New disease perspectives and goals of therapy in **CLL**

Zeljka Skunca,MD,PhD

DEFINITION

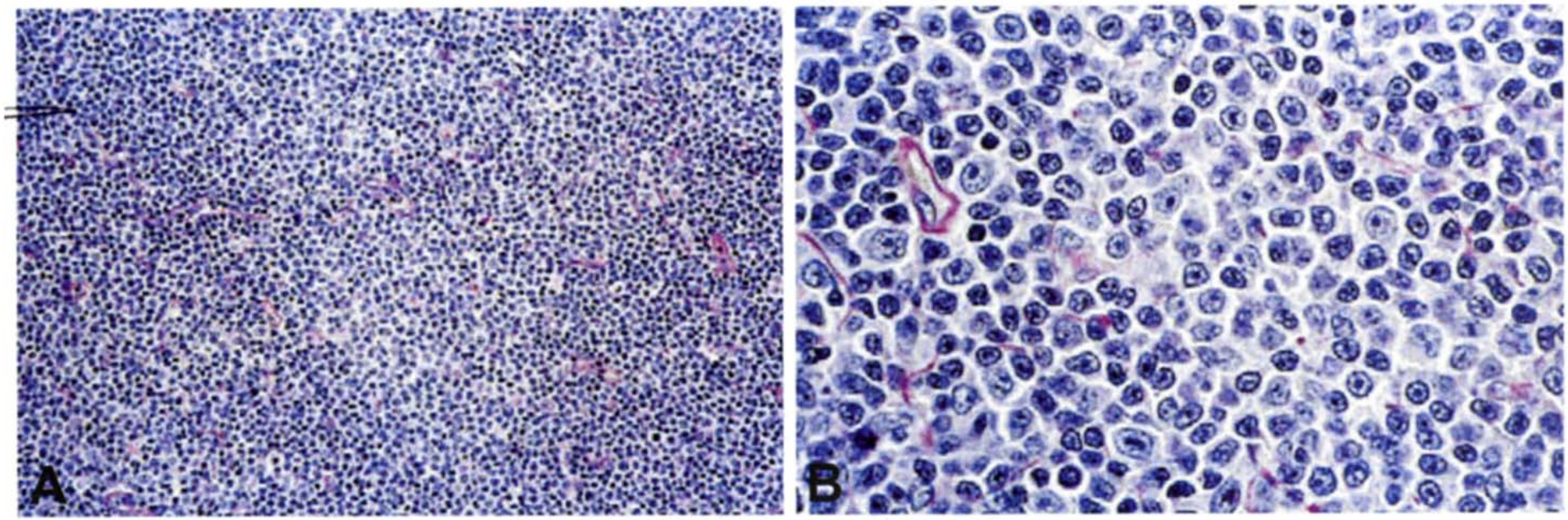
- Monomorphic small, round, to slighly irregular B lymphocytes in the peripheral blood (PB), bone marrow (BM), spleen and lymph nodes, admixed with prolympocytes and paraimunoblasts forming proliferation centres in tissue infiltrates.(WHO 2008.)

CRITERIA FOR DEFINITION

- The CLL cells usualy coexpress CD5 and CD23
- In the PB must be ≥ 5x10e9/L monoclonal lymphocytes with a CLL phenotype.
- In the BM ≥ 40% monoclonal lymphocytes

Epidemiology

- CLL is the most common leukemia of adults in Western contries.
- 2-6 cases per 100.000 person per year



Chronic lymphocytic leukaemia, lymph node. **A** A proliferation centre embedded in a darker background of small lymphocytes (PAS stain). **B** High magnification showing a clustering of larger lymphoid cells (prolymphocytes and paraimmunoblasts) in the proliferation centre.

Comparison of historical and current views of CLL biology

Historical view		Current view
CLL is a clinically heterogeneous disease with a homogeneous cellular origin.	➡	CLL is a clinically heterogeneous disease originating from B lymphocytes that may differ in activation, maturity, or cellular subgroup.
CLL is a disease derived from naive B lymphocytes.	➡	CLL is a disease derived from antigen-experienced B lymphocytes that differ in the level of immunoglobulin variable (v) gene mutations.
Leukemic-cell accumulation occurs because of an inherent apoptotic defect involving the entire mass of leukemic cells.	➡	Investigators believe leukemic cell accumulation occurs because of survival signals from the external environment.
CLL is a disease of lymphocyte accumulation.	➡	CLL is a disease of lymphocyte accumulation with a higher associated level of proliferation than was previously recognized.
Prognostic markers identify patients at various risk levels (low, intermediate, or high in the Rai staging categories, and A, B, or C in the Binet categories) with an acknowledged heterogeneity in clinical outcomes among patients in the low- and intermediate-risk categories.	➡	New molecular biomarkers are used in both diagnosis and prognosis to better assess patients.

Laboratory findings in CLL impacting classification

The French-American-British classification	
Typical CLL	>90% of cells are small
CLL/PLL	11%–54% of cells are prolymphocytes
Atypical CLL	Heterogeneous morphology; <10% prolymphocytes
Marrow involvement	
Diffuse involvement	Usually advanced disease; worse prognosis
Nodular, interstitial, or combination (nondiffuse involvement)	Associated with less advanced disease; better outcomes

IWCLL* update of the NCI-WG criteria for diagnosing CLL

Update of the NCI-WG criteria for CLL diagnosis

- A peripheral blood B-lymphocyte count of at least 5×10^9/L, with up to 55% of the cells being prolymphocytes
- The lymphocytes should be monoclonal B lymphocytes expressing B-cell surface antigens (CD19, CD20, CD23) with light chain restriction and the T-cell antigen CD5
- Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains
- Variations of the intensity of expression of these markers may exist and do not prevent inclusion of a patient in CLL clinical trials

*International Workshop on CLL.

