Autologous transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia achieves outcomes similar to allogeneic transplantation: results of CALGB Study 10001 (Alliance)

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Supplemental Data

Supplemental Table 1: Induction Treatments by Transplant Type*

Induction Agents	Allo-SCT	Auto-SCT	No SCT on study
Cyclophosphamide	11	14	20
Daunorubicin	13	19	20
Doxorubicin	3	0	2
Vincristine	15	19	24
Methotrexate	1	0	0
Cytarabine	0	1	0
L-Asparaginase	13	17	21
Pegylated asparaginase	0	1	0
IT Cytarabine	0	0	2
IT Methotrexate	4	4	1
Rituximab	2	0	0
Prednisone	5	9	9
Dexamethasone	5	8	8
Imatinib	7	12	9

Abbreviations: Allo, allogeneic; Auto, autologous, IT, intrathecal; SCT, stem cell transplantation;

* None were statistically significantly different.

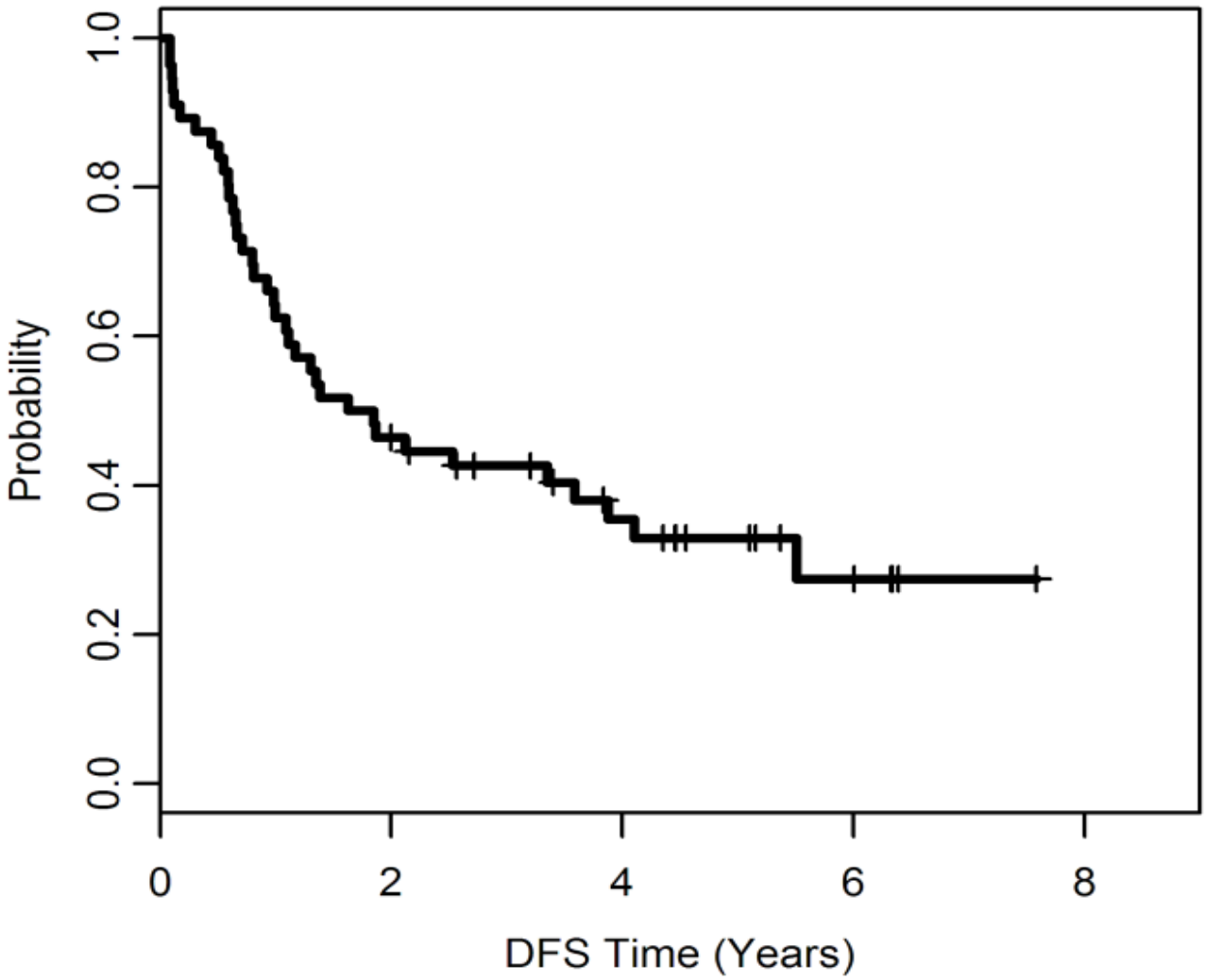
Supplemental table 2: Patient outcome based on exposure to imatinib during induction

