

# Combination of Ponatinib and Blinatumomab in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Early Results from a Phase II Study

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# Ponatinib + Blinatumomab in Ph+ ALL: Background

- Standard of care in newly diagnosed Ph+ ALL: chemotherapy plus TKI
  - 5-year OS with 1<sup>st</sup> or 2<sup>nd</sup> generation TKIs: 35-50%<sup>1-3</sup>
  - T315I mutations are dominant mechanism of relapse (up to 75% at relapse)<sup>3</sup>
- Ponatinib: pan-BCR-ABL TKI with activity in T315I mutations
  - Combination of hyper-CVAD + ponatinib: higher rates of complete molecular response (CMR) and 5-year OS of 74%, without need for HSCT in most pts<sup>4</sup>
- Blinatumomab
  - Effective monotherapy in R/R Ph+ ALL: CR/CRh rate of 36%<sup>5</sup>
  - Combination of dasatinib + blinatumomab safe and effective in newly diagnosed Ph+ ALL: high rates of molecular response, 1-year OS of 94%<sup>6</sup>

<sup>1</sup>Daver N et al. *Haematologica* 2015;100(5):563-61

<sup>2</sup>Ravandi F et al. *Cancer* 2015;121(23):4158-64

<sup>3</sup>Rousselot P et al. *Blood* 2016;128(6):774-82

<sup>4</sup>Jabbour E et al. *Lancet Hematol* 2018;5(12):e618-27

<sup>5</sup>Martinelli G et al. *J Clin Oncol* 2017;35(16):1795-1802

<sup>6</sup>Foa R et al. *N Engl J Med* 2020;383:1613-23

# Ponatinib + Blinatumomab in Ph+ ALL: Endpoints

- **Primary endpoint**
  - Frontline: CMR rate
  - Relapsed/refractory: CR/CRp rate
- **Secondary endpoints**
  - Event-free survival
  - Overall survival
  - Safety

# Ponatinib + Blinatumomab in Ph+ ALL: Eligibility

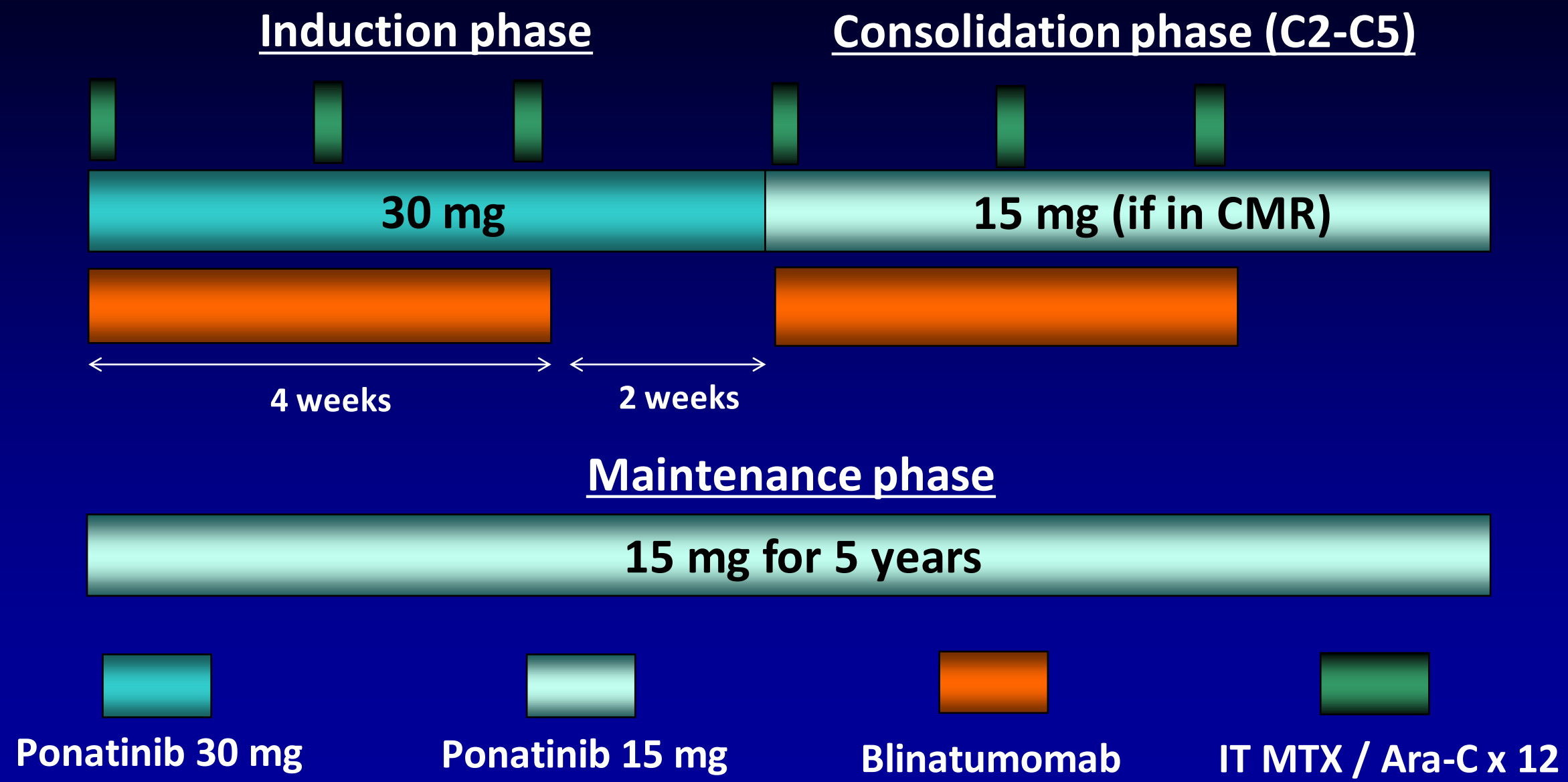
## Inclusion criteria

- Newly diagnosed Ph+ ALL, relapsed/refractory Ph+ ALL, or lymphoid accelerated or blast phase CML
  - Previous therapy with 1-2 courses of chemotherapy  $\pm$  TKI was allowed in newly diagnosed cohort
- Age  $\geq$  18 years
- ECOG performance status  $\leq$  2
- Adequate hepatic function
  - Bilirubin  $\leq$  2 mg/dL
  - AST and ALT  $\leq$  3 x ULN