Rai and Binet staging systems for classification of CLL

System	Stage	Definition	Median survival
Rai staging system			
	0 (low risk)	Lymphocytosis only	11.5 years
	I (intermediate risk)	Lymphocytosis and lymphadenopathy	11.0 years
	II (intermediate risk)	Lymphocytosis in blood and marrow with splenomegaly and/or hepatomegaly (with or without lymphadenopathy)	7.8 years
	III (high risk)	Lymphocytosis and anemia (hemoglobin <11 g/dL or hematocrit <33%)	5.3 years
	IV (high risk)	Lymphocytosis and thrombocytopenia (platelet count <100,000/mm^3)	7.0 years
Binet staging			
	A	Enlargement of <3 lymphoid areas (cervical, axillary, inguinal, spleen, liver); no anemia or thrombocytopenia	11.5 years
	B	Enlargement of ≥3 lymphoid areas	8.6 years
	C	Anemia (hemoglobin <10 g/dL or thrombocytopenia platelet count <100,000/mm^3), or both	7.0 years

NCCN CLL indications for treatment

NCCN CLL indications

- Significant disease-related symptoms:
  - — Fatigue
  - — Night sweats
  - — Weight loss
  - — Fever without infection
- Threatened end-organ function
- Bulky disease (spleen >6 cm beneath costal margin, lymph nodes >10 cm)
- Lymphocyte doubling time ≤6 months*
- Progressive anemia
- Platelet count <100,000 cells/mm^3
- Eligible for clinical trial†

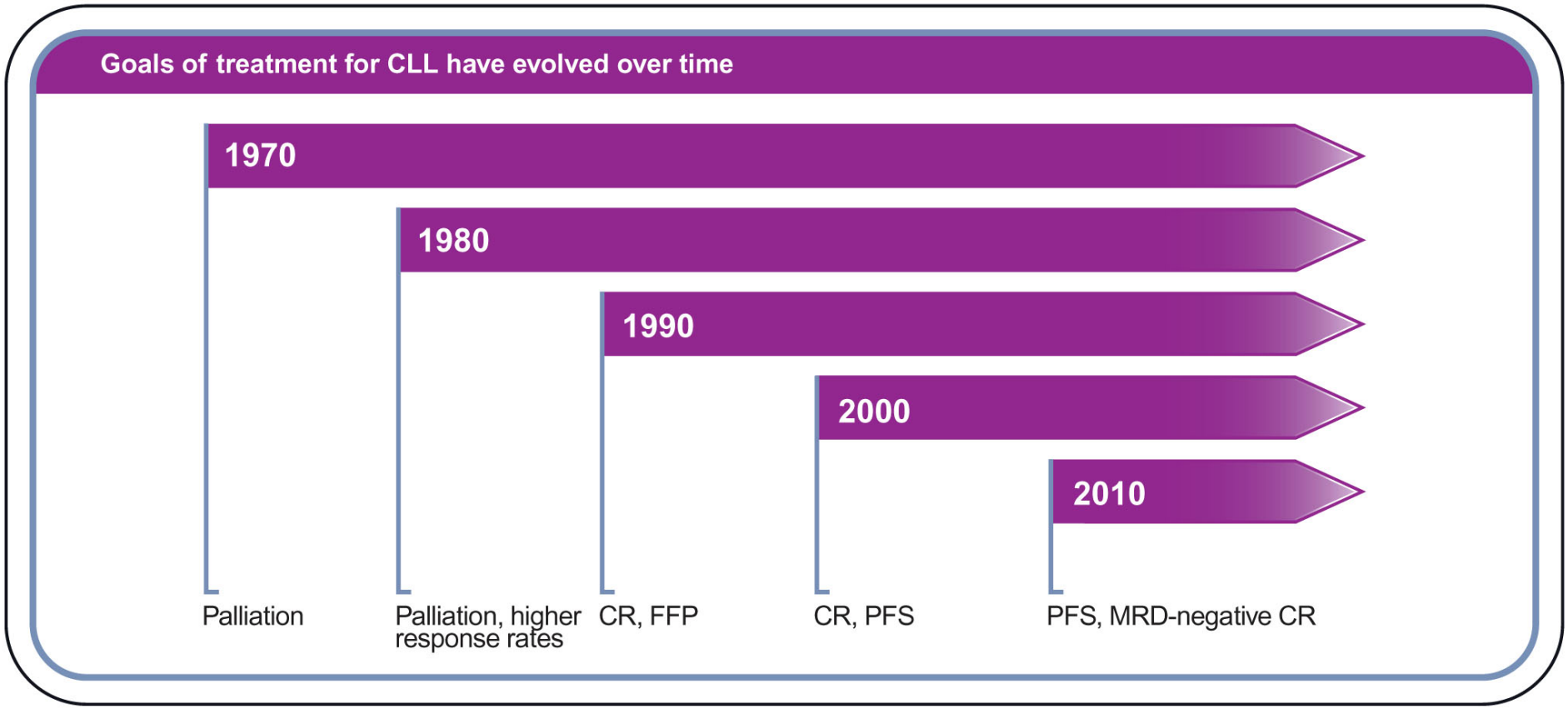
*Absolute lymphocyte count alone is not an indication for treatment.
†Given incurability with conventional therapy, consider a clinical trial as first line of treatment.

Markers that identify poor prognosis in CLL

Routinely available markers
Advanced Rai or Binet stage
Atypical morphology
Peripheral lymphocyte doubling time <12 months
Serum markers: elevated thymidine kinase and sCD23
Immunophenotyping: dim surface IgM/IgD, CD20+, CD22+, CD5+, CD19+, CD79a+, CD23+, CD43+
High β_2-microglobulin level
Diffuse marrow histology
Poor response to chemotherapy
Investigational markers
Lack of IgV_H gene mutation
Expression of ZAP-70 protein
FISH studies showing trisomy 12q, del 11q, del 17p, del 6q

sCD23=soluble CD23; FISH=fluorescence in situ hybridization.

