Haematological Malignancy Research Network: Real-World Disease Management and Outcomes in Chronic Myeloid Leukaemia

Synopsis

Audit Title	Real-World Disease Management and Outcomes in Chronic Myeloid Leukaemia
Design	Disease Registry (population-based cohort)
Subjects	Patients newly diagnosed with chronic myeloid leukaemia 1st September, 2004 to 31st August, 2019
Size	555
Primary Objectives	To describe the disease management of chronic myeloid leukaemia in chronic phase
Secondary Objectives	To examine treatment duration, response, progression-free and overall survival
Primary Endpoint	Treatment pathways by line of treatment
Secondary Endpoint	Progression-free and overall survival

Contents

Abbreviations

AlloSCT	Allograft Stem Cell Transplant
AP	Accelerated Phase
BP	Blast Phase
BSC	Best Supportive Care
CCyR	Complete cytogenetic remission
CML	Chronic Myeloid Leukaemia
CML-CP	Chronic Myeloid Leukaemia in Chronic Phase
CP	Chronic Phase
HMDS	Haematological Malignancy Diagnostic Service
HMRN	Haematological Malignancy Research Network
HU	Hydroxycarbamide
ICD-O-3	Classification of Diseases for Oncology, 3rd Edition
IFN	Interferon
MMR	Major Molecular Response (≤0.1%)
MR	Molecular Response (≤1.0%)
MR^2	Molecular Response (≤1.0%) or complete cytogenetic remission
NHS	National Health Service
OS	Overall Survival
PFS	Progression-free survival
SCT	Stem Cell Transplant
TKI	Tyrosine Kinase Inhibitor
TTD	Time to Treatment Discontinuation

Objectives

1. To describe the disease management and complete treatment pathways for chronic myeloid leukaemia in chronic phase with a focus in those treated with two or more TKIs.
2. To examine response, treatment duration, progression-free and overall survival.

Setting & Study Design

The Haematological Malignancy Research Network (HMRN) is an ongoing population-based cohort, which was established in 2004 to provide robust, generalizable data to inform clinical practice and research[1]. The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3.8 million (Yorkshire and the Humber & Yorkshire Coast Cancer Networks) and collects detailed information about all haematological malignancies diagnosed in the region. With an emphasis on primary-source data, prognostic factors, sequential treatment/response history, and socio-demographic details are recorded to clinical trial standards. This is done for all patients newly diagnosed with a haematological malignancy in the HMRN region; there are around 2,500 each year of which approximately 30 are cases of chronic myeloid leukaemia (CML). All haematological malignancy diagnoses within the region are made at a single specialist haematopathology laboratory – the Haematological Malignancy Diagnostic Service (HMDS) and it is from here that all HMRN patients are ascertained. A sophisticated custom-designed web database is used to handle clinical diagnoses, specimen tracking and reporting; all diagnoses, including disease transformations and progressions, are automatically coded to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3).

CML diagnosis is based on the demonstration of a BCR-ABL fusion transcript expressed by the Philadelphia (Ph) chromosome by RQ-PCR and/or the demonstration of t(9;22)(q34;q11) by conventional karyotyping or interphase FISH. As per standard practice, response to therapy

[1] Alexandra Smith, Debra Howell, Simon Crouch, Dan Painter, John Blase, Han-I Wang, Ann Hewison, Timothy Bagguley, Simon Appleton, Sally Kinsey, Cathy Burton, Russell Patmore, Eve Roman; Cohort Profile: The Haematological Malignancy Research Network (HMRN): a UK population-based patient cohort, International Journal of Epidemiology, Volume 47, Issue 3, 1 June 2018, Pages 700–700g, https://doi.org/10.1093/ije/dyy044

is monitored using either molecular or cytogenetic tests or both; specifically, patients are monitored by quantitative PCR on peripheral blood, supplemented by bone marrow karyotyping when if it was clinically indicated. ABL kinase mutational analysis is carried out when the transcript ratio has increased over two sequential samples or on clinical demand. Testing for T315I mutation is also performed for patients who fail to respond to first line TKI and all patients who acquire TKI resistance over the course of their treatment.

Data Collection and Processing

Data collection is initiated six months after date of diagnosis; research nurses working to agreed operating procedures and data standards visit each of the 14 hospitals in the region and abstract a core clinical dataset from the patients' medical records. The information collected includes demographic details, baseline blood count data and first line treatment. All details are abstracted onto structured forms and entered onto the web-based system, which integrates HMRN and HMDS data. An important feature of data acquisition is the emphasis on primary source information; data from radiology reports, blood tests, clinical examination, and clinician summaries are recorded, enabling embedded algorithms in the database system to automatically generate stage and prognostic scores. Further data abstraction from the medical records has been undertaken to capture information on subsequent treatment lines. Information on date and cause of death were obtained from the NHS Central Register.

Data Analysis

The analysis has included all adult (18+ years) patients newly diagnosed with CML in **chronic phase** (ICD-O-3: 9875/3) by HMDS between 1st September, 2004 to 31st August, 2019 whilst resident in the HMRN region and treated within the Network. Subjects were described in terms of their baseline demographic and prognostic characteristics and each patient's treatment pathway characterised from date of diagnosis to date of death or, for patients still alive, end of follow up.

Standard statistical methods were used to describe the demographics and disease management of CML with data presented as proportions, means and medians with corresponding ranges and confidence intervals where appropriate.

Disease management has been examined by treatment line and type of treatment including the proportion of patients who undergo an allogenic stem cell transplant, with a focus in those previously treated with two or more TKIs. Reason for treatment discontinuation has been examined (treatment failure/intolerance), ("Time to Treatment Discontinuation" (TTD)) and time spent in each disease state including time spent in Accelerated Phase (AP) or Blast Phase (BP). If tested, the proportion of subjects with T315I mutation in those that have not responded to treatment has been described.

Standard time to event analyses including Kaplan-Meier has been used to estimate progression-free and overall survival by line of treatment and TTD. The endpoints are defined below:

Disease Response

Disease response has been defined as either a major molecular response (MMR, ≤ 0.1% BCR-ABL1) or as a MR^2, which is a molecular response (MR, ≤ 1.0% BCR-ABL1) or complete cytogenetic remission (CCyR). Time to response was measured from the initiation of treatment to achieving a MR^2 ("Time to MR^2") or MMR ("Time to MMR") and duration of response measured from the date an MR or MMR was achieved to loss of response for each line of treatment or regimen.

Time to Treatment Discontinuation (TTD)

In those that have discontinued treatment, Time to Treatment Discontinuation (TTD) was defined as the time from the initiation of treatment to the date of discontinuation or death. It was also reported for all patients censoring at the end of follow-up for those patients still on treatment.

Overall survival (OS)

OS was defined as the time (in years) from initiation of treatment (i.e., the index date) to death (any cause). Patients who did not die within the study observation period were censored on the last date they were known to be alive, according to national central register.

Progression-free survival (PFS)

PFS was defined from the initiation of treatment (i.e., the index date) to the earliest documentation of disease progression to AP/BC or date of death from any cause. For patients who did not have disease progression or died, the last date of follow-up of the medical records was used as the censor date.

Duration of disease state

Time spent in accelerated phase and blast crisis was defined from date of disease progression to remission, or date of death if remission was not achieved.

Relative Survival

Relative survival (RS) was also estimated to examine the CML-specific mortality rate. The Stata program strel (v1.2.7) was used to estimate RS and corresponding 95% Confidence Intervals (95%CI); with age and sex-specific background mortality rates being obtained from national life tables. RS was estimated for treatment lines 1 to 4 and regimen if more than 25 patients received treatment.

Results

In total, there was 555 newly diagnosed cases 1st September, 2004 to 31st August, 2019 whilst resident in the HMRN region and treated within the Network, with a male predominance (55.3%) and a median age of 59.9 years old (Table 1). The performance status of the majority of patients was good (ECOG 0/1: 72.1%) and whilst hepatomegaly was relatively uncommon (9.5%), splenomegaly affected 239 patients (43.1%). Median follow-up time was 8.5 years.

Whilst TKIs are the mainstay in the management of CML, patients frequently receive other interventions including allografts and many will receive supportive care mainly in the form of blood products. Interferon is occasionally given and Hydroxycarbamide (HU) is also given to help reduce the white cell count, and 256 of the patients received it at some stage of their treatment pathway, especially at diagnosis prior to commencing a TKI. To illustrate the level of supportive care given the complete treatment pathways for 30 patients initially treated with HU are shown in Appendix I to demonstrate the complexity of the pathways. The results of this report will, however, focus on TKIs and the majority of patients were initially treated

with a TKI (n=539, 97.1%). The remaining 16 patients either received hydroxycarbamide only (n=7) or were treated with a supportive/palliative intent only (n=9), as expected these patients were on average older with a median age of 88.7 years.

Table 2 describes the TKIs by line of therapy and baseline demographic factors and Figure 1 the sequential TKIs treatment for those patients who commenced imatinib, dasatinib and nilotinib. As expected imatinib was the most common TKI at first line with 483 patients receiving it. In total, 225 patients went onto receive a second line TKI; with 58.2% receiving Nilotinib. In total, 22 patients received an allograft for their CML treatment and seven after disease progression to blast crisis or accelerated phase. Figure 2 shows at what stage in their pathway they were transplanted. Table 3 summarises the year treatment began by TKI, as expected, Imatinib was the only drug available in 2004-2005, from 2006 Nilotinib was introduced and Dasatinib in 2007 at second line.

Of the 539 patients treated with a TKI, 62.3% received a response, either an MMR or M^2 and median time to response was 474 days. Of these 278/539 achieved an MMR and 58 only an M^2 (Table 4). In total 134 patients lost their response, and median time to loss of response was 273 days. Tables 5-7 shows the response rates at second, third and fourth line respectively.

Table 8 summarises the reasons why a patient switched TKI, the most common reason being either a response was not achieved or loss of response. A relatively high proportion, however, switched as they were unable to tolerate the therapy and this differed by type of TKI, and was generally higher in those who were treated with Dasatinib. A relatively small proportion of patients were tested for the T315I mutation (Table 9), and of those tested 16.2% had the mutation at first line (1L) and 40% at second and third line.

Tables 10 – 13 and Figures 3 – 10 summarises overall survival (OS) by treatment lines and TKI. At first line, 5-year OS was 78.0% and did not differ by TKI (Figure 4), as expected survival was poorer in those who did not achieve an MMR with a 5-year OS of 66.5% compared to 88.3% in those that did achieve an MMR (Figure 5). Reaching an MMR within 6 or 12 months of starting treatment did not have a strong influence on outcome (Figures 6-7)

A similar figure for 5-year OS at second line (78.5%) compared to first line was seen, however, more variation was observed by regimen with those receiving Bosutinib having the poorest outcome (Figure 9). Having an MMR was again predictive of survival (Figures 10-12).

At 3rd line, 5-year OS was 72.3% (Table 12, Figure 13) and differences were seen by TKI, with Bosutinib having a 5-year OS of 91.5% and Ponatinib 46.9%, and was 88.9% in those who achieved an MMR (Figures 15-17). By fourth line (Table 13, Figures 18-19) 5-year OS had reduced to 58.8%.

Similar trends were seen for PFS compared to OS (Tables 14-17 and Figures 20-36) primarily as only 21 patients' disease had progressed to blast crisis (n=12) or an accelerated phase (n=9). For all BC/AP patients, median time in BC/AP was 93.8 days (5th-95th percentile:25-503 days); the corresponding mean was 172.1 (sd: 163.5). The median time for those in blast crisis was 78 (5th-95th percentile:33-530) and mean was 142 days (sd 146.1), the respective time for those in accelerated phase was 154 (5th-95th percentile:7-503) and 212 days (sd 185.1). At third line, three patients progressed: accelerated phase (n=1), blast crisis (n=2) and the mean time in state 276 days (213.8), median 249 days (5th-95th: 78-503). Figure 37 shows the treatments given in this phase, ranging from hydroxycarbamide to intensive chemotherapy (DA, FLAG-Ida) and allografts.

Tables 18-21 and Figures 38 -45 summarise time to treatment discontinuation (TTD) by treatment line. Censoring at the end of the study follow-up for those still on treatment, the median time for first line was 3.3 years, this decreased to 1.2 years in those who had discontinued treatment (Table 18); the respective means were 6.5 and 2.4 years. TTD decreased at second line to a median of 2.4 years (Table 19, Figures 40-41), 1.6 years at third line (Table 20, Figures 42-43) and 1.0 years at fourth line (Table 21, Figures 44-45).

Table 22 and Figures 46-49 summarise the relative survival (RS) estimates for treatment lines 1 to 4. At first line (Figure 46), there was a disparity between OS and RS, with a 5-year OS of 77.8% and 5-year RS of 89.2% indicating that patients were dying from competing

causes of death. The magnitude between OS and RS diminished with increasing line of treatment, for example at fourth line (Figure 49), 5-year OS was 63.8% and 5-year RS was 64.8% indicating that patients were dying as a consequence of their CML.

Table 1 Baseline characteristics newly diagnosed CML diagnosed 1st September 2004 to 31st August 2019

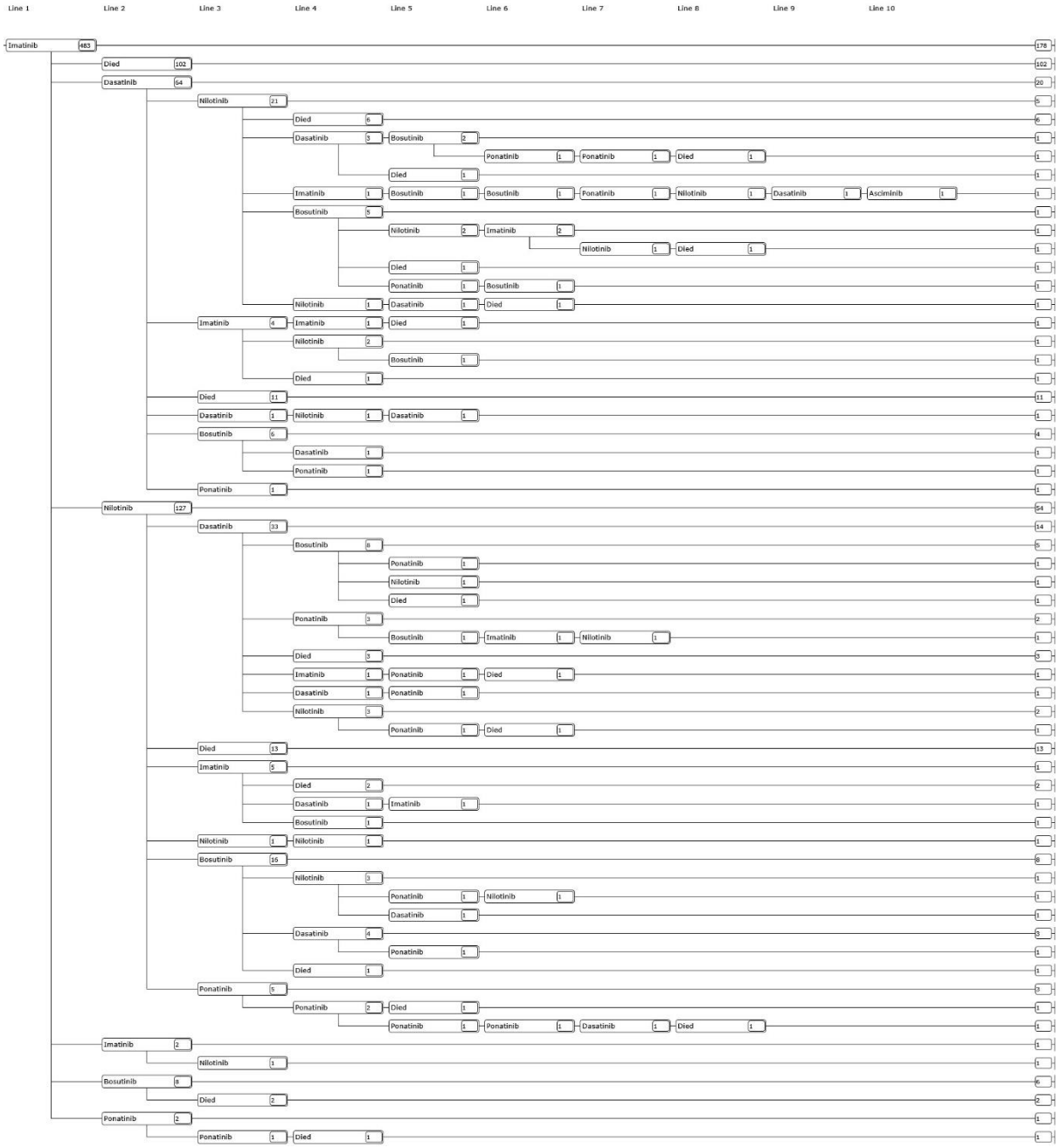
		Total n (%)
Total		555 (100)
Sex	Male	307 (55.3)
	Female	248 (44.7)
Age at diagnosis (years)	Mean (SD)	59.5 (17.5)
	Median (Range)	59.9 (18.7 - 96.4)
Performance Status - ECOG	0	236 (42.5)
	1	164 (29.5)
	2	43 (7.7)
	3 / 4	16 (2.9)
	Not Known	96 (17.3)
Hb (g/dl)	Mean (sd)	11.8 (2.1)
WBC Count (10^9/L)	Mean (sd)	40.8 (20.9)
Lymphocytes (10^9/L)	Mean (sd)	6.8 (9.8)
Neutrophils (10^9/L)	Mean (sd)	74.2 (74.9)
Monocytes (10^9/L)	Mean (sd)	4.1 (7.3)
PCV (10^9/L)	Mean (sd)	35.7 (6.5)
Platelets (10^9/L)	Mean (sd)	530.0 (459.4)
Splenomegaly	No	270 (48.6)
	Yes	239 (43.1)
	Not known	46 (8.3)
Hepatomegaly	No	448 (80.7)
	Yes	53 (9.5)
	Not known	54 (9.7)
Follow up time (years)	Median (95% CI)	8.5 (8.0 - 9.2)

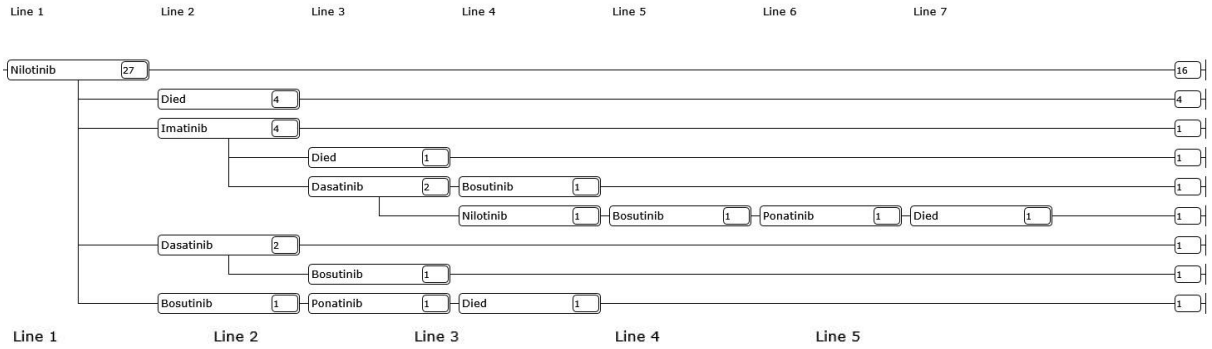
Eastern Co-operative Oncology Group (ECOG), performance status was not routinely collected until 2012

Table 2 Tyrosine Kinase Inhibitors by Treatment Line

	1L	2L	3L	4L	5L	6L	7L	8L	9L	10L
Total	539 (100)	225 (100)	107 (100)	48 (100)	21 (100)	9 (100)	5 (100)	1 (100)	1(100)	1(100)
Sex:										
Male	301 (55.8)	127 (56.4)	64 (59.8)	30 (62.5)	14 (66.7)	6 (66.7)	2 (40.0)	1 (100)	1 (100)	1 (100)
Female	238 (44.2)	98 (43.6)	43 (40.2)	18 (37.5)	7 (33.3)	3 (33.3)	3 (60.0)			
Age at treatment (years)										
Mean (SD)	58.8 (17.1)	56.7 (15.4)	56.2 (15.3)	57.0 (13.4)	57.3 (13.8)	57.4 (12.8)	61.1 (13.9)	-	-	-
Median (Range)	59.3 (18.7 - 94.7)	56.7 (19.3 - 88.4)	56.2 (19.4 - 89.0)	57.4 (19.7 - 82.5)	55.3 (37.2 - 82.0)	55.2 (40.1 - 80.4)	55.3 (49.1 - 81.0)	-	-	-
Imatinib	483 (89.6)	16 (7.1)	10 (9.3)	3 (6.3)	1 (4.8)	3 (33.3)	-	-	-	-
Dasatinib	27 (5.0)	66 (29.3)	36 (33.6)	10 (20.8)	3 (14.3)	-	1 (20.0)	-	1 (100)	-
Nilotinib	27 (5.0)	131 (58.2)	26 (24.3)	12 (25.0)	3 (14.3)	1 (11.1)	2 (40.0)	1 (100)	-	-
Bosutinib	1 (0.2)	10 (4.4)	26 (24.3)	17 (35.4)	6 (28.6)	2 (22.2)	-	-	-	-
Ponatinib	1 (0.2)	2 (0.9)	9 (8.4)	6 (12.5)	8 (38.1)	3 (33.3)	2 (40.0)	-	-	-
Asciminib	-	-	-	-	-	-	-	-	-	1 (100)

