Managing Chronic Myeloid Leukemia

Jorge Cortes, MD
Jane and John Justin Distinguished Chair in Leukemia Research
Section Chief of AML & CML
Deputy Chairman, Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

September 22, 2015

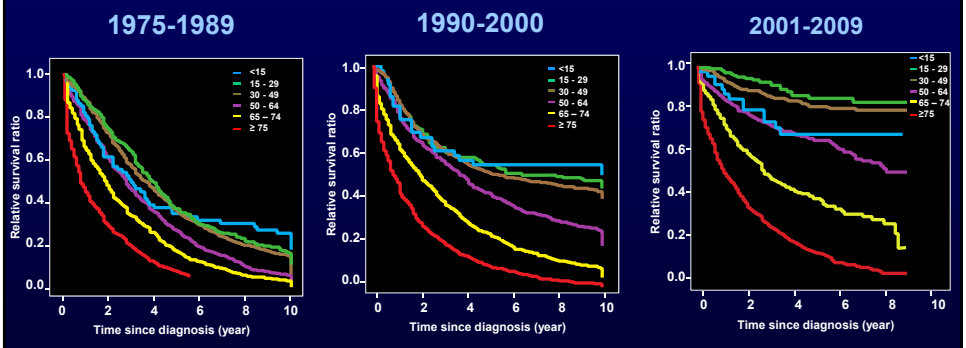
Managing Chronic Myeloid Leukemia

Welcome and Introductions

What is New in CML in 2015

Jorge Cortes, MD
Chief, CML and AML Sections
Department of Leukemia
MD Anderson Cancer Center
Houston, Texas

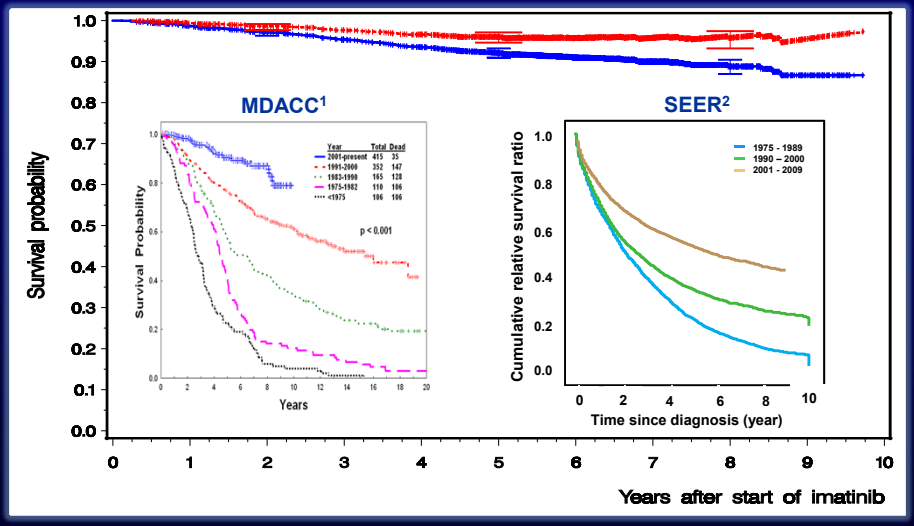
Cumulative Relative Survival by Time Period and Age - SEER



Chen Y, et al. Leuk Lymphoma. 2013;54(7):1411-1417.

OS of Imatinib-Treated Patients - EUTOS

- 2290 pts enrolled in imatinib clinical trials in Europe
- Median follow-up 77 mo
- Cause of death: CML 4%; unrelated/unknown 7%



[1]Kantarjian et al. Blood 2012; 119: 1981-7 [2]Chen et al. Leuk Lymphoma. 2013; 54: 1411-7 Pfirrmann et al. ASH 2014; Abstract #153

The CML Journey

Diagnosis

Staging | Monitoring

Treatment selection | Treatment Continuation | Treatment discontinuation

Patient Education

The CML Journey

Comorbidities

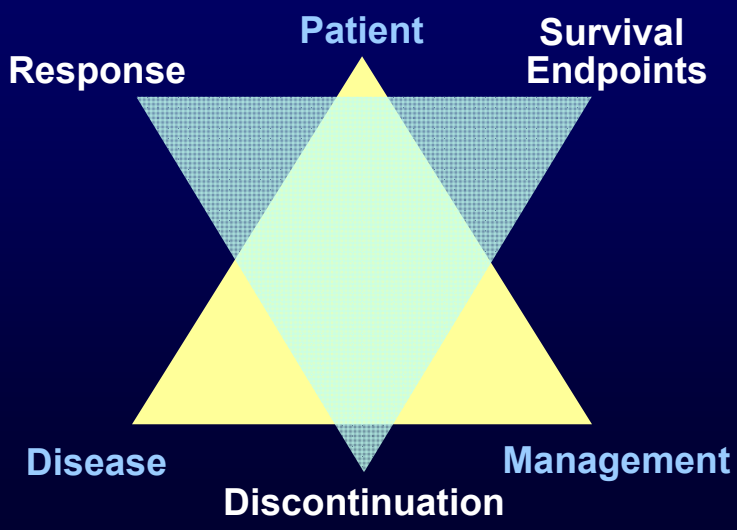
Concomitant Medications

Adherence | Adherence

Adverse Events (Identification and Management)

