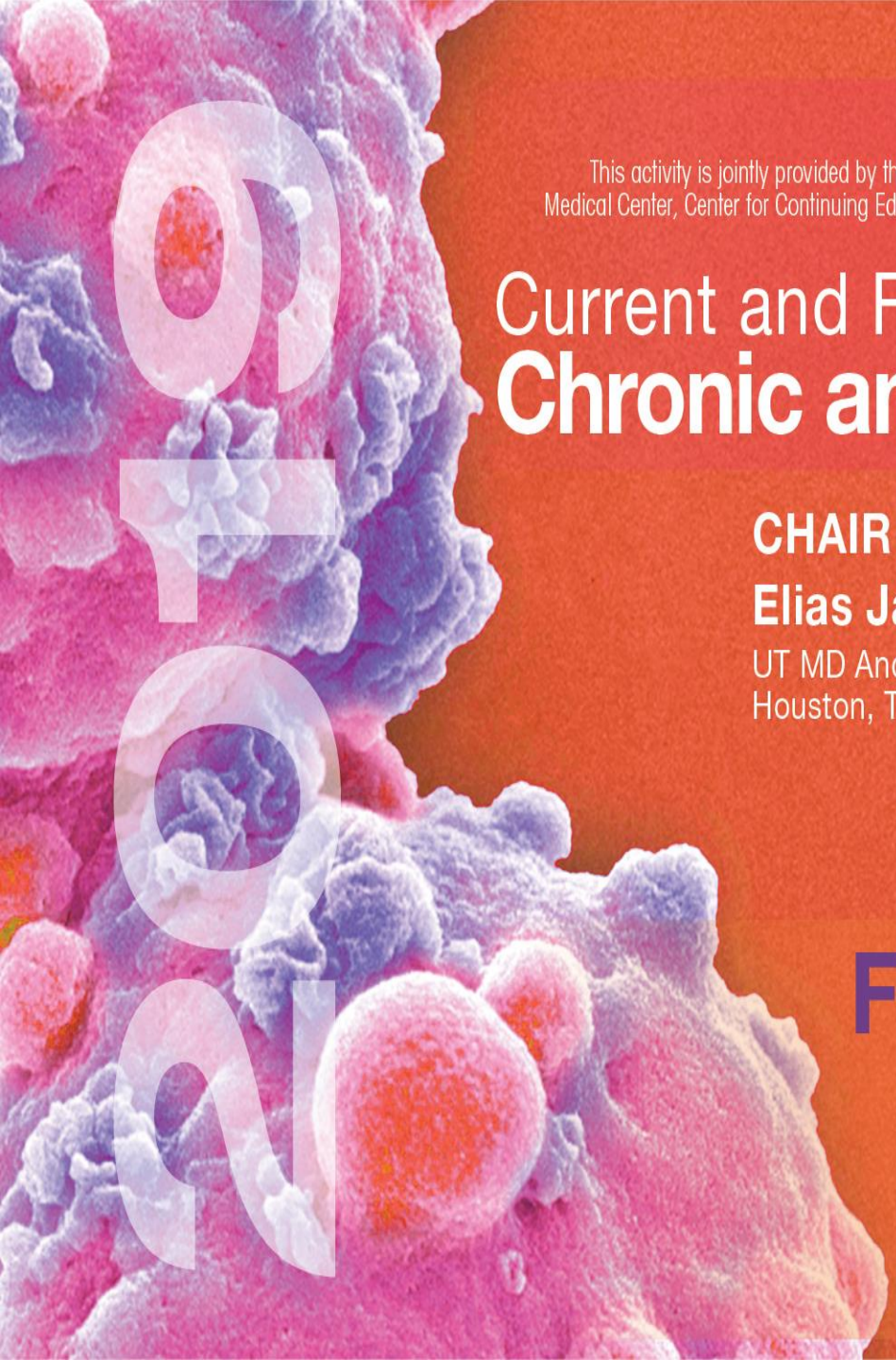

This activity is jointly provided by the University of Nebraska Medical Center, Center for Continuing Education and Bio Ascend.

UNIVERSITY OF NEBRASKA MEDICAL CENTER
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Bio Ascend

Current and Future Directions in **Chronic and Acute Leukemias**

2019

CHAIR

Elias Jabbour, MD
UT MD Anderson Cancer Center
Houston, Texas

FACULTY

Susan O'Brien
University of California, Irvine
Irvine, California

Hagop Kantarjian
UT MD Anderson Cancer Center
Houston, Texas

Friday, September 13
6:00 AM – 7:45 AM

This activity is supported by an independent educational grant from Pfizer Inc.

How I Treat CML in 2019

Elias Jabbour, MD
Houston
September 2019

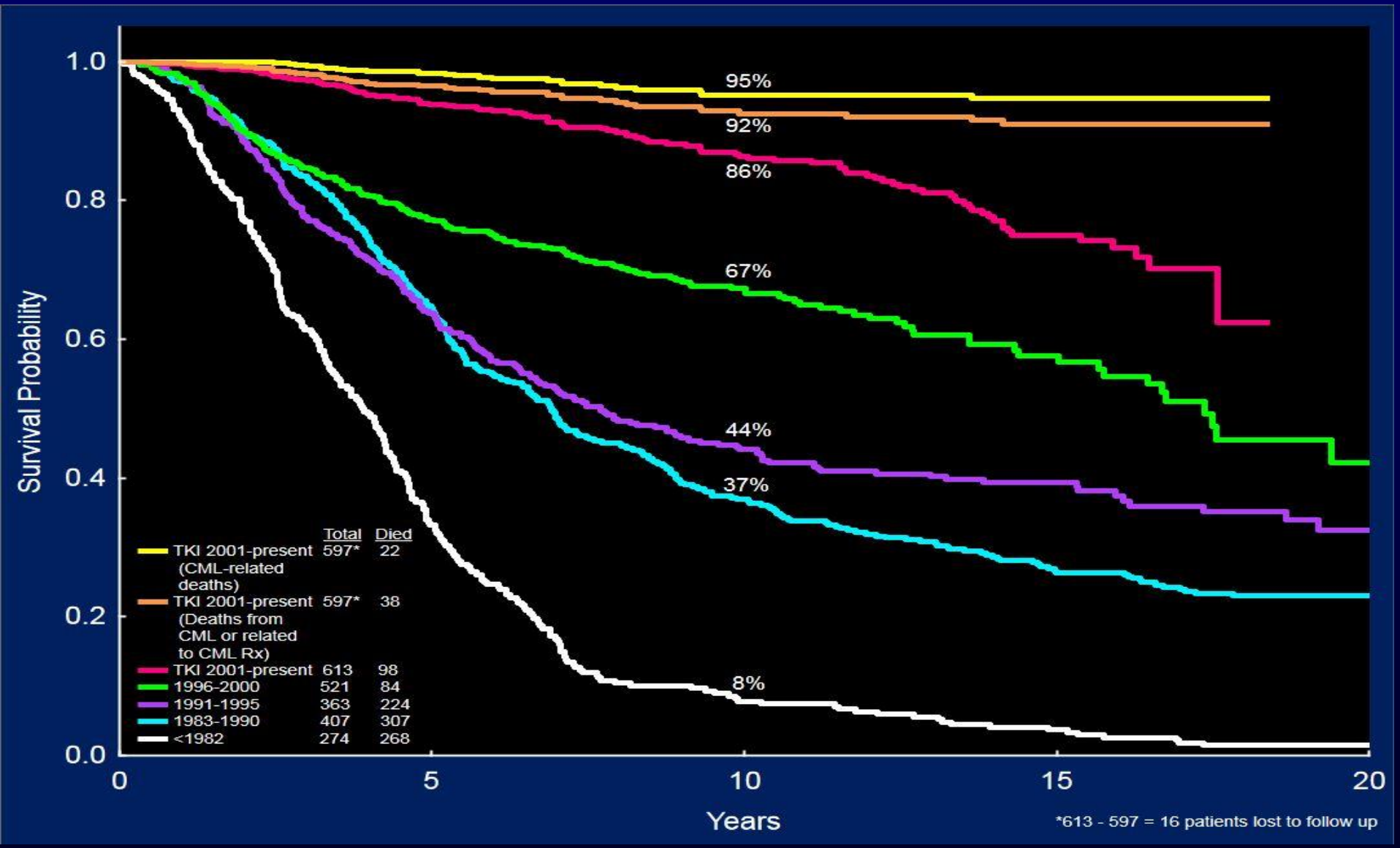
Disclosures

Grants/Research Support, Consultant: *AbbVie Inc., Bristol-Myers Squibb Company, Pfizer Inc., Seattle Genetics, Inc., Takeda Pharmaceutical Company Limited*