Figure 1 Sequential Tyrosine Kinase Inhibitors




Line 1
Line 2
Line 3
Line 4
Line 5
Line 6
Line 7
Nilotinib 27
Died 4
Imatinib 4
Died 1
Dasatinib 2
Bosutinib 1
Nilotinib 1
Bosutinib 1
Ponatinib 1
Died 1
Dasatinib 2
Bosutinib 1
Bosutinib 1
Ponatinib 1
Died 1
16
4
1
1
1
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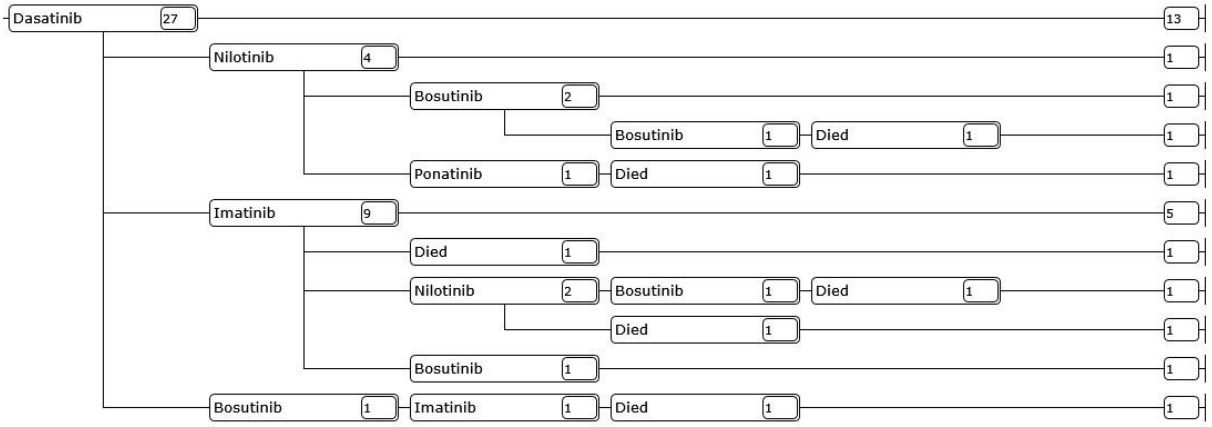
1
1
Line 1
Line 2
Line 3
Line 4
Line 5


Dasatinib 27
Nilotinib 4
Bosutinib 2
Bosutinib 1
Died 1
Ponatinib 1
Died 1
Imatinib 9
Died 1
Nilotinib 2
Bosutinib 1
Died 1
Died 1
Bosutinib 1
Bosutinib 1
Imatinib 1
Died 1
13
1
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1
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1

Figure 2 Complete Treatment Pathways for allografted patients

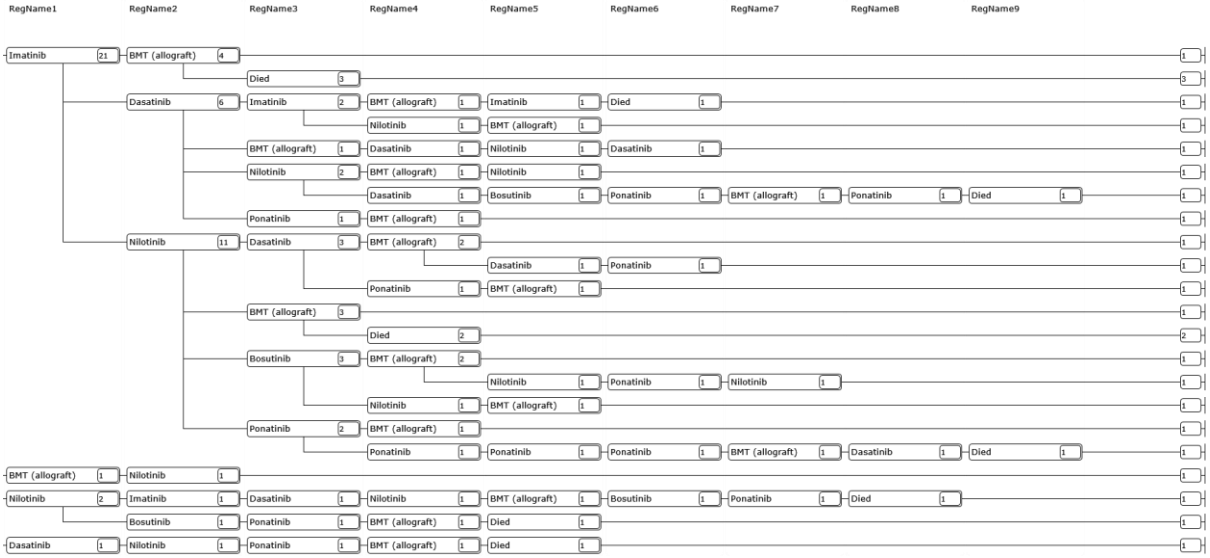


Table 3 Year treatment started by tyrosine kinase inhibitor (TKI)

Year	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib	Total
Total	**516 (53.9)**	**203 (21.2)**	**144 (15.0)**	**62 (6.5)**	**31 (3.2)**	**1 (0.1)**	**957 (100)**
2004	7 (100)	-	-	-	-	-	7 (100)
2005	25 (100)	-	-	-	-	-	25 (100)
2006	24 (92.3)	2 (7.7)	-	-	-	-	26 (100)
2007	42 (87.5)	1 (2.1)	5 (10.4)	-	-	-	48 (100)
2008	37 (69.8)	6 (11.3)	10 (18.9)	-	-	-	53 (100)
2009	26 (63.4)	5 (12.2)	10 (24.4)	-	-	-	41 (100)
2010	32 (65.3)	4 (8.2)	13 (26.5)	-	-	-	49 (100)
2011	34 (54.8)	9 (14.5)	19 (30.6)	-	-	-	62 (100)
2012	25 (50.0)	17 (34.0)	6 (12.0)	-	2 (4.0)	-	50 (100)
2013	41 (43.6)	33 (35.1)	10 (10.6)	8 (8.5)	2 (2.1)	-	94 (100)
2014	43 (52.4)	22 (26.8)	10 (12.2)	7 (8.5)	-	-	82 (100)
2015	36 (41.9)	33 (38.4)	9 (10.5)	6 (7.0)	2 (2.3)	-	86 (100)
2016	34 (47.9)	21 (29.6)	9 (12.7)	6 (8.5)	1 (1.4)	-	71 (100)
2017	34 (40.0)	23 (27.1)	14 (16.5)	10 (11.8)	4 (4.7)	-	85 (100)
2018	45 (58.4)	13 (16.9)	7 (9.1)	4 (5.2)	8 (10.4)	-	77 (100)
2019	29 (37.7)	12 (15.6)	12 (15.6)	13 (16.9)	10 (13.0)	1 (1.3)	77 (100)
2020	2 (9.1)	2 (9.1)	10 (45.5)	6 (27.3)	2 (9.1)	-	22 (100)
2021	-	-	-	2 (100)	-	-	2 (100)
Line 1	483 (89.6)	27 (5.0)	27 (5.0)	1 (0.2)	1 (0.2)	-	539 (100)
2004	7 (100)	-	-	-	-	-	7 (100)
2005	25 (100)	-	-	-	-	-	25 (100)
2006	24 (100)	-	-	-	-	-	24 (100)
2007	41 (100)	-	-	-	-	-	41 (100)
2008	35 (100)	-	-	-	-	-	35 (100)
2009	25 (96.2)	-	1 (3.8)	-	-	-	26 (100)
2010	30 (85.7)	-	5 (14.3)	-	-	-	35 (100)
2011	31 (73.8)	-	11 (26.2)	-	-	-	42 (100)

Year	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib	Total
2012	24 (75.0)	3 (9.4)	5 (15.6)	-	-	-	32 (100)
2013	37 (84.1)	4 (9.1)	2 (4.5)	-	1 (2.3)	-	44 (100)
2014	40 (93.0)	2 (4.7)	1 (2.3)	-	-	-	43 (100)
2015	31 (83.8)	5 (13.5)	-	1 (2.7)	-	-	37 (100)
2016	31 (86.1)	5 (13.9)	-	-	-	-	36 (100)
2017	32 (82.1)	6 (15.4)	1 (2.6)	-	-	-	39 (100)
2018	43 (95.6)	1 (2.2)	1 (2.2)	-	-	-	45 (100)
2019	27 (96.4)	1 (3.6)	-	-	-	-	28 (100)
Line 2	16 (7.1)	131 (58.2)	66 (29.3)	10 (4.4)	2 (0.9)	-	225 (100)
2006	-	2 (100)	-	-	-	-	2 (100)
2007	-	1 (20.0)	4 (80.0)	-	-	-	5 (100)
2008	-	3 (23.1)	10 (76.9)	-	-	-	13 (100)
2009	-	1 (12.5)	7 (87.5)	-	-	-	8 (100)
2010	2 (16.7)	2 (16.7)	8 (66.7)	-	-	-	12 (100)
2011	3 (20.0)	6 (40.0)	6 (40.0)	-	-	-	15 (100)
2012	1 (8.3)	10 (83.3)	1 (8.3)	-	-	-	12 (100)
2013	1 (3.8)	25 (96.2)	-	-	-	-	26 (100)
2014	-	17 (70.8)	6 (25.0)	1 (4.2)	-	-	24 (100)
2015	2 (8.0)	22 (88.0)	1 (4.0)	-	-	-	25 (100)
2016	2 (11.1)	11 (61.1)	2 (11.1)	3 (16.7)	-	-	18 (100)
2017	-	13 (61.9)	6 (28.6)	1 (4.8)	1 (4.8)	-	21 (100)
2018	2 (12.5)	10 (62.5)	3 (18.8)	-	1 (6.3)	-	16 (100)
2019	2 (9.5)	7 (33.3)	7 (33.3)	5 (23.8)	-	-	21 (100)
2020	1 (14.3)	1 (14.3)	5 (71.4)	-	-	-	7 (100)
Line 3	10 (9.3)	26 (24.3)	36 (33.6)	26 (24.3)	9 (8.4)	-	107 (100)
2007	1 (50.0)	-	1 (50.0)	-	-	-	2 (100)
2008	1 (33.3)	2 (66.7)	-	-	-	-	3 (100)
2009	1 (16.7)	3 (50.0)	2 (33.3)	-	-	-	6 (100)
2010	-	2 (100)	-	-	-	-	2 (100)
2011	-	3 (60.0)	2 (40.0)	-	-	-	5 (100)
2012	-	4 (80.0)	-	-	1 (20.0)	-	5 (100)

Year	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib	Total
2013	1 (9.1)	3 (27.3)	4 (36.4)	3 (27.3)	-	-	11 (100)
2014	1 (10.0)	2 (20.0)	3 (30.0)	4 (40.0)	-	-	10 (100)
2015	3 (18.8)	3 (18.8)	7 (43.8)	2 (12.5)	1 (6.3)	-	16 (100)
2016	-	2 (28.6)	4 (57.1)	1 (14.3)	-	-	7 (100)
2017	2 (15.4)	1 (7.7)	7 (53.8)	3 (23.1)	-	-	13 (100)
2018	-	-	3 (37.5)	1 (12.5)	4 (50.0)	-	8 (100)
2019	-	1 (7.7)	2 (15.4)	7 (53.8)	3 (23.1)	-	13 (100)
2020	-	-	1 (25.0)	3 (75.0)	-	-	4 (100)
2021	-	-	-	2 (100)	-	-	2 (100)

Table 4 Response to First Line Tyrosine Kinase Inhibitor and Time to Response (days)

		Any Response (MMR or MR²)		MMR				MR² Only		Loss of Response (MMR or MR²)	
	Total	Yes	Time to response (days) (95% CI)	Yes	6 months	12 months	Time to response (days) (95% CI)	Yes	Time to response (days) (95% CI)	Yes	Time to loss of response (days)
Total	539 (100)	336 (62.3)	474.0 (427.0 - 518.0)	278 (51.6)	28 (5.2)	118 (21.9)	587.0 (541.0 - 662.0)	58 (10.8)	NR	134 (39.9)	273.0 (206.0 - 365.0)
Imatinib	483 (100)	298 (61.7)	479.0 (449.0 - 529.0)	242 (50.1)	19 (3.9)	100 (20.7)	599.0 (545.0 - 671.0)	56 (11.6) -	NR	119 (39.9)	273.0 (210.0 - 399.0)
Nilotinib	27 (100)	18 (66.7)	425.0 (182.0 - 698.0)	18 (66.7)	6 (22.2)	11 (40.7)	425.0 (182.0 - 698.0)	2 (7.4)	NR	3 (16.7)	44.0 (28.0 - .)
Dasatinib	27 (100)	19 (70.4)	427.0 (273.0 - 730.0)	17 (63.0)	3 (11.1)	6 (22.2)	579.0 (273.0 - 1077.0)	-	-	12 (63.2)	216.0 (85.0 - 1177.0)
Bosutinib	1 (100)	1 (100)	-	1 (100)	-	1 (100)	-	-	-	-	-
Ponatinib	1 (100)	-	-	-	-	-	-	63 (11.7)	NR	-	-

95%CI=95% Confidence Intervals
NR = Not reached

Table 5 Response to Second Line Tyrosine Kinase Inhibitor and time to response (days)

		Any Response (MMR or MR²)		MMR				MR² Only		Loss of Response (MMR or MR²)	
	Total	Yes	Time to response (days) (95% CI)	Yes	6 Months	12 Months	Time to response (days) (95% CI)	Yes	Time to response (days) (CI)	Yes	Time to loss of response (days)
Total	225 (100)	152 (67.6)	209.0 (181.0 - 247.0)	127 (56.4)	67 (29.8)	102 (45.3)	301.0 (213.0 - 364.0)	29 (12.9)	NR	40 (26.3)	245.0 (115.0 - 428.0)
Imatinib	16 (100)	10 (62.5)	312.0 (19.0 - .)	7 (43.8)	5 (31.3)	6 (37.5)	514.0 (19.0 - .)	3 (18.8)	NR	2 (20.0)	259.0 (259.0 - .)
Nilotinib	131(100)	90 (68.7)	207.0 (177.0 - 249.0)	77 (58.8)	39 (29.8)	58 (44.3)	280.0 (207.0 - 414.0)	16 (12.2)	NR	24 (26.7)	227.0 (113.0 - 436.0)
Dasatinib	66 (100)	44 (66.7)	202.0 (155.0 - 247.0)	37 (56.1)	20 (30.3)	32 (48.5)	231.0 (183.0 - 749.0)	8 (12.1)	NR	13 (29.5)	307.0 (84.0 - 547.0)
Bosutinib	10 (100)	7 (70.0)	323.0 (64.0 - 512.0)	5 (50.0)	2 (20.0)	5 (50.0)	323.0 (64.0 - .)	2 (20.0)	-	1 (14.3)	-
Ponatinib	2 (100)	1 (50.0)	-	1 (50.0)	1 (50.0)	1 (50.0)	-	-	-	-	-

95%CI=95% Confidence Intervals
NR = Not reached

Table 6 Response to Third Line Tyrosine Kinase Inhibitor and time to response (days)

	Total	Any Response (MMR or MR²)		MMR				MR² Only		Loss of Response (MMR or MR²)	
		Yes	Time to response (days) (95% CI)	Yes	6 months	12 months	Time to response (days) (95% CI)	Yes	Time to response (days) (95% CI)	Yes	Time to loss of response (days)
Total	107 (100)	61 (57.0)	206.0 (99.0 - 391.0)	51 (47.7)	36 (33.6)	41 (38.3)	447.0 (190.0 - 629.0)	10 (9.3)	NR	19 (31.1)	295.0 (117.0 - 384.0)
Imatinib	26 (100)	3 (30.0)	365.0 (78.0 - .)	14 (53.8)	2 (20.0)	2 (20.0)	552.0 (92.0 - .)	1 (10.0)	NR	-	-
Nilotinib	36 (100)	16 (61.5)	294.0 (86.0 - 951.0)	22 (61.1)	8 (30.8)	10 (38.5)	105.0 (78.0 - 447.0)	2 (7.7)	NR	5 (31.3)	301.0 (77.0 - .)
Dasatinib	26 (100)	25 (69.4)	99.0 (78.0 - 206.0)	12 (46.2)	17 (47.2)	20 (55.6)	629.0 (63.0 - .)	3 (8.3)	NR	11 (44.0)	204.0 (72.0 - 329.0)
Bosutinib	9 (100)	16 (61.5)	111.0 (49.0 - 629.0)	1 (11.1)	9 (34.6)	9 (34.6)	-	4 (15.4)	NR	2 (12.5)	-
Ponatinib	8 (100)	1 (11.1)	-	1 (12.5)	-	-	-	-	NR	1 (100)	-

95%CI=95% Confidence Intervals
NR = Not reached

Table 7 Response to Fourth Line Tyrosine Kinase Inhibitor and time to response (days)

		Any Response (MMR or MR^2)		MMR				MR^2 Only		Loss of Response (MMR or MR^2)	
	Total	Yes	Time to response (days) (95% CI)	Yes	6 months	12 months	Time to response (days) (95% CI)	Yes	Time to response (days) (95% CI)	Yes	Time to loss of response (days)
Total	48 (100)	26 (54.2)	277.0 (79.0 - 372.0)	16 (33.3)	16 (33.3)	18 (37.5)	391.0 (82.0 - 1043.0)	5 (10.4)	NR	8 (29.6)	164.0 (66.0 - 740.0)
Imatinib	12 (100)	-	-	5 (41.7)	-		-	-	NR	-	-
Nilotinib	10 (100)	7 (58.3)	163.0 (28.0 - .)	2 (20.0)	5 (41.7)	5 (41.7)	169.0 (28.0 - .)	1 (8.3)	NR	3 (42.9)	378.0 (68.0 - .)
Dasatinib	17 (100)	6 (60.0)	301.0 (16.0 - .)	8 (47.1)	2 (20.0)	4 (40.0)	301.0 (16.0 - .)	1 (10.0)	NR	1 (12.5)	-
Bosutinib	6 (100)	11 (64.7)	277.0 (24.0 - 391.0)	1 (16.7)	8 (47.1)	8 (47.1)	391.0 (31.0 - .)	2 (11.8)	NR	4 (40.0)	164.0 (66.0 - .)
Ponatinib	5 (100)	2 (33.3)	-	1 (20.0)	1 (16.7)	1 (16.7)	-	1 (16.7)	NR	-	-

95%CI=95% Confidence Intervals
NR = Not reached

Table 8 Reason for Switching Tyrosine Kinase Inhibitor

		Switched to Second Line		Switched to Third Line			Switched to Fourth Line		
	Total	No response/ loss of response	Intolerance	Total	No response/ loss of response	Intolerance	Total	No response/ loss of response	Intolerance
Total	225 (100)	173 (76.9)	52 (23.1)	107 (100)	67 (62.6)	40 (37.4)	48 (100)	35 (72.9)	13 (27.1)
Imatinib	204 (100)	164 (80.4)	40 (19.6)	7 (100)	67 (62.6)	40 (37.4)	5 (100)	5 (100)	-
Nilotinib	6 (100)	3 (50.0)	3 (50.0)	63 (100)	5 (71.4)	2 (28.6)	12 (100)	8 (66.7)	4 (33.3)
Dasatinib	14 (100)	6 (42.9)	8 (57.1)	34 (100)	39 (61.9)	24 (38.1)	19 (100)	11 (57.9)	8 (42.1)
Bosutinib	-	-	-	2 (100)	21 (61.8)	13 (38.2)	10 (100)	9 (90.0)	1 (10.0)
Ponatinib	1 (100)	-	1 (100)	1 (100)	1 (50.0)	1 (50.0)	2 (100)	2 (100)	-

Table 9 Tested for T315I Mutation by Treatment Line

	1L				2L			3L			
	Tested	Mutation	Suspicious	WT	Tested	Mutation	WT	Tested	Mutation	Suspicious	WT
Total	37 (100)	6 (16.2)	4 (10.8)	27 (73.0)	15 (100)	6 (40.0)	9 (60.0)	8 (100)	3 (37.5)	2 (25.0)	3 (37.5)
								2 (100)	1 (50.0)	-	1 (50.0)
Imatinib	34 (100)	6 (17.6)	3 (8.8)	25 (73.5)	-	1 (100)	-	4 (100)	1 (25.0)	1 (25.0)	2 (50.0)
Nilotinib	1 (100)	-	-	1 (100)	3 (42.9)	4 (57.1)	3 (42.9)	2 (100)	1 (50.0)	1 (50.0)	-
Dasatinib	2 (100)	-	1 (50.0)	1 (50.0)	2 (33.3)	4 (66.7)	2 (33.3)	2 (100)	1 (50.0)	1 (50.0)	-
Bosutinib	-	-	-	-	1 (100)	-	1 (100)	-	-		
Ponatinib	-	-	-	-				-			

