

Obefazimod Reduces Inflammation-Driven Tumor Burden in a Murine Model of Colitis-Associated Cancer

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Introduction

- > Patients with IBD have an increased risk of CRC, highlighting the need for sustained, deep control of intestinal tissue inflammation with a treatment ideally suitable for long-term use [1–3]
- > Obefazimod (Obe) is an oral, once-daily, small molecule that enhances the expression of microRNA-124, thereby restoring intestinal immune balance through regulation of Th17 cells and macrophage activity
- > Obe has shown efficacy in patients with moderately to severely active ulcerative colitis (UC) in two Phase 2 induction trials and subsequent open-label maintenance (OLM) studies with up to 5 to 7 years of treatment [4–6], as well as in the Phase 3 ABTECT induction and maintenance trials [7]
- > This study evaluated whether Obe provides sustained control of deep intestinal inflammation and protects against carcinogenic events in an experimental mouse model of colitis-associated CRC

Methods

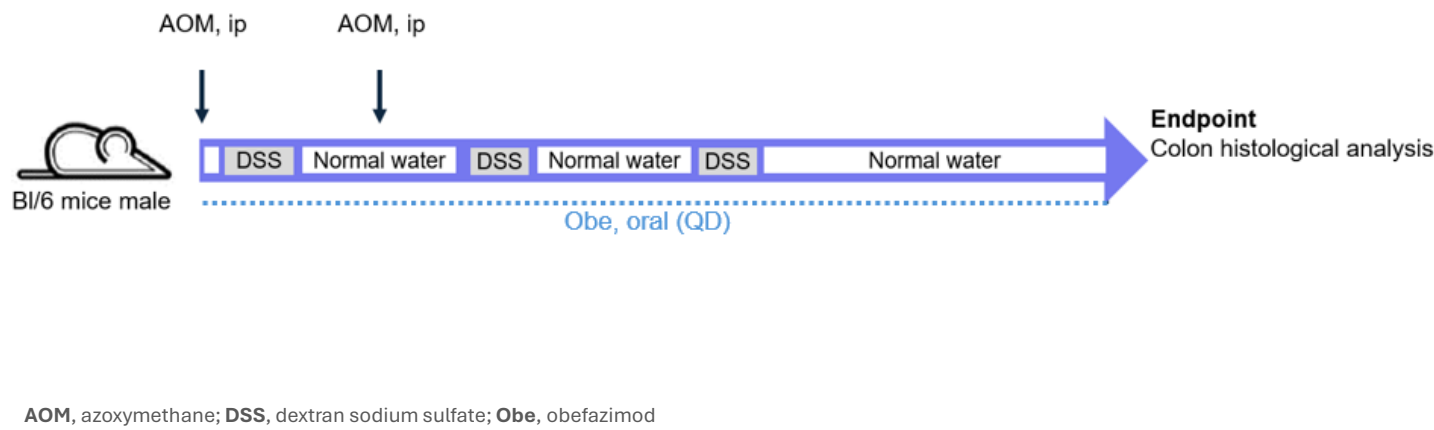
Murine Model

- > A murine colitis associated colon cancer model induced by intraperitoneal administration of the carcinogen azoxymethane (AOM) followed by 3 cycles of oral administration of the pro-inflammatory agent dextran sodium sulfate (DSS) separated by recovery periods, was used to evaluate the effect of oral administration of Obe (**Fig 1**) [8]
- > C57/BL6 males received Obe orally at 40 mg/kg for 97 days
- > Body weight was followed as a clinical parameter

