How I Treat CML in 2019.

Focus on Resistance to Second Generation TKIs

Elias Jabbour, MD

Sao Paolo

March 2019

Therapy of CML in 2019

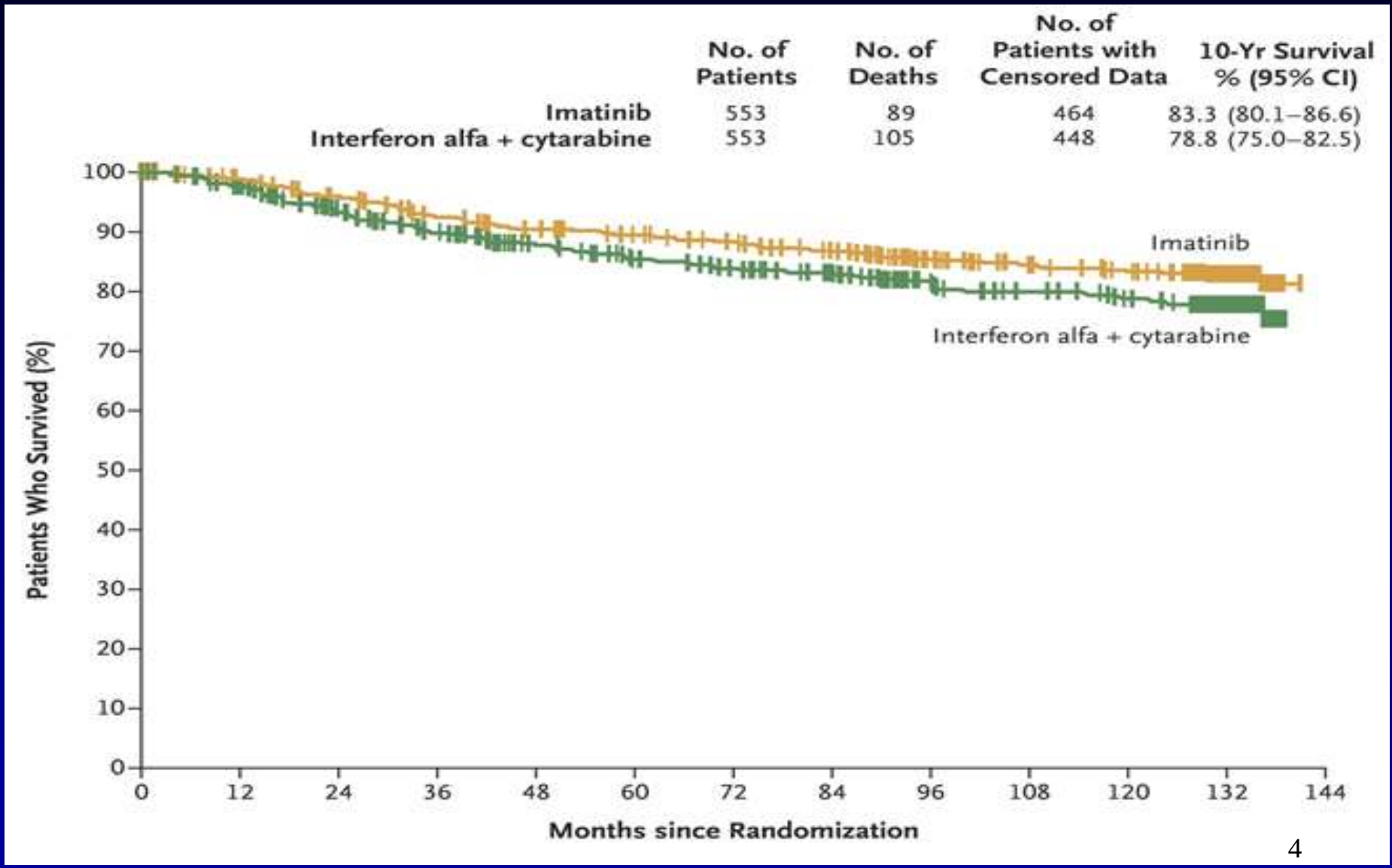
- Frontline
  - Imatinib 400 mg daily
  - Dasatinib 100 mg daily
  - Nilotinib 300 mg BID
  - Bosutinib 400 mg daily
- Second/third line
  - Nilotinib, dasatinib, bosutinib, ponatinib, omacetaxine
  - Allogeneic SCT
- Other
  - Decitabine, peginterferon α-2a
  - Hydroxyurea, cytarabine, combos of TKIs and with TKIs

Sequence of Frontline and Salvage Strategies in CML

	Choice of TKI	
Frontline Rx	**Dasatinib 50mg/D**	**Imatinib 400mg/D**
Salvage for Resistance	**-Ponatinib 30mg/D unless intolerance or cardiovascular risk factors**	**-Dasatinib 50→100mg/D or bosutinib 300-500 mg/D -if failure then ponatinib**
Salvage for toxicities	**Bosutinib 300-500mg/D**	**Dasatinib or bosutinib**

- **I do not use nilotinib frontline because of 10-yr CV problems 10-12+%**
- **Always adjust TKI dose if side-effects before considering change of TKI**

Survival With Imatinib vs IFN + Ara-C in Newly Dx CML (IRIS; 10-yr)



Hochhaus. *N Engl J Med.* 2017;376:917.

CML Frontline Therapy

- Up to 16, and 8 main studies compared new-generation TKIs to imatinib frontline: ENESTnd (nilotinib), DASISION (dasatinib), BFORE (bosutinib), EPIC (ponatinib), others
- All showed higher rates of favorable early surrogate endpoints: CGCR, MMR, MR4.5, ↓ AP/BP
- Increased uncommon toxicities with newer TKIs: PAOD-MI-TIA, pancreatitis, pleural effusions; HT and pulmonary HT, ↑ BS, vasospastic reactions, ↑ non-CML deaths

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. JCO. 34: 2333; 2016

ENESTnd – The 6-Year Update

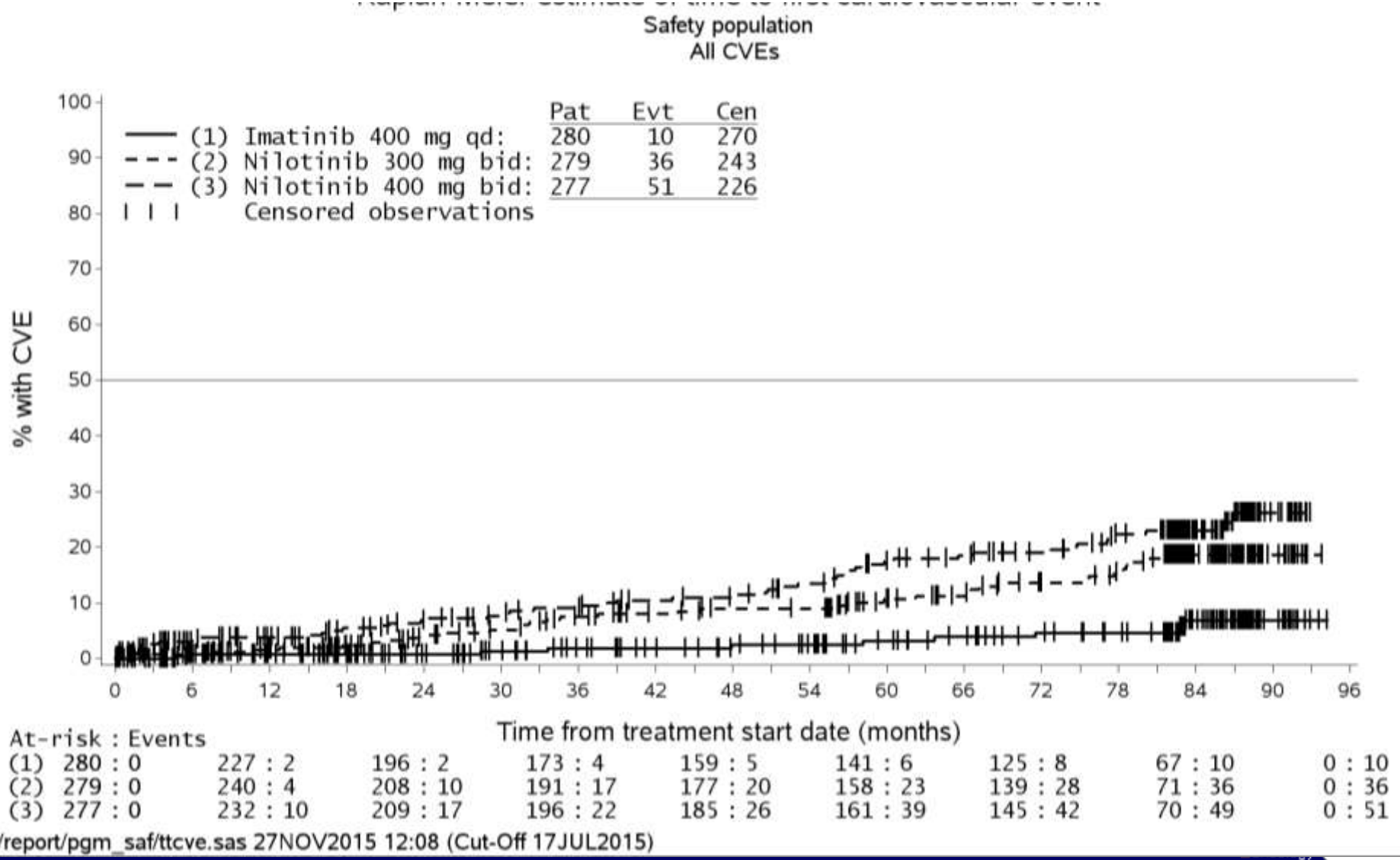
- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281) or imatinib (n=283)
- Minimum follow-up 6 yrs

