

T- and NK-cell Immunomodulatory Reprogramming by Cemsidomide, a Novel and Potent MonoDAC® Degradar, in Relapsed/Refractory Multiple Myeloma: Biomarker Results from CFT7455-1101 Arm B2 Cohort.

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INTRODUCTION

Patients with relapsed/refractory multiple myeloma (RRMM) who are penta-drug exposed, face limited treatment options and harbor immune compartments compromised by both disease and prior therapy, including resistance to lenalidomide and pomalidomide frequently associated with Cereblon (CRBN) pathway dysregulation. Cemsidomide is a novel, highly potent oral CRBN-based IKZF1/3 MonoDAC® degrader with retained activity in lenalidomide- and pomalidomide-resistant preclinical models, positioning it as a candidate for patients who have exhausted current immunomodulatory agents.

AIM

To characterize the peripheral immune pharmacodynamic profile of cemsidomide in combination with dexamethasone during Cycle 1 of CFT7455-1101 trial in heavily pretreated RRMM patients with emphasis on T-cell activation and fitness and NK-cell functional reprogramming.

METHOD

- Patients and treatment:** 62 patients were included in this analysis and received daily cemsidomide orally on a 14 days on/14 days off schedule across four different doses levels (37.5ug [n=8], 62.5ug [n=15], 75ug [n=20], 100ug [n=19]), with weekly dexamethasone (20 or 40mg, age-stratified per USPI).
- Sample collection:** Peripheral blood was collected predose at C1D1, C1D7, C1D14, C1D21 and C2D1.
- Immunophenotyping:** T- and NK- cell subsets were profiled by multiparameter flow cytometry.
- Cytokine expression:** Serum cytokines were measured using MSD S-plex proinflammatory panel 1.

