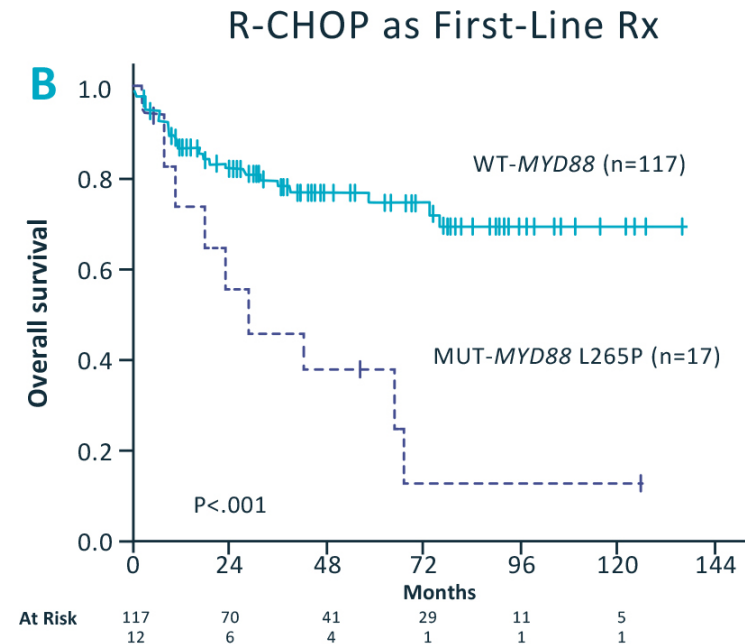
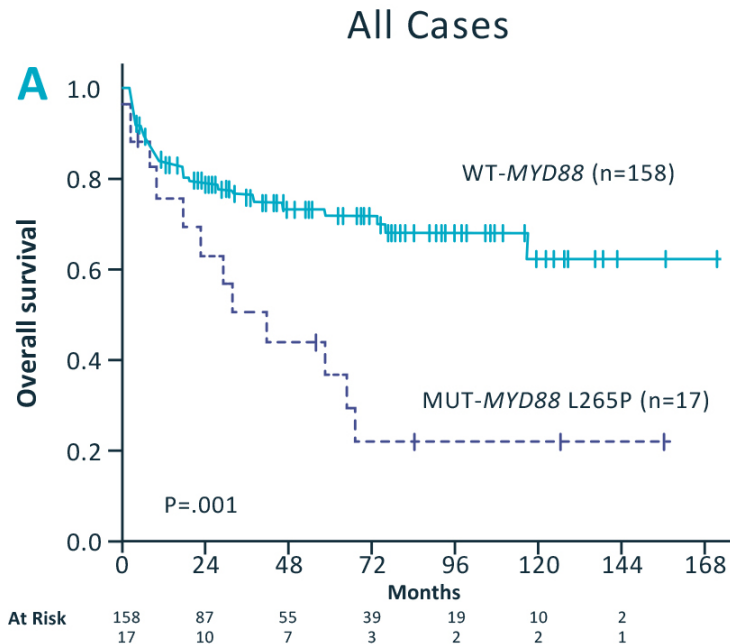


Novel Approach to the Potential
Treatment of Patients with B-Cell Lymphomas
Harboring the MYD88 L265P Mutation:
Combination Treatment with TLR Antagonist and Rituximab

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MYD88 L265P oncogene over-activates TLR7- and TLR9-mediated signaling pathways that promote B-cell survival and proliferation¹



MYD88 L265P in DLBCL patients is associated with decreased overall survival, including in those treated with first-line R-CHOP²

DLBCL patients harboring only the MYD88 L265P mutation (n=5 of 66 evaluable) did not respond to ibrutinib in Phase 2 clinical trial³

