264 MALT1 inhibitor

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead discovery/optimization
Target (MoA)	MALT1 inhibition
Brief Description	MALT1 protease is essential to mediate the immune-suppressive function of Tregsin the tumor microenvironment and acute genetic blockade or pharmacologic inhibition enhances antitumor immunity
Organization	Center for Drug Design and Discovery

Differentiation

□ **Unmet Needs**

- MALT1 protease is essential to mediate the immunosuppressive function of Tregs in the tumor microenvironment. Various immunosuppressive cytokines and secretory factors from tumors have been reported to polarize the tumor microenvironment into immunosuppressive one by promoting differentiation toward Treg, MDSC, and other immunosuppressive subset of immune cells, and resulting immunosuppression can markedly attenuate the efficacy of cancer immunotherapeutic

□ **Innovations**

- T reg modulation (reduction in numbers or inducing phenotypical changes) in the tumor microenvironment to augment antitumor immunity (broadly applicable immune oncology strategy across various tumor types
- Pharmacologic inhibition of MALT1 causes Treg cells to prime tumors for immune checkpoint therapy, yet does not cause systemic autoimmunity
- Inhibition of MALT1 protease activity in cells (EC50 's up to 250 nM)

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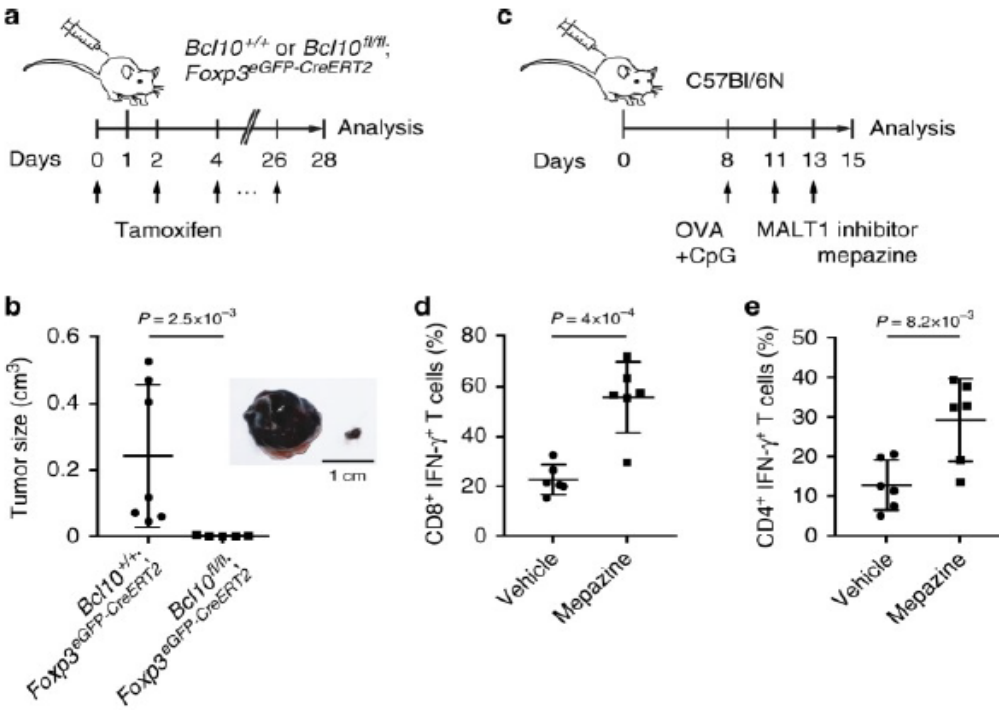
Key Data

Genetic modification schematics



Inhibition of CARD11-BCL10-MALT1 signaling enhances anti-tumor immunity. **a** Schematic representation of the B16F1 tumor model combined with the acute deletion of Bcl10 in regulatory T cells (Tregs): on day 1, 1 × 10^5 B16F1 tumor cells were subcutaneously injected into the flanks of Bcl10 ;Foxp3 and Bcl10 ;Foxp3 mice. Tamoxifen was administered every other day deleting the Bcl10 alleles in newly emerging Tregs until the final analysis on day 28. **b** Quantification of the tumor size in Bcl10 ;Foxp3 and Bcl10 ;Foxp3 mice on day 28 after tamoxifen treatment. Representative tumors of Bcl10 ;Foxp3 (left) and Bcl10 ;Foxp3 (right) male mice are depicted on the right side of the graph. Scale bar represents 1 cm. Statistical significance between genotypes was assessed by a twotailed Mann–Whitney U test. **c** Schematic representation of the B16-OVA tumor model in wild-type mice combined with a pharmacological inhibition of the MALT1 protease activity: B16-OVA cells were subcutaneously injected into the flanks of C57Bl/6 mice, followed by a vaccination with OVA + CpG on day 8. On days 11 and 13, mice were treated with either the MALT1 inhibitor mepazine or vehicle PBS/5% DMSO and analyzed on day 15. **d, e** Quantification of the ratio of tumor-infiltrating d CD8 IFN-γ cells to the frequency of CD8 cells and e CD4 Foxp3 IFN-γ cells to the total percentage of CD4 Foxp3 T cells after re-stimulation of enriched tumor-infiltrating lymphocytes with phorbol myristate acetate (PMA) (100 nM)/ionomycin (1 μM). Statistical significance was calculated with a two-tailed unpaired Student's t test.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

Contact Information

Contact Person	Stefaan Allemeersch
Email	stefaan.allemeersch@cistim.be
URL	http://www.cd3.eu/pipeline/