Results from a Phase IIa Study of the Anti-CXCL12 Spiegelmer® Olaptesed Pegol (NOX-A12) in Combination with Bendamustine/Rituximab in Patients with Chronic Lymphocytic Leukemia

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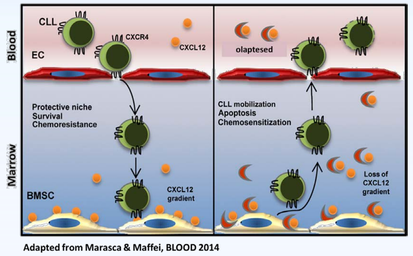
BACKGROUND



Adapted from Marasca & Maffei, BLOOD 2014

Olaptesed pegol is a novel, L-stereoisomer RNA aptamer (Spiegelmer®) that binds and neutralizes CXCL12/SDF-1, a chemokine which attracts and activates immune- and non-immune cells via interaction with the receptors, CXCR4 and CXCR7. Signaling of CXCL12 is pivotal to the interactions of leukemic cells with bone marrow microenvironment. The therapeutic concept of olaptesed is to inhibit such tumor-supporting pathways and thereby to mobilize and sensitize CLL cells to therapy.

Here we aim to assess the activity and safety of olaptesed in combination with bendamustine and rituximab (BR) in patients with relapsed / refractory CLL.

METHODS

28 relapsed or refractory CLL patients were enrolled and treated in this open-label, single-arm Phase IIa study:

- For PK/PD investigation, administration of 1,2 or 4 mg/kg olaptesed alone to 3 pts/group (+ additional replacement pt) (pilot group only)
- Subsequently, dose titration with intravenous (IV) olaptesed at 1,2 and 4 mg/kg at cycles 1, 2 and 3, respectively, 1h before rituximab (RTX) treatment
- During cycles 4 to 6, olaptesed dosed at the highest individually titrated dose
- RTX administered IV at 375 mg/m² on day 1 of 1st 28-day cycle and 500 mg/m² on day 1 of subsequent cycles
- Bendamustine (70 - 100 mg/m²) given IV on days 2-3 (cycle 1) or days 1-2 (cycles 2-6) of each 28-day cycle following RTX
- Clinical response assessed according to NCI-WG Guidelines (Hallek et al. Blood 111; 2008: 5446-56).

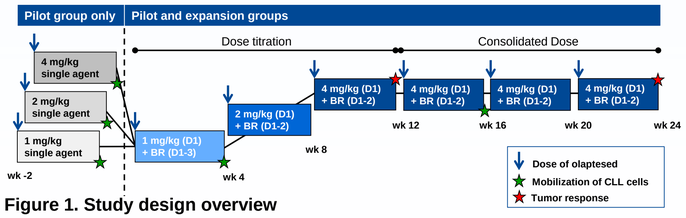


Figure 1. Study design overview

RESULTS

Patient Characteristics		
Number/gender	N = 28	12 w, 16 m
Age (years)	41 - 79	median 67
Binet stage	A:	6
	B:	11
	C:	11
Prior treatment	1 line	17
	2 lines	10
	3 lines	1
Fludarabine / Bendamustine	naive:	5
	pretreated:	23

- Rapid mobilization of CLL cells by a single dose of olaptesed, lasting throughout the observation time of 72h (Fig. 2, left panel)
- Notably, RTX depletes CLL cells in cycle 1 at 3-24h so mobilization only observed at 1h (Fig. 2, middle panel).
- However in cycle 4, effective mobilization still observed for up to 24h (Fig. 2, right panel).

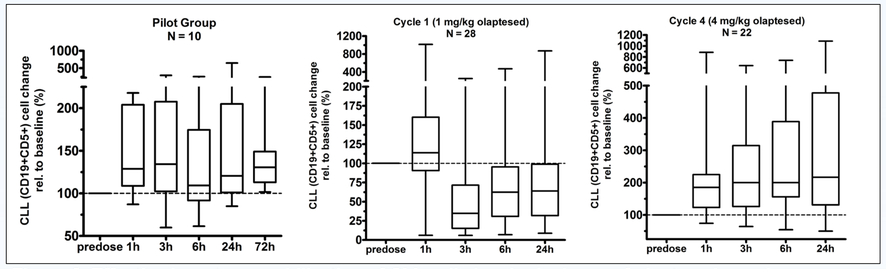


Figure 2. Effective long-term mobilization of CLL cells by single doses of olaptesed pegol.

