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UChicago Medicine

The Changing Landscape for Chronic Leukemias: CLL & CML

Richard A Larson, MD

University of Chicago

Disclosures – Richard A. Larson, MD

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Not your Grandfather's Buick!

A few important facts about CLL

- Two names for the same disease:
  - Chronic lymphocytic leukemia (CLL)
  - Small lymphocytic lymphoma (SLL)
- The median age at diagnosis is about 72 years.
- Most patients do not have symptoms at diagnosis.
- Half of cases are indolent.
  - Monoclonal B-cell lymphocytosis (<5,000/ul)
- Half of cases are aggressive. Half are not.
- About 10% are familial.

A few more facts about CLL

- Treatment is generally effective and well-tolerated.
- Median survival after any of the frontline regimens is longer than 6-7 years.
- CLL is generally not thought to be curable, but this may be changing.
- Newer agents are more expensive.
- Combinations work better than single agents.
- Many new trials are underway.

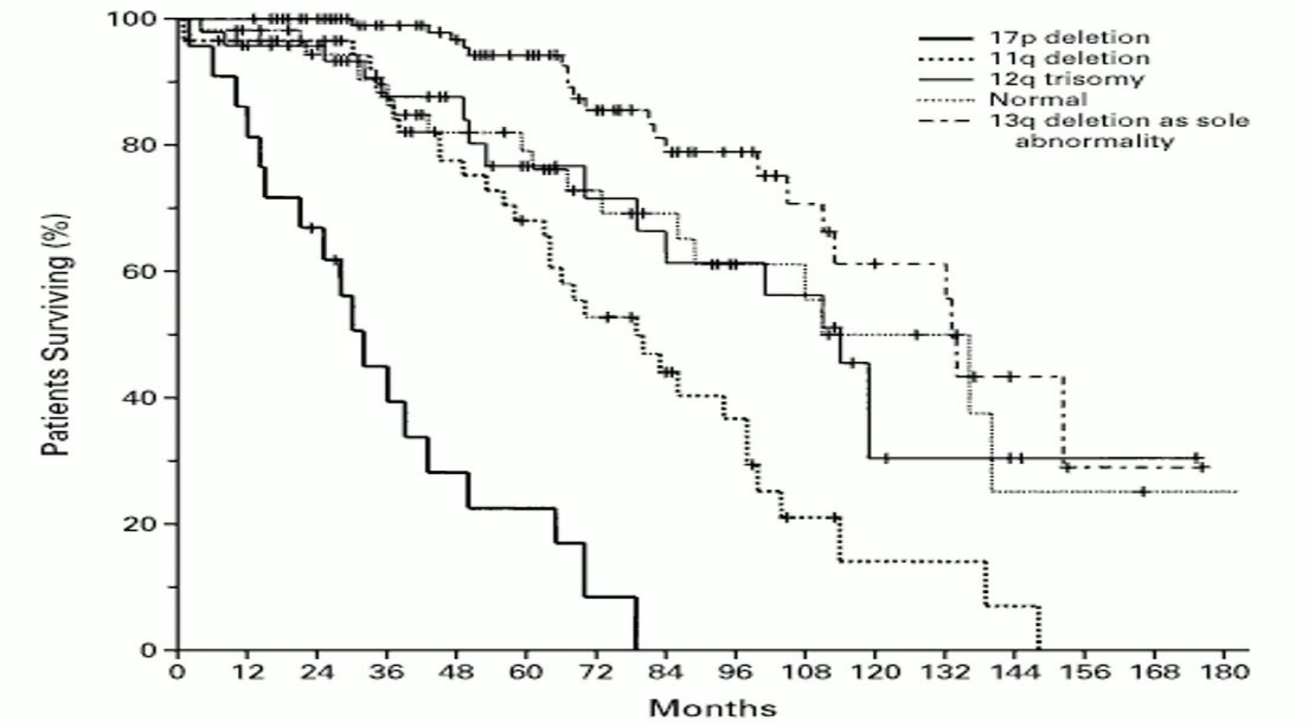
Modified Rai & Binet clinical staging systems

Risk Group	Rai Stage	Description	Binet Stage
Low:	0	**Lymphocytosis** in blood or bone marrow	A
Intermediate:	I	Lymphocytosis + enlarged **lymph nodes**	
	II	Lymphocytosis + enlarged liver or **spleen** with or without lymphadenopathy	B
High:	III	Lymphocytosis + **anemia** (Hgb <11 g/dL) with or without enlarged liver, spleen, or lymph nodes	C
	IV	Lymphocytosis + **thrombocytopenia** (platelet count <100,000/uL) with or without anemia or enlarged liver, spleen, or lymph nodes	

Whom to treat, when, and how?

