Supplementary Materials

Supplementary methods

Patient consent and ethical conduct

Patient consent was required for data collection from medical records for all living patients in the Netherlands and in the United Kingdom (UK) for living patients at centers where data were collected by an independent researcher; for deceased patients, data were collected by the direct care team to preserve patient confidentiality. This study was conducted in accordance with the Declaration of Helsinki.

Response to treatment

To ensure consistency, molecular responses (major molecular response [MMR], MR4, and MR4.5) were derived from the recorded *BCR-ABL1* transcript levels (after applying conversion factors as required to ensure *BCR-ABL1* values from all centers were standardized to the International Scale[1]) according to European LeukemiaNet (ELN) 2013 criteria.[2] Hematologic and cytogenetic responses were taken as recorded; however, if cytogenetic responses were missing, complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR) were derived from *BCR-ABL1* values where available (CCyR defined as *BCR-ABL1* between >0.1% and <1%; PCyR defined as *BCR-ABL1* between 1% and 10%).[2,3] Where patients' level of response at baseline was not available, the best response to the previous tyrosine kinase inhibitor (TKI) was taken as the baseline response level, which may have led to an underestimation of the level of response achieved during bosutinib treatment if patients had deteriorated between the best response on the previous TKI and bosutinib initiation.

Adverse events

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03.[4]

Statistical analyses

Sample size

As a retrospective, non-interventional, single cohort study, no formal power calculation was carried out. Approximately 210 patients across the UK and the Netherlands had been prescribed bosutinib in normal clinical practice at the time the study was initiated, and it was therefore anticipated that approximately 100 patients in total from across the UK and the Netherlands would be included, which was deemed adequate to produce results of sufficient reliability for the outcomes of interest.

Patients lost to follow-up

Patients with no response data recorded within 6 months prior to the data collection date (chosen as MR is routinely collected at 6-monthly intervals) were considered to be lost to follow-up (LTFU), and the date of last documented response was used as the date on which the patient was LTFU.

Treatment duration

Treatment duration was evaluated as the time from bosutinib initiation to discontinuation. For patients still on bosutinib at data collection or LTFU, treatment duration was the time from bosutinib initiation to the date of data collection or the LTFU date, respectively.

Overall survival

Overall survival (OS) was evaluated from the time between bosutinib initiation and death due to all causes; patients who were alive or LTFU were censored on the date of data collection or date LTFU, respectively. OS at 1 and 2 years after bosutinib initiation was estimated by Kaplan–Meier analysis. OS is presented as Kaplan–Meier plots.

Logistic regression analyses

Independent associations between relevant baseline variables and cumulative CCyR, MMR, and MR4 were evaluated using multivariable logistic regression analyses. Baseline variables included in the analyses were reason for bosutinib initiation, age at chronic myeloid leukemia (CML) diagnosis, duration of CML at bosutinib initiation, number of different TKI therapies prior to bosutinib initiation, number of comorbidities (<2 vs. ≥2), presence of cytopenia (≥1 of anemia [Hb <80 g/L], neutropenia [<1.0 x10^9/L], lymphopenia [<0.5 x10^9/L], and thrombocytopenia [<50 x10^9/L]) at bosutinib initiation), and bosutinib dose at initiation. Sex was evaluated as a confounder.

Subgroup analyses

Post hoc analyses were carried out to evaluate cumulative treatment response in patients in chronic phase at baseline stratified according to whether patients switched to bosutinib due to resistance or intolerance to prior TKI therapy. Data were analyzed using the available data and denominators are presented where data were missing. Data were analyzed using Stata v14 (StataCorp). Percentages are reported to the nearest whole number and, therefore, percentages may not total 100% due to rounding.

Supplementary references

1. Müller MC, Cross NCP, Erben P, et al. Harmonization of molecular monitoring of CML therapy in Europe. Leukemia. 2009;23:1957-1963.

2. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122:872-884.

3. Branford S, Fletcher L, Cross NCP, et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood. 2008;112:3330-3338.

4. National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (v4.03). Published June 2010. https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed August 19, 2021.

