

## Treatment outcome in a population-based, ‘real-world’ cohort of patients with chronic myeloid leukemia

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## Supplementary information

### Treatment outcome in a population based 'real-world' cohort of chronic myeloid leukemia patients

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## **Supplementary results**

### TKI intolerance

Considering all treatment lines for analysis, side effects were reported in 177/305 patients treated with imatinib (58%), 58/139 patients treated with nilotinib (42%) and 61/116 patients treated with dasatinib (53%) in any line. Cytopenia (in particular thrombocytopenia), fatigue and infections were reported frequently (>5%) during all three forms of treatment (supplemental table S2). Gastrointestinal complaints (in particular diarrhea) were far more common in patients treated with imatinib and dasatinib, whereas rash was more often observed during imatinib and nilotinib treatment. Imatinib showed high rates of fluid retention (both superficial and periorbital) and musculoskeletal symptoms, while pleural effusion was observed frequently during dasatinib treatment. Lastly, cardiovascular events were observed at a high rate (5.8%) during nilotinib treatment. Actions following the different adverse events are shown in supplemental table S2.

## Supplementary tables

**SI table S1.** Events, competing risks and censors per cumulative incidence competing risk analysis.

Analysis	Event	Competing risk	Censor
Time to CCyR (Overall)	First CCyR	- Death - Progression	- End of follow up without event or competing risk
Time to CCyR (On initial treatment)	First CCyR on first line treatment	- Death - Progression - First line TKI discontinuation without CCyR achievement	- End of follow up without event or competing risk
Time to MMR (Overall)	First MMR	- Death - Progression	- End of follow up without event or competing risk
Time to MMR (On initial treatment)	First MMR on first line treatment	- Death - Progression - First line TKI discontinuation without MMR achievement	- End of follow up without event or competing risk
Time to MR <sup>4.0</sup> (Overall)	First MR <sup>4.0</sup>	- Death - Progression	- End of follow up without event or competing risk
Time to MR <sup>4.0</sup> (On initial treatment)	First MR <sup>4.0</sup> on first line treatment	- Death - Progression - First line TKI discontinuation without MR4.0 achievement	- End of follow up without event or competing risk
Time to MR <sup>4.5</sup> (Overall)	First MR <sup>4.5</sup>	- Death - Progression	- End of follow up without event or competing risk
Time to MR <sup>4.5</sup> (On initial treatment)	First MR <sup>4.5</sup> on first line treatment	- Death - Progression - First line TKI discontinuation without MR4.5 achievement	- End of follow up without event or competing risk
All cause TKI discontinuation	First line TKI discontinuation	- Death	- End of follow up without event or competing risk
TKI discontinuation due to failure	First line TKI discontinuation due to reported failure	- Death - TKI discontinuation due to all other reasons	- End of follow up without event or competing risk
TKI discontinuation due to intolerance	First line TKI discontinuation due to reported intolerance	- Death - TKI discontinuation due to all other reasons	- End of follow up without event or competing risk
Effective and tolerable first line treatment	First line TKI continuation at least one year after achieving MMR	- Death - Progression - HSCT	- End of follow up without event or competing risk
CML-related death	Death proceeded by CML progression	- Death due to all other causes	- End of follow up without event or competing risk - HSCT
TKI stop eligibility	Eligibility for a TKI stop attempt according to the EURO-SKI criteria	- Death - Progression - First line TKI failure - Less than 3 years on first and second line TKI	- End of follow up without event or competing risk

Abbr: CCyR, complete cytogenetic response; MMR, major molecular response; MR<sup>4.0</sup>, BCR-ABL1 0.01% on international scale;

