C1.**PRELIMINARY RESULTS OF THE CLL11 (BO21004) TRIAL**

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Background:

Chronic lymphocytic leukemia (CLL) is characterized by the expansion of the malignant clone leading to compromised bone marrow and immune function. One important goal of therapy is to reduce the tumor burden and to restore normal haematopoetic function. In preclinical experiments, the novel type II, glycoengineered anti-CD20 mAb obinutuzumab (GA101) demonstrated increased B-cell depleting activity in blood, lymph nodes and spleen of cynomolgus monkeys compared to rituximab (R) (Mössner et al., Blood 2010). We participated in a large randomized, prospective phase 3 trial (CLL11, BO21004) in untreated CLL patients with coexisting medical conditions to compare outcome and safety of GA101+Clb (GClb) or rituximab+Clb (RClb) with Clb alone. During the safety run-in phase we observed a very rapid removal of lymphocytes from peripheral blood of six patients after first administration of GClb (Goede et al, Leukemia, 2013). We present the changes in B-cells, hemoglobin (Hb), platelets and neutrophils from baseline to end of treatment as observed in the stage 1 analysis of the CLL11 trial.

Methods:

Treatment-naïve CLL patients with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min were eligible. Patients received Clb alone (0.5 mg/kg po d1, d15 q28 days, 6 cycles), GClb (100 mg iv d1, 900 mg d2, 1000 mg d8 and d15 of cycle 1, 1000 mg d1 cycles 2-6), or RClb (375 mg/m2 iv d1 cycle 1, 500 mg/m2 d1 cycles 2-6). The B-cells, Hb, platelet and absolute neutrophil count (ANC) counts were measured at baseline, during treatment and at the end of treatment. Immunoglobulin levels were measured in all patients at baseline and at the end of treatment.

Results:

The median number of treatment cycles received was 6 in all treatment arms and patients received similar total cumulative doses of Chlorambucil. Both RClb and GClb induced a rapid and more profound reduction in lymphocytes than Clb alone. GClb achieved lymphocyte reduction faster and to a deeper level than RClb (Table 1).

In the Clb treatment arm, the median hemoglobin level remained relatively stable during treatment, while a clear trend towards an improvement was observed in the anti-CD20 containing arms.

Platelet count slightly decreased during Clb treatment and improved with GClb and RClb. Neutrophil count dropped below baseline in all three treatment arms. There were no changes in the median IgA, IgG and IgM levels for all three treatment arms during chemoimmunotherapy.

Conclusions:

The addition of CD20 monoclonal antibodies to Clb leads to a faster and deeper decrease of lymphocytes from peripheral blood than Clb alone. GClb induces an almost immediate and complete lymphocyte depletion whilst RClb acts more gradually. Despite the profound B-cell depletion with GClb and RClb, immunoglobulin levels remain unchanged until the end of treatment. Overall the data suggests that GA101 may have superior B-cell depleting activity compared to rituximab which could result in enhanced recovery of bone marrow function and increased efficacy as previously reported (Goede et al JCO 2013 abstract 4005 ASCO).

Table 1: Absolute lymphocyte count (median, range)

	BL	C1D15	C2D1	C4D1	C6
Clb	71.07 (4.64-437.86)	47.30 (2.88-296.13)	23.17 (0.88-221.55)	11.30 (0.52-195.80)	7.51 (0.60-158.50)
G-Clb	54.36 (0.41-764.00)	1.05 (0.04-33.92)	1.02 (0.05-126.00)	0.90 (0.10-20.20)	0.83 (0.14-6.63)
Clb	71.07 (4.64-437.86)	47.30 (2.88-296.13)	23.17 0.88-221.55)	11.30 (0.52-195.80)	7.62 (0.60-158.50)
R-Clb	52.69 (0.00 – 558.72)	10.14 (0.00 – 426.00)	3.42 (0.00-120.90)	1.61 (0.00-62.27)	1.26 (0.00 – 83.50)