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Presentation CT232

Preliminary Results of a Phase 1, First-in-Human, Dose-Escalation Study of the Anti-CCR8 Antibody Denikitug in Participants With Advanced Solid Tumors

Bruno Bockorny[1], Christopher Chen[2], Jaffer Ajani[3], David Sommerhalder[4], Minal Barve[5], Meredith McKean[6], Sandip Patel[7], Renu Jain[8], Brian Weist[8], Julika Huber[8], Vaishnavi Ganti[8], Ling Han[8], Anna Seto[8], Lars Mueller[8], Nataliya V Uboha[9]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Stanford University School of Medicine, Palo Alto, CA, USA; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]NEXT Oncology, San Antonio, TX, USA; [5]Mary Crowley Cancer Research/SCRI, Dallas, TX, USA; [6]Sarah Cannon Research Institute, Nashville, TN, USA; [7]University of California San Diego, Moores Cancer Center, San Diego, CA, USA; [8]Gilead Sciences, Inc., Foster City, CA, USA; [9]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA

Disclosure Information

Bruno Bockorny, MD

I have the following relevant financial relationships to disclose:

- Employee of the Dana-Farber Cancer Institute
- Consultant for Blueprint Medicine; BioLineRx; Boxer; Enlivex; Foster & Eldridge, LLC; N1X10; Phelps Dunbar, LLP; Rango; and SpringWorks
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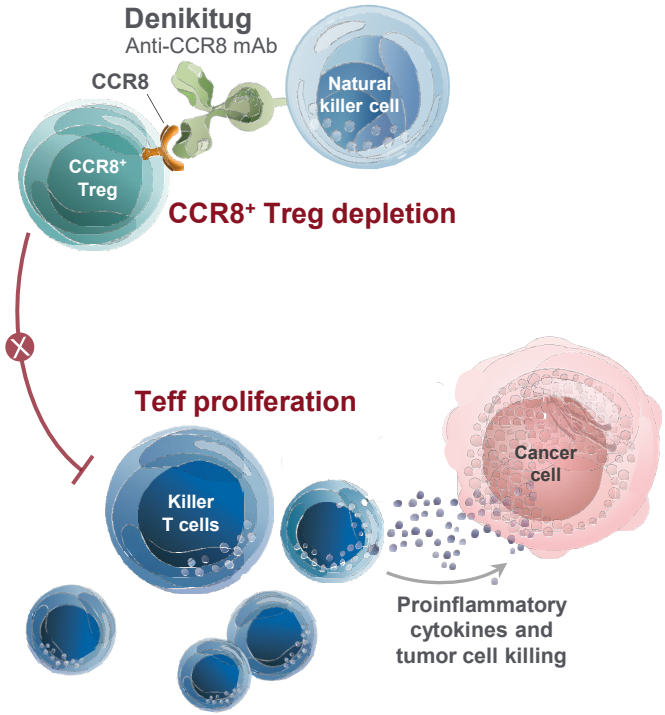
Background and Objective

- Regulatory T cells (Tregs) suppress effector T-cell (Teff) activity, and Treg accumulation in the tumor microenvironment (TME) is associated with poor prognosis and immunotherapy (IO) resistance[1–5]
- C-C motif chemokine receptor 8 (CCR8) is enriched on intratumoral Tregs (itTregs),[2,4,5] supporting its potential as a differentiated target for Treg depletion and modulation of immunosuppression within the TME
  - Preclinical models show that CCR8$^+$ itTreg depletion can enhance antitumor immune activity and overcome IO resistance[2]

Objective: To report preliminary Phase 1 safety and efficacy of denikitug, an anti-CCR8 monoclonal antibody (mAb), in advanced solid tumors (NCT05007782)[6]



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5. De Simone M, et al. *Immunity*. 2016;45:1135–47. 6. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT05007782 (accessed March 3, 2026).