Colon Analysis

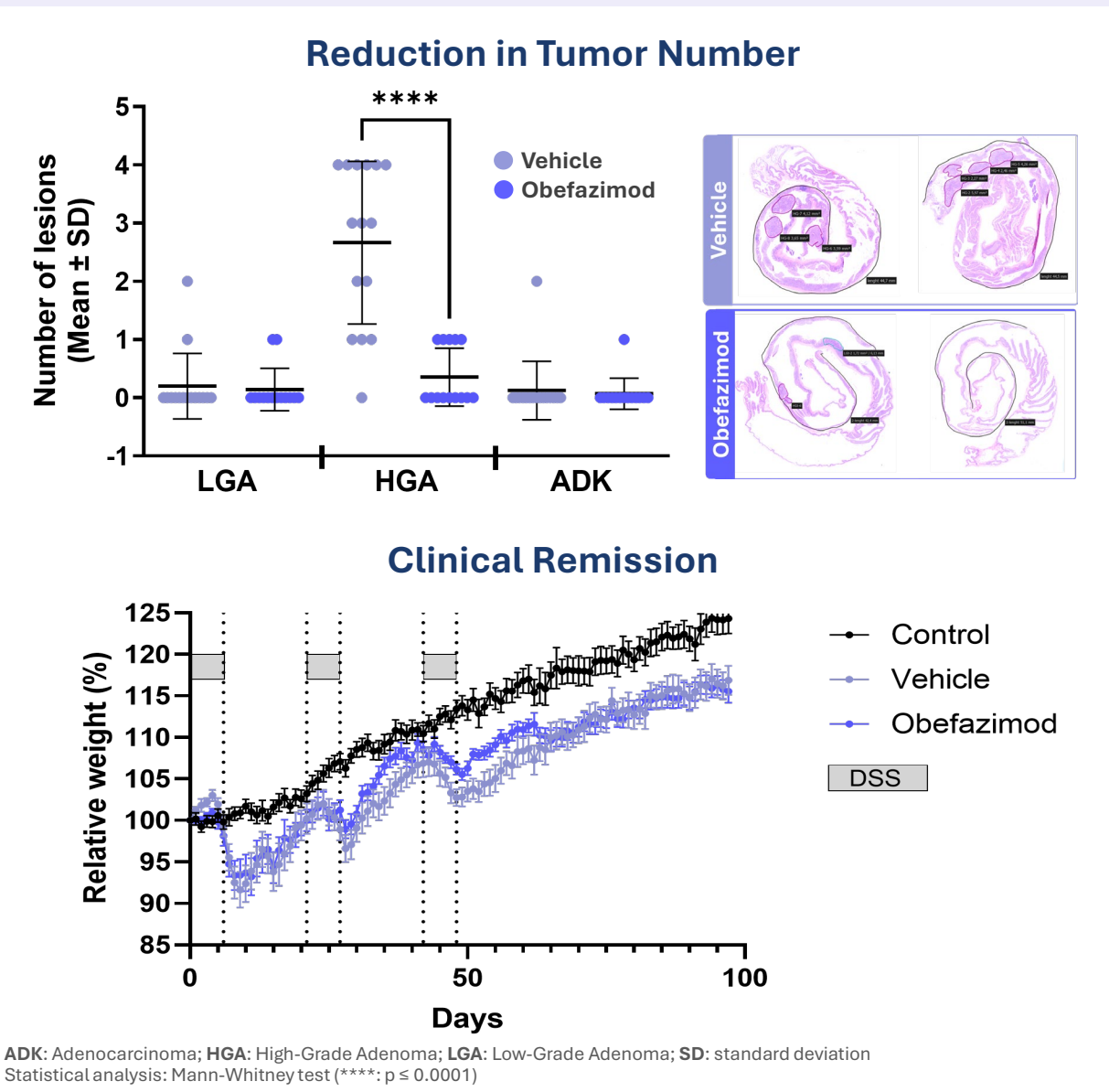
- > The colon was fixed for paraffin inclusion. Histological analysis was performed after hematoxylin and eosin stain (HES) coloration
 - Tumor number, size, and histological stage defined as low-grade dysplasia/adenomas (nuclear hyperchromasia, polarity changes, and increased nuclear-to-cytoplasmic ratio), high-grade dysplasia/adenomas (additional loss of nuclear polarity) and adenocarcinomas (cancerous crypts invading the muscularis mucosa) were assessed
 - Immunostainings were performed to quantify Ki-67, β -catenin, vimentin, E-cadherin, TGF- β , IL-6, F4/80, cleaved caspase-3 and CDX2

Study Design (Figure 1)



