Autoimmune hemolytic anemia in Chronic Lymphocytic Leukemia

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CLL and Immune Status

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Special Article

Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

By WILLIAM DAMESHEK

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Special Article

Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

By William Dameshek

Clinical case

- 68-year-old male
- Past medical history: diabetes mellitus, hypertension, COPD, non-granulomatous anterior uveitis
- August 2012: Lymphocytosis (13.800/µl)
- November 2012: **CLL diagnosis**
  - Hb 14.9, WBC 22.690 (17.900 lymphocytes), platelet 241.000
  - Inmunophenotype: $CD5^+$, $CD20^+$, $CD79b^+$, $CD23^+$, Kappa restriction

Clinical case

- No symptoms
- PS: 0/CIRS: 4
- No lymphadenopathy or organomegaly

Other laboratory parameters

- LDH 362 (N <243)
- Beta-2 microglobulin: 3.27mg/L (N < 1.80)
- ZAP-70: 50%
- Unmutated *IGHV* genes
- FISH: trisomy 12

CLL - Stage A(0)

February 2014-December 2014: Disease progression to CLL Stage B(I)

- **Symptoms**: Assymptomatic, PS: 0
- **Physical findings:** Generalized peripheral lymphadenopathy (**~3** cm). No splenomegaly, no hepatomegaly
- **CT scan**: consistent with CLL (no bulky disease, SUV < 3)
- **Laboratory findings**
  - Hemoglobin: 12.8
  - Platelets: 196.000
  - WBC count: 40.690 (64% lymphocytes) (LDT < 1 yr)

January 2015 (Emergencies Department)

- **Symptoms**: Fever > 38ºC with cough, fatigue, PS: 1
- **Physical findings:** Pallor, generalized cutaneous and oral mucosa petechiae, generalized peripheral lymphadenopathy (**~3-4** cm). No splenomegaly, no hepatomegaly
- **Laboratory findings**
  - Hemoglobin: 6.2
  - Platelets: 4.000
  - WBC count: 43.810 (41.180 lymphocytes, 880 neutrophil count)

Clinical case

  - Corrected reticulocyte count: 0.05%
- Positive Direct Antiglobulin Test (C3d++/IgG-)
- LDH 244 (N <243)
- Bilirrubin: 22 (N<17)
- Haptoglobins: 3.02 (N:0.3-2.0)

CLL - Stage C(IV)

(Evans syndrome: AHAI DAT-positive and ITP)

Therapy and treatment results

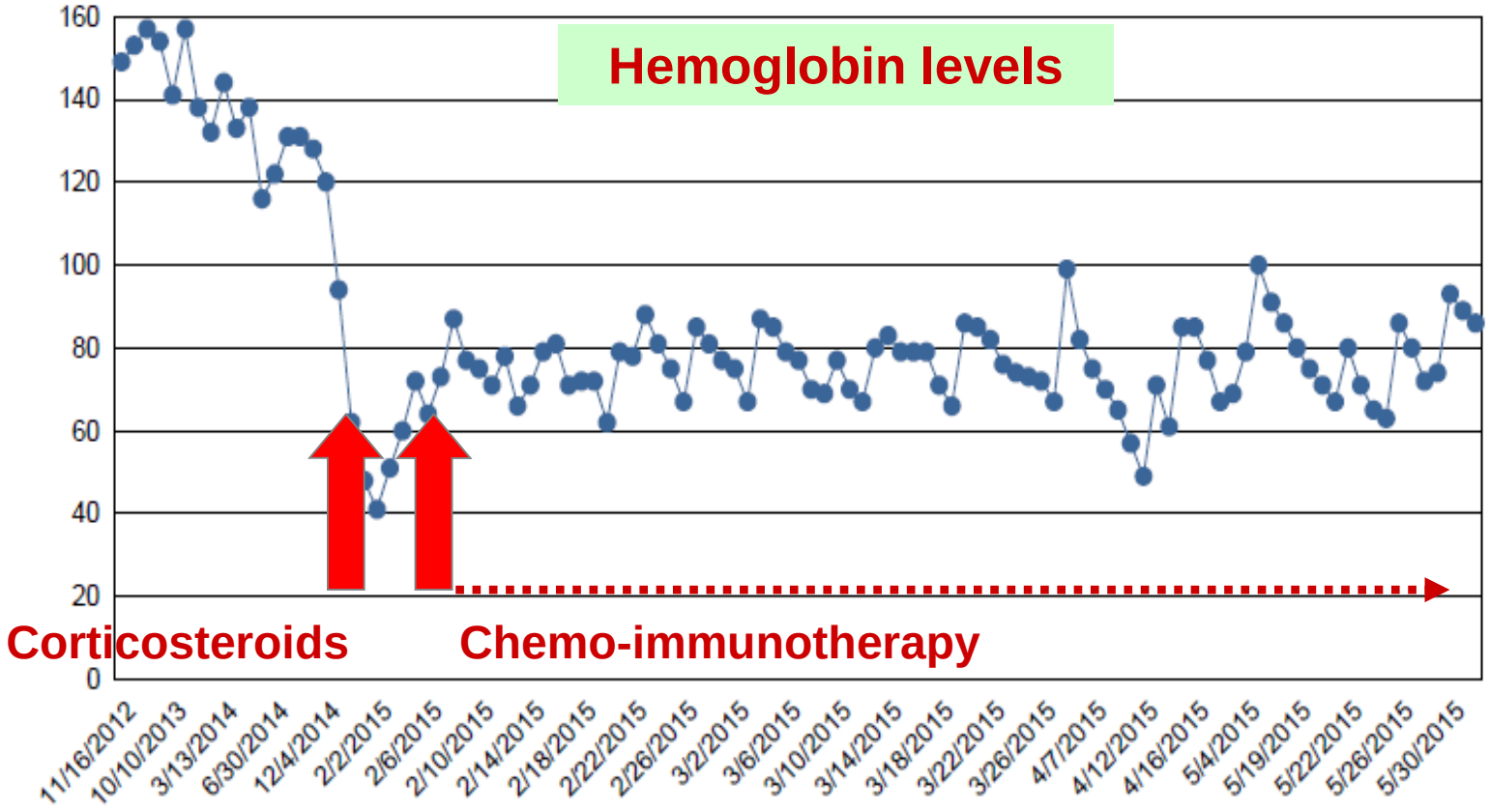
- 31 January 2015: Prednisone 1mg/kg/day and Immunoglobulin infusion 1gr/Kg on days 1 and 2