Support

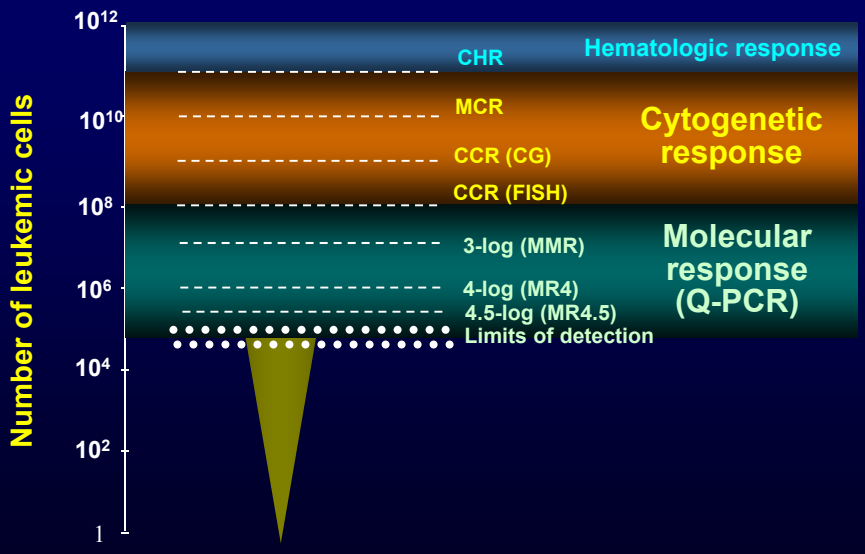
Predictors of Outcome in CML



Evolution of Frontline Therapy

- 1990s: IFN (±ara-C, ±HHT)
- 2000: Imatinib 400mg
- 2001: Imatinib 800mg
- 2005: Nilotinib, dasatinib
- 2012: Ponatinib

Evaluating Response in CML

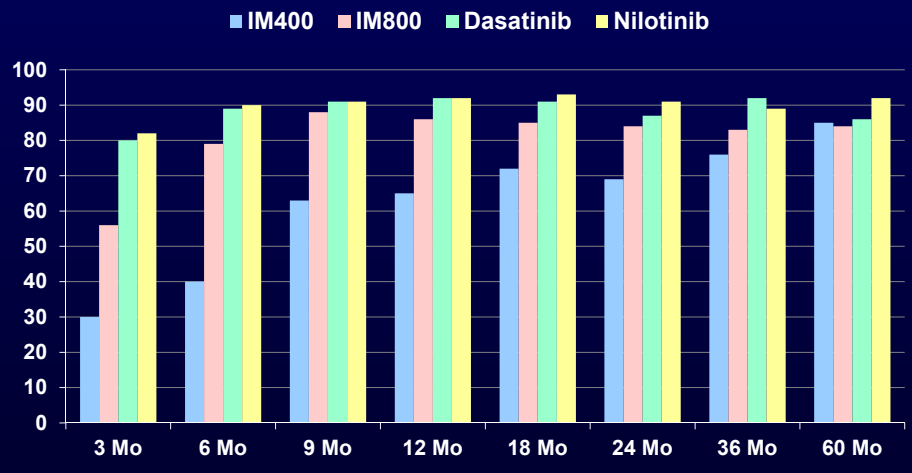


What Do We Get?

Response	Translates into:
Complete hematologic response (CHR)	Improved symptoms
Complete cytogenetic response (CCyR)	Significantly improved survival
Major molecular response (MMR)	Modest improvement in event-free survival, possible longer duration CCyR
"Complete" molecular response (CMR)	Possibility of considering treatment discontinuation (clinical trials only)

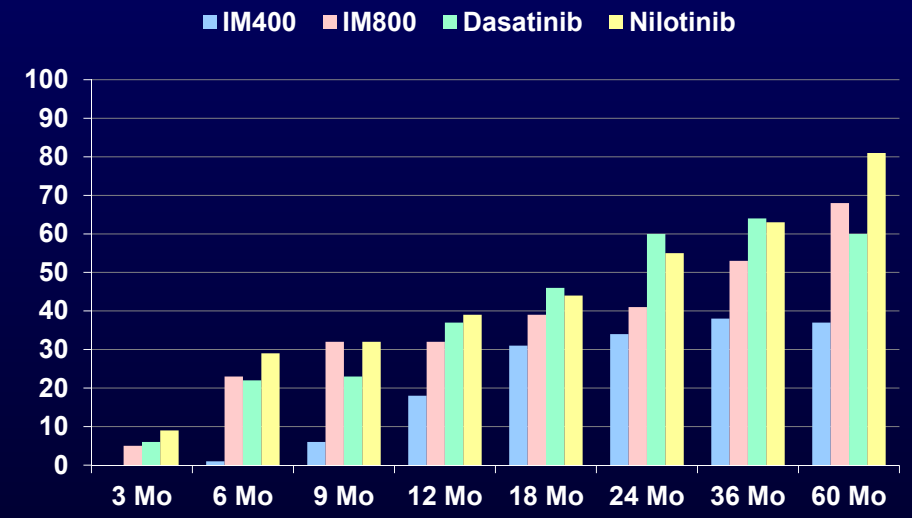
TKI Frontline Therapy in CML
CCyR AT Time Periods (ITT)

- 487 patients with CML frontline therapy: imatinib 400 mg (n=71), imatinib 800 mg (n=201), nilotinib (n=109), dasatinib (n=107)



Jain et al. Lancet Hematology 2015; 2; e118-e128

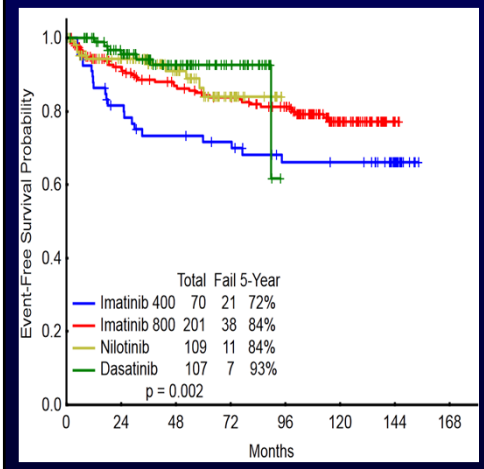
TKI Frontline Therapy in CML
MR4.5 AT Time Periods (ITT)



