LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

CML Living with a Chronic Disease

Welcome & Introduction

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CML Living with a Chronic Disease

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CML: Living with a Chronic Disease

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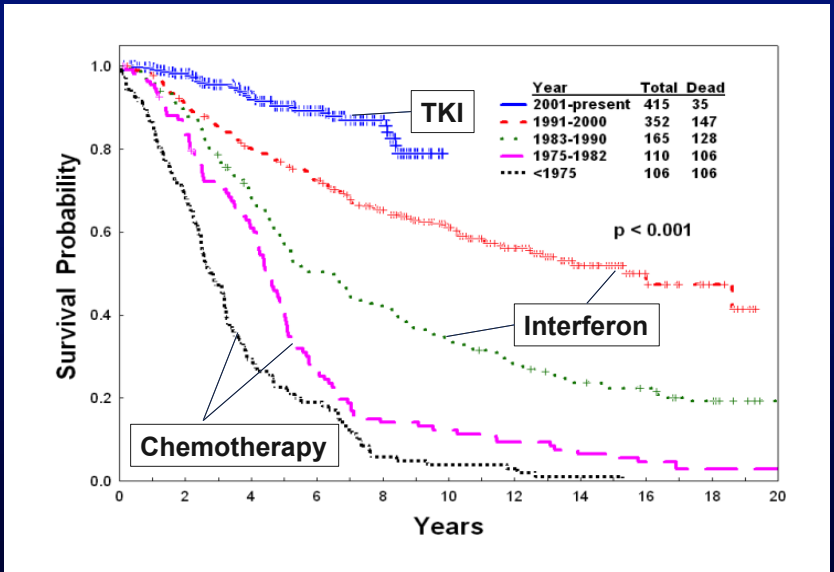
Survival in Early Chronic Phase CML



Kantarjian HM, et al. *Blood*. 2012; 119(9): 1981-1987.

Some Important Topics in CML 2013

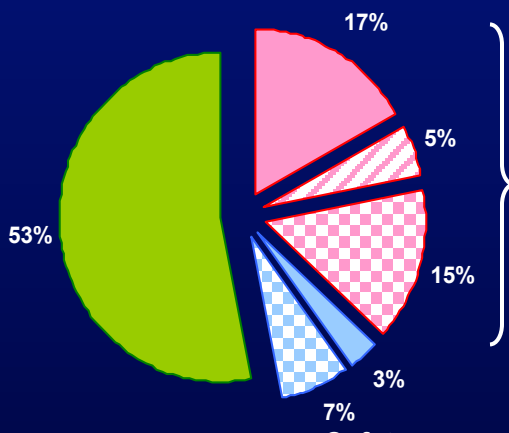
- Initial therapy
- Early response
- Deeper responses
- Treatment discontinuation: planned and unplanned
- New treatment options
- Clinical trials

Results With Imatinib in Early CP CML – The IRIS Trial at 8-Years

- 304 (55%) patients on imatinib on study
- Projected results at 8 years:
  - CCyR 83%
    - 82 (18%) lost CCyR, 15 (3%) progressed to AP/BP
  - Event-free survival 81%
  - Transformation-free survival 92%
    - If MMR at 12 mo: 100%
  - Survival 85% (93% CML-related)
- Annual rate of transformation: 1.5%, 2.8%, 1.8%, 0.9%, 0.5%, 0%, 0%, & 0.4%

Deininger M, et al. Blood 2009; 114(22): 1126.

IRIS 8-Year Update



- No CCyR
- Lost CCyR
- CCyR Other
- Safety
- Lost-regained CCyR
- Sustained CCyR on study

Deininger M, et al. Blood . 2009;114(22):1126.

Nilotinib vs Imatinib in Newly Diagnosed Chronic Phase CML

- 846 pts randomized to nilotinib 300 mg BID (n=282), nilotinib 400 mg BID (n=281), or imatinib 400 mg QD (n=283)
- Minimum follow-up 48 mo

Outcome	Nil 300	Nil 400	IM 400
% CCyR*	87	85	77
% MMR**	76	73	56
% BCR-ABL ≤0.0032%**	40	37	23
% Transformed AP/BP	3.2	2.1	6.7
% 4-yr EFS	95	97	93
% 4-yr OS	94	97	93

* by 24 months, ** by 48 months

Kantarjian HM, et al. *Blood.* 2012;120: Abstract 1676.

