

Effect of comorbidities on response outcomes with first-line tyrosine kinase inhibitors, dasatinib versus imatinib, in patients with chronic myeloid leukemia in chronic phase: exploratory post hoc analysis of DASISION

CML-081

Massimo Breccia,¹ Michael Mauro,² Elias Jabbour,³ Giuseppe Saglio,⁴ Antonio Jiménez-Velasco,⁵ Philipp le Coutre,⁶ Irene DeGutis,⁷ Wasiulla Khan,^{7*} Oumar Sy,⁷ Rene Swanink,⁸ Jorge E. Cortes⁹

¹Department of Translational and Precision Medicine, Policlinico Umberto 1, Sapienza University, Rome, Italy; ²Memorial Sloan Kettering Cancer Center, New York, NY, USA; ³The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ⁴Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; ⁵Hospital Universitario Carlos Haya, Malaga, Spain;

⁶Charité Universitätsmedizin Berlin, Berlin, Germany; ⁷Bristol Myers Squibb, Princeton, NJ, USA; ⁸Bristol Myers Squibb, Braine-l'Alleud, Belgium; ⁹Georgia Cancer Center, Augusta University, Augusta, GA, USA

*Affiliation at the time of the study.

Introduction

- In the 5-year follow-up of the phase 3 DASISION study (NCT00481247), dasatinib demonstrated faster and deeper molecular responses than imatinib when administered as first-line therapy for chronic myeloid leukemia in chronic phase (CML-CP)¹
 - Major molecular response (MMR) by 5 years: 76% vs 64%, $P = 0.0022$
 - Molecular response with a 4.5-log reduction in *BCR-ABL1* transcript levels (MR^{4.5}): 42% vs 33%, $P = 0.0251$
- More than 50% of patients with CML-CP have at least one comorbidity at diagnosis²
 - The most frequent comorbidities include hypertension, other cardiovascular disorders, and diabetes
 - The Charlson Comorbidity Index (CCI) score is used to evaluate the impact of comorbidities on patient mortality. It predicts 10-year survival in patients with multiple comorbidities, with points being attributed to each comorbidity based on severity³
 - Comorbidities, in addition to other considerations, may influence first-line treatment choice for most patients and should be considered when selecting tyrosine kinase inhibitor (TKI) therapy
- In this exploratory post hoc analysis of DASISION at 5 years' follow-up, we investigated the effect of comorbidities in patients with CML-CP treated with dasatinib and imatinib

Objective

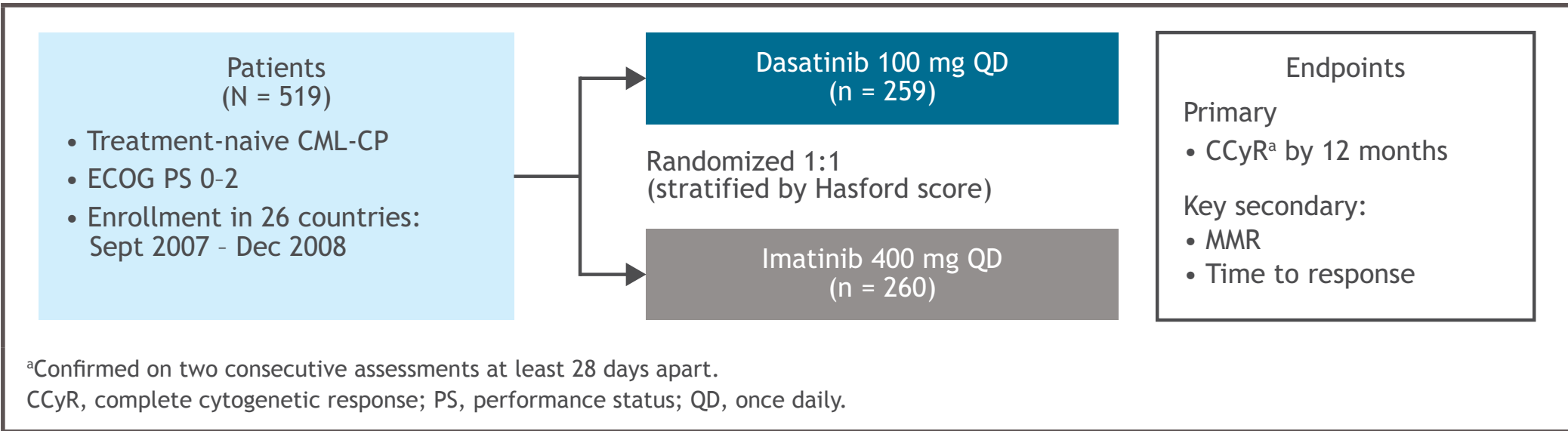
- To assess the impact of comorbidities on efficacy and safety outcomes with 5 years of follow-up in patients with CML-CP randomized to dasatinib or imatinib in the DASISION trial