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
6y OS	92	96	92	HR 0.9/0.46

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

Hochhaus. Leukemia 30: 1044; 2016

ENEST-nd-CV Events



Hochhaus et al., Leukemia 2016

Generic Imatinib in India: Survival of the Cheapest

- 1367 pts newly diagnosed CML: 1193 “innovator”, 174 generic
- CP 90% & 83%; AP 7% & 10%; BP 4% & 7%

	Innovator	Generic
CCyR	67	64
MMR	22	14
MR4	17	24
AP/BP	8	7
AEs		
Edema, any grade	12	6
Myalgia, any grade	15	10
Rash, grade 3	<1	3
Thrombocytopenia, any grade	6	9
Neutropenia, any grade	5	3
Anemia, any grade	9	6

Madhav et al. ASH 2016; abstract #630

Lower-Dose Dasatinib Newly Diagnosed CML-CP

- 59 pts, median age 46 y (range, 22-80 y)
- Dasatinib 50 mg/d

No. Response/total	3 mos	6 mos	12 mos
PCR <10%	56/59 (95%)	48/49 (98%)	23/23 (100%)
PCR < 1%	43/59 (73%)	42/49 (86%)	22/23 (96%)
CCyR	26/59 (44%)	43/49 (88%)	21/23 (91%)
MMR	17/59 (29%)	33/49 (67%)	19/23 (83%)
MR 4.0	2/59 (3%)	16/49 (33%)	17/23 (74%)
MR 4.5*	0/59	9/49 (18%)	11/23 (48%)

Naqvi et al. Cancer. 2018;124(13):2740-2747.

Frontline CML Therapy in 2019+

- Dasatinib 50mg daily produces similar efficacy and significantly less toxicity than 100mg daily
- Current frontline: dasatinib 50mg daily+venetoclax 400mg daily. Aim to achieve high rates of durable CMRs and Rx discontinuation=molecular cures

Rx Endpoints When Comparing Second TKIs to Imatinib in Frontline Rx

- Lower incidence of early transformation to AP-BP
- Survival
- Molecular cure
- Long-term safety
- Cost; cost-effectiveness = “Rx value”

Monitoring Patients with CML While on TKI Therapy

- Adequate monitoring required to optimize outcome
  - —Not too much, not too little
- CCyR is gold standard: survival benefit
- MMR may decrease probability of relapse
- CMR offers hope for treatment discontinuation (clinical trials only)
- Mutation analysis only when clinical failure
- Results should be interpreted in the context of alternative options

The Simple Guide to Molecular Monitoring

- If it is going down, it is good
- If it is stable, it is OK
- If it is going up, monitor more frequently
  - Not a failure by itself
- If continues to go up (> 1 log w/o MMR)
  - Check CG
  - If CG relapse
    check mutation analysis

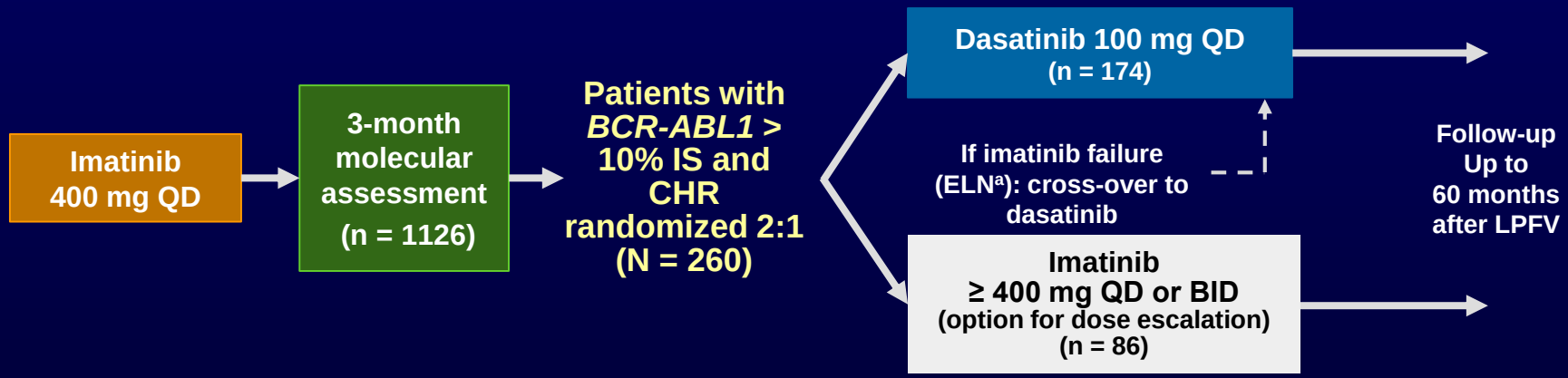
BCR-ABL Transcripts < 10% at 6 mos Associated with Better Outcome

Response					
3 Mo	6 Mo	No.	% Survival	% PFS	% FFS
≤ 10	≤1	342	97	97	87
≤ 10	1-10	42	100	97	79
≤ 10	> 10	10	89	90	51
> 10	≤ 1	18	100	100	76
> 10	1-10	36	100	94	79
> 10	> 10	35	74	69	11

Brandford. Blood 122: abst 254; 213

DASCERN: Study Design

- Randomized, open-label, international phase 2b trial in adults with CML-CP with CHR but *BCR-ABL1* >10% IS at 3 months after initial treatment with imatinib 400 mg QD



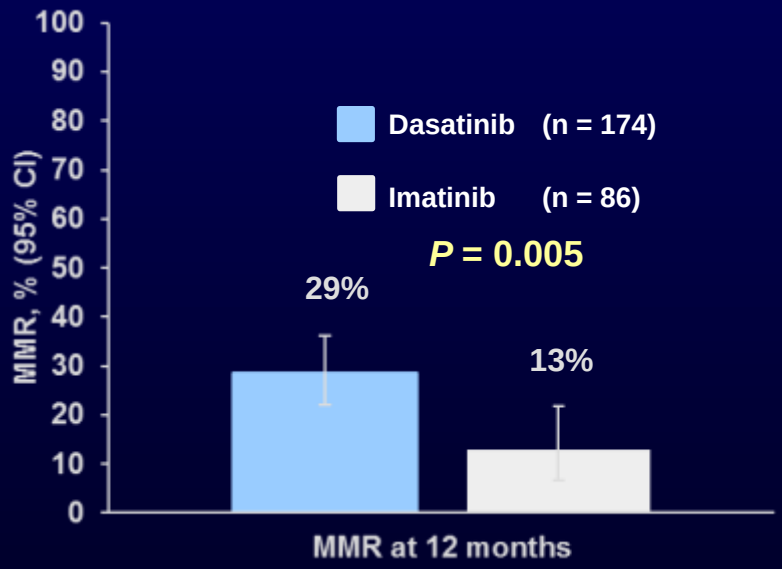
- Stratified by Sokal and time from molecular assessment to randomization
  - Randomization may occur up to 8 weeks after the 3-month molecular assessment

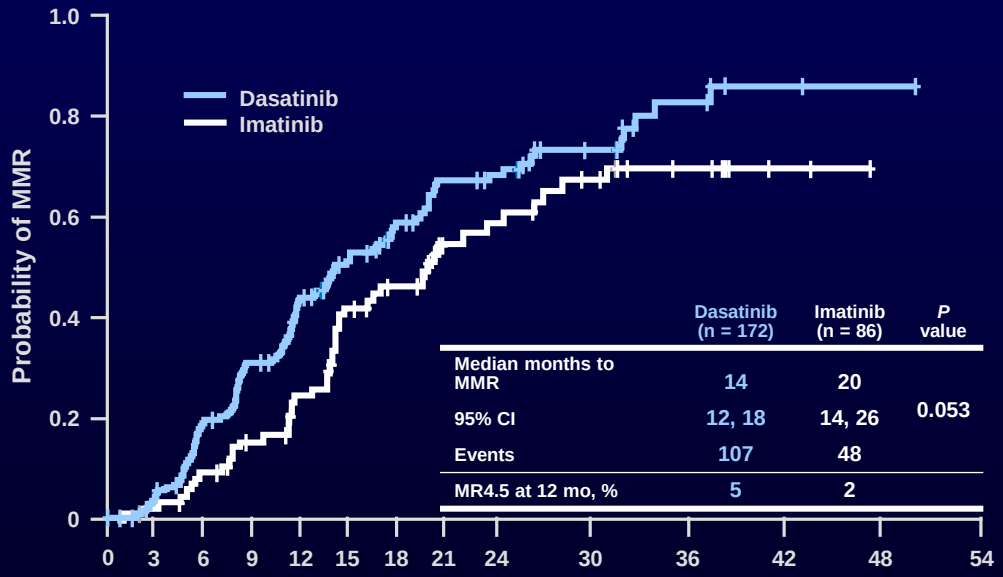
[a]Patients initially randomized to imatinib, meeting ELN 2013 failure criteria, and without dasatinib-resistant mutations were crossed over to the dasatinib arm.

