Chronic Lymphocytic Leukemia

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Chronic Lymphocytic Leukemia

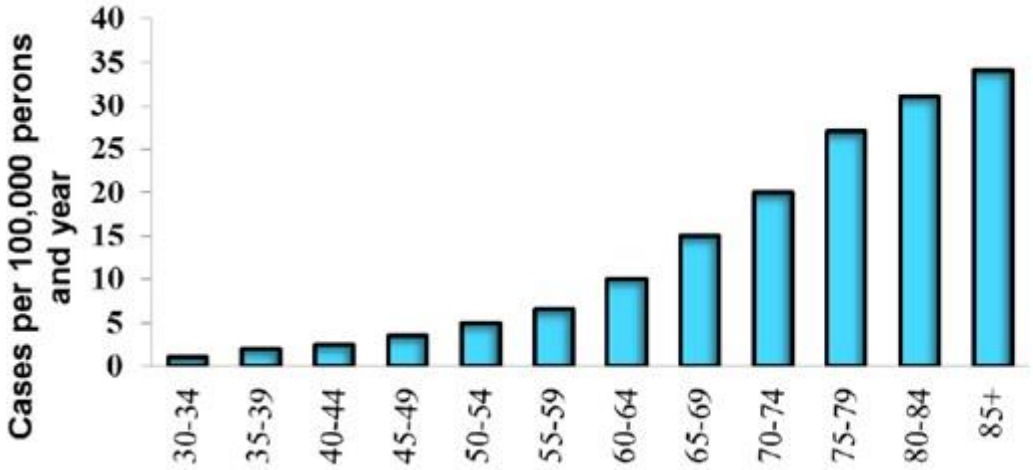
- Statistics
- Clinical features
- Diagnosis
- Staging, prognosis
- Treatment
- Complications

Statistics

- Most frequent leukemia in Western world
- 25 - 30% of all leukemias
- Incidence rate: 5-6/100 000/ year
- More common in men than women (2:1 ratio)

Statistics

- CLL incidence increases with age
- Median age at diagnosis 72 years



Increasing age-adjusted incidence

Etiology

- Unknown
- No association with radiation or chemicals
- Genetic predisposition
  - Familial predisposition can be documented in 5-10% of patients with CLL

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Clinical features

- Asymptomatic: 50 % or more

- Fatigue, fever, weight loss
- Lymphadenopathy (painless)
- Splenomegaly / hepatomegaly
- Anemia
- Thrombocytopenia, bleeding

