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APRIL 5-10

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BMS-986442 (AGEN1777), a novel TIGIT/CD96 bispecific antibody, demonstrates superior monotherapy and combination activity versus conventional anti-TIGIT antibodies in preclinical models

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Disclosure Information

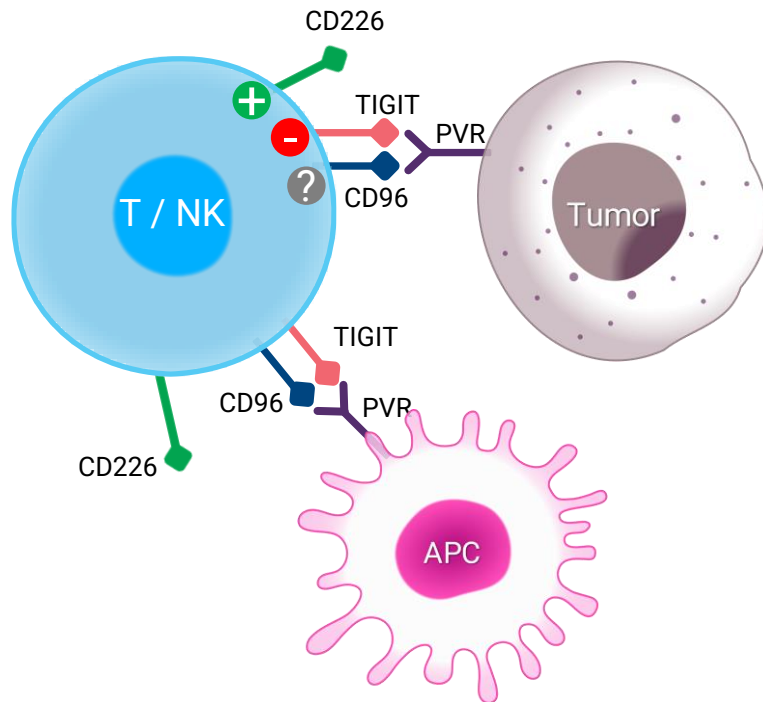
The logo for the AACR Annual Meeting 2024 is located in the top right corner. It features a stylized circular graphic composed of several curved segments in shades of blue, green, and yellow, arranged in a circular pattern. To the left of this graphic, the text "ANNUAL MEETING" is written in a large, bold, black sans-serif font. Below it, "2024 • SAN DIEGO" is written in a smaller, black sans-serif font.

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- Full-time employee with stock/stock options at Agenus

TIGIT and CD96 regulate key inhibitory and co-stimulatory pathways in T and NK cells



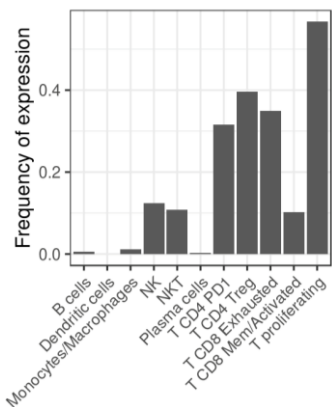
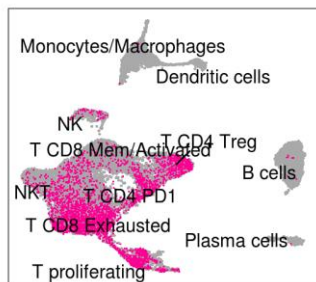
- Shared mechanism that limits CD226 (DNAM-1) co-stimulatory signaling to potentially inhibit innate (NK cell) and adaptive (T cell) immunity in the TME¹
- PVR, the shared ligand of TIGIT and CD96, is overexpressed on cancer cells and myeloid APCs, and linked to poor prognosis across various cancers^{2,3}
- The role of CD96 as a co-inhibitory versus co-stimulatory receptor remains controversial due to differences in signaling domains between mouse (ITIM) and human (ITIM, YxxM)
- Anti-TIGIT monoclonal antibodies (mAbs) have not shown promising activity as monotherapy in advanced solid tumors