CML: The Past and Today

Parameter	Before 2000	Today
Course	Fatal	Indolent
Prognosis	Poor	Excellent
10-yr survival	10%	84%–90%
Frontline Rx	Allo-SCT; IFN-α	Imatinib; dasatinib; nilotinib; bosutinib
Second-line Rx	?	Bosutinib; ponatinib; allo-SCT

CML. Survival at MDACC 1975 - 2019

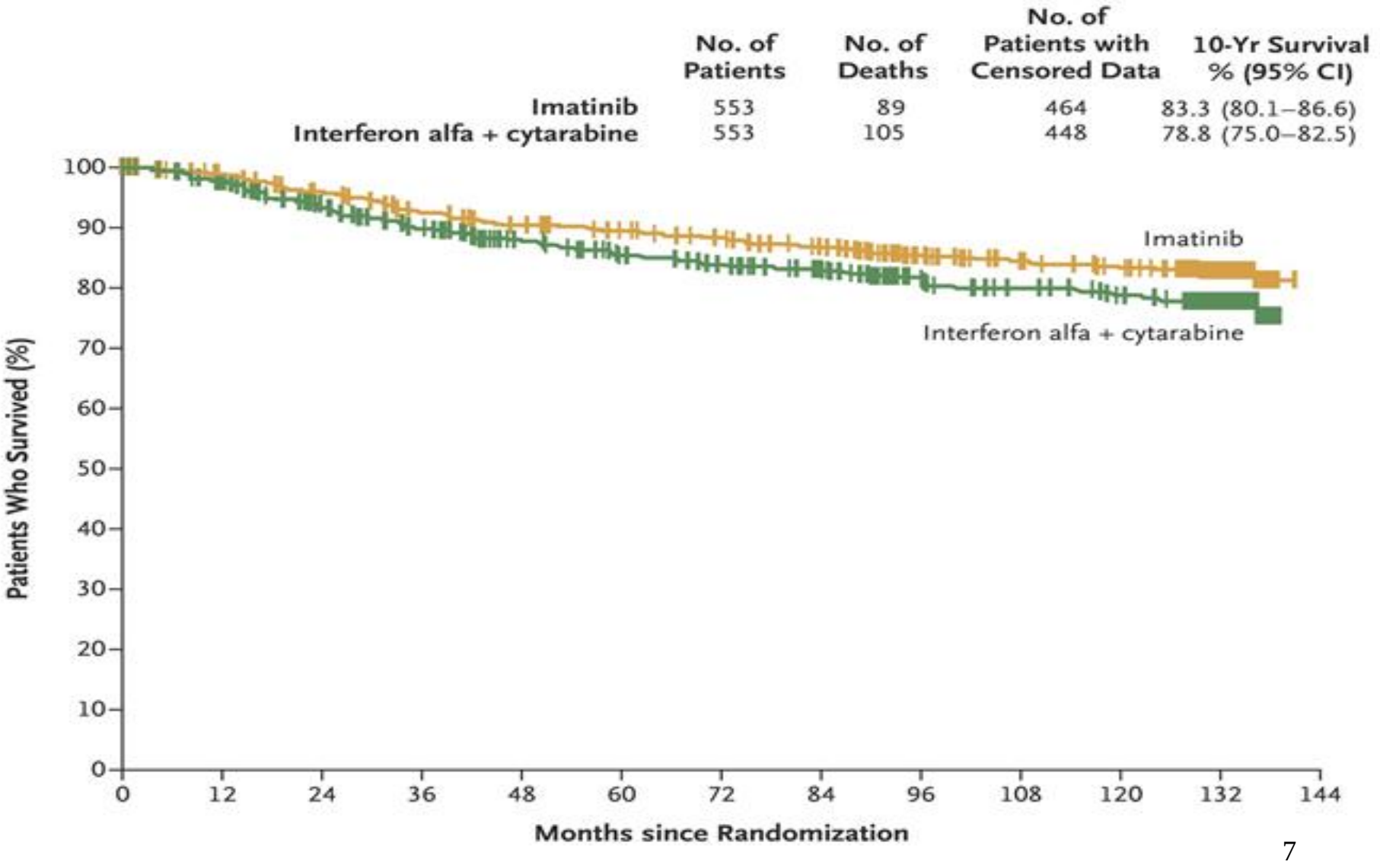


Harrison's Principles of Internal Medicine. 2014. And unpublished update 2019.

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

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

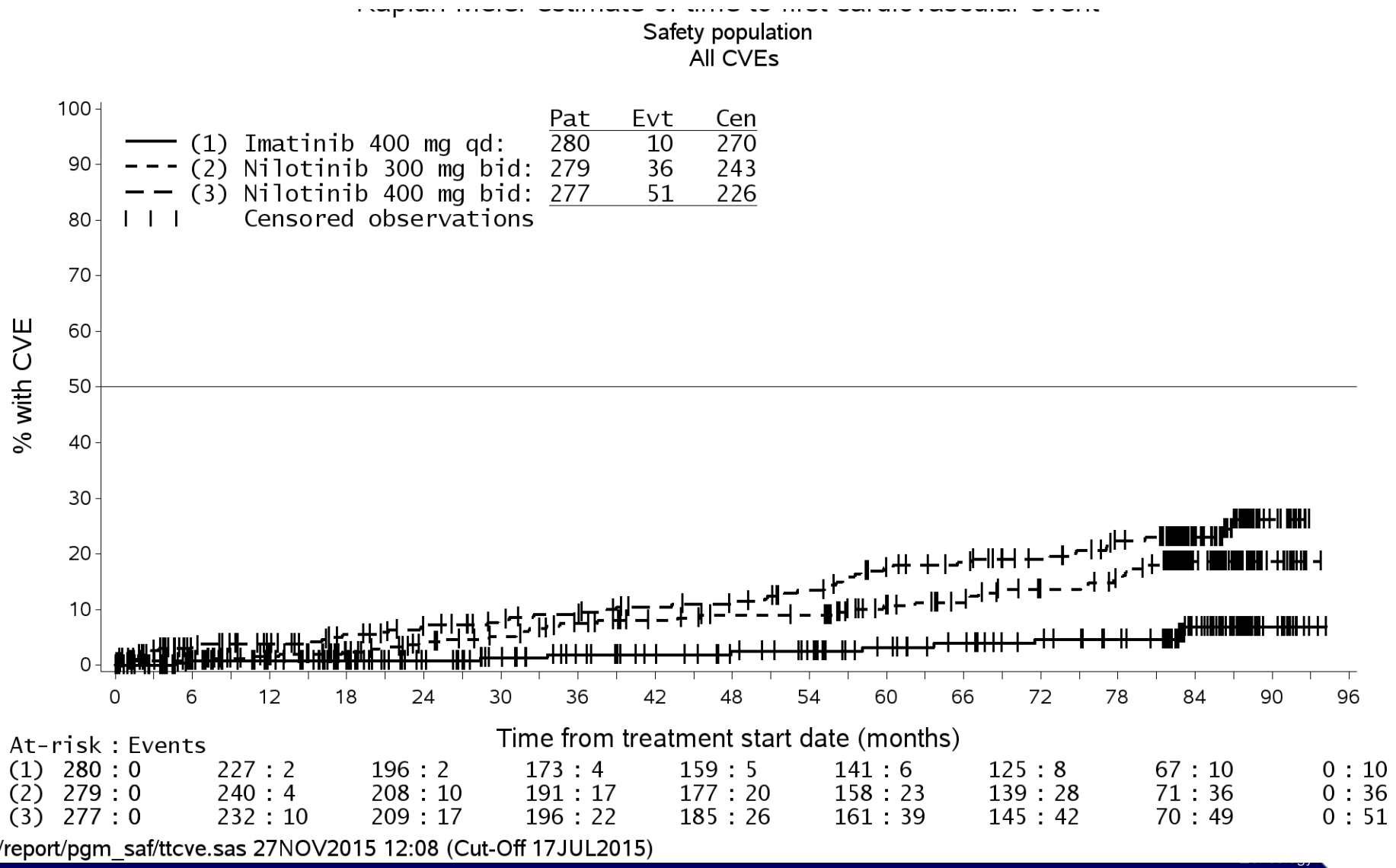
- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281) or imatinib (n=283)
- Minimum follow-up 6 yrs

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

BFORE – The 2-Year Report

	Bosutinib n=268	Imatinib n=268	P value
BCR-ABL1 ≤10% at 3 mo, % (95% CI)	75.2 (69.8–80.6)	57.3 (51.0–63.5)	<0.001
MMR 12 mo, %	47	36	0.0126
MMR 24 mo, %	61	51	0.0146
AP/BP, %	2.2 (1.1/1.1)	2.6 (2.2/0.4)	
EFS events, n (%)*	14 (5)	17 (6)	
Deaths, n (%)†	3 (1)	9 (3)	
OS, % (95% CI)	99 (97–100)	97 (94–99)	

