Achieving early cytogenic or molecular landmark response is predictive of outcomes in heavily pretreated patients with chronic-phase chronic myeloid leukemia treated with ponatinib in the phase 2 PACE trial: 5-year data

P670

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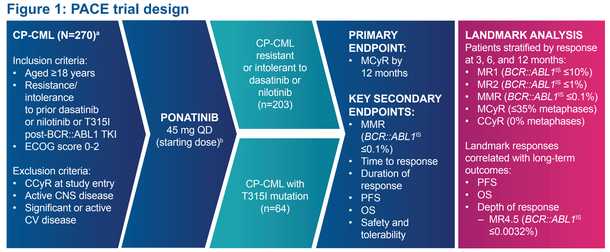
Background

- In chronic-phase chronic myeloid leukemia (CP-CML), poor outcomes are associated with sequential tyrosine kinase inhibitor (TKI) therapy and/or the presence of *BCR::ABL1* mutations[1,2]
- Ponatinib is the only BCR::ABL1 inhibitory TKI currently approved to potently inhibit all known native and single resistance-mutation variants of BCR::ABL1, including T315I[3,4]
- Early landmark response to treatment with BCR::ABL1 TKIs in patients with newly diagnosed CP-CML has been associated with improved long-term outcomes.[5–7] However, landmark analyses in patients treated with multiple prior TKIs are limited
- The phase 2 PACE trial demonstrated clinical efficacy of ponatinib in heavily pretreated patients with CP-CML resistant or intolerant to dasatinib or nilotinib or with the T315I mutation[8]
- We performed a post hoc analysis of patients with CP-CML in the PACE trial with landmark cytogenetic and molecular responses at 3, 6, and 12 months

Methods

- PACE was a single-arm, open-label, international, multicenter, phase 2 trial (NCT01207440)[4]

Figure 1: PACE trial design



[a] Three patients who had not received prior dasatinib or nilotinib did not have T315I confirmed at baseline and were not evaluable for efficacy
[b] Dose reduction recommendations were applied in October 2013 to manage adverse events, per protocol, in response to concerns regarding an accumulation of arterial occlusive events with continued follow-up across the ponatinib clinical program

CCyR, complete cytogenetic response; CNS, central nervous system; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; QD, once daily

- Following protocol amendment in 2013, the ponatinib dose was reduced to 15 mg QD for patients who achieved MCyR and 30 mg QD for patients who did not achieve MCyR
- At the data cutoff date (Feb 6, 2017), median follow-up was 56.8 months[8]
- A post hoc landmark analysis was conducted to correlate early molecular and cytogenetic responses with long-term efficacy outcomes

Results

Table 1: Baseline characteristics by MMR at 3 months

Characteristic	Achievement of MMR at 3 months		Overall
	No MMR (n=200)	MMR (n=33)	(n=233)
Age, years, median (range)	60 (18–87)	54 (26–79)	60 (18–87)
Male, n (%)	105 (53)	22 (67)	127 (55)
Median time from diagnosis to first dose, years (range)	7.6 (0.5–27.4)	5.3 (1.4–22.3)	7.1 (0.5–27.4)
Prior TKI therapy, n (%)			
1 TKI	12 (6)	2 (6)	14 (6)
2 TKIs	66 (33)	11 (33)	77 (33)
≥3 TKIs	122 (61)	20 (61)	142 (61)
Resistant/intolerant to most recent dasatinib or nilotinib, n (%)			
Resistant only	121 (61)	23 (70)	144 (62)
Resistant and intolerant	38 (19)	7 (21)	45 (19)
Intolerant only	32 (16)	2 (6)	34 (15)
Best response of MMR or better to most recent dasatinib/nilotinib, n (%)	7 (4)	1 (3)	8 (3)
***BCR::ABL1*IS status at baseline, n (%)**			
>10%	159 (80)	18 (55)	177 (76)
>1%–10%	37 (19)	14 (42)	51 (22)
>0.1%–1%	4 (2)	1 (3)	5 (2)
Mutation status, n (%)			
No mutation detected	112 (56)	9 (27)	121 (52)
T315I	37 (19)	16 (48)	53 (23)
Mutations other than T315I	51 (26)	8 (24)	59 (25)

[a] 34 of 267 patients with CP-CML who were evaluable for efficacy in PACE were not evaluable for this analysis