No response

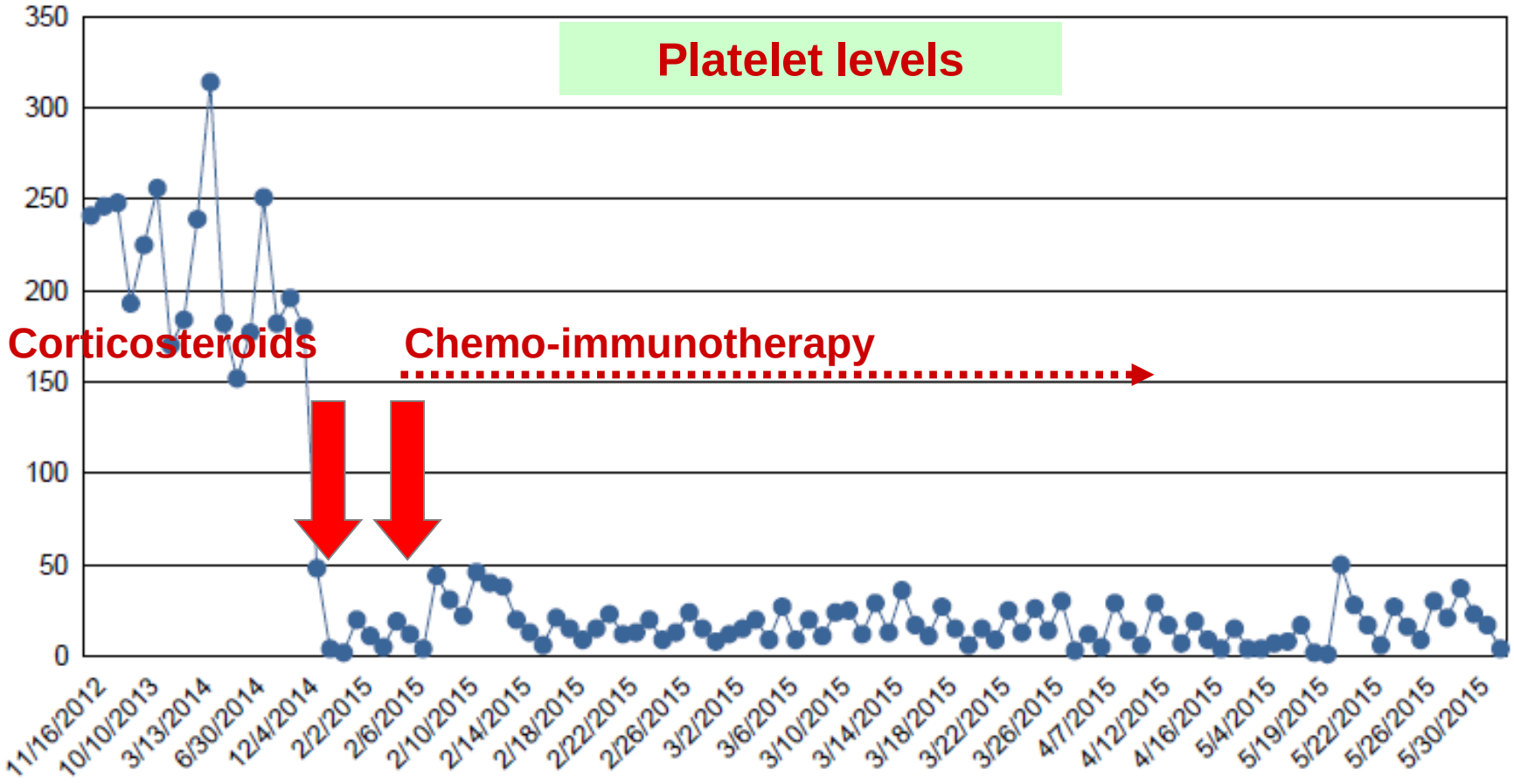
- Bone marrow aspiration: massive infiltration by CLL cells.

- 6 February 2015: chemo-immunotherapy with Bendamustine (70mg/m^2 days 1 and 2) and Rituximab (375mg/m^2).

