CML – Success of Precision Medicine

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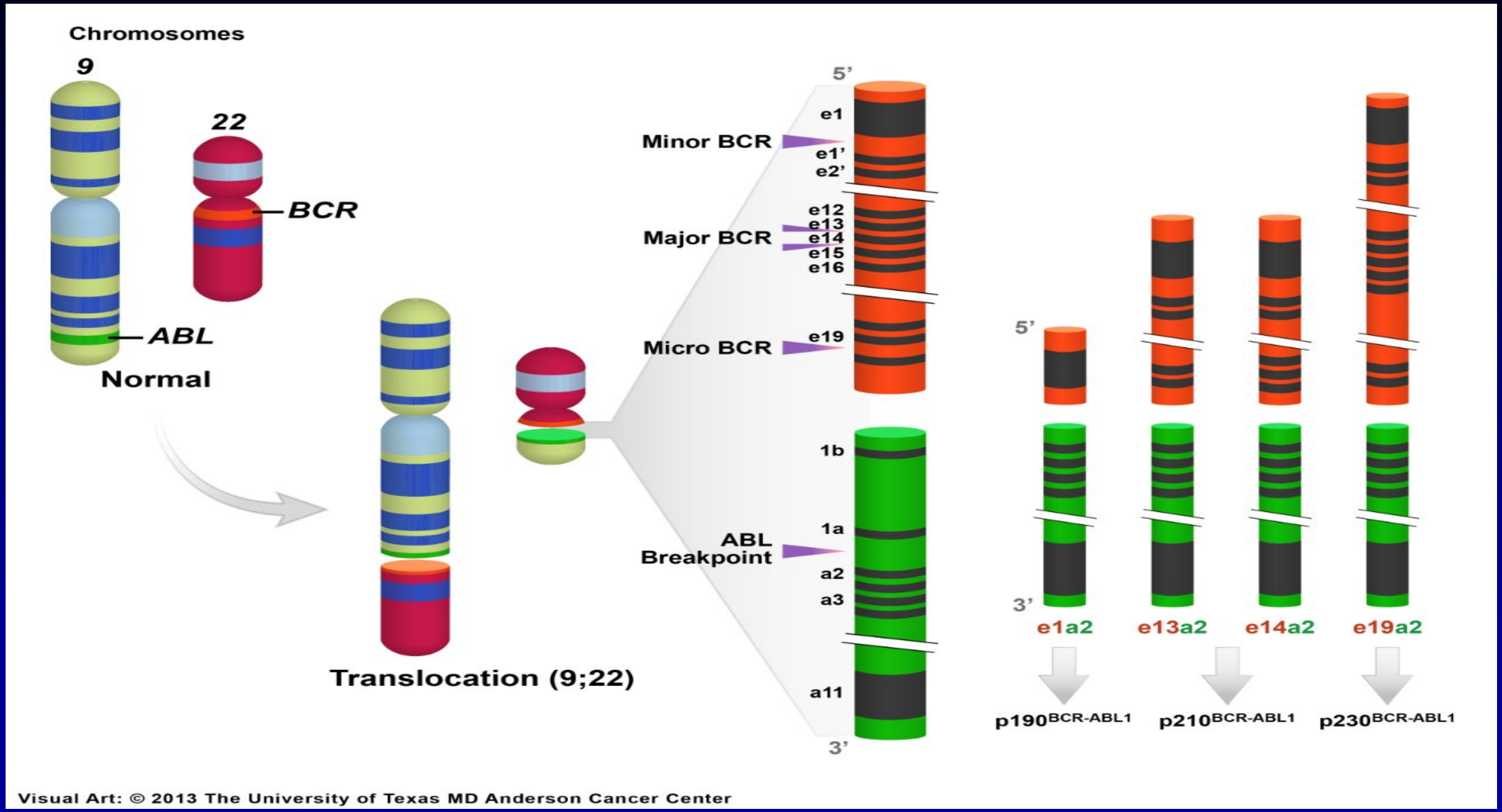
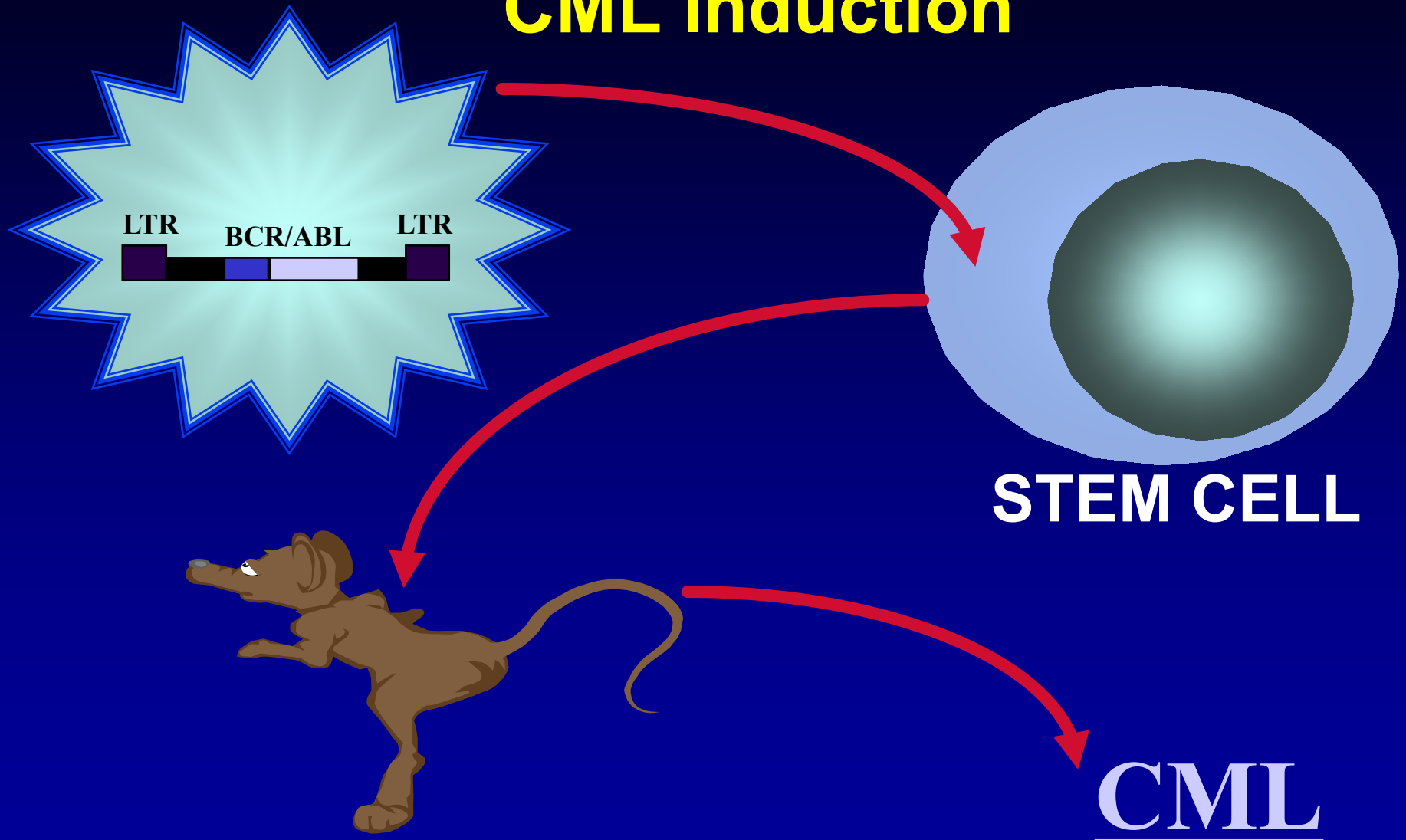
July 2022

CML Ph-Associated CG and Molecular Events



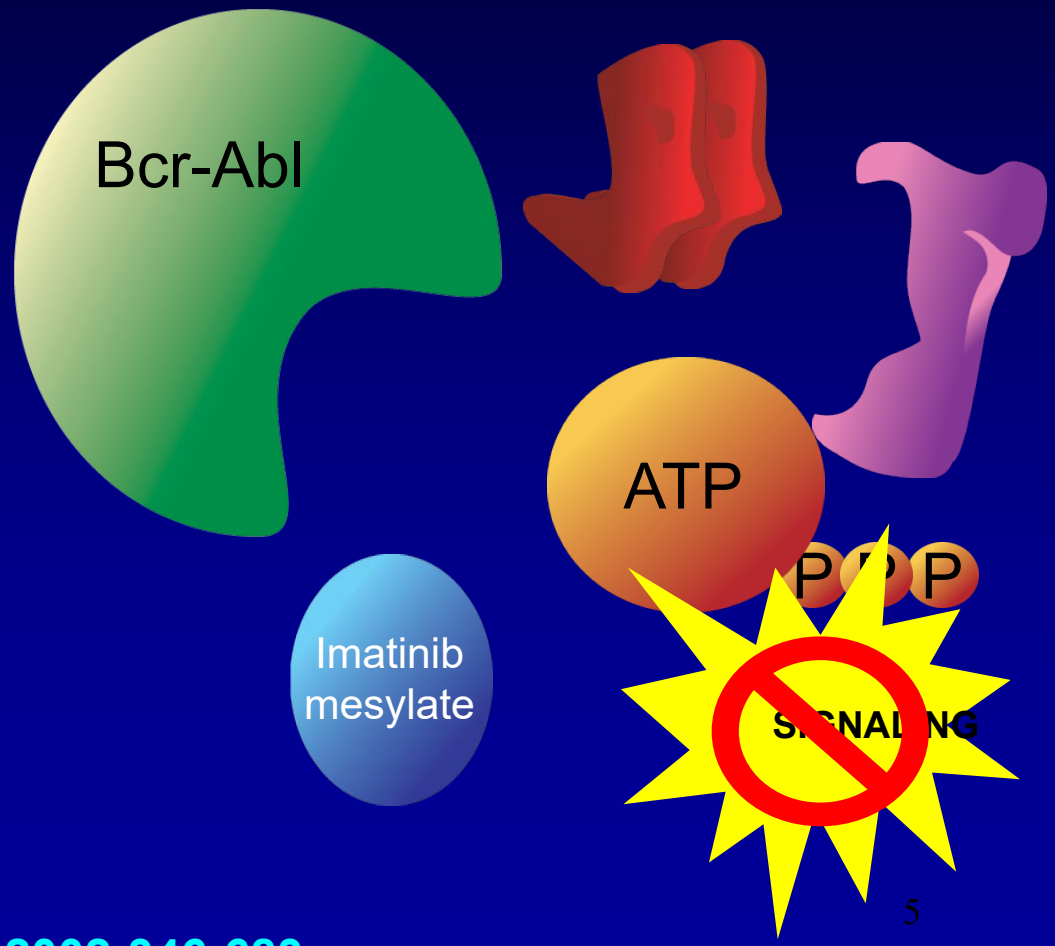
BCR-ABL Expression Sufficient for CML Induction



(Daley et al., Science 1990)

Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage and Antman. N Engl J Med. 2002;346:683.

Developmental Therapeutics in CML

FDA Approval		
Agent	**Salvage**	**Frontline**
Interferon	1986	1986
Imatinib	2001	2002
Dasatinib	2006	2010
Nilotinib	2007	2010
Ponatinib	2012	
Bosutinib	2012	2017
Asciminib	2022	
Omacetaxine	2012	

Kantarjian. NEJM 346:645;2002. Kantarjian. NEJM 354:2542;2006. Talpaz. NEJM 354; 2531: 2006. Kantarjian. NEJM 362:2260:2010. Kantarjian. Lancet Oncol 12: 841; 2011. Cortes. NEJM 367: 2075; 2012. Cortes. Blood 120: 2573; 2012. Cortes. AJH e-Pub 2/2013.