WT=Wild Type

Overall Survival

Table 10 Overall survival from start of first line treatment by regimen

		Vital status		Median survival (95% CI)	5-year survival % (95% CI)	10-year survival % (95% CI)
	Total	Alive	Dead			
Total	539	373 (69.2)	166 (30.8)	NR	78.0 (74 - 81.4)	64.2 (59.1 - 68.9)
Imatinib	483	330 (68.3)	153 (31.7)	NR	77.7 (73.4 - 81.3)	63.5 (58 - 68.4)
Dasatinib	27	21 (77.8)	6 (22.2)	NR	81.3 (60.8 - 91.8)	77.4 (56.5 - 89.2)
Nilotinib	27	20 (74.1)	7 (25.9)	NR	77.3 (53 - 90.1)	-
Bosutinib	1	1 (100)	-	-	-	-
Ponatinib	1	1 (100)	-	-	-	-
Major Molecular Response						
No	261 (100)	158 (60.5)	103 (39.5)	NR	66.5 (60.1 - 72.2)	51.2 (43.2 - 58.7)
Yes	278 (100)	215 (77.3)	63 (22.7)	NR	88.3 (83.5 - 91.8)	75.2 (68.5 - 80.7)
Major Molecular Response at 6 months						
No	511 (100)	352 (68.9)	159 (31.1)	NR	77.5 (73.4 - 81.1)	63.6 (58.3 - 68.4)
Yes	28 (100)	21 (75.0)	7 (25.0)	NR	84 (62.2 - 93.8)	74.7 (45.5 - 89.8)
Major Molecular Response at 12 months						
No	421 (100)	279 (66.3)	142 (33.7)	NR	76.1 (71.5 - 80.1)	61.8 (56 - 67)
Yes	118 (100)	94 (79.7)	24 (20.3)	NR	84.1 (74.8 - 90.2)	73.3 (61.1 - 82.3)

NR = Not reached

Figure 3 Overall survival from start of first line treatment

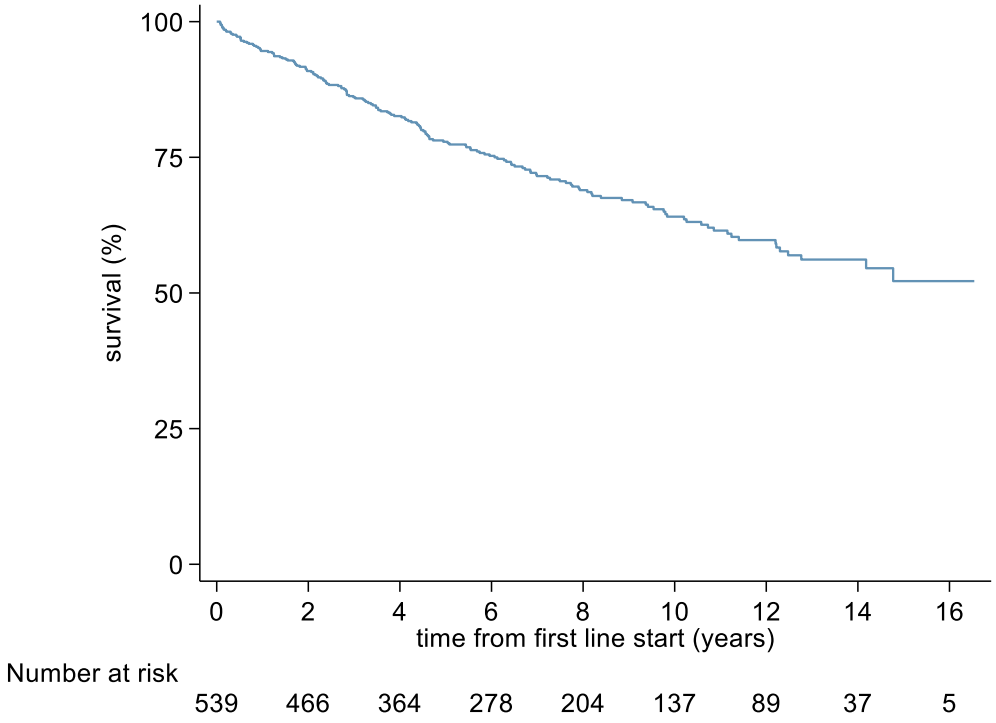


Figure 4 Overall survival from start of first line treatment by regimen

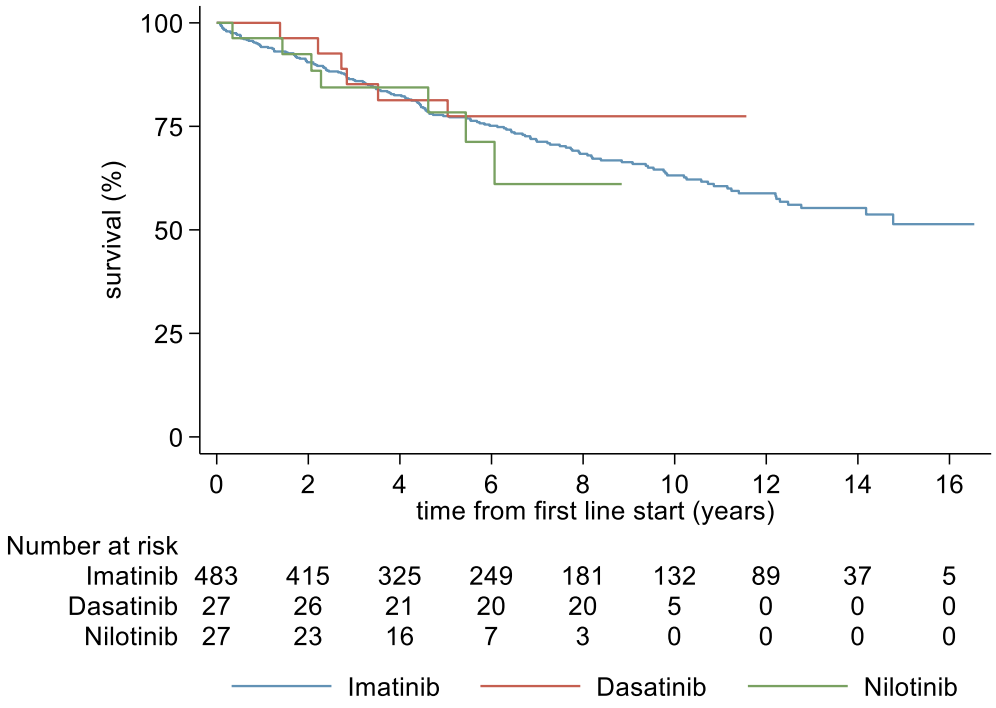


Figure 5 Overall survival from start of first line treatment by Major Molecular Response

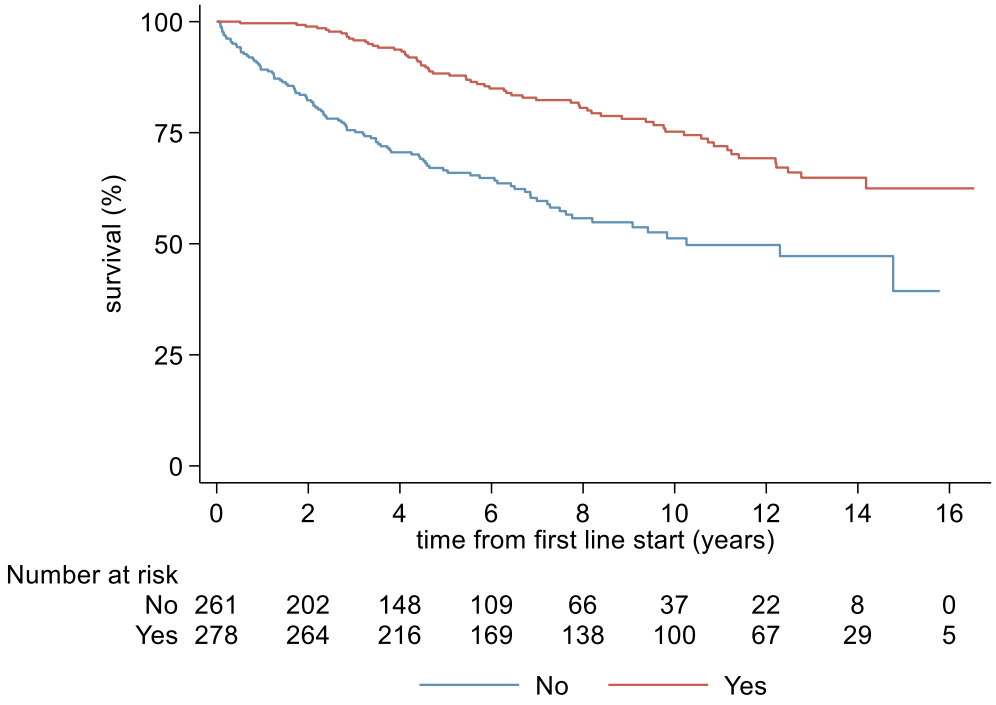


Figure 6 Overall survival from start of first line treatment by Major Molecular Response at 6 months

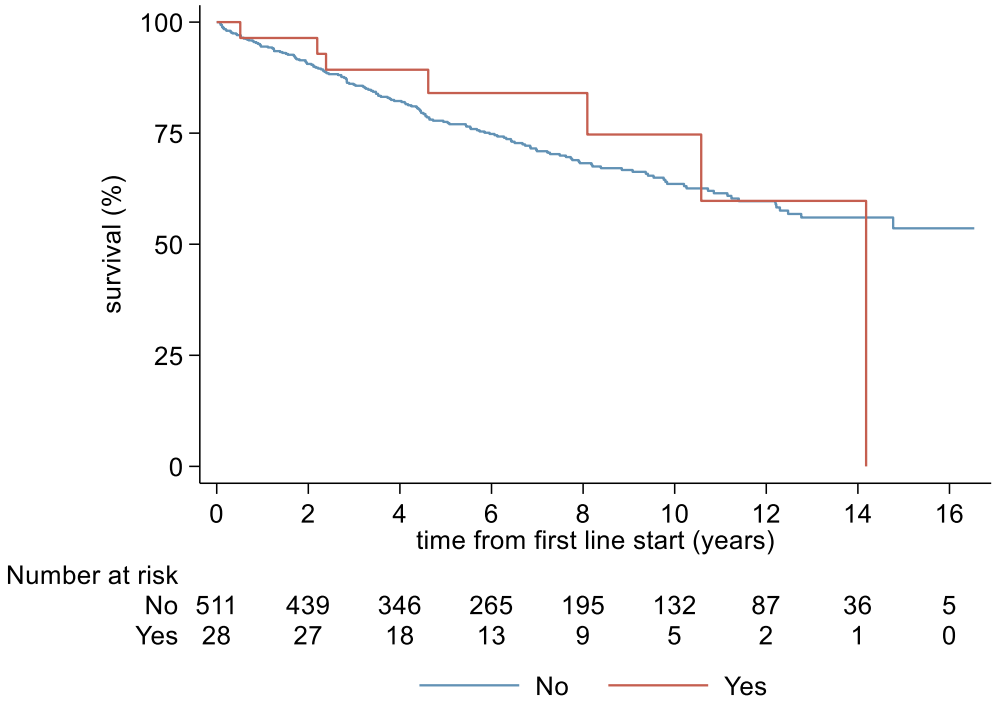


Figure 7 Overall survival from start of first line treatment by Major Molecular Response at 12 months

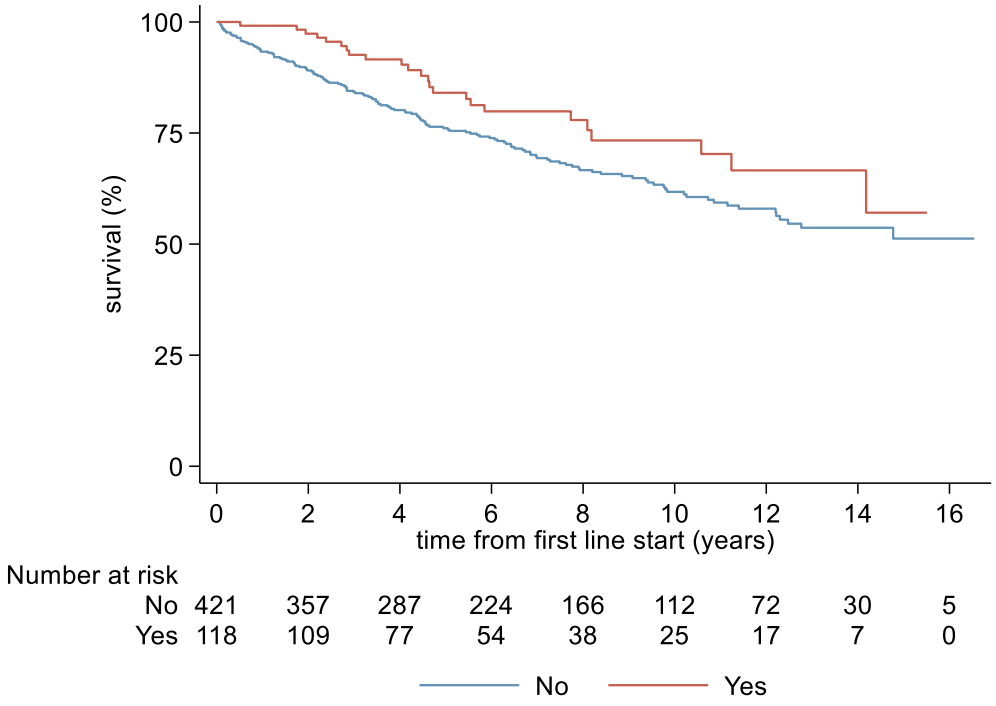


Table 11 Overall survival from start of second line treatment by regimen

	Total	Vital status		Median survival (95% CI)	5-year survival % (95% CI)	10-year survival % (95% CI)
		Alive	Dead			
Total	225 (100)	165 (73.3)	60 (26.7)	13.5 (9.3 - .)	78.5 (72 - 83.7)	56.2 (45.4 - 65.8)
Imatinib	16 (100)	11 (68.8)	5 (31.3)	NR	66 (40.9 - 82.5)	49.5 (23.3 - 71.2)
Dasatinib	66 (100)	42 (63.6)	24 (36.4)	9.3 (6.6 - .)	78.8 (64.6 - 87.8)	46.4 (30.3 - 61)
Nilotinib	131 (100)	105 (80.2)	26 (19.8)	13.5 (9.6 - .)	83.0 (74.8 - 88.7)	65.3 (40.1 - 82)
Bosutinib	10 (100)	6 (60.0)	4 (40.0)	2.5 (1.5 - .)	-	-
Ponatinib	2 (100)	1 (50.0)	1 (50.0)	-	-	-
Major Molecular Response						
No	102 (100)	62 (60.8)	40 (39.2)	9.3 (6.5 - .)	66.6 (55.8 - 75.3)	48.4 (35.1 - 60.4)
Yes	123 (100)	103 (83.7)	20 (16.3)	13.5 (9.6 - .)	89.3 (81.5 - 94)	67.4 (48.4 - 80.7)
Major Molecular Response at 6 months						
No	158 (100)	107 (67.7)	51 (32.3)	13.5 (9.1 - .)	74 (65.8 - 80.5)	53.9 (42 - 64.4)
Yes	67 (100)	58 (86.6)	9 (13.4)	NR	90.3 (77.9 - 95.9)	75.9 (57.3 - 87.2)
Major Molecular Response at 12 months						
No	123 (100)	78 (63.4)	45 (36.6)	13.5 (9.0 - .)	69.8 (60.3 - 77.5)	51.7 (39.1 - 63)
Yes	102 (100)	87 (85.3)	15 (14.7)	NR	90.4 (81.5 - 95.1)	68.4 (47.8 - 82.2)

NR = Not reached

Figure 8 Overall survival from start of second line

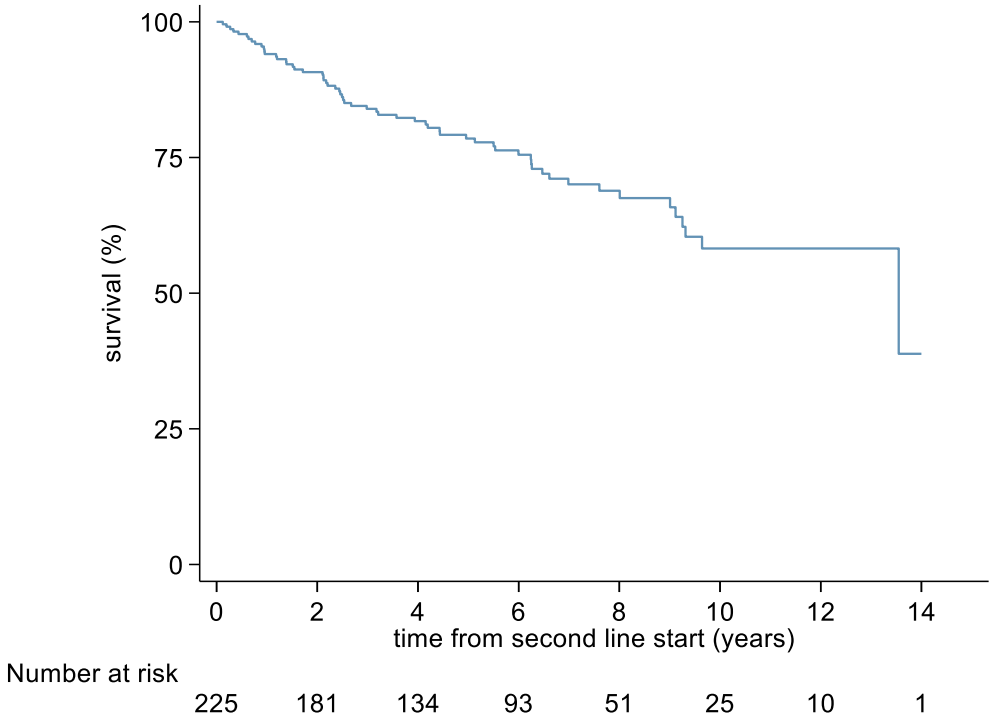


Figure 9 Overall survival from start of second line by second line regimen

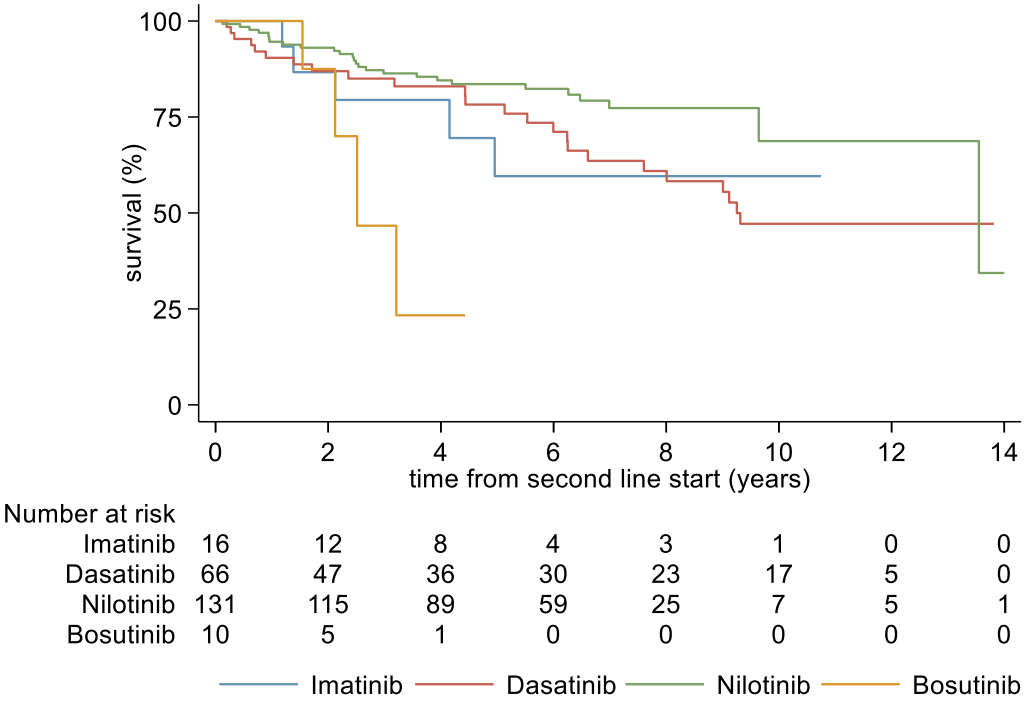


Figure 10 Overall survival from start of second line treatment by Major Molecular Response

