ALL– Management of Ph-positive and Ph-like ALL in 2019

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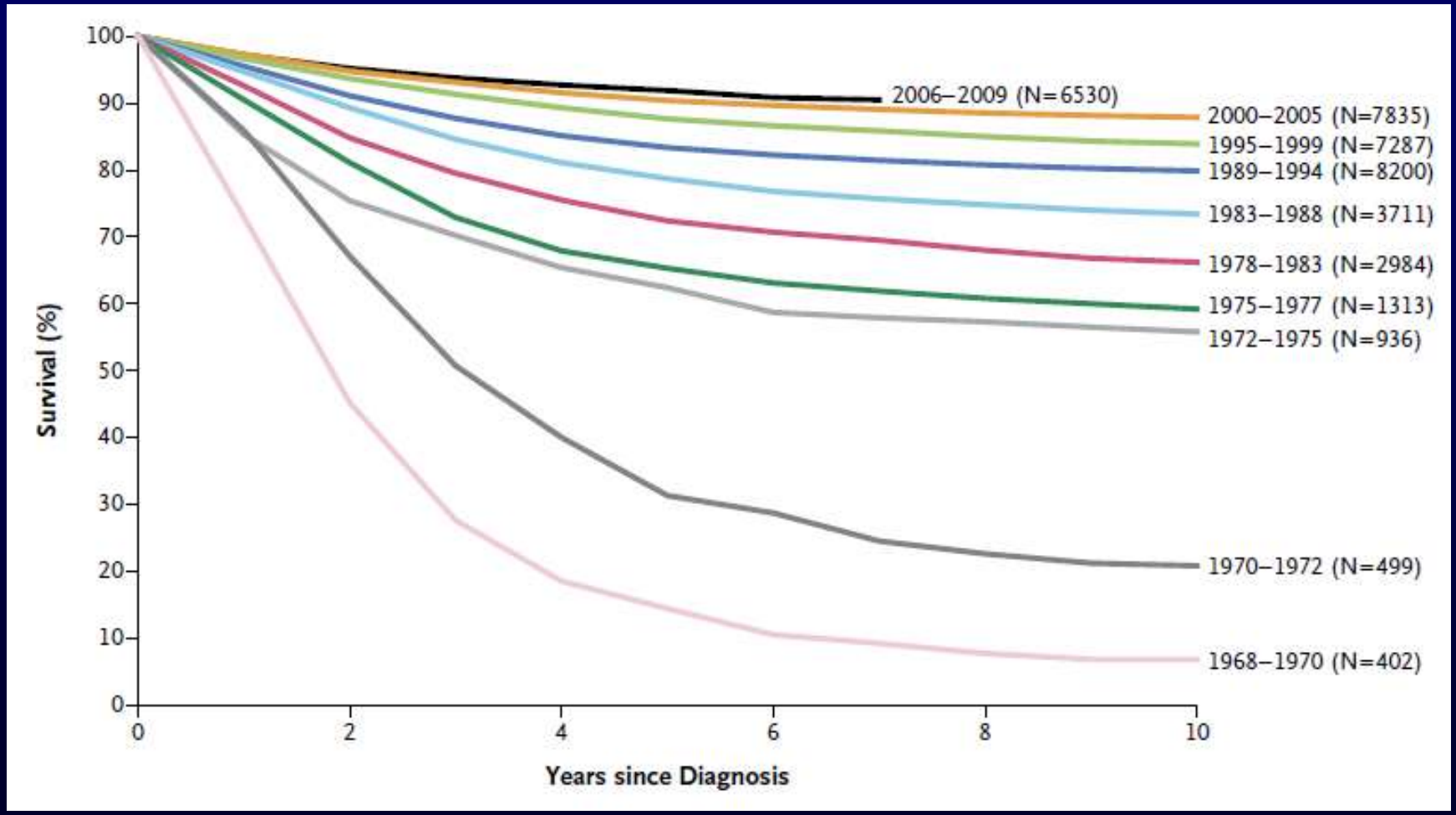
March, 2019

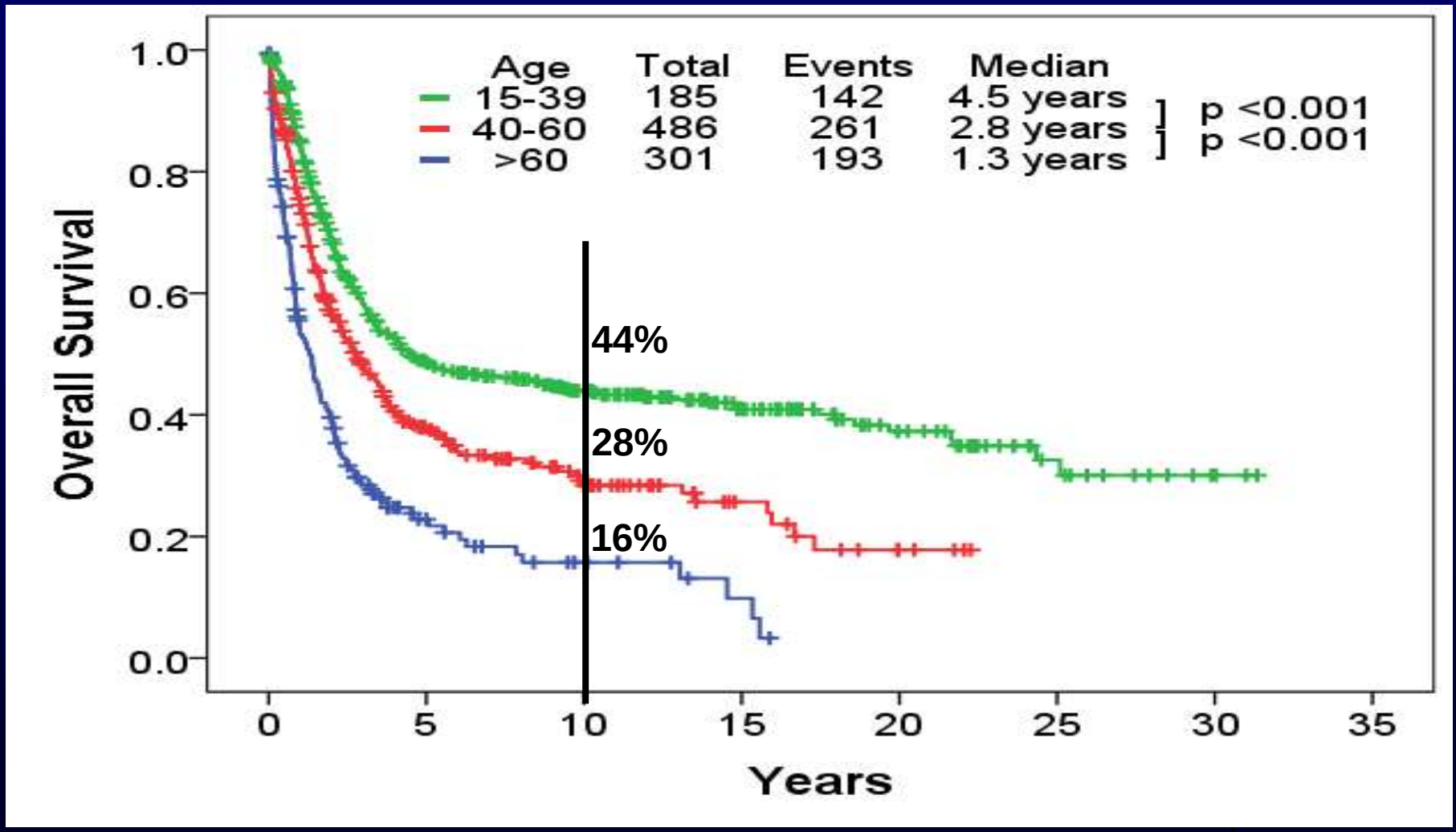
Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials



Hunger. NEJM. 2015;373(16):1541-1552

Survival of 972 Adults with Ph-negative ALL

- 972 pts Rx 1980-2016; median F/U 10.4 years



Sasaki. Blood 2016; 128:3975

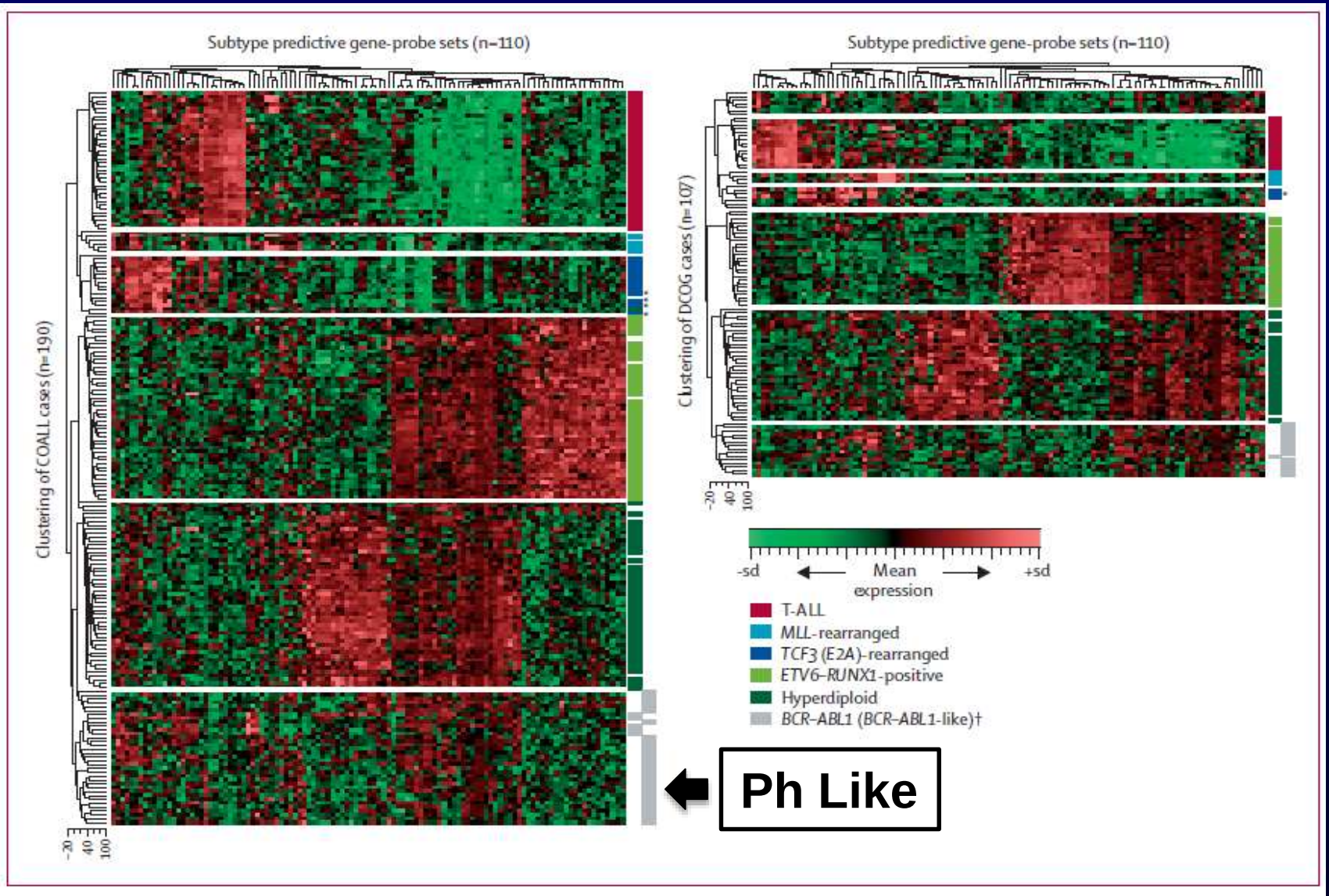
Reasons Why Pediatric ALL Does Better Than Adult ALL