Dasatinib vs Imatinib in Newly Diagnosed Chronic Phase CML

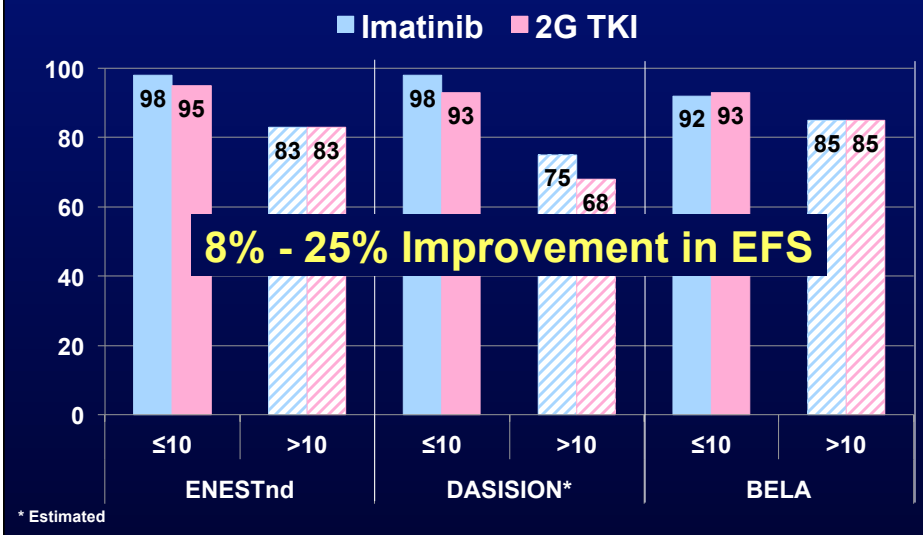
- 519 pts randomized to dasatinib 100 mg QD (n=259) or imatinib 400 mg QD (n=260)
- Minimum follow-up 36 mo

Outcome*	Das 100	IM 400
% CCyR	86	82
% MMR	68	55
% BCR-ABL ≤0.0032%	22	12
% Transformed AP/BP	4	6
% 3-yr PFS	91	91
% 3-yr OS	94	93

* by 24 months

Hochhaus A, et al. *J Clin Oncol.* 2012; Abstract 6504.

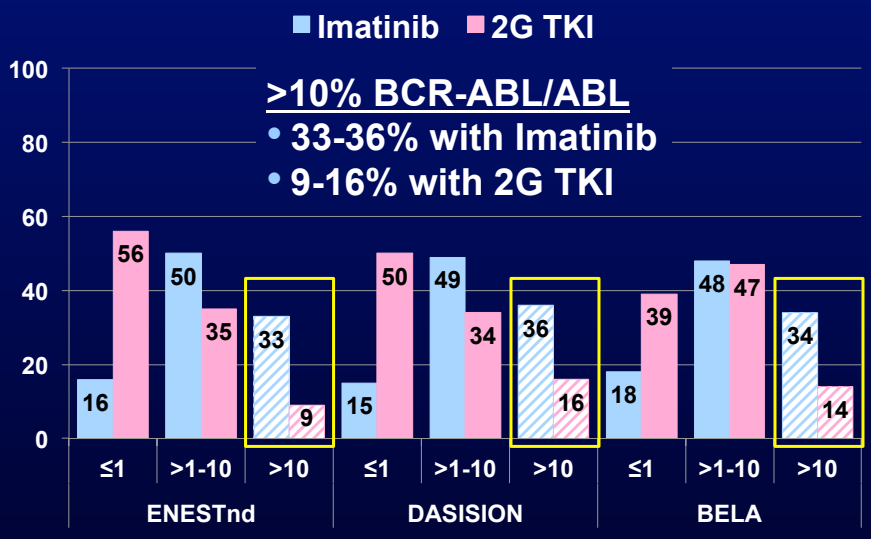
3-Year EFS by Molecular Response at 3 Months