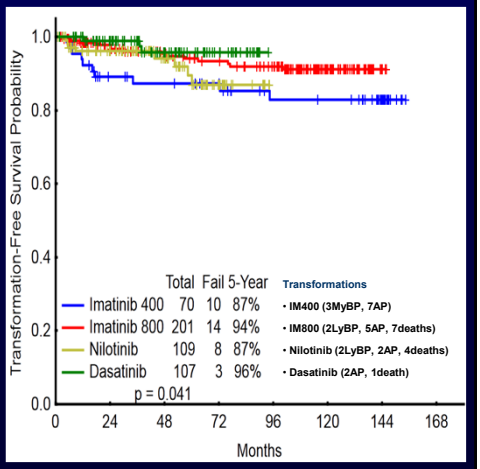
Jain et al. Lancet Hematology 2015; 2; e118-e128

TKI Frontline Therapy in CML
Long-Term Outcome By Response Time

Event-Free Survival



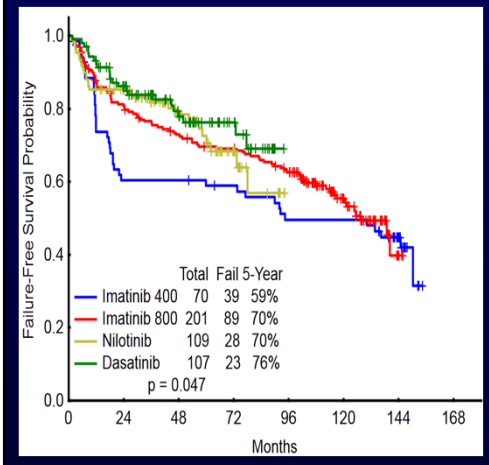
Transformation-Free Survival



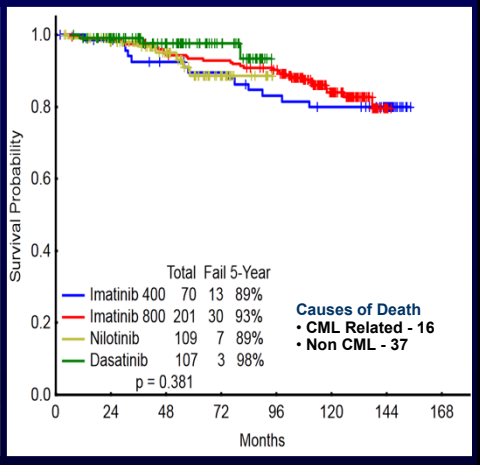
Jain et al. Lancet Hematology 2015; 2; e118-e128

TKI Frontline Therapy in CML
Long-Term Outcome By Response Time

Failure-Free Survival



Overall Survival



Jain et al. Lancet Hematology 2015; 2; e118-e128

DASISION – The Final Report

- 519 pts randomized to dasatinib (n=259) or imatinib (n=260)
- Minimum follow-up 5 yrs

Outcome (%)	Dasatinib	Imatinib	P value or HR
Discontinued	39	37	
12m cCCyR	77	66	P=0.007
5y MMR	76	64	P=0.0022
5y MR4.5	42	33	P=0.025
3m <10%	84	64	
5y AP/BP	4.6	7.3	
5y OS	91	90	HR 1.01
5y PFS	85	86	HR 1.06