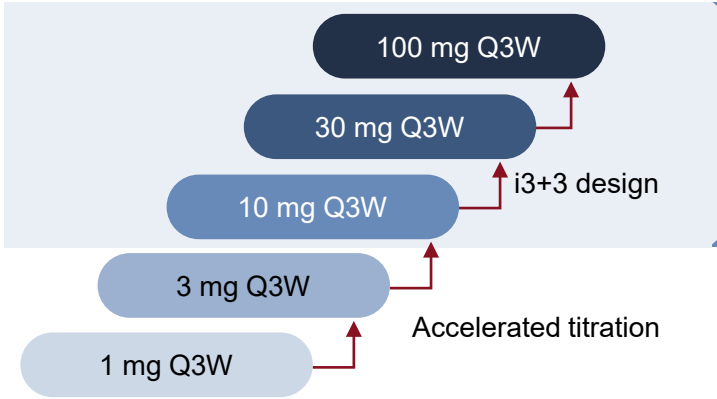
Study Design (NCT05007782)

Denikitug Monotherapy[a] | **Denikitug Plus Zimberelimab**

Key Eligibility

- Advanced solid tumors intolerant to or ineligible for therapies with known benefit
- ≥18 years of age
- ECOG PS 0–2
- Adequate organ function

Part A (n=16): Dose Escalation



Part B (n=41): Paired Tumor Biopsy

Evaluable biopsies[b] (n=26)

- Gastric/EGJ adenocarcinoma
- Breast cancer
- HNSCC
- NSCLC
- Gynecologic cancer

Primary endpoints, Part A

- Safety and tolerability

Secondary endpoints, Parts A and B

- Pharmacokinetic and immunogenicity analyses

Key exploratory endpoints, Parts A and B

- Preliminary efficacy (ORR, DCR, TTR, DOR)
- Biomarker analyses

Treatment duration and response follow-up: 1 year. Data as of March 24, 2026, unless otherwise noted.

[a]Sample size per dose level: 1 mg (n=1), 3 mg (n=1), 10 mg (n=19), 30 mg (n=19), 100 mg (n=17).
[b]Evaluable biopsies were fresh tissue obtained during screening and on-treatment (C2D5) from the same anatomical site with sufficient tumor content and tissue quality to allow successful biomarker analysis.
C2D5, cycle 2 day 5; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EGJ**, esophagogastric junction; **HNSCC**, head and neck squamous cell carcinoma; **i3+3**, interval 3+3 design; **NSCLC**, non–small cell lung cancer; **ORR**, objective response rate; **Q3W**, every 3 weeks; **TTR**, time to response.

Baseline Characteristics

	All (Parts A and B; N=57)
Age, median (range), years	59 (31–87)
Female, n (%)	35 (61)
ECOG PS, n (%)	
0	16 (28)
1	41 (72)
Prior lines of therapy, n (%)	
Median (range)[a]	3 (0–8)
<2 lines	9 (16)
≥2 lines	48 (84)
Prior anti–PD-(L)1 therapy, n (%)	38 (67)
Time on study, median (range), weeks	20.7 (2.4–88.9)

[a]Participants with 0 prior lines presented with metastatic disease after failing adjuvant therapy.

	All (Parts A and B; N=57)
Metastasis, n (%)	
Liver	18 (32)
Brain	1 (2)
Tumor type, n (%)[b]	
NSCLC	14 (25)
Gastric/EGJ adenocarcinoma	11 (19)
Gynecologic cancer[c]	10 (18)
Breast cancer	8 (14)
HNSCC	5 (9)
Other tumor types[d]	9 (16)

[b]Percentages may not total 100% due to rounding.
[c]Included cervical, endometrial, vulvar, and vaginal cancers.
[d]Included anal, cholangiocarcinoma, colorectal, melanoma, ovarian, pancreatic, and sarcoma tumors.

Anti–PD-(L)1, anti–programmed cell death protein 1 or anti–programmed cell death ligand 1; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EGJ**, esophagogastric junction; **HNSCC**, head and neck squamous cell carcinoma; **NSCLC**, non–small cell lung cancer.

