

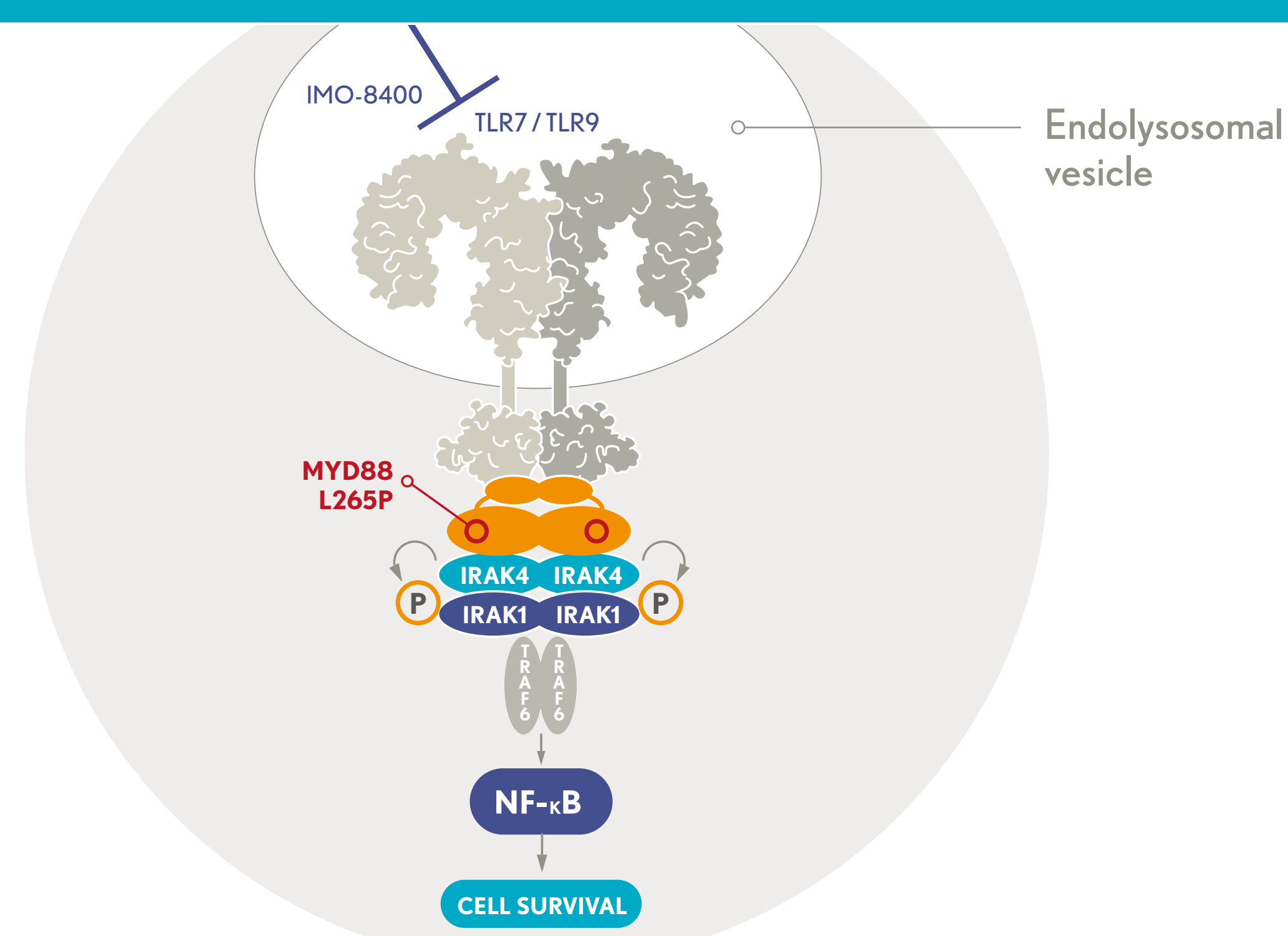
IMO-8400 Inhibits Tumor Growth and Signaling Pathways in Waldenström's Macroglobulinemia: a Novel Therapeutic Approach in Development

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RATIONALE AND OBJECTIVES

- MYD88 L265P is an oncogenic mutation present in over 90% of patients with Waldenström's macroglobulinemia (WM)¹ and in other B-cell lymphomas²
- MYD88 is an adaptor molecule in toll-like receptor (TLR) signaling; the L265P mutation oncogenic activity recently was associated with over-activation of the TLR signaling pathway³