Cortes et al. ASCO 2018

Generic Imatinib Overview

Study	Design	Results
Poland	N=726 with generic 99 frontline, 627 switched from brand	Frontline: 3 mo BCR-ABL <10% 66%, 12 mo MMR 50% Switch: 84% maintained or improved response; response lost: 10% MR4.5, MMR 1%, CCyR 0.3%
MDACC	N=27 switched brand → generic	21 MR4.5: all maintained 6 no MR4.5: all improved (2 MR4.5)
India	N=1367 newly diagnosed: 1193 brand, 174 generic	CCyR: brand 67% v generic 64%; MR4 17% v 24% EFS: 68 m v 58 m (p=0.012); TFS: 75 m v 67 m (p=0.03); OS: 78 m v 72 m (p=0.148)
Canada	N=334 frontline (matched cohorts: 167 brand, 167 generic)	Switched to another TKI: generic 22% (15% toxicity), brand 10% (5% toxicity) Discontinued: 8% v 2%

Sacha et al. ASH 2016; abstract #629; Madhav et al. ASH 2016; abstract #630; Klil-Drori A, et al. *ASH* 2017; abstract #315; Aboudalle I, et al. ASH 2017; abstract #2906

CML Therapy in 2019

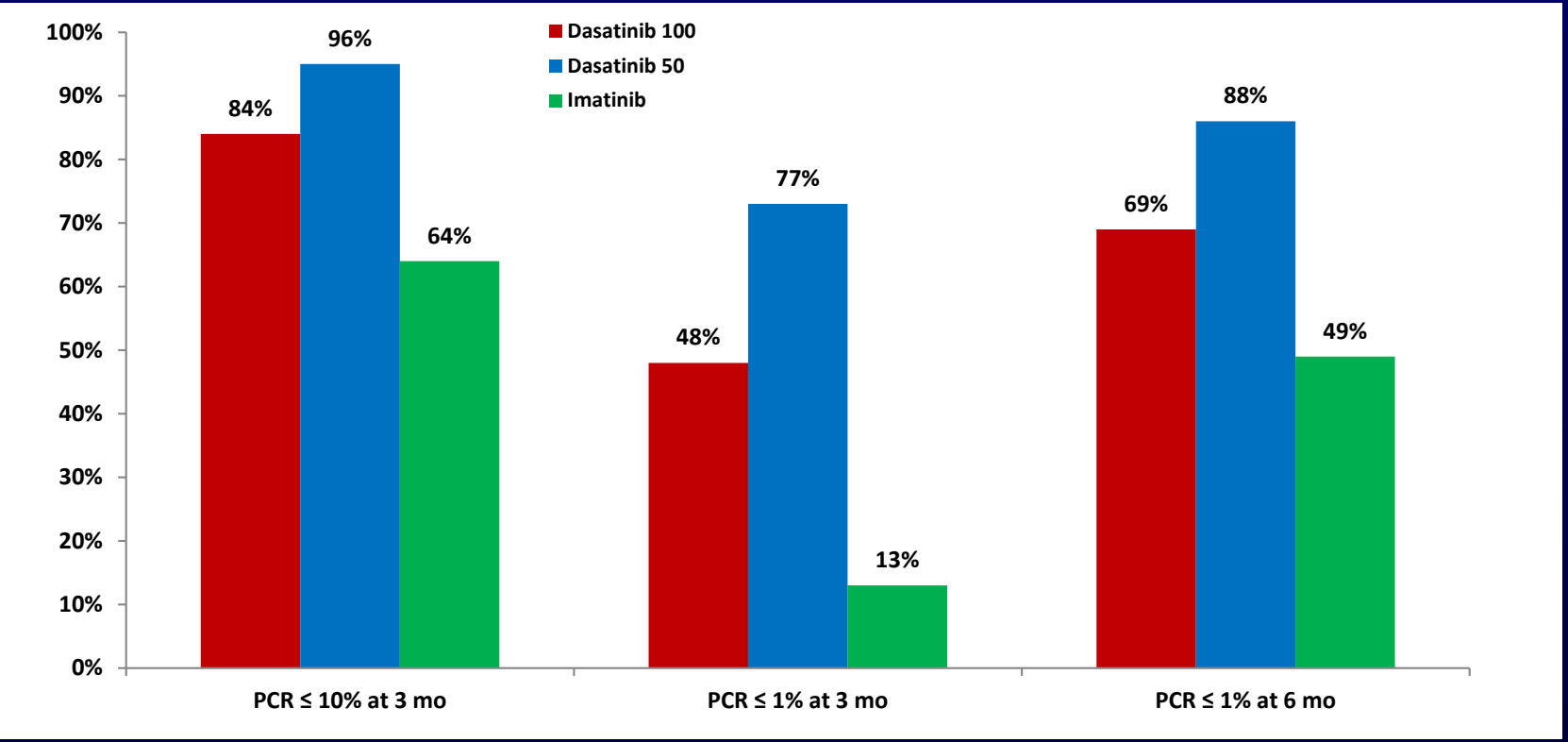
- Imatinib for lower-risk Sokal and older pts (≥ 65-70 yrs); or for all CMLs until second TKIs prices lower?
- Second TKIs for high-risk Sokal
- Second TKIs for younger pts (< 50 yrs) in whom Rx DC important (?); but higher cost and toxicities

Low-dose Dasatinib in CML-CP. Response

No. Response/ Total (%)	3 month	6 month	12 month	18 month	24 month	30 month
BCR-ABL1 transcripts (IS) ≤10%	78/81 (96)	79/81 (98)	---	---	---	---
PCR ≤1%	62/81 (77)	73/81 (88)	---	---	---	---
CCyR	40/81 (49)	70/81 (86)	76/81 (94)	61/65 (94)	44/47 (94)	18/18 (100)
MMR	27/81 (33)	53/81 (65)	65/81 (80)	57/65 (88)	41/47 (87)	18/18 (100)
MR4.0	5/81 (6)	28/81 (35)	48/81 (59)	48/65 (74)	31/47 (66)	15/18 (83)
MR4.5	3/81 (4)	21/81 (26)	40/81 (49)	44/65 (68)	27/47 (57)	14/18 (78)

Naqvi. Cancer (In Press); 2018.

Low-dose Dasatinib in CML-CP. Response



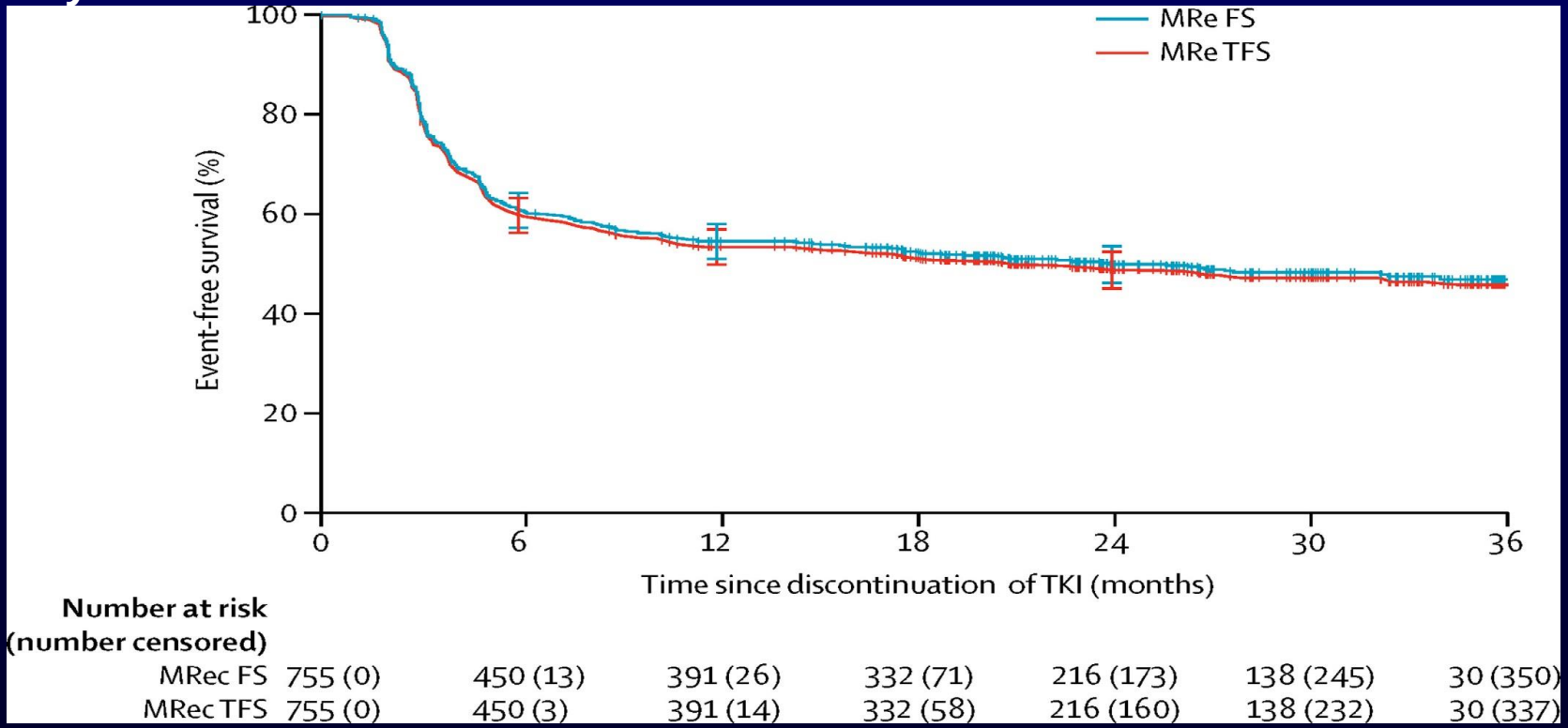
Naqvi. Cancer (In Press); 2018.

