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Chronic Lymphocytic Leukemia

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Disclosures

Data and Safety Monitoring Board	Bayer HealthCare Pharmaceuticals

Case presentation 4: Dr Chen

87-year-old man

- 2012: Diffuse adenopathy: CLL (del11q, trisomy 12)
  - Observed
- 2014: Obinutuzumab/chlorambucil x 6
  - Discontinued chlorambucil early due to cytopenias
- 2015: Progressive disease
- Ibrutinib: excellent response
  - Develops atrial fibrillation requiring oral rivaroxaban
- Currently: No bulky nodes, creatinine ~1.0; WBC normal

Case presentation 5: Dr Brenner

58-year-old woman

- 2010: Standard-risk CLL

    – FCR x 6 with CR

- 2015: Bone marrow: Extensive replacement
    by CLL (asymptomatic)

  – Multiple cytogenetic abnormalities, including 17p deletion

- Currently on ibrutinib in complete remission

Biomarkers in CLL

Informing therapy

CLL: Risk stratification
Staging remains important

- Modified Rai

  - Low: Lymphocytosis in blood or marrow

  - Intermediate: Enlarged nodes, splenomegaly and/or hepatomegaly

  - High: Anemia (Hb <11) or thrombocytopenia (Plt < 100)

- Binet

  - A: 2 involved nodal sites without cytopenias

  - B: Organomegaly; more nodal sites, without cytopenias

  - C: Hb < 10 and/or Plt < 100.

Genetic aberrations and survival in CLL

Dohner et al. *NEJM* 343:1910; 2000
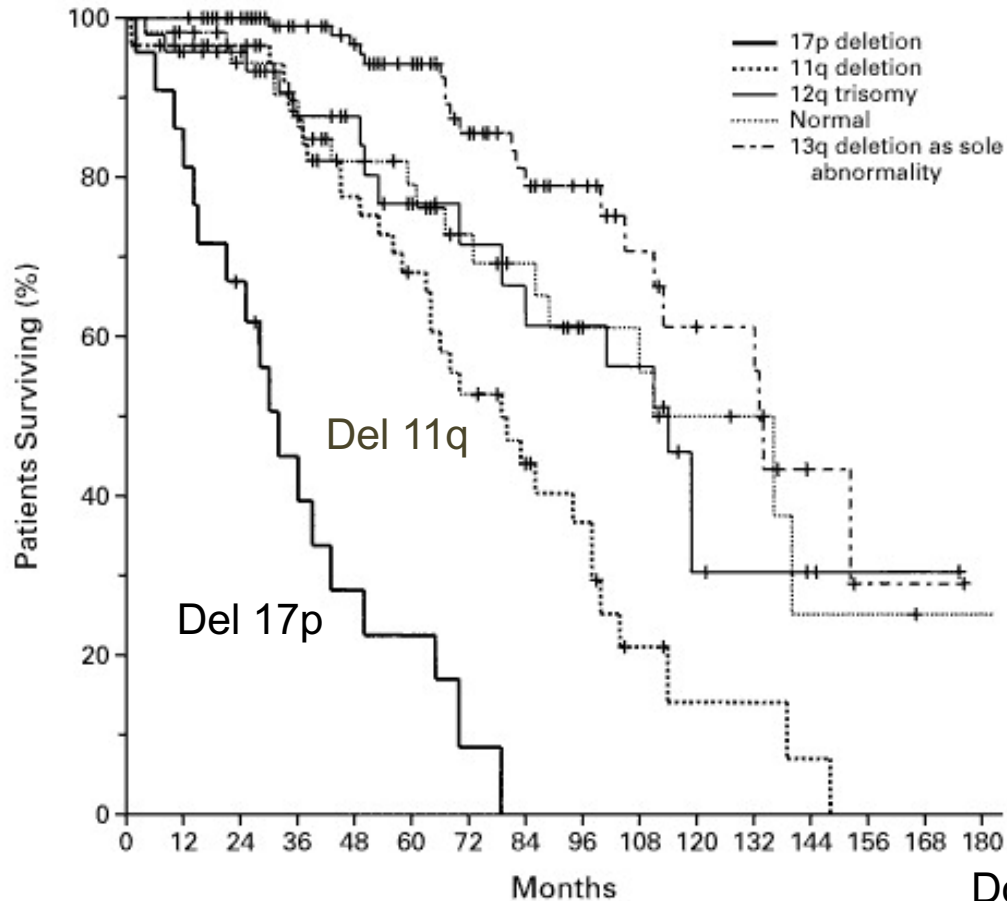
Clonal evolution in CLL is common, and has prognostic implications