CEMSIDOMIDE BACKGROUND

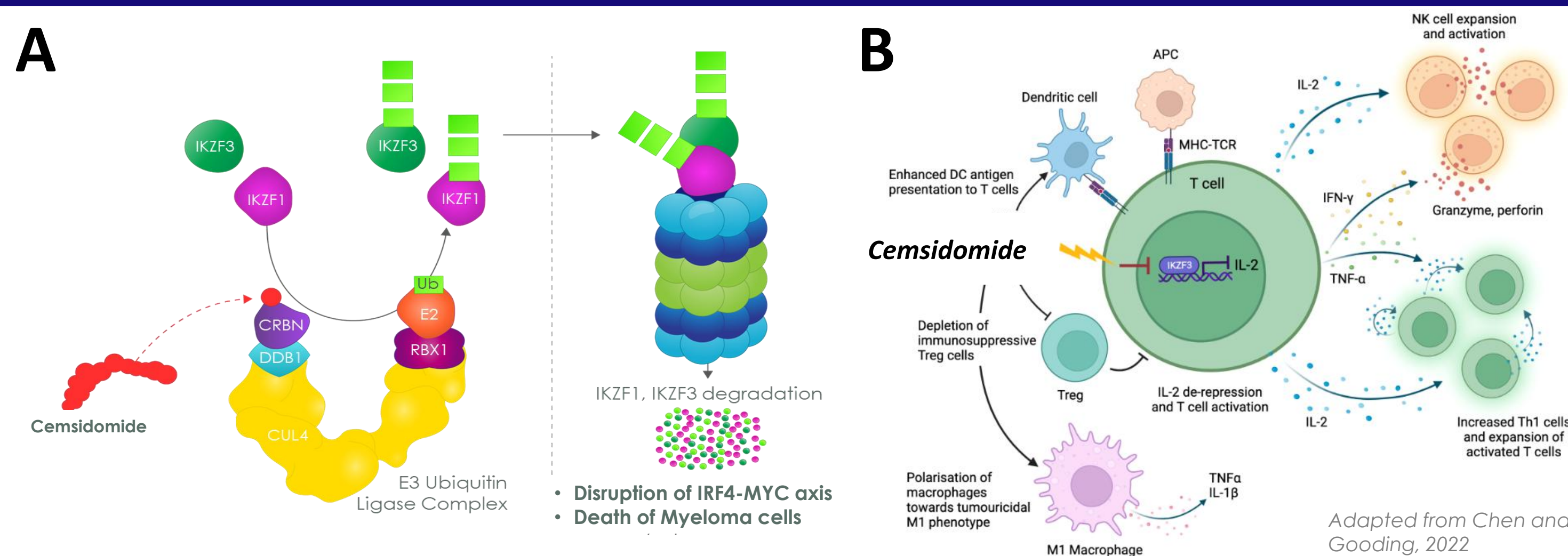


Figure 1: Cemsidomide mechanism of action on the plasma cells & immune cells

(A): Cemsidomide binds to CRBN creating a new surface that facilitates the recruitment and ubiquitination of IKZF1 and IKZF3, leading to the proteasomal degradation of both proteins, a process leading to the disruption of the IRF4-MYC axis and death of the myeloma cells. (B): By degrading IKZF3, IL2 repression is lifted, leading to IL2 elevation, which translates in T-cell and NK-cell activation.

