Contemporay Management of CML in 2025

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Sea Island; July 24, 2025

Disclosures

- Has no relevant financial relationships

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	2021	2024
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.

Commonly Used Terminologies for TKIs

- First-generation TKI – Imatinib
- Second-generation TKIs – Dasatinib, bosutinib, nilotinib
- Third-generation TKIs – Here it gets a bit different
  - Third generation = third wave of *BCR::ABL1* TKIs +*T315I* effective: ponatinib, asciminib
  - Some CML experts wish to distinguish the third wave of TKIs ABL1 KD binding = ponatinib; olverembatinib -- vs "Specifically Targets the ABL Myristoyl Pocket" (STAMP) inhibitors = asciminib, TGRX678, TERN701)

Jabbour E, et al. Clin Lymphoma Myeloma Leuk. 2015;15:323-334.

CML TKIs in 2025

Approved TKIs

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

Investigational TKIs

- Olverembatinib(T315I; ABL-KDi)
- ELVN-001 (T315I; ABL1-KDi)
- TGRX-678 (T315I; STAMPi)
- TERN-701 (T315I;STAMPi)

STAMPi = Specifically Targets the ABL Myristoyl Pocket inhibitor

CML. Response Definitions

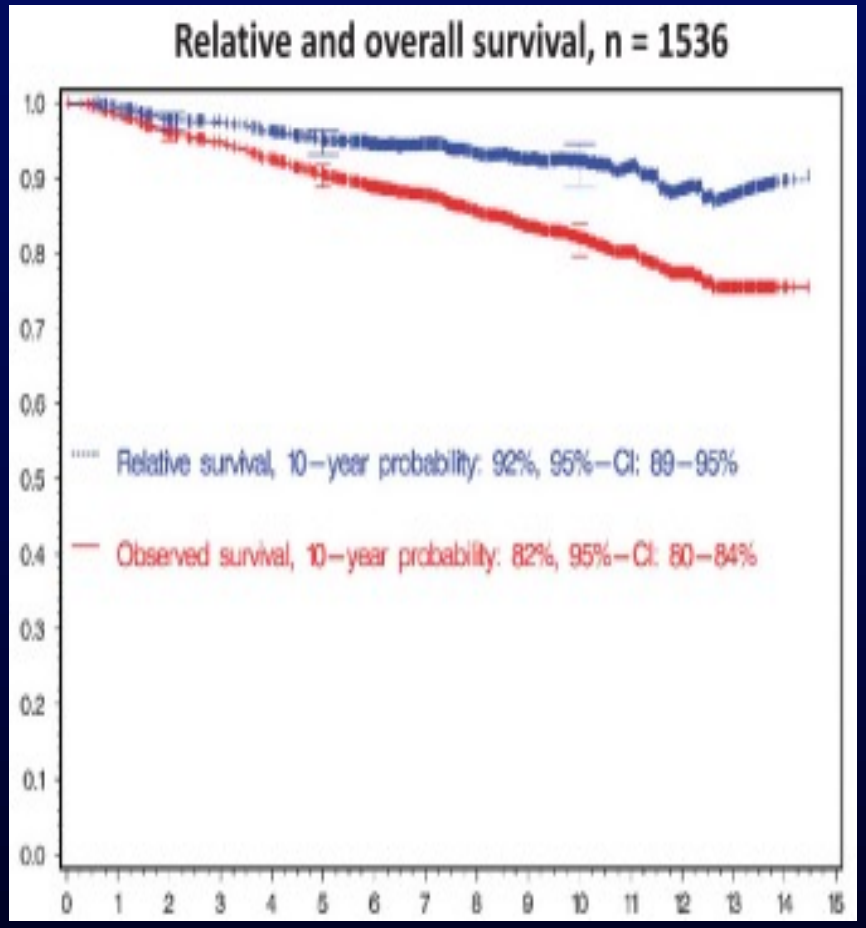
BCR::ABL1 (International scale)	Log reduction in *BCR::ABL1*	Response definition	
100	-	Baseline	
≤10	1	≈ Major Cytogenetic Response (MCyR)	
≤1	2	≈ Complete Cytogenetic Response (CCyR)	
≤0.1	3	Major Molecular Response (MMR)	
≤0.01	4	MR4	Deep Molecular Response (DMR)
≤0.0032	4.5	MR4.5	
≤0.001	5	MR5	