Frontline CML Therapy in 2019+

- Dasatinib 50mg daily produces similar efficacy and significantly less toxicity than 100mg daily
- Current frontline: dasatinib 50mg daily+venetoclax 200mg daily. Aim to achieve high rates of durable CMRs and Rx discontinuation=molecular cures

TKIs Rx DC and Rx-Free Remissions in CML

- 758 pts Rx with TKIs for >3 yrs and in Deep MR for >1 yr Relapse=loss of MMR; *BCR-ABL* transcripts [IS] >0.1%
- 2-yr molecular RFS 61%

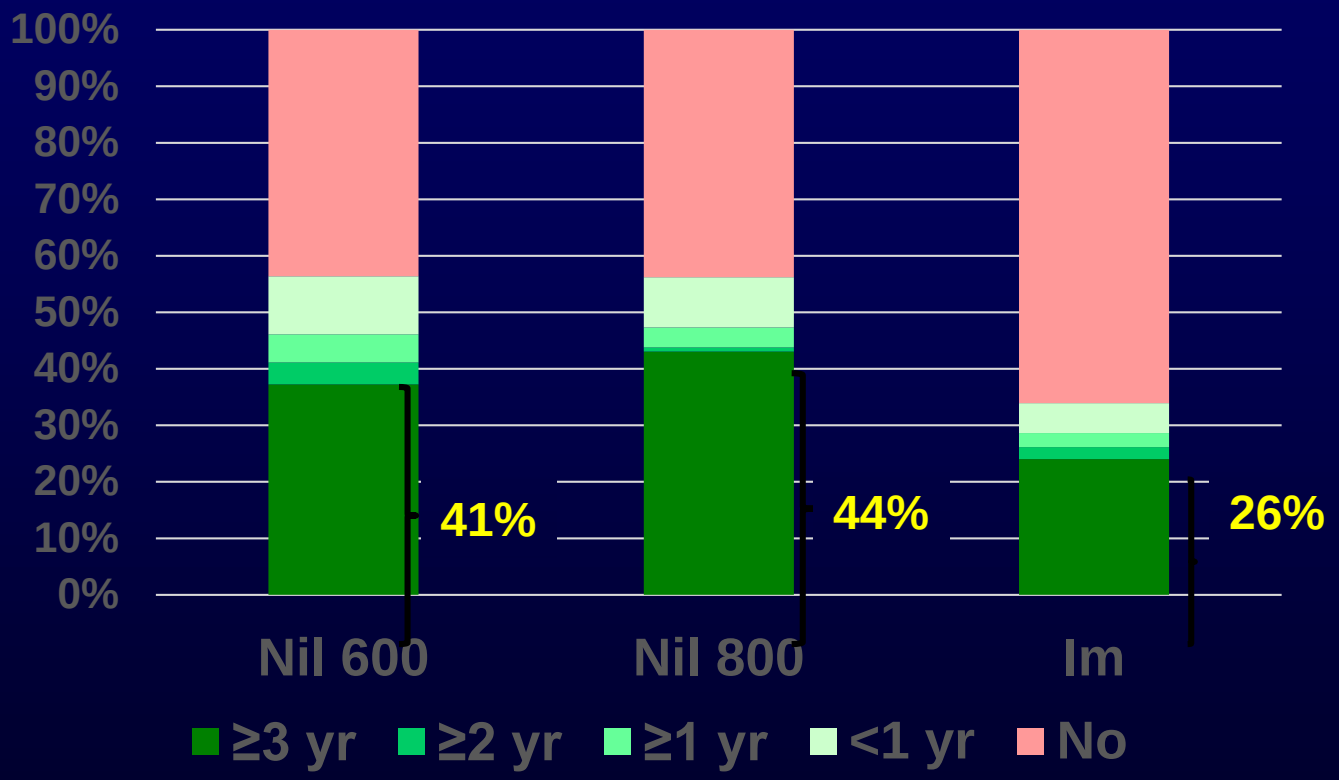


Number at risk (number censored)							
MRec FS	755 (0)	450 (13)	391 (26)	332 (71)	216 (173)	138 (245)	30 (350)
MRec TFS	755 (0)	450 (3)	391 (14)	332 (58)	216 (160)	138 (232)	30 (337)

Saussele. Lancet Oncology 19: 747-757, 2018

ENESTnd - Probability of Sustained MR4.5

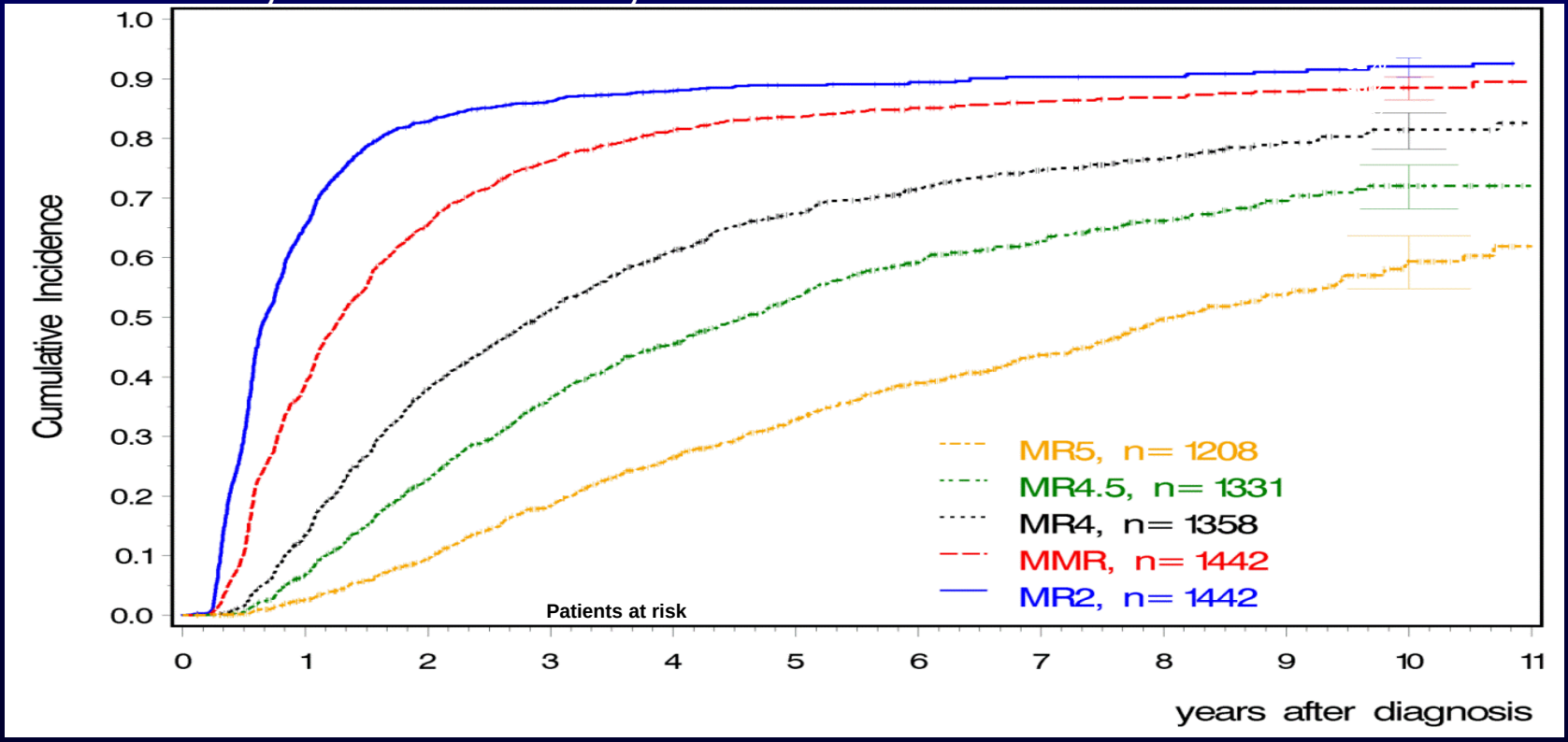
- Cumulative incidence MR4.5: Nil 600 56%, Nil 800 55%, Imatinib 33%



Hochhaus A, et al. *Blood*. 2015;126 [abstract 2781].

