4054 Molecular Response with Nilotinib in Patients with Philadelphia Negative (Ph-) Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENEST1st Sub-Analysis.

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Background: The cytogenetic hallmark of chronic myeloid leukemia (CML) is a translocation, t(9;22)(q34;q11), resulting in the Philadelphia (Ph) or derivative 22 chromosome. Cytogenetic studies indicate that 90-95% of cases have the Ph chromosome or recognized variant (Ph+ CML), with the remaining 5-10% having a normal or near normal karyotype despite the presence of the BCR-ABL fusion (Ph-negative, BCR-ABL-positive CML). Tyrosine kinase inhibitors (TKIs) have been approved

for the treatment of patients with Ph+ CML. The effect of TKIs in patients with Ph- CML has not been described in detail.

Objective: ENEST1st (Evaluating Nilotinib Efficacy and Safety in clinical Trials as First-Line Treatment) sub-group analysis was planned to explore the effect of nilotinib in patients with Ph- CML.

Patients and Methods: ENEST1st (NCT01061177) is a phase 3b, multicenter, open-label study of nilotinib 300 mg twice daily (BID) in adults with newly diagnosed BCR-ABL+ CML-CP. Patients with confirmed Ph- CML-CP were included in the sub-analysis. Primary endpoint was rate of MR4 (defined as BCR-ABL ≤ 0.01% on the International Scale [BCR-ABLIS] or undetectable BCR-ABL in cDNA with ≥ 10,000 ABL transcripts) at 18 mo.

Results: Of the 1089 patients included in ENEST1st study, 30 patients (2.7%) were Ph- (only one of those had a cytogenetic aberration [del9q34]), 983 patients (90.3%) were Ph+ and 76 (7.0%) patients had an unknown karyotype at baseline. Among these patients, 28 pts (2.7%) Ph- and 952 pts (90.5%) Ph + with b2a2 and/or b3a2 BCR-ABL transcripts and treated with imatinib for ≤ 3 mo were analyzed for molecular response (MR).

Median age of patients with Ph- CML was 51.5 years (range, 21.0 to 75.0). EUTOS score was low in 86.7% and high in 6.7% of patients (6.7% missing). Sokal risk score was low, intermediate, and high in 33.3%, 30.0%, and 23.3% of patients, respectively (13.3% missing).

In Ph+ CML patients, the median age was 53.0 years (range, 18.0 to 91.0). EUTOS score was low in 82.0% and high in 9.2% of pts (8.9% missing). Sokal risk score was low, intermediate, and high in 34.8%, 37.2%, and 18.1% of pts, respectively (9.9% missing).

The MR4 rate at 18 mo in Ph- population was 39.3% (95% CI, 21.2% - 57.4%). The cumulative incidence of MR4 by18 mo was 60.7% (95% CI, 42.6% - 78.8%). Rates of cumulative MMR (BCR-ABLIS ≤0.1%) and MR4.5 (BCR-ABLIS ≤0.0032%) by 18 mo were 85.7% (95% CI, 72.8% - 98.7%) and 46.4% (95% CI, 28.0% - 64.9%), respectively.

For the Ph+ CML population, the MR4 rate at 18 mo was 38.1% (95% CI, 35.0% - 41.2%).

The cumulative incidence of MR4 by 18 mo was 48.1% (95% CI, 44.9% - 51.3%). Rates of cumulative MMR (BCR-ABLIS ≤0.1%) and MR4.5 (BCR-ABLIS ≤0.0032%) by 18 mo were 76.8% (95% CI, 74.1% - 79.5%) and 31.4% (95% CI, 28.5% - 34.4%), respectively.

Rates of MMR, MR4, and MR4.5 at 18 and 24 mo among Ph- population and the Ph+ CML population are summarized in the Table.

The 3-month BCR-ABL level has been shown to be predictive of MR in the Ph+ CML population.

Among Ph- population not pretreated with imatinib (n = 14), 85.7% achieved BCR-ABLIS ≤ 1%, no patients had BCR-ABLIS > 1% to ≤ 10% and > 10% at 3 mo. Two patients did not have the assessment at 3 mo.

Among patients with Ph+ CML not pretreated with imatinib (n = 802), 70.0% , 17.0%, and 2.7% of patients achieved BCR-ABLIS ≤ 1% , > 1% to ≤ 10%, and >10% respectively. Eighty-five patients did not have the assessment at 3 mo.

Most common AEs experienced by the Ph- population were hypophosphatemia (25%), rash (18%), pruritus (14%), nasopharyngitis (14%), alanine aminotransferase increase (14%), and blood bilirubin increase (14%). In the Ph+ population, the list of most common AEs includes rash (22%), pruritus (17%), headache (16%), and fatigue (14%).

Conclusions: The MR rates observed in Ph- CML subgroup are similar to the rates observed in Ph+ CML patients. These results indicate that nilotinib is active in this previously unexplored population as well and larger studies should be conducted to confirm the results. The safety results observed in Ph-CML patients are similar to the ones observed in the Ph+ CML pts.

Nilotinib 300 mg BID[5]	MR at 18 and 24 mo	
	18 mo	24 mo
MMR		
Ph- (n = 28)	60.7%	50.0%
Ph+ (n = 952)	66.0%	61.4%
MR[4]		
Ph-	39.3%	35.7%
Ph+	38.1%	40.4%
MR[4.5]		
Ph-	25.0%	7.1%
Ph+	20.9%	22.5%

aCML patients with typical b2a2 and/or b3a2 BCR-ABL transcripts and ≤3 mo of prior imatinib

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