Safety Summary

Adverse Events, n (%)	All (Parts A and B; N=57)[a,b]
Any grade TEAEs	**56 (98)**
Treatment-related	43 (75)
Grade ≥3 TEAEs	**42 (74)**
Treatment-related[c]	14 (25)
Serious TEAEs	**31 (54)**
Treatment-related	5 (9)
TEAEs leading to discontinuation	**8 (14)**
Treatment-related	8 (14)
TEAEs leading to death	**1 (2)**
Treatment-related	0 (0)

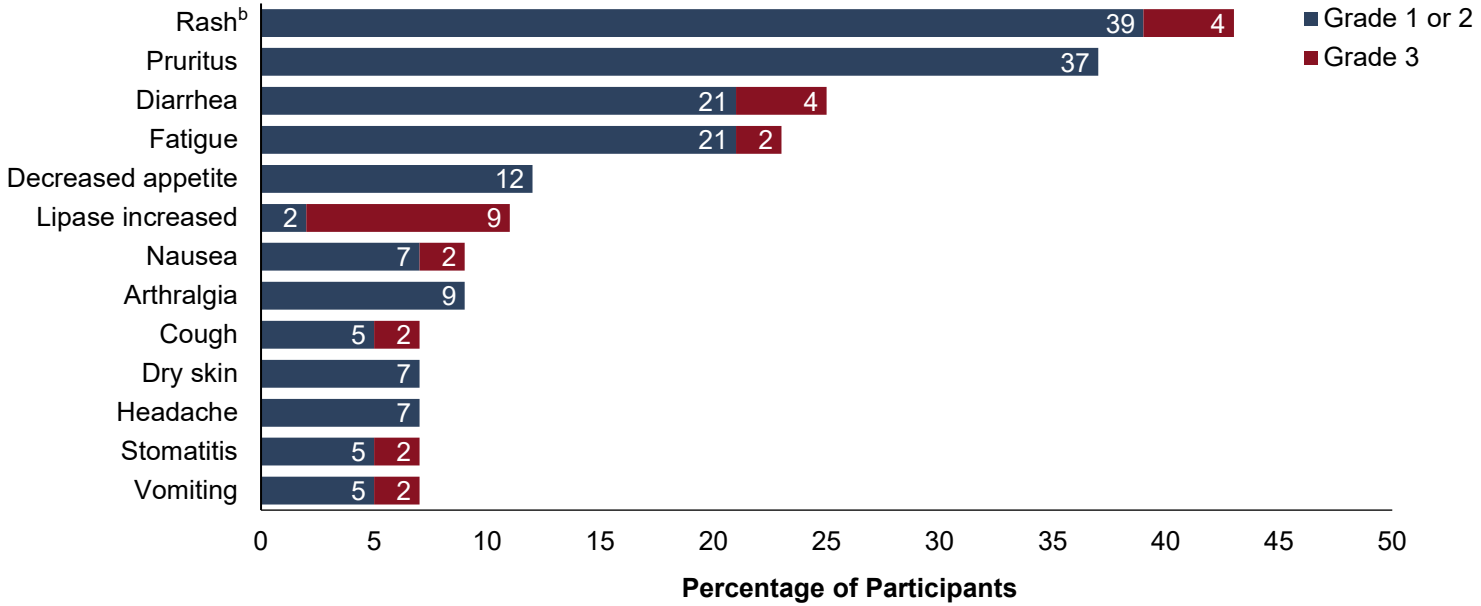
[a]The safety evaluable population included all participants who received ≥1 dose of denikitug.
[b]There were no dose-limiting toxicities reported in the dose-escalation portion of the study (Part A).
[c]There were no Grade 4 or 5 treatment-related adverse events.

TEAE, treatment-emergent adverse event.