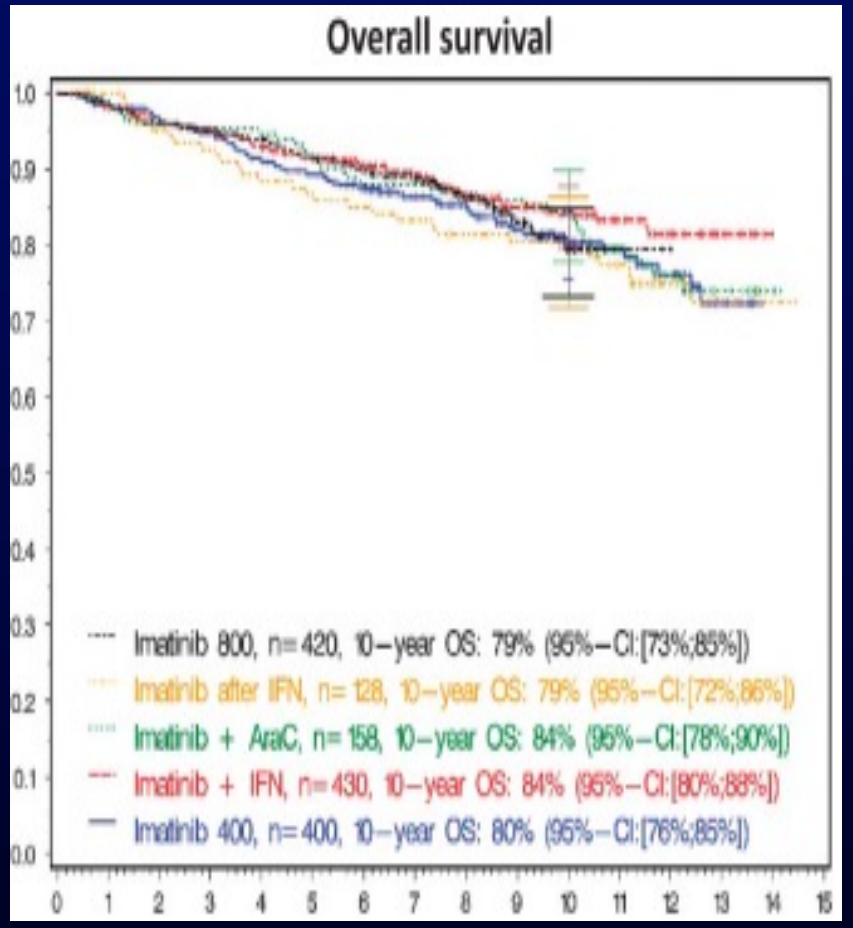
Frontline Rx in CML-CP

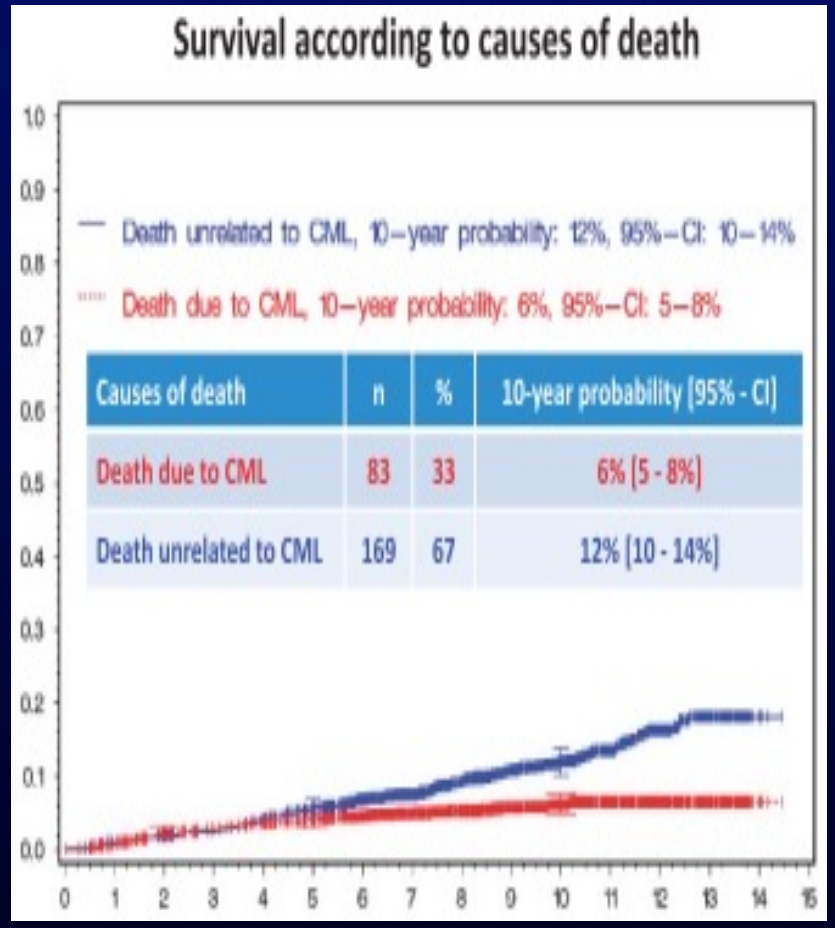
Efficacy of Imatinib-based Rx in CMLIV: 10-Yr FU

- 1551 pts newly Dx CML-CP randomized to IMA 400, IMA 800, IMA+IFN, IMA+ara-C, IMA after IFN
- 10-yr OS 82%, 10-yr relative OS 92% ; 10-yr CML death 6%, non-CML deaths 12%. 10-yr BP 5.8%
- Only 417 pts = 26.5% switched from imatinib to 2nd TKIs; BUT resistance about 150 = 10%
- Allo SCT138 (9%) ;91 (6%) in CP
- MVA OS; risk score, co-morbidities, smoking, ACA, non-academic center

92%
89%
81%







Causes of death	n	%	10-year probability [95% - CI]
Death due to CML	83	33	6% [5 - 8%]
Death unrelated to CML	169	67	12% [10 - 14%]

Hehlmann. Leukemia 31: 2398; 2017.

Re-Assessing 8 Established Rx Traditions in CML

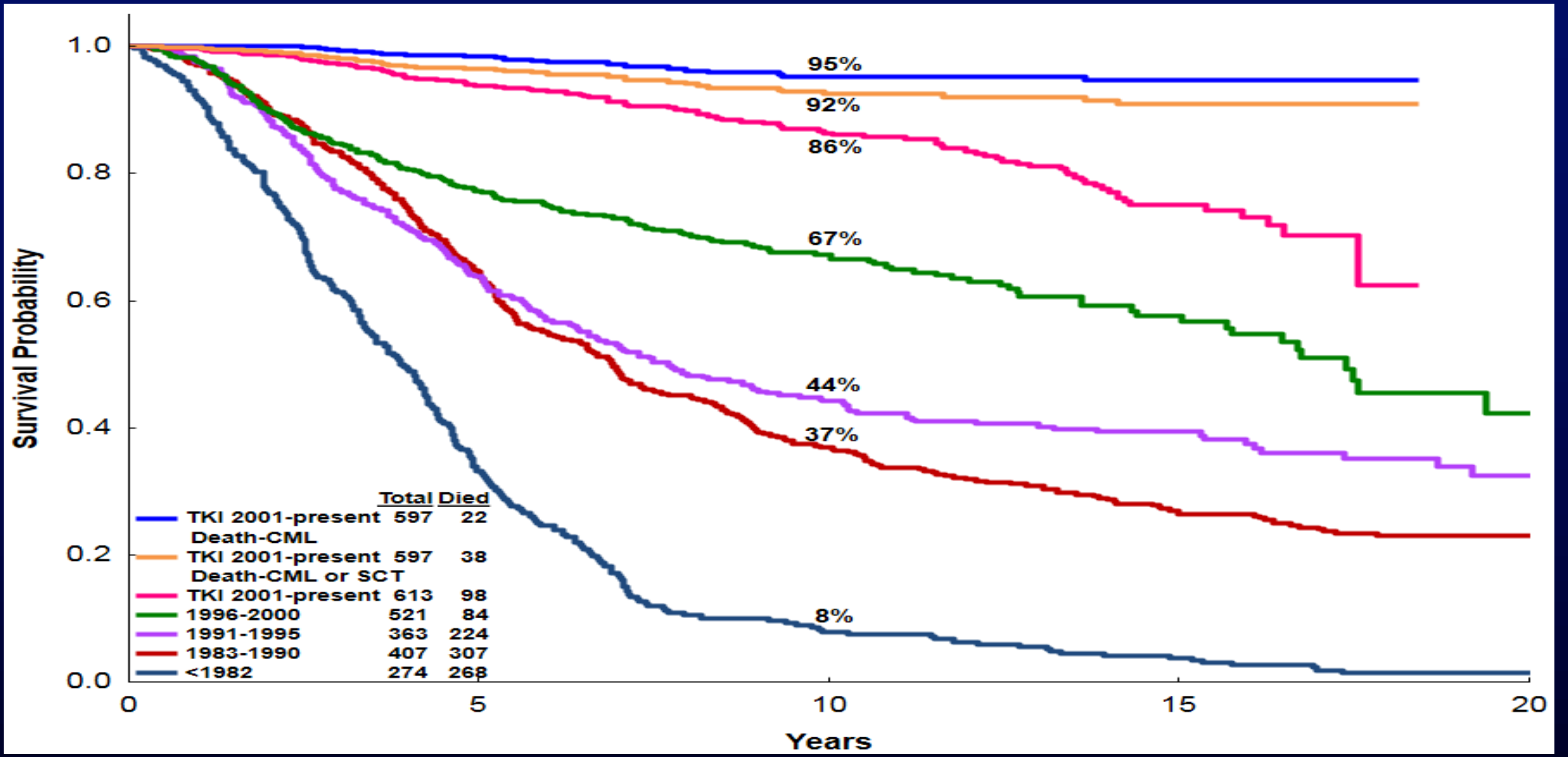
- **Use of TKIs at MTD-1**: Lower doses TKIs (OBD) may be as effective, safer, in both frontline (e.g. dasatinib 50 mg/D) and later lines Rxs (e.g. ponatinib 15-30 mg/D)
- **Use best TKI frontline; ignore cost**: Generic TKIs $500-5,000/yr (imatinib, dasatinib) = better "Rx value"
- **High Failure rate of frontline TKIs = 40%**: Distinguish "failure" as resistance (PCR> 1-10%). **Resistance only 10%/10 years**
- **TKI toxicity = change TKI** : TKIs toxicities= always better to reduce TKI dose, except if prohibitive toxicity
- **Change TKI Rx for PCR levels 0.1-1%**: Do not do so
- **Pursue TFR aggressively** by rotating TKIs for persistent PCR>0.01% to attain TFR: More harm than good
- **NCCN/ENL milestones important**: Not as much
- **If PCR 1-10% = change TKI**: Not needed in older CML; pts may still live normal life in chronic phase

Senapati. Blood Cancer Journal 13:58; 2023. Kantarjian. Lancet Haematology 10: e860-e864; 2023

CML Frontline Therapy – Aims

- Improve survival -- Current 10-year relative survival 92%
- Improve durable deep molecular response (DMR) =↑TFR -- possible
- Reduce short-term and long-term side effects
- Cost of frontline TKI<$40,000/yr for good "treatment value"

