx

Longlasting remission, cure?

‘Slow go’

„Light“ th: CLB, F-mono

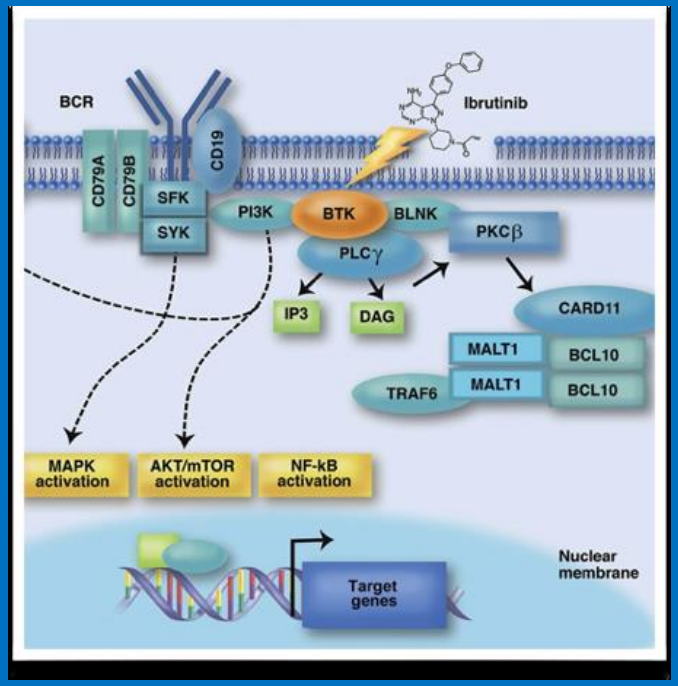
→ Control of symptoms

‘No go’

Paliative therapy

Balducci L & Extermann M, *Oncologist* 2000; 5:224–237.

Ibrutinib – Bruton kinase inhibitor



Approved initially in 2014 for RR, now approved for frontline use

Pro:

Ease of administration

Once daily dosing

Increased PFS compared to previously available treatments

Con:

AEs from off target effects

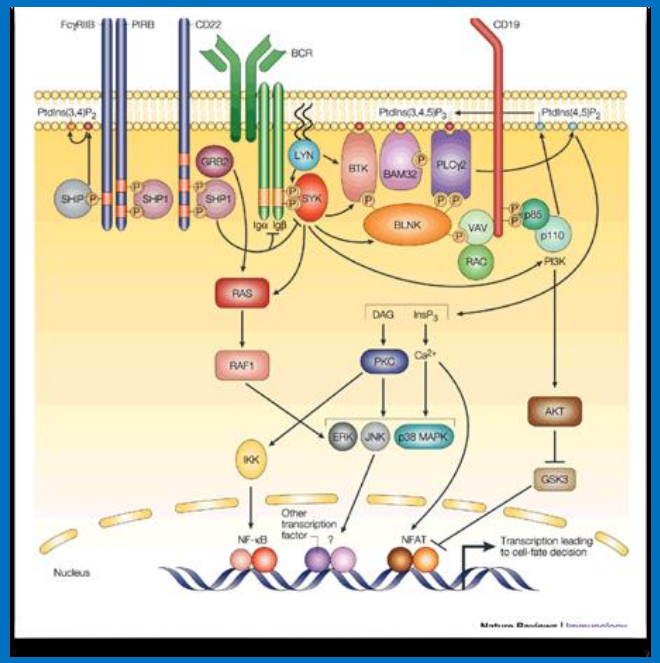
Diarrhea

Afib/hypertension

Thrombocytopenia

Increased bleeding risk, and bruising

Idelalisib Phosphoinositide 3-kinase delta (PI3K) inhibitor



Approved in 2014 for relapsed patients in combination with rituximab

Pro:

