Ponatinib for the Treatment of Philadelphia-Positive Acute Lymphocytic Leukemia

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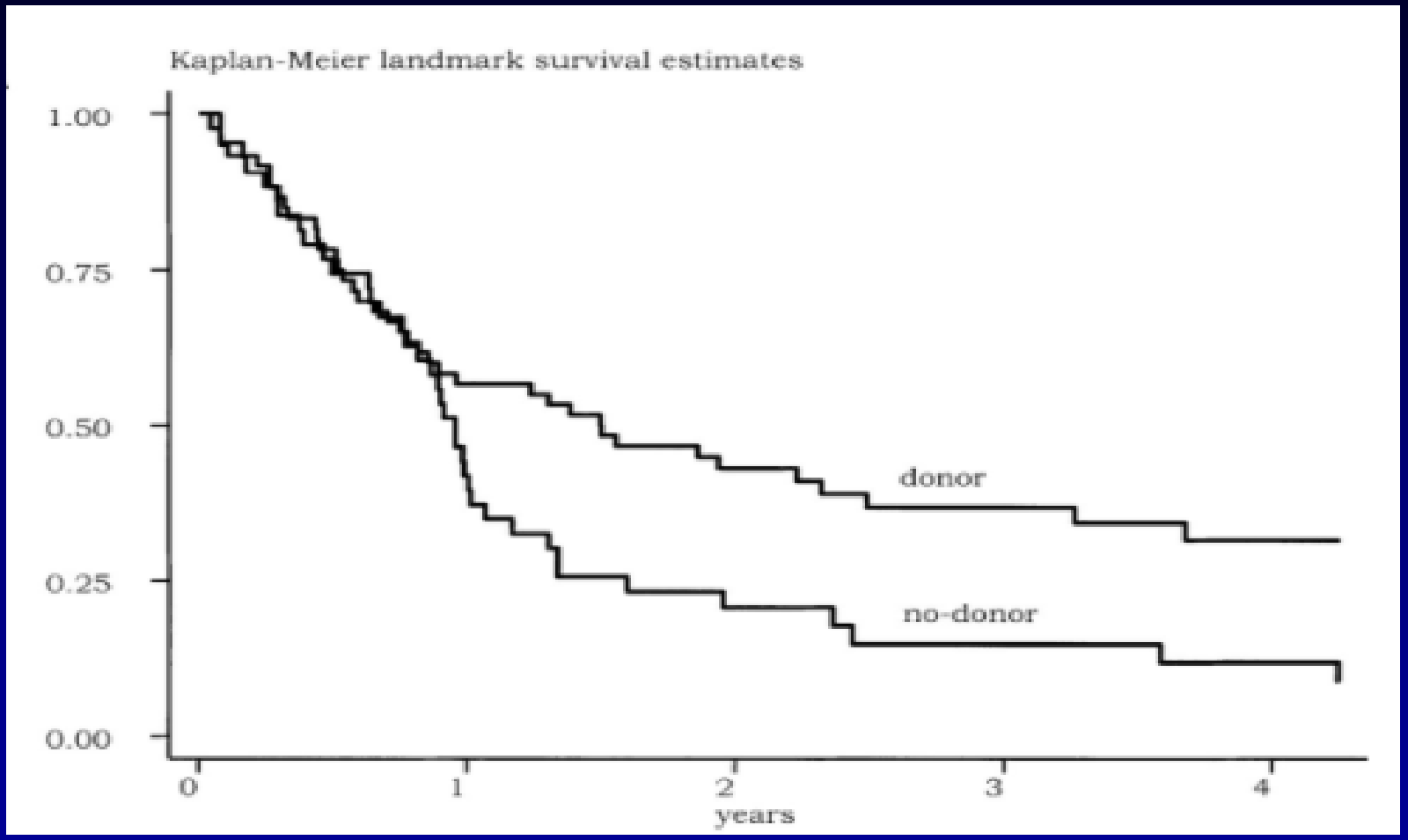
Reasons for Recent Success in Adult ALL Rx

- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx

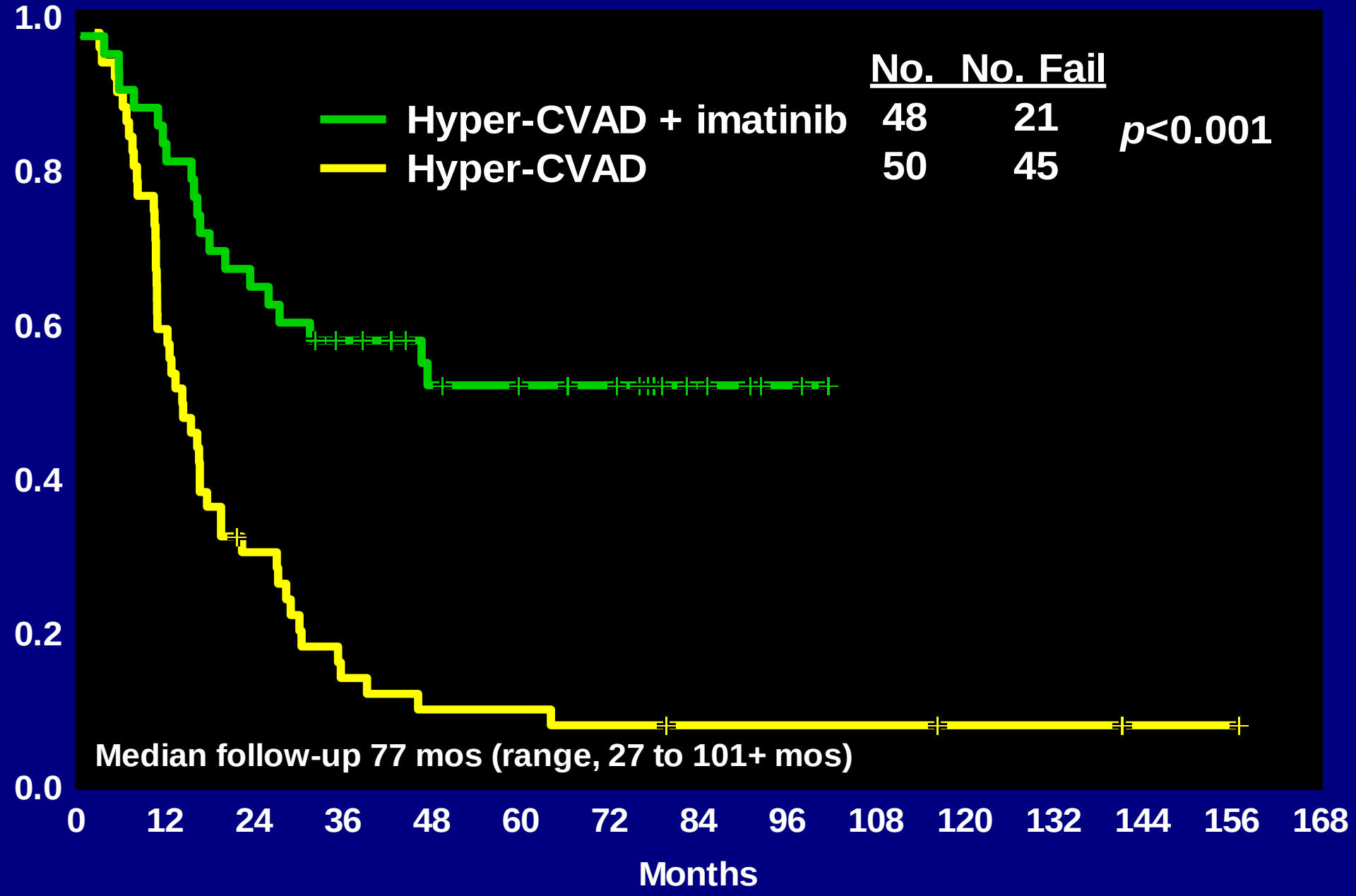
SCT for Ph+ ALL. Pre-TKI



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

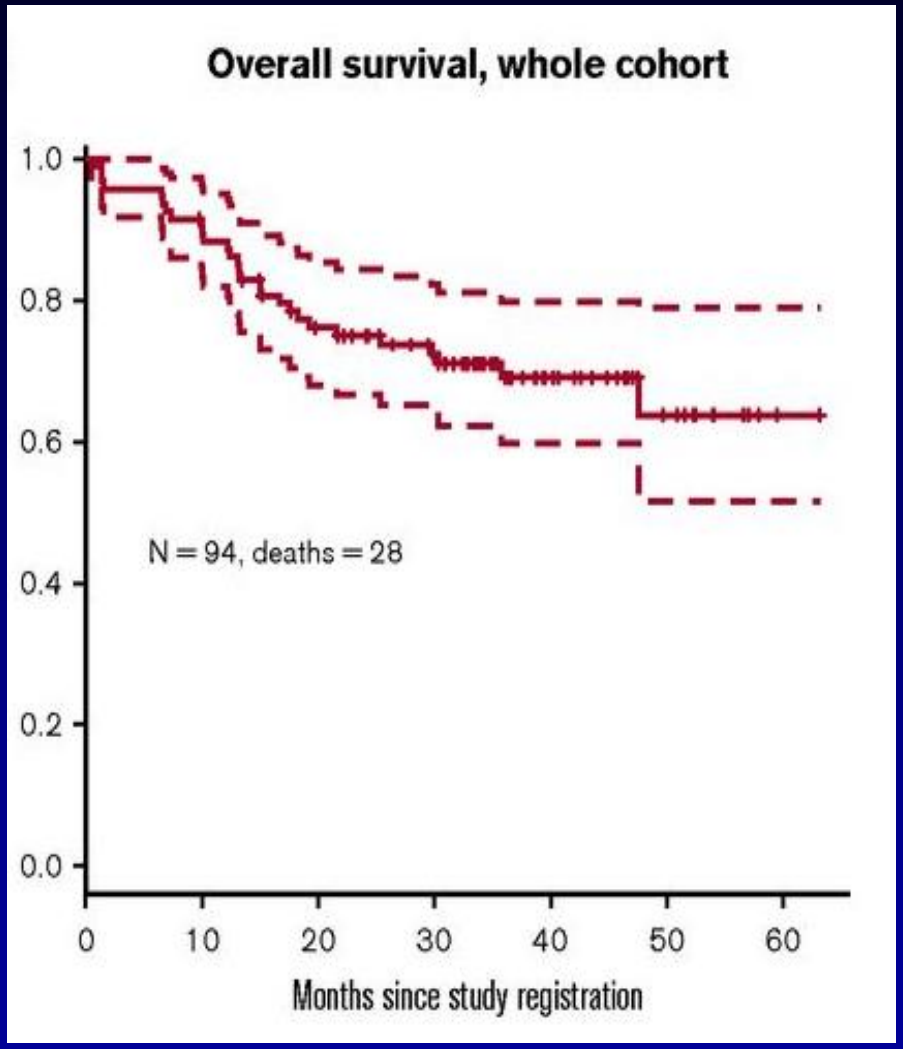
Dombret H et al *Blood* 2002

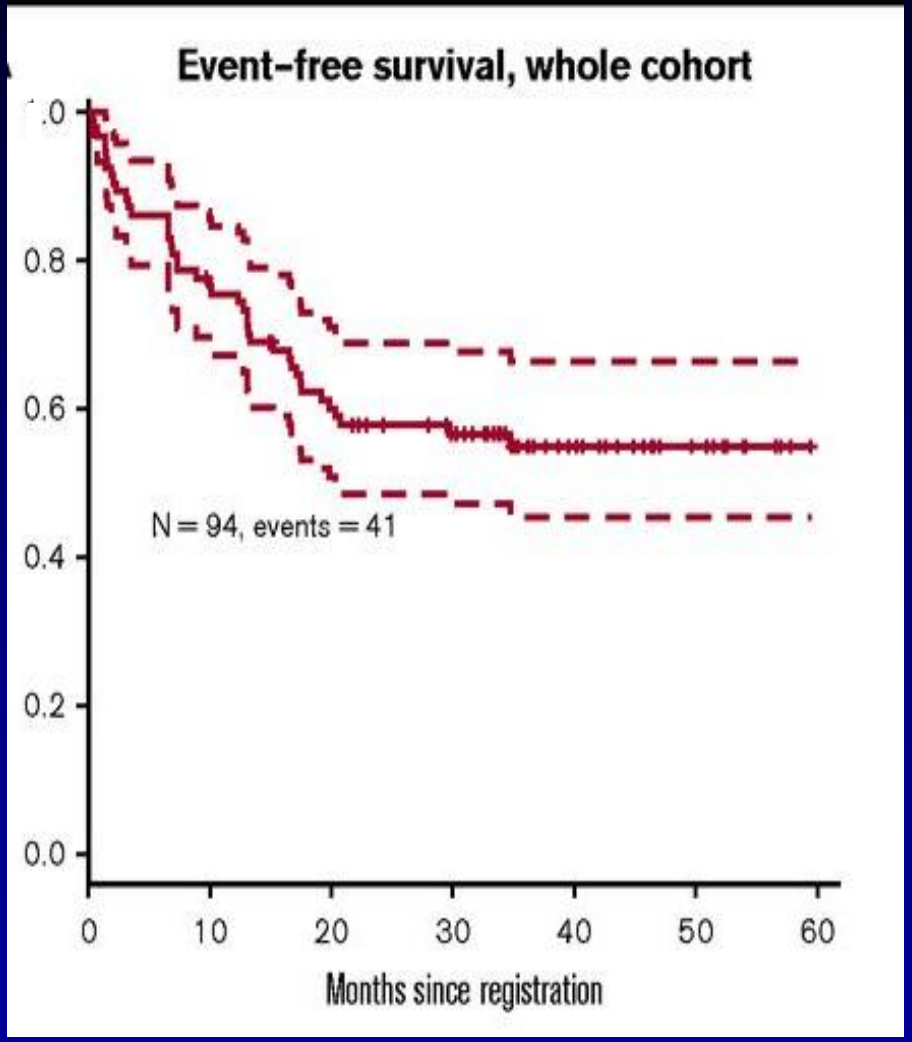
Survival in Ph-ALL by Regimen (Excluding Primary Refractory)



Daver N. Haematologica. 2015;100(5):653-661.