TIGIT and CD96 are frequently co-expressed on TILs

A

Metastatic Melanoma

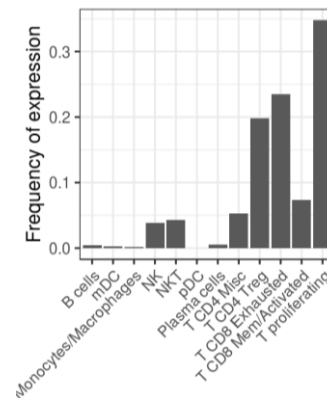
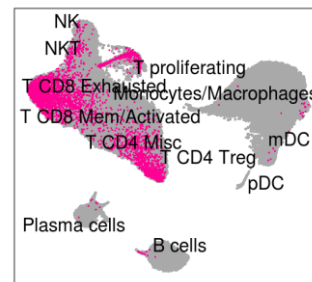
TIGIT & CD96



B

NSCLC

TIGIT & CD96

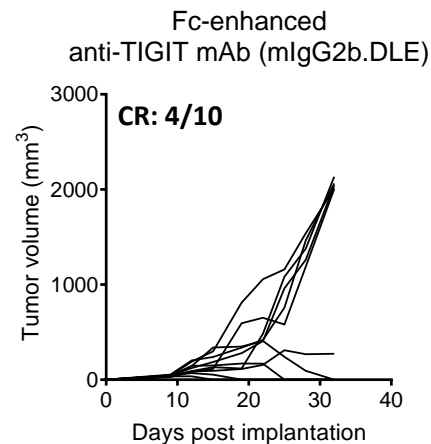
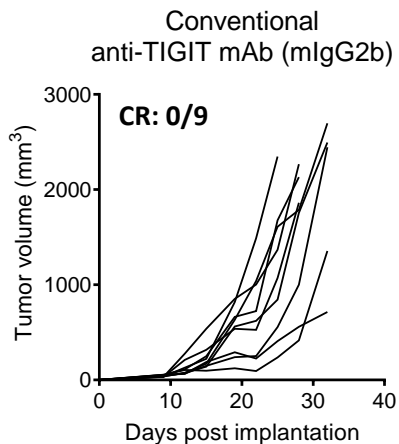
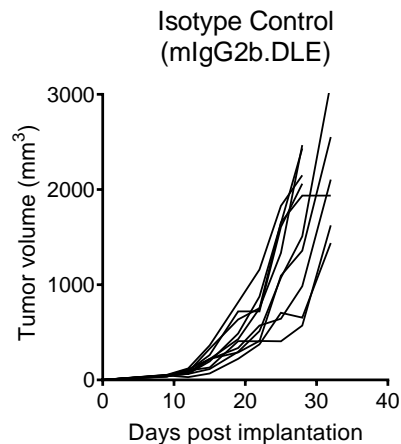
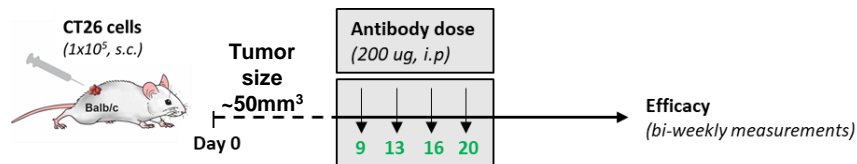


Single-cell RNA-seq analysis of TILs isolated from 32 patients with metastatic melanoma treated with nivolumab and/or ipilimumab, and 5 untreated patients with non-metastatic NSCLC showed **co-expression** of TIGIT and CD96 (pink)

TIGIT mAbs with a conventional IgG Fc domain lack single agent activity in syngeneic mouse models



CT26 Colon Carcinoma (Subcutaneous)



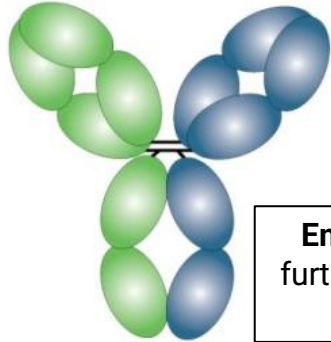
How do we raise the bar?

A question of target biology (i.e., requirement for combination), a drug-intrinsic problem, or a bit of both?