SUPPLEMENTARY TABLE S1 Multivariable associations between baseline variables and cumulative responses to bosutinib

Variable, OR (95% CI)	Cumulative CCyR	Cumulative MMR	Cumulative MR4
Reason for initiation of bosutinib (intolerance *vs*. resistance)	19.64 (3.31–116.6)	14.76 (2.99–72.80)	3.32 (0.79–13.94)
Age at CML diagnosis (years)	0.97 (0.93–1.02)	1.00 (0.95–1.04)	1.01 (0.97–1.05)
Duration of CML (years)	0.98 (0.89–1.07)	1.01 (0.93–1.10)	1.01 (0.94–1.10)
Number of different TKIs	0.48 (0.14–1.71)	0.76 (0.27–2.11)	0.71 (0.29–1.77)
Cytopenia *vs.* no cytopenia	3.13 (0.29–34.08)	2.12 (0.28–15.82)	1.62 (0.34–7.64)
≥2 *vs.* <2 comorbidities	2.32 (0.57–9.42)	1.27 (0.37–4.37)	1.08 (0.32–3.60)
Dose at initiation 100 mg *vs.* 500 mg	0.23 (0.03–1.55)	0.59 (0.12–3.00)	0.90 (0.18–4.36)
Dose at initiation 200 mg *vs.* 500 mg	0.38 (0.05–2.77)	0.46 (0.09–2.48)	0.84 (0.18–4.06)
Dose at initiation 300 mg *vs.* 500 mg	1.08 (0.17–6.92)	2.63 (0.51–13.54)	0.90 (0.23–3.52)
Dose at initiation 400 mg *vs.* 500 mg	3.46 (0.36–33.49)	4.56 (0.57–36.77)	0.60 (0.09–4.06)

Abbreviation: CCyR, complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukemia; MMR, major molecular response; MR, molecular response; OR, odds ratio; TKI, tyrosine kinase inhibitor.

SUPPLEMENTARY TABLE S2 Patients in chronic phase at baseline achieving optimal responses during the first 12 months of bosutinib treatment

Response, n (%)	3 months	6 months	12 months
Optimal	54 (64)	54 (64)	40 (48)
Warning	11 (13)	11 (13)	17 (20)
Failure	3 (4)	2 (2)	0
Only CHR recorded	3 (4)	4 (5)	1 (1)
No data available	13 (15)	13 (15)	26 (31)
Total	84 (100)	84 (100)	84 (100)

Optimal, warning and failure were defined based on European LeukemiaNet 2013 criteria for second-line TKI therapy[2] using available *BCR-ABL1* levels and documented cytogenetic responses.
Abbreviations: CHR, complete hematologic response; TKI, tyrosine kinase inhibitor.

SUPPLEMENTARY TABLE S3 Medical treatment following bosutinib discontinuation

n (%)	Patients discontinuing bosutinib (n=33)
Patients receiving follow-up medical treatment	20 (61)
Follow-up medical treatment[a]	
Imatinib	5 (15)
Nilotinib	2 (6)
Dasatinib	8 (24)
Ponatinib	3 (9)
Bosutinib	1 (3)
Other	3 (9)
No follow-up medical treatment recorded	13 (39)

Abbreviation: TKI, tyrosine kinase inhibitor

[a]Not mutually exclusive. One patient had ponatinib followed by bosutinib, and one patient had donor lymphocyte infusion followed by imatinib.

SUPPLEMENTARY TABLE S4 Grade 3-4 adverse events leading to dose reduction or discontinuation

Adverse event, n	No dose changes	Dose reduction	Dose discontinuation		Total
			Temporary	Permanent	
Hematologic					
Anemia	1	-	-	-	1
Neutropenia	-	1	-	-	1
Thrombocytopenia	3	2	-	1	6
Non-hematologic					
ALT increased	-	1	1 (14 days)	1	3
Atrial fibrillation	1	-	-	-	1
Cardiac failure	-	1	-	-	1
Diarrhea	1	1	1 (14 days)	-	3
Fatigue	-	1	-	-	1
Hepatotoxicity	-	1	-	-	1
Pain in extremity	-	-	1 (12 days)	-	1
Vomiting	-	-	-	1	1
Other	1	1	-	-	2
Grand Total	7	9	3	3	22

Abbreviation: ALT: alanine aminotransferase.

