Sponsor
Novartis Pharmaceuticals

Generic Drug Name
N/A

Trial Indication(s)
Chronic Myeloid Leukemia

Protocol Number
CABL001AUS09

Protocol Title
Assessing Real-world Clinical Outcomes of 3L+ Therapies among Patients with Chronic Myeloid Leukemia and those with T315I Mutation in the United States (ARC Study)

Clinical Trial Phase
IV

Phase of Drug Development
NA

Study Start/End Dates

Study start date: 01/12/2020

Study Completion date: 23/12/2021

Reason for Termination

NA

Study Design/Methodology

The study was a retrospective, non-interventional patient chart review and used a panel of oncologists/hematologists from the US to collect real-world clinical outcomes of patients with CML-CP in 3L+ and those with the T315I mutation.

This study included two distinct cohorts of CML-CP patients; that is, patients with CML-CP who initiated 3L for CML-CP (i.e., 3L cohort) and patients with CML-CP with T315I mutation (i.e., T315I cohort).

Study design for the analyses of the 3L cohort:

- The index date: date of initiation of 3L therapy for CML-CP

- The study period: period of ≥ 24 months following the index date unless the patient died before

- Patient characteristics were measured at CML diagnosis and at the index date

- The clinical outcomes of interest were measured during the study period

Study design for the analyses of the T315I cohort:

- The index date: date of initiation of a line of therapy identified as the T315I line of interest (i.e., identification of T315I mutation before initiation or over the course of line of therapy)

- The study period: period of ≥ 24 months following the index date unless the patient died before

- Patient characteristics were measured at CML diagnosis and at the index date.
- The clinical outcomes of interest were measured during the study period

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

- To evaluate treatment patterns in patients with CML-CP who were previously treated with TKI or other CML treatments and were relapsed/refractory to/were intolerant/had other reasons for switching of CML therapy

Secondary objective(s)

- To evaluate the effectiveness of TKI and other CML treatments used in 3L+ settings in patients with CML-CP; specifically, the molecular response, cytogenetic response, and hematologic response achieved in real-world settings (e.g., 3L, 4L, 5L)
- To evaluate the effectiveness of TKI and other treatments used in a line of therapy with the identification of T315I mutation in patients with CML-CP; specifically, the molecular response, cytogenetic response, and hematologic response achieved in real-world settings
- To conduct a targeted literature search to better understand what is already known about molecular response in CML-CP in a real-world setting
- To evaluate treatment patterns in patients with CML-CP with T315I mutation
- To evaluate real-world BCR-ABL testing frequency per the latest NCCN guidelines in 3L settings in patients with CML-CP

- To evaluate real-world BCR-ABL testing frequency per the latest NCCN guidelines in patients with CML-CP with T315I mutation

Test Product (s), Dose(s), and Mode(s) of Administration
NA

Statistical Methods

Data collected was reported using descriptive statistics (i.e., frequency, proportion, mean, standard deviation, median, range). Time to MR was estimated using KM analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Physician selection

Physicians were eligible to participate in the study if they fulfilled all of the following criteria:

- Completed medical subspecialty training
- Reported hematology, medical oncology, or any other oncology subspecialties as the primary medical subspecialty
- Were responsible for treatment decisions and follow-up for ≥ 1 adult patient with Ph+ CML-CP who received a 3L or those with the T315I mutation since January 2013 (the date from which molecular monitoring response on the International Scale (IS) became a more standard procedure/commonly available)
- Had access to molecular monitoring results reported on the IS, and with a sensitivity level of precision for molecular response of MR3 (BCR-ABL1/ABL1 ≤ 0.1% or 3-log reduction) or better

Patient selection

Participating physicians were directed to provide information on patients who were included into the following separate cohorts. Each participating physician contributed up to 5 patient medical charts from each cohort.

For the 3L cohort:

- Adult patients diagnosed with Ph+ CML-CP who initiated a 1L therapy, switched to a 2L therapy, and initiated a 3L therapy for CML-CP
- All lines of therapy (TKIs or other CML treatments) received outside of an interventional clinical trial setting
- 3L therapy was initiated on or after January 1st, 2013 (when molecular monitoring became a common practice in CML monitoring) and no later than November 30th, 2018, to have a minimum of 2 years of follow-up after therapy initiation, except if the patient died before

For the T315I cohort:

- Adult patients diagnosed with Ph+ CML-CP who initiated ≥ 1 line of therapy for Ph+ CML-CP and T315I mutation was identified
- All lines of therapy (TKIs or other CML treatments) received outside of an interventional clinical trial setting
- Line of therapy identified as the T315I line of interest was initiated on or after January 1st, 2013 and no later than November 30th, 2018, to have a minimum of 2 years of follow-up after therapy initiation, except if the patient died before

For both cohorts:

- Patients with Ph+ CML-CP for whom the physician had complete information on the CML related care from CML diagnosis and for ≥ 2 years after the initiation of line of therapy of interest (i.e., 3L or line of therapy identified as the T315I line of interest), unless the patient died before. Complete information included: CML treatments, treatment duration, routine laboratory (e.g., complete blood count (CBC), BCR-ABL), CML status (e.g., SOKAL risk score, CP/accelerated phase (AP)/ blast crisis (BC)), medications, and clinical status (e.g., history, physical exam)
- The physician had access to molecular monitoring results reported on the IS from initiation of the line of therapy of interest and with a sensitivity level of precision for molecular response of MR3 (BCR-ABL1/ABL1≤0.1% or 3-log reduction) or better

Of note, the cohorts were not mutually exclusive such that patients included in the 3L cohort with T315I mutation were included in the T315I cohort. Thereafter, there was an oversampling of patients with T315I mutation. Patients from the T315I cohort from the oversampling with a 3L were not included in the 3L cohort.

Exclusion criteria
Excluded patients:
- Physicians and patients who did not meet study inclusion criteria detailed above were excluded.

Participant Flow
A total of 162 patients with an erenumab prescription were entitled to employer-sponsored occupational health care. Of these patients, half met the responder definition (n=82) of two or more erenumab prescriptions with no evidence of switch to other CGRPi and were thus included in the main analyses. A one-to-one age and sex matched control group of migraine patients not receiving CGRP to control for potential changes in patient behavior and health care practices during the COVID-19 pandemic was included. The patients in the control group were selected based on having received at least one triptan prescription for migraine after 2018.

Baseline Characteristics

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3L Cohort

Patient demographic and clinical characteristics

		Reasons for termination of second-line therapy[1]	
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]
	N= 164	N= 42	N= 80
Patient characteristics			
Age at Ph+ CML-CP diagnosis, years			
Mean [SD]	57.6 [12.3]	61.6 [11.7]	55.4 [14.0]
Median	58.0	62.0	56.0
Range	[18.0, 84.0]	[30.0, 84.0]	[18.0, 79.0]
Age groups, N (%)			
18-54 years	58 (35.4%)	13 (31.0%)	32 (40.0%)
55-64 years	53 (32.3%)	13 (31.0%)	22 (27.5%)
65-74 years	40 (24.4%)	9 (21.4%)	20 (25.0%)
≥75 years	13 (7.9%)	7 (16.7%)	6 (7.5%)
Year of Ph+ CML-CP diagnosis, N (%)			
2000-2004	4 (2.4%)	3 (7.1%)	1 (1.3%)
2005-2009	3 (1.8%)	1 (2.4%)	2 (2.5%)
2010-2014	87 (53.0%)	15 (35.7%)	42 (52.5%)
2015-2018	70 (42.7%)	23 (54.8%)	35 (43.8%)
Female, N (%)	73 (44.5%)	21 (50.0%)	32 (40.0%)
Race/ethnicity, N (%)			
White - Non-Hispanic/Latino	107 (65.2%)	27 (64.3%)	45 (56.3%)
Black or African American - Non-Hispanic/Latino	25 (15.2%)	6 (14.3%)	15 (18.8%)
Hispanic/Latino	17 (10.4%)	5 (11.9%)	10 (12.5%)
East Asian[3]	8 (4.9%)	2 (4.8%)	6 (7.5%)
Asian Indian[4]	6 (3.7%)	2 (4.8%)	3 (3.8%)
North American Native	1 (0.6%)	0 (0.0%)	1 (1.3%)
Other[5]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insurance type at Ph+ CML-CP diagnosis[6], N (%)			
Commercial/private insurance	103 (62.8%)	25 (59.5%)	50 (62.5%)

		Reasons for termination of second-line therapy[1]	
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**
	N= 164	**N= 42**	**N= 80**
Medicare	51 (31.1%)	18 (42.9%)	20 (25.0%)
Medicaid	20 (12.2%)	4 (9.5%)	10 (12.5%)
Military insurance (VA or active military)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[7]	1 (0.6%)	0 (0.0%)	0 (0.0%)
No insurance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown/Not sure	1 (0.6%)	0 (0.0%)	1 (1.3%)
Follow-up with complete care information			
Duration of follow-up from diagnosis of Ph+ CML-CP[8], months			
Mean [SD]	84.5 [36.9]	80.0 [50.8]	82.8 [33.6]
Median	80.3	70.1	80.0
Range	[22.3, 228.8]	[22.3, 228.8]	[22.3, 220.8]
<12 months, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥12 months, N (%)	164 (100.0%)	42 (100.0%)	80 (100.0%)
≥24 months, N (%)	161 (98.2%)	40 (95.2%)	79 (98.8%)
≥36 months, N (%)	157 (95.7%)	38 (90.5%)	77 (96.3%)
Clinical profile at CML diagnosis			
Sokal score[9], N (%)			
Low risk (<0.8)	46 (28.0%)	13 (31.0%)	22 (27.5%)
Intermediate risk (0.8 to ≤1.2)	77 (47.0%)	13 (31.0%)	41 (51.3%)
High risk (>1.2)	22 (13.4%)	6 (14.3%)	9 (11.3%)
Unknown	19 (11.6%)	10 (23.8%)	8 (10.0%)
ECOG performance status[10], N (%)			
Grade 0	65 (39.6%)	14 (33.3%)	34 (42.5%)
Grade 1	79 (48.2%)	21 (50.0%)	38 (47.5%)
Grade 2	19 (11.6%)	7 (16.7%)	8 (10.0%)
Grade 3	1 (0.6%)	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Additional clinical characteristics			
Patients for whom comorbidities were known at third-line initiation, N (%)	163 (99.4%)	42 (100.0%)	80 (100.0%)
Modified Charlson Comorbidity Score at third-line initiation[11]			
Mean [SD]	0.5 [1.1]	0.9 [1.5]	0.4 [0.9]

		Reasons for termination of second-line therapy[1]	
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**
	N= 164	**N= 42**	**N= 80**
Median	0.0	0.0	0.0
Range	[0.0, 5.0]	[0.0, 5.0]	[0.0, 4.0]
0, N (%)	126 (77.3%)	27 (64.3%)	65 (81.3%)
1, N (%)	17 (10.4%)	5 (11.9%)	8 (10.0%)
2, N (%)	6 (3.7%)	2 (4.8%)	2 (2.5%)
≥3, N (%)	14 (8.6%)	8 (19.0%)	5 (6.3%)

3L: third-line; CML: chronic myeloid leukemia; CP: chronic phase; ECOG: Eastern Cooperative Oncology Group; Ph+: Philadelphia chromosome positive; SD: standard deviation; TKI: tyrosine kinase inhibitors; VA: Veterans Affairs

Notes:

[1] Physicians could select more than one reason for termination of second-line therapy (not mutually exclusive).