Ease of administration-BID dosing

No cardiac toxicity

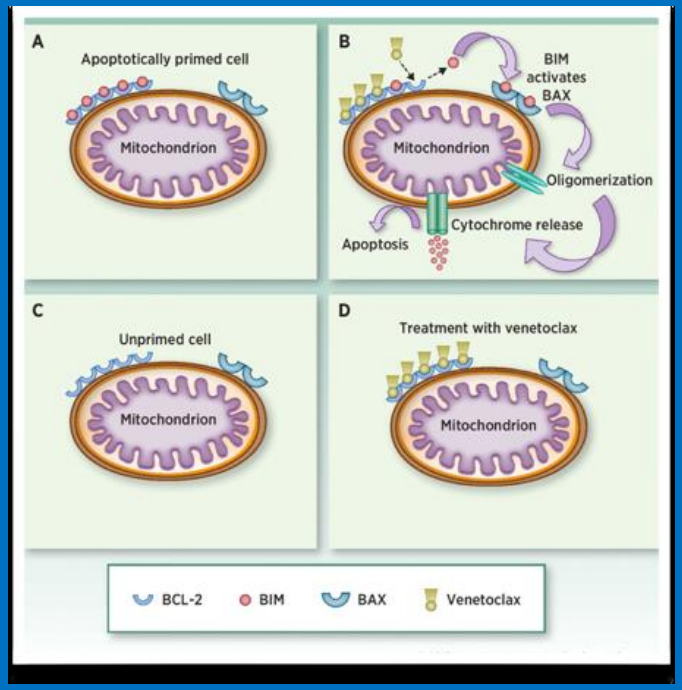
Low TLS risk

Con:

Colitis, pneumonitis, transaminitis

Risk of CMV reactivation, PCP pneumonia, sepsis, and infections

Venetoclax BCL2 inhibitor



Approved in 2016 for patients with 17p deletion who have received one prior therapy.

Pro:

BCR-independent mechanism of action

Ease of administration-once daily dosing

No cardiac toxicity

Impressive overall response rate and short time to response and

MRD negativity

Con:

Tumor lysis- dose ramp up

Grade 3/4 neutropenia

low incidence of febrile neutropenia

Nausea/diarrhea

Female, born. 08/1949

mal

09/2006 reffered for leukocytosis with lymphocytosis

FH: Mother DM, father + IM.

SA: Administrative, Financial office

MH: Usual children diseases

Since 35 years hypertension - Lokren, Gopten, Vasexten

Since 40 years DM II. type, PAD - Metformin

Dyslipoproteinemia - Atoris (od 6/06)

Problems with varices – Glyvenol

NO: By blood draw accidentaly leukocytosis and lymfocytosis

Subj.: Appetite good, not loosing weight, stool, urination no problems, temperature normal, sweating, itching usual, breathing OK, DK no oedema

Nonsmoker, alkohol no, medication – viz, no alergies

Menopausis at 50, labours 2, gynekol. no controls

Obj.: Eupnoe, no cyanosis, no icterus, no haemorrhagic diathesis, periph. lymph nodes not enlarged,
Abdomen unable to be palpated.
Height 172 cm, weight 137kg,
BP 160/80, ECOG 0, Karnofsky 100%

KO: Leu: **120,9**, SEG: **9**, B: 1, Ly: **88**, Mo: **2**, Gumpr.sh: 85,
Ne: **8,4**, Ly: **82,3**, Mo: **8,6**, Eo: **0,2**, Ba: 0,5,
Ne: **10,1**, Ly: **99,5**, Mo: **10,4**, Eo: 0,2, Ba: **0,6**,
Ery: 4,40, HB: 138, HTC: 0,417, MCV: 94,8,
MCH: 31,3, MCHC: 330, RDW: 14,2,
Rtc: 13, abs.: 0,057;
Plt: 253, MPV: 9,4, PCT: 0,237, PDW: 16,6,

Bioch.: Fe: 14,4,
Kreat.: 68,0, Uric acid: **445**, LD: 3,30,
CB: 74,0, ELFO no abnormality
Beta-2-m: 1,84,
Vitamin B12: 438, folic acid: 5,8, Ferritin: 264,5,

06.04.2007 = half a year later

No problems. Endokrinology hypothyreosis not confirmed.