- Mayo Clinic:
  - The rate of clonal evolution measured by FISH increased with duration of follow-up with only one occurrence in the first 2 years (n = 71; 1.4%) but 17 occurrences (n = 63; 27%) among patients tested after 5+ years.
- Germany:
  - Following a median observation time of 42.3 months after first genetic study, 11 out of the 64 (17%) patients showed clonal evolution with the following newly acquired aberrations: del(17p13) (n = 4), del(6q21) (n = 3), del(11q23) (n = 2), +(8q24) (n = 1).

Shannafelt et al. *JCO* 24:4624 2006
Stilgenbauer et al. *Haematologica* 92:1240 2007

# Mutations driving CLL and their evolution in progression and relapse
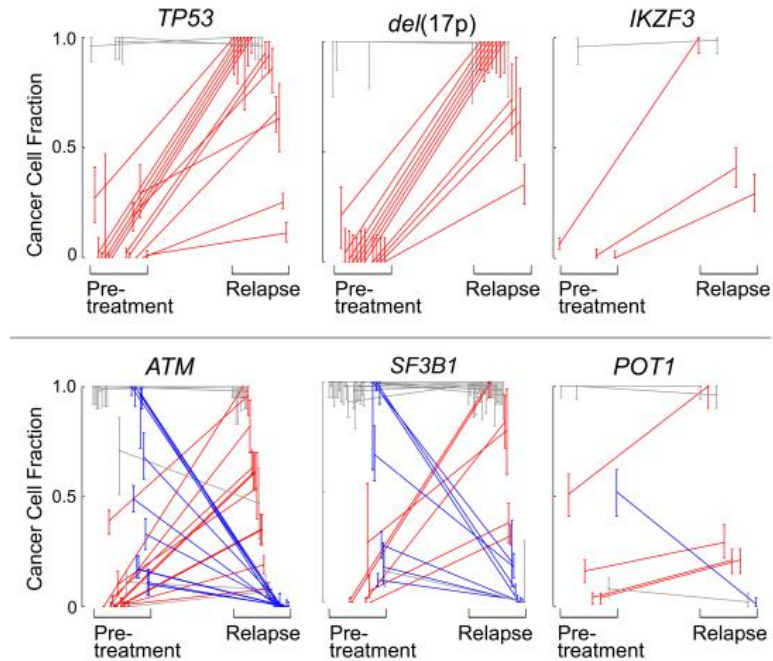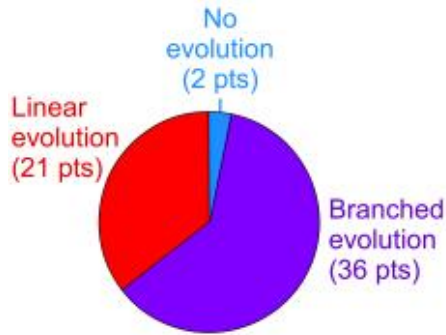
CLL International Prognostic Index (2016)

	Adverse Factor	Grade
Age	>65 years	1
Clinical Stage	Rai I-IV or Binet B-C	1
β_2-microglobulin level	>3.5 mg/L	2
IGHV mutation status	Unmutated (>98% homology with germline)	2
Del(17p) and/or *TP53* mutation	Present	4

Risk	Score	5-year Overall Survival (p<0.001 for all)
Low	0-1	93%
Intermediate	2-3	79%
High	4-6	63%
Very High	7-10	23%