## Exclusion criteria

- Uncontrolled, active CV disease
  - History of MI, CVA, or revascularization within 3 months
  - Congestive heart failure with reduced LVEF
  - Atrial or ventricular arrhythmia
  - History of arterial or venous thromboembolism
  - Uncontrolled hypertension ( $>140/90$ )
- Significant CNS pathology (excluding CNS leukemia)

# Ponatinib + Blinatumomab in Ph+ ALL: Regimen



# Ponatinib + Blinatumomab in Ph+ ALL: Patients (N=35)

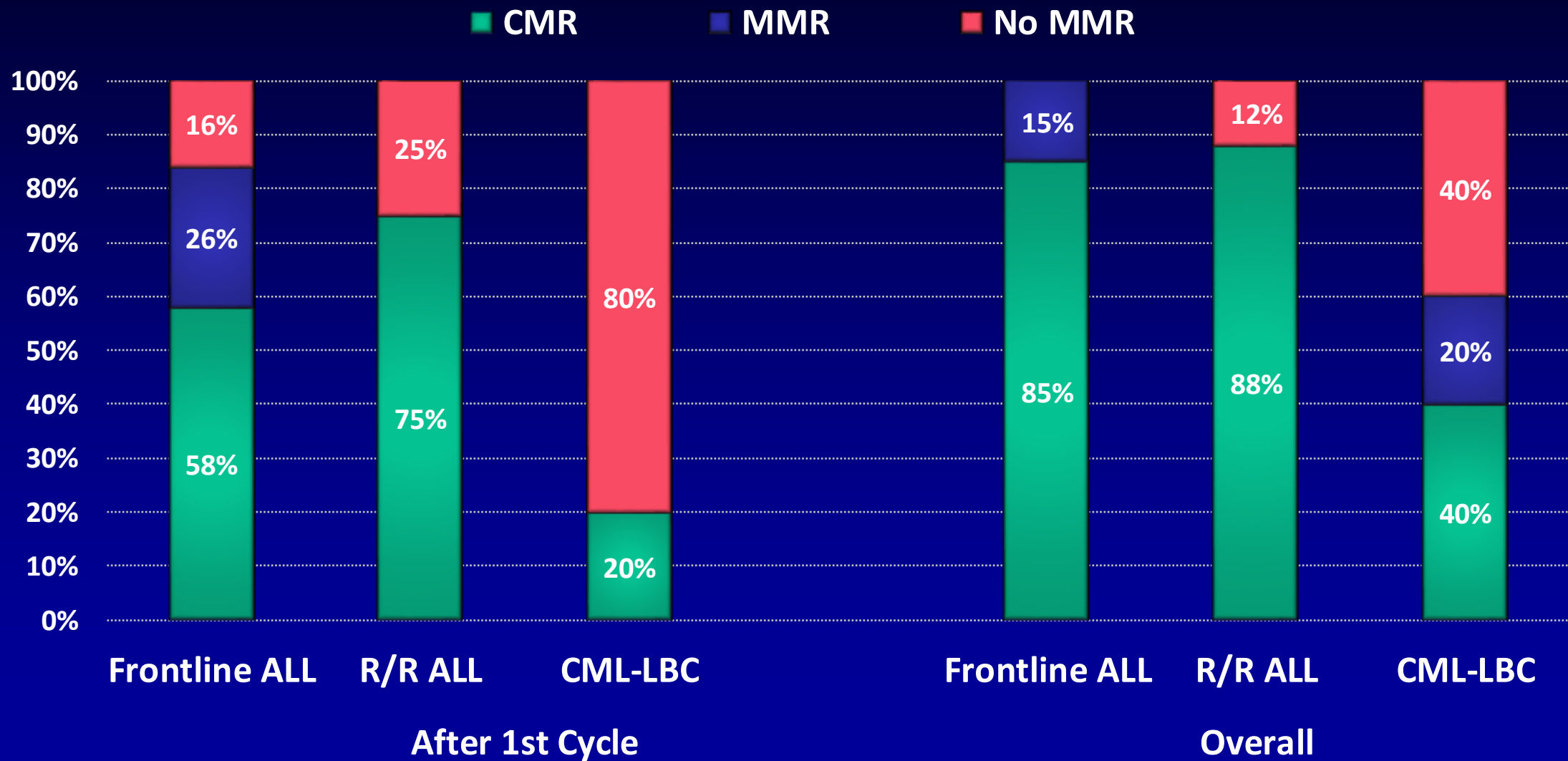
Characteristic	Category	Total N = 35	Frontline Ph+ ALL N = 20	R/R Ph+ ALL N = 10	CML-LBC N=5
N (%) / median [range]					
Age (years)		59 [24-83]	62 [34-83]	36 [24-61]	70 [57-82]
WBC (x10 <sup>9</sup> /L)		9.9 [0.3-316.2]	8.9 [0.3-316.2]	8.8 [2.1-99.5]	96.6 [2-275.5]
CNS involvement		2 (6)	0	0	2 (40)
CD19 expression		99.8 [74.9-100]	99.8 [74.9-100]	99.9 [98.3-100]	99.7 [98.3-99.9]
BCR-ABL1 transcript	p190	23 (66)	14 (70)	9 (90)	0
	p210	12 (34)	6 (30)	1 (10)	5 (100)
Line of therapy	Frontline	23 (66)	20 (100)	0	3 (60)
	Primary refractory	1 (3)	0	1 (10)	0
	Salvage 1	5 (14)	0	4 (40)	1 (20)
	Salvage 2+	6 (17)	0	5 (50)	1 (20)