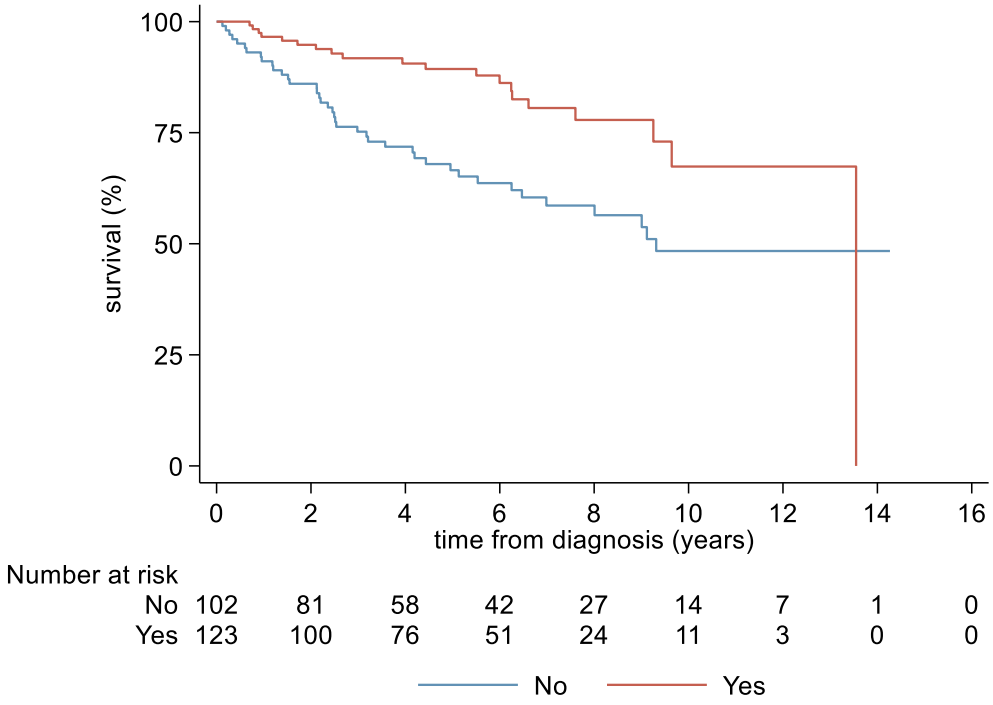


Figure 11 Overall survival from start of second line treatment by Major Molecular Response at 6 months

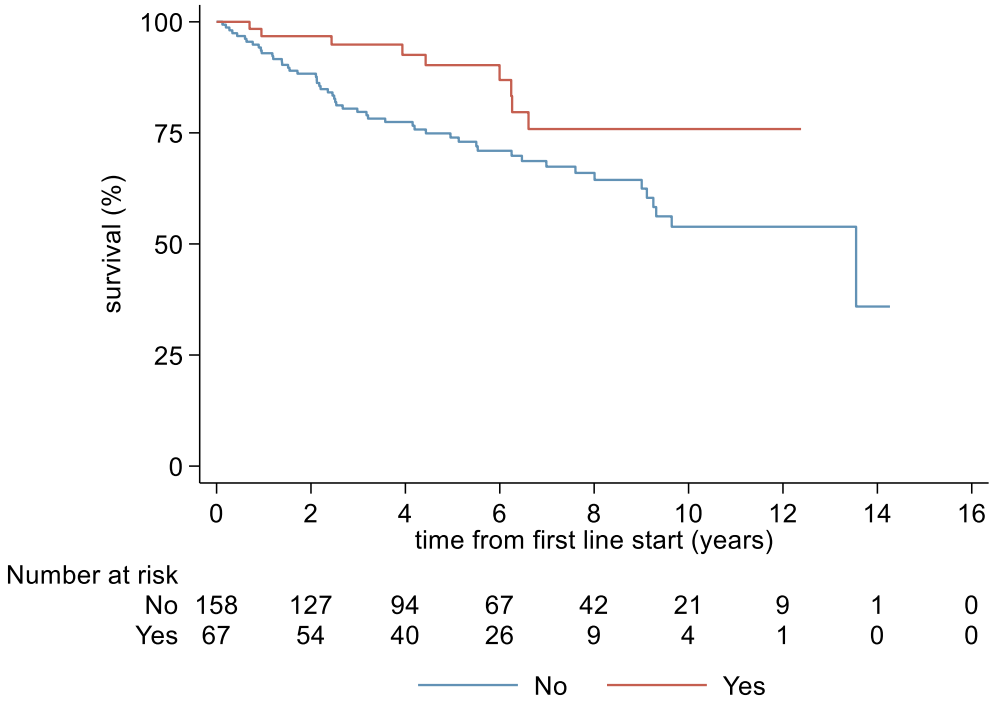


Figure 12 Overall survival from start of second line treatment by Major Molecular Response at 12 months

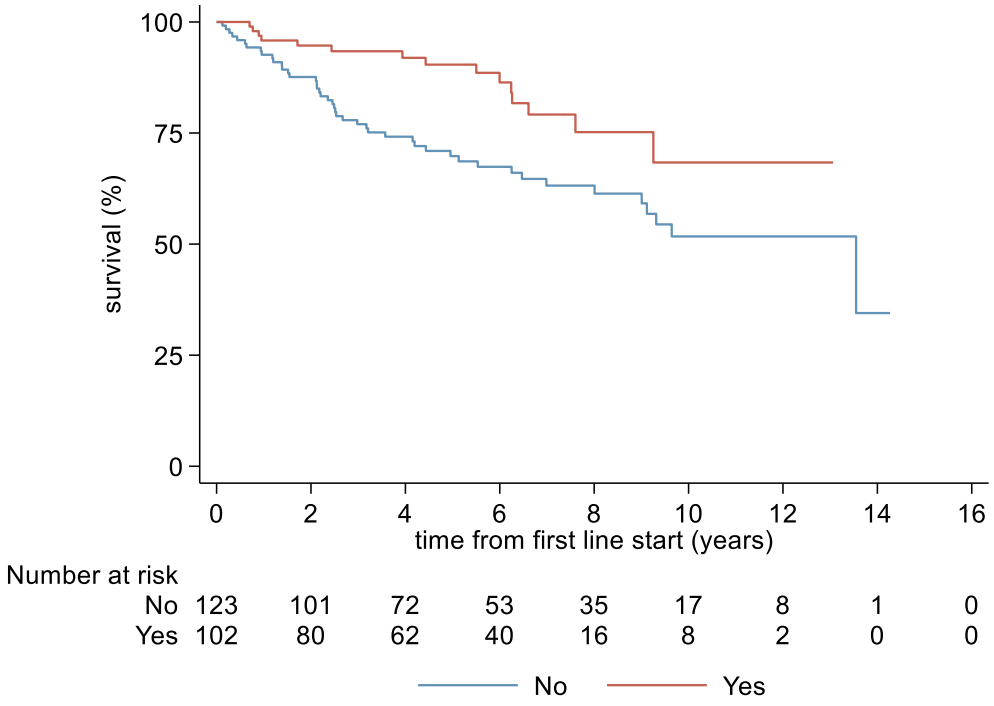


Table 12 Overall survival from start of third line treatment by regimen

	Total	Vital status		Median survival (95% CI)	5-year survival % (95% CI)	10-year survival % (95% CI)
		Alive	Dead			
Total	107	75 (70.1)	32 (29.9)	NR	72.3 (60.9 - 81)	49.5 (32.3 - 64.6)
Imatinib	10 (100)	5 (50.0)	5 (50.0)	6.4 (0.1 - .)	60.6 (25.1 - 83.4)	48.5 (16 - 75.1)
Dasatinib	36 (100)	29 (80.6)	7 (19.4)	. (6.2 - .)	76 (55 - 88.1)	67.5 (41.7 - 83.9)
Nilotinib	26 (100)	13 (50.0)	13 (50.0)	8.7 (5.1 - .)	73 (49.5 - 86.9)	35.2 (13 - 58.5)
Bosutinib	26 (100)	24 (92.3)	2 (7.7)	-	91.5 (70 - 97.8)	-
Ponatinib	9 (100)	4 (44.4)	5 (55.6)	1.8 (0.1 - .)	46.9 (12 - 76.3)	-
Major Molecular Response						
No	56 (100)	32 (57.1)	24 (42.9)	6.2 (4.3 - .)	57.4 (41.5 - 70.4)	46 (30.3 - 60.4)
Yes	51 (100)	43 (84.3)	8 (15.7)	NR	88.9 (72.8 - 95.7)	58.6 (28.6 - 79.6)
Major Molecular Response at 6 months						
No	71 (100)	46 (64.8)	25 (35.2)	NR	65 (51.1 - 75.9)	55.7 (41.1 - 68)
Yes	36 (100)	29 (80.6)	7 (19.4)	8.9 (6.4 - .)	88.4 (68.1 - 96.1)	40.5 (10.4 - 69.7)
Major Molecular Response at 12 months						
No	66 (100)	42 (63.6)	24 (36.4)	NR	64.3 (49.8 - 75.6)	54.6 (39.6 - 67.3)
Yes	41 (100)	33 (80.5)	8 (19.5)	8.9 (6.4 - .)	85.9 (66.2 - 94.5)	41.2 (11.2 - 69.9)

NR = Not reached

Figure 13 Overall survival from start of third line

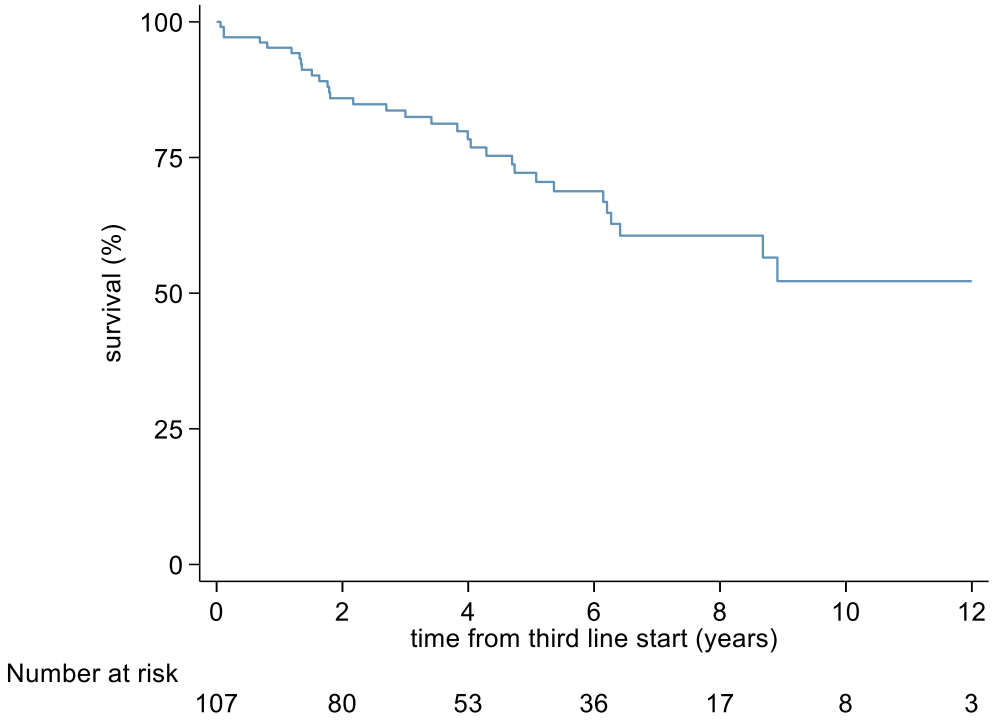


Figure 14 Overall survival from start of third line by third line regimen

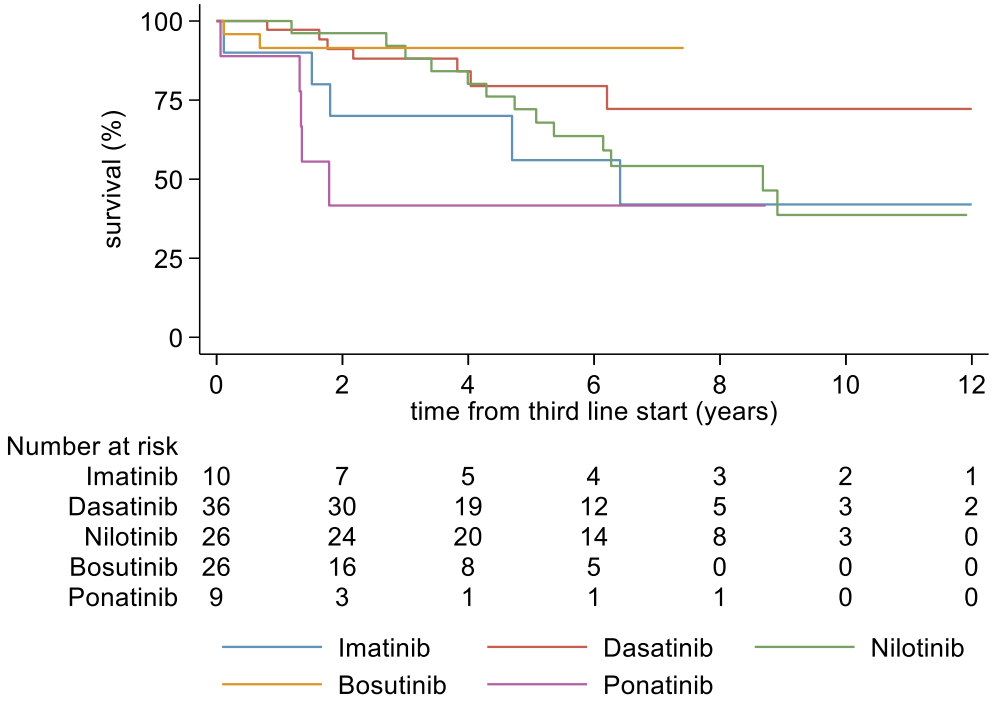


Figure 15 Overall survival from start of third line treatment by Major Molecular Response

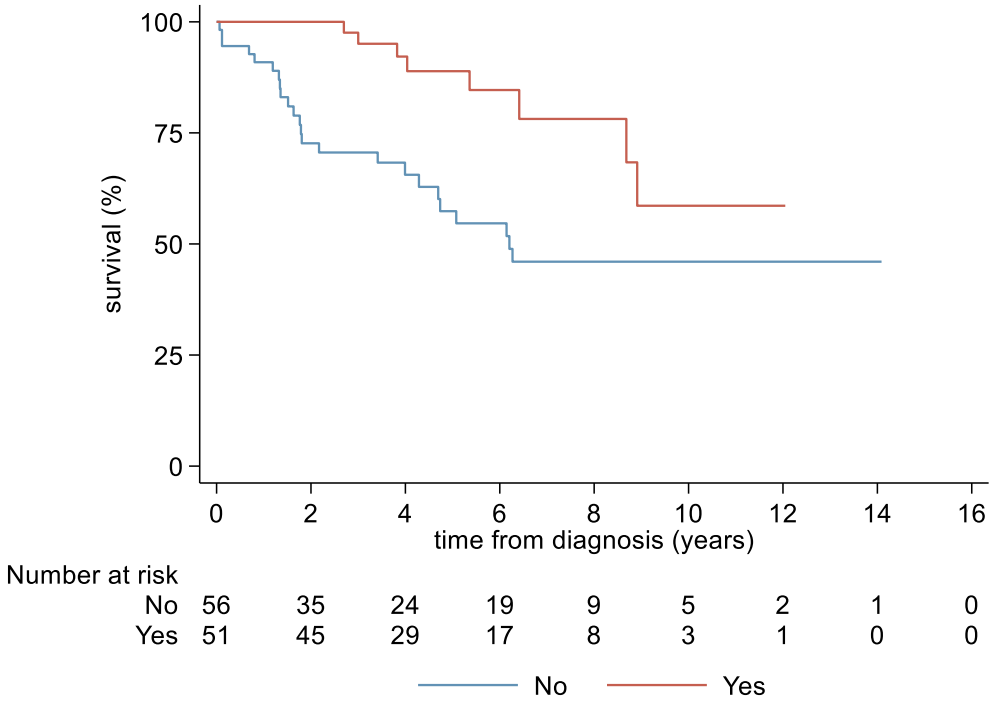


Figure 16 Overall survival from start of third line treatment by Major Molecular Response at 6 months

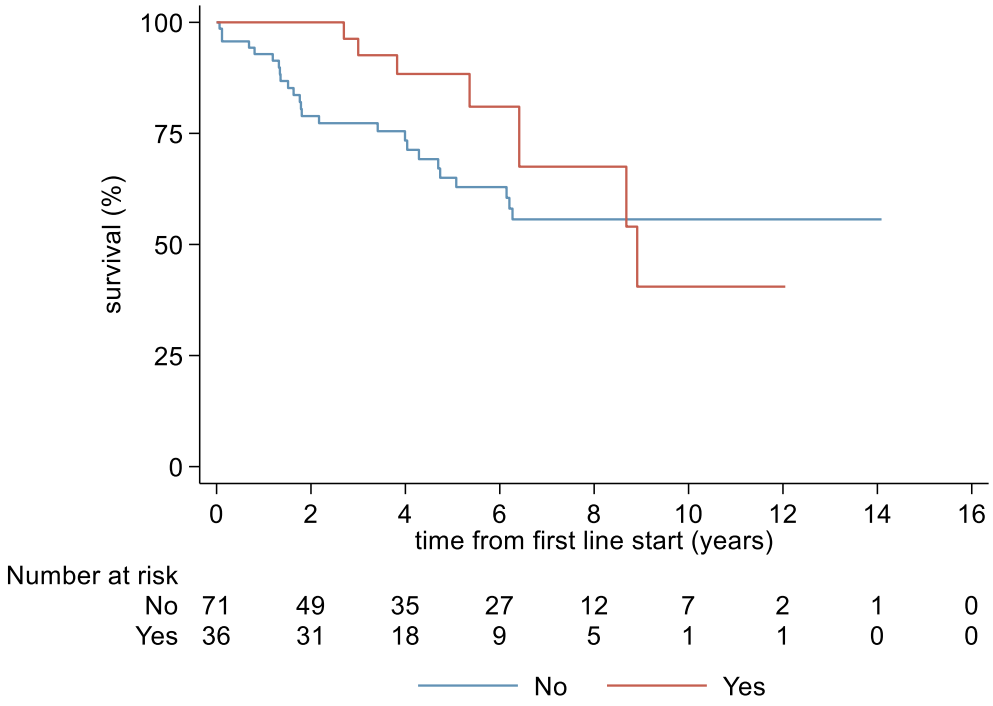


Figure 17 Overall survival from start of third line treatment by Major Molecular Response at 12 months

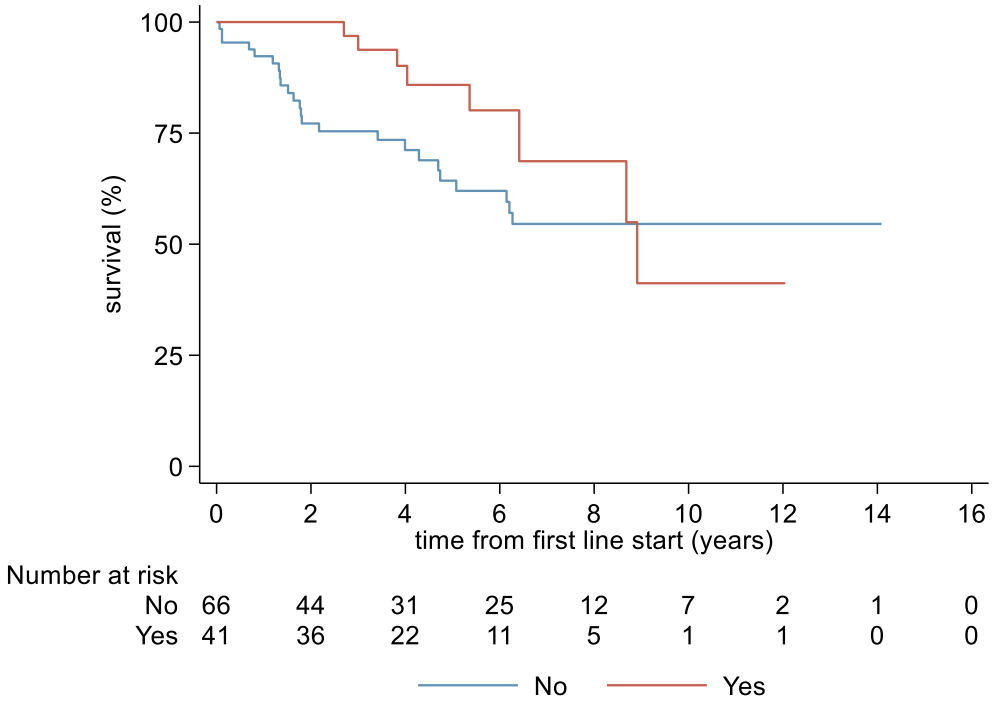


Table 13 Overall survival from start of fourth line treatment by regimen

	Total	Vital status		Median survival (95% CI)	5-year survival % (95% CI)	10-year survival % (95% CI)
		Alive	Dead			
Total	46	32 (69.6)	14 (30.4)	NR	58.8 (37.8 - 74.9)	52.3 (30.3 - 70.4)
Imatinib	3	1 (33.3)	2 (66.7)	6.0 (3.7 - .)	66.7 (5.4 - 94.5)	-
Dasatinib	10	8 (80.0)	2 (20.0)	4.0 (3.2 - .)	50 (5.8 - 84.5)	-
Nilotinib	12	9 (75.0)	3 (25.0)	NR	68.2 (28.6 - 88.9)	68.2 (28.6 - 88.9)
Bosutinib	16	11 (68.8)	5 (31.3)	NR	55.4 (17.4 - 81.9)	-
Ponatinib	5	3 (60.0)	2 (40.0)	NR	-	-