Obj.: No anemia, no icterus, no haemorrhagic diathesis, small neck lymph nodes, pther periferal nodes not enlarged, hepar and spleen ?,

KO: Leu: **164,5**, Ne: **11,8**, Ly: **79,5**, Mo: 8,0, Eo: **0,3**, Ba: 0,4,
Ne: **19,3**, Ly: **130,8**, Mo: **13,1**, Eo: 0,4, Ba: **0,7**
Ery: 4,21, HB: 132, HTC: 0,401, MCV: 95,3, MCH: 31,4, MCHC: **329**, RDW: 14,6,
Plt: 239, MPV: 9, PCT: 0,214, PDW: 16,7,

5.5.2008 = 1,75 year

Subj. Sweating
Obj.: No anemia, no icterus, no haemorrhagic diathesis, periferal lymph nodes cca 2-3cm, right neck, left axilla and inguina, liver and spleen ?,

KO: Leu: **297,9**, Ne: **7,2**, Ly **71,3**, Mo: **21,2**, Eo: **0,1**, Ba: 0,2,
Ne: **21,4**, Ly: **212,4**, Mo: **63,3**, Eo: 0,2, Ba: **0,5**
Ery: 3,99, HB: 126, HTC: 0,393, MCV: 98,5, MCH: 31,5,
MCHC: **320**, RDW: 15,6,
Plt: 248, MPV: 8,7, PCT: 0,216, PDW: 16,6,

Fludara + Cyclophosphamide (Rituximab not available)

No problems, she feels better, organomegaly disappeared.

KO: Leu: 7,8, Ne: **31,6**, **Ly: 58,0**, **Mo: 9,5, Eo: 0,4, Ba: 0,5,**
Ne: 2,4, Ly: 4,5, Mo: 0,7,
Ery: 3,85, HB: 123, HTC: 0,357, MCV: 92,7, MCH: 31,9,
MCHC: 344, RDW: **16,6,**
Plt: 216, MPV: 8,2, PCT: 0,177, PDW: 16,5,

Bioch.: Urea: 5,5, Kreat.: 56,0, Uric acid: 271,
Bilirubin: 8,2, ALT: 0,39, AST: 0,38, GGT: 0,43, ALP: 0,92,
LD: 3,20, Beta-2-mikro: **2,98**

29.6.2009 = one year later

Subj. no problems..

Obj.: no change

KO: Leu: 10,7, Ne: **38,4**, **Ly: 53,7**, **Mo: 6,7, Eo: 1,0, Ba: 0,2,**
Ne: 4,1, Ly: 5,7, Mo: 0,7, Eo: 0,1,
Ery: 3,88, HB: 130, HTC: 0,373, MCV: 95,9, MCH: 33,4,
MCHC: 348, RDW: 13,4,
Plt: 221, MPV: 8,1, PCT: 0,179, PDW: 16,8,