# Ponatinib + Blinatumomab in Ph+ ALL: Response Rates

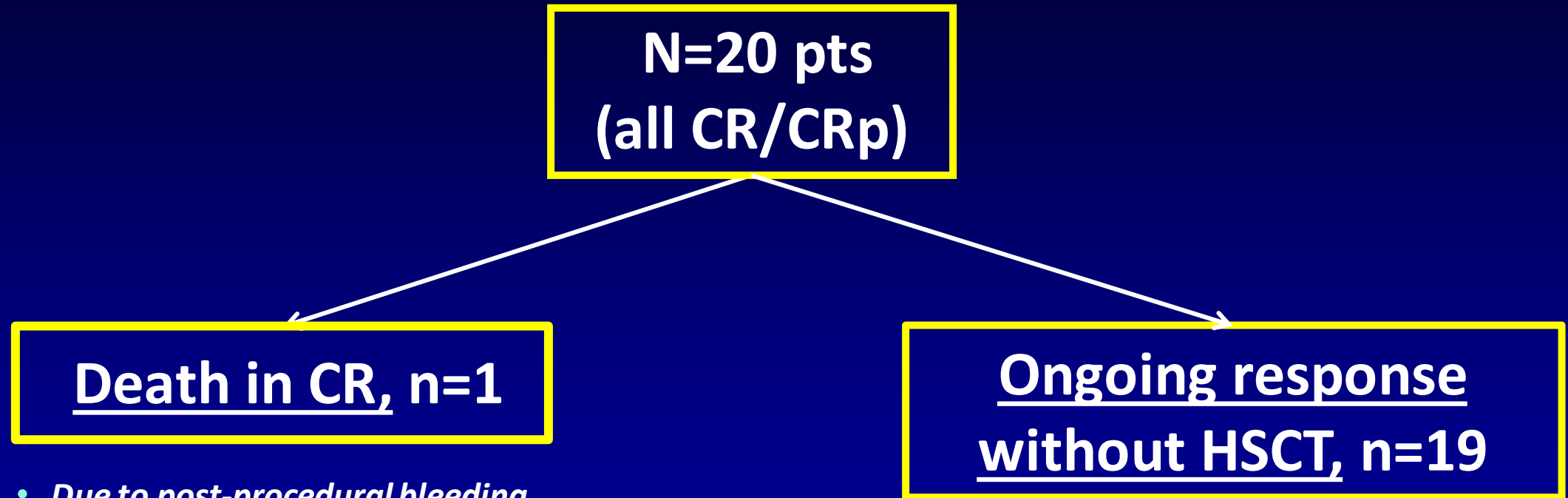
Response, n/N (%)	All N = 35	Frontline Ph+ ALL N = 20	R/R Ph+ ALL N = 10	CML-LBC N=5
<b>CR/CRp*</b>	<b>27/28 (96)</b>	<b>14/14 (100)</b>	<b>8/9 (89)</b>	<b>5/5 (100)</b>
<i>CR</i>	25 (89)	13 (93)	8 (89)	4 (80)
<i>CRp</i>	2 (7)	1 (7)	0	1 (20)
MMR	30/33 (91)	20/20 (100)	7/8 (88)	3/5 (60)
<b>CMR</b>	<b>26/33 (79)</b>	<b>17/20 (85)</b>	<b>7/8 (88)</b>	<b>2/5 (40)</b>
Early death	0	0	0	0

\* 6 frontline pts and 1 salvage pt in MRD+ CR at start

# Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



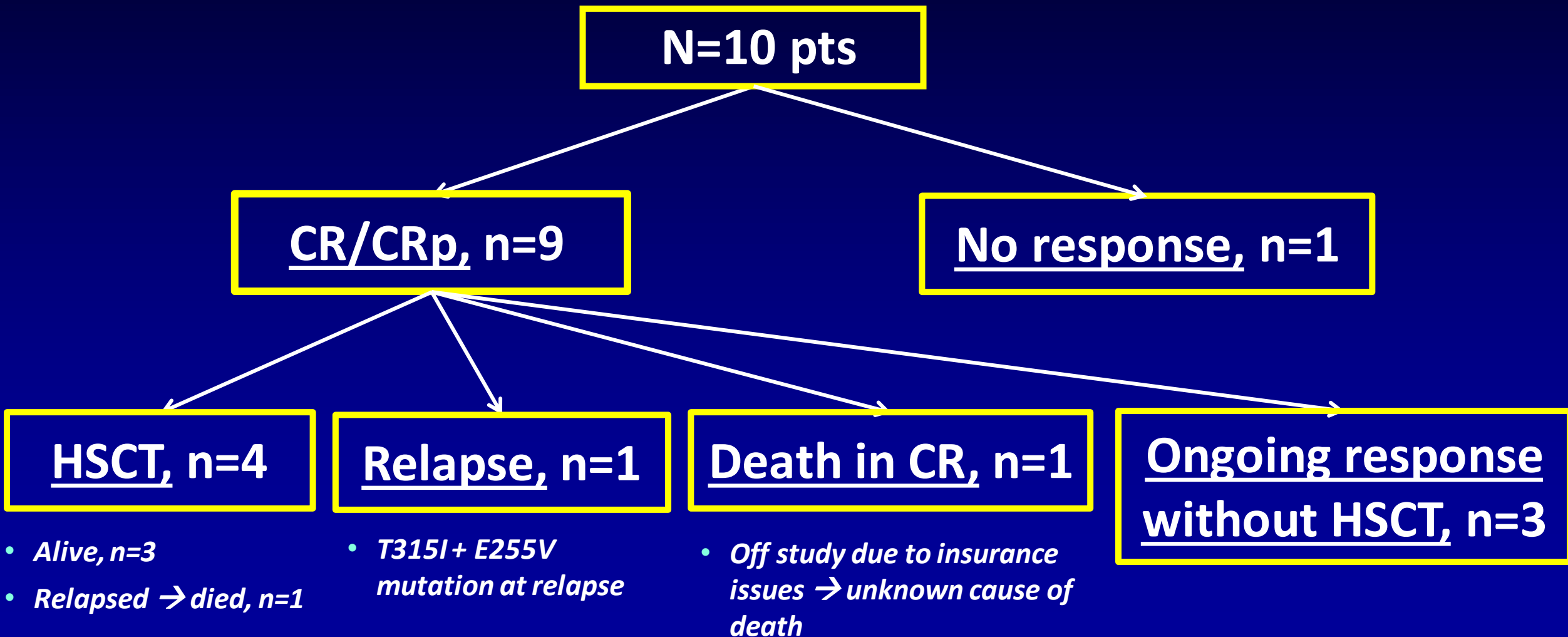
# Ponatinib + Blinatumomab in Ph+ ALL: Disposition (Frontline Ph+ ALL)