Methods

Study design

- DASISION was an open-label, randomized, multicenter, phase 3 trial (Figure 1)

Figure 1. Study design



- Eligible patients included those with newly diagnosed CML-CP
 - Patients were excluded if they had uncontrolled or serious cardiovascular disease; however, those with common cardiovascular risk factors including uncontrolled hypertension or angina, congestive heart failure > 3 months before enrollment, and myocardial infarction > 6 months before enrollment were eligible
- Patients were stratified by Hasford score and randomized 1:1 to dasatinib or imatinib
- The primary endpoint was rate of CCyR by 12 months

Exploratory subgroup analysis based on CCI score

- Efficacy and safety data were retrospectively stratified based on CCI score categories 2-4, 5-6, and ≥ 7 (higher scores indicate a higher comorbidity burden)
- Rates of MMR and MR^{4.5} were compared between treatment groups using unstratified Cochran-Mantel-Haenszel tests
- Time to MMR and MR^{4.5} were evaluated using Kaplan-Meier methodology with HRs based on Cox proportional-hazards models and P values from unstratified log-rank tests

Results

Baseline characteristics

- In total, 14 patients (3%) had CCI 2-4, 260 (50%) had CCI 5-6, and 245 (47%) had CCI ≥ 7 (Figure 2)
- The baseline characteristics were generally balanced between treatments in each CCI group (Table 1)
- The median average daily dose was lower in the dasatinib arm compared with the imatinib arm in all groups (Table 2)
- The median duration of therapy was ~60 months, independent of the treatment arm or CCI score