Entity	Prognosis	% Pediatric	% Adult
Hyperdiploid	Favorable	25-30	5
t(12;21), *ETV6-RUNX1*	Favorable	20-25	2
Ph+ALL	Unfavorable	5	25
Ph-like ALL	Unfavorable	10	25

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 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T

Ph-like ALL



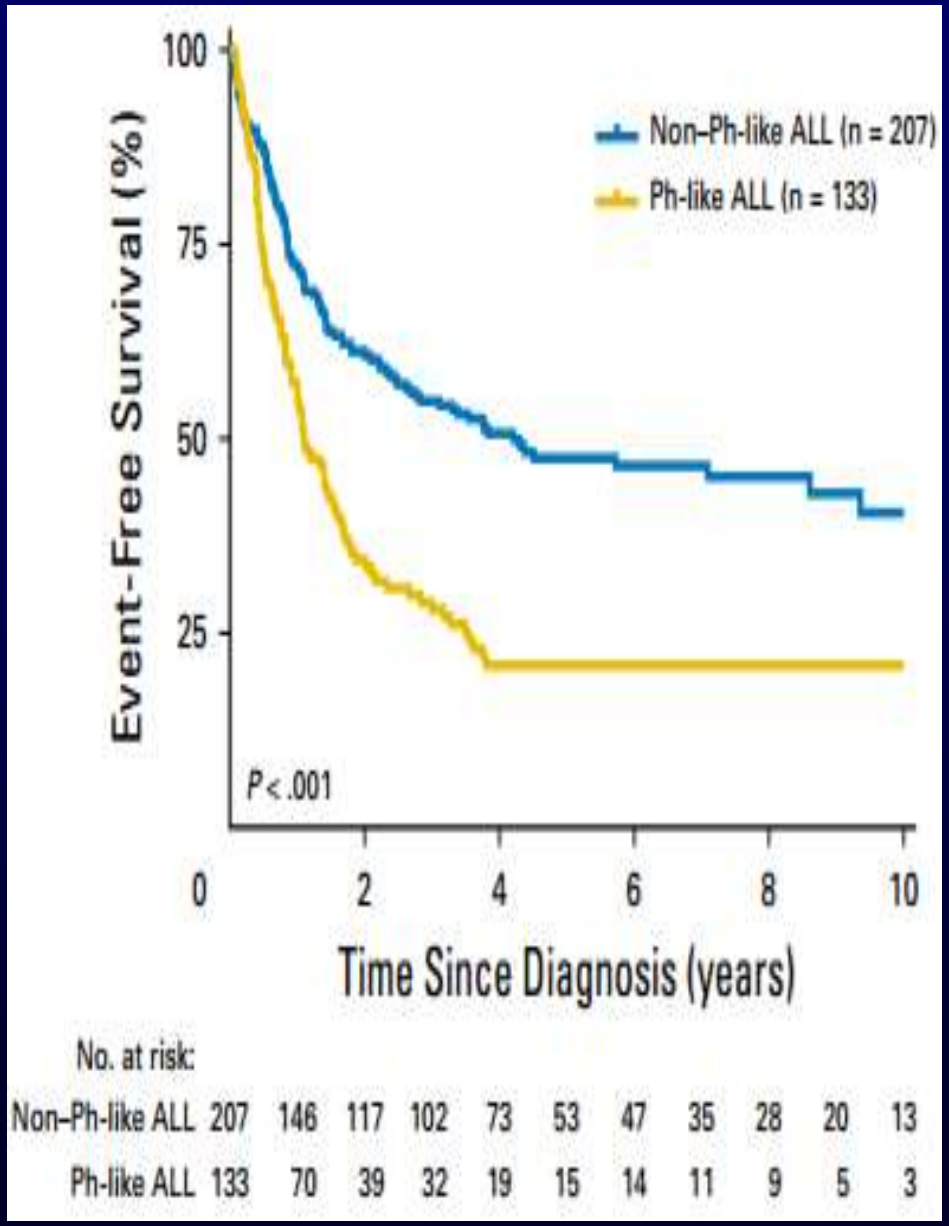
Den Boer. Lancet Oncology 2009

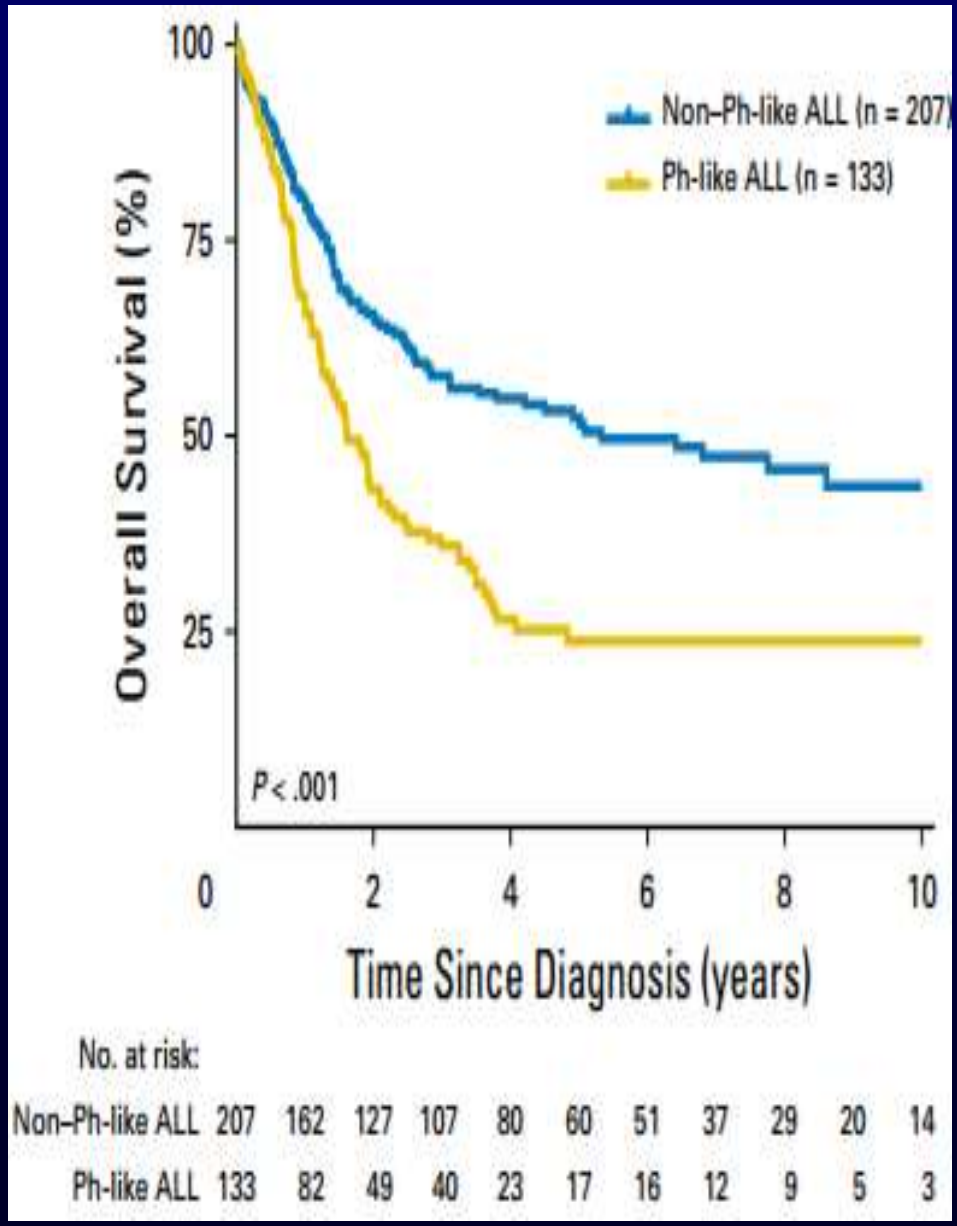
Ph-like ALL - Characteristics

- Gene expression profile similar to Ph+ ALL
- No Ph chromosome or BCR-ABL1
- Negative for most recurrent genetic abnormalities (MLL-rearrangement, ETV6-RUNX1, E2A-rearrangement, hyperdiploidy)
- IKZF1 alterations---IKAROS for lymphoid lineage development