Hyper-CVAD + Dasatinib in Ph+ ALL





Ravandi F, et al. *Blood Advances*. 2016;1:250-259.

ChemoRx-free Regimen in Ph-positive ALL

- Steroids x 35 days; dasatinib 140mg/D x 3 mos--if no CMR→Clofarabine + CTX and/or allo SCT
- 60 pts; median age 42 yrs (19-59); median FU 28 mos
- CHR 97%; **CMR 19%**
- 46 no CMR: 14 relapses (8 with p210); 12 deaths in CMR

Category	No	% 2.5 –yr OS	% DFS
Total	60	58	49
p190	33	-	57
p210	18	-	40
CMR 3 mos	-	-	75

Chiaretti. Blood 126: abst 81; 2015

Low-intensity chemo Rx + Dasatinib in Ph + ALL ≥ 55 yrs

- 71 pts (2007-2010); median age 69 yrs (58-83)
- Dasatinib 100-140 mg/D, VCR 1mg Q wk, Dex 20-40 mg/D x 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-Asp C1,3,5; ara-C C2,4,6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- T315I at Dx 23% by NGS
- 36 relapses; T315I in 75%

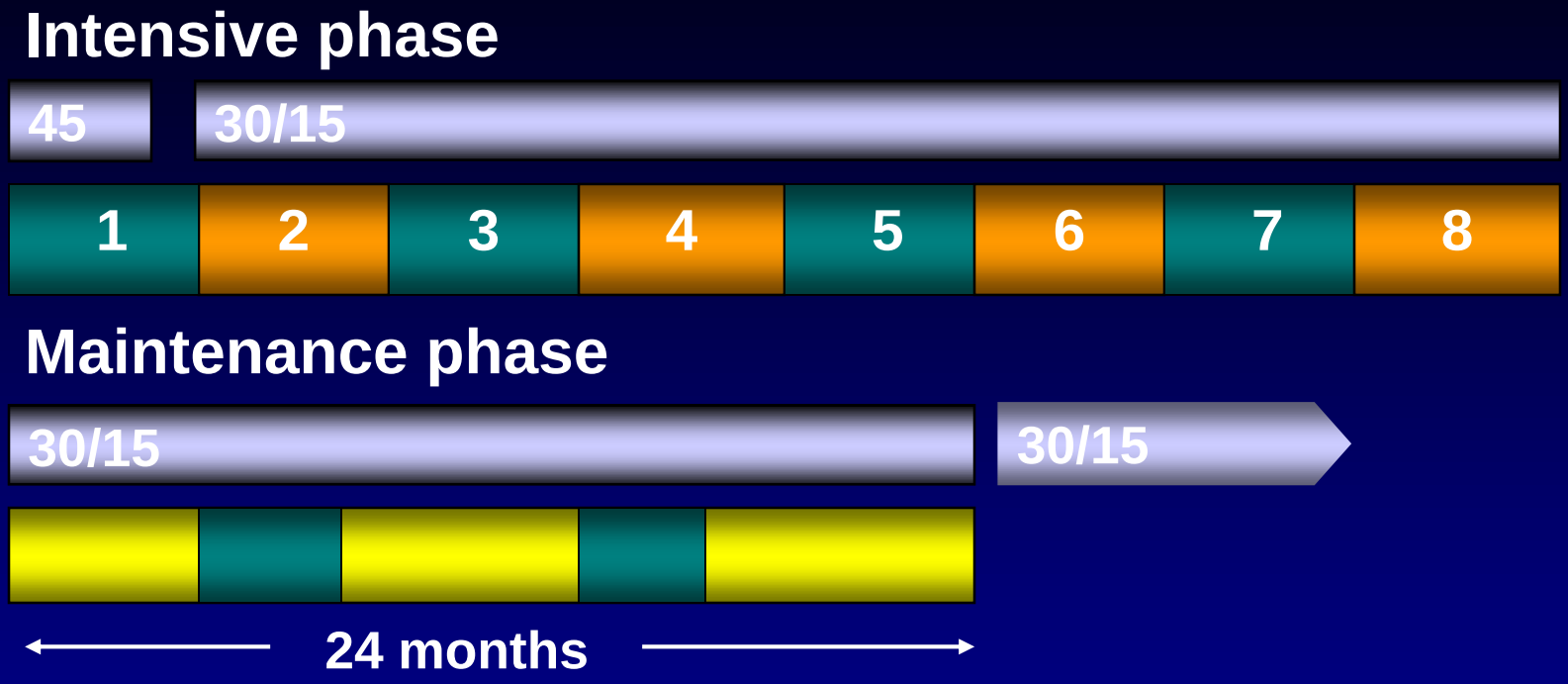
Rousselot. Blood 2016;128(6):774-82

Hyper-CVAD + Ponatinib in Ph-Positive ALL. Background

- Combination of cytotoxic chemotherapy with TKIs highly effective
- Ponatinib more potent BCR-ABL inhibitor
- Ponatinib suppresses T315I clones, commonly causing relapse (30% in our studies; 63% in French study)
- Ponatinib high activity: CCyR 50-60% in pts failing 2-3 TKIs or with T315I
- Significant vascular toxicity with ponatinib

Fielding. Blood. 2014; 123:843; Ravandi. Blood. 2010; 116: 2070; Cortes. NEJM. 2013;369:1783

Hyper-CVAD + Ponatinib. Design



- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Jabbour. Lancet Onc. 16:1547;2015

Hyper-CVAD + Ponatinib in Ph-Positive ALL. Patient Characteristics

Parameter N=76		N (%)/ Median [range]
Age (yrs)		47 (21-80)
≥ 60 yrs		20 (26)
Sex	Female	36 (47)
PS	2	8 (11)
WBC (x 10^9/L)		13.6 (0.9-629.4)
CNS +		5 (7)
CD20 +		26 (34)
Transcript	190	56 (74)
	210	19 (25)
	Unknown	1 (1)
CG	Ph+	55 (72)
	Diploid/IM (FISH or PCR+)	21 (28)

