

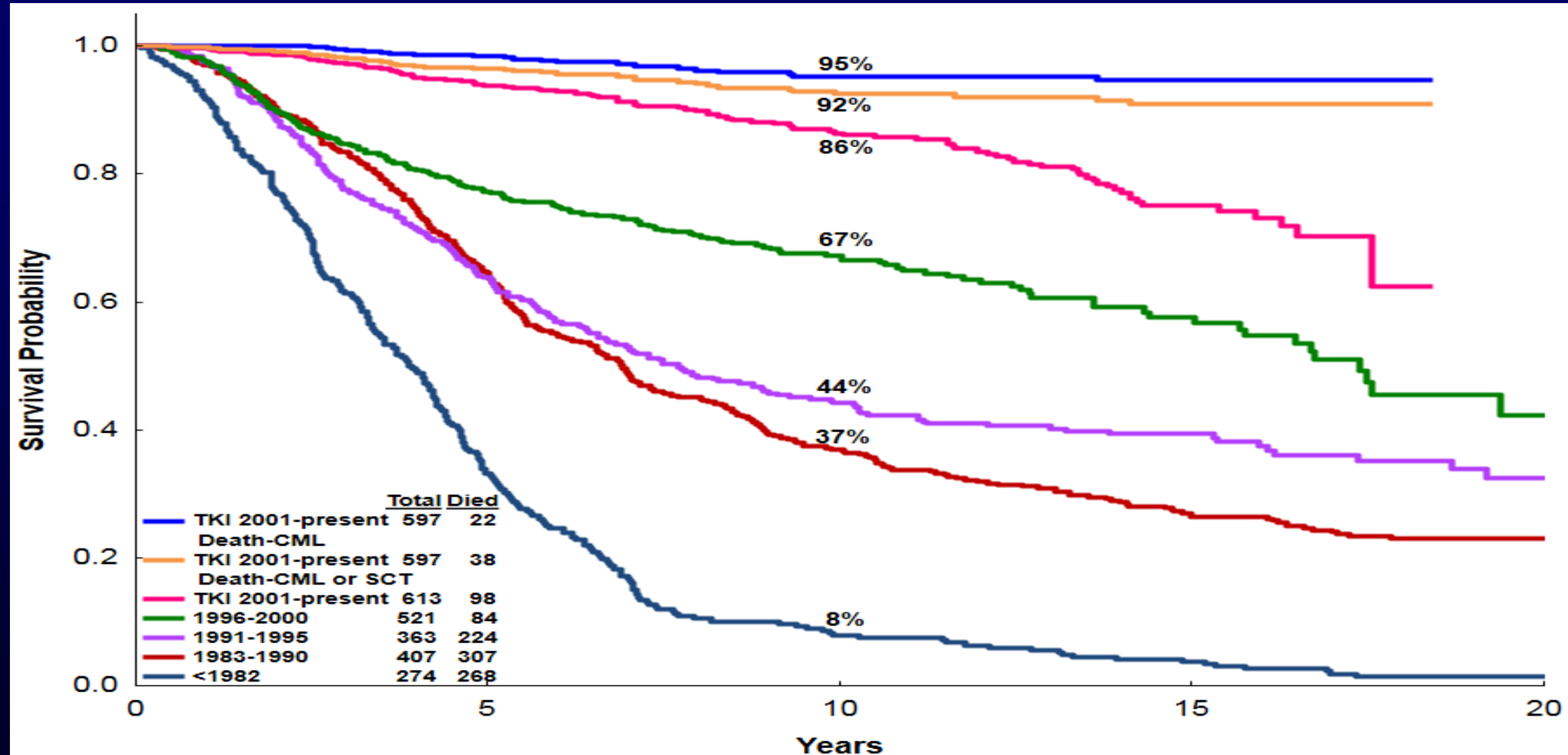
CML and Ph-positive ALL in 2025: What is new at MDACC?

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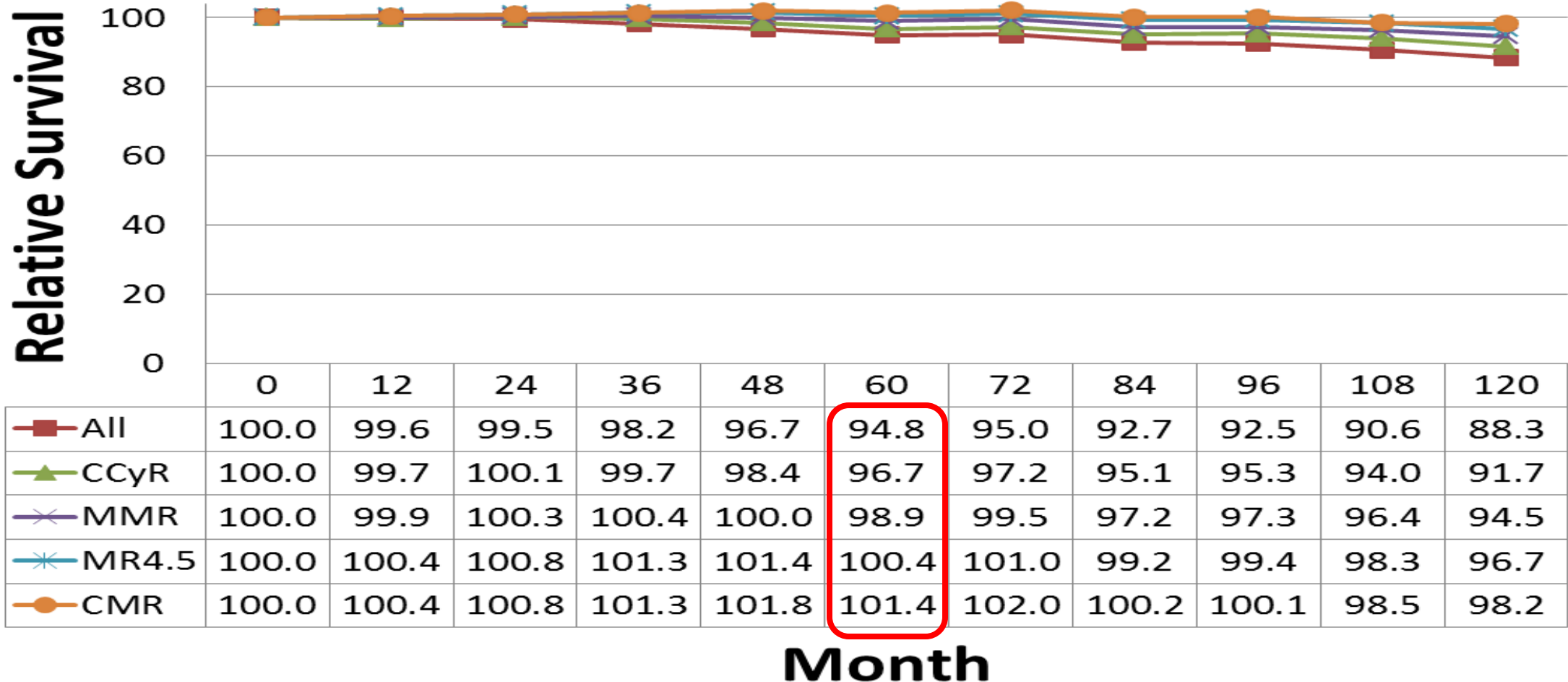
**The University of Texas MD Anderson
Cancer Center, Houston, TX**

CML. Survival at MDACC 1975 - 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]



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

How Do I Treat Frontline CML-CP in 2025

- Generic imatinib 400 mg daily (use CostPlus or similar; < \$50/month); lower than out-of-pocket cost on insurance
- Dasatinib 100 mg daily (FDA/SOC); 50 mg daily equally effective and half price
- Bosutinib 400 mg daily (200-300-400 escalation to avoid GI/early DC)
- Nilotinib 300 mg BID; lower to 150 mg BID or 200 mg daily once in MR2/MMR to avoid AOE
- Asciminib 80 mg daily
- Any of above 5 good if endpoint is survival
- High risk Sokal – 2nd GEN TKIs better
- If TFR is important (younger CML) – 2nd GEN TKIs
- TKI choice also depends on : 1) **age** (e.g. dasatinib 20 mg daily if age 70+); 2) **cost** (generic imatinib affordable even to poorest); 3) **Rx aim** (survival vs TFR); 4) **co-morbidities** – eg avoid dasatinib if COPD, PH; avoid bosutinib if GI/hepatic/renal issues; avoid nilotinib if history of AOE or diabetes; etc

5 Factors Determine Frontline Rx in CML: Age, Rx Aim, Cost, CML Risk, Comorbidities

Factor	Category	TKI
Age and Rx aim	-- Younger/TFR	Dasatinib 50 mg Bosutinib 200-400 mg
	-- Older/Survival	Imatinib 400 mg
Cost	Cannot afford out of pocket expenses	Imatinib generic (Cost Plus \$500/yr)
CML risk	High Sokal	Dasatinib, bosutinib
Comorbidities	AOEs, DM, COPD, renal, pancreatitis	Select TKI that causes least problems

CML Frontline Therapy

- Up to 17, and 9 main studies compared new-generation TKIs to imatinib frontline: ENESTnd (nilotinib), DASISION (dasatinib), BFORE (bosutinib), EPIC (ponatinib), ASC\$ FIRST (asciminib)
- All showed higher rates of favorable early surrogate endpoints: CGCR, MMR, MR4.5, ↓ AP/BP; **none has shown survival benefit**
 - Very good salvage options**
- Increased uncommon toxicities with newer TKIs: PAOD-MI-TIA, pancreatitis, pleural effusions; HT and pulmonary HT, ↑ BS, vasospastic reactions, ↑ non-CML deaths

CML Failure and Rx Changes

- CML failure from 1)TKI side effects, or 2) resistance
- If side effects, adjust TKI dose before changing to 2nd TKIs
- If resistance, check BCR:: ABL1 mutation and decide on 2nd or 3rd generation TKI based on mutations, prior TKIs, co-morbidities, etc
- Resistance = CG relapse (PCR >1%, or >0.5% consistently)

CML. Criteria for Failure and Suboptimal Response to Frontline TKI – ELN 2020

Time (mo)	Response		
	Failure	Warning	Optimal
3	BCR-ABL1 >10% if confirmed within 1-3 months	BCR-ABL1 >10%,	BCR-ABL1 ≤10%
6	BCR-ABL1 >10%	BCR-ABL1 >1-10%	BCR-ABL ≤1%
12		BCR-ABL1 >0.1-1%	BCR-ABL1 ≤0.1%
Any time	>1%, resistance mutations, high-risk ACA	BCR-ABL1 >0.1-1% Loss of ≤0.1% (MMR)	BCR-ABL1 ≤0.1%

- For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR4)
- A change of treatment may be considered if MMR is not reached by 36–48 months

Sequence of Frontline and Salvage Strategies in CML

	Choice of TKI	
Frontline Rx	Dasatinib 50mg/D	Imatinib 400mg/D
Salvage for Resistance	-Ponatinib 45mg/D if T315I; 30mg/D if no guiding mutations – reduce to 15 mg/D when PCR<1%	-Dasatinib 50→100mg/D or bosutinib 300-500 mg/D -if failure then ponatinib
Salvage for toxicities	Bosutinib 300-500mg/D	Dasatinib or bosutinib

- Avoid use of nilotinib frontline because of 10-yr CV problems 24+%
- Always adjust TKI dose if side-effects before considering change of TKI

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/azacitidine, cytarabine, hydrea – can be added to TKIs
- Allo SCT

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*

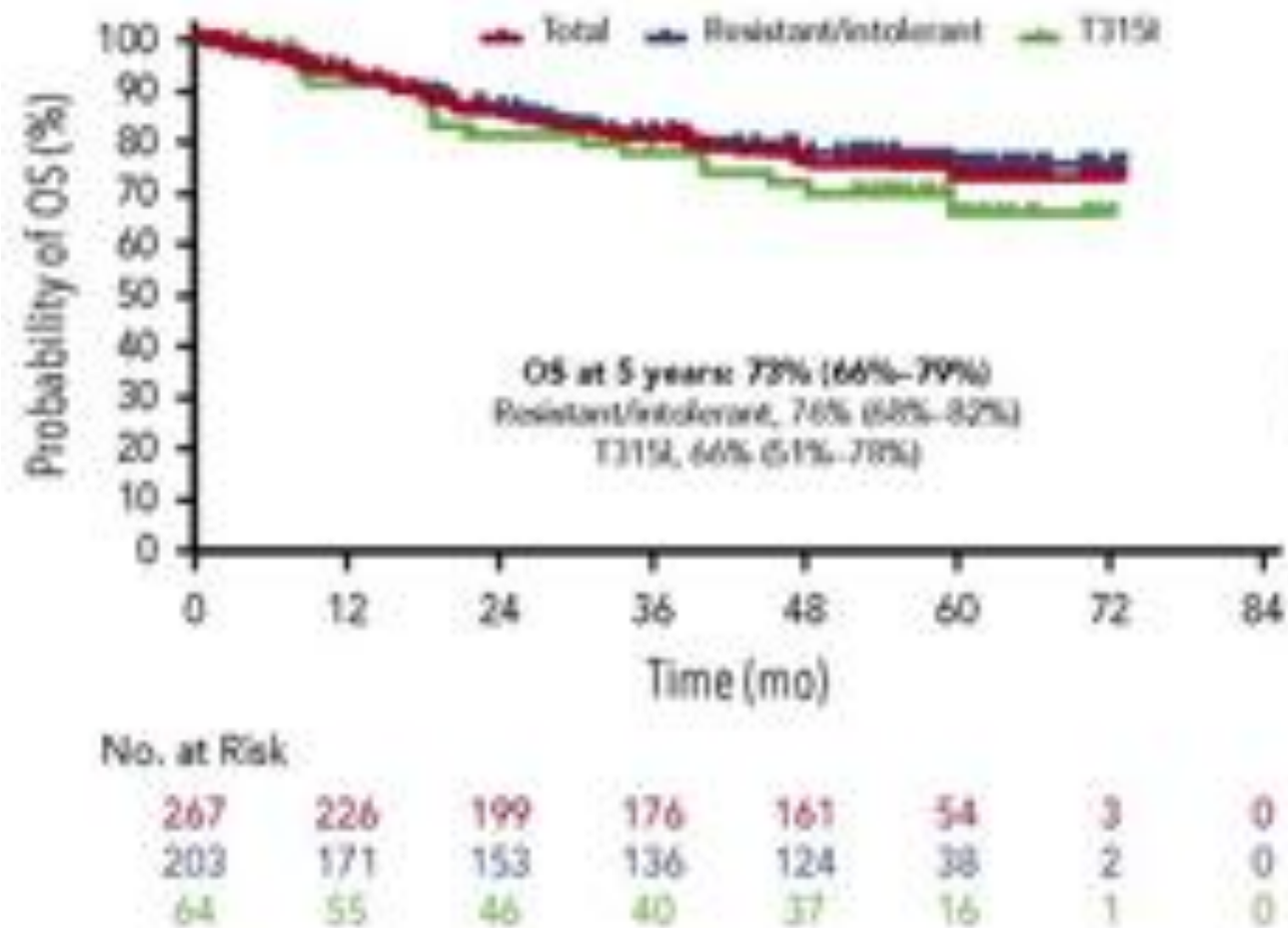
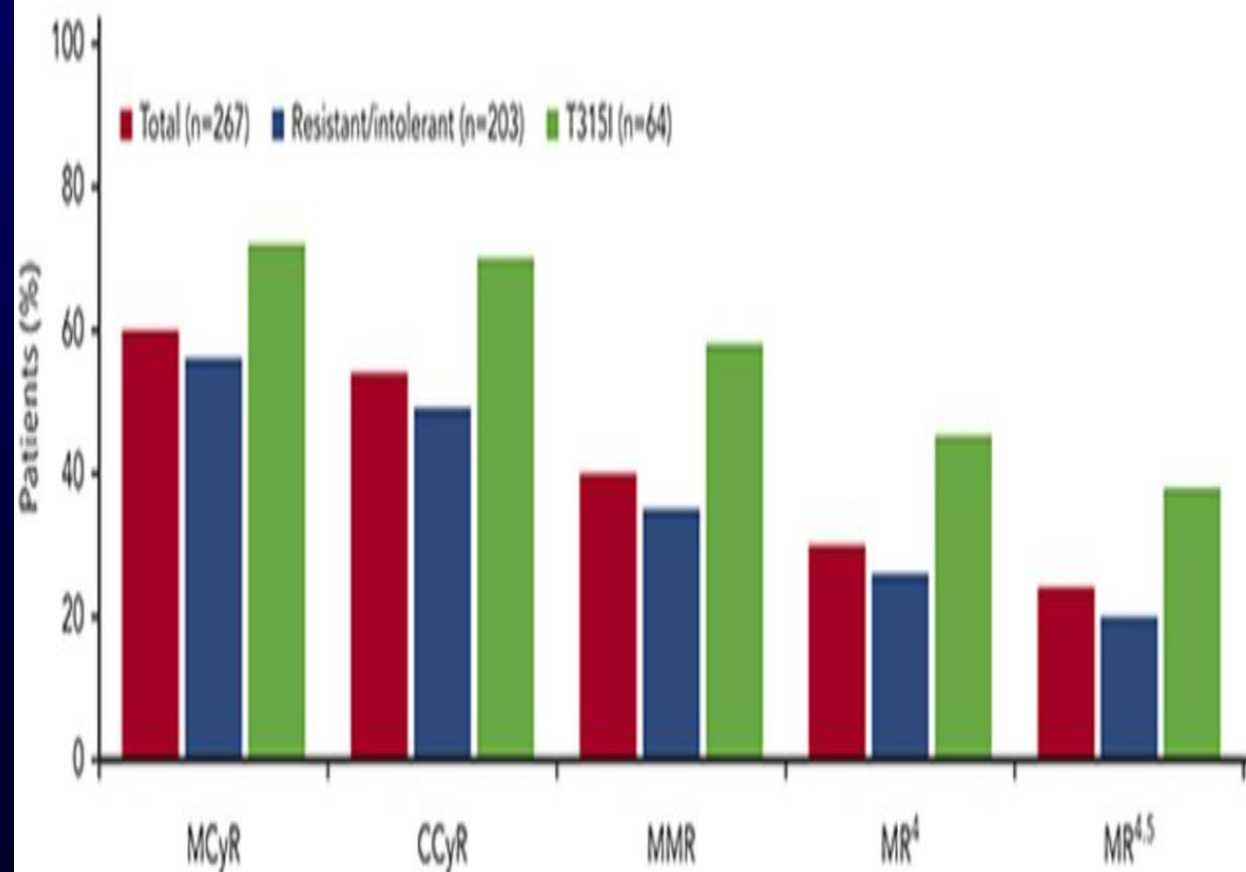
*Includes imatinib-intolerant patients. NR, not reported.