Allogeneic SCT	**Continues in remission**	**Relapse after response**	**Dead**
No imatinib	3	1	4
Imatinib	4	0	3
Autologous SCT			
No imatinib	3	0	4
Imatinib	5	1	6

Abbreviations: SCT, stem cell transplantation;

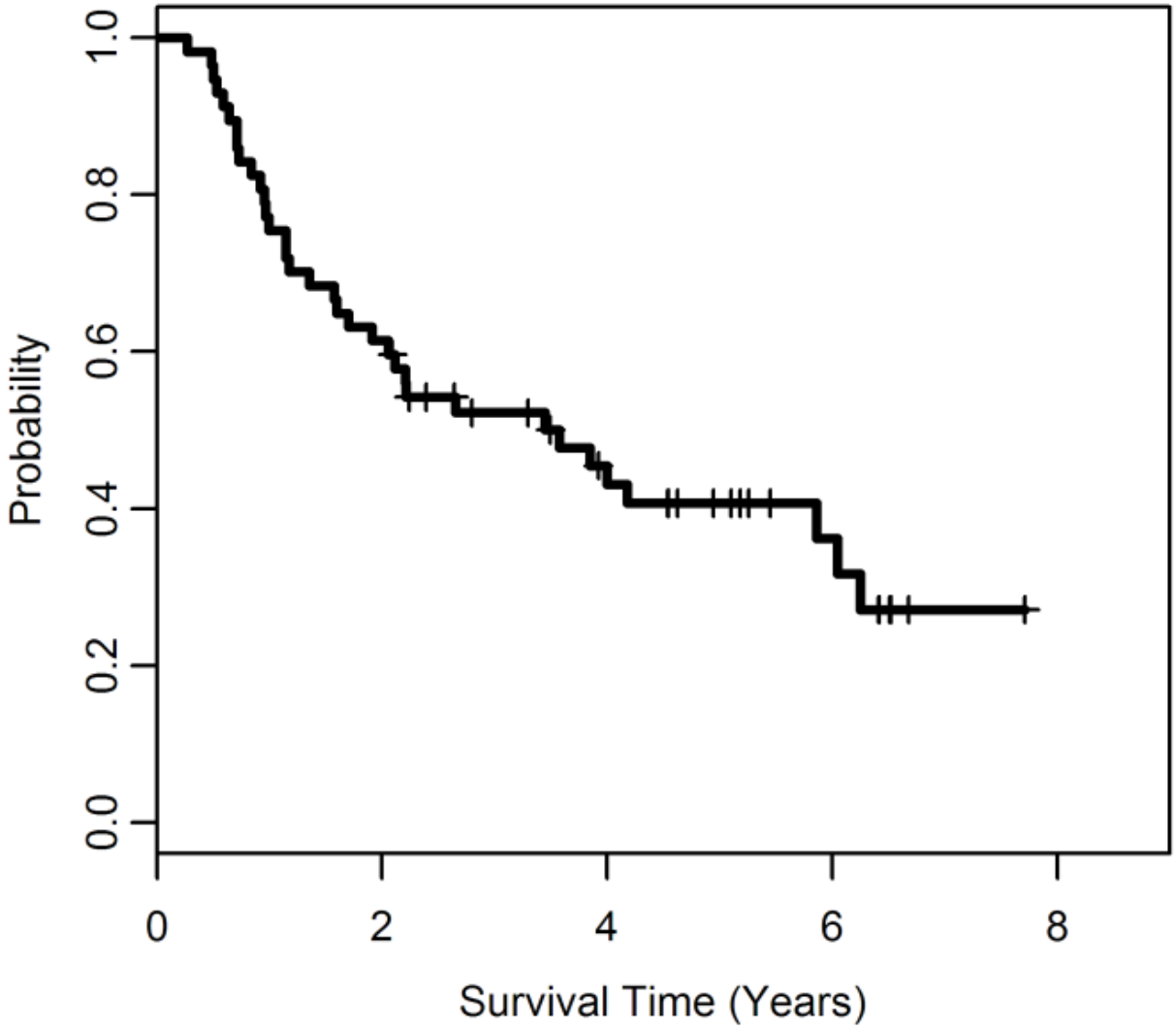
Supplemental Figure 1A: Disease-Free Survival (DFS) of the Whole Cohort (n=56)