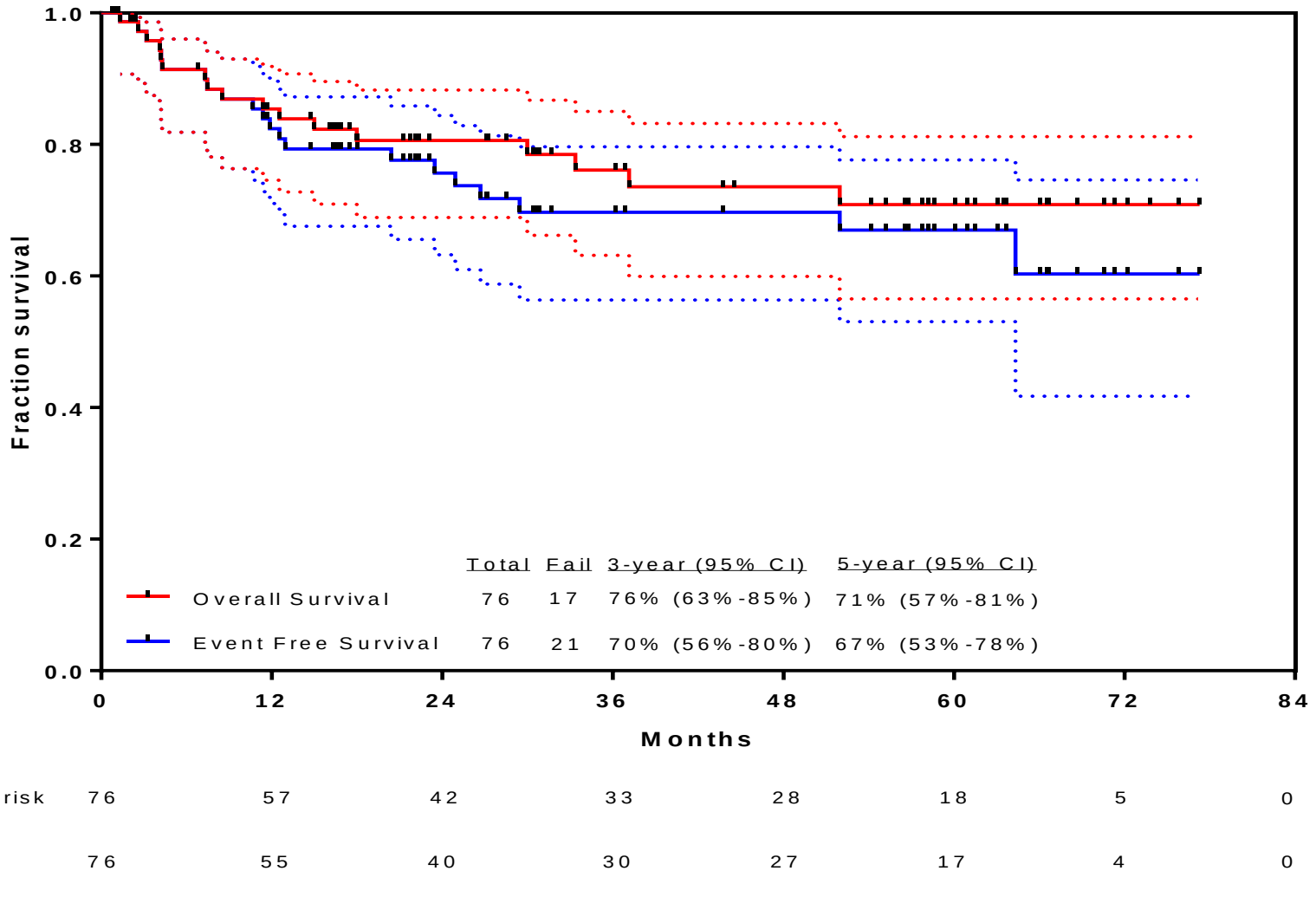
Hyper-CVAD + Ponatinib in Ph-Positive ALL. Overall Results

Parameter	N (%)
CR*	65/65 (100)
CCyR**	55/55 (100)
MMR***	74/76 (97)
CMR***	63/76 (83)
Flow negativity***	74/75 (99)
Early death	0 (0)

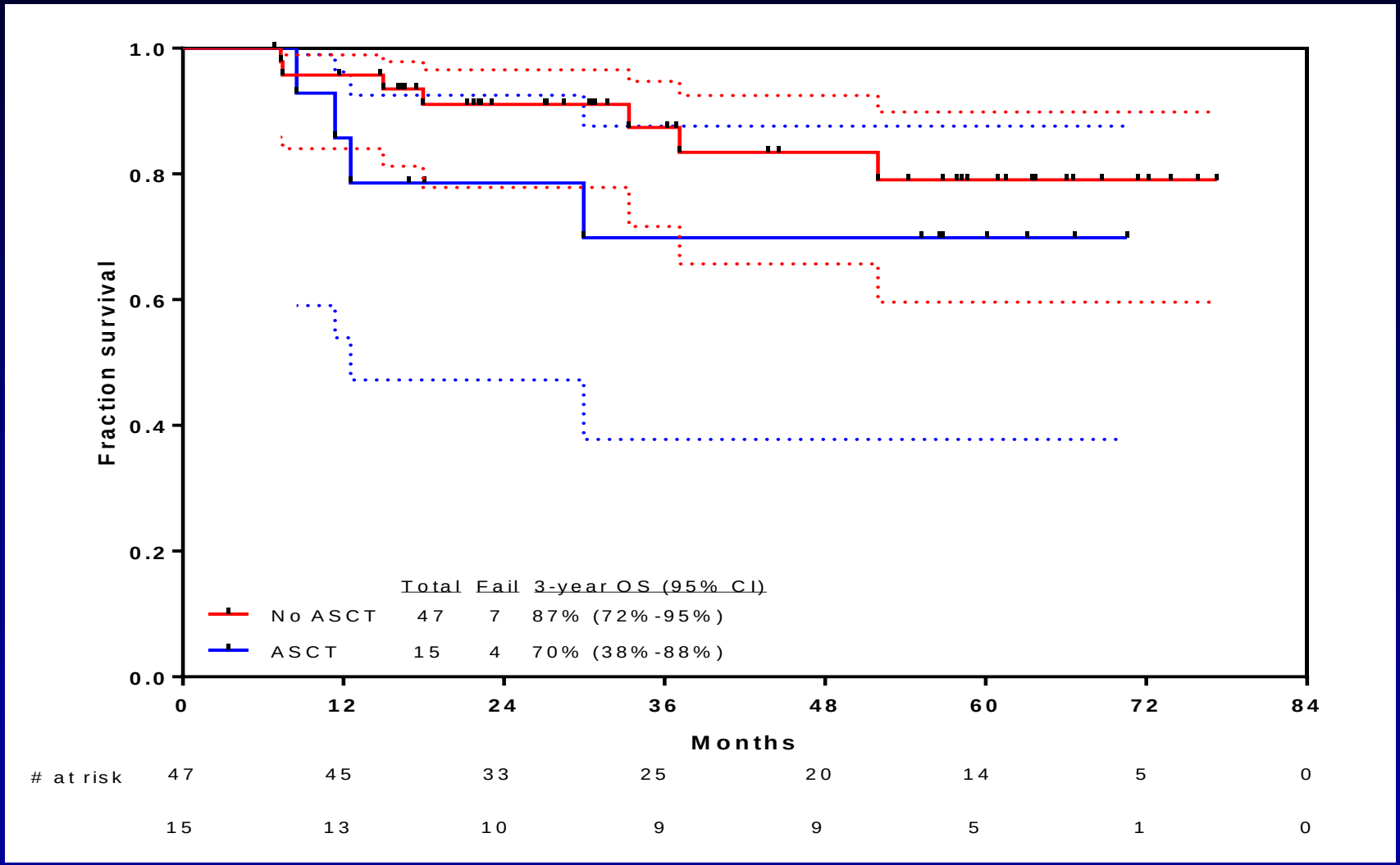
- * 11 pts in CR at start
- ** 21 pts diploid by CG at start or insufficient metaphases
- *** 1 pts no sample