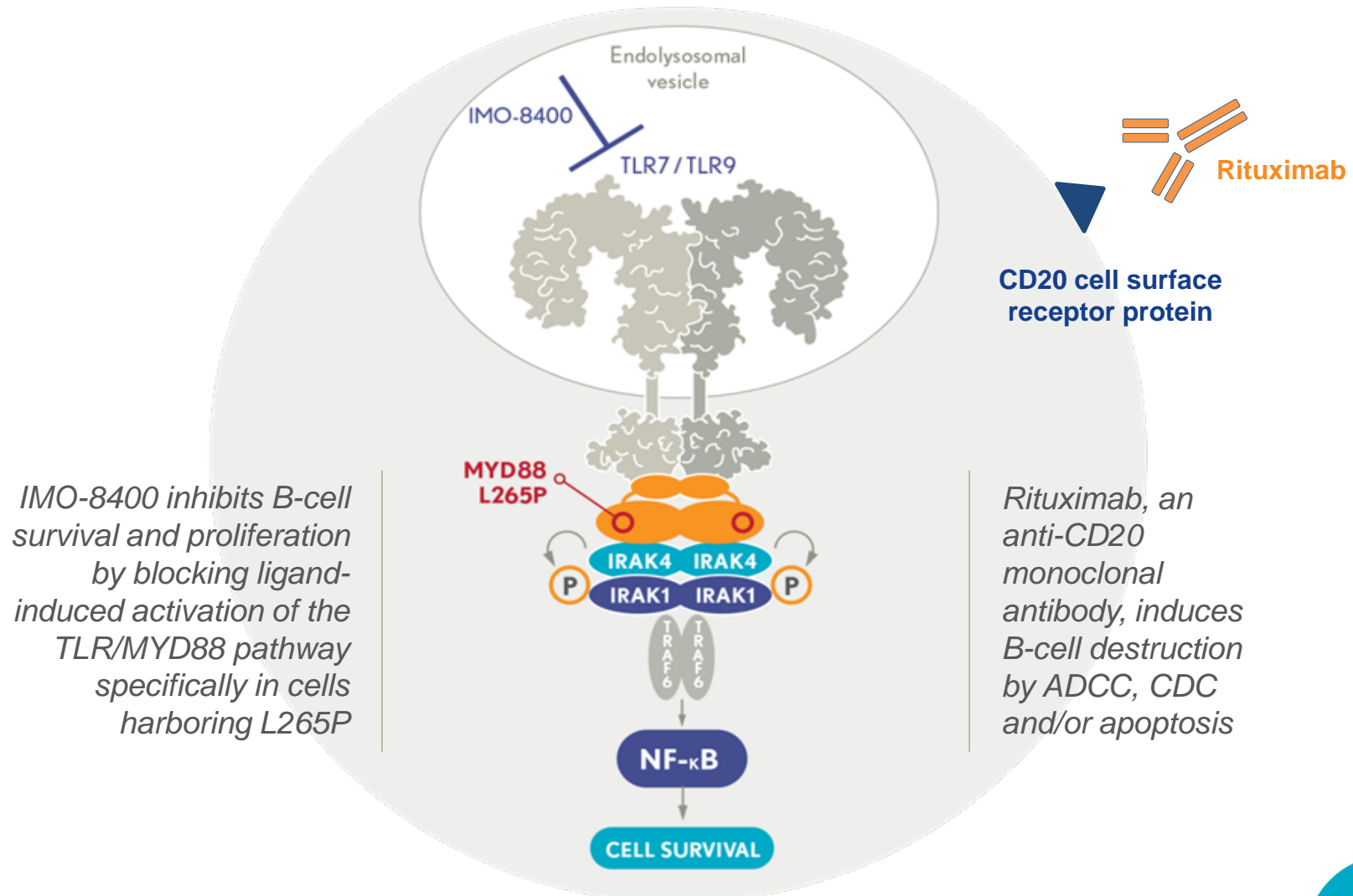
¹ Lim *et al.* AACR 2013 Abstract #2332 | ² Fernandez-Rodriguez *et al.* Leukemia 2014, 28:2104-6 | ³ deVos *et al.* EHA 2013 Abstract #S1180