BMS-986442: Differentiated TIGIT & CD96 bispecific antibody with dual targeting in the DNAM pathway

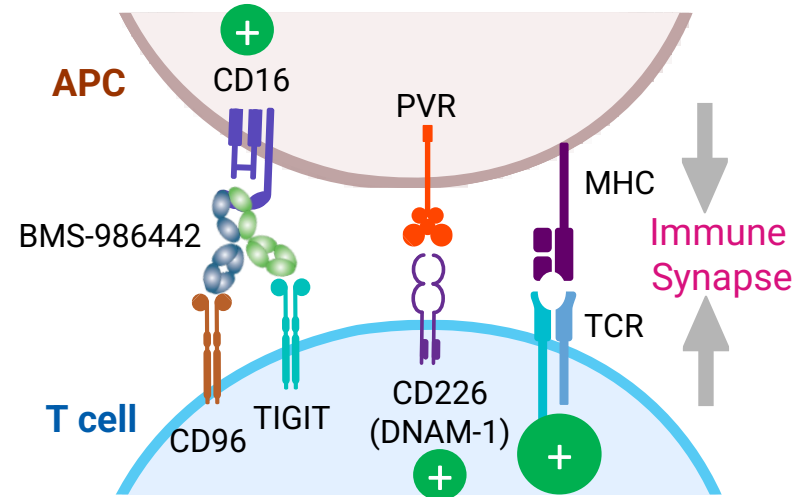
BMS-986442 (AGEN1777) is differentiated from 1st gen TIGIT mAbs by targeting 2 receptors in the DNAM pathway to potently enhance T and NK cells and overcome TIGIT resistance

Fc-enhanced
TIGIT/CD96 bi-specific



Dual blockade of both
TIGIT and CD96 pathways

Enhanced Fc-FcγR interactions
further increase T cell priming and
APC activation

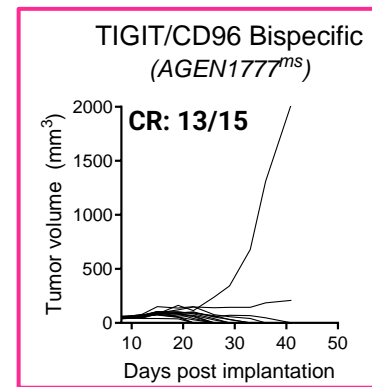
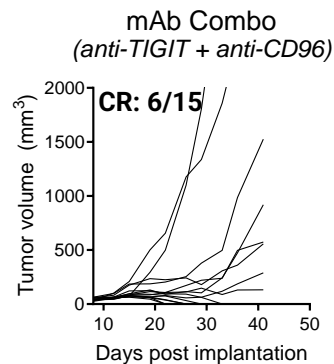
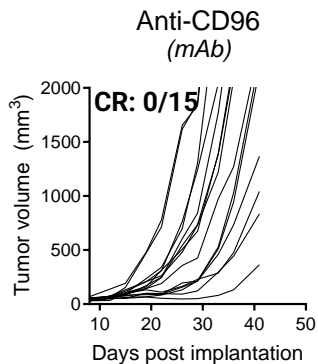
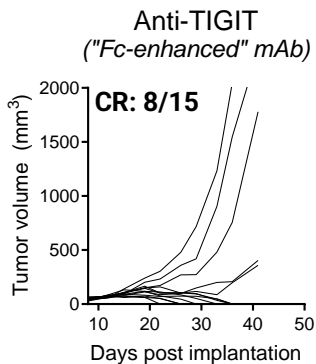
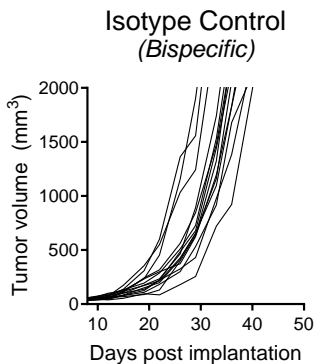


TIGIT-CD96 bispecific delivers superior tumor control

Outperforms combination of TIGIT and CD96 mAbs



CT26 Colon Carcinoma (Subcutaneous)



