Asciminib as a bridge - therapy before allogeneic hemopoietic stem cell transplantation and in post-transplant period for chronic myeloid leukemia

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Background: Asciminib is a novel BCR::ABL1 inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP) and has shown efficacy and a good safety profile according to the results of a phase I and III studies in patients with Ph-positive chronic myeloid leukemia (CML) failing prior tyrosine kinase inhibitors (TKIs). While pre-transplant use of 2-nd generation TKIs (nilotinib / dasatinib) does not change the risk associated with allogeneic hemopoietic stem cell transplantation (allo-HSCT) recipients, there are some reports of TKI therapy, in particular ponatinib inducing GVHD. There is yet no data available for patients receiving asciminib.

Aim: To evaluate the safety and effectiveness of pre- and post-transplant asciminib in allo-HSCT candidates.

Materials and Methods: In Russia, asciminib is available under the Managed Access Program (MAP) approved by Novartis. In the MAP program 68 patients with CML were enrolled. We reviewed data of 12 patients across 2 contributing centers, who underwent allo-HSCT between August 2021 and August 2022. The median age of this cohort was 41 years (range 28-59) and 8(58%) patients were male. The median duration of CML before asciminib was 2.8 years (range 0.3-15).

CML status before asciminib: all patients were without cytogenetic and molecular response. Six patients had complete hematological response, 6 patients were without complete hematological response (including cytopenia). Three patients were in the 1st chronic phase CML, 4 patients had a history of accelerated phase and five patients had a history of blast crisis. The median duration of asciminib before allo-HSCT was 194 days (61-377 days). Nine (75%) patients had *BCR::ABL1* mutations, and seven (58%) had *BCR:ABL1*^{t315i}. Four (33%) patients had additional chromosomal abnormalities. The majority of patients (84%) received ≥3 TKIs, 4 patients (33%) had a history of ponatinib treatment. In five (41%) patients, the initial dose of

asciminib was 40 BID, seven (59%) patients started with 200 mg BID. On asciminib 11patients (92%) did not develop adverse events (AEs) of any grade. Only 1 (8%) patient developed AEs (neutropenia 3 grade, thrombocytopenia 4 grade), but was able to continue treatment at reduced dose 20 mg BID. Disease status pre-transplant for 4 patients was complete hematological response, 1patient achieved complete cytogenetic response (CCyR), 2 and 1 had major molecular response (MMR) and MR4 molecular response, respectively. Four patients were without hematological response (Fig.1).

Results

All patients received allo-HSCT with reduced dose intensity conditioning regimen. GVHD prevention with PtCyTxMMF/PtCyCsA or monoCy/monoCsA (in cases of relative donors and bone marrow source) was given. Eight (67%) patients had relative donors (5 match relative donors and 3 haplo donors) and 4 pts (33%) – match unrelated donor (9/10, 8/10) with transplant source PBSC.

No unusual toxicity was observed during conditioning (Tab.1). Median engraftment time was D+20 (range 18-24). Primary and secondary graft failures were recorded in 1 patient each. The 1-year overall survival was 70% (Fig.2).

In the post-transplant period, four (33%) patients continued to receive asciminib for the treatment of minimal residual disease (MRD), with the achievement of CMR in 3(25%) cases (Tab.2). One patient developed VOD grade 1 with resolution during therapy on D+10. Two patients developed liver aGVHD gr.2, which did not require correction of the underlying immunosuppressive therapy. No action was taken on asciminib. Two patients developed intestinal aGVHD gr.3 requiring glucocorticosteroids and ruxolitinib treatment. Asciminib was interrupted until resolution aGVHD. The cumulative incidence of acute GVHD (1-3 grade up to 100 days) was 18% (Fig.3).

aGVHD was not significantly associated with asciminib.

Eight(67%) patients are alive with median follow-up after allo-HSCT of 135 days. Cause of death were: 1case sepsis, 2 case - progression CML, 1 case- secondary graft failure. Non-relapse mortality was 18% at 12 months(Fig.4).

Conclusions

Finally, asciminib had promising results for the treatment of highly pre-treated CML patients from the Phase 1 data and ASCEMBL study. In our observation (limited with small dataset) asciminib was effective as bridge- therapy before allo-HSCT in highly pretreated patients with low rate of severe toxicity and acceptable rate of aGVHD.

It seems that in patients with advanced phases, asciminib is a promising drug to improve the status of the disease before allo-HSCT and with no increase of rate of aGVHD after allo-HSCT.

Pre-transplantation asciminib treatment does not adversely impact transplantation outcomes.

