EPIC: A Phase 3 Trial of Ponatinib Compared with Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CP-CML)

Abstract #519

Lipton JH, Chuah C, Guerci-Bresler A, Rosti G, Simpson D, Assouline S, Etienne G, Nicolini FE, Le Coutre P, Clark R, Stenke L, Andorsky D, Oehler V, Lustgarten S, Rivera VM, Clackson T, Haluska FG, Baccarani M, Cortes JE, Guilhot F, Hochhaus A, Hughes T, Kantarjian H, Shah NP, Talpaz M, Deininger MW

EPIC: Introduction

- Ponatinib is an oral TKI with potent activity against BCR-ABL[1]
  - Approved in the US and EU for adult patients with refractory CML or Ph+ ALL and those with the T315I mutation*
- In phase II, pts with fewer prior TKIs had better responses and less discontinuations; multivariate analyses suggest increased activity in younger, less heavily treated pts with shorter time since diagnosis[2]
- The phase III EPIC (Evaluation of Ponatinib vs Imatinib in CML) trial was established to assess safety and efficacy of ponatinib compared with imatinib in newly diagnosed CP-CML
- On 18 October 2013, EPIC was terminated due to arterial thrombotic events in the ponatinib clinical program and patient safety considerations
- Safety and efficacy data available up to the point of termination (median follow-up 5.1 months) are presented (data as of 01 Apr 2014)

**See approved prescribing information.*

1. O'Hare T, et al. *Cancer Cell*. 2009;16:401-412. 2. Cortes JE, et al. *N Engl J Med*. 2013;369:1783-1796.

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EPIC: Study Design

Newly diagnosed Ph$^+$ CP-CML
Target accrual N = 528

Stratified by Sokal risk score[1]
Low (<0.8) vs intermediate (0.8 to ≤1.2) vs high (>1.2)

RANDOMIZED

Ponatinib 45 mg qd orally
- Dose modification allowed to manage AEs
- Max dose: 45 mg qd

Imatinib 400 mg qd orally
- Dose modification allowed to manage AEs
- Dose escalation allowed in case of suboptimal response
- Max dose: 800 mg qd (400 mg bid)

Endpoints Analyzed
- BCR-ABL^{IS} <10% rate at 3 mo
- MMR, MR4, and MR4.5 rates at 3, 6, 9, and 12 mo
- MMR, MR4, and MR4.5 rates by at least 3, 6, 9, and 12 mo
- MMR, MR4, and MR4.5 rates at any time (best response)
- Time to MMR, MR4, and MR4.5
- CCyR rates at any time, at 6 and 12 mo, and by 6 and 12 mo
- Safety

None of the prospectively defined endpoints could be analyzed due to trial termination

1. Sokal JE, et al. *Blood*. 1984;63:789-799.
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EPIC: Demographic and Baseline Characteristics

	Ponatinib n = 155	Imatinib n = 152	Overall N = 307
Median age (range), years	**55 (18-89)**	**52 (18-86)**	**53 (18-89)**
Median time from diagnosis to treatment (range) , months	0.95 (0.16-3.91)	1.05 (0.13-5.56)	0.99 (0.13-5.56)
Male, n (%)	97 (63)	92 (61)	189 (62)
ECOG PS, n (%)			
0	116 (75)	119 (78)	235 (77)
1	37 (24)	32 (21)	69 (23)
2	1 (1)	1 (1)	2 (1)
Sokal score, n (%)			
Low risk	64 (41)	62 (41)	126 (41)
Intermediate risk	64 (41)	67 (44)	131 (43)
High risk	27 (17)	23 (15)	50 (16)
Total no. CV risk factors* and disease history, n (%)			
0	43 (28)	49 (32)	92 (30)
1	37 (24)	43 (28)	80 (26)
2	24 (15)	28 (18)	52 (17)
≥3	50 (32)	32 (21)	82 (27)

*CV risk factors included hypertension, hypercholesterolemia, diabetes, obesity, and smoking.
Only median time from diagnosis to treatment was statistically different between arms ($P<.05$).