[2] The resistance or lack of efficacy subgroup includes patients for whom physicians reported Resistance and/or Lack of efficacy as a reason for termination of second-line therapy.

[3] East Asian nationalities included: China, Hong Kong, Macao, Taiwan, Japan, South Korea, North Korea, Mongolia, and Vietnam.

[4] Asian Indian nationalities included: Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Afghanistan, and Sri Lanka.

[5] Physicians did not report other race/ethnicity.

[6] Physicians could select more than one option (not mutually exclusive).

[7] One patient was reported as having supplement to Medicare.

[8] The duration of follow-up was measured from the diagnosis of Ph+ CML-CP to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

[9] The Sokal score is calculated using the following formula: exp (0.0116 x (age [years] – 43.4)) + (0.0345 x (spleen size [cm] – 7.51) + (0.188 x ((platelets [10^9/L]/700)2 – 0.563)) + (0.0887 x (blasts [%] – 2.10)). Sokal et al. (1984) proposed three risk groups:

- low-risk (score <0.8)
- intermediate-risk (score 0.8 - 1.2)
- high-risk (score >1.2)

Source: Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in “good-risk” chronic granulocytic leukemia. Blood 1984; 63:789-99.

[10] Grade 0 (the patient was fully active; no restriction); grade 1 (the patient was restricted in strenuous physical activities; fully ambulatory and able to carry out light work); grade 2 (the patient was capable of all self-care but unable to carry out any work activities; was up and about >5 percent of waking hours); grade 3 (the patient was capable of only limited self-care; confined to bed or chair >50 percent of waking hours); grade 4 (the patient was completely disabled; could not carry out any self-care; totally confined to bed or chair).

[11] Charlson comorbidity score excluding chronic myeloid leukemia.

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T315I Cohort

Descriptive data

Patient demographic and clinical characteristics

	All patients N= 128
Patient characteristics	
Age at Ph+ CML-CP diagnosis, years	
Mean [SD]	58.8 [11.9]
Median	60.0
Range	[18.0, 81.0]
Age groups, N (%)	
18-54 years	36 (28.1%)
55-64 years	44 (34.4%)
65-74 years	37 (28.9%)
≥75 years	11 (8.6%)
Year of Ph+ CML-CP diagnosis, N (%)	
2000-2004	1 (0.8%)
2005-2009	2 (1.6%)
2010-2014	65 (50.8%)
2015-2018	60 (46.9%)
Year T315I mutation was detected, N (%)	
2010	0 (0.0%)
2011	1 (0.8%)
2012	0 (0.0%)
2013	4 (3.1%)
2014	22 (17.2%)
2015	16 (12.5%)
2016	13 (10.2%)
2017	30 (23.4%)
2018	41 (32.0%)
2019	1 (0.8%)
Female, N (%)	64 (50.0%)
Race/ethnicity, N (%)	
White - Non-Hispanic/Latino	88 (68.8%)
Black or African American - Non-Hispanic/Latino	14 (10.9%)

	All patients N= 128
Hispanic/Latino	14 (10.9%)
East Asian[1]	5 (3.9%)
Asian Indian[2]	5 (3.9%)
North American Native	2 (1.6%)
Other[3]	0 (0.0%)
Unknown/Not sure	0 (0.0%)
Insurance type at Ph+ CML-CP diagnosis[4], N (%)	
Commercial/private insurance	65 (50.8%)
Medicare	47 (36.7%)
Medicaid	20 (15.6%)
Military insurance (VA or active military)	1 (0.8%)
Other[5]	1 (0.8%)
No insurance	0 (0.0%)
Unknown/Not sure	0 (0.0%)
Follow-up with complete care information	
Duration of follow-up from diagnosis of Ph+ CML-CP[6], months	
Mean [SD]	78.0 [28.9]
Median	76.2
Range	[8.1, 226.3]
<12 months, N (%)	1 (0.8%)
≥12 months, N (%)	127 (99.2%)
≥24 months, N (%)	124 (96.9%)
≥36 months, N (%)	123 (96.1%)
Clinical profile at CML diagnosis	
Sokal score[7], N (%)	
Low risk (<0.8)	31 (24.2%)
Intermediate risk (0.8 to ≤1.2)	57 (44.5%)
High risk (>1.2)	29 (22.7%)
Unknown	11 (8.6%)
ECOG performance status[8], N (%)	
Grade 0	53 (41.4%)
Grade 1	63 (49.2%)
Grade 2	10 (7.8%)
Grade 3	2 (1.6%)
Grade 4	0 (0.0%)
Unknown/Not sure	0 (0.0%)

	All patients N= 128
Additional clinical characteristics	
Patients for whom comorbidities were known at initiation of the line with the identification of the T315I mutation, N (%)	128 (100.0%)
Modified Charlson Comorbidity Score at initiation of the line with the identification of the T315I mutation[9]	
Mean [SD]	0.3 [1.0]
Median	0.0
Range	[0.0, 5.0]
0, N (%)	108 (84.4%)
1, N (%)	9 (7.0%)
2, N (%)	5 (3.9%)
≥3, N (%)	6 (4.7%)

CML: chronic myeloid leukemia; CP: chronic phase; ECOG: Eastern Cooperative Oncology Group; Ph+: Philadelphia chromosome positive; SD: standard deviation; TKI: tyrosine kinase inhibitors; VA: Veterans Affairs

Notes:

[1] East Asian nationalities included: China, Hong Kong, Macao, Taiwan, Japan, South Korea, North Korea, Mongolia, and Vietnam.

[2] Asian Indian nationalities included: Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Afghanistan, and Sri Lanka.

[3] Physicians did not report other race/ethnicity.

[4] Physicians could select more than one option (not mutually exclusive).

[5] One patient was reported as having supplement to Medicare.

[6] The duration of follow-up was measured from the diagnosis of Ph+ CML-CP to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

[7] The Sokal score is calculated using the following formula: exp (0.0116 x (age [years] – 43.4)) + (0.0345 x (spleen size [cm] – 7.51) + (0.188 x ((platelets [10^9/L]/700)2 – 0.563)) + (0.0887 x (blasts [%] – 2.10)). Sokal et al. (1984) proposed three risk groups:

- low-risk (score <0.8)
- intermediate-risk (score 0.8 - 1.2)
- high-risk (score >1.2)

Source: Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in “good-risk” chronic granulocytic leukemia. Blood 1984; 63:789-99.

[8] Grade 0 (the patient was fully active; no restriction); grade 1 (the patient was restricted in strenuous physical activities; fully ambulatory and able to carry out light work); grade 2 (the patient was capable of all self-care but unable to carry out any work activities; was up and about >5 percent of waking hours); grade 3 (the patient was capable of only limited self-care; confined to bed or chair >50 percent of waking hours); grade 4 (the patient was completely disabled; could not carry out any self-care; totally confined to bed or chair).

[9] Charlson comorbidity score excluding chronic myeloid leukemia.

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Outcome data

Data were abstracted for 164 patients who received a 3L for Ph+ CML-CP.

- 42 charts (25.6%) reported termination of 2L due to intolerance or management of adverse events
- 80 charts (48.8%) reported termination of 2L due to resistance or lack of efficacy
- 15 patients (9.1%) had a 4L and 3 patients (1.8%) had a 5L
- 104 charts (63.4%) had a last response on 2L of MR2 or lower
- 108 charts (65.9%) did not have a T315I mutation on or before 3L

Primary outcome Results

Treatment patterns by line of therapy

	Across all lines	First-line	Second-line	Third-line
	N= 164	N= 164	N= 164	N= 164
Description of line of therapy				
Number of lines of therapy				
Mean [SD]	3.1 [0.4]			
Median	3.0			
Range	[3.0, 5.0]			
≥3 lines of therapy, N (%)	164 (100.0%)			
≥4 lines of therapy, N (%)	15 (9.1%)			
≥5 lines of therapy, N (%)	3 (1.8%)			
≥6 lines of therapy, N (%)	0 (0.0%)			
Total number of lines, N	510			

	Across all lines N= 164	First-line N= 164	Second-line N= 164	Third-line N= 164
Treatment received, N (%)				
Imatinib	145 (28.4%)	135 (82.3%)	6 (3.7%)	4 (2.4%)
In combination with hydroxyurea	9 (1.8%)	9 (5.5%)	0 (0.0%)	0 (0.0%)
Dasatinib	110 (21.6%)	15 (9.1%)	77 (47.0%)	17 (10.4%)
In combination with hydroxyurea	4 (0.8%)	1 (0.6%)	3 (1.8%)	0 (0.0%)
Nilotinib	89 (17.5%)	4 (2.4%)	51 (31.1%)	31 (18.9%)
In combination with hydroxyurea	3 (0.6%)	0 (0.0%)	1 (0.6%)	2 (1.2%)
Bosutinib	60 (11.8%)	0 (0.0%)	22 (13.4%)	33 (20.1%)
In combination with hydroxyurea	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Ponatinib	78 (15.3%)	1 (0.6%)	4 (2.4%)	67 (40.9%)
In combination with hydroxyurea	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (2.4%)
Omacetaxine	8 (1.6%)	0 (0.0%)	1 (0.6%)	7 (4.3%)
In combination with hydroxyurea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Interferon	5 (1.0%)	0 (0.0%)	2 (1.2%)	1 (0.6%)
In combination with hydroxyurea	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hydroxyurea	15 (2.9%)	9 (5.5%)	1 (0.6%)	4 (2.4%)
Calendar year of line of therapy initiation, N (%)				
2001-2004	4 (0.8%)	4 (2.4%)	0 (0.0%)	0 (0.0%)
2005-2008	4 (0.8%)	2 (1.2%)	2 (1.2%)	0 (0.0%)
2009-2012	40 (7.8%)	30 (18.3%)	10 (6.1%)	0 (0.0%)
2013-2016	261 (51.2%)	108 (65.9%)	104 (63.4%)	49 (29.9%)
2017-2021	201 (39.4%)	20 (12.2%)	48 (29.3%)	115 (70.1%)
Duration of line of therapy[1], months				
Mean [SD]	23.5 [20.8]	19.8 [20.7]	16.0 [13.2]	35.1 [22.7]