Den Boer et al. Lancet Oncology 2009. Mullighan et al. N Engl J Med. 2009

Ph-Like ALL-- Survival and EFS

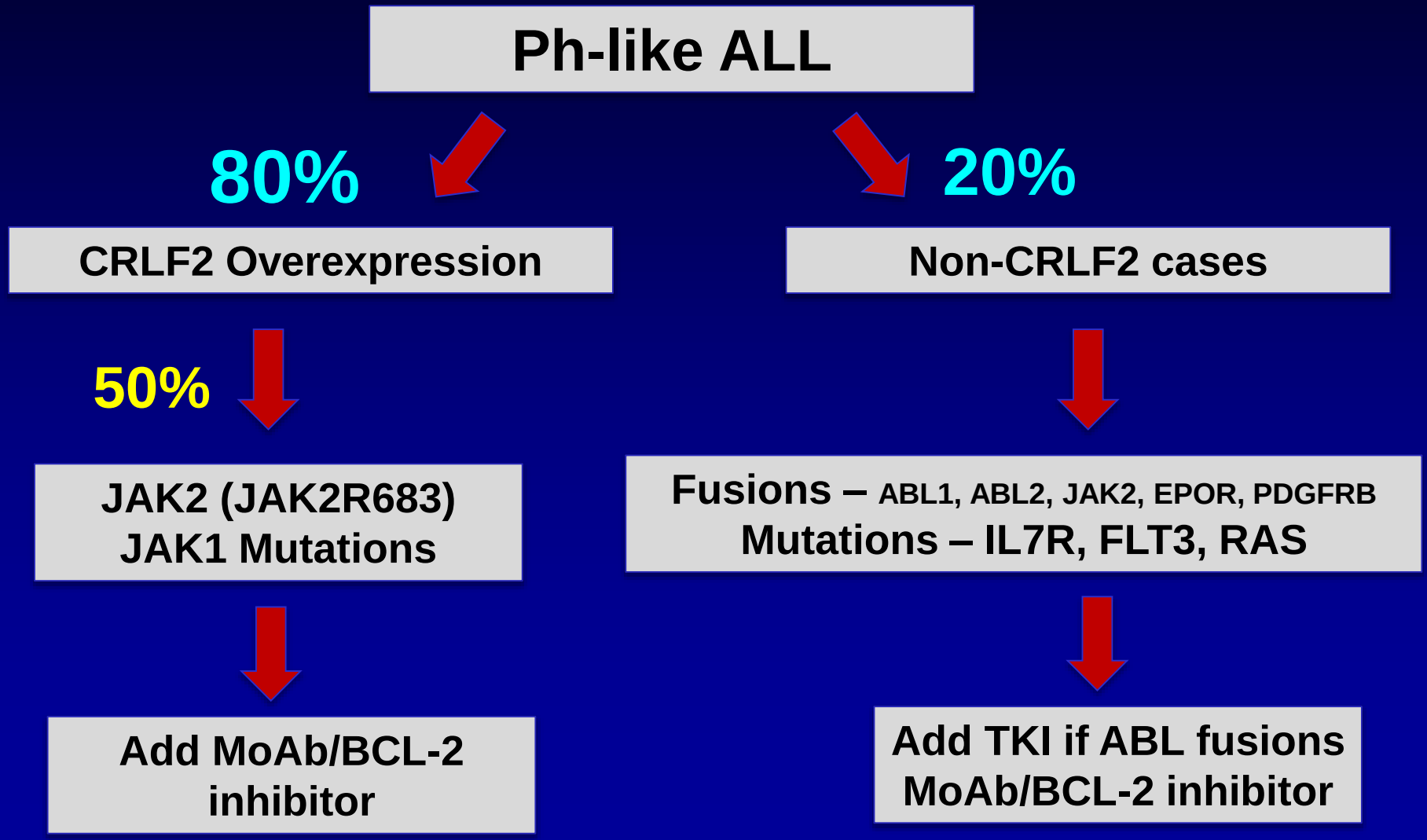




Roberts, et al. JCO 35:394; 2017

Ph-like ALL Molecular Lesions

- Ph-like 25-30% of ALL; poor prognosis

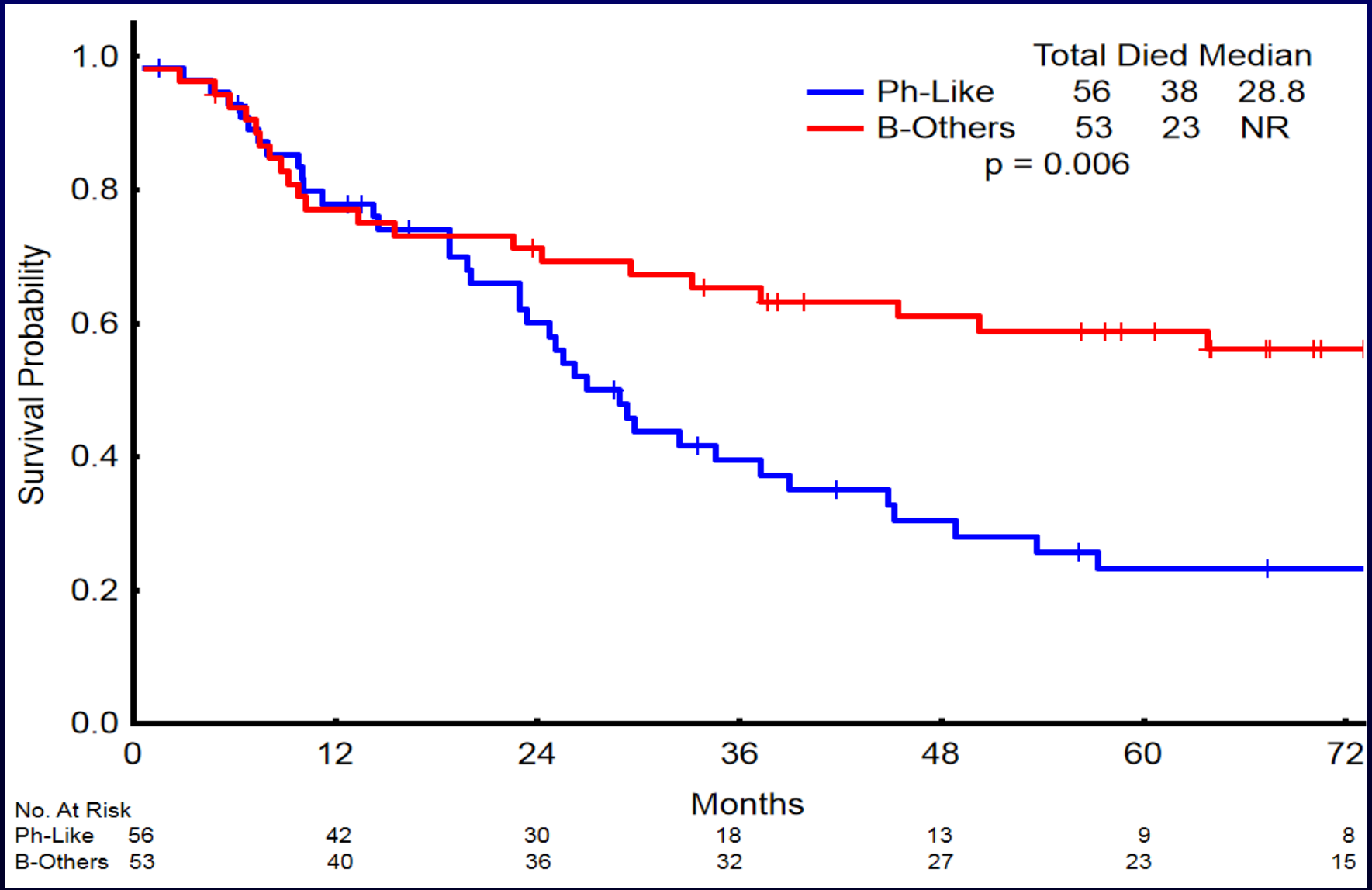


Ph-like ALL. Higher MRD + Rate

B-ALL Categories (N=155)				
	Ph-Like	Ph+	B-other	p-value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	0.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<0.001
Negative	10 (30)	19 (56)	27(87)	

Jain. Blood 2017; 129:572-581

Ph-like ALL – Worse Survival



Jain. Blood 2017; 129:572-581

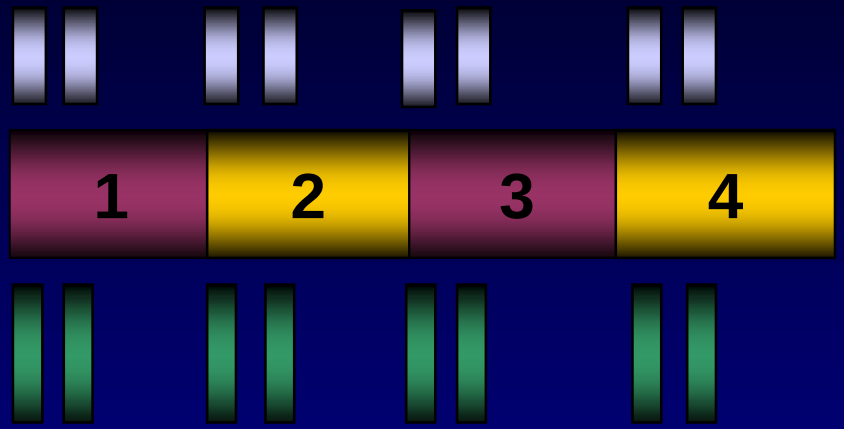
Ph-like ALL. Summary and Future Directions

- Ph-like 25-30% of ALL; poor prognosis
- 50-80% have CRLF2 rearrangement, of which 50% have JAK mutations
- ABL and JAK fusions in CRLF2 non-rearranged cases
- FISH and RT-PCR identifies fusions
- Plans: add TKI if ABL fusions, and antibodies/venetoclax if CRLF2+, to frontline and salvage ALL

Hyper-CVAD + Blinatumomab in FL B-ALL

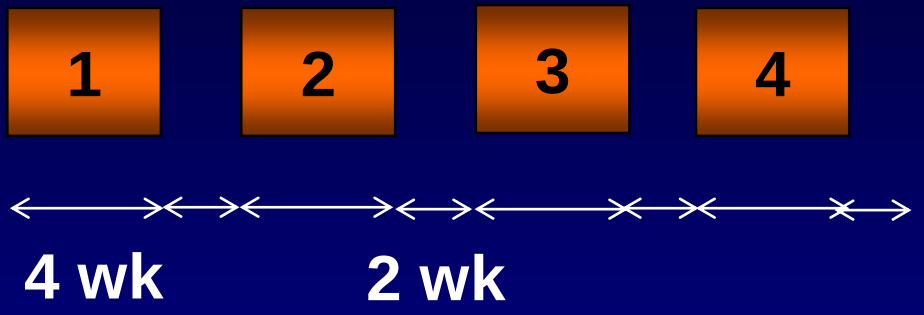
Treatment schedule

Intensive phase



Blinatumomab phase

*After 2 cycles of chemo for Ho-Tr, Ph-like, t(4;11)