CLL IPI predicts overall survival
Superior to Stage and IgH mutation status
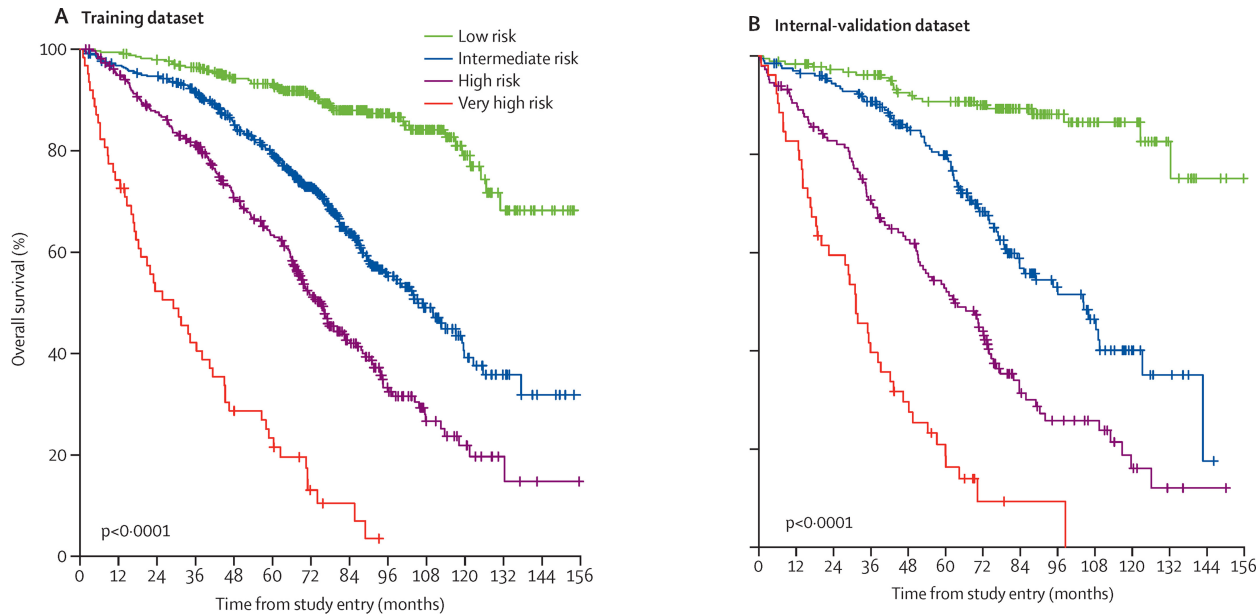
Potential therapeutic implications of CLL-IPI

CLL-IPI category	OS at 5 years (%)	Potential clinical consequence
Low risk	93.2	Do not treat
Intermediate risk	79.3	Do not treat except if the disease is really symptomatic
High risk	63.3	Treatment indicated except if the disease is asymptomatic
Very high risk	23.3	If you need to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials.

CLL: Which biomarkers to evaluate, and when?

Diagnosis

- Rai or Binet

- Del 17p/TP53 mutation

- IGHV

- Beta-2 microglobulin

Eichhorst and Hallek, *Hematology 2016* 149-155

CLL: Which biomarkers to evaluate, and when?

Diagnosis/Treatment

- Rai or Binet

- Del 17p/TP53 mutation

- IGHV

- Beta-2 microglobulin

- Karyotype

- Del 11q

Eichhorst and Hallek, *Hematology 2016* 149-155

CLL: Which biomarkers to evaluate, and when?

Diagnosis/Treatment

- Rai or Binet
- Del 17p/TP53 mutation
- IGHV
- Beta-2 microglobulin
- Karyotype
- Del 11q

Relapse treatment

Del 17p/TP53 mutation

Karyotype

Del 11q

Eichhorst and Hallek, *Hematology 2016* 149-155

CLL biomarkers: future issues

- Prognostic vs. predictive biomarkers

- Novel therapies (ibrutinib) may replace chemoimmunotherapy for selected patients as upfront therapy. CLL-IPI has not been demonstrated to be predictive in this setting.