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].

Ponatinib in CML—CP (PACE)

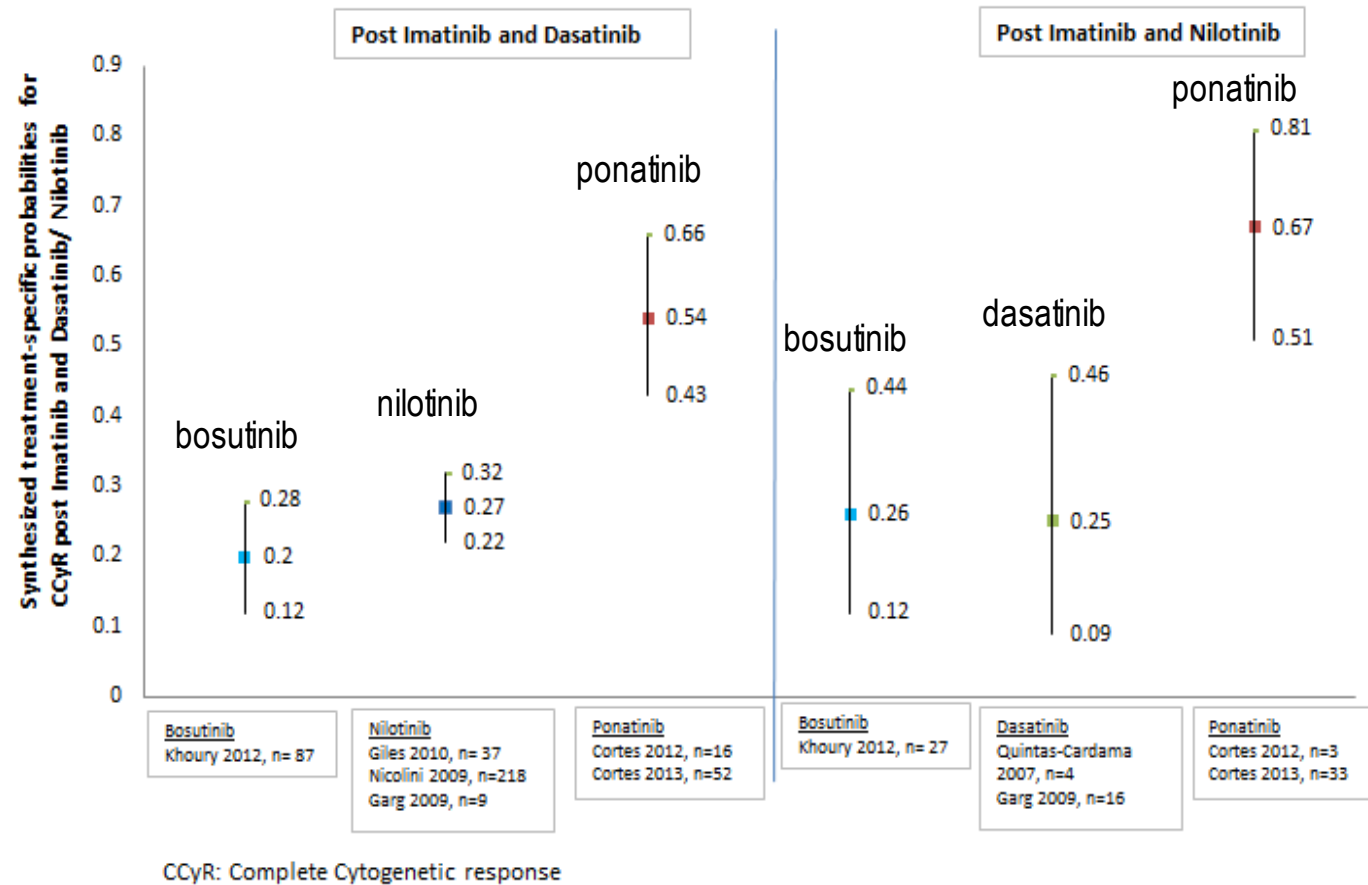
- 449 pts Rx; 270 in CP
- CG major 60%, MMR 40%, 5-yr OS 73%

Response at Any Time



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



OPTIC-Ponatinib Dose Range

- 283 pts in CML CP resistant or intolerant to 2+ TKIs; randomized to ponatinib starting dose 45, 30, 15mg/D. All reduced to 15mg/D once $\text{PCR} \leq 1\%$ (CGCR)

% PCR $\leq$ 1% 12 mos	45-15 (n=91)	30-15 (n=90)	15 (n=88)
Overall	48	34	24
No mutations	41	36	26
T315I	60	25	6
Other	53	43	33
$\leq$ 2 TKIs	48	42	26
3 + TKIs	49	30	22
% severe arterio-occlusive disease	0-4	3-4	0

Ponatinib in T315I-Mutated CML-CP (OPTIC)

- 283 pts; 67 with T315I+ CML-CP, resistant to 2+ TKIs
- Randomization to PONA 45, 30, 15mg ID; reduce to 15mg/D once MR2

Parameter	45-15	30-15	15-15
% MR2			
T315I	64	25	16
Overall	60	41	40
% 4-yr OS			
T315I	86	70	75
Overall	88	86	88
%TE-AOES	8	14	5

- Conclusion—In T315I-mut CML, ponatinib 45mg/D better and reduce to 15mg once MR2

Adjusted-dose Ponatinib in CML-CP (PACE; OPTIC)

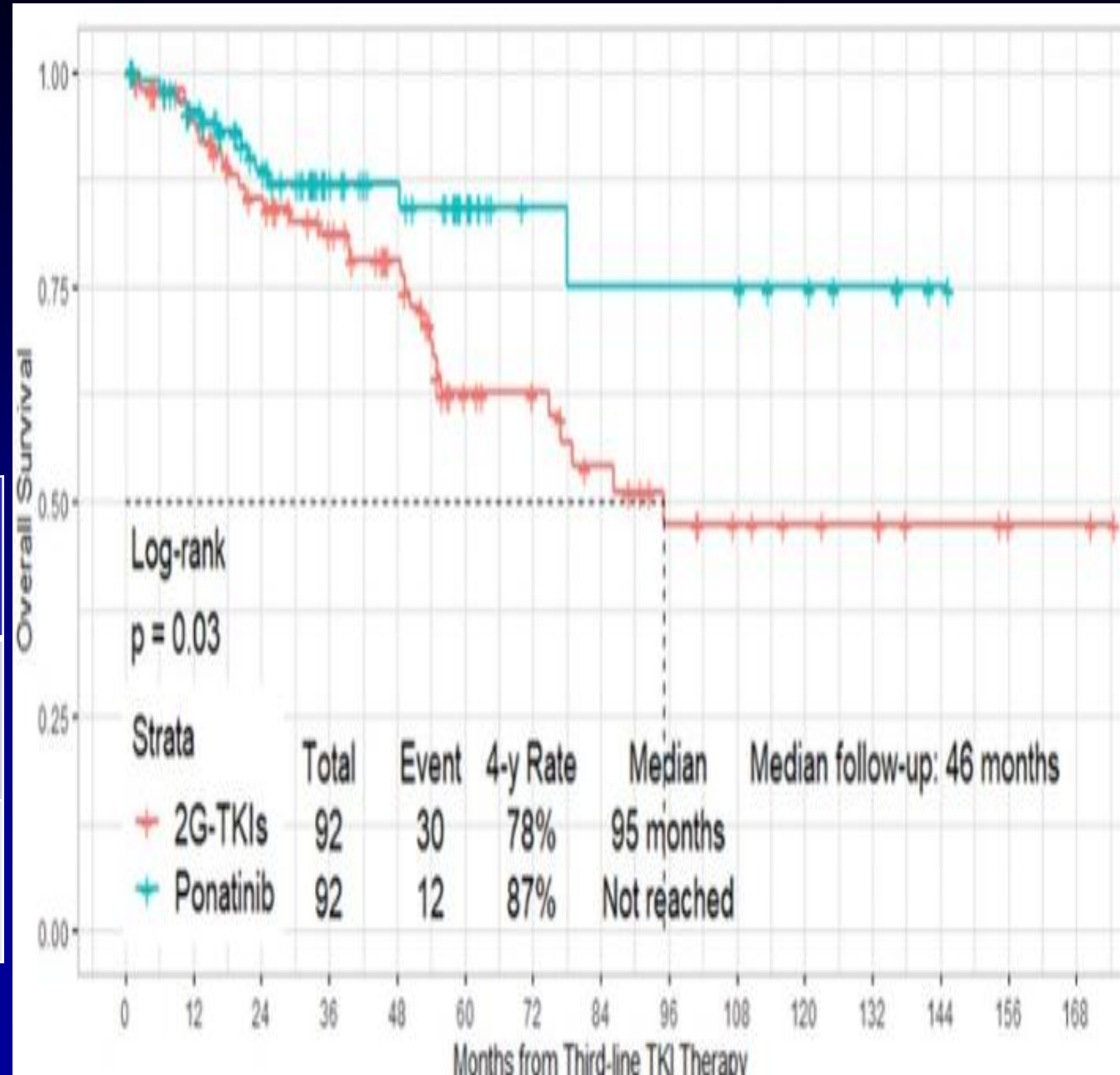
- 364 pts—PACE 270 (resist +intol), OPTIC 94 (all resist or T315I)
- PACE—45mg; adjust for AEs
- OPTIC 45mg; reduce to 15mg in MR2 (PCR<1%)
- Prior 2+TKIs 93-99%; 3+TKIs 53-60%

Parameter	PACE	OPTIC
2-yr MR2	52	56
2-yr PFS	68	80
2-yr OS	86	91
Median time on Rx	12.6	19.5
Exposure-adjusted TE-AOEs/100 pts-yrs	16	7.6

Third-Line TKI Therapy in CML Chronic Phase

- 354 pt in CML-CP Rx with 3-L TKI : 204 from MDACC, 63 from PACE, 87 from OPTIC
- 3-L Rx: dasatinib 69; nilotinib 64; bosutinib 40; ponatinib 181 (51%)
- PCR 16% at time of 3-L Rx
- MVA—Ponatinib favorable

Outcome	Ponatinib	2GN TKI	p value
% 4-yr PFS	75	58	<0.001
% 4-yr OS	87	78	0.03



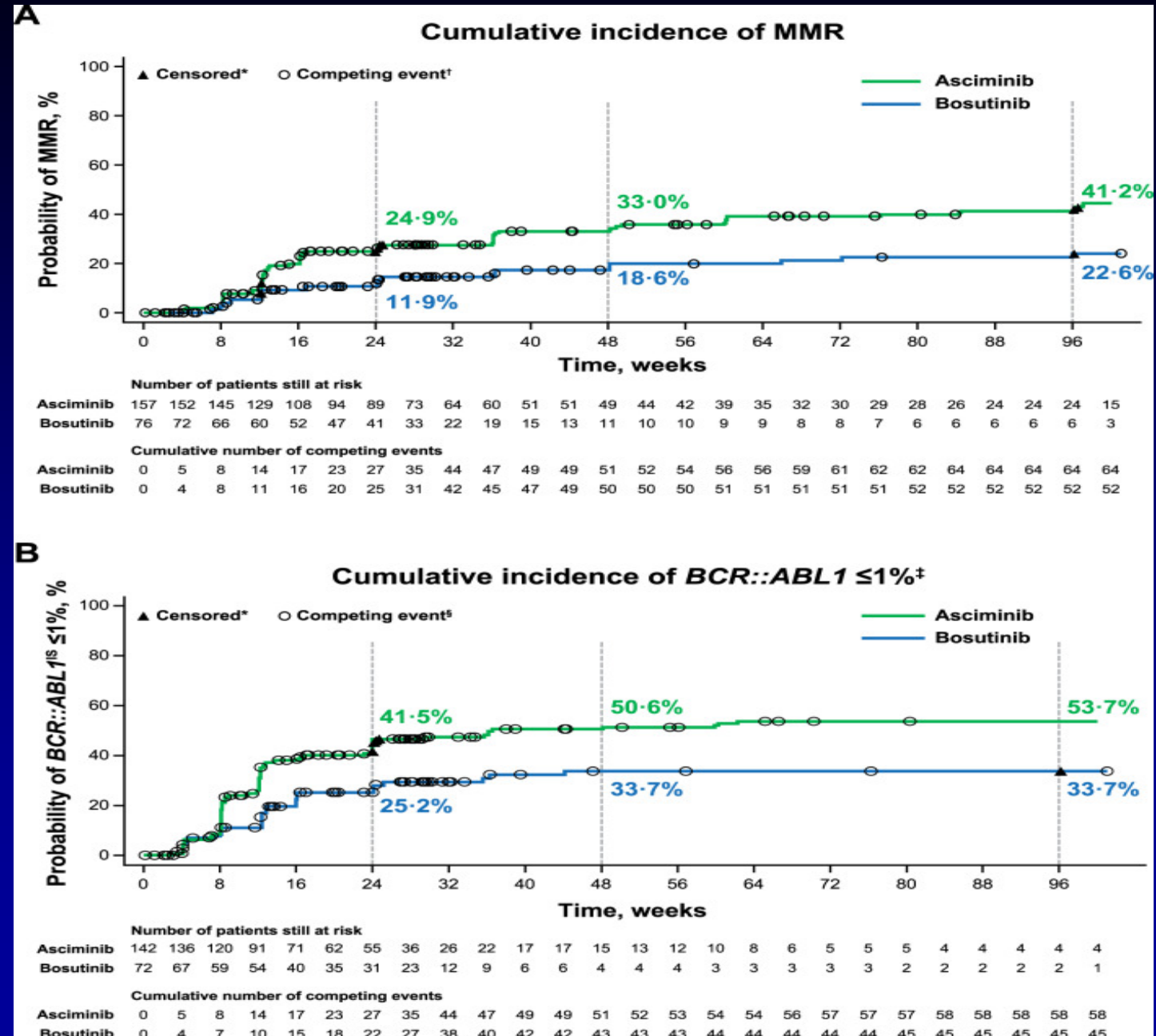
When and How to Use Ponatinib ?