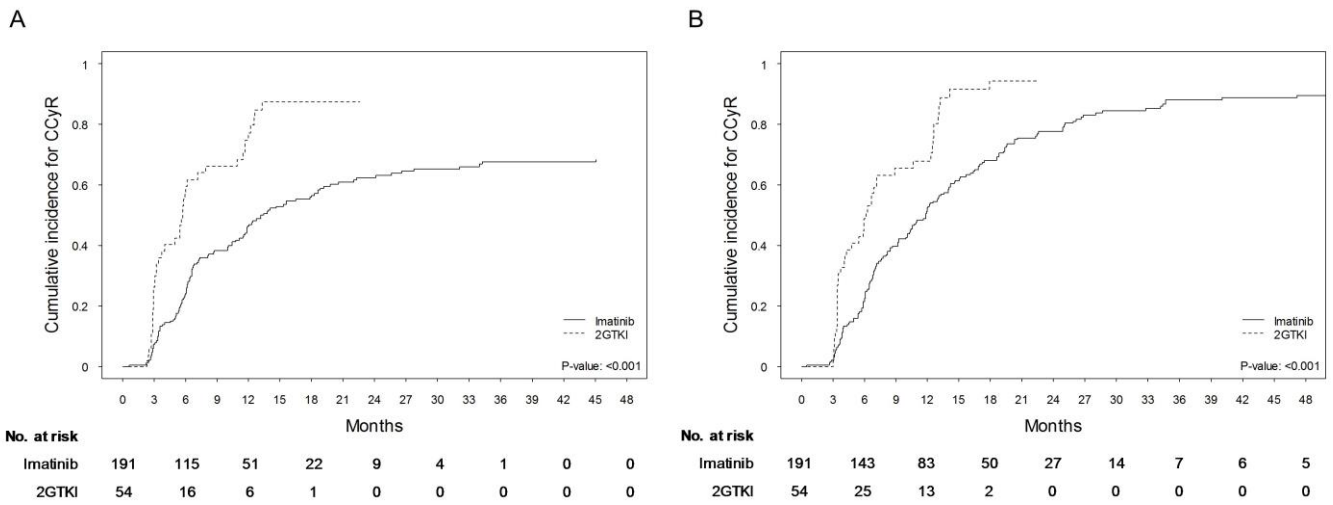
MR<sup>4.5</sup>, BCR-ABL1 0.0032% on international scale; TKI, tyrosine kinase inhibitor; HSCT, hematopoietic stem cell transplantation