Hyper-CVAD + Ponatinib in Ph-Positive ALL. Survival

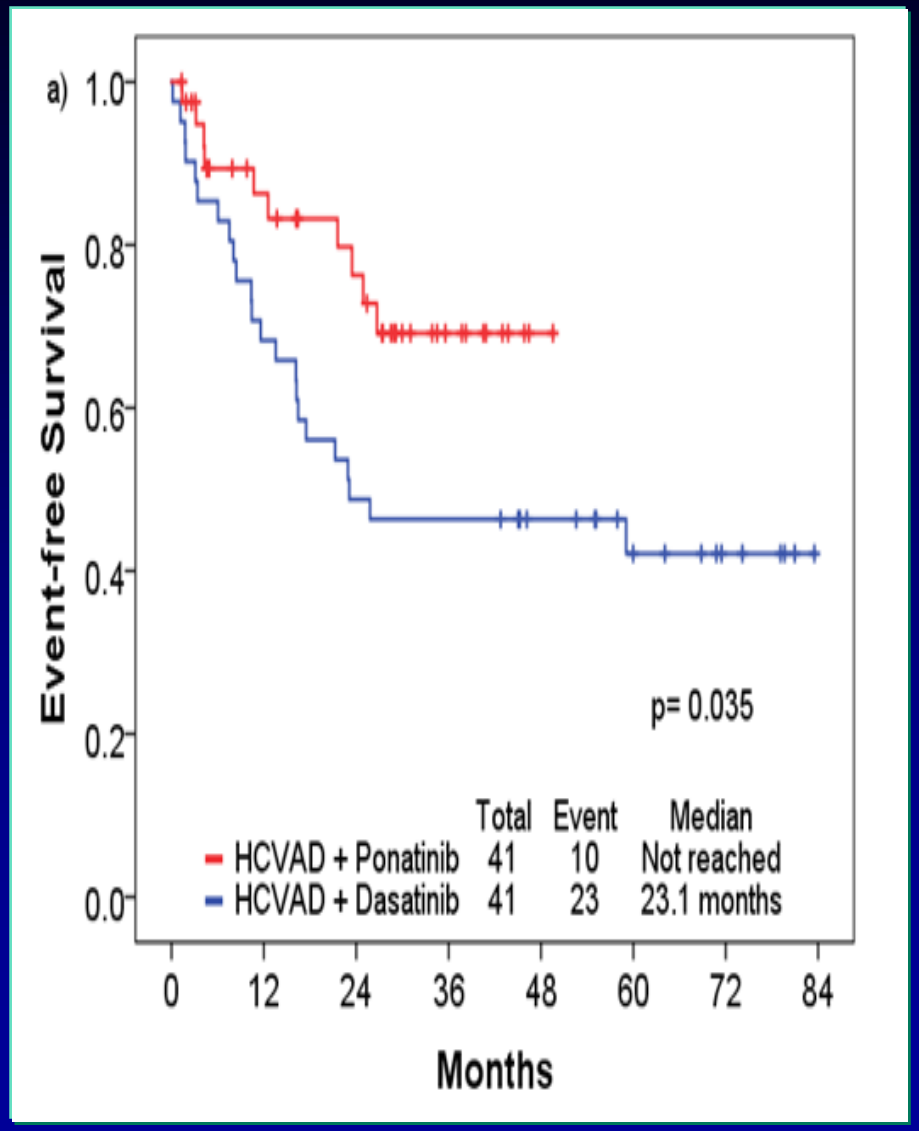
- Median follow up of 36 months (<1-77)

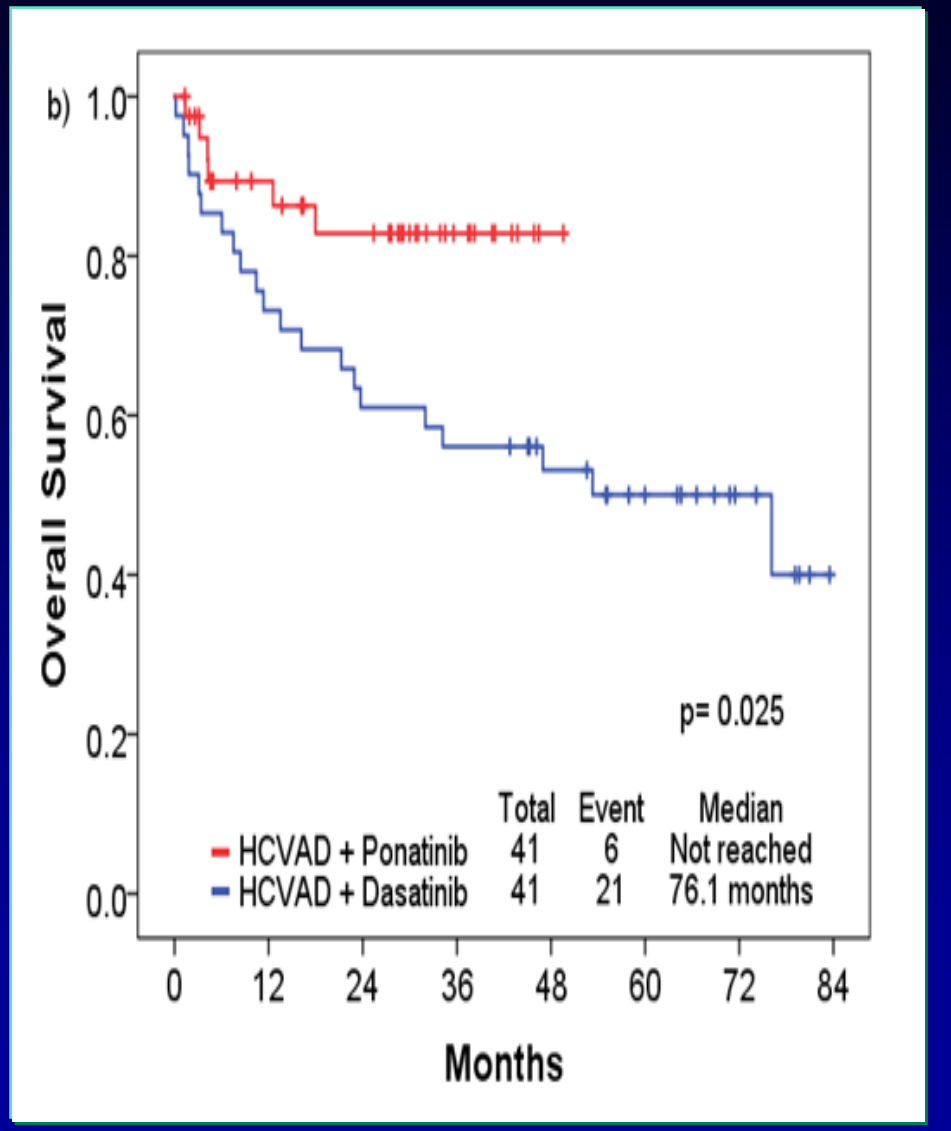


Hyper-CVAD + Ponatinib in Ph+ ALL. Landmark Analysis at 6 Months by SCT



Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph-Positive ALL.