12.12.2011 = two years later

No problems

Obj.: No important change

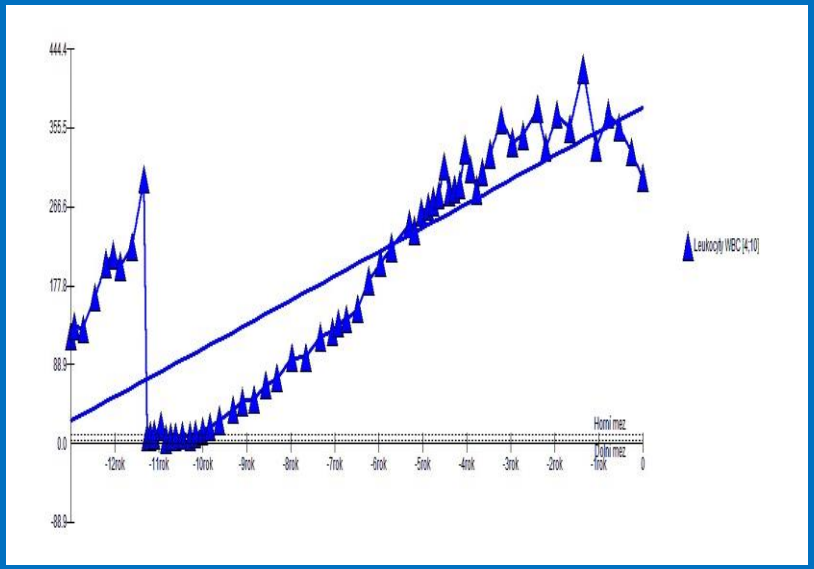
KO: Leu: **97,13**, Ne: **5,7**, Ly: **92,0**, Mo: **1,9**, Eo: **0,1**, Ba: 0,3,
Ne: 5,49, Ly: **89,37**, Mo: **1,87**, Eo: 0,12, Ba: **0,28**,
Ery: 3,94, HB: 128, HTC: 0,395, MCV: 100,3, MCH: 32,5,
MCHC: **324**, RDW: 14,7,
Plt: 208, MPV: **10,8**, PCT: 0,22, PDW: 13,1,