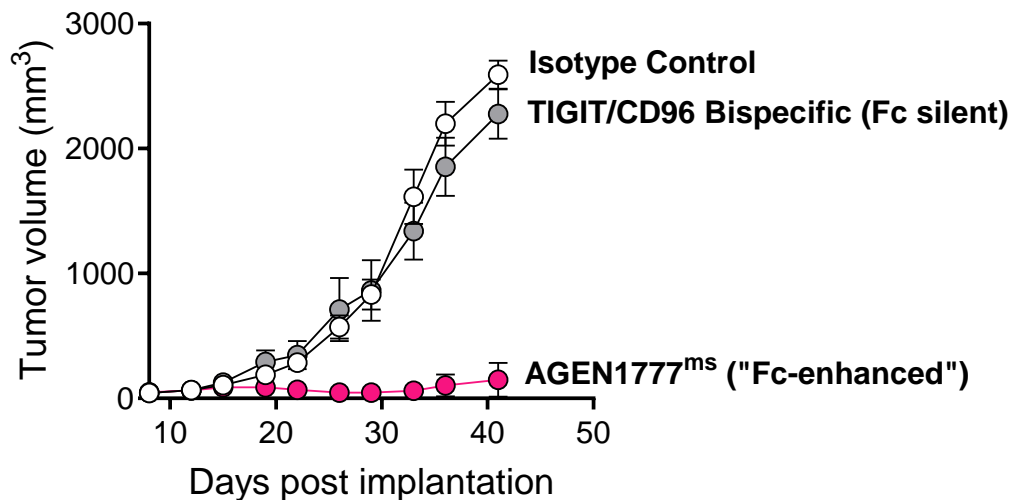
AGEN1777^{ms} is a mouse surrogate anti-TIGIT/CD96 bispecific antibody

FcγR interactions are critical for tumor control

Co-blockade alone is insufficient: Anti-TIGIT/CD96 bispecific requires FcγR co-engagement to promote anti-tumor immunity



CT26 Colon Carcinoma
(Subcutaneous)

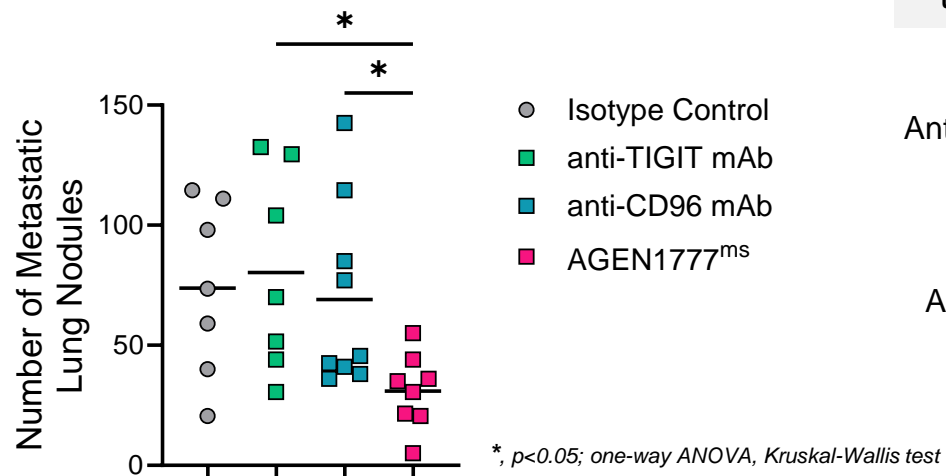


AGEN1777^{ms} is a mouse surrogate anti-TIGIT/CD96 bispecific antibody

AGEN1777^{ms} controls lung metastases in IO refractory orthotopic 4T1 breast carcinoma

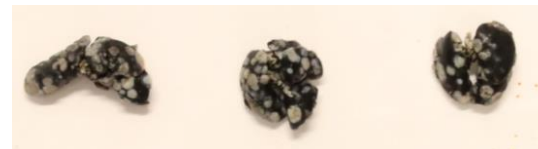


4T1 Breast Carcinoma (Orthotopic)