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EPIC: Status and Disposition at Time of Termination

From Aug ‘12 to Oct ‘13, 307 patients were randomized (58% of target enrollment)

	Ponatinib n = 155*	Imatinib n = 152	Overall N = 307
Median follow-up, months (range)	5.0 (0.03–17.6)	5.3 (0.5–14.1)	5.1 (0.03–17.6)
Discontinued, n (%)	155 (100)	152 (100)	307 (100)
Study termination	130 (84)	141 (93)	271 (88)
Adverse event	14 (9)	2 (1)	16 (5)
Withdrawal of consent	7 (5)	1 (1)	8 (3)
Lack of efficacy	0	4 (3)	4 (1)
Death	1 (1)	2 (1)	3 (1)
Physician decision	2 (1)	0	2 (1)
Progressive disease	0	1 (1)	1 (<1)
Lost to follow-up	0	1 (1)	1 (<1)
Other	1 (1)	0	1 (<1)

*1 patient was randomized but not treated and not included in safety analyses.

AEs Leading to Discontinuation:

Ponatinib: rash (n = 4), thrombocytopenia (n = 3), abdominal pain (n = 2), weight loss (n = 1), ALT increase (n = 1), AST increase (n = 1), pancreatitis (n = 1), acute myocardial infarction (n = 1), diarrhea (n = 1), nausea (n = 1), fatigue (n = 1), headache (n = 1), peripheral arterial occlusive disease (n = 1)

Imatinib: eye hemorrhage (n=1), diarrhea (n=1)

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EPIC: Study Drug Exposure

	Ponatinib n = 154	Imatinib n = 152
Median (range) duration of exposure, days	114 (2-432)	141 (14-419)
Median (range) dose intensity, mg/day	39 (9-45)	400 (186-574)
Any dose reductions, n (%)	55 (36)*	10 (7)
Dose interruptions of at least 3 days, n (%)	87 (57)	30 (20)

*Additional 60 (39%) patients in ponatinib arm had a dose reduction following issuance of dose reduction recommendations post clinical hold to new patient enrollment (Oct 2013).

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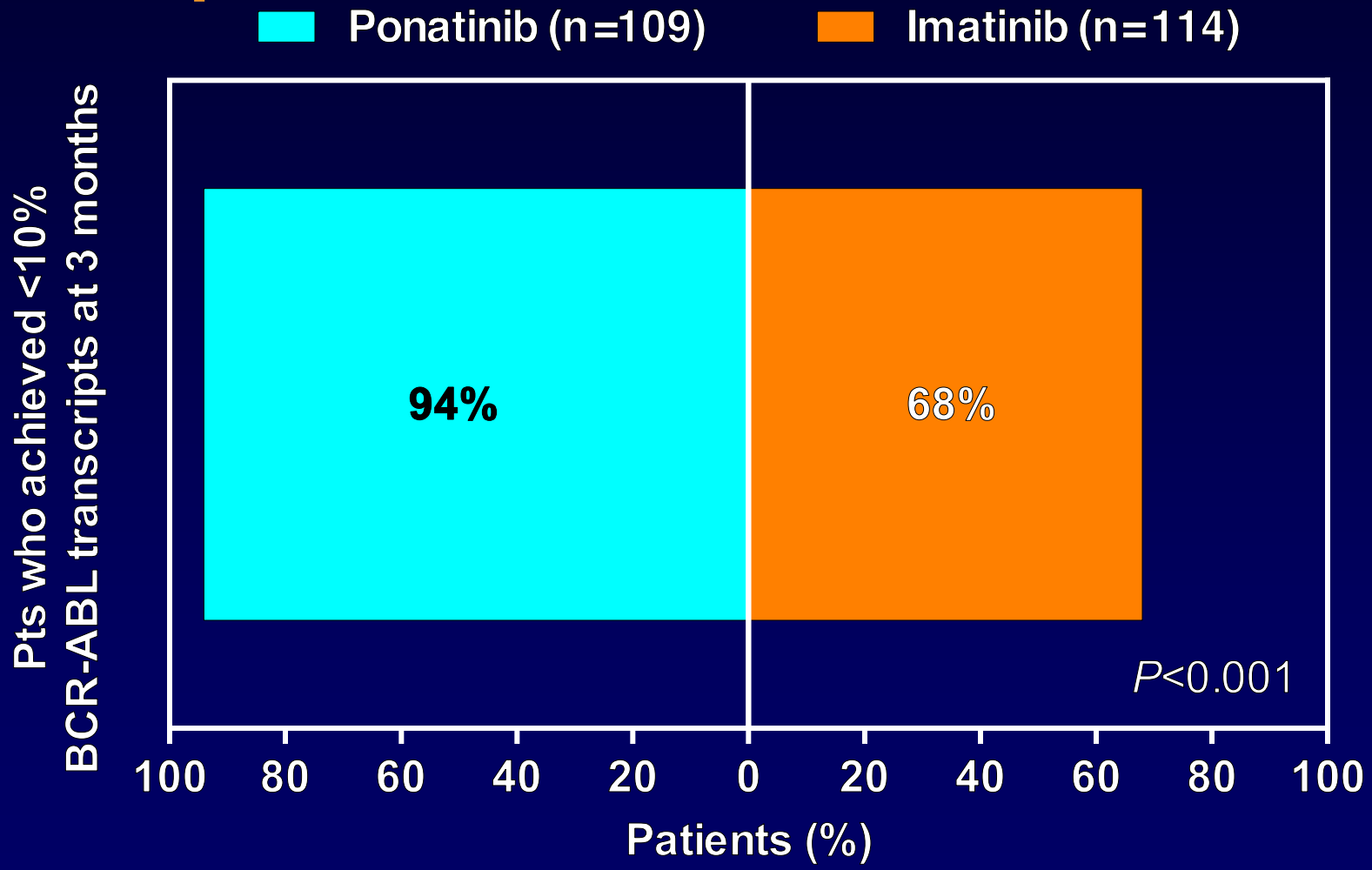
EPIC: Achievement of <10% BCR-ABL Transcripts at 3 Months: Evaluable Patients