CLL treatment expectations by decade

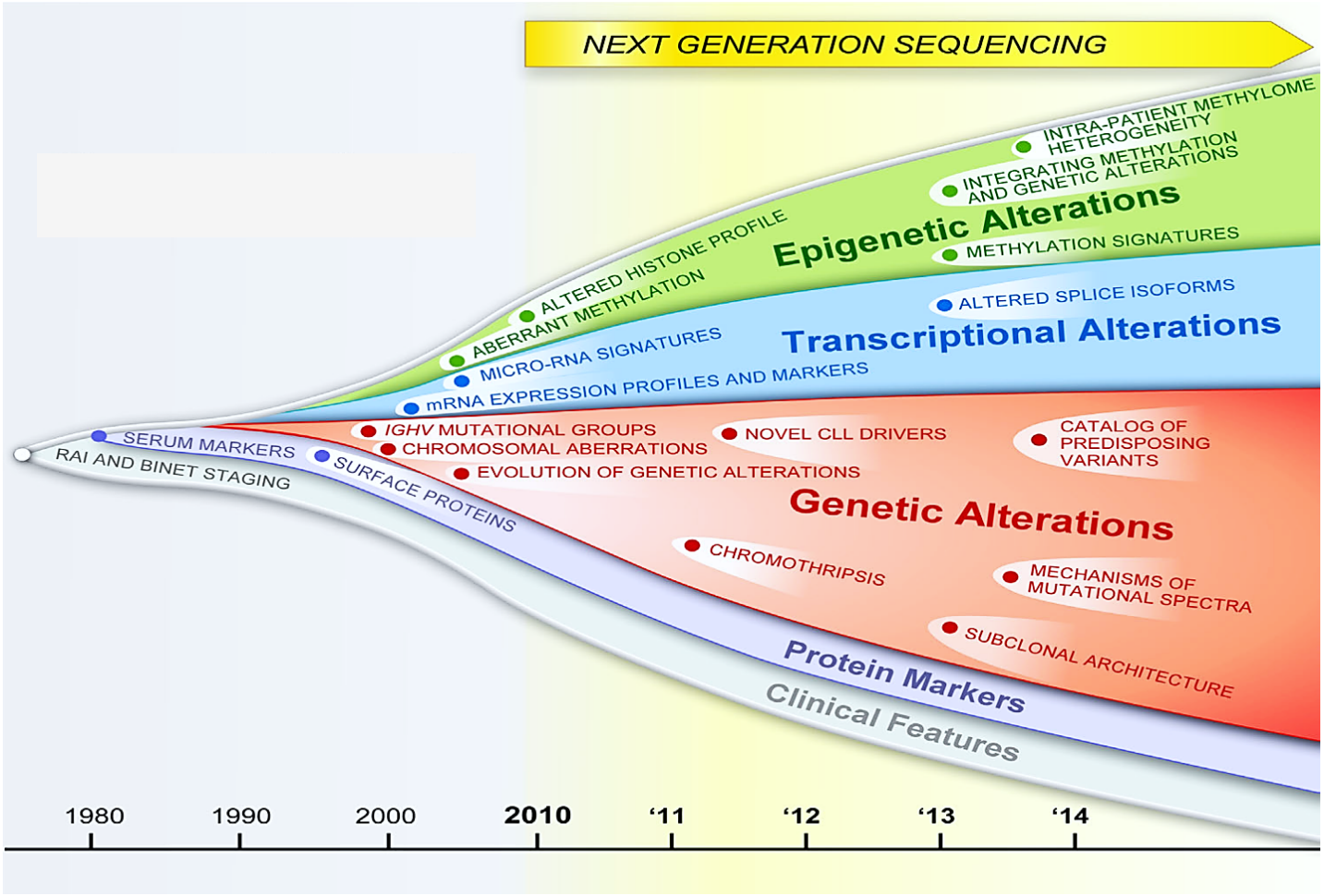


FFP=freedom from progression.

2008 revision of the NCI-WG criteria for response in CLL

Treatment goals in CLL	Definition
Complete response (CR)	At ≥2 months posttherapy: • Absence of lymphadenopathy >1.5 cm, hepatomegaly, splenomegaly, and constitutional symptoms • Normalization of CBC (neutrophils >1,500/μL, platelets >100,000/μL, hemoglobin >11 g/dL) • Lymphocytes <4,000/μL • Additional assessments in clinical trials: - Minimal residual disease (MRD) <1 CLL cell per 10,000 leukocytes - Bone marrow biopsy shows normal cellularity, lymphocytes <30%
Partial response (PR)	At ≥2 months posttherapy: • A decrease in the number of blood lymphocytes by ≥50% from the value before therapy • Reduction in lymphadenopathy (by CT scans in clinical trials or by palpation in clinical practice) as defined by - Decrease in lymph node size by ≥50% - No increase in any lymph node, and no new enlarged node(s) detected • Normalization of CBC (neutrophils >1,500/μL or 50% improvement over baseline; platelets >100,00/μL or 50% improvement over baseline; hemoglobin >11 g/dL or ≥50% over baseline)
Stable disease (SD)	No CR or PR, no progressive disease
Progressive disease (PD)	At least 1 of the following: • Lymphadenopathy (≥50% increase) • ≥50% increase in hepatomegaly or splenomegaly • Transformation to a more aggresive histology (Richter's transformation) • Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL
Progressive-free survival (PFS)	The time from study entry until objective disease progression or death
Treatment failure	Includes the following responses: • Stable disease • Nonresponse • Progressive disease • Death from any cause
Relapse	Patient achieved CR or PR but at ≥6 months shows evidence of disease progression
Refractory	Treatment failure or disease progression within 6 months of the last antileukemic therapy
Minimal residual disease (MRD)	For patients who have achieved a CR, eradication of disease cells as determined by flow cytometry or PCR (<1 CLL cell per 10,000 leukocytes)