- No proven benefit from early treatment prior to symptoms.
- Constitutional symptoms: fatigue, weight loss, sweats
- Bulky lymphadenopathy
- Symptomatic splenomegaly
  - Splenic sequestration; early satiety; abdominal distension
- Anemia (Hemoglobin <10 g/dl)
  - Autoimmune hemolysis
- Thrombocytopenia (platelets <100,000/ul)
- Lymphocytosis alone is not a useful marker of disease progression.

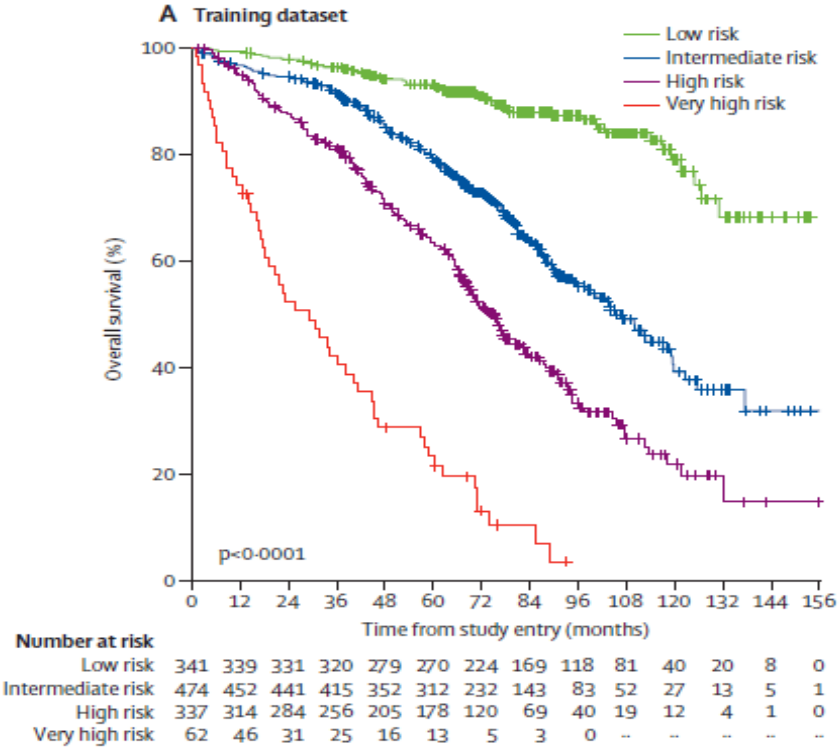
Chromosomal abnormalities predict survival in CLL



Dohner et al. NEJM 2000; 343: 1910-1916

CLL: Factors influencing prognosis

- Patient factors (age, PS, comorbidities)
- Stage (Rai or Binet)
- IGHV mutational status
- FISH panel
- CLL-IPI: meta-analysis of >3400 patients
  - TP53 status
  - IGHV mutational status
  - B2M >3.5mg/L
  - Clinical stage (Rai II-IV)
  - Age > 65 years



The International CLL-IPI Working Group. Lancet Oncol 2016; 17: 779-790

Currently available, standard and novel CLL drugs

- Chlorambucil – oral
- Cyclophosphamide – IV, oral
- Fludarabine – IV, (oral)
- Pentostatin – IV
- Bendamustine – IV
- Methylprednisolone - IV
- Lenalidomide – oral (off label)

- Monoclonal antibodies
  - Rituximab (anti-CD20)
  - Obinutuzumab (anti-CD20)
- Kinase inhibitors
  - Ibrutinib (Oral BTK inhibitor)
  - Acalabrutinib (Oral BTK inhib.)
  - Idelalisib (Oral PI3K delta inhibitor)
  - Duvelisib (Oral PI3K$\delta\gamma$ inhibitor)
- Venetoclax (Oral BCL2 inhibitor)

How to choose?