Post-transplant asciminib induced improvement in molecular response in this heavily pre-treated cohort of patients. The majority of patients attained deep molecular response.

More data obtained on larger cohort is needed in order to assess its impact on long-term survival.

Table 1. Baseline characteristics

Patient №	1	2	3	4	5	6	7	8	9	10	11	12
Age, sex	47/F	34/M	57/M	59/F	31/F	42/F	52/M	35/M	41/M	28/M	30/M	33/F
Disease phase at diagnosis	CP1	CP1	CP1	CP1	CP1	CP1	CP1	CP1	CP1	AP1	CP1	AP1
History of CML progression	BC	BC	AP	CP1	AP	CP1	BC	CP1	BC	AP1	AP	BC
Previous TKI	Ima/ Dasa/ Nilo	Ima/ Dasa/ Nilo/ Pona	Ima/ Bosu/ Pona	Ima/ Rado/ Pona	Ima/ Nilo/ Bosu/ Dasa	Ima/ Nilo/ Dasa/ Bosu	Ima/ Nilo/ Dasa/ Ima	Ima/ Dasa	Ima/ Nilo/ Dasa/ Bosu	Ima/ Bosu	Ima/ Nilo/ Dasa	Ima/ Bosu/ Dasa
ABL-kinase domain mutation	F317 V	T315I	T315I	T315I	T315I	none	T315I	T315I	F317L	T315I, V299 L	none	none
History of ACA in Ph+ cells/atypical type bcr-abl	none	+21, +der(22), del(11)(q23)	+Y, +8	-	-	p190	p190	p190	t(6;9;22), t(Y;5)	p190	-7, +8/ GE16	-
Disease phase before asciminib	CP2	CP2	AP	CP1	CP2	CP1	CP3	CP1	CP3	CP2	CP2	CP2
Asciminib starting dose	40 BD	200 BD	200 BD	200 BD	40 BD	40 BD	200 BD	200 BD	40 BD	200 BD	40 BD	40 BD
Disease status at HSCT	no CHR	no CHR	CHR	no CHR	CHR	no CHR	CMR	MMR	no CHR	CHR	no CHR	CHR
Donor/ Conditioning	Haplo/ RIC	MRD/ RIC	Haplo/ RIC	MRD/ RIC	MRD/ RIC	MUD m/m / RIC	MUD/ RIC	MUD/ RIC	MRD/ RIC	MRD/ RIC	MUD m/m / RIC	MUD/ RIC
Acute GVHD (Gr)	no	no	no	no	Gr 1	Gr 3	no	Gr 3	no	Gr1	Gr 3	no

Patient №	1	2	3	4	5	6	7	8	9	10	11	12
Start asciminib Post-HSCT	yes	no	no	yes	yes	yes	no	no	no	yes	no	no
Response	Primary graft failure	CMR	CMR	CHR	CMR	CMR	sepsis	CMR	progression	CMR	CMR	Secondary graft failure
Mortality Status	died	alive	alive	alive	alive	alive	died	alive	died	alive	alive	died

Notes: F - Female, M - male, CP1 - chronic phase 1, CP2 - 2nd chronic phase, CP3 - 3d chronic phase, AP - acceleration phase, BC - blast crisis, Ima - Imatinib, Nilo - Nilotinib, Dasa - Dasatinib, BD - twice daily, CHR - complete hematological response, MMR - major molecular response, CMR - complete molecular response, Haplo - Haplo-identical donor, MRD - match related donor, MUD - match unrelated donor, RIC - Redused Intensity Conditioning, Gr - Grade.

Table 2. Asciminib after allo-HSCT

Pts	Cause	Dose	Day	Response
1	MRD	40 mg BD	+60	CMR
2	MRD	20 mg BD	+30	impossible to assess (death)
3	MRD	40 mg BD	+30	CMR
4	MRD	40 mg BD	+60	CMR

Notes: MRD - match related donor, BD - twice daily, CMR - complete molecular response.