CML – in 2022

Approved TKIs

- Imatinib
- Nilotinib
- Dasatinib
- Ponatinib (T315I)
- Bosutinib
- Asciminib
- Radotinib (Korea)
- [Omacetaxine]

New TKIs

- HQP1351(T315I; China)
- K 0706
- PF-114 (Russia)

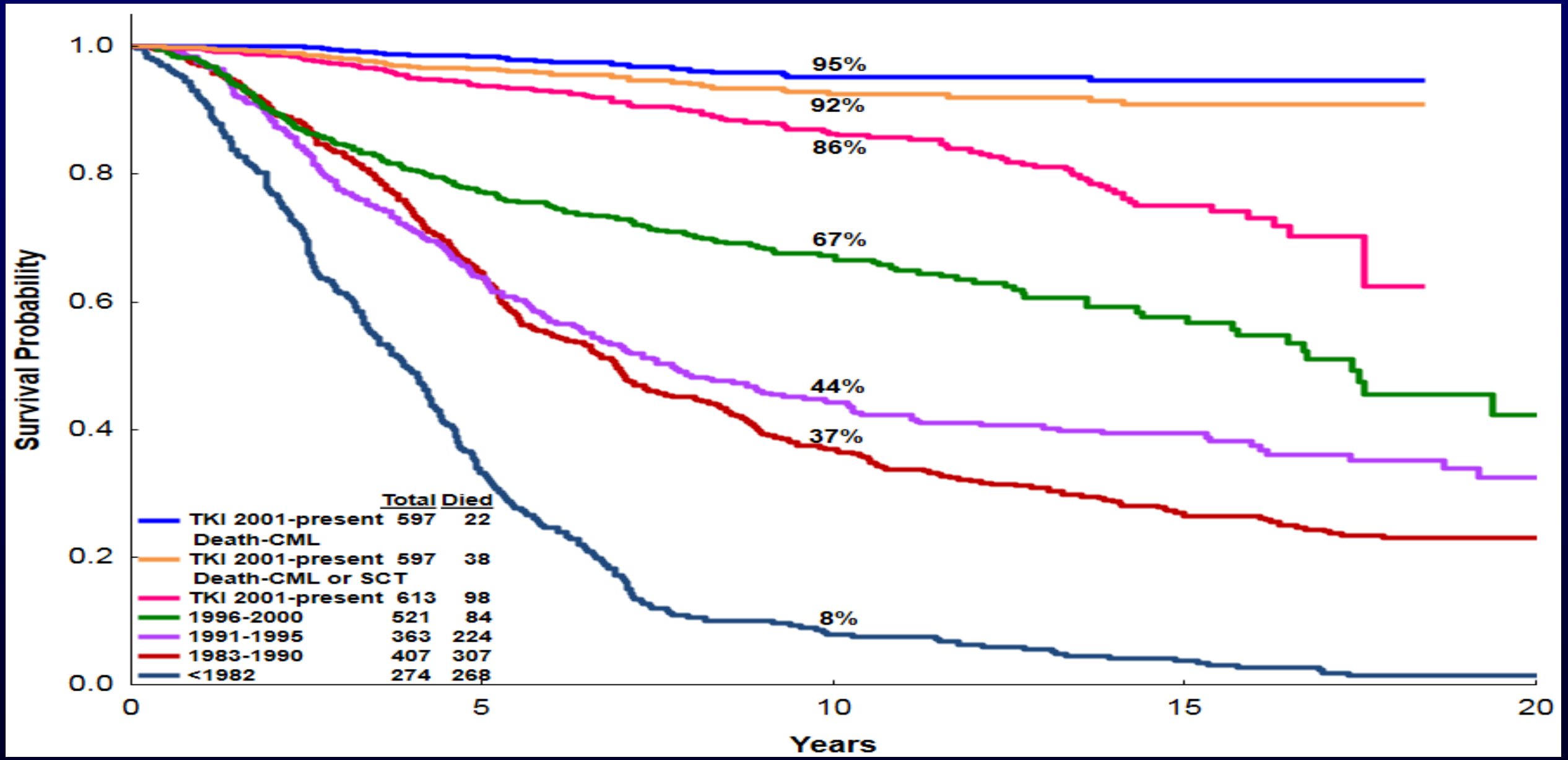
CML. The Past and Today

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, asciminib ; allo SCT

Rx Endpoints in CML

- Survival
- Rx DC and “Rx-free remission”
- Long-term safety
- Cost; cost-effectiveness = “Rx value”

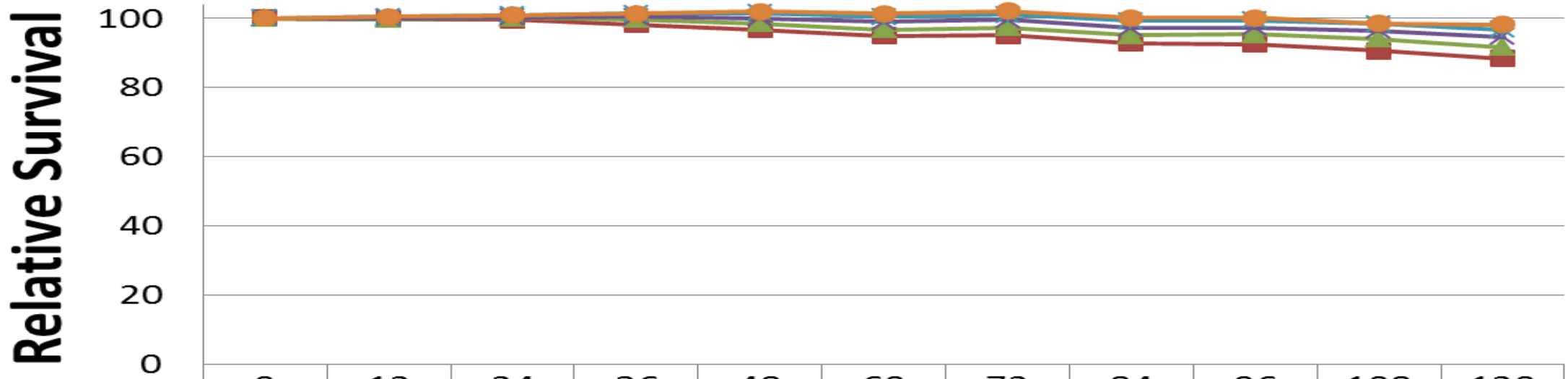
CML. Survival at MDACC 1975 - 2019



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

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

Month

Sasaki . Lancet Hematology 2: e186-193; 2015

CML Frontline Therapy

- Up to 16, and 8 main studies compared new generation TKIs to imatinib frontline: ENEST-nd (nilotinib), DASISION (dasatinib), BELA (bosutinib), EPIC (ponatinib), others
- All showed higher rates of favorable early surrogate endpoints: CG CR, MMR, MR4.5, ↓ AP/BP
- None showed survival benefit (maybe because highly active second TKIs salvage Rx)
- Increased uncommon toxicities with newer TKIs: PAOD-MI-TIA, pancreatitis, pleural effusions; HT and pulmonary HT, ↑BS, vasospastic reactions, ↑non-CML deaths

Important Frontline CML Randomized Trials

response at, %	DASISION		ENESTnd		BFORE		TOPS	
	DAS 100	IMA 400	NIL 300	IMA 400	BOS 400	IMA 400	IMA 800	IMA 400
MMR 3m	8	0.4	9	1	4.1	1.7	12	3
MMR 12m	46	28	44	22	47	37	47	40
CCyR 12m	77	66	80	65	77	66	70	66
AP/BP	2.3	5.0	1	6	2.2	2.6	1.9	3.2
PFS	94	92	96	94	NR	NR	97	94
OS	95	95	97	96	99	97	99	98

Generic vs Patent Imatinib-Chinese Experience

- 442 pts Tx with generic (n=236) or patent imatinib (n=206)

% 4-yr Outcome	Generic	Patent
CG CR	97	97
MMR	88	90
MR4	55	68
MR4.5	33	39
PFS	94	96
OS	96	98

Dou. Blood 734: abst 2940; 2019

Dasatinib vs Nilotinib Aiming to Achieve DMR (MR4.5)

- 454 pts with CML CP randomized to dasatinib 100mg/D or nilotinib 300mg BID (n=227 in each)
- No difference in PFS, EFS, OS

% 3yr	Dasatinib	Nilotinib
PFS	99.0	98.8
EFS	65.4	67.2
OS	99	98.8
CGCR	78.9	78.4
MR4.5	44.5	40.5

Matsumura. Blood 136: abst 45; 2020

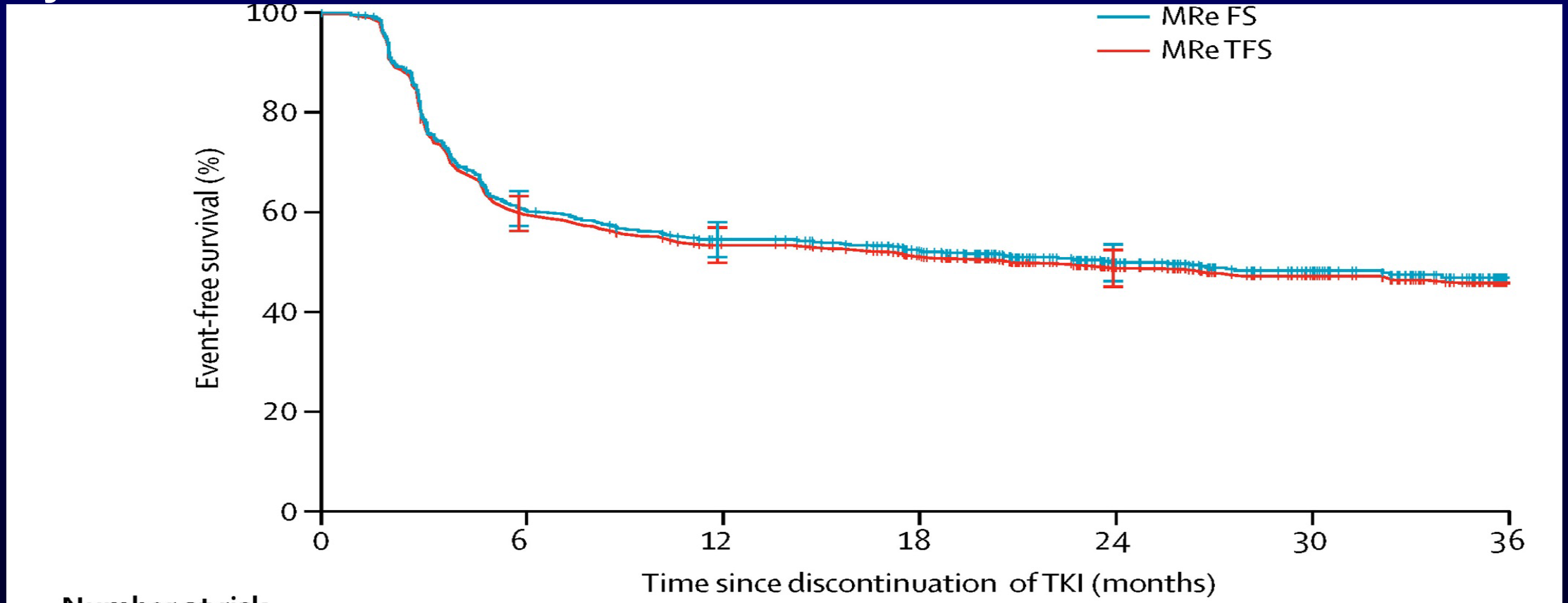
Deep Molecular Response and Rx-Free Remission