- Oral vs IV (clinic visits and chair time)
- Cost, guidelines, pathways, & formulary restrictions
- Sequential single agents vs combinations
- Predictive biomarkers (TP53 mutation or del(17p))
- Frailty (“fitness”)
- What’s left for second (or third) line

Frontline and later line CLL recommendations

- Younger, clinically fit patients (<65 years old)
  - FCR (fludarabine + cyclophosphamide + rituximab X 6 months)
- Older (>65 years old) or frail adults
  - Ibrutinib or acalabrutinib (with or without rituximab or obinutuzumab)
  - Bendamustine + rituximab
  - Chlorambucil + obinutuzumab
  - Venetoclax (time-limited)
- CLL with del(17p), mutated *TP53,* or unmutated *IGHV*
  - Ibrutinib or acalabrutinib
  - Venetoclax
  - Idelalisib; Duvelisib
  - Non-myeloablative stem cell transplantation or CAR T-cells

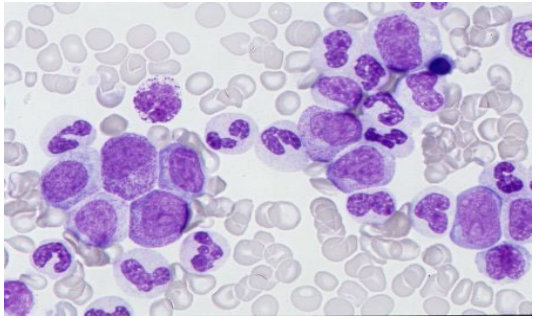
RA Larson. Section Editor for Leukemia, UpToDate, 2022

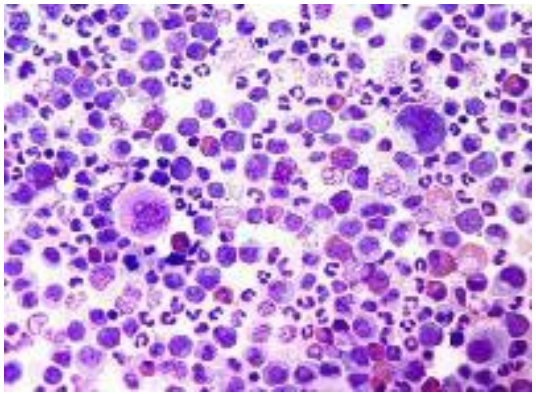
Chronic Myeloid Leukemia (CML)

Outcomes with tyrosine kinase inhibitor (TKI) therapy.

Learning Objectives

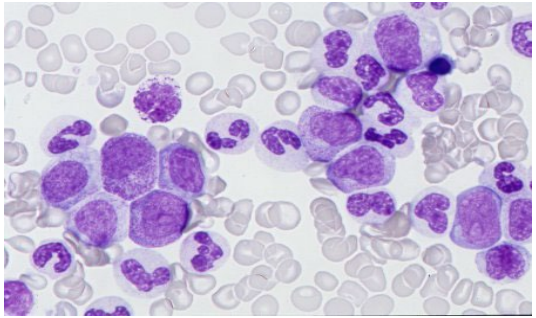
- Survival with CML now approaches that of the general population.
- Risk assessment is still important (Sokal vs ELTS).
- Asciminib – a non-ATP competitive inhibitor of BCR::ABL1
- Should the goal be Survival or Treatment-free Remission (TFR)?
- Discontinuation and Treatment-free Remission.