TIGIT/CD96 bispecific promotes superior tumor control compared to anti-TIGIT mAb

Anti-TIGIT mAb



AGEN1777^{ms}



Representative images

AGEN1777^{ms} is a mouse surrogate anti-TIGIT/CD96 bispecific antibody

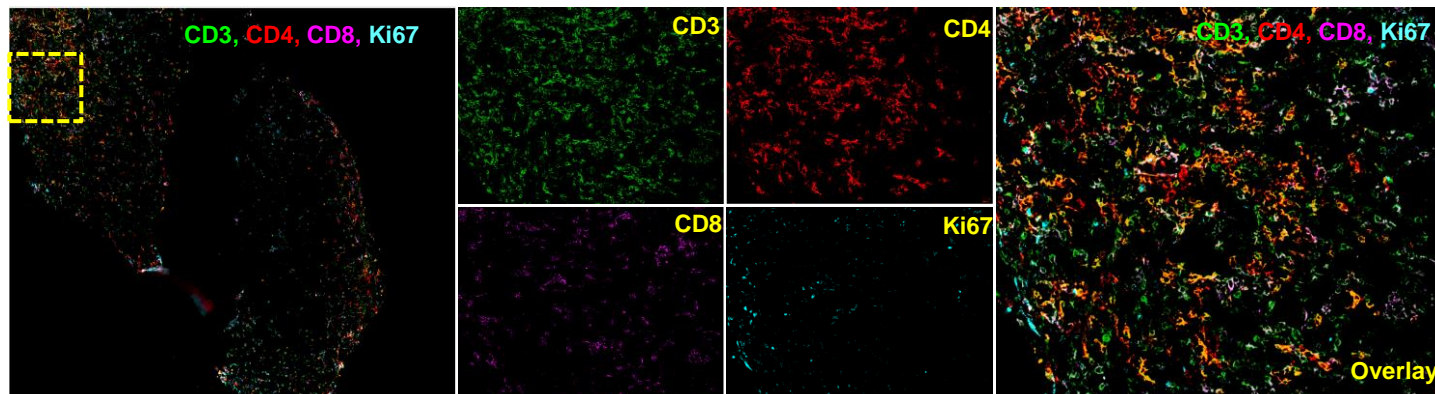
AGEN1777^{ms} increases activated tumor-infiltrating lymphocytes (TILs) in CT26 tumor-bearing mice

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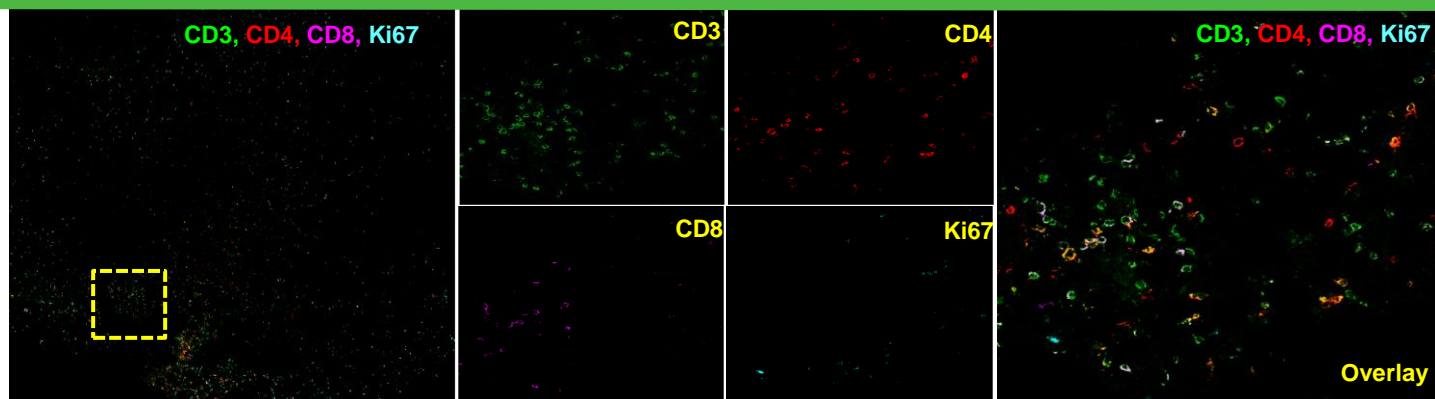
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AGEN1777^{ms}