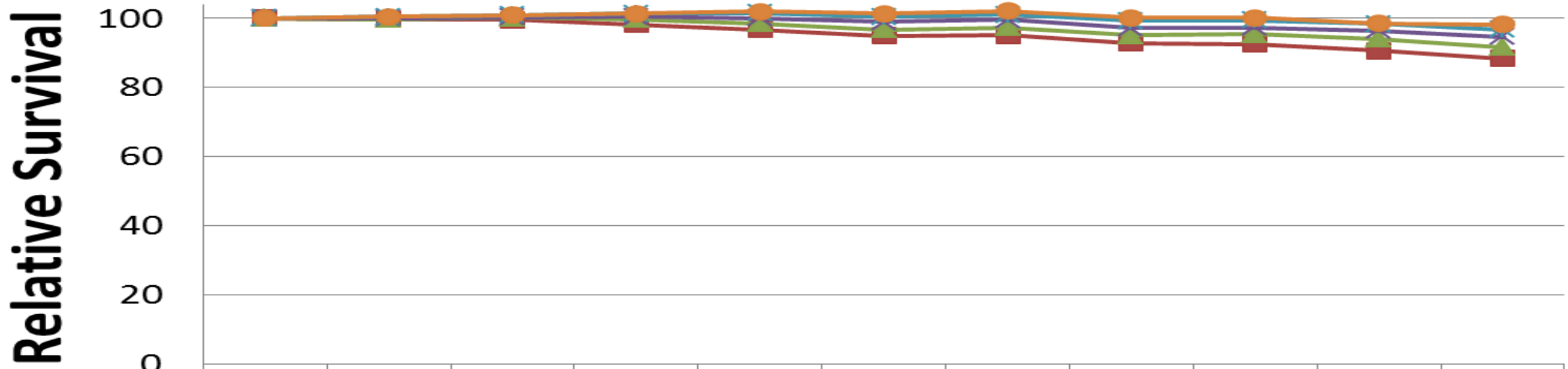
CML. Survival at MDACC 1975 - 2019



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

Therapy of CML in 2025

- Frontline
  - imatinib 400 mg daily
  - dasatinib 100 mg daily (50 mg at MD Anderson)
  - nilotinib 300 mg BID
  - bosutinib 400mg daily
  - asciminib 80 mg daily
- Second / third line
  - nilotinib, dasatinib, bosutinib, ponatinib, asciminib omacetaxine
  - allogeneic SCT
- Other
  - decitabine, peg IFN, omacetaxine (only 2-5days/mo)
  - hydrea, cytarabine, combos with TKIs

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Dose Below MTD vs Optimal Biologic Dose (OBD)

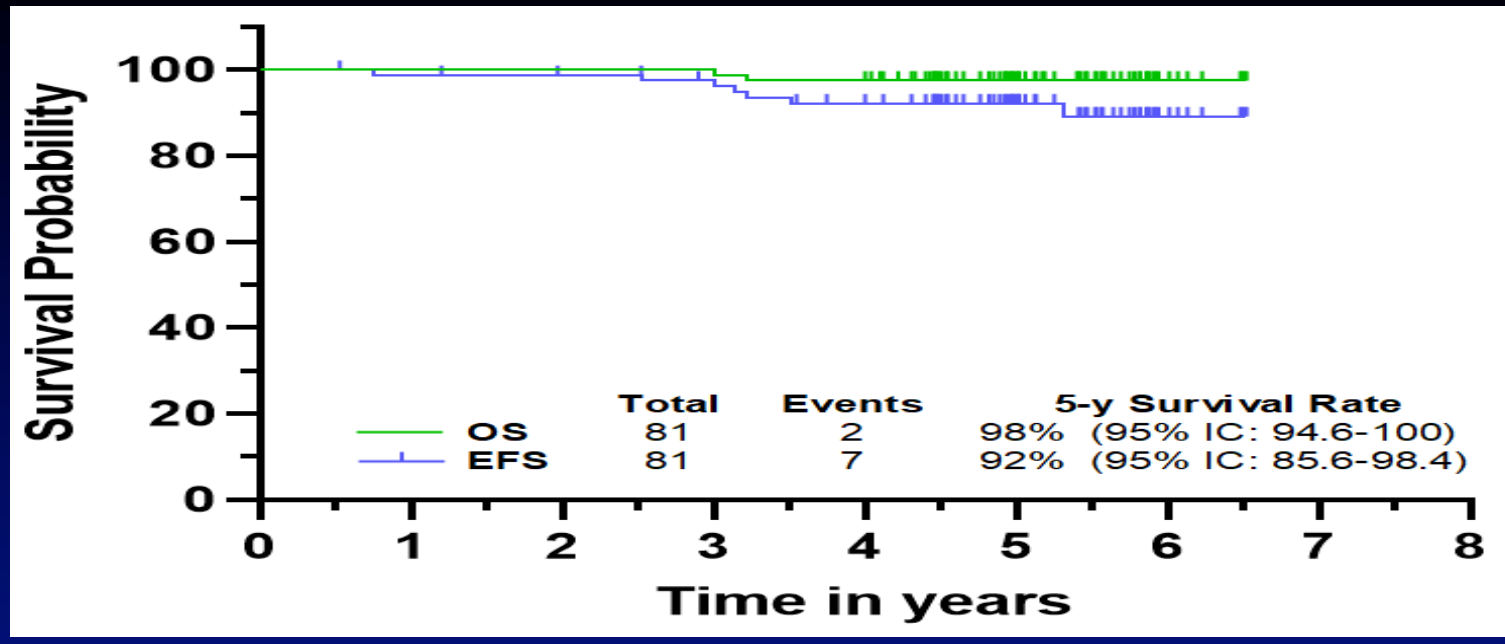
- Most cancer research 1960-2010 used drug dose below MTD in phase 2-3 and in FDA drug approval – Logical then since chemoRx for 3-12 mos; expected serious AEs in < 25%
- With novel targeted therapies, Rx for many years, or life-long = new toxicities with chronic use not anticipated from phase 1-3 studies
- Optimal Biologic Dose (OBD) = dose that maintains efficacy similar to that of dose below MTD, but lowers toxicities significantly, improves compliance, and lowers Rx costs

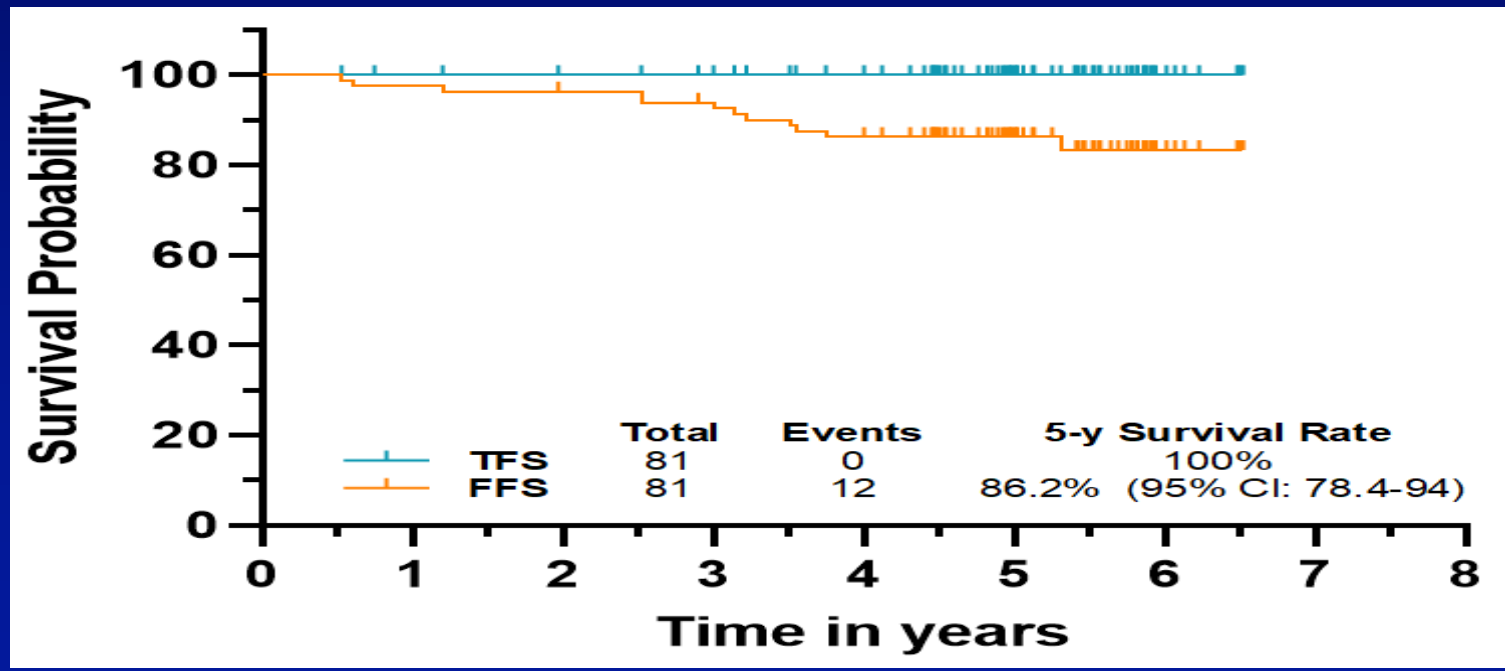
Senapati. Blood Cancer Journal 13:58; 2023.