Final Results CML-IV. Molecular Response with Imatinib

- 1538 pts newly diagnosed CML-CP randomized to imatinib 400, imatinib 800, imatinib + IFN, imatinib + ara-C, or imatinib after IFN



Kalmanti L, et al. *Leukemia.* 2015;29(5):1123-1132. Hehlmann R, et al. *Blood.* 2017;130(suppl): Abstract 897.

Cost of TKIs in CML--2019

TKI	Annual WAC ($/yr)
9 generic imatinibs	4,400 – 82,000
Gleevec(400mg/D)	121,000
Nilotinib (300 BID)	153,000
Dasatinib (100mg/D)	232,000
Bosutinib (400mg/D)	170,000

Shih. Lancet Hematology. Online June 2019

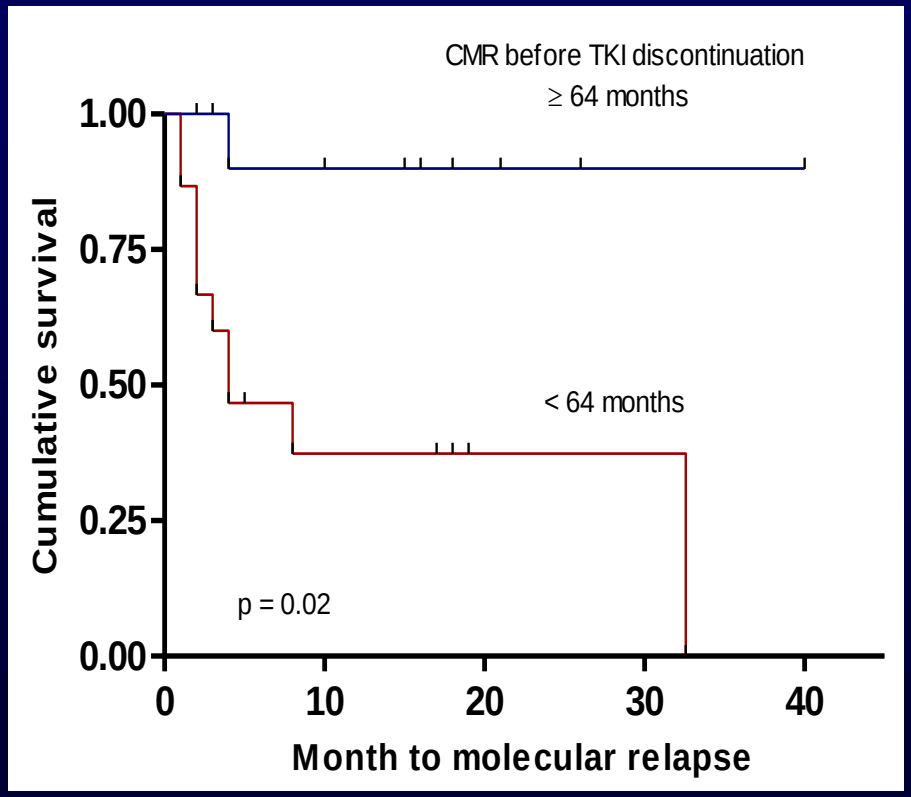
Cost-Benefit of TKIs. "Treatment Value" with Survival as Rx Endpoint

- Using frontline second TKIs vs imatinib generic (at 1/3 of patent price) results in cost of $800,000/QALY
- Simply stated, cost per additional year lived in $800,000, 16x more than accepted threshold of $50,000/QALY
- Therefore, we need strong justification to use second TKIs as frontline CML Rx (vs generic imatinib)

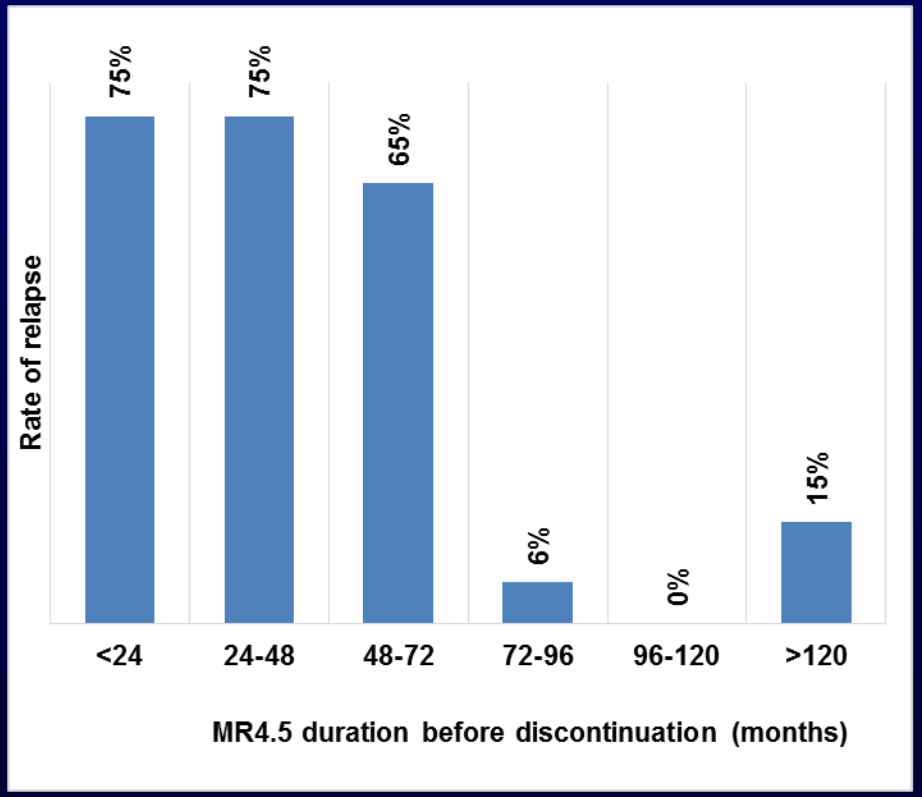
Padula. JNCI 108; 2016. Kantarjian. Lancet Oncology 13: May 2016. Chhatwal. Cancer 121:3372;2015

Outcome of CML Patients After TKI Discontinuation - MDACC

Initial Report



Updated Report



Benjamini et al. Leuk & Lymphoma 2014; 55(12):2879-86; Chamoun et al. ASH 2016; abstract #1923

TKIs Rx DC in Clinical Practice--Requirements

Parameter	Yes	No
Sokal risk	low-intermediate	high
BCR-ABL transcripts	quantifiable-B2A2, B3A2 (e13a2 or e14a2)	not quantifiable
CML past Hx	chronic	AP-BP
Response to first TKI	optimal	failure
Duration of all TKIs Rx	> 8 yrs	< 3 yrs
Depth of molecular response	CMR (MR 4.5)	less than MR 4.0
Duration of molecular response	> 2-3 yrs	< 2 yrs
Monitoring availability/center-pt	ideal (q2 mo in yrs 1-2)	poor; non-compliant

CML Monitoring

- Establish confirmed CGCR in first year (BM at 6-12 mo)
- In CGCR

  - FISH and QPCR every 6 mos

  - If MMR (QPCR < 0.1%), may monitor with QPCR only (watch for false results)

  - If QPCR ↑ by 0.5 – 1 log and/or loss of MMR (PCR> 0.1%) → monitor more frequently
- Mutations studies if resistance / need to change TKIs
- Change TKI only for loss of CGCR, not based on MMR/QPCR