Cortes et al. ASH 2018; abstract #788

DASCERN: Early Intervention For Patients with BCR-ABL >10% at 3 months

- 260 pts with CHR, but *BCR-ABL1* > 10% IS at 3 mos after initial treatment with 400 mg imatinib QD
- Randomized 2:1 to dasatinib 100 mg daily or imatinib ≥400 mg daily
- Primary endpoint MMR at 12 mo



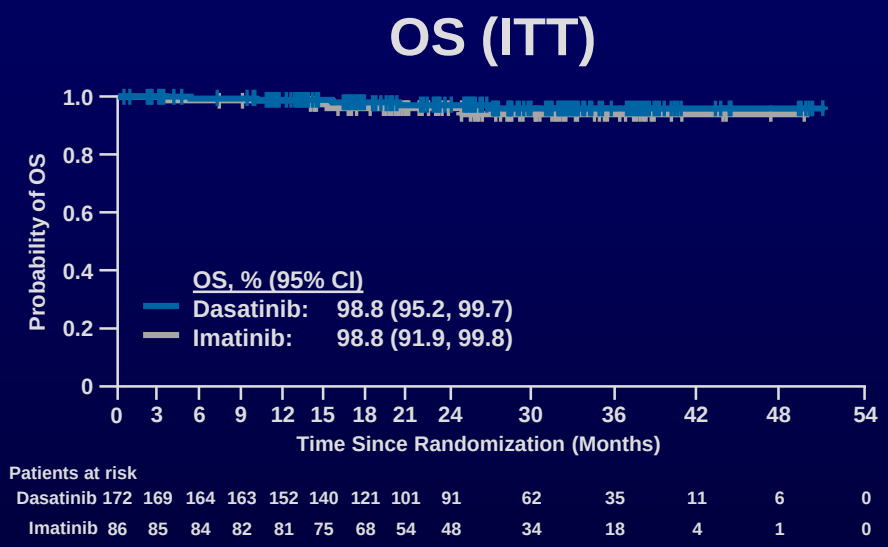


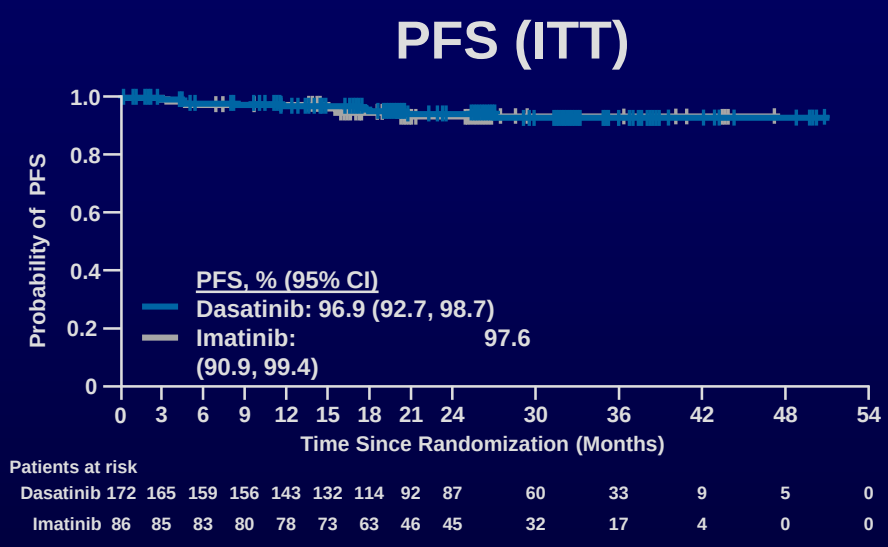
	Dasatinib (n = 172)	Imatinib (n = 86)	*P* value
Median months to MMR	14	20	0.053
95% CI	12, 18	14, 26	
Events	107	48	
MR4.5 at 12 mo, %	5	2	

CI = confidence interval; ITT = intent-to-treat; MMR = major molecular response.

Cortes et al. ASH 2018; abstract #788

DASCERN Secondary Endpoint: Survival Outcomes



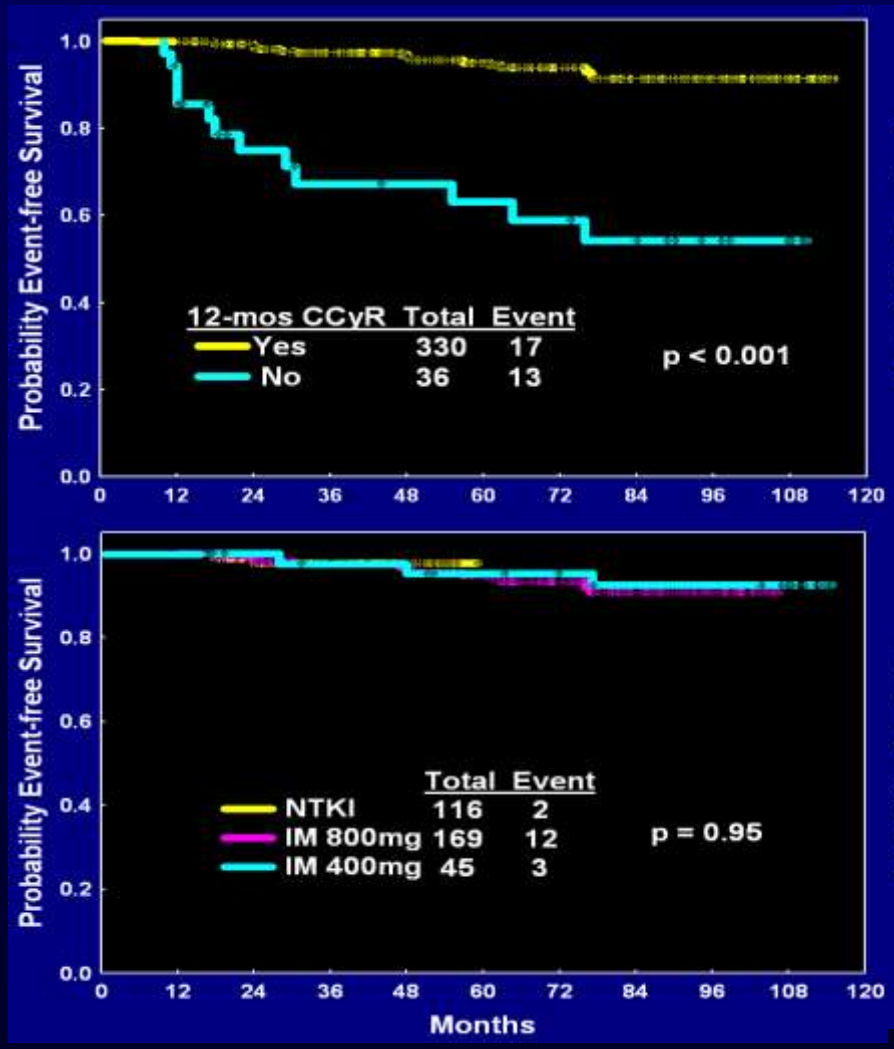


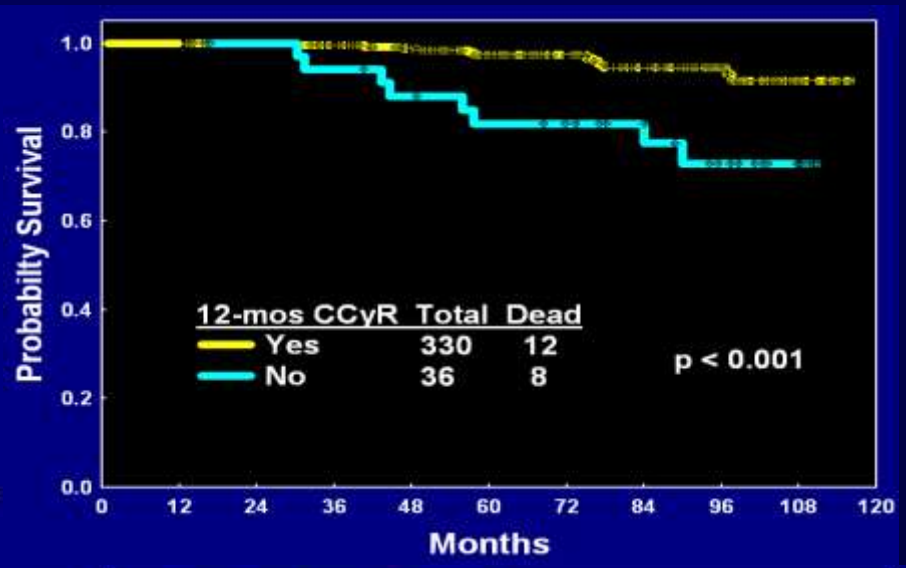
- **Median duration of follow-up:**
  - **30 months (range 12-56) in patients randomized to dasatinib**
  - **30 months (range 12-65) in patients randomized to imatinib**