	Across all lines N= 164	First-line N= 164	Second-line N= 164	Third-line N= 164
Median	16.8	12.9	11.9	32.6
Range	[0.3, 137.0]	[0.3, 137.0]	[0.5, 66.3]	[1.9, 102.0]
Most frequent treatment sequences from first- to third-line of therapy				
Treatment sequence, N (%)				
Imatinib, dasatinib, ponatinib	22 (13.4%)			
Imatinib, dasatinib, nilotinib	19 (11.6%)			
Imatinib, dasatinib, bosutinib	17 (10.4%)			
Imatinib, nilotinib, ponatinib	16 (9.8%)			
Imatinib, nilotinib, dasatinib	10 (6.1%)			
Imatinib, bosutinib, ponatinib	10 (6.1%)			
Imatinib, nilotinib, bosutinib	7 (4.3%)			
Dasatinib, nilotinib, bosutinib	4 (2.4%)			
Imatinib and hydroxyurea, dasatinib, nilotinib	3 (1.8%)			
Nilotinib, bosutinib, ponatinib	2 (1.2%)			
Death, progression to AP/BC[2] or HSCT				
Patients who died after initiation of third-line therapy, N (%)				
Anytime following the initiation of third-line therapy	15 (9.1%)			
During the course of third-line therapy	4 (2.4%)			
Patients who progressed to AP/BC after initiation of third-line therapy[2], N (%)				
Anytime following the initiation of third-line therapy	8 (4.9%)			
During the course of third-line therapy	5 (3.0%)			
Patients who underwent HSCT after initiation of third-line therapy, N (%)				
Anytime following the initiation of third-line therapy	1 (0.6%)			
During the course of third-line therapy	1 (0.6%)			

	Across all lines	First-line	Second-line	Third-line
	N= 164	N= 164	N= 164	N= 164
Patients developed graft versus host disease after undergoing HSCT[3], N (%)				
Patients had <3 months of follow-up following HSCT[4]	0 (0.0%)			
Patients had 3 to <6 months of follow-up following HSCT[4]	0 (0.0%)			
Patients had ≥6 months of follow-up following HSCT[4]	0 (0.0%)			
Patients who were still on the third-line therapy as of the data collection date, N (%)	110 (67.1%)			

3L: third-line; AP: accelerated phase; BC: blast crisis; HSCT: hematopoietic stem cell transplant; SD: standard deviation

Notes:

[1] The duration of the line of therapy was measured from the initiation of the line of therapy to i) end of the line of therapy, ii) death, iii) last date for which the physician had complete care information, or iv) data collection date (ie. patient was still on the line of therapy at data collection), whichever occured first.

[2] An accelerated phase was defined as: 1. Peripheral blood myeloblasts ≥15% and <30%; 2. With peripheral blood myeloblasts and promyelocytes combined ≥30%; 3. Peripheral blood basophils ≥20%; 4. Platelet count ≤100 x 10^9/L unrelated to therapy; 5. Additional clonal cytogenetic abnormalities in Ph+ cells.
Source: National Comprehensive Cancer Network (NCCN) guidelines referencing the modified criteria used at MD Anderson Cancer Center
A blast crisis was defined as: 1. ≥30% blasts in the blood, marrow, or both; 2. Extramedullary infiltrates of leukemic cells.
Source: National Comprehensive Cancer Network (NCCN) guidelines referencing the International Bone Marrow Transplant Registry

[3] Graft versus host disease information was collected for the full launch only. The 27 patient charts collected during the soft launch were excluded for this analysis.

[4] The duration of follow-up was measured from the HSCT date to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

Secondary Outcome Results

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Third-line therapy response

		Reasons for termination of second-line therapy[1]				
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]	Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
Molecular monitoring frequency following the initiation of third-line therapy						
Molecular monitoring during 0-6 months following the initiation of third-line therapy, N (%)						
Every month	17 (10.4%)	3 (7.1%)	8 (10.0%)	12 (11.5%)	10 (9.3%)	
Every 6 weeks	15 (9.1%)	0 (0.0%)	3 (3.8%)	15 (14.4%)	14 (13.0%)	
Every 2 months	21 (12.8%)	5 (11.9%)	7 (8.8%)	10 (9.6%)	10 (9.3%)	
Every 3 months	98 (59.8%)	28 (66.7%)	56 (70.0%)	57 (54.8%)	65 (60.2%)	
Every 6 months	9 (5.5%)	4 (9.5%)	4 (5.0%)	6 (5.8%)	5 (4.6%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Molecular monitoring during 7-12 months following the initiation of third-line therapy, N (%)						
Every month	9 (5.5%)	2 (4.8%)	4 (5.0%)	6 (5.8%)	6 (5.6%)	
Every 6 weeks	19 (11.6%)	0 (0.0%)	5 (6.3%)	17 (16.3%)	16 (14.8%)	
Every 2 months	10 (6.1%)	0 (0.0%)	3 (3.8%)	4 (3.8%)	3 (2.8%)	
Every 3 months	99 (60.4%)	29 (69.0%)	56 (70.0%)	59 (56.7%)	65 (60.2%)	
Every 6 months	14 (8.5%)	3 (7.1%)	8 (10.0%)	8 (7.7%)	7 (6.5%)	

		Reasons for termination of second-line therapy[1]				
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]	Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0%)	
Molecular monitoring during 13-24 months following the initiation of third-line therapy, N (%)						
Every month	3 (1.8%)	2 (4.8%)	0 (0.0%)	1 (1.0%)	2 (1.9%)	
Every 6 weeks	18 (11.0%)	0 (0.0%)	7 (8.8%)	17 (16.3%)	17 (15.7%)	
Every 2 months	12 (7.3%)	0 (0.0%)	3 (3.8%)	5 (4.8%)	3 (2.8%)	
Every 3 months	75 (45.7%)	17 (40.5%)	45 (56.3%)	44 (42.3%)	48 (44.4%)	
Every 4 months[4]	5 (3.0%)	3 (7.1%)	1 (1.3%)	3 (2.9%)	3 (2.8%)	
Every 6 months	30 (18.3%)	10 (23.8%)	16 (20.0%)	19 (18.3%)	19 (17.6%)	
Once a year	4 (2.4%)	1 (2.4%)	1 (1.3%)	2 (1.9%)	3 (2.8%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Molecular monitoring during >24 months following the initiation of third-line therapy, N (%)						
Every month	1 (0.6%)	1 (2.4%)	0 (0.0%)	1 (1.0%)	1 (0.9%)	
Every 6 weeks	17 (10.4%)	0 (0.0%)	5 (6.3%)	15 (14.4%)	16 (14.8%)	
Every 2 months	10 (6.1%)	1 (2.4%)	2 (2.5%)	3 (2.9%)	3 (2.8%)	
Every 3 months	68 (41.5%)	12 (28.6%)	44 (55.0%)	41 (39.4%)	43 (39.8%)	
Every 4 months[4]	5 (3.0%)	3 (7.1%)	1 (1.3%)	3 (2.9%)	3 (2.8%)	

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
Every 6 months	39 (23.8%)	13 (31.0%)	20 (25.0%)	25 (24.0%)	23 (21.3%)	
Once a year	7 (4.3%)	3 (7.1%)	1 (1.3%)	3 (2.9%)	6 (5.6%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0%)	
Third-line therapy response						
Molecular response achieved during third-line therapy, N (%)						
Best response within 12 months following third-line therapy initiation						
BCR-ABL > 10% OR less than 1-log reduction	8 (4.9%)	4 (9.5%)	3 (3.8%)	8 (7.7%)	8 (7.4%)	
MR1: BCR-ABL ≤10% OR 1-log reduction	22 (13.4%)	3 (7.1%)	9 (11.3%)	21 (20.2%)	19 (17.6%)	
MR2: BCR-ABL ≤1% OR 2-log reduction	30 (18.3%)	10 (23.8%)	18 (22.5%)	21 (20.2%)	19 (17.6%)	
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	47 (28.7%)	12 (28.6%)	26 (32.5%)	25 (24.0%)	28 (25.9%)	
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	32 (19.5%)	6 (14.3%)	16 (20.0%)	21 (20.2%)	20 (18.5%)	
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	20 (12.2%)	6 (14.3%)	6 (7.5%)	6 (5.8%)	9 (8.3%)	
Not tested for molecular response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	5 (3.0%)	1 (2.4%)	2 (2.5%)	2 (1.9%)	5 (4.6%)	

		Reasons for termination of second-line therapy[1]				
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]	Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
Best response during entire course of third-line therapy[5]						
BCR-ABL > 10% OR less than 1-log reduction	8 (4.9%)	4 (9.5%)	3 (3.8%)	8 (7.7%)	8 (7.4%)	
MR1: BCR-ABL ≤10% OR 1-log reduction	22 (13.4%)	3 (7.1%)	9 (11.3%)	21 (20.2%)	19 (17.6%)	
MR2: BCR-ABL ≤1% OR 2-log reduction	19 (11.6%)	6 (14.3%)	11 (13.8%)	15 (14.4%)	13 (12.0%)	
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	38 (23.2%)	9 (21.4%)	22 (27.5%)	17 (16.3%)	23 (21.3%)	
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	28 (17.1%)	7 (16.7%)	11 (13.8%)	16 (15.4%)	18 (16.7%)	
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	46 (28.0%)	13 (31.0%)	23 (28.8%)	26 (25.0%)	24 (22.2%)	
Not tested for molecular response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	3 (1.8%)	0 (0.0%)	1 (1.3%)	1 (1.0%)	3 (2.8%)	
Last response during entire course of third-line therapy						
BCR-ABL > 10% OR less than 1-log reduction	14 (8.5%)	5 (11.9%)	8 (10.0%)	13 (12.5%)	12 (11.1%)	
MR1: BCR-ABL ≤10% OR 1-log reduction	30 (18.3%)	8 (19.0%)	10 (12.5%)	26 (25.0%)	26 (24.1%)	
MR2: BCR-ABL ≤1% OR 2-log reduction	15 (9.1%)	3 (7.1%)	10 (12.5%)	11 (10.6%)	10 (9.3%)	