IMO-8400, a synthetic oligonucleotide-based antagonist of TLRs 7, 8 and 9

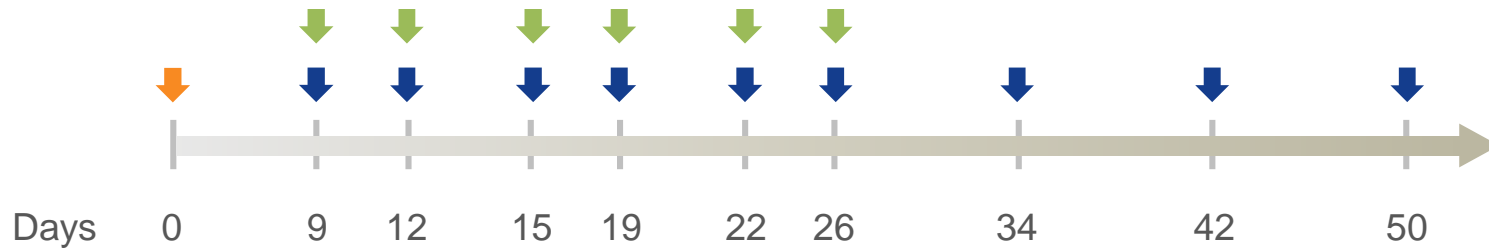
- Inhibited TLR signaling and decreased tumor cell viability in B-cell lymphoma cell lines harboring MYD88 L265P mutation
- Tumor growth inhibition in xenograft models correlated with reduced tumor-secreted cytokines and with inhibition of MYD88 L265P-driven signaling pathways including JAK/STAT, NF- κ B and p38
- Well tolerated in Phase 1 and Phase 2 clinical trials in healthy volunteers and patients with psoriasis, with no pattern of hematological or other toxicity observed through 12 treatment weeks
- Most common treatment-related adverse events in more than one subject were injection site reactions
- Ongoing Phase 1/2 monotherapy clinical trials in Waldenström's macroglobulinemia and DLBCL harboring MYD88 L265P mutation

* AACR 2014, Abstract #2570; ASH 2014, Abstract #3101

IMO-8400 and rituximab: potentially complementary mechanisms for treatment of MYD88 L265P-positive B-cell malignancies



IMO-8400 and rituximab in ABC-DLBCL OCI-Ly10 xenograft model



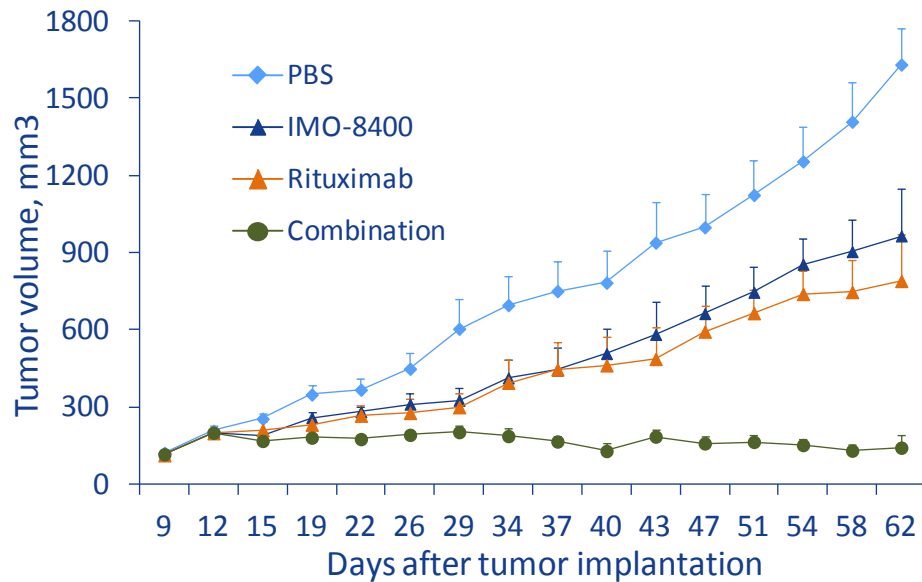
↓ 5 x 10⁶ OCI-Ly10 cells, s.c.

↓ IMO-8400: 25 mg/kg, i.p.

↓ Rituximab: 10 mg/kg, i.p.