Therapy and treatment results



Therapy and treatment results

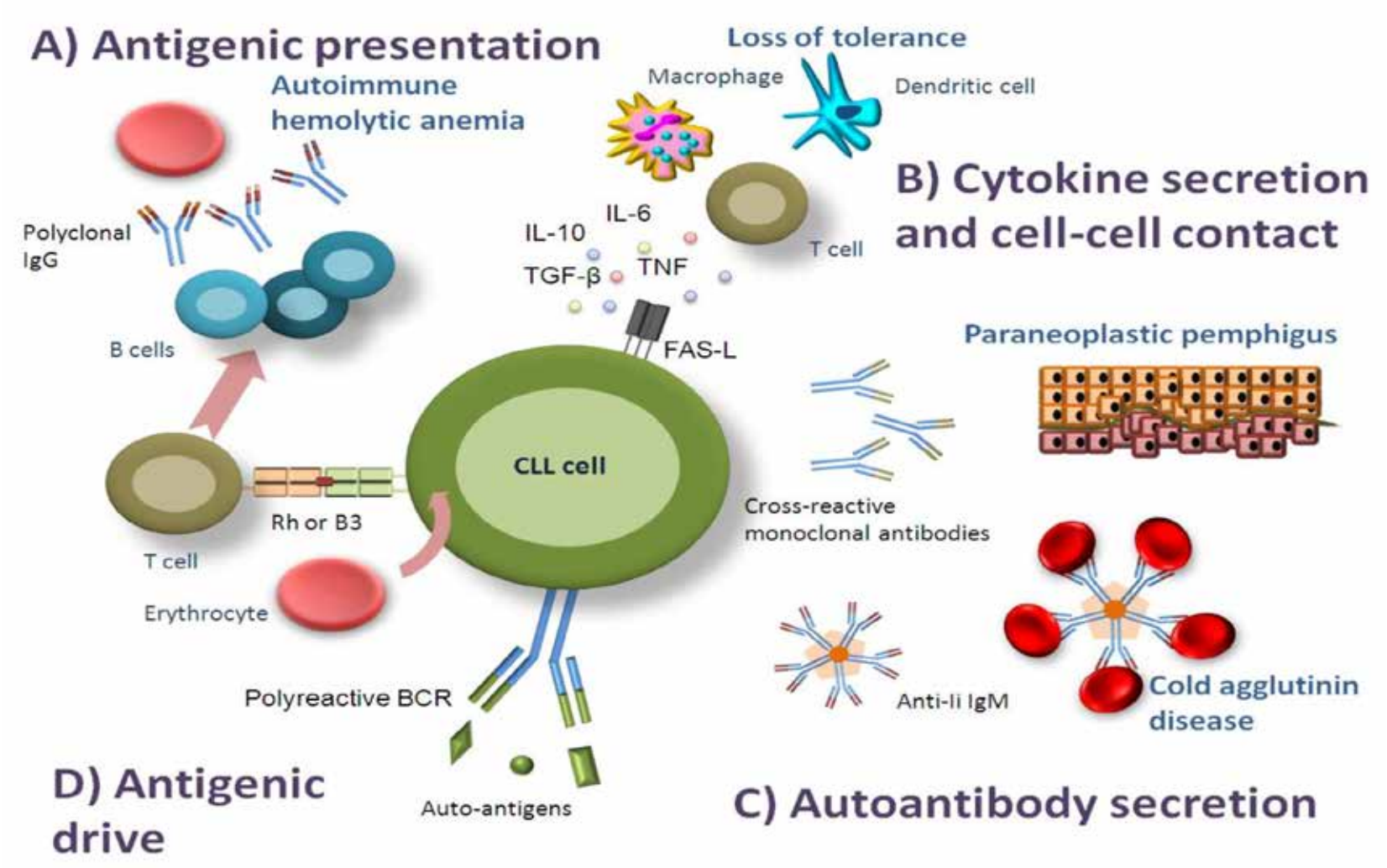


Therapy and treatment results

- After two cycles of chemo-immunotherapy with bendamustine and rituximab
  - Quick disappearance of lymphadenopathy (+2 months after therapy)
  - Improvement of anemia and persistent thrombocytopenia.
  - Corrected reticulocyte count: 1.3%