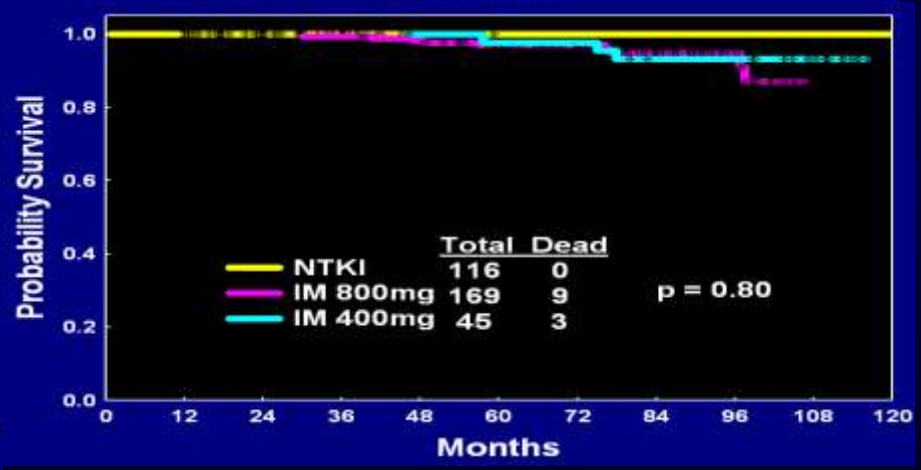
CI = confidence interval; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.

Cortes et al. ASH 2018; abstract #788

EFS and Survival by 12-month Response-CCyR vs Others with TKI Frontline Rx

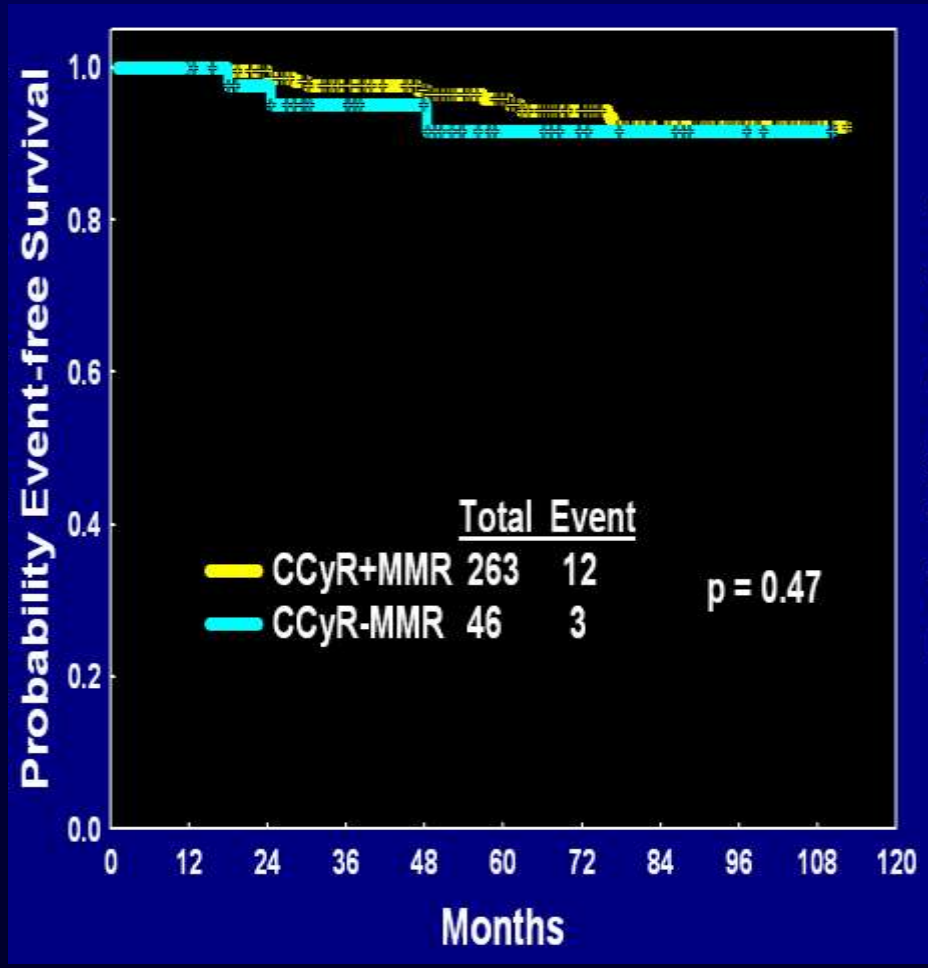


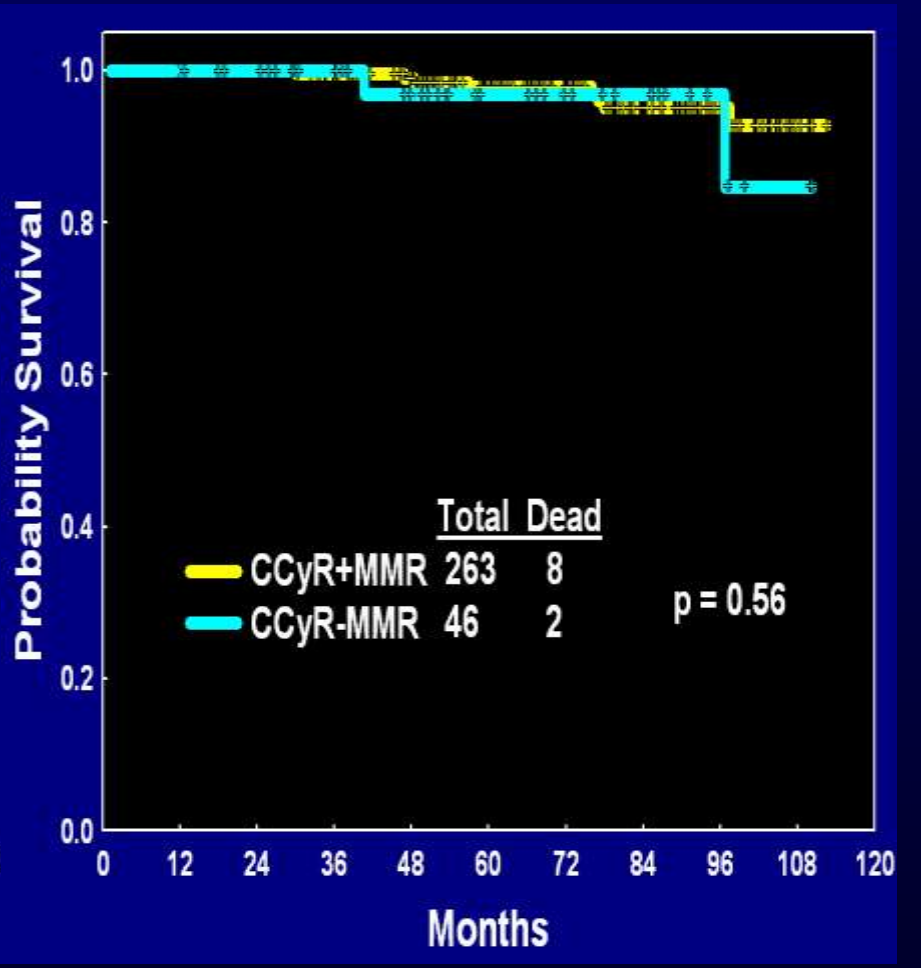




Jabbour. Blood. 2011;118:4541-6.

EFS and Survival by 12-month Response-CCyR with vs without MMR with TKI Frontline Rx





Jabbour. Blood. 2011;118:4541-6.