Figure 18 Overall survival from start of fourth line

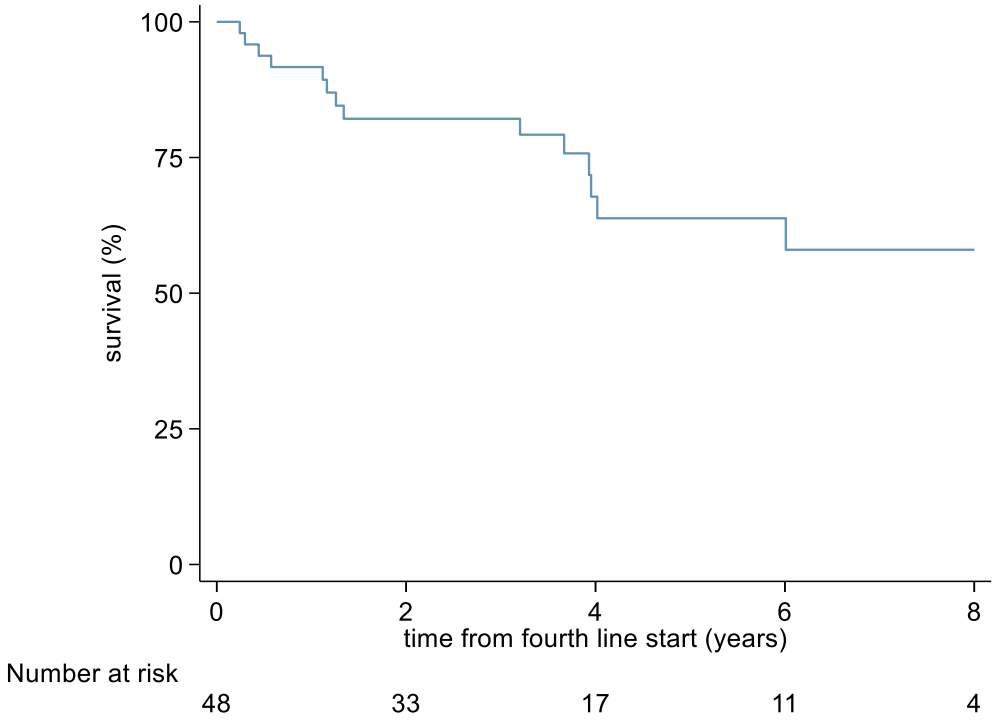
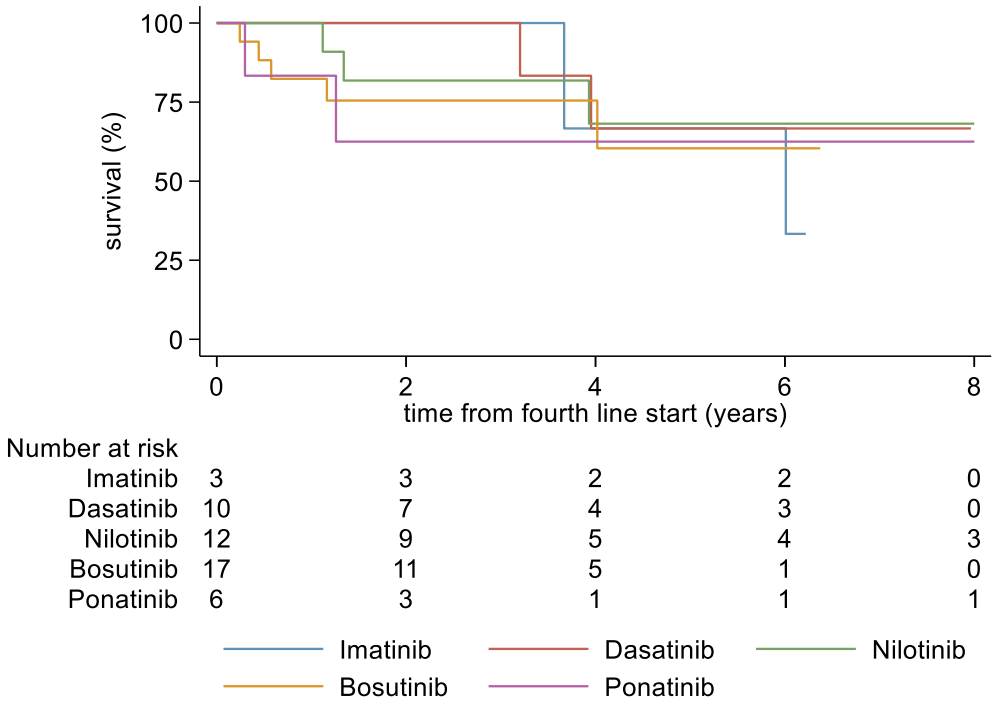


Figure 19 Overall survival from start of fourth line by regimen



Progression-free survival

Table 14 Progression-free survival from start of first line treatment by regimen

	Total	PFS		Median PFS (95% CI)	5-year PFS % (95% CI)	10-year PFS % (95% CI)
		Yes	No			
Total	539 (100)	368 (68.3)	171 (31.7)	NR	76.5 (72.4 - 80)	63.9 (58.7 - 68.5)
Imatinib	483 (100)	325 (67.3)	158 (32.7)	NR	76 (71.6 - 79.7)	62.9 (57.5 - 67.9)
Dasatinib	27 (100)	21 (77.8)	6 (22.2)	NR	81.3 (60.8 - 91.8)	77.4 (56.5 - 89.2)
Nilotinib	27 (100)	20 (74.1)	7 (25.9)	NR	77.9 (53.9 - 90.4)	-
Bosutinib	1 (100)	1 (100)	-	-	-	-
Ponatinib	1 (100)	1 (100)	-	-	-	-
Major Molecular Response						
No	261 (100)	153 (58.6)	108 (41.4)	10.3 (7.2 - .)	66.5 (60.1 - 72.2)	51.2 (43.2 - 58.7)
Yes	278 (100)	215 (77.3)	63 (22.7)	NR	88.3 (83.5 - 91.8)	75.2 (68.5 - 80.7)
Major Molecular Response at 6 months						
No	511 (100)	347 (67.9)	164 (32.1)	NR	77.5 (73.4 - 81.1)	63.6 (58.3 - 68.4)
Yes	28 (100)	21 (75.0)	7 (25.0)	14.2 (10.6 - .)	84 (62.2 - 93.8)	74.7 (45.5 - 89.8)
Major Molecular Response at 12 months						
No	421 (100)	274 (65.1)	147 (34.9)	NR	76.1 (71.5 - 80.1)	61.8 (56 - 67)
Yes	118 (100)	94 (79.7)	24 (20.3)	NR	84.1 (74.8 - 90.2)	73.3 (61.1 - 82.3)

NR = Not reached

Figure 20 Progression-free survival from start of first line treatment

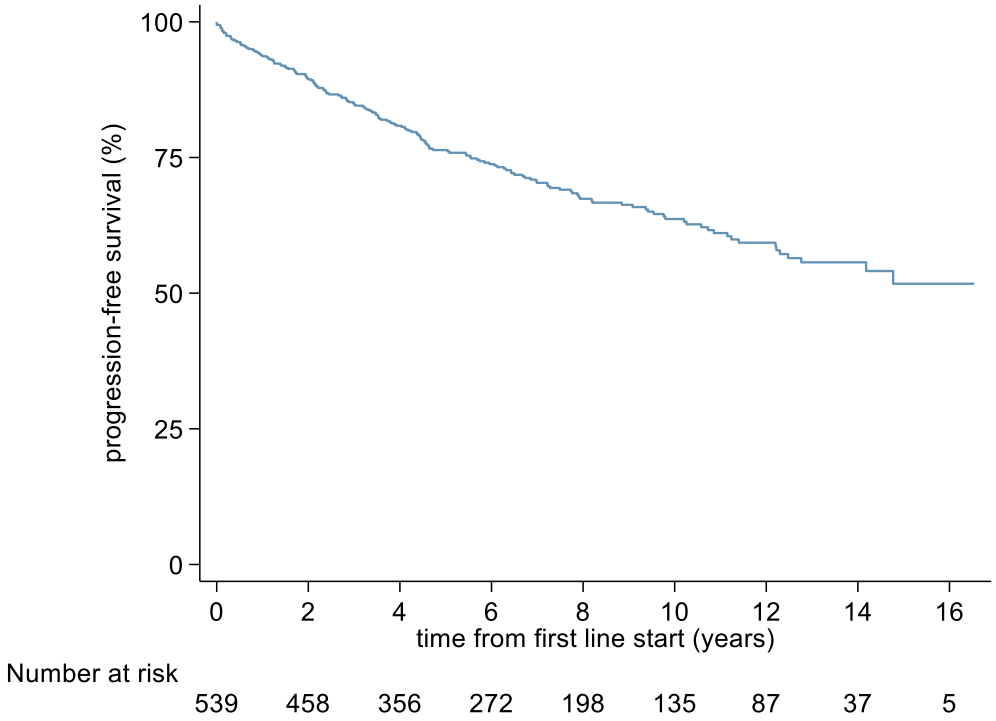


Figure 21 Progression-free survival from start of first line treatment by regimen

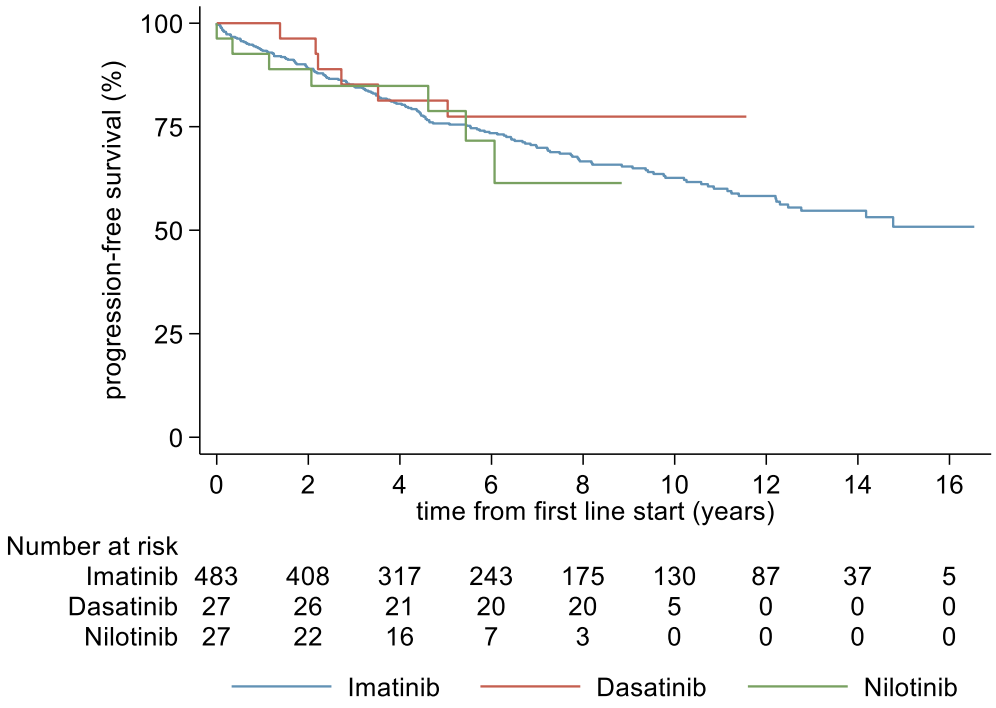


Figure 22 Progression-free survival from start of first line treatment by Major Molecular Response

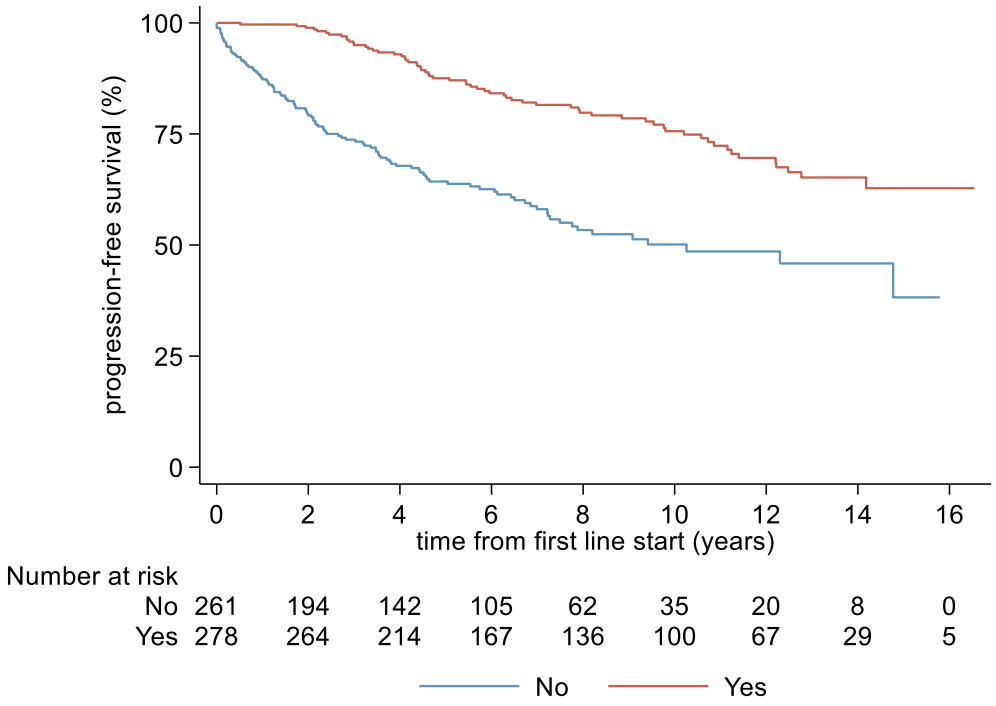


Figure 23 Progression-free survival from start of first line treatment by Major Molecular Response at 6 months

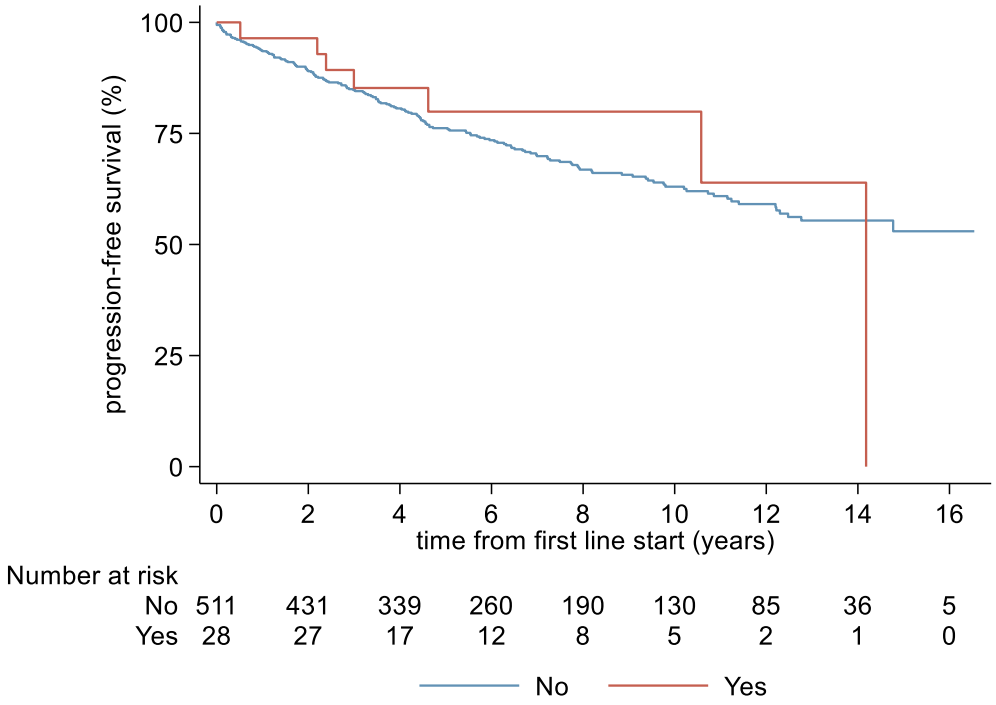


Figure 24 Progression-free survival from start of first line treatment by Major Molecular Response at 12 months

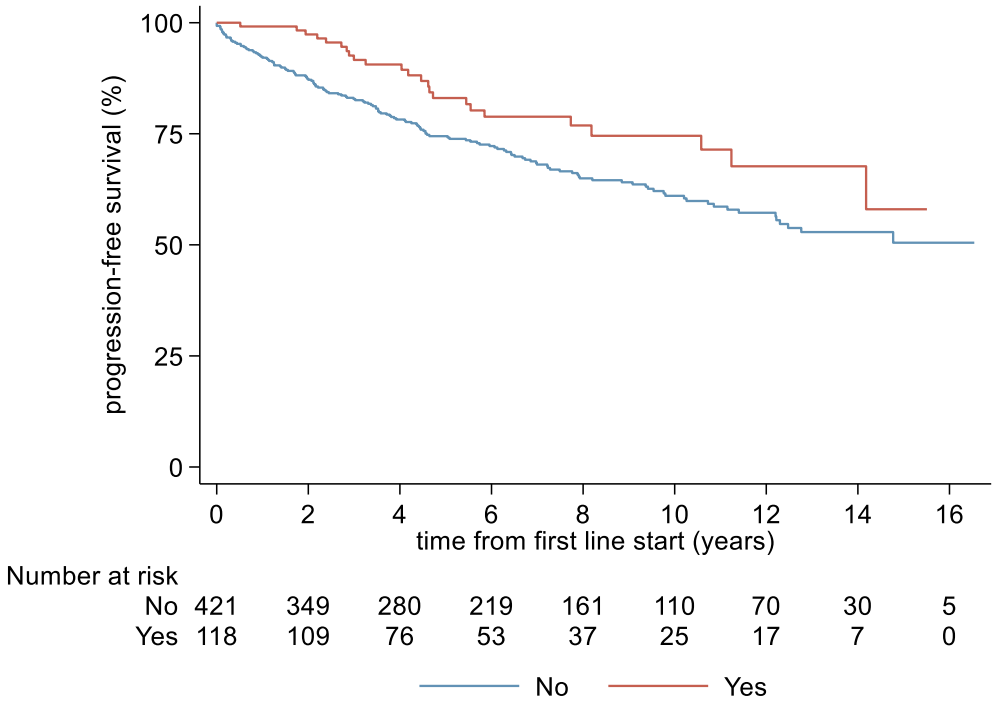


Table 15 Progression-free survival from start of second line treatment by regimen

	Total	PFS		Median PFS (95% CI)	5-year PFS % (95% CI)	10-year PFS % (95% CI)
		Yes	No			
Total	225	164 (72.9)	61 (27.1)	13.5 (9.3 - .)	75 (68.2 - 80.5)	57.4 (46.8 - 66.7)
Imatinib	16 (100)	11 (68.8)	5 (31.3)	NR	60 (27.5 - 81.7)	60 (27.5 - 81.7)
Dasatinib	66 (100)	41 (62.1)	25 (37.9)	9.0 (6.2 - .)	69.8 (55.6 - 80.3)	43.2 (27.9 - 57.5)
Nilotinib	131 (100)	105 (80.2)	26 (19.8)	13.5 (9.6 - .)	81.4 (73.4 - 87.3)	68.5 (47.7 - 82.4)
Bosutinib	10 (100)	6 (60.0)	4 (40.0)	2.5 (1.5 - .)	-	-
Ponatinib	2 (100)	1 (50.0)	1 (50.0)	-	-	-
Major Molecular Response						
No	102 (100)	61 (59.8)	41 (40.2)	9.0 (5.5 - .)	65.9 (53.8 - 73.5)	48.4 (35.1 – 60.3)
Yes	123 (100)	103 (83.7)	20 (16.3)	13.5 (9.6 - .)	87.6 (79.4 - 92.7)	69 (49.8 - 82.1)
Major Molecular Response at 6 months						
No	158 (100)	106 (67.1)	52 (32.9)	13.5 (9.0 - .)	73.8 (64.5 - 79.4)	54.0 (42.2 - 64.5)
Yes	67 (100)	58 (86.6)	9 (13.4)	NR	86.9 (74.1 - 93.6)	79.6 (63 - 89.4)
Major Molecular Response at 12 months						
No	123 (100)	77 (62.6)	46 (37.4)	9.6 (6.6 - .)	68.2 (58.7 - 76.1)	51.8 (39.3 – 63.6)
Yes	102 (100)	87 (85.3)	15 (14.7)	NR	88.3 (79 - 93.6)	70.6 (49.7 - 84.1)

NR = Not reached

Figure 25 Progression-free survival from start of second line

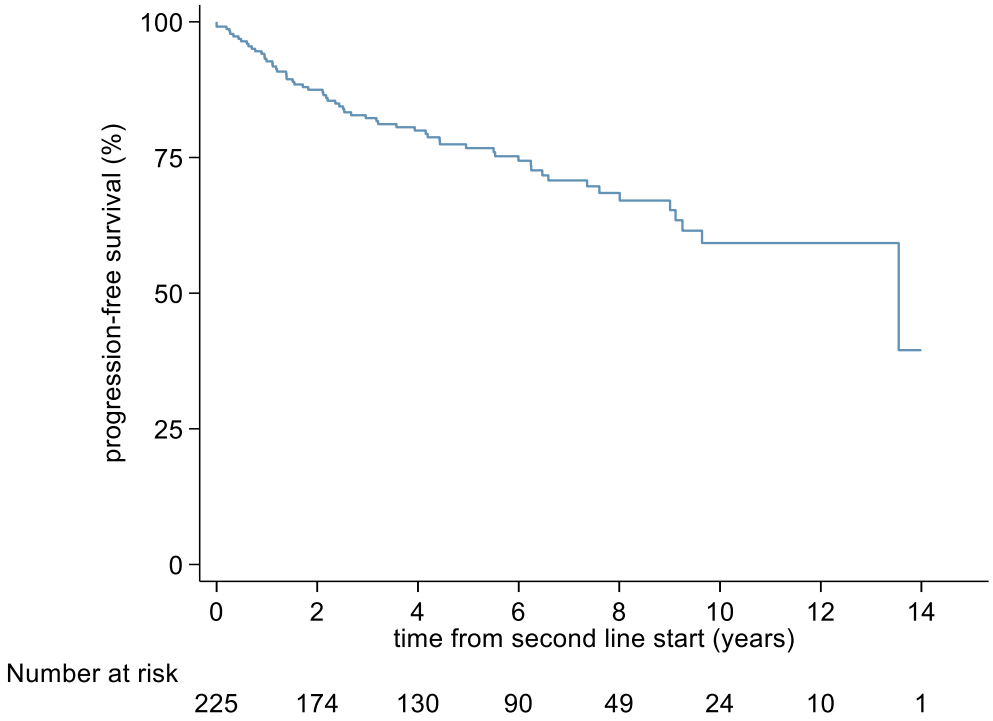


Figure 26 Progression-free survival from start of second line by second line regimen