Treatment-Related Adverse Events

- Common TRAEs were consistent with an immunomodulatory mechanism of action

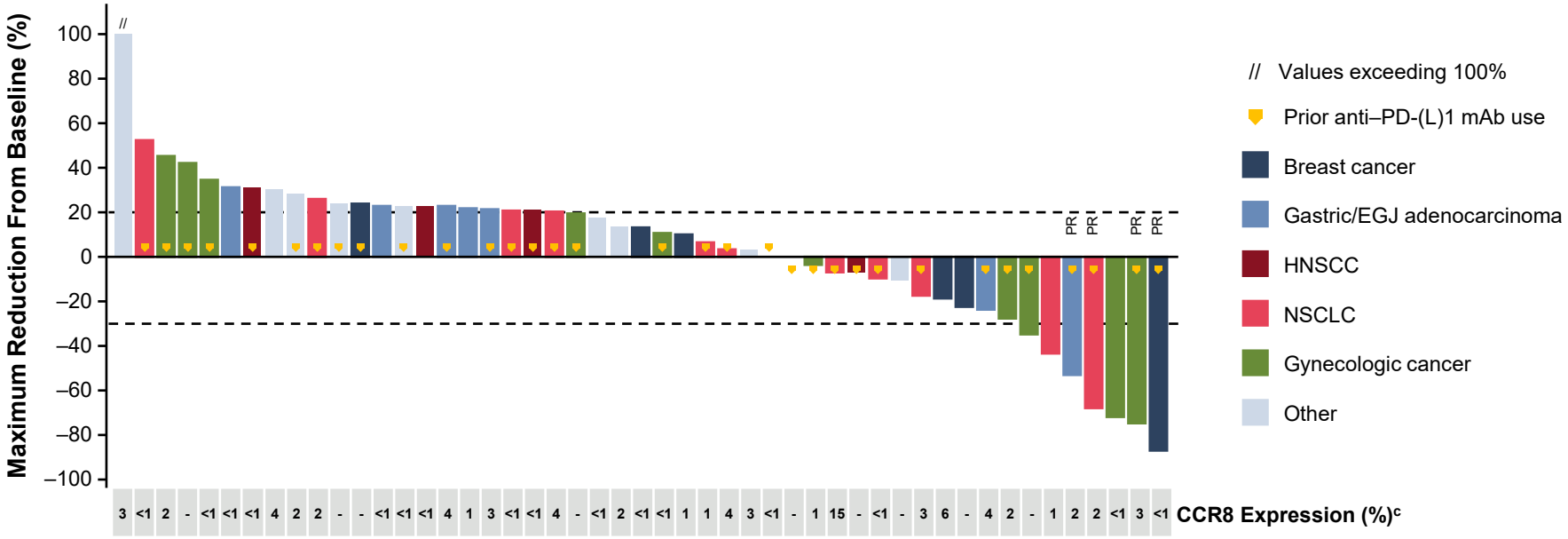
TRAEs in >5% of Participants (N=57)[a]



[a]The safety evaluable population included all participants who received ≥1 dose of denikitug. Multiple AEs were counted only once, at the highest severity grade, for each participant.
[b]Combines rash and maculopapular rash.
AE, adverse event; **TRAE,** treatment-related adverse event.

Efficacy

Tumor Reductions Observed Across a Variety of Tumor Types[a,b]



- Dose levels for confirmed PRs were 10 mg (n=3) and 100 mg (n=1)
- In this heterogeneous participant population, no clear relationship was observed between CCR8 expression and RECIST response

[a]Efficacy analyses were conducted on the efficacy evaluable population and included all treated participants with measurable baseline disease and at least one postbaseline tumor assessment.
[b]Three participants had a ≥30% tumor reduction but did not have a confirmed PR due to new lesions, uPR with subsequent PD, or post-progression PR following a new lesion.
[c]CCR8 expression was determined by immunohistochemistry (433H) applying a digital scoring algorithm ([#CCR8⁺ cells/totals cells] X 100) to a pathologist-determined region of interest; digital scores were confirmed by pathologist review.
Anti–PD-(L)1, anti–programmed cell death protein 1 or anti–programmed cell death ligand 1; **CCR8**, C-C motif chemokine receptor 8; **EGJ**, esophagogastric junction; **HNSCC**, head and neck squamous cell carcinoma; **mAb**, monoclonal antibody; **NSCLC**, non–small cell lung cancer; **PD,** progressive disease; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **uPR,** unconfirmed partial response.