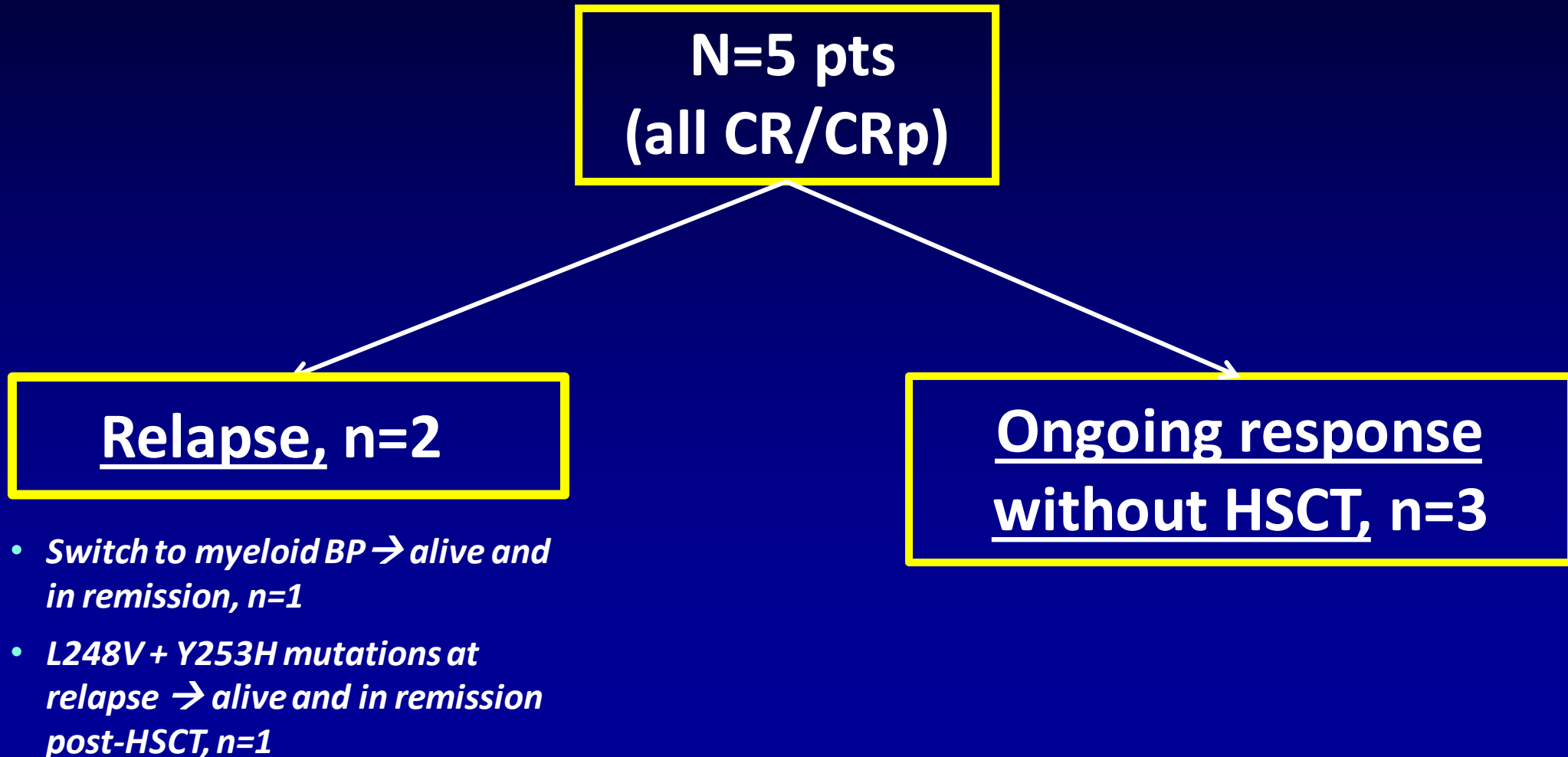
- *Due to post-procedural bleeding and hypovolemic shock*

**No pts in frontline cohort underwent HSCT in CR1 and none has relapsed with median CR duration of 6 months (range, 1+ to 33+)**

