

Final results of a Phase 1/2 study of SYK inhibitor Entospletinib in combination with Obinutuzumab in patients with relapsed/refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Alexey V Danilov*, Vi Lam, Bria Thurlow, Byung Park, Adam Kittai
*City of Hope National Medical Center, Duarte, CA Adanilov@coh.org

Introduction

Therapeutic resistance and intolerance of Bruton tyrosine kinase (BTK) inhibitors is an emerging need in CLL. SYK is integral to the activation of BTK and the B-cell receptor (BCR) signaling cascade and is overexpressed in CLL. We have shown that BAFF-mediated SYK activation triggered BCR signaling and rendered protection of CLL cells from spontaneous apoptosis *in vitro* as well as disrupted BAFF-BCR cross-talk (Fig 1). Single agent small molecule SYK inhibitor entospletinib was efficacious in treatment of patients with R/R CLL. Here we report final results of a single arm, open label, investigator-initiated phase 1/2 clinical trial which evaluated safety and efficacy of entospletinib in combination with obinutuzumab, a glycoengineered monoclonal anti-CD20 antibody, in patients with R/R CLL (NCT03010358).

Methods

Patients enrolled in the Phase 1 dose-escalation portion of the trial included adults with CLL or non-Hodgkin lymphoma (Phase 1 part only) after ≥ 1 prior therapy. Patients were enrolled at 2 dose levels to receive entospletinib 200 or 400 mg twice-daily orally according to 3+3 design (Table 1). The primary endpoint for the phase 1 portion of the study was to determine the RP2D of the combination. All patients received single agent entospletinib as part of a 7-day run-in. Thereafter, patients received entospletinib on days 1-28 of each 28-day cycle continuously, and obinutuzumab intravenously in standard doses for 6 cycles. Once the RP2D was determined, a phase 2 study enrolled patients with R/R CLL only, where complete response (CR) was the primary endpoint. A total of 24 patients (22 CLL, 2 follicular lymphoma) were enrolled.

Phase I

Twelve patients were enrolled in the phase 1 part of the study. The phase 2 part of the study included 17 patients with CLL. Of 6 patients who received entospletinib 200 mg on the Phase 1 part of the study, one patient experienced a DLT (grade 3 asymptomatic AST/ALT abnormalities) attributed to entospletinib. No DLTs were observed among the six patients who received entospletinib 400 mg. Thus, entospletinib 400 mg twice-daily was determined to be the RP2D in combination with obinutuzumab.