**SI table S2. Adverse events per TKI and actions taken on the adverse events**

	Imatinib n=305		Nilotinib n=139		Dasatinib n=116		No action		Interruption		Reduction		Switch		Stop		Unknown	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Hematologic adverse events</b>	<b>67</b>	<b>22,0</b>	<b>20</b>	<b>14,4</b>	<b>23</b>	<b>19,8</b>												
Thrombocytopenia*	30	9,8	14	10,1	12	10,3	19	33	9	16	18	32	7	12	1	2	3	5
Leukopenia*	15	4,9	0	0,0	2	1,7	9	50	3	17	5	28	1	6	0	0	0	0
Anemia*	13	4,3	4	2,9	2	1,7	7	37	1	5	7	37	2	11	1	5	1	5
Pancytopenia*	9	3,0	2	1,4	7	6,0	2	11	2	11	6	33	6	33	2	11	0	0
<b>Biochemical adverse events</b>	<b>9</b>	<b>3,0</b>	<b>7</b>	<b>5,0</b>	<b>6</b>	<b>5,2</b>												
Elevated serum creatinine	6	2,0	0	0,0	2	1,7	6	75	0	0	1	13	1	13	0	0	0	0
Elevated serum ALAT	2	0,7	2	1,4	1	0,9	1	20	2	40	2	40	0	0	0	0	0	0
Elevated serum bilirubine	0	0,0	2	1,4	0	0,0	0	0	1	50	0	00	1	50	0	0	0	0
Elevated serum GGT	0	0,0	0	0,0	2	1,7	1	50	0	0	0	0	0	0	0	0	1	50
Elevated serum amylase	0	0,0	0	0,0	1	0,9	1	100	0	0	0	0	0	0	0	0	0	0
Elevated serum ASAT	1	0,3	1	0,7	0	0,0	0	0	0	0	1	50	0	0	0	0	1	50
Elevated serum lipase	0	0,0	1	0,7	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
Electrolyte disorders	0	0,0	1	0,7	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
Hypoalbuminemia	0	0,0	0	0,0	0	0,0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Nonhematologic</b>																		
<b>Gastrointestinal complains</b>	<b>63</b>	<b>20,7</b>	<b>5</b>	<b>3,6</b>	<b>20</b>	<b>17,2</b>												
Diarrhea	28	9,2	2	1,4	11	9,5	6	14	6	14	12	28	18	42	0	0	1	2
Nausea	15	4,9	1	0,7	5	4,3	2	10	0	0	10	48	9	43	0	0	0	0
Vomiting	13	4,3	1	0,7	3	2,6	4	22	1	6	4	22	8	44	0	0	1	6
Abdominal discomfort	6	2,0	1	0,7	1	0,9	1	13	0	0	1	13	6	75	0	0	0	0
Pancreatitis	1	0,3	0	0,0	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
<b>Pulmonary</b>	<b>8</b>	<b>2,6</b>	<b>8</b>	<b>5,8</b>	<b>21</b>	<b>18,1</b>												
Pleural effusion	2	0,7	3	2,2	16	13,8	0	0	3	14	2	10	14	67	2	10	0	0
Dyspnea	5	1,6	4	2,9	4	3,4	3	21	0	0	4	29	5	36	2	14	0	0
Pleuritis	1	0,3	0	0,0	1	0,9	0	0	0	0	0	0	1	50	1	50	0	0
Pulmonary hypertension	0	0,0	1	0,7	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
<b>Fluid retention</b>	<b>38</b>	<b>12,5</b>	<b>7</b>	<b>5,0</b>	<b>4</b>	<b>3,4</b>												
Superficial edema	18	5,9	5	3,6	3	2,6	3	12	0	0	12	46	10	39	1	4	0	0
Periorbital edema (+eyelid edema)	16	5,2	2	1,4	1	0,9	2	10	1	5	4	19	12	57	1	5	1	5