	All patients	Reasons for termination of second-line therapy[1]		Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
		Intolerance or management of adverse events	Resistance or lack of efficacy[2]			
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	33 (20.1%)	6 (14.3%)	20 (25.0%)	16 (15.4%)	20 (18.5%)	
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	29 (17.7%)	7 (16.7%)	10 (12.5%)	14 (13.5%)	18 (16.7%)	
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	40 (24.4%)	13 (31.0%)	20 (25.0%)	23 (22.1%)	21 (19.4%)	
Not tested for molecular response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown/Not sure	3 (1.8%)	0 (0.0%)	2 (2.5%)	1 (1.0%)	1 (0.9%)	
CCyR achieved during third-line therapy, N (%)						
CCyR achieved within 12 months following third-line therapy initiation[6]						
Yes, CCyR was achieved	114 (69.5%)	26 (61.9%)	56 (70.0%)	64 (61.5%)	70 (64.8%)	
No, CCyR was not achieved	17 (10.4%)	5 (11.9%)	4 (5.0%)	15 (14.4%)	14 (13.0%)	
Not tested for cytogenetic response	31 (18.9%)	11 (26.2%)	19 (23.8%)	24 (23.1%)	23 (21.3%)	
Unknown/Not sure	2 (1.2%)	0 (0.0%)	1 (1.3%)	1 (1.0%)	1 (0.9%)	
CCyR achieved during entire course of third-line therapy[6]						
Yes, CCyR was achieved	116 (70.7%)	26 (61.9%)	57 (71.3%)	65 (62.5%)	72 (66.7%)	
No, CCyR was not achieved	15 (9.1%)	5 (11.9%)	3 (3.8%)	14 (13.5%)	12 (11.1%)	
Not tested for cytogenetic response	31 (18.9%)	11 (26.2%)	19 (23.8%)	24 (23.1%)	23 (21.3%)	
Unknown/Not sure	2 (1.2%)	0 (0.0%)	1 (1.3%)	1 (1.0%)	1 (0.9%)	

		Reasons for termination of second-line therapy[1]				
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]	Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
CHR achieved during third-line therapy, N (%)						
CHR achieved within 12 months following third-line therapy initiation[7]						
Yes, CHR was achieved	146 (89.0%)	35 (83.3%)	74 (92.5%)	91 (87.5%)	96 (88.9%)	
No, CHR was not achieved	6 (3.7%)	1 (2.4%)	2 (2.5%)	5 (4.8%)	5 (4.6%)	
Not tested for hematologic response	11 (6.7%)	6 (14.3%)	4 (5.0%)	7 (6.7%)	7 (6.5%)	
Unknown/Not sure	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	
CHR achieved during the course of third-line therapy[7]						
Yes, CHR was achieved	146 (89.0%)	35 (83.3%)	74 (92.5%)	91 (87.5%)	96 (88.9%)	
No, CHR was not achieved	6 (3.7%)	1 (2.4%)	2 (2.5%)	5 (4.8%)	5 (4.6%)	
Not tested for hematologic response	11 (6.7%)	6 (14.3%)	4 (5.0%)	7 (6.7%)	7 (6.5%)	
Unknown/Not sure	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	
Molecular response achieved after third-line therapy initiation, N (%)						
MR4.5: BCR-ABL1/ABL1 ≤0.0032% OR 4.5-log reduction						
Patients for whom the sensitivity limit of detection for BCR-ABL was MR4.5 or better[8], N (%)	128 (78.0%)	37 (88.1%)	59 (73.8%)	84 (80.8%)	84 (77.8%)	
Patients who achieved MR4.5 anytime after the initiation of third-line therapy[9,10]						

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
3 months, N (%)	2 (1.6%)	0 (0.0%)	2 (3.4%)	1 (1.2%)	1 (1.2%)	
6 months, N (%)	12 (9.4%)	3 (8.1%)	4 (6.8%)	3 (3.6%)	6 (7.1%)	
12 months, N (%)	20 (15.6%)	6 (16.2%)	6 (10.2%)	6 (7.1%)	9 (10.7%)	
18 months, N (%)	34 (26.6%)	10 (27.0%)	15 (25.4%)	16 (19.0%)	20 (23.8%)	
24 months, N (%)	36 (28.1%)	11 (29.7%)	16 (27.1%)	17 (20.2%)	21 (25.0%)	
Anytime following the initiation of third-line therapy [crude rate]	47 (36.7%)	14 (37.8%)	23 (39.0%)	26 (31.0%)	25 (29.8%)	
Patients who achieved MR4.5 or better during the course of third-line therapy[11]	46 (35.9%)	13 (35.1%)	23 (39.0%)	26 (31.0%)	24 (28.6%)	
Among patients who achieved MR4.5 or better during the course of third-line therapy, response was sustained for[11,12], N (%)						
<6 months	2 (4.3%)	0 (0.0%)	1 (4.3%)	1 (3.8%)	1 (4.2%)	
6-12 months	6 (13.0%)	0 (0.0%)	5 (21.7%)	5 (19.2%)	1 (4.2%)	
13-24 months	6 (13.0%)	2 (15.4%)	2 (8.7%)	2 (7.7%)	3 (12.5%)	
>24 months	32 (69.6%)	11 (84.6%)	15 (65.2%)	18 (69.2%)	19 (79.2%)	
KM estimates[13]						
Median time to MR4.5[14], months	0.0	0.0	0.0	0.0	0.0	0.0
Overall rate, (%) and (95% CI)	47.2 (36.9, 58.8)	44.4 (28.4, 64.4)	48.2 (33.0, 66.1)	44.5 (31.7, 59.7)	38.1 (26.5, 52.5)	36.0 (25.7, 48.8)
Patients at risk, N (%)	123 (96.1%)	36 (97.3%)	56 (94.9%)	80 (95.2%)	80 (95.2%)	82 (97.6%)
3 month-rate, (%) and (95% CI)	1.6 (0.4, 6.2)	0.0 (0.0, 0.0)	3.4 (0.9, 13.1)	1.2 (0.2, 8.2)	1.2 (0.2, 8.2)	1.2 (0.2, 8.2)
Patients at risk, N (%)	106 (82.8%)	31 (83.8%)	53 (89.8%)	71 (84.5%)	69 (82.1%)	77 (91.7%)

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
6 month-rate, (%) and (95% CI)	10.0 (5.8, 16.9)	8.7 (2.9, 24.7)	7.0 (2.7, 17.5)	3.9 (1.3, 11.5)	7.8 (3.6, 16.5)	3.6 (1.2, 10.9)
Patients at risk, N (%)	85 (66.4%)	25 (67.6%)	50 (84.7%)	59 (70.2%)	58 (69.0%)	71 (84.5%)
12 month-rate, (%) and (95% CI)	17.5 (11.6, 25.8)	18.4 (8.7, 36.6)	10.5 (4.8, 21.8)	8.4 (3.9, 17.9)	12.1 (6.5, 22.0)	7.5 (3.4, 15.9)
Patients at risk, N (%)	67 (52.3%)	19 (51.4%)	40 (67.8%)	47 (56.0%)	45 (53.6%)	60 (71.4%)
18 month-rate, (%) and (95% CI)	31.5 (23.6, 41.3)	32.6 (18.9, 52.4)	26.7 (17.0, 40.4)	24.1 (15.5, 36.4)	29.1 (19.8, 41.5)	20.6 (13.2, 31.4)
Patients at risk, N (%)	64 (50.0%)	17 (45.9%)	39 (66.1%)	46 (54.8%)	43 (51.2%)	59 (70.2%)
24 month-rate, (%) and (95% CI)	33.5 (25.4, 43.4)	36.2 (21.8, 56.0)	28.5 (18.6, 42.3)	25.7 (16.8, 38.1)	30.6 (21.1, 43.1)	21.9 (14.2, 32.9)
MR4: BCR-ABL1/ABL1 ≤0.01% OR 4-log reduction						
Patients for whom the sensitivity limit of detection for BCR-ABL was MR4 or better[8], N (%)	151 (92.1%)	39 (92.9%)	70 (87.5%)	96 (92.3%)	100 (92.6%)	
Patients who achieved MR4 anytime after the initiation of third-line therapy[9,10]						
3 months, N (%)	7 (4.6%)	3 (7.7%)	3 (4.3%)	2 (2.1%)	6 (6.0%)	
6 months, N (%)	22 (14.6%)	7 (17.9%)	7 (10.0%)	5 (5.2%)	14 (14.0%)	
12 months, N (%)	54 (35.8%)	12 (30.8%)	23 (32.9%)	27 (28.1%)	31 (31.0%)	
18 months, N (%)	67 (44.4%)	18 (46.2%)	29 (41.4%)	35 (36.5%)	41 (41.0%)	
24 months, N (%)	73 (48.3%)	18 (46.2%)	34 (48.6%)	41 (42.7%)	42 (42.0%)	
Anytime following the initiation of third-line therapy [crude rate]	78 (51.7%)	21 (53.8%)	35 (50.0%)	42 (43.8%)	46 (46.0%)	

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
Patients who achieved MR4 or better during the course of third-line therapy[11]	74 (49.0%)	20 (51.3%)	34 (48.6%)	42 (43.8%)	42 (42.0%)	
Among patients who achieved MR4 or better during the course of third-line therapy, response was sustained for[11,12], N (%)						
<6 months	5 (6.8%)	0 (0.0%)	3 (8.8%)	3 (7.1%)	3 (7.1%)	
6-12 months	9 (12.2%)	0 (0.0%)	5 (14.7%)	5 (11.9%)	1 (2.4%)	
13-24 months	13 (17.6%)	4 (20.0%)	5 (14.7%)	4 (9.5%)	8 (19.0%)	
>24 months	47 (63.5%)	16 (80.0%)	21 (61.8%)	30 (71.4%)	30 (71.4%)	
KM estimates[13]						
Median time to MR4, months	17.9	17.9	33.4	18.8	26.7	0.0
Overall rate, (%) and (95% CI)	59.1 (50.2, 68.3)	62.4 (45.4, 79.4)	52.9 (40.8, 66.1)	55.6 (44.3, 67.6)	51.0 (40.5, 62.5)	47.3 (37.4, 58.4)
Patients at risk, N (%)	141 (93.4%)	35 (89.7%)	66 (94.3%)	91 (94.8%)	91 (91.0%)	93 (96.9%)
3 month-rate, (%) and (95% CI)	4.7 (2.3, 9.6)	7.9 (2.6, 22.5)	4.3 (1.4, 12.8)	2.1 (0.5, 8.1)	6.1 (2.8, 13.1)	2.1 (0.5, 8.1)
Patients at risk, N (%)	119 (78.8%)	29 (74.4%)	61 (87.1%)	81 (84.4%)	77 (77.0%)	87 (90.6%)
6 month-rate, (%) and (95% CI)	14.4 (9.6, 21.2)	18.6 (9.3, 35.1)	10.2 (5.0, 20.2)	5.4 (2.3, 12.5)	13.4 (8.0, 22.0)	5.3 (2.2, 12.2)
Patients at risk, N (%)	73 (48.3%)	21 (53.8%)	44 (62.9%)	49 (51.0%)	51 (51.0%)	62 (64.6%)
12 month-rate, (%) and (95% CI)	38.8 (31.0, 47.7)	33.7 (20.6, 51.9)	32.5 (22.8, 45.1)	33.4 (24.2, 45.0)	33.3 (24.4, 44.4)	29.5 (21.2, 40.0)
Patients at risk, N (%)	56 (37.1%)	13 (33.3%)	37 (52.9%)	39 (40.6%)	39 (39.0%)	53 (55.2%)
18 month-rate, (%) and (95% CI)	50.1 (41.7, 59.2)	54.4 (38.2, 72.2)	42.0 (31.1, 54.7)	44.5 (34.2, 56.3)	46.7 (36.5, 58.2)	38.7 (29.5, 49.6)
Patients at risk, N (%)	48 (31.8%)	12 (30.8%)	32 (45.7%)	33 (34.4%)	36 (36.0%)	47 (49.0%)