Evaluable: Patients with an assessment at 3 months or later

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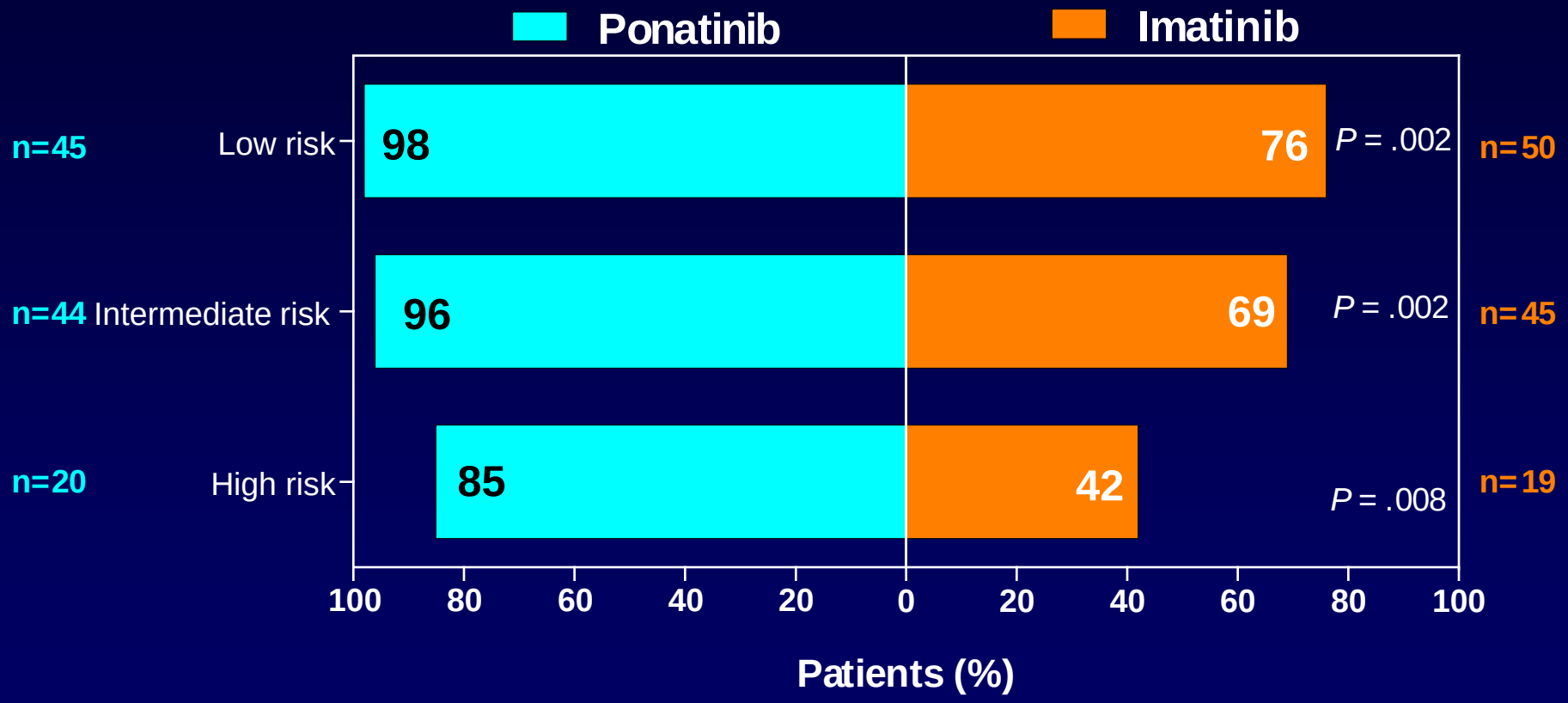
EPIC: Achievement of <10% BCR-ABL Transcript Levels at 3 Months by Sokal Risk Score: Evaluable Patients