# Ponatinib + Blinatumomab in Ph+ ALL: Disposition (R/R Ph+ ALL)

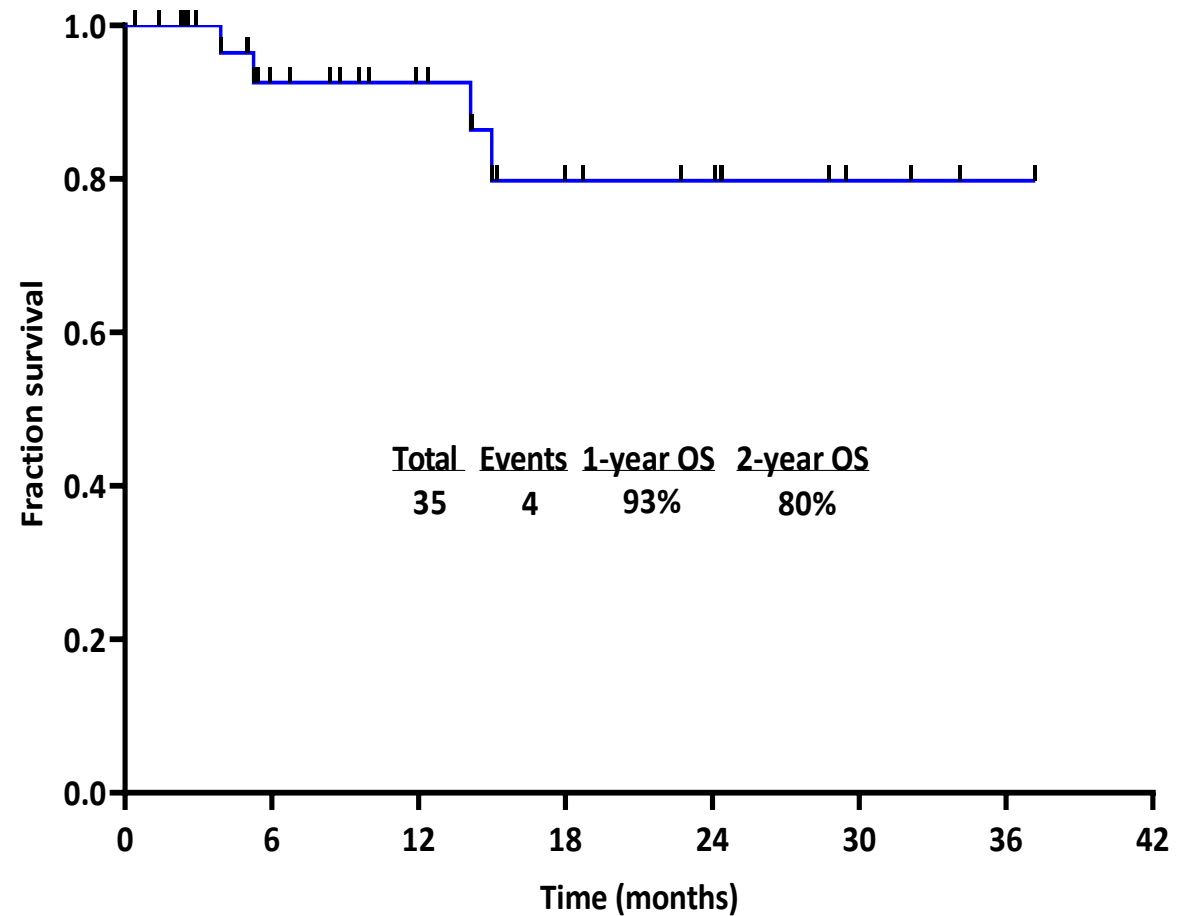
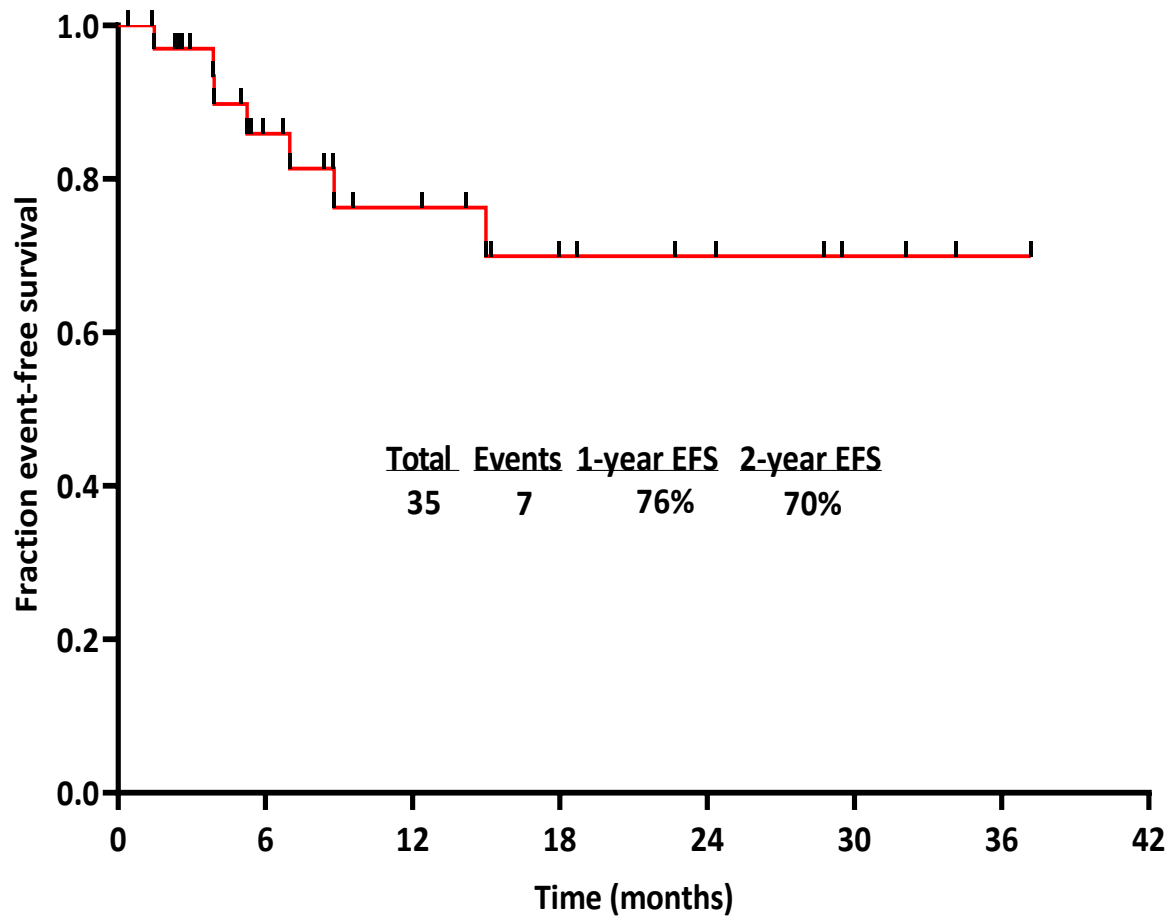