Maintenance phase

Hyper-CVAD

Rituximab or Ofatumumab

MTX-Ara-C

IT MTX, Ara-C

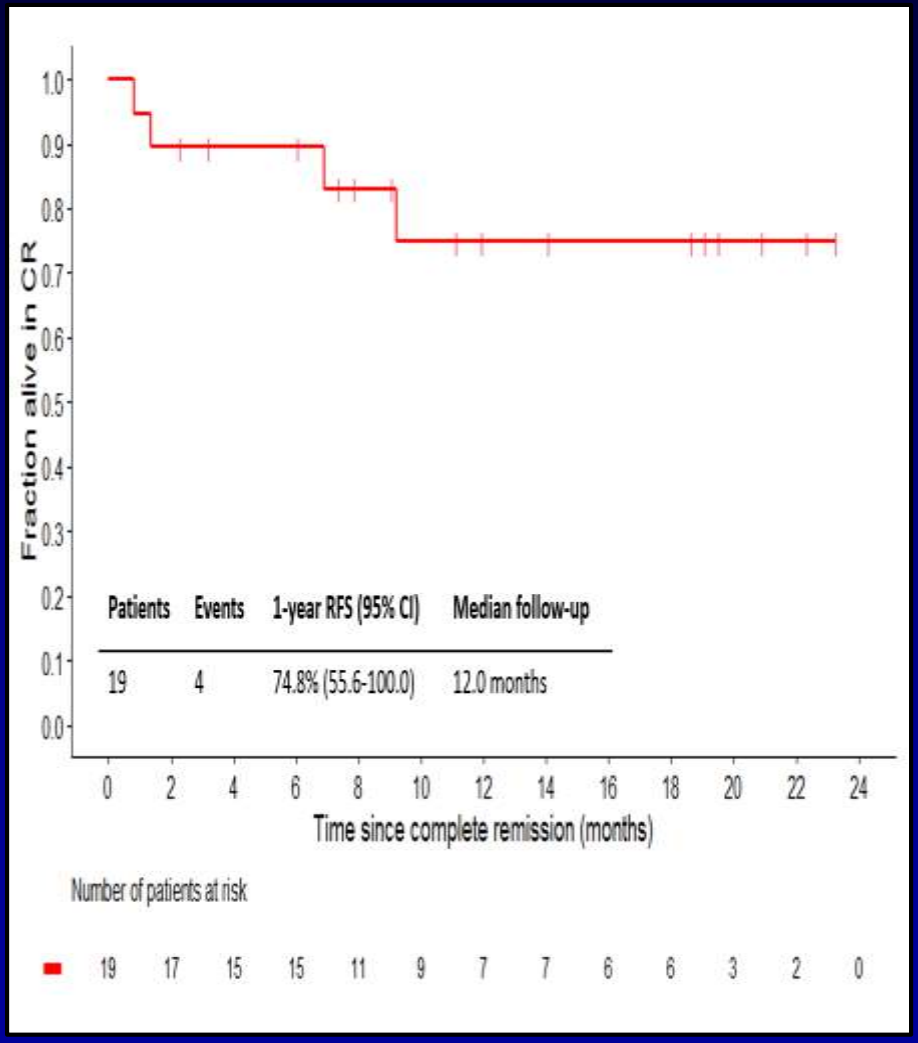
POMP

Blinatumomab

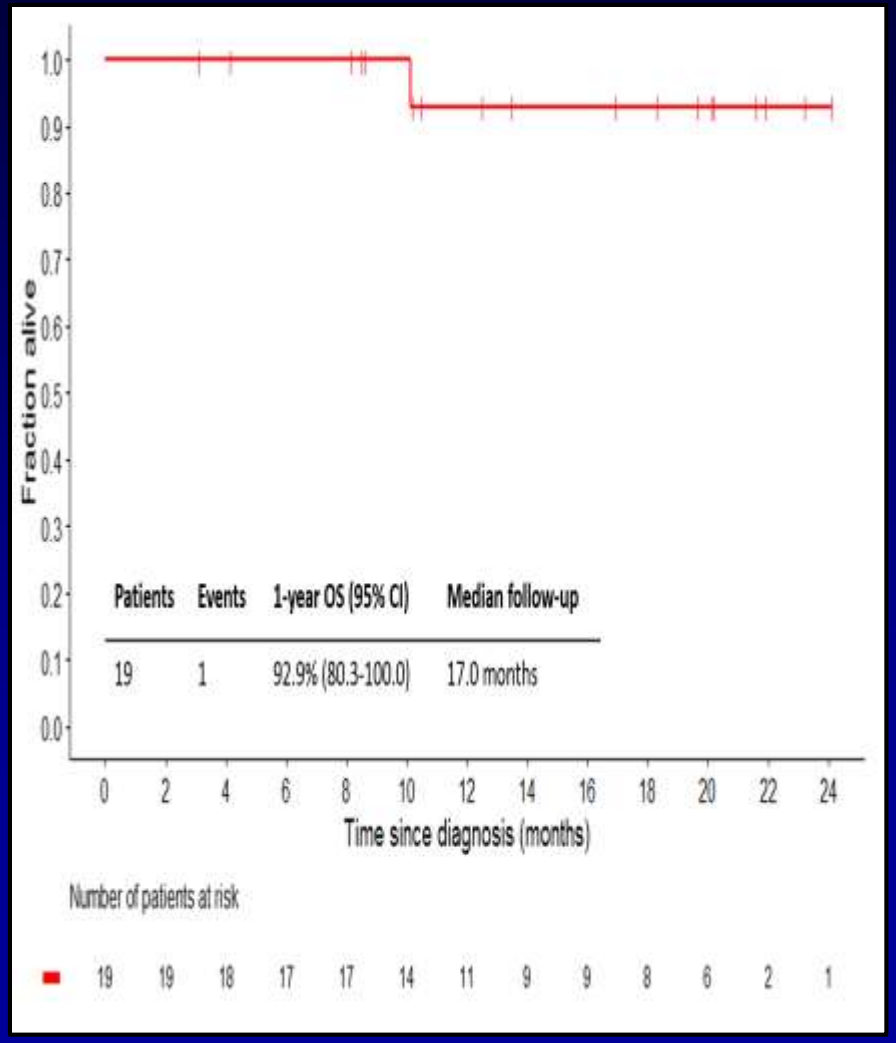
Richard-Carpentier. Blood 132: abst 32; 2018