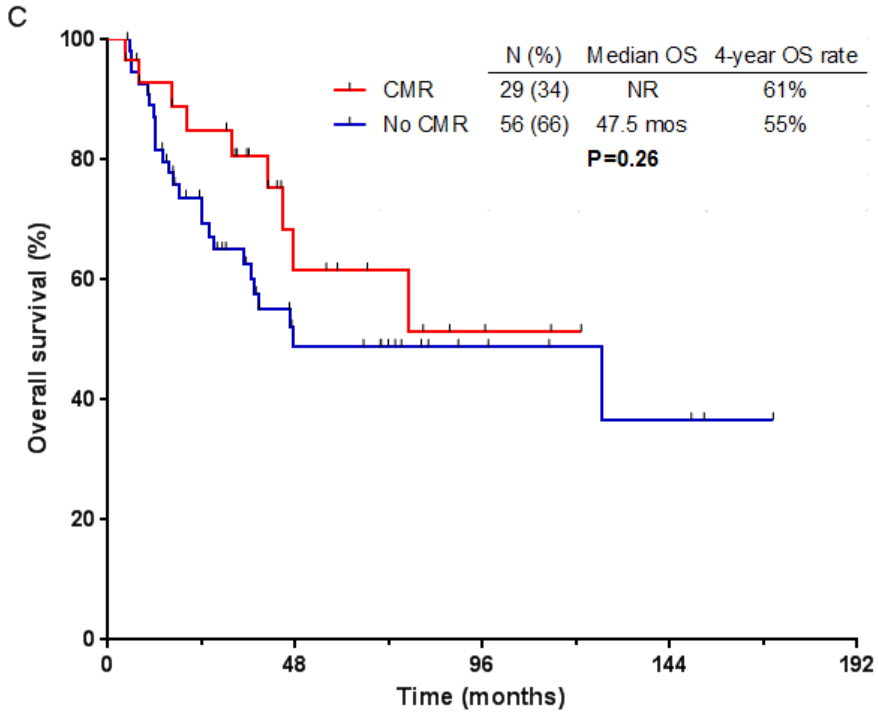




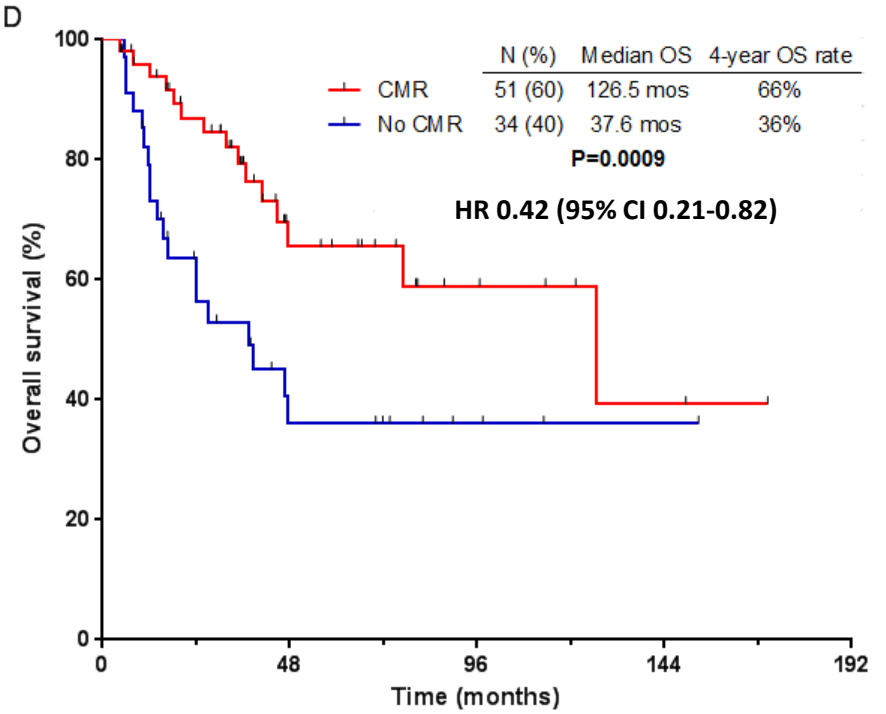
Sasaki. Cancer. 2016; 122(23):3650-3656

CMR in Ph-Positive ALL. OS for CMR vs. others

At CR



At 3 months



- **MVA for OS**

  CMR at 3 months (HR 0.42 [95% CI 0.21-0.82], P=0.01)

Short. Blood. 2016;128(4):504-7

SLIDE NON AUTORIZZATA
DAL RELATORE

SLIDE NON AUTORIZZATA
DAL RELATORE

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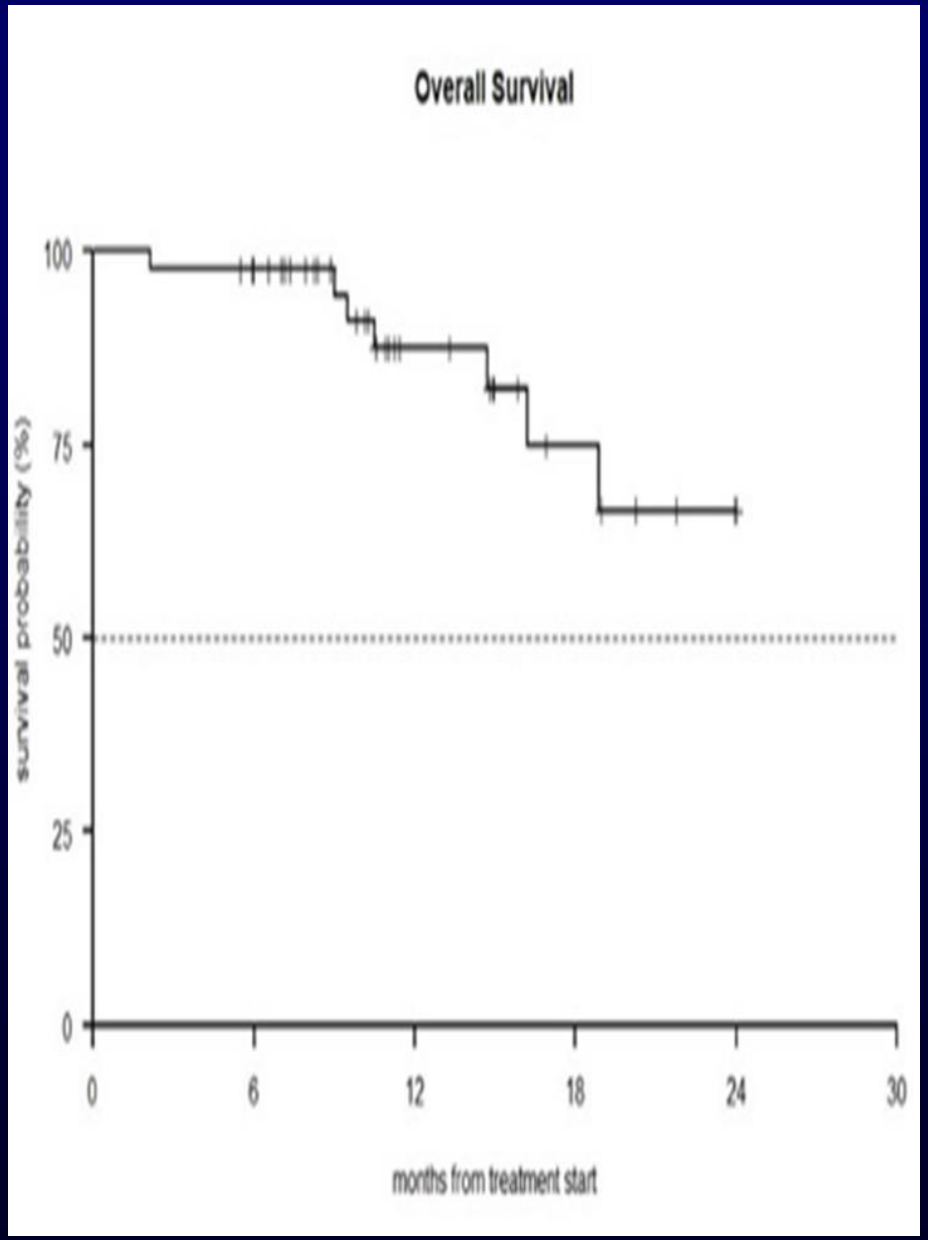
Ponatinib and Steroids in Ph-positive ALL