* Estimated

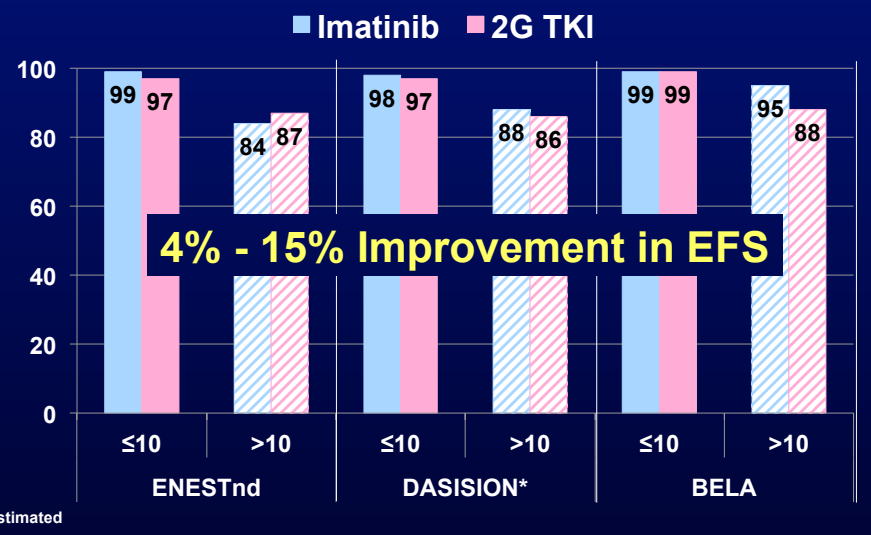
Hochhaus A, et al. Blood. 2012; 120:Abstract 167. Saglio G, et al. Blood. 2012; 120:Abstract 1675. Brummendorf TH, et al. Blood. 2012;120: Abstract 69.

Molecular Response at 3 Months by Therapy



Hochhaus A, et al. Blood. 2012; 120:Abstract 167. Saglio G, et al. Blood. 2012; 120:Abstract 1675. Brummendorf TH, et al. Blood. 2012;120: Abstract 69.

3-Year OS by Molecular Response at 3 Months



* Estimated

Hochhaus A, et al. Blood. 2012; 120:Abstract 167. Saglio G, et al. Blood. 2012; 120:Abstract 1675. Brummendorf TH, et al. Blood. 2012;120: Abstract 69.

Early Response to TKI: 3 months or 6 months?

- 58/489 (12%) pts on frontline TKI had no MCyR at 3 months
- 5-y EFS 77%, OS 88%, TFS 94%
- By 6 months, 52 (90%) still on TKI (4 intolerance, 1 loss CHR, 1 BP)

5-yr Outcome	% by Response at 6 months	
	MCyR	No MCyR
OS	100	79
EFS	85	66
TFS	95	94

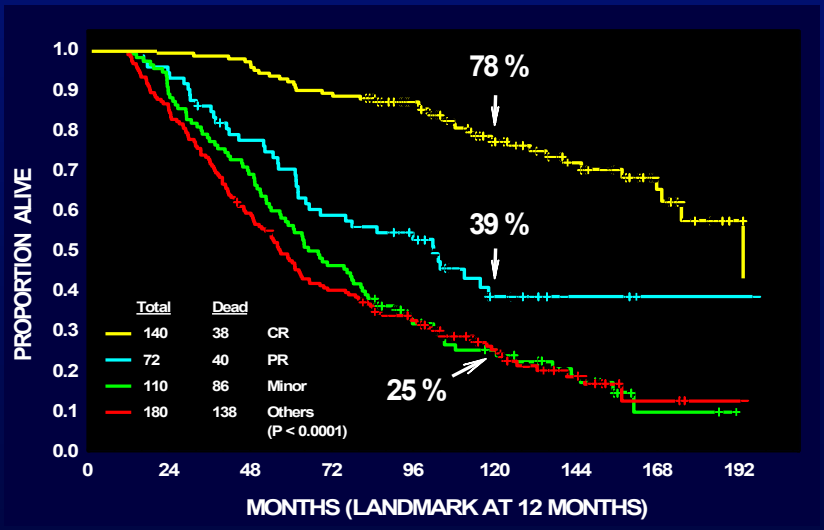
- Conclusion: Waiting for 6 month response better discriminates for poor outcome.

Nazha A, et al. *Blood.* 2012;120: Abstract 3757.

Early Response: What to Do?