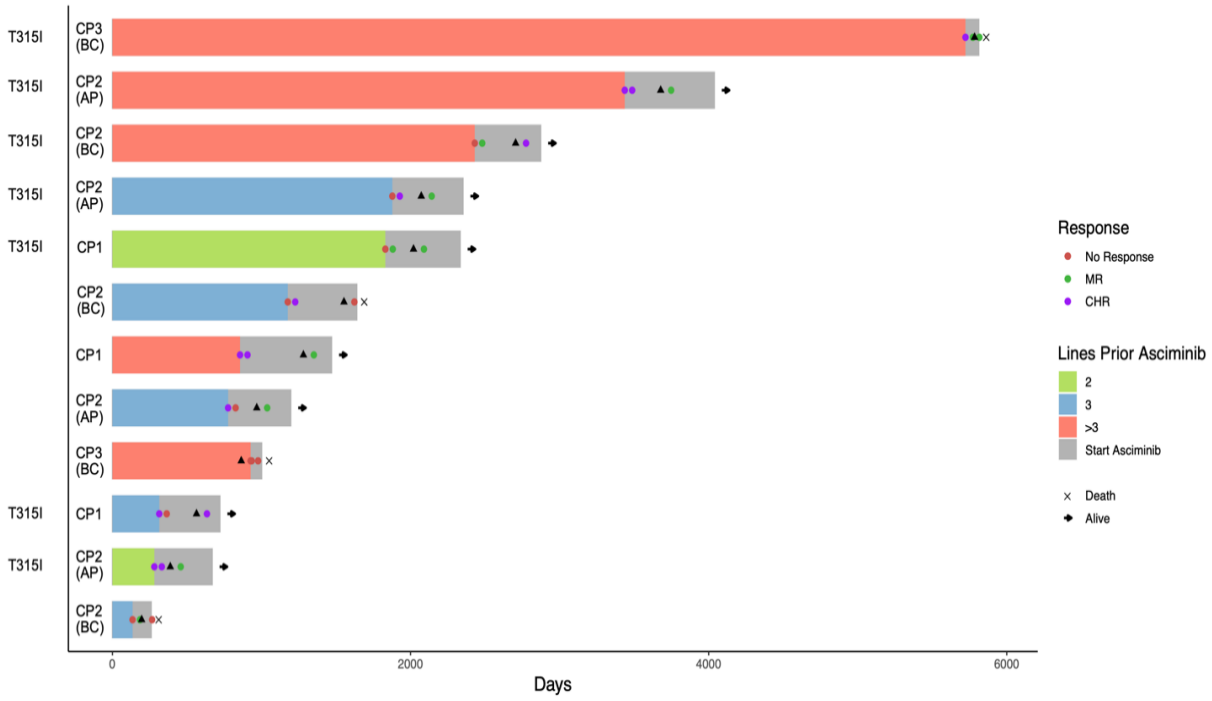

Figure 1. Summary graph of Asciminib treatment in CML patients

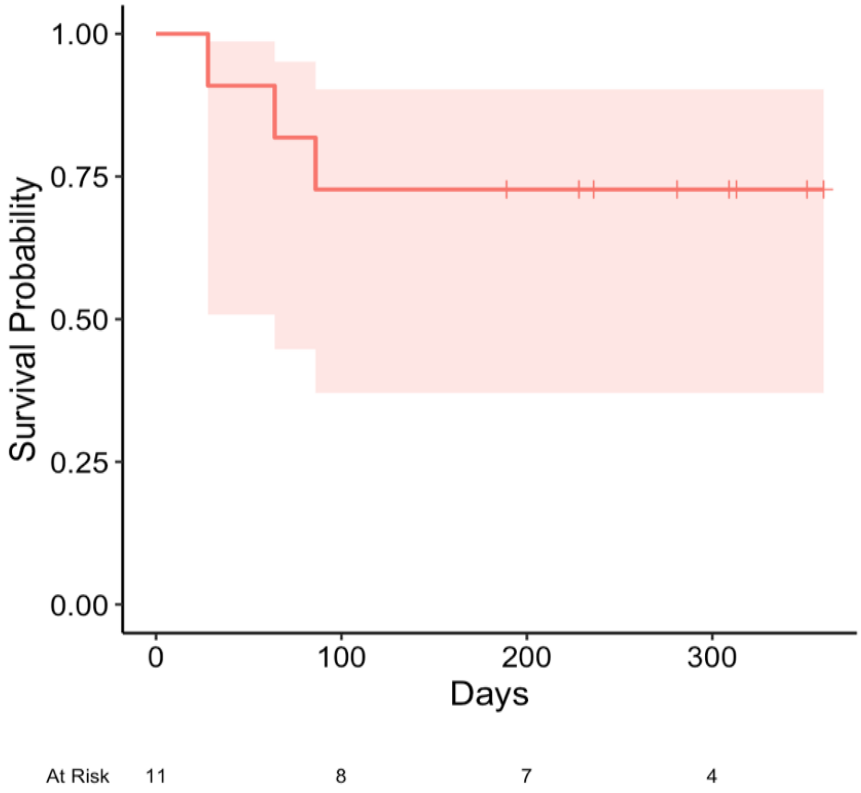

Figure 2. 1-year overall survival