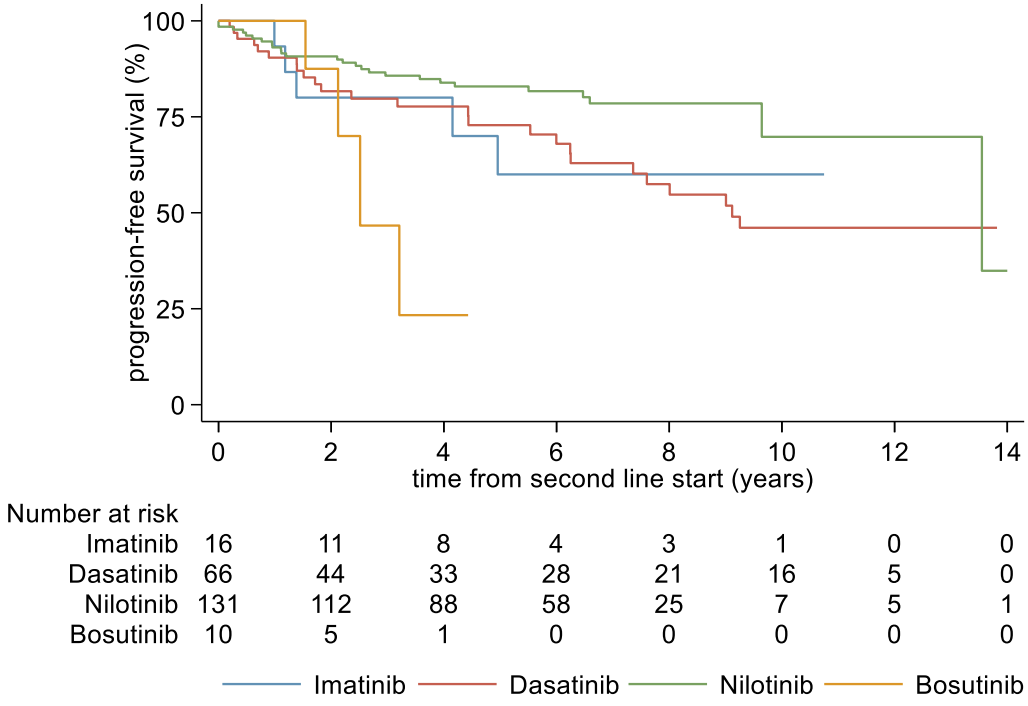


Figure 27 Progression-free survival from start of second line treatment by Major Molecular Response

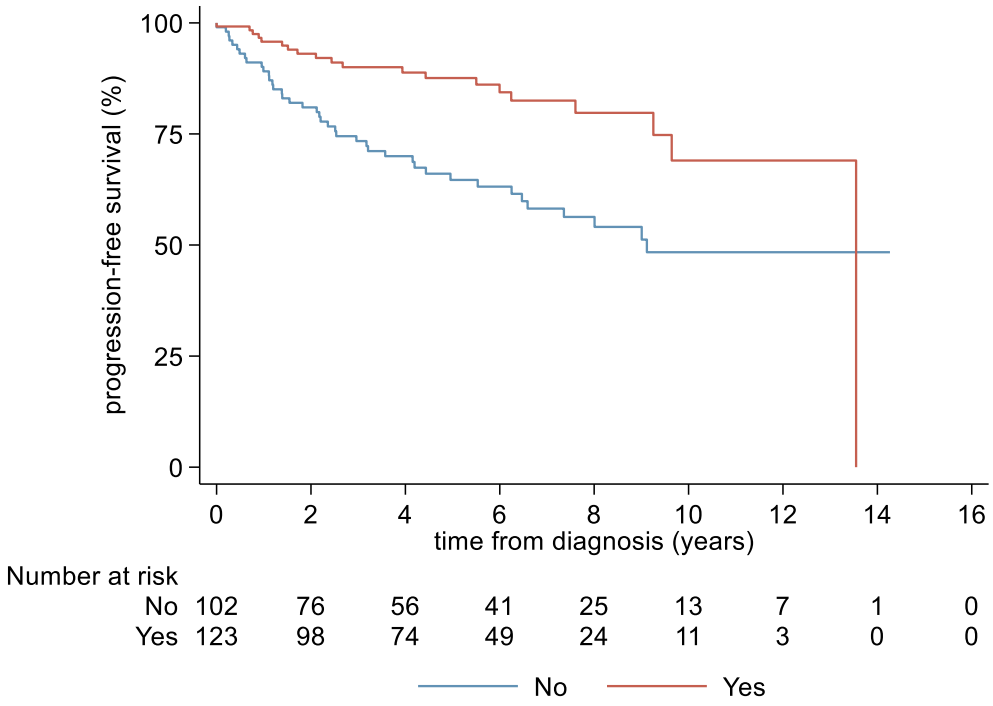


Figure 28 Progression-free survival from start of second line treatment by Major Molecular Response at 6 months

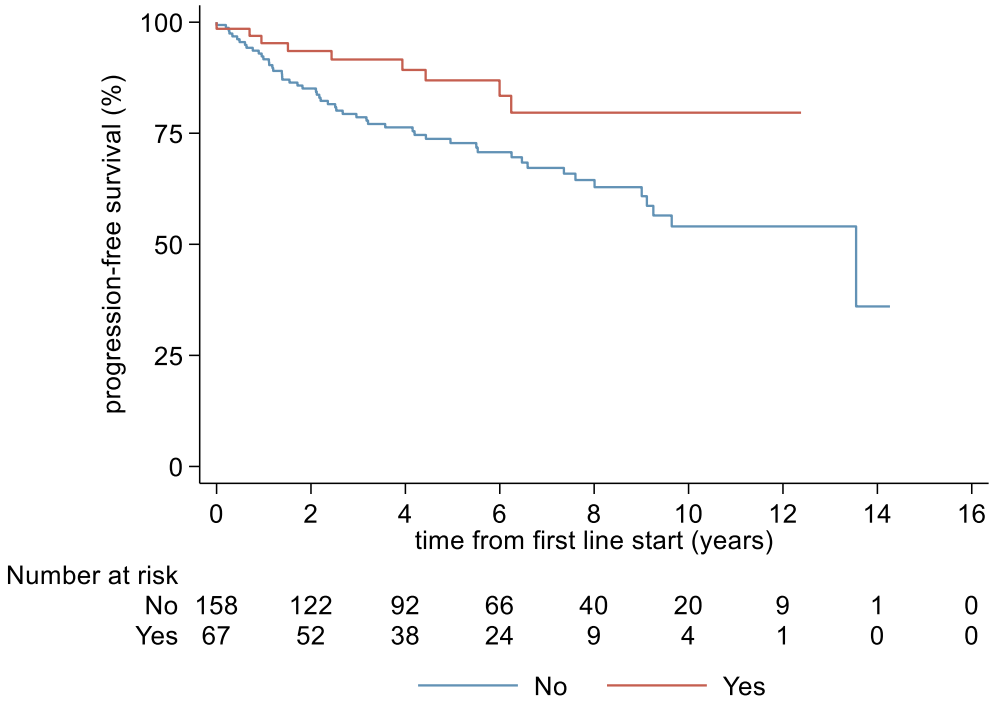


Figure 29 Progression-free survival from start of second line treatment by Major Molecular Response at 12 months

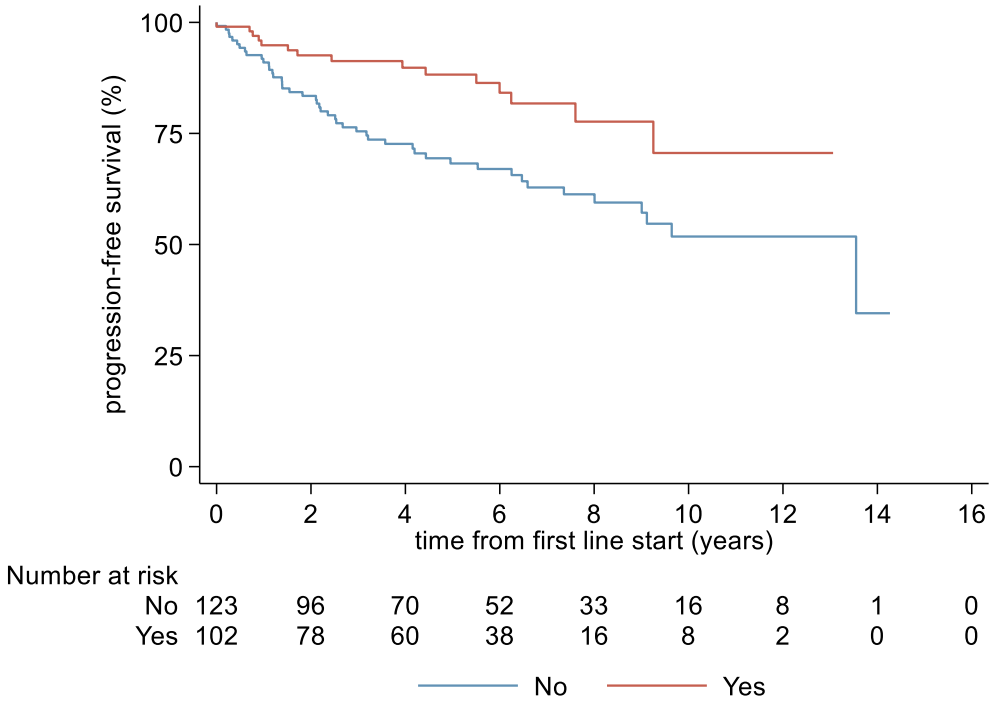


Table 16 Progression-free survival from start of third line treatment by regimen

	Total	PFS[1]		Median PFS (95% CI)	5-year PFS % (95% CI)	10-year PFS % (95% CI)
		Yes	No			
Total	107 (100)	74 (69.2)	33 (30.8)	NR	72.1 (61.1 – 80.4)	51.4 (35.3 - 65.4)
Imatinib	10 (100)	4 (40.0)	6 (60.0)	1.8 (0.1 - .)	50 (18.4 - 75.3)	33.3 (6.3 - 64.6)
Dasatinib	36 (100)	29 (80.6)	7 (19.4)	NR	79.8 (59.6 - 91.0)	73.7 (50.7 - 87.2)
Nilotinib	26 (100)	13 (50.0)	13 (50.0)	8.7 (4.7 - .)	72.2 (50.2 - 85.6)	38.9 (16.9 - 60.6)
Bosutinib	26 (100)	24 (92.3)	2 (7.7)	NR	93.0 (71.5 – 97.9)	-
Ponatinib	9 (100)	4 (44.4)	5 (55.6)	1.8 (0.0 - .)	41.7 (10.9 - 70.8)	-
Major Molecular Response						
No	56 (100)	31 (55.4)	25 (44.6)	6.1 (3.4 - .)	56.9 (41.4 – 69.8)	45.1 (29.4 – 59.5)
Yes	51 (100)	43 (84.3)	8 (15.7)	NR	88.9 (72.8 - 95.7)	58.6 (28.6 - 79.6)
Major Molecular Response at 6 months						
No	71 (100)	45 (63.4)	26 (36.6)	NR	64.6 (50.9 - 75.3)	55.1 (40.6 – 67.4)
Yes	36 (100)	29 (80.6)	7 (19.4)	8.9 (6.4 - .)	88.4 (68.1 – 96.1)	40.5 (10.4 - 69.7)
Major Molecular Response at 12 months						
No	66 (100)	41 (62.1)	25 (37.9)	NR	63.9 (49.8 – 75.0)	53.9 (38.9 - 66.6)
Yes	41 (100)	33 (80.5)	8 (19.5)	8.9 (6.4 - .)	85.8 (66.2 - 94.3)	41.2 (11.5 - 69.9)

[1] Accelerated phase (n=1), Blast crisis (n=2) mean time in state 276 days (213.8), median 249 days (5th-95th: 78-503)
NR = Not reached

Figure 30 Progression-free survival from start of third line

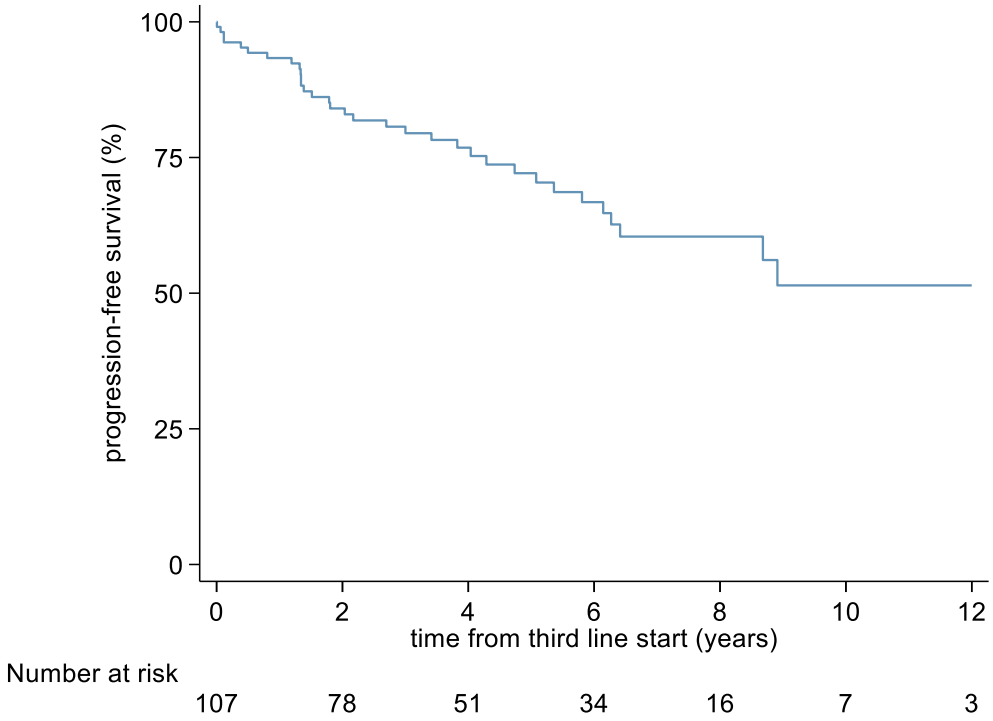


Figure 31 Progression-free survival from start of third line by third line regimen

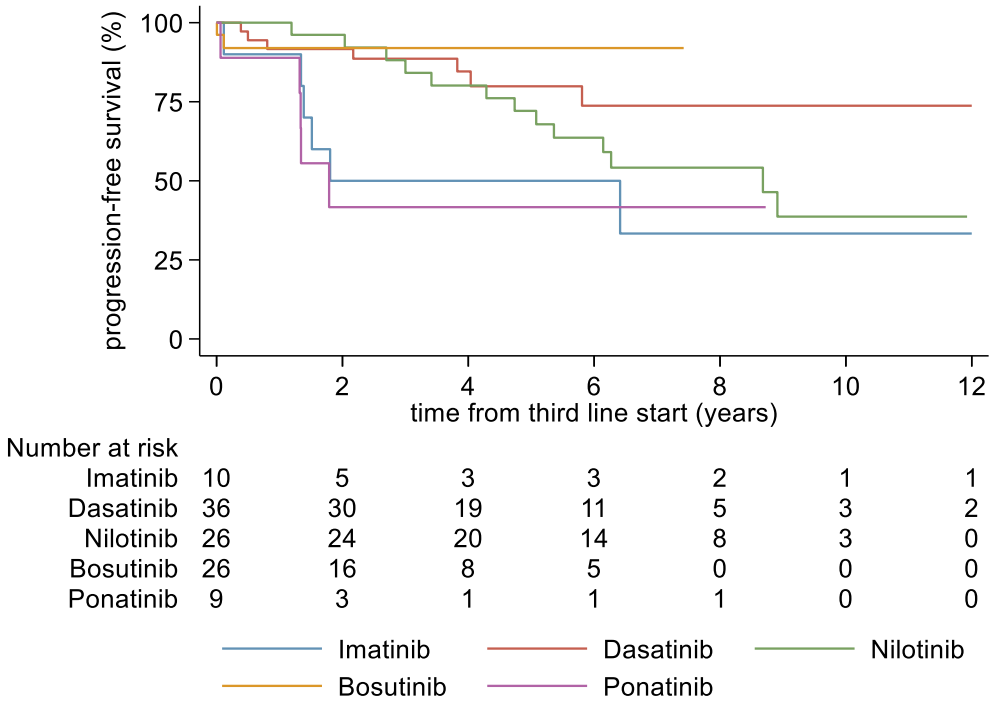


Figure 32 Progression-free survival from start of third line treatment by Major Molecular Response

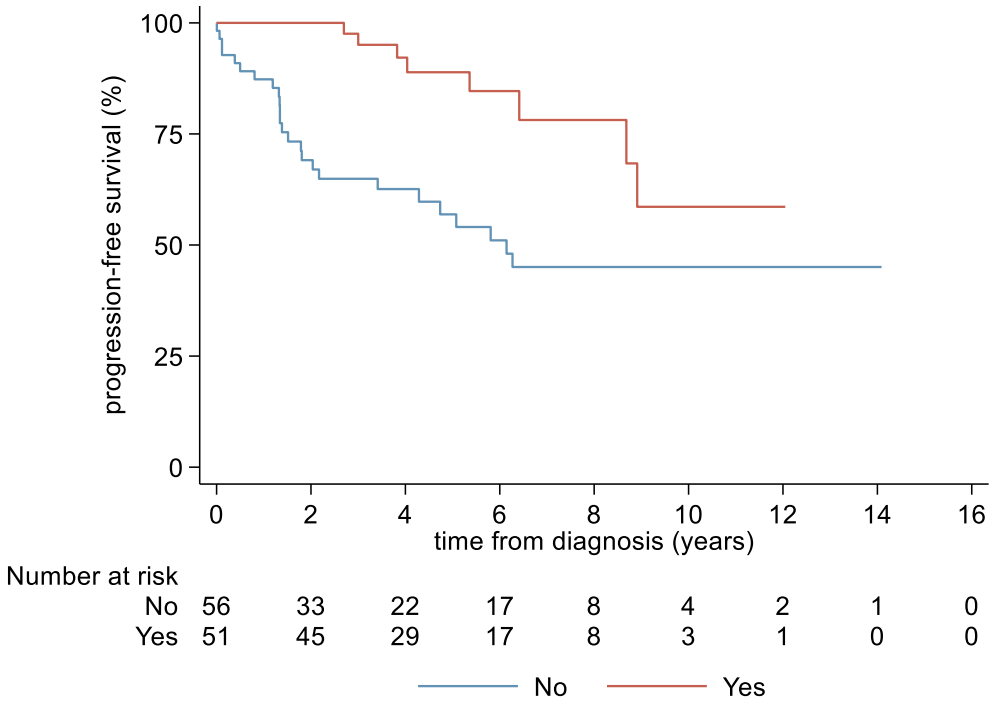


Figure 33 Progression-free survival from start of third line treatment by Major Molecular Response at 6 months

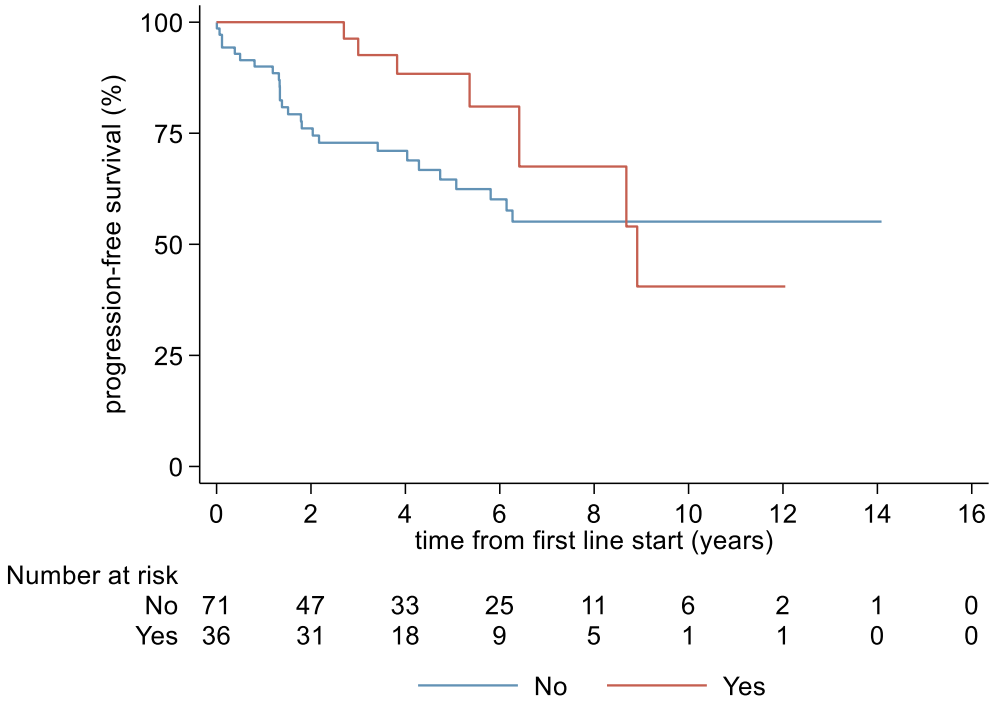


Figure 34 Progression-free survival from start of third line treatment by Major Molecular Response at 12 months