- TLR signaling activates IRAK1/IRAK4, TRAF6, BTK, and NF-κB and JAK/STAT pathways
- Human B-cells express TLR7 and TLR9
- We hypothesize that antagonizing TLR7/TLR9 will block MYD88 L265P-driven signaling and inhibit tumor cell viability,⁴ providing a novel potential approach to the treatment of WM
- IMO-8400 is an antagonist of TLR7/TLR9 that has been well tolerated in prior clinical trials and has shown clinical activity in patients with an autoimmune disease
- Current objectives are to evaluate IMO-8400 effects on signaling pathways and tumor cell survival in MYD88 L265P-positive WM models, including an xenograft tumor model

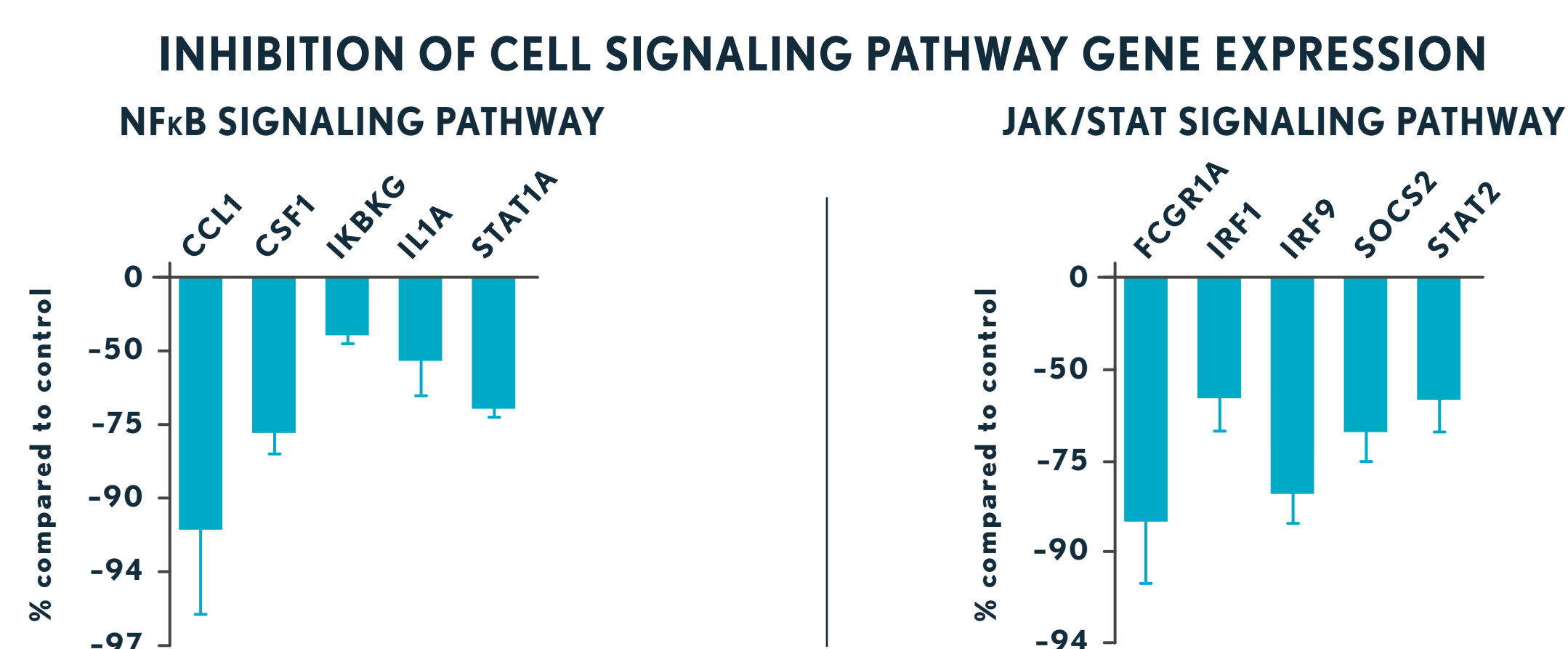
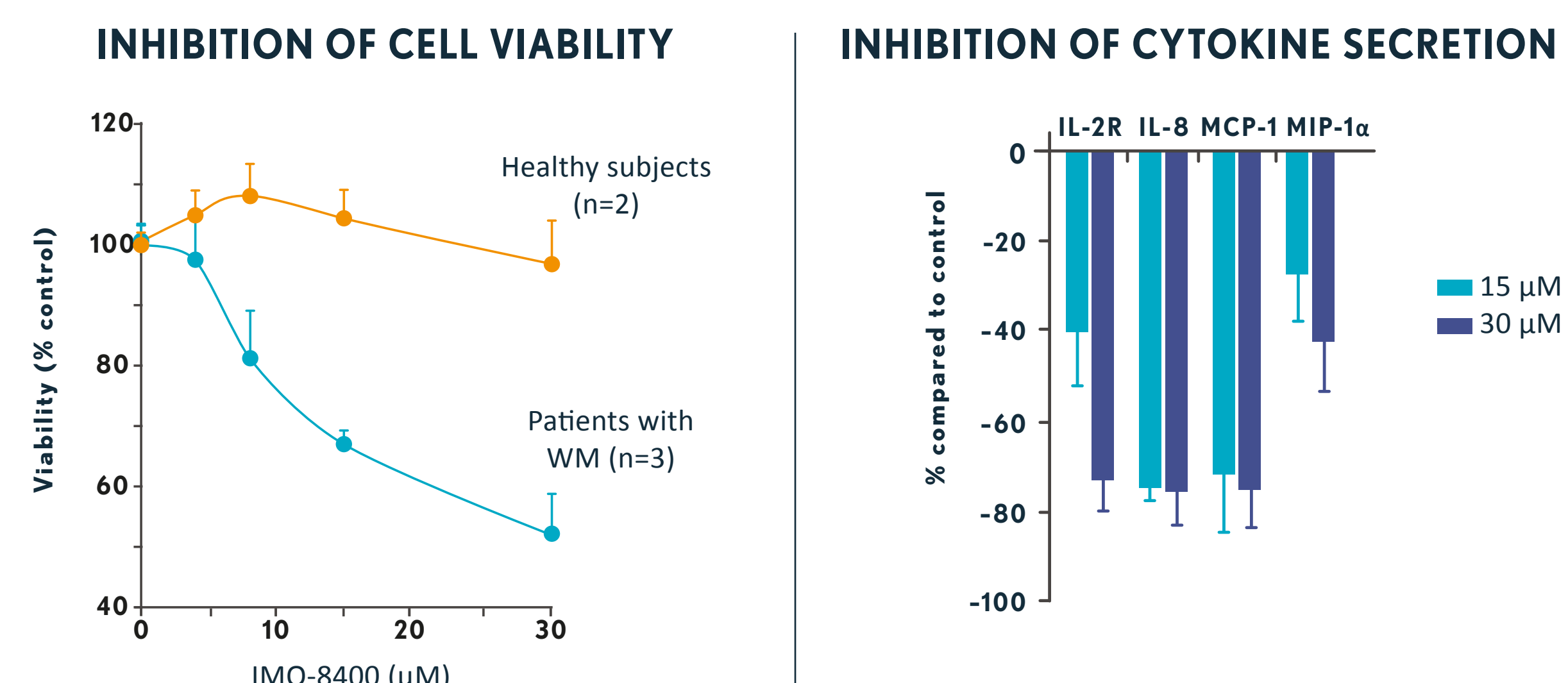
IMO-8400 INHIBITS MYD88 L265P-DRIVEN SIGNALING AND CELL SURVIVAL



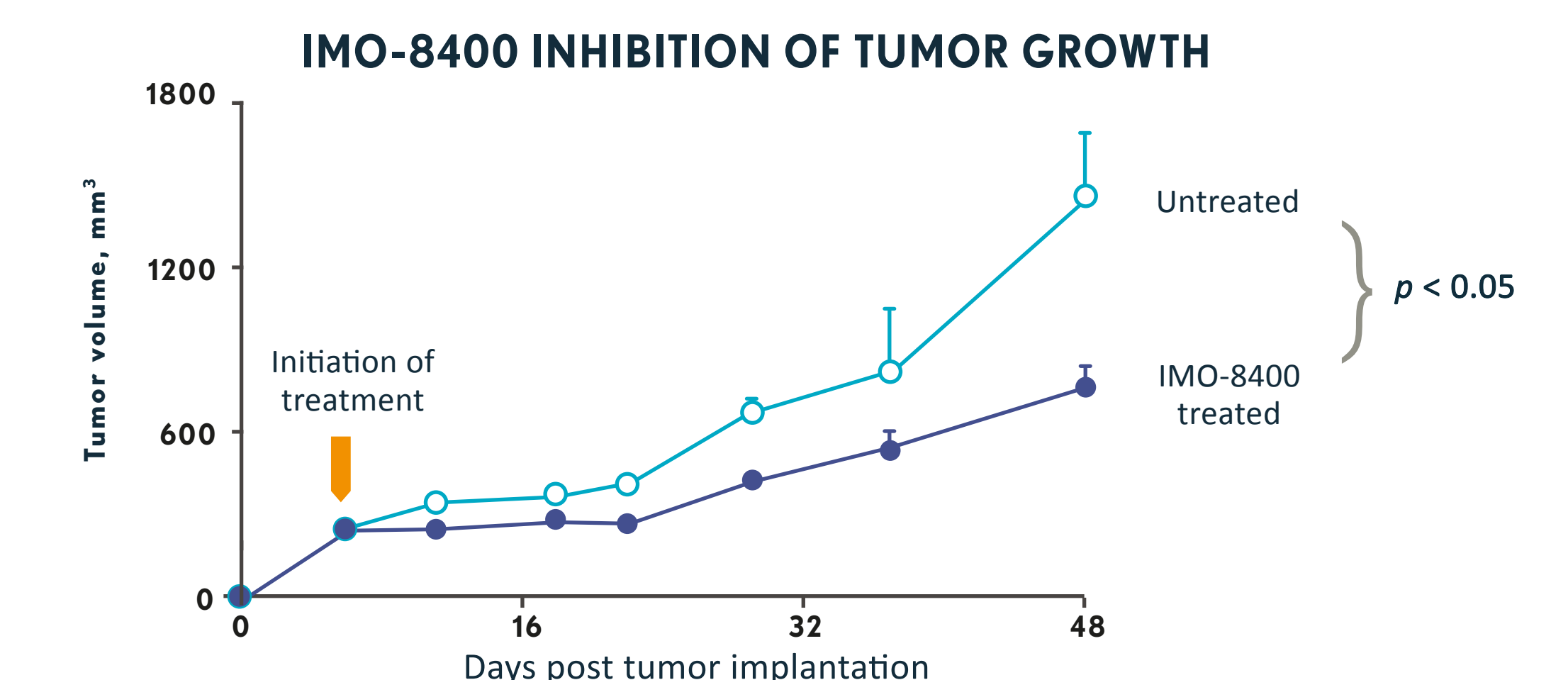
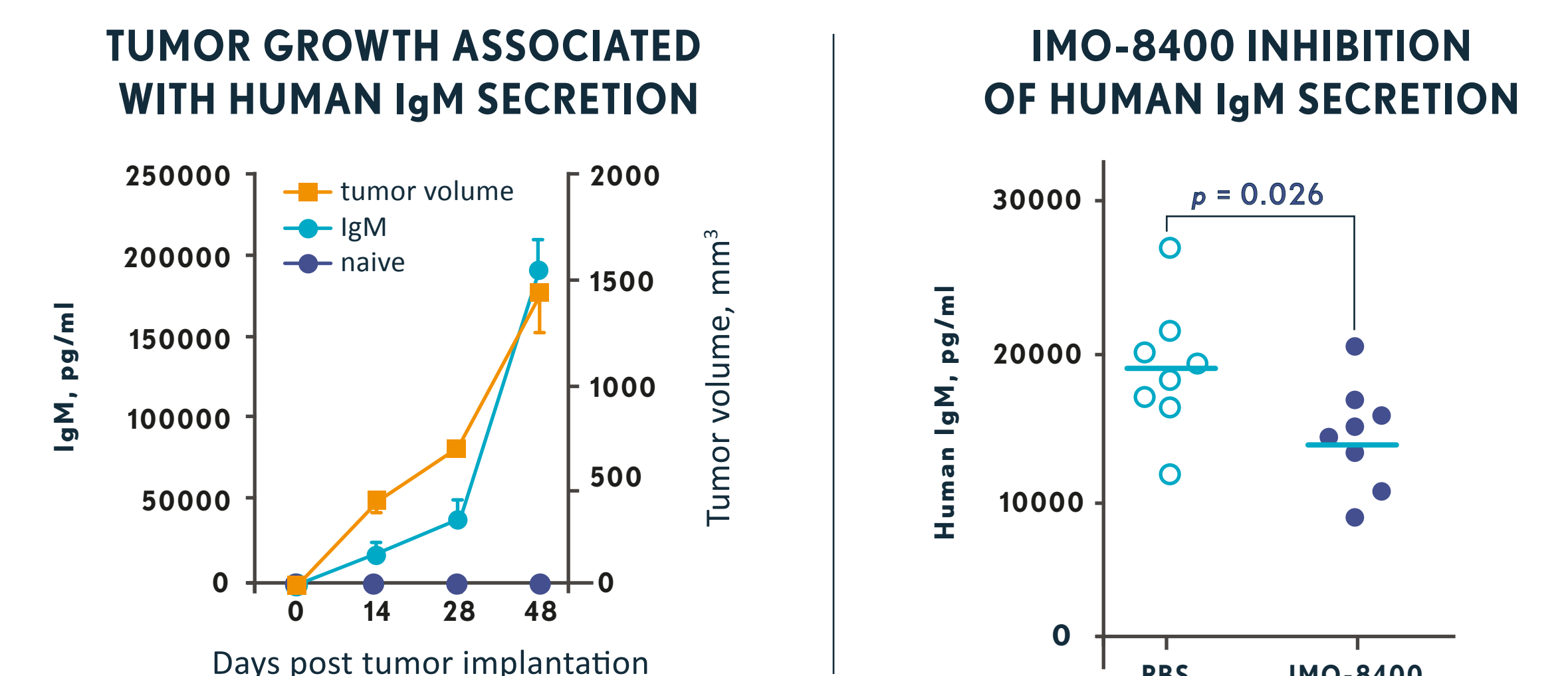
EXPERIMENTAL CONDITIONS

- Primary bone marrow cells from WM patients
 - N=3, all MYD88 L265P-positive by allele-specific PCR
 - Cell cultures incubated for 48 to 72 h with IMO-8400 at varying concentrations
- MWCL-1 cell culture and xenograft model
 - MYD88 L265P mutation shown by Sanger sequencing