Figure 2. CCI stratification in DASISION, overall study population

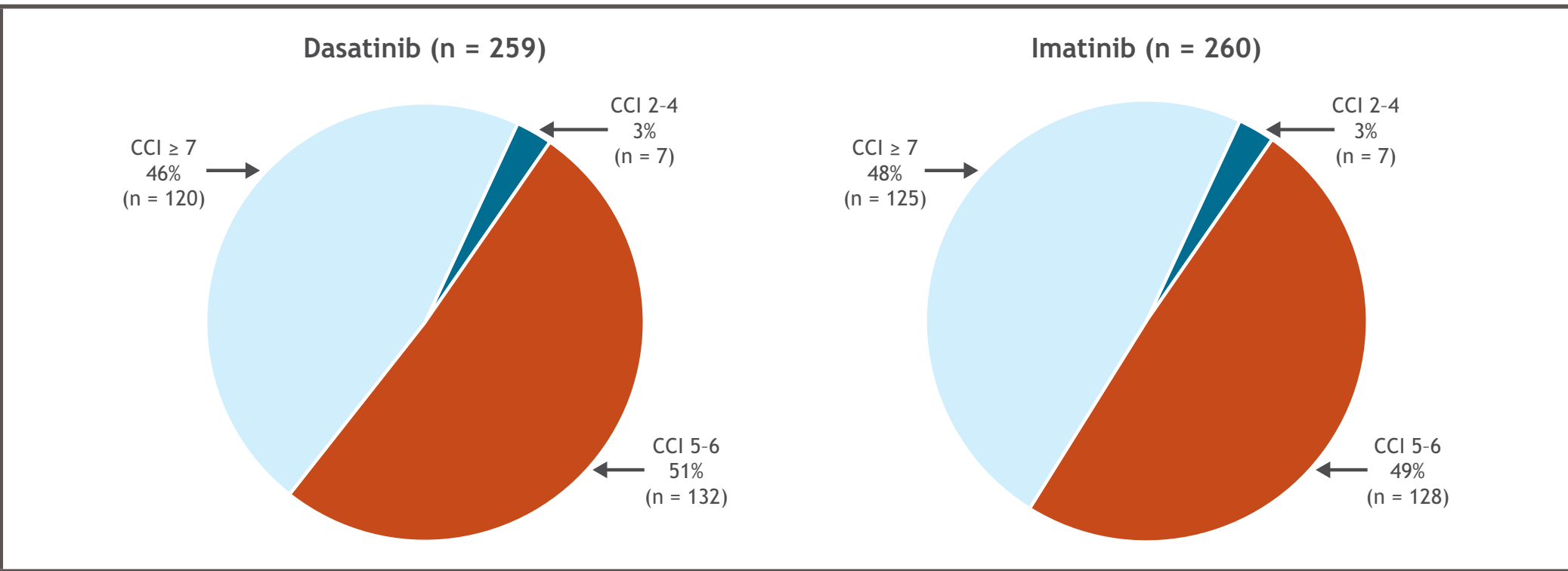


Table 1. Baseline characteristics by CCI group

	CCI 2-4		CCI 5-6		CCI ≥ 7	
	Dasatinib (n = 7)	Imatinib (n = 7)	Dasatinib (n = 132)	Imatinib (n = 128)	Dasatinib (n = 120)	Imatinib (n = 125)
Age, median (range), years	26 (20-50)	45 (29-59)	37 (18-64)	37 (18-65)	58 (28-84)	58 (23-78)
Male sex, %	71	71	57	66	53	59
ECOG PS, %						
0	100	71	80	81	85	77
1	0	29	20	18	15	22
2	0	0	0	1	0	1
Hasford score, %						
Low risk (≤ 780)	43	71	50	48	14	17
Intermediate risk (> 780 and ≤ 1480)	57	14	30	34	68	62
High risk (> 1480)	0	14	20	18	18	21

Table 2. Drug exposure by CCI group

	CCI 2-4		CCI 5-6		CCI ≥ 7	
	Dasatinib (n = 7)	Imatinib (n = 7)	Dasatinib (n = 132)	Imatinib (n = 128)	Dasatinib (n = 120)	Imatinib (n = 125)
Average daily dose, median (range), mg/day	98.5 (96.0-100.0)	400.0 (318.6-418.9)	99.5 (67.3-138.5)	400.0 (160.0-740.2)	94.2 ^a (20.6-126.7)	399.2 ^b (124.5-733.2)
Duration of therapy, median (range), months	60.2 (29.8-65.1)	60.1 (3.2-61.0)	60.8 (0.0-72.1)	60.8 (1.3-74.5)	60.2 ^a (0.0-71.8)	60.1 ^b (0.3-71.8)

^an = 119; ^bn = 123.

Efficacy findings

Response rates

- While dasatinib had improved response rates in the CCI 2-4 group, the small number precludes any clinical correlation
 - MMR rate: 85.7% for dasatinib vs 57.1% for imatinib ($P = 0.2542$)
 - MR^{4.5} rate: 71.4% for dasatinib vs 14.3% for imatinib ($P = 0.0374$)
- Dasatinib significantly improved response rates in patients in the CCI 5-6 group versus imatinib (Figure 3A)
- In the cohort with a higher comorbidity burden (CCI ≥ 7 group), dasatinib had a numerically higher response rate than imatinib; however, it was not statistically significant (Figure 3B)
- MMR rates were numerically greater with dasatinib compared with imatinib at 12, 24, 36, and 60 months (Table 3)

Time to MMR

- Median time to MMR in both the CCI 5-6 group and the CCI ≥ 7 group was significantly shorter with dasatinib than imatinib (Figures 4A and 4B)
 - CCI 5-6: 15.0 vs 24.0 months (HR = 1.64; 95% CI, 1.23-2.19; $P = 0.0006$)
 - CCI ≥ 7 : 12.0 vs 21.4 months (HR = 1.41; 95% CI, 1.04-1.91; $P = 0.0279$)