- DMR = PCR<0.01-<0.0032 = MR4-4.5
- Durable DMR >2 yr + stop = 50% TFR
- Durable DMR > 5 yr + stop = 80+% TFR

Chamoun. Jounal of Hematology & Oncology 12: 1; 2019

TKIs Rx DC and Rx-Free Remissions in CML

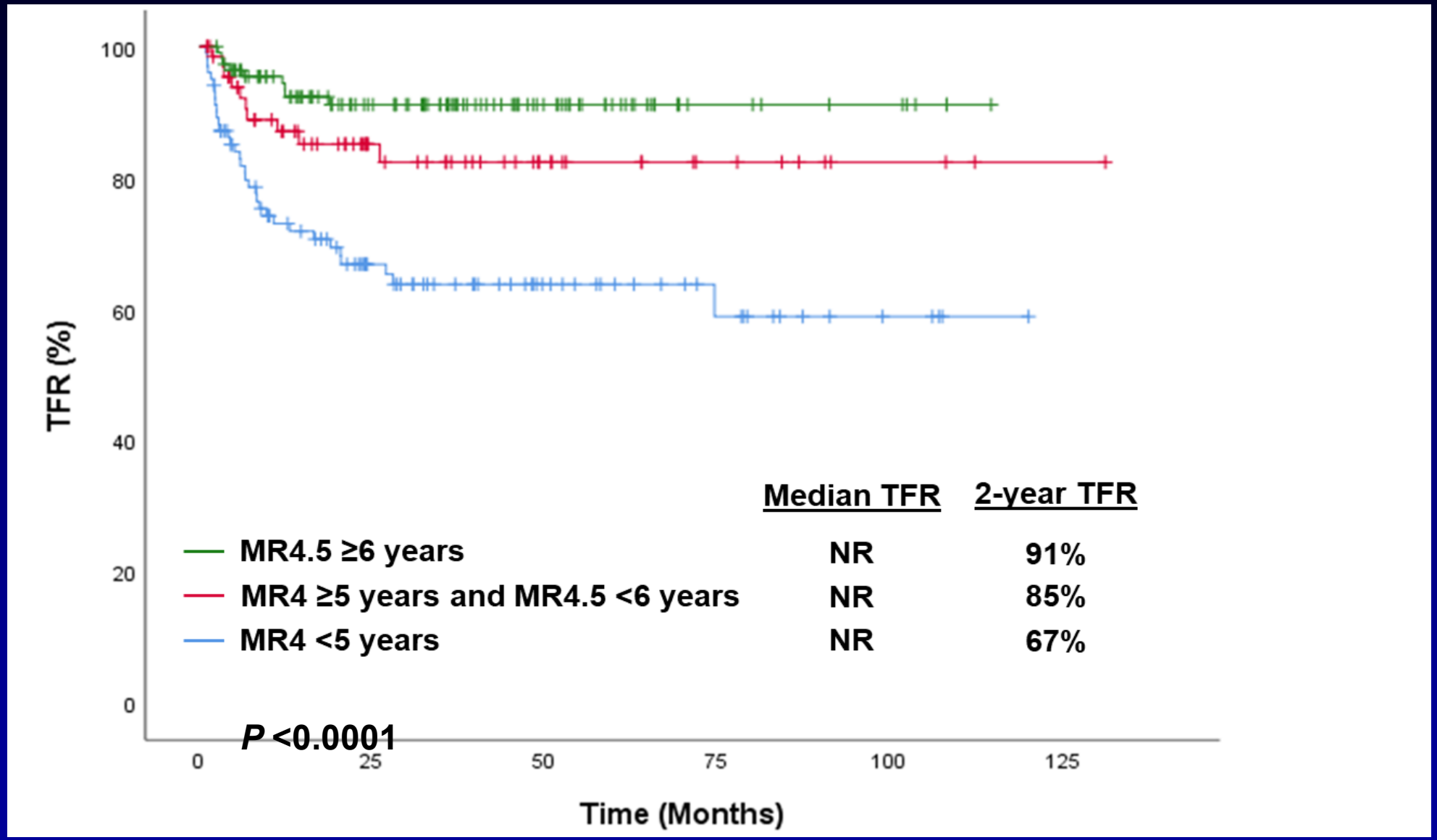
- 758 pts Rx with TKIs for >3 yrs and in Deep MR for >1 yr Relapse=loss of MMR; *BCR-ABL* transcripts [IS] >0.1%
- 2-yr molecular RFS 61%



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

Treatment-free Remission in CML Patients: Rates by MR4 and MR4.5 durations



Haddad. AJH: March 31; 2022

CML. Tangible Measures of Success

- Patients with CML live their near-normal life expectancy, with high quality of life and minimal Rx side effect
- CML potentially curable – on TKIs : DMR (MR4+) 80%; durable DMR (2-5+years) 70-80% = 55-65% of total . Rx DC success 50-80% = TFR/“molecular cure” 30- 50% of total
- But… there are interesting observations, and expected or unintended consequences

Strategies to Improve on TFR/Molecular Cure – Combos of TKIs Plus…

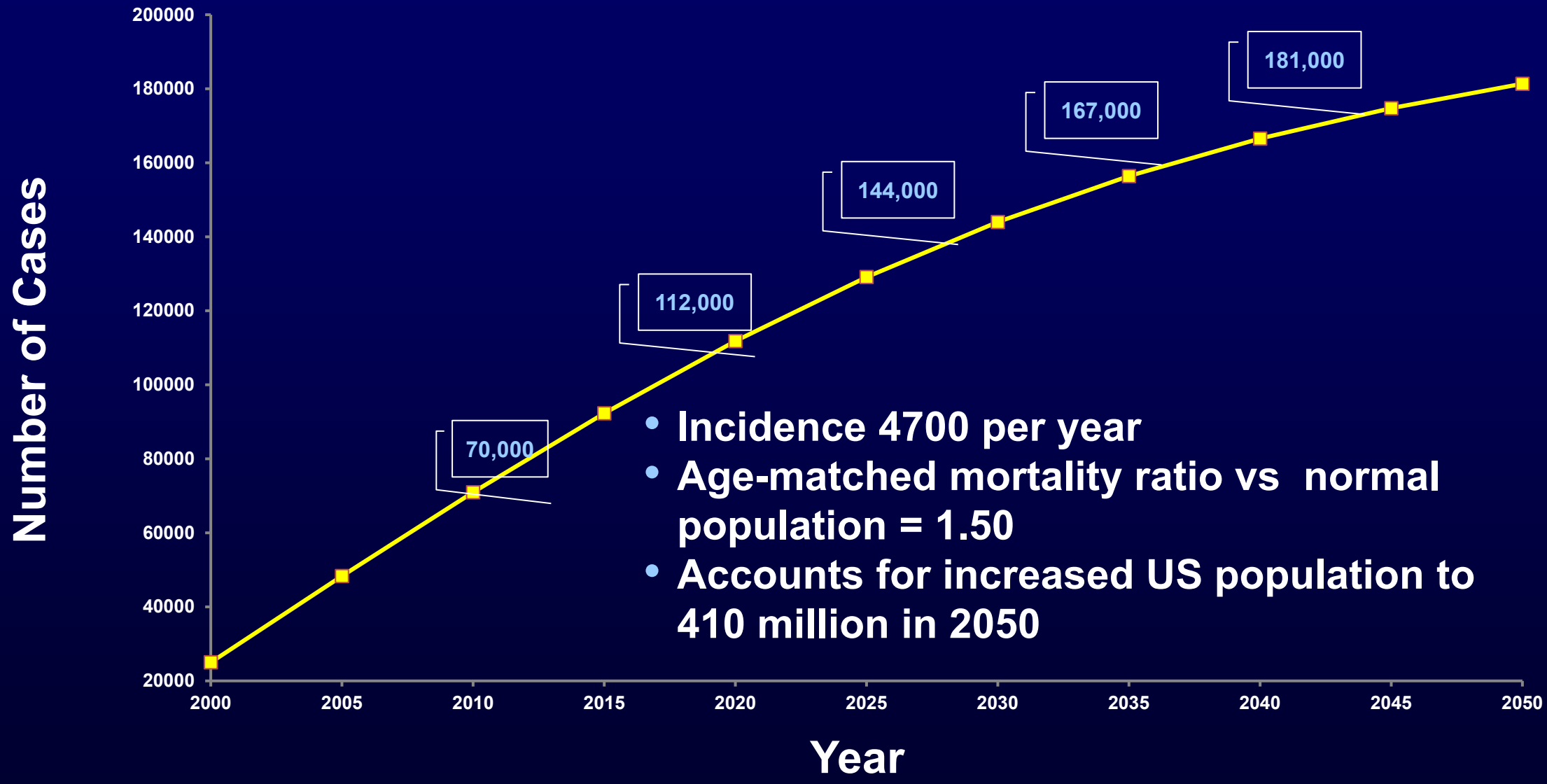
- Interferon
- JAK2 inhibitors (ruxolitinib)
- HMAs
- Asciminib
- Venetoclax

- None worked so far – Problem: need safe, effective and easy-to-deliver Rx to combine (patients may not accept IV,SQ, even minimally toxic drugs)
- Current MDACC trial – Dasatinib + oral decitabine 3days/mo

CML. Interesting Observations and Expected or Unintended Consequences

- CML increasing prevalence and Rx implications -- cost of Rx, expertise, too rapid and unnecessary rotations of TKIs
- Diminishing role of allo SCT; but now increasing due to increased prevalence
- Developments of resistance through target (ABL kinase domain) mutations
- Long-term chronic administration = unexpected long-term side-effects
- Targeted Rxs and “Optimal Biologic Dose” vs MTD
- High prices of cancer drugs

CML - Increasing Prevalence Over Time



- Incidence 4700 per year
- Age-matched mortality ratio vs normal population = 1.50
- Accounts for increased US population to 410 million in 2050

Wang. Blood 127: 2742; 2016

CML -- Low Incidence BUT High Prevalence

- Before 2000 -- Incidence 4-5,000/yr; median survival 6 yrs. Prevalence is when incidence/yr = deaths/yr. so 4-5,000 x 6 = 25-30,000
- Since 2000 -- CML mortality started to decrease drastically, from 10-20%/year to 0.5% under "ideal" conditions
- 2012 -- Incidence 4,700/yr; median survival >20 ---Prevalence ↑annually by 4,700 new cases until incidence- deaths/yr --2040; prevalence = 35 x incidence = 180-200,000. World = 25 x US; World prevalence 4.5-5 million
- 2022 -- New parameters: Increased expertise; increased incidence (9,000/yr) due to increased population (US 330 million; world 8 billion); Mark Cuban effect = every CML patient can be treated at a cost of $565/yr; allo SCT cost $20-30,000 1x – US 500,000; World 12-15 million

Huang. Cancer 118: 3123; 2012

Cost of TKIs in 2022 –The "Mark Cuban Effect"

Agent	Dose (mg/D)	AWP for 1 Yr ($ US)
Generic imatinib	400	5,300 / 565(Mark Cuban)
Dasatinib	100	228,000
Dasatinib	50	127,000
Dasatinib	20	63,000
Nilotinib	300 BID	240,000
Nilotinib	150-200 BID	120,000
Bosutinib	400	250,000
Ponatinib	45 or 30 or 15	270,000
Asciminib	40 BID	258,000
Asciminib	200 BID	1,289,000

