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Safety and Efficacy of adding pegylated Interferon–α2b to standard Dose Dasatinib in newly diagnosed CP-CML

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Rationale: Dasatinib (DAS) and interferon have different modes of action and may have synergistic activity in CML, due to both antineoplastic and immunostimulatory mechanisms. Addition of pegylated interferon (PegIFN) to imatinib therapy in CP CML has in previous clinical trials (French

SPIRIT and NordCML002) resulted in deeper molecular response. Thus, an optimal combination of DAS and PegIFN may increase the proportion of patients who reach deep molecular response with potential for treatment-free remission (TFR).

Design: Newly diagnosed CP-CML patients were treated with DAS (Sprycel, BMS) 100mg OD as single drug for three months. Thereafter weekly subcutaneous injections of Peg-IFN α2b (PegIntron, MSD) was added to DAS; from end of month 3 (M3) to M6, 15µg/week, thereafter 25µg/week until M15. Primary end points were safety and the rate of MMR at M12. The doses of PegIFN were lower than in the SPIRIT study to increase adherence.

Population: Forty patients were included at 14 university centers. One patient was lost to follow-up and one patient stopped DAS before starting PegIFN due to headache. Hence, 40 patients were evaluated for toxicity and 39 were analysed for efficacy. Mean and median age was 48 years (range 19-71). The proportions of high risk patients were 27% (Sokal), 16% (Hasford), and 18% (EUTOS).Data from M0 to M12 are reported here.

Safety and dosing: Treatment was well tolerated with expected DAS and PegIFN related side effects. Six patients had seven serious adverse events, all hospitalizations. 1 episode each of bradycardia/atrial fibrillation (possibly PegIFN-related), headache (DAS), fever (PegIFN), anaphylaxis-like reaction (PegIFN) , fever/malaise/headache (PegIFN), pneumonia and a knee effusion (both unrelated). One pleural effusion occurred (3%). Grade 3-4 neutropenia and thrombocytopenia occurred in 6 and 9 patients respectively. Prolonged hematological toxicity (>2months) occurred in 8 patients, causing dosing problems in 5. One patient suffered grade 3 depression. Grade 3 flu-like symptoms occurred in 2 patients. One patient had lipase elevation grade 3 and one patient developed hypothyroidism attributed to PegIFN. Grade 2 dermal problems like rash and acne occurred in about 20%, attributable to both drugs. 94% (DAS) and 76% (PegIFN) of assigned dose was given. Dose reductions occurred in 19 patients for DAS and 20 patients for PegIFN. Two patients discontinued DAS and switched to nilotinib, 1 for headache at M3 and 1 at M12 for lack of efficacy/hematological toxicity. Two patients could not start PegIFN for hematological toxicity (one lost to follow-up after M6). PegIFN was discontinued because of bradycardia/atrial fibrillation (1 pat), anaphylaxis (1 patient), flu-like syndrome (2 pats) and long-term hematological toxicity (2 pats). At 12 months 31/38 pats (82%) were still on PegIFN, much higher than in French Spirit or NordCML002.

Efficacy: We have used the DAS arm of the Dasision study (Kantarjian NEJM 2010) as a historical control. Early response at M3 was very similar between studies. In the present and the Dasision cohorts respectively, 18% vs 16% missed the 10% BCR-ABL^{IS} landmark, 66% vs 56% achieved a CCyR and 10% vs 8% achieved MMR. At M6, three months after introduction of PegIFN, a steep increase in MMR was observed compared with Dasision. This was also reflected in deep responses, MR4.0 (see tables) and MR4.5 at M12, 23% vs 5%. The primary efficacy endpoint was MMR at M12, 81% vs 46%.

MMR	DAS+PegIFN (%)	DAS (Dasision)(%)	Difference (%)
M3	**10**	**8**	**2**
M6	**55**	**27**	**28**
M9	**70**	**39**	**31**
M12	**81**	**46**	**35**

MR4.0	DAS+PegIFN (%)	DAS (Dasision)(%)	Difference (%)
M3	**3**	**0**	**3**
M6	**24**	**6**	**18**
M9	**38**	8	**30**
M12	**45**	**12**	**33**

Progressions and treatment failure defined by ELN 2013: Failures: No progression was noted. At M3, 2 patients still had >95% Ph+ metaphases (MF). At M6, four patients (11%) had > 35% Ph+MF or >10% BCR-ABL levels. At M12, one patient failed CCgR and two more patients failed <1% BCR-ABL. No BCR-ABL mutations were detected in "failure" patients.

Conclusion: The combination of DAS and low dose PegIFN can be safely administered in newly diagnosed CP CML. No unexpected autoimmune phenomena were observed, and pleural effusions were rare. Efficacy appears very promising with high early MMR rates and deep molecular responses. A randomized comparison DAS +/- PegIFN is warranted.

Support: Study drug from BMS and MSD. Grant from BMS.

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Extra tables FYI, not for ASH submission

MMR	DAS+PegIFN (%)	Dasision(%)	006	Radich
M3	10	8	37	19
M6	55	27	67	33
M9	70	39	71	43
M12	81	46	81	58

MR4.0	DAS+PegIFN (%)	(Dasision)(%)	006	Radich
M3	3	0	18	9
M6	24	6	33	19
M9	38	8	33	23
M12	45	12	56	27