Kantarjian. Lancet Haematology 10: e860-e864; 2023

Low-Dose Dasatinib Frontline Rx in CML

- 83 patients with newly diagnosed CML-CP Rx with low-dose dasatinib 50 mg daily (March 2016 - April 2018). Median FU 5 yrs
- %5-yr MMR 95%; MR4.5 82%;CMR 70%
- No cases of CML AP or BP
- 2 deaths unrelated to CML
- 5-yr OS 98%
- Only 5 pts (6%) changed to other TKIs for possible suboptimal response or resistance





Gener. CLML 23: 742-748;2023

Dasatinib 70 mg vs 100mg in ND CML. (India)

- 120 pts randomized. Median age 39 yrs (29-50)
- ELTs Low 28%, Int 40%, High 32%

% Parameter	70	100	pValue
3-mos PCR<10%	93	97	NS
6-mos PCR<10%	100	98	NS
6-mos CCyR	97	82	NS
6-mos MMR	33	37	NS
6-mos DMR	5	13	NS
12 mos CCyR/MMR/DMR	100/81/28	98/71/27	NS
↓ PLTS	15	43	.029
Effusion	5	10	-

EHA 2025. S168

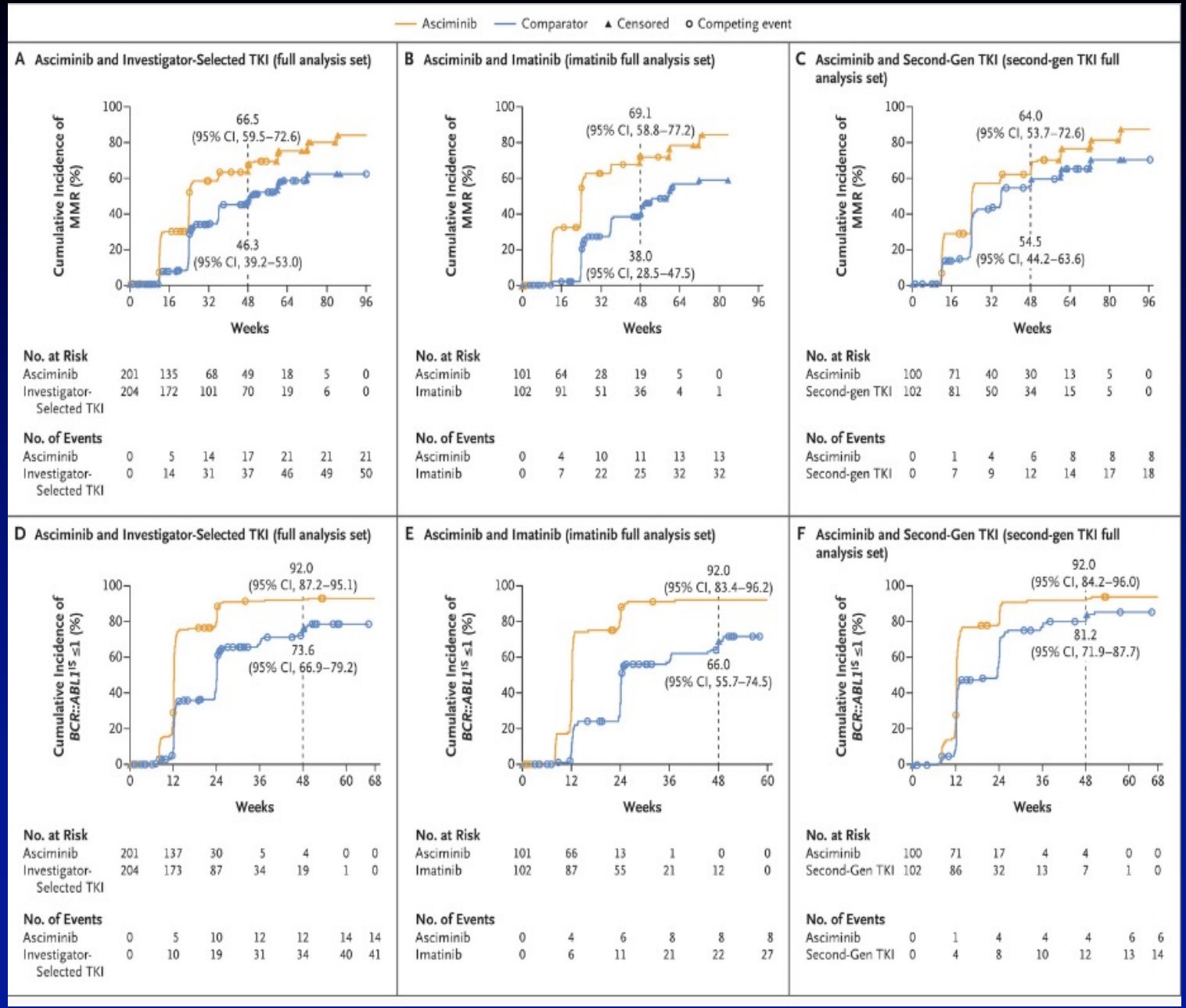
TKIs OBD vs MTD

TKI	MTD (FDA approved) Frontline/ later line	OBD	Lowest Effective
Imatinib (mg/D)	400/400	400	100-300
Dasatinib (mg/D)	100/100	50	20
Bosutinib (mg/D)	100-200-300-400/500	400	100-300
Nilotinib (mg BID)	300 BID/400 BID	300 BID	150-200/D
Ponatinib (mg/D)	---/45	30; 45 if T315I	7.5-15 (once PCR<1%)