- Standard practice —1) T315I mutation or; 2) Failure of 2 TKIs including second generation TKI—use 45mg daily
- My suggestion—T315I mutation (use 45 mg/D); or resistance to second TKI without guiding mutations —use 30mg/D

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)
- 2-yr OS 97% vs 99%
- Asciminib AOE 8/157 (5%) with median FU 2.3 yrs
- Bottomline: early MMR does not translate into OS benefit

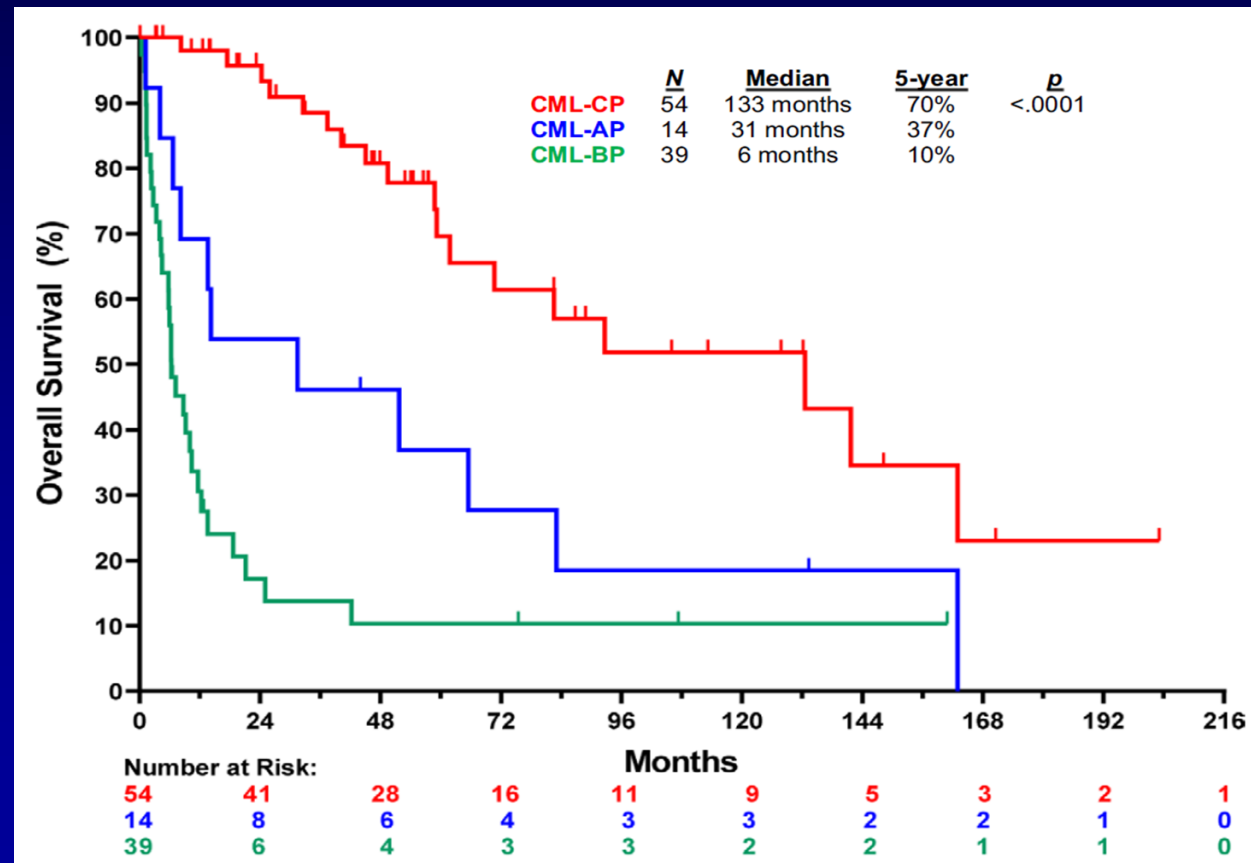
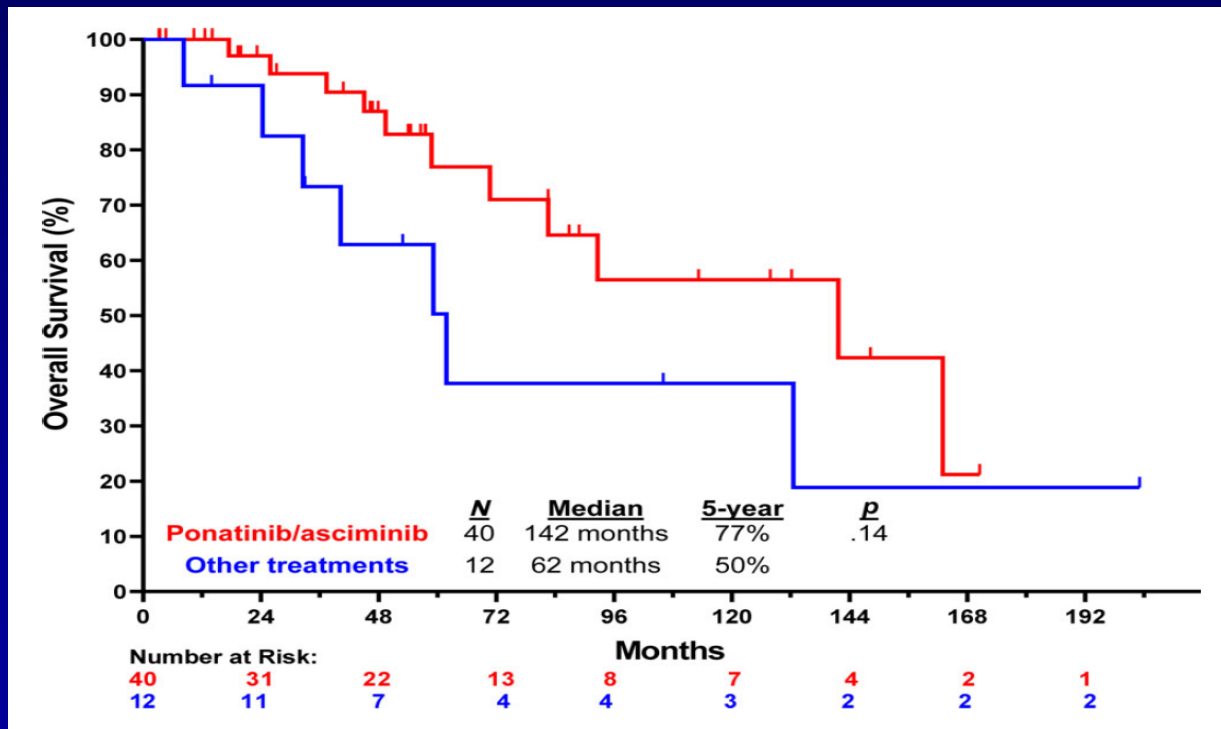
Parameter	Asciminib	Bosutinib
% 2-yr MMR	38	16
% 2-yr PFS	94	91
% 2-yr OS	97	99
% G 3-4 AEs	56	68
% AEs & DC	8	26



Outcomes of CML with T315I mutation

- 107 pts -- 54 CP, 14 AP, 39 BP . Median prior Rx 3 (1-9). Median Dx-T315I 41 mos
- Post-T315I: ponatinib (43%), chemo +/- TKI (36%), 2G-TKIs (10%), asciminib (7%), ASCT (17%)
- CML-CP: 5-yr OS 77% with ponatinib/asciminib vs. 50% with other therapies
- MVA: - worse OS with AP (HR, 4.35), BP (HR, 16.6), and >2 prior TKIs (HR, 2.33); better OS with ponatinib/asciminib (HR, 0.46) and ASCT (HR, 0.06)

CML Phase	Median OS (mos)	% 5-yr OS
CP	132	70
AP	31	37
BP	6	10



Asciminib Phase 1 Trial in T315I-Mutated CML CP

- 48 pts with CML-CP and T315I Rx with ASCI 200mg BID. 2 TKIs 83%. Median exposure 3.5 yrs
- MMR 86%, MR4 31%
- 26 ponatinib “exposed” - MMR 38%
- AOE 12.5%

Rx of *T315I*-mutated CML

- Ponatinib 45 mg/D until PCR<1%, then 15 mg/D
- If ponatinib toxicity after dose adjustment, many consider asciminib 200 mg BID -- BUT \$650.000/year = not good Rx value
- **Alternatives: allo SCT (young); omacetaxine, HMA, araC +/- VEN until *T315I* clone disappears; then add 2nd GEN TKI (old).**
- If ponatinib resistance, asciminib may not be effective

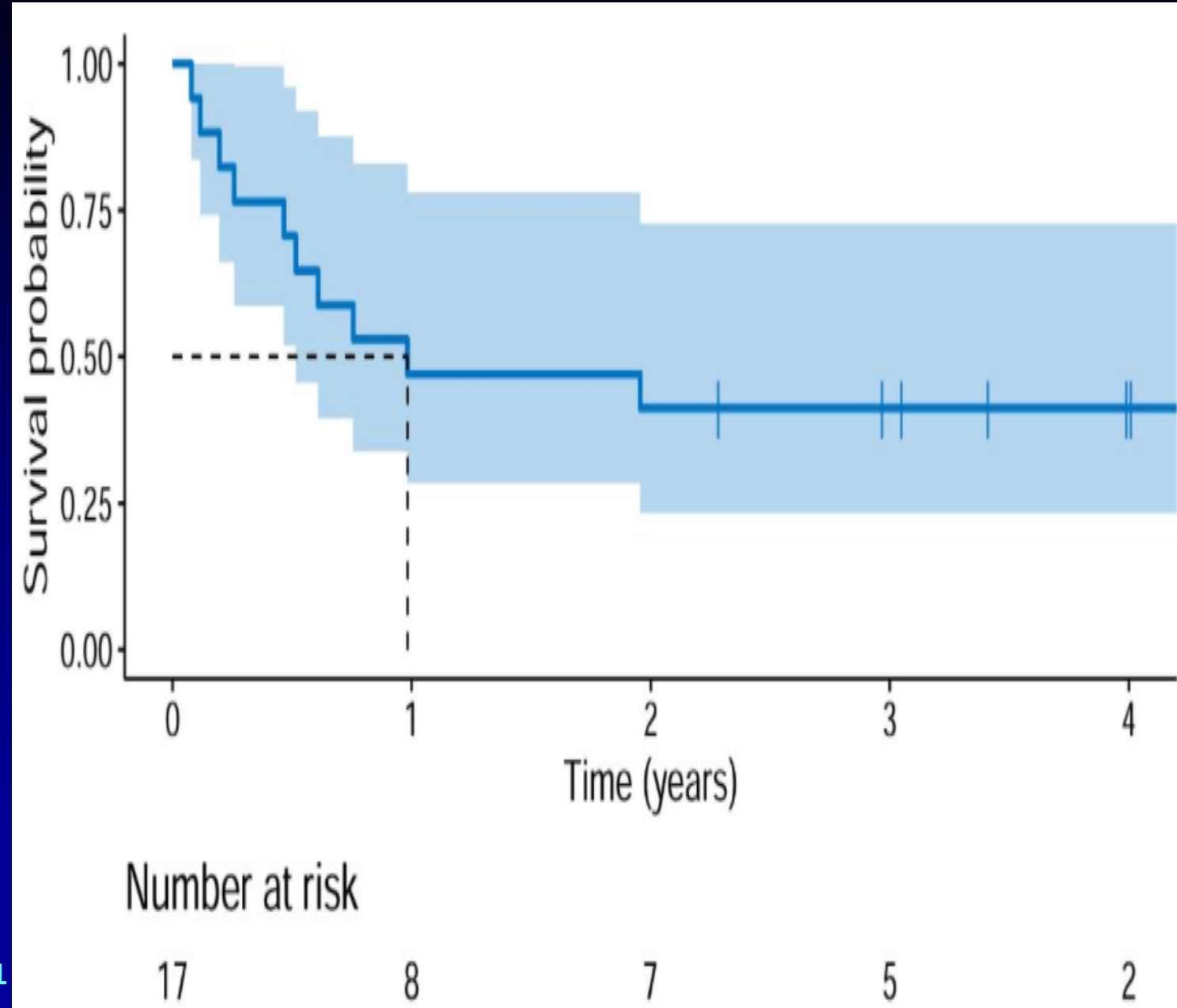
Olverembatinib Active in CML

- 80 pts Rx with OLVER 30, 40, 50 mg QoD; 65 (78%) 3+TKIs. Prior PONA 46 (57%); prior ASCI 25 (31%)

CML Phase/prior Rx	No (CCyR/MMR)	% CCyR	% MMR
Chronic	51	61	42
Prior PONA	26/30	58	37
Resist	19/21	53	43
Int	4/6	3	17
Prior ASCI	8/12	50	33
Advanced CML	14/17	21	18

FLAG-IDA + Ponatinib in CML Myeloid BP

- 17 pts in CML-MBP
Rx with FLAG-IDA + ponatinib
- 11/17 back to CP;
CG CR 5/17; MMR 5/17
- Rx related death 3;
allo SCT 12
- Median OS 12 mos



Ponatinib-Based Rx in CML-BP

- 76 pt with CML-myeloid BP: 50 first Rx, 21 salvage
- Additional Rxs: IC 28, IC+VEN 7, HMA+VEN 18, HMA 6, PONA alone 17— Later HSCT 15
- ORR 50%; CR + CRi 40%. CCyR 28%
- Median OS 8.5 mo; 2 yr OS 27%

Parameter	% ORR	% 2 yr OS	
-First line	62	68	P=.005
Salvage	27	14	
-Combo	56	-	P=.06
Mono	29	-	
-HSCT	-	71	
No HSCT	-	38	