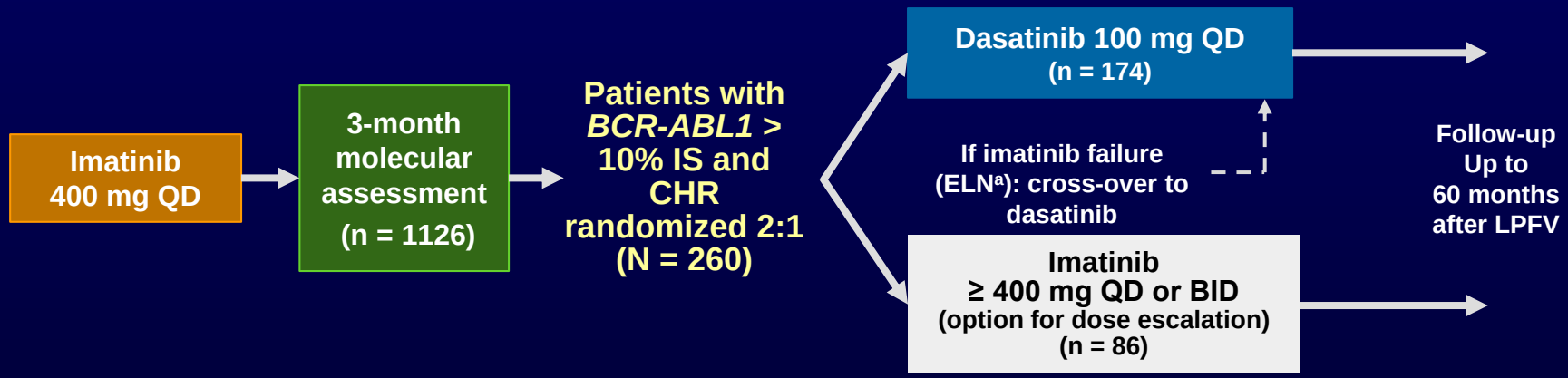
BCR-ABL Transcripts < 10% at 6 mos Associated with Better Outcome

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

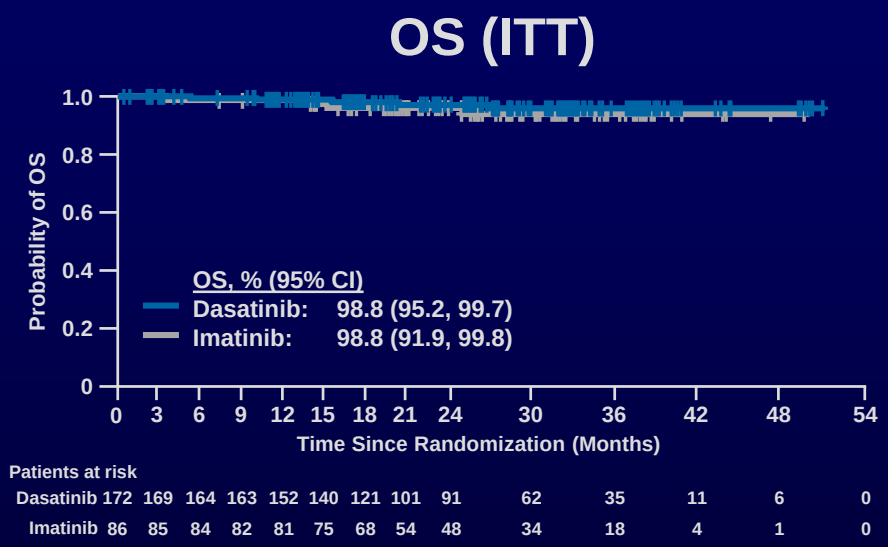


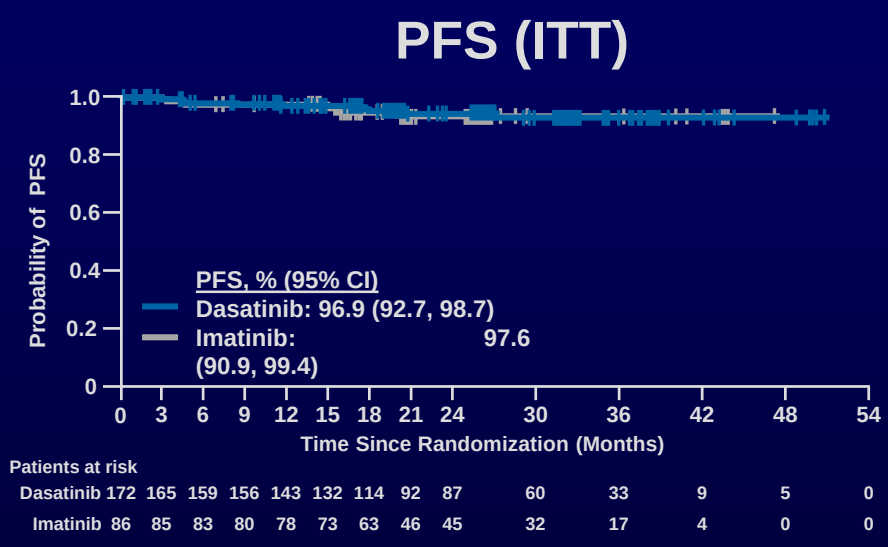
- Stratified by Sokal and time from molecular assessment to randomization
  - Randomization may occur up to 8 weeks after the 3-month molecular assessment

[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 Secondary Endpoint: Survival Outcomes



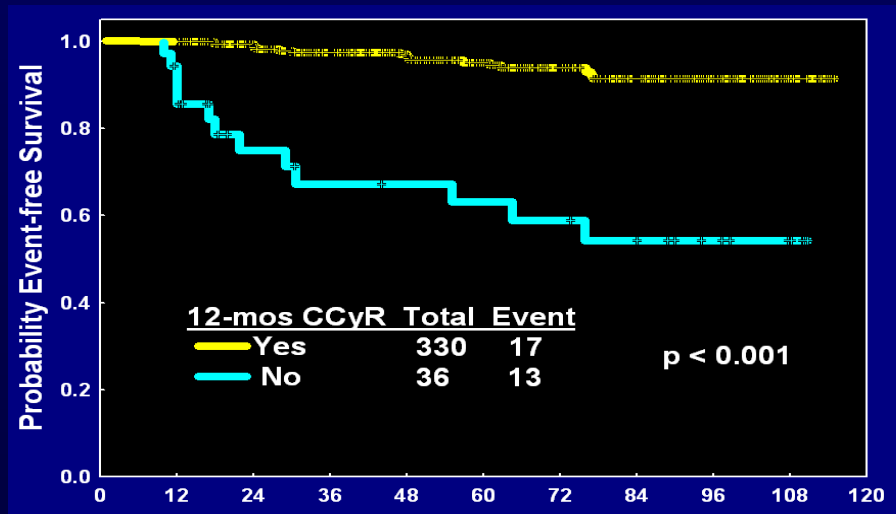


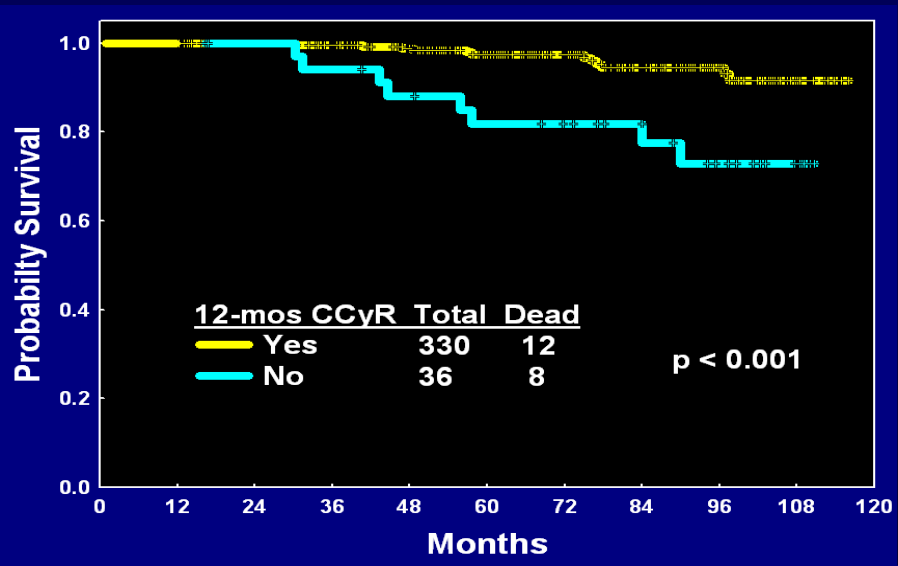
- **Median duration of follow-up:**
  - **30 months (range 12-56) in patients randomized to dasatinib**
  - **30 months (range 12-65) in patients randomized to imatinib**

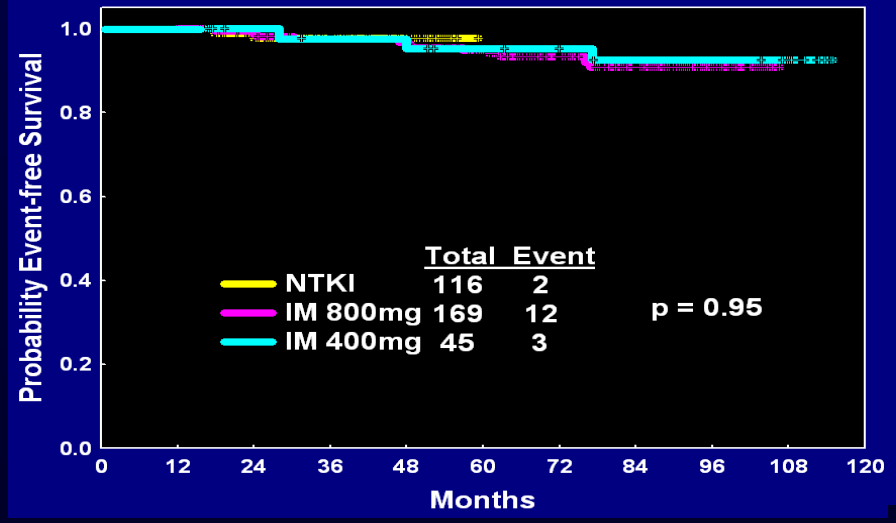
CI = confidence interval; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.

