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Restoring Immune Function of Tumor-Specific CD4$^+$ T Cells during Recurrence of Melanoma

Goding SR et al. J Immunol 2013; 190:4899-4909

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Background

- Melanoma
  - Stages and Therapy
- Adoptive T Cell Transfer
- Reccurence
  - Tregs
  - PD-1
  - LAG-3
  - TIGIT
  - TIM-3

Melanoma

- Surgery
  - with or without lymph node sampling
- Chemotherapy (*CHT*)
  - systemic or regional
- Biologic therapy
  - IFN, IL-2, TNF
- Targeted therapy
  - mAbs, Signal transduction inhibitors, Oncolytic viruses, Angiogenesis inhibitors
- Radiation therapy

Melanoma

- Stage *0 (melanoma in situ)*
  - Surgery
- Stage I & II *(invasive melanoma)*
  - Surgery + lymph node sampling
- Stage III *(regional metastasis)*
  - Surgery + biologic therapy
  - Targeted therapy + regional CHT (+ biologic therapy)
- Stage IV *(distant metastasis)* and Reccurent Melanoma
  - Targeted therapy
  - Biologic therapy
  - CHT
  - Palliative therapy (Surgery, Radiotherapy)

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Adoptive Cell Transfer (ACT)

- Tumor-Specific T cells
  - Tumor-infiltrating Lymphocytes (TIL)
  - genetically engineered T cells
- In vitro reproduction
- Lymphodepletion
- Re-Infusion

Jennifer Makalowski and Hinrich Abken (2013). Adoptive Cell Therapy of Melanoma: The Challenges of Targeting the Beating Heart, Melanoma - From Early Detection to Treatment, Dr. Ht Duc (Ed.), ISBN: 978-953-51-0961-7, InTech, DOI: 10.5772/53619.

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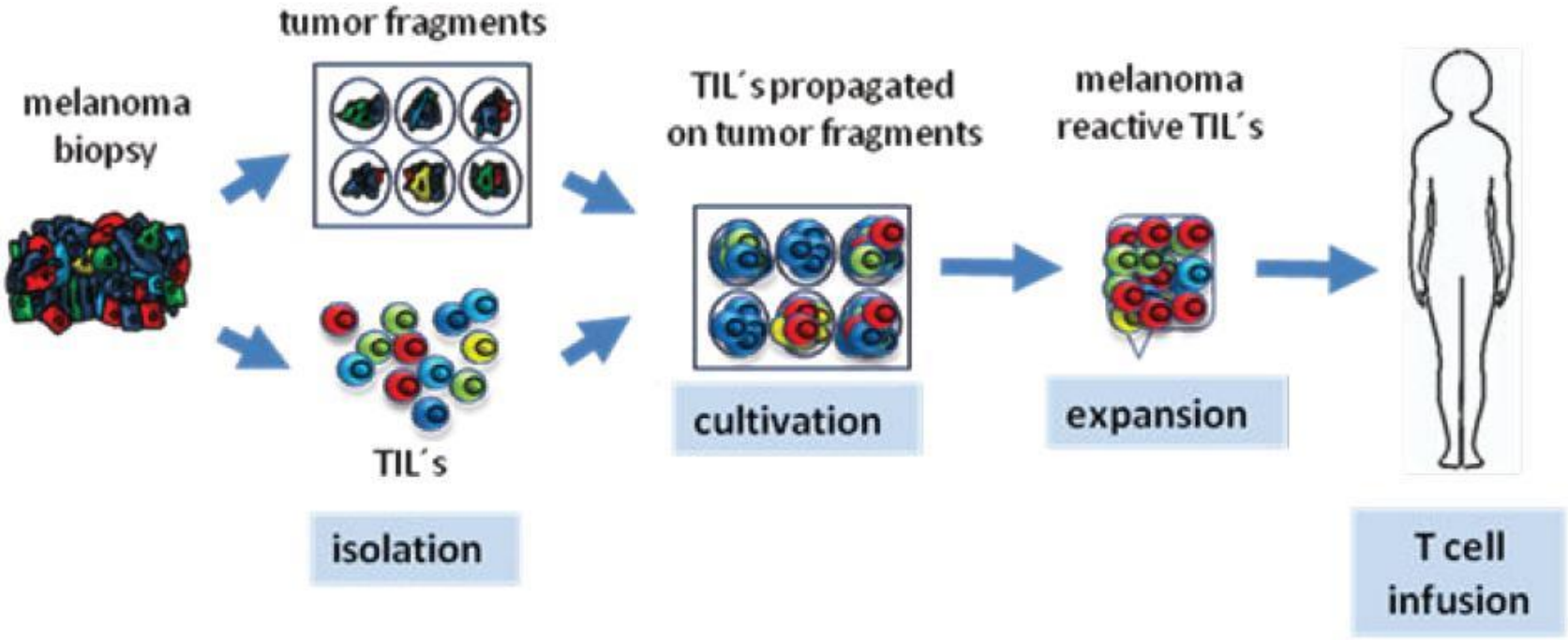
Adoptive Cell Transfer



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Adoptive Cell Transfer (ACT)

- Effective as primary treatment
  - under regulatory T cell (*Treg*) depletion
- Less effective for treatment of recurring melanoma
  - effector T cell (T_E) inhibiting molecules
    - Programmed cell death protein 1 (*PD-1*)
    - Lymphocyte-activation gene 3 (*LAG-3*)
    - T cell immunoreceptor with Ig and ITIM domains (*TIGIT*)
    - T cell immunoglobulin mucin-3 (*TIM-3*)

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Materials and Methods

- Mice
  - Tyrp1$^{B\text{-}w}$RAG$^{-/-}$ TRP-1-specific CD4^{+} TCR transgenic mice
    - were crossed with
  - Foxp3-DTR mice
    - to create
  - tyrp1$^{B\text{-}w}$RAG$^{-/-}$ Foxp3-DTR TRP-1-specific CD4^{+} TCR transgenic mice
    - no CD8+ T cells
    - T cell receptor is TRP-1 specific
    - Tregs can be inactivated with DT
  - C57BL/6 RAG$^{-/-}$ mice

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Materials and Methods

- Tumor Line
  - B16.F10 (H-2^b): TRP-1^+ spontaneous murine melanoma
  - injected s.c. at $2x10^5$ cells/mouse

