Evalstotug (BA3071): a potent conditionally active biologic (CAB) anti–CTLA-4 antibody designed to enable high exposures, extended dosing, and reduced immune-mediated toxicity

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October 11, 2024

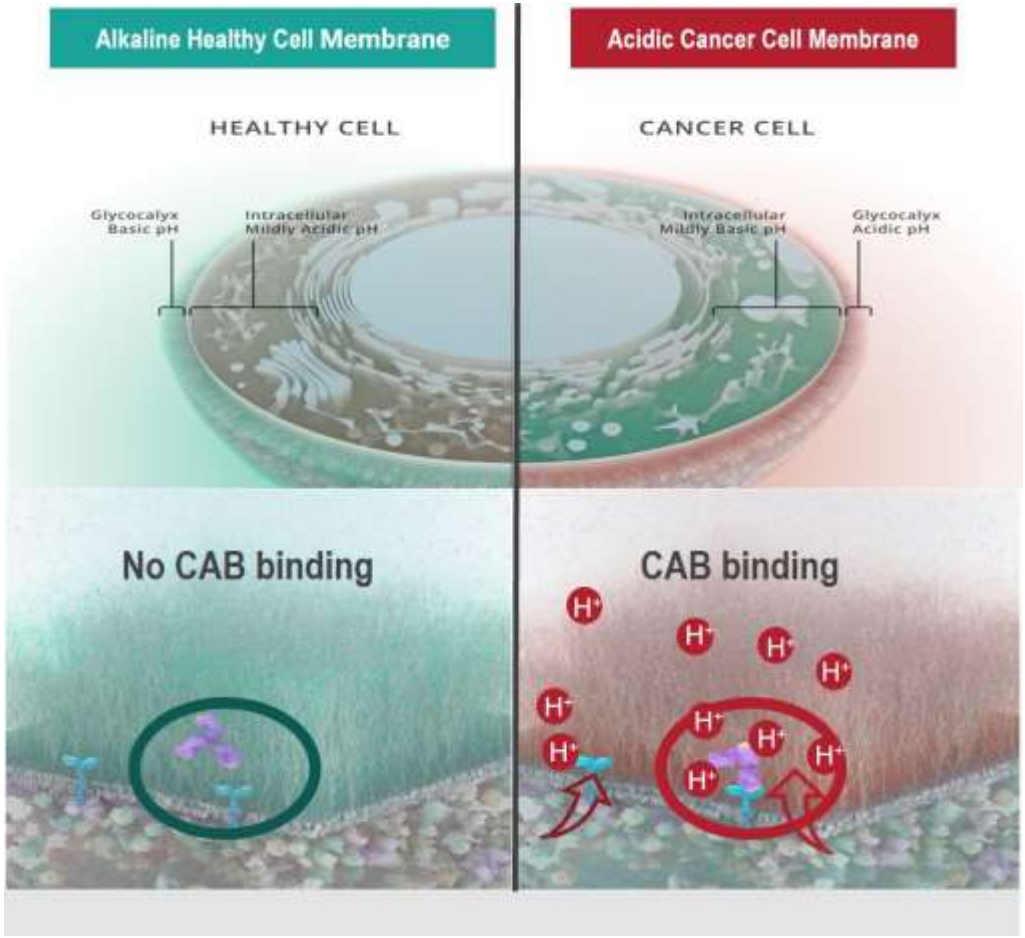
Abbreviation: CTLA-4, cytotoxic T-lymphocyte associated protein 4.

Disclosures

- William J. Boyle is an employee of BioAtla, Inc.

CAB technology widens the therapeutic index

- **Minimally altered in CDRs** to permit binding only within the acidic TME[1]
- CABs are **not masked or caged by a blocking peptide** and do not require enzymatic cleavage for activation
- Designed to **reduce immune-related AEs**, enhance antitumor immunity, avoid tissue-mediated drug disposition, and improve pharmacokinetics