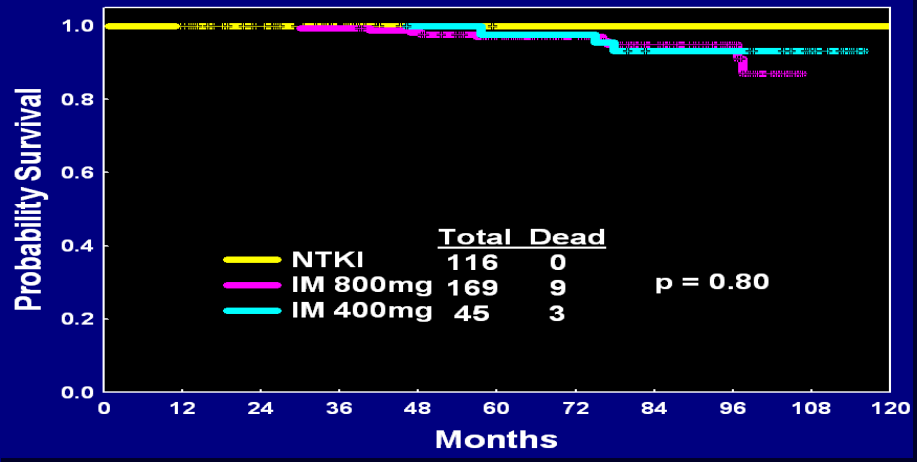
Cortes et al. ASH 2018; abstract #788

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



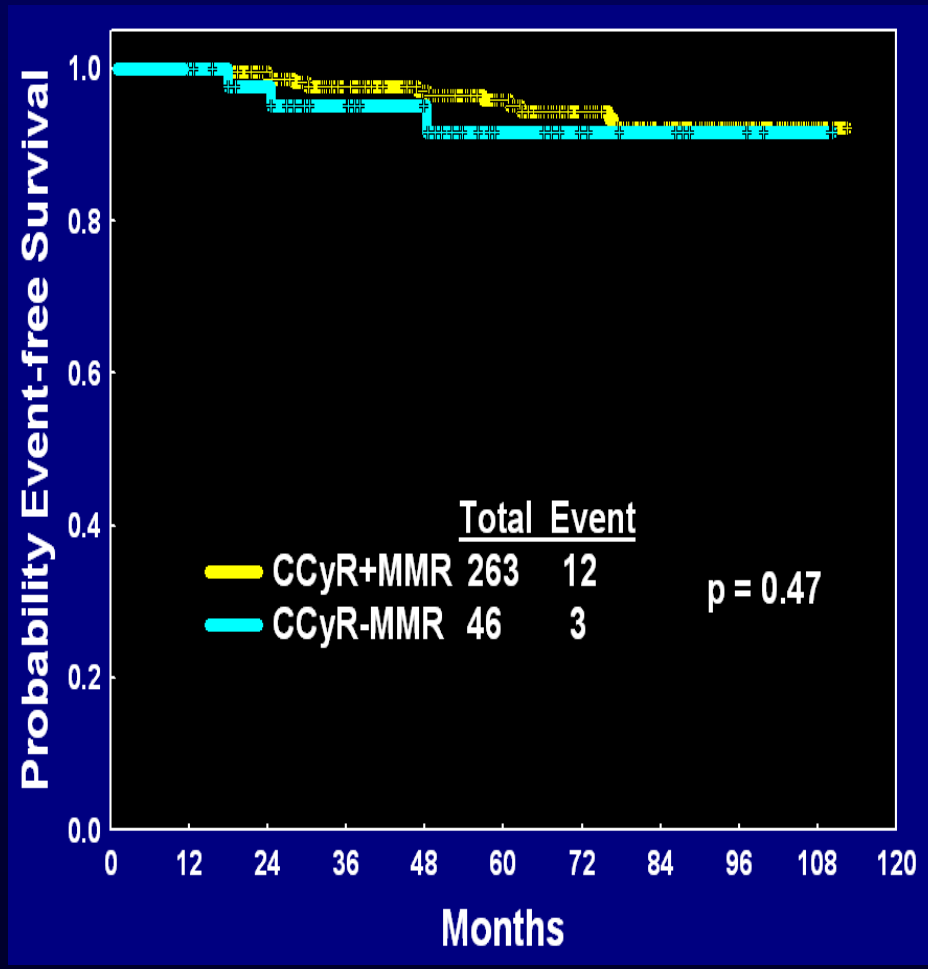


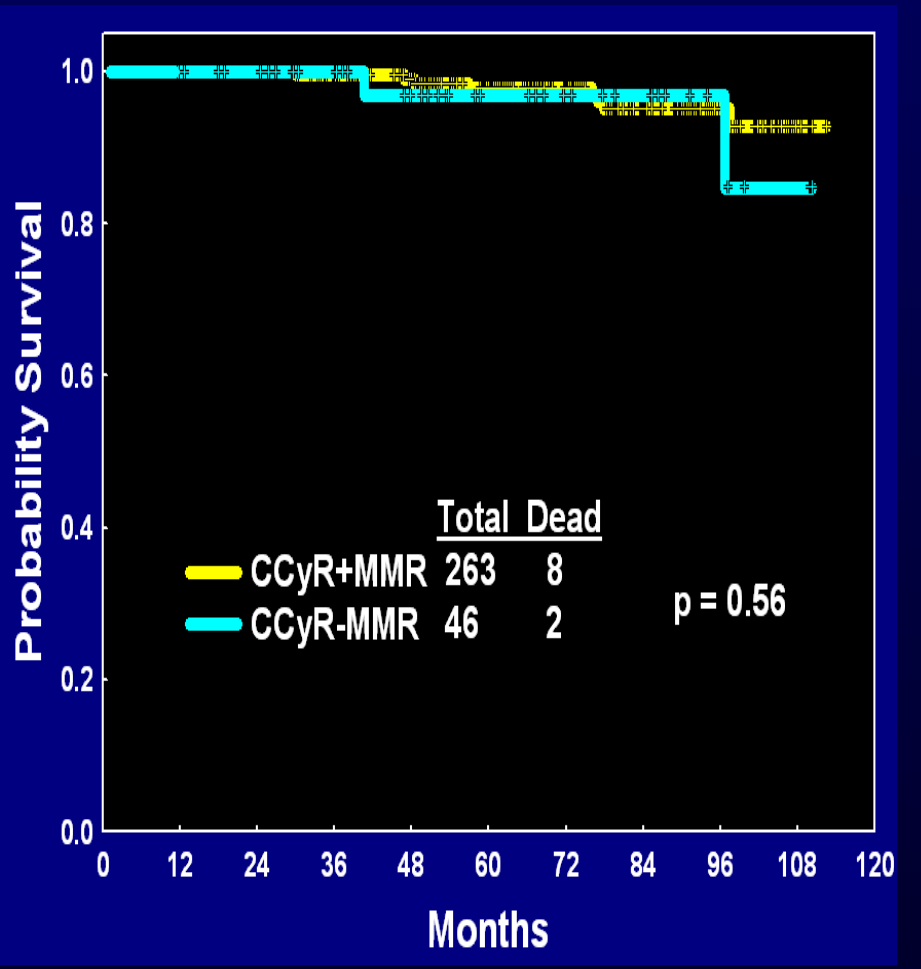




Jabbour. Blood. 2011;118:4541-6.