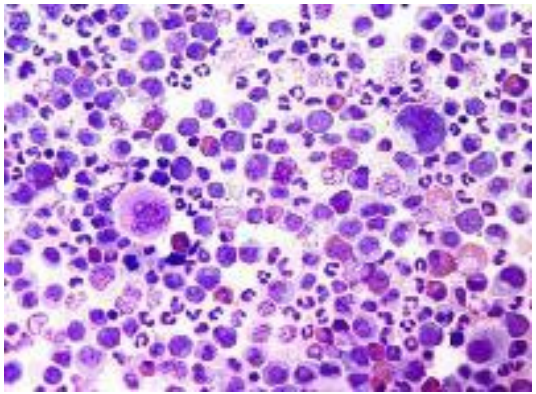




Case History

- 49-year-old man with mild fatigue
- Mild splenomegaly (5 cm) on exam
- WBC 82,000/uL (2% blasts, 3% basophils)
- Hemoglobin 11 g/dL
- Platelets 520,000/uL
- RT-PCR for BCR::ABL1 positive
- Bone marrow: 95% cellular with granulocytic hyperplasia
- Cytogenetics: 46 XY, t(9;22)(q34;q11)
- Diagnosis:
  chronic myeloid leukemia in chronic phase





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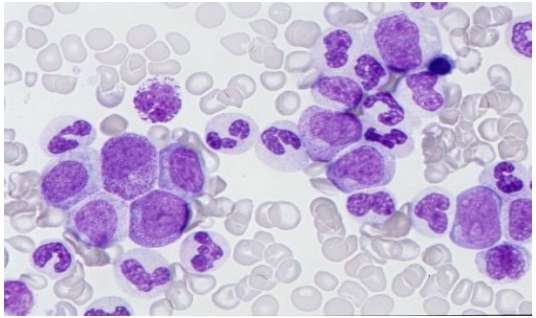
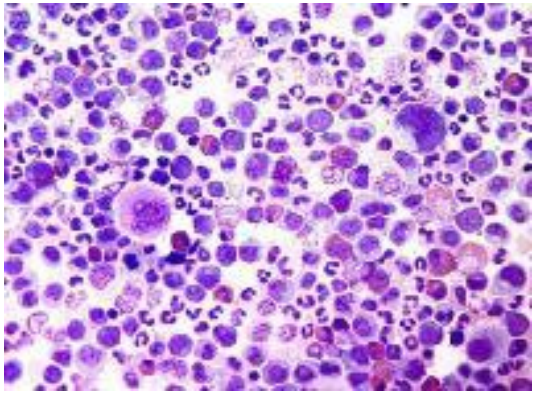
- Cytogenetics: 46 XY, t(9;22)(q34;q11)
- Diagnosis:
  chronic myeloid leukemia in chronic phase
- Sokal risk score = 0.75 (Low)
- ELTS score = 1.315 (Low)





Comparison of Sokal and ELTS prognostic scores (EUTOS Long Term Survival score)

Score	Calculation	Definition of risk groups
Sokal	Exp 0.0116 × (**age** - 43.4) + 0.0345 × (**spleen** - 7.51) + 0.188 × [(**platelet count**/700)^2 - 0.563] + 0.0887 × (**blood blasts** - 2.10)	Low-risk: < 0.8 Intermediate-risk: 0.8 - 1.2 High-risk: > 1.2
ELTS	0.0025 × (**age**/10)^3 + 0.0615 × **spleen size** + 0.1052 × **peripheral blood blasts** + 0.4104 × (**platelet count**/1000)$^{-0.5}$	Low-risk: < 1.5680 Intermediate-risk:1.5680- 2.2185 High-risk: > 2.2185

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To calculate Sokal and ELTS scores, go to http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html.

Which is better – Sokal or ELTS?

N = 5154 patients	Low Risk		Intermediate Risk		High Risk	
	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
% of patients	38%	55%	38%	28%	23%	13%
10-yr OS	89%	88%	81%	79%	75%	68%
6-yr Leukemia-related death	3%	2%	4%	5%	8%	12%

- ELTS: EUTOS score for **long-term survival considering leukemia-related death**; age given in years; spleen size in cm below costal margin measured by palpation; blasts in percent of peripheral blood differential; platelet count, 10E9/L. All values are pre-treatment.
- To calculate Sokal and ELTS scores, go to http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html ; or UpToDate.