Hyper-CVAD + Blinatumomab in FL B-ALL
Outcome

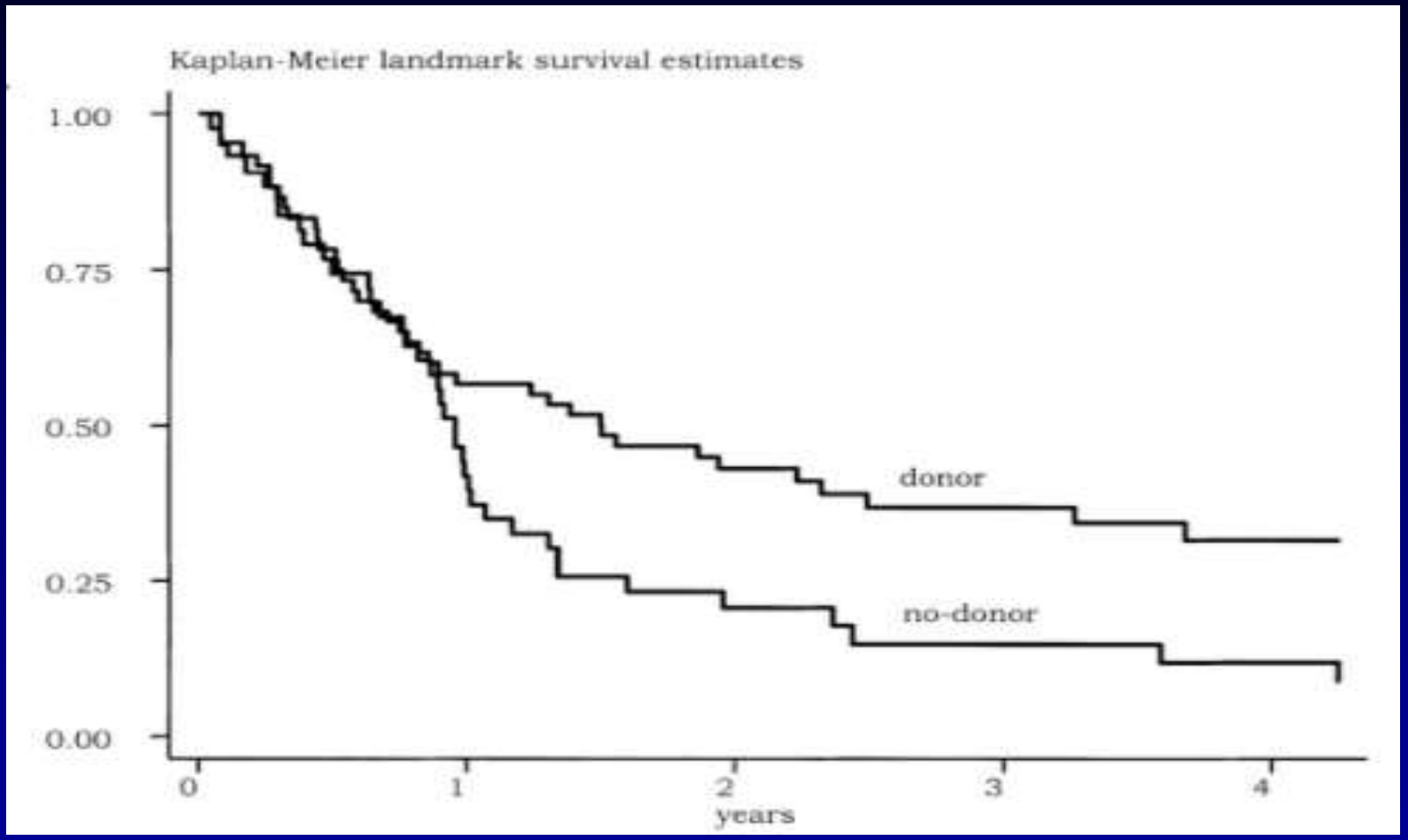
RFS



OS



SCT for Ph+ ALL. Pre-TKI

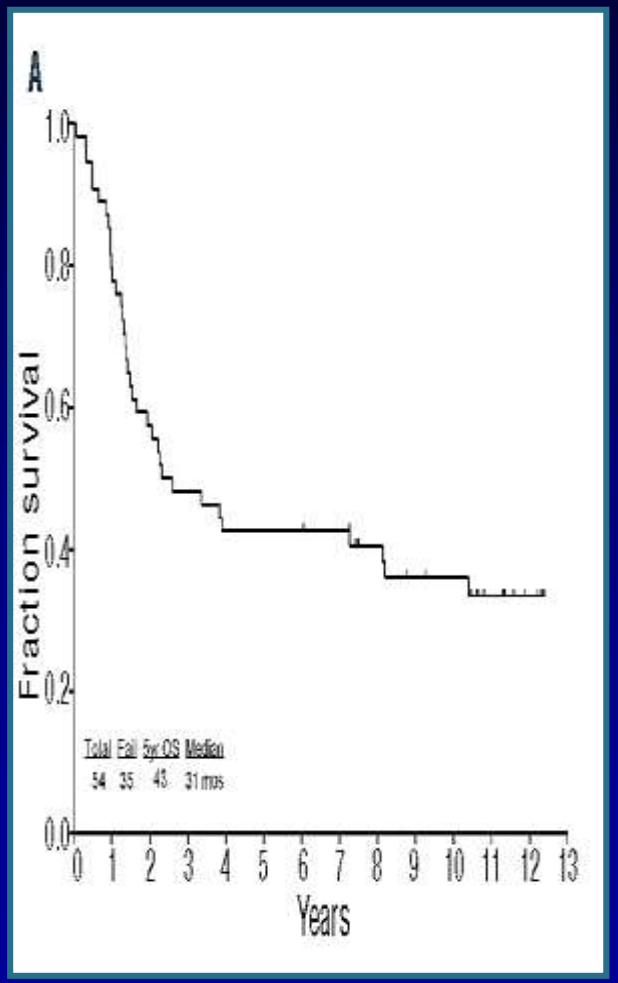


- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

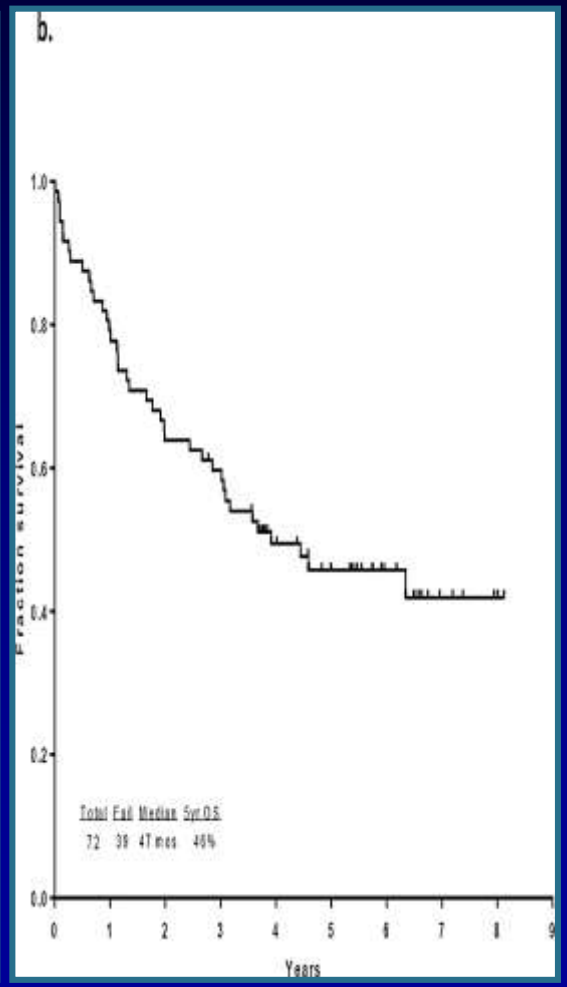
Dombret H et al *Blood* 2002

TKI for Ph+ ALL

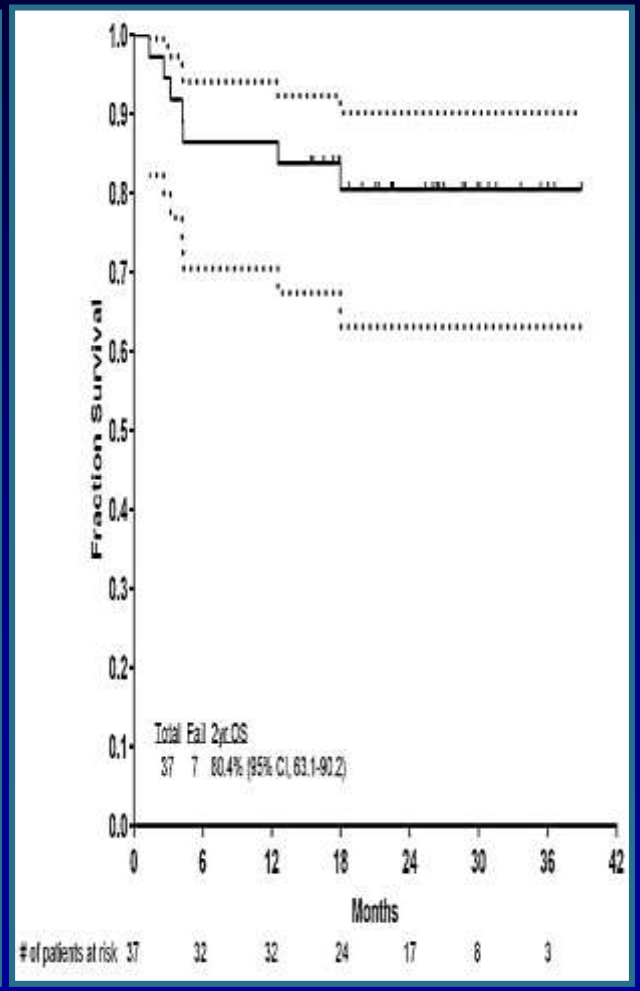
Imatinib; 5-yr OS=43%



Dasatinib; 5-yr OS=46%



Ponatinib; 5-yr OS=71%



Daver, Haematologica 2015; Ravandi, Cancer 2015; Jabbour, Lancet Onc 2015; Jabbour, Lancet Hematology 2018

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

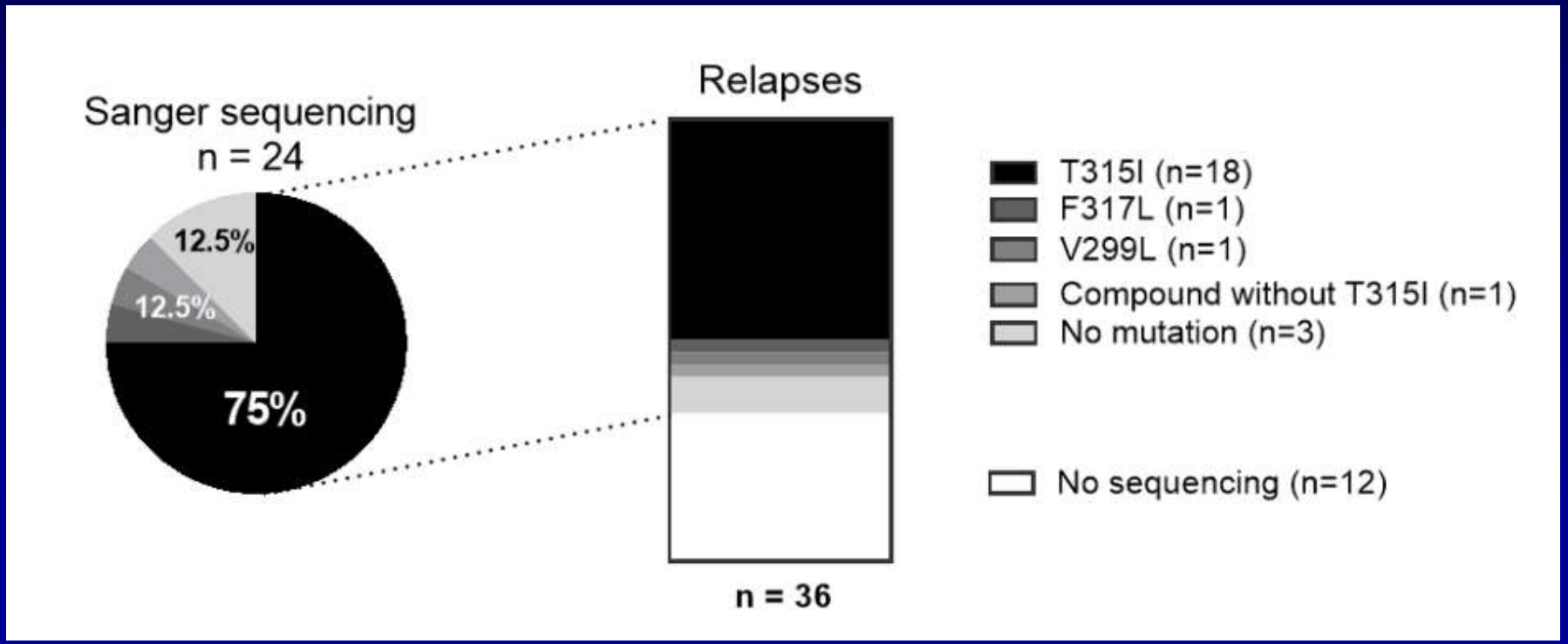
Low-intensity chemo Rx + Dasatinib in Ph + ALL ≥ 55 yrs

- 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

T315I Mutations at Diagnosis and Relapse in Ph+ ALL

- **T315I kinase domain mutation present in 18/24 patients (75%) at time of relapse**



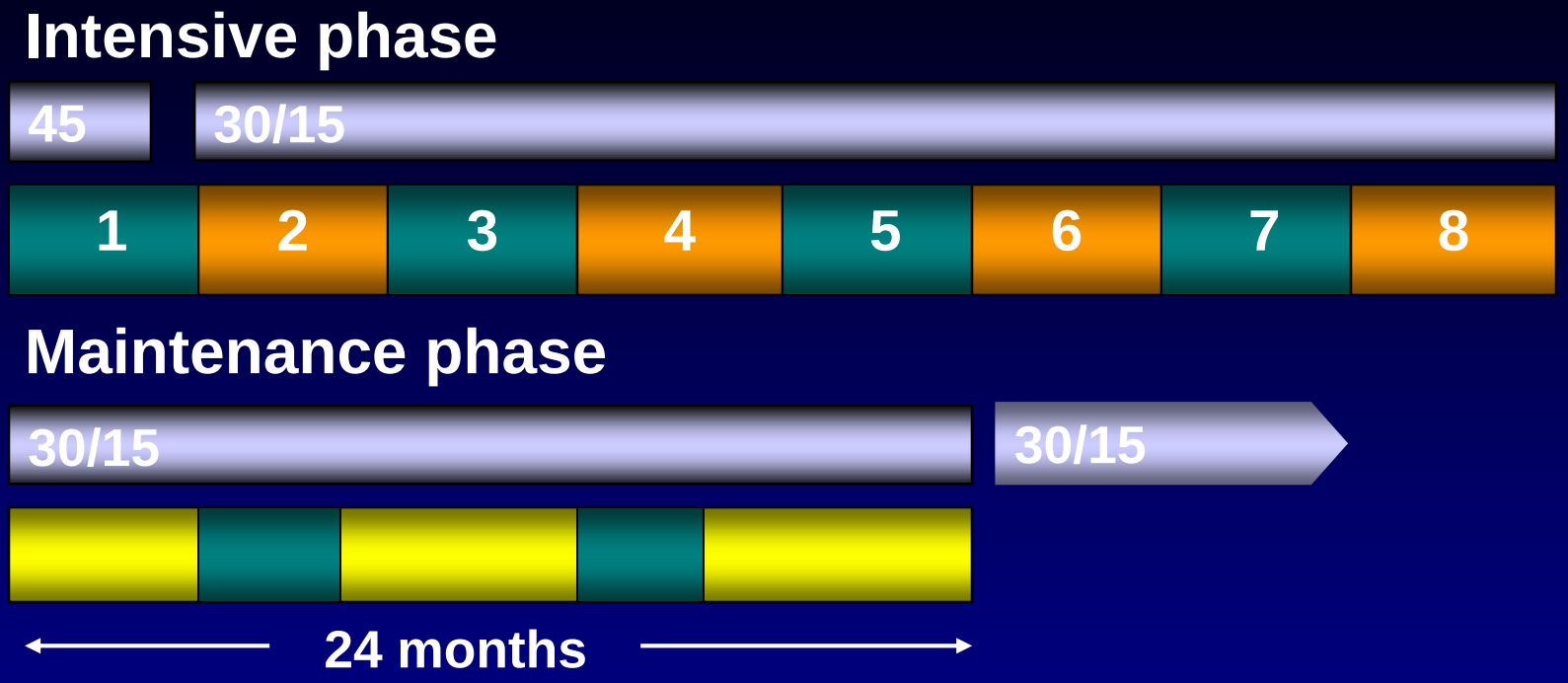
Rousselot. Blood 2016;128(6):774-82

Nilotinib+Low-intensity Chemo Rx in Newly-Dx Older Ph-positive ALL

- 79 Rx; 72 evaluable. Median age 65 yrs (55-85)
- Nilotinib 400mg BID; decadron/VCR
- CR 68/72=94%; 24 had allo SCT
- PCR negative 58% post consolidation 2
- 11 deaths in CR; 6 post SCT
- 4-yr EFS 42%, 4-yr OS 47%
- 4-yr OS 61% with SCT vs 39% without SCT

Ohmann. Blood 132: abst 31; 2018

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. Jabbour. Lancet Hematology 2018

