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Cretostimogene Induces Acute Th1 Skewed Inflammation in BCG-Unresponsive CIS-Containing Non-Muscle Invasive Bladder Cancer (BOND-003 Cohort C)

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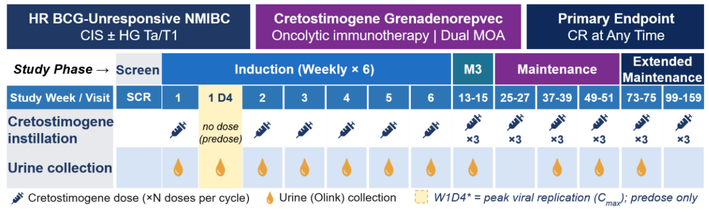
BACKGROUND

- Cretostimogene grenadenorepvec is an oncolytic immunotherapy that lyses Rb-E2F–altered tumor cells and amplifies anti-tumor immunity via a GM-CSF transgene
- BOND-003 Cohort C is a Phase 3 study in patients with CIS–containing, BCG-unresponsive NMIBC[1]
- As of 23 June 2025:
  - CR rate at any time was 75.5%
  - Median DOR: 27.9 months and ongoing
- Urinary cytokines (a surrogate of local immune milieu) were profiled post-treatment to characterize the immune-mediated MOA

METHODS

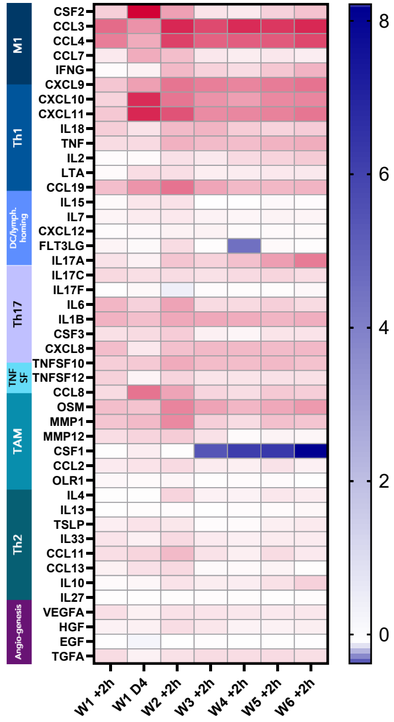
- Serial urine collected pre-dose (−2 hr) and post-dose (+2 hr) across treatment phases from BOND-003 Cohort C biomarker consented participants (n=60)
- Tested with Olink Target 48 Cytokine panel
- Results of Week 1-6 (induction phase) are displayed as raw NPX (log_2-scaled) or ΔNPX (log_2 fold-change) vs. within-subject baseline (W1).

Figure 1. BOND-003 Cohort C: Urine Collection Relative to Cretostimogene Dosing.



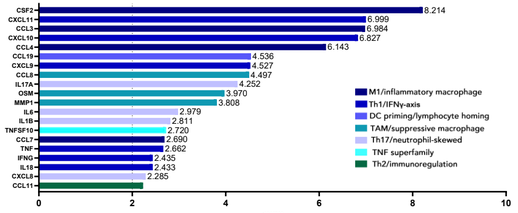
RESULTS

Figure 2. Cretostimogene drives coordinated, multi-lineage inflammatory cytokine induction



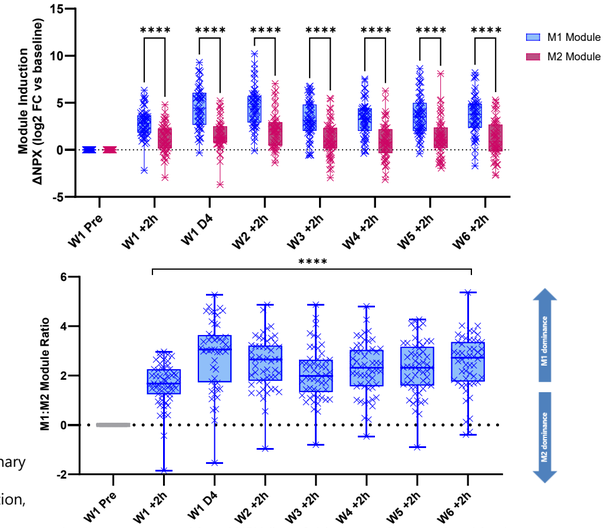
Median ΔNPX (log_2 fold-change vs. W1 Pre) across 45 urinary analytes at post-dose induction timepoints (W1 +2h–W6 +2h), grouped by functional module. Red indicates induction, blue suppression, white no change; rows are grouped by functional module. Coordinated induction of Th1, Th17, M1, DC-priming, and TNF-superfamily analytes is evident at post-dose timepoints. Most groups peaked early (W1D4–W2 post-dose); Th17 cytokines peaked later (~Week 6). Th2 and immunoregulatory cytokines remained largely below the limit of detection and were not induced.