Isotype
Control

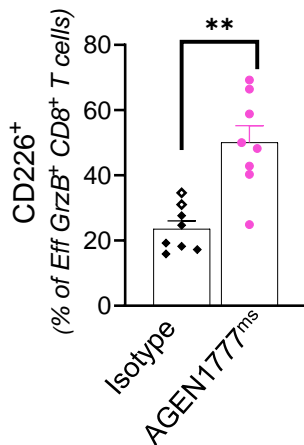


AGEN1777^{ms} enhances the frequency of intratumoral CD226⁺ CD8⁺ T cell subsets in the TME

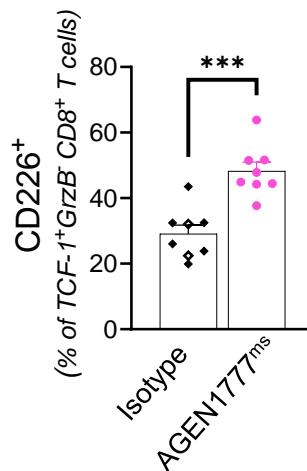
Enhanced frequency of CD226⁺ effector and memory CD8⁺ T cells

Efficacy was not dependent on intratumoral Treg depletion

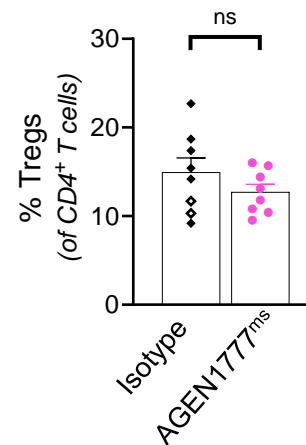
Effector GrzB⁺ CD8⁺ T cells



Memory precursor CD8⁺ T cells

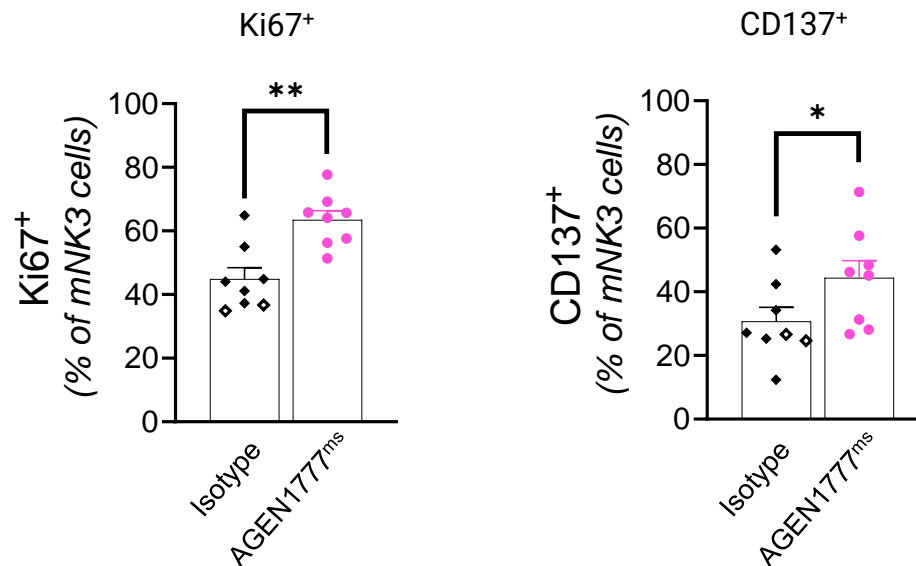


Regulatory T cells



AGEN1777^{ms} enhances the frequency and activation of cytotoxic NK cells in the TME