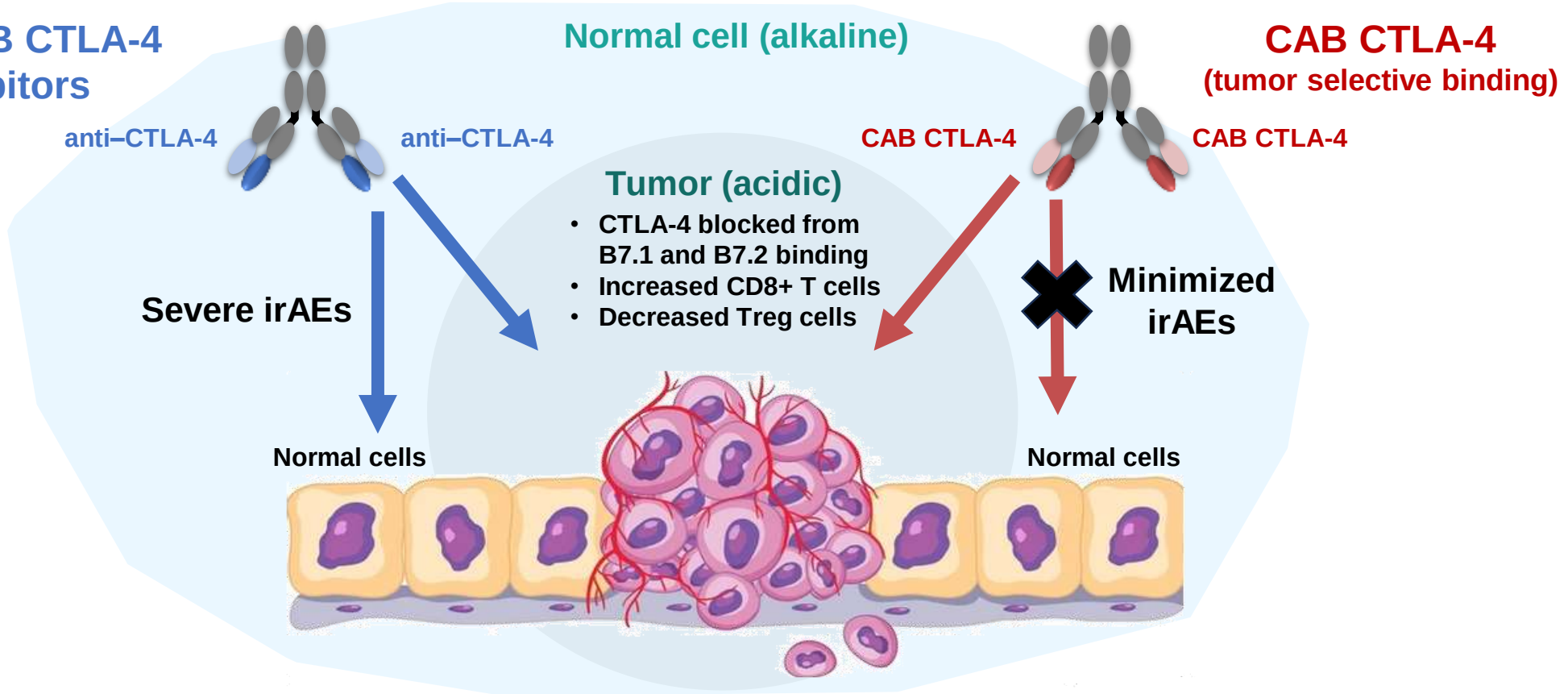


Abbreviations: AE, adverse event; CAB, Conditionally Active Biologic; TME, tumor microenvironment.

1. Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

Evalstotug (CAB CTLA-4)

Selectively active in the acidic TME[1] to reduce irAEs



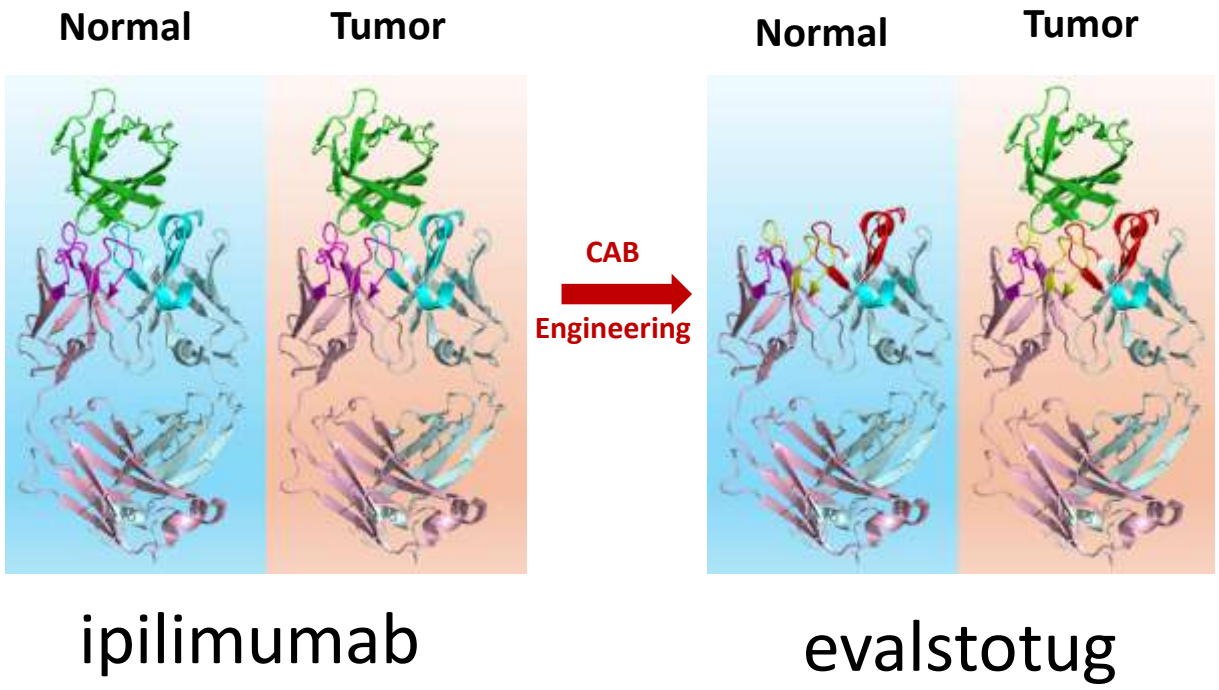
Abbreviations: CAB, Conditionally Active Biologic; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; irAE, immune-related adverse event; TME, tumor microenvironment; Treg, regulatory T cells.

1. Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

Evalstotug is a CAB-derivative of ipilimumab

Preserved efficacy with reduced toxicity in combination with PD-1

- Ipilimumab (ipi) CDR's modified to bind at tumor cell acidic pH, but not at normal pH leading to evalstotug:
  - Preserved affinity and epitope
  - Equivalent E_{Max} and EC_{50} in preclinical models
    - Same $T_{1/2}$ and exposure in primates and humans
    - Both ipi and evalstotug have not reached their maximal activity
  - Same effects on intratumoral lymphocytes;
    - Increased CD8+ from CTLA-4 blocking
    - Decreased Tregs from ADCC
- Substantially reduced G.I. toxicity in combination treatment in primates and humans
- Enables higher dosing in combination therapy:
  - Reduced toxicity in monotherapy and in combination with PD-1
  - Increased efficacy

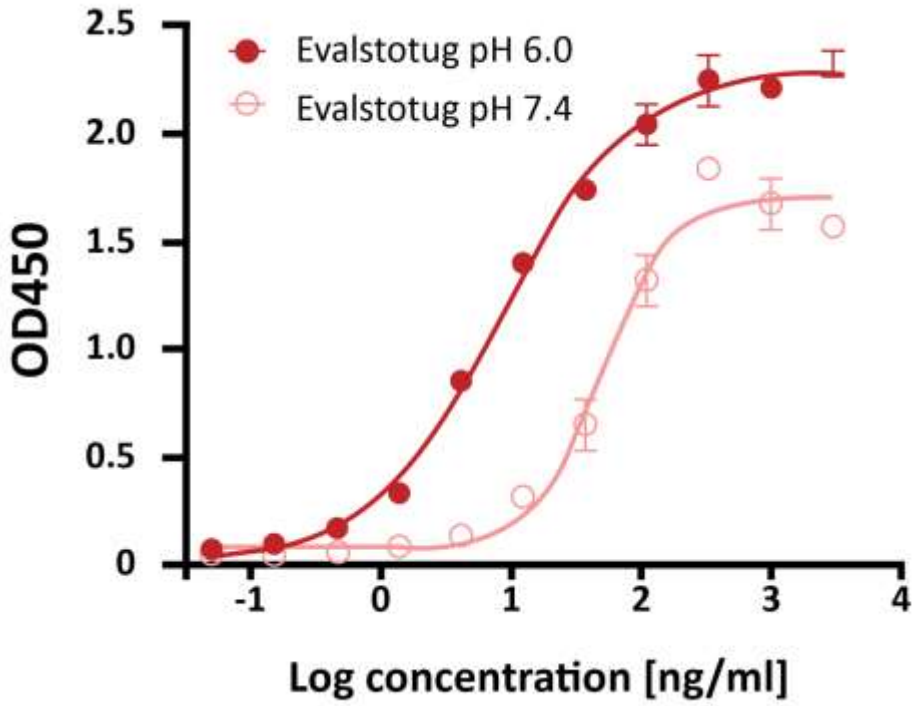


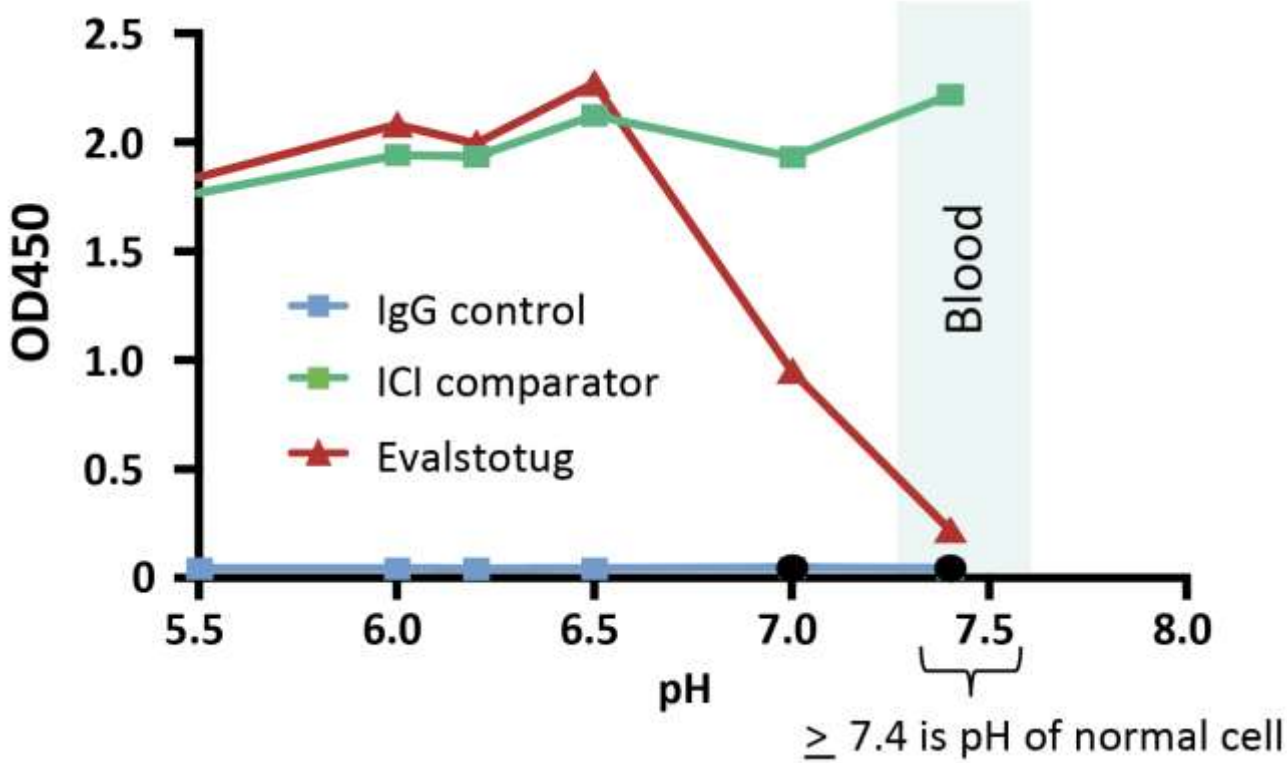
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CAB, Conditionally Active Biologic; CD, cluster of differentiation; CDR, complementarity-determining region; CTLA-4, cytotoxic T-lymphocyte associated protein 4; EC_{50}, concentration producing 50% E_{max}; E_{max}, maximum effect; PD-1, programmed cell death protein 1, $t_{1/2}$, half-life; Treg, regulatory T cells.

1. Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

Reversible binding in the TME

Comparison of evalstotug binding to CTLA-4 in different pH conditions

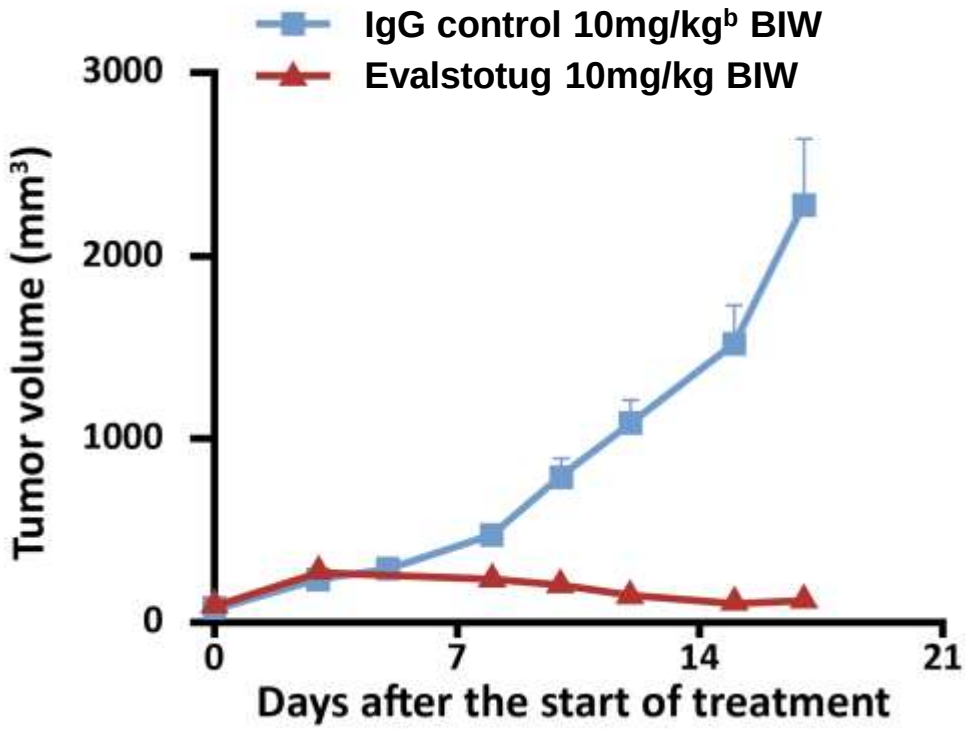


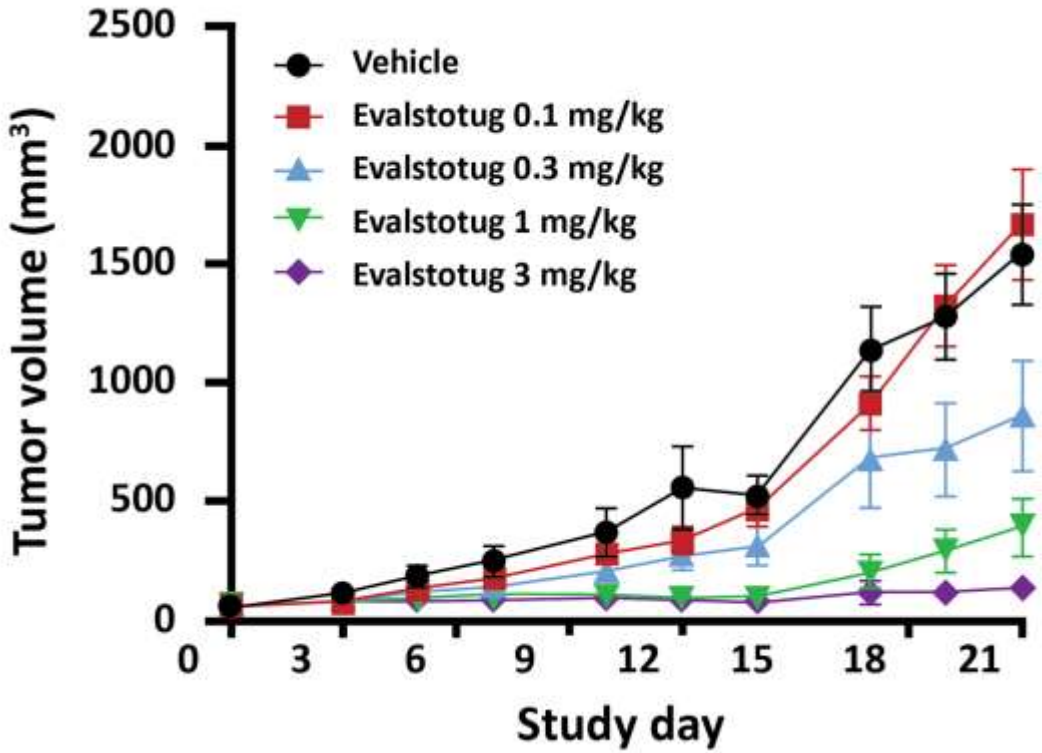


Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; OD450, optical density at 450 nm; TME, tumor microenvironment.
Note: Figures modified from Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