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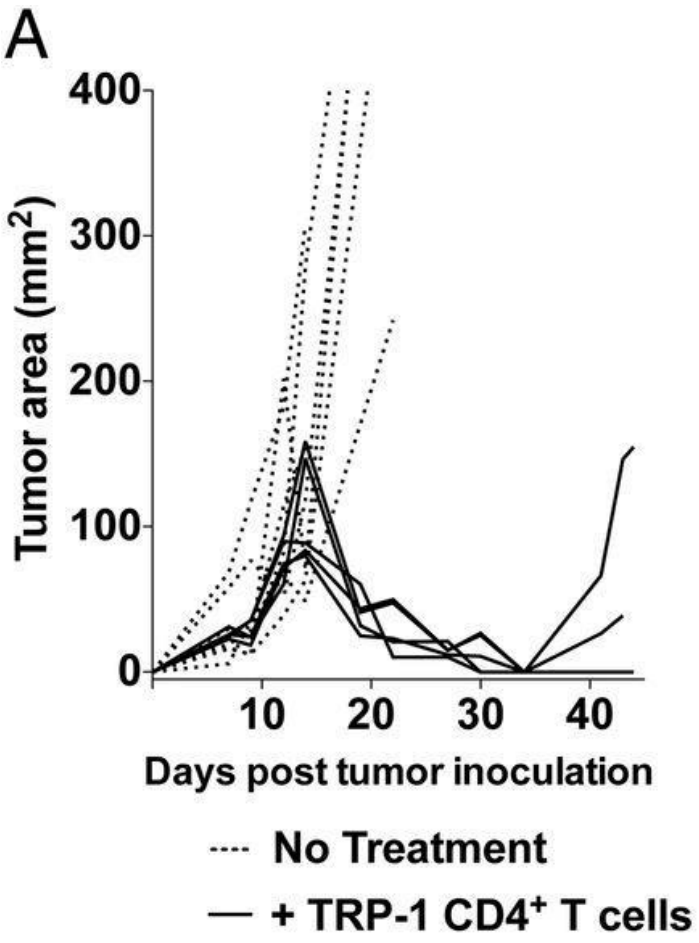
Results

- Tumor-specific Foxp3^{+} Tregs expand during recurrence
  - CD57BL/6 mice
  - ACT 10 days after tumor inoculation
  - Recurrence variable (30 to 120 d)



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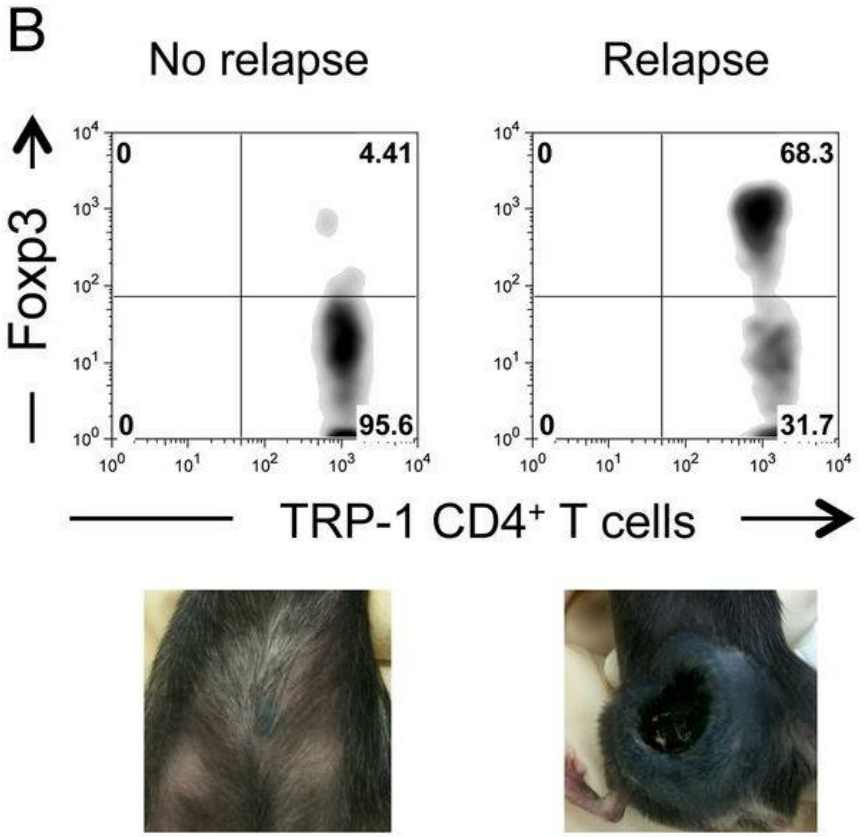
Results

- Tumor-specific Foxp3+ Tregs expand during recurrence
  - higher levels of Tregs in mice with relapse



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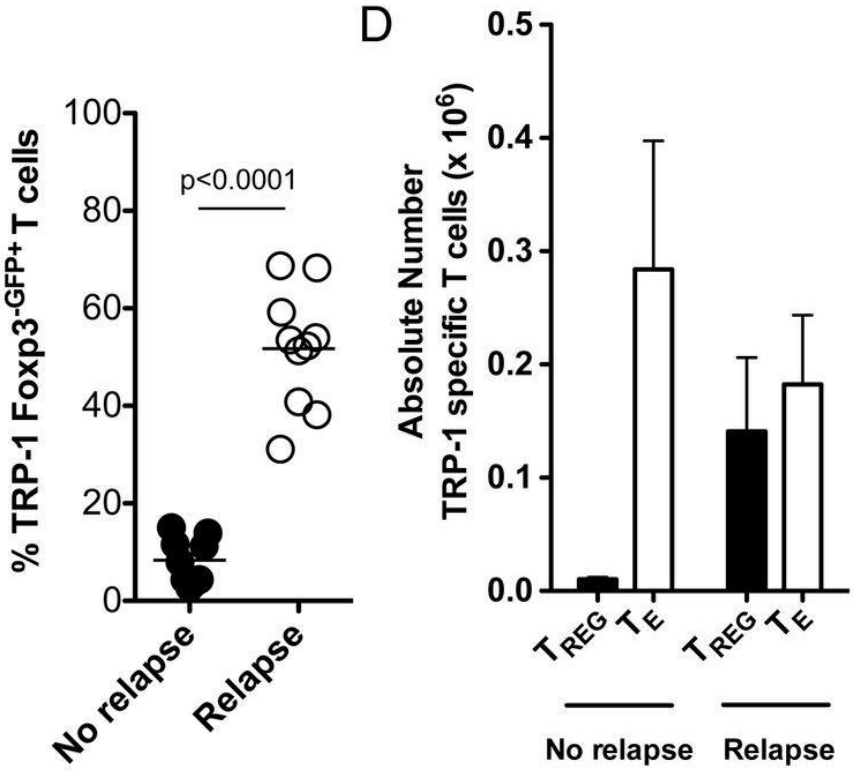
Results

- Tumor-specific Foxp3+ Tregs expand during recurrence
  - higher levels of Tregs in mice with relapse
  - T_E approximately the same