Figure 1. SYK inhibitor ENTOSpletinib abrogates BAFF-BCR cross-talk in CLL

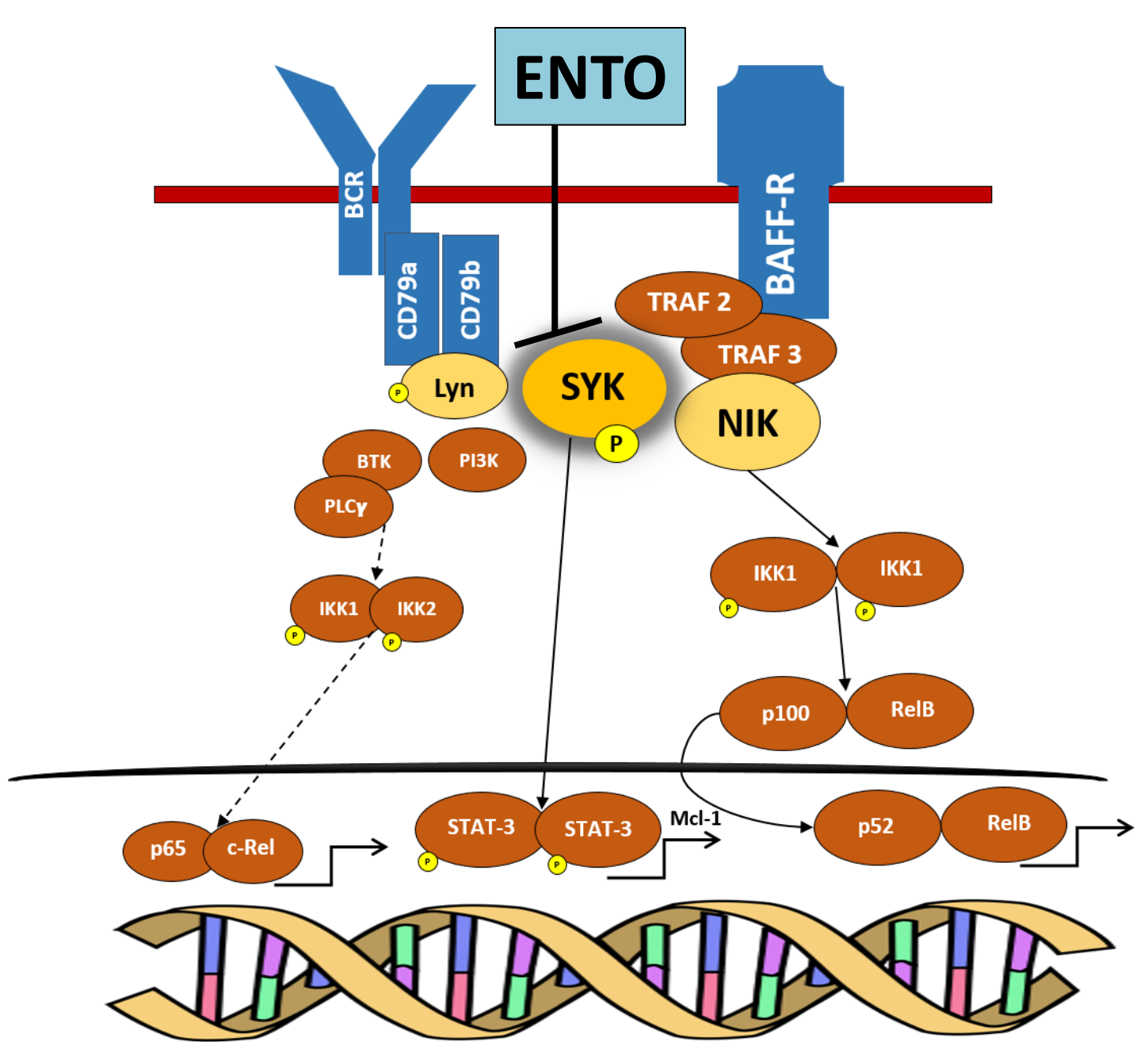


Table 1. Phase I Dosing Schema

Dose level	Entospletinib starting on day -7 of the run-in phase	Obinutuzumab (cycles 1-6)
-1	200 mg po daily	C1D1 – 100 mg IV
1	200 mg po BID	C1D2, 8, 15 – 1000 mg IV
2	400 mg po BID	C2-6 – 1000 mg IV on day 1

Table 2. Patient Characteristics (n=21, CLL)

Characteristics	All patients N = 21	(%)
Age		
< 65 years	7	(33.3)
≥ 65 years	14	(66.7)
Sex		
Male	15	(71.4)
Female	6	(28.6)
ECOG performance status		
0	8	(38.1)
1	12	(57.1)
2	1	(4.8)
FISH		
Deletion 13q	14	(66.7)
Trisomy 12	3	(14.2)
Deletion 11q	2	(9.5)
Deletion 17p	5	(23.8)
Complex Karyotype (CK, ≥ 3 abnormalities)	6	(28.6)
CK + TP53 aberration	5	(23.8)
≥ 5 abnormalities	1	(4.8)
Mutational Status		
TP53	9	(42.9)
Notch1	2	(9.5)
SF3B1	4	(19.0)
High Risk CLL**	13	(61.9)
Prior Treatments		
1	6	(28.6)
2	8	(38.1)
≥ 3	7	(33.3)
Fludarabine	12	(57.1)
Bendamustine	14	(66.7)
Ibrutinib	7	(33.3)
Idelalisib	1	(4.8)

Table 3. Adverse Events (all pts)