Figure 3. MMR and MR^{4.5} rates at any time by CCI subgroup

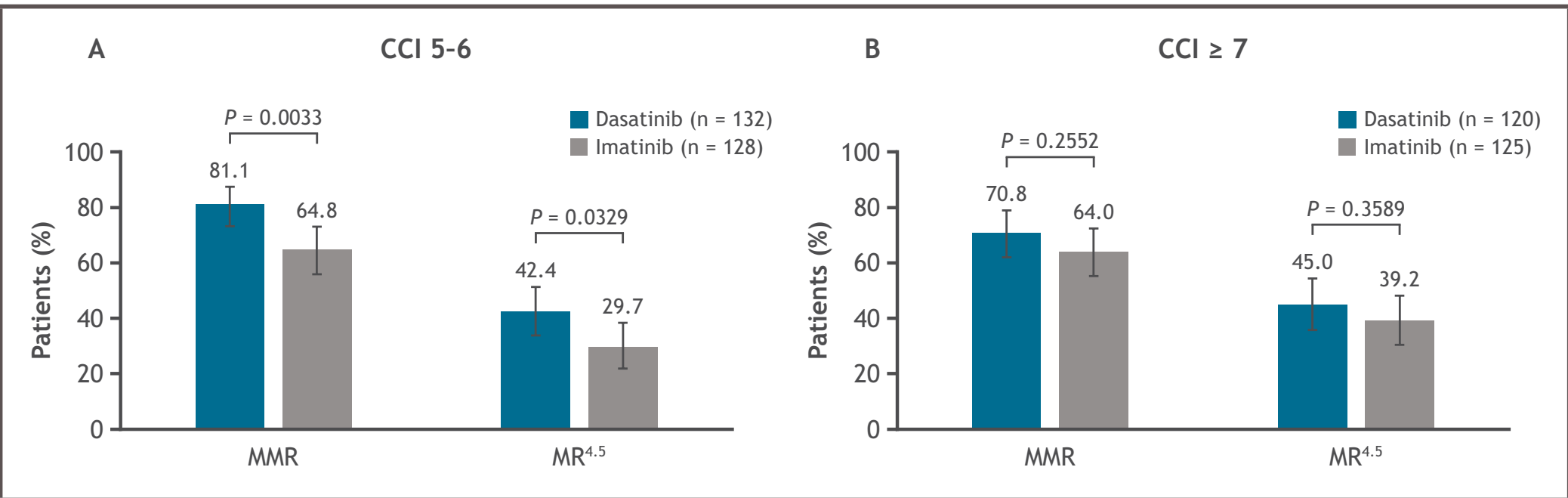
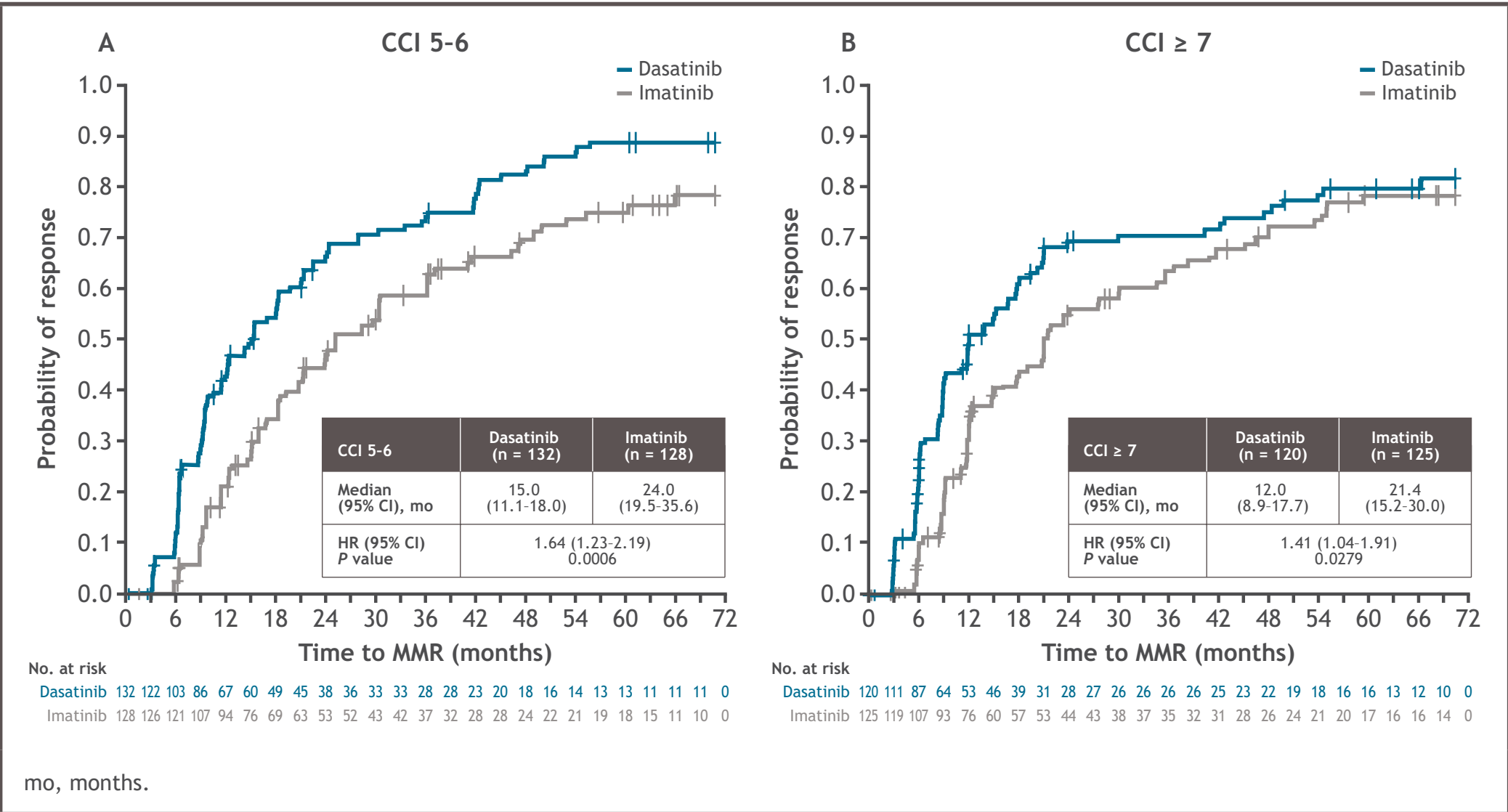