} BM infiltration

- Recurrent infections
- AIHA, ITP

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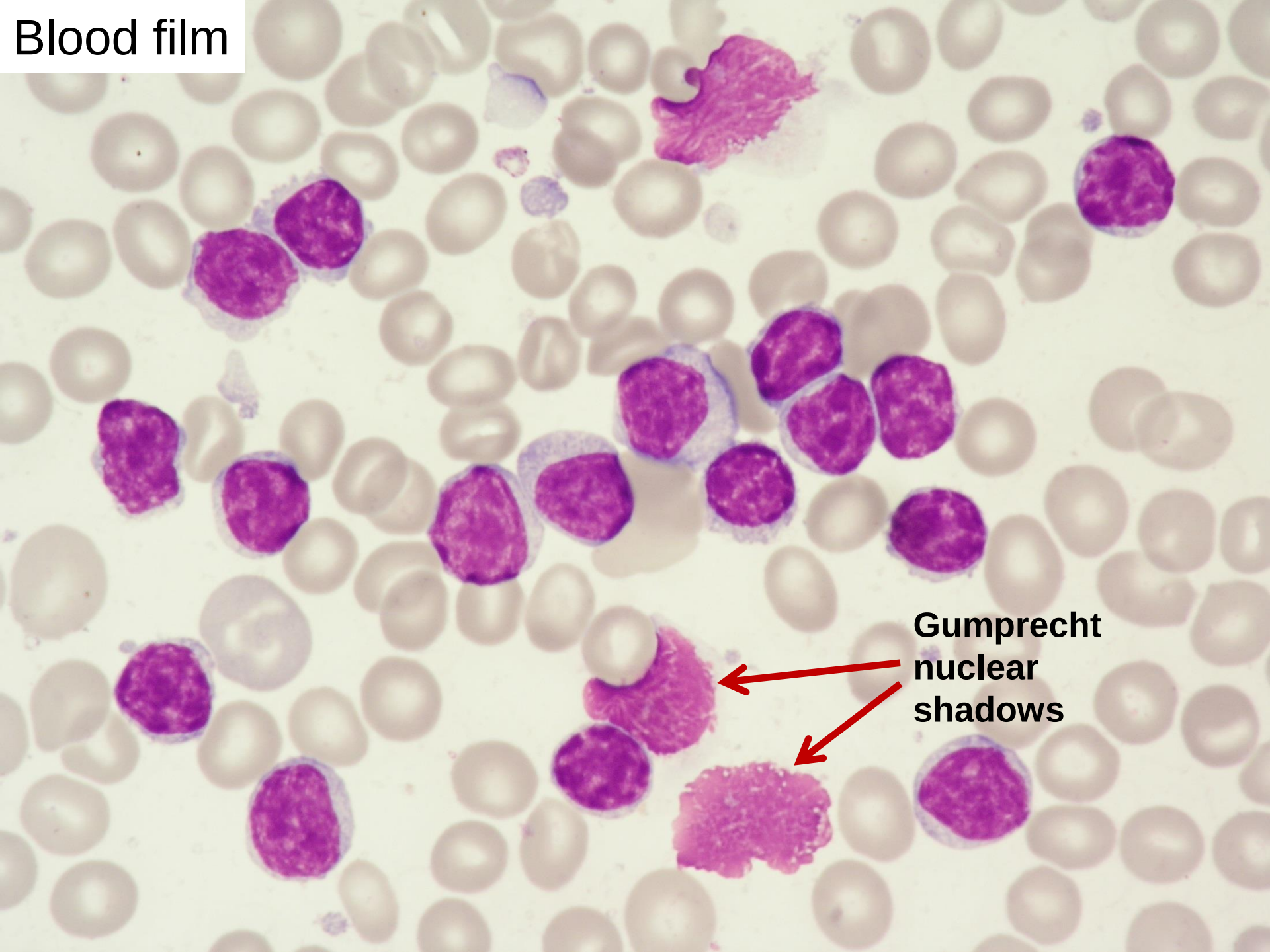
Diagnosis of CLL

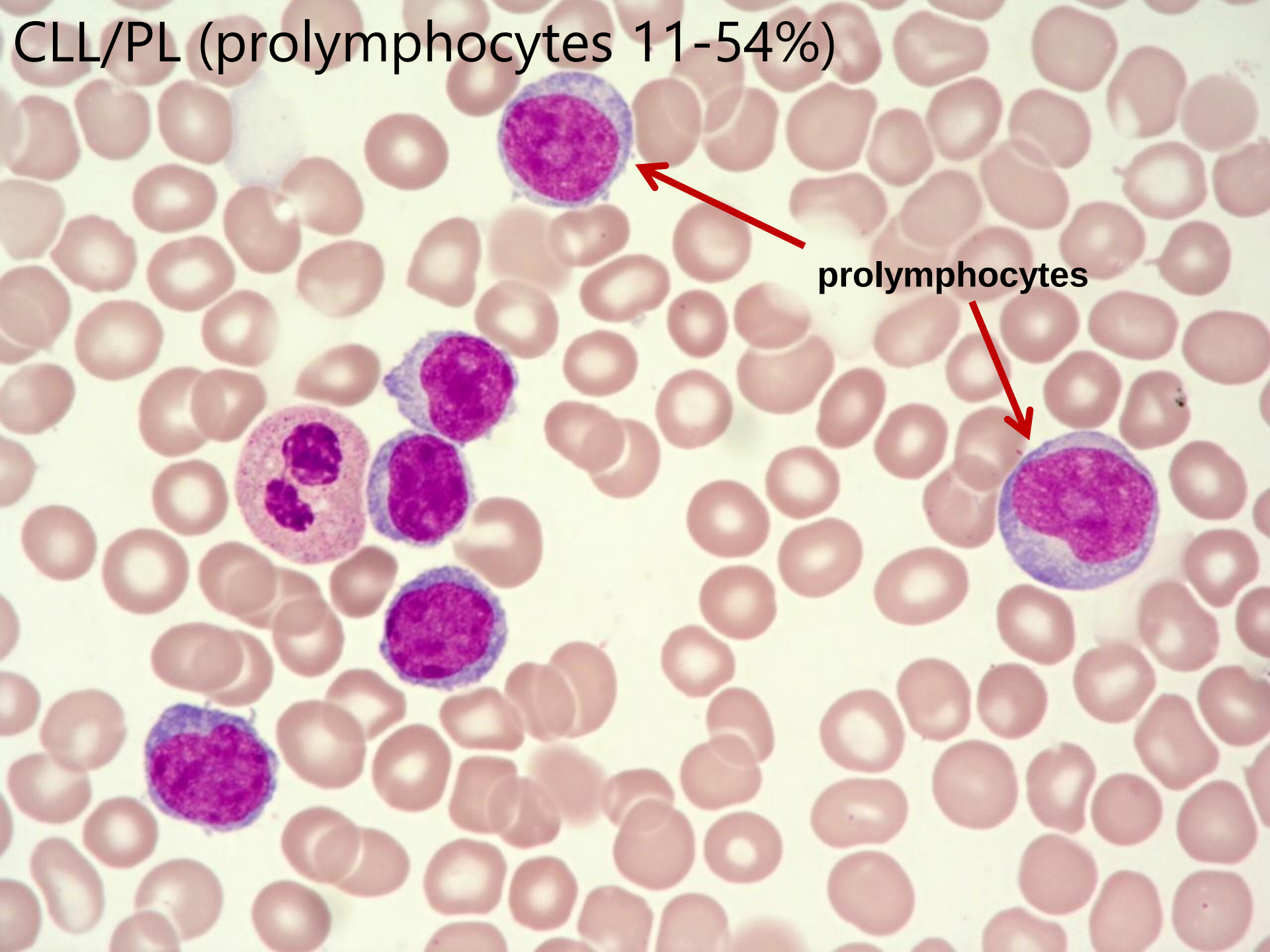
- Presence of at least $5x10^9$ B lymphocytes/L (5000/µL) in the peripheral blood
- Typical immunophenotype
- < 55% atypical lymphoid cells (prolymphocytes) in peripheral blood