- Clonal evolution emphasizes importance of longitudinal evaluation of cytogenetics, particularly if therapeutic decisions will be impacted by findings.

Venetoclax in CLL

Venetoclax in relapsed CLL

D Absolute Lymphocyte Count

Roberts et al, *NEJM* 374:311 2016
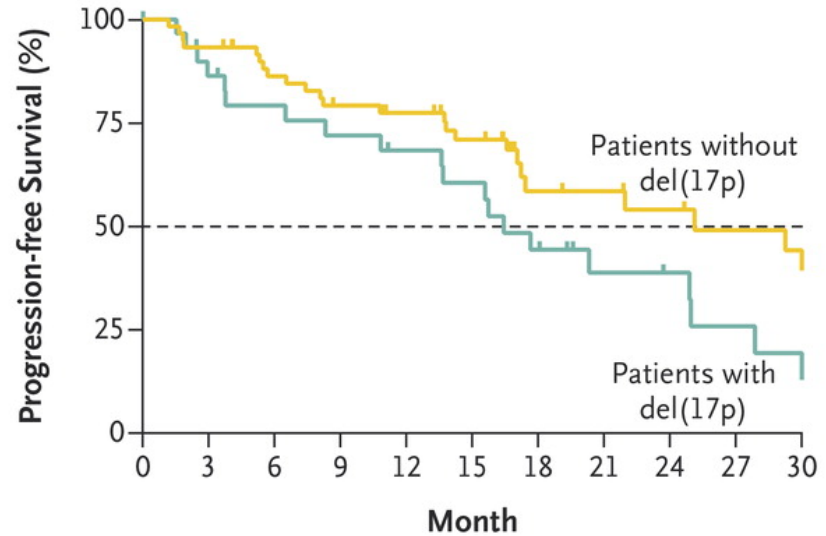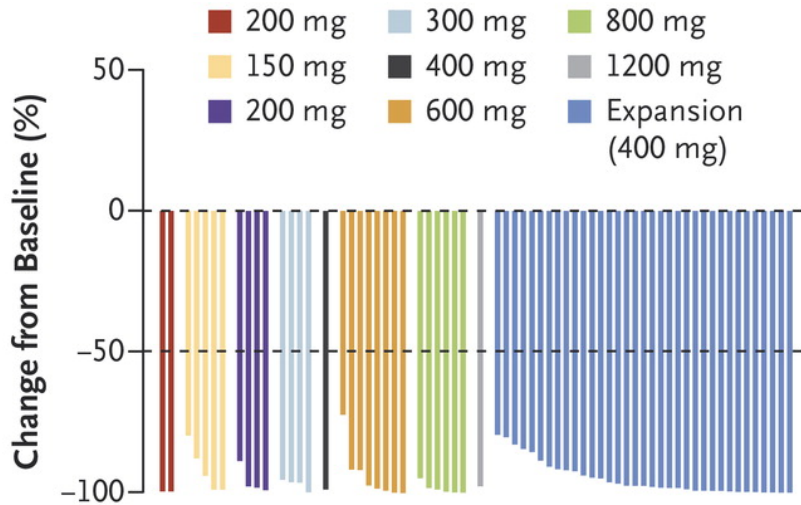
Clinicopathological features and outcomes of CLL on venetoclax

- In relapsed/refractory CLL, approximately 80% of patients respond to venetoclax, irrespective of risk factors for chemoimmunotherapy.

- 67 patients on 3 early phase venetoclax trials:

  - 25 (37%) experienced PD; including 17 with Richter's transformation

  - Fludarabine refractoriness and complex karyotype were associated with progression.

  - Del(17p) and TP53 mutation were <u>not</u> associated with progression

Venetoclax current FDA approval in CLL

17p deletion

At least one prior therapy

MURANO trial
Venetoclax/rituximab (VR) vs. bendamustine/rituximab (BR)

PFS outcomes for VR vs BR

Seymour et al. *Proc ASH* 2017;Abstract LBA-2.