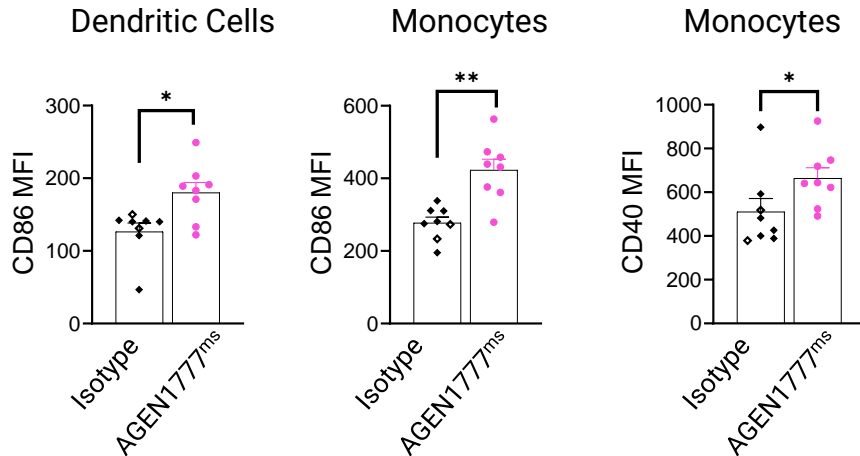
Enhanced frequency of tumor-infiltrating cytotoxic NK cells



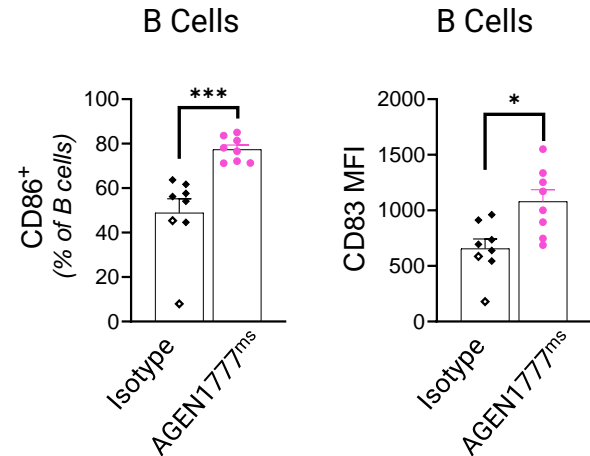
**, p<0.05; **, p<0.01; Mann-Whitney test*

AGEN1777^{ms} enhances the activation of intratumoral professional antigen-presenting cells

Enhanced activation of intratumoral dendritic cells and monocytes



Enhanced frequency of activated intratumoral B cells



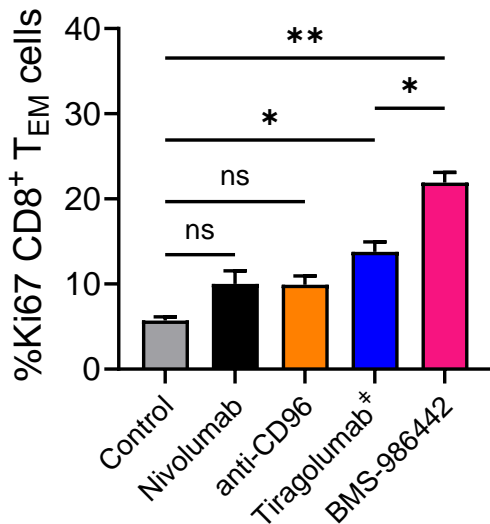
*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; Mann-Whitney test

Similar increases in the frequencies of activated B cells, dendritic cells and monocytes observed in the inguinal lymph node of AGEN1777^{ms}-treated mice

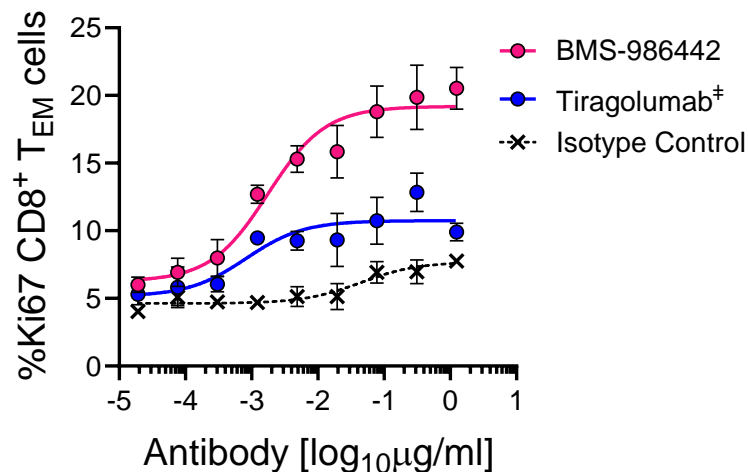
BMS-986442 (AGEN1777) demonstrates superior CD8 memory recall versus conventional anti-TIGIT mAb