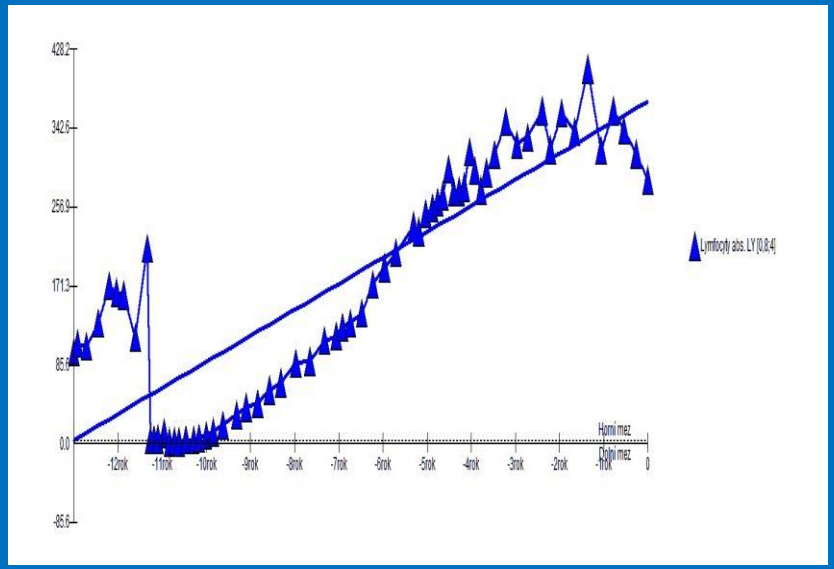
21.11.2014 – 6 years later

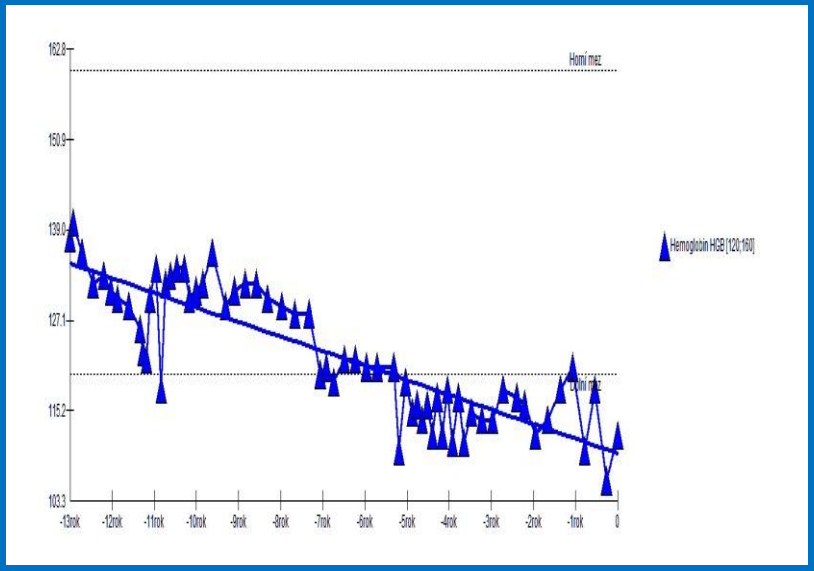
No problems

Obj.: No important change

KO: Leu: **280,29**, Ne: **0,8**, Ly: **96,0**, Mo: **2,3**, Eo: **0,1**, Ba: 0,8,
Ne : 2,58, Ly: **268,95**, Mo **6,38**, Eo : 0,16, Ba : **2,22**
Ery: 3,69, HB: **114**, HTC: 0,389, MCV: **105,4**, MCH: 30,9,
MCHC: **293**, RDW: **18,8**,
Plt: 191, MPV: 10,2, PCT: 0,200, PDW: 12,1,


444.4
355.5
266.6
177.8
88.9
0.0
-88.9
Horní mez
Dolní mez
-12rok
-11rok
-10rok
-9rok
-8rok
-7rok
-6rok
-5rok
-4rok
-3rok
-2rok
-1rok
0
Leukocyty WBC [4;10]


428.2
342.6
256.9
171.3
85.6
0.0
-85.6
Horní mez
Dolní mez
-12rok
-11rok
-10rok
-9rok
-8rok
-7rok
-6rok
-5rok
-4rok
-3rok
-2rok
-1rok
0
Lymfocyty abs. LY [0,8;4]


162.8
150.9
139.0
127.1
115.2
103.3
Horní mez
Dolní mez
-13rok
-12rok
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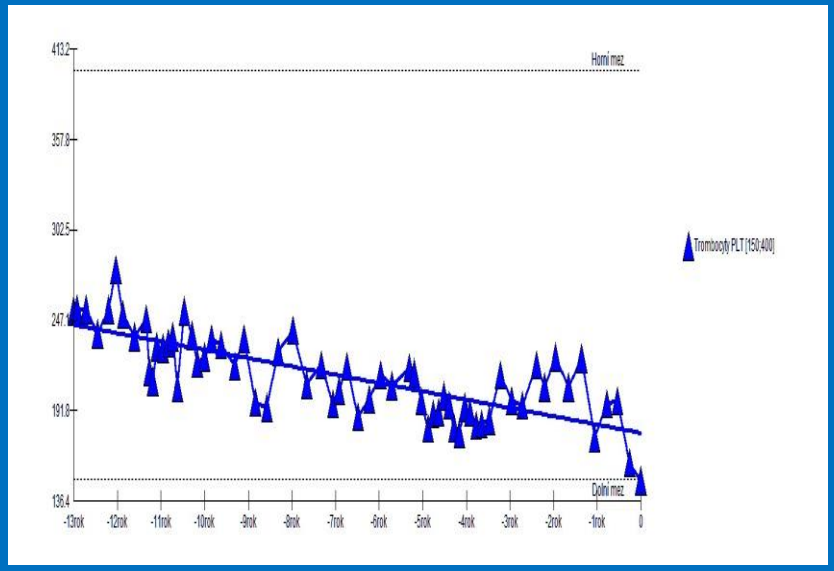
-10rok
-9rok
-8rok
-7rok
-6rok
-5rok
-4rok
-3rok
-2rok
-1rok
0
Hemoglobin HGB [120;160]


413.2
357.8
302.5
247.1
191.8
136.4
Horní mez
Dolní mez
-13rok
-12rok
-11rok
-10rok
-9rok
-8rok
-7rok
-6rok
-5rok
-4rok
-3rok
-2rok
-1rok
0
Trombocyty PLT [150;400]