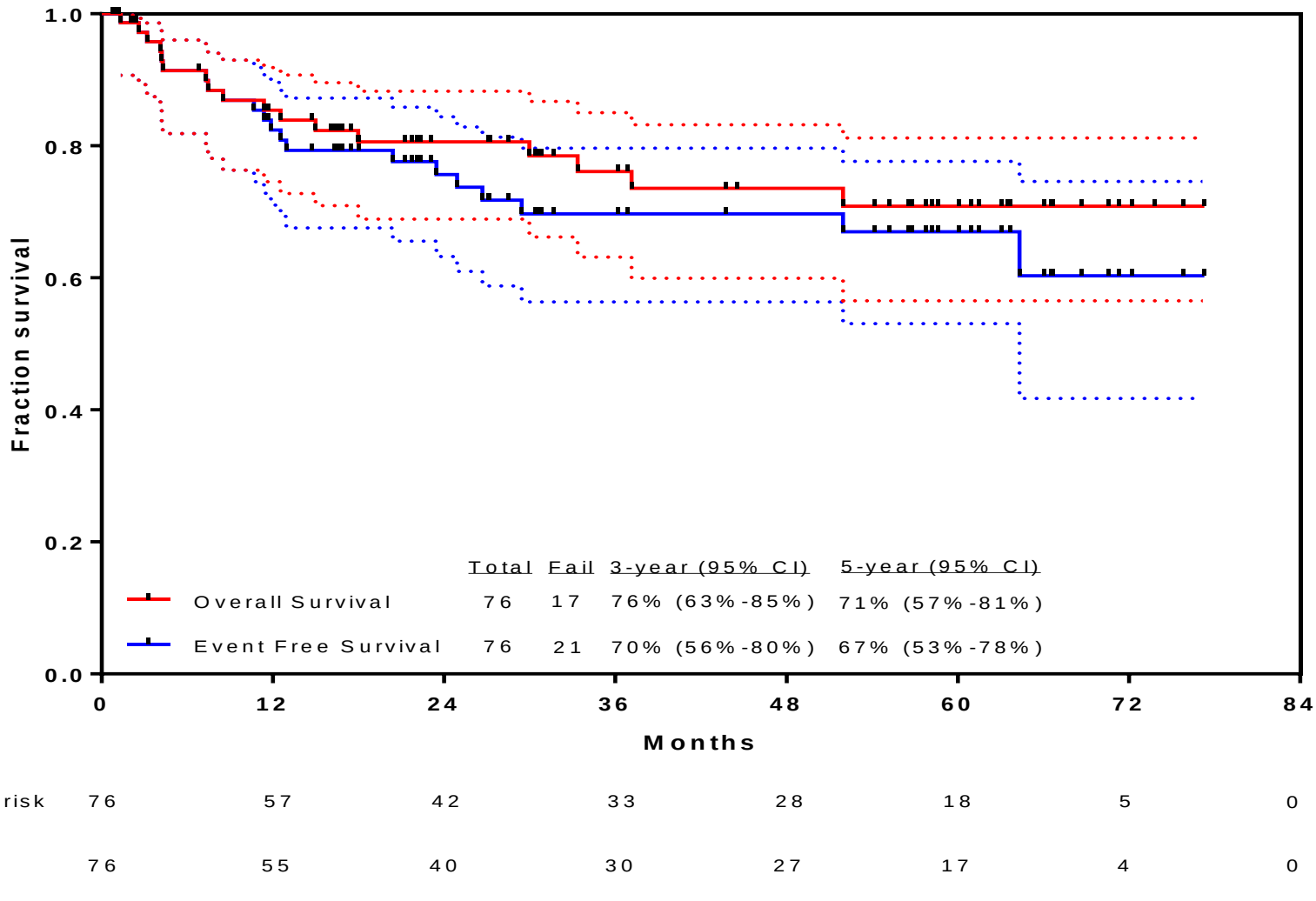
Hyper-CVAD + Ponatinib in Ph-Positive ALL. Overall Results

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)

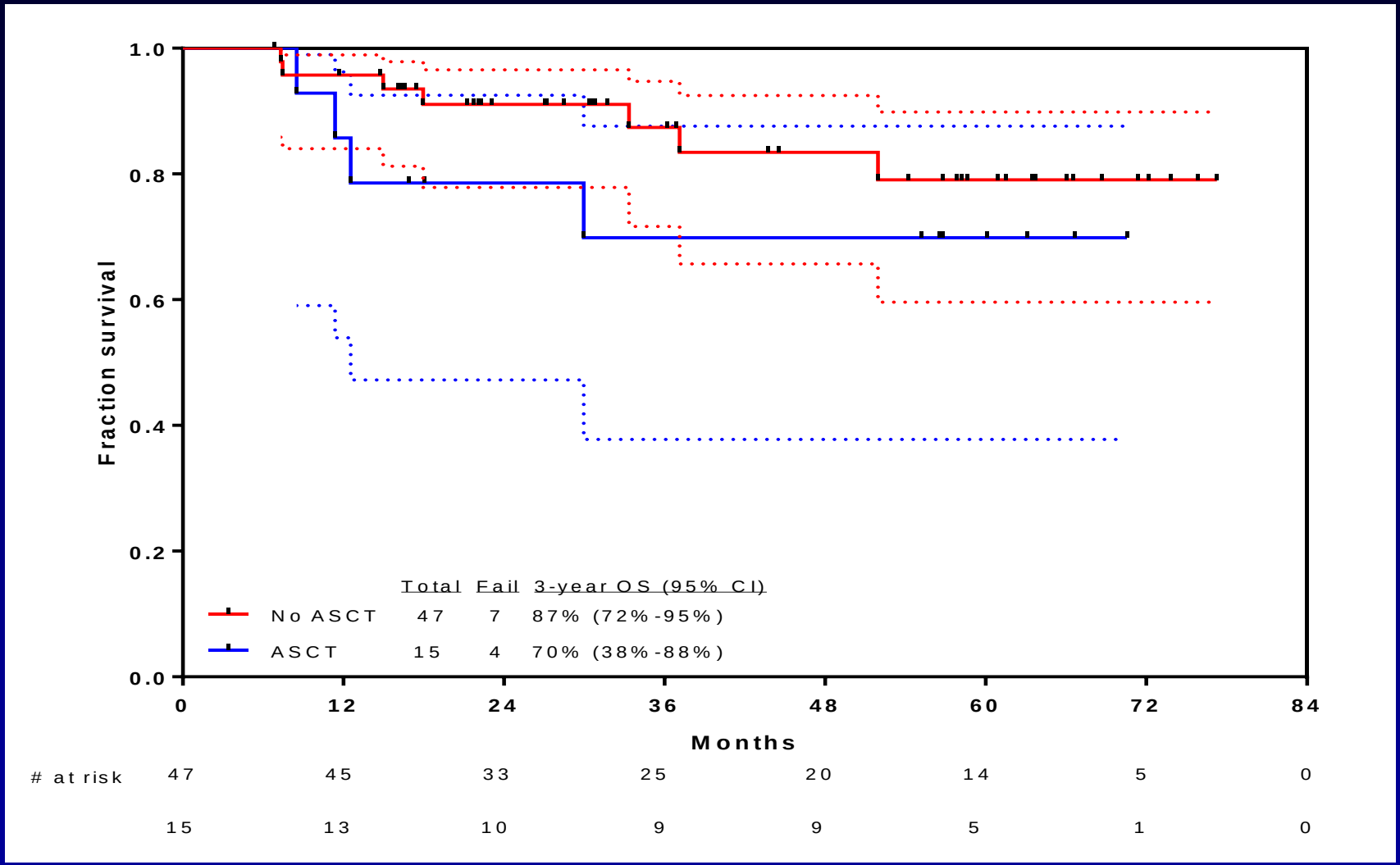
- * 11 pts in CR at start
- ** 21 pts diploid by CG at start or insufficient metaphases
- *** 1 pts no sample

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

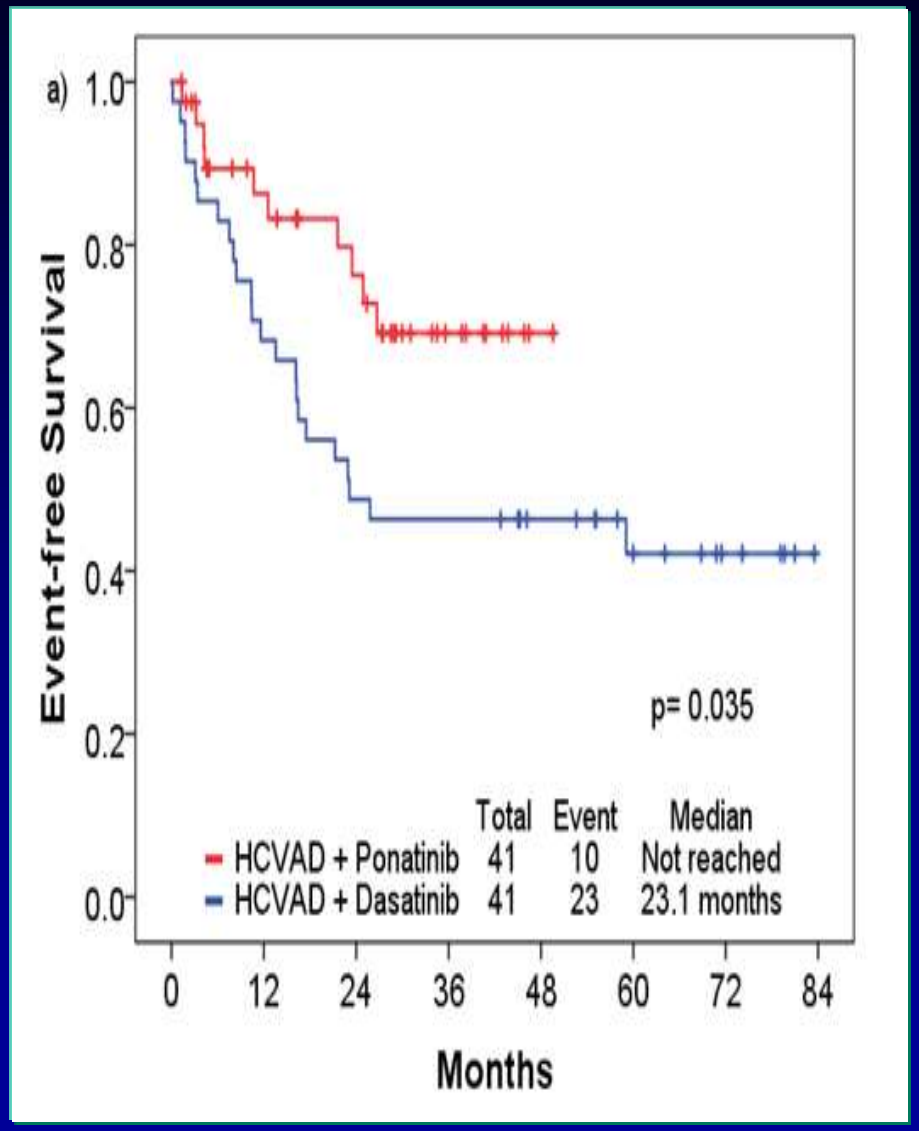
- Median follow up of 36 months (<1-77)