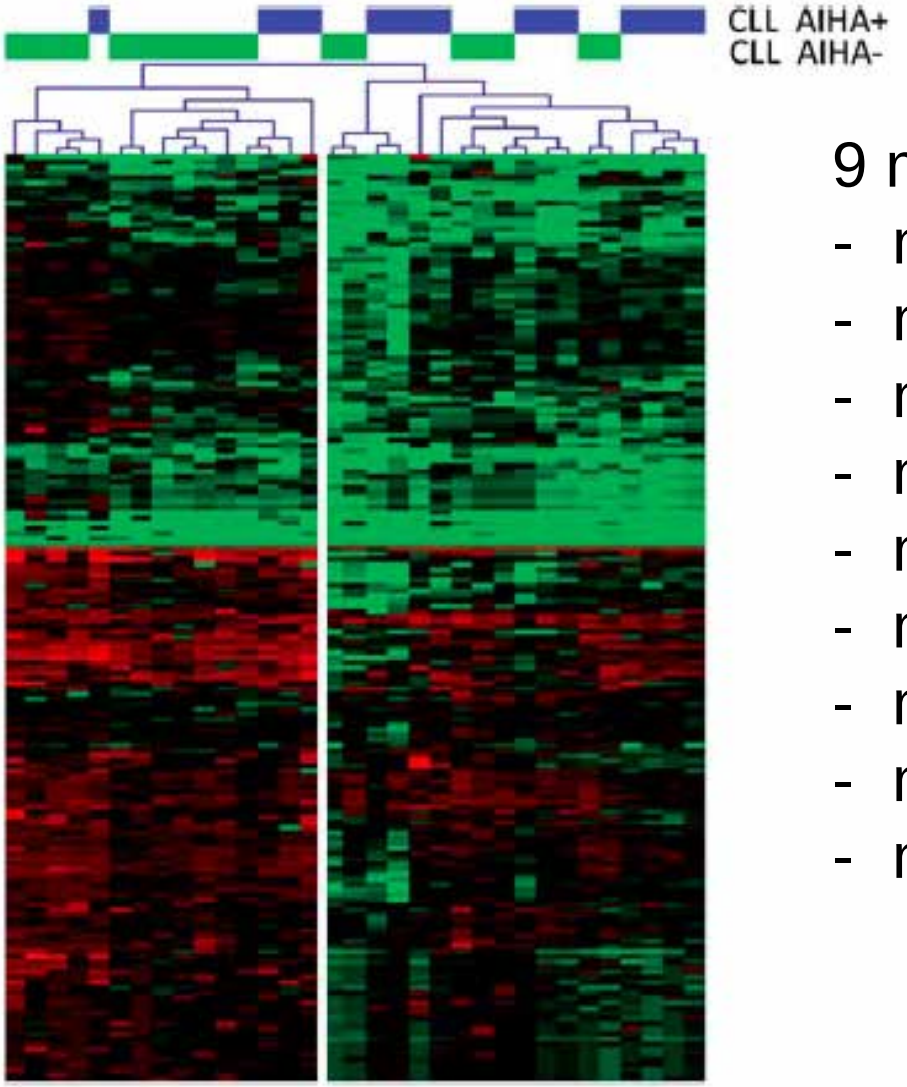
- Eltrombopag treatment planned

Pathogenesis of autoimmune phenomena



Hodgson et al. Haematologica 2011

MicroRNA signature in autoimmune hemolytic anemia (AIHA) and CLL

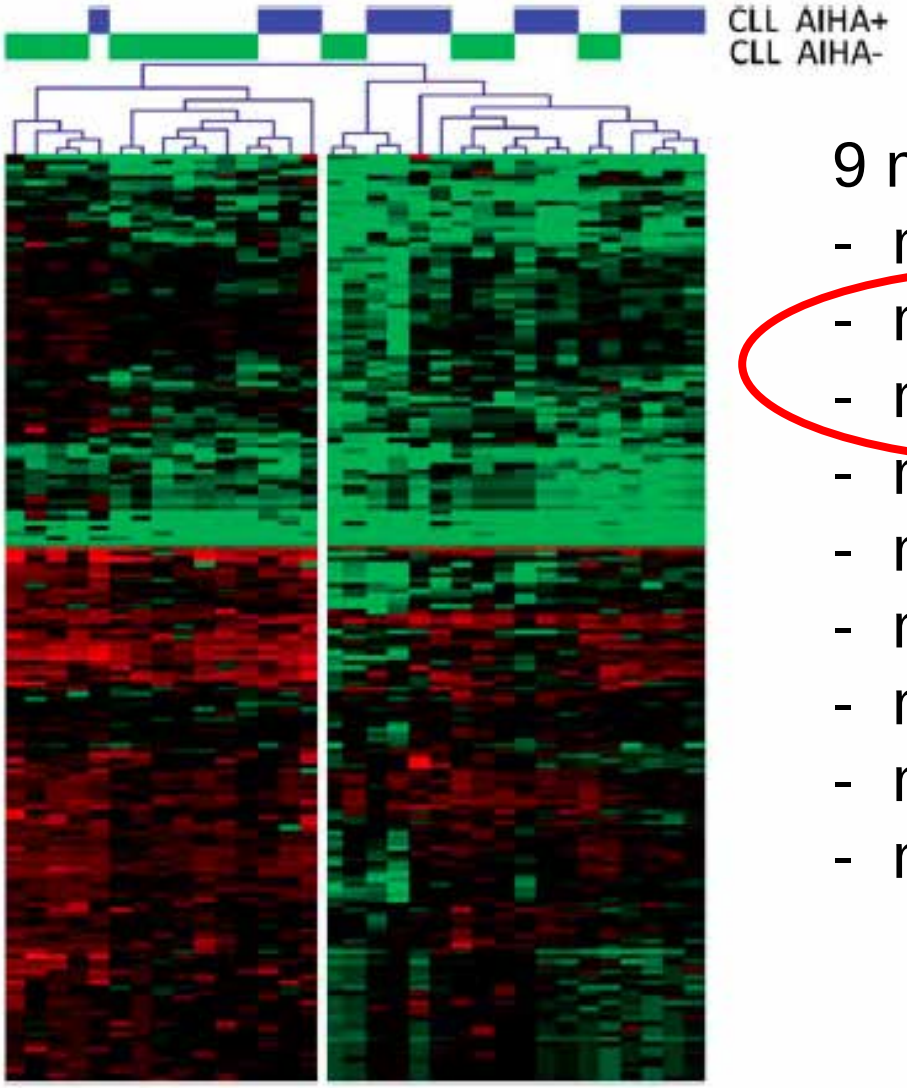


9 miRNAs downregulated

- mir-19a
- mir-20a
- mir-146b-5p
- mir-29c
- mir-186
- mir-223
- mir-324-3p
- mir-484
- mir-660

Ferrer et al. Leukemia and Lymphoma 2013

MicroRNA signature in AIHA and CLL



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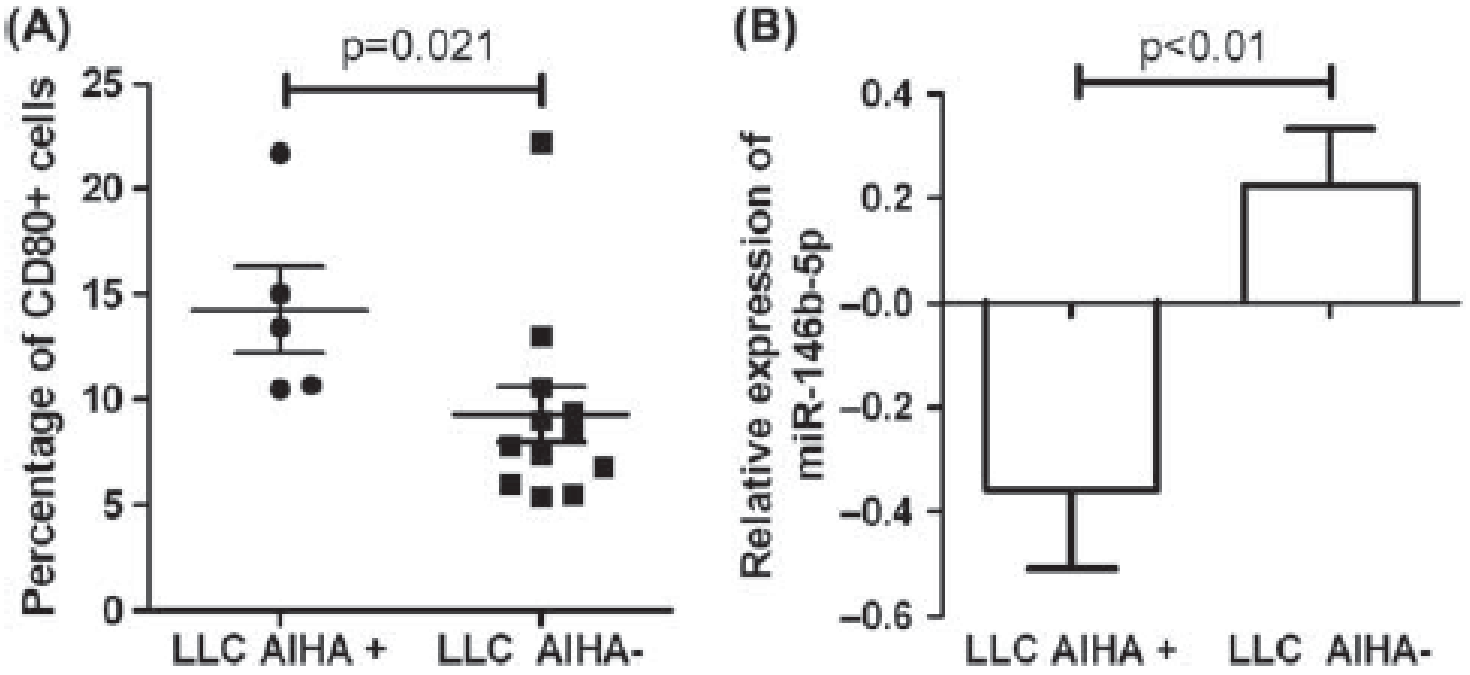
Involved in autoimmune phenomena