RESULTS

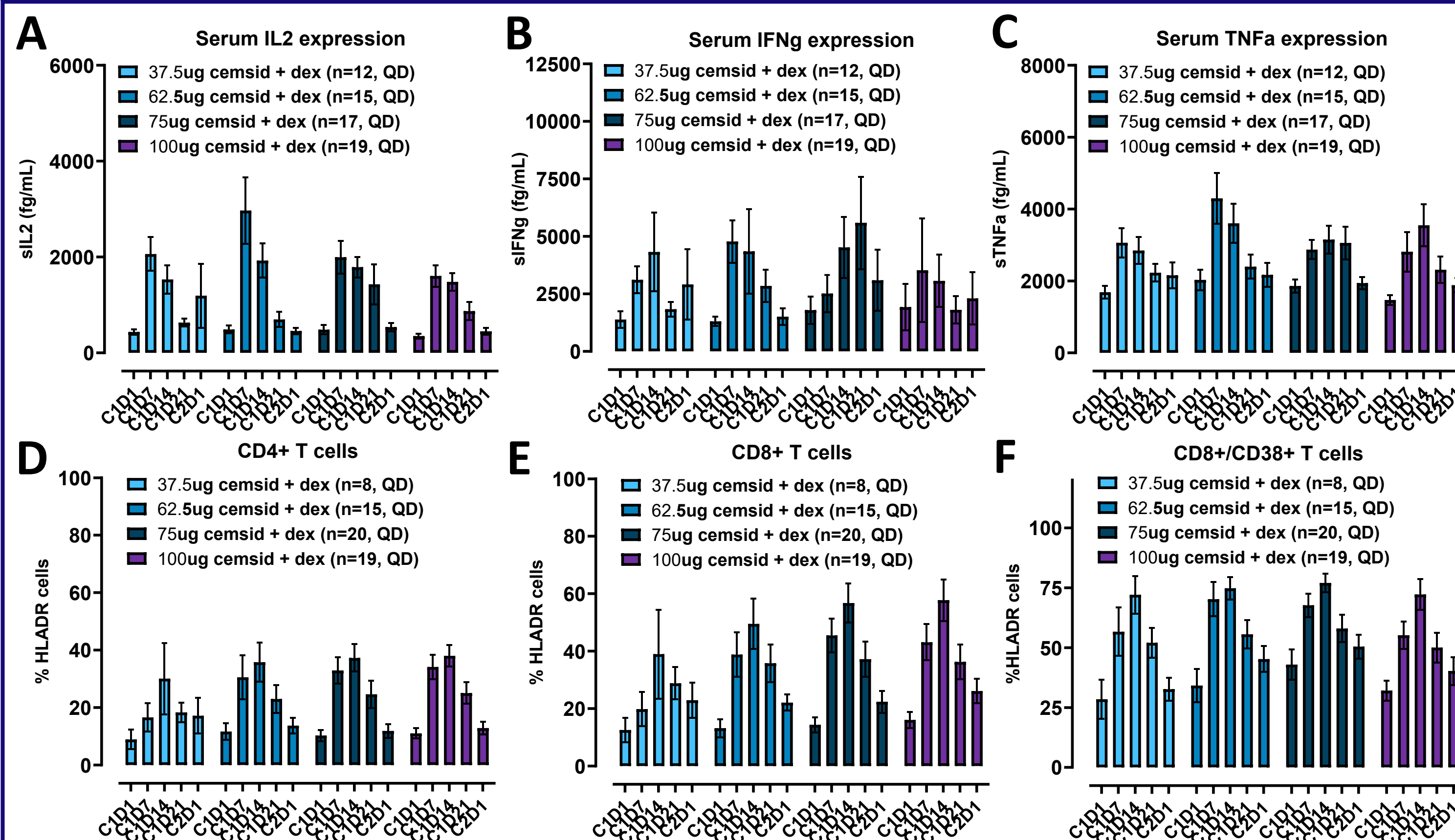


Figure 2: Cemsidomide induces coordinated T-cell activation across soluble and cellular readouts at all dose levels

(A-C): serum IL2 (A), IFNγ (B) and TNFα (C) levels are measured by MSD S-plex and show 4-6x (sIL2), 3-4x (sIFNγ) and 2-3x (sTNFα) increase from baseline. CD4+ (D) and CD8+ T cells (E) exhibit a 3-4x elevation in the activation marker HLADR. The activated CD8+ T cells (F) co-expressing CD38 show a 3x increase of HLADR in parallel. All readouts show a cyclical pattern marked by an elevation upon cemsidomide/dex administration (with a peak at C1D14) before returning to baseline during the off-treatment period.

CONCLUSIONS and PRELIMINARY INSIGHTS FROM CFT7455-1102 (CEMSIDOMIDE/ELRANATAMAB COMBO)

Collectively, cemsidomide enhanced immune fitness in this heavily pretreated population, activating both T and NK compartments while expanding, through replication, competent, cytotoxicity armed effectors. Altogether, these data support continued cemsidomide development including in combination with T-cell redirecting therapies.

In this light, in our ongoing Phase 1b CFT7455-1102 study, in which cemsidomide is combined with the BCMA T-cell Engager elranatamab, preliminary data on the first 2 patients enrolled show cemsidomide elevates CD8+ effector memory T cells and activates T cells while not driving exhaustion, consistent with the Phase 1 study with cemsidomide plus dex. Further samples and biomarkers will be collected across our CFT7455-1102 study to confirm and expand our understanding of cemsidomide's role in immune modulation and its complementarity with a BCMA T-cell engager such as elranatamab.

Figure 6: In data from the first 2 patients, cemsidomide in combination with elranatamab drives CD8+ Tem shift, associated with T-cell expansion, T-cell activation while preventing T-cell exhaustion.

(A,E): % CD4+ and CD8+ T cells detected at different timepoint. Cemsidomide and elranatamab combination drive the expansion of CD8+ T cells, including in CD4+ -skewed patient. (B,F): Cemsidomide drives the CD8+ Tem shift despite patients harboring different immunophenotype at baseline. (C,G): Cemsidomide and elranatamab drive T-cell activation, proliferation and elicit an increase in Gzmb+ CD8+ Tem, indicating the expanding population is further armed for cytotoxicity. (D, H): Cemsidomide prevents T-cell exhaustion.