Tumor regression with dose response

Preclinical model with human CTLA-4 knock-in mice[a]





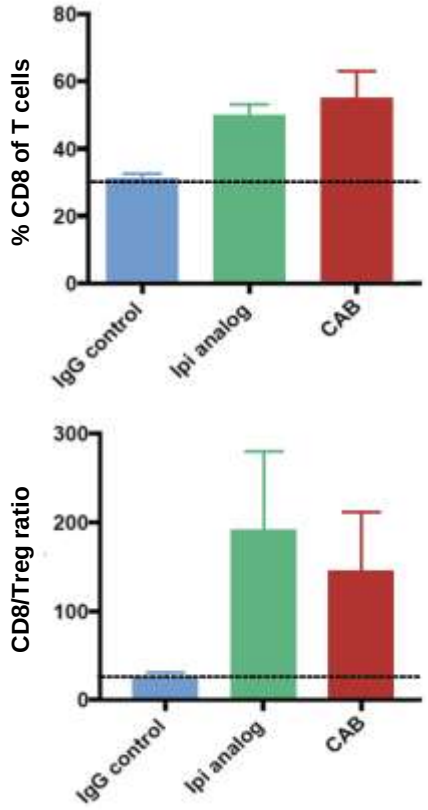
Abbreviations: BIW, twice a week; CTLA-4, cytotoxic T-lymphocyte associated protein 4; IgG, immunoglobulin G.
Note: Figures modified from Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.
[a]Human CTLA-4 knock-in mice were xenografted with mouse MC-38 syngeneic colon adenocarcinoma tumor cell line.
[b]Equivalent to 1 mg/kg anti–CTLA-4 human dose.

Evalstotug modulated T cells in the TME and periphery

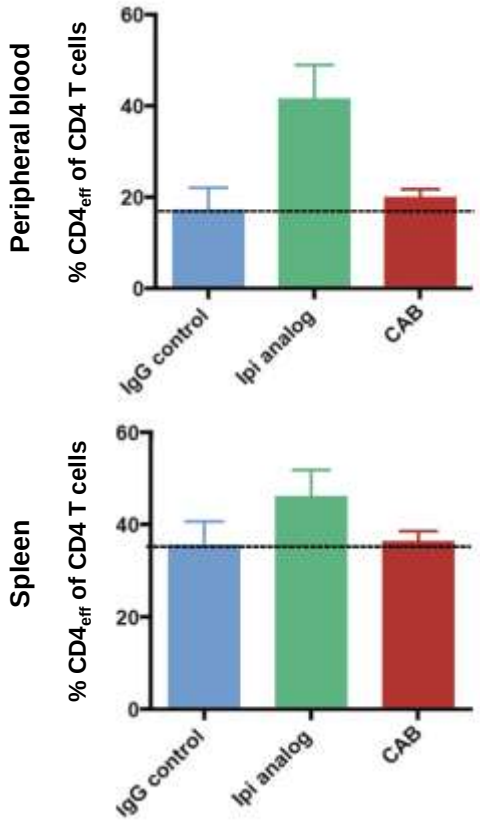
Potential mechanism for reduced immune-related toxicities

