1675 Early Response (Molecular and Cytogenetic) and Long-Term Outcomes in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Exploratory Analysis of DASISION 3-Year Data

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Background: In the randomized phase 3 DASISION trial in patients (pts) with newly diagnosed CML-CP, dasatinib 100 mg once daily (QD) demonstrated improved efficacy over imatinib 400 mg QD and an acceptable tolerability profile (NEJM 2010 362 2260). At 3 years (y) pts achieved high rates of progression free survival (PFS) (91% both arms) and overall survival (OS) (94%, dasatinib; 93%, imatinib). Compared with pts receiving imatinib, pts receiving dasatinib achieved higher rates of cytogenetic and molecular responses, shorter time to responses, and fewer transformations to accelerated/blast phase (AP/BP) (JCO 2012 30 6504). Marin et al reported that BCR-ABL levels at 3 and 6 months (mo) with imatinib were significantly correlated with 8-y PFS and OS (JCO 2012 30 232), and Hanfstein et al proposed BCR-ABL levels of 10% at 3 mo and 1% at 6 mo as clinically important landmarks correlated with 5-y PFS and OS (Leukemia 2012 Epub). The aim of this exploratory analysis was to investigate the impact of early molecular and cytogenetic response on the outcome of pts enrolled in the DASISION trial.

Methods: Pts with CML-CP were randomized to receive dasatinib 100 mg QD (n=259) or imatinib 400 mg QD (n=260). Methods have been previously reported (NEJM 2010

362 2260). PFS and OS rates were obtained from Kaplan-Meier estimates. Qualifying events for PFS included: increasing white blood cells, loss of complete hematologic response or major cytogenetic response, transformation to AP/BP, or death.

Results: More dasatinib v imatinib pts achieved a partial cytogenetic response (PCyR) or complete CyR (CCyR) at 3 mo (81% v 67%) and at 6 mo (91% v 81%). Significantly higher rates of 3-y PFS were observed in pts with PCyR/CCyR at 3 mo (P<.0001, P=.0026 for dasatinib, imatinib) or at 6 mo (P=.0172, <.0001). Of pts with 3-mo molecular analyses (235 dasatinib, 239 imatinib), more pts treated with dasatinib achieved BCR-ABL ≤10% (84% v 64%) or ≤1% (48% v 13%). Of pts with 6-mo molecular analyses (236 dasatinib, 236 imatinib), more pts treated with dasatinib achieved BCR-ABL ≤10% (89% v 83%) or ≤1% (70% v 50%). Pts with BCR-ABL ≤10% at 3 mo had significantly better 3-y PFS (dasatinib: 93.1% v 68.2%, P=.0003; imatinib: 95.9% v 75.3%, P<.0001) and OS (dasatinib: 95.9% v 85.9%, P=.0348; imatinib: 96.0% v 88.0%, P=.0036). Pts with BCR-ABL ≤1% at 6 mo had significantly better PFS (dasatinib: 94.9% v 84.6%, P=.0020; imatinib: 97.4% v 83.8%, P=.0016) and with imatinib significantly better OS (97.4% v 93.6%, P=.0215). The difference between BCR-ABL ≤1% v >1-10% at 6 mo was not significant. Pts with BCR-ABL ≤10% and ≤1% at 3 and 6 mo had a lower risk of transformation within 3 y (Table); transformation was associated with a high risk of death (overall 50% mortality within 7 mo). In addition, pts receiving imatinib who had a poor response at 3 mo (BCR-ABL >10%) who achieved ≤10% at 6 mo still had a higher risk of transformation in comparison with those who achieved an initial deeper response at 3 mo. However, no patient on dasatinib with BCR-ABL >10% at 3 mo and ≤10% at 6 mo transformed.

Conclusions: More pts treated with dasatinib achieved a faster, deeper cytogenetic and molecular response, which was associated with better 3-y outcomes and lower risk of transformation to AP/BP. The clinical importance of achieving deeper levels of cytogenetic response (CCyR) at 6 mo will be presented. Early response landmarks may identify pts at higher risk for transformation, poor outcome, and those who may benefit from alternate treatments to improve responses and thereby minimize exposure to risk over time. More pts starting on imatinib compared with dasatinib transformed to AP/BP than those receiving dasatinib. These exploratory data highlight the clinical importance of a fast and deep response, with the potential to reduce the risk of transformation and improve long-term outcomes. OS data at 3 y in DASISION are immature and longer-term follow up is planned.

Table: Landmark analysis of transformation to AP/BP within 3 y based on BCR-ABL level

	Relative risk of transformation Hazard ratio [95%CI] Pts transformed, n/N	
BCR-ABL level	**Dasatinib** **100 mg QD**	**Imatinib** **400 mg QD**
At 3 mo		
>10% v ≤10%	6 [2, 20] 5/37 v 6/198	6 [2, 19] 11/85 v 4/154
>1% v ≤1%	3 [1, 10] 8/123 v 3/112	- - 15/207 v 0/32
At 6 mo		
>10% v ≤10%	13 [3, 46] 5/26 v 5/210	10 [3, 31] 7/41 v 5/197
>1% v ≤1%	6 [2, 24] 7/72 v 3/164	12 [2, 94] 11/121 v 1/117

"-" indicates no pts transformed in one of the groups so the hazard ratio could not be calculated

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