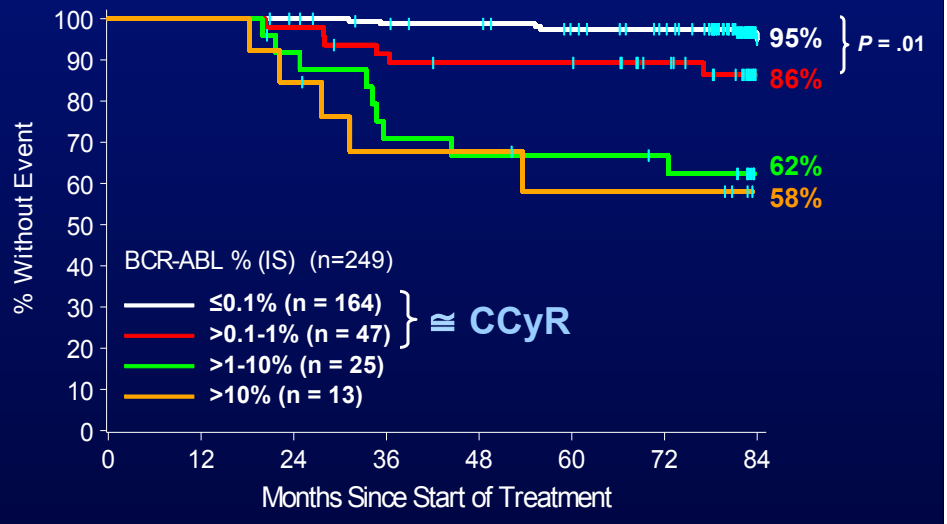
- Response at 3 or 6 months is predictive of long-term outcome
- Strong correlation with response duration; weak correlation with transformation or survival
- Most patients with suboptimal response at 3 months will still have a good outcome
- No data that change in therapy at 3 months changes outcome
- Very important to assess at 6 months

IFNα in CML
Survival by CG Response



Kantarjian et al. Cancer 2003; 97: 1033

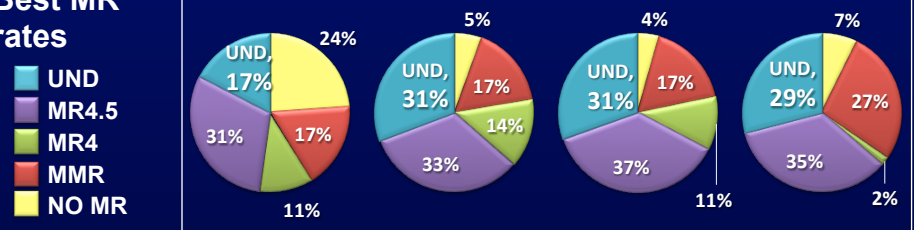
IRIS - EFS by Molecular Response
With Imatinib at 18 Months



Event = AP-BP on IM; death any cause on IM; loss of CHR or MCyR; or ↑ WBC.

Hughes T, et al. Blood 2010; 116: 3758-65

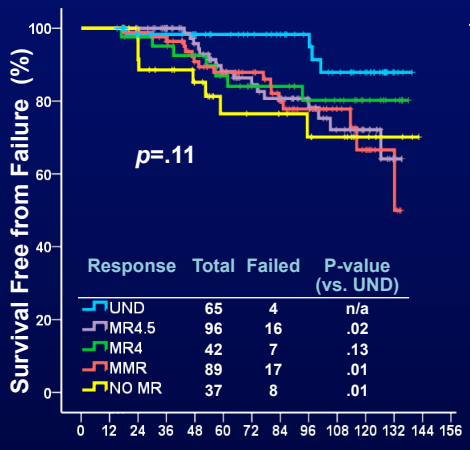
Molecular Response in CML
MR Rates at 36 Months (CCyR patients)

TKI	IM 400 N=52	IM 800 N=148	NILO N=48	DASA N=56
CCyR (%)	46 (88)	144 (97)	46 (96)	55 (98)
Best MR rates				
Median F/U, months (range)	124 (13-142)	100 (4-132)	31 (3-77)	36 (2-73)

Falchi L, et al. Blood. 2012; 120:Abstract 164.

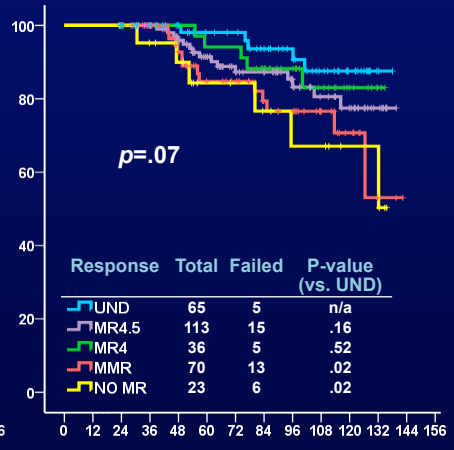
Molecular Response in CML
FFS by MR at 18 and 24 months