Adverse Event	All Patients (N=23)	
	Any Grade	Grade ≥ 3
Adverse Events - All	22 (95.7)	15 (65.2)
Hematologic AEs:		
Neutrophil count decreased	11 (47.8)	10 (43.5)
Platelet count decreased	5 (21.7)	4 (17.4)
Anemia	3 (13.0)	1 (4.3)
Febrile neutropenia	2 (8.7)	2 (8.7)
Non-hematologic Adverse Events:		
Fatigue	11 (47.8)	2 (8.7)
Infusion related reaction	10 (43.5)	4 (17.4)
Nausea	8 (34.8)	1 (4.3)
Diarrhea	7 (30.4)	0
Fever	8 (34.8)	0
Alanine aminotransferase increased	5 (21.7)	3 (13.0)
Aspartate aminotransferase increased	5 (21.7)	3 (13.0)
Infection	5 (21.7)	1 (4.3)
Creatinine increased	4 (17.4)	0

Phase II

Efficacy was analyzed in the 21 patients with CLL, of which 17 received entospletinib at RP2D (400 mg twice daily). Patients with CLL had a median age of 66 years (Table 2). Thirteen patients (62%) had *TP53* aberration (n=9), CK (n=6), or *NOTCH1* or *SF3B1* mutation. The median number of prior therapies was two (range, 1-6). Seven patients had received prior ibrutinib (4 patients discontinued due to intolerance and 2 due to progression). Median follow-up was 31 mos. Among the 21 efficacy-evaluable participants with CLL, the ORR was 67% (95%CI, 43–85%). Three patients (14%, 95%CI 3–36%) achieved a CR, and 11 patients (53%) had a partial response (PR). Two out of 3 patients with confirmed CR had undetectable MRD in the bone marrow. Median event-free survival was 27.5 months (95%CI: 16 months–NR), treatment duration – 31 months (95%CI: 27–40; Figure 2). Thirteen patients with high-risk CLL had an ORR of 54% (5 PRs and 2 CRs). Among the eight patients who had previously received kinase inhibitors, ORR was 62.5% (all PRs).

Treatment-related adverse events were reported in 96% of patients (Table 3). Grade 3 or higher AEs occurred in 65%. Neutropenia (43.5%; including 4 patients [17%] who had transient grade 4 neutropenia attributed to obinutuzumab) was the most common grade ≥ 3 hematologic toxicity. The median onset of neutropenia was 7 days after the first obinutuzumab infusion, median duration was 28 days. Growth factor support was not required and grade ≥ 3 infection occurred in only 1 patient. Only one patient on study discontinued therapy due to adverse events (recurrent AST/ALT abnormalities which resolved upon cessation of entospletinib).

Pharmacodynamic analysis demonstrated that treatment with entospletinib led to rapid downmodulation of pSTAT3 and the anti-apoptotic protein MCL1 in CLL cells. Furthermore, six months of combination therapy was accompanied by a reduction in IFN γ secretion in CD4 $^{+}$ T-cells and a reversal of exhausted phenotype, as evidenced by downregulation of PD-1 (Figure 3).

Conclusions

The combination of entospletinib and obinutuzumab shows an acceptable safety profile. Efficacy of this combination (EFS 27.5 months in predominantly high-risk population) compares favorably with chlorambucil/obinutuzumab in R/R CLL (13 months), thus warranting continued exploration of the regimen.

References

- Paiva C, Rowland TA, Sreekantham B, Godbersen C, Best SR, Kaur P, et al. SYK inhibition thwarts the BAFF - B-cell receptor crosstalk and thereby antagonizes Mcl-1 in chronic lymphocytic leukemia. *Haematologica*. 2017;102(11):1890-900.
- Chiron D, Bellanger C, Papin A, Tessoulin B, Dousset C, Maiga S, et al. Rational targeted therapies to overcome microenvironment-dependent expansion of mantle cell lymphoma. *Blood*. 2016;128(24):2808-18.