		Reasons for termination of second-line therapy[1]				
	All patients	Intolerance or management of adverse events	Resistance or lack of efficacy[2]	Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
24 month-rate, (%) and (95% CI)	55.5 (46.9, 64.4)	54.4 (38.2, 72.2)	49.8 (38.5, 62.4)	53.0 (42.3, 64.7)	48.1 (37.8, 59.5)	45.6 (36.0, 56.5)
MR3: BCR-ABL1/ABL1 ≤0.1% OR 3-log reduction						
Patients for whom the sensitivity limit of detection for BCR-ABL was MR3 or better[8], N (%)	164 (100.0%)	42 (100.0%)	80 (100.0%)	104 (100.0%)	108 (100.0%)	
Patients who achieved MR3 anytime after the initiation of third-line therapy[9,10]						
3 months, N (%)	17 (10.4%)	5 (11.9%)	7 (8.8%)	4 (3.8%)	10 (9.3%)	
6 months, N (%)	53 (32.3%)	12 (28.6%)	19 (23.8%)	20 (19.2%)	26 (24.1%)	
12 months, N (%)	102 (62.2%)	25 (59.5%)	49 (61.3%)	53 (51.0%)	60 (55.6%)	
18 months, N (%)	112 (68.3%)	29 (69.0%)	55 (68.8%)	58 (55.8%)	66 (61.1%)	
24 months, N (%)	114 (69.5%)	30 (71.4%)	56 (70.0%)	59 (56.7%)	68 (63.0%)	
Anytime following the initiation of third-line therapy [crude rate]	115 (70.1%)	30 (71.4%)	57 (71.3%)	60 (57.7%)	68 (63.0%)	
Patients who achieved MR3 or better during the course of third-line therapy[11]	112 (68.3%)	29 (69.0%)	56 (70.0%)	59 (56.7%)	65 (60.2%)	
Among patients who achieved MR3 or better during the course of third-line therapy, response was sustained for[11,12], N (%)						
<6 months	8 (7.1%)	1 (3.4%)	6 (10.7%)	4 (6.8%)	5 (7.7%)	
6-12 months	22 (19.6%)	1 (3.4%)	16 (28.6%)	10 (16.9%)	12 (18.5%)	
13-24 months	12 (10.7%)	4 (13.8%)	4 (7.1%)	4 (6.8%)	5 (7.7%)	

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
>24 months	70 (62.5%)	23 (79.3%)	30 (53.6%)	41 (69.5%)	43 (66.2%)	
KM estimates[13]						
Median time to MR3, months	7.4	8.8	8.5	9.0	9.0	11.3
Overall rate, (%) and (95% CI)	78.8 (71.4, 85.4)	85.4 (70.5, 95.2)	74.0 (63.6, 83.4)	68.8 (58.5, 78.7)	73.7 (63.7, 82.8)	60.9 (51.3, 70.6)
Patients at risk, N (%)	142 (86.6%)	34 (81.0%)	72 (90.0%)	96 (92.3%)	93 (86.1%)	99 (95.2%)
3 month-rate, (%) and (95% CI)	10.5 (6.7, 16.3)	12.3 (5.3, 27.0)	8.8 (4.3, 17.6)	3.9 (1.5, 10.0)	9.4 (5.2, 16.8)	3.9 (1.5, 10.0)
Patients at risk, N (%)	98 (59.8%)	25 (59.5%)	58 (72.5%)	72 (69.2%)	70 (64.8%)	80 (76.9%)
6 month-rate, (%) and (95% CI)	33.5 (26.6, 41.5)	31.0 (18.9, 48.1)	24.3 (16.2, 35.4)	20.9 (14.0, 30.5)	24.6 (17.3, 34.2)	19.6 (13.1, 28.7)
Patients at risk, N (%)	40 (24.4%)	10 (23.8%)	27 (33.8%)	30 (28.8%)	28 (25.9%)	43 (41.3%)
12 month-rate, (%) and (95% CI)	67.8 (59.9, 75.4)	67.2 (51.4, 82.2)	62.7 (52.0, 73.5)	59.0 (48.7, 69.6)	62.7 (52.5, 72.9)	53.1 (43.6, 63.2)
Patients at risk, N (%)	27 (16.5%)	5 (11.9%)	20 (25.0%)	23 (22.1%)	20 (18.5%)	36 (34.6%)
18 month-rate, (%) and (95% CI)	76.1 (68.5, 83.0)	0.818046712	71.0 (60.5, 80.8)	65.9 (55.5, 76.0)	70.8 (60.7, 80.2)	58.6 (49.0, 68.4)
Patients at risk, N (%)	25 (15.2%)	4 (9.5%)	19 (23.8%)	22 (21.2%)	18 (16.7%)	35 (33.7%)
24 month-rate, (%) and (95% CI)	77.8 (70.4, 84.6)	85.4 (70.5, 95.2)	72.5 (62.0, 82.0)	67.4 (57.0, 77.3)	73.7 (63.7, 82.8)	59.7 (50.2, 69.5)
MR2: BCR-ABL1/ABL1 ≤1% OR 2-log reduction						
Patients for whom the sensitivity limit of detection for BCR-ABL was MR3 or better[8], N (%)	164 (100.0%)	42 (100.0%)	80 (100.0%)	104 (100%)	108 (100%)	
Patients who achieved MR2 anytime after the initiation of third-line therapy[9,10]						
3 months, N (%)	63 (38.4%)	15 (35.7%)	28 (35.0%)	33 (31.7%)	35 (32.4%)	

	All patients	Reasons for termination of second-line therapy[1]		Last response on 2L was MR2 or lower	No T315I on or before 3L	ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower
		Intolerance or management of adverse events	Resistance or lack of efficacy[2]			
	N= 164	N= 42	N= 80	N= 104	N= 108	N= 104
6 months, N (%)	119 (72.6%)	31 (73.8%)	59 (73.8%)	65 (62.5%)	73 (67.6%)	
12 months, N (%)	131 (79.9%)	34 (81.0%)	67 (83.8%)	73 (70.2%)	78 (72.2%)	
18 months, N (%)	133 (81.1%)	35 (83.3%)	68 (85.0%)	74 (71.2%)	80 (74.1%)	
24 months, N (%)	133 (81.1%)	35 (83.3%)	68 (85.0%)	74 (71.2%)	80 (74.1%)	
Anytime following the initiation of third-line therapy [crude rate]	133 (81.1%)	35 (83.3%)	68 (85.0%)	74 (71.2%)	80 (74.1%)	
Patients who achieved MR2 or better during the course of third-line therapy[11]	131 (79.9%)	35 (83.3%)	67 (83.8%)	74 (71.2%)	78 (72.2%)	
Among patients who achieved MR2 or better during the course of third-line therapy, response was sustained for[11,12], N (%)						
<6 months	19 (14.5%)	2 (5.7%)	12 (17.9%)	9 (12.2%)	16 (20.5%)	
6-12 months	22 (16.8%)	5 (14.3%)	13 (19.4%)	12 (16.2%)	10 (12.8%)	
13-24 months	13 (9.9%)	2 (5.7%)	7 (10.4%)	5 (6.8%)	5 (6.4%)	
>24 months	77 (58.8%)	26 (74.3%)	35 (52.2%)	48 (64.9%)	47 (60.3%)	
KM estimates[13]						
Median time to MR2, months	3.1	3.1	3.2	3.6	3.2	3.9
Overall rate, (%) and (95% CI)	86.2 (79.4, 91.6)	93.4 (77.2, 99.3)	86.2 (77.3, 92.8)	78.3 (68.8, 86.6)	79.1 (69.6, 87.2)	73.0 (64.0, 81.3)
Patients at risk, N (%)	98 (59.8%)	26 (61.9%)	51 (63.8%)	68 (65.4%)	70 (64.8%)	70 (67.3%)
3 month-rate, (%) and (95% CI)	38.7 (31.7, 46.6)	36.0 (23.5, 52.5)	35.3 (25.9, 46.8)	32.2 (24.0, 42.1)	32.7 (24.7, 42.5)	31.9 (23.9, 41.9)
Patients at risk, N (%)	36 (22.0%)	9 (21.4%)	19 (23.8%)	30 (28.8%)	27 (25.0%)	35 (33.7%)
6 month-rate, (%) and (95% CI)	74.5 (67.4, 81.1)	76.3 (62.3, 88.0)	75.2 (65.2, 84.1)	65.7 (56.2, 75.0)	69.8 (60.6, 78.5)	63.5 (54.2, 72.7)

		Reasons for termination of second-line therapy[1]				
	All patients	**Intolerance or management of adverse events**	**Resistance or lack of efficacy[2]**	**Last response on 2L was MR2 or lower**	**No T315I on or before 3L**	**ITT sensitivity analysis[15]: Last response on 2L was MR2 or lower**
	N= 164	**N= 42**	**N= 80**	**N= 104**	**N= 108**	**N= 104**
Patients at risk, N (%)	15 (9.1%)	3 (7.1%)	10 (12.5%)	13 (12.5%)	14 (13.0%)	24 (23.1%)
12 month-rate, (%) and (95% CI)	83.8 (77.0, 89.4)	86.8 (72.7, 95.8)	84.6 (75.6, 91.6)	76.5 (67.1, 84.9)	75.5 (66.2, 83.8)	71.8 (62.8, 80.3)
Patients at risk, N (%)	11 (6.7%)	1 (2.4%)	9 (11.3%)	11 (10.6%)	11 (10.2%)	23 (22.1%)
18 month-rate, (%) and (95% CI)	86.2 (79.4, 91.6)	93.4 (77.2, 99.3)	86.2 (77.3, 92.8)	78.3 (68.8, 86.6)	79.1 (69.6, 87.2)	73.0 (64.0, 81.3)
Patients at risk, N (%)	11 (6.7%)	1 (2.4%)	9 (11.3%)	11 (10.6%)	11 (10.2%)	23 (22.1%)
24 month-rate, (%) and (95% CI)	86.2 (79.4, 91.6)	93.4 (77.2, 99.3)	86.2 (77.3, 92.8)	78.3 (68.8, 86.6)	79.1 (69.6, 87.2)	73.0 (64.0, 81.3)

3L: third-line; BCR-ABL: break point cluster region - Abelson; CCyR: complete cytogenetic response; CI: confidence interval; CHR: complete hematologic response; CML: chronic myeloid leukemia; CP: chronic phase; ITT: intent-to-treat; KM: Kaplan-Meier; MR: molecular response; Ph+: Philadelphia chromosome positive; SD: standard deviation; TKI: tyrosine kinase inhibitors

Notes:

[1] Physicians could select more than one reason for termination of second-line therapy (not mutually exclusive).