MC38 syngeneic tumor xenograft models in hCTLA4 knock-in mice at identical doses

Tumor infiltrating lymphocytes

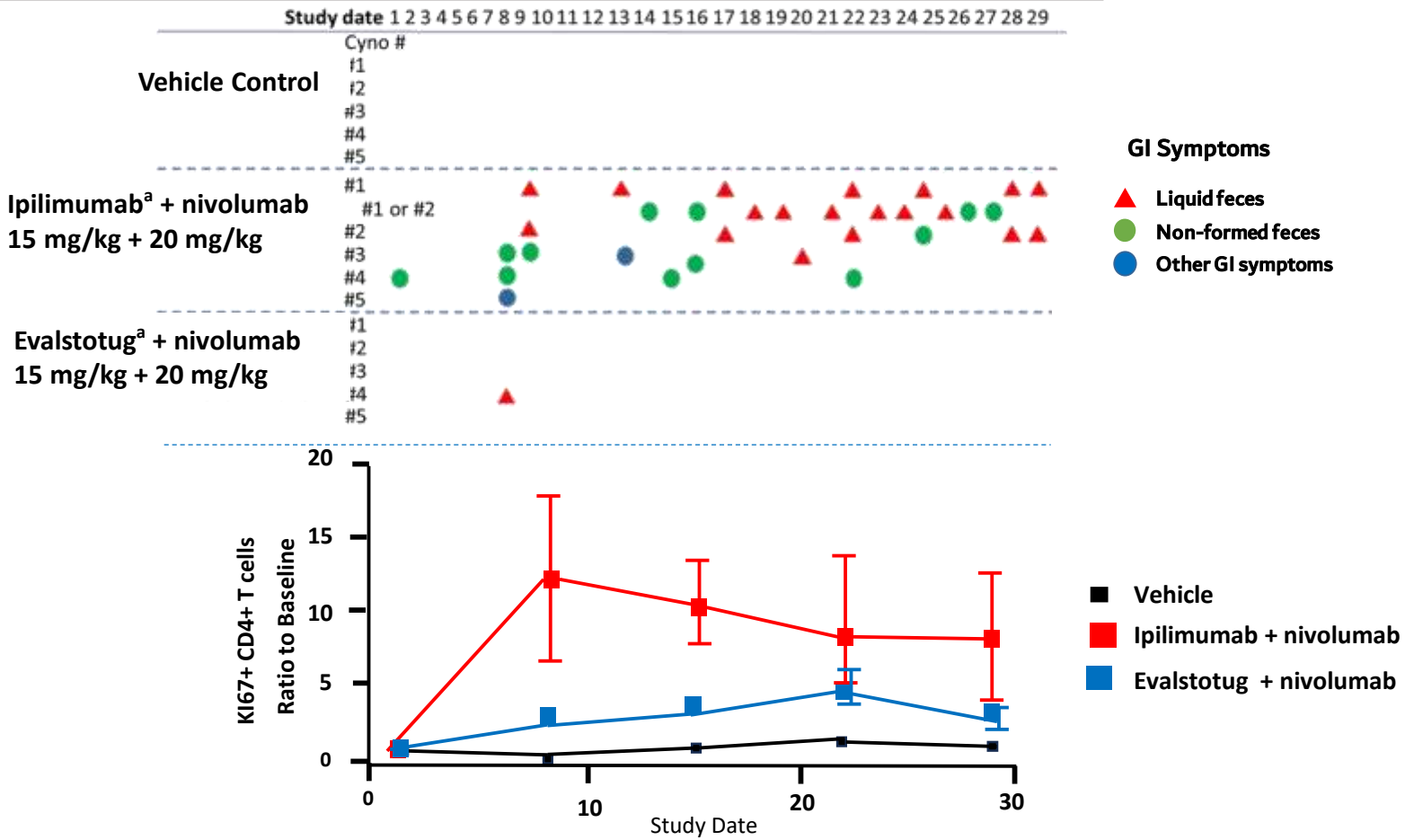


Normal tissue lymphocytes



Abbreviations: CAB, conditionally active biologic; CD, cluster of differentiation; $CD4_{eff}$, helper T cells; CTLA-4, cytotoxic T-lymphocyte associated protein 4; IgG, immunoglobulin G; Ipi, ipilimumab; TME, tumor microenvironment; Treg, regulatory T cell.
Note: Figure modified from Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

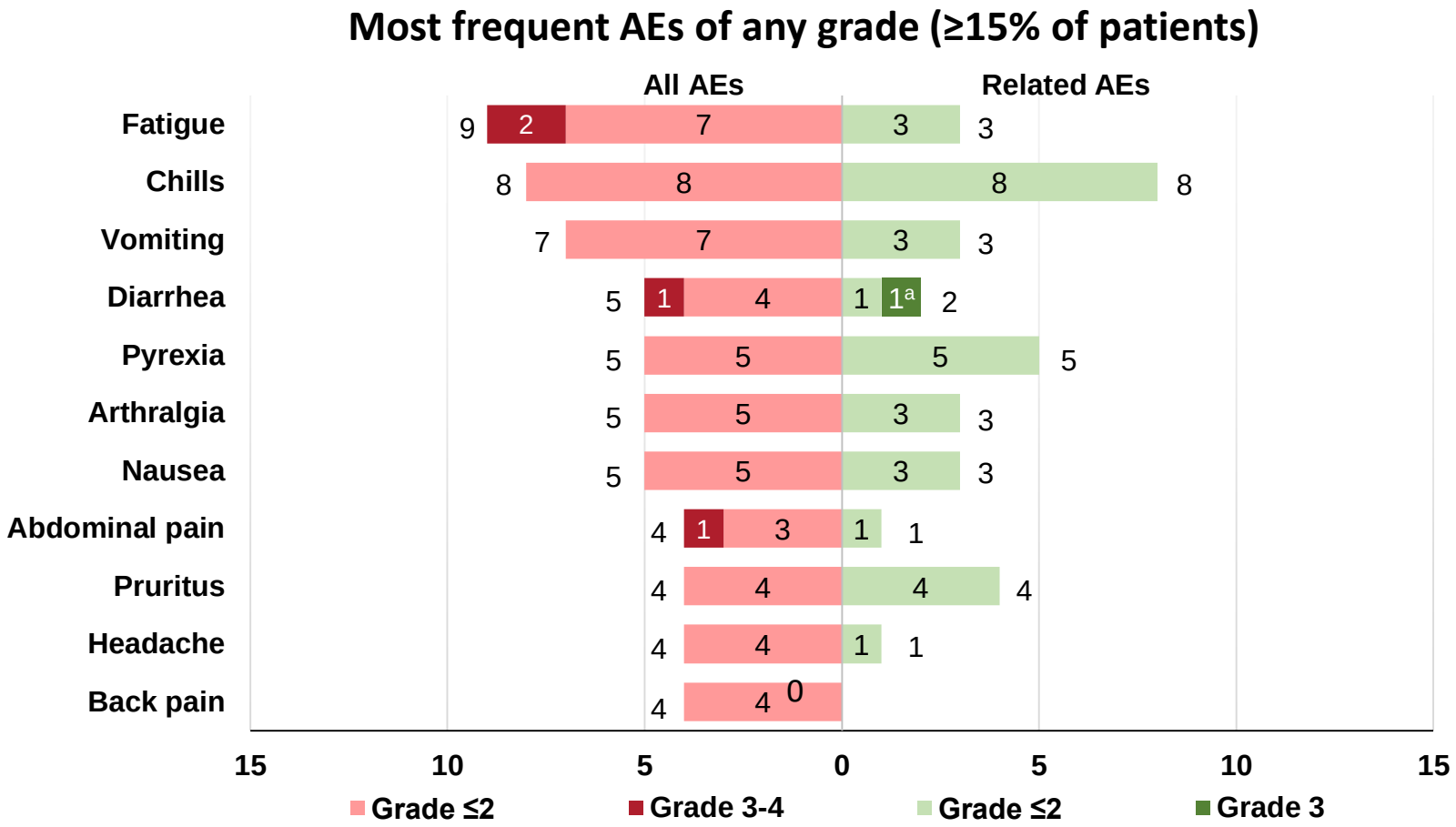
Evalstotug reduced GI toxicity in primates