Table 3. MMR rates by CCI subgroup over time

	CCI 2-4			CCI 5-6			CCI ≥ 7		
	Dasatinib (n = 7)	Imatinib (n = 7)	P	Dasatinib (n = 132)	Imatinib (n = 128)	P	Dasatinib (n = 120)	Imatinib (n = 125)	P
12 months	57.1	14.3	0.11	44.7	24.2	0.0005	47.5	32.8	0.02
24 months	71.4	14.3	0.04	64.4	46.1	0.0031	62.5	48.0	0.02
36 months	85.7	57.1	0.25	69.7	56.3	0.025	63.3	54.4	0.16
60 months	85.7	57.1	0.25	81.1	64.1	0.0021	70.0	64.0	0.32

Figure 4. Time to MMR (CCI 5-6 and ≥ 7 groups)



Safety

- Grade 3/4 treatment-related adverse events (TRAEs) were reported in 0% of patients with dasatinib vs 14% with imatinib in the CCI 2-4 group, 8% vs 9% in patients with CCI 5-6, and 24% vs 13% in patients with CCI ≥ 7 (Table 4)
 - The incidence of pleural effusion was higher in the dasatinib group in both the CCI 5-6 and CCI ≥ 7 groups compared with imatinib
- Grade 3-4 TRAEs leading to discontinuation did not occur in the CCI 2-4 group, and were reported with similar frequency with dasatinib and imatinib in both CCI 5-6 (1% vs 1%) and CCI ≥ 7 groups (8% vs 7%)
- No deaths occurred in the CCI 2-4 group; a similar percentage of patients treated with dasatinib and imatinib died in the CCI 5-6 group (8% vs 9%) and CCI ≥ 7 group (13% vs 11%)
- Dose escalations were more frequent in the imatinib group in all cohorts, while both dose interruptions and dose reductions were more common in the dasatinib group (Table 5)
- The patients in the CCI ≥ 7 subgroup had noticeably more dose reductions associated with dasatinib