Evolution and growth in our understanding of CLL heterogeneity over time



Gruber and Wu. Semin Hematol 51:177-187, 2014

Evidence for clonal evolution occurring in CLL

- **A. Sequential analyses of:**
  - **Karyotype and FISH abnormalities**
    - **Shanafelt *et al*. J Clin Oncol 2006**
  - **Global DNA abnormalities by comparative genomic hybridization and SNP profiling**
    - **Grubor *et al*. Blood 113: 1294-1303, 2009**
    - **Braggio, Kay *et al*. Leukemia 2102**

- **B. Analyses of DNA abnormalities by next generation sequencing of CLL genomes**

Clonal evolution

A. Sequential analyses of FISH abnormalities, microRNA abnormalities, and global DNA abnormalities

~25% of patients develop a new genetic abnormality over time in coding or non-coding genes

- Occurs more frequently in:
  - Unmutated-CLL clones and in Mutated-CLL clones of patients that eventually require therapy
  - $CD38^+$ clones
  - $ZAP\text{-}70^+$ clones
  - $CD49d^+$ clones
- Most common new lesions:
  - del(13q)
  - del(17p) – harbinger of accelerated disease
- Greater the number of clonal aberrations patients have the shorter time to treatment and survival

Summary of consistent findings

B. Analyses of DNA abnormalities by next generation sequencing of CLL genomes

- **Genomic complexity exists in CLL of a degree less than that of solid tumors and DLCBL; similar to AML**
- **Over 20 recurrent mutations were identified. Most common abnormality is in NOTCH1**
- **Specific mutations associate with at least 7 biological pathways**
- **Mutations appear to fall into two categories: initiating clonal driver mutations and secondary, subclonal mutations**
- **Subclonal mutations often emerge after therapy but many/most exist prior to therapy**

Summary

All CLL clones are heterogeneous *at all points in time*

This heterogeneity can be genetic/fixed or physiologic/dynamic

Those clonal submembers that divide are more likely to upregulate AID and therefore develop new genetic changes

The degree of intraclonal genetic heterogeneity correlates with CLL disease progression and shorter time-to-treatment and survival

Over time, and especially with therapy, these intraclonal genetic variants can outcompete the initial major clonal submembers – Clonal Evolution

Treatment of the elderly patient with CLL

5 year mortality rate according to comorbidity rate

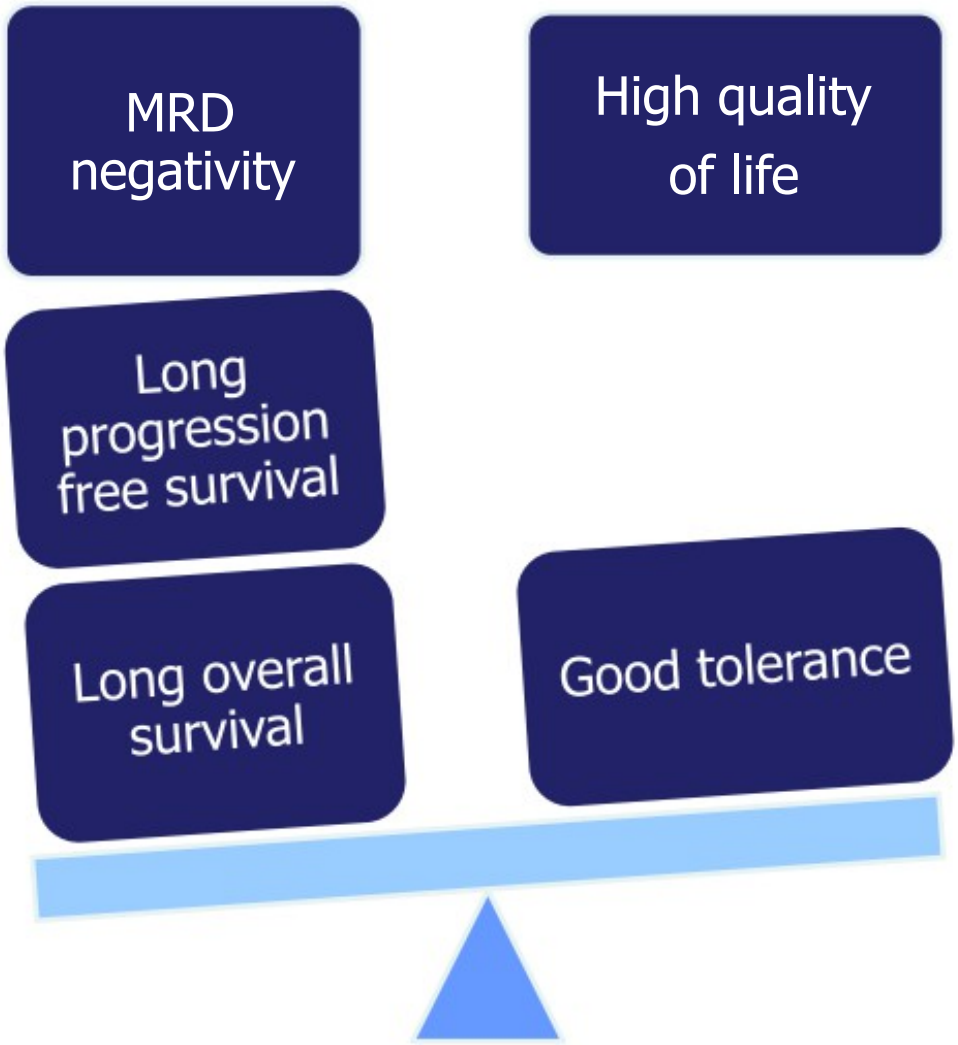
60% of all patients with CLL requiring treatment