Rx of CML Post Frontline TKI Failure – Summary 2025

- **Frontline Rx excellent (and getting better and safer)**
- **Most patients can remission on first frontline TKI with proper monitoring, patience, and TKIs dose adjustment (2/3rd at 10 years)**
- **2nd line options equivalent; ponatinib post 2nd GEN resistance**
- **3rd line - ponatinib better efficacy:safety profile with dose adjustments; asciminib FDA approved**

Management of Ph-Positive ALL. A Success Story

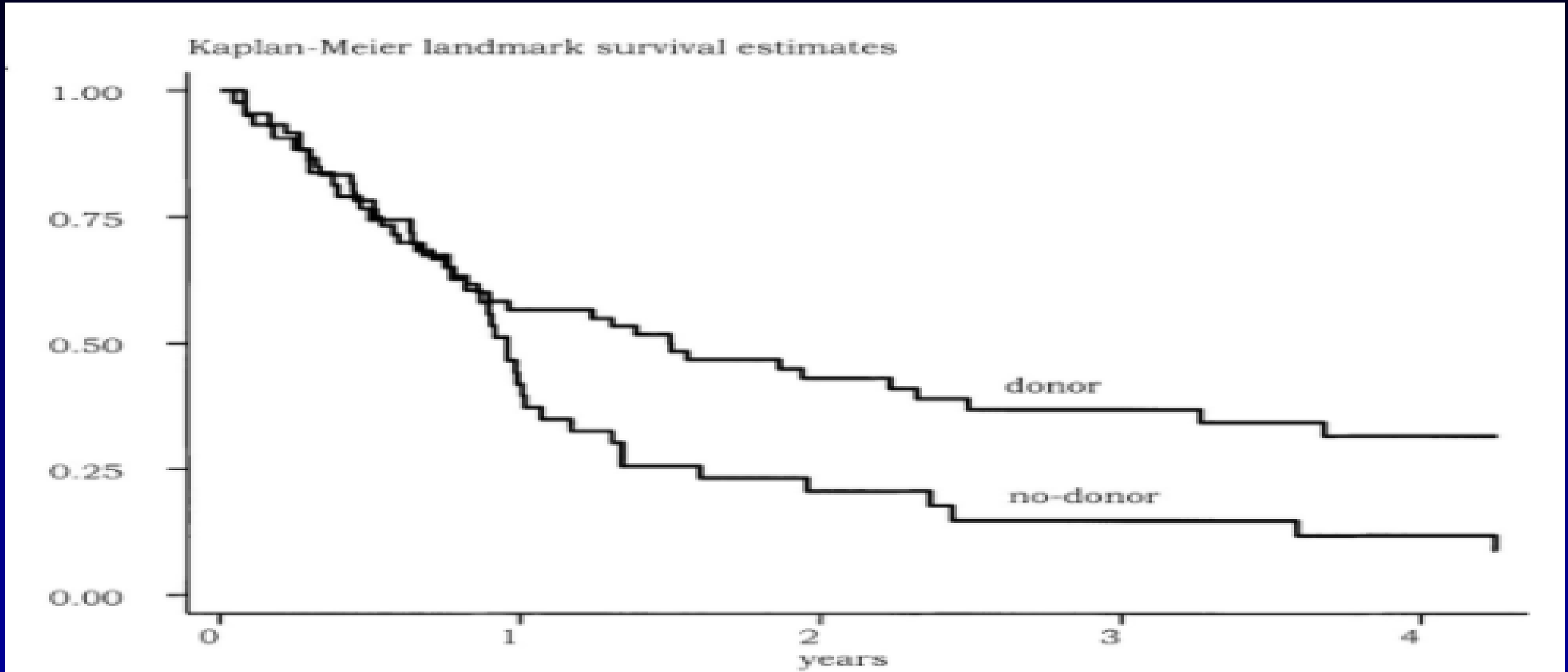
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**The University of Texas MD Anderson Cancer Center,
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Fall 2024

SCT for Ph+ ALL. Pre-TKI



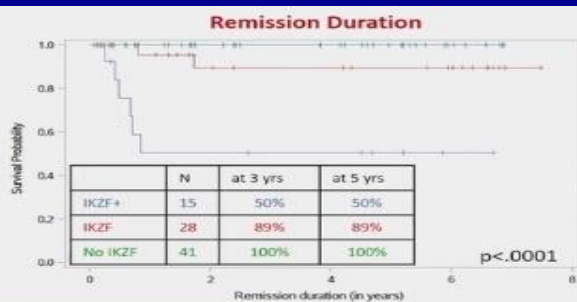
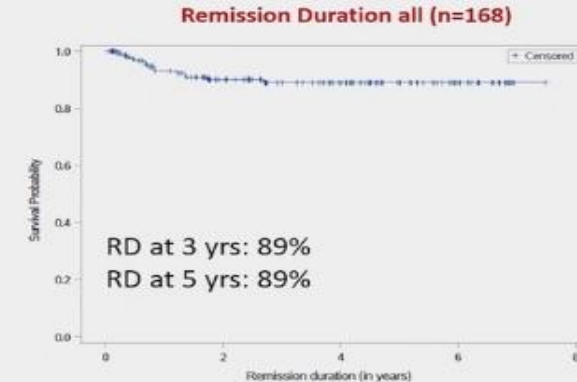
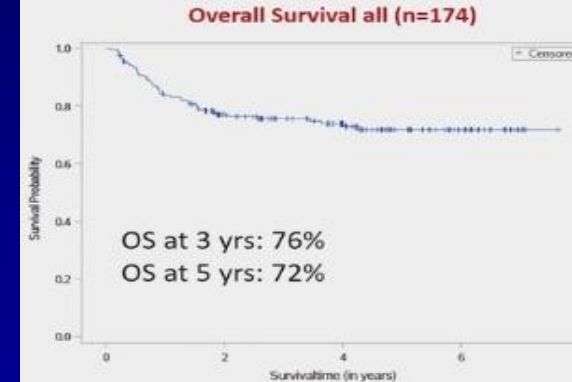
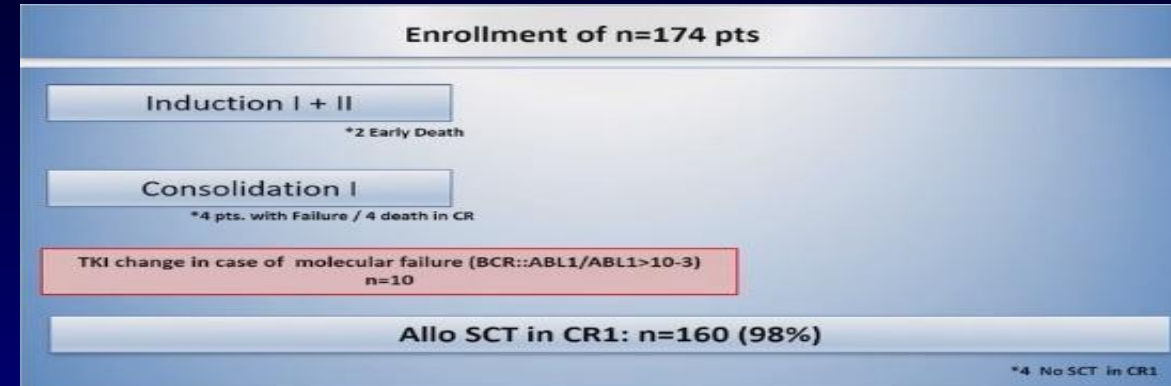
- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

Ph-Positive ALL on GMALL

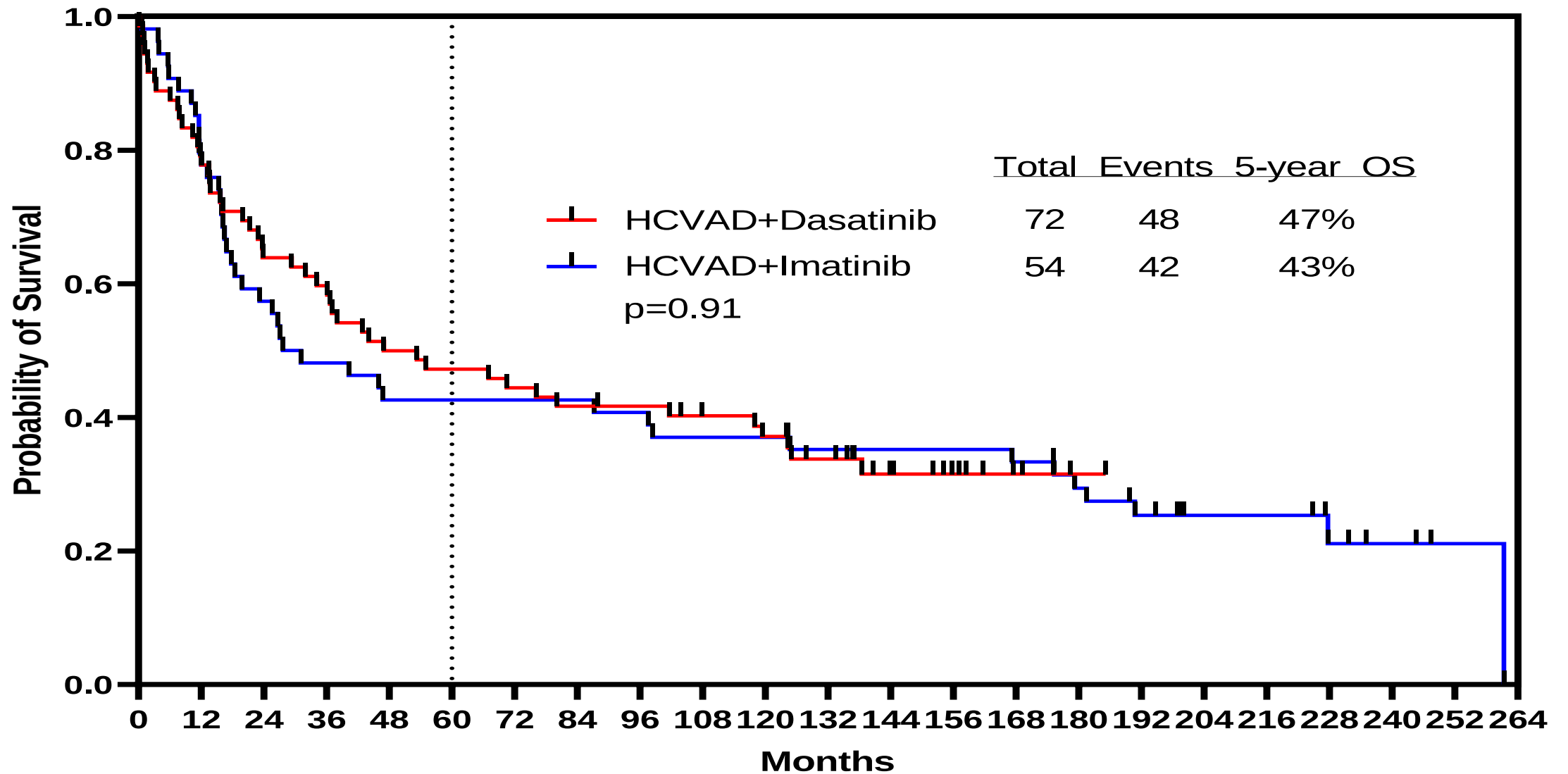
- 174 pts; median age 42 yrs (18-55)
- Imatinib 600mg/D + LI ChemoRx; **then allo HSCT 160/174 (92%; 98% of CRs; median time to SCT 4 mos)**
- CR 85% post induction; CR 96% overall
- Molecular CR 9% post induction, 42% post C3
- 3-yr OS 76%; 3-yr OS post HSCT 81%; Rx mortality 16%**

	after Induction I	pre Consolidation I	after Consolidation I
Evaluable cytology	165	174	174
CR/CRu	85%	96%	94%
PR	9%	2%	0%
Failure	4%	1%	2%
Early Death	1%	1%	3%**

	After Induction I	Pre Consolidation I	After Consolidation I
MRD Total	174	150	144
MRD Evaluable	139 (80 %)	150 (87%)	144 (87%)
Mol CR	9 %	24 %	42%
Mol Fail	81%	58%	38%
$\geq 10^{-2}$			17%
$<10^{-2} \geq 10^{-3}$			41%
$<10^{-3} \geq 10^{-4}$			43%
Mol IMR	25%	18%	21 %