Evaluable: Patients with an assessment at 3 months or later

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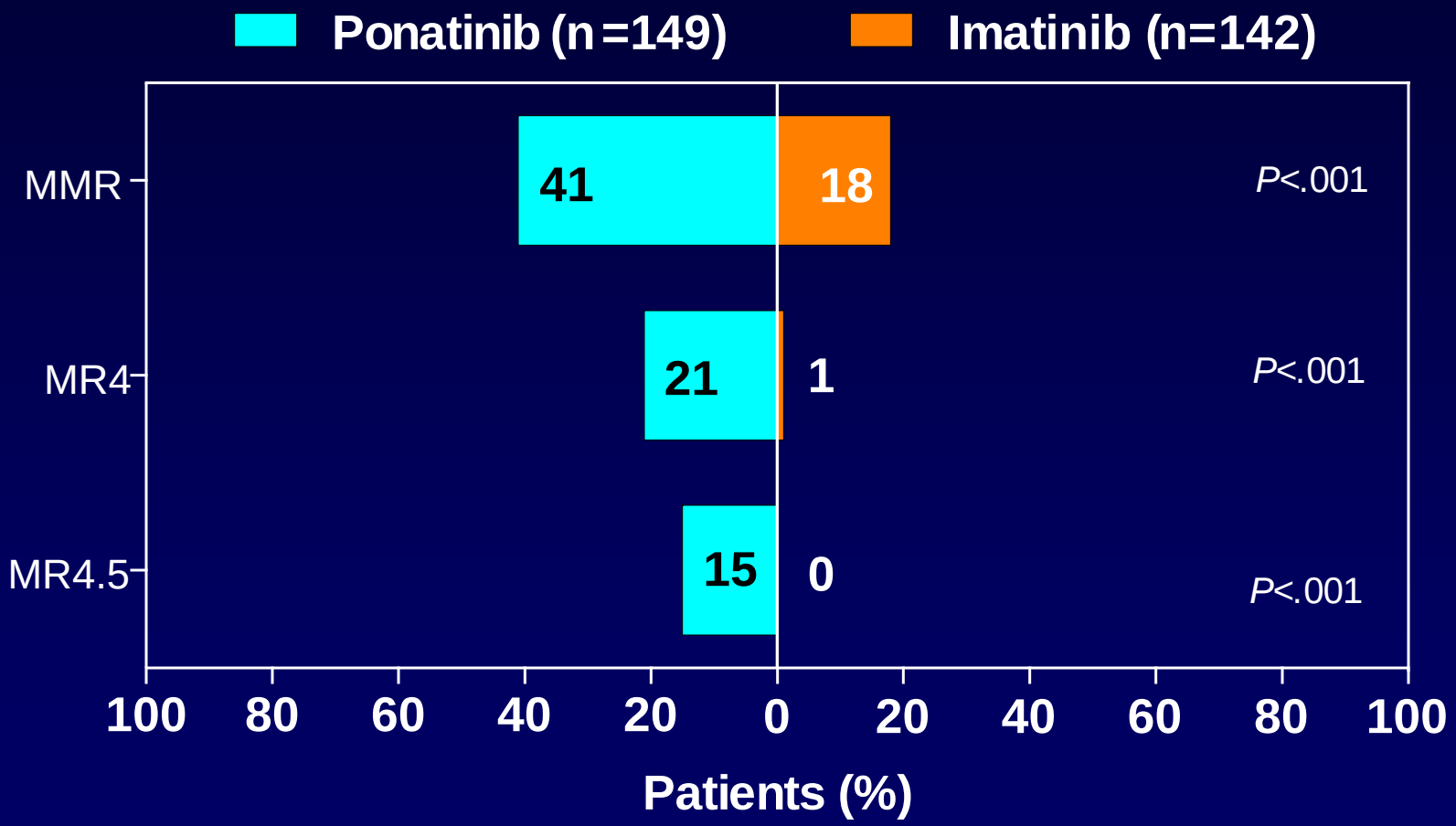
EPIC: Best Overall Molecular Response at Any Time: Evaluable Patients