 - Cell cultures incubated for 24 to 72 h with IMO-8400 at varying concentrations
 - Xenograft studies in NOD-SCID mice (n=8) dosed by i.p. injection with IMO-8400 (25 mg/kg) or saline (PBS) twice/week for 3 weeks followed by once/week for 3 weeks. Treatment was initiated when mean tumor volumes reached approximately 270 mm³

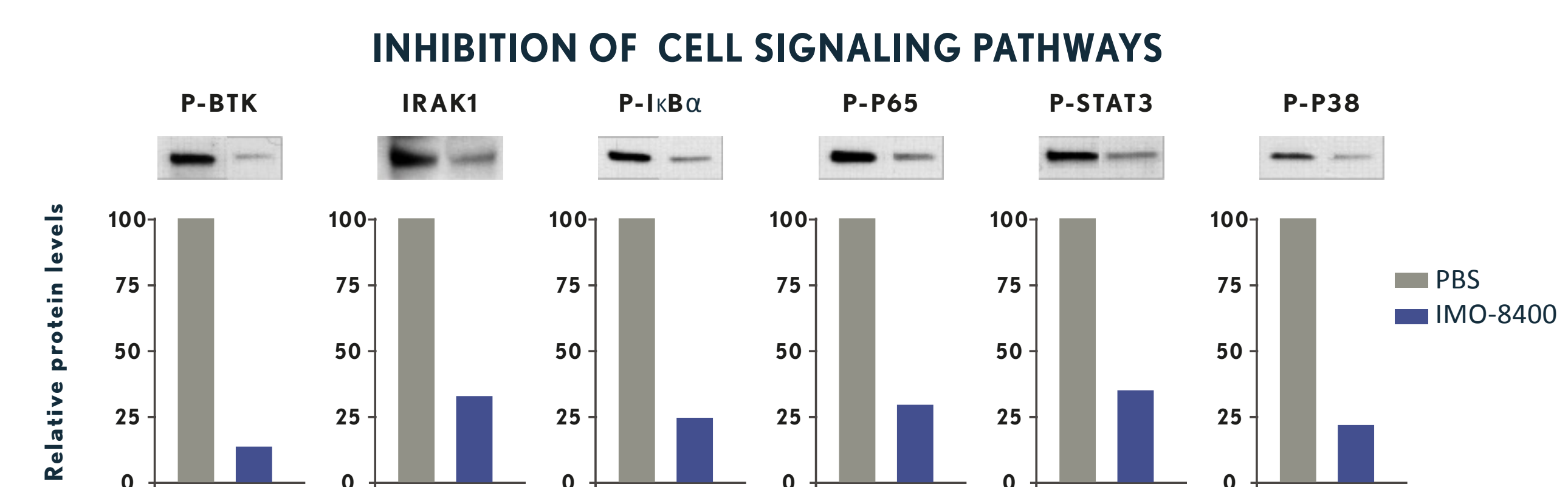
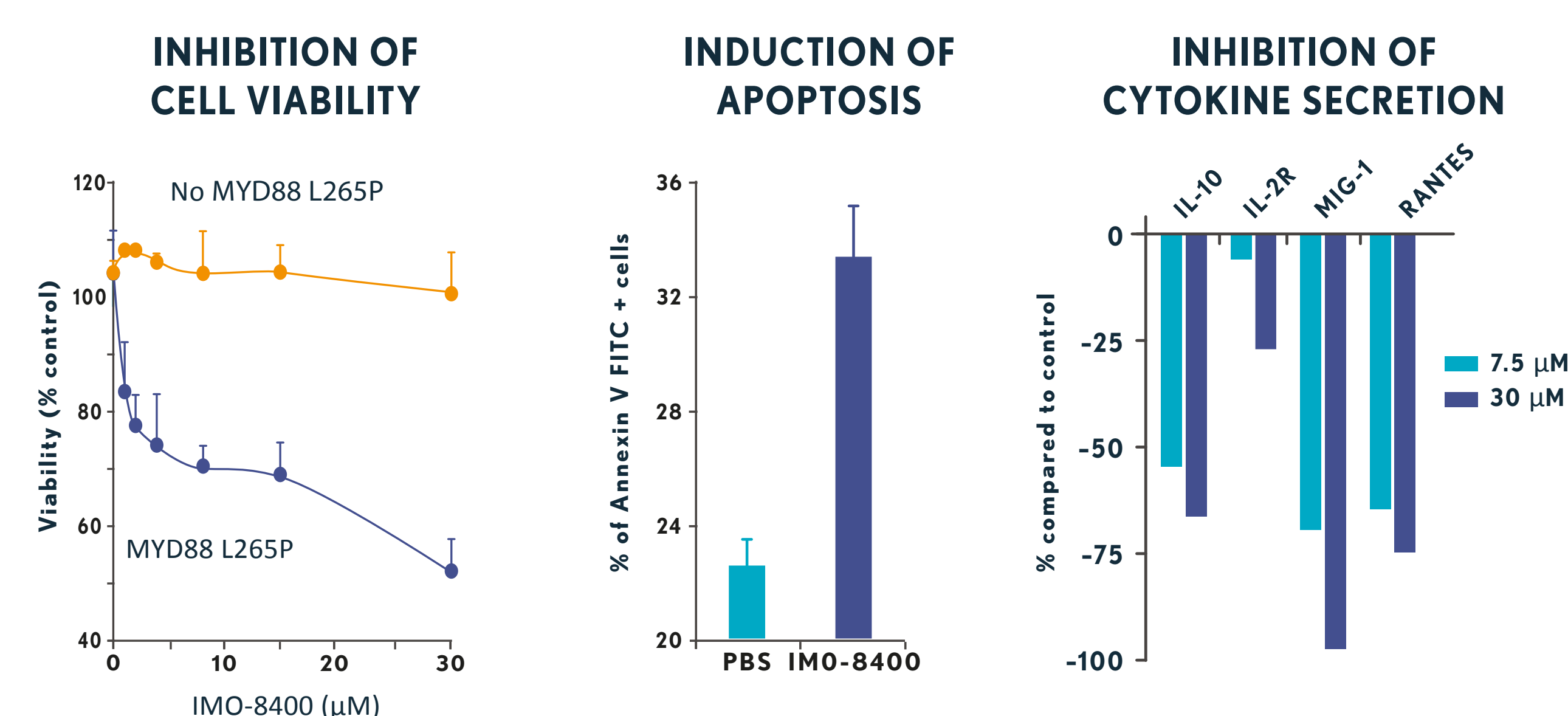
IMO-8400 BLOCKS SIGNALING PATHWAYS AND INHIBITS CELL VIABILITY IN WM PRIMARY BONE MARROW CELLS BEARING MYD88 L265P