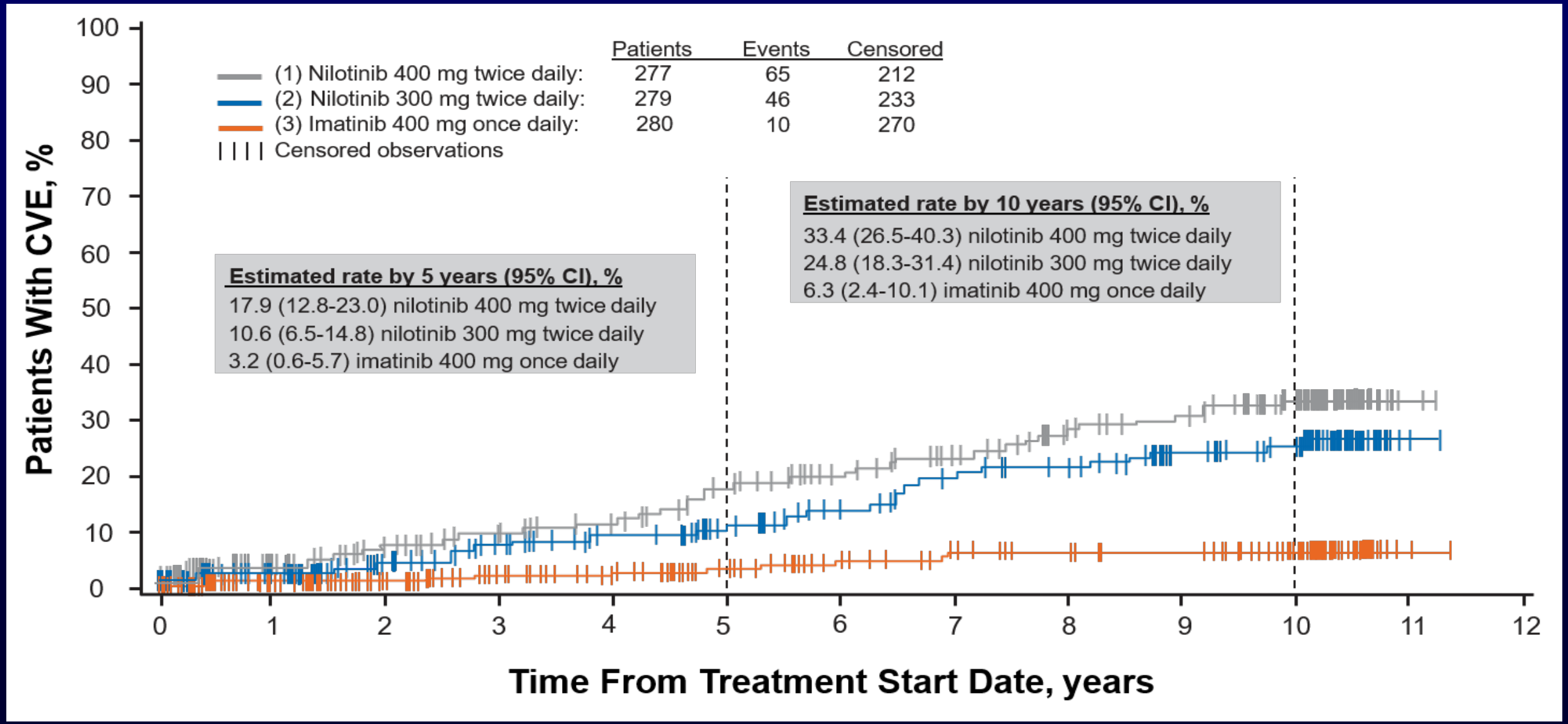
- Mark Cuban CostPlus generic company sells generic drugs at cost + 15% profit – generic imatinib $47.5/mo = $ 565/year = $17,000/30yrs

Redbook . March 21, 2022

Lessons From TKIs Development in CML Optimal Biologic Dose vs MTD

- BCR::ABL1 TKIs were the true original targeted Rxs
- But, developed in the classical pattern of cancer drugs, i.e. chronic use at dose identified as < MTD (accounted for with Course 1, not as chronic Rx = chronic new toxicities)
- Daily targeted (chronic) Rxs in cancer better developed at “Optimal Biologic Dose” (OBD) = as effective and less toxic

Nilotinib vs Imatinib in CML(ENESTnd)--10-Yr Results
Cardiovascular Events

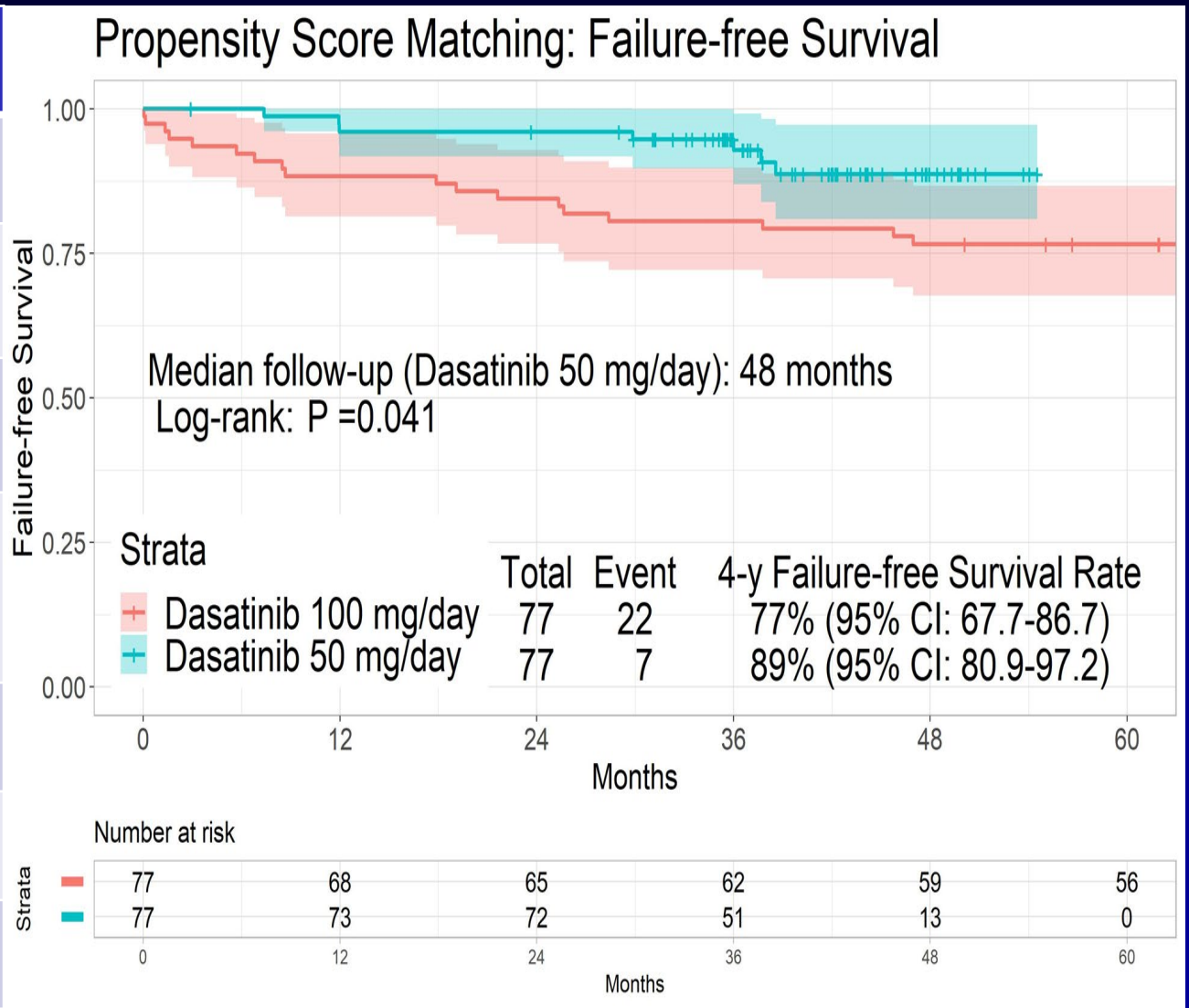


Kantarjian. Leukemia 35: 440; 2021.

Dasatinib 50 vs 100mg/D in CML-CP

- 233 pts with CML-CP Rx with dasatinib 50mg/D (n=83) or 100mg (n=150)
- Propensity score matching of 77 pts in each group

Parameter	DAS 50	DAS 100	p Value
%1-yr MR4	63	43	.009
%1-yr MR4.5	53	36	.03
%1-yr CMR	46	33	.06
% pleural effusions	5 (G3-4 3%)	21 (G3-4 10%)	.016
% 4-yr FFS	89	77	.04
TFS	100	100	-
EFS	95	92	NS



Sasaki. Blood 138: abst 631; 2021

Dasatinib 20mg/D in Older CML

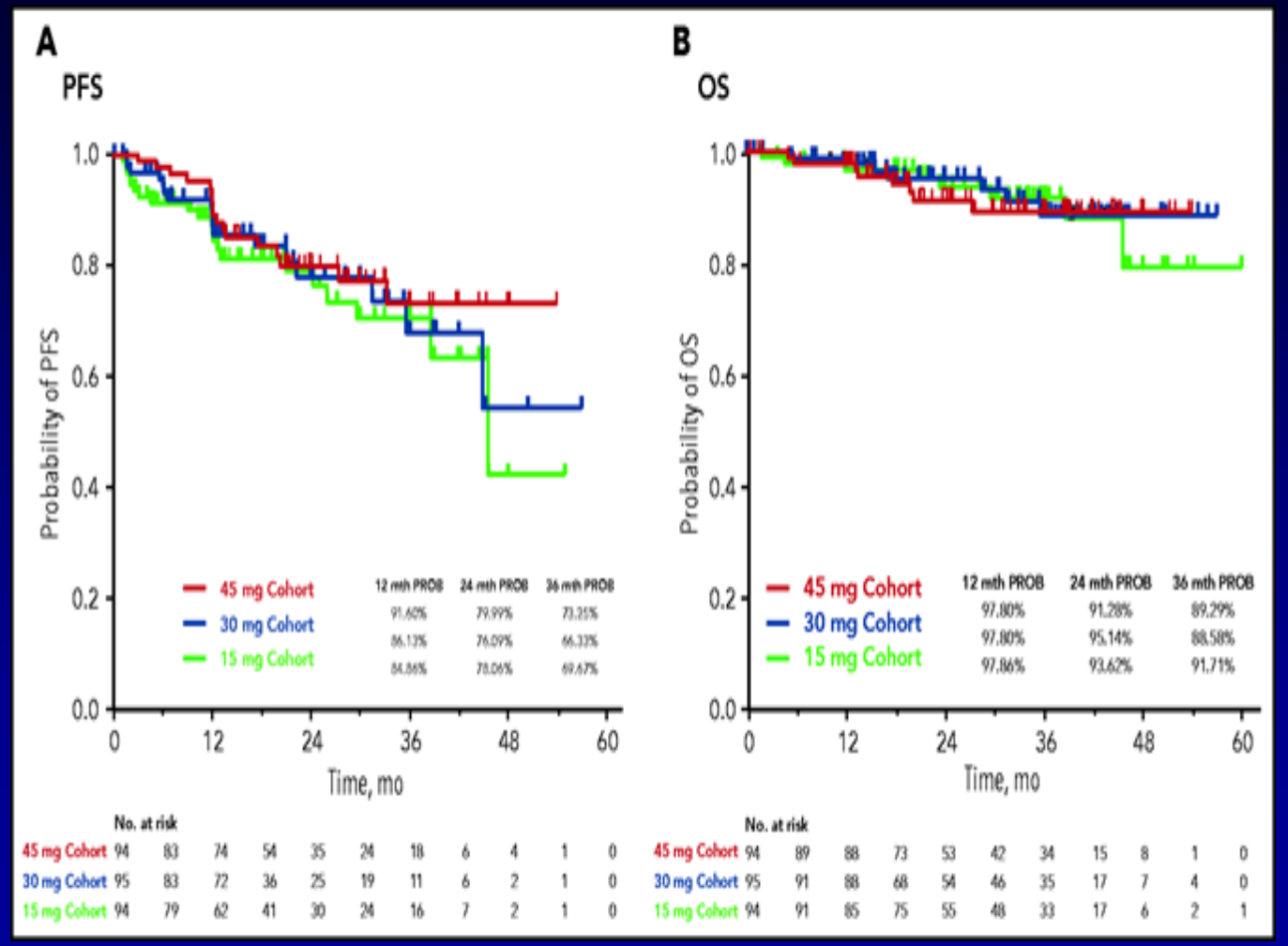
- 52 pts > 70 yrs (median age 77.5 yrs) Rx with dasatinib 20mg/D. Median FU 12 mos.
- Cumulative MMR at 12 mos 31/52 = 60%
- 12-mo MR4 14= 27%. MR4.5 7 = 13%
- Rx DC due to failure (n=3) or side-effects (n=3). None DC for progression
- 4 pleural effusions G 1-2