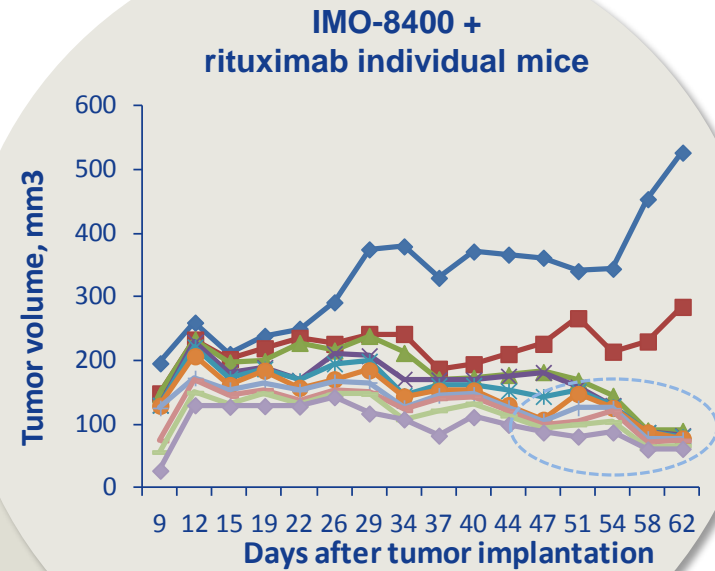
- Groups (n=10 each)
 - PBS, IMO-8400, rituximab, IMO-8400 + rituximab combination
- Treatment initiated on day 9 when tumor nodules reach ~100 mm³
- Terminated when average of tumor volume reached ~1.5 grams
- Analyzed tumor-secreted cytokines in serum
- Collected and saved tumor nodules for further analyses

Antitumor activity of IMO-8400 plus rituximab in OCI-Ly10 ABC-DLBCL xenograft model