Efficacy

Radiographic Response and Disease Control Were Observed in Heavily Pretreated Participants

- Median prior lines of therapy was 6 for responders and 2 for those with disease control

	Efficacy Evaluable Population (n=52)[a]
Best overall response, n (%)	
cCR	0 (0)
cPR	4 (8)
SD	20 (38)
PD	28 (54)
ORR,[b] n (%)	4 (8)
DCR,[c] n (%)	24 (46)
Median (range) TTR, months	4 (2.1–4.1)
Median (range) DOR, months	4.3 (3.7–14.6)

[a]The efficacy evaluable population included all treated participants with measurable disease at baseline and at least one postbaseline tumor assessment.
[b]ORR = cCR + cPR.
[c]DCR = cCR + cPR + SD.

cCR, confirmed complete response; **cPR**, confirmed partial response; **DCR,** disease control rate; **DOR**, duration of response; **ORR**, objective response rate; **PD**, progressive disease; **SD**, stable disease; **TTR**, time to response.

Pharmacodynamic Effects Within the TME

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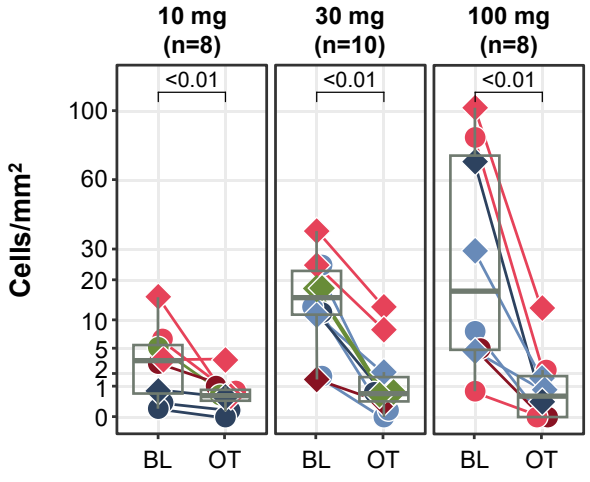
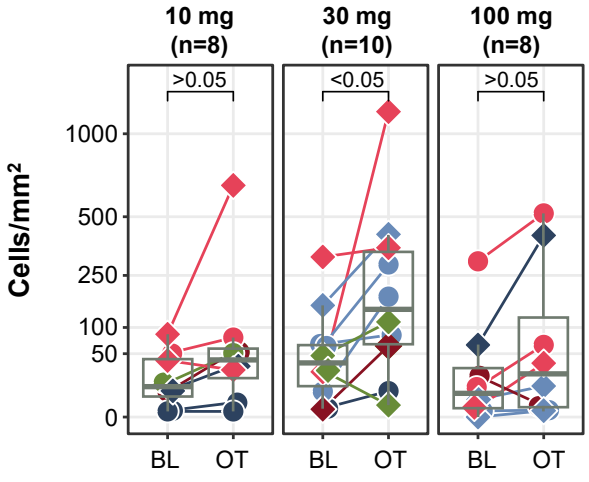
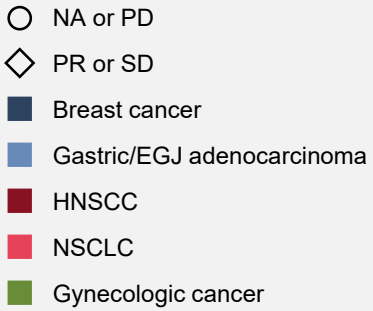
Paired Tumor Biopsy Cohorts (Part B)

CCR8⁺ Treg Density



Ki67⁺ CD8⁺ T-Cell Density





- Denikitug treatment led to depletion of CCR8⁺ Tregs and a trend of modest increase in Ki67⁺ CD8⁺ T cells; similar trends were observed in peripheral blood (data not shown)

Immune environment density changes were evaluated in paired tumor biopsies (n=26) via mIF. Evaluable biopsies were fresh tissue obtained during screening and on-treatment (C2D5) from the same anatomical site with sufficient tumor content and tissue quality to allow successful biomarker analysis. Clinical response data for biomarker analyses were based on an October 28, 2025, data cut-off.