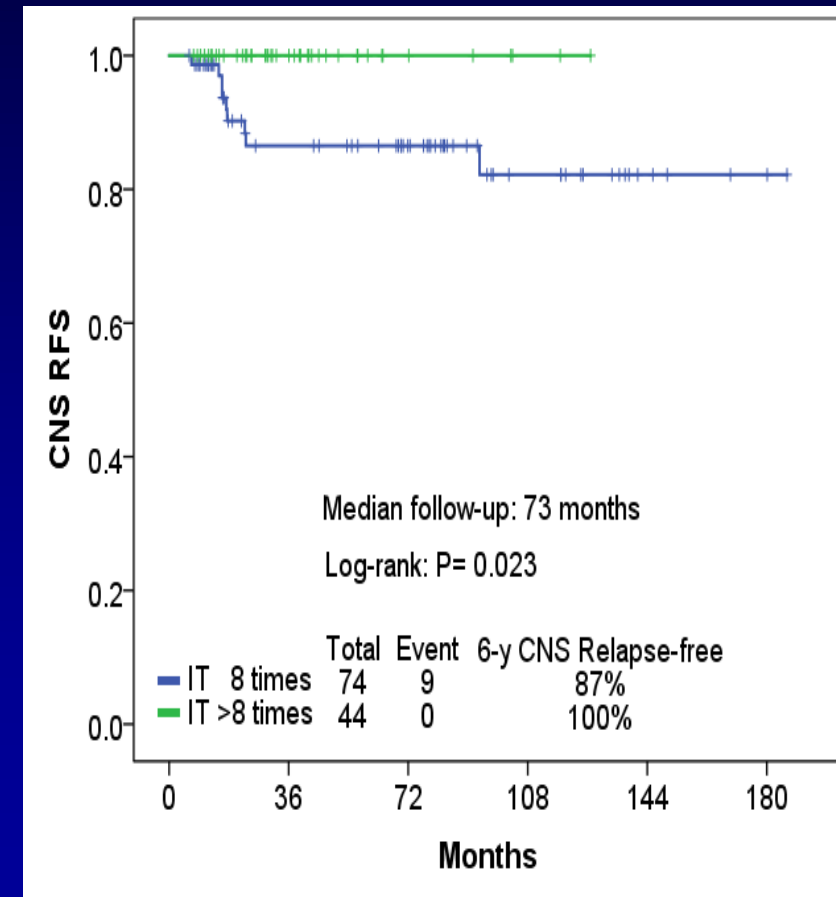
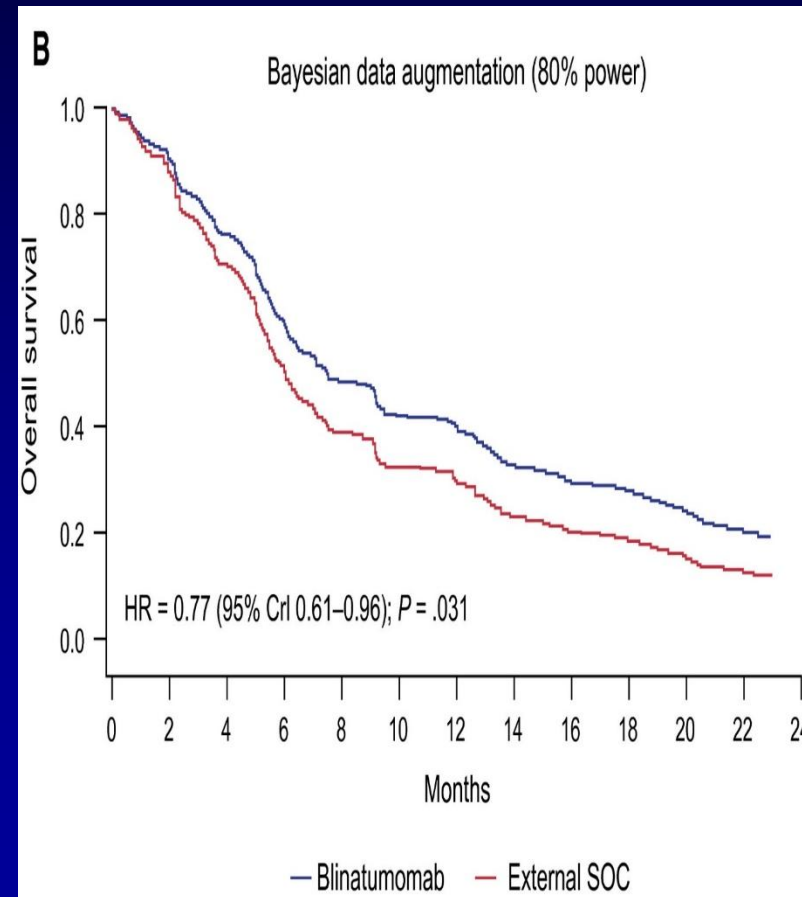
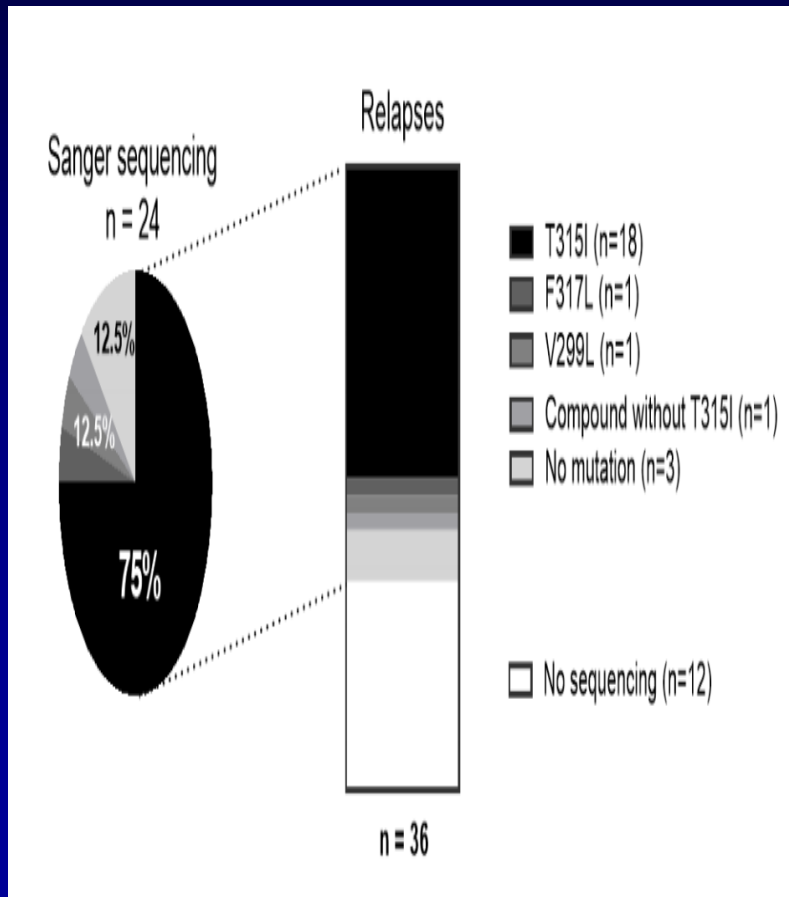


Ph-positive ALL 1st/2nd Generation TKI. Survival



Reasons for Rx Changes in Ph-positive ALL

- T315I KD mutation present in 18/24 patients (75%) Rx with Dasatinib at time of relapse
- Blinatumomab > ChemoRx CR/CRh 36% vs 25%; 1-yr OS 41% vs 31%
- More IT needed

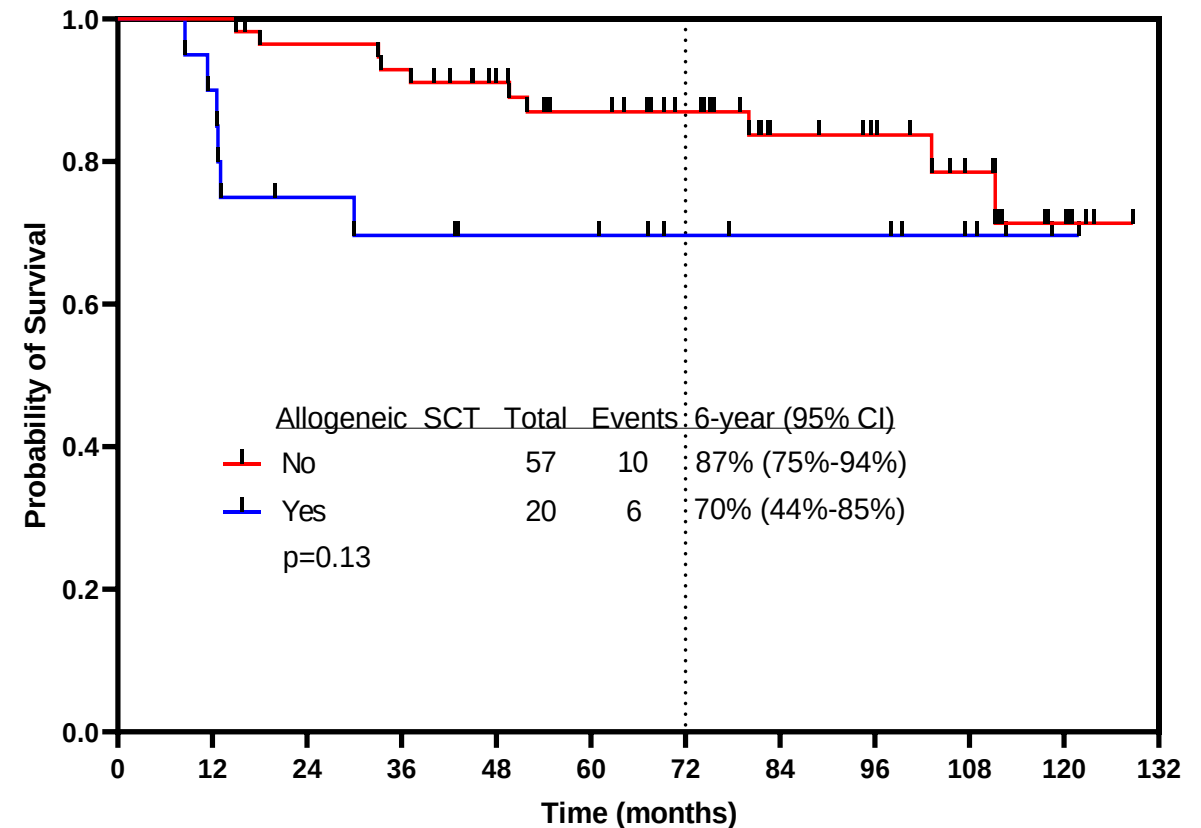
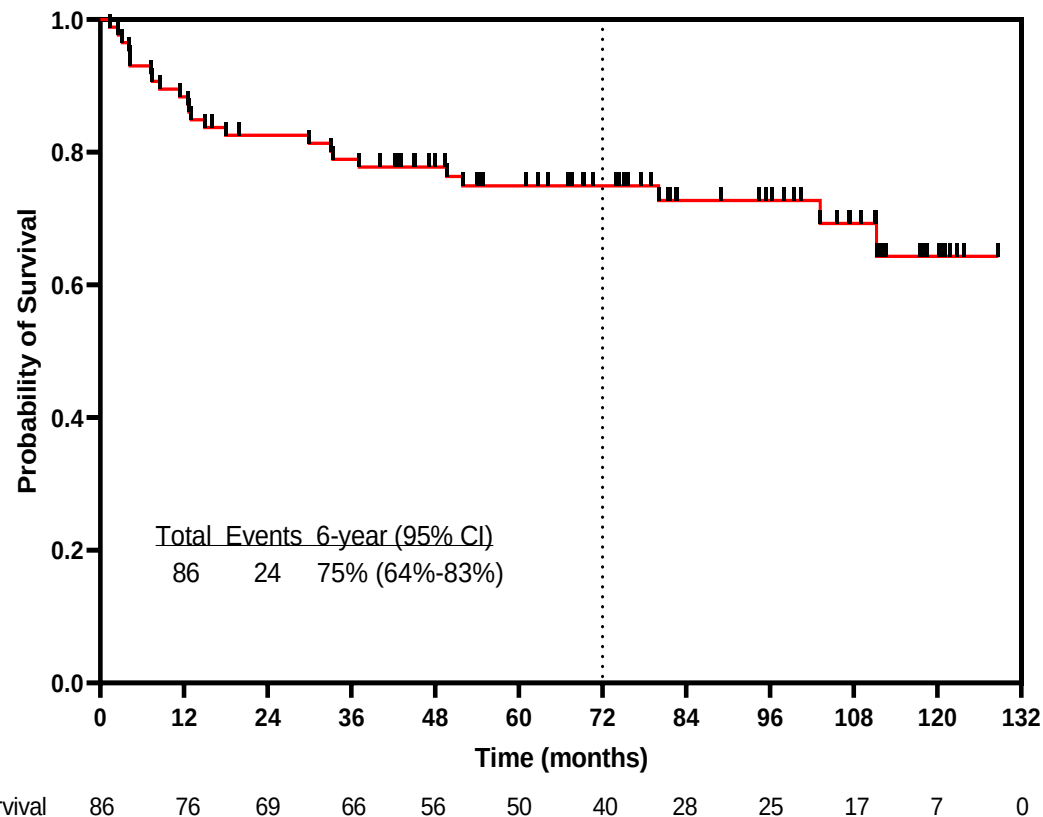


HyperCVAD + Ponatinib in Ph-positive ALL. Long-Term F/U of more than 6 years

- 86 pts Rx; median age 47 yrs (39-61); median FU 80 mos (61-109)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); **CMR 84%; 6-yr OS 75%, EFS 65%; 20 pts (23%) ASCT**