Kumagai. Blood 138: abst 36601; 2021. Murai. Lancet Haematology 8: e 902-911; 2021

Ponatinib Dose and Outcome in CML-CP

- 283 pts with CML-CP and T315I mutation or resistance to 2+TKIs randomized to ponatinib 45, 30 or 15m/D until PCR<1%, then reduced to 15mg/D

% 3-yr	45-15		30-15		15	
	Other	T315	Other	T315	Other	T315
PCR <1%	54	60	41	25	44	10
PFS	71	75	75	49	74	61
OS	90	86	93	79	94	85



- Interpretation—use 45mg/D if T315I; otherwise 30mg/D OK

Deininger. Blood 140: abst 307;2021 Cortes. Blood 138: 2042–2050; 2021

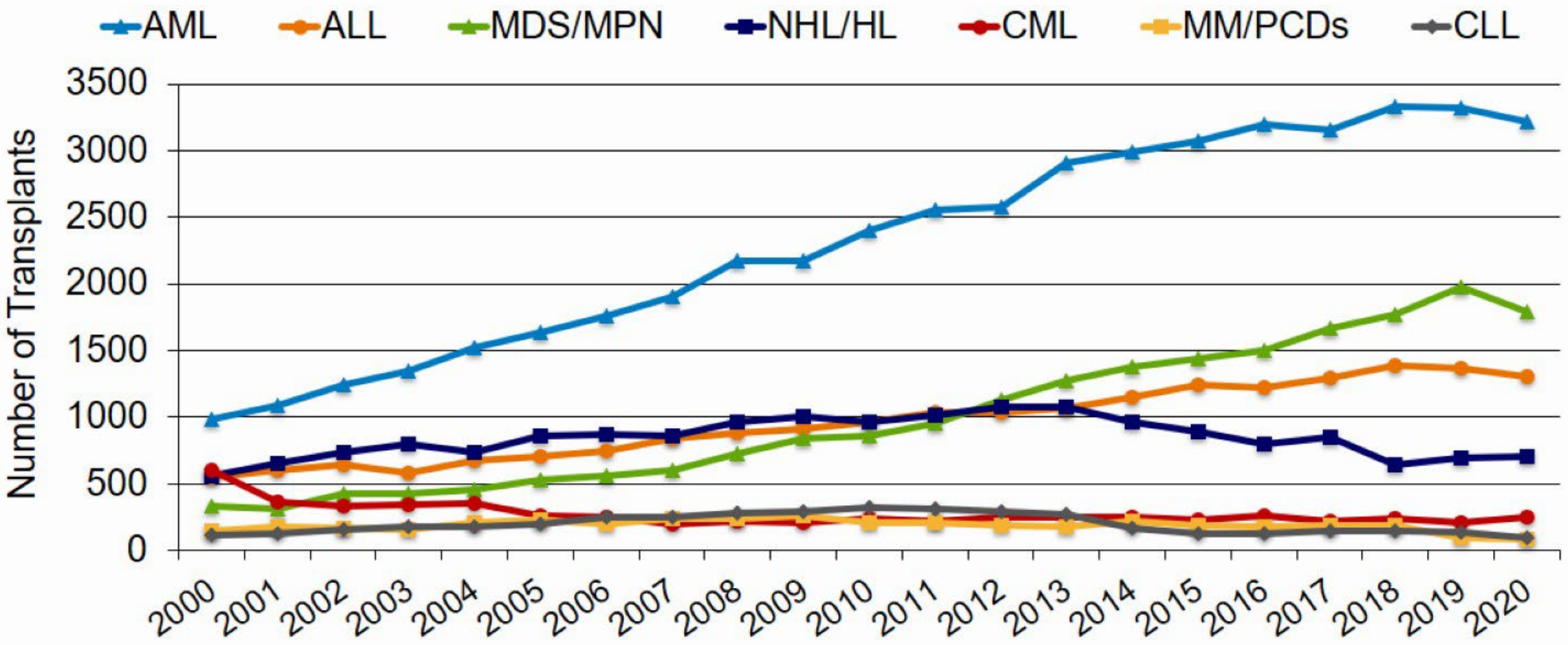
What Are The Optimal TKIs Doses

Drug	Salvage			Frontline		
	Initial approval	Current	Should be	Initial attempt	Approved	Should be
Imatinib	400 mg QD	400 mg QD		400 mg QD	400 mg QD	
Dasatinib	70 mg BID	100 mg QD		100 mg QD	100 mg QD	50 mg QD
Nilotinib	400 mg BID	400 mg BID		300-400 mg BID	300 mg BID	150-300 mg BID
Bosutinib	500 mg QD	500 mg QD	400 mg QD?	500 mg QD	400 mg QD	200-400 mg QD
Ponatinib	45 mg QD	45 mg QD	30 mg QD?	45 mg QD	--	--

CML – TKIs and Allo SCT

- 2000 – Incidence 5,000 cases; prevalence 30,000 -- allo SCT first line Rx 20-50% of "eligible candidates" = 2,500-3,000 SCT
- 2000-2012 – Allo SCT 2nd-3rd+ line Rx; failure rate <2% per year; but prevalence increasing (100,000+ in 2021) – allo SCT decreased drastically to <500/year then increased slowly
- 2022 – prevalence 130,000+; with "total TKIs failures" and cure aim in younger patients (<60-65 yrs) = SCT 1000+/yr
- BUT IBMTR quote , 500 SCT in 2020. So "resistance" rate lower OR less patients offered allo SCT and managed with TKIs

Number of Allogeneic HCTs in the US by Selected Disease



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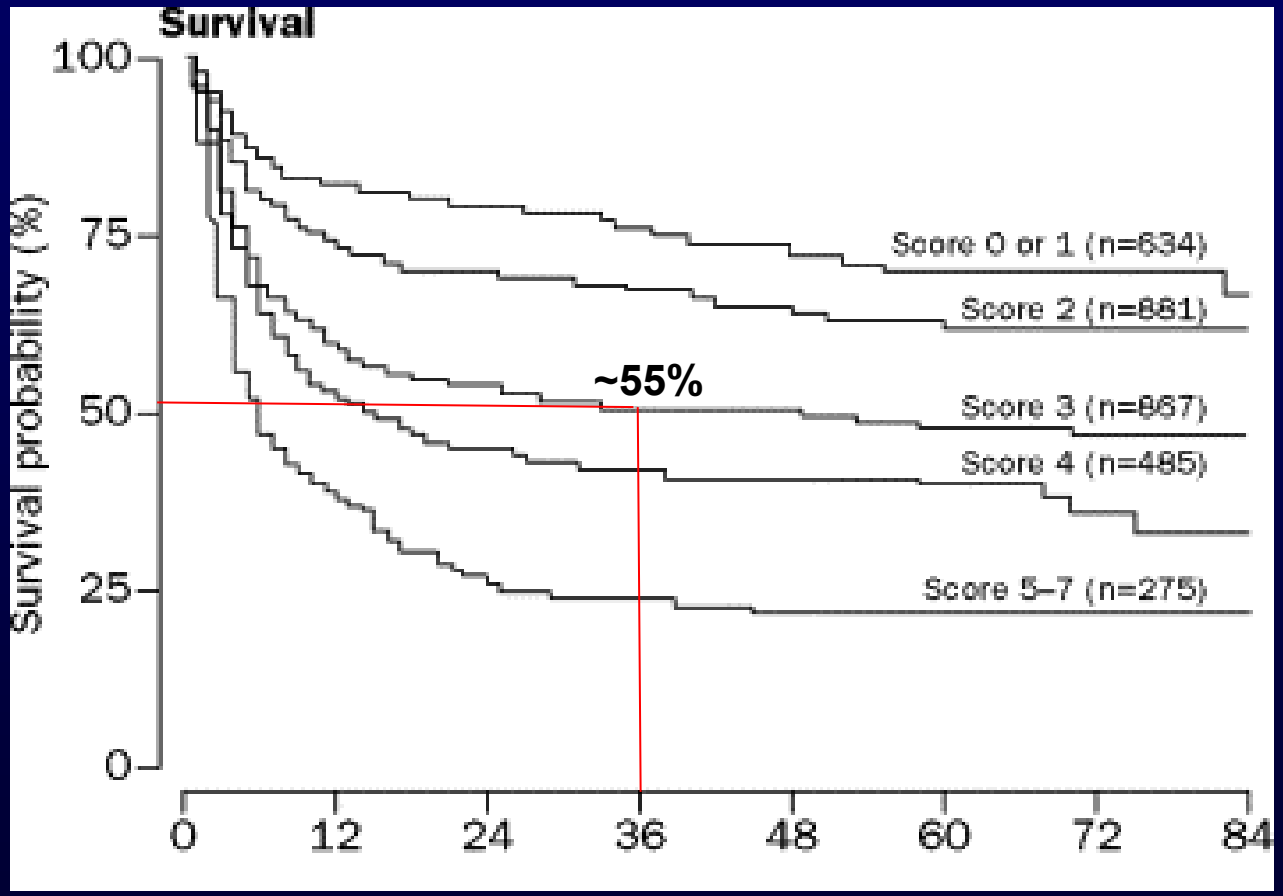
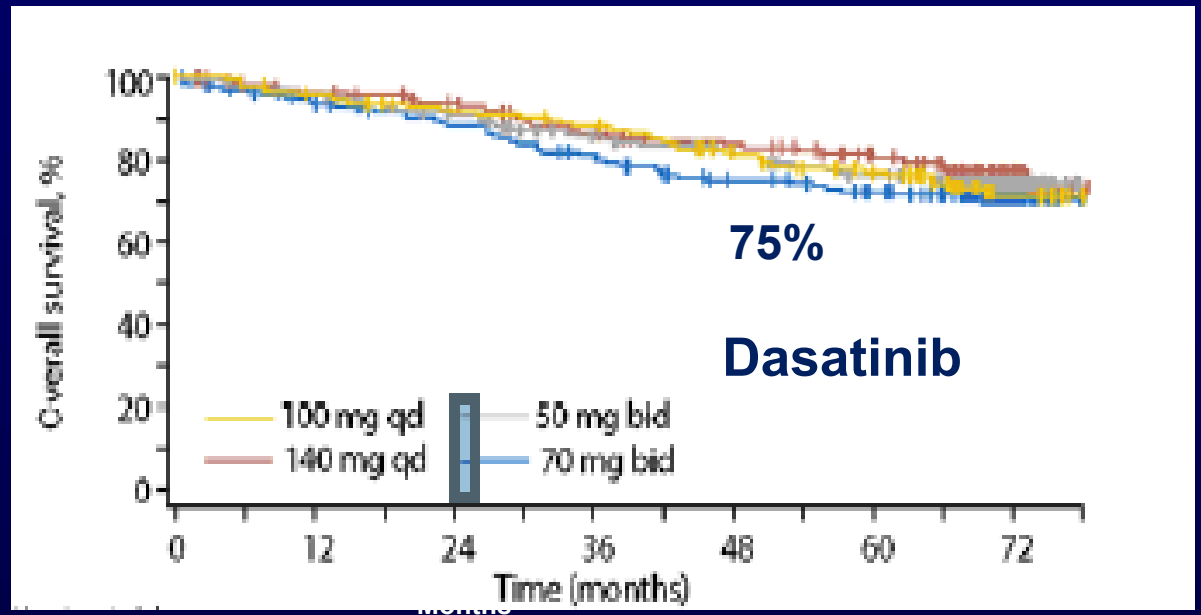
Abbreviations –
AML: Acute myelogenous leukemia;
ALL: Acute lymphoblastic leukemia;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
NHL: Non-Hodgkin lymphoma;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia;
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
CLL: Chronic lymphocytic leukemia