- Among 267 patients with CP-CML, 94% received ≥2 prior TKIs and 61% received ≥3 prior TKIs (**Table 1**)

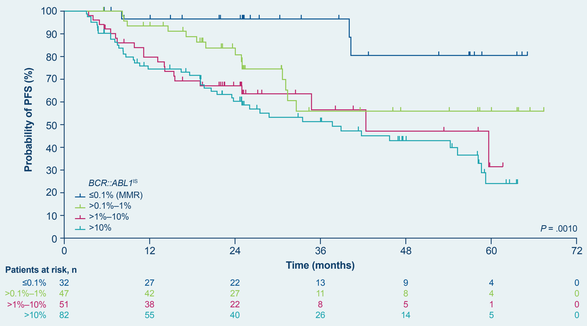
Objective

To investigate the association of early landmark responses to ponatinib with long-term survival outcomes

Results

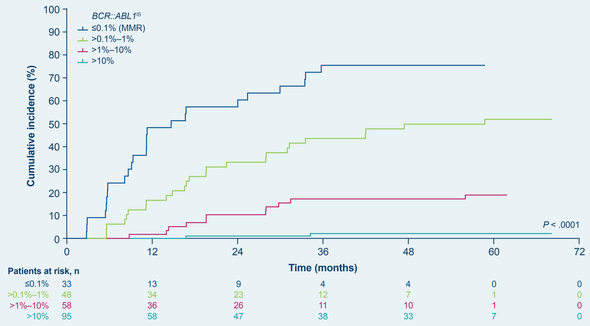
- Achievement of MMR at 3 months was associated with significantly improved PFS at 4 years compared with lack of MMR at 3 months (**Figure 3A; Table 2**)
- Patients with molecular response of MMR at 3 months achieved deeper cumulative responses (MR4.5) at any time at significantly higher rates than nonresponders (**Figure 3B**)

Figure 3A: PFS by molecular response at 3 months[a]



[a] For PFS, patients who did not have disease progression or death were censored at the last response assessment[8]

Figure 3B: Cumulative incidence rate of MR4.5 by molecular response at 3 months



Key takeaways

- **In this highly resistant pretreated patient population, early molecular responses achieved with ponatinib were significantly associated with improved long-term survival outcomes**
- **Deeper molecular responses were significantly correlated with higher rates of MR4.5 responses over time**

Landmark responses

- At the final analysis, 148 of 267 (55%) patients achieved the primary endpoint of MCyR at 12 months[8]
- For the PACE study, the MMR by 5 years was 40% (108 of 267 patients)[8]
- Molecular response of MR1, MR2, or MMR at 3 months was reached by 49%, 34%, and 14% of patients, respectively (**Figure 2**)
- At 3 months, 51% of patients had MCyR and 39% had CCyR
- In general, patients who achieved a landmark response of MMR at 3 months were younger, more recently diagnosed, and more likely to have had a mutation detected at study entry compared with patients who did not achieve MMR at 3 months (**Table 1**)
- Patients with cytogenetic response of MCyR or CCyR at 3 months had significantly improved PFS at 4 years compared with patients who did not achieve MCyR or CCyR (**Figure 4; Table 2**)
- Among landmark evaluable patients, 34% received 2 prior TKIs and 61% received ≥3 prior TKIs
- Patients with MMR at 3 months had numerically higher probability of OS after 4 years (**Figure 5A; Table 2**)
- Patients with cytogenetic responses of MCyR or CCyR were significantly more likely to have improved OS at 4 years compared with patients who did not achieve a cytogenetic response (**Figure 5B–C; Table 2**)
- Similar improvement in long-term outcomes were observed for patients with landmark responses at 6 months and 12 months (**Table 2**)