- Tests to establish diagnosis:
- Complete blood count and differential (blood smear)
- Immunophenotyping of lymphocytes

Hallek M et al., Blood 2018

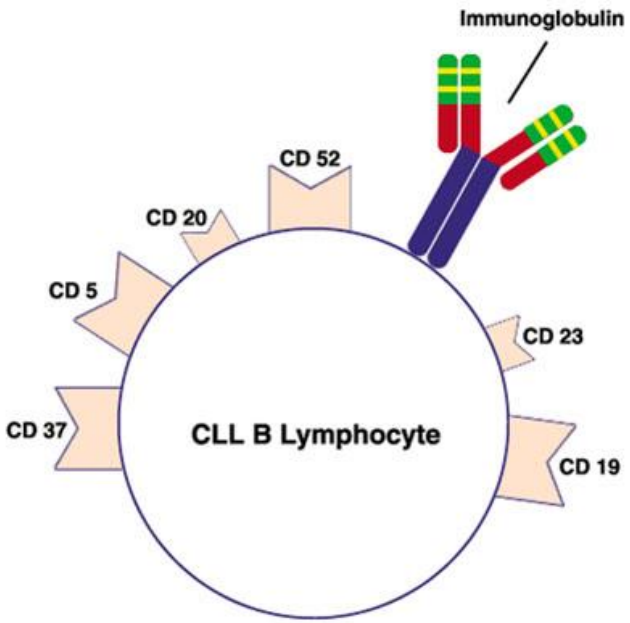

Blood film
Gumprecht nuclear shadows

CLL/PL (prolymphocytes 11-54%)



CLL immunophenotype

Marker	Expression
CD5	Positive
CD23	Positive
CD79b	Dim/negative
FMC7	Negative
sIg	Dim
CD22	Dim/negative
CD20	Dim
CD43	Positive
CD11c	Dim
CD10	Negative
CD81	Negative
CD200	Positive



Differential diagnosis

- Non-neoplastic lymphocytosis:
  - Infections (infectious mononucleosis etc.)
  - Microscopic differential, flow-cytometry

- Neoplastic conditions other than CLL:
  - Leukemic phase of lymphomas (MCL)
  - Hairy cell leukemia, prolymphocytic leukemia
  - Bone marrow examination, lymph node biopsy, cytogenetics

MBL

- Monoclonal B-cell lymphocytosis (MBL)
  - Monoclonal B-cell populations of up to $5x10^9/L$
  - Found in up to 12% of healthy individuals
  - Precedes virtually all cases of CLL
  - Requires follow-up