die because of leukemia

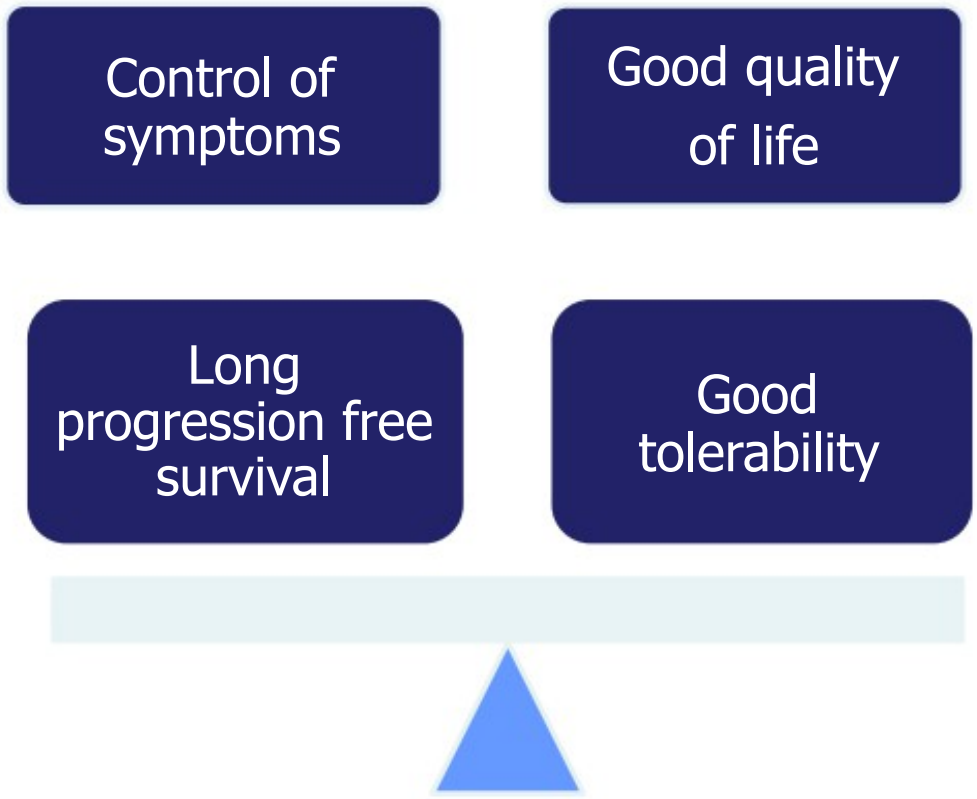
- independent from their burden of comorbidities