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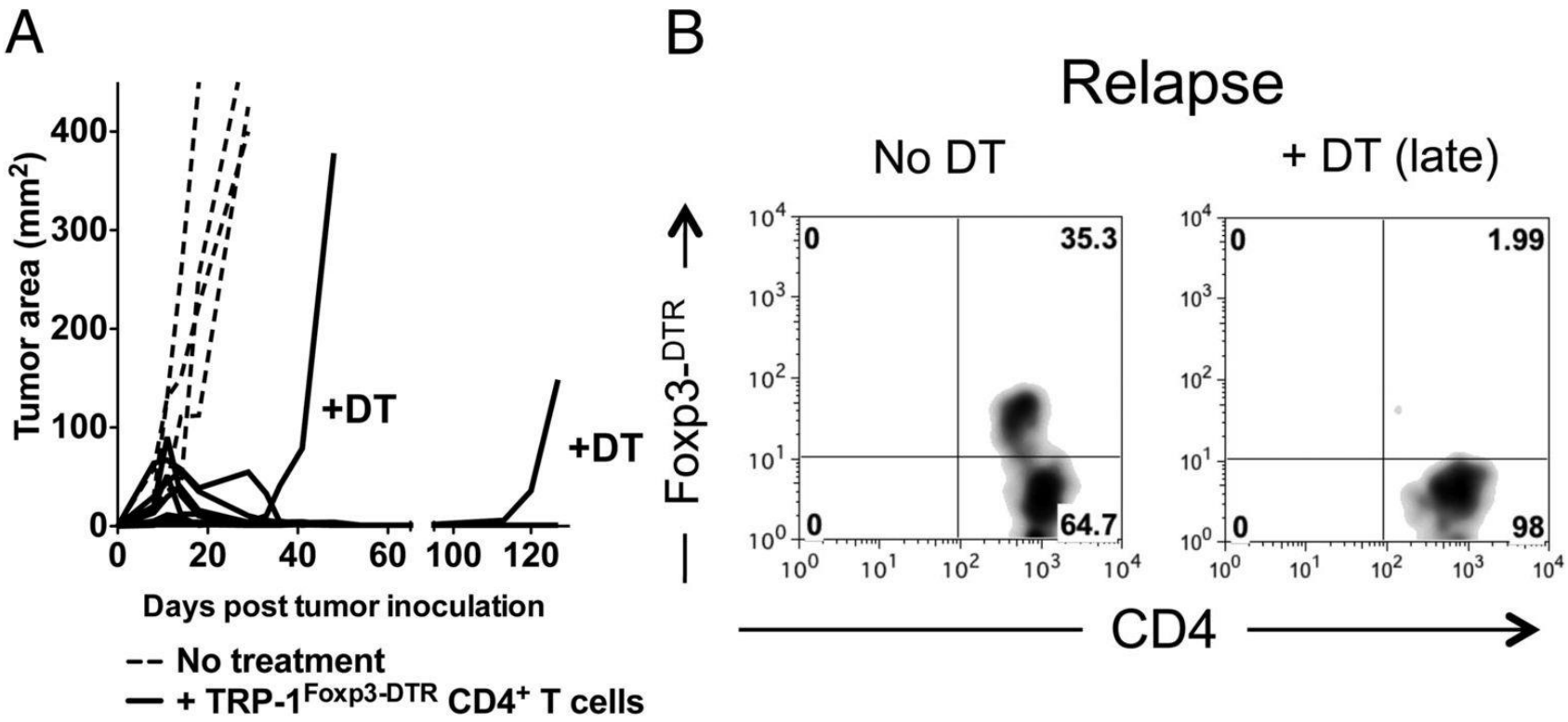
Results

- Depletion of tumor-specific Foxp3^{+} T cells does not treat recurrence



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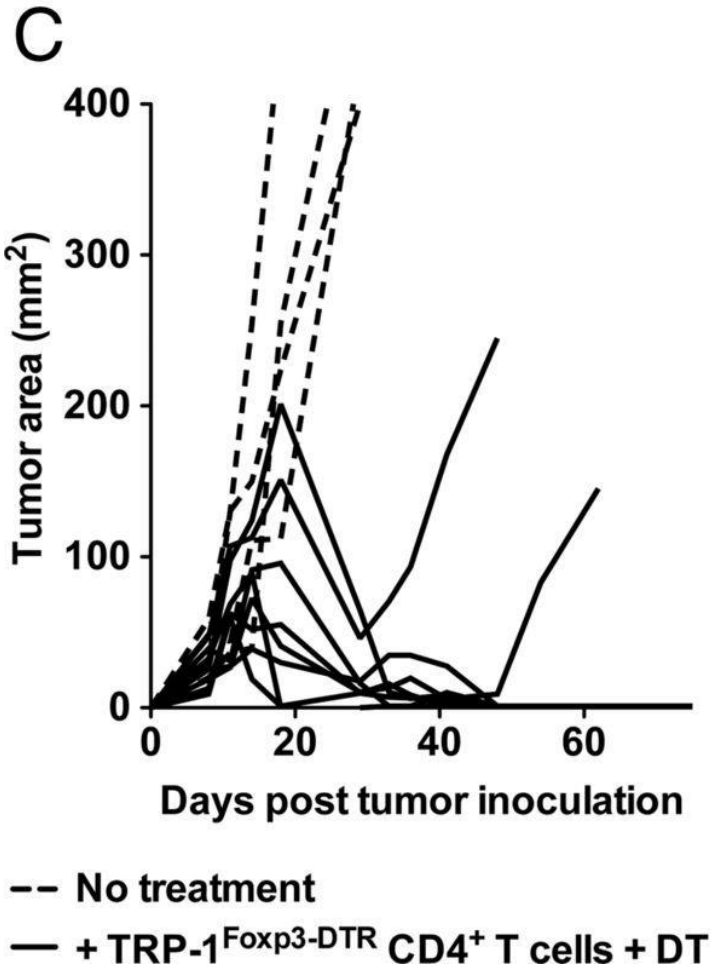
Results

- Depletion of tumor-specific Foxp3+ T cells does not treat recurrence
  - It also doesn‘t prevent it