[2] The resistance or lack of efficacy subgroup includes patients for whom physicians reported Resistance and/or Lack of efficacy as a reason for termination of second-line therapy.

[3] Patients were required to have ≥24 months of follow-up following the initiation of third-line therapy, unless they died before.

[4] Molecular monitoring every 4 months was not an option in the question, but one physician reported conducting molecular monitoring every 4 months.

[5] Best response during course of therapy was re-coded when level of best response within first 12 months or level of last response was superior to that of best response during course of therapy.

[6] A complete cytogenetic response indicates that no Ph+ metaphases are present in the sample.
Source: National Comprehensive Cancer Network (NCCN) guidelines

[7] A complete hematologic response was defined as: 1. Complete normalization of peripheral blood counts with leukocyte count $<10x10^9$/L; 2. Platelet count $<450x10^9$/L; 3. No immature cells in peripheral blood samples; 4. No palpable splenomegaly.
Source: National Comprehensive Cancer Network (NCCN) guidelines

[8] The sensitivity level of detection was defined as the most precise sensitivity level of detection for BCR-ABL1/ABL1 reported following the initiation of third-line therapy. If the sensitivity following the initiation of third-line therapy was not reported, the most precise of the current sensitivity level of detection and the sensitivity level of detection between January 1st, 2013 and November 30th, 2018 was used.

[9] Only molecular response reported with a correspondingly similar or higher sensitivity level of detection are reported.

[10] The molecular responses were assessed from the third-line therapy initiation to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

[11] The molecular responses were assessed from the third-line therapy initiation to i) end of third-line therapy, ii) death, iii) last date for which the physician had complete care information, or iv) data collection date, whichever occured first.

[12] If a patient reached a given molecular response level and lower molecular response levels are not reported, the duration that the response was sustained for was imputed the lower molecular response based on the information reported for the higher molecular response.

[13] Patients were censored at i) end of third-line therapy, ii) death, iii) last date for which the physician had complete care information, iv) data collection date, v) date of progression to AP/BC or vi) date of HSCT, whichever occured first.

[14] A median time of zero indicates that less than 50% of patients reached the level of molecular response.

[15] The sensitivity analysis used an intent-to-treat approach where patients were censored at i) death, ii) last date for which the physician had complete care information, iii) data collection date, iv) date of progression to AP/BC or v) date of HSCT, whichever occured first.

[8] The sensitivity level of detection was defined as the most precise sensitivity level of detection for BCR-ABL1/ABL1 reported following the initiation of third-line therapy. If the sensitivity following the initiation of third-line therapy was not reported, the most precise of the current sensitivity level of detection and the sensitivity level of detection between January 1st, 2013 and November 30th, 2018 was used.

[9] Only molecular response reported with a correspondingly similar or higher sensitivity level of detection are reported.

[10] The molecular responses were assessed from the third-line therapy initiation to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

[11] The molecular responses were assessed from the third-line therapy initiation to i) end of third-line therapy, ii) death, iii) last date for which the physician had complete care information, or iv) data collection date, whichever occured first.

[12] If a patient reached a given molecular response level and lower molecular response levels are not reported, the duration that the response was sustained for was imputed the lower molecular response based on the information reported for the higher molecular response.

[13] Patients were censored at i) end of third-line therapy, ii) death, iii) last date for which the physician had complete care information, iv) data collection date, v) date of progression to AP/BC or vi) date of HSCT, whichever occured first.

[14] A median time of zero indicates that less than 50% of patients reached the level of molecular response.

[15] The sensitivity analysis used an intent-to-treat approach where patients were censored at i) death, ii) last date for which the physician had complete care information, iii) data collection date, iv) date of progression to AP/BC or v) date of HSCT, whichever occured first.

3L cohort Mutation testing

	Across all lines N= 164	First-line N= 164	Second-line N= 164	Third-line N= 164
Mutation testing was performed on or before the initiation of the line of therapy[1], N (%)	416 (81.6%)	113 (68.9%)	136 (82.9%)	151 (92.1%)
Unknown mutation profile testing status on or before the initiation of the line of therapy[2], N (%)	17 (3.3%)	10 (6.1%)	7 (4.3%)	0 (0.0%)
BCR-ABL1/ABL1 mutation testing among patients for whom previous line of therapy was terminated because of resistance or lack of efficacy, N (%)	180 (35.3%)		93 (56.7%)	80 (48.8%)
Testing performed[1]	155 (86.1%)		75 (80.6%)	73 (91.3%)
Testing not performed[3]	19 (10.6%)		12 (12.9%)	7 (8.8%)
Unknown/Not sure[2]	6 (3.3%)		6 (6.5%)	0 (0.0%)
BCR-ABL1/ABL1 mutation testing among patients for whom MR2 was not achieved within 12 months following previous line of therapy initiation, N (%)	110 (21.6%)		62 (37.8%)	42 (25.6%)
Testing performed[1]	97 (88.2%)		52 (83.9%)	40 (95.2%)
Testing not performed[3]	9 (8.2%)		6 (9.7%)	2 (4.8%)
Unknown/Not sure[2]	4 (3.6%)		4 (6.5%)	0 (0.0%)

MR: molecular response

Notes:

[1] Physicians reported one of the following on or before the initiation of the line of therapy: A- ≥1 BCR-ABL1 mutations other than T315I, B- no BCR-ABL1 mutations other than T315I, C- T315I mutation, D- testing was performed on a previous line of therapy, but T315I mutation was not detected.

[2] Physicians reported that the BCR-ABL1 mutations testing status on or before the initiation of the line of therapy was unknown, and no BCR-ABL1 mutations testing was reported for a previous line of therapy.

[3] Physicians reported that no BCR-ABL1 mutations testing was performed on or before the initiation of the line of therapy, and no BCR-ABL1 mutations testing was reported for a previous line of therapy.

NOVARTIS

T315I Outcome data

Data were abstracted for 128 patients who received a 3L for Ph+ CML-CP.

- 76 charts (59.4%) for which 2L was identified as the T315I line of interest
- 51 charts (39.8%) for which 3L was identified as the T315I line of interest

Treatment patterns by line of therapy

	Across all lines	Line identified as the T315I line of interest	First-line	Second-line	Third-line
	N= 128	N= 128	N= 128	N= 128	N= 93
Description of line of therapy					
Number of lines of therapy					
Mean [SD]	2.8 [0.5]				
Median	3.0				
Range	[2.0, 5.0]				
≥2 lines of therapy, N (%)	128 (100.0%)				
≥3 lines of therapy, N (%)	93 (72.7%)				
≥4 lines of therapy, N (%)	5 (3.9%)				
≥5 lines of therapy, N (%)	1 (0.8%)				
≥6 lines of therapy, N (%)	0 (0.0%)				
Total number of lines, N	355				
Line identified as the T315I line of interest[1], N (%)				76 (59.4%)	51 (54.8%)

	Across all lines	Line identified as the T315I line of interest	First-line	Second-line	Third-line
	N= 128	N= 128	N= 128	N= 128	N= 93
Treatment received, N (%)					
Imatinib	90 (25.4%)	2 (1.6%)	86 (67.2%)	3 (2.3%)	1 (1.1%)
In combination with hydroxyurea	9 (2.5%)	0 (0.0%)	9 (7.0%)	0 (0.0%)	0 (0.0%)
Dasatinib	71 (20.0%)	20 (15.6%)	23 (18.0%)	45 (35.2%)	3 (3.2%)
In combination with hydroxyurea	7 (2.0%)	4 (3.1%)	3 (2.3%)	4 (3.1%)	0 (0.0%)
Nilotinib	36 (10.1%)	7 (5.5%)	12 (9.4%)	15 (11.7%)	8 (8.6%)
In combination with hydroxyurea	4 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	3 (3.2%)
Bosutinib	34 (9.6%)	9 (7.0%)	2 (1.6%)	23 (18.0%)	9 (9.7%)
In combination with hydroxyurea	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Ponatinib	106 (29.9%)	87 (68.0%)	0 (0.0%)	40 (31.3%)	64 (68.8%)
In combination with hydroxyurea	5 (1.4%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	5 (5.4%)
Omacetaxine	8 (2.3%)	2 (1.6%)	0 (0.0%)	1 (0.8%)	7 (7.5%)
In combination with hydroxyurea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Interferon	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
In combination with hydroxyurea	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hydroxyurea	8 (2.3%)	1 (0.8%)	5 (3.9%)	1 (0.8%)	1 (1.1%)
Calendar year of line of therapy initiation, N (%)					
2001-2004	1 (0.3%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
2005-2008	2 (0.6%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)
2009-2012	13 (3.7%)	0 (0.0%)	13 (10.2%)	0 (0.0%)	0 (0.0%)
2013-2016	206 (58.0%)	55 (43.0%)	100 (78.1%)	78 (60.9%)	28 (30.1%)
2017-2021	133 (37.5%)	73 (57.0%)	13 (10.2%)	49 (38.3%)	65 (69.9%)
Duration of line of therapy[2], months					

	Across all lines N= 128	Line identified as the T315I line of interest N= 128	First-line N= 128	Second-line N= 128	Third-line N= 93
Mean [SD]	22.6 [19.7]	27.7 [20.1]	17.1 [16.8]	19.6 [16.9]	34.7 [22.1]
Median	14.4	30.2	12.1	13.4	31.6
Range	[0.1, 97.0]	[1.6, 87.3]	[1.0, 93.3]	[0.1, 82.7]	[2.8, 97.0]
Most frequent treatment sequences					
Treatment sequence, N (%)					
Imatinib, dasatinib, ponatinib	21 (16.4%)				
Imatinib, bosutinib, ponatinib	11 (8.6%)				
Dasatinib, ponatinib	10 (7.8%)				
Imatinib, nilotinib, ponatinib	8 (6.3%)				
Nilotinib, ponatinib	8 (6.3%)				
Dasatinib, bosutinib, ponatinib	6 (4.7%)				
Imatinib, ponatinib, bosutinib	6 (4.7%)				
Imatinib, dasatinib	5 (3.9%)				
Imatinib, ponatinib	4 (3.1%)				
Imatinib and hydroxyurea, dasatinib, ponatinib	3 (2.3%)				
Death, progression to AP/BC[3] or HSCT					
Patients who died after initiation of the line identified as the T315I line of interest, N (%)					
Anytime following the initiation of the line identified as the T315I line of interest	14 (10.9%)				
During the course of the line identified as the T315I line of interest	5 (3.9%)				
Patients who progressed to AP/BC after initiation of the line identified as the T315I line of interest[3], N (%)					

	Across all lines	Line identified as the T315I line of interest	First-line	Second-line	Third-line
	N= 128	N= 128	N= 128	N= 128	N= 93
Anytime following the initiation of the line identified as the T315I line of interest	6 (4.7%)				
During the course of the line identified as the T315I line of interest	1 (0.8%)				
Patients who underwent HSCT after initiation of the the line identified as the T315I line of interest, N (%)					
Anytime following the initiation of the line identified as the T315I line of interest	2 (1.6%)				
During the course of the line identified as the T315I line of interest	1 (0.8%)				
Patients developed graft versus host disease after undergoing HSCT[4], N (%)					
Patients had <3 months of follow-up following HSCT[5]	0 (0.0%)				
Patients had 3 to <6 months of follow-up following HSCT[5]	0 (0.0%)				
Patients had ≥6 months of follow-up following HSCT[5]	0 (0.0%)				
Patients who were still on the line identified as the T315I line of interest as of the data collection date, N (%)	64 (50.0%)				

AP: accelerated phase; BC: blast crisis; HSCT: hematopoietic stem cell transplant; SD: standard deviation

Notes:

[1] Physicians identified the line of therapy corresponding to the T315I line of interest. The line during which the T315I mutation was detected is not necessarily the line identified as the T315I line of interest (i.e., the T315I mutation was detected at the end of second-line therapy but the physician identified the third line as the T315I line of interest).