Goede et al., submitted

Treatment aims in physically fit CLL patients

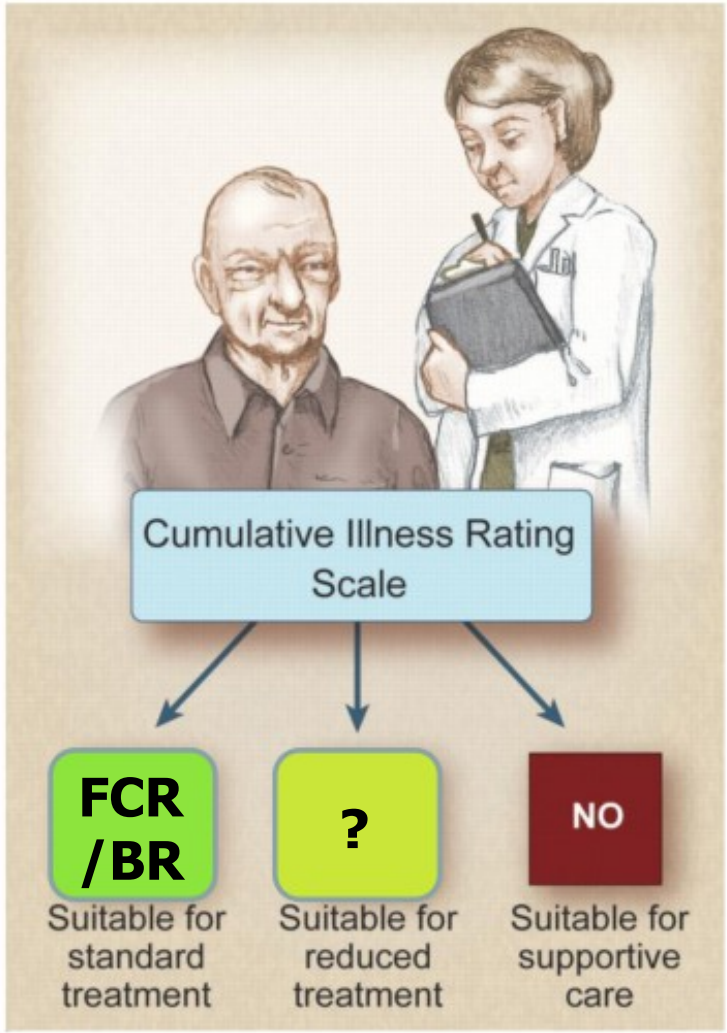


Treatment aims in less fit CLL patients



Fitnes-adapted therapy of CLL

Cumulative Illness rating Scale (CIRS)*



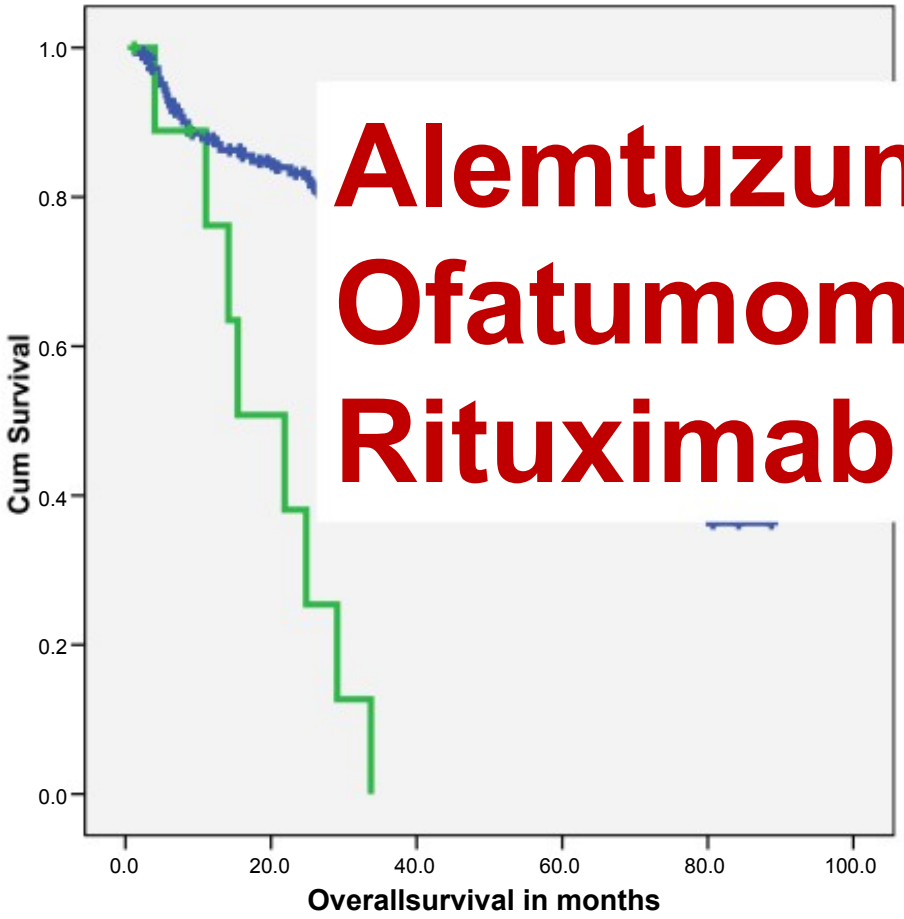
* Balducci L & Extermann M, Oncologist 2000; 5:224-237

Improvement of prognosis in elderly CLL patients with Clb + Rituximab?

	therapy	n	CR	ORR
Catovsky et al., Lancet 2007	Clb	200	6%	66%
Hillmen et al., ASH 2010	ClbR	100	12%	80%
Foa et al., ASH 2011	ClbR	85	17%	81%

Elderly patients with poor risk

CLL5 study: 156 patients treated with Clb or F



Alemtuzumab?
Ofatumomab?
Rituximab + HDP/Dexa?

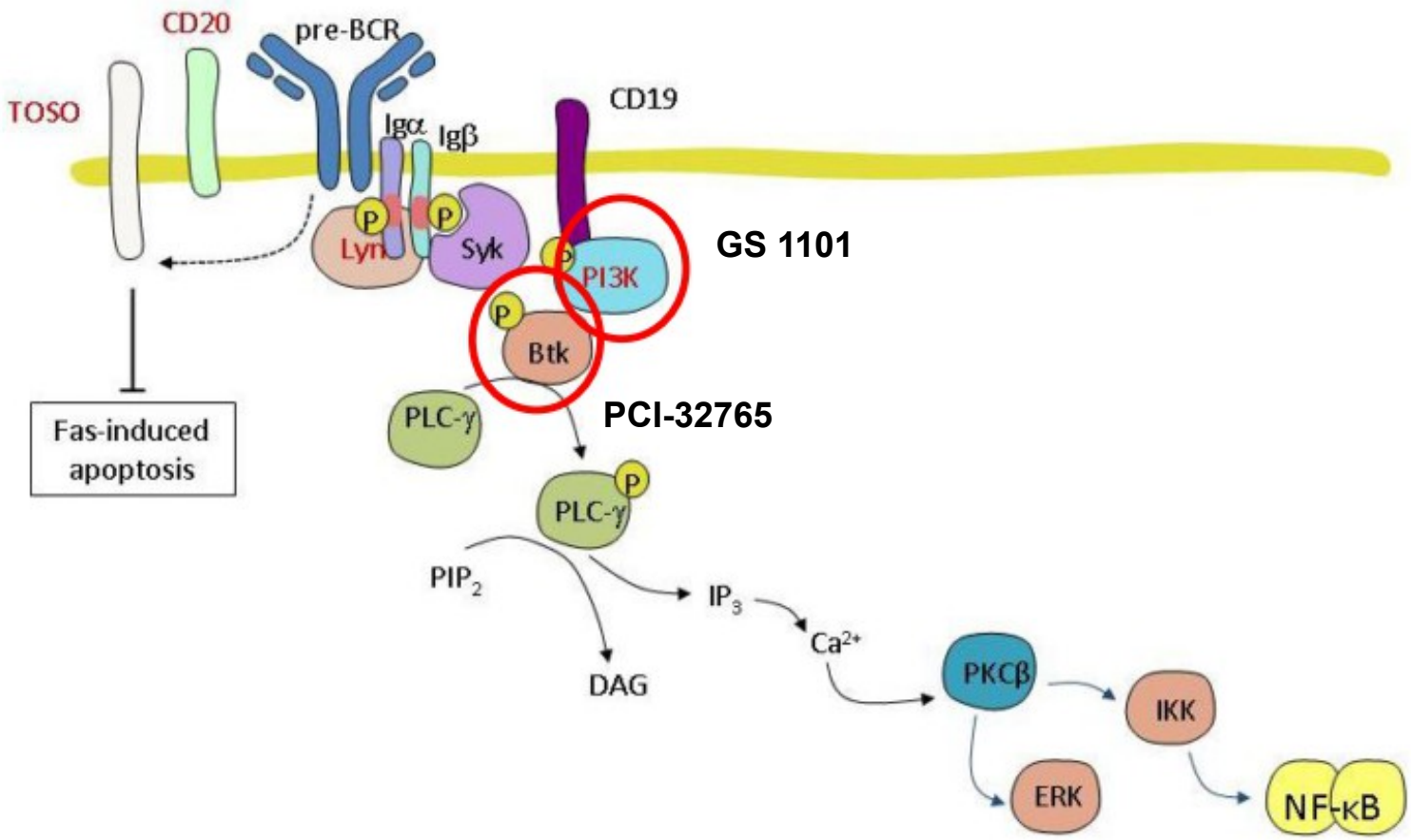
Median OS:
No del(17p) (n=146) 69 months
Del(17p) (n=10): 21 months
P < 0.001