BL, baseline; **C2D5**, cycle 2 day 5; **CCR8**, C-C motif chemokine receptor 8; **CD8**, cluster of differentiation 8; **EGJ**, esophagogastric junction; **HNSCC**, head and neck squamous cell carcinoma; **Ki67**, Kiel 67; **mIF**, multiplex immunofluorescence; **NA**, first tumor assessment not reached or response unevaluable; **NSCLC**, non-small cell lung cancer; **OT**, on-treatment; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **TME**, tumor microenvironment; **Treg**, regulatory T cell.

Patient Case: Clinical Response and Biomarker Dynamics

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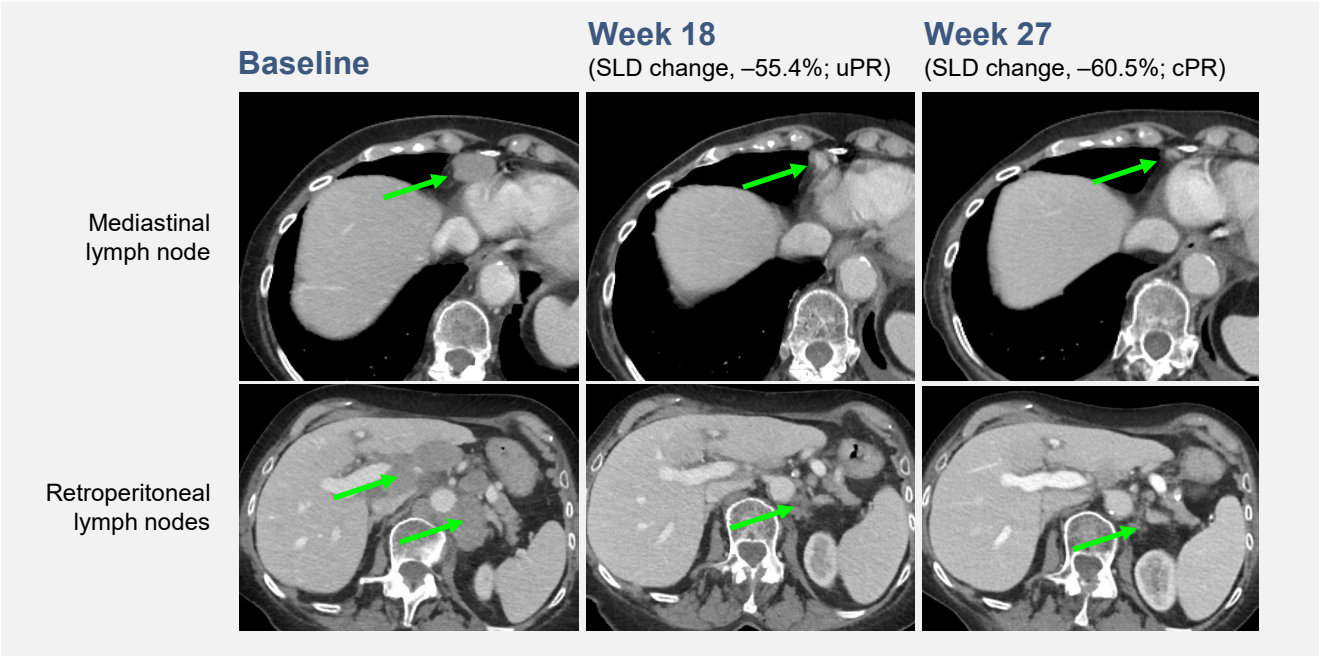
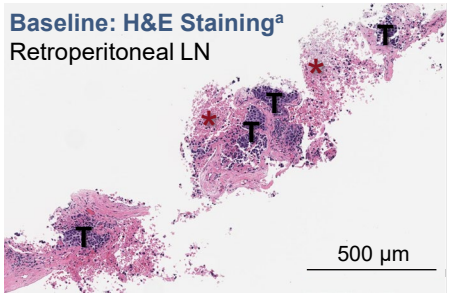
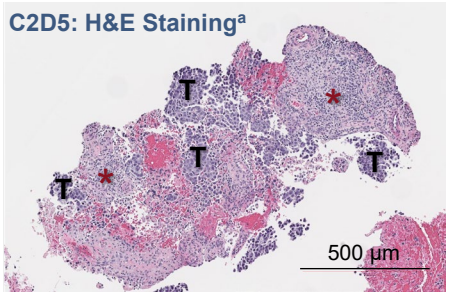
- 78-year-old female, squamous metastatic NSCLC with cPR maintained for 14.6 months
  - <1% TPS; 5 prior lines of treatment, including progression on pembrolizumab-based regimens