SUPPLEMENTARY TABLE S5 Distribution of adverse events leading to dose reduction or discontinuation according to bosutinib dose at the time of the adverse event

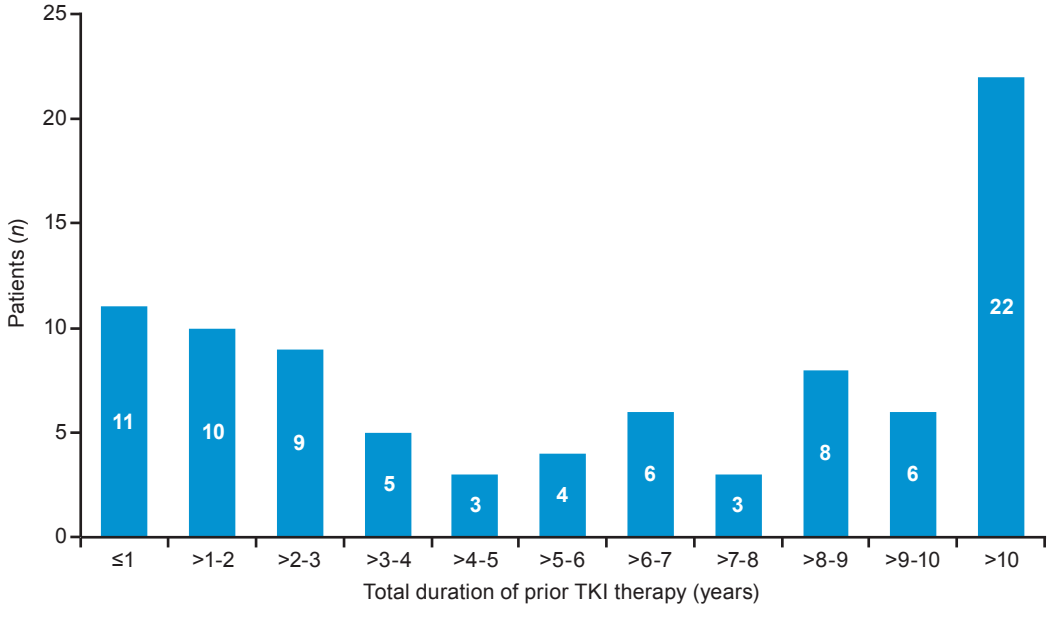
	Bosutinib dose at the time of the adverse event (mg/day)													
Adverse event, n	**100**	**130[a]**	**150[a]**	**200**	**250[a]**	**300**	**350[a]**	**400**	**450[a]**	**500**	**550[a]**	**600**	**750[a,b]**	**Total**
Hematologic														
Neutropenia	-	1	-	1	-	-	-	-	-	-	-	-	-	2
Thrombocytopenia	-	-	-	2	-	2	-	1	-	-	-	-	-	5
Non-hematologic														
Abdominal distension	-	-	-	-	-	-	-	1	-	-	-	-	-	1
Abdominal pain	-	-	-	-	-	-	1	1	-	-	-	-	-	2
Acne	-	-	-	-	-	-	-	-	-	1	-	-	-	1
ALT increased	4	-	2	4	1	4	-	5	-	3	-	-	-	23
Asthenia	-	-	-	-	-	-	-	-	-	1	-	-	-	1
Bone pain	2	-	-	-	-	1	-	-	-	-	-	-	-	3
Cardiac failure	-	-	-	-	-	-	-	3	-	-	-	-	-	3
Chest pain	1	-	-	2	-	1	-	-	-	1	-	-	-	5
Creatinine increased	-	-	-	-	-	2	-	1	-	-	-	-	-	3
Diarrhea	-	-	2	4	-	5	-	-	-	4	-	1	-	16
Dizziness	1	-	-	-	-	-	-	1	-	-	-	-	-	2
Dyspnea	1	-	-	-	-	-	-	1	-	-	-	-	-	2
Fatigue	2	-	-	1	-	3	-	1	-	-	-	-	-	7
Headache	-	-	-	2	-	1	-	-	-	-	-	-	-	3
Hepatotoxicity	-	-	-	-	-	1	-	-	-	-	-	-	-	1
Hypertension	-	-	-	-	-	1	-	-	-	-	-	-	-	1
Nausea	1	-	-	2	-	2	-	3	-	1	-	-	-	9
Pain in extremity	-	-	-	-	-	-	-	-	-	2	-	-	-	2
Pain	-	-	-	3	-	1	-	1	-	-	-	-	-	5
Pleural effusion	-	-	-	1	-	2	-	3	-	2	-	-	-	8
Rash	-	-	-	2	-	1	-	-	-	2	-	-	1	6
Vomiting	-	-	-	-	1	1	-	1	-	-	-	-	-	3
Other	3	-	-	4	-	7	-	3	1	4	1	-	-	23
Total	**15**	**1**	**4**	**28**	**2**	**35**	**1**	**26**	**1**	**21**	**1**	**1**	**1**	**137**