Abbreviations: CD, cluster of differentiation; Cyno, cynomolgus macaque; GI, gastrointestinal; QW, once weekly.
Note: Ipilimumab and evalstotug had the same half-life and exposure in this model. Figure modified from Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.
[a]Ipilimumab analog or evalstotug 15 mg/kg (≈11 mg/kg human dose) + nivolumab 20 mg/kg (≈14.6 mg/kg human dose) both administered QW for 4 weeks.

Ph1 dose escalation of evalstotug; 70 mg to 1000 mg cleared

Most related AEs were low grade; no grade 4/5 related AEs were observed



Only 2 patients with grade 3 related immune-mediated AEs (DKA; lipase increase with gastritis/diarrhea) among 21 treated patients

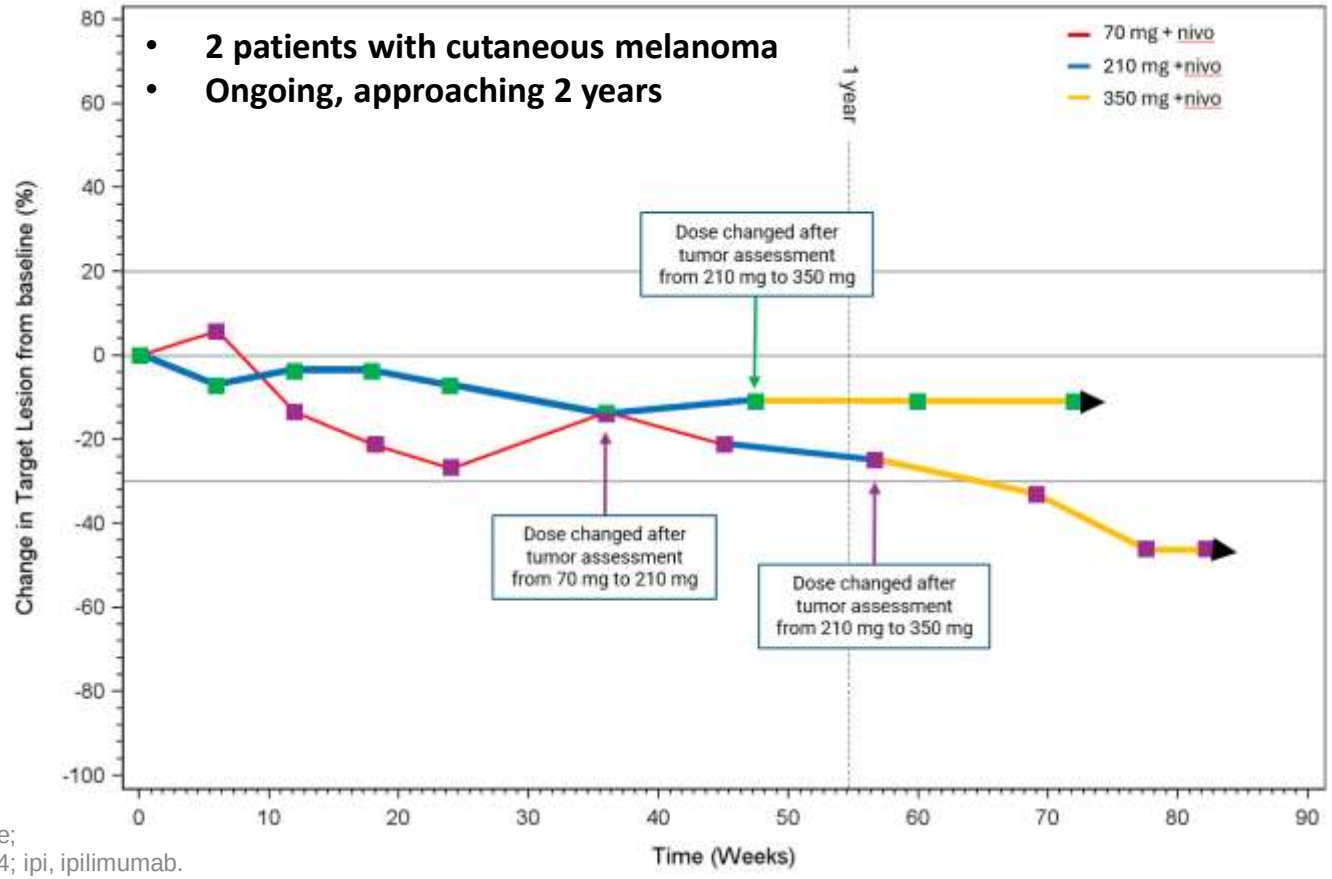
Abbreviation: AE, adverse event; DKA, diabetic ketoacidosis.
Note: Data from 03/29/24 data cut.
[a]Immune-mediated AE that occurred with increased lipase and gastritis.