CLL5 study : Unpublished data

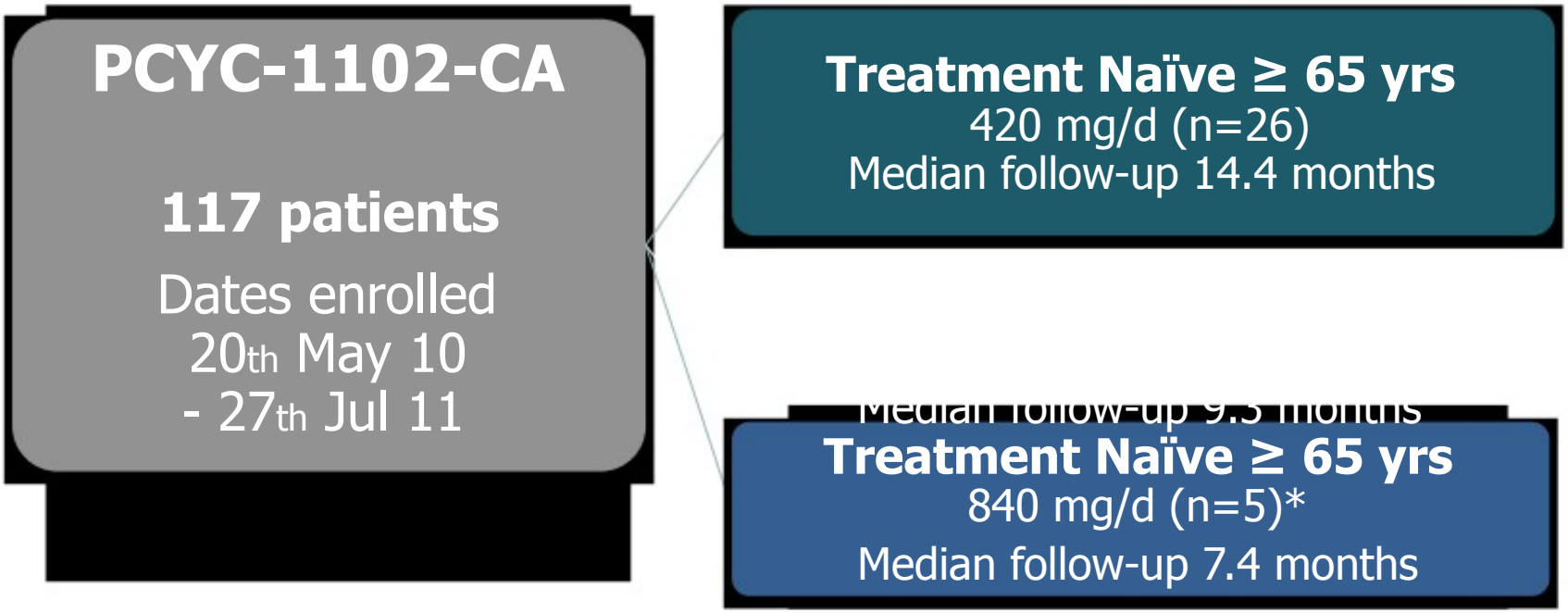
Treatment of relapsed/refractory CLL with antibodies

	Alemtuzumab Stilgenbauer et al., 2012	Ofatumumab Wierda et al., 2011	Rituximab + HDP Castro et al., 2008	Rituximab + Dexa Smolej et al., 2012
N	40	89	14	54
Median age	65	NA	59	65
ORR	73%	44%	93%	67%
CR	3%	0%	36%	13%
Median PFS	11 mo	5 mo	15 mo	6 mo
Median OS	18 mo	16 mo	median OS n.r. after 40 mo	14 mo.