CML. Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

Time (mo)	Response		
	Failure	Warning	Optimal
3	No CHR, And/or Ph+ >95%	BCR-ABL >10%, and/or Ph+ 36-95%	BCR-ABL ≤10%, and/or Ph+ <35%
6	BCR-ABL >10% and/or Ph+ >35%	BCR-ABL 1-10%, and/or Ph+ 1-35%	BCR-ABL <1%, and/or Ph+ ≤35%
12 and beyond	BCR-ABL >1% and/or Ph+ >0%	BCR-ABL >0.1-1%	BCR-ABL <0.1%
Any	Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+	CCA/Ph- (-7, or 7q-)	BCR-ABL <0.1%

Baccarani. Blood 2013; 122: 872-84

Important Response Categories in CML

Response	Translates into:
BCR-ABL ≤ 10% at 6 mos; CCyR later	Significantly improved survival
MMR	Modest improvement in EFS; possible longer duration CCyR; no survival benefit
CMR	Possibility of Rx discontinuation

Case 1

- 63 yr old man with CML treated frontline with nilotinib 300mg bid. Achieved CGCR and PCR less than 0.1%. After 3 yrs had CG relapse with PCR 50%, FISH 60%, mutation T315I. Next treatment option:
  - a) dasatinib 100mg daily
  - b) bosutinib 500mg daily
  - c) ponatinib 30mg daily
  - d) allogeneic SCT

Case 1

- 63 yr old man with CML treated frontline with nilotinib 300mg bid. Achieved CGCR and PCR less than 0.1%. After 3 yrs had CG relapse with PCR 50%, FISH 60%, mutation T315I. Next treatment option:
  - a) dasatinib 100mg daily
  - b) bosutinib 500mg daily
  - c) ponatinib 30mg daily
  - d) allogeneic SCT

Case 2

- 55 yr old woman with CML treated with dasatinib 100mg daily. Achieved CGCR and MMR but had hematologic relapse after 4 yrs. BM 2% blasts, CG 80% Ph+. PCR 80%. Mutations negative. Next treatment option:
  - a) nilotinib 400mg bid
  - b) bosutinib 500mg daily
  - c) ponatinib 30mg daily
  - d) allogeneic SCT

Case 2

- 55 yr old woman with CML treated with dasatinib 100mg daily. Achieved CGCR and MMR but had hematologic relapse after 4 yrs. BM 2% blasts, CG 80% Ph+. PCR 80%. Mutations negative. Next treatment option:
  - a) nilotinib 400mg bid.
  - b) bosutinib 500mg daily
  - c) ponatinib 30mg daily.
  - d) allogeneic SCT

Therapy of CML Post Frontline Failure

- Dasatinib 100 mg/D
- Nilotnib 400 mg BID
- Bosutinib 500 mg/D
- Ponatinib 45 mg/D approved dose (T315I; failure≥2 TKIs)
- Omacetxine, hydrea, HMA, LD ara-C can be added to TKI

Response and PFS with 2nd-Gen TKIs in Imatinib-Resistant CP-CML

TKI	Dasatinib[1,2]		Nilotinib		Bosutinib
Follow-up	**2 years[1,2]** (minimum follow-up)	**6 years[3]** (data lock at 6y)	**2 years[4]** (minimum follow-up)	**4 years[5]** (minimum follow-up)	**2 years[6]** (minimum follow-up)
Number of pts	167*	167*	226	321*	200
Discontinued, n (%)	NR	114 (69)	197/321 (61)	224 (70)	108 (54)
MCyR	63%*	NR	56%	59*	58%
CCyR	50%*	NR	41%	45*	46%
PFS, %	80*	49*	64*	57*	81*

***Includes imatinib-intolerant patients. NR, not reported.**

1. Sprycel® (dasatinib). Official prescribing information. November 2012.
2. Shah NP, et al. J Clin Oncol. 2010;28:15s (abstract 6512).
3. Shah NP, et al. Blood. 2014;123:2317-24.
4. Kantarjian HM et al. Blood. 2011;117:1141-1145.
5. Giles FJ, et al. Leukemia. 2013;27:107-12.
6. Gambacorti-Passerini C, et al. Am J Hematol. 2014 [Epub ahead of print].

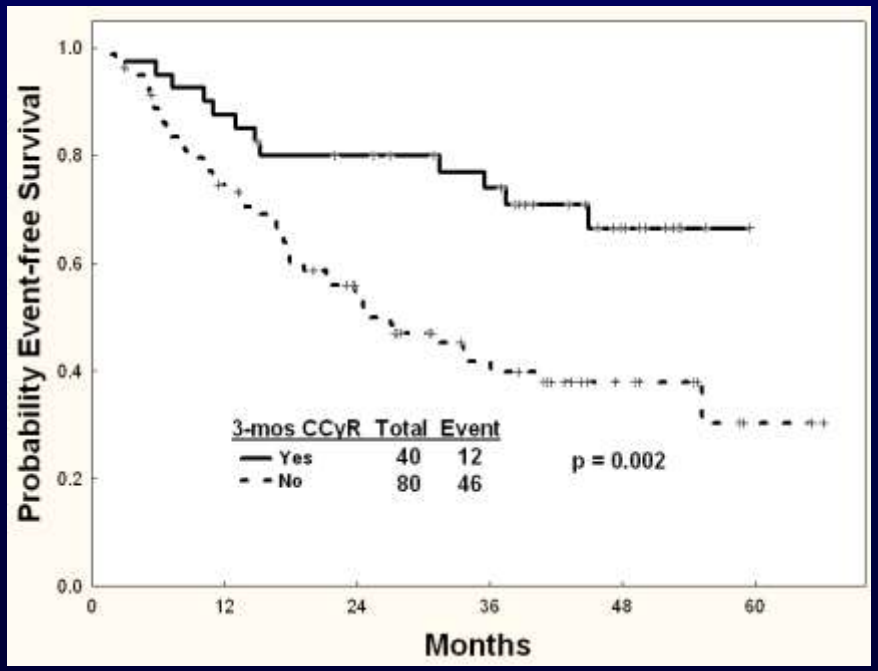
2nd Line TKI in CML CP

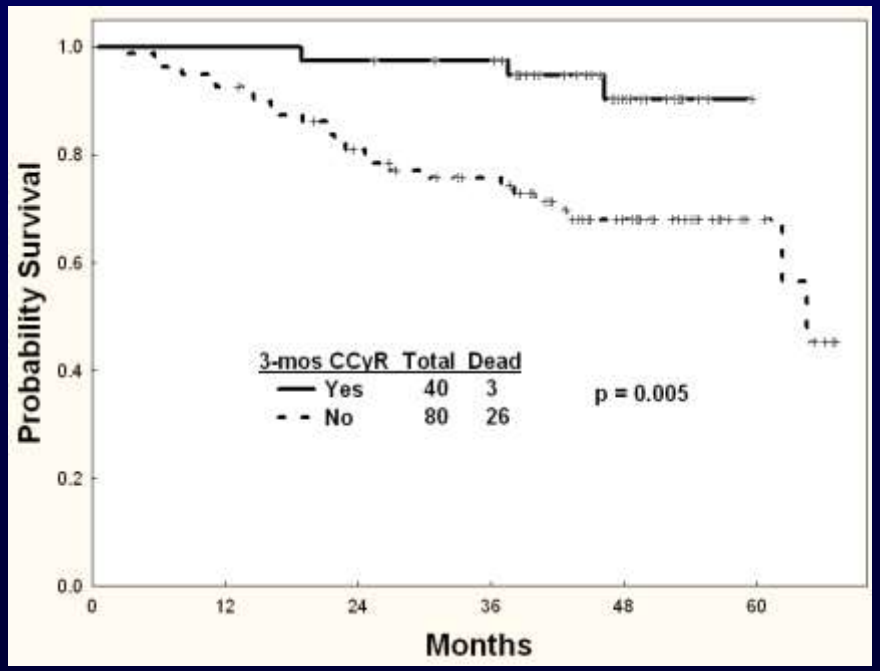
- 621 pts treated with 2nd TKI: dasatinib 55%, nilotinib 31%, bosutinib 6%, other (7%)
- 1st TKI: imatinib (85%), ponatinib (7%), nilotinib (5%), dasatinib (3%) or bosutinib (<1%)
- Reason to switch: resistance 55%, intolerance 45%
- Median F/U: 50 mo (0.1-139 mo)
- Response: CCyR 50%; Best molecular: MMR 13%, MR4.5 38%
- MVA: specific TKI no impact in OS or TFS; nilotinib or other inferior EFS and FFS

Chamoun et al. ASH 2017; abstract #1594

Predictors of Outcome to 2nd Line TKI in CML

- 123 pts treated with dasatinib (n=78) or nilotinib (n=45) after imatinib failure
- Median follow-up 76 months (range, 25-109)
- MCyR 63%, CCyR 59%, 3-yr EFS 53%, 3-yr OS 84%
- 3-mo CCyR33%