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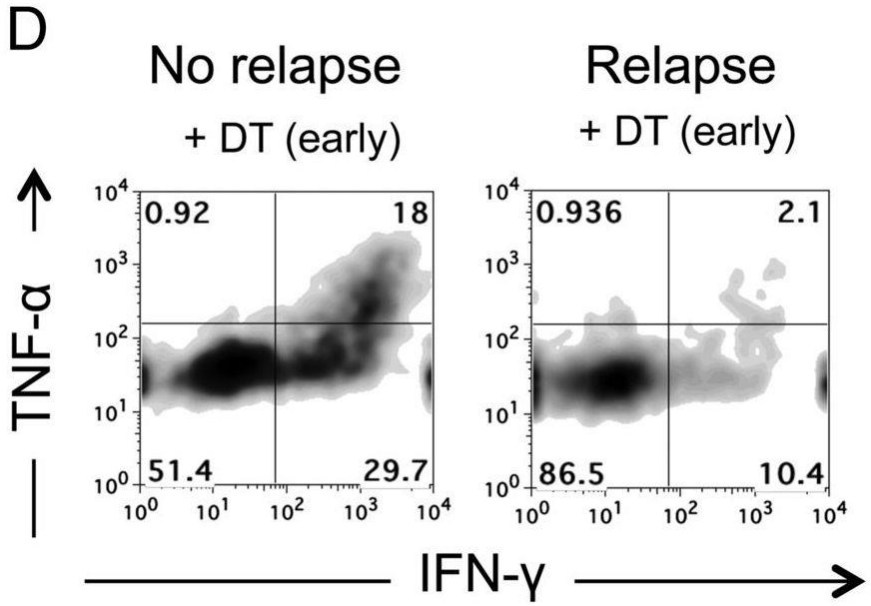
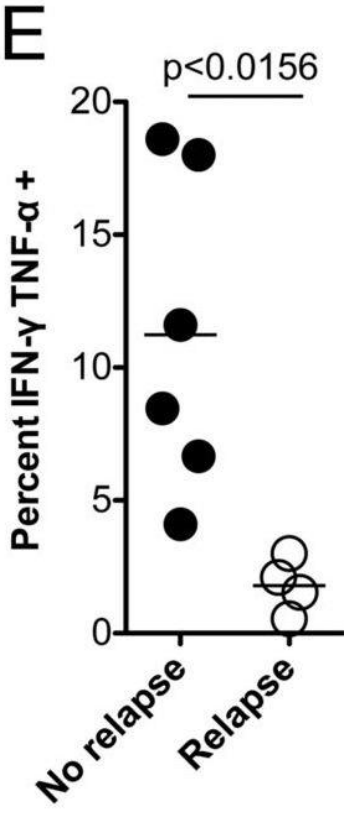
Results

- Depletion of tumor-specific Foxp3+ T cells does not treat recurrence
  - Differences in IFN and TNF production suggest intrinsic dysfunction of CD4$^+$ T_E





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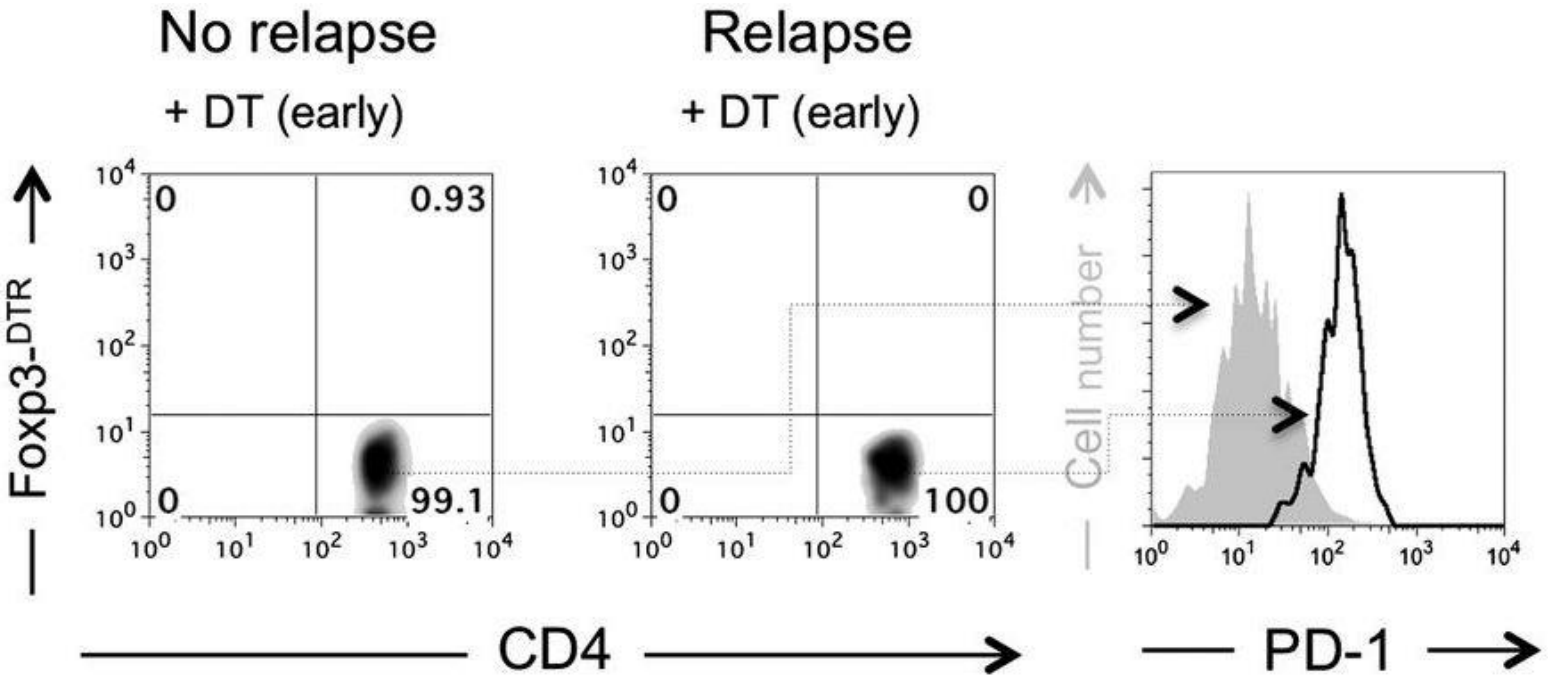
Results

- Tumor-specific CD4+ T cells become exhausted during cancer recurrence



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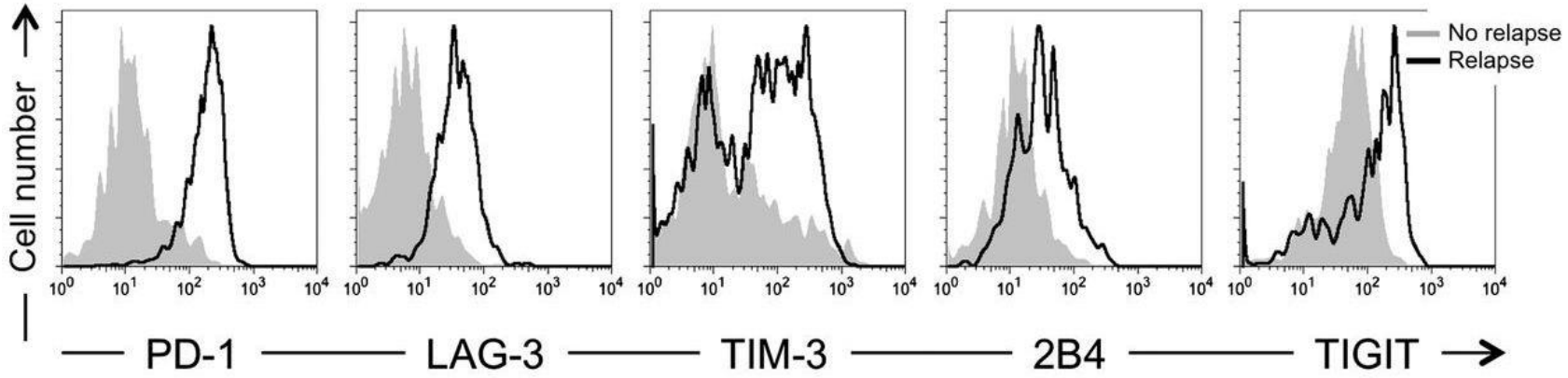