The median was 1.7 years (95% Confidence Interval (CI) was 1.1, 4.1)

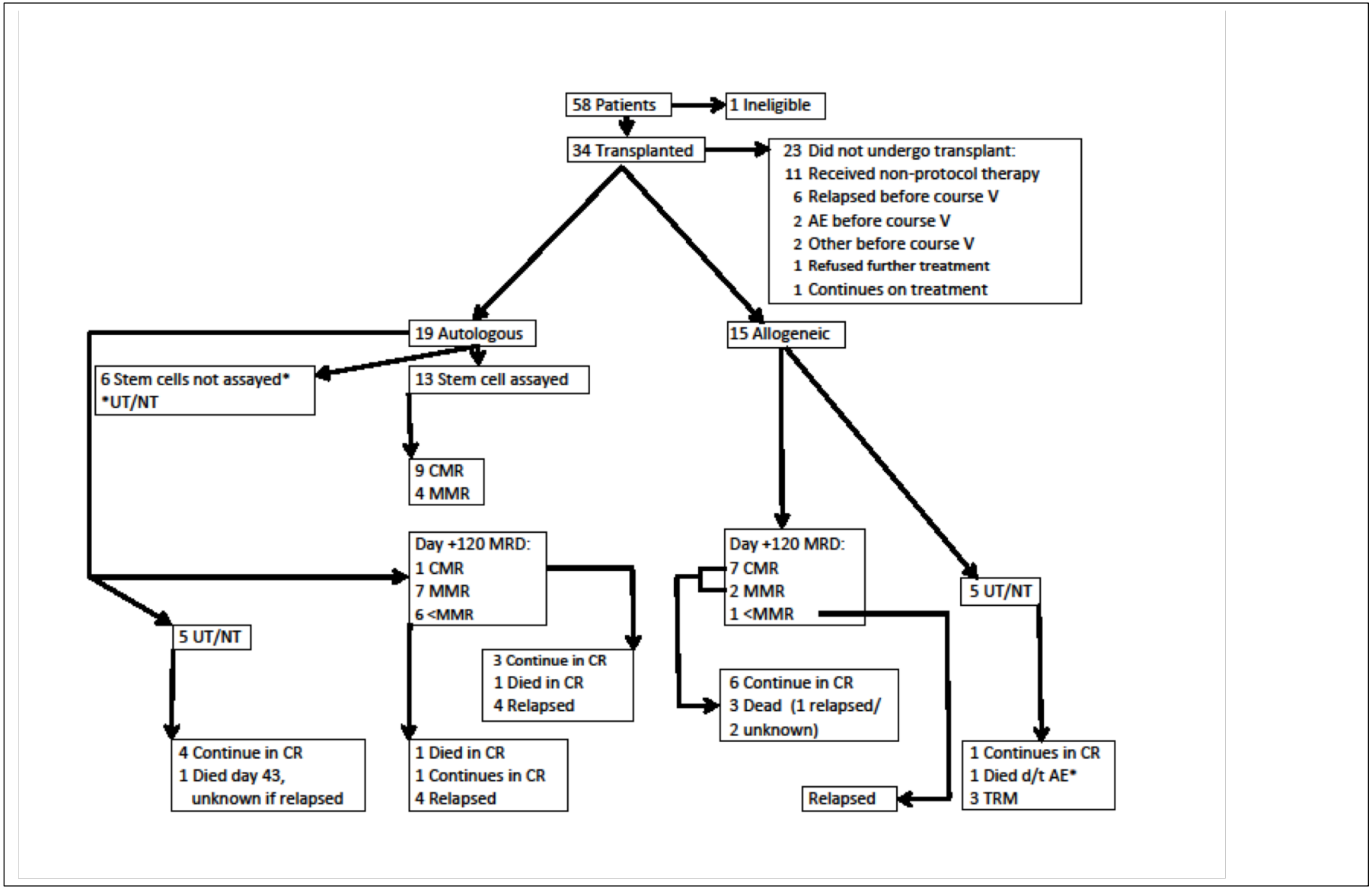


Supplemental Figure 1B: Overall Survival (OS) for the Whole Cohort (n=57)