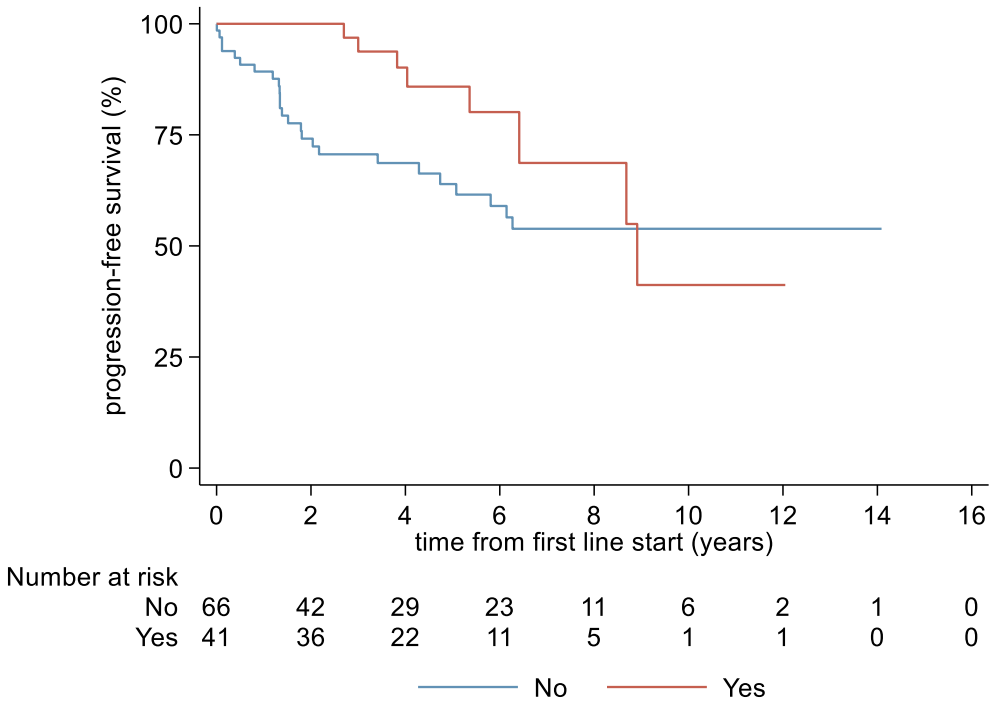


Table 17 Progression-free survival from start of fourth line treatment by regimen

	Total	PFS		Median PFS (95% CI)	5-year PFS % (95% CI)	10-year PFS % (95% CI)
		Yes	No			
Total	48 (100)	33 (68.8)	15 (31.3)	NR	63.7 (45.1 - 77.4)	57.9 (37.7 - 73.6)
Imatinib	3 (100)	1 (33.3)	2 (66.7)	5.6 (0.4 - .)	66.7 (5.4 - 94.5)	-
Dasatinib	10 (100)	8 (80.0)	2 (20.0)	NR	68.6 (21.3 - 91.2)	-
Nilotinib	12 (100)	8 (66.7)	4 (33.3)	NR	58.2 (21.3 - 82.7)	58.2 (21.3 - 82.7)
Bosutinib	17 (100)	12 (70.6)	5 (29.4)	NR	60.4 (24.4 - 83.5)	-
Ponatinib	6 (100)	4 (66.7)	2 (33.3)	NR	62.5 (14.2 - 89.3)	-

NR = Not reached

Figure 35 Progression-free survival from start of fourth line

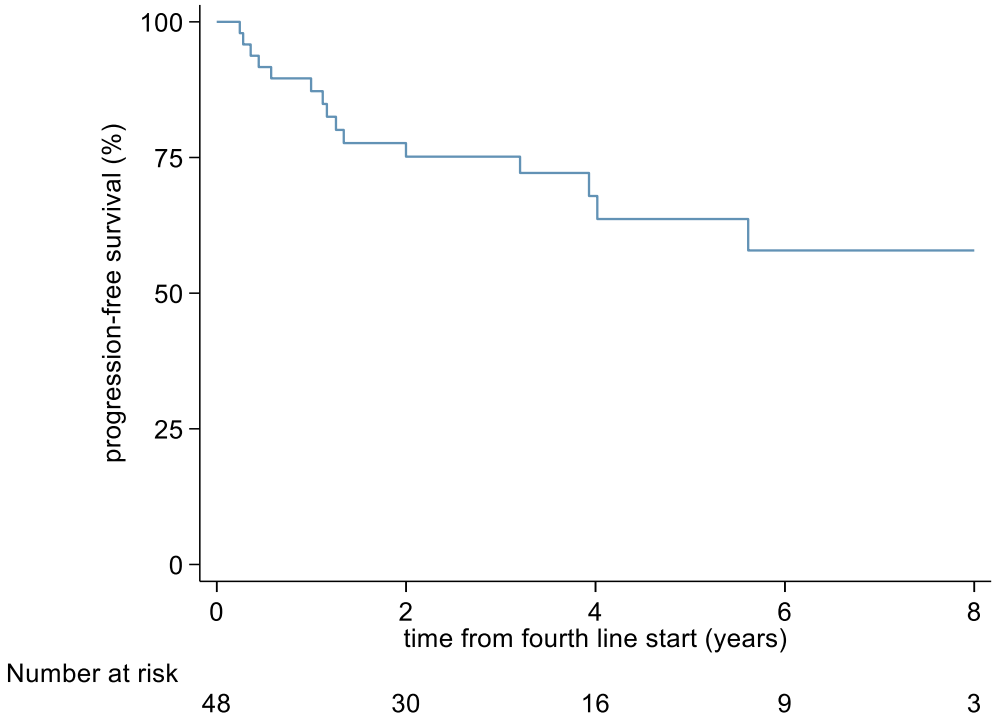


Figure 36 Progression-free survival from start of fourth line by third line regimen

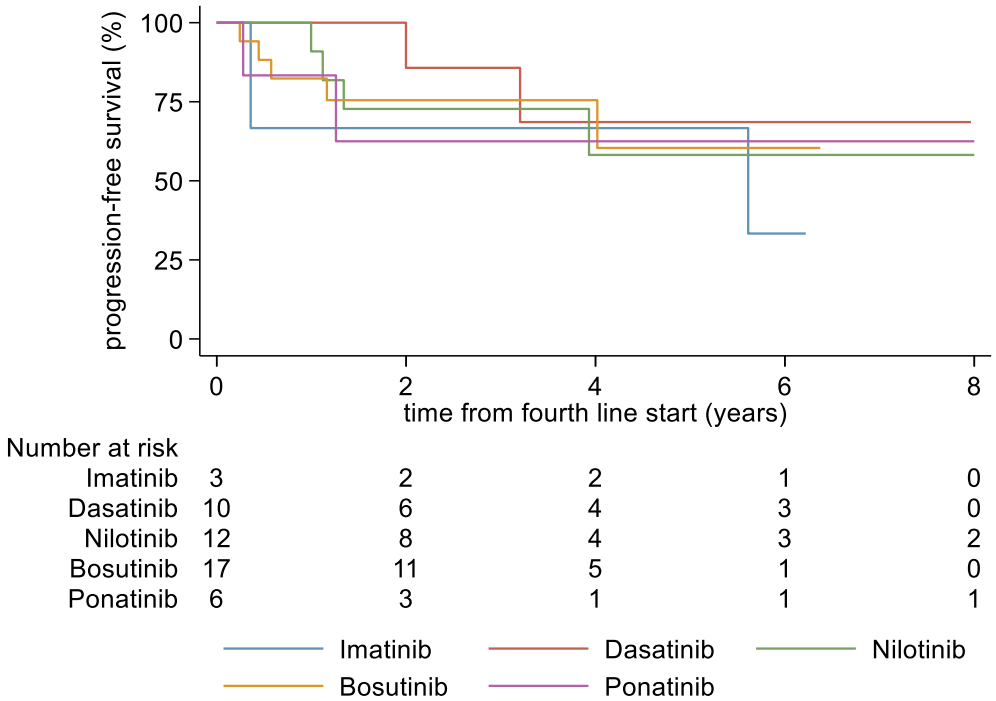


Figure 37 Treatment Pathways for subjects in Blast Crisis/Accelerated Phase

Time to treatment discontinuation

Table 18 Time to treatment discontinuation (TTD) for first line treatment by regimen

	Total	Discontinuation		Median TTD, years (95% CI)	Mean TTD, years (95% CI)	Discontinued only	Median TTD, years (95% CI)	Mean TTD, years (95% CI)
		No	Yes					
Total	539 (100)	192 (35.6)	347 (64.4)	3.3 (2.5 - 4.3)	6.5 (5.9 - 7.1)	347 (64.4)	1.2 (0.9 - 1.4)	2.4 (2.1 - 2.7)
Imatinib	483 (100)	164 (34.0)	319 (66.0)	3.1 (2.4 - 4.0)	6.3 (5.7 - 7.0)	319 (66.0)	1.2 (1.0 - 1.5)	2.5 (2.1 - 2.8)
Dasatinib	27 (100)	12 (44.4)	15 (55.6)	5.3 (0.5 - .)	5.8 (4.0 - 7.5)	15 (55.6)	0.5 (0.1 - 3.2)	2.0 (0.8 - 3.1)
Nilotinib	27 (100)	16 (59.3)	11 (40.7)	NR	5.6 (4.2 - 7.1)	11 (40.7)	0.5 (0.0 - 4.2)	1.6 (0.4 - 2.7)
Bosutinib	1 (100)	-	1 (100)	-	-	1 (100)	-	-
Ponatinib	1 (100)	-	1 (100)	-	-	1 (100)	-	-

Figure 38 Time to treatment discontinuation (TTD) for first line treatment by regimen

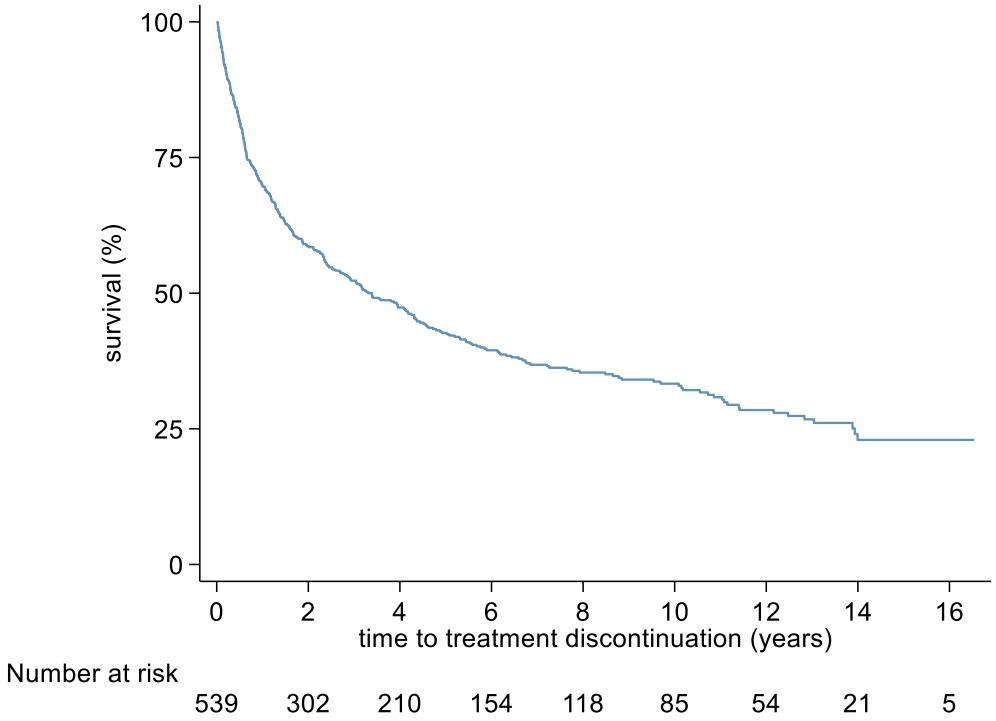


Figure 39 Time to treatment discontinuation (TTD) for first line treatment by regimen

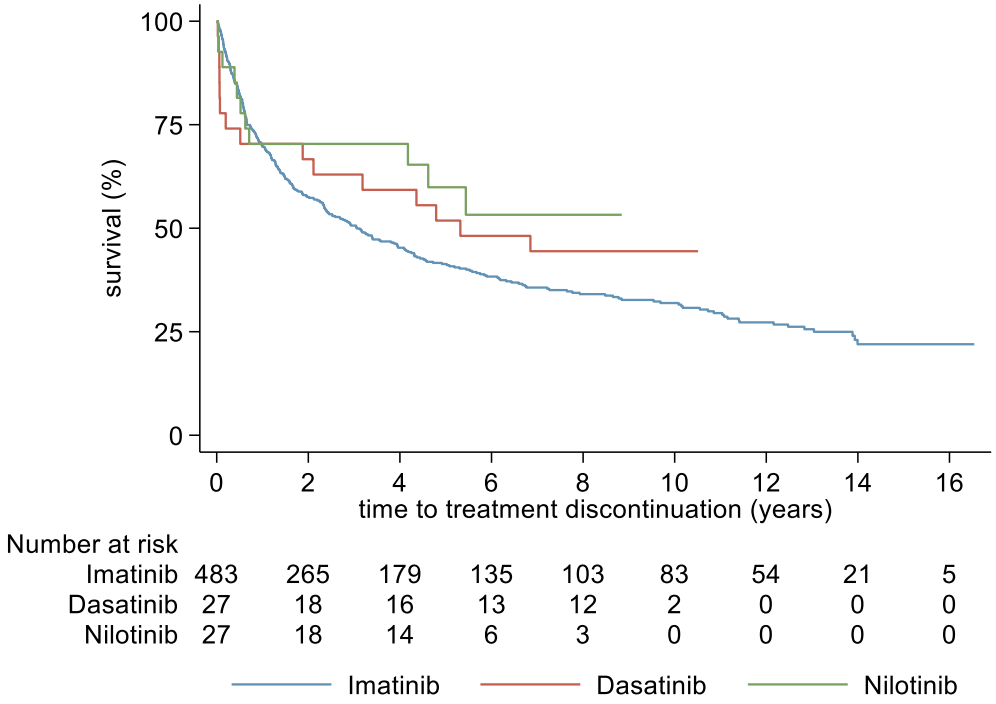


Table 19 Time to treatment discontinuation (TTD) for second line treatment by regimen

	Total	Discontinuation		Median TTD, years (95% CI)	Mean TTD, years (95% CI)	Discontinued only	Median TTD, years (95% CI)	Mean TTD, years (95% CI)
		No	Yes					
Total	225	77 (34.2)	148 (65.8)	2.4 (1.7 - 3.8)	4.7 (3.9 - 5.4)	148 (65.8)	1.1 (0.7 - 1.4)	1.9 (1.6 - 2.3)
Imatinib	16 (100)	6 (37.5)	10 (62.5)	2.2 (0.4 - .)	4.0 (1.7 - 6.3)	10 (62.5)	1.2 (0.0 - 2.2)	1.4 (0.5 - 2.2)
Dasatinib	66 (100)	18 (27.3)	48 (72.7)	1.7 (1.1 - 3.8)	3.5 (2.5 - 4.5)	48 (72.7)	1.1 (0.6 - 1.7)	2.1 (1.4 - 2.7)
Nilotinib	131 (100)	46 (35.1)	85 (64.9)	2.5 (1.8 - 4.9)	5.0 (4.0 - 6.1)	85 (64.9)	1.1 (0.4 - 1.6)	2.0 (1.4 - 2.5)
Bosutinib	10 (100)	6 (60.0)	4 (40.0)	3.2 (0.2 - .)	2.7 (1.5 - 3.9)	4 (40.0)	0.2 (0.2 - .)	1.0 (-0.3 - 2.2)
Ponatinib	2 (100)	1 (50.0)	1 (50.0)	2.1 (2.1 - .)	2.3 (2.0 - 2.6)	1 (50.0)	-	-

Figure 40 Time to treatment discontinuation (TTD) for second line treatment

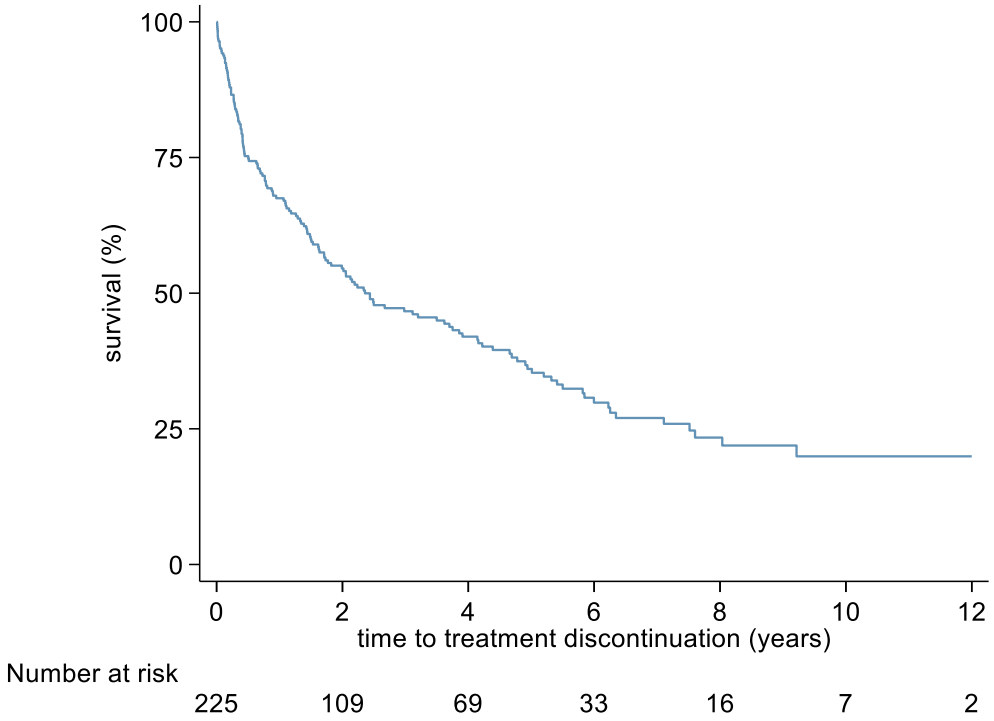


Figure 41 Time to treatment discontinuation (TTD) for second line treatment by regimen

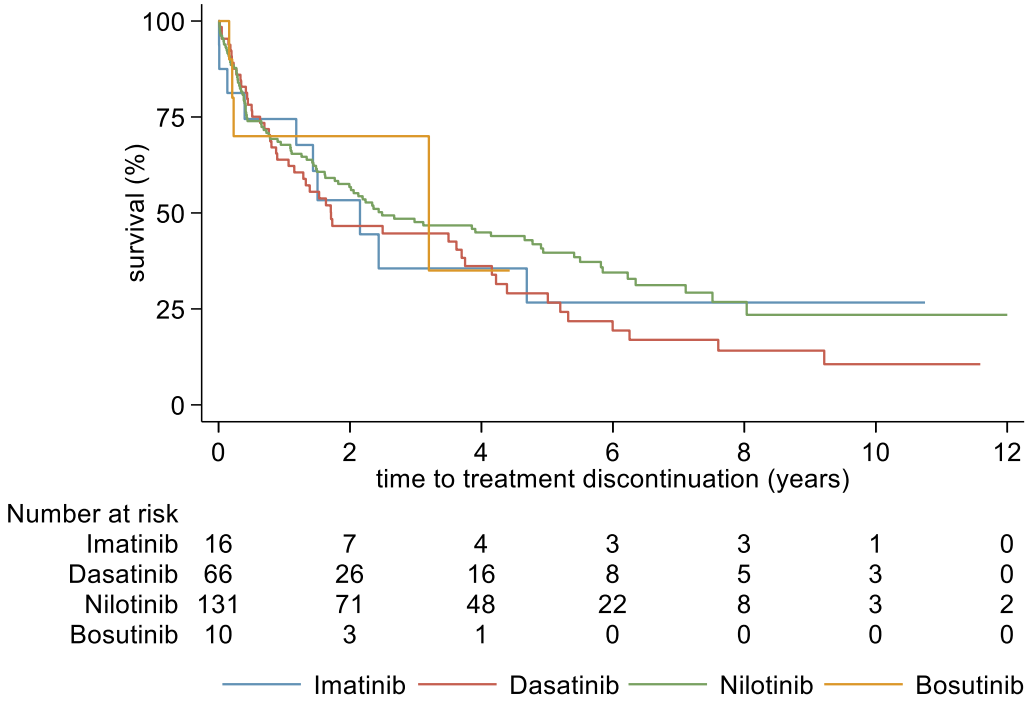


Table 20 Time to treatment discontinuation (TTD) for third line treatment by regimen