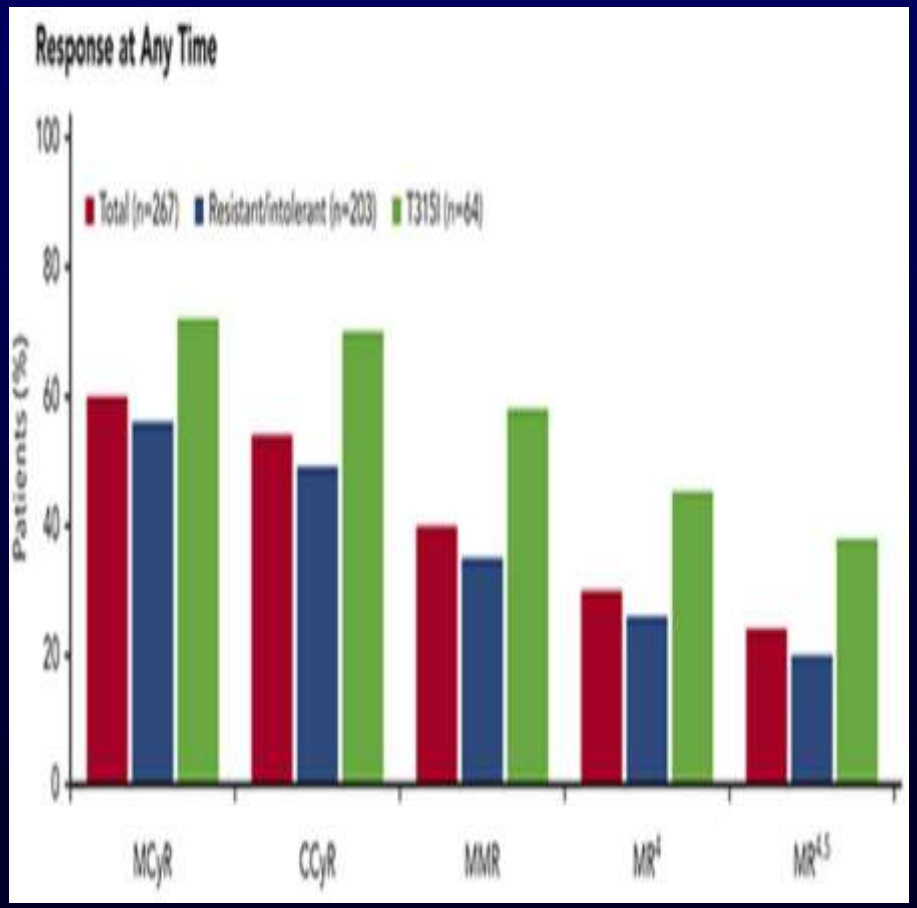


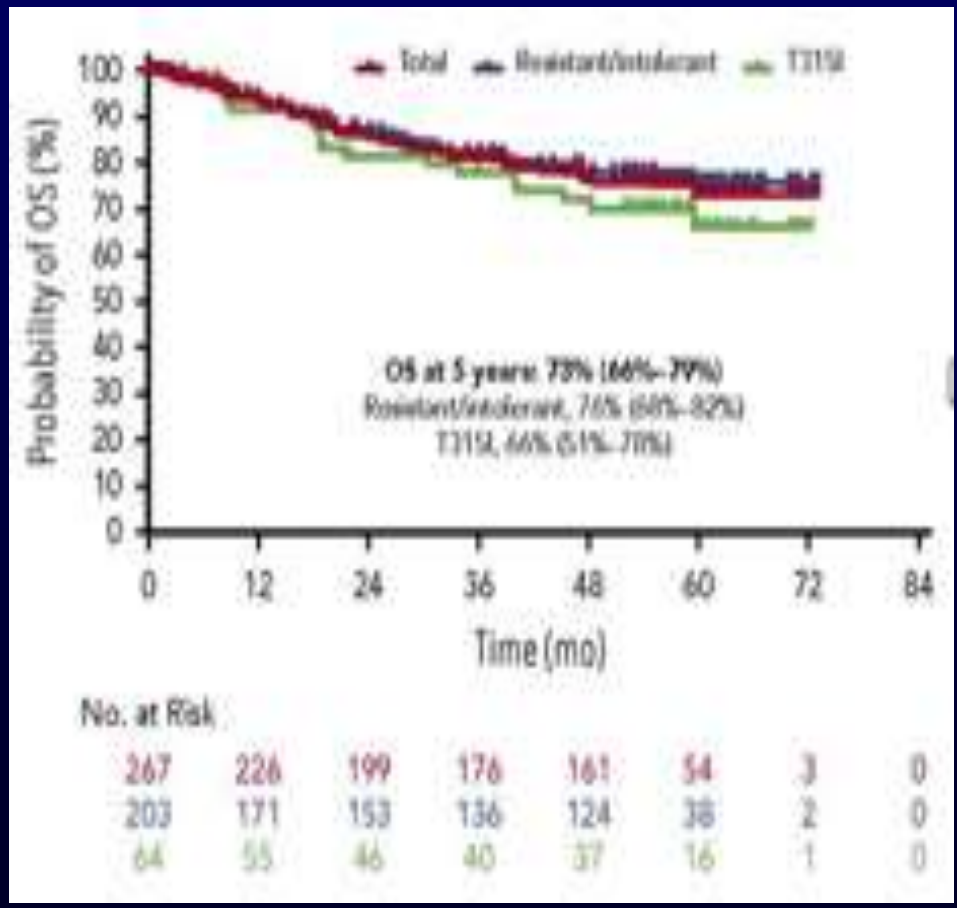
- MVA: 3-mo CCyR only factor independently associated with EFS (p<0.001) and OS (p=0.03)

Jabbour et al. Blood. 2010;116: Abstract 2289. Jabbour et al. Clin Lymphoma Myeloma Leuk. 2013 Jan 11. [Epub ahead of print]

Ponatinib in CML—CP (PACE)

- 449 pts Rx; 270 in CP
- CG major 60%, MMR 40%, 5-yr OS 73%

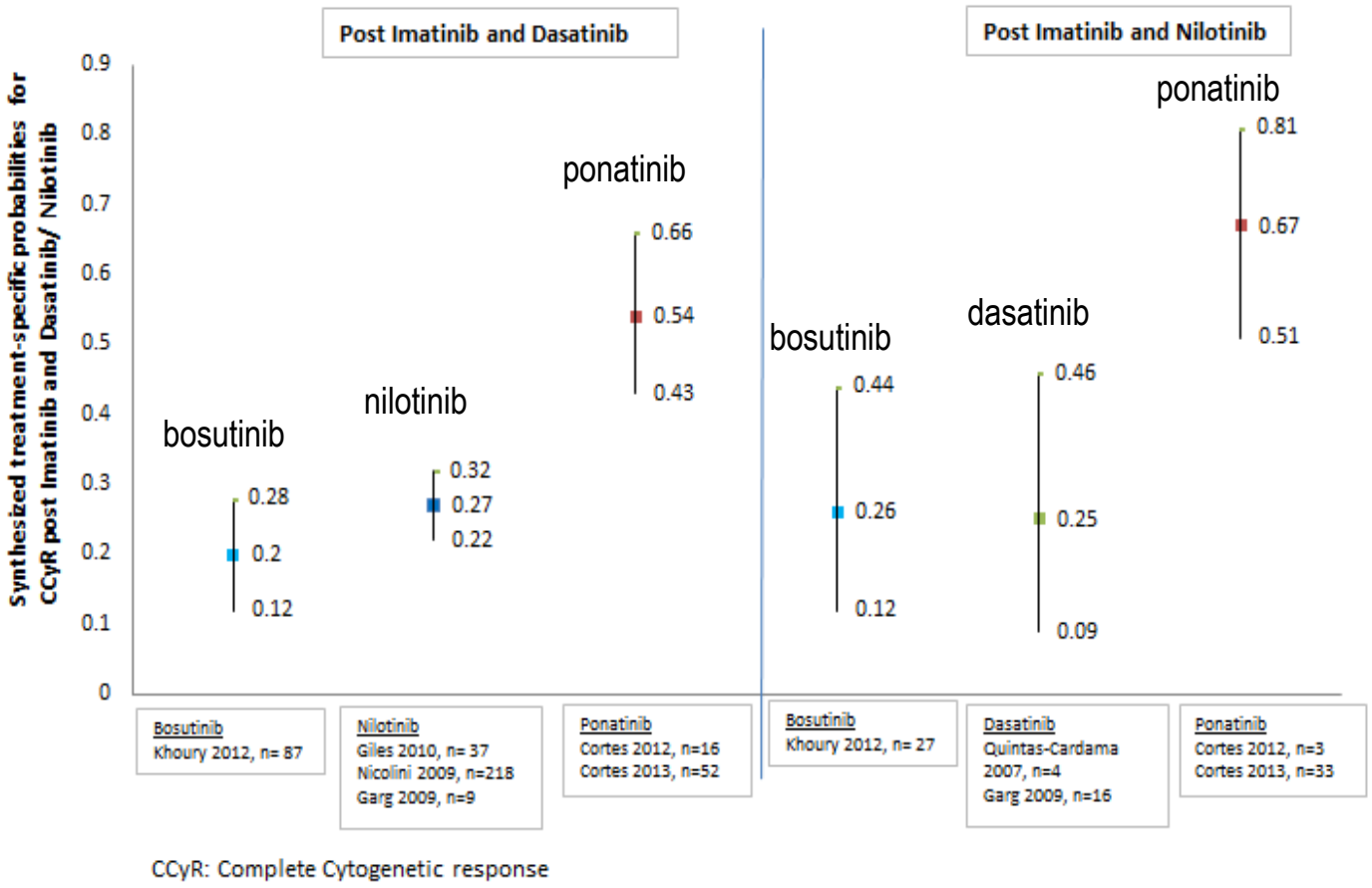




Cortes. Blood 132: 393; 2018

Comparative Efficacy of Third-line Therapy After Failure of Imatinib and Dasatinib or Nilotinib

