Abstract: S156

Title: FRONTLINE ASCIMINIB COMBINATION IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS. THE FASCINATION TRIAL.

Abstract Type: Oral Presentation

Session Title: Evolution of clinical management in CML

Background:

"The **F**rontline **asci**minib in combi**nation"** - FASCINATION study (NCT03906292) is a multicenter, prospective, open-label, interventional phase II trial to evaluate efficacy and tolerability of asciminib – a first-in-class BCR::ABL1 inhibitor specifically targeting the ABL myristoyl pocket (STAMP) - as first-line treatment in combination with conventional ATP-competing BCR::ABL1 inhibitors (nilotinib, dasatinib, or imatinib) for patients (pts) with chronic myeloid leukemia (CML) in chronic phase.

Aims:

The aim of the study was to pilot asciminib in combination with ATP competing tyrosine kinase inhibitors (TKI) as first-line therapies in CML pts to improve the rate of deep molecular response (MR^4) after 1 year of therapy. A higher rate of patients in deep molecular response compared to standard therapies could increase the proportion of patients in treatment-free remission (TFR) over time. Here, we report results of the pre-planned interim analysis of the primary endpoint according to the protocol.

Methods:

Adult pts with newly diagnosed *BCR::ABL1*-positive CML were included in the study until 3 months after diagnosis. A <4 week pretreatment with hydroxyurea was permitted. Pts treated for <6 weeks with nilotinib 300 mg BID, dasatinib 100 mg QD, or imatinib 400 mg QD were eligible for recruitment and allocated to one of four respective cohorts (Table). Cohorts were filled consecutively and were designed to allow assessment of QD and BID asciminib-based combinations to optimize quality of life (QoL) and compliance. Asciminib therapy was commenced 12 weeks after start of nilotinib, dasatinib, or imatinib, and after complete recovery of normal hematopoiesis. Dose of asciminib was based on pharmacokinetic data (area under the curve) of the combination cohorts within the phase I trial (NCT02081378). Nilotinib 300 mg BID was combined with asciminib 20 mg BID (cohort 1), or asciminib 40 mg QD (cohort 2), dasatinib 100 mg QD was combined with asciminib 80 mg QD (cohort 3), and imatinib 400 mg QD was combined with asciminib 60 mg QD (cohort 4). The primary endpoint was the rate of MR^4 (BCR::ABL1 transcripts ≤0.01% on the International Scale, IS) at month 12.

Results:

Between 2019 and 2022, 144 pts were recruited from 21 sites in Germany. Two pts were screening failures and 17 pts did not tolerate the initial TKI and were excluded from the study before start of asciminib. Combination therapy was commenced in 125 pts (66% male). Median age at diagnosis was 45.5 years (range, 19.0-89.0), 57.3, 28.1, and 14.6% were low, intermediate, and high risk according to the ELTS score, respectively. Adverse events grade 3-4 were observed in 37.6% of the pts. A total of 21 pts (17%) discontinued the combination therapy within the first 12 months due to dermal toxicity (n=4), gastroenterological toxicity (n=4), treatment failure/progression (n=3), cytopenia (n=2), papillitis/ocular papilla edema (n=1), polyneuropathy (n=1), pain (n=1), incompliance (n=1), and withdrawal of consent (n=4). One patient who progressed to blast phase received an allogeneic stem cell transplantation. A total of 114 pts were eligible for evaluation of molecular response at month 12. According to intention to treat, rate of MR^4 at month 12 was 37.7% (95%-CI: 30.1-45.8%).

Summary/Conclusion:

The combination of asciminib as frontline therapy with ATP competing BCR::ABL1 inhibitors is associated with a

high rate of deep molecular response but also impaired tolerability. Longer follow up is planned to investigate asciminib maintenance treatment after deep molecular response and TFR.

Cohort	TKI combination	Number of recruited patients	Number of patients eligible for molecular response at month 12	Number of patients with MR^4 at month 12 (%)
1	Nilotinib 300 mg BID + asciminib 20 mg BID	30	28	9 (32.1)
2	Nilotinib 300 mg BID + asciminib 40 mg QD	32	31	13 (41.9)
3	Dasatinib 100 mg QD + asciminib 80 mg QD	32	27	9 (33.3)
4	Imatinib 400 mg QD + asciminib 60 mg QD	31	28	12 (42.9)
	Total	125	114	43 (37.7)

Keywords: Chronic myeloid leukemia, BCR::ABL, Clinical trial, Tyrosine kinase inhibitor