Macular edema	4	1,3	0	0,0	0	0,0	1	25	0	0	0	0	3	75	0	0	0	0
<b>Musculoskeletal</b>	<b>30</b>	<b>9,8</b>	<b>5</b>	<b>3,6</b>	<b>5</b>	<b>4,3</b>												
Myalgia	11	3,6	2	1,4	3	2,6	1	6	1	6	10	63	3	19	1	6	0	0
Muscle cramps	10	3,3	1	0,7	1	0,9	4	29	1	7	6	43	3	21	0	0	0	0
Musculoskeletal pain	8	2,6	2	1,4	1	0,9	1	9	0	0	4	36	4	36	2	18	0	0
Gout	1	0,3	0	0,0	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
<b>Cardiovascular events</b>	<b>4</b>	<b>1,3</b>	<b>8</b>	<b>5,8</b>	<b>1</b>	<b>0,9</b>												
Ischemic heart disease	1	0,3	3	2,2	1	0,9	3	60	0	0	0	0	2	40	0	0	0	0
Cerebro vascular event	0	0,0	2	1,4	0	0,0	2	100	0	0	0	0	0	0	0	0	0	0
Peripheral arterial occlusive disease	2	0,7	2	1,4	0	0,0	1	25	0	0	1	25	2	50	0	0	0	0
Venous thromboembolic event	1	0,3	1	0,7	0	0,0	1	50	0	0	0	0	1	50	0	0	0	0
<b>Non-ischemic cardiac events</b>	<b>9</b>	<b>3,0</b>	<b>5</b>	<b>3,6</b>	<b>1</b>	<b>0,9</b>												
Cardiac arrhythmia	4	1,3	2	1,4	1	0,9	7	100	0	0	0	0	0	0	0	0	0	0
Cardiac valvular problem	1	0,3	0	0,0	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
Congestive heart failure	4	1,3	2	1,4	0	0,0	6	86	0	0	1	14	0	0	0	0	0	0
Symptomatic QT prolongation	0	0,0	1	0,7	0	0,0	0	0	0	0	1	100	0	0	0	0	0	0
<b>Neurological</b>	<b>5</b>	<b>1,6</b>	<b>6</b>	<b>4,3</b>	<b>3</b>	<b>2,6</b>												
Headache	2	0,7	3	2,2	3	2,6	0	0	0	0	3	38	5	63	0	0	0	0
Dizziness	2	0,7	1	0,7	0	0,0	0	0	1	33	1	33	1	33	0	0	0	0
Polyneuropathy	1	0,3	2	1,4	0	0,0	1	33	2	67	0	0	0	0	0	0	0	0
<b>Other</b>																		
Rash	34	11,1	10	7,2	4	3,4	6	12	2	4	11	22	30	61	0	0	0	0
Infection	33	10,8	7	5,0	7	6,0	40	82	4	8	5	10	0	0	0	0	0	0
Fatigue	25	8,2	8	5,8	6	5,2	8	20	2	5	14	35	16	40	0	0	0	0
Bleeding	5	1,6	0	0,0	3	2,6	5	63	0	0	0	0	1	13	0	0	2	25
Anorexia	4	1,3	0	0,0	3	2,6	0	0	2	29	2	29	2	29	1	14	0	0
Second malignancies	7	2,3	2	1,4	1	0,9	10	100	0	0	0	0	0	0	0	0	0	0
Pruritus	4	1,3	3	2,2	1	0,9	0	0	1	13	2	25	4	50	1	13	0	0
Surgical intervention	1	0,3	1	0,7	2	1,7	3	75	0	0	0	0	0	0	0	0	1	25
Alopecia	0	0,0	2	1,4	0	0,0	0	0	0	0	2	100	0	0	0	0	0	0
Mucositis	4	1,3	0	0,0	0	0,0	0	0	1	25	1	25	2	50	0	0	0	0
Hypertension	0	0,0	1	0,7	1	0,9	1	50	0	0	0	0	1	50	0	0	0	0
Raynaud phenomonom	0	0,0	0	0,0	1	0,9	0	0	0	0	0	0	1	100	0	0	0	0
Depression	0	0,0	0	0,0	1	0,9	0	0	0	0	0	0	0	0	0	0	1	100
Gynaecomasty	2	0,7	0	0,0	0	0,0	0	0	0	0	0	0	2	100	0	0	0	0
Allergic reaction	2	0,7	0	0,0	0	0,0	1	50	0	0	0	0	1	50	0	0	0	0
Diabetes mellitus	0	0,0	1	0,7	0	0,0	1	100	0	0	0	0	0	0	0	0	0	0
Insomnia	1	0,3	0	0,0	0	0,0	0	0	0	0	0	0	1	100	0	0	0	0