# Ponatinib + Blinatumomab in Ph+ ALL: Disposition (CML-LBP)



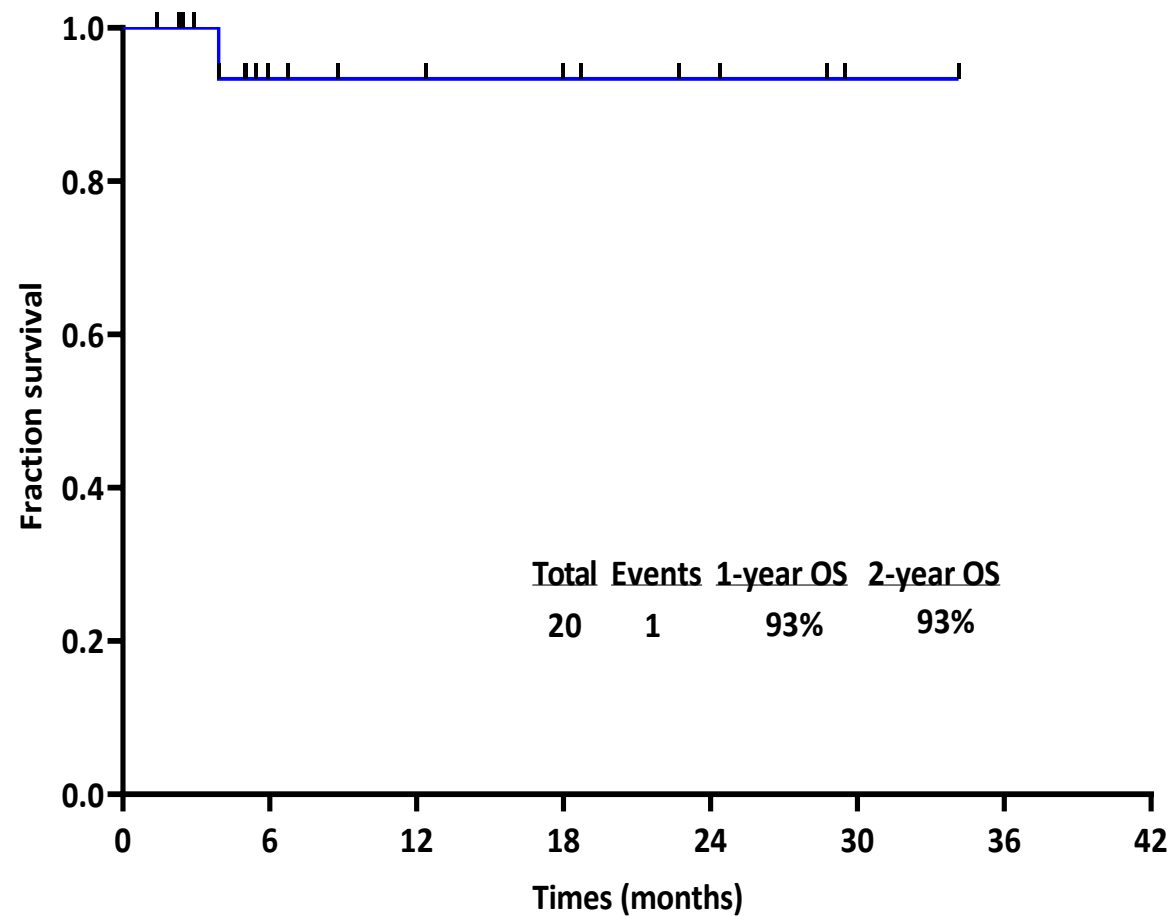
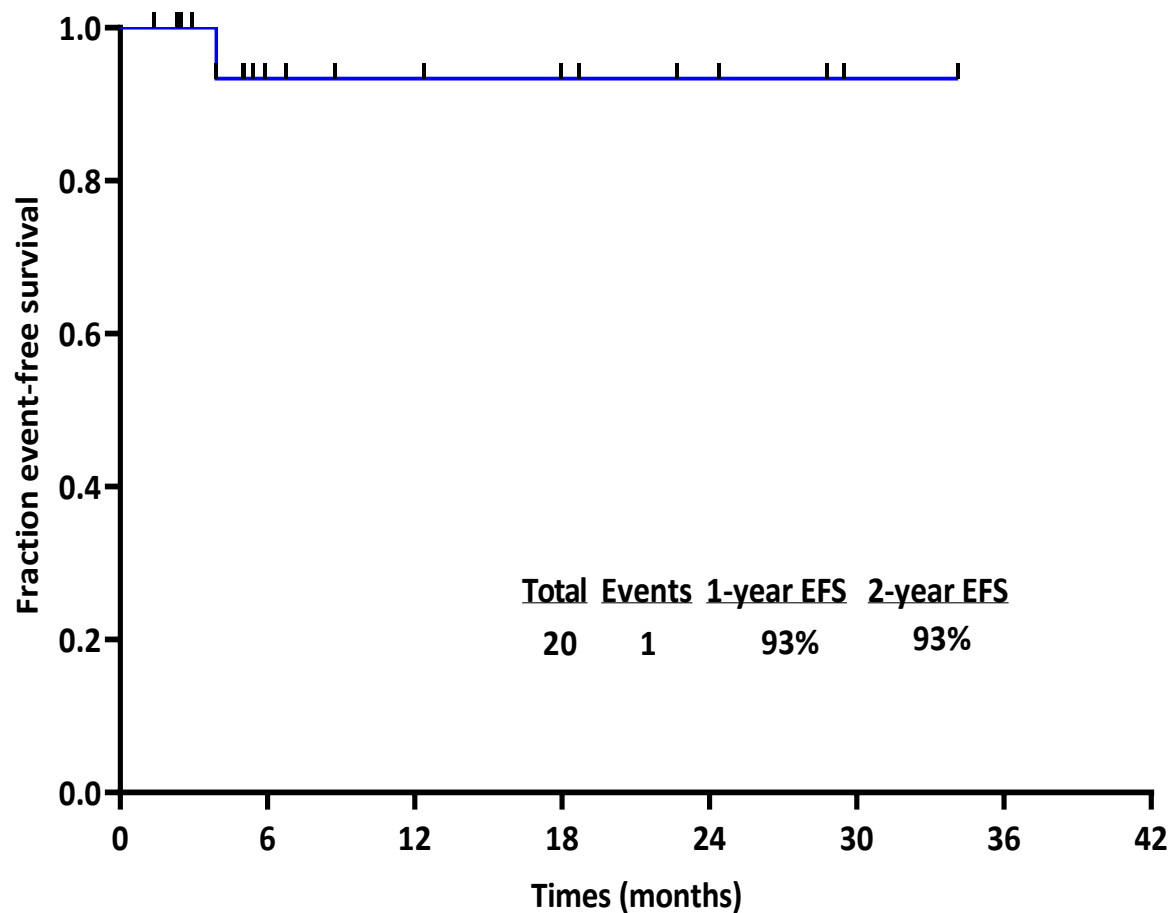
# Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Entire Cohort