Median time to MMR: Ponatinib 100 (56-219) days; imatinib 169 (113-409) days
Evaluable: Patients with an assessment at each time point or later

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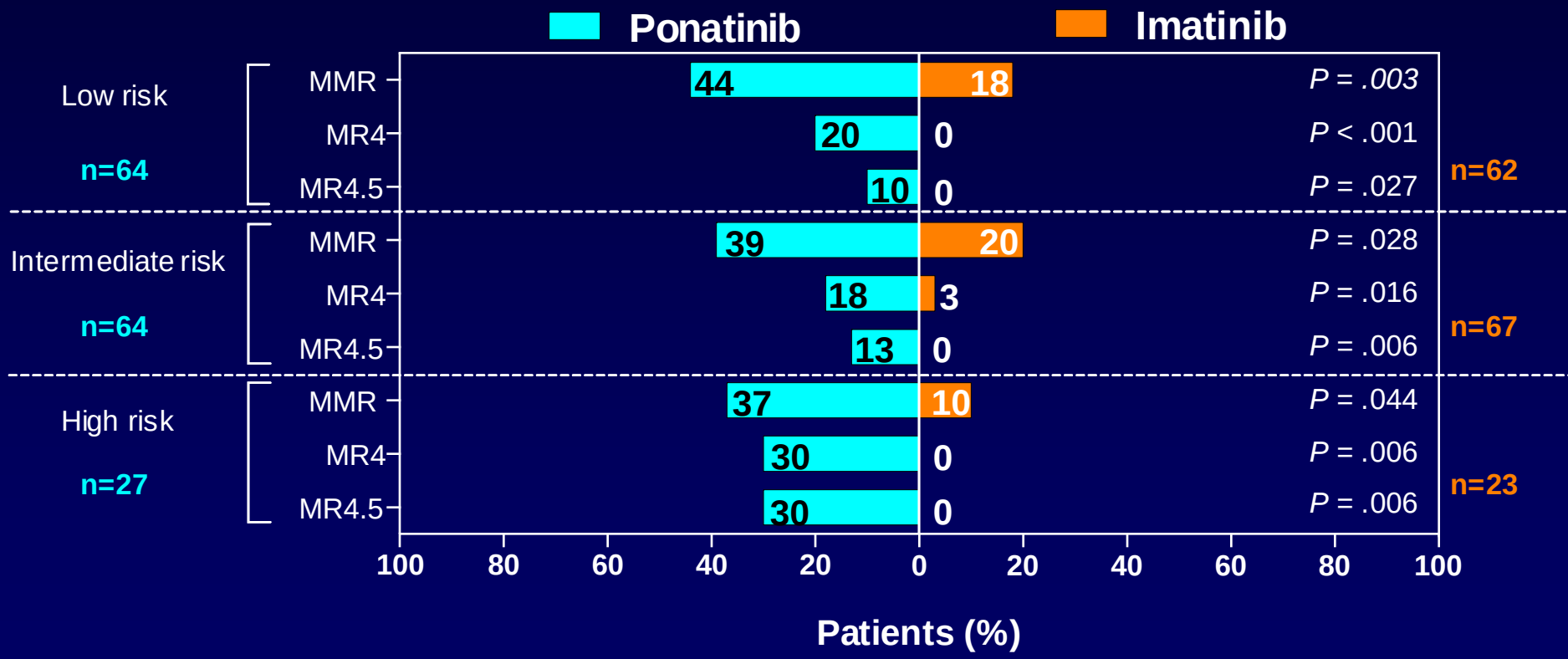
EPIC: Best Molecular Response at Any Time by Sokal Risk Score: Evaluable Patients



Evaluable: Patients with an assessment at each time point or later

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EPIC: Patients With Treatment-Emergent AEs (>15%)