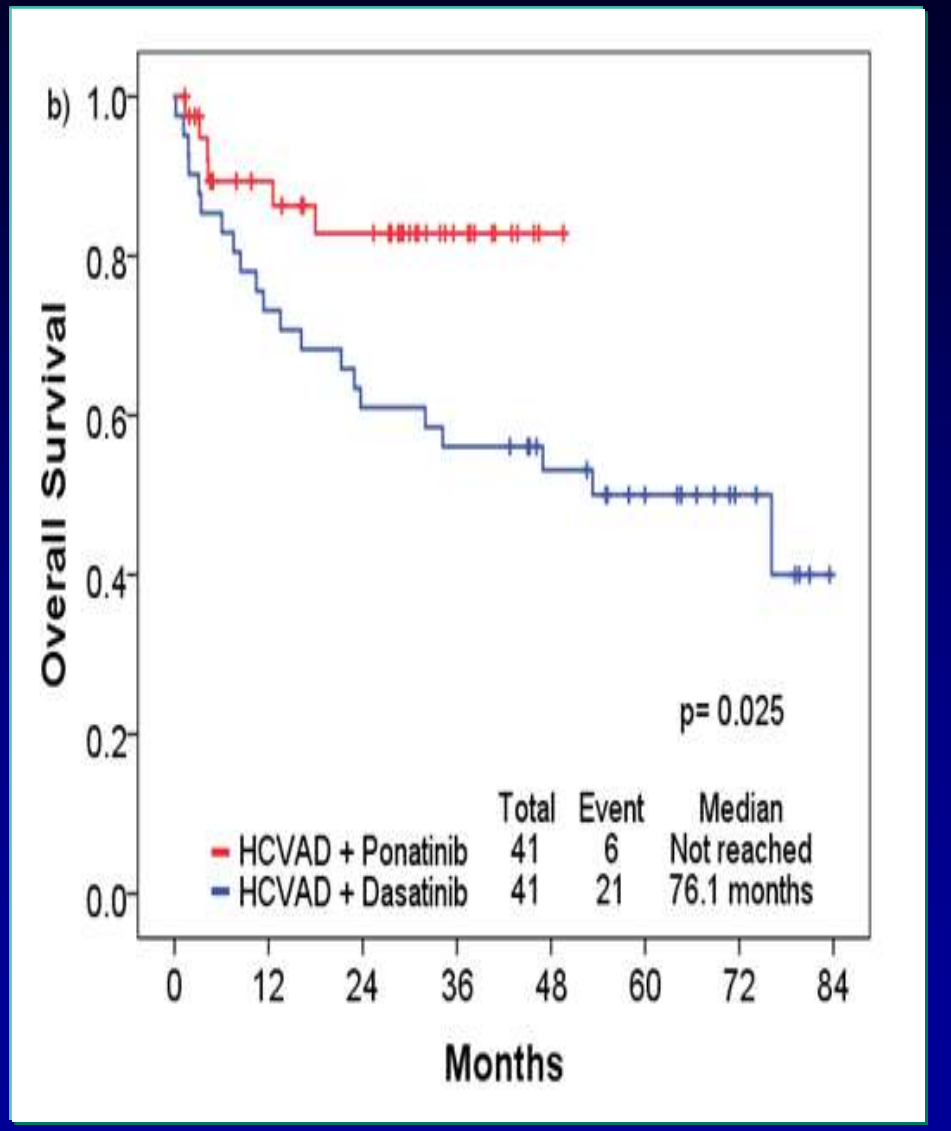


Hyper-CVAD + Ponatinib in Ph+ ALL. Landmark Analysis at 6 Months by SCT



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

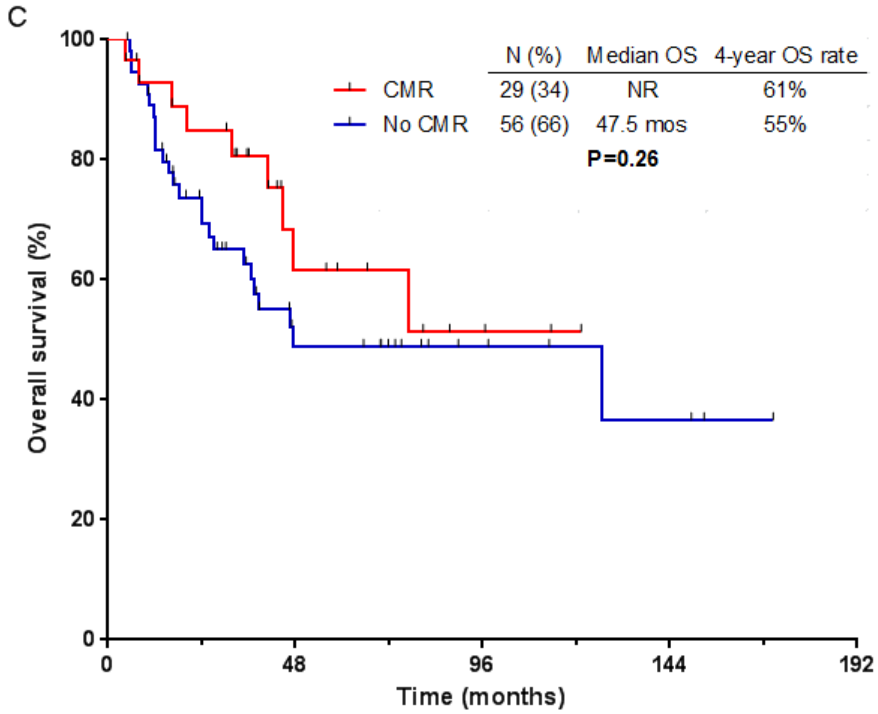




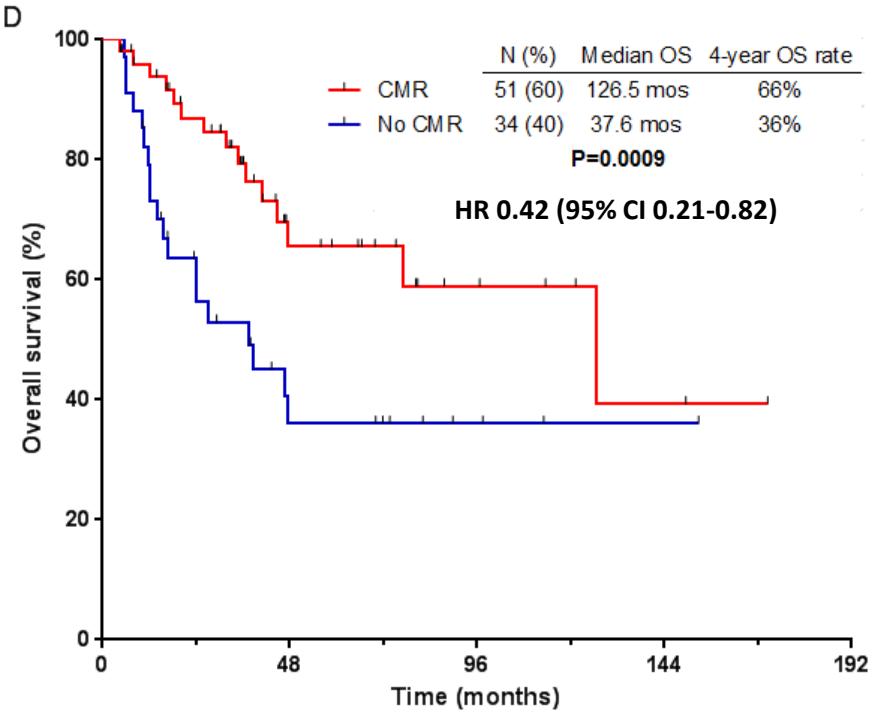
Sasaki. Cancer. 2016; 122(23):3650-3656

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

At CR



At 3 months



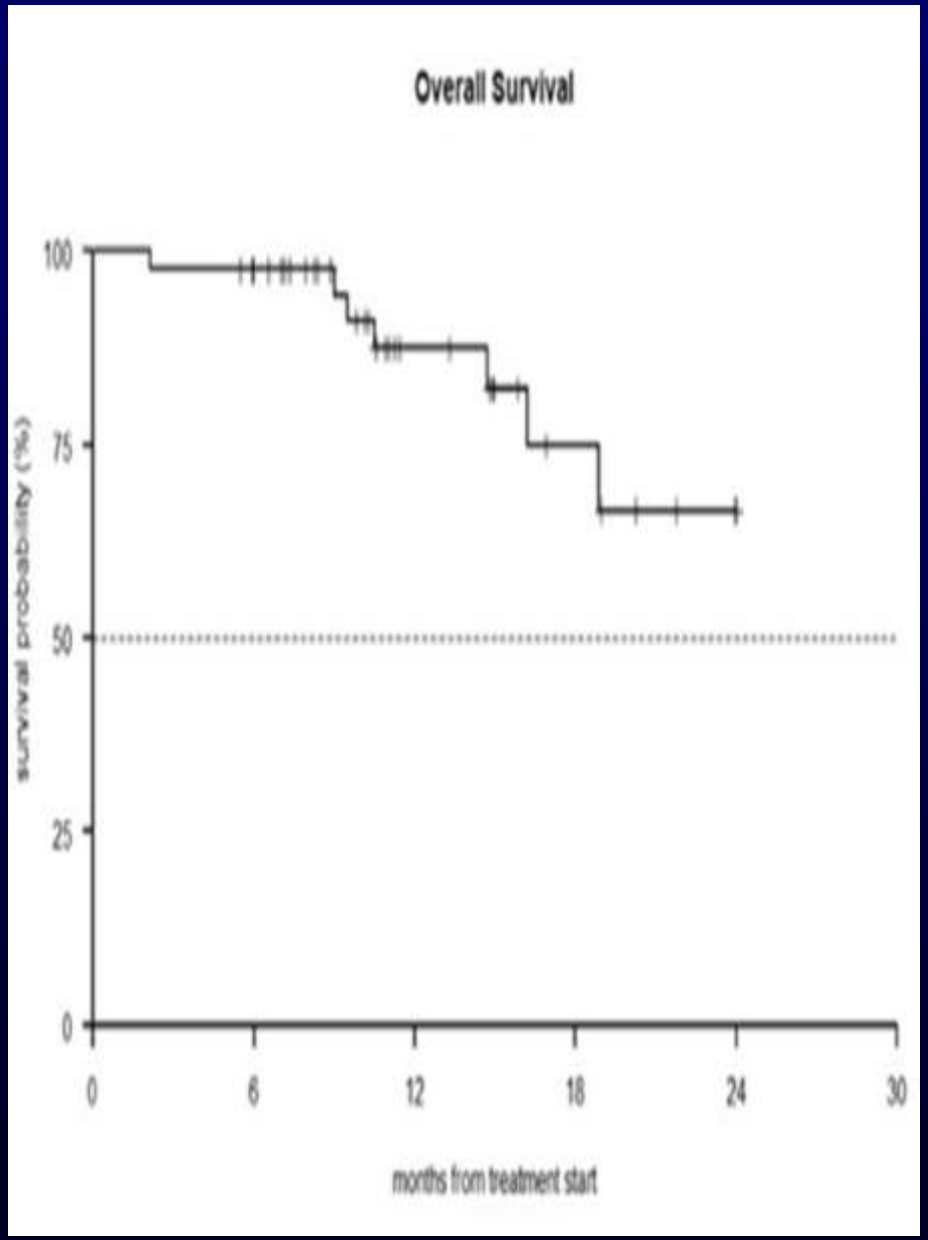
- **MVA for OS**

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

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

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



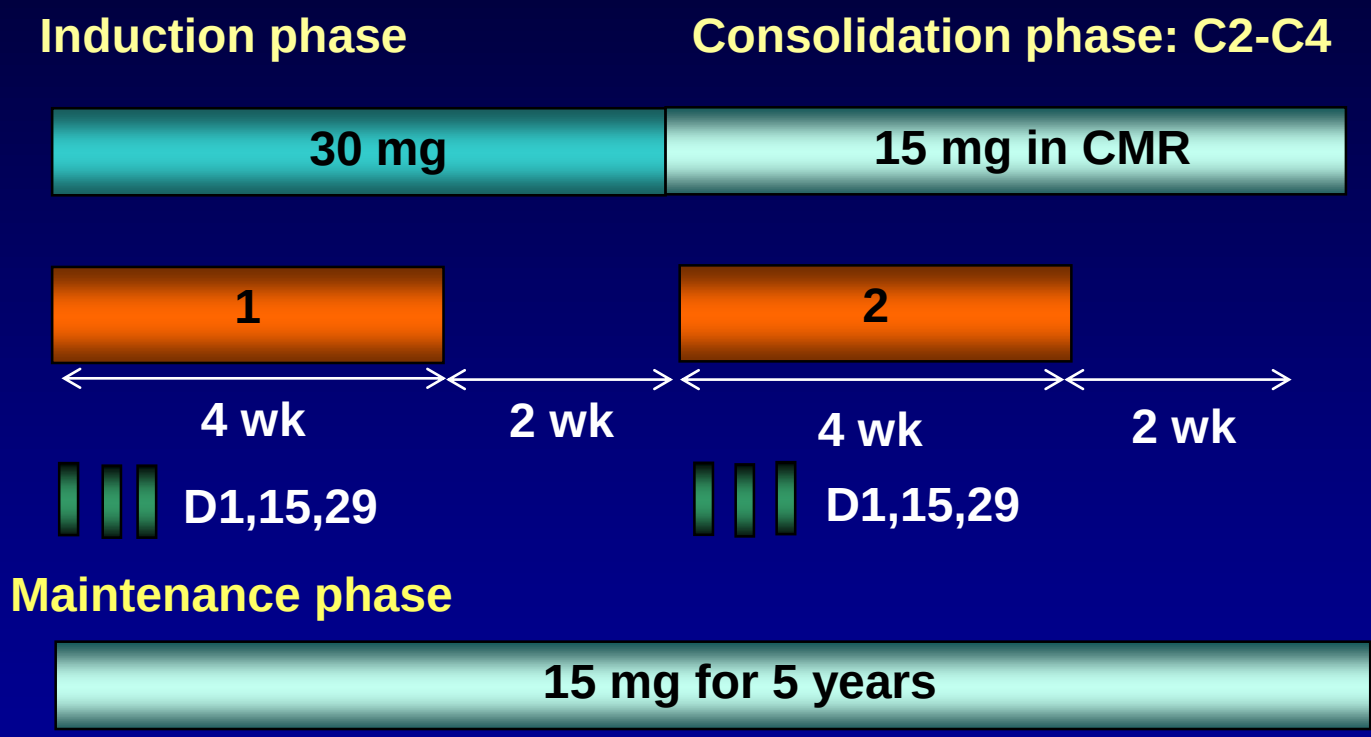
Martinelli. Blood 130: abst 99; 2017

Blinatumomab and Inotuzumab in R-R Ph-positive ALL