IMO-8400 TREATMENT INHIBITS TUMOR GROWTH IN A MYD88 L265P-POSITIVE MWCL-1 XENOGRFT MODEL



IMO-8400 BLOCKS SIGNALING PATHWAYS AND INHIBITS CELL VIABILITY IN MWCL-1 CELL LINE BEARING MYD88 L265P



CONCLUSIONS

- IMO-8400 inhibits cell growth, cytokine secretion, and key cell signals including IRAK1/IRAK4, BTK, and NF-κB and JAK/STAT in MYD88 L265P-positive WM primary bone marrow cells
- Implantation of MYD88 L265P-positive MWCL-1 cells in immunocompromised mice produces tumor growth that correlates with increased human IgM
- Studies in the MWCL-1 mouse model show that IMO-8400 reduces tumor growth, consistent with cell culture studies showing IMO-8400 inhibits cell signaling, induces cancer cell apoptosis, and inhibits cell viability
- Based on promising preclinical data from studies of IMO-8400 in cell-based assays and tumor models and clinical safety in early trials, IMO-8400 is currently being evaluated in a Phase 1/2 clinical trial in patients with WM
- This is the first clinical approach to block the activity of the oncogenic mutation present in over 90% of patients with WM; for further information visit www.iderapharma.com or www.clinicaltrials.gov/show/NCT02092909

1. Treon SP, Hunter ZR. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *Blood*. 2013 May 30;121(22):4434-6.
2. Ngo VN, Staudt LM et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature*. 2011; 470:115-9.
3. Lim K-H, Barton GM, Staudt LM. Oncogenic MYD88 mutants require Toll-like receptors. *Cancer Res*. 2013; 73, Suppl 1: 2332.
4. Bhagat L et al. IMO-8400, a selective antagonist of TLRs 7, 8 and 9, inhibits MYD88 L265P mutation-driven signaling and cell survival: a potential novel approach for treatment of B-cell lymphomas harboring MYD88 L265P mutation. *AACR 2014 Abstract #2570*.