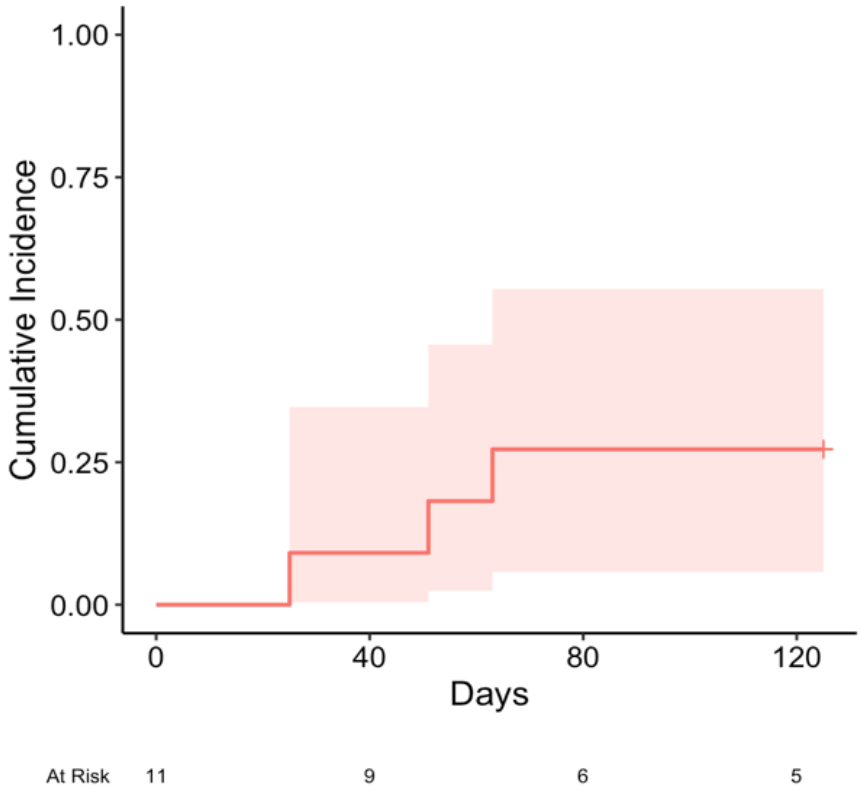

Figure 3. Cumulative incidence of aGVHD

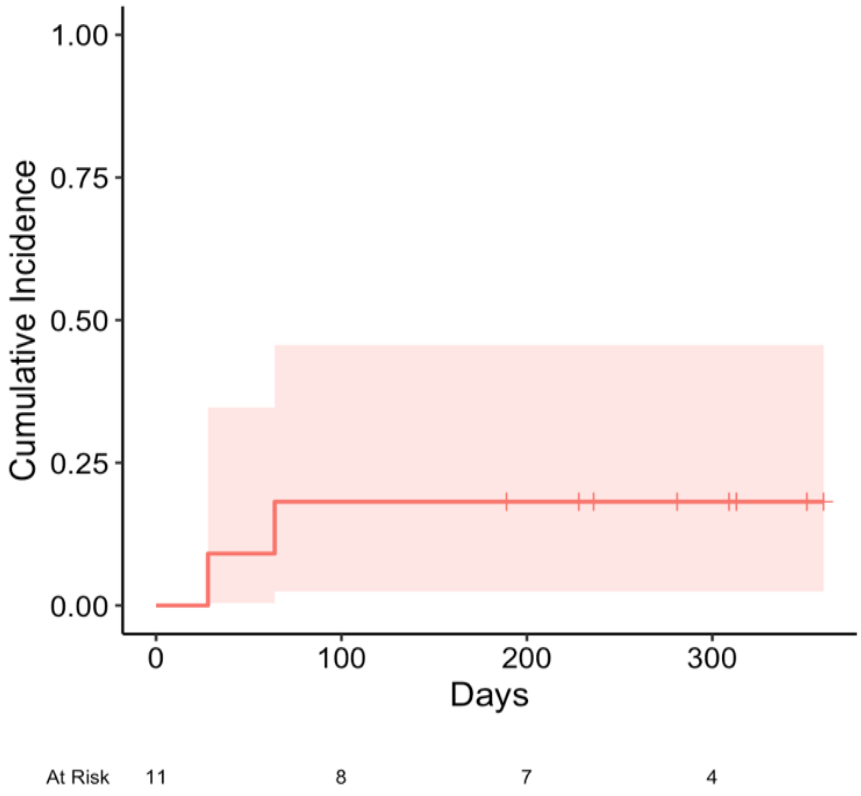

Figure 4. NRM by asciminib