Figure 3. Robust GM-CSF expression associated with M1/Th1/Th17-dominant local response



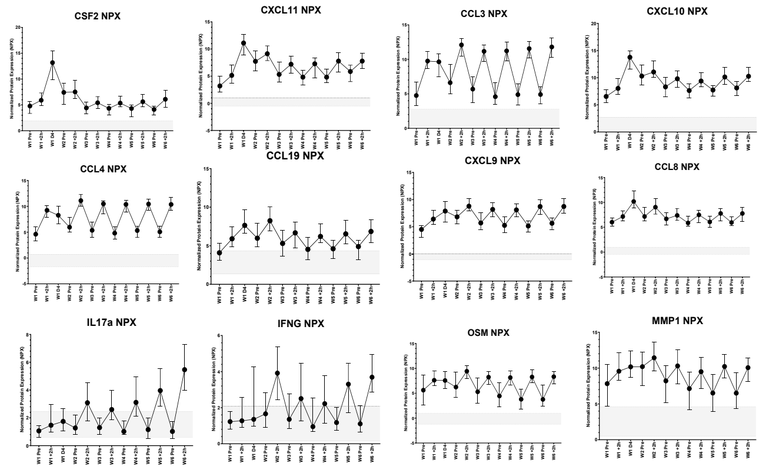
Maximum ΔNPX (log_2 fold-change vs. baseline) per analyte during induction (W1–6), for analytes increasing ΔNPX > 2 over baseline, colored by functional group. GM-CSF (CSF2) shows the largest induction (~300-fold peak at W1 D4).

Figure 4. Cretostimogene shifts NMIBC myeloid compartment from immunosuppressive (M2) to inflammatory (M1) phenotype during induction.



Analyses use per-subject ΔNPX (log_2 fold-change from each subject's Week 1 pre-dose baseline), computed per analyte. Box plots show median and IQR (Tukey whiskers) with subjects overlaid; the dotted line marks baseline (ΔNPX = 0), above which reflects a shift toward M1. (a) M1 module (CSF2, CCL3, CCL4, CCL7) versus M2/TAM module (CCL8, OSM, MMP1, MMP12, CSF1, CCL2, OLR1) induction (per-subject median ΔNPX); M1 significantly exceeds M2 at every post-dose timepoint. (b) Combined M1:M2 ratio (M1 − M2 median ΔNPX), which increases significantly from baseline. Data were analyzed by a mixed-effects model (REML) with subject as a random effect: (a) two-way (module × time) with Šídák's correction; (b) Dunnett's test versus baseline. ****p<0.0001.

Figure 5. Cretostimogene induces acute, transient, multi-lineage inflammatory cytokine responses that resolve between instillations



Longitudinal urinary NPX (median ± IQR) for representative induced analytes across paired pre/post-dose timepoints (W1–W6). Representative analytes span M1/inflammatory-macrophage (CSF2, CCL3, CCL4), Th1/IFN-γ-axis (CXCL9, CXCL10, CXCL11, IFN-γ), DC-priming (CCL19), Th17/neutrophil (IL-17A), and M2/TAM (CCL8, OSM, MMP1) modules. Values are raw NPX (log_2-scaled); dotted lines denote the least- and most-conservative plate-specific LODs. Post-dose induction with return toward baseline before subsequent dosing indicates repeated acute, self-limiting immune activation.

CONCLUSION

- Cretostimogene induces a transient, potentially GM-CSF–driven acute inflammatory program—Th1/IFN-γ, Th17 inflammation, DC priming (CCL19), cytotoxic/apoptotic signaling (TRAIL), and M1 myeloid polarization—without Th2, regulatory cytokine induction, resolving between doses with preserved bladder homeostasis.
- These data provide mechanistic support for cretostimogene's MOA—productive, immunogenic anti-tumor inflammation—consistent with the high, durable CR rates in BOND-003 Cohort C.

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Abbreviations: BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ; CR: complete response; GM-CSF: granulocyte-macrophage colony-stimulating factor; MOA: mechanism of action; NMIBC: non-muscle invasive bladder cancer; NPX: normalized protein expression; Th1: T helper type 1 **References:** 1 Tyson et al., Lancet Oncology, 2026.