\*Cytopenia ≥ CTC grade 3 and/or requiring adjustment of treatment

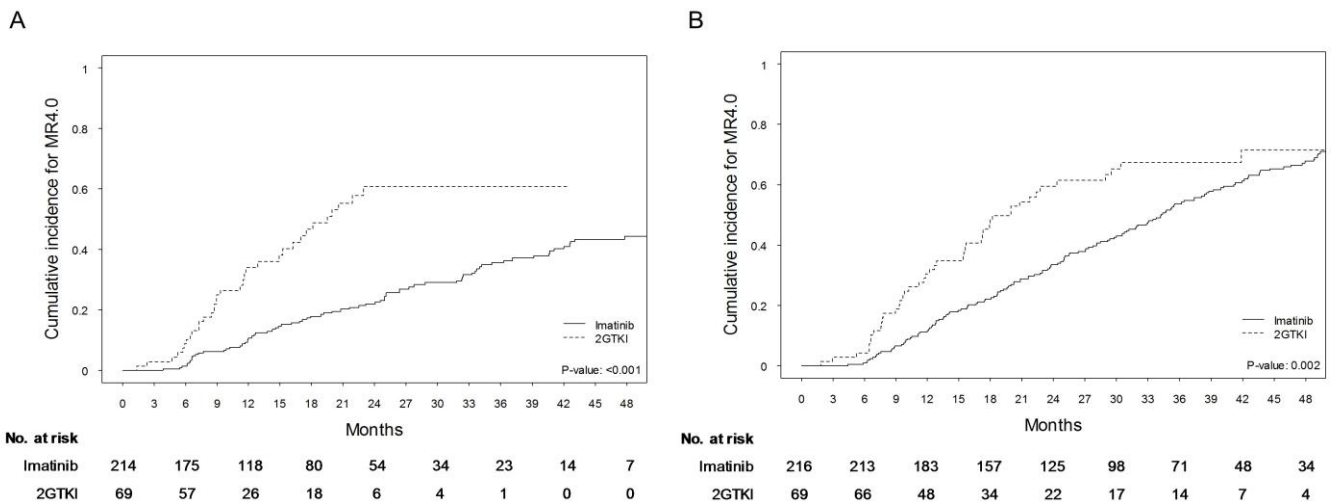
## Supplementary figures



**SI figure S1.** CCyR achievement on frontline imatinib and 2GTKIs

- Cumulative incidence of CCyR on initial treatment
- Cumulative incidence of overall CCyR rate (including switch)

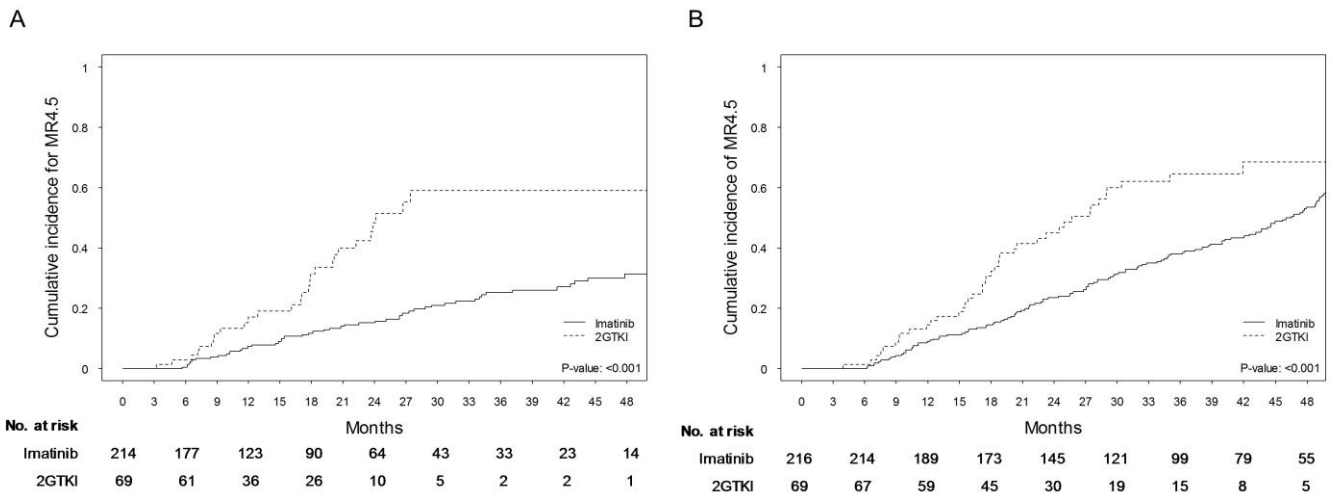
Abbreviations: CCyR, complete cytogenetic response, 2GTKIs, second generation tyrosine kinase inhibitors.



**SI figure S2.** MR<sup>4.0</sup> achievement on frontline imatinib and 2GTKIs

- Cumulative incidence of MR<sup>4.0</sup> on initial treatment
- Cumulative incidence of overall MR<sup>4.0</sup> rate (including switch)