Cortes et al. ASH 2014; Abstract #154

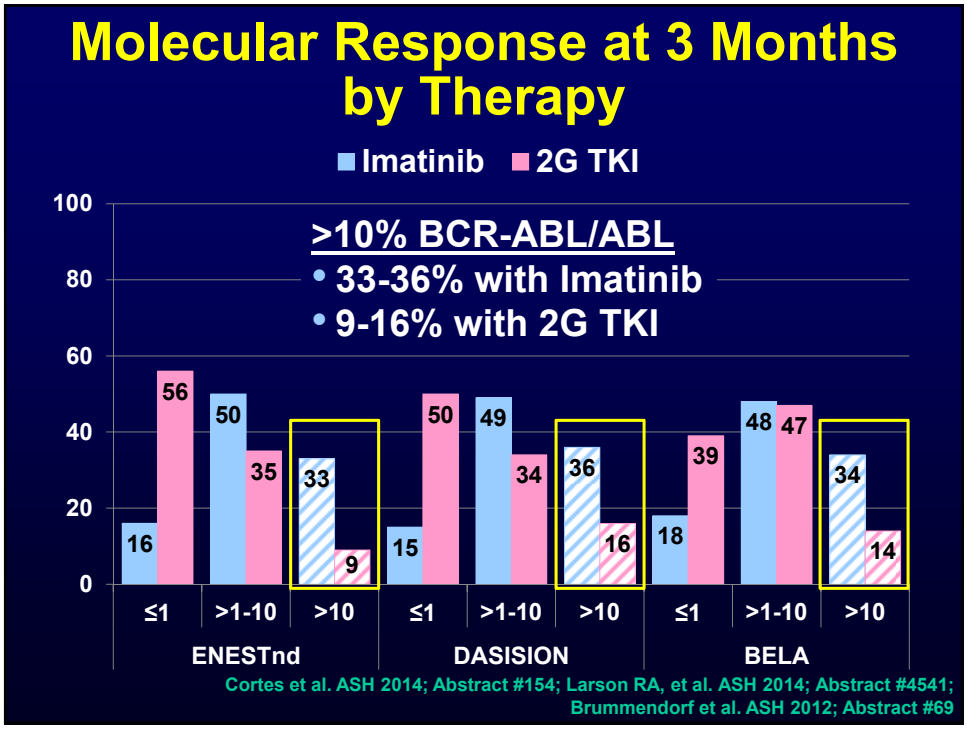
ENESTnd – The 6-Year Report

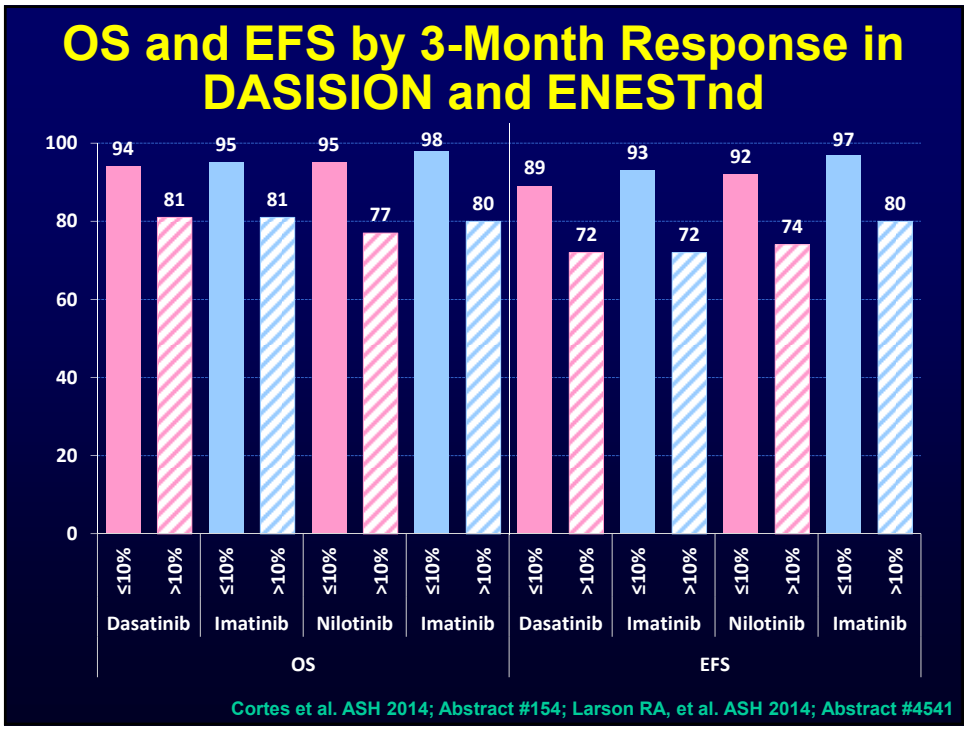
- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281) or imatinib (n=283)
- Minimum follow-up 6 yrs

Outcome (%)	Nil 600	Nil 800	Imatinib	P value or HR
Discontinued*	40	38	50	
5y MMR*	77	77	60	P<0.0001
6y MR4.5	56	55	33	P<0.0001
3m <10%	91	89	67	
6y AP/BP	3.9	2.1	7.4	P=0.06/0.003
5y OS*	94	96	92	HR 0.8/0.44
5y EFS*	95	97	93	HR 0.61/0.37

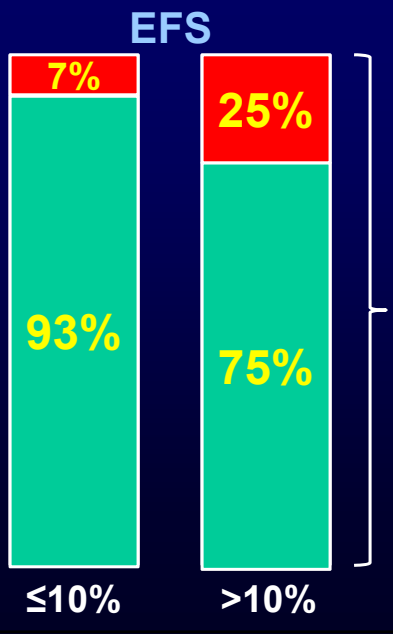
* 5-yr data from Larson et al ASCO 2014; Abstract #7073

Larson RA, et al. *Blood*. 2014; Abstract #4541


Molecular Response at 3 Months by Therapy
Imatinib
2G TKI
>10% BCR-ABL/ABL
• 33-36% with Imatinib
• 9-16% with 2G TKI
100
80
60
40
20
0
16
56
50
35
33
9
15
50
49
34
36
16
18
39
48
47
34
14
≤1
>1-10
>10
≤1
>1-10
>10
≤1
>1-10
>10
ENESTnd
DASISION
BELA
Cortes et al. ASH 2014; Abstract #154; Larson RA, et al. ASH 2014; Abstract #4541;
Brummendorf et al. ASH 2012; Abstract #69


OS and EFS by 3-Month Response in DASISION and ENESTnd
100
80
60
40
20
0
94
81
95
81
95
77
98
80
89
72
93
72
92
74
97
80
≤10%
>10%
Dasatinib
Imatinib
Nilotinib
Imatinib
OS
EFS
Cortes et al. ASH 2014; Abstract #154; Larson RA, et al. ASH 2014; Abstract #4541

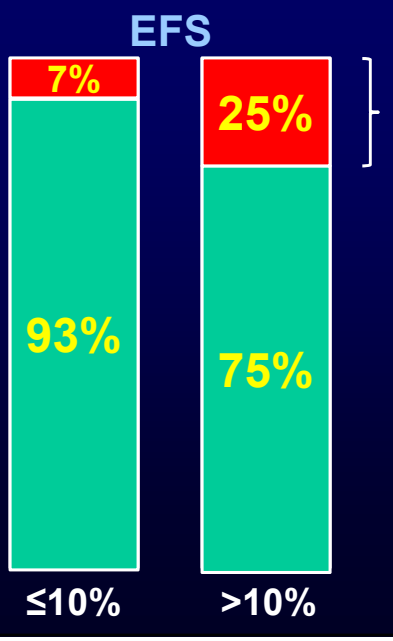
What Do I Do With the Slow Responder?



Change therapy to all of these?

- Only 15-25% need help
- At most 10-15% would benefit

What Do I Do With the Slow Responder?



Or better identify the 20% who may need help?

- Small difference in survival (88% vs 98%)
- Some deaths not-related to CML
- Effective salvage therapy

What is the dog doing?

- **Coming out**
- **Sinking**
- **Not moving**

Perro semihundido. Goya.