Figure 1: Synthesized treatment-specific probabilities (and 95% Credible Intervals) of achieving CCyR post Imatinib and Dasatinib/ Nilotinib

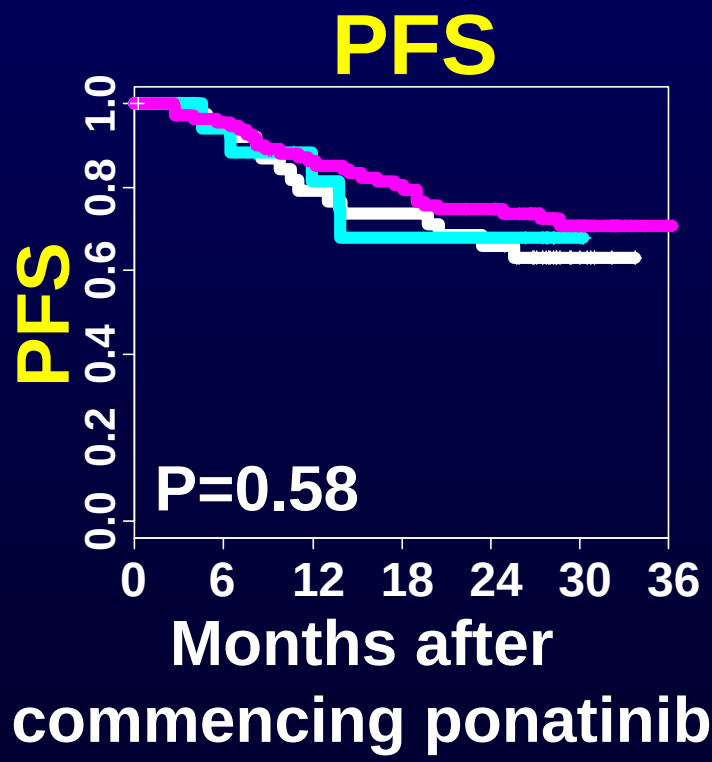


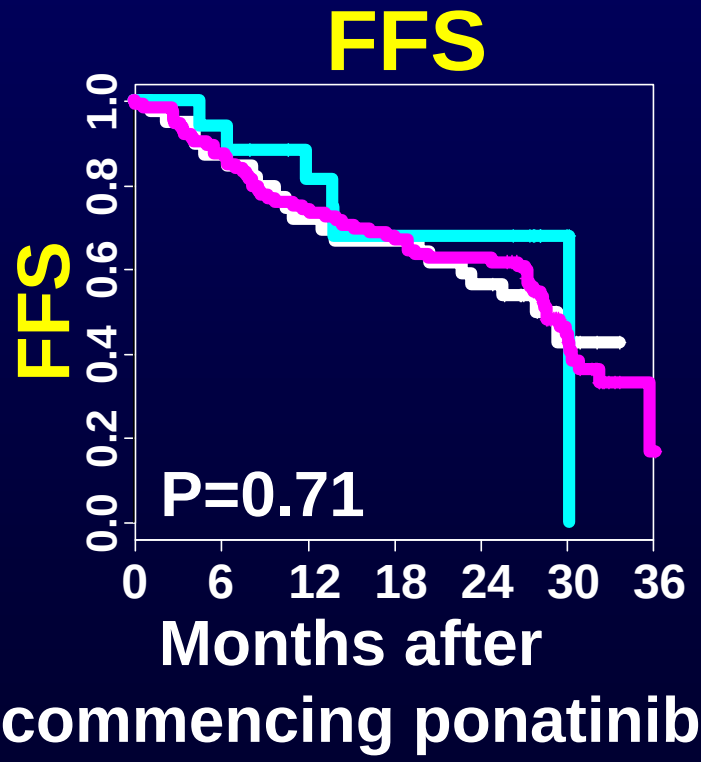
CCyR: Complete Cytogenetic response

Lipton JH, et al. *Blood*. 2014;124:abstract 4551.

Outcome After Ponatinib for Patients with CML CP without T315I

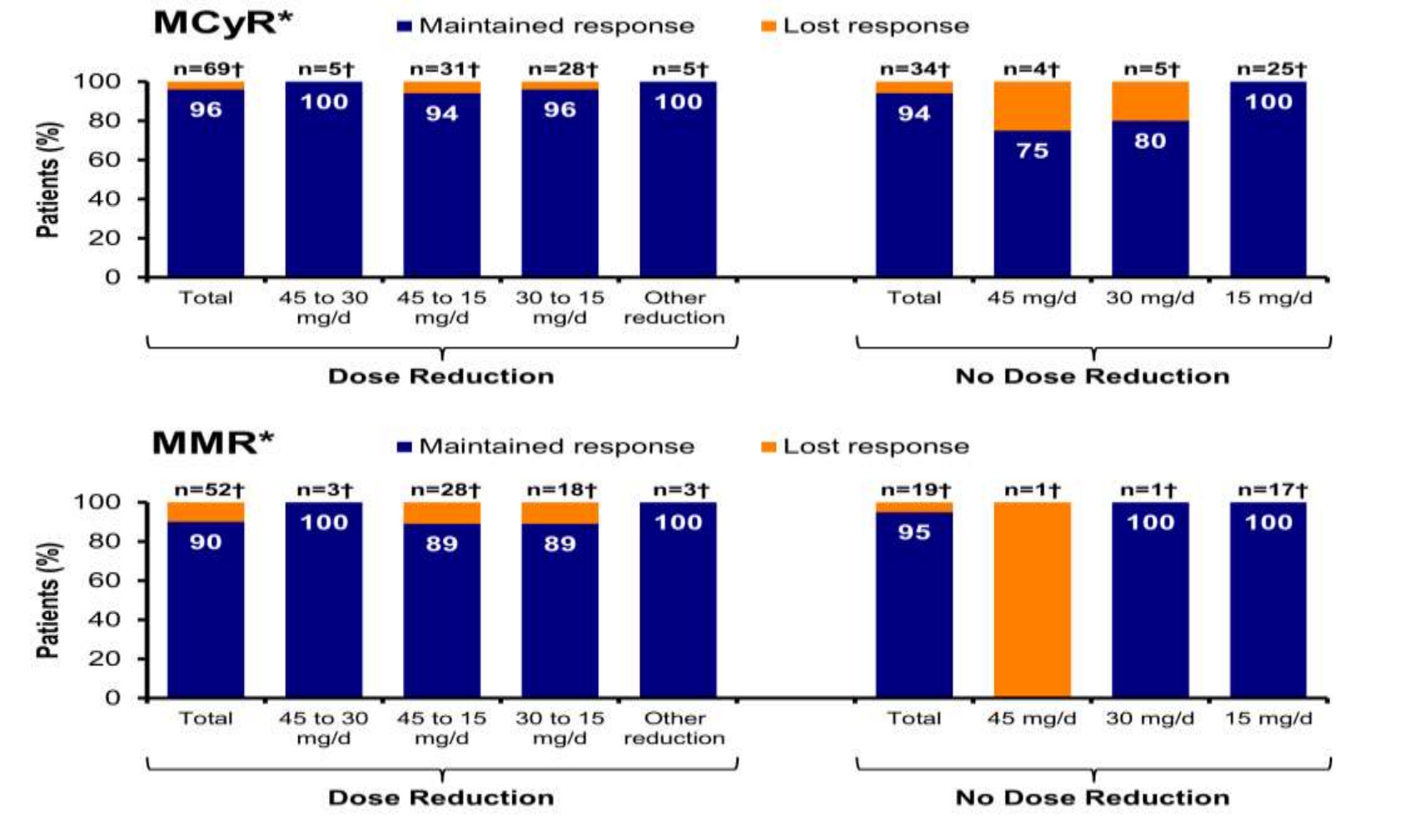
- No mutation (112)
- 1 mutation (39)
- >1 mutation (17)