Intra-patient dose escalation of anti-CTLA-4 leads to increased response in melanoma patients

CAB-CTLA-4 (evalstotug) enables higher dosing to (~5 mg/kg); not possible with ipi

As of October 4, 2024:

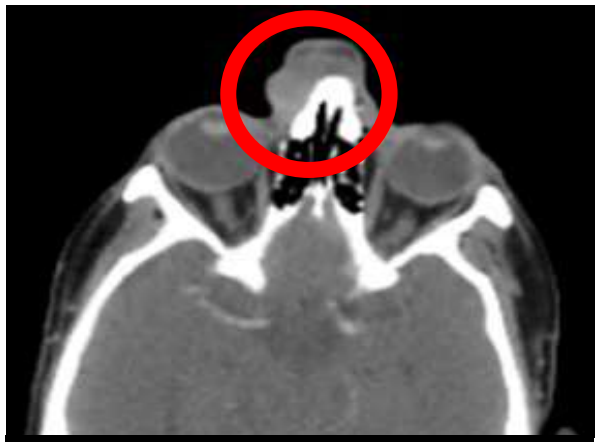
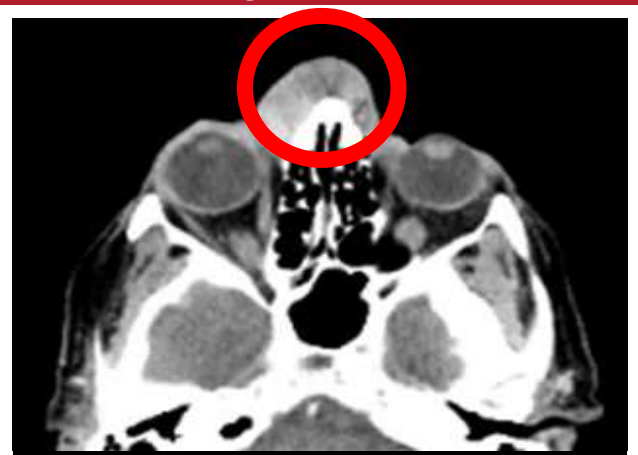
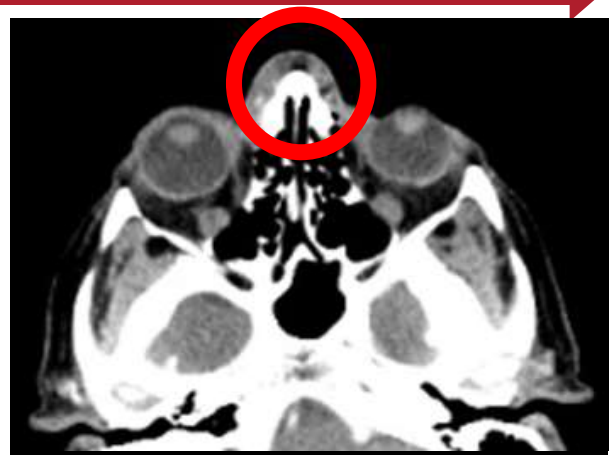
- Phase 1 dose escalation study conducted among patients with median of 3 prior lines of treatment
- Among 8 patients who received 350 mg evalstotug in combination with nivolumab, 1 cCR (cervical cancer) and 2 cPRs (melanoma and gastric)



Abbreviations: CAB, Conditionally Active Biologic; cCR, confirmed complete response; cPR, confirmed partial response; CTLA-4 cytotoxic T-lymphocyte associated protein 4; ipi, ipilimumab.
Note: Data from 04/30/24 data cut.
[a]Among evaluable patients (received at least 1 post-treatment scan).
[b]Patient with cutaneous melanoma enrolled at evalstotug 210 mg was dose escalated to 350 mg at 52 weeks. Dose escalation was well-tolerated.
[c]Patient with cutaneous melanoma enrolled at evalstotug 70 mg was dose escalated to 210 mg at 42 weeks and 350 mg at 69 weeks. Dose escalations were well-tolerated.

Confirmed PR associated with increased dosing

75-year-old female with stage IV cutaneous melanoma (BRAF+)

70 mg evalstotug	210 mg (SD)	350 mg (PR)
November 2022	August 2023	March 2024
		
Baseline First dosed at 70 mg evalstotug	**Tumor assessment – SD** Therapy well-tolerated. Became symptomatic with nasal obstruction, and biopsy showed persistence of disease. Dose escalated to 210 mg with resultant SD and symptom improvement	**Tumor assessment – PR** Therapy well-tolerated for >1 year. Further dose escalated to 350 mg with resultant PR

Note: Patient received adjuvant pembrolizumab before enrollment.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; PR, partial response; SD, stable disease.

Conclusions

- Preclinical & clinical data demonstrate that ipi & evalstotug are similar, i.e. epitope, affinity, T1/2 and tumor exposure, and efficacy
- Preclinical & clinical data demonstrate that ipi & evalstotug are NOT similar with respect to normal tissue environment and safety; e.g., reduced irAEs and extended treatment
- Evalstotug enables higher dosing which can lead to improved efficacy, which is not permissible with ipi
- Evolving Ph1 and Ph2 data[1,2] data supports safety profile that is generally well tolerated at higher doses even when combined with PD-1
- Extended Ph1 and initial Ph2 study will be presented in November 2024

Abbreviations: AE, adverse event; PD-1, programmed cell death protein 1; PFS, progression-free survival.

1. Thomas J, et al. Poster presented at: The American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 – June 4, 2024; Chicago, IL.
2. BioAtla R&D Day July 25th 2024, Ph2 monotherapy data

Questions?