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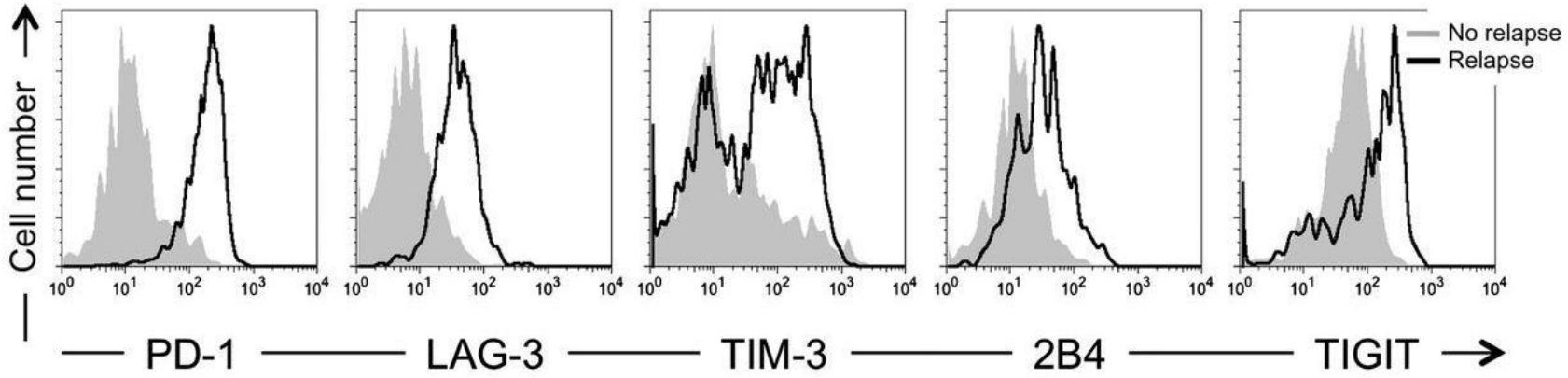

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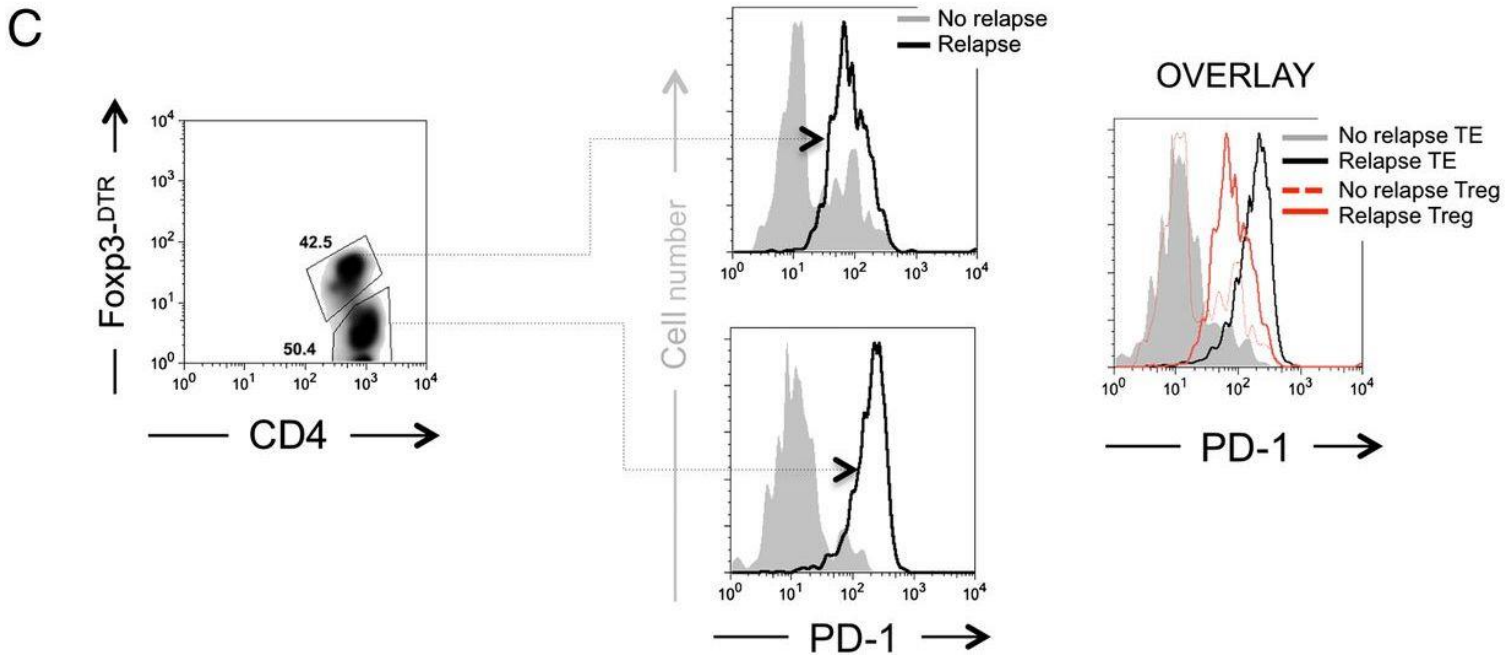