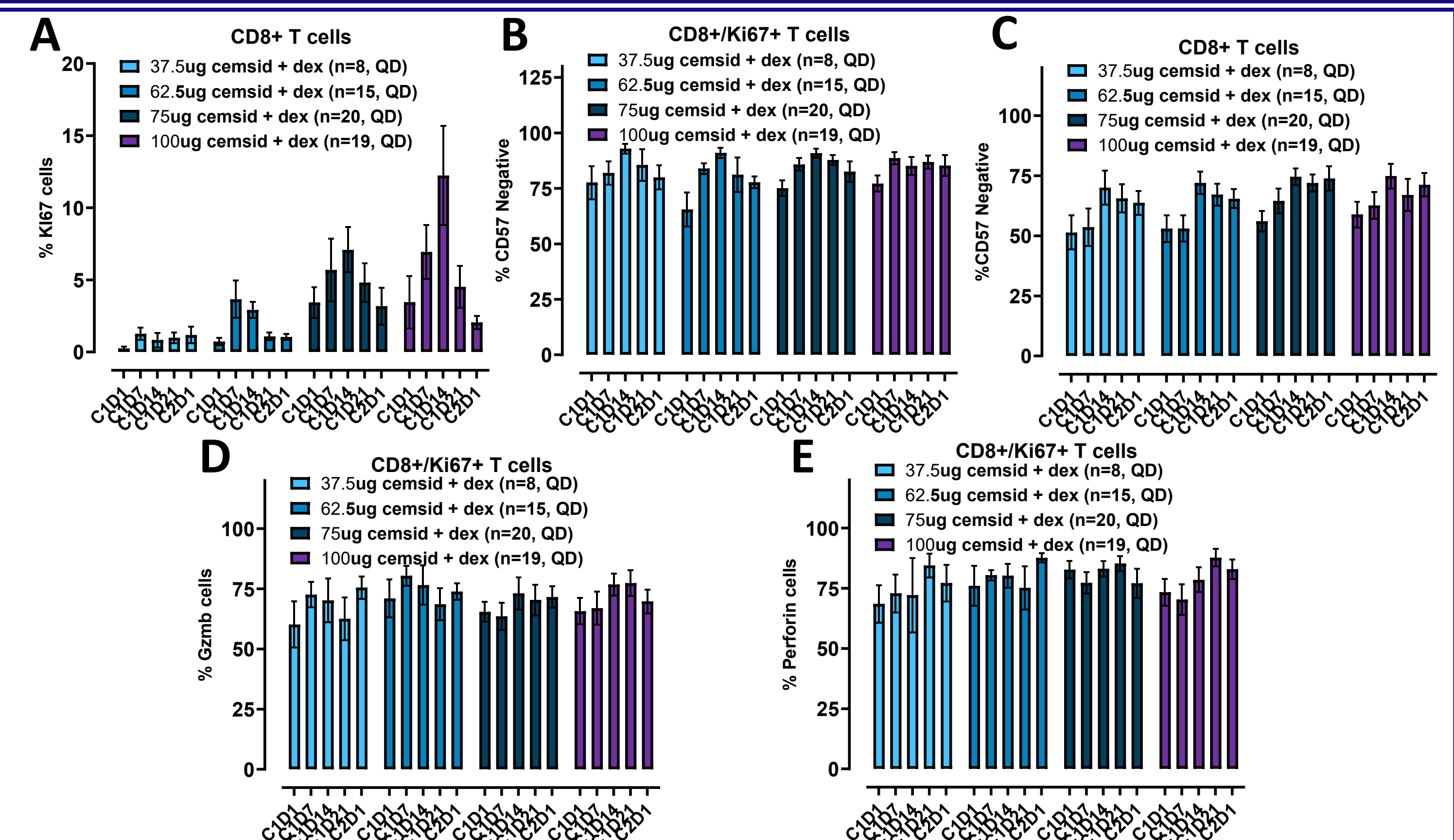


Figure 3: Proliferating CD8+ T cells enrich for a fit, non-senescent, cytotoxicity armed phenotype

(A) Cemsidomide and DEX treatment induces robust proliferation, more pronounced at 75ug and 100ug. (B,C) The proliferating pool enriches for non-senescent (CD57-) cells and both total and proliferating CD8+ compartments shift toward a fit phenotype. (D,E) Proliferating cells retain or slightly increase Gzmb and Perforin content, indicating the expanding population is armed for cytotoxicity.