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

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

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

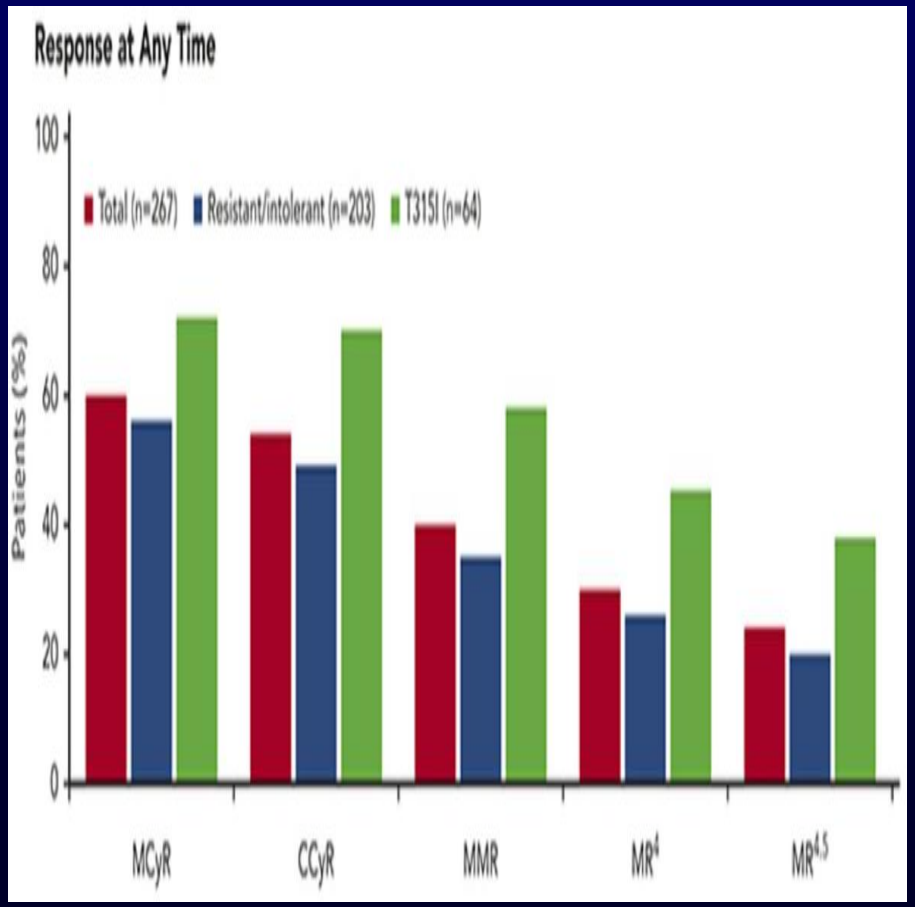
Chamoun et al. ASH 2017; abstract #1594

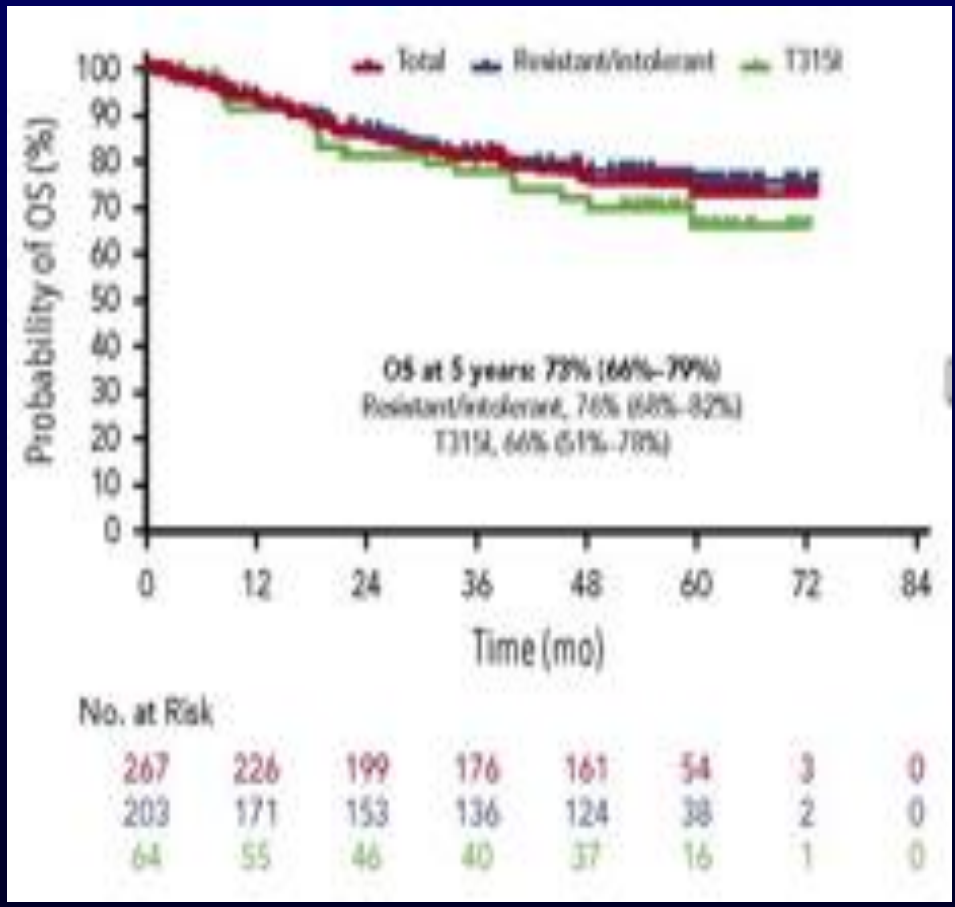
CML. Role and Timing of allo SCT

Status	TKIs	Allo SCT
AP-BP	Interim Rx to MRD	ASAP
IM failure in CP, T315I	Ponatinib	If no/loss response to ponatinib
IM failure in CP – no CE, no mutations, good initial response	Long-term second line TKIs	Third line post second TKI failure
IM failure in CP – CE, bad mutations, no CG response	Interim Rx to MRD	Second line
Older ≥65 – 70 post IM failure	Long-term	May forgo allo SCT for many yrs of QOL

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

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

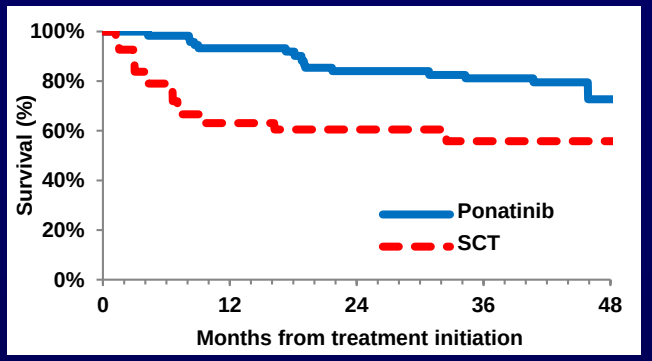
Khan M, et al. *Blood.* 2017;130(suppl): Abstract 2882.

Ponatinib or SCT for T315I CML

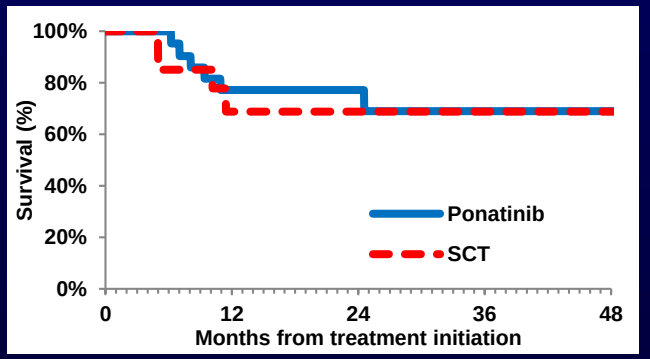
- Pts ≥18 yrs with CML T315I in any stage enrolled in PACE (n=449) or EBMT (1999-2010; n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36

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

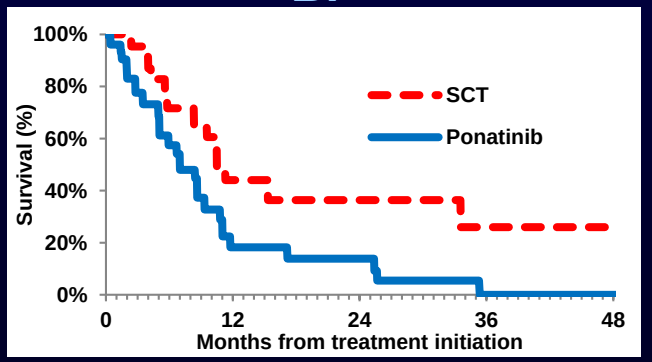
CP



AP



BP



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

Use of Ponatinib in CML and Ph+ ALL

- Ponatinib 30mg daily (not 45mg daily as FDA approved), and reduce to 15mg daily for side effects or in CMR
- Watch for: veno-occlusive disease (heart, CNS, mesenteric, peripheral), pancreatitis, severe hypertension, skin rashes
- Use in CML: 1) T315I; 2) post second TKI failure (do not wait for failure of multiple TKIs) and if no guiding mutations
- Use in Ph+ ALL: preferred TKI

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.

CML Summary – 2019

- Frontline therapy good (and getting better, safer and cheaper?)
- 2nd line options grossly equivalent; 3rd line ponatinib better (new ones safer?)
- CCyR (PCR of 1%) 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
- Dose reductions effective and safe in most instances (e.g dasatinib 50 mg)
- TFR feasible for a few if done right (better to wait for long MR4.5); integrating biology and depth/duration of response
- Patients comorbidities be optimized

Leukemia Questions?

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