Parameter	Blinatumomab	Inotuzumab
No. Rx	45	38
No. CR/marrow CR (%)	16 (36)	25 (66)
% MRD negative in CR	88	63
Median OS (mos)	7.1	8.1
% later allo SCT	44	32

Martinelli. JCO 35: 1795; 2017. Stock. Proceedings ASCO 2018

Blinatumomab-ponatinib in Ph-Positive ALL

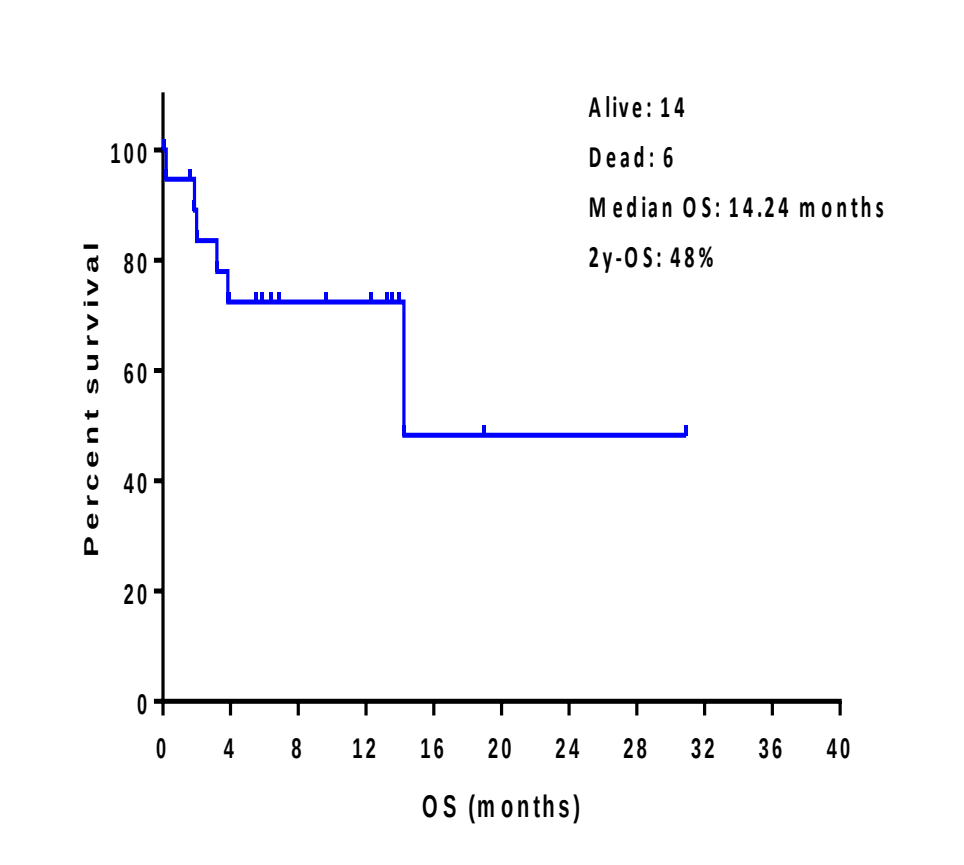


Blinatumomab IT MTX, Ara-C Ponatinib 30 mg Ponatinib 15 mg

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

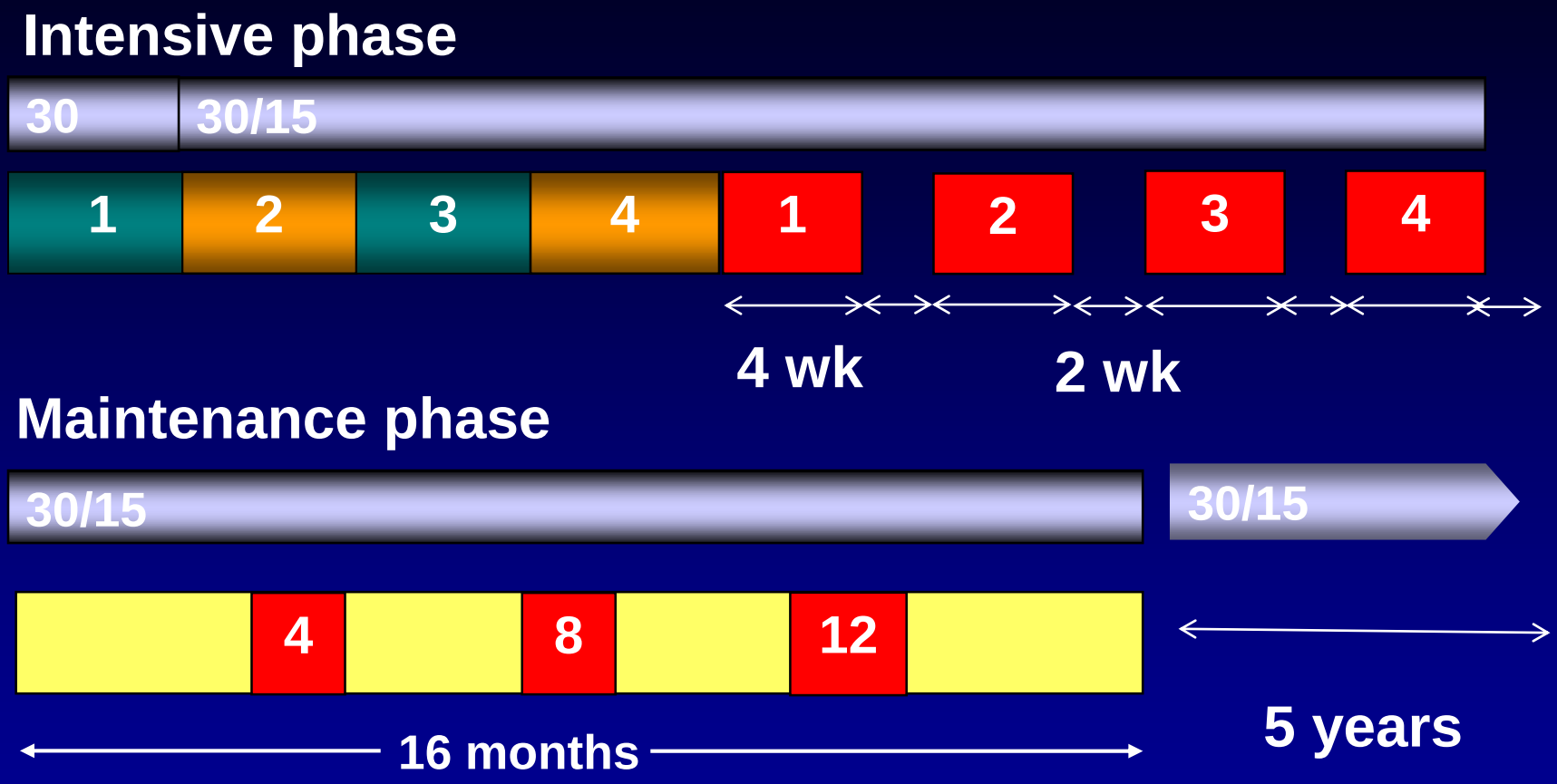
Blinatumomab-Ponatinib in Ph+ ALL. Retrospective Experience (N=20)

- 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

Mini-MTX-cytarabine

Ponatinib 30 mg →15 mg

Vincristine + prednisone

Blinatumomab

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