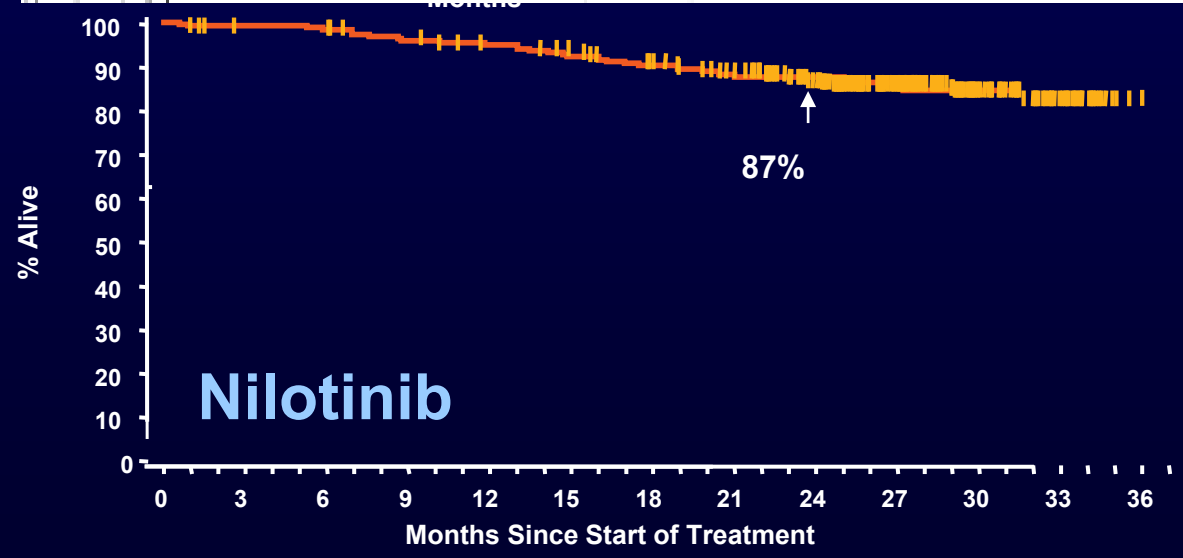
Timing of Allogeneic SCT

- General —Failure of multiple TKIs
- Consider allo SCT for candidate patients with resistance (not toxicity) to a second generation TKIs and no guiding mutations (3rd GEN TKIs expensive + toxic)
- DO NOT/may not consider allo SCT in older patient (e.g. age 65-70+) regardless of molecular or CG status– Continue most appropriate TKI, and consider adding LD araC, AZA, omacetaxine, or even hydrea
- Dogma of " must achieve CG CR at all cost" not relevant in older patients – may live normal life expectancy in chronic phase with Ph+ > 5-80% or PCR> 1-10%

Overall Survival With TKI After Imatinib Failure or With SCT







Shah. Blood; 2014[E-pub ahead of print.
Kantarjian. Blood 2009; 114: Abs # 1129;
Gratwohl . Lancet 1998; 352: 1087-92

Lessons From TKIs Development in CML –Target Mutations as Cause of Resistance

- CML experts predicted that cancer/CML cells are smart and will soon develop resistance mechanisms
- Fortunately CML cells not that smart – mutations in target first identified in CML with targeted Rx, but now a common trend – with FLT3 and IDH inhibitors in AML, with BTKis and venetoclax in CLL, etc.. But these were overcome with newer generation TKIs

CML. Mutations and Resistance

Mutation	IC_{50}-fold increase relative to WT (W=1)				
	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
M244V	0.9	0.9	2.0	1.2	3.2
L248R	14.6	22.9	12.5	30.2	6.2
L248V	3.5	3.5	5.1	2.8	3.4
G250E	6.9	4.3	4.4	4.6	6.0
Q252H	1.4	0.8	3.1	2.6	6.1
Y253F	3.6	1.0	1.6	3.2	3.7
Y253H	8.7	0.6	2.6	36.8	2.6
E255K	6.0	9.5	5.6	6.7	8.7
E255V	17.0	5.5	3.4	10.3	12.9
D276G	2.2	0.6	1.4	2.0	2.1
E279K	3.6	1.0	1.6	2.0	3.0
E292L	0.7	1.1	1.3	1.8	2.0
V299L	1.5	26.1	8.7	1.3	0.6
T315A	1.7	6.0	58.9	2.7	0.4
T315I	17.5	45.4	75.0	39.4	3.0
T315V	12.2	29.3	738.8	57.0	2.1
F317L	2.6	2.4	4.5	2.2	0.7
F317R	2.3	33.5	114.8	2.3	4.9
F317V	0.4	11.5	21.3	0.5	2.3
M343T	1.2	1.1	0.9	0.8	0.9
M351T	1.8	0.7	0.9	0.4	1.2
F359I	6.0	2.9	3.0	16.3	2.9
F359V	2.9	0.9	1.5	5.2	4.4
L384M	1.3	0.5	2.2	2.3	2.2
H396P	2.4	0.4	1.1	2.4	1.4
H396R	3.9	0.8	1.6	3.1	5.9
F486S	8.1	2.3	3.0	1.9	2.1
L248R + F359I	11.7	39.3	13.7	96.2	17.7

Adapted from Redaelli S et al. *Am J Hematol.* 2012;87:E125-E128.

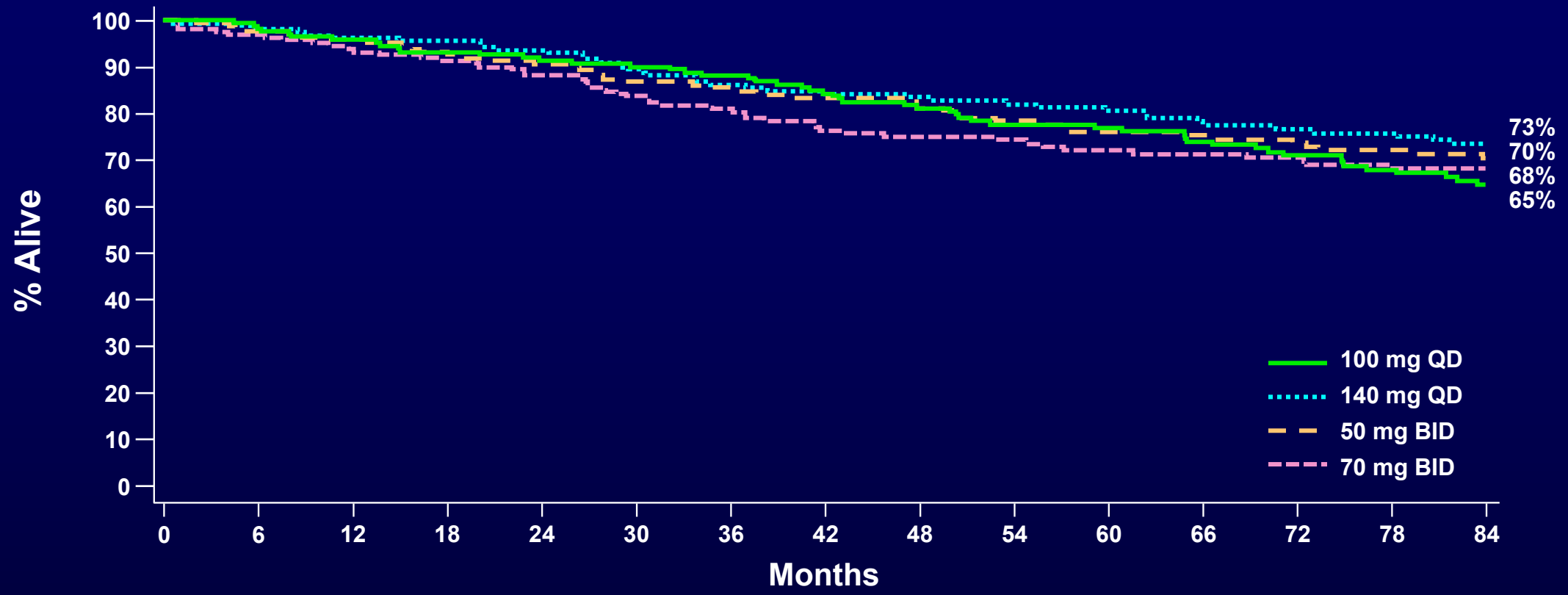
Sensitive	<2-fold difference
Moderately sensitive	2.1- to 4-fold difference
Resistant	4.1- to 10-fold difference
Highly resistant	>10-fold difference

Eiring et al. Genome Biol. 2014; 15 (9): 461.