	Total	Discontinuation		Median TTD, years (95% CI)	Mean TTD, years (95% CI)	Discontinued only	Median TTD, years (95% CI)	Mean TTD, years (95% CI)
		No	Yes					
Total	107 (100)	33 (30.8)	74 (69.2)	1.6 (0.7 - 2.7)	3.8 (2.8 - 4.7)	74 (69.2)	0.5 (0.3 - 1.1)	1.5 (1.0 - 1.9)
Imatinib	10 (100)	1 (10.0)	9 (90.0)	0.1 (0.0 - 1.5)	1.5 (0.0 - 3.0)	9 (90.0)	0.1 (0.0 - 1.5)	1.0 (-0.3 - 2.3)
Dasatinib	36 (100)	11 (30.6)	25 (69.4)	1.4 (0.4 - 4.5)	4.2 (2.6 - 5.9)	25 (69.4)	0.4 (0.3 - 1.4)	1.4 (0.5 - 2.4)
Nilotinib	26 (100)	6 (23.1)	20 (76.9)	2.9 (1.6 - 4.9)	4.4 (2.8 - 6.0)	20 (76.9)	2.2 (0.8 - 4.0)	2.6 (1.7 - 3.5)
Bosutinib	26 (100)	14 (53.8)	12 (46.2)	3.1 (0.2 - .)	3.7 (2.3 - 5.1)	12 (46.2)	0.2 (0.0 - 0.7)	0.6 (0.1 - 1.1)
Ponatinib	9 (100)	1 (11.1)	8 (88.9)	0.6 (0.0 - 1.3)	0.8 (0.3 - 1.4)	8 (88.9)	0.4 (0.0 - 1.3)	0.6 (0.3 - 0.9)

Figure 42 Time to treatment discontinuation (TTD) for third line treatment

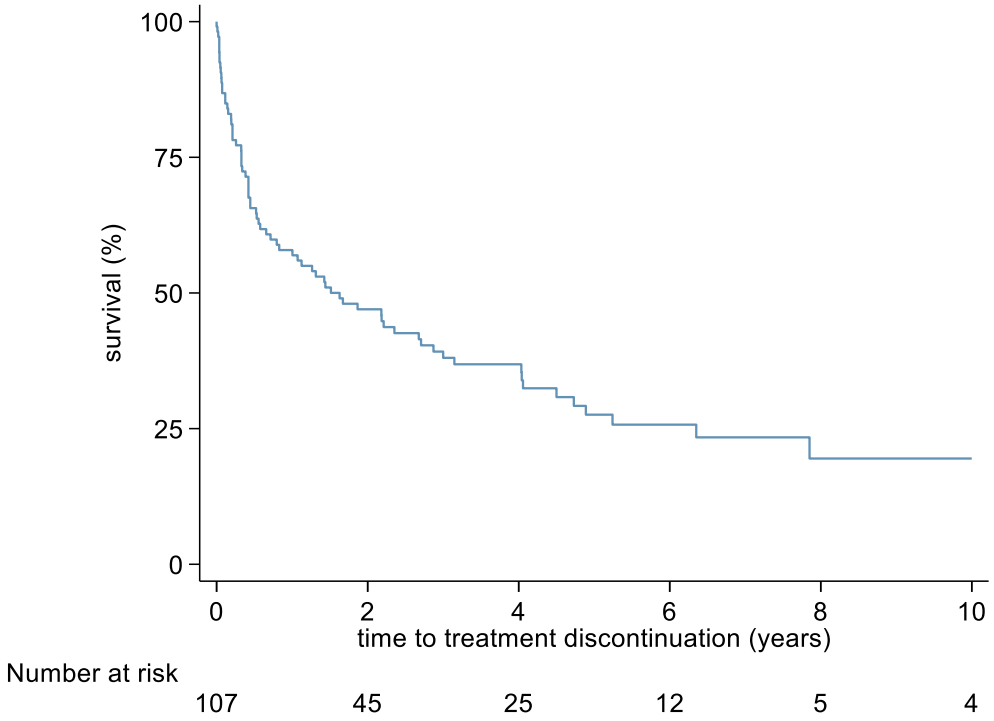


Figure 43 Time to treatment discontinuation (TTD) for third line treatment by regimen

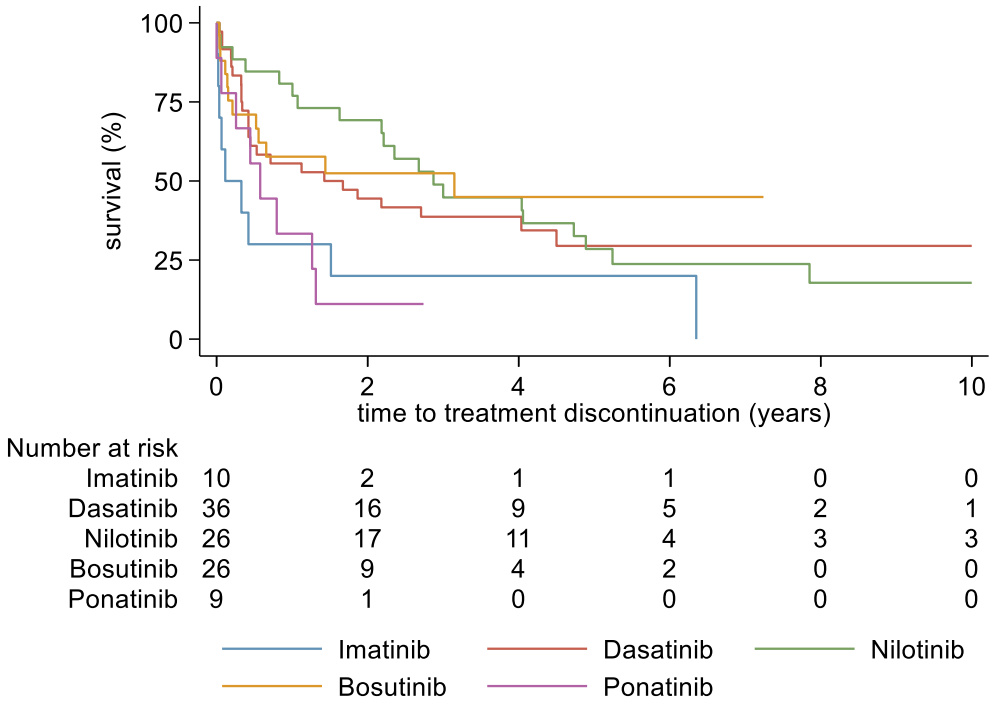


Table 21 Time to treatment discontinuation (TTD) for fourth line treatment by regimen

	Total	Discontinuation		Median TTD, years (95% CI)	Mean TTD, years (95% CI)	Discontinued only	Median TTD, years (95% CI)	Mean TTD, years (95% CI)
		No	Yes					
Total	48 (100)	15 (32.6)	31 (67.4)	1.0 (0.3 - 5.8)	3.1 (2.0 - 4.3)	31 (67.4)	0.3 (0.2 - 0.6)	1.0 (0.4 - 1.6)
Imatinib	3 (100)	-	3 (100)	0.1 (0.0 - .)	0.2 (-0.0 - 0.4)	3 (100)	0.1 (0.0 - .)	0.2 (-0.0 - 0.4)
Dasatinib	10 (100)	4 (40.0)	6 (60.0)	3.2 (0.0 - .)	3.1 (1.5 - 4.7)	6 (60.0)	0.2 (0.0 - .)	1.9 (0.2 - 3.6)
Nilotinib	12 (100)	3 (25.0)	9 (75.0)	0.6 (0.0 - .)	2.9 (0.8 - 5.1)	9 (75.0)	0.2 (0.0 - 2.1)	1.4 (-0.3 - 3.1)
Bosutinib	17 (100)	8 (47.1)	9 (52.9)	1.2 (0.3 - .)	3.2 (1.8 - 4.6)	9 (52.9)	0.3 (0.0 - 0.8)	0.5 (0.2 - 0.7)
Ponatinib	6 (100)	2 (33.3)	4 (66.7)	0.3 (0.2 - .)	1.3 (0.1 - 2.5)	4 (66.7)	0.2 (0.2 - .)	0.5 (0.0 - 0.9)

Figure 44 Time to treatment discontinuation (TTD) for fourth line treatment

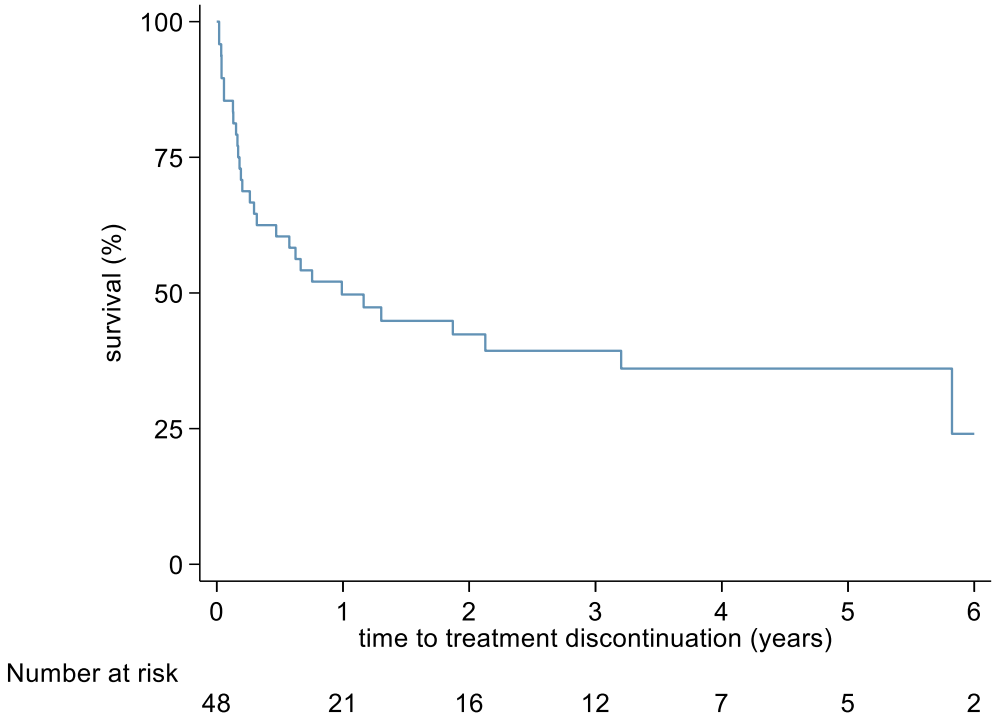


Figure 45 Time to treatment discontinuation (TTD) for fourth line treatment by regimen

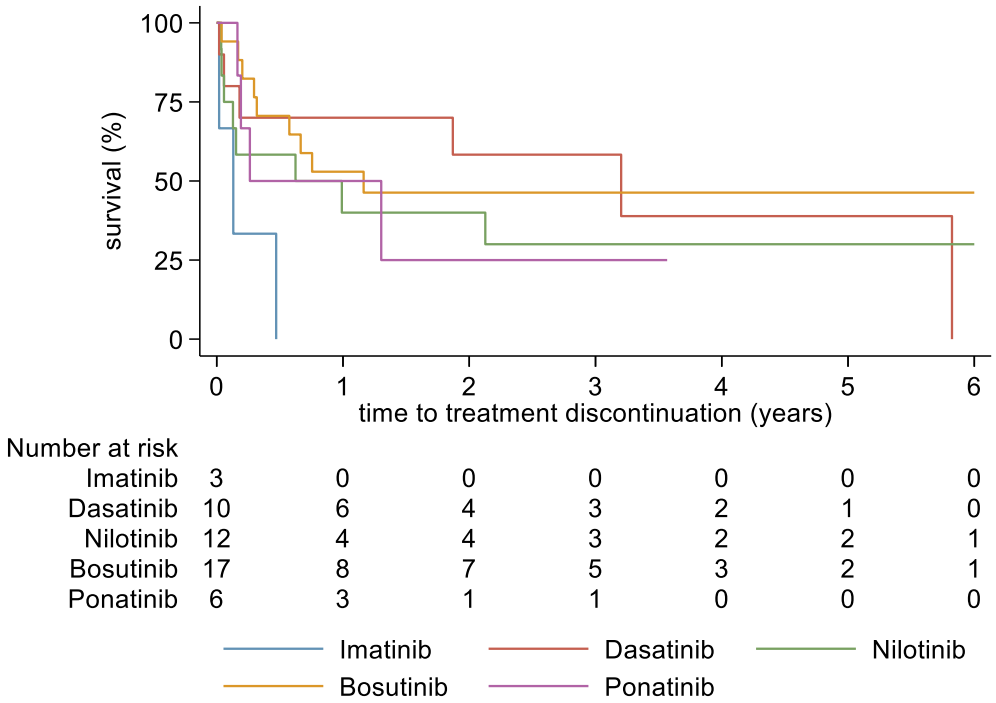


Table 22 Relative Survival by Treatment Line

		5-year		10-year	
Total	N	OS (95%CI)	RS (95%CI)	OS (95%CI)	RS (95%CI)
1L	539 (100)	77.8 (73.9 - 81.3)	89.2 (84.8 - 92.4)	64.1 (59 - 68.8)	83.9 (77.7 - 88.6)
Imatinib	483 (89.6)	77.5 (73.2 - 81.2)	89.9 (85 - 93.3)	63.3 (57.8 - 68.2)	83.8 (77 - 88.8)
Dasatinib	27 (5.0)	81.4 (61 - 91.8)	81.9 (61.1 - 92.2)	78.2 (64.4 - 87.2)	84.2 (67.4 - 92.8)
Nilotinib	27 (5.0)	78.1 (54 - 90.6)	79.7 (54.2 - 92)	59.3 (28.5 - 80.4)	69 (28 - 89.7)
2L	225 (100)	78.4 (71.8 - 83.6)	85.7 (78 - 90.9)	57.1 (45.8 - 66.9)	69.1 (54.6 - 79.7)
Dasatinib	66 (29.3)	78.2 (64.4 - 87.2)	84.2 (67.4 - 92.8)	46.3 (30.3 - 60.8)	56.7 (36 - 72.9)
Nilotinib	131 (58.2)	83.5 (75.6 - 89.1)	87.8 (78.9 - 93.1)	70.5 (52.1 - 82.8)	76.3 (54.9 - 88.6)
3L	107 (100)	72.3 (61.1 - 80.7)	77.5 (64.9 - 86)	52.4 (37.2 - 65.6)	63.9 (44 - 78.3)
Dasatinib	36 (33.6)	80 (60.3 - 90.6)	81.7 (60.8 - 92.2)	80 (60.3 - 90.6)	81.7 (60.8 - 92.2)
Nilotinib	26 (24.3)	72.1 (50.2 - 85.6)	75.9 (51.3 - 89.2)	40.2 (19 - 60.7)	48.5 (21.5 - 71.2)
Bosutinib	26 (24.3)	91.4 (69.9 - 97.8)	91.5 (69.8 - 97.8)	-	-
4L	48 (100)	63.8 (44.7 - 77.9)	64.8 (45.2 - 78.9)	56.8 (35.2 - 73.7)	58.2 (35.8 - 75.2)

Figure 46 Overall & Relative Survival at First Line

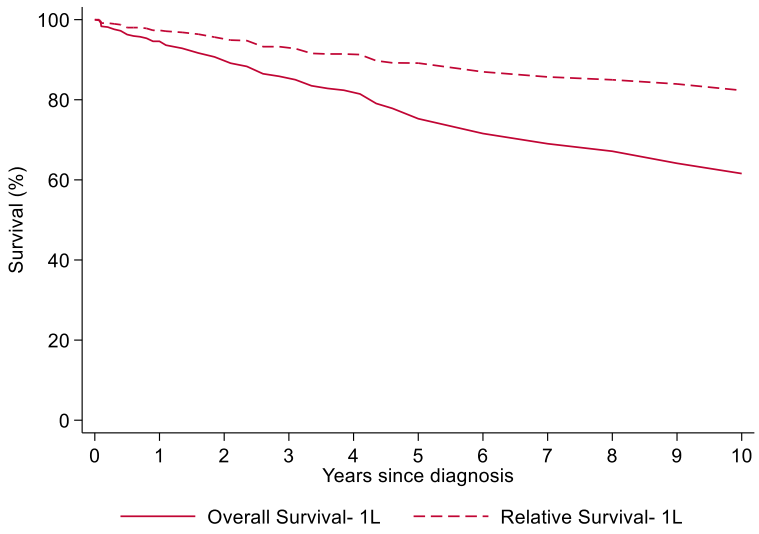


Figure 47 Overall & Relative Survival at Second Line

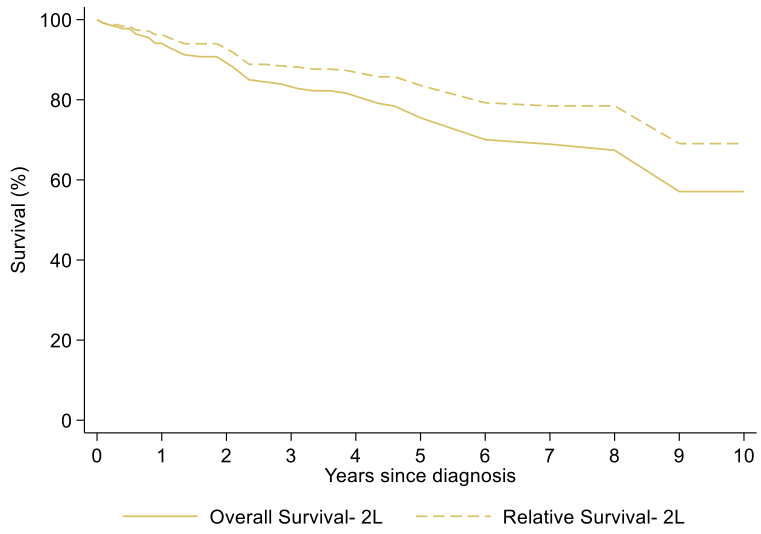


Figure 48 Overall & Relative Survival at Third Line

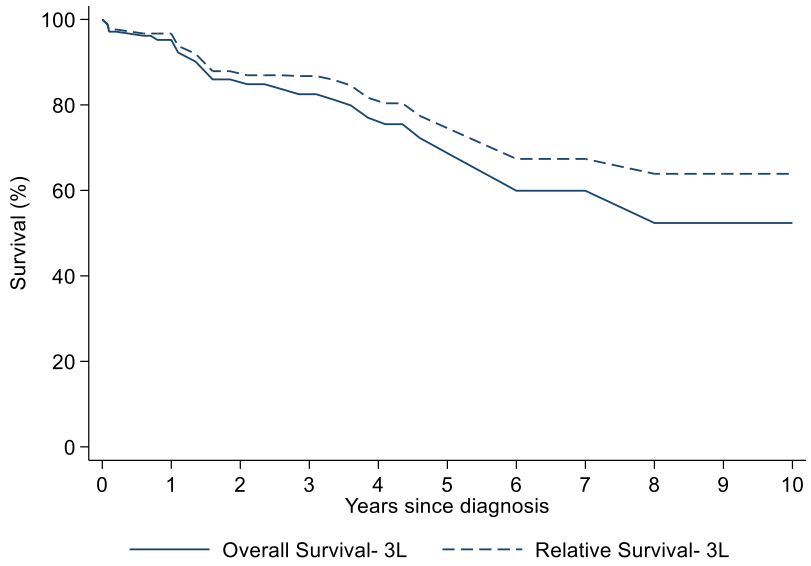
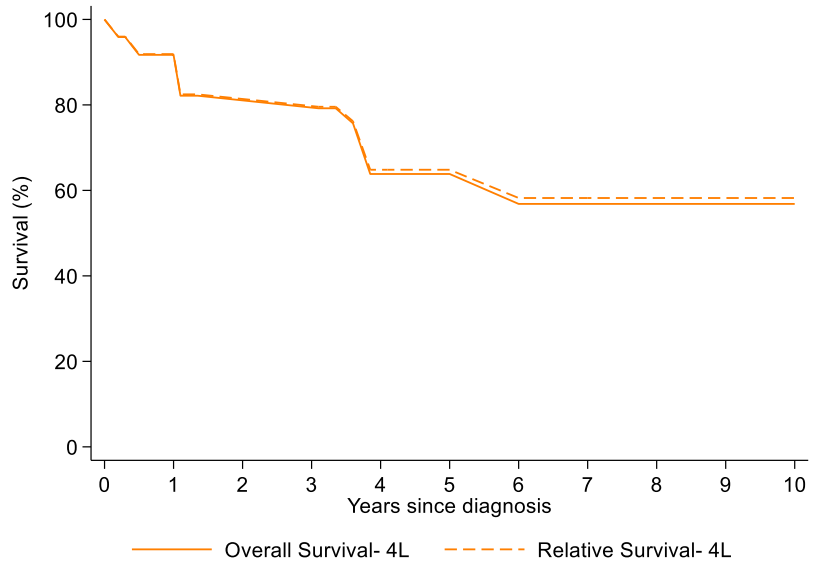


Figure 49 Overall & Relative Survival at Fourth Line



Appendix I Complete Treatment Pathways for 30 patients initially treated with Hydroxycarbamide