CMV memory recall assay



BMS-986442 enhances CD8⁺ T effector memory cell activation over conventional anti-TIGIT mAb



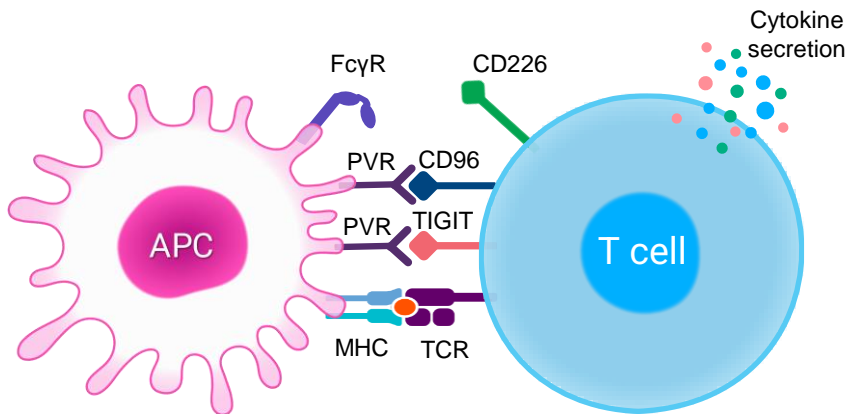
BMS-986442 promotes superior T cell responsiveness alone and in combination with anti-PD-1

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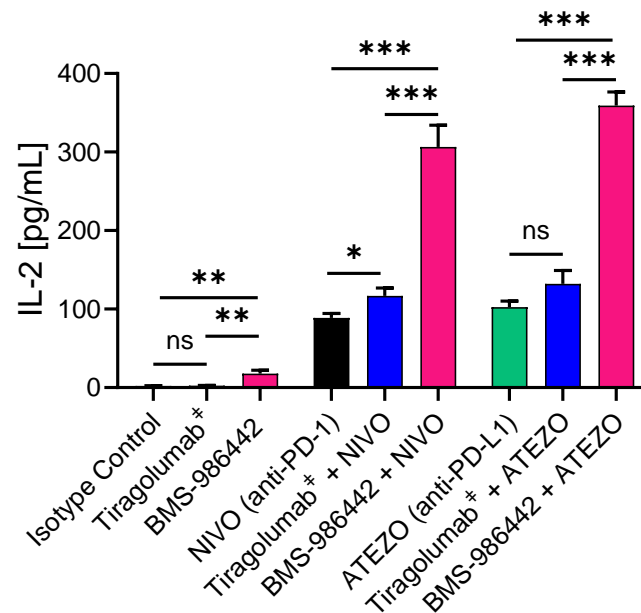
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T cell : APC priming assay



BMS-986442 promotes superior T cell activation compared to conventional anti-TIGIT mAb



† analogue of tiragolumab

Source data: Agenus, internal data not published



- Dual blockade of TIGIT and CD96 could represent a promising approach to overcome the limitations of conventional anti-TIGIT therapy
- Enhanced Fc γ R co-engagement leverages novel mechanisms to :
 - ✓ Enhance T cell priming and activation
 - ✓ Activate APCs
 - ✓ Promote cytotoxic NK cell activation
- BMS-986442 demonstrates superior immune activation as monotherapy and in combination with PD-(L)1 blockade compared to conventional anti-TIGIT mAb
- BMS-986442 is currently in a Phase 1/2 clinical study in combination with nivolumab \pm chemotherapy for the treatment of solid tumors and NSCLC (NCT05543629)

Acknowledgments

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