Table 4. Safety by CCI subgroup

Adverse events, %	CCI 2-4		CCI 5-6		CCI ≥ 7	
	Dasatinib (n = 7)	Imatinib (n = 7)	Dasatinib (n = 132)	Imatinib (n = 128)	Dasatinib (n = 119)	Imatinib (n = 123)
TRAEs						
Any grade	14	43	78	88	85	80
Pleural effusion	0	0	18.2	0.8	41.2	0.8
Grade 3-4	0	14	8	9	24	13
Treatment-related SAEs	0	0	14	6	20	11
TRAEs leading to discontinuation						
Any grade	0	14	8	1	22	12
Grade 3-4	0	0	1	1	8	7
All deaths	0	0	8	9	13	11

Treatment-related was defined as certain, probable, or possible relationship to study drug as per investigator assessment. Includes events reported between first dose and 30 days after last dose of study therapy. SAE, serious adverse event.

Table 5. Dose modification by CCI subgroup

Dose modification, %	CCI 2-4		CCI 5-6		CCI ≥ 7	
	Dasatinib (n = 7)	Imatinib (n = 7)	Dasatinib (n = 132)	Imatinib (n = 128)	Dasatinib (n = 119)	Imatinib (n = 123)
Any dose escalation	0	14	11	29	7	18
Any dose interruption	86	43	60	52	77	52
Any dose reduction	14	29	23	12	54	22

Conclusions

- This exploratory post hoc analysis showed that dasatinib was effective across all CCI groups and, in agreement with existing studies, suggested that comorbidities do not negatively affect TKI activity
- Dasatinib demonstrated significantly higher molecular response rates versus imatinib in patients with CCI 5-6, and had a comparable response to imatinib at any time in patients with a higher comorbidity burden (CCI ≥ 7)
- Dasatinib was associated with significantly reduced time to response than imatinib in both cohorts with a higher comorbidity burden
- In patients with a high comorbidity burden (CCI ≥ 7), dasatinib was associated with an increased number of grade 3-4 AEs
 - However, dasatinib had a similar frequency of treatment-related grade 3-4 AEs leading to discontinuation compared with imatinib in each subgroup
 - Pleural effusion was more common in patients treated with dasatinib compared with imatinib in both the CCI 5-6 and CCI ≥ 7 groups
- From both a safety and efficacy perspective, these findings support the use of dasatinib as first-line treatment in patients with CML-CP and a substantial comorbidity burden

References

- Cortes JE, et al. *J Clin Oncol* 2016;34:2333-2340.
- Hoffmann VS, et al. *Leukemia* 2015;29:1336-1343.
- Charlson ME, et al. *J Chron Dis* 1987;40:373-383.

Acknowledgments

- We thank the patients and families for making this trial possible and the clinical study teams who participated
- This study was funded by Bristol Myers Squibb
- All authors contributed to and approved the presentation
- Medical writing and editorial assistance was provided by Laura Bella, PhD, formerly of Caudex, funded by Bristol Myers Squibb

Disclosures

MB: consultancy fees and/or honoraria from AbbVie, Bristol Myers Squibb/Celgene, Incyte, Novartis, and Pfizer; MJM: consultancy fees and honoraria from Bristol Myers Squibb, Novartis, Pfizer, and Takeda; research funding from Sun Pharma/SPARC; EJ: advisory role and research funding from AbbVie, Adaptive Biotechnologies, Angen, Bristol Myers Squibb, Genentech, Pfizer, and Takeda; GS: research funding from Ariad, Bristol Myers Squibb, Incyte, Novartis, Pfizer, and Roche; ALJ: none; PDL: honoraria from Incyte, Novartis, and Pfizer; ID, WK: employee and current equity holder of/in Bristol Myers Squibb; OS, RS: employee of Bristol Myers Squibb; JEC: consultancy fees from Amphivena Therapeutics, BiolineRx; consultancy fees and research funding from Astellas, Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Novartis, Pfizer, and Takeda; research funding from Arog, Immunogen, Merus, Sun Pharma, and Telios; and consultancy, board of directors or advisory committees, and research funding from BioPath Holdings.

Previously presented at the 62nd American Society of Hematology Annual Meeting; December 5-8, 2020.