[2] The duration of the line of therapy was measured from the initiation of the line of therapy to i) end of the line of therapy, ii) death, iii) last date for which the physician had complete care information, or iv) data collection date (ie. patient was still on the line of therapy at data collection), whichever occured first.

[3] An accelerated phase was defined as: 1. Peripheral blood myeloblasts ≥15% and <30%; 2. With peripheral blood myeloblasts and promyelocytes combined ≥30%; 3. Peripheral blood basophils ≥20%; 4. Platelet count ≤100 x 10^9/L unrelated to therapy; 5. Additional clonal cytogenetic abnormalities in Ph+ cells.
Source: National Comprehensive Cancer Network (NCCN) guidelines referencing the modified criteria used at MD Anderson Cancer Center

A blast crisis was defined as: 1. ≥30% blasts in the blood, marrow, or both; 2. Extramedullary infiltrates of leukemic cells.
Source: National Comprehensive Cancer Network (NCCN) guidelines referencing the International Bone Marrow Transplant Registry

[4] Graft versus host disease information was collected for the full launch only. The 25 patient charts collected during the soft launch were excluded for this analysis.

[5] The duration of follow-up was measured from the HSCT date to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

Mutation testing

	Across all lines	Line identified as the T315I line of interest	First-line	Second-line	Third-line
	N= 128	N= 128	N= 128	N= 128	N= 93
Mutation testing was performed on or before the initiation of the line of therapy[1], N (%)	317 (89.3%)	128 (100.0%)	100 (78.1%)	118 (92.2%)	93 (100.0%)
Unknown mutation profile testing status on or before the initiation of the line of therapy[2], N (%)	4 (1.1%)	0 (0.0%)	3 (2.3%)	1 (0.8%)	0 (0.0%)
BCR-ABL1/ABL1 mutation testing among patients for whom previous line of therapy was terminated because of resistance or lack of efficacy, N (%)	133 (37.5%)	78 (60.9%)		75 (58.6%)	55 (43.0%)
Testing performed[1]	126 (94.7%)	78 (60.9%)		68 (90.7%)	55 (100.0%)
Testing not performed[3]	6 (4.5%)	0 (0.0%)		6 (8.0%)	0 (0.0%)
Unknown/Not sure[2]	1 (0.8%)	0 (0.0%)		1 (1.3%)	0 (0.0%)
BCR-ABL1/ABL1 mutation testing among patients for whom MR2 was not achieved within 12 months following previous line of therapy initiation, N (%)	98 (27.6%)	55 (43.0%)		64 (50.0%)	31 (24.2%)

	Across all lines	Line identified as the T315I line of interest	First-line	Second-line	Third-line
	N= 128	N= 128	N= 128	N= 128	N= 93
Testing performed[1]	94 (95.9%)	55 (100.0%)		60 (93.8%)	31 (100.0%)
Testing not performed[3]	3 (3.1%)	0 (0.0%)		3 (4.7%)	0 (0.0%)
Unknown/Not sure[2]	1 (1.0%)	0 (0.0%)		1 (1.6%)	0 (0.0%)

MR: molecular response

Notes:

[1] Physicians reported one of the following on or before the initiation of the line of therapy: A- ≥1 BCR-ABL1 mutations other than T315I, B- no BCR-ABL1 mutations other than T315I, C- T315I mutation, D- testing was performed on a previous line of therapy, but T315I mutation was not detected.

[2] Physicians reported that the BCR-ABL1 mutations testing status on or before the initiation of the line of therapy was unknown, and no BCR-ABL1 mutations testing was reported for a previous line of therapy.

[3] Physicians reported that no BCR-ABL1 mutations testing was performed on or before the initiation of the line of therapy, and no BCR-ABL1 mutations testing was reported for a previous line of therapy.

Response on the line of therapy identified as the T315I line of interest[1]

	All patients N= 128
Molecular monitoring frequency following the initiation of the line of therapy identified as the T315I line of interest	
Molecular monitoring during 0-6 months following the initiation of the line of therapy identified as the T315I line of interest, N (%)	
Every month	14 (10.9%)
Every 6 weeks	11 (8.6%)
Every 2 months	19 (14.8%)
Every 3 months	76 (59.4%)
Every 6 months	6 (4.7%)
Other	0 (0.0%)
Unknown/Not sure	0 (0.0%)
Molecular monitoring during 7-12 months following the initiation of the line of therapy identified as the T315I line of interest, N (%)	
Every month	8 (6.3%)
Every 6 weeks	13 (10.2%)
Every 2 months	15 (11.7%)
Every 3 months	79 (61.7%)
Every 6 months	8 (6.3%)
Other	0 (0.0%)
Unknown/Not sure	0 (0.0%)
Molecular monitoring during 13-24 months following the initiation of the line of therapy identified as the T315I line of interest, N (%)	
Every month	1 (0.8%)
Every 6 weeks	16 (12.5%)
Every 2 months	14 (10.9%)
Every 3 months	67 (52.3%)
Every 4 months[3]	5 (3.9%)
Every 6 months	14 (10.9%)
Once a year	2 (1.6%)
Other	0 (0.0%)
Unknown/Not sure	0 (0.0%)
Molecular monitoring during >24 months following the initiation of the line of therapy identified as the T315I line of interest, N (%)	
Every month	0 (0.0%)
Every 6 weeks	16 (12.5%)
Every 2 months	12 (9.4%)
Every 3 months	56 (43.8%)
Every 4 months[3]	5 (3.9%)

	All patients N= 128
Every 6 months	27 (21.1%)
Once a year	2 (1.6%)
Other	0 (0.0%)
Unknown/Not sure	1 (0.8%)
Response during the line of therapy identified as the T315I line of interest	
Molecular response achieved during the line of therapy identified as the T315I line of interest, N (%)	
Best response within 12 months following initiation of the line of therapy identified as the T315I line of interest	
BCR-ABL > 10% OR less than 1-log reduction	0 (0.0%)
MR1: BCR-ABL ≤10% OR 1-log reduction	18 (14.1%)
MR2: BCR-ABL ≤1% OR 2-log reduction	32 (25.0%)
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	40 (31.3%)
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	17 (13.3%)
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	18 (14.1%)
Not tested for molecular response	0 (0.0%)
Unknown/Not sure	3 (2.3%)
Best response during entire course of the line of therapy identified as the T315I line of interest[4]	
BCR-ABL > 10% OR less than 1-log reduction	0 (0.0%)
MR1: BCR-ABL ≤10% OR 1-log reduction	18 (14.1%)
MR2: BCR-ABL ≤1% OR 2-log reduction	28 (21.9%)
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	27 (21.1%)
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	17 (13.3%)
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	37 (28.9%)
Not tested for molecular response	0 (0.0%)
Unknown/Not sure	1 (0.8%)
Last response during entire course of the line of therapy identified as the T315I line of interest	
BCR-ABL > 10% OR less than 1-log reduction	8 (6.3%)
MR1: BCR-ABL ≤10% OR 1-log reduction	29 (22.7%)
MR2: BCR-ABL ≤1% OR 2-log reduction	15 (11.7%)
MR3: BCR-ABL ≤ 0.1% OR 3-log reduction	26 (20.3%)
MR4: BCR-ABL≤ 0.01% OR 4-log reduction	15 (11.7%)
MR4.5: BCR-ABL ≤ 0.0032% OR 4.5-log reduction	31 (24.2%)
Not tested for molecular response	0 (0.0%)
Unknown/Not sure	4 (3.1%)

	All patients N= 128
CCyR achieved during the line of therapy identified as the T315I line of interest, N (%)	
CCyR achieved within 12 months following initiation of the line of therapy identified as the T315I line of interest[5]	
Yes, CCyR was achieved	98 (76.6%)
No, CCyR was not achieved	7 (5.5%)
Not tested for cytogenetic response	22 (17.2%)
Unknown/Not sure	1 (0.8%)
CCyR achieved during entire course of the line of therapy identified as the T315I line of interest[5]	
Yes, CCyR was achieved	98 (76.6%)
No, CCyR was not achieved	7 (5.5%)
Not tested for cytogenetic response	22 (17.2%)
Unknown/Not sure	1 (0.8%)
CHR achieved during the line of therapy identified as the T315I line of interest, N (%)	
CHR achieved within 12 months following initiation of the line of therapy identified as the T315I line of interest[6]	
Yes, CHR was achieved	118 (92.2%)
No, CHR was not achieved	3 (2.3%)
Not tested for hematologic response	6 (4.7%)
Unknown/Not sure	1 (0.8%)
CHR achieved during the course of the line of therapy identified as the T315I line of interest[6]	
Yes, CHR was achieved	118 (92.2%)
No, CHR was not achieved	3 (2.3%)
Not tested for hematologic response	6 (4.7%)
Unknown/Not sure	1 (0.8%)
Molecular response achieved after initiation of the line of therapy identified as the T315I line of interest, N (%)	
MR4.5: BCR-ABL1/ABL1 ≤0.0032% OR 4.5-log reduction	
Patients for whom the sensitivity limit of detection for BCR-ABL was MR4.5 or better[7], N (%)	107 (83.6%)
Patients who achieved MR4.5 anytime after the initiation of the line of therapy identified as the T315I line of interest[8,9]	
3 months, N (%)	1 (0.9%)
6 months, N (%)	8 (7.5%)
12 months, N (%)	18 (16.8%)
18 months, N (%)	23 (21.5%)
24 months, N (%)	27 (25.2%)