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 N=18 (41%)	No MCyR N=26 (59%)
OS	100	79
EFS	85	66
TFS	95	94

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

Nazha et al. Haematologica 2013; 98: 1686-8

Effect of Reduced Dosing on 3 Month PCR by Total Dose and Number of Missed Days

	Imatinib		Dasatinib	
Percent prescribed dose	No. (%) (N=327)	3 mo PCR < 10%	No. (%) (N=315)	3 mo PCR < 10%
100%	272 (83)	78%	222 (71)	96%
80-99%	42 (13)	62%	48 (13)	85%
<80%	13 (4)	46%	45 (4)	80%
Total missed days median (range)	13.5 (1-48)		14 (1-58)	
0	272 (83)	78%	222 (71)	96%
0-14	41 (13)	59%	48 (15)	85%
> 14	14 (4)	57%	45 (14)	80%

- Probability of achievement of RQ-PCR <10% decreases with increased numbers of missed doses and decreased total dosing

Apperley JF, et al. Blood. 2013;122: Abstract 93.

TIDEL II – Outcome by EMR

- 25 pts with BCR-ABL >10% at 3 months
- Inferior outcome (OS, TFS, MMR)
- MMR at 24 mo = 24%
- 4 → IM800, 18 → Nilotinib, 3 → Withdrawn

6 mo BCR-ABL/ABL	No. (%)	
>10%	6 (24)	
1-10%	10 (40)	<10% @ 6 mo = 64%
<1%	6 (24)	
Withdrawn	3 (12)	

- 78 pts missed TIDEL-II endpoints

Management	No.	No. MMR @ 24 mo
Remained on imatinib	14	12 (86)
Changed to nilotinib*	54	21 (39)

* Median time to change 7 mo (range, 2 to 19)

Yeung et al. Blood 2015; 125: 915-923

TKI Frontline Therapy in CML Treatment Discontinuation

	F/U (mo)	IM400	Nilotinib	Dasatinib	Bosutinib
			Percentage		
ENESTnd*¥	>72	55	46-45	Less than 70% have successful outcome	
DASISION	>60	37		39	
BELA	>24	29			37

* Nilotinib 300mg BID shown.
¥ Includes patients who discontinued into extension study; rates are 39% imatinib and 38-44% nilotinib if all excluded

Saglio G, et al. ASH 2013; 92; Cortes et al. ASH 2013; 653; Cortes et al. ASH 2011; Abstract #455

Factors Influencing Early Discontinuation of 2nd Generation TKI

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

When Do I Change Therapy?

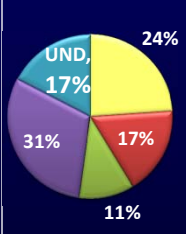
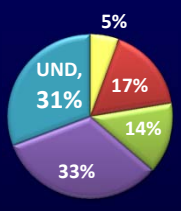
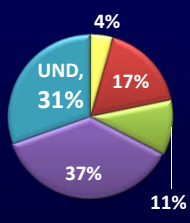
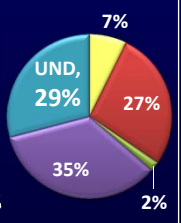
I do:

- European Leukemia Net failure (mostly)
- Loss of complete cytogenetic response (CCyR)
- Intolerance (true)

I don't:

- Increase in PCR (unless loss CCyR)
- PCR still detectable
- 1st instance of adverse events

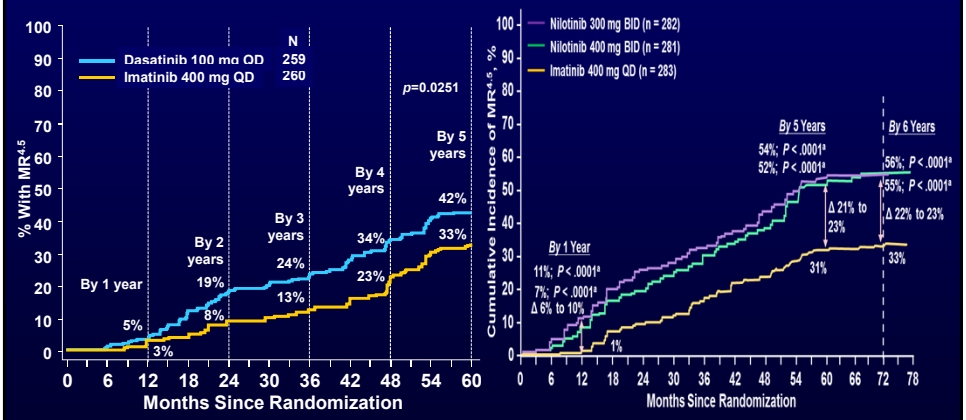
Molecular Response in CML
MR Rates at 36 Months (CCyR patients)

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 UND MR4.5 MR4 MMR NO MR				
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.

Cumulative Rates of $MR^{4.5}$ with Imatinib, Dasatinib and Nilotinib

DASISION **ENESTnd**



Cortes et al. ASH 2014; Abstract #154; Larson RA, et al. *Blood*. 2014; Abstract #4541

Factors associated with Sustained Undetectable PCR (multivariable analysis, N= 495)

- Older age
- Higher baseline platelets
- TKI modality (non-IM400)
- CCyR at 3 months