Figure 2. Event-free survival (top) and duration of treatment (bottom)

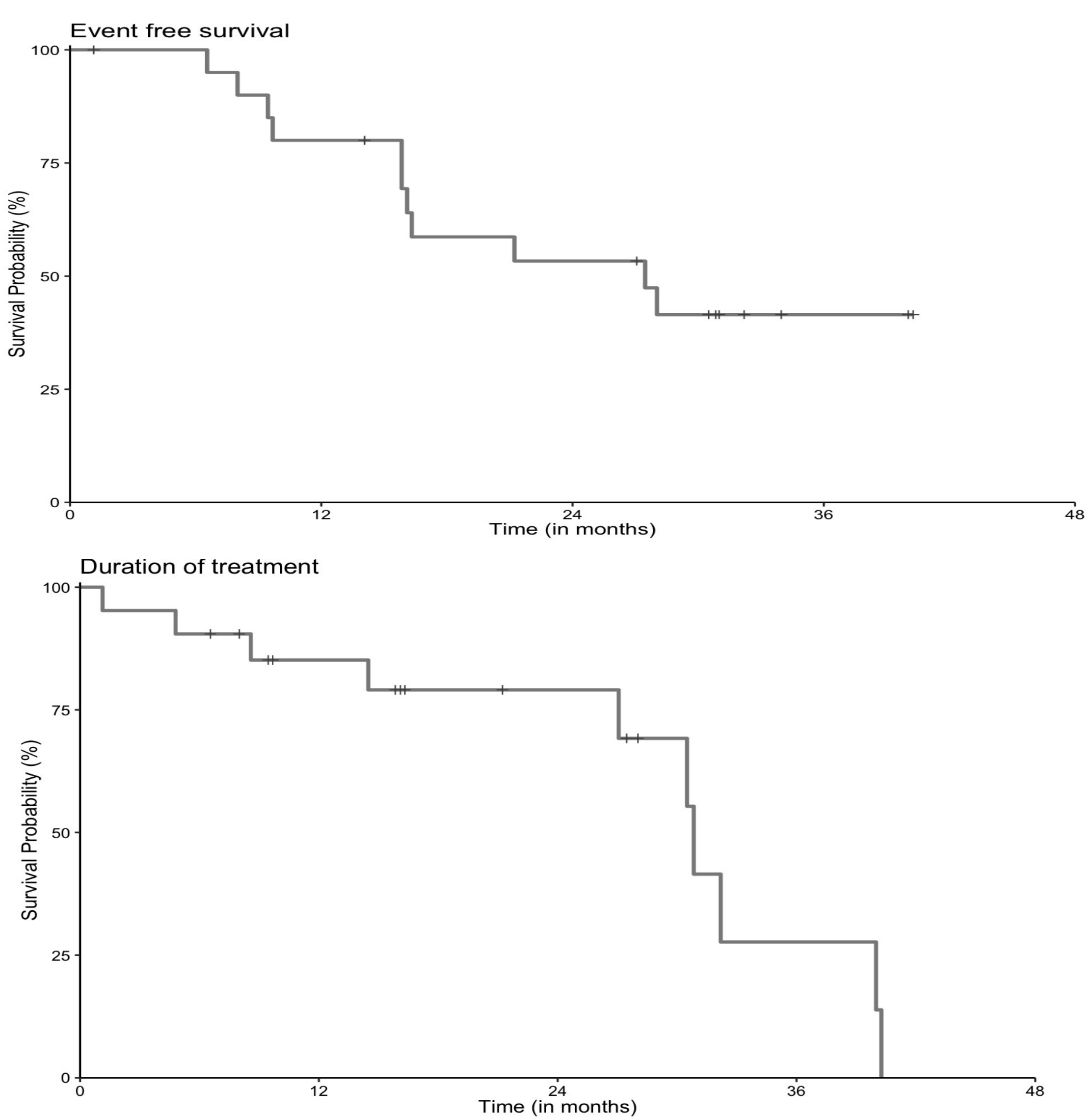


Figure 3. Immune effects of combination therapy with ENTO-OBIN in CLL