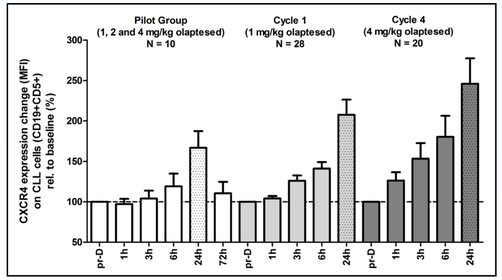


Figure 3. Increase of CXCR4 expression on CLL cell surface in the course of long-term mobilization.

- CXCR4 expression levels increased on CLL cell surface in the periphery after olaptesed treatment (Fig. 3)
- This increase (peak at 24h) reflects the extended circulation of CLL cells in the periphery due to the sustained blockade of CXCL12 by olaptesed (Fig. 3)

Reduction of lymphadenopathy by ≥ 50% was achieved in 17 out of 22 evaluable patients with reported enlarged lymph nodes by the end of treatment. Concomitantly, rapid reduction of lymphocytosis in peripheral blood with normalization by treatment cycle 2 – 3 was observed and the CLL to leukocyte ratio improved significantly (Fig. 4).

Efficacy was assessed at end of cycle 6. In the intent-to-treat population, the overall response rate was 82%: four patients (14%) achieved a complete response (2 confirmed, 2 investigator reported) and nineteen patients (68%) achieved a partial response.

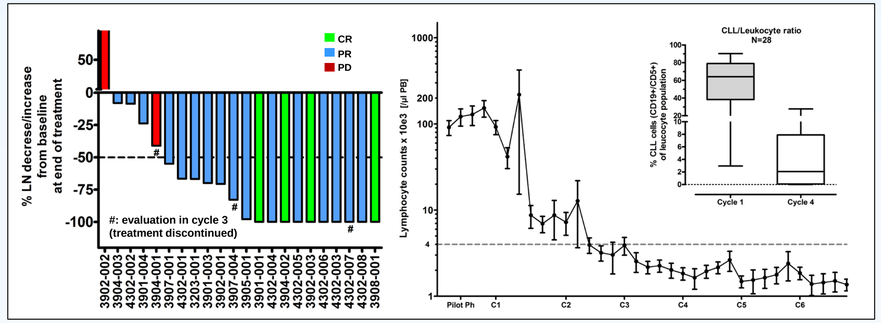


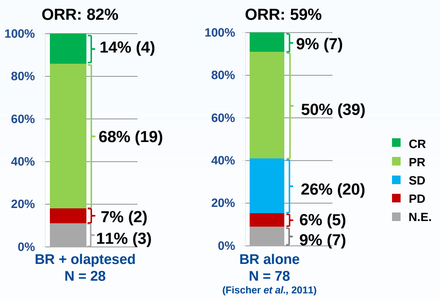
Figure 4. Lymphadenopathy and lymphocyte count /ratio changes.

Notably, all 8 high-risk patients [defined as relapsed within 24m after fludarabine/bendamustine treatment (n=5) or presenting a TP53-deletion/mutation (n=3]) responded to treatment with olaptesed + BR with a partial or even complete response. Treatment with olaptesed at 1, 2 and 4 mg/kg in combination with BR was safe and well tolerated. The observed adverse reactions were qualitatively and quantitatively as expected for patients treated with BR.

CONCLUSION

Olaptesed in combination with BR was safe and well tolerated.

Compared with historical data, olaptesed showed superiority over baseline therapy (Fischer *et al.*, 2011) with regards to overall response rate and increasing rates of complete remission, warranting further development of this Spiegelmer® in CLL.



ACKNOWLEDGEMENTS & DISCLOSURES

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AK, TD and KR are employees of NOXXON.