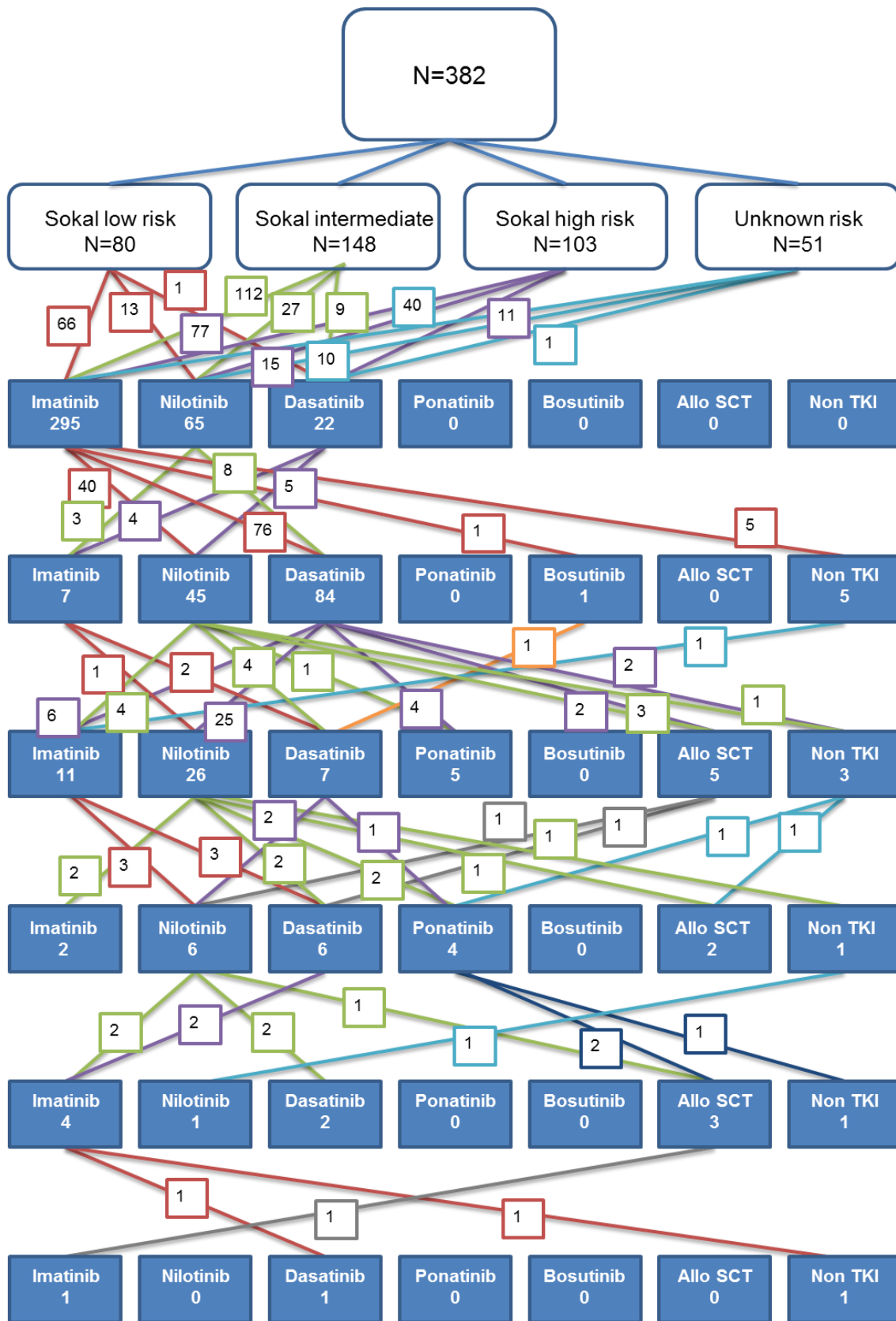
Abbreviations: MR<sup>4.0</sup>, BCR-ABL1 0.01% on international scale, 2GTKIs, second generation tyrosine kinase inhibitors.



**SI figure S3.** MR<sup>4.5</sup> achievement on frontline imatinib and 2GTKIs

- Cumulative incidence of MR<sup>4.5</sup> on initial treatment
- Cumulative incidence of overall MR<sup>4.5</sup> rate (including switch)

Abbreviations: MR<sup>4.5</sup>, BCR-ABL1 0.032% on international scale, 2GTKIs, second generation tyrosine kinase inhibitors.



**SI figure S4.** Treatment lines and patterns

Treatment patterns for 382 CML patients in chronic phase at diagnosis treated with a first line TKI

Abbreviations: Allo SCT, allogeneic stem cell transplantation