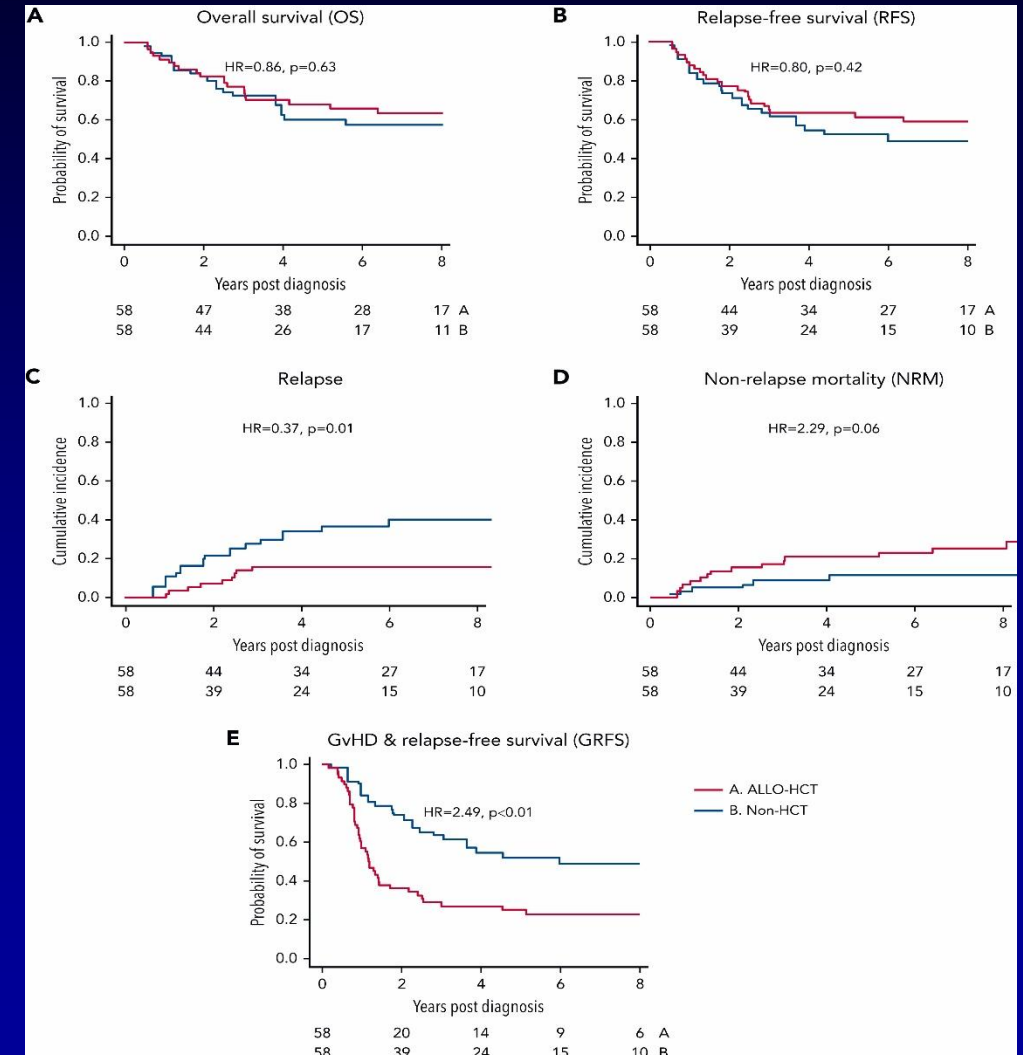
OS

6-mos-landmark



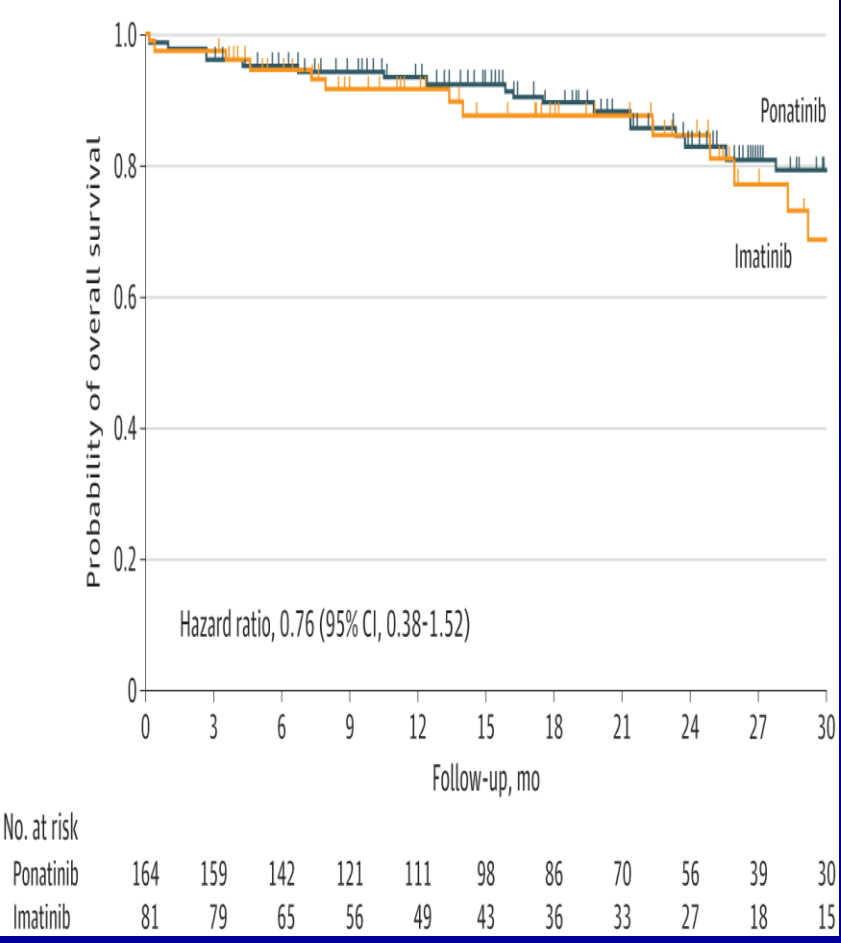
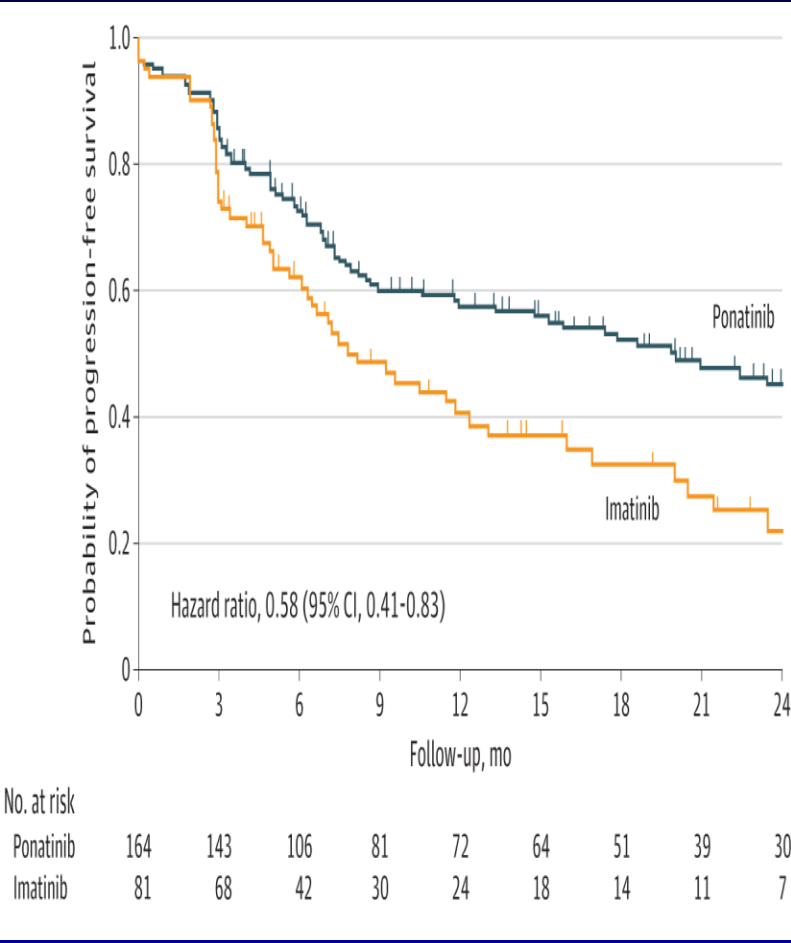
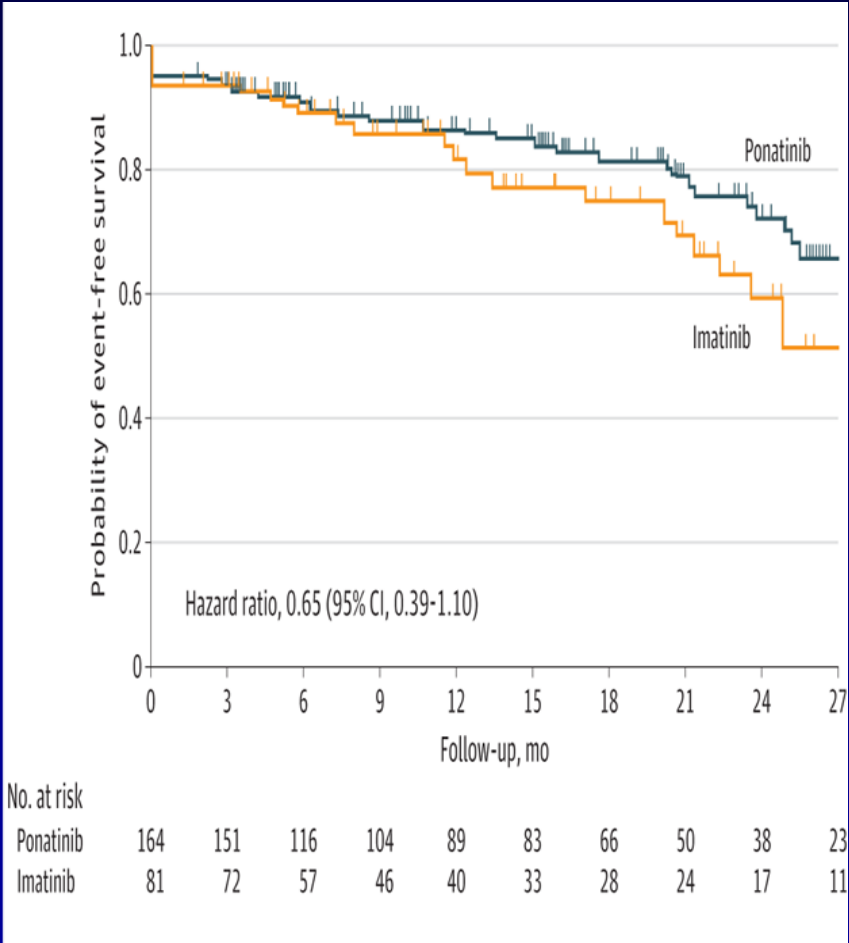
No Benefit of Allogeneic SCT in Patients with Ph+ ALL who Achieve CMR

- Propensity score analysis of patients who achieved CMR within 3 months
- Allogeneic SCT → lower risk of relapse but higher NRM
- No impact of SCT on OS or RFS



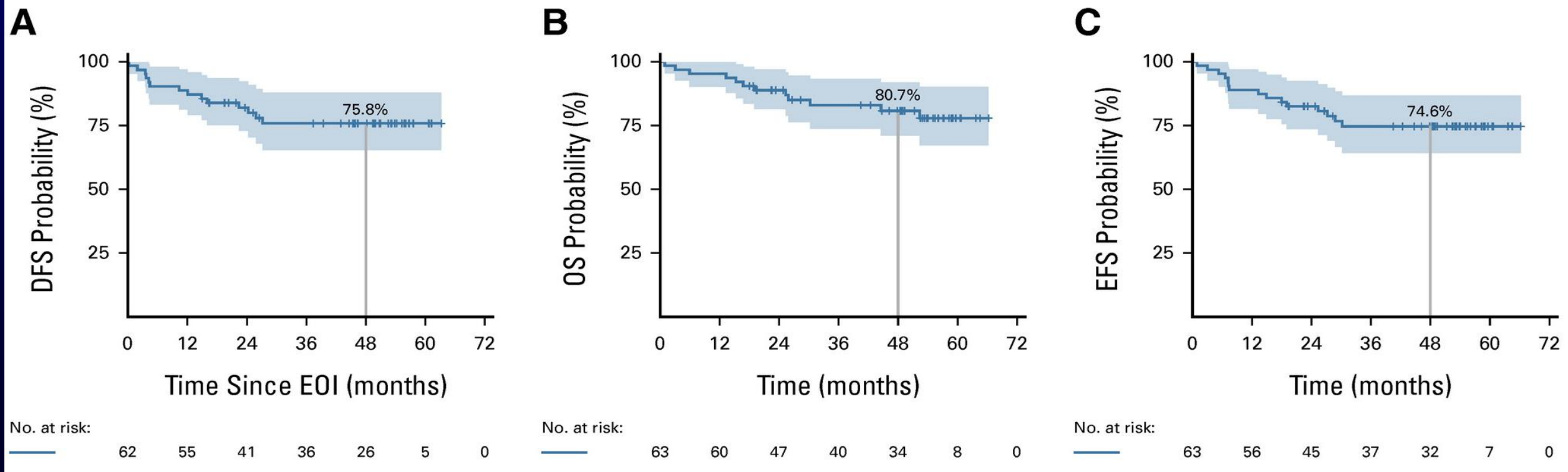
Ponatinib vs Imatinib in Newly Dx Ph+ALL. PhALLCON Phase 3 Trial

- 245 pts randomized (2:1) to ponatinib 30 mg/D (n=164) or imatinib (n=81) , both with VCR-Dex for 90 days; then continuation of TKIs and chemoRx.
- Primary endpoint MR4 CR at 90 days: 34.4% vs 16.7% (p = 0.002)

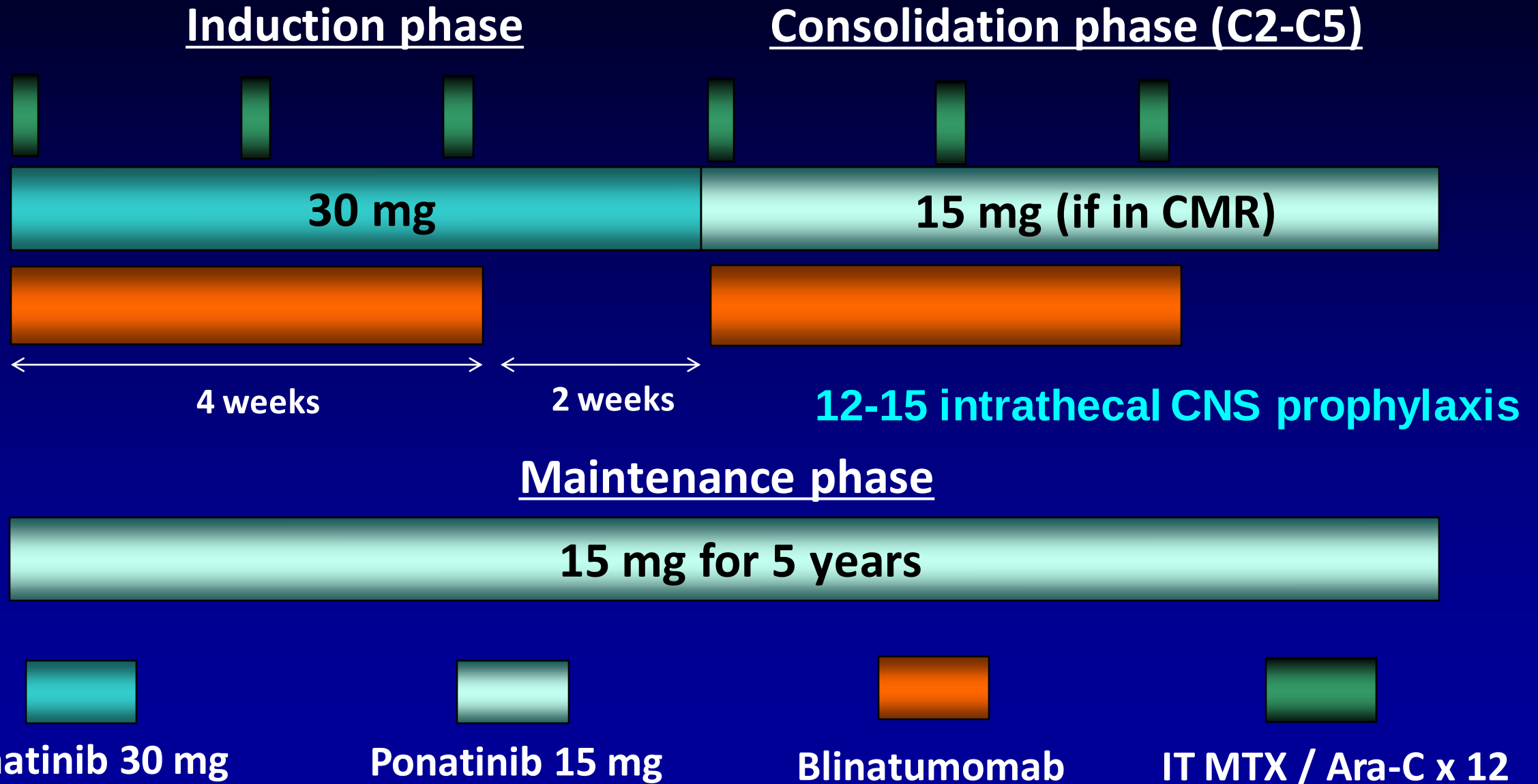


Dasatinib + Blinatumomab (D-ALBA) in Newly- Dx Ph+ ALL– Final Update

- 63 pts Rx; median age 54 yrs (24-82). Median FU 53 mos
- Molecular response (CMR/PNQ) 27/29 non-SCT = 93%
- 30/63 (48%) allo SCT–6 allo SCT in CR2
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal. 6 deaths
- 4-yr OS 81%, DFS 76%, EFS 75%
- Outcome better if MR (EOI): DFS 100% vs 69% (p=.016); worse if *IKZF1*+: DFS 82% vs 45% (p=.026)



Ponatinib + Blinatumomab in Ph+ ALL. Regimen



Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

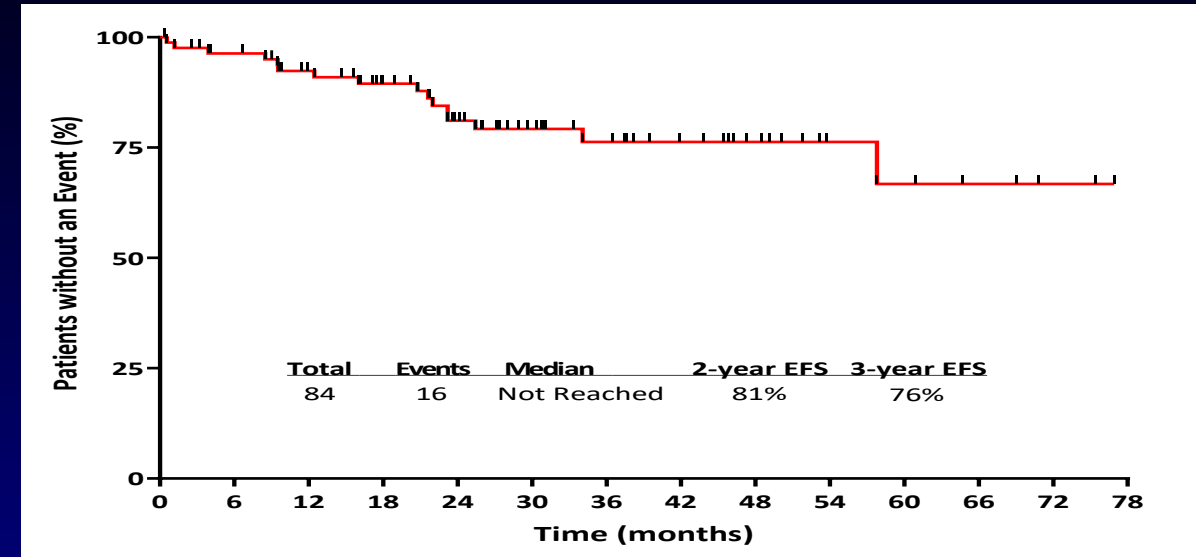
- 84 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs. Median FU 29 mos
- Only 2 pt had SCT (2%)
- Median F/U 29 months. 3-yr EFS 76%, OS 89%
- 10 relapses (9 p190): 5 CNS, 4 BM, 1 CRLF2+ (Ph-). 3-yr cumulative relapse 12%