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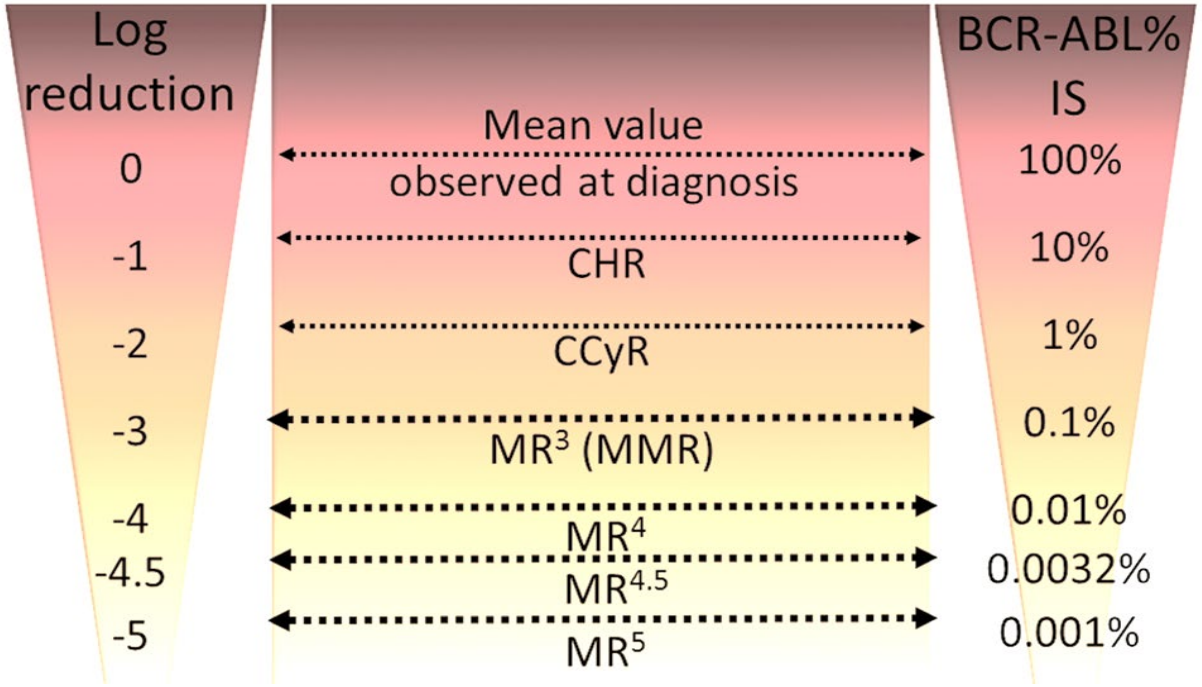
Quantitative RT-PCR for BCR::ABL1 transcripts (International Scale)



Baccarani M et al. Am Soc Clin Oncol Education Book. 2014: 167-75.

2020 European LeukemiaNet Recommendations for newly diagnosed CML

Time:	Optimal Response	Warning	Failure
3 months	BCR::ABL1 ≤10%	BCR::ABL1 >10%	>10% if confirmed
6 months	BCR::ABL1 <1%	BCR::ABL1 >1-10%	BCR::ABL1 >10%
12 months	BCR::ABL1 ≤0.1% (MMR)	BCR::ABL1 >0.1-1%	BCR::ABL1 >1%
Thereafter, >12 months	Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos	BCR::ABL1 >0.1% -7 or del(7q) in Ph- cells	BCR::ABL1 >1% ABL1 mutations. New chromosome abnormalities

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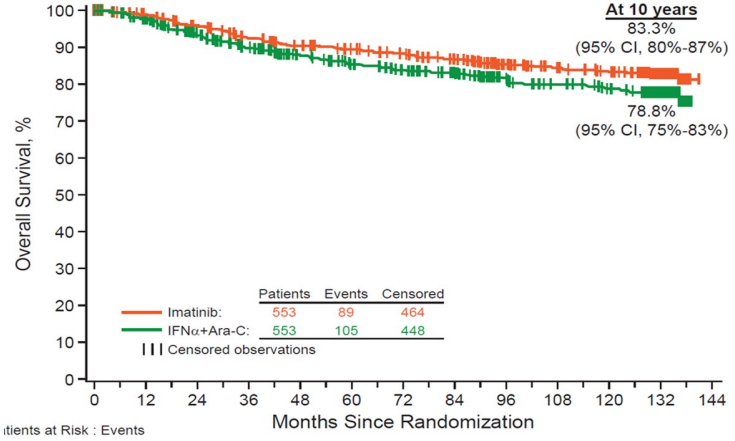
Baccarani et al. Blood 2013 Aug 8; 122(6): 872-84
Hochhaus, et al. Leukemia 2020; 34: 966-84

