Abstract: P673

Title: ASCIMINIB MANAGMENT IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS WITH T315I MUTATION.

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Session Title: Chronic myeloid leukemia - Clinical

Background:

Asciminib mechanism of action differs from other tyrosine kinase inhibitors (TKIs) for it is a Specifically Targeting the ABL Myristoyl Pocket (STAMP) ABL kinase inhibitor, that has a potential efficacy against BCR::ABL1 clones with ATP-binding site mutations, including T315I. In clinical trials in patients (pts) with Ph-positive chronic myeloid leukemia (CML) with T315I mutation, failing other TKIs, it has shown an efficacy and a good safety profile. Asciminib is in use in clinical practice in Russia in Managed Access Program (MAP) supported by Novartis

Aims:

To present the updated results of the asciminib use in CML patients with the T315I mutation under the MAP in 3 centers of Russia.

Methods:

In total 82 pts received asciminib in MAP with doses 40/200 mg BID. Twenty-nine were in a 200 mg BID dose group, the data of 24 of them are presented, while 5 pts, who undergone bone marrow transplantation, were excluded from the analysis. Twenty-three pts had T315 mutation, one patient had F317L (T315I detected, but later not confirmed). All pts were adult (>18 years) with Ph-positive CML in chronic phase (CP): 3 were in a second CP after an accelerated phase and 1 – after a blast crisis, all of them had no alternative therapeutic options. Response monitoring and toxicity control were performed according to the MAP treatment plan. Complete cytogenetic response (CCyR - corresponded to BCR::ABL1 ≤1% or MR2), major molecular response (MMR) and deep molecular response (MR4) were assessed by cumulative incident function (CIF) with Gray's test for comparison responses in subgroups. Survival analysis was performed by Kaplan-Meier method.

Results:

Median (Me) age at asciminib start was 49 years (range 32-71), the female proportion was 63%. Me of CML duration before asciminib was 6,9 years (range 1-34). All pts received ≥2 prior TKIs, 45% had ≥ 4 prior TKIs. With the Me follow-up period of 21 months (range 6-39); 5 (21%) pts discontinued asciminib (4 due to resistance, 1 due to a clinician decision in achieved MR4). Nine pts had additional chromosomal abnormalities (ACAs) and/or additional BCR::ABL1 mutations in an anamnesis; their responses are presented in a table 1. Six (25%) of 24 pts had ACAs before asciminib, 4 of them achieved MMR , and one of them (№1) was resistant and lost CCyR. Six pts had additional BCR::ABL1 mutations in an anamnesis, 5 of them achieved MMR and 1 pt (№9) was resistant to therapy.

Two-years overall survival at 24 months was 100%. Survival rate without treatment discontinuation was 74%. CIF of CCyR, MMR and MR4 at 24 month was 57%, 57% and 34%, respectively. Thirteen (54%) pts were ponatinib-pretreated, and CIF of MMR in ponatinib-naive pts compared to ponatinib-pretreated pts was significantly higher: 90% vs. 25% (p=0.001). In total 4 pts lost CCyR or MMR (table 1).

Thirteen (54%) pts experienced adverse events (AEs) of any grade and 4 (17%) had AEs of grade 3 (neutropenia, hypercholesterinemia). No one discontinued treatment due to toxicity.

Summary/Conclusion:

Highly pre-treated CML pts with T315I mutation are able to achieve a response with asciminib 200 mg BID,

especially in ponatinib-naive group. In our pts a safety profile was good with no evidence of severe toxicity. Asciminib shows effectiveness in highly resistant pts with T315I mutation with/without other genetic events (combined mutations, ACAs), though some of them still a challenge for clinicians. Overcoming the resistance by adding other therapy should be investigated.

Table 1. Characteristics of the pts with additional genetic events.

N of pts	ACAs (n=6)	BCR::ABL1 mutations (n=6)	Response to asciminib	Loss of response	Additional therapy
1	-7, del 7p, del 16q;	T315I	CCyR	loss of CCyR	-
2*	der9, der17, der22	F317L (T315I in anamnesis)	MMR	loss of CCyR	Bosutinib*
3*	der22	T315I, F359V	CCyR	loss of CCyR	Dasatinib*
4	trisomy 8	T315I, F317L	MMR	-	-
5	der22	T315I	MMR	loss of MMR	-
6	trisomy 8	T315I, S348L	MMR	-	-
7	-	T315I, G250E	MR4	-	-
8	-	T315I, E255K	MR4	-	-
9	-	H396R, F317V, T315I	No	-	-

* Two pts achieved CCyR/MMR on the asciminib monotherapy, then lost the responses. MR4 was achieved on combined therapy asciminib + bosutinib/dasatinib.

Keywords: BCR::ABL, Asciminib, Chronic myeloid leukemia, Mutation status