Results

Figure 2. Clinical Observations and Tumor Histological Analysis

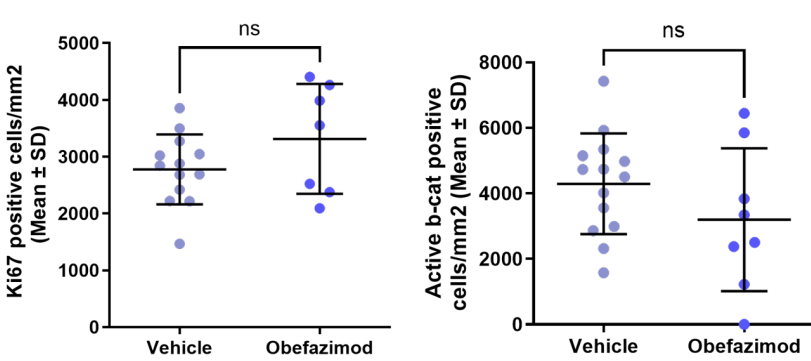


Author's Conclusions

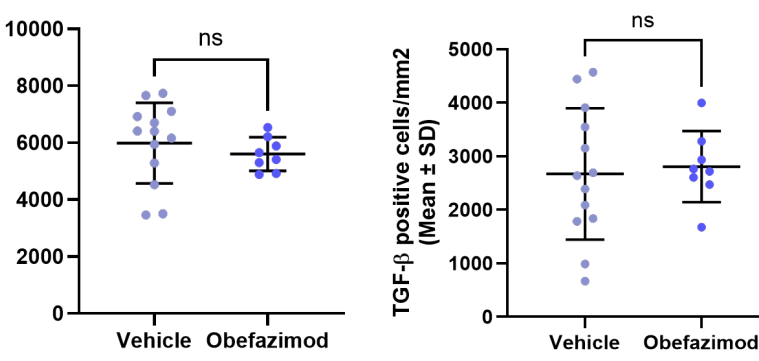
- > **Obefazimod significantly reduced tumoral lesions, especially high-grade adenomas, in mice with persistent chronic colonic inflammation and exposure to a carcinogen**
- > Additional tissue characterization did not support direct tumor-intrinsic or immune-mediated anti-tumor effect while reduced hyperplasia and regenerative epithelial changes in adjacent tissue are consistent with attenuation of inflammation-driven tissue remodeling
- > Our data suggest a deep and efficient control of inflammation by restoring mucosal immune balance, and thus, significantly reducing tumor and improving clinical score by preventing the progression of low to high grade dysplasia associated with inflammation [10]
- > No increased colorectal cancer incidence was observed with obefazimod in open label, long term clinical studies. Additional human clinical studies would be required to assess the potential beneficial effect of Obe on CRC incidence in IBD patients

Figure 3. Tissue Characterization by Biomarker Immunostaining

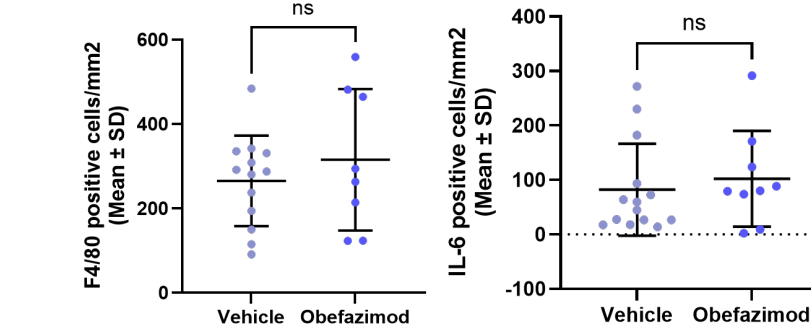
Tumor-Cell Proliferation & Wnt-Pathway Activity



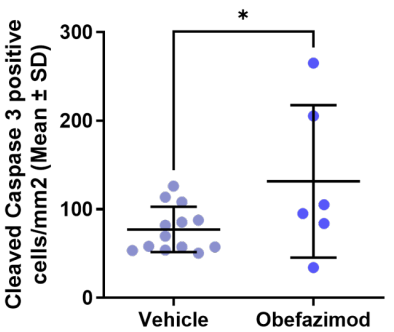
Stromal Markers



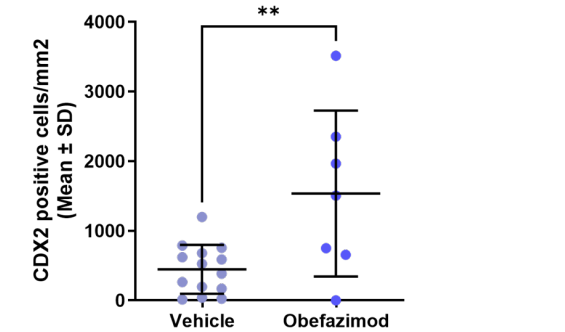
Macrophage Infiltration Marker



Apoptosis Marker



Epithelial Marker



- > Mice subjected to the AOM/DSS developed a large number of tumors in the colon, while their oral treatment with Obe at 40 mg/kg once decreased tumor burden with decreased high-grade dysplasia (**Fig 2**)
- > Investigation of biomarkers indicated no detectable effect of Obe on tumor-cell proliferation or Wnt-pathway activity, consistent with no significant differences in stromal content or activation. Similarly, IL-6 expression and the extent of macrophage infiltration within tumor lesions did not differ (**Fig 3**)
- > In contrast, Obe-treated mice showed increased apoptosis and preserved epithelial CDX2 marker; loss of which is associated with greater tumor aggressiveness [9] (**Fig 3**)