Ferrer et al. Leukemia and Lymphoma 2013

MicroRNA signature in AIHA and CLL

mir-146b-5p modulates the expression of CD80 a molecule that regulates B-T cell synapse and is associated with APC capacity of CLL cells



Ferrer et al., Leukemia and Lymphoma 2013

Autoimmune phenomena in CLL

- **Common**
  - AIHA (4.5% to 11%)
  - Immune thrombocytopenia (2%-5%)
  - PRCA (< 1%)
  - Immune neutropenia (?) (LGL)
- **Infrequent**
  - Autoimmune disorders preceeding CLL

    (e.g. pernicious anemia)

  -- Concomitant autoimmune disorders/CLL

  (e.g. Cold agglutinin disease, paraneoplastic pemphigus, neuropathies)

Anemia/Thrombocytopenia: Immune or marrow failure?: Some clues

	Immune	Bone marrow f.
Prior history of IC	Yes	No
Ongoing or recent Rx	No	Yes
Onset	Abrupt	Gradual
Plt count/Hb level	Very low	Moderately low
Bone marrow	Not massively infiltrated Glicoforine ++ / Factor VIII	Packed
Indirect signs hemolysis	Yes; but not always!	No
Espherocytes/Large Plts.	Yes; not striking	No
Laboratory tests	AIHA : DAT(+) ITP : No reliable tests	DAT(-)
Dissociated Hb /Plt count	Possible	No
Response to corticosteroids	Yes	No