Figure 2: Patients achieving landmark responses

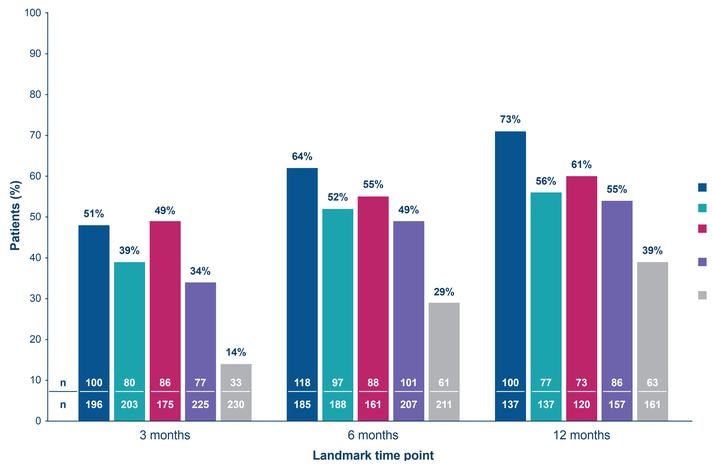


Figure 4: PFS by cytogenetic response at 3 months

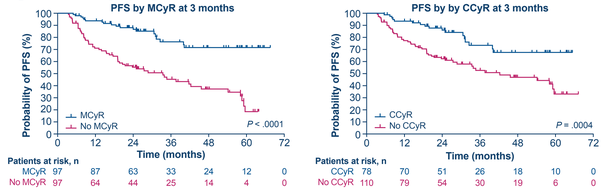
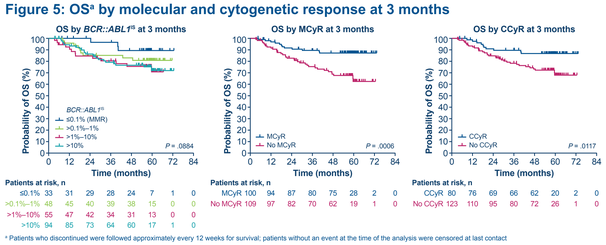


Figure 5: OS[a] by molecular and cytogenetic response at 3 months



[a] Patients who discontinued were followed approximately every 12 weeks for survival; patients without an event at the time of the analysis were censored at last contact

Table 2: Summary of Kaplan-Meier–estimated 4-year PFS and 4-year OS by molecular and cytogenetic response at 3, 6, and 12 months

Landmark response	PFS			OS		
	n	4-yr rate, %	*P*-value	n	4-yr rate, %	*P*-value
3-month molecular, % *BCR::ABL1*IS						
≤10% (MR1)	82	61	.0218	86	81	.5896
>10%	79	52		89	79	
≤1% (MR2)	75	66	.0002	77	85	.0683
>1%	133	52		148	79	
≤0.1% (MMR)	32	80	.0010	33	89	.0884
>0.1%	180	54		197	80	
3-month cytogenetic						
MCyR	97	71	<.0001	100	87	.0006
No MCyR	97	37		109	69	
CCyR	78	68	.0004	80	87	.0017
No CCyR	110	47		123	73	
6-month molecular, % *BCR::ABL1*IS						
≤10% (MR1)	84	69	.0012	88	90	.0069
>10%	55	51		73	80	
≤1% (MR2)	95	70	<.0001	101	86	.0673
>1%	86	52		106	82	
≤0.1% (MMR)	57	83	<.0001	61	93	.0067
>0.1%	128	53		150	82	
6-month cytogenetic						
MCyR	116	64	<.0001	118	85	.0208
No MCyR	57	43		72	78	
CCyR	95	72	<.0001	97	87	.0088
No CCyR	75	41		90	79	
12-month molecular, % *BCR::ABL1*IS						
≤10% (MR1)	68	80	.0002	73	97	.0001
>10%	38	53		48	81	
≤1% (MR2)	82	76	.0004	86	93	.0047
>1%	59	56		72	85	
≤0.1% (MMR)	61	81	.0005	63	97	.0017
>0.1%	84	57		99	85	
12-month cytogenetic						
MCyR	97	75	<.0001	100	93	.0012
No MCyR	32	53		41	81	
CCyR	74	83	<.0001	77	96	.0002
No CCyR	51	55		60	81	

Conclusions

- In this heavily pretreated CP-CML population, achieving cytogenetic and molecular responses at 3 and 6 months was associated with improved long-term PFS and OS
- Deeper molecular response at 3 months correlated with increased likelihood of achieving MR4.5 at any time
- Patients with no response at three months may still have a later response and a favorable long-term outcome and therapy may be continued if there is good tolerance
- These results underscore the potential utility of assessing cytogenetic and molecular responses at early time points, as they are strong predictors of favorable long-term outcomes
- The results of this retrospective analysis confirm that achievement of early and deep responses, particularly *BCR::ABL1*IS ≤10%, with ponatinib within 12 months improves long-term outcomes in patients with heavily pretreated CP-CML

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