18 months



Response	Total	Failed	P-value (vs. UND)
UND	65	4	n/a
MR4.5	96	16	.02
MR4	42	7	.13
MMR	89	17	.01
NO MR	37	8	.01

24 months

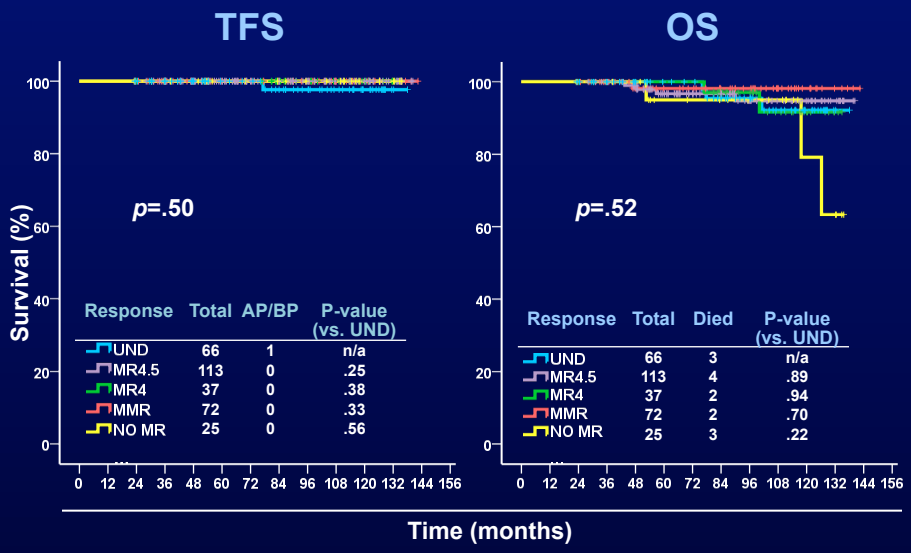


Response	Total	Failed	P-value (vs. UND)
UND	65	5	n/a
MR4.5	113	15	.16
MR4	36	5	.52
MMR	70	13	.02
NO MR	23	6	.02

Time (months)

Falchi L, et al. Blood. 2012; 120:Abstract 164.

Molecular Response in CML
TFS and OS by MR at 24 months



Falchi L, et al. Blood. 2012; 120:Abstract 164.

So What Do We Get?

Response	Translates into:
CHR	Decreased symptoms
CCyR	Significantly improved survival
MMR	Improvement in EFS, possible longer duration CCyR
CMR	Possibility of considering treatment discontinuation (clinical trials only)

TKI Frontline Therapy in CML Treatment Discontinuation

		Percentage				
	F/U (mo)	IM400	IM800	Nilotinib	Dasatinib	Bosutinib
ENESTnd*¥	>36	38		29		
DASISION	>36	31			30	
BELA	>24	29				37
MDACC	>36	29	24	18	8	

* Nilotinib 300mg BID shown.
¥ Includes patients who discontinued into extension study; rates are 26% imatinib and 22% nilotinib if all excluded

Alattar et al. ASH 2011; Abstract #745; Saglio et al. ASH 2011; Abstract #452; Kantarjian et al. ASCO 2011; Abstract #6510; Cortes et al. ASH 2011; Abstract #455

Factors Influencing Early Discontinuation of 2nd Generation TKI

- Adverse events
- Lack of efficacy
- Availability of alternative options
- Decrease tolerance to adverse events
- Unreasonable expectations regarding toxicity
- Suboptimal management of AEs
- Lack of familiarity

Imatinib Treatment Discontinuations The STIM Trial

- 100 pts treated with imatinib for ≥3 yrs with CMR (≥5-log ⇓) sustained for ≥2 yrs
  - —51 prior IFN, 49 no prior IFN
- Median follow-up 34 mo (9-50 mo)
- Probability of CMR 24 mo after stop: 39% (95% CI: 29%, 48%)
- Higher relapse in male, high-risk Sokal, no prior IFN, <5 yrs on imatinib
- MVA: High Sokal (HR 2.56; p=.008) and imatinib therapy ≤ 60 mo (HR 0.58; p=.047)
- 10/61 relapses did not return to CMR after imatinib re-start

Mahon et al. ASH 2011; Abstract #603

Predictive Factors for Sustained Undetectable Transcripts

- Older age
- Higher hemoglobin
- Higher platelets
- Non-IM 400 therapy
- Deep response at 3 months

Falchi L, et al. Blood. 2012; 120:Abstract 164.