Falchi et al. Am J Hematol 2013; 88: 1024-9

Adherence to Imatinib

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

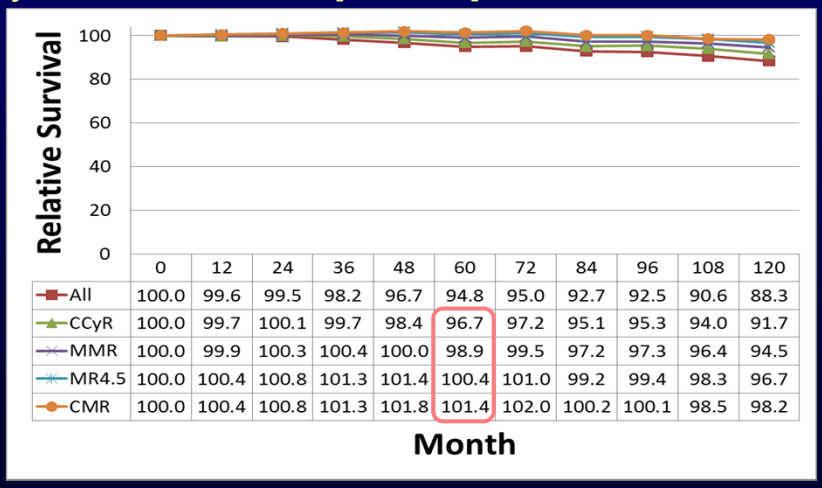
Response	% Response at 6 yrs by Adherence Rate		P value
	>90% N=64	≤90% N=23	
MMR	94	14	<0.0001
CMR	44	0	0.002

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

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

Relative Survival with TKI by Response to Therapy

- 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]

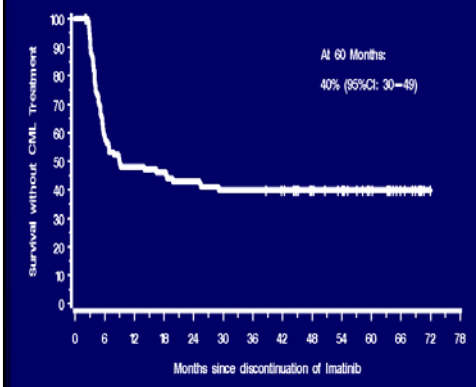


	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.6	99.5	98.2	96.7	94.8	95.0	92.7	92.5	90.6	88.3
CCyR	100.0	99.7	100.1	99.7	98.4	96.7	97.2	95.1	95.3	94.0	91.7
MMR	100.0	99.9	100.3	100.4	100.0	98.9	99.5	97.2	97.3	96.4	94.5
MR4.5	100.0	100.4	100.8	101.3	101.4	100.4	101.0	99.2	99.4	98.3	96.7
CMR	100.0	100.4	100.8	101.3	101.8	101.4	102.0	100.2	100.1	98.5	98.2

Sasaki et al. Lancet Hematology 2015

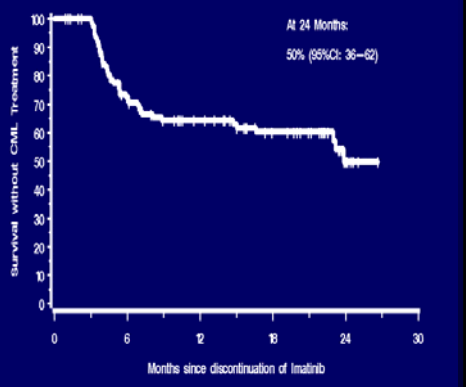
Imatinib Treatment Discontinuation STIM1 and STIM2

STIM1



- 100 pts
- Median follow-up 55 mo (range, 9-72)

STIM2



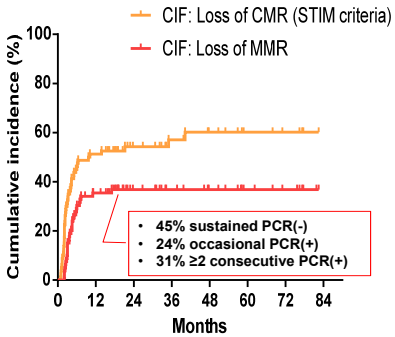
- 127 pts
- Median follow-up 16 mo (range, 0-27)

Mahon f, et al. Blood. 2013;122: Abstract 255 and Abstract 654.

Loss of MMR as Trigger to Restart TKI

- 80 pts discontinued imatinib after ≥2 yrs sustained MR$^{4.5}$

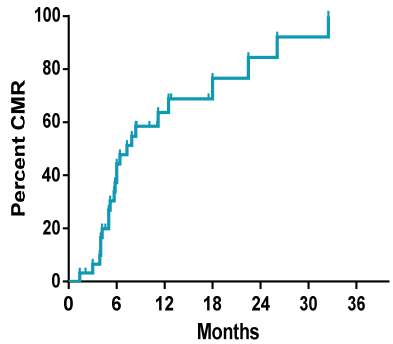
Probability of Relapse



Pts at risk

CMR loss	80	40	24	16	12	7	5	1
MMR loss	80	49	31	22	17	10	7	1

CMR After Re-Star of Imatinib*



Pts at risk 31 18 8 4 3 2

* All patients regained MMR

Rousselot P, et al. Blood. 2013;122: Abstract 381.

Minimum Requirements for TKI Treatment Discontinuation

- Deep molecular response (MR4.5/CMR)
- Sustained (2-5 yrs)
- Close monitoring (Q mo x6 mo, Q 2 mo x6 mo, q 3 mo x12 mo, Q 6 mo thereafter)
- Resume upon relapse
- Define what constitutes relapse

EURO-SKI - Adverse Events After TKI *Withdrawal* (n=200)

- 222 AEs in 98 pts were reported
- 57 AEs in 31 patients were related to treatment stop, no grade 4

Adverse event	Number			
	Patients		AEs	
	Grade 1-4	Grade 3	Grade 1-4	Grade 3
Musculoskeletal pain, joint pain, arthralgia	23	3	39	6
Other (sweating, skin disorders, folliculitis, depressive episodes, fatigue, urticaria, weight loss)	8	0	18	3

Musculoskeletal pain in CML patients after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J. Richter et al. J Clin Oncol. 2014 Sep 1;32(25):2821-3.

Tyrosine kinase inhibitor withdrawal syndrome: a matter of c-kit ? Response to Richter et al. Ph. Rousselot et al.