Asciminib vs TKI Choice in Newly Dx CML

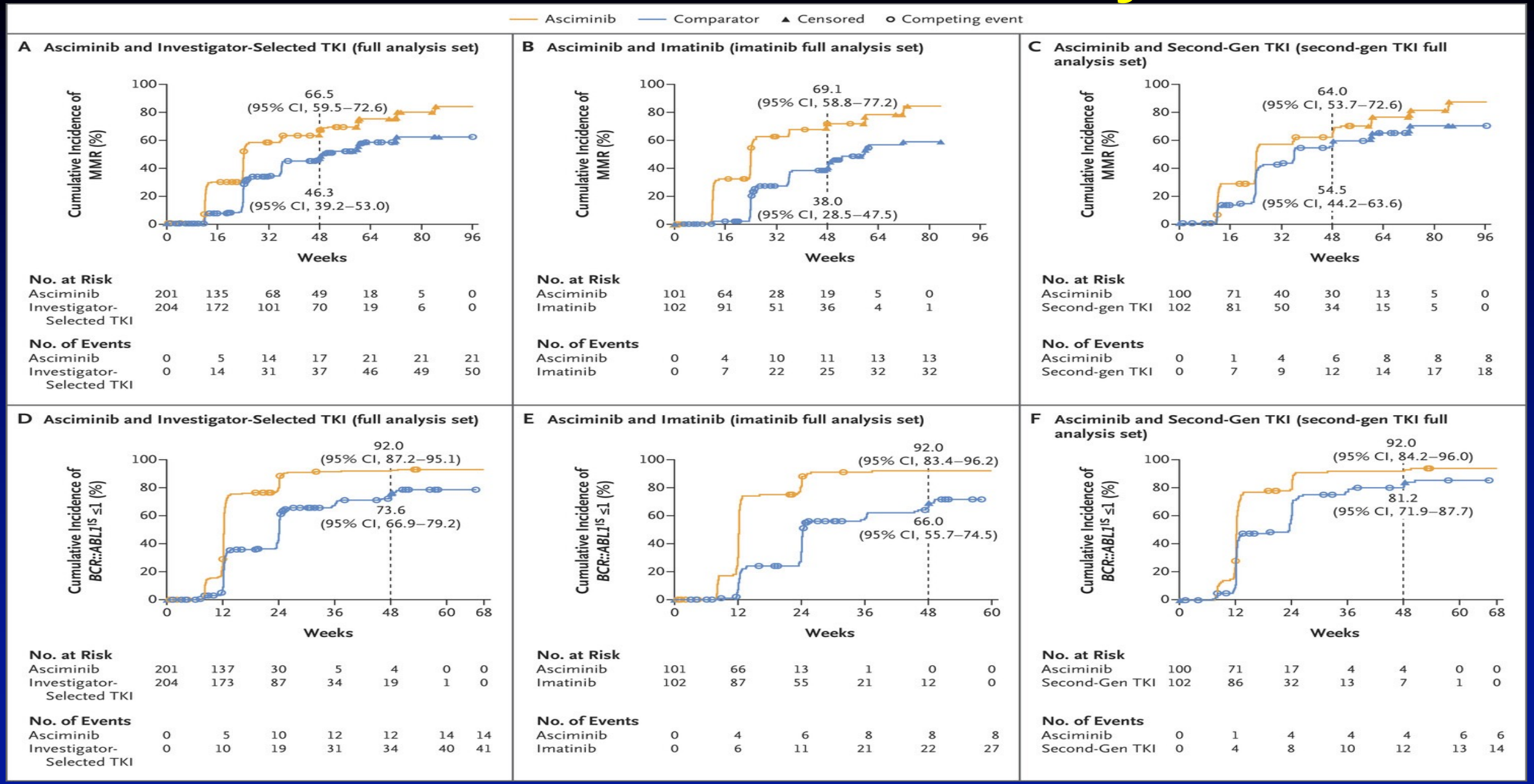
- 405 pts randomized (1:1 and 1:1) to asciminib (n=201) or Investigator Choice TKI (n=204; 50% imatinib)

Parameter	% 48-wk MMR	P value
ASCI vs IMA	68 vs 40	<.001
ASCI vs 2nd TKI	66 vs 58	NS
ASCI vs TKI choice	68 vs 49	<.001



Hochhaus. NEJM June 4; 2024

Asciminib vs TKI Choice in Newly Dx CML



Hochhaus. NEJM June 4; 2024

Asciminib Frontline Rx in CML (ASC4 FIRST)

- 405 pts --201 pts randomized to ASCI, 204 to investigator-selected TKI. Median FU 16 mos
- Side effects lower with ASCI; no comparison to 2nd GEN TKIs; no OS data; DC rates on IMA and 2nd GEN higher than previous (2.5%/yr); mutation/resistance rates?

Parameter	ASCI	IS-TKI	IMA	p value
% 1-yr MMR	67.7	49.0	-	<.001
% 1-yr MMR	69.3 66	- 58	40.2	<.001 NS
% AOEs	1	1	-	-
% Rx DC	4.5	8.2-11.9	11.1	-
% Rx ongoing	86	75	62	-

Hochhaus. NEJM 391: 885-898; 2024. Cortes. Blood 144: abst 475; 2024

Best Frontline TKI Therapy Today

- Generic imatinib if survival is the endpoint; $500x30 yrs = $15,000 total cost for lifetime Rx
- Generic dasatinib 50mg QD if *earlier* TFR is the endpoint. Dasatinib 50 mg/D = $3,850/yr
- Generic dasatinib 50-100mg QD if high risk Sokal
- Once patient achieves good molecular response, can reduce any TKI to lower dose levels

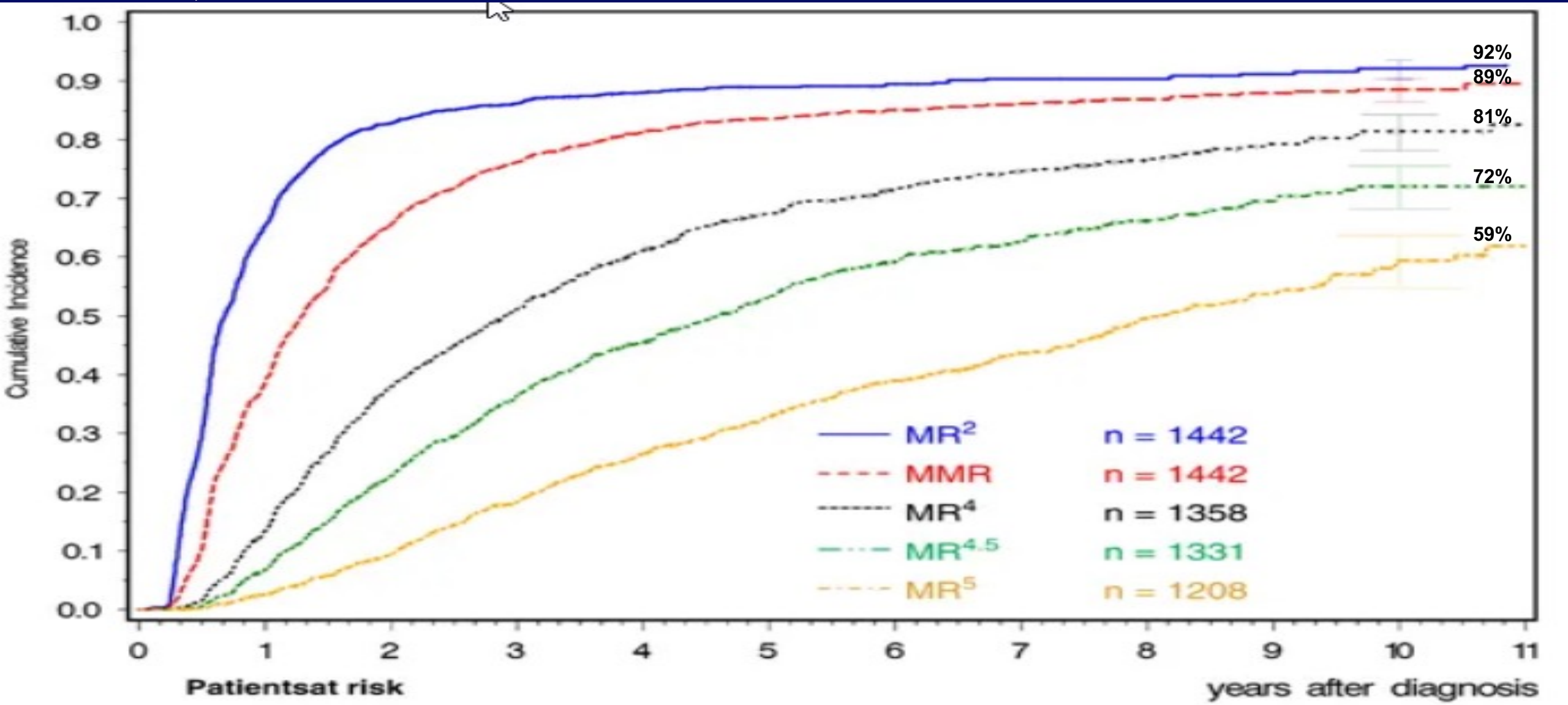
Senapati. Blood Cancer Journal 13:58; 2023.