Median follow-up: 12 months (range, 1-37)



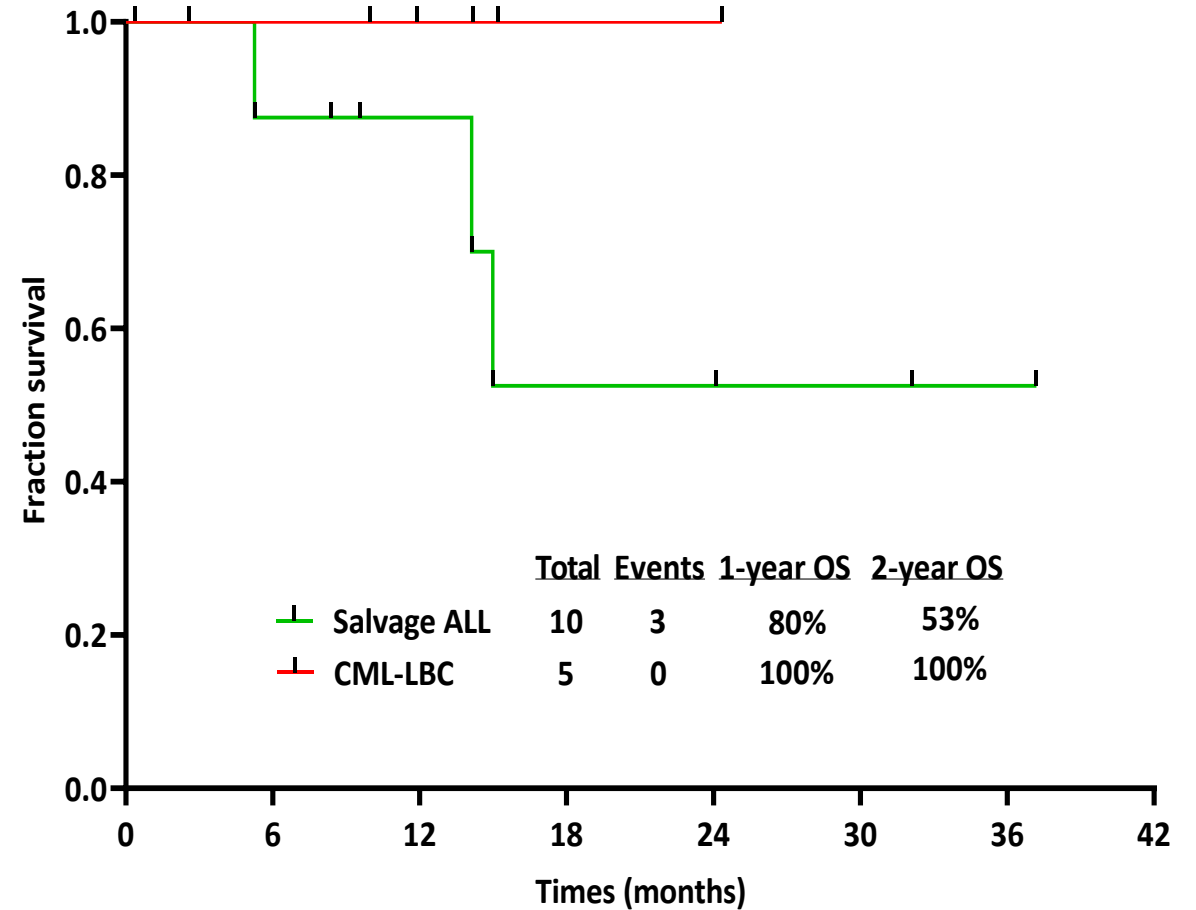
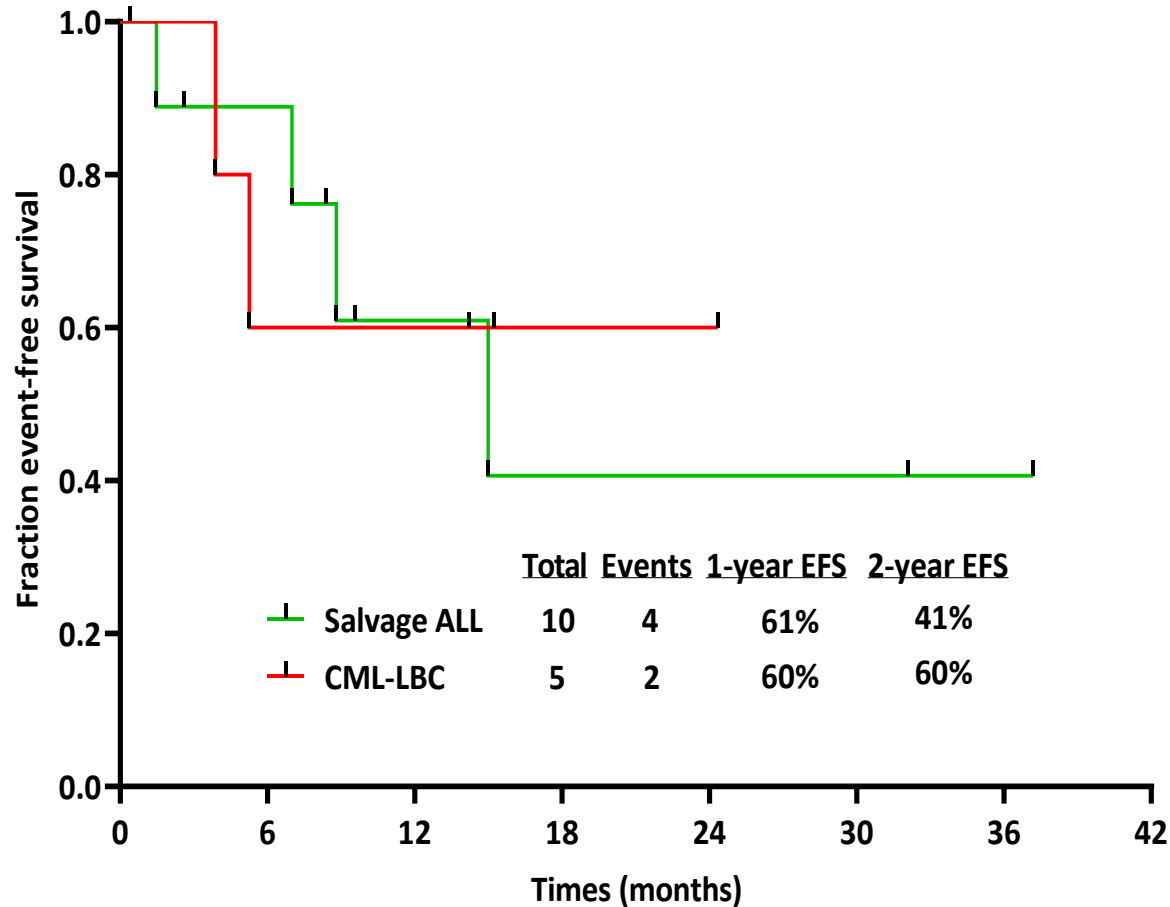
# Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort

Median follow-up: 12 months (range, 1-37)



# Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for R/R and CML-LBP Cohorts

Median follow-up: 12 months (range, 1-37)



# Ponatinib + Blinatumomab in Ph+ ALL: Related Adverse Events

Adverse events	Grade 1, N (%)	Grade 2, N (%)	Grade 3, N (%)
Elevated lipase	0	0	2 (6)
Fever / febrile neutropenia	1 (3)	3 (9)	1 (3)
ALT increased	1 (3)	1 (3)	1 (3)
Cerebrovascular ischemia	0	1 (3)	1 (3)
Hypertension	0	0	1 (3)
Pancreatitis	0	0	1 (3)
Deep vein thrombosis	0	0	1 (3)
Encephalopathy	0	0	1 (3)
Rash	4 (11)	4 (11)	0
Cytokine release syndrome	0	2 (6)	0
Constipation	3 (9)	3 (9)	0
Fatigue	3 (9)	2 (6)	0
Tremor	1 (3)	1 (3)	0

# Ponatinib + Blinatumomab in Ph+ ALL: Conclusions

- Ponatinib + blinatumomab is safe and effective in Ph+ ALL
- In frontline Ph+ ALL: CR/CRp 100%, CMR 85%, 2-year OS 93%
  - No frontline pts underwent HSCT in CR1 and none has relapsed
- In R/R Ph+ ALL: CR/CRp 89%, CMR 88%, 2-year OS 53%
- Combination of ponatinib + blinatumomab is a promising chemotherapy-free, HSCT-sparing regimen for Ph+ ALL