Case No 2

Male, born. 10.10.1939

FH: Father + pneumonia, mother+ CMA, son + v.s. neo cerebri, IM (?), otherwise neg.
SH: Retired, technician, exposition 0,
PH: No severe disease
Dyspnoea, anginous pains, palpitations. Evaluated cardiologically, TRD, ORL; Diuretics with no effect.
Lab. evaluation: anemia, leucocytosis – reffered to haematol.
Subj.: Good appetite, weight loss 5 kg after + of son, stool, urine normal, no febrills, no sweating or itching, DE not swelling.
Non-smoker, alcohol neg., medication non, no alergies

Obj.: Eupnoe, no cyanosis, no icterus, no haemorrhagic diathesis, pale skin, periph. LN small, generalised, up to 1 cm in diameter, tonsills normal, thyroidea norm., breathing clear, no strange fenomenons, heart action regular, P 78/min., discret systolic murmur, abdomen no signs of peritonitis, spleen and liver not palpable, DE no swelling
TK 125/70, High 183, Weight 87 kg, BSA 2,09,
T 36,7C,
ECOG 1, Karnofsky 90%,

Lab. (Euromedics s.r.o., 7.9.12):

KO: Leu: **20,9**, Seg.: **10**, B: 1. Ly: **89**, Gumpr. shadows often

Ery: 1,87, Hb: **71**, Hk: **28,5**,

MCV: **109,8**, MCH: 38,0, MCHC: 346,

Thr: 157

Our results 20.9.2012:

FW: **36**/ **77**,

KO: Leu: **25,56**, SEG: **5,7**, Ly: **93,3**, Ba: 0,5, Pl.c.: 0,5, Gumpr.sh.: 21,

Ne: **4,9**, Ly: **94,2**, Mo: **0,6**, Eo: **0,2**, Ba: 0,1,

Ne abs.: **1,23**, Ly abs.: **24,09**, Mo abs.: 0,16,

Ery: **1,71**, Hb: **64**, HTC: **0,193**,

MCV: **112,9**, MCH: **37,4**, MCHC: 332, RDW: **18,1**,

Plt: 186, MPV: 10,1, PCT: 0,190, PDW: 10,7,

Reticulocytes SIS: 15,0,
Quick test INR: 1,02, APTT: **23,5**,
Bioch.: Na: 139, K: 4,5, Cl: 106, Ca: 2,14, Fe: **43,9**,
Urea: 7,2, Kreat.: 74, Uric acid: 310,
MDRD: 1,50, creat. clearence 96,8 ml/min.
Bilirubin: 8,9, ALT: 0,27, AST: 0,32, GGT: 0,70, ALP: 1,33,
Tot. protein: **63,6**,
Alb.%: **69,80**, A1G%: **5,20**, A2G%: 7,70, B1G%: 6,50, B2G%: **1,90**, GG%: **8,90**,
Alb.: 44,4, A1G: 3,31, A2G: 4,9, B1G: 4,13, B2G: 1,2, GG: 5,66, A/G: 2,311,
IgG: 7,0, IgA: **0,53**, IgM: **0,14**, I-ELFO: Neg.
TSH: 1,000, Vitamin B12: 200, Folic acid: 13,1, Ferritin: **399,8**,
Glycemia: **5,8**, Haptoglobin: 1,02,
Beta-2-mikro: **3,35**, LD: 3,0, CRP: 1,8,
Blood gropup: A pos, DAT: **4+**, IgG:**4+** Kell: neg, Screening antibodies neg,

Will we treat the patient ?

How ?

Negative prognostic factors

- Unmutated IgHv genes
- Cytogenetic abnormalities -del 17p (p53), del11q (ATM),
- Expression of CD 38
- Increased LD a β-2-microglobulin
- Prolymphocytes > 10%
- *Difuse infiltration of BM*

What to think about before the therapy ??

- Factors linked to the disease
- Clinical stage
- Genetics (FISH - del17p13)
  - PrimoTx x second line x refractoriness

- Factors linked to the patient
  - Fitness / komorbidities
  - Patient wishes

- Thank you for your attendance