- 44 pts ≥ 60 yrs (9 pts < 60 yrs); median age 68 (27-85)
- Ponatinib 45mg/D x 6 weeks x 8 = 1 yr of Rx; steroids during induction; TIT Q mo
- CHR 42/42=100% post induction
- 6-mos CHR 90%, CGCR 90%, **CMR 13/32=40%**
- **Estimated 2-yr 60%**
- 13 SAEs and 2 deaths from ponatinib



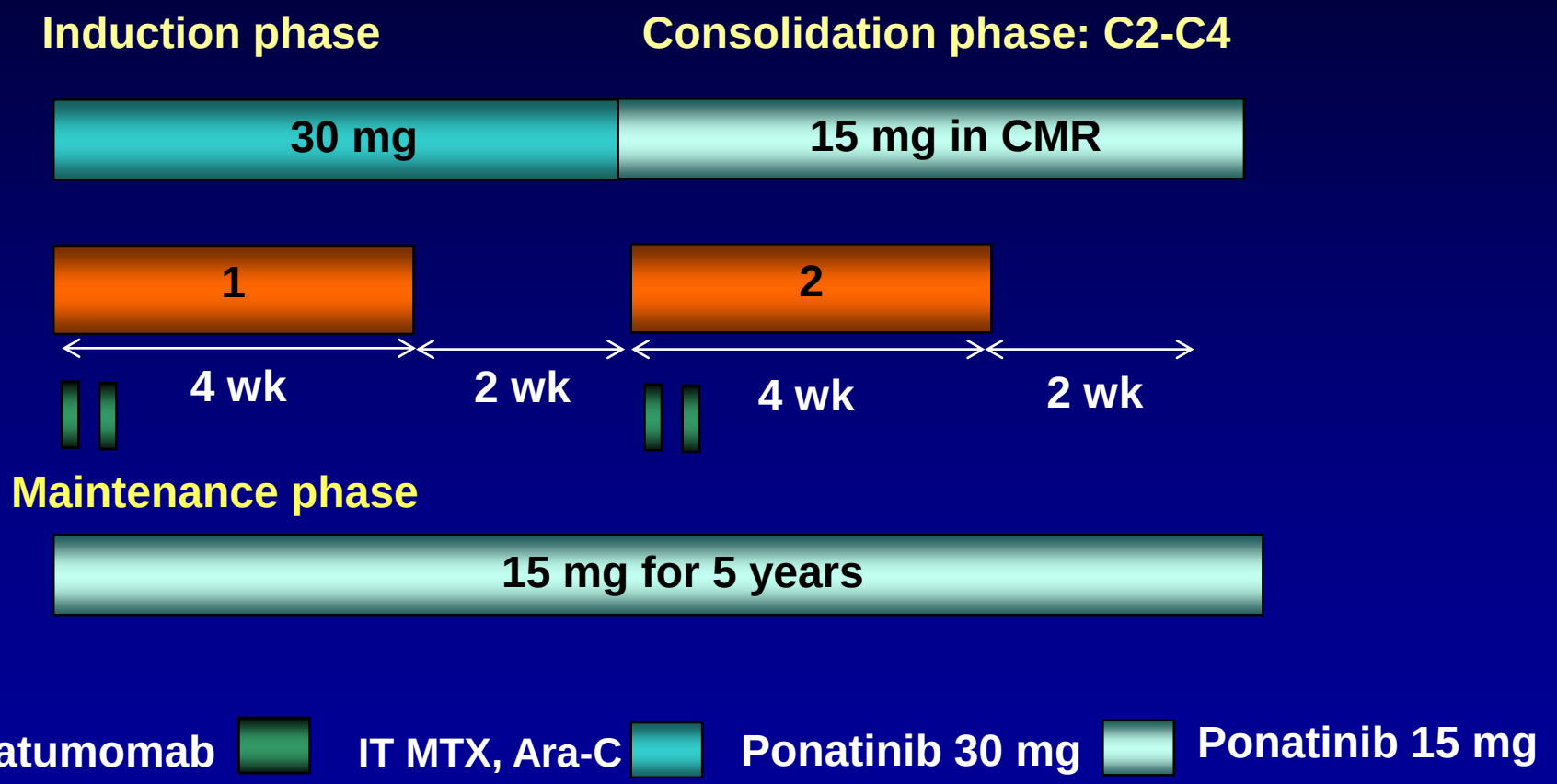
Martinelli. Blood 130: abst 99; 2017

Blinatumomab in Ph-positive ALL

- Single agent blinatumomab
- R/R Ph+ ALL to 2+ generation TKI (n=45)
- T3151 (n=10); ≥ 2 TKI (n=27); prior ponatinib (n=23)
- Primary endpoint **CR/CRh 16/45=36%**
- Secondary endpoints
  - Complete MRD response in CR: 88%
  - Proceed to alloHSCT: 44%
  - Median RFS 6.7 mo
  - **Median OS 7.1 mo**