Mahon et al. ASH 2014; Abstract #151

2nd Generation TKI in CML CP Post-Imatinib Resistance

Response	Percentage		
	Dasatinib†	Nilotinib‡	Bosutinib
FU (mo)	>24	>24	24*
CHR	89	77	86
MCyR	59	56	54
CCyR	44	41	41
24 mo PFS**	80%	64%	79%
24 mo OS**	91%	87%	92%

† 6-yr PFS 49%, OS 71%, TFS 76%
‡ 4-yr PFS 57%, OS 78%

* Median
** All patients

Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd Generation TKI in CML CP Post-Imatinib Failure

Toxicity	Dasatinib	Nilotinib	Bosutinib
Pleural effusion	++	-	-
Liver	+	+	+
Transaminases	+	+	++
Bilirubin	-	++	-
Rash	+	+	++
Diarrhea	-	-	++
Lipase	- (+)	++	-
Glucose	-	++	-
Hypophosphatemia	++	++	+
Bleeding	+	-	-
QTc	++	++	-

Response to Bosutinib 3rd Line Therapy

- Src & Abl inhibitor, no effect over c-kit or PDGFR
- 119 pts who failed imatinib (600mg) & dasatinib or nilotinib
- Minimum 4-yr follow-up

Response, %	IM + D resistant (n = 38)	IM + D intolerant (n = 50)	IM + NI resistant (n = 26)
CHR	68	76	76
MCyR	39	42	38
CCyR	22	40	31
PCyR	17	2	7
4-yr sustained MCyR	43	87	78
Discontinued 2º AEs	21	44	12

- 4-yr Cumulative PD o death 24%

IM, imatinib; D, dasatinib; NI, nilotinib.

Gambacorti-Passerini et al. ASH 2014; Asbtract #4559

Ponatinib Phase 2 Study Responses to Therapy

- Ponatinib 45 mg daily
- 93% ≥2 prior TKI, 58% ≥3 prior TKI
- Median follow-up 38.4 mo (0.1-48.6 mo)

	Percentage						
	CP-CML				AP	BP	Ph+ ALL
	MCyR	CCyR	MMR	MR4.5	MaHR	MaHR	MaHR
R/I	55	48	33	19	62	32	50
T315I	72	70	58	34	61	29	36
Total**	59	53	39	22	61	31	41
Median mo to response	2.8	2.8	5.5	NR	0.7	1.0	0.7

Cortes et al. ASH 2014; Abstract #3135; Kantarjian et al. ASCO 2014; Abstract #7081

Arterio-Thrombotic Events with TKI

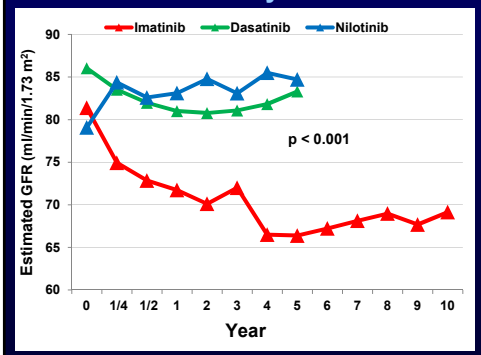
	Imatinib	Other TKI
ENESTnd	3	10-16
DASISION	2	5
BELA	3	3
EPIC	2	8
PACE*		13 (27)
Bosutinib Phase 2		6

Larson et al. ASH 2014: Abstract #4541; Cortes et al, ASH 2014: Abstract #156; Lipton et al, ASH 2014: Abstract #519; Cortes et al. ASCO 2014: Abstract #7060

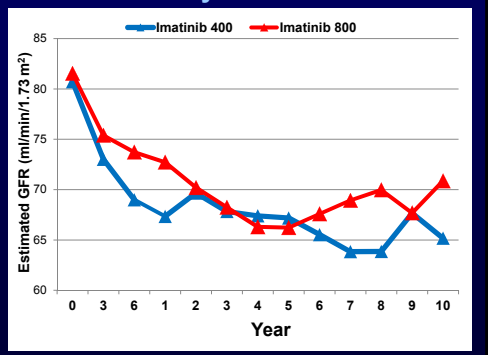
Renal Dysfunction with TKI

- 475 pts treated with imatinib (n=253), dasatinib (n=99), or nilotinib (n=116)

eGRF by TKI



eGRF by Imatinib Dose



- ARF (↑ creatinine ≥0.3 mg/dl): IM 6%, dasatinib 1%, nilotinib 2%
- CRF (GFR ≤60 ml/min/1.73 m^2 x ≥90 d): IM 22%, dasatinib 5%, nilotinib 4%
- No effect of ARF or CRF on outcome

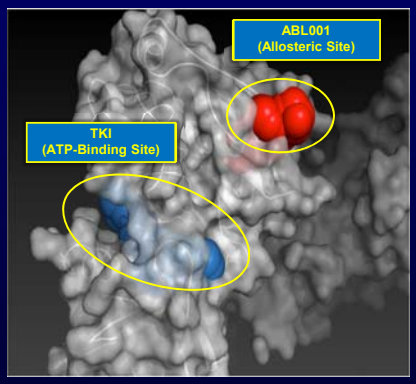
Yilmaz M, et al. *Blood.* 2013;122: Abstract 1488.

Simultaneous Binding of Two Inhibitors to BCR-ABL

Wild-Type BCR-ABL Protein

TKIs

- Bind to ATP-binding site (active site) of ABL kinase domain[1]
- Resistance may emerge to current TKIs as a result of point mutations in the ATP-site of the BCR-ABL1 kinase domain[2]



ABL001

- A potent and selective allosteric inhibitor of BCR-ABL[3]
- Binds to a distinct allosteric site (other than active site) on ABL kinase domain[3]
- Binds to BCR-ABL in combination with nilotinib or imatinib without cross competition[3]

1. Shah NP, et al. *Cancer Cell*. 2002; 2:117-125.
2. Zhang JM, et al. *Nat Rev Cancer*. 2009; 9:28-39.
3. http://www.novartis.com/downloads/investors/event-calendar/2013/investor-day-full-presentation.pdf Slide 177

What Am I Doing to Make Treatment Discontinuation More Palatable?