Swerdlow et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood 2016

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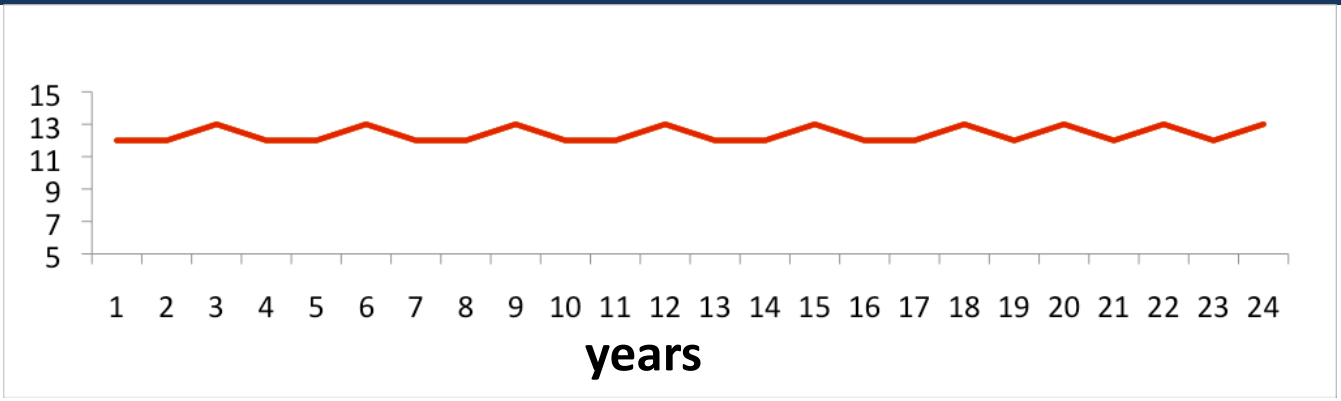
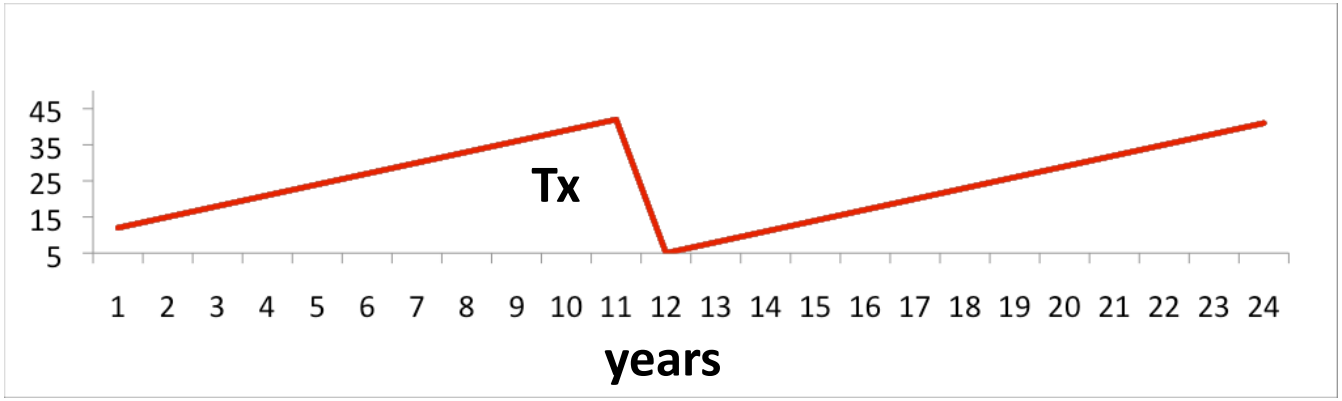
CLL: Highly variable clinical course