Kantarjian. Lancet Haematology. Online August 28, 2023

Improving TFR Rates in CML-CP

CML IV–Molecular Response With Imatinib

- 1551 pts newly Dx CML-CP randomized to imatinib 400, imatinib 800, imatinib + IFN, imatinib + ara-C, or imatinib after IFN



Kalmanti. Leukemia 29: 1123; 2015.

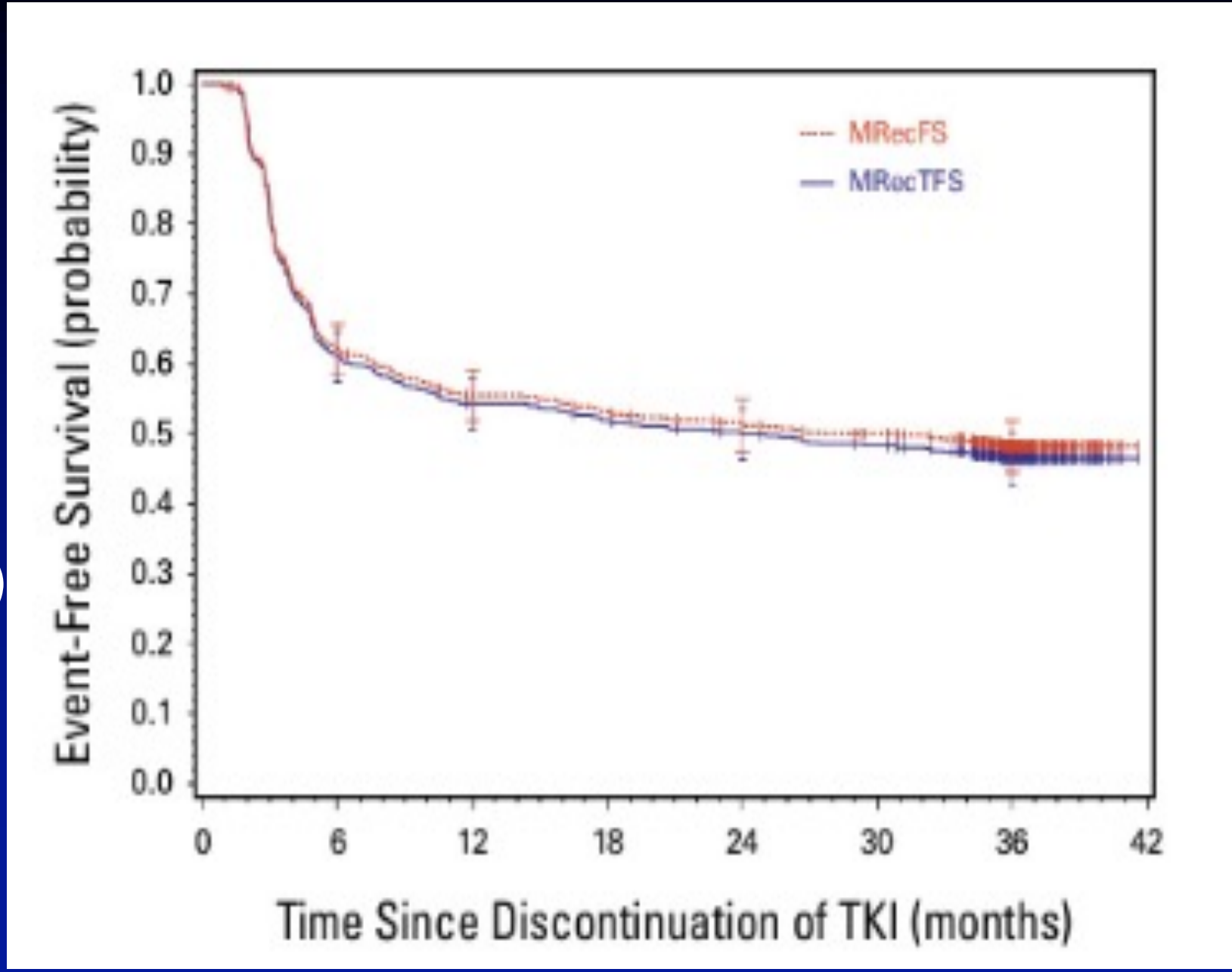
Deep Molecular Response and Rx-Free Remission

- 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

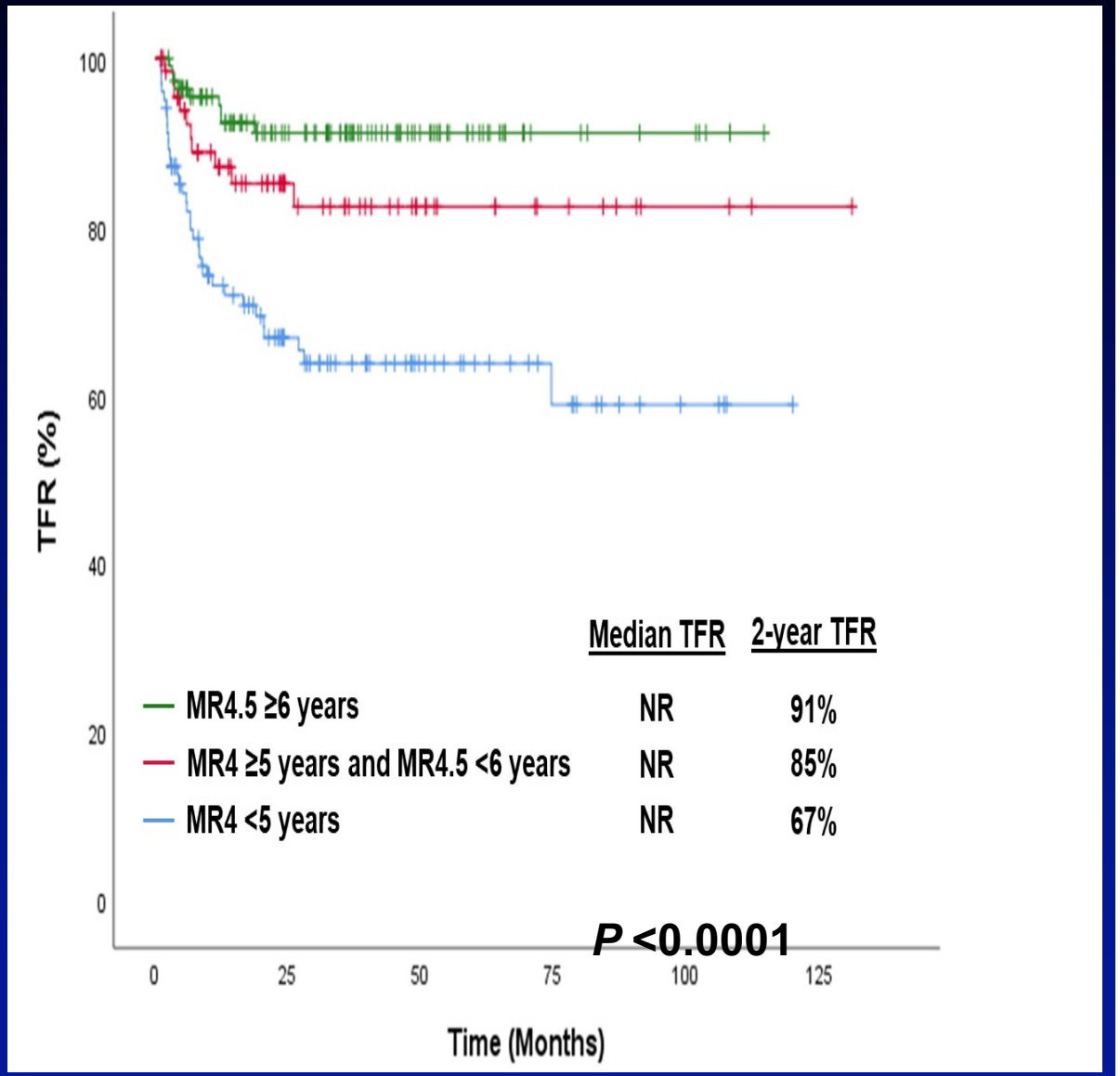
TFR in CML (EURO-SKI)