CML Therapy Post Frontline Failure

- Dasatinib 100 mg/D
- Nilotinib 400 mg BID
- Bosutinib 300-500 mg/D
- Ponatinib 30-45 mg/D (T315I; failure> 2 TKIs)
- Asciminib 40 mg BID (third line therapy, ie failure > 2 TKIs);200 mg BID for T315I but data minimal
- Omacetaxine, decitabine/azacytidine, cytarabine, hydrea – can be added to TKIs
- Allo SCT

OS by Dasatinib Dose After Imatinib Failure

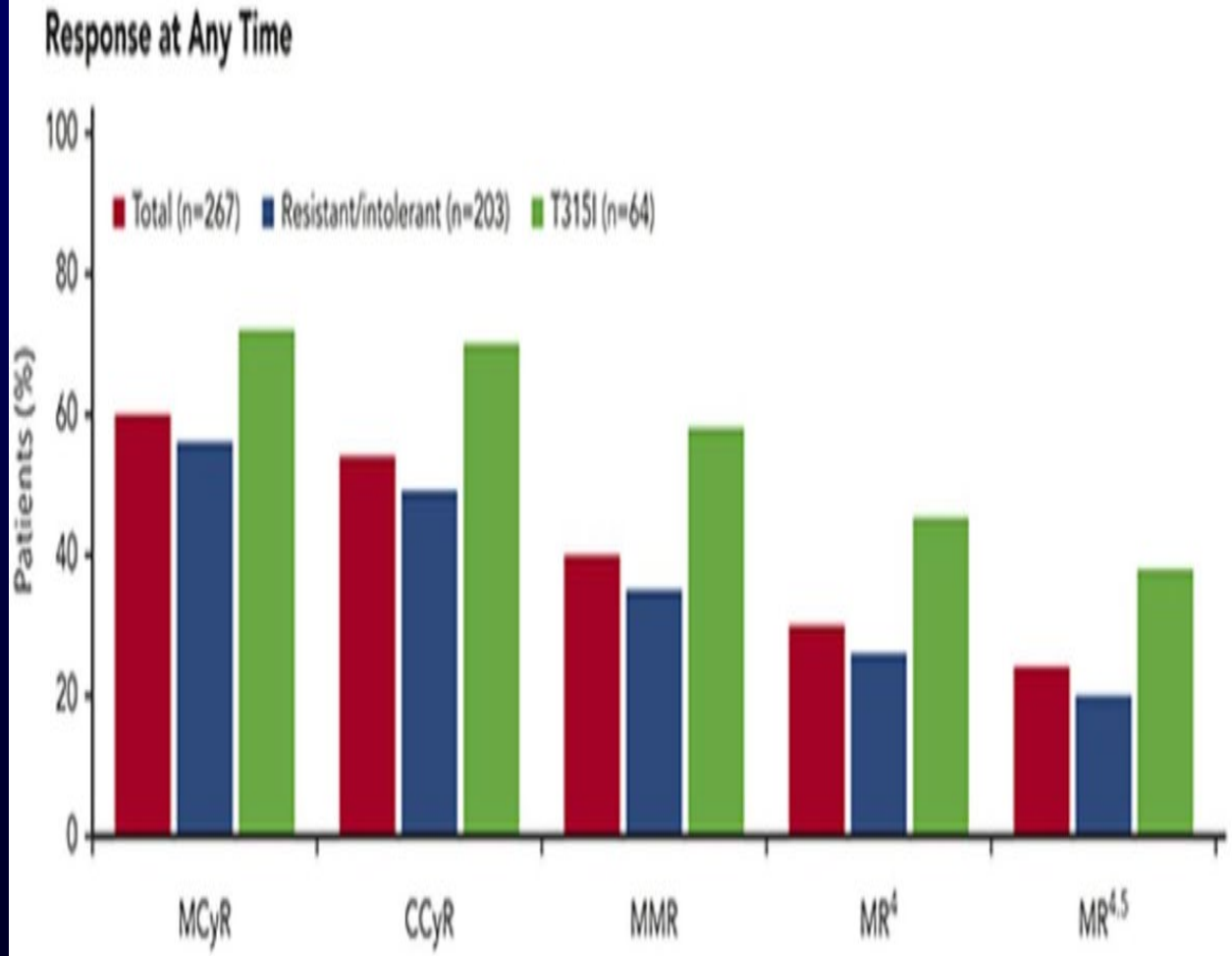


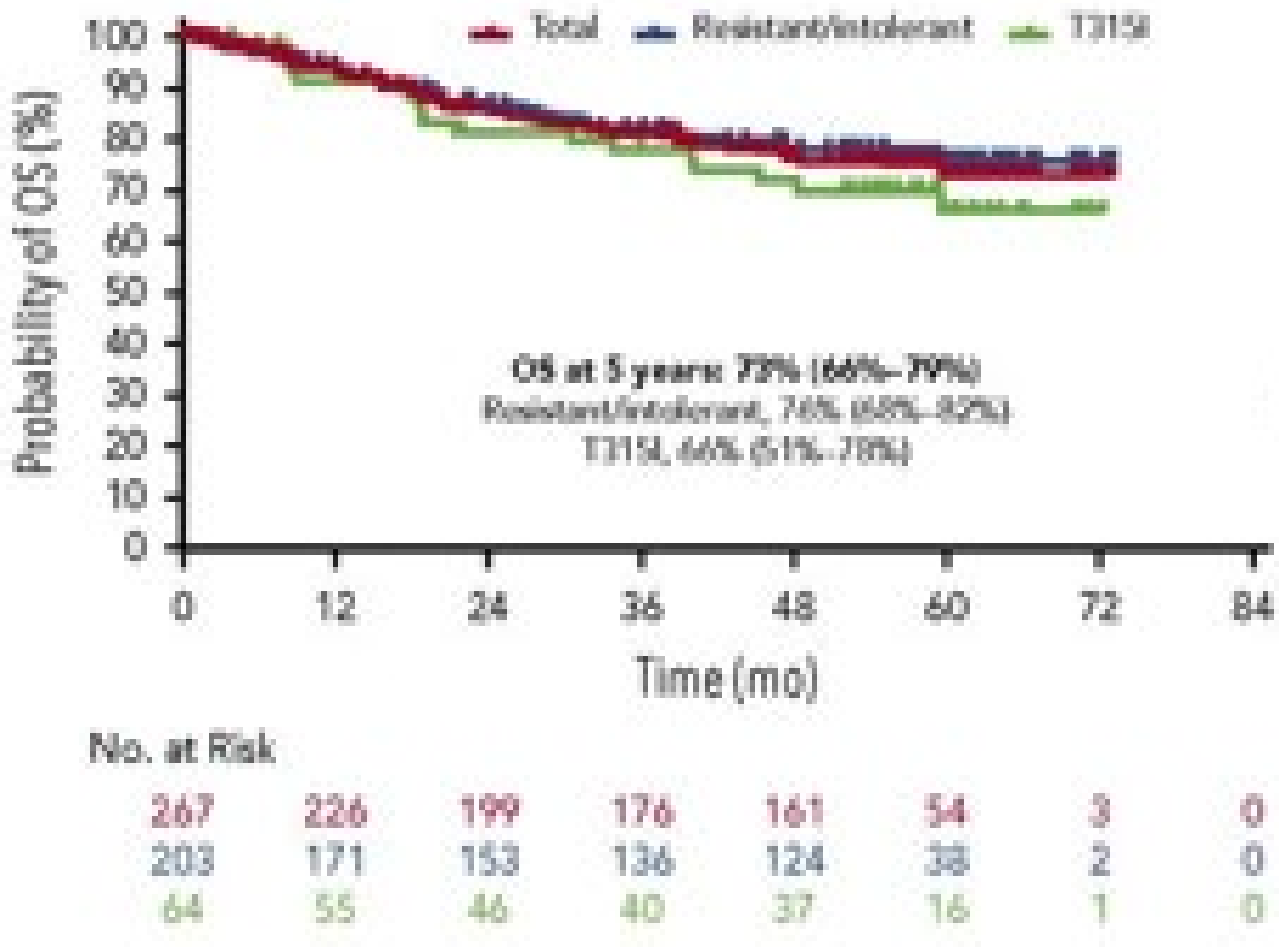
	Imatinib-resistant	Imatinib-intolerant	Overall
OS, % (95% CI)	63 (53–71)	70 (52–82)	65 (56–72)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (33–51)

Shah . AJH 91: 896; 2016

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

Ponatinib Real-life Experience (Italy)

- 666 pts: CP 515, AP 50, BP 101
- Prior 2 TKIs 259 (39%), 3 TKIs 260 (29%), 3+TKI 147 (22%)
- T315I 46 (7%)
- Baseline HT 27%, thrombosis 5%, CAHD 5%, CHF 2%
- 593 evaluable for response. Median FU 14 mos
- MR2 71%, MR3 59%, MR4 40%

Response	CP (n=515)	AP-BP (n=151)
MR2	444/515 (86%)	20/151 (50)
MR3	382/515 (74%)	56/151 (37)
MR4	222/515 (43)	44/151 (29)

- Dose reductions 20% due to AEs, 46% by choice
- Rx DC 22%: intolerance 7%, 1^0R 3%, 2^0R 6%
- Time to Rx DC 47 mo in CP
- 5-yr OS??

Breccia. Hemasphere 6: abst P697; 2022

Asciminib vs Bosutinib 3rd Line Rx in CML-CP

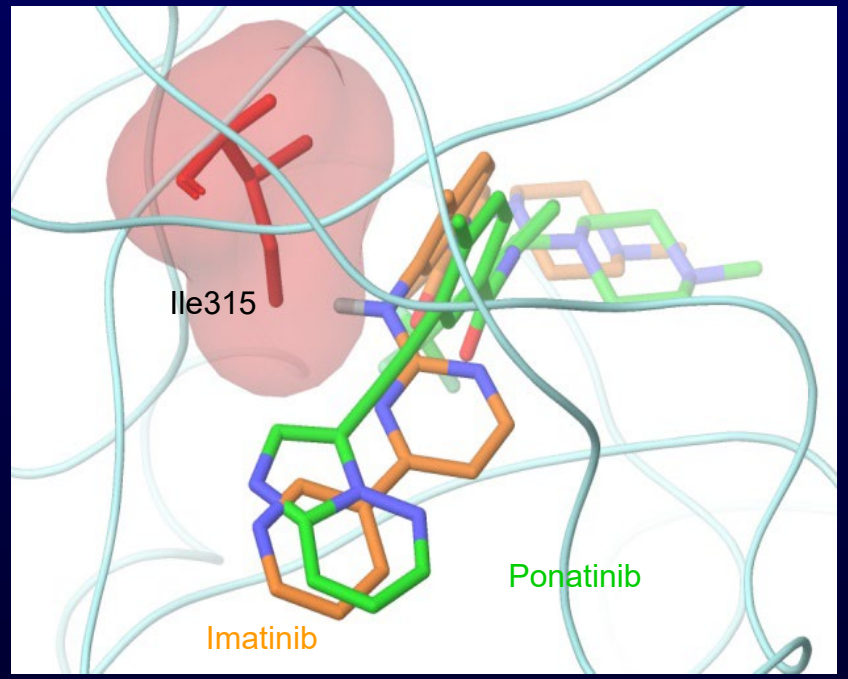
- 233 pt failing 2+ TKIs randomized (2:1) to asciminib 40mg BID (n=157) or bosutinib 500mg/D (n=76)

Parameter	Asciminib	Bosutinib
% 2-yr MMR	38	16
% 2-yr PFS	94	91
% 2-yr OS	97	99
% G 3-4 AEs	56	68
% AEs & DC	36	51

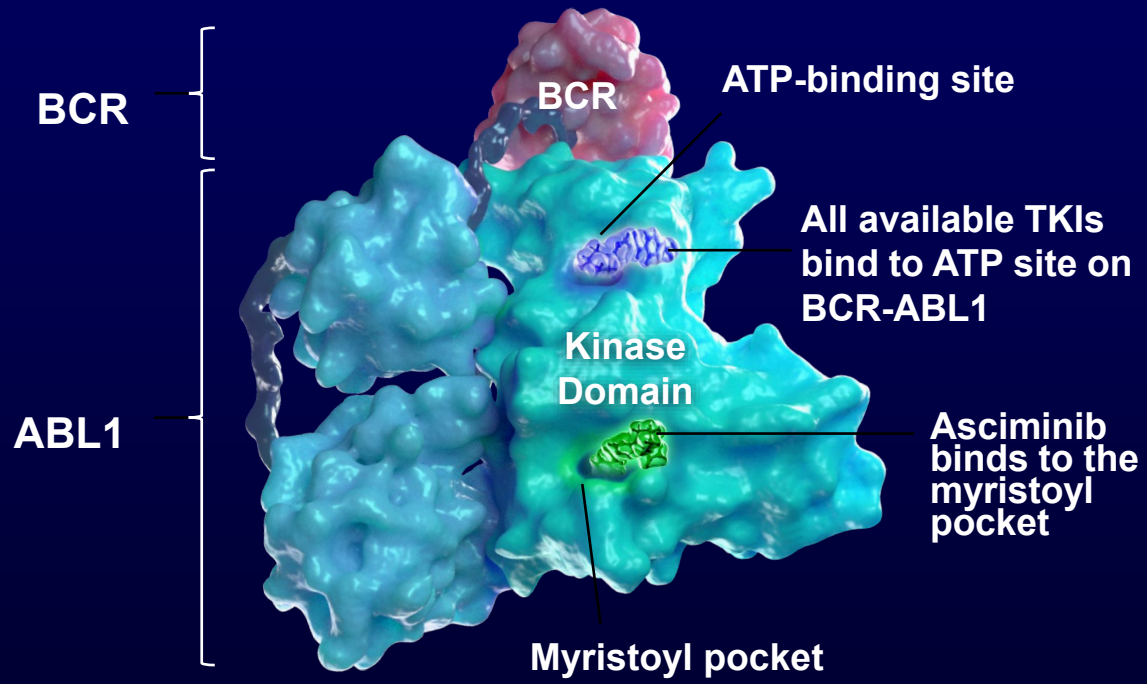
Rea. HemaSphere 6: abst S155; 2022

Ponatinib or Asciminib?