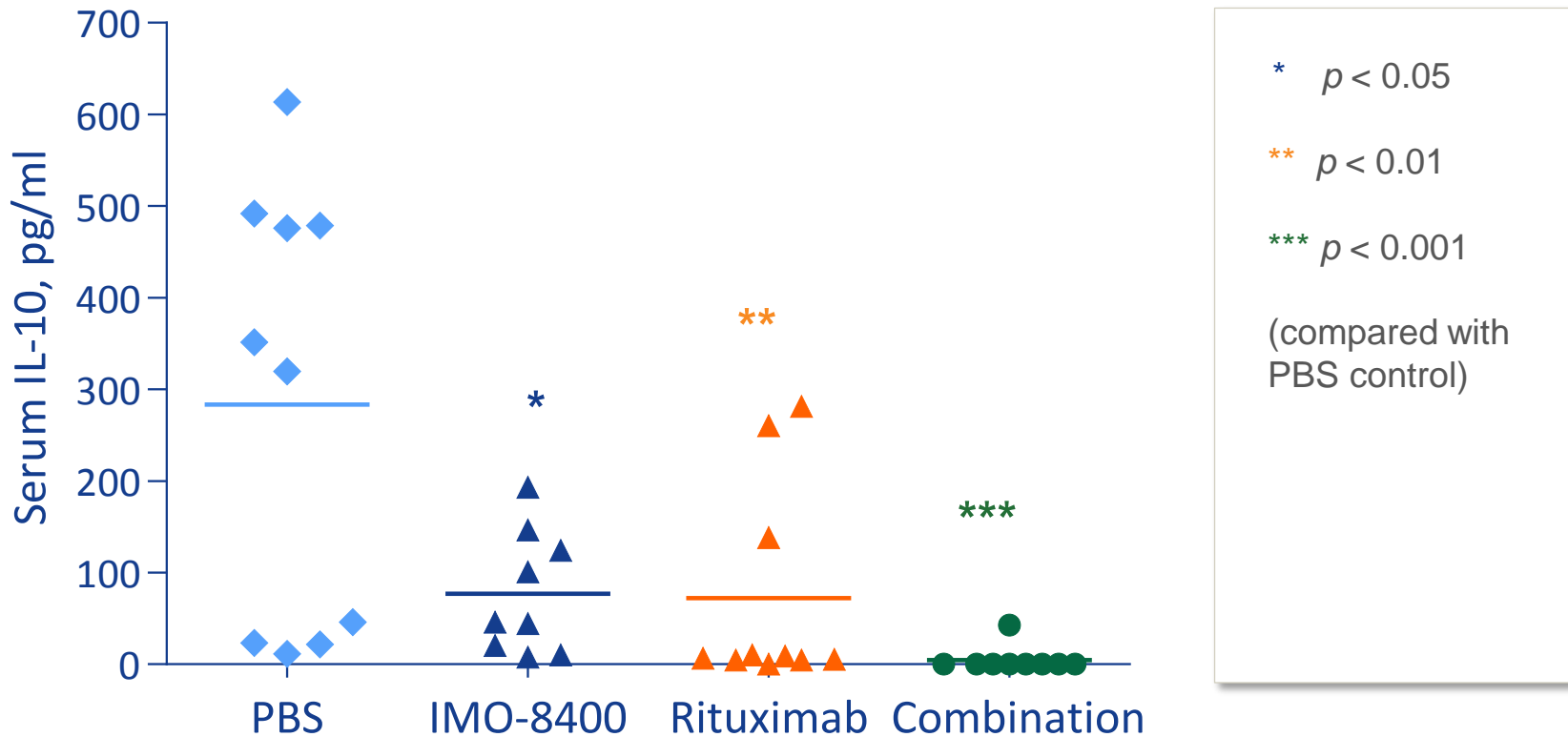


Combination vs. IMO-8400: $p=0.0003$

Combination vs. rituximab: $p=0.003$

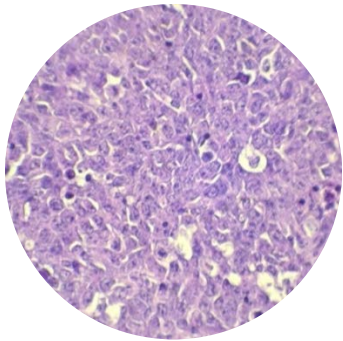


Correlated to the tumor growth inhibition, treatment suppressed OCI-Ly10 secretion of human IL-10

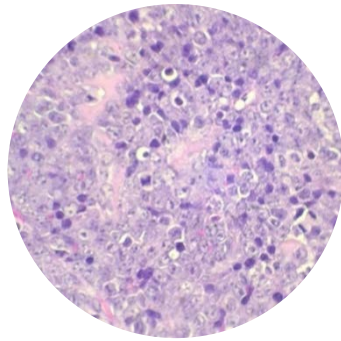


Serum samples collected at day 35 post tumor implantation were analyzed by human 25-plex assay.

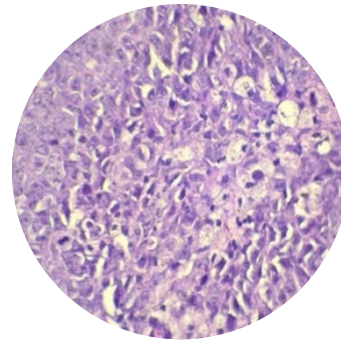
Combination treatment reduced tumor burden