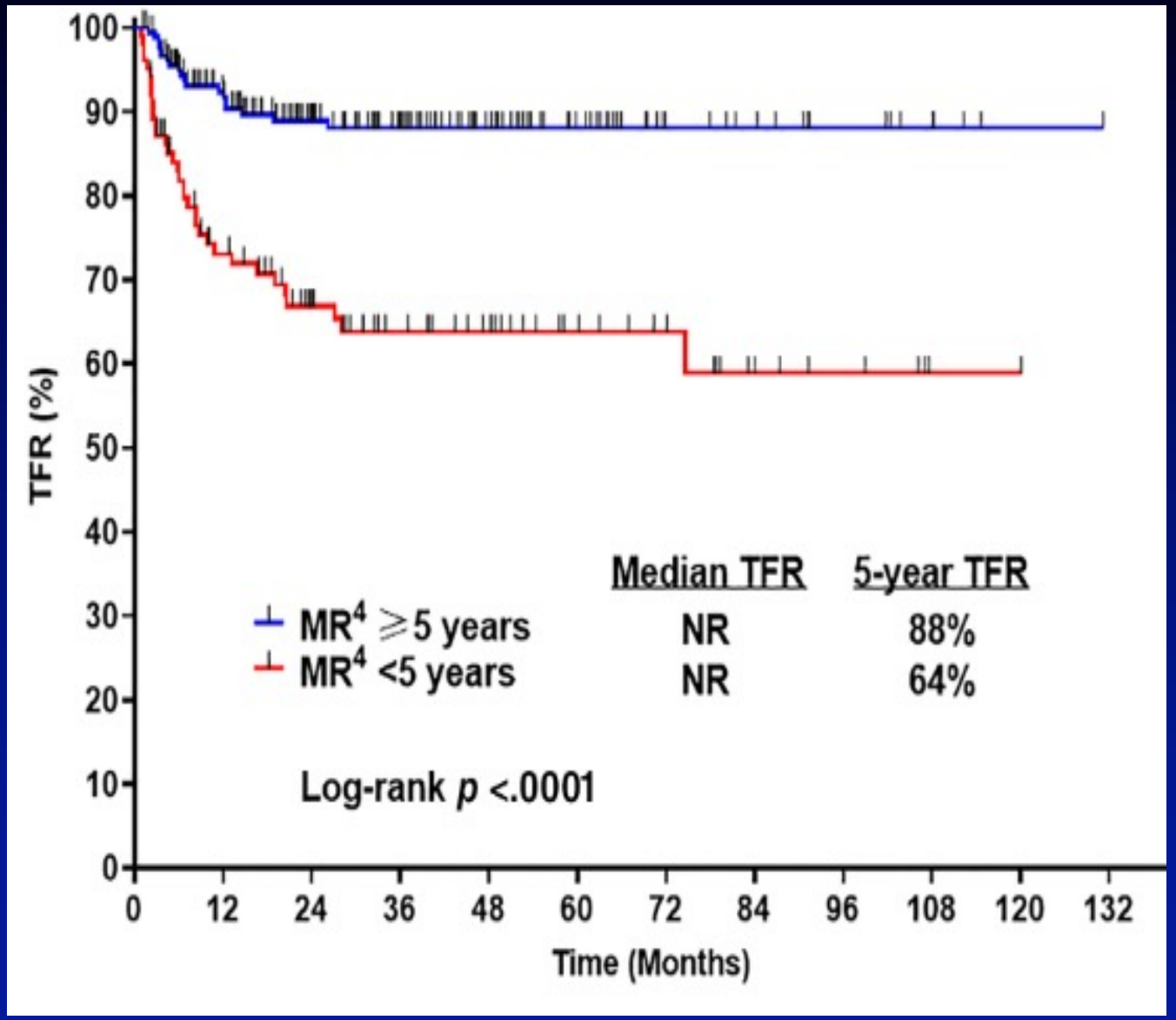
- 728 pts on TKI for 3+ yrs and DMR (*BCR::ABL1* < 0.01%) for 1+ year had Rx DC to attempt TFR
- 3-yr TFR rate 46%
- MVA: Duration of TKI Rx, peripheral blasts at Dx, e14a2 (= better)



Mahon. J Clin Oncol 42: 1875-1880; 2024

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





Haddad . Am J Hematol. 2022 ;97:856-864

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Senapati. Blood Cancer Journal 13:58; 2023. Kantarjian. Lancet Haematology 10: e860-e864; 2023

Rx of CML Post TKI Toxicities

PS-- Always adjust TKI dose before considering change		
Frontline TKI	**Second line TKI**	**Third+ line TKI**
Imatinib	Dasatinib Bosutinib Nilotinib	Ponatinib 15-30 mg/D Asciminib 40 mg BID Allo SCT, HMAs, LD araD, HU, etc
Dasatinib	Bosutinib Nilotinib Imatinib	As above
Nilotinib	Dasatinib Bosutinib Imatinib	As above

Prohibitive Toxicities Needing Change of TKI

- Recurrent pleural effusions
- Pulmonary hypertension
- Arterio-occlusive or vaso-occlusive events
- Pancreatitis
- Neurologic problems (dementia-like, Parkinson)
- Immune-related events: pneumonitis, myocarditis, hepatitis, nephritis
- Bosutinib-associated enterocolitis

Senapati. Blood Cancer Journal 13:58; 2023

CML. Response Milestones and MDACC Recommendations in Frontline Rx (*BCR::ABL1* IS)

Time (mo)		Response	
		Consider TKI change	Continue same TKI
3		No CHR; Ph 100%	CHR
6		Imatinib Rx; > 10% (no change if 2nd GEN TKI)	≤ 10%
12	and beyond	Imatinib Rx, > 1% (2nd GEN TKI, wait longer if 1-10%; or if older) resistance mutations; high risk ACAs	≤ 1%; MR2

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, i.e., failure > 2 TKIs); 200 mg BID for T315I but data minimal
- Omacetaxine, decitabine/azacitidine, cytarabine, hydrea – can be added to TKIs
- Allogeneic SCT– underutilized, highly curative, cost-effective, one-time therapy

Rx of CML Post Frontline TKI Resistance

PS – Always check for mutations to direct TKI Rx as indicated; if not

Frontline TKI	Second line TKI	Third+ line TKI
Imatinib	Dasatinib Bosutinib Nilotinib (do not rotate 2nd GEN TKIs if resistance)	Ponatinib Asciminib Allo SCT, others
Dasatinib Bosutinib	Ponatinib -- 30 mg till PCR<1% then 15 mg/D --T315I – 45 mg/D till PCR<1% then 15 mg/D	Asciminib Allo SCT, others

Asciminib Second Line Rx in CML

- 101 pts. Prior DASA 45%, NILO 10%, BOSU 5%. On TKI > 1 yr 66%. Reason DC: no efficacy 56%, intolerance 44%. BR::ABL1 1-10% 31%, > 10% 30%