University of Rochester

Cretostimogene Induces Acute Th1-Skewed Inflammation in BCG-Unresponsive CIS-Containing Non-Muscle Invasive Bladder Cancer

BOND-003 Cohort C

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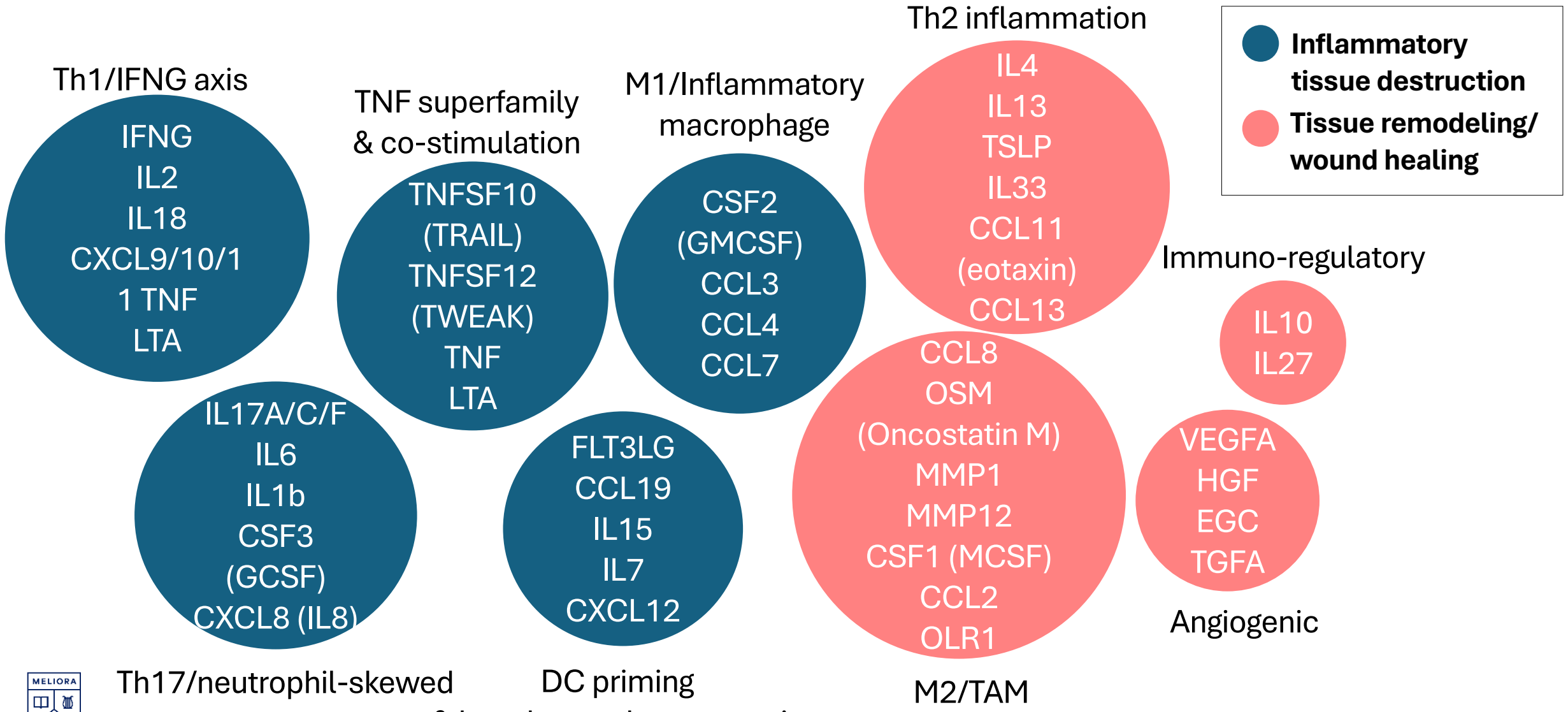
September 17, 2026
Rochester, NY