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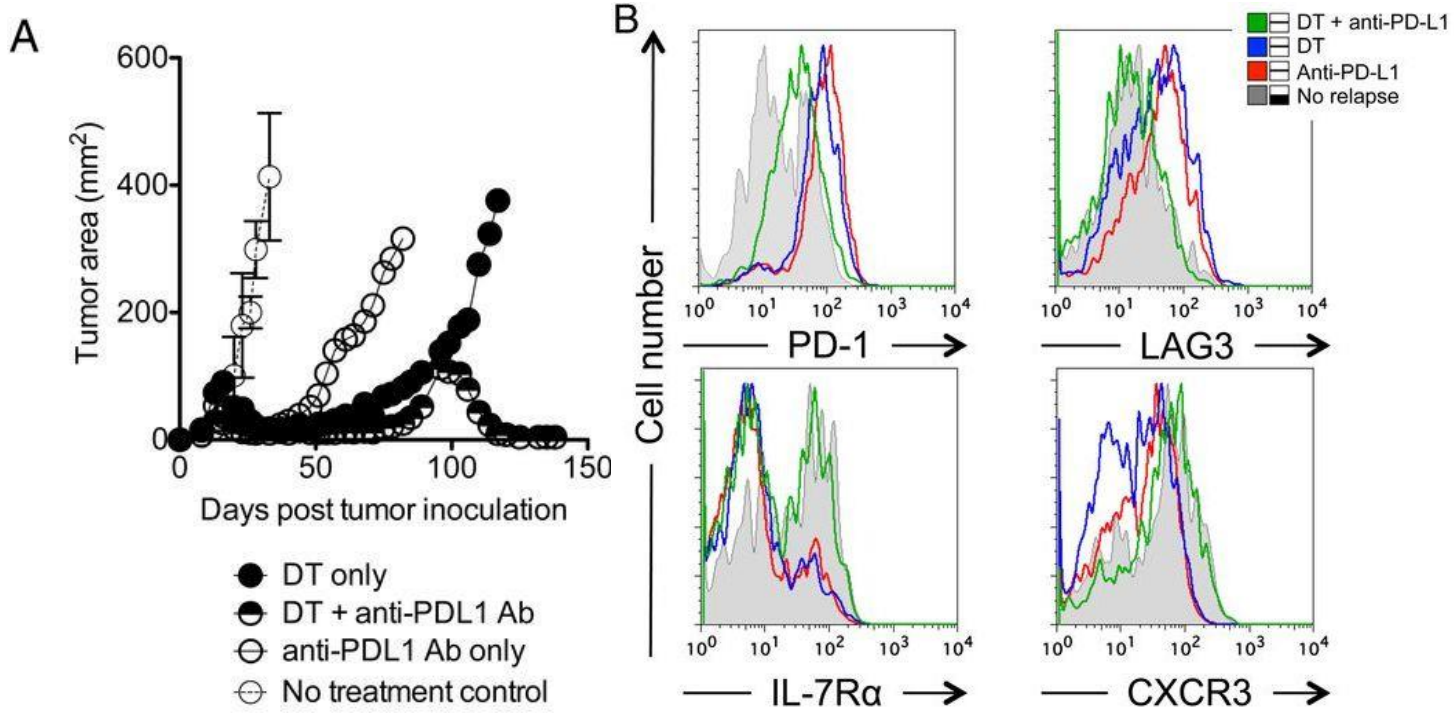
Results

- PD-L1-specific blockade restores antitumor immunity and treats recurrence only in combination with tumor-specific Treg ablation



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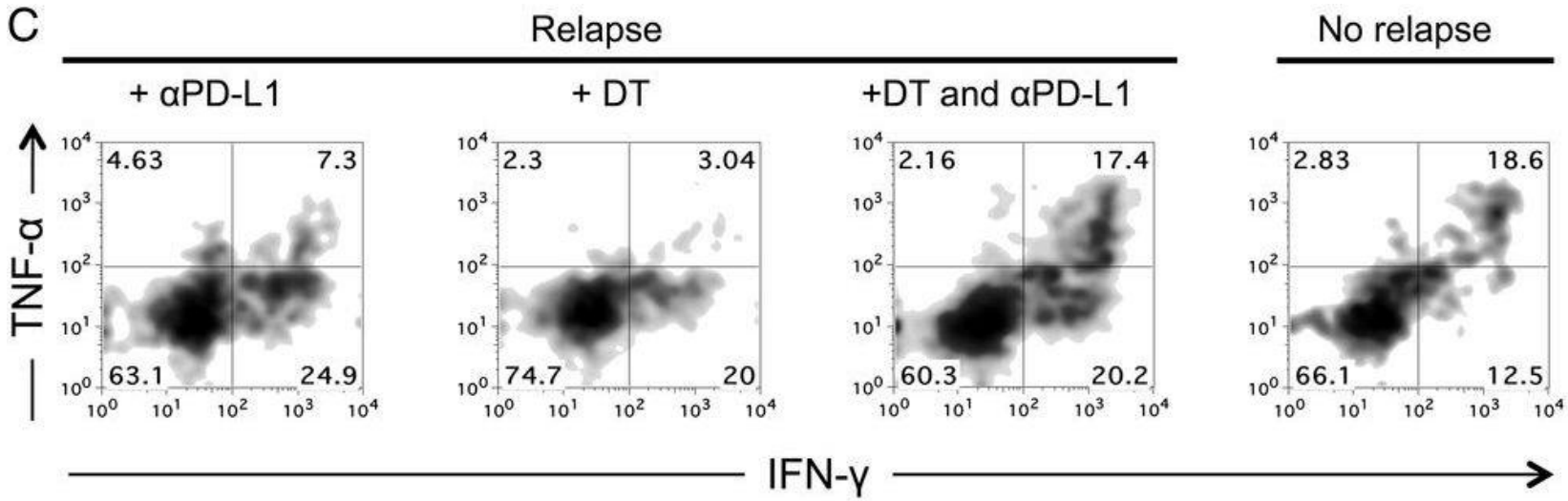

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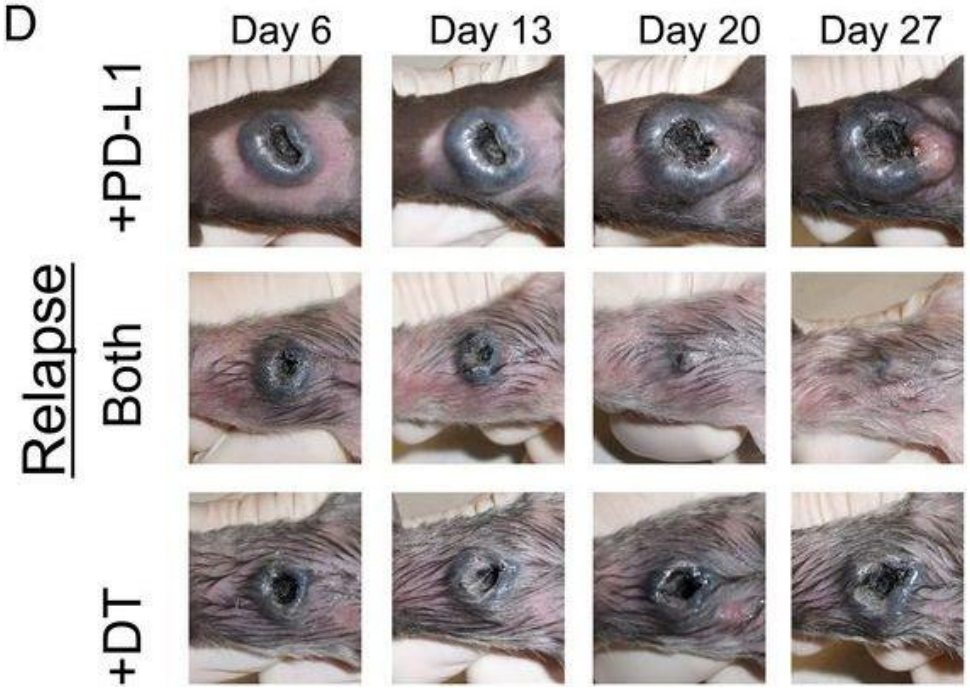