	All patients N= 128
Anytime following the initiation of the line of therapy identified as the T315I line of interest [crude rate]	43 (40.2%)
Among patients who achieved MR4.5 or better during the course of the line of therapy identified as the T315I line of interest[10]	37 (34.6%)
Duration of sustained response[11], N (%)	
<6 months	1 (2.7%)
6-12 months	11 (29.7%)
13-24 months	3 (8.1%)
>24 months	21 (56.8%)
Unknown[12]	1 (2.7%)
KM estimates[13]	
Median time to MR4.5, months[13]	39.8
Overall rate, (%) and (95% CI)	54.3 (40.2, 69.6)
Patients at risk, N (%)	100 (93.5%)
3 month-rate, (%) and (95% CI)	1.0 (0.1, 6.8)
Patients at risk, N (%)	84 (78.5%)
6 month-rate, (%) and (95% CI)	8.3 (4.2, 15.9)
Patients at risk, N (%)	63 (58.9%)
12 month-rate, (%) and (95% CI)	20.4 (13.3, 30.5)
Patients at risk, N (%)	47 (43.9%)
18 month-rate, (%) and (95% CI)	27.3 (18.9, 38.3)
Patients at risk, N (%)	44 (41.1%)
24 month-rate, (%) and (95% CI)	31.9 (22.8, 43.5)
MR4: BCR-ABL1/ABL1 ≤0.01% OR 4-log reduction	
Patients for whom the sensitivity limit of detection for BCR-ABL was MR4 or better[7], N (%)	121 (94.5%)
Patients who achieved MR4 anytime after the initiation of the line of therapy identified as the T315I line of interest[8,9]	
3 months, N (%)	1 (0.8%)
6 months, N (%)	13 (10.7%)
12 months, N (%)	36 (29.8%)
18 months, N (%)	44 (36.4%)
24 months, N (%)	57 (47.1%)
Anytime following the initiation of the line of therapy identified as the T315I line of interest [crude rate]	60 (49.6%)
Among patients who achieved MR4 or better during the course of the line of therapy identified as the T315I line of interest[10]	54 (44.6%)
Duration of sustained response[11], N (%)	
<6 months	7 (13.0%)

	All patients N= 128
6-12 months	12 (22.2%)
13-24 months	10 (18.5%)
>24 months	24 (44.4%)
Unknown[12]	1 (1.9%)
KM estimates[13]	
Median time to MR4, months	18.7
Overall rate, (%) and (95% CI)	62.2 (51.2, 73.2)
Patients at risk, N (%)	114 (94.2%)
3 month-rate, (%) and (95% CI)	0.8 (0.1, 5.9)
Patients at risk, N (%)	91 (75.2%)
6 month-rate, (%) and (95% CI)	11.9 (7.1, 19.7)
Patients at risk, N (%)	58 (47.9%)
12 month-rate, (%) and (95% CI)	35.2 (26.6, 45.5)
Patients at risk, N (%)	40 (33.1%)
18 month-rate, (%) and (95% CI)	44.4 (34.8, 55.3)
Patients at risk, N (%)	29 (24.0%)
24 month-rate, (%) and (95% CI)	59.7 (49.2, 70.4)
MR3: BCR-ABL1/ABL1 ≤0.1% OR 3-log reduction	
Patients for whom the sensitivity limit of detection for BCR-ABL was MR3 or better[7], N (%)	128 (100.0%)
Patients who achieved MR3 anytime after the initiation of the line of therapy identified as the T315I line of interest[8,9]	
3 months, N (%)	10 (7.8%)
6 months, N (%)	39 (30.5%)
12 months, N (%)	77 (60.2%)
18 months, N (%)	84 (65.6%)
24 months, N (%)	85 (66.4%)
Anytime following the initiation of the line of therapy identified as the T315I line of interest [crude rate]	88 (68.8%)
Among patients who achieved MR3 or better during the course of the line of therapy identified as the T315I line of interest[10]	81 (63.3%)
Duration of sustained response[11], N (%)	
<6 months	8 (9.9%)
6-12 months	24 (29.6%)
13-24 months	15 (18.5%)
>24 months	33 (40.7%)
Unknown[12]	1 (1.2%)
KM estimates[13]	

	All patients N= 128
Median time to MR3, months	8.5
Overall rate, (%) and (95% CI)	75.2 (66.1, 83.5)
Patients at risk, N (%)	112 (87.5%)
3 month-rate, (%) and (95% CI)	8.0 (4.4, 14.3)
Patients at risk, N (%)	75 (58.6%)
6 month-rate, (%) and (95% CI)	33.3 (25.5, 42.7)
Patients at risk, N (%)	32 (25.0%)
12 month-rate, (%) and (95% CI)	67.6 (58.6, 76.3)
Patients at risk, N (%)	17 (13.3%)
18 month-rate, (%) and (95% CI)	73.6 (64.6, 81.9)
Patients at risk, N (%)	17 (13.3%)
24 month-rate, (%) and (95% CI)	73.6 (64.6, 81.9)
MR2: BCR-ABL1/ABL1 ≤1% OR 2-log reduction	
Patients for whom the sensitivity limit of detection for BCR-ABL was MR3 or better[7], N (%)	128 (100.0%)
Patients who achieved MR2 anytime after the initiation of the line of therapy identified as the T315I line of interest[8,9]	
3 months, N (%)	46 (35.9%)
6 months, N (%)	92 (71.9%)
12 months, N (%)	107 (83.6%)
18 months, N (%)	109 (85.2%)
24 months, N (%)	109 (85.2%)
Anytime following the initiation of the line of therapy identified as the T315I line of interest [crude rate]	110 (85.9%)
Among patients who achieved MR2 or better during the course of the line of therapy identified as the T315I line of interest[10]	109 (85.2%)
Duration of sustained response[11], N (%)	
<6 months	16 (14.7%)
6-12 months	29 (26.6%)
13-24 months	17 (15.6%)
>24 months	46 (42.2%)
Unknown[12]	1 (0.9%)
KM estimates[13]	
Median time to MR2, months	3.1
Overall rate, (%) and (95% CI)	95.9 (89.1, 99.0)
Patients at risk, N (%)	76 (59.4%)
3 month-rate, (%) and (95% CI)	36.6 (28.8, 45.6)
Patients at risk, N (%)	25 (19.5%)

	All patients N= 128
6 month-rate, (%) and (95% CI)	77.1 (69.0, 84.3)
Patients at risk, N (%)	8 (6.3%)
12 month-rate, (%) and (95% CI)	91.8 (85.6, 96.1)
Patients at risk, N (%)	2 (1.6%)
18 month-rate, (%) and (95% CI)	95.9 (89.1, 99.0)
Patients at risk, N (%)	2 (1.6%)
24 month-rate, (%) and (95% CI)	95.9 (89.1, 99.0)

BCR-ABL: break point cluster region - Abelson; CCyR: complete cytogenetic response; CI: confidence interval; CHR: complete hematologic response; CML: chronic myeloid leukemia; CP: chronic phase; KM: Kaplan-Meier; MR: molecular response; Ph+: Philadelphia chromosome positive; SD: standard deviation; TKI: tyrosine kinase inhibitors

Notes:

[1] Physicians identified the line of therapy corresponding to the T315I line of interest. The line during which the T315I mutation was detected is not necessarily the line identified as the T315I line of interest (i.e., the T315I mutation was detected at the end of second-line therapy but the physician identified the third line as the T315I line of interest).

[2] Patients were required to have ≥24 months of follow-up following the initiation of the line identified as the T315I line of interest, unless they died before.

[3] Molecular monitoring every 4 months was not an option in the question, but one physician reported conducting molecular monitoring every 4 months.

[4] Best response during course of therapy was re-coded when level of best response within first 12 months or level of last response was superior to that of best response during course of therapy.

[5] A complete cytogenetic response indicates that no Ph+ metaphases are present in the sample.
Source: National Comprehensive Cancer Network (NCCN) guidelines

[6] A complete hematologic response was defined as: 1. Complete normalization of peripheral blood counts with leukocyte count $<10x10^9$/L; 2. Platelet count $<450x10^9$/L; 3. No immature cells in peripheral blood samples; 4. No palpable splenomegaly.
Source: National Comprehensive Cancer Network (NCCN) guidelines

[7] The sensitivity level of detection was defined as the most precise sensitivity level of detection for BCR-ABL1/ABL1 reported following the initiation of the line identified as the T315I line of interest. If the sensitivity following the initiation of the line identified as the T315I line of interest, the most precise of the current sensitivity level of detection and the sensitivity level of detection between January 1st, 2013 and November 30th, 2018 was used.

[8] Only molecular response reported with a correspondingly similar or higher sensitivity level of detection are reported.

[9] The molecular responses were assessed from the initiation of the line identified as the T315I line of interest to i) death, ii) last date for which the physician had complete care information, or iii) data collection date, whichever occured first.

[10] The molecular responses were assessed from initiation of the line identified as the T315I line of interest to i) end of the T315I line of interest, ii) death, iii) last date for which the physician had complete care information, or iv) data collection date, whichever occured first.

[11] If a patient reached a given molecular response level and lower molecular response levels are not reported, the duration that the response was sustained for was imputed the lower molecular response based on the information reported for the higher molecular response.

[12] The "unknown" option was not included in the original survey. Upon recontact, one physician provided the date of molecular response for one patient but not the duration of sustained response.

[13] Patients were censored at i) end of line of therapy identified as the T315I line of interest, ii) death, iii) last date for which the physician had complete care information, iv) data collection date, v) date of progression to AP/BC or vi) date of HSCT, whichever occured first.

Safety Results
Not applicable.

Other Relevant Findings
NA

Conclusion
The results of the analyses highlight the unmet treatment needs in earlier and later lines of therapy, as well as compliance with NCCN mutation testing guidelines. A sizeable proportion of patients were observed with short earlier lines of therapy and reasons for termination including lack of efficacy, resistance, and intolerance. Most patients also did not achieve MR3 or better within 12 months after initiation of first- and second-line therapies. As treatment repeatedly failed, patients exhausted their treatment options, leading to a high percentage of patients receiving a 3G TKI as third-line therapy. A large proportion of patients—both in the overall sample and across all subgroups of interest—did not reach important treatment milestones during later lines of therapy. Over 90% of patients were tested for BCR-ABL/ABL1 mutations prior to third line TKI therapy; in just a few cases, the third line TKI therapy was not recommended based on the mutation profile.

Patients with CML-CP in 3L+ have rapidly cycled between first-generation TKI and second-generation TKI in 1L and 2L. Rates of MR3 did not improve between earlier lines, with lack of efficacy/resistance being the most important reasons for discontinuation; intolerance became more prevalent in 2L. Findings highlight the need for novel therapeutics with improved safety/efficacy to prolong treatment in earlier lines and for patients in later lines who exhaust treatment options quickly.

Date of Clinical Study Report
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