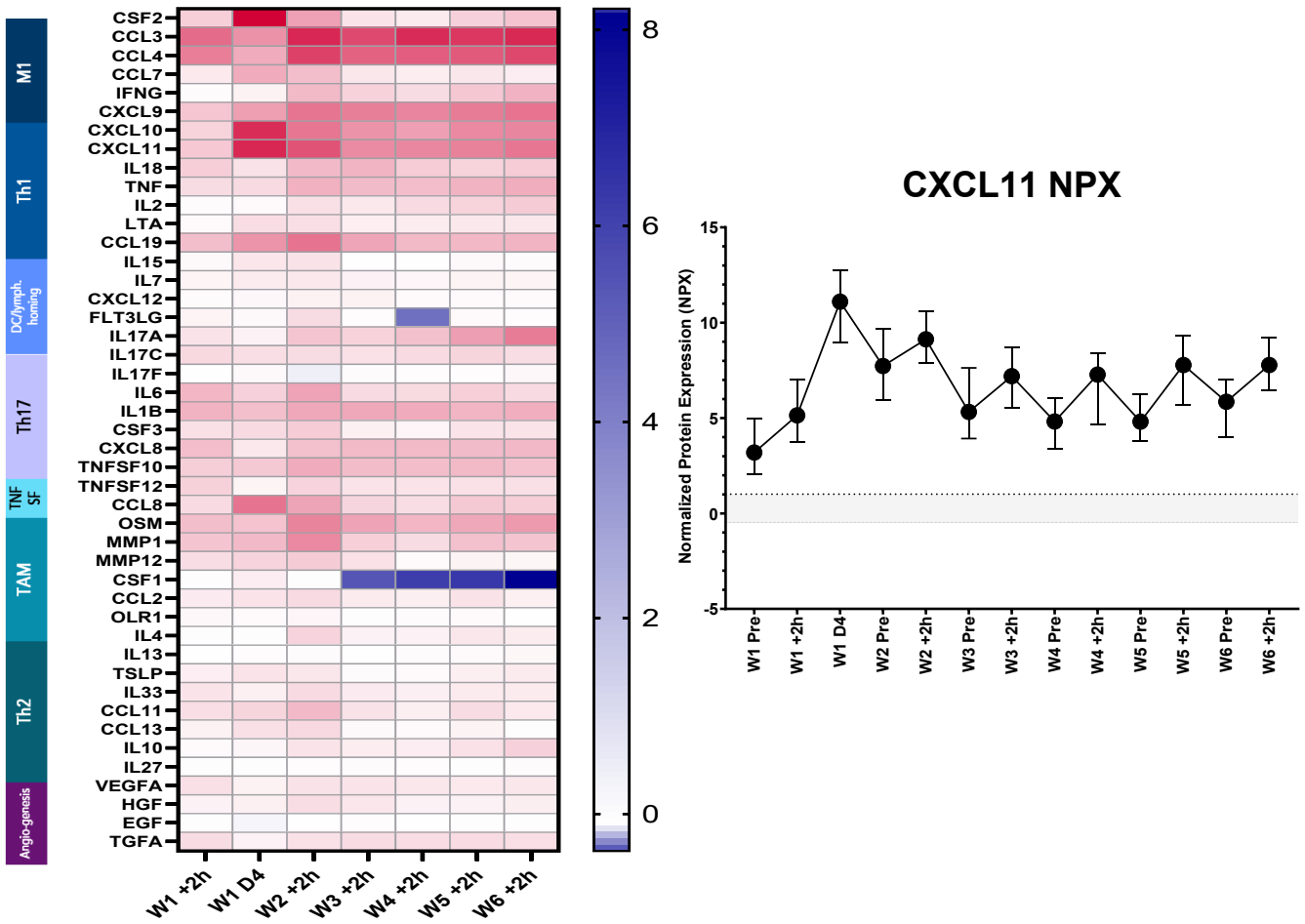
Does cytokine/chemokine induction define the immune response to Cretostimogene?

- Used Olink Target 48 multiplex panel to measure baseline and post-treatment urinary cytokines/chemokines that represent different lineages and components of the immune response.
- Urine and blood collected prior to and 2 hours post-instillation and on W1D4.
- Compared pre-treatment week 1 cytokine/chemokine levels with post-treatment levels at weeks 1-6.
- Identified cytokines/chemokines that characterize the immune response mediated by Cretostimogene.

Olink Target48 panel cytokine/chemokine signatures



Cretostimogene drives coordinated multi-lineage inflammatory cytokine induction



- Robust induction across M1, Th1/IFNγ, Th17, DC-priming, and TNF-superfamily cytokines (TRAIL), up to ~300-fold (GM-CSF/CSF2), at post-dose timepoints.
- Peak in cytokine levels with each induction treatment.
- Levels return to near-baseline between instillations.
- Creto induces a profound remodeling of the TME to a pro-inflammatory milieu throughout induction.