Parameter	%
CR-CRi	97
% CMR	78
% NGS-MRD negative	95
% 3-yr OS	89

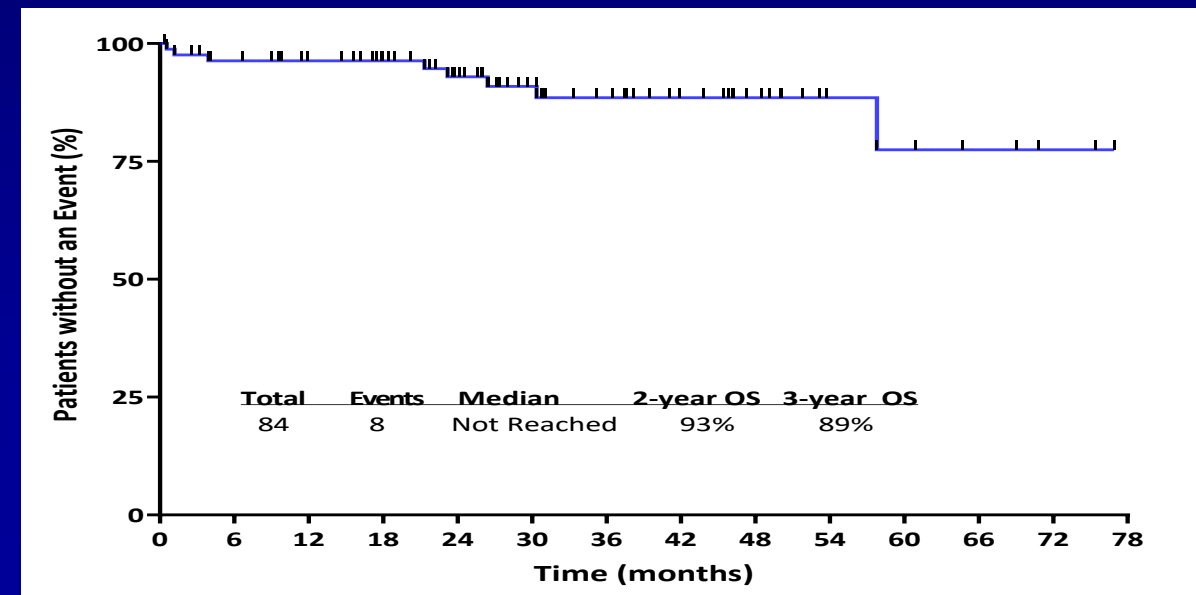
Jabbour. Lancet Haematol. 2023;10(1):e24-e34

Kantarjian JCO. 2024;42(36):4246-4251

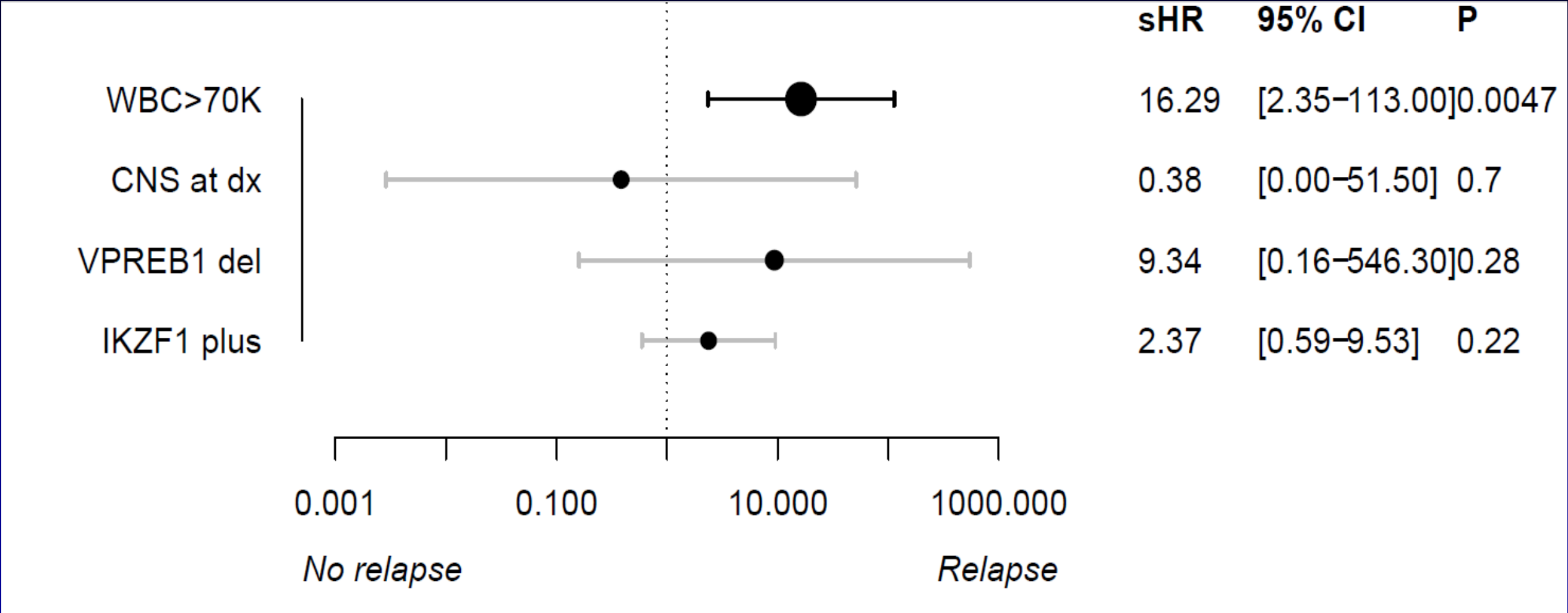
Event-Free Survival



Overall Survival



Ponatinib + Blinatumomab in Ph+ ALL. MVA for Relapse Risk

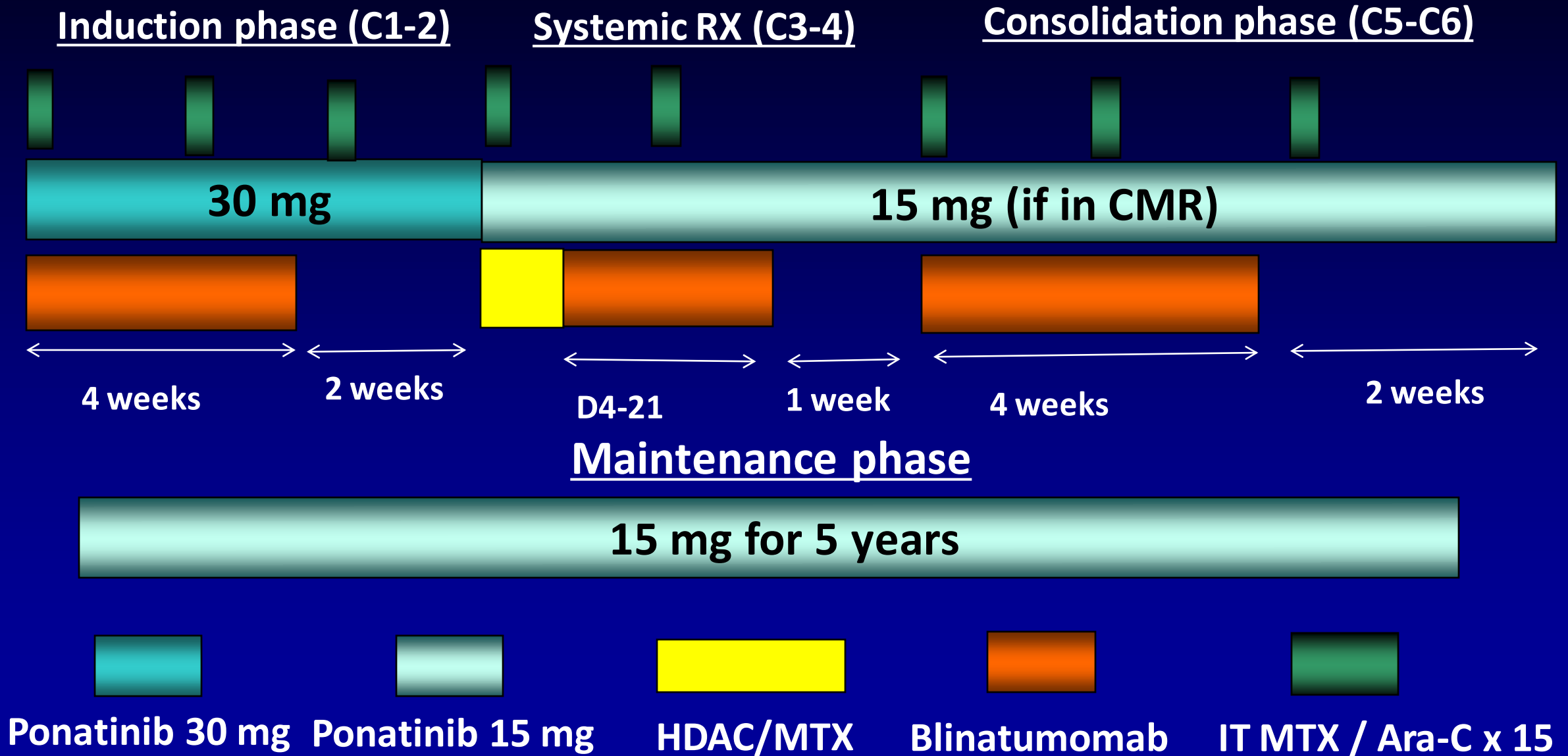


MVA: WBC >70K at Dx was only factor independently predictive of relapse

Ponatinib vs Dasatinib + Blinatumomab in Ph+ ALL

Parameter	Pona+Blina (n=84; 5 blina)	Dasa+Blina (n=63; 2+blina)	Dasa+ Blina (n=24; 3 blina)	Pona+ Blina (n=133; 2-5 blina)
Median age (yrs)	50	54	73	57
% PCR neg	78	93 (+PNQ)	63	73
% NGS-clonseq neg	95			
% 4-yr OS	89	82	75	18-mo OS 92%
% allo SCT	2	48	5	12
Relapses (CNS)	10 (5)	9 (4)	8 [3 T315I]	4 (1)

Ponatinib + Blinatumomab in Ph-positive ALL. Regimen (WBC $\geq$ 70K)

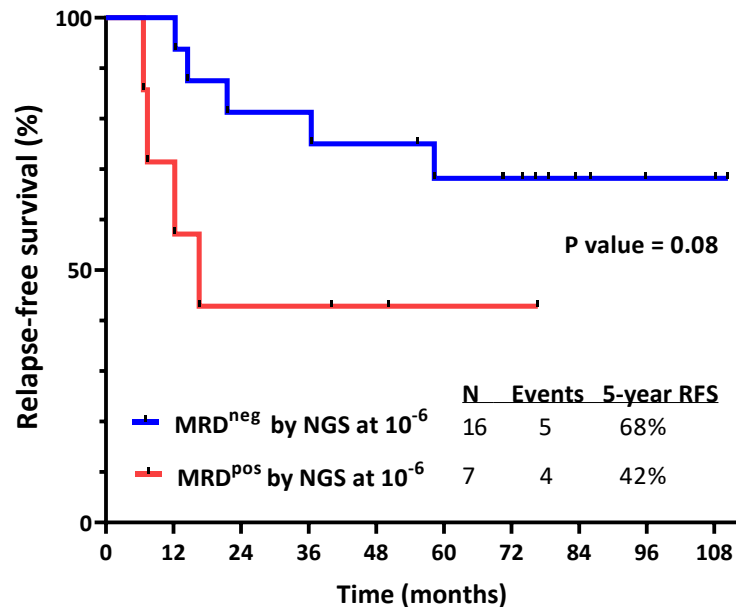


NGS MRD in Ph+ ALL.

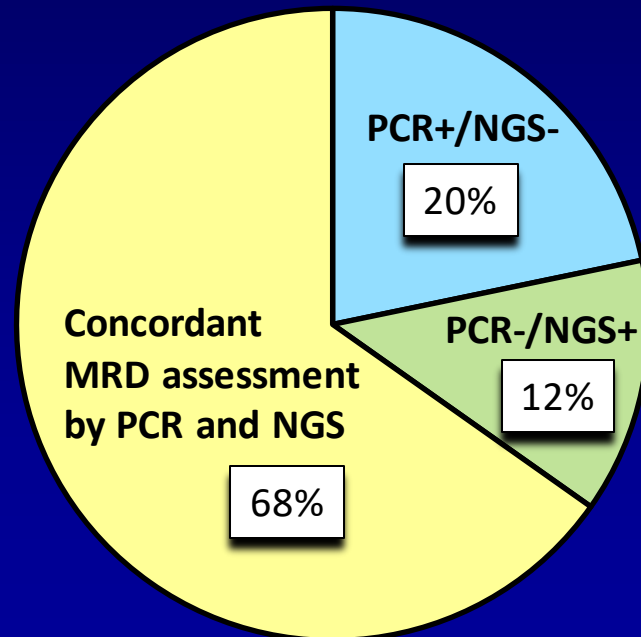
Adults with Ph+ ALL
undergoing frontline therapy
(n=44 in retrospective cohort)
(n=74 in validation cohort)

Comparison of MRD assessment by RT-PCR for *BCR::ABL1*
and next-generation sequencing for IG/TR (sensitivity 10^{-6})

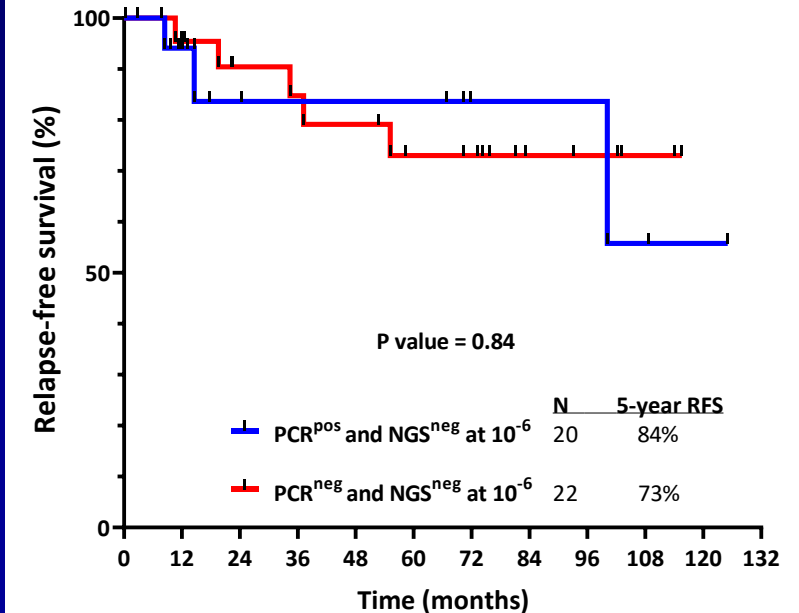
NGS MRD in first 6 months of
treatment is prognostic for RFS and OS