Treatments for chronic phase CML

- FDA approved for frontline and second-line indications:
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Bosutinib
  - Interferon (during pregnancy)
- FDA approved for second-line indication:
  - Ponatinib
  - Omacetaxine mepesuccinate
- FDA approved for third-line indication:
  - Asciminib
- Allogeneic hematopoietic stem cell transplantation



10-year survival with imatinib

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Stopping TKI Therapy in CML

Why discontinue tyrosine kinase inhibitor (TKI) therapy?

Common side-effects from TKIs in CML

	Imatinib		Dasatinib		Nilotinib	
	All grades	**Gr 3&4**	All grades	**Gr 3&4**	All grades	**Gr 3&4**
Fatigue	++++	**+**	+++	**+**	++++	**+**
Skin rash	++++	**++**	+++	**+**	++++	**+**
Nausea	++++		++++		+++	**+**
Diarrhea	++++	**++**	++++	**+**	+++	**+**
Myalgia	+++++		++++			
Headache	+++		++++		++++	
Edema	++++	**++**	++++	**++**	+++	
Pl. Effusion	++	**+**	++++	**++**	++	**+**
Hyperglycemia					++++	**+++**
Elevated Lipase	++++	**++**			++++	**+++**
Elevated ALT	++++	**++**		**+**	+++++	**+++**

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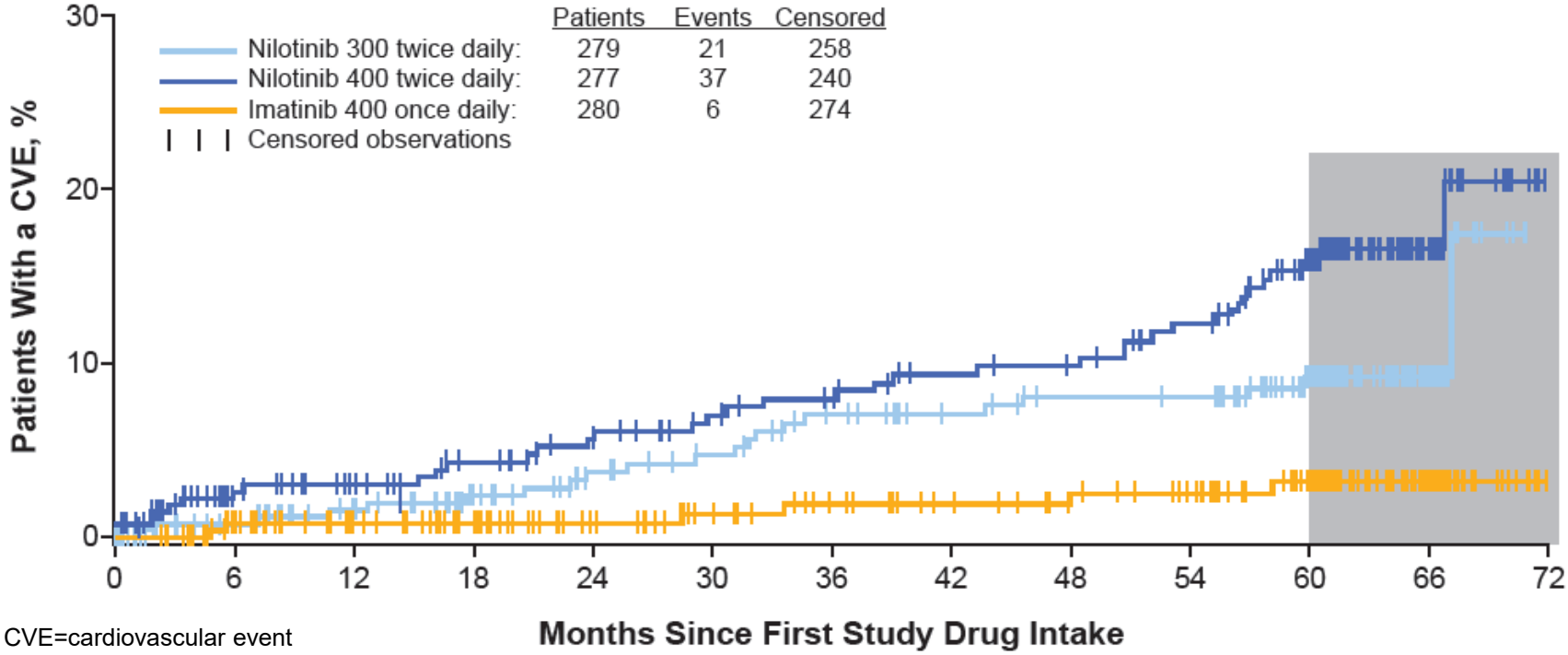
2+, 1-5%; 3+, 5-10%; 4+, 10-50%; 5+, >50%