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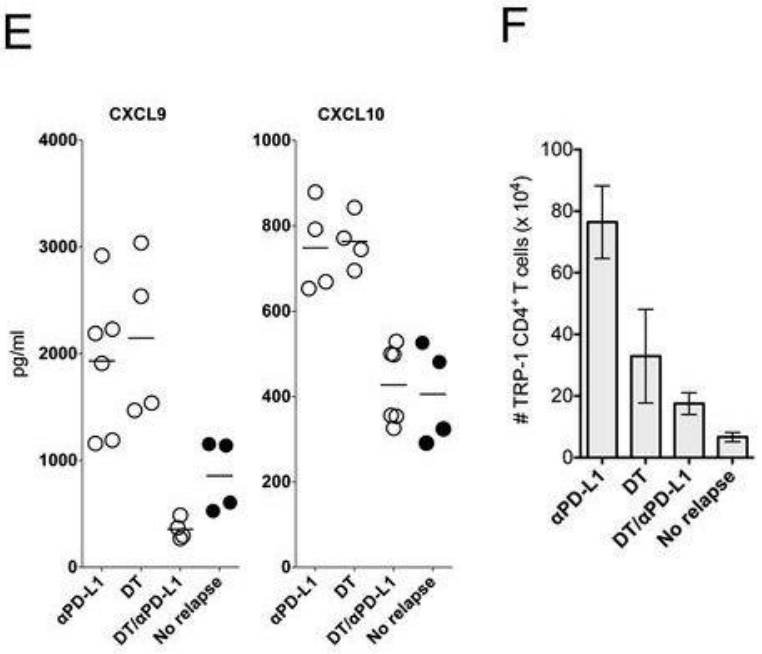

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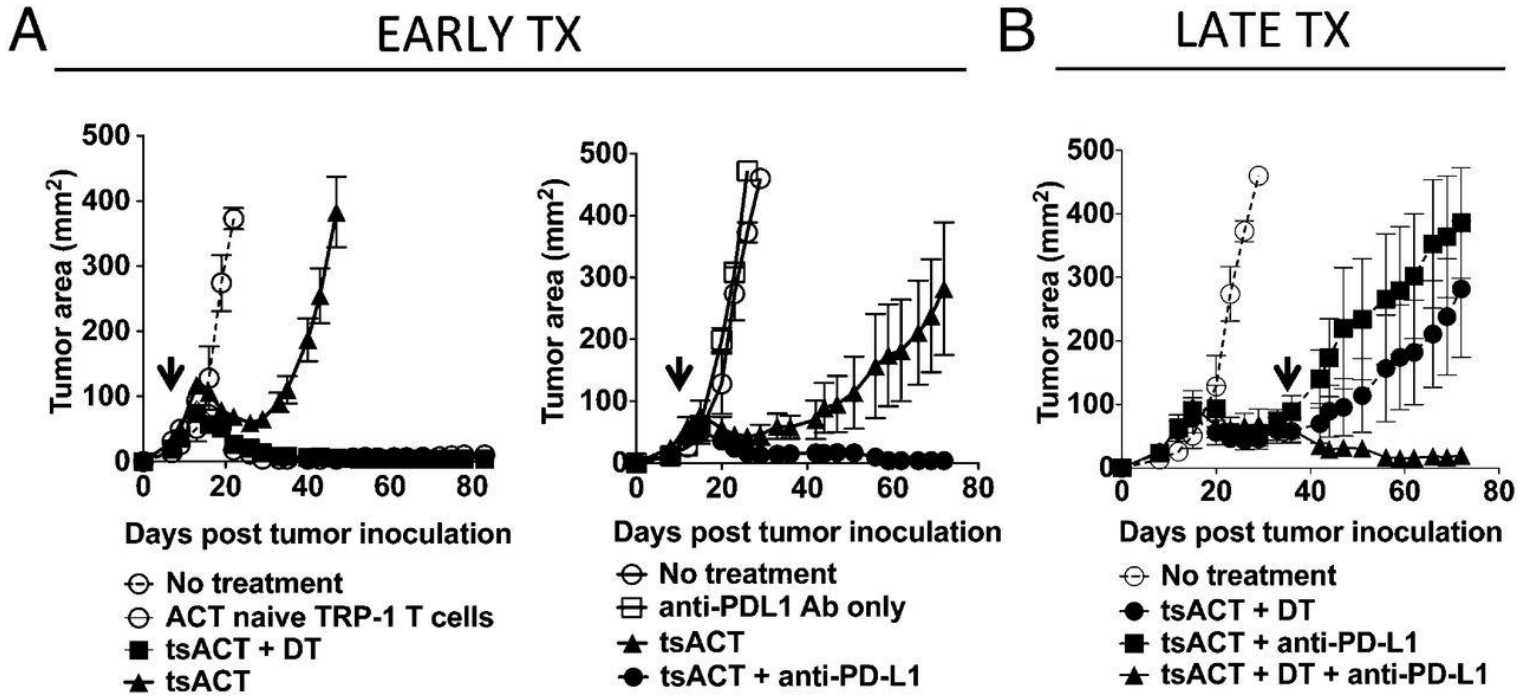
Results

- Disparate treatment requirements between primary and recurrent cancer



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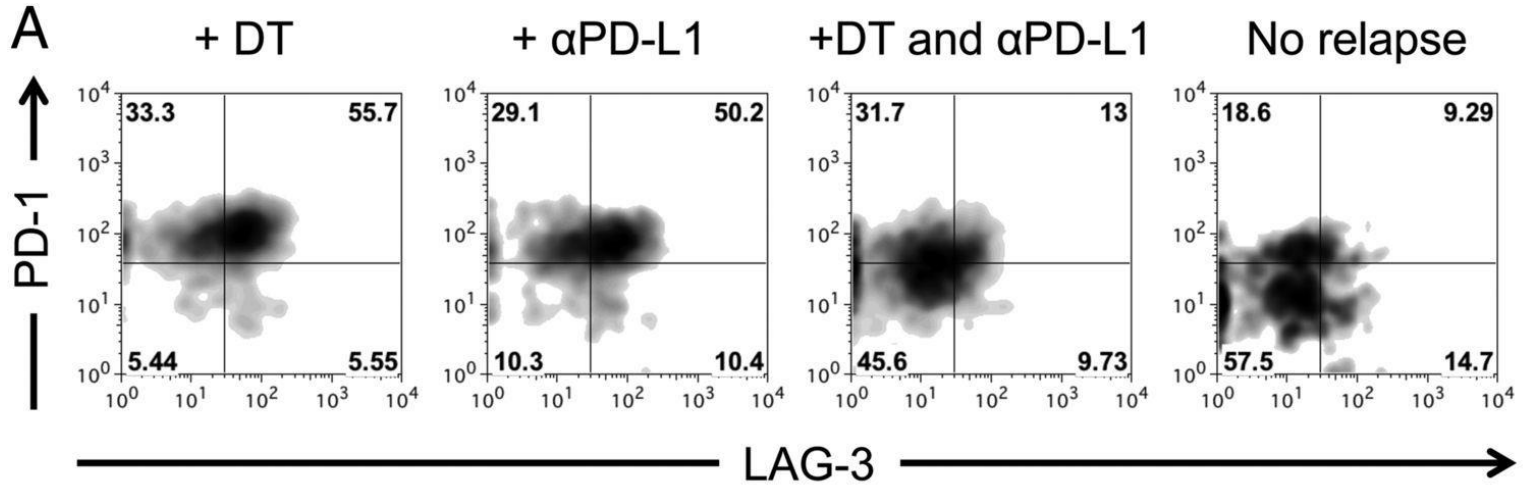
Results