T = tumor
*** = immune infiltrate in tumor stroma**

[a]Images were acquired at the same magnification and reviewed by a pathologist.
C2D5, cycle 2 day 5; **cPR**, confirmed partial response; **H&E**, hematoxylin and eosin; **LN**, lymph nodes; **NSCLC**, non–small cell lung cancer; **SLD**, sum of longest diameters; **TPS**, tumor proportion score; **uPR**, unconfirmed partial response.

Patient Case: Biomarker Results

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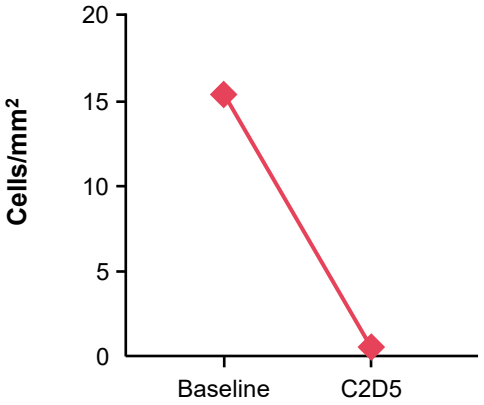
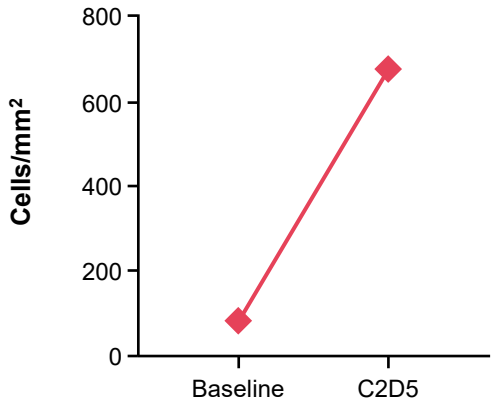
- Effective CCR8$^+$ Treg depletion and Ki67$^+$ CD8$^+$ T-cell expansion observed in paired tumor biopsies

CCR8$^+$ Treg Density



97% depletion of CCR8$^+$ Tregs

Ki67$^+$ CD8$^+$ T-Cell Density



7.8-fold increase in Ki67$^+$ CD8$^+$ T cells

C2D5, cycle 2 day 5; **CCR8**, C-C motif chemokine receptor 8; **CD8**, cluster of differentiation 8; **Ki67**, Kiel 67; **Treg**, regulatory T cell.

Conclusions

- Denikitug is pharmacologically active at doses ≥10 mg
  - As evidenced by changes in key biomarkers, including depletion of CCR8^{+} itTregs and increases in activated Teffs
- Antitumor activity was observed in heavily pretreated participants
  - Including those who were refractory to or had progressed on prior anti–PD-(L)1 therapy
- Denikitug monotherapy demonstrated a manageable safety profile; observed TRAEs were consistent with an immunomodulatory MoA
- The results support further evaluation of denikitug as monotherapy and as a potential combination partner with other treatments, such as anti–PD-(L)1 immunotherapies

Anti–PD-(L)1, anti–programmed cell death protein 1 or anti–programmed cell death ligand 1; **CCR8**, C-C motif chemokine receptor 8; **itTreg**, intratumoral regulatory T cell; **MoA**, mechanism of action; **Teff**, effector T cell; **TRAE**, treatment-related adverse event.

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- Correspondence: Bruno Bockorny, bbockorn@bidmc.harvard.edu