The median overall survival was 3.6 years (95% CI 1.9, 6.2)



Consort Diagram of CALGB 10001



* Died due to adverse event (died d/t AE) refers to death after day 100

Abbreviations: AE, adverse event; CMR, complete molecular remission; CR, complete remission; d/t, due to; MMR, major molecular remission; MRD, minimal residual disease; NT, not tested; TRM, treatment-related mortality; UT, unknown transcript;

Treatment Dosing Information

Course I: Remission induction with any standard 4-5 drug regimen with or without imatinib.

Course II: Enrolled on study. Imatinib 400 mg orally (PO) twice daily (BID) days 1-28

Course III: CNS prophylaxis

Intrathecal Methotrexate (Mtx) 15 mg once per week x 3 weeks (Days lll-1. III-8, III-15)

Intravenous (IV) Vincristine (VCR) 2 mg once per week x 3 weeks (Days III- 1, III-8, III-15)

IV Mtx 1000 mg/m^2 over 3 hours once per week x 3 (Days lll-1, III-8, III-15)

PO Mtx 25 mg/m^2 every 6 hours x 4 doses beginning 6 hours after starting IV Mtx (Days III-I & III-2, III-8 & III-9, III-15 and III-16)

IV Leucovorin (Lcv) 25 mg/m^2 6 hours after last PO Mtx dose (Days III-2, III-9, III-16)

PO Lcv 5 mg/m^2 beginning 12 hours after IV Lcv x 8 doses (Days III-3 & III-4, III-10

& III-11, III-17 & III-18) or until serum Mtx level <0.05 μM

Cotrimoxazole double strength (DS) one tablet PO BID 3 days/week

Course IV: Imatinib 400 mg PO BID days 1-28, to be followed by Course V

Course V: Allogeneic Transplant

Fractionated total body irradiation (13.2 Gy) on days -7 through -4

Etoposide 60 mg/kg (based on corrected body weight) IV over 4 hours on day -3

Tacrolimus 0.05 mg/kg/day continuous intravenous infusion (CIVI) on days -1 through +3 followed by tacrolimus 0.03 mg/kg/day CIVI on days 4 through +14. Tacrolimus 0.03 mg/kg/day CIVI on days +14 through +56 or in divided doses every 12 hours or oral formulation (when tolerated) at a ratio of 1:4 (IV:PO) in two divided doses daily based on last IV dose. Following day +56, tacrolimus should be tapered according to institutional guidelines.

Filgrastim (G-CSF) 5 μg/kg subcutaneously (SC) beginning on day +4 until absolute neutrophil count (ANC) >1.5x10^9/L for one day

Course V: Autologous Transplant

Etoposide 10 mg/kg/day (corrected body weight) CIVI over 96 hours on days 1-4

Cytarabine 2000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4

G-CSF 10 μg/kg/day SC beginning on day 14. G-CSF must continue until peripheral blood stem cell collection was completed or white blood cell count >50x10^9/L

Imatinib 400 mg PO BID was started after collection of stem cells was completed and continued until 72 hours prior to transplant

Fractionated total body irradiation (13.2 Gy) on days -8 through -5

Etoposide 60 mg/kg (based on corrected body weight) IV over 4 hours on day -4

Cyclophosphamide 100 mg/kg (corrected body weight) IV over 2 hours on day -2

G-CSF 5 μg/kg SC beginning on day 0 until ANC >1.5x10^9/L for two days or ≥5x10^9/L for one day

Course V: Only for patients unable to undergo SCT

Etoposide 10 mg/kg/day (corrected body weight) CIVI over 96 hours on days 1-4

Cytarabine 2000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4

G-CSF 10 μg/kg/day SC beginning on day 14. G-CSF must continue until peripheral blood stem cell collection was completed or white blood cell count >50x10^9/L

Course VI: Maintenance after recovery of blood counts

For patients who underwent allogeneic transplant, Imatinib 400 mg PO once daily days 1-28 for a minimum of 12 months until two negative reverse-transcriptase polymerase chain reaction (RT-PCR) assays three months apart or until relapse

For patients who underwent autologous transplant, Imatinib 400 mg PO twice daily days 1-28 for a minimum of 12 months until two negative RT-PCR assays three months apart or until relapse

Supplemental Table 3: Grade ≥3 (≥10%) adverse events related to stem cell transplantation step.