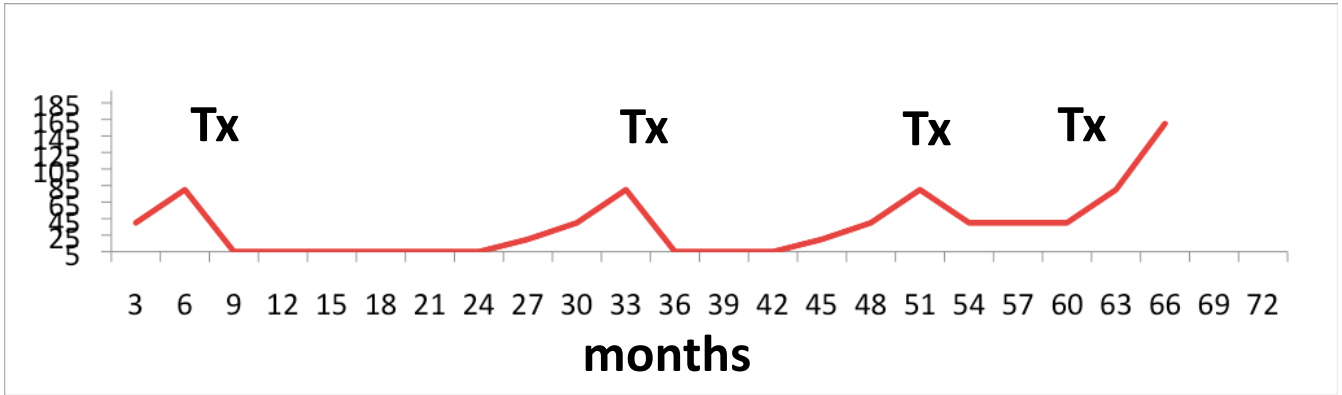
Stable



Slow progression



Fast progression



CLL: ‚classical' prognostic factors

- **Poor prognosis:**
- ↑ Clinical stage (Rai or Binet)
- ↑ Serum markers for tumor burden
  - LDH
  - Beta-2-microglobulin
  - Thymidine kinase
- ↓ Lymphocyte doubling time (< 1 year)

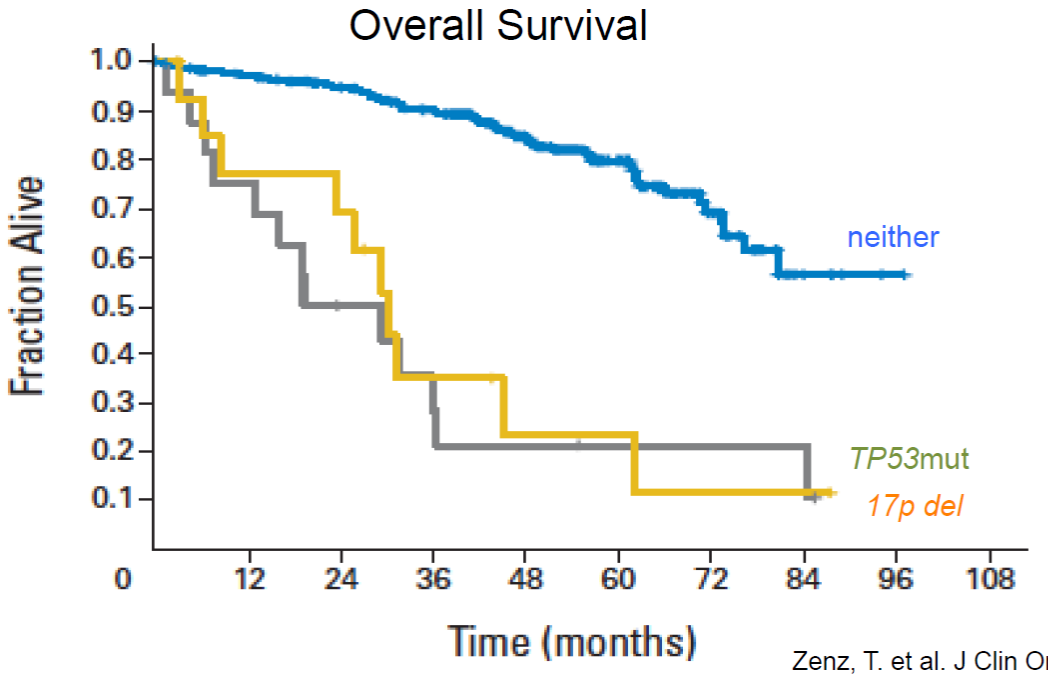
CLL staging system: Rai

Stage (Rai)	Description	Median survival
0	Lymphocytosis	> 10
I	Lymphocytosis + lymphadenopathy	7-11
II	Lymphocytosis + spleno/hepatomegaly	7-8
III	Lymphocytosis + anemia (Hb < 110 g/L)	4-5
IV	Lymphocytosis + thrombocytopenia (PLT < $100x10^9$/L)	4-5

Rai KR et al. Clinical staging of chronic lymphocytic leukemia, Blood 1975

CLL: TP53 mutation or del(17p)

- Strongest predictor of poor survival
- Found in 7 to 10 %
- Implications for therapy choices