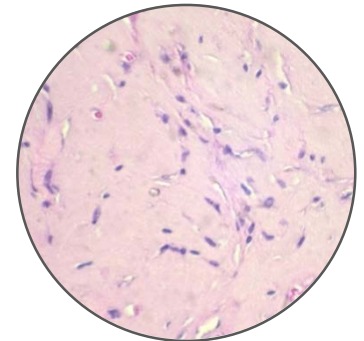
PBS



IMO-8400



Rituximab

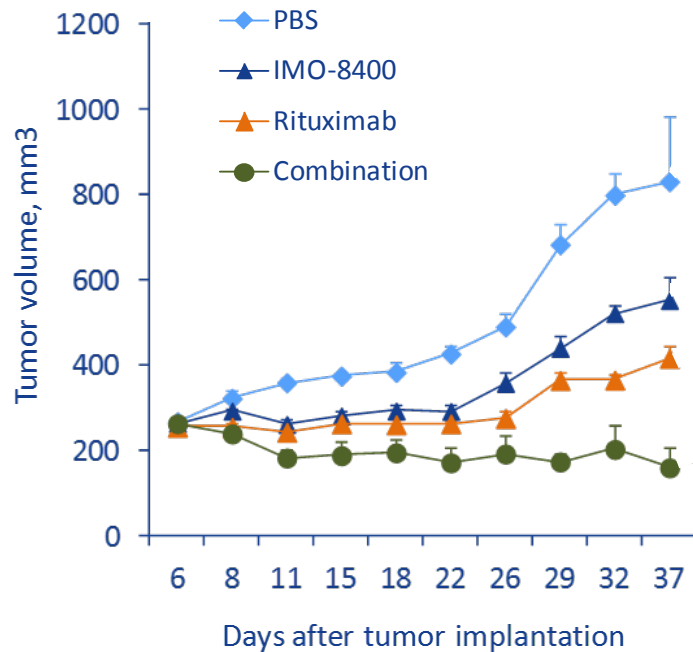


Combination

- A. Representative sections obtained from PBS vehicle control treated OCI-Ly10 xenotransplants showed a monotonous population of very large malignant lymphocytes with prominent nucleoli and occasional mitoses.
- B. IMO-8400 treated tumors showed multiple necrotic areas.
- C. Rituximab treated tumors showed multiple areas with necrosis and presence of apoptotic neoplastic cells.
- D. Treatment with IMO-8400 and rituximab resulted in disappearance of almost all the malignant lymphocytes. The residual tumor nodules were primarily fibrotic cells.

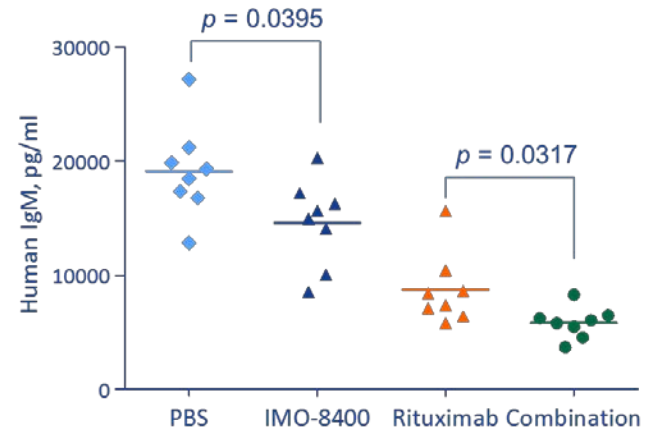
Antitumor activity of IMO-8400 plus rituximab in MWCL-1 Waldenström's macroglobulinemia xenograft model

Anti-tumor activity



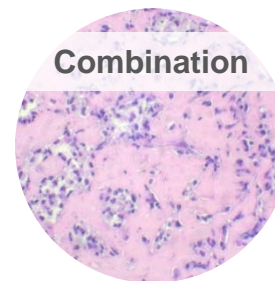
NOD-SCID mice (n=8/group) were implanted s.c with 10⁷ MWCL-1 on day 0. Treatment was initiated on day 6 when tumor volumes reached 200-300 mm³.

Effect on tumor IgM production



Serum samples collected at day 14 post tumor implantation were analyzed for human IgM by ELISA.

Tumor histology



Similar to OCL-Ly10 model, combination treatment resulted in disappearance of most malignant lymphocytes. The residual tumor nodules were primarily fibrotic cells.

Summary: TLR antagonist plus rituximab in xenograft models of B-cell lymphomas with MYD88 L265P

- The oncogenic mutation MYD88 L265P is associated with a poor clinical response to R-CHOP therapy in DLBCL patients
 - Endogenous ligands of TLRs 7, 8, and 9 drive MYD88 L265P oncogenic activity
- IMO-8400, an antagonist of TLRs 7, 8, and 9, plus rituximab has anti-tumor activity in xenograft models with the MYD88 L265P mutation
 - OCI-Ly10 ABC-DLBCL and MWCL-1 Waldenström's macroglobulinemia
- Idera is currently conducting clinical trials of IMO-8400 monotherapy in patients with Waldenström's macroglobulinemia or DLBCL with the MYD88 L265P mutation
- Rituximab plus IMO-8400 may offer an alternative for patients with B-cell lymphomas and the MYD88 L265P oncogenic mutation who have not responded to R-CHOP