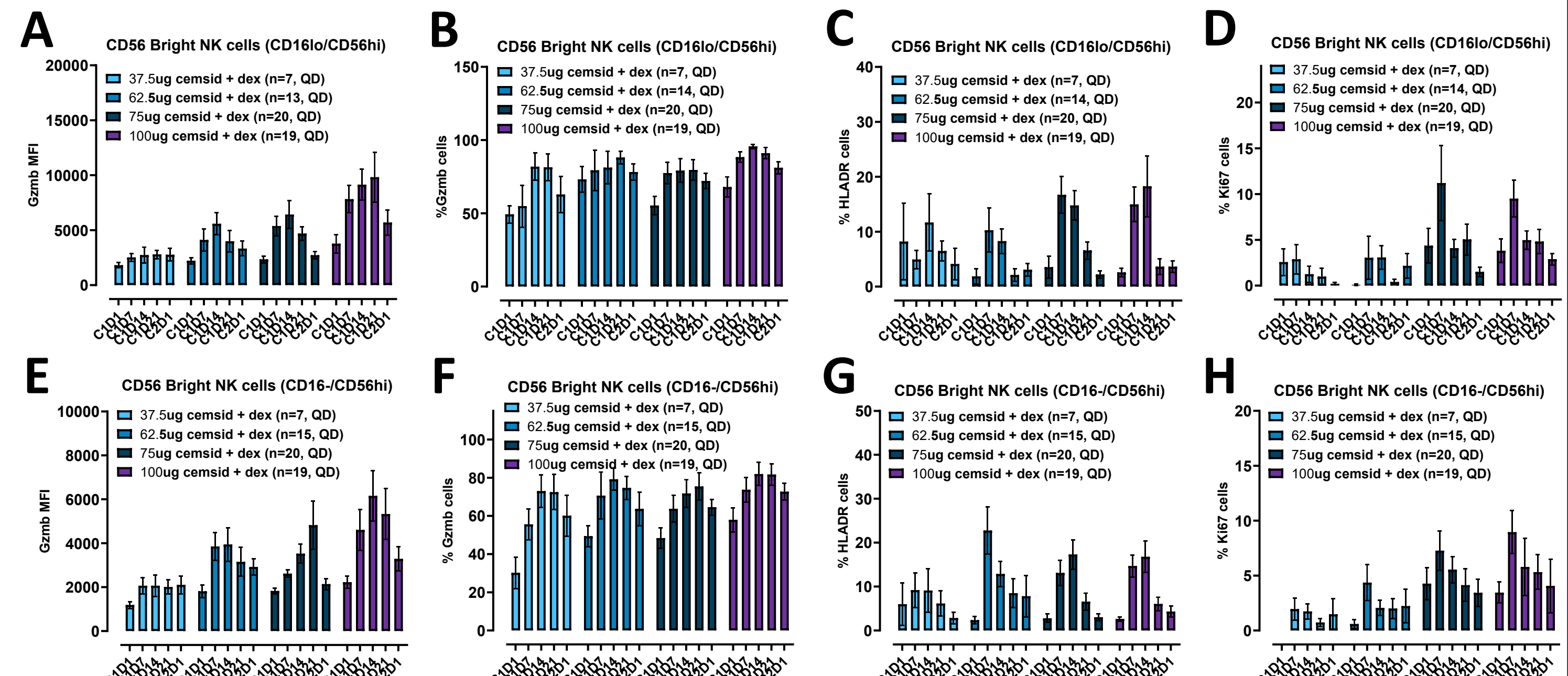


Figure 4: Functional reprogramming of cytokine-producing CD56 bright NK cells (immature [CD16-/CD56hi] and intermediate [CD16lo/CD56hi] NK cells)

Cemsidomide with DEX elicit an elevation (up to 2.5x) of Gzmb MFI expression (A, E) and an increased fraction of Gzmb+ cells within CD56 bright NK subsets (B,F). These cells are activated (HLADR upregulation up to 7x) (C, G) and show proliferative activity at the highest 2 dose levels (D, H). As in T cells, the CD56 bright NK readouts are cyclical, peaking during the treatment phase and returning to baseline level at C2D1.