- Simultaneous blockade of PD-L1 and LAG-3 in vivo treats recurring tumors, overcoming the necessity to deplete tumor-specific Tregs



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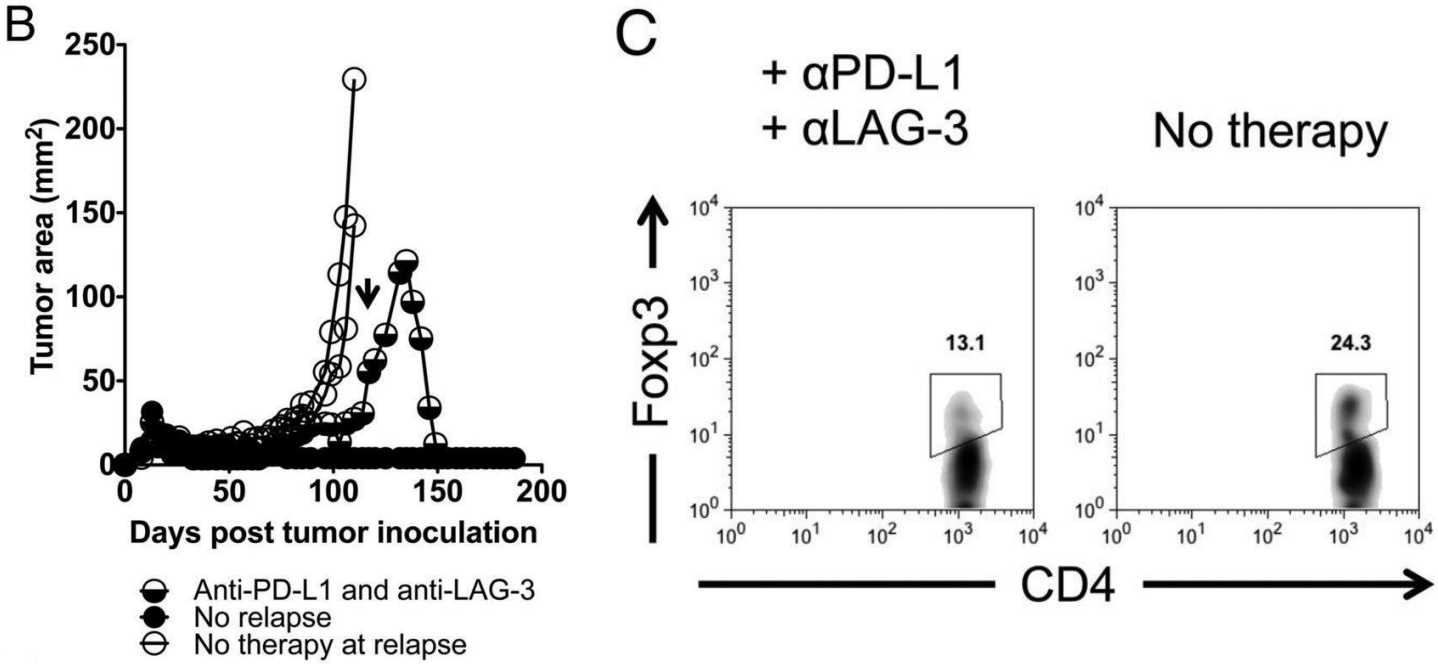

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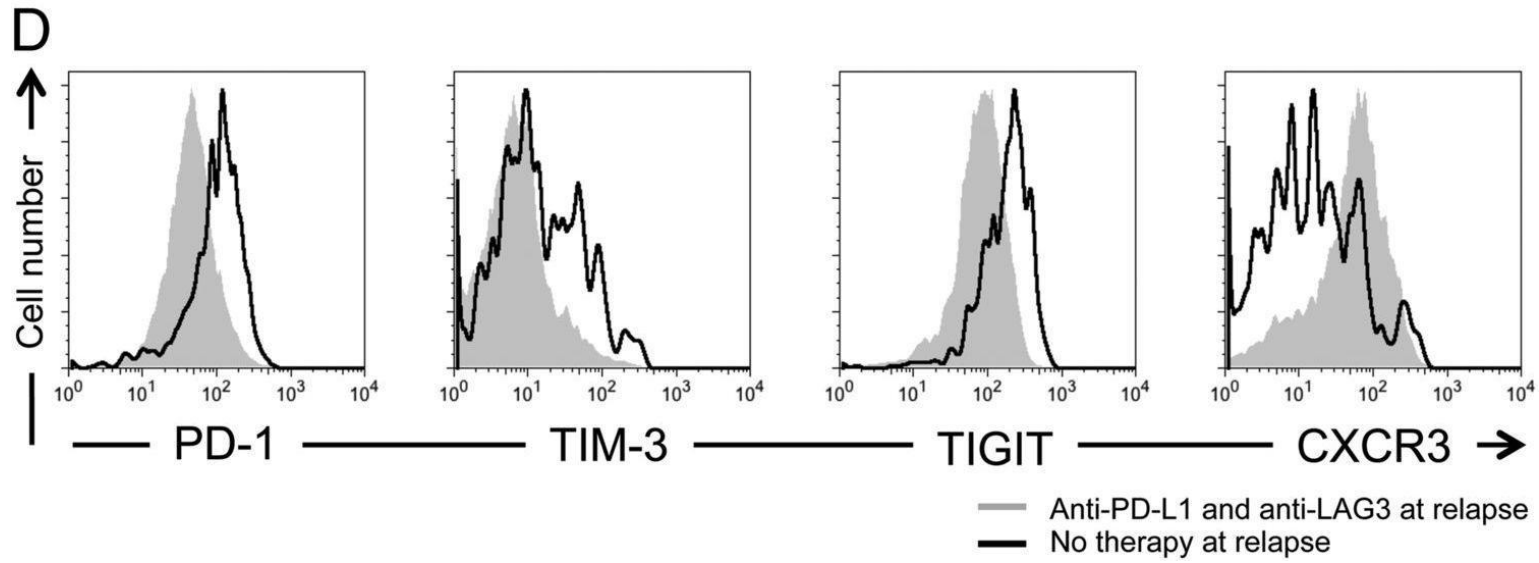

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Discussion

- Treg-mediated suppression and chronic exhaustion of $CD4^+$ T cells are are intertwined during melanoma recurrence.
- Suppression of antitumor immunity is not Treg dependent
- Anti-LAG-3 mAbs have the same effect as Treg depletion
- Impact of endogenous Tregs, B cells and CD8+ T cells?