Discordance between MRD assessment
by PCR and NGS is relatively common

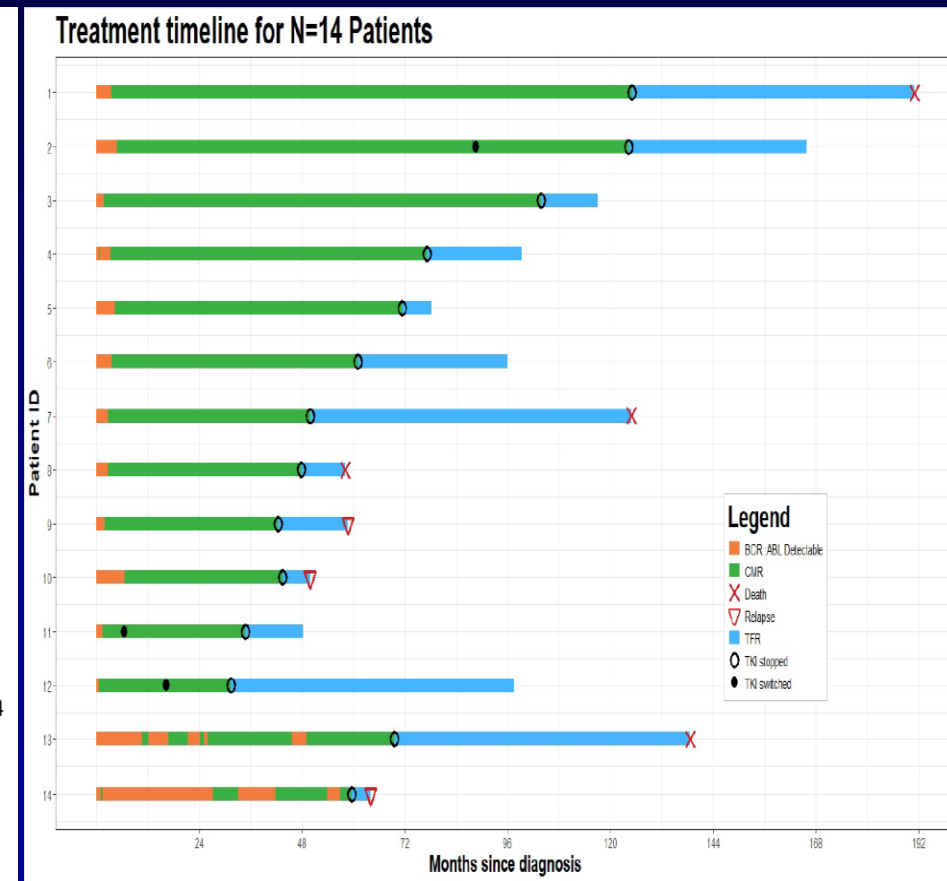
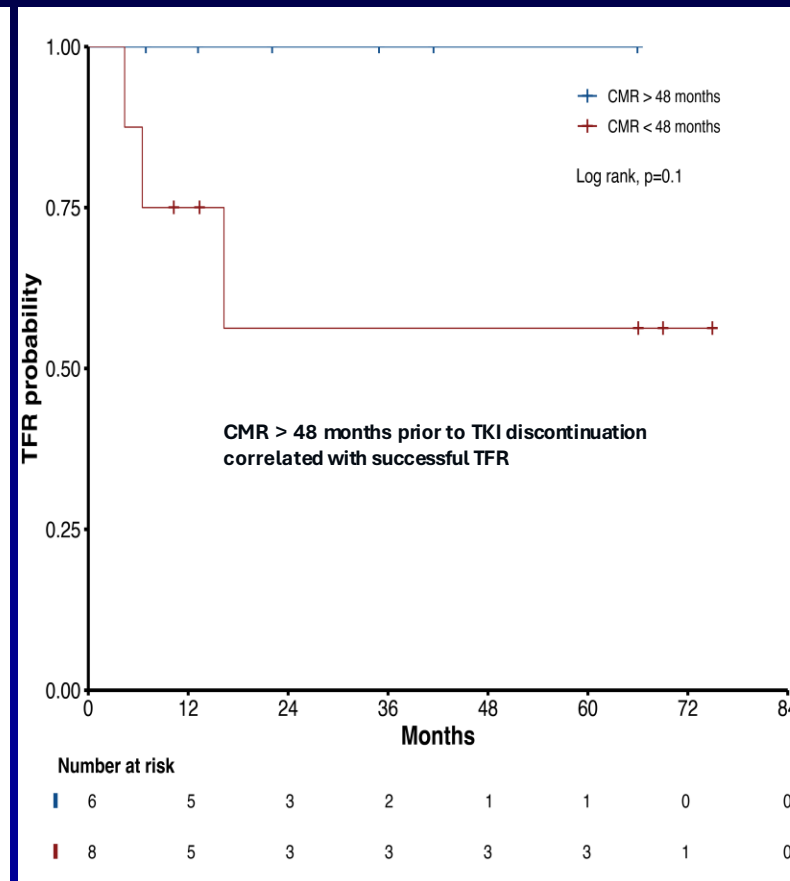
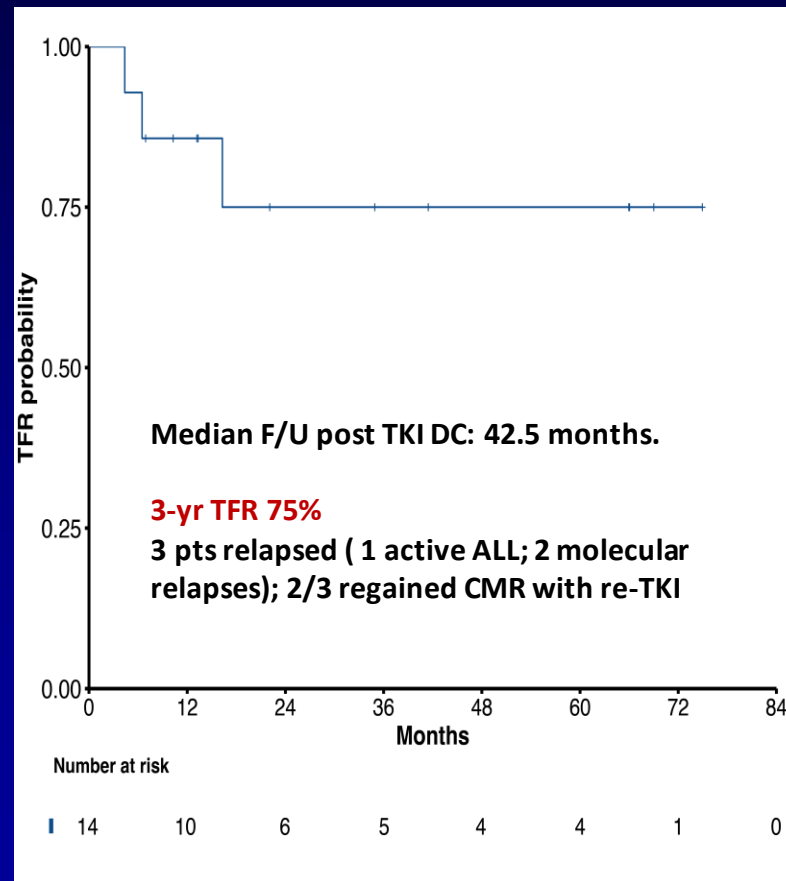


RT-PCR for *BCR::ABL1* is not prognostic in
patients who achieve NGS MRD negativity

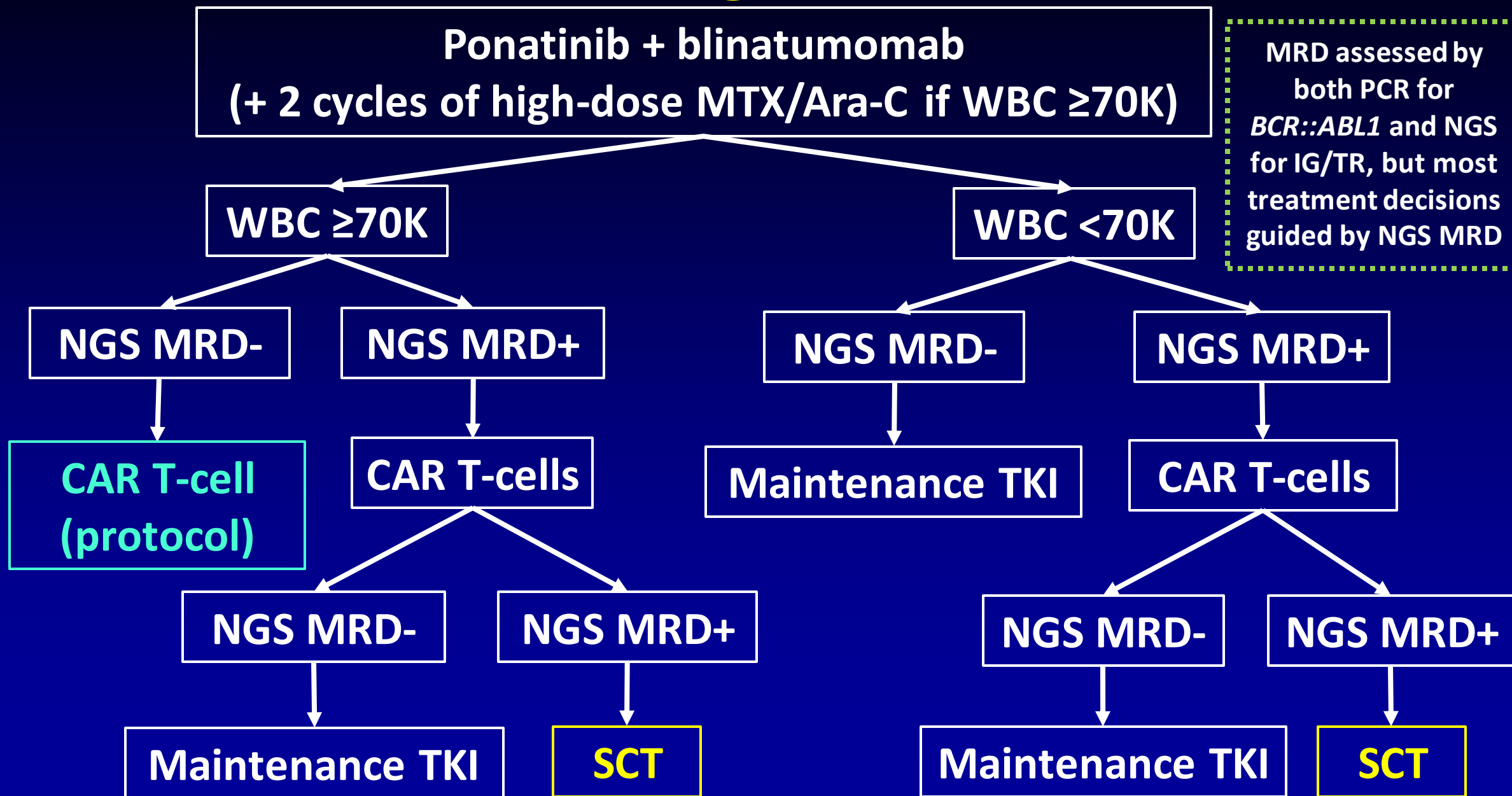


TKI DC/TFR in Ph+ ALL Without Allo HSCT

- 14/238 pts (6%); median age 61 yrs; Median time on TKI 60 mos (31-125); median time in CMR 46 mos (2.7-121)
- Rx HCVAD + added TKI: Ima 2, dasa 6, pona 4, blina-pona 2
- Reason for TKI DC: pleural effusions 4, AOE/VOE 4, pulmmonary hypertension 2, pancreatitis 1, cytopenia 1, other 2
- 11pts (79%) remained in TFR. None of 8 in CMR 4+yrs prior to TKI DC had relapse



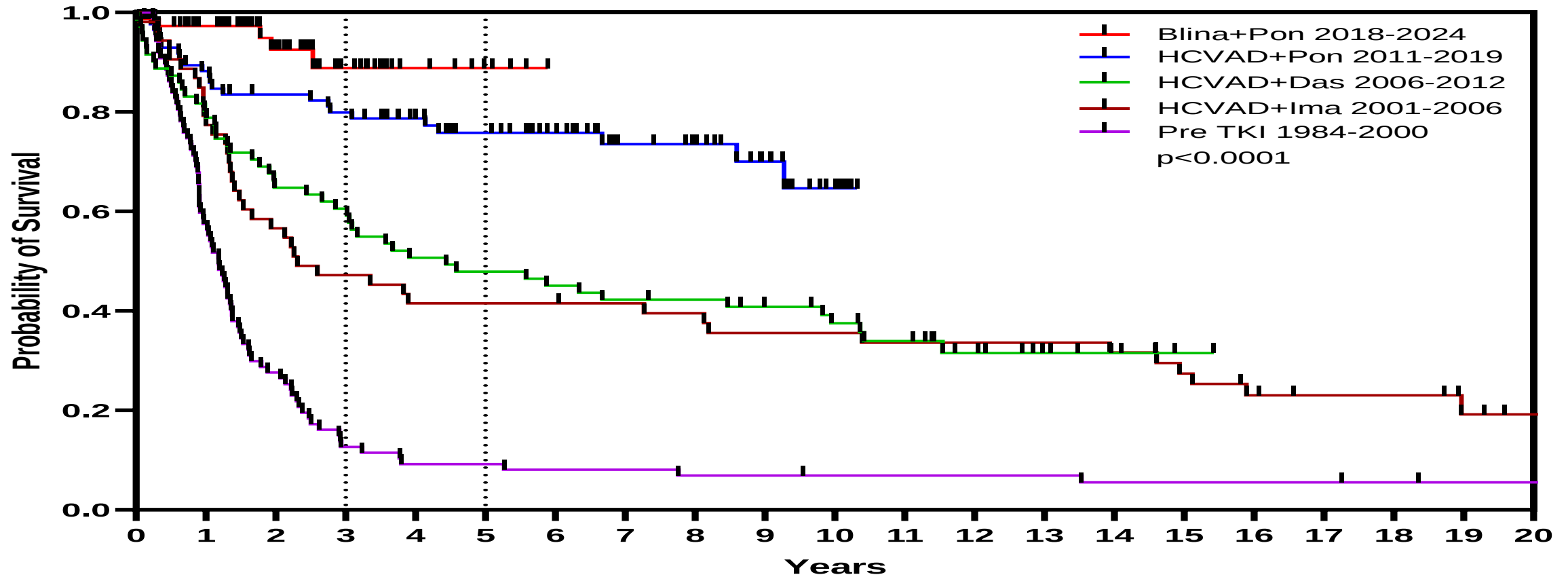
MDACC Research Algorithm for Ph+ ALL



In Conclusion...

- Do we need allo-SCT? --
 - Identify patients who can be cured without allo-SCT; e.g. **3-mos CMR, MRD negative by NGS** (lack of *IKZF1^{plus}*)
- **Ponatinib** best TKI-- 3 mos-CMR 86%; 6-year OS rate 76% (HCVAD-ponatinib)
 - **Ponatinib > Imatinib**: Phase III PhaLLCON
- How much chemoRx— Risk of CNS relapses
 - **15 IT** vs HDAC/MTX?
 - Consider CAR T-cell?
- New drugs to be explored--
 - **SQ Blina, asciminib, olverembatinib**
- Duration of TKI maintenance---TFR
 - At least 4-5 years of NRD-negativity by NGS
 - In pts without HR features (High WBC and/or *IKZF1^{plus}*)

ALL. Survival by Decade (MDACC 1984-2024)



	Total	Events	3yr OS	5yr OS	Median
Blin+Pon 2018-2024	76	5	89%	89%	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

$p < 0.0001$

Thank You

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