Ponatinib



Asciminib



O'Hare . Cancer Cell. 2009;16:401-412; Manley. Leuk Res. 2020; 98:106458

Ponatinib and Asciminib in CML CP-- Summary of Real-World Results (EHA)

Parameter	Ponatinib	Asciminib
N reported	515	≈ 210-250
% MR2 (CGCR)	86	57-70
% MMR	74	22-53
% MR4	43	16-42

HemaSphere 6: abst 697; 706, 708, 709, 712; 2022

3 New BCR-ABL TKIs in CML

- HQP1351 (China)
- K0706
- PF-114 (Russia)

Turkina. Blood 134: abst 1638; 2019

Olverembatinib (HQP1351) in CML

- 101 pts with CML in CP (n=86) or AP (n=15)
- Olverembatinib 1-60mg Qod
- 83% Rx with 2+ TKIs
- T315I-mut 62%
- CG CR 62%. MMR 51%

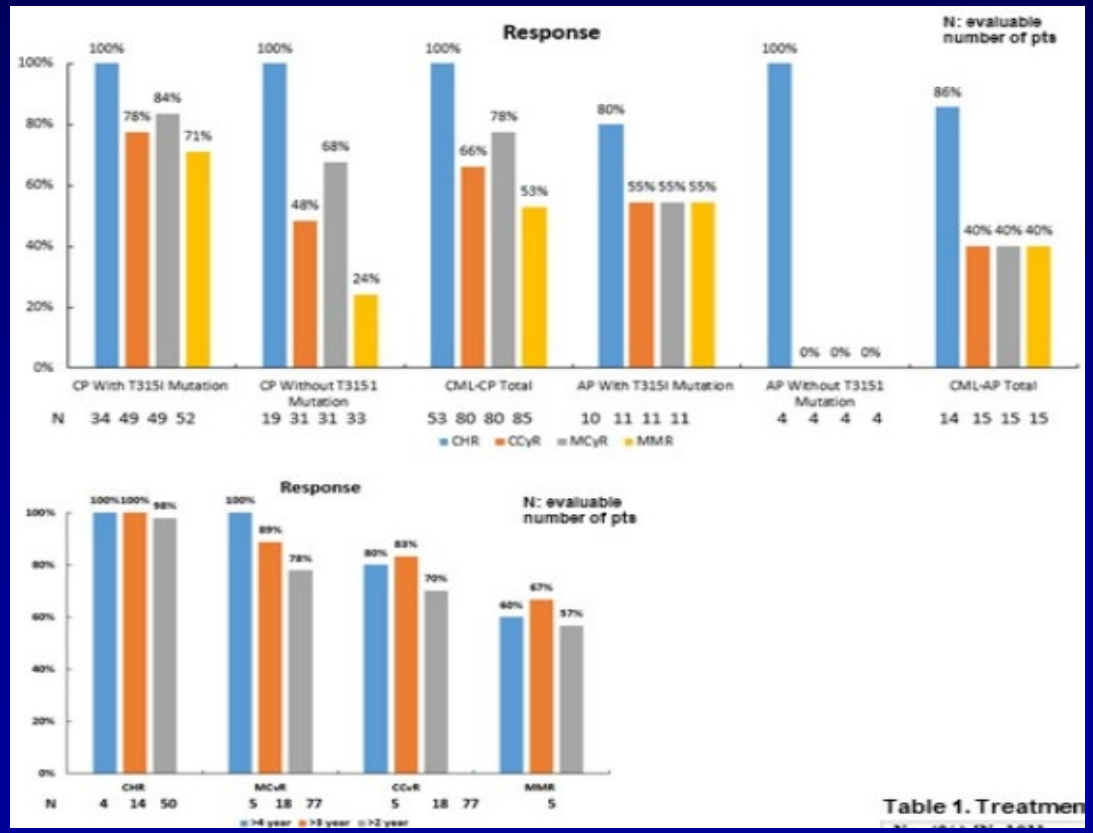
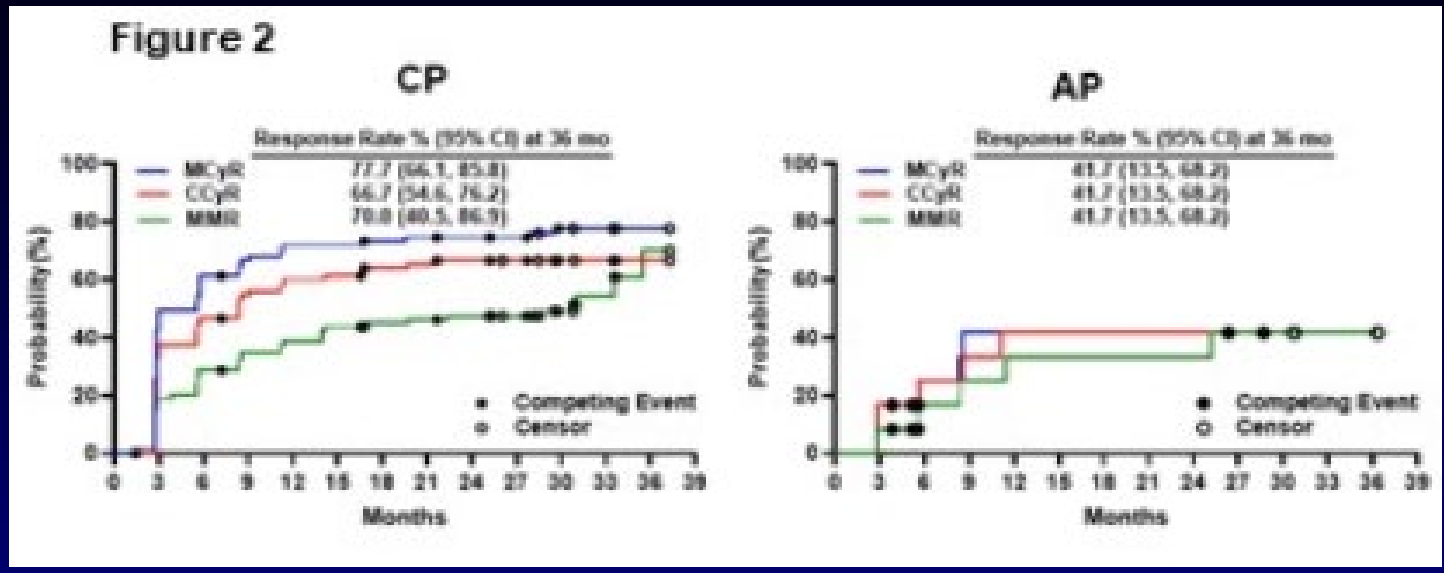
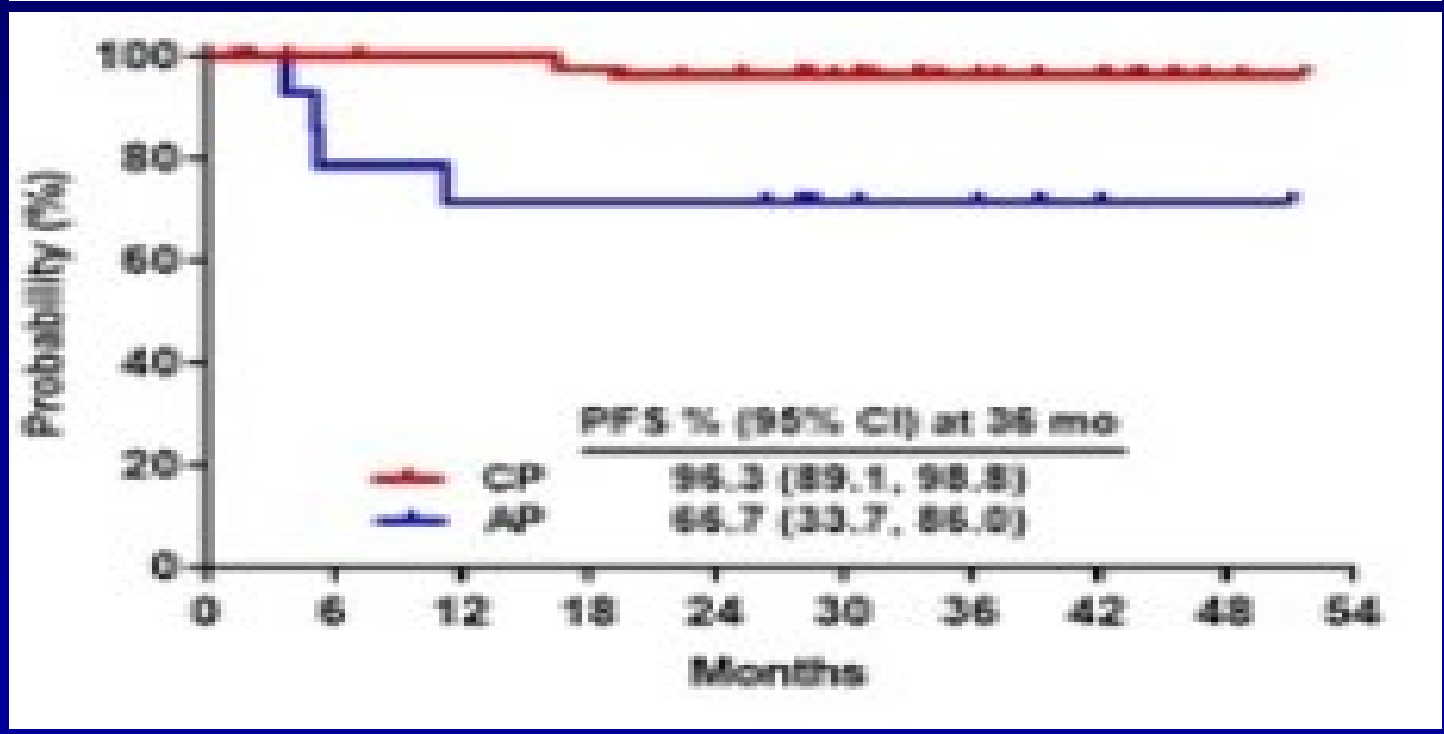


Table 1. Treatmen





Qian. Blood 140: abst 311; 2021

CML Summary 2022

- Frontline Rx excellent (and getting better and safer)
- Rx DC feasible (better to wait for long DMR > 3-5 yrs = high TFR “cure” rate)
- Strategies to increase rate of TFR
- 2nd line options equivalent; ponatinib post 2nd GEN resistance
- 3rd line - ponatinib better efficacy:safety profile with dose adjustments; asciminib FDA approved

Leukemia Questions?

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