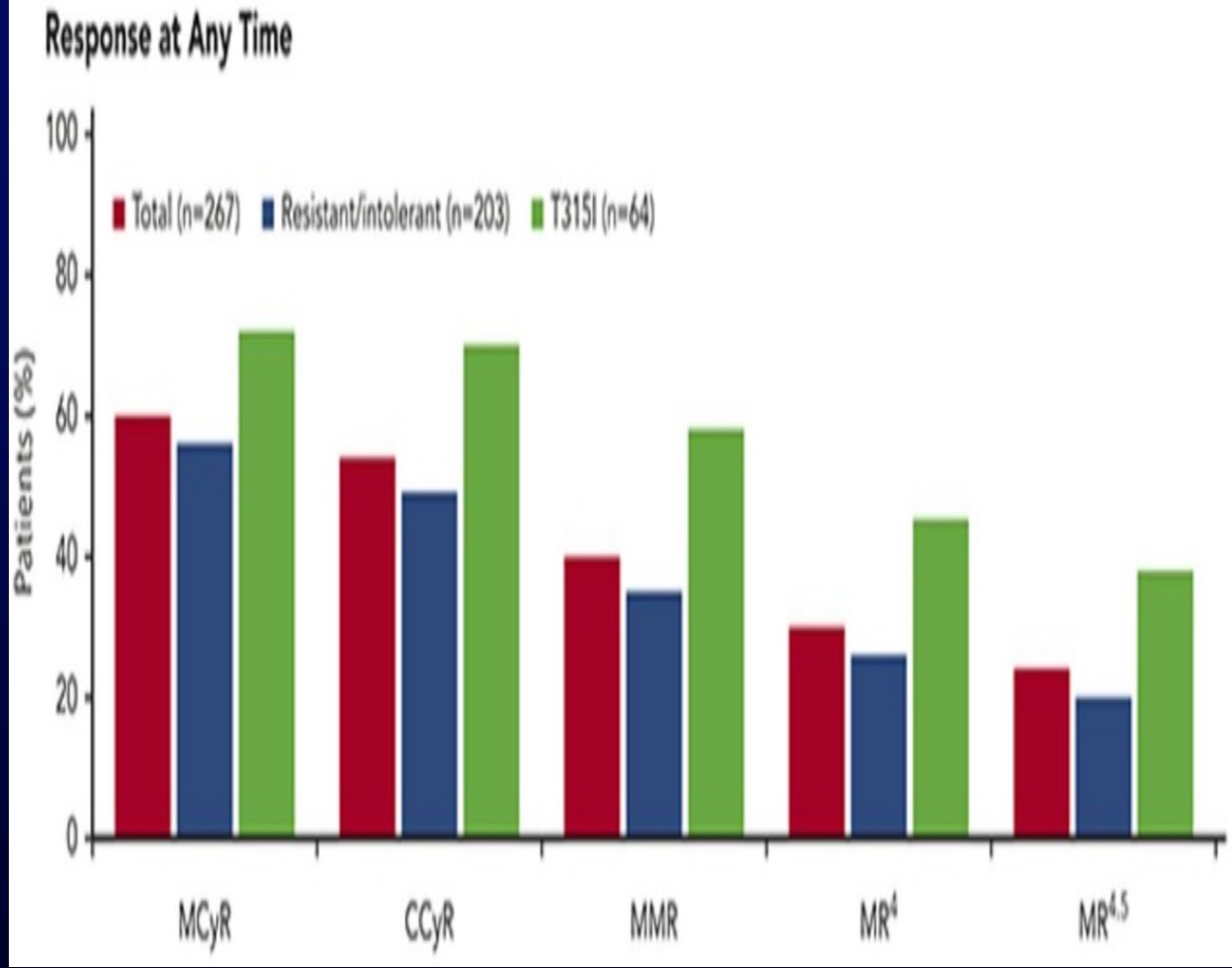
Parameter	Percent
6-mo MR2	82
6-mo MR3	44
-Prior intol.	58
-Prior no efficacy	35

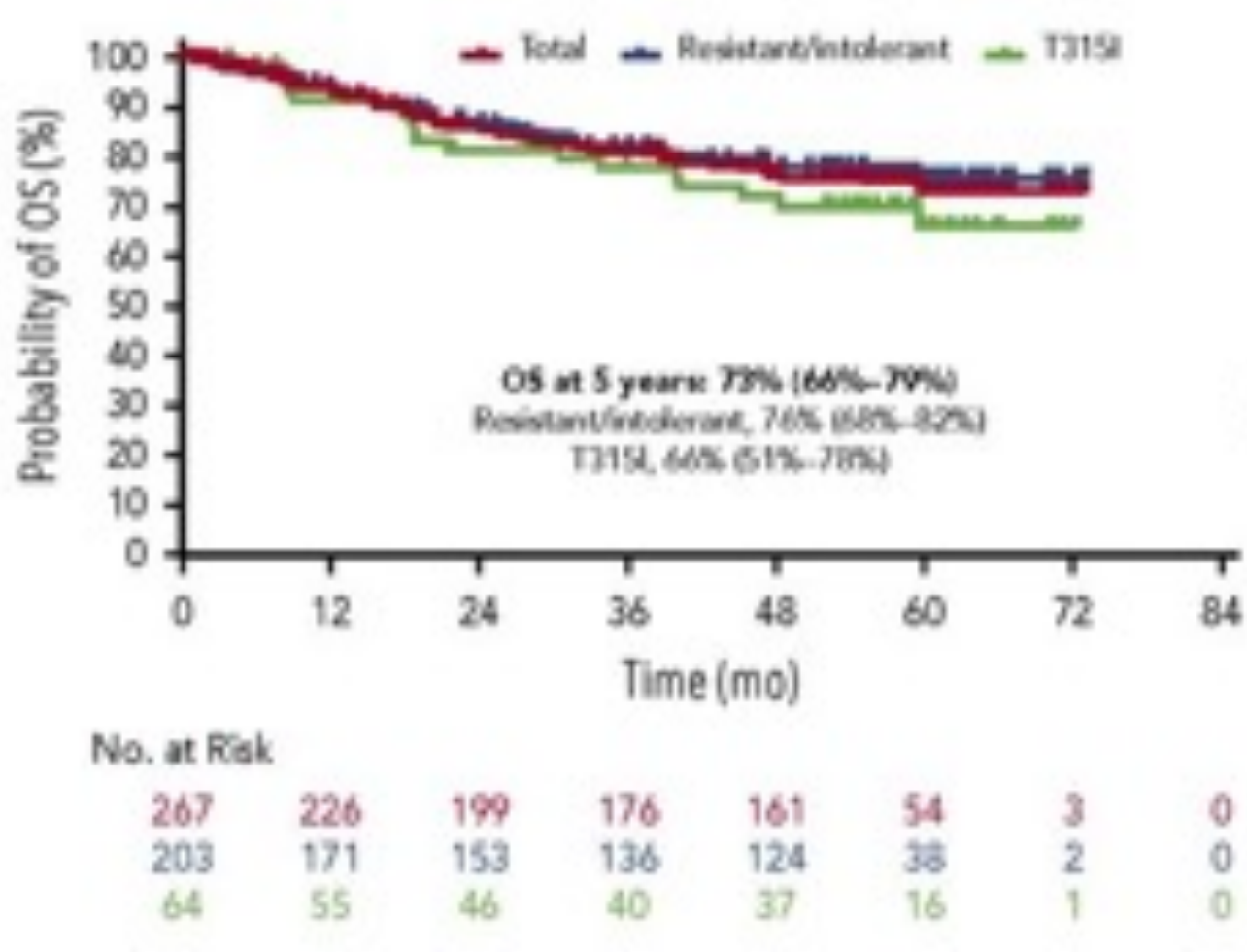
- AEs G3+: HT 9%, plts↓ 7%. Rx DC 4

Andorsky. JCO 43 (Suppl 16): abst 6516; 2025

Ponatinib in CML—CP (PACE)

- 449 pts Rx; 270 in CP, failure 2+ prior TKIs = 3rd+ line therapy
- CG major 60%, MMR 40%, 5-yr OS 73%





Cortes. Blood 132: 393; 2018

CML – Later Line Therapy

- Olverembatinib
- Asciminib (STAMPi)
- TGRX-706 (STAMPi)
- TERN-701 (STAMPi)
- ELVN-001

Leukemia Questions?

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