Zenz, T. et al. J Clin Oncol (2010) 28:4473-4479

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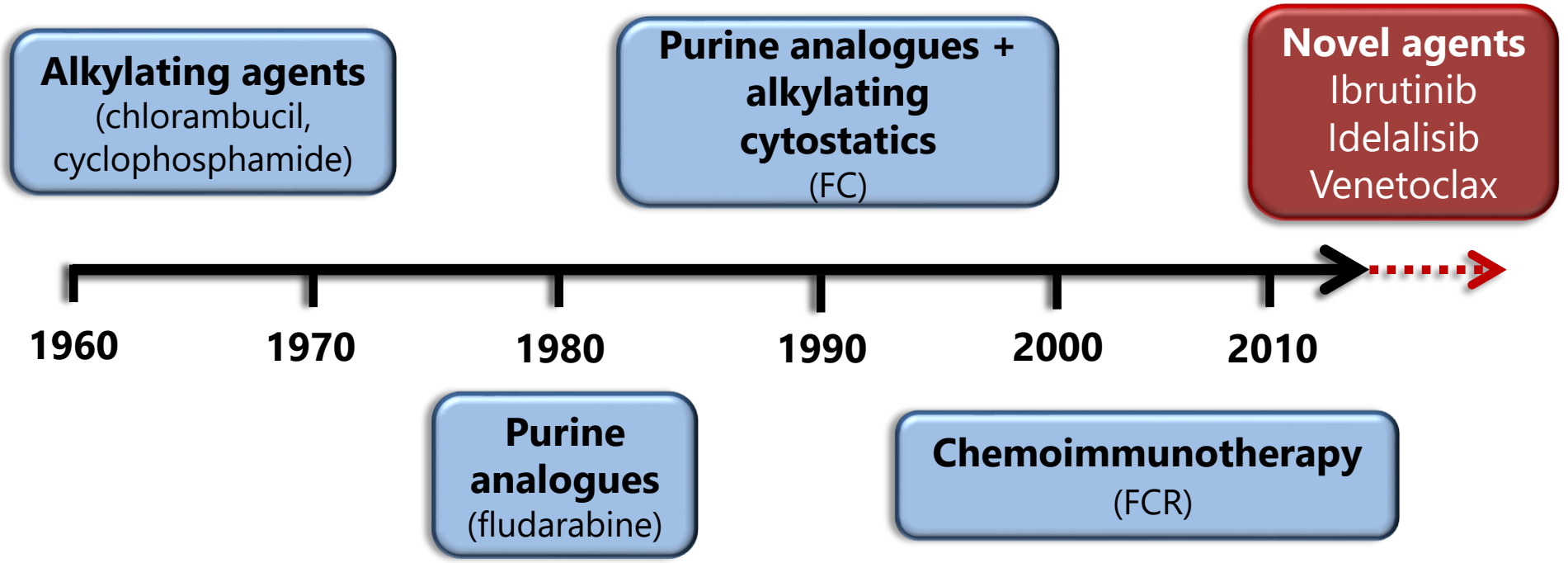
When to treat? The concept of active disease

- Bulky disease: massive (>6 cm) or progressive splenomegaly or massive (>10cm) or rapidly progressive lymphoadenopathies
- Progressive bone marrow failure: appearance or worsening of anemia or thrombocytopenia
- Autoimmune anemia or thrombocytopenia NOT responsive to steroids
- Lymphocyte doubling time (LDT) < 6 months or a >50% increase in the absolute lymphocyte count in 2 months
- Systemic symptoms: weight loss (>10% in the last 6 months), fever (for two weeks in the absence of infections), night sweats, extreme fatigue

Hallek et al. Blood 2018

Therapy



Symptom palliation

Higher ORR
Better PFS

Best ever reported results
MRD status

Cure?

Treatment options

- **Chemoimmunotherapy**
  - Rituximab + fludarabine + cyclophoshamide (FCR)
  - Rituximab + Bendamustine
  - Rituximab + Chlorambucil
- **Targeted treatment** (small molecules)
  - BCR inhibitors (ibrutinib, idelalisib)
  - BCL2 inhibitor (venetoclax)
- **Allogenic stem cell transplantation**
  - Fit young patients

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Complications in CLL

- **Histologic transformation (Richter‘s syndrome)**
  - Transformation to a highly aggressive lymphoma (DLBCL), up to 10 % during CLL course
- **Infections**
  - Most frequent cause of morbidity and mortality in CLL
- **Autoimmune complications**
  - Occur in up to 25 % of CLL patients, AIHA, ITP
- **Secondary malignancies**

Conclusions

- Most common type of leukemia in western countries
- Disease typically occurs in elderly patients
- Highly variable clinical course
- Only patients with active or symptomatic disease require therapy
- Bone marrow evaluation is not required for the diagnosis
- New therapeutic agents – potential to improve the outcome of patients with CLL