Adherence to Imatinib

- 87 pts on imatinib for ≥2 years
- Compliance measured by : self reporting, pill count and microelctronic monitoring system (MEMS)

Response	% Response at 6 yrs by Adherence Rate		P value
	>90% N=64	≤90% N=23	
MMR	94	14	<0.0001
CMR	44	0	0.002

- Poor correlation between 3 methods
- MVA for molecular response: adherence (MMR and CMR) and OCT1 (CMR)

Bazeos et al. Blood 2009; 114: abst# 3290

Bosutinib in CP CML After Imatinib Resistance or Intolerance

- 288 pt CML-CP with IM resistance (200) or intolerance (88)
- Bosutinib 500 mg orally daily
- Median follow-up 41 months (minimum 36 months)

Response	Percentage	
	IM Resistant	IM Intolerant
CHR	86	85
MCyR	58	60
CCyR	48	51
MMR*	64	65
CMR*	49	61
2-yr OS	88	98
3-yr Progression or detah	21	7
Discontinued therapy	56	63

- Median dose intensity: IM-resistant 485 mg/d, IM-intolerant : 394 mg/d

*Among pts in CCyR; overall (all patients) MMR 41%, CMR 34%

Cortes J, et al. *Blood*. 2012; Abstract 3779.

Ponatinib Phase 2 Study - PACE Response Characteristics CP-CML

- 93% failed ≥2 TKI, 58% failed ≥3 TKI

Response Rate, n (%)	N=267
Any Cytogenetic Response	180 (67)
MCyR	149 (56)
CCyR	124 (46)
MMR	91 (34)
$MR^{4.5}$	39 (15)
BCR-ABL ≤10% at 3 months, n/N(%)	142/240 (59)
1 prior approved TKI	14/16 (88)
Median Time to Response*, months [range]	
MCyR	2.8 [1.6 – 11.3]
MMR	5.5 [1.8 – 19.2]

- 91% MCyR sustained at 12 months (K-M)

Cortes J, et al. *Blood.* 2012;120: Abstract 163.

Omacetaxine for CML CP After Failure to ≥2 TKI

- 122 pts with CML CP (n=81) or AP (n=41) with ≥2 prior TKI
- Omacetaxine 1.25 mg/m^2 BID x14d, then x7d

Response, %	CP N=81	AP N=41
Primary endpoint	MCyR 20% CCyR 10%	MaHR 27% CHR 24%
Median duration, mo	17.7	9
Median PFS, mo	9.6	4.7
Median OS, mo	33.9	16

- 11 pts (9 CP, 2 AP) ongoing response
- Median 35 cycles over median 39 months
- Median response duration: 14 mo CP, 24 mo AP

Kantarjian HM, et al. *Blood.* 2012;120: Abstract 2767.

Some Safety Notes on New (and Old) Drugs

- **Imatinib:** Nothing new after 13+ years
- **Dasatinib:** Pleural effusion, occasional pulmonary hypertension
- **Nilotinib:** QTc, peripheral arterial occlusive disease
- **Bosutinib:** Diarrhea, rash, liver
- **Ponatinib:** Arterial thrombosis, pancreatitis, liver
- **Omacetaxine:** Myelosuppression
- **All:** Fatigue

Take Home Message – CML 2013 ¼

- Great therapy for CML
- Early response (3 months) predictive of response
  - Should not change at 3 months
  - Monitor at 6 months and decide
- Deeper molecular responses improve event-free survival
  - No impact on transformation or survival
  - No clear benefit for CMR (except discontinuation?)
- Few patients can discontinue safely
  - New approaches: IFN, AZA, JAK2 inhinbitors, etc
- Excellent new drugs: ponatinib, bosutinib, omacetaxine

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Question and Answer Session

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MY CML TRACKER

An interactive online tool to help you keep track of appointments, questions to ask your doctor, medications, side effects, test results and more.

- **Visit www.LLS.org/cmltracker**

CO-PAY ASSISTANCE PROGRAM

The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified CML patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

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OTHER RESOURCES FOR PATIENTS

- **CML Online Chat – www.LLS.org/chat**
- **CML Blog – www.LLS.org/cmlblog**
- **Cancer and Your Finances Webcast – www.LLS.org/webcasts**

For more information about CML, other LLS programs and support services, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**