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Disclosures

SD: AbbVie, Celtrion, Ferring, Fresenius Kabi, Hospira, Johnson & Johnson, Medac, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celtrion, Sandoz, Boehringer Ingelheim. J CA, CJR, DJ, FC, MdiR, DS, NC, JS, AG: Abivax. J CP, MH, BL: none. J BS: AbbVie, AltruBio, Abivax, AlfaSigma, BMS, Boehringer Ingelheim, CED Service GmbH, Dr. Falk Pharma, Eli Lilly, Endpoint Health, Falk, Ferring, Galapagos, Gilead, Janssen, Landos, Materia Prima, PredictImmune, MSD, Pfizer, Takeda, T1x bio, GDH: (consultant or speaker's fees) Abbvie, Abivax, Agomab, Alimentiv, Anaptys Bio, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celtrion, Eli Lilly, Exelion Biosciences, Galapagos, Glaxo Smith Kline, Dr Falk Pharma, Pfizer, J&J, Merck, Mirador, Polipharma, ProCise Diagnostics, Prometheus Biosciences, Sorriso Pharma, Spyre, Takeda, Ventyx, LPB, Abbvie, Abivax, Adacety, Alimentiv, Amgen, Applied Molecular Transport, Arena, Banoak, Biogen, BMS, Celtrion, Connect BioPharm, Cytoke Pharma, Enterra, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GSK, IAC Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Lilly, Medac, Mopac, Morphic, MSD, Nordic Pharma, Novartis, Oncodesign Precision Medicine, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Par Immune, Pfizer, Prometheus, Protagonist, Roche, Samsung, Sandoz, Sanofi, Satisfay, Takeda, Telavant, Theravance, Thermo Fischer, Tigenix, Tillots, Viatrix, VectrBio, Ventyx, Yasopia. J BES: Abbvie, Abivax, Adiso Therapeutics, Agomab, Alimentiv, Amgen, AnaptysBio, Arena Pharmaceuticals, Artigen Therapeutics, Astra Zeneca, Biologic Design, Biora Therapeutics, Boehringer Ingelheim, BMS, Celtrion, Equillum, Enterra, Enveda Biosciences, Evimmune, Ferring, Fzata, Galapagos, Genentech, Gilead Sciences, GSK, Gossamer Bio, Imhotep, Index Pharmaceuticals, Innovation Pharmaceuticals, Kaleido, Kalliope, Lilly, Merck & Co., Microba, Microbiotica, Mitsubishi Tanabe, Mobius Care, Morphic Therapeutics, MRM Health, Nexus Therapeutics, Nimbus Discovery, Odyssey Therapeutics, OSE Immunotherapeutics, Janssen, Palisade Bio, Pfizer, Protagonist Therapeutics, Q32 Bio, Rasayana Therapeutics, Recludix Therapeutics, Relstone Biopharma, Sanofi, Sorriso Therapeutics, Spyre Therapeutics, Takeda, Target RWE, Teva, TLL Pharmaceutical, T1X, Trex Bio, Union Therapeutics, Ventyx Biosciences. J DTR: (consultant/speaker's fees) AbbVie, Abivax, AltruBio, Athos Therapeutics, Bristol-Myers Squibb, Celtrion, Connect BioPharma, Eli Lilly, Genentech, Iterative Health, Janssen Pharmaceuticals, J&J, Merck, Odyssey Therapeutics, Pfizer, Sanofi, Spyre, Takeda, Vedanta Biosciences, Ventyx. J BV: Abbvie, Agomab, Allasigma, Biogen, Biora Therapeutics, BMS, Celtrion, Eli Lilly, Falk, Ferring, Galapagos, Landos, Materia Prima, J&J, Pfizer, Sandoz, Sanofi, Sossel Heptares Neura, Takeda, Tillots Pharma, Truvion and Viatrix, Alimentiv, Anaptys Bio, Applied Strategic, AstraZeneca, Atheneum, BenevolentAI, Biora Therapeutics, Boxer Capital, BMS, Domain Therapeutics, Guidepoint, Landos, Merck, Mirador Therapeutics, Mylan, Neura, Inotrem, Ipsos, Sanofi, Santa Ana Bio, Sapphire Therapeutics, Sossel Heptares, Thelios Pharma, Vagustim, Viatrix. RA: AbbVie, Abivax, Adiso, Alimentiv, Bristol Meyer Squibb, Celtrion, Genentech, Geneoscopy, Janssen, Pfizer, Takeda.

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