Martinelli. JCO 35: 1795; 2017

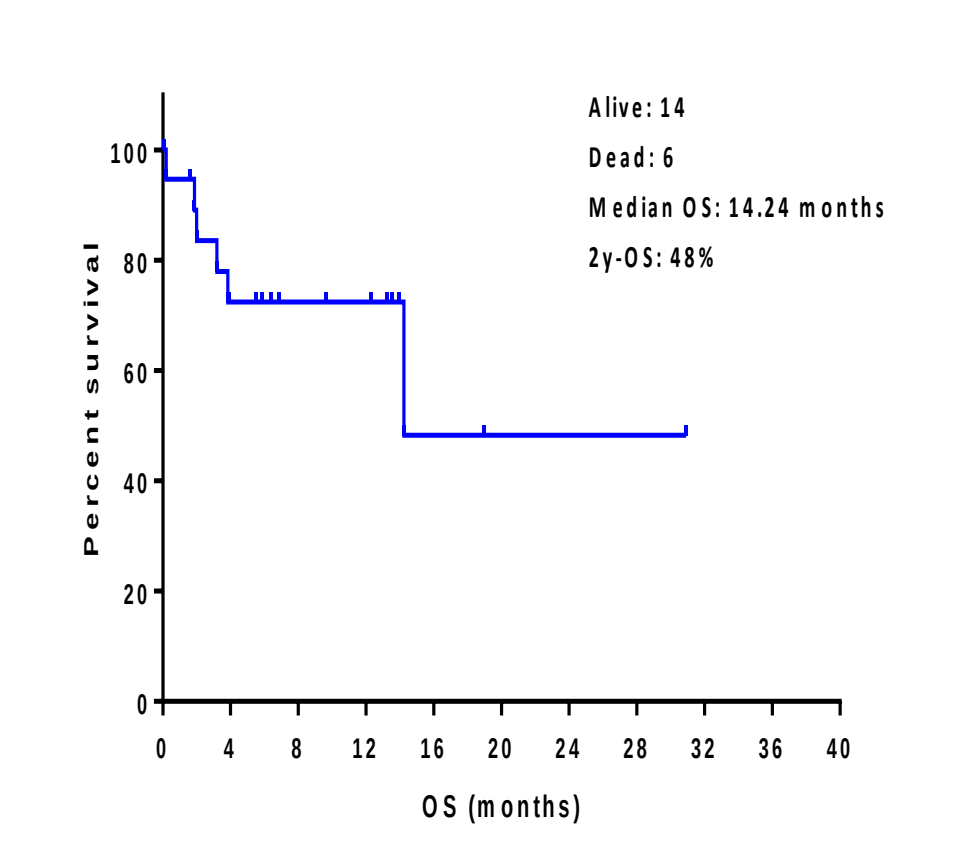
Blinatumomab-ponatinib in Ph-Positive ALL



Assi. Clin Lymphoma Myeloma Leuk. 2017;17(12):897-901

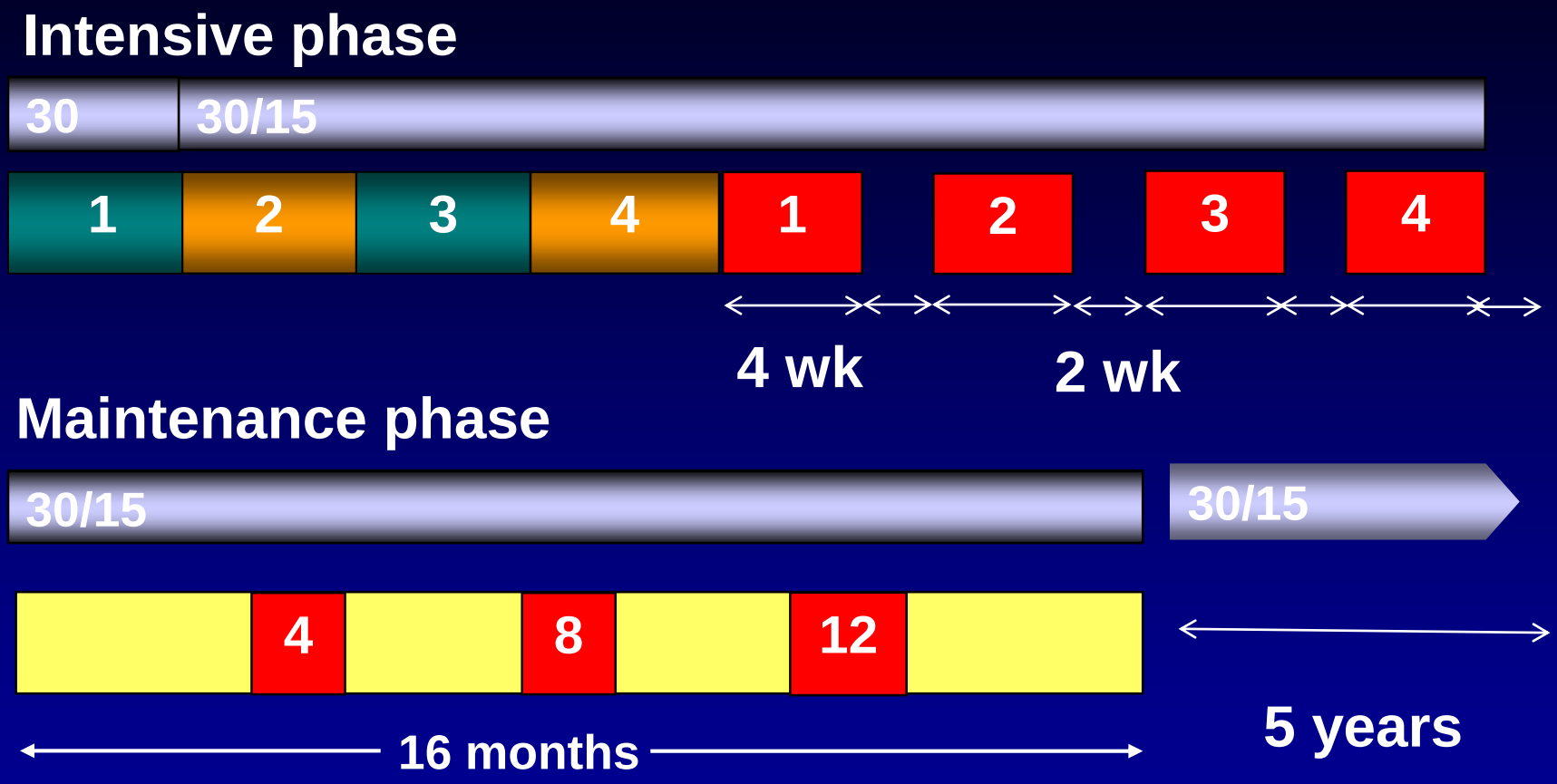
Blinatumomab-Ponatinib in Ph+ ALL. Retrospective Experience (N=20)

- R/R Ph+ ALL or CML-LBC
  - Molecular (n=10)
  - Hematologic (n=10)
- Median follow-up: 6 months
- 13/20 (65%) responded
  - 8/10 with MRD +
  - 5/10 with overt relapse



Assi. Clin Lymphoma Myeloma Leuk. 2017;17(12):897-901

Hyper-CVD + Ponatinib + Blinatumomab in Ph-positive ALL (N=60)



CNS prophylaxis (N=12)

Mini-Hyper-CVD

Ponatinib 30 mg →15 mg

Mini-MTX-cytarabine

Vincristine + prednisone

Blinatumomab

Ph-Positive ALL. General Guidelines

- Combinations of chemo Rx + TKIs
- Early and daily continuous and indefinite TKIs better than later intermittent or limited-duration TKIs
- Newer TKIs better than imatinib
- Ponatinib best TKI?
- Today – allo SCT in CR1

  Future – allo SCT in CR1 if no CMR

Questions in Ph-positive ALL

- Do we need allo SCT? --not always; never?
  - Identify patients who can be cured without allo-SCT; e.g. 3-mos CMR, others
- Ponatinib best TKI?-- 3 mos-CMR 83%; 5-year OS rate 70%
  - Phase III low-dose CT + Imatinib vs low-dose CT + ponatinib
- How much chemoRx-- low-Intensity versus intensive chemo Rx?
  - Mini-HCVD-Ponatinib-Blinatumomab
- Can we cure Ph-positive ALL without chemoRx or allo SCT?--ponatinib+blinatumomab

Thank You