IC: immune cytopenia
Rx: treatment

Prognostic significance of autoimmune cytopenia

	Autoimmune cytopenia	Clinical and biological associations	Impact on survival	C “immune” vs C “non-immune”
Mauro et al. Blood 2000	AHAI	Older age Male High white cell count	No	NA
Zent et al. BJH 2008	AHAI ITP	Advanced stage Male High ZAP-70 Unmutated *IGHV* genes Poor risk cytogenetics	No	Yes (better outcome)
Visco et al. Blood 2008	ITP	High white cell count High ZAP-70 Unmutated *IGHV* genes	Negative	NA
Visco et al. Haematologica 2010	AHAI	Unmutated *IGHV* genes	Negative	NA
Dearden et al. Blood 2010	AHAI	Older age Beta 2 microglobulin increased	Negative	NA
Moreno et al. Blood 2010	AHAI ITP	High white cell count Short doubling lymphocyte count High CD38 Beta 2 microglobulin increased	No	Yes (better outcome)
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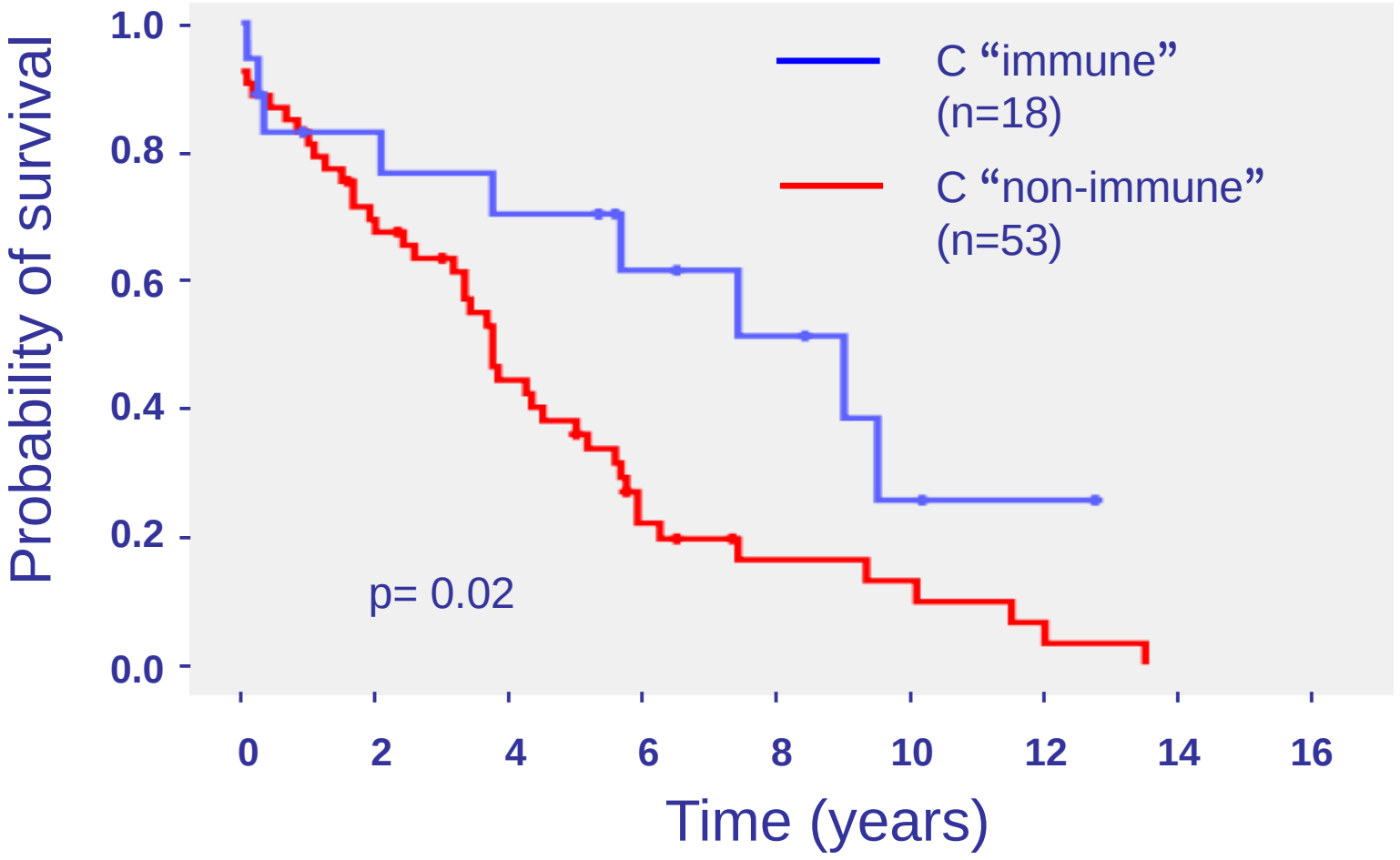
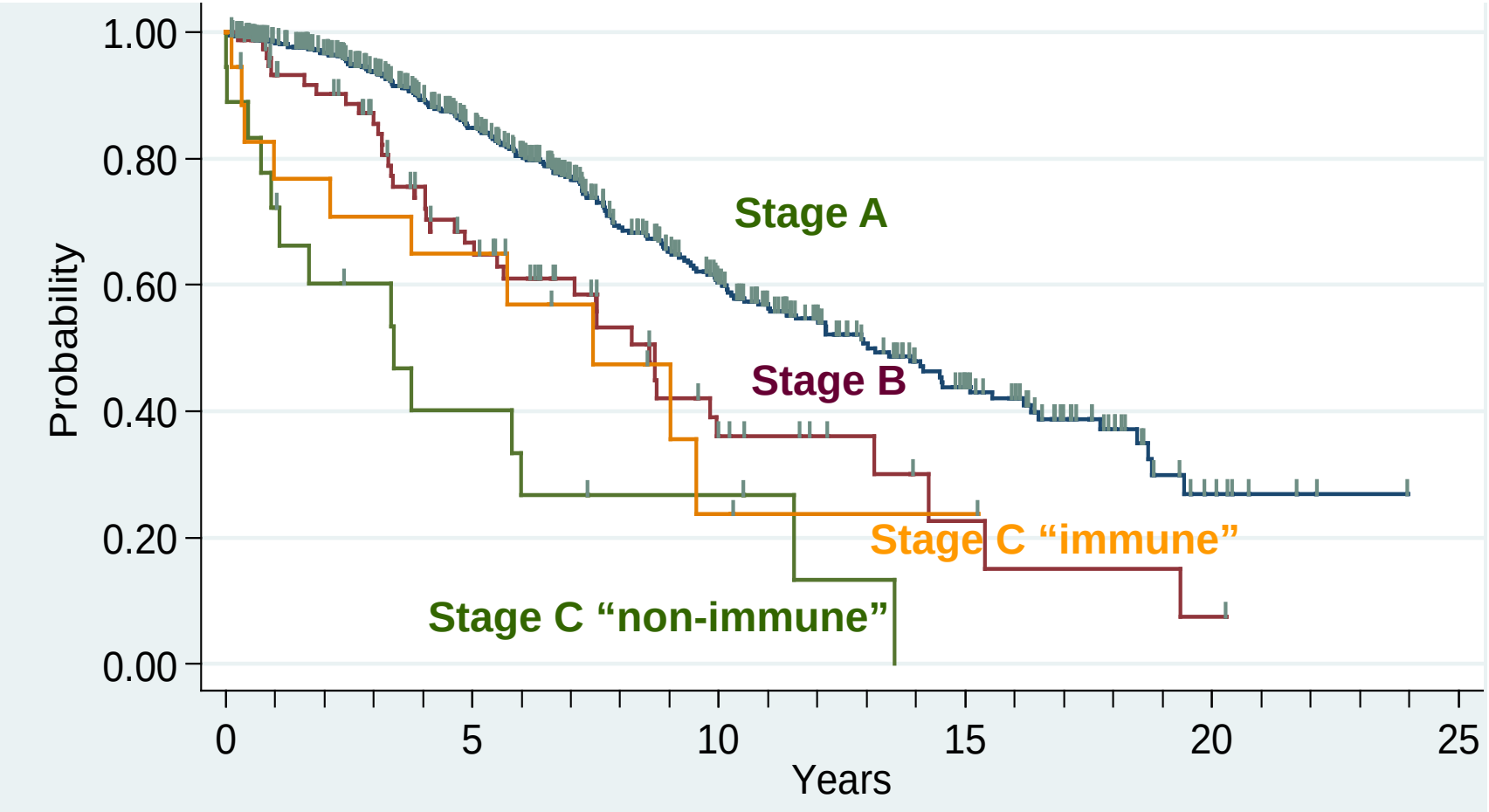
C “immune” *vs*. C “non-immune” (at diagnosis, no prior therapy)



Moreno et al. Blood 2010;
See also Zent et al. BJH 2008; Visco et al. Leukemia and Lymphoma 2014

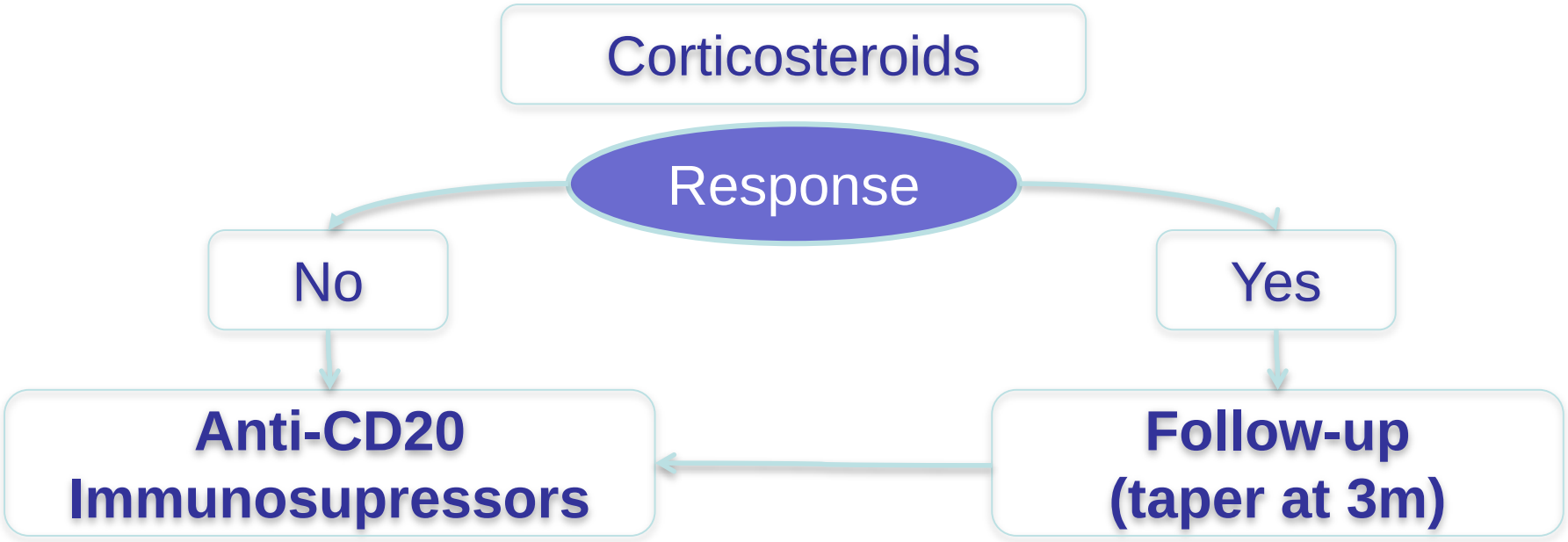
Modified Binet staging system including stage C “immune” category