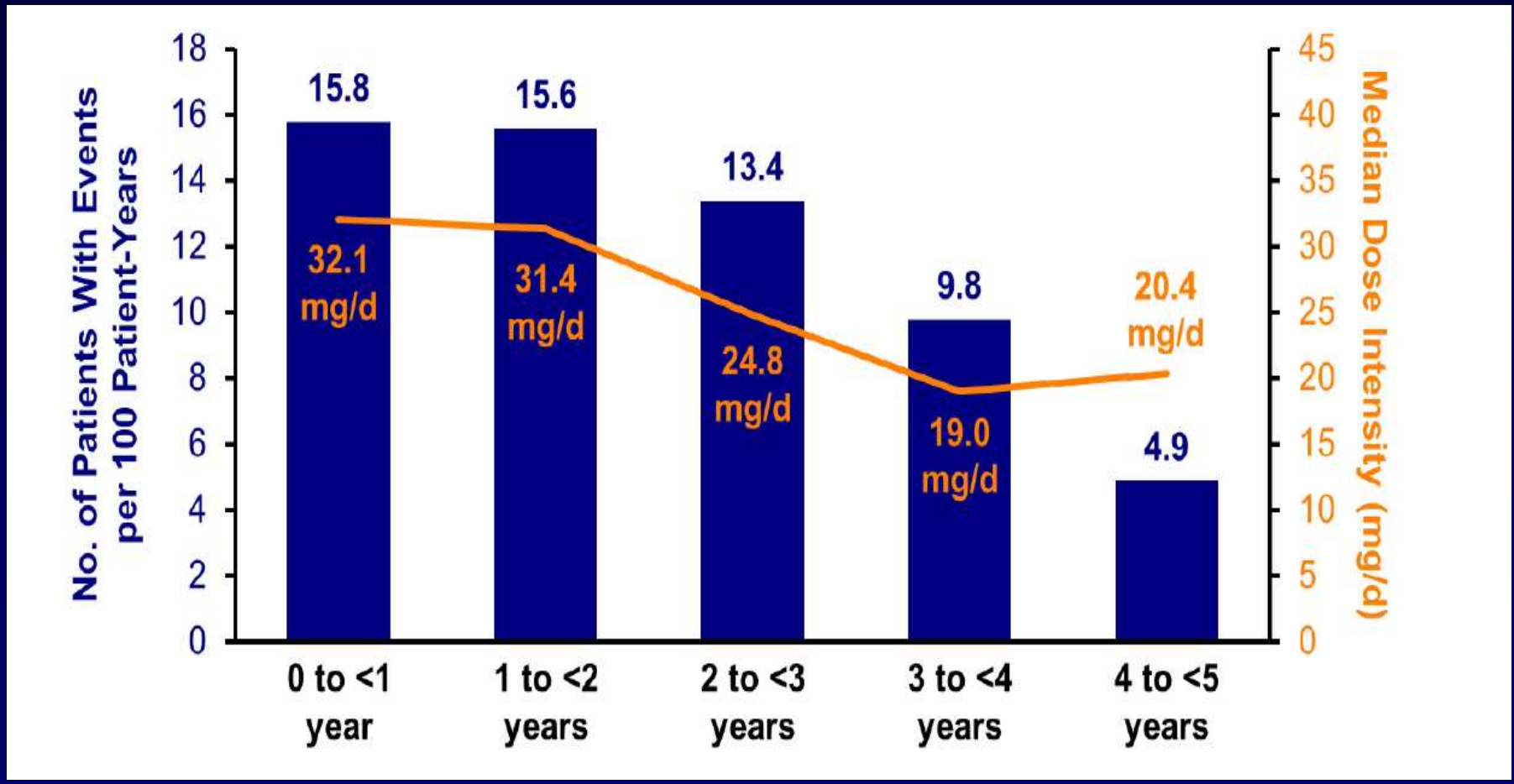


Parker WT, et al. *Blood.* 2013;122: Abstract 651.

Impact of Prospective Dose Reductions



Exposure-Adjusted Incidence Rates for Newly Occurring AOE



3rd Line TKI in CML

- 185 pts Rx with 3rd TKI: nilotinib 36%, dasatinib 35%, ponatinib 12%, imatinib 10%, bosutinib 7%
- Median time from Dx: 58 mo (3 – 199 mo)
- 1st TKI: intolerance 44%, resistance 67%; 2nd TKI: intolerance 60%, resistance 49%

Response	%
CCyR	38
MMR	41
MR4	33
MR4.5	29

- MVA predictors of CCyR and MMR: ponatinib, Hgb, intolerance

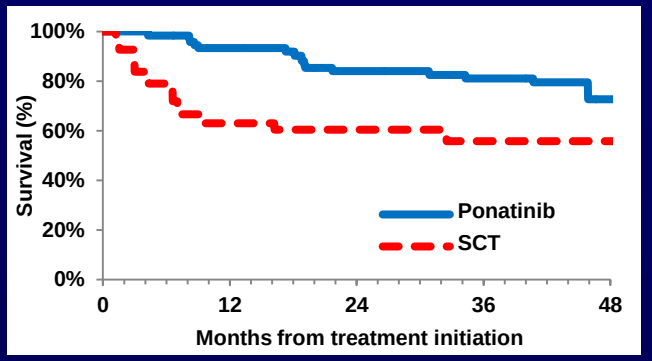
Khan M, et al. *Blood.* 2017;130(suppl): Abstract 2882.

Ponatinib or SCT for T315I CML

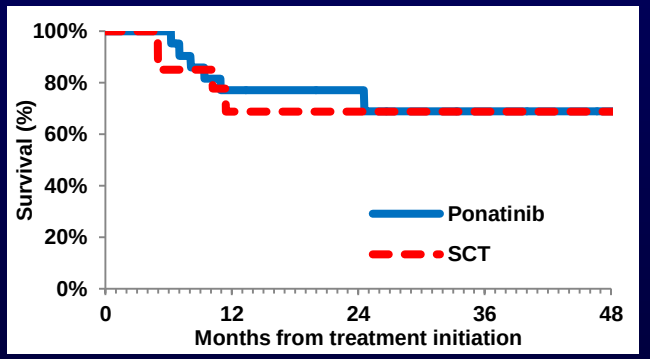
- Pts ≥18 yrs with CML T315I in any stage enrolled in PACE (n=449) or EBMT (1999-2010; n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36

Disease group	Median survival (mo)	
	PACE	EBMT
CP	NR	103
AP	NR	56
BP	7	11
Ph+ ALL	7	32

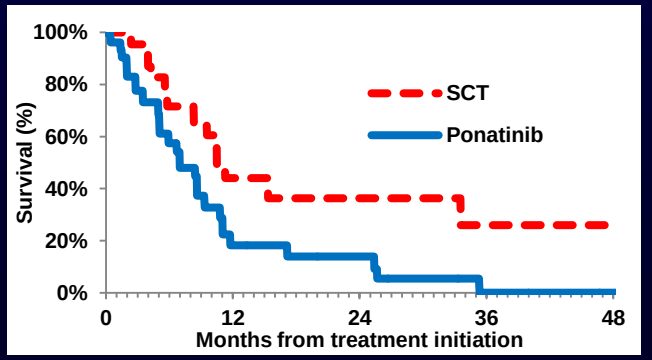
CP



AP



BP



Nicolini et al et al, Cancer. 2017;123(15):2875-2880

Ponatinib Toxicities of Concern CML Therapy?

- Optimal dose: 30 vs. 45 mg daily?
  - Awaiting OPTIC Data
- Incidence of toxicities of concern
  - Pancreatitis 7%
  - Skin rashes 40%; severe 4-7%
  - Vasoocclusive disorders (cardiac, CNS, PAOD) 12%
  - Hypertension 67%; severe 20%

New TKI Under Development

TKI	Features	Current status
Asciminib (ABL-001)	Allosteric inhibitor	• Completed phase 1, single agent and combination • Pivotal phase 3 3rd line vs bosutinib started
Radotinib	2nd generation	• Approved in South Korea 1st and 2nd line • Pending studies elsewhere
PF-114	Ponatinib analog, not binding VEGFR	• Nearing MTD • Starting phase 2
HQP1351	Active against T315I	• Phase 1 completed
K0706	3rd generation	• Phase 1 ongoing

CMLBP-MDACC Experience (1997-2016)

- 477 pts Rx: lymphoid BP 28%; TKI alone 35%, TKI + ChemoRx 48%; allo SCT 22%
- MHR 50%; CGCR 21%; MHR with TKI alone 43%; TKI + chemo 64%
- Median OS 12 mos
- MVA for OS: TKI combo, allo SCT, lymphoid BP favorable

Jain. Cancer 2017. Epub ahead of print.

Summary – CML 2019

- Excellent therapy for CML
- CGCR is endpoint of Rx = improves survival
- Aim for PCR<10% by 6 mos, and for CG CR by 12+mos—these are only indications to change Rx
- Deeper molecular responses (MMR) improve EFS; no impact on transformation or survival; benefit for CMR in DC Rx??
- Better prognostic models identifying the best sequential therapy
- Role of NGS: Detecting higher-risk patients (compound mutations etc..)
- Patients comorbidities be optimized

Thank You

Leukemia Questions?

- Email: ejabbour@mdanderson.org
- Cell: 713.498.2929
- Office: 713.792.4764