Apperley. Lancet 2015; 385: 1447-59
Steegmann et al. Leuk Lymph 2012; 53:2351

Incidence of Adverse Vascular Events on ENESTnd



CVE=cardiovascular event

What is “treatment-free remission” (TFR) and when it is appropriate to consider?

- Prospective discontinuation of TKI therapy with more frequent molecular monitoring.
  - Goal is to maintain deep molecular remission without treatment.
  - Eliminate chronic side-effects (e.g. fatigue, rash, GI)
  - Reduce complications of treatment (vascular toxicity)
  - Reduce costs
- Best results are achieved after >5 years of total therapy and >2 years in deep molecular remission (<0.01% IS transcript level)

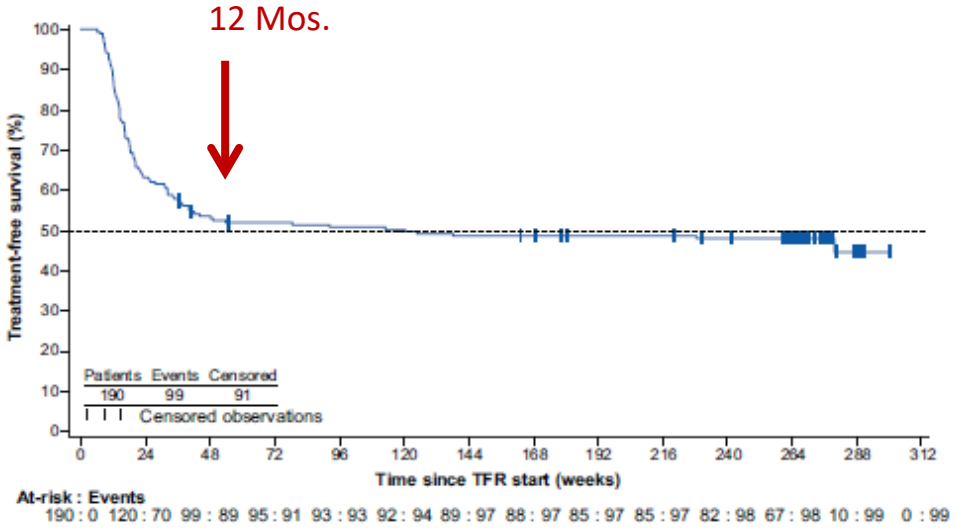
TFR – warnings!

- Psychological stress & anxiety
- Non-adherence to follow up (monitoring is mandatory)
- “TKI withdrawal” syndrome
- Molecular recurrence & hematologic relapse
- Need for retreatment

ENESTfreedom Study: TFR after frontline nilotinib

- Chronic phase CML, n=190
- Frontline nilotinib for >3 years.
- Sustained $MR^{4.5}$ for >1 year.

Sokal score at Diagnosis	TFR at 5 years, n/N (%)	
Low	32/63	51%
Intermediate	19/50	38%
High	8/29	28%
Missing	20/48	42%



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Radich et al. Leukemia 2021

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rlarson@uchicago.edu