Abbreviation: ALT: alanine aminotransferase.

[a]Bosutinib tablets are 100 mg and 500 mg; non-standard dosing reflects the average daily dose where alternate daily doses differed.

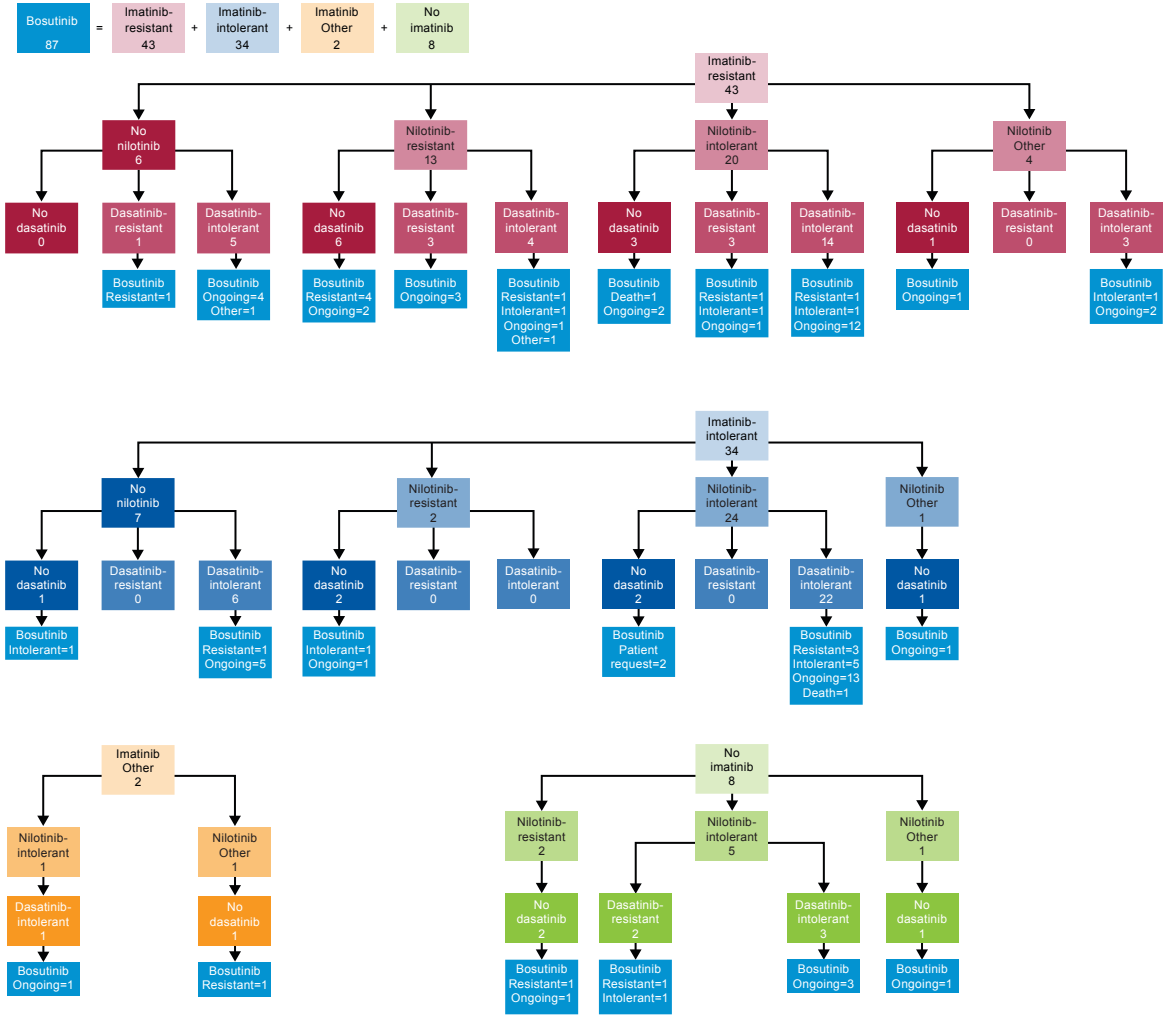
[b]Maximum daily bosutinib dose is 600 mg; 750 mg dose was at patient's request