CCyR on TKI
Minimum 2yr on therapy
Stable CCyR
No CMR

- IFN
- AZA
- Omacetaxine
- Ruxolitinib
- HH/Smo Inhibitors
- Checkpoint Inhibitors

Eltrombopag for TKI-Associated Thrombocytopenia

- Patients with CML and platelets <50 x 10^9/L or MF and <100 x 10^9/L after ≥3 months of therapy with TKI
- Eltrombopag 50 mg orally daily
  - Dose escalation allowed every 2 weeks up to 300 mg
- 16 pts treated (11 CML, 5 MF)
  - CML: nilotinib 2, dasatinib 3, ponatinib 4, bosutinib 1, imatinib 1
  - MF: ruxolitinib 5
- CML: 10/11 complete response
  - 1 Hgb and 1 neutrophil improvement
  - 4 improved cytogenetic response
  - 2 tolerated TKI dose escalation
- MF: 2/5 non-sustained response

Borthakur G, et al. Blood. 2013: Abstract #4022 [Updated 12/2014]

Monitoring Patterns in a Community Setting in the US

Cytogenetic Response Monitoring

Testing status	<6 mo	6 ≤ 12 mo	12 ≤ 18 mo	18+ mo
Total N	418	360	284	242
Tested at milestone, %	32	31	16	27
CCyR, %	22	55	56	62
No CCyR, %	78	45	44	38
Switched TKI, %	9	36	20	88
Not tested at milestone, %	68	69	84	73

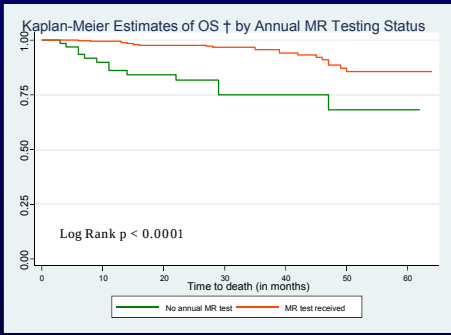
Molecular Response Monitoring

Testing status @ mo	0-3	3 ≤ 6	6 ≤ 9	9 ≤ 12	12 ≤ 15	15 ≤ 18	≥18
Total N	418	400	388	378	370	364	353
Tested at milestone, %	31	35	43	39	41	39	81
CMR, %	0	9	14	20	22	29	52
MMR, %	3	13	23	15	26	23	20
No CMR/MMR, %	85	60	52	55	43	41	27
Unknown	12	18	11	10	9	7	1
Not tested at milestone, %	69	65	57	61	59	61	19

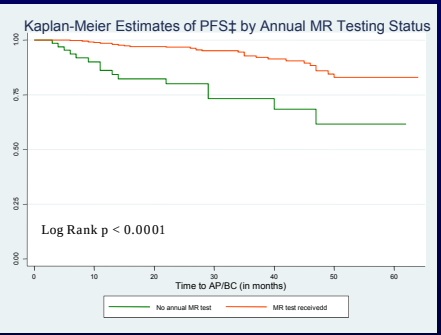
Chen et al. 2014

Overall Survival and Progression-Free Survival of CML Patients in Chronic Phase Treated with First-line TKI

Overall Survival



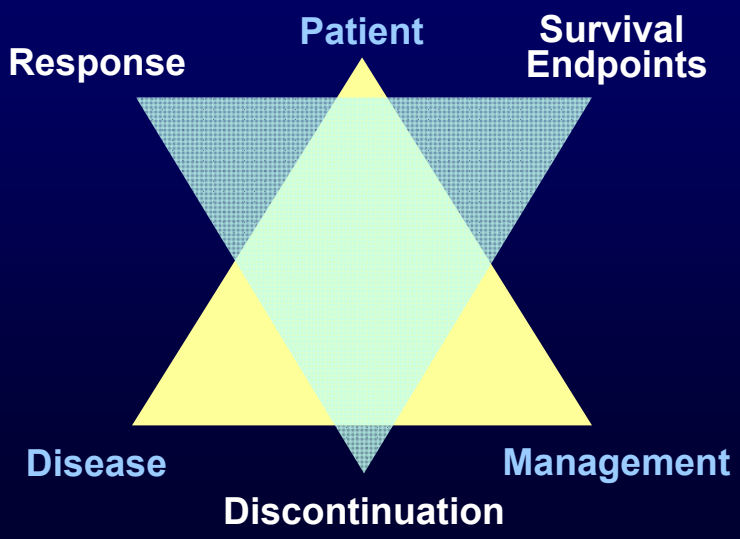
Progression-Free Survival



- After adjusting for confounding variables (age, gender, baseline KPS, payer type, co morbidities), annual MR testing remained the driving impact OS (HR=0.341; 95% CI, 0.162-0.717, P-value=0.0065) and PFS (HR=0.319; 95% CI, 0.161-0.632, P-value=0.0019).

Chen et al. 2014

Predictors of Outcome in CML



"If I seem unduly clear to you, you must have misunderstood what I said"

Alan Greenspan

See you in NY – November 1st, 2015

Team TNT

Questions?

jcortes@mdanderson.org

713-794-5783

Managing Chronic Myeloid Leukemia

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

Resources to Make Informed Treatment Decisions

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

The Leukemia & Lymphoma Society (LLS) offers:

- **Live, Online Chats provide a friendly forum to share experiences with others.**
  - **WEBSITE: www.LLS.org/chat**
- **LLS' Financial Assistance Program for PCR Testing can provide up to $1,000 of your PCR testing costs, for uninsured patients or patients that are not covered in full by insurance, during your enrollment period.**
  - **WEBSITE: www.LLS.org/pcr TOLL-FREE PHONE: (877) 614-9242**
- **What to ask: For a list of suggested questions to ask about certain topics, download and print any of the following guides.**
  - **WEBSITE: www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/publications**
- **Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.**
  - **EMAIL: infocenter@LLS.org PHONE: (800) 955-4572**