New treatment options in CLL

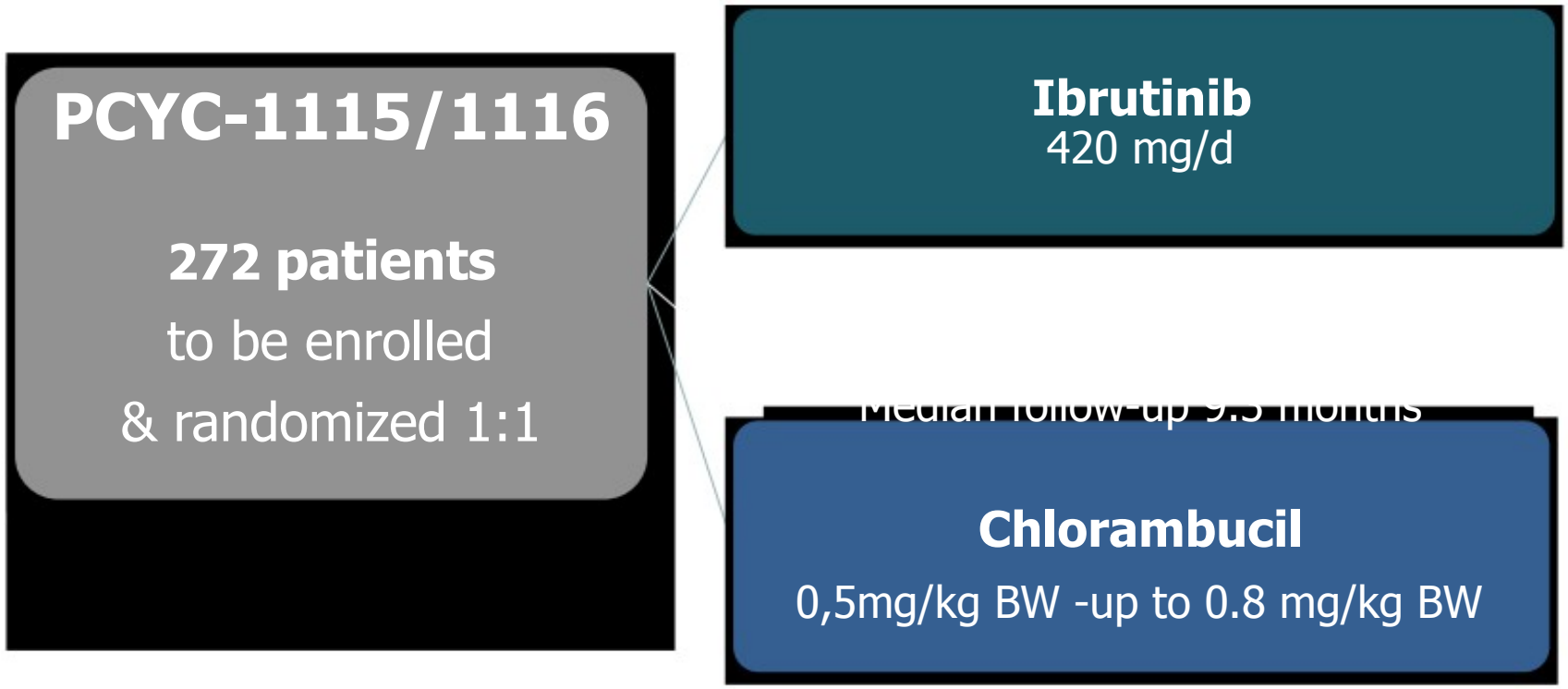


Btk-inhibitor ibrutinib in previously untreated patients with CLL/SLL ≥ 65 years

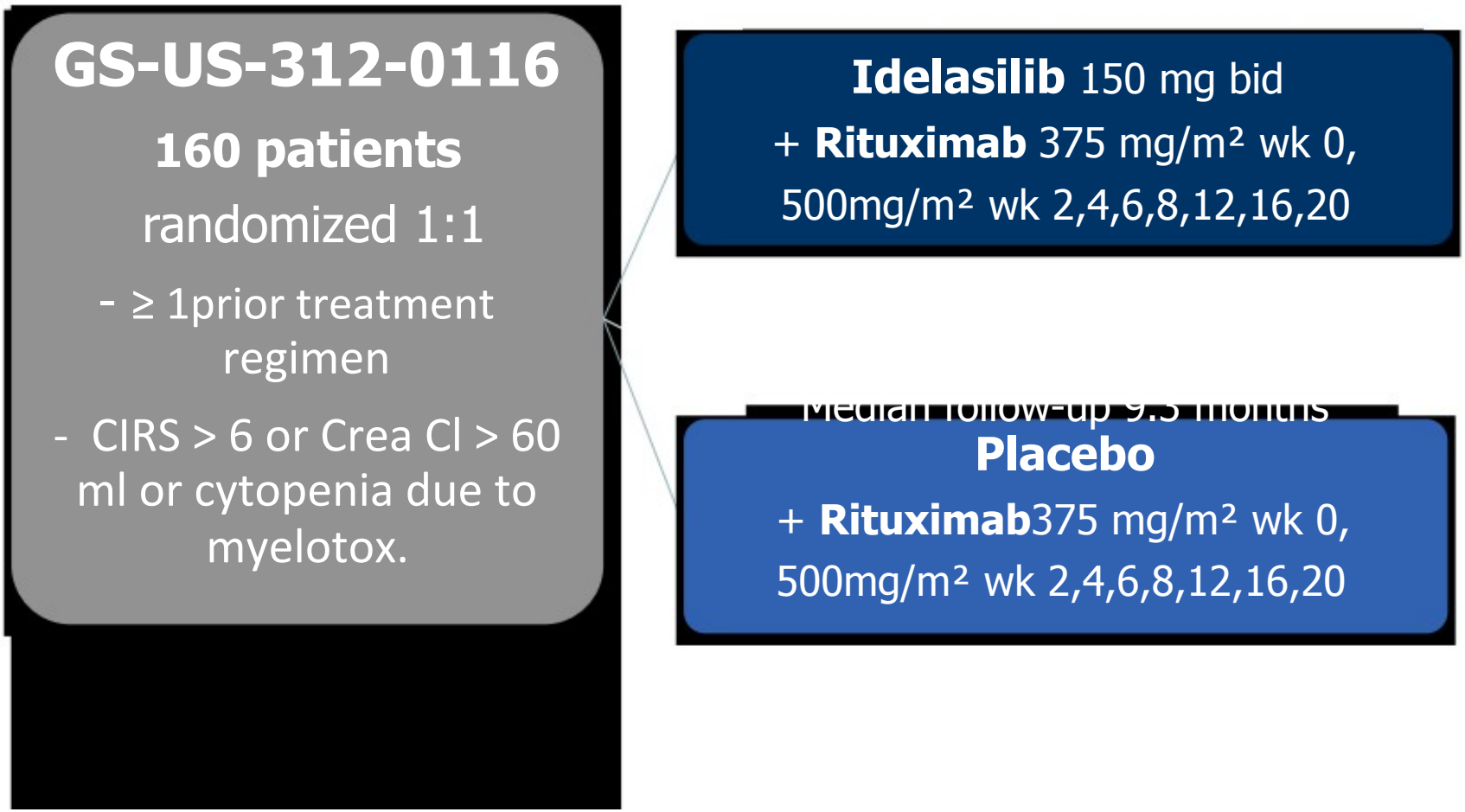


O`Brien et al., EHA 2012

Ibrutinib versus chlorambucil in previously untreated patients with CLL/SLL ≥ 65 years



Idelalisilib + Rituximab versus Placebo + Ritxuimab in pretreated unfit patients



Treatment of comorbid CLL patients

Binet Stage	Del(17p) or p53 mut	First line treatment
A, asymptomatic B	Irrelevant	None
C, symptomatic B	no	CLB, CLB-AntiCD20?
	yes	A, O or R+HDS
Relapse		
Early (< 2 year) = refractory disease	no	No standard: BR, FCR lite
	yes	A, O or R+HDS
Late (> 2 year)	no	Repeat first line

Thank you very much for your attention!