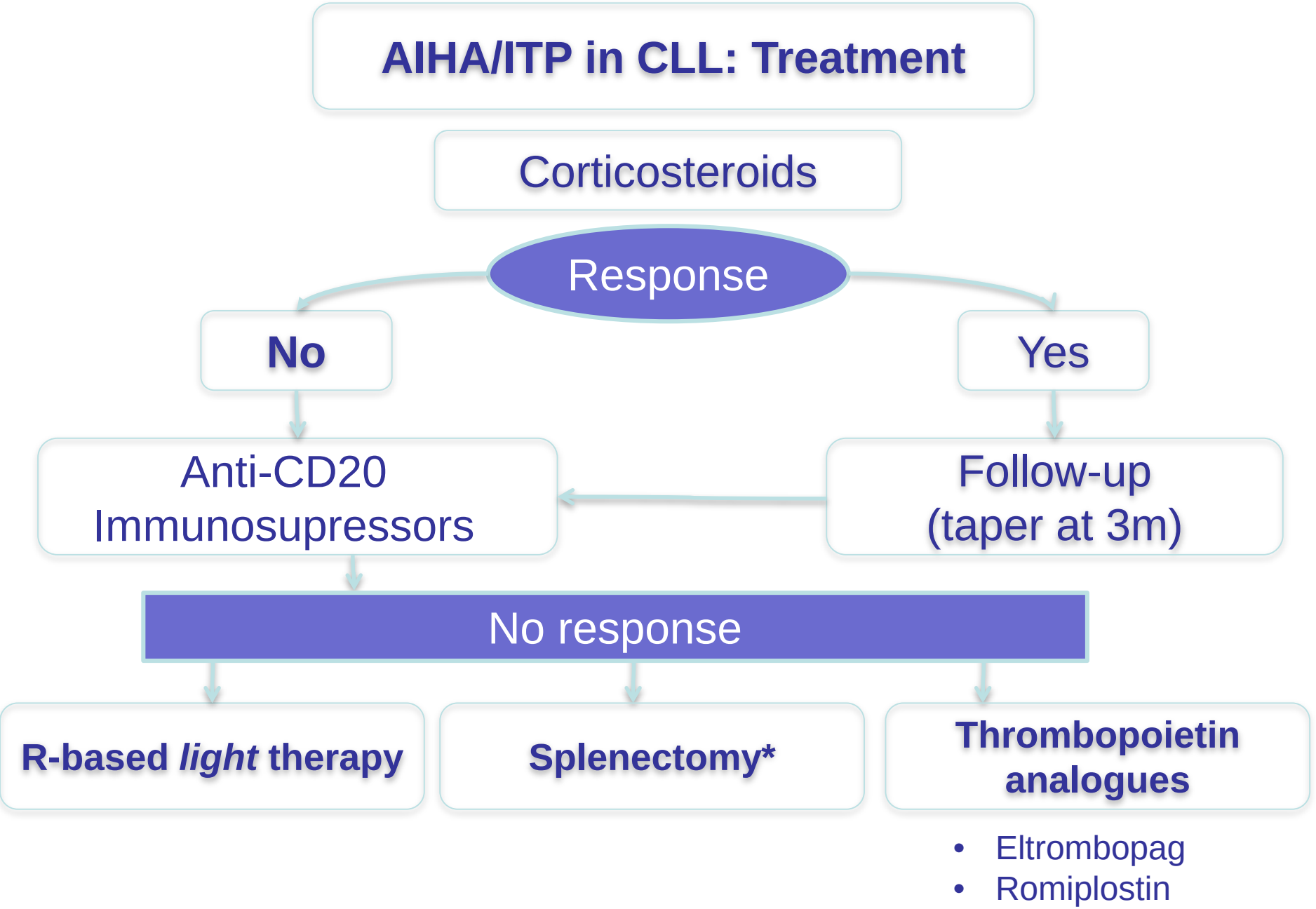


Moreno et al. Blood 2010

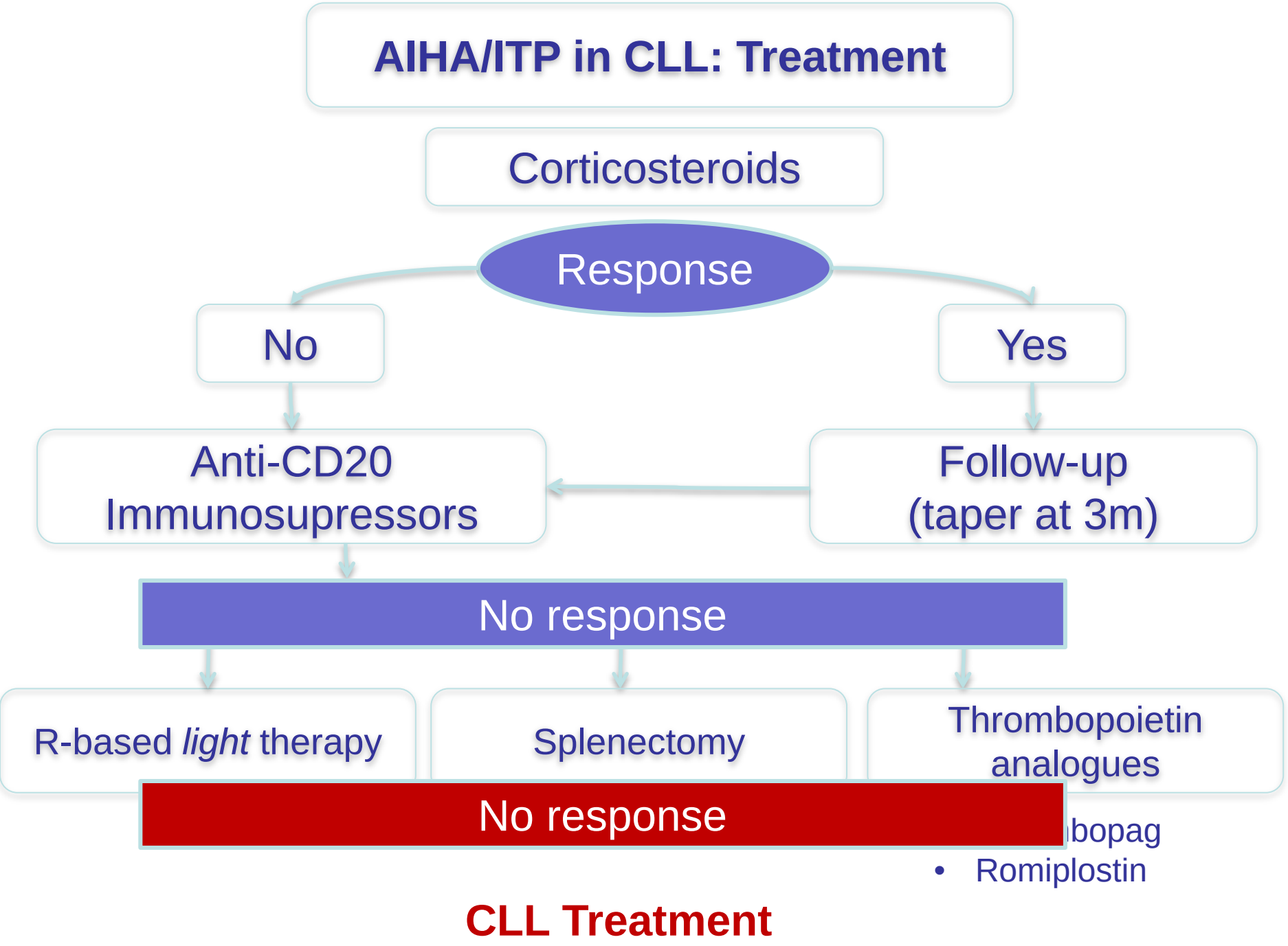
Dearden C Blood 2010 (Inside Blood)

AIHA/ITP in CLL: Treatment





* Role of splenectomy increasingly controversial



CLL Treatment

Treatment of autoimmune cytopenia

- Combination therapies:
  - Corticosteroids + rituximab may increase reponse rate and its duration.
  - Rituximab, cyclophosphamide, dexamethasone (RCD): high *overall* response rate.
  - Bendamustine +Rituximab is effective in AIHA
  - Rituximab, dexamethasone and cyclosporine: high response in ITP
  - BCRi (i.e Ibrutinib)- case report showing controversial results, including effectiveness in AIHA
- Other:
  - Intravenous immunoglobulin (bleeding!).
  - Platelets/Red-blood cells tranfusion.

Modern therapy minimizes the risk of developing AIHA

Treatment regimen	AIHA prevalence	Remarks
Chlorambucil	5-12%	Unselected patients
Chlorambucil	2-12%	Selected patients (trials) Previously untreated
Fludarabine	11-23%	Unselected Advanced and heavily pretreated
Fludarabine	8-11%	Selected patients (trials) Previously untreated
Fludarabine plus Cyclophosphamide	1-5%	Selected patients (trials) Previously untreated
FCR	<1-5.8%	Selected patients (trials) Previously untreated

Di Raimondo et al. Leukemia and Lymphoma 1993; Myint et al. BJH 1995; Catovsky et al. Blood 2004; Leporrier et al. Blood 2001; Moreno et al. Blood 2010; Mauro et al. Blood 2000; Eichhorst et al. Blood 2006; Dearden et al. Blood 2008; Eichhorst et al. Blood 2009; Borthakur et al. BJH 2007; Hallek et al. Lancet 2010

Modern therapy minimizes the risk of developing AIHA

Treatment regimen	AIHA prevalence	Remarks
FCR+ibrutinib	NA	Selected patients (trial)
Ibrutinib *vs* Ofatumumab	0 *vs* 2%	Selected patients (trial)
Ibrutinib	1.5%	Selected patients (trial)
Ofatumumab	2-10%	Selected patients (observational study) Heavily pretreated
GA-101+Chlorambucil	NA	Selected patients (trial)

Brown J et al. Blood 2015; Montillo et al. Blood 2014 (ASH abstract); Rogers et al. Blood 2014 (ASH abstract); Moreno C et al. Haematologica 2015; Goede et al. N Engl J Med 2014

Take-home messages

- Autoimmune cytopenias (AC) frequently complicate CLL.
- The risk of AC is much lower with current than with older therapies.
- The possibility of cytopenia of immune origin needs to be taken into account in cases *advanced* disease (Rai III, IV; Binet C) without high tumor burden.
- The prognostic significance of autoimmune cytopenia may vary depending on the cohort investigated (i.e., pre-treated, whole series, advanced disease).
- Autoimmune cytopenia not responding to conventional therapy is an indication for CLL therapy.

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ON TP53 ANALYSIS IN CHRONIC
LYMPHOCYTIC LEUKEMIA
Technical approaches and data interpretation, troubleshooting, predictive and therapeutic implications
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