Supplementary Figure S1. Distribution of total time on prior TKI therapy



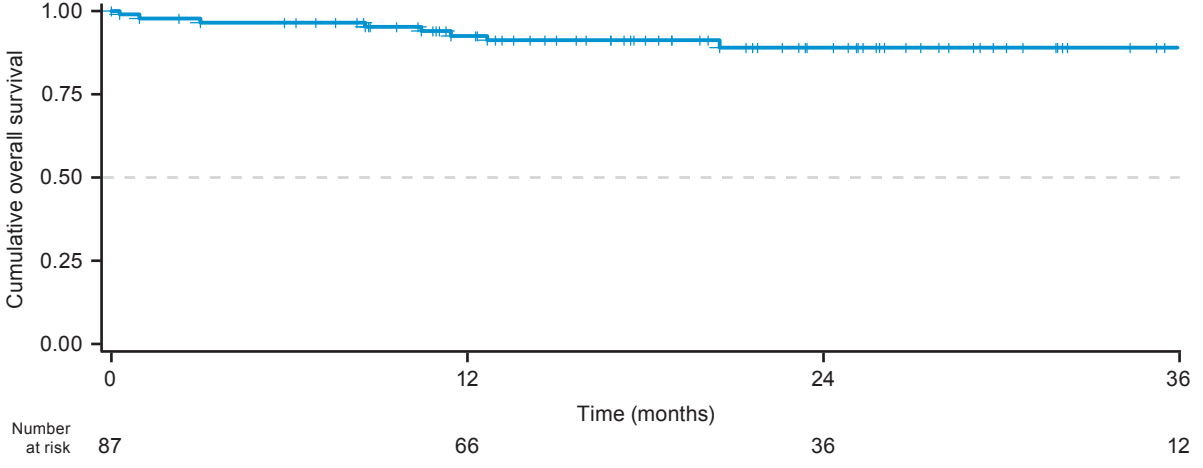
TKI: tyrosine kinase inhibitor.

Supplementary Figure S2. Summary of patients' TKI treatment pathways*



*TKI treatment was not necessarily received in the order shown. 'Other' refers to discontinuation for reasons other than resistance or intolerance.
TKI: tyrosine kinase inhibitor.

Supplementary Figure S3. Overall survival in the overall patient population*



*Date of death not available for one patient.