Preferred Term	Ponatinib, n = 154		Imatinib, n = 152	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Non-hematologic				
Rash	58 (38)	10 (7)	25 (16)	2 (1)
Abdominal pain	55 (36)	4 (3)	15 (10)	0
Headache	50 (33)	1 (1)	20 (13)	0
Constipation	41 (27)	0	3 (2)	0
Increased lipase	41 (27)	22 (14)	11 (7)	3 (2)
Myalgia	40 (26)	1 (1)	27 (18)	0
Nausea	34 (22)	2 (1)	52 (34)	0
Fatigue	32 (21)	1 (1)	30 (20)	0
Arthralgia	29 (19)	2 (1)	23 (15)	1 (1)
Pyrexia	28 (18)	0	7 (5)	1 (1)
Dry skin	27 (18)	1 (1)	5 (3)	0
Hypertension	27 (18)	7 (5)	3 (2)	0
Diarrhea	20 (13)	1 (1)	41 (27)	1 (1)
Vomiting	18 (12)	1 (1)	28 (18)	0
Peripheral edema	14 (9)	0	22 (15)	0
Muscle spasm	11 (7)	0	52 (34)	2 (1)
Periorbital edema	1 (1)	0	33 (22)	0
Hematologic				
Thrombocytopenia	38 (25)	19 (12)	21 (14)	10 (7)

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EPIC: Patients With Treatment-Emergent SAEs (≥2 Patients)

Preferred Term	Ponatinib, n = 154		Imatinib, n = 152	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Non-hematologic				
Pancreatitis	5 (3)	5 (3)	0	0
Atrial fibrillation	3 (2)	2 (1)	0	0
Acute myocardial infarction	2 (1)	2 (1)	0	0
Angina pectoris	2 (1)	0	0	0
Cardiac failure	2 (1)	1 (0.6)	0	0
Abdominal pain	2 (1)	1 (0.6)	0	0
Pyrexia	2 (1)	0	1 (0.7)	1 (0.7)
Pneumonia	2 (1)	1 (0.7)	1 (0.7)	0
Peripheral arterial occlusive disease	2 (1)	2 (1)	0	0
Pleural effusion	0	0	2 (1)	1 (0.7)
Hematologic				
Thrombocytopenia	3 (2)	3 (2)	0	0

1 patient each in the ponatinib arm & the imatinib arm had grade 5 pneumonia

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EPIC: Patients With Treatment-Emergent Vascular Occlusive Events

	Ponatinib, n = 154 n (%)		Imatinib, n = 152 n (%)	
	AE	SAE	AE	SAE
Arterial thrombotic events	11 (7)	10 (7)	3 (2)	1 (0.7)
Cardiovascular	5 (3)	4 (3)	1 (0.7)	0
Cerebrovascular	3 (2)	3 (2)	1 (0.7)	1 (0.7)
Peripheral vascular	3 (2)	3 (2)	1 (0.7)	0
Venous thromboembolic events	1 (0.6)	1 (0.6)	0	0
Total vascular occlusive events	12 (8)*	11 (7)	3 (2)	1 (0.7)

*15 events reported in 12 patients; 3 patients had multiple events.

- Time to onset of vascular occlusive events:
  - Ponatinib 10-233 days; imatinib 2-156 days
- Of the 12 patients treated with ponatinib with vascular occlusive events, 11 had at least 1 risk factor or relevant medical history

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EPIC: Vascular Occlusive Events

List of Vascular Occlusive AEs (serious AEs indicated by *)	
Ponatinib n = 12[a]	**Imatinib n = 3[a]**
Cardiac discomfort (n = 1)	Electrocardiogram ST-segment depression (n = 1)
Coronary artery stenosis (n = 1)	Peripheral vascular disorder (n = 1)
Intermittent claudication (n = 1)	Hypoxic-ischemic encephalopathy (n = 1)*
Acute myocardial infarction (n = 2)*	
Angina pectoris (n = 2)*	
Coronary artery disease (n = 2)*	
Cerebrovascular accident (n = 1)*	
Dysarthria (n = 1)*	
Peripheral artery thrombosis (n = 1)*	
Retinal vein thrombosis (n = 1)*	
Transient ischemic attack (n = 1)*	
Peripheral arterial occlusive disease (n = 2)*	

[a]Patients can have more than 1 event

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EPIC: Summary

- Despite early termination, preliminary analyses suggest improved efficacy of ponatinib over imatinib (median follow-up 5.1 months)
  - <10% BCR-ABL at 3 months: 94% ponatinib vs 68% imatinib (*P*<.001) – endpoint correlates with OS
  - Higher response rates that were deeper and more rapid
- There were more adverse events in the ponatinib arm
  - Higher incidence of grade 3/4 AEs and SAEs
  - More patients experienced vascular occlusive events
- A dose-ranging trial of ponatinib in refractory CML to evaluate benefit/risk of alternate dosing regimens is planned

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