		Grade of AE						
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**		**Total**
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Hematologic AE								
Blood/Bone Marrow								
Hemoglobin	Allo	7	*(54%)*	0		0		13
	Auto	14	*(74%)*	1	*(5%)*	0		19
Leukocytes (total WBC)	Allo	0		4	*(31%)*	0		13
	Auto	0		2	*(11%)*	0		19
Lymphopenia	Allo	3	*(23%)*	0		0		13
	Auto	2	*(11%)*	0		0		19
Neutrophils	Allo	0		12	*(92%)*	0		13
	Auto	1	*(5%)*	16	*(84%)*	0		19
Platelets	Allo	3	*(23%)*	9	*(69%)*	0		13
	Auto	2	*(11%)*	15	*(79%)*	0		19
Transfusion: Platelets	Auto	2	*(11%)*	0		0		19
Transfusion: pRBCs	Auto	2	*(11%)*	0		0		19
SUMMARY								
Maximum Hematologic AE	**Allo**	**0**		**12**	***(92%)***	**0**		**13**
	Auto	**2**	***(11%)***	**16**	***(84%)***	**0**		**19**
Non-Hematologic AE								
Constitutional Symptoms								
Fatigue (asthenia, lethargy, malaise)	Auto	3	*(16%)*	0		0		19
Dermatology/Skin								
Rash/Desquamation	Allo	2	*(15%)*	0		0		13
Gastrointestinal								
Dehydration	Auto	2	*(11%)*	0		0		19
Diarrhea	Auto	3	*(16%)*	0		0		19
Esophagitis	Auto	2	*(11%)*	0		0		19
Mucositis/stomatitis	Allo	10	*(77%)*	0		0		13
	Auto	7	*(37%)*	1	*(5%)*	0		19

	Arm	Grade of AE 3-Severe n (%)	4-LifeThr n (%)	5-Lethal n (%)	Total
Nausea	Allo	2 *(15%)*	0	0	13
	Auto	5 *(26%)*	0	0	19
Vomiting	Auto	2 *(11%)*	0	0	19
Infection					
Febrile neutropenia (fever of unknown origin)	Allo	4 *(31%)*	0	0	13
	Auto	8 *(42%)*	1 *(5%)*	0	19
Infection (documented clinically or by culture	Allo	4 *(31%)*	0	1 *(8%)*	13
	Auto	5 *(26%)*	0	0	19
Infection without neutropenia	Auto	2 *(11%)*	00	0	19
Metabolic/Laboratory					
Phosphate serum-low (hypophosphatemia)	Allo	2 *(15%)*	0	0	13
Potassium serum-low (hypokalemia)	Auto	4 *(21%)*	1 *(5%)*	0	19
Sodium serum-low (hyponatremia)	Auto	2 *(11%)*	0	0	19
Pain					
Pain	Auto	2 *(11%)*	0	0	19
SUMMARY					
Maximum Non-Hematologic AE	**Allo**	**10** ***(77%)***	**0**	**2*** ***(15%)***	**13**
	Auto	**12** ***(63%)***	**4** ***(21%)***	**0**	**19**
SUMMARY					
Maximum Overall AE	**Allo**	**0**	**11** ***(85%)***	**2†** ***(15%)***	**13**
	Auto	**2** ***(11%)***	**16** ***(84%)***	**0**	**19**

* Two patients are reported but only one patient is listed because the table presents only ≥10% Grade ≥3 toxicities.

† Two additional patients died within 100 days of transplant but are not included in this table because the Table lists only Grade ≥3 if occurred ≥10% of cases. Both died without blood count recovery; one after allo-SCT and one after auto-SCT.

Abbreviations: AE, adverse events; Auto, autologous; Allo, allogeneic; pRBCs, packed red blood cells; Thr, threatening; WBC, white blood cell count;

Supplemental Table 4: Distribution of mutations in 7 of 10 patients at relapse following stem cell transplantation

Mutation	Frequency (numbers)
Y253H	3
T315I	2
E255K/V	2
None	3