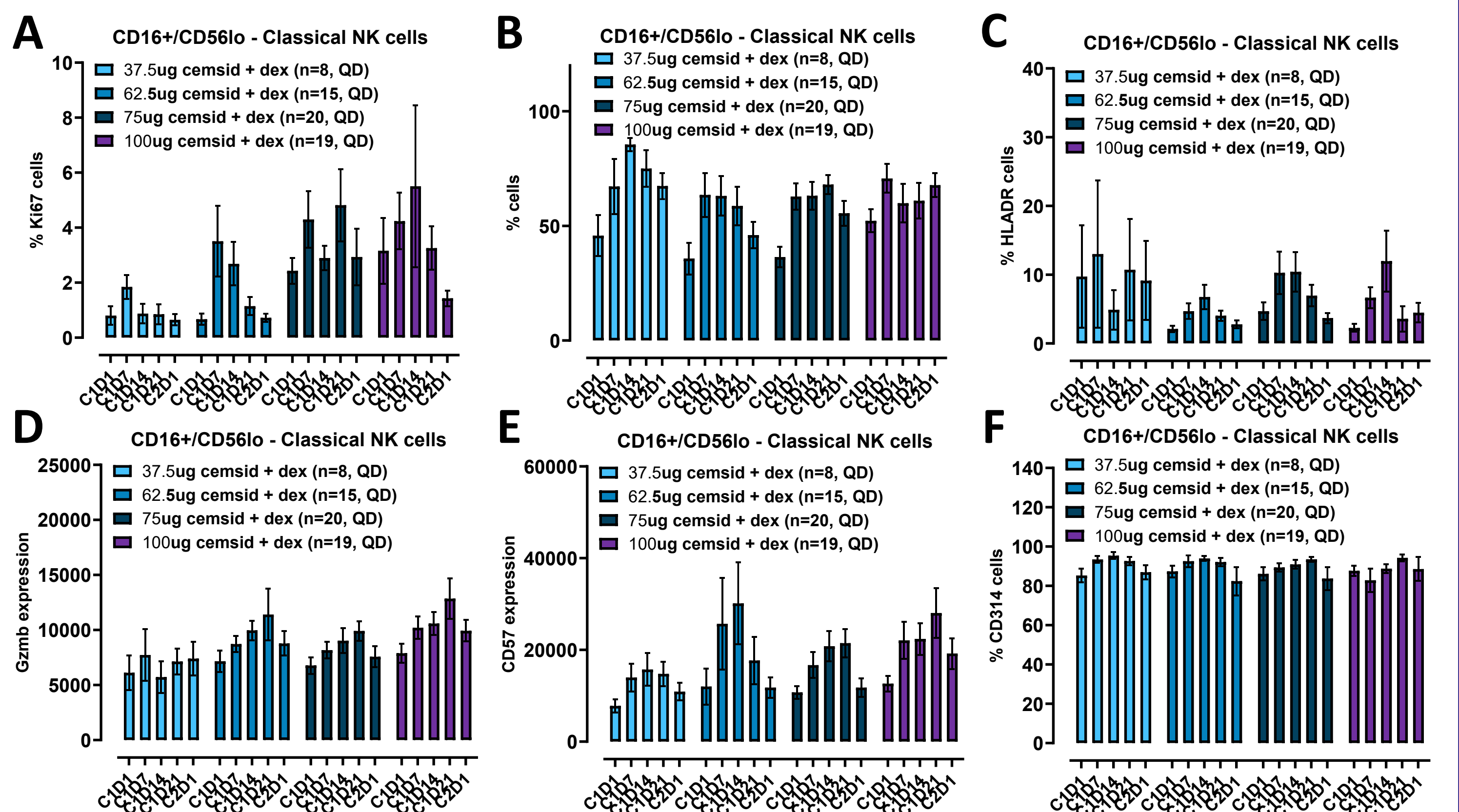
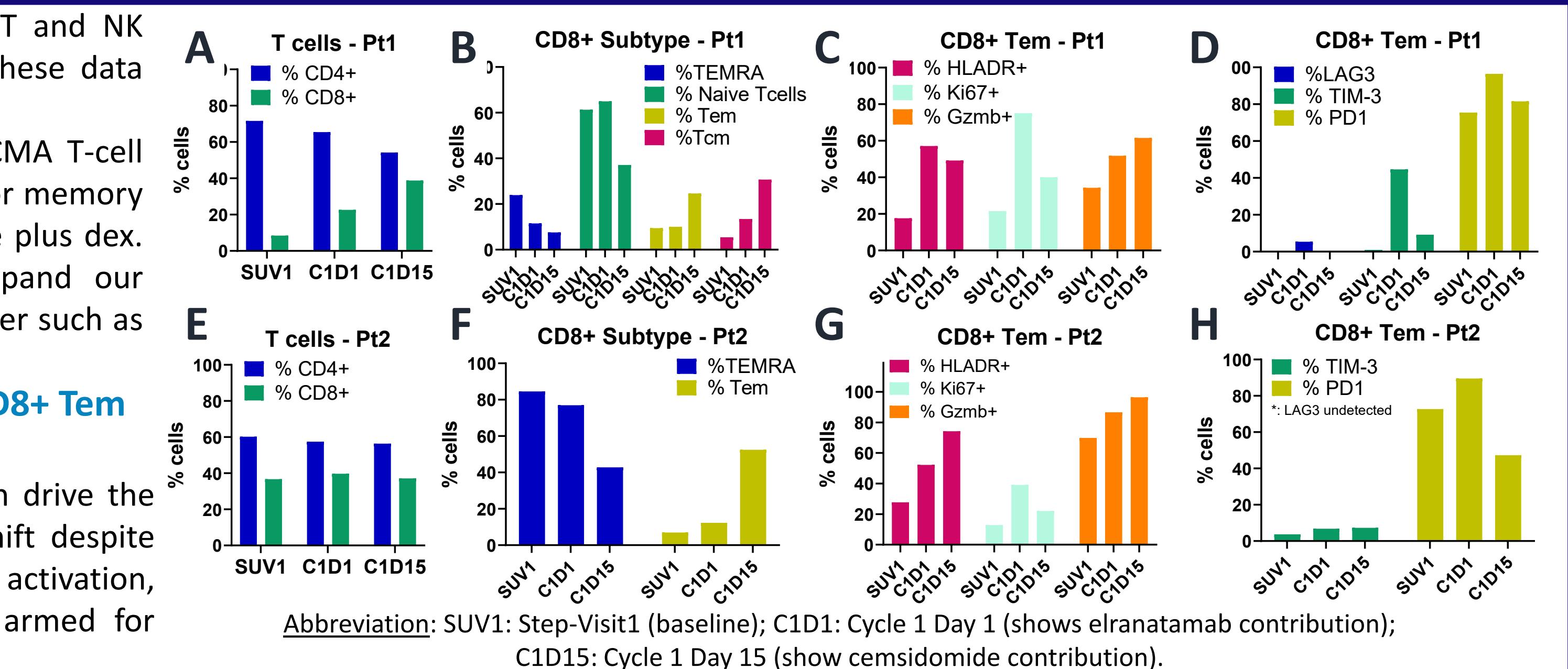


Figure 5: Mature cytotoxic NK cells are expanded, activated, and armed with preserved CD314
Cemsidomide and dexamethasone also engage the mature cytotoxic NK population primarily responsible for antibody-dependent cellular cytotoxicity (ADCC)-mediated killing. The combination expands this population (measured by Ki67 (A) and % cells (B)) and activates it (upregulation of HLADR (C)). Gzmb content detected by MFI (D) increases during the on-treatment, and CD57 expression (E) rises, reflecting maturation toward terminally differentiated cytotoxic effectors. CD314/NKG2D (F) is preserved or slightly upregulated across all dose levels preserving the activating receptor, crucial for sustained cytotoxic function.



Abbreviation: SUV1: Step-Visit1 (baseline); C1D1: Cycle 1 Day 1 (shows elranatamab contribution); C1D15: Cycle 1 Day 15 (show cemsidomide contribution).

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