Impact of lenalidomide pre-apheresis on markers of T cell fitness and pharmacodynamic biomarkers in newly diagnosed multiple myeloma patients with suboptimal response to autologous stem cell transplantation

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Disclosures

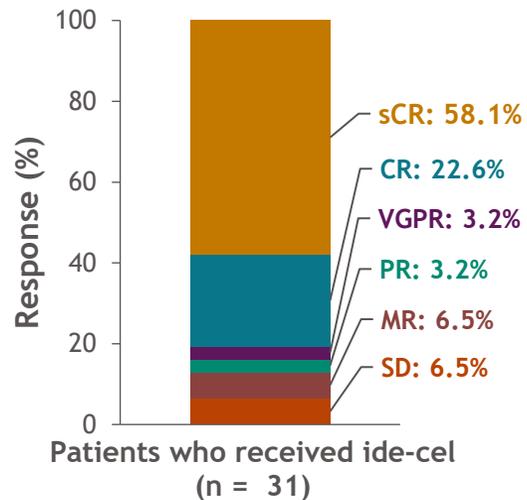- Dr Basudhar is an employee of and holds stock ownership with Bristol Myers Squibb

Ide-cel delivered promising complete responses in patients with NDMM suboptimal response after frontline ASCT

Karmma-2 study design[1]:

Frontline ASCT → Limited response → Cohort 2c PR, MR, or SD → Ide-cel infusion 300–450 x 10^6 CAR T cells → LEN maintenance N=8/31 / No LEN maintenance N=23/31

Median time to ide-cel: 5.8 mo (4.1 – 14.3)

sBCMA: 27 ng/mL (6.5-257)

Promising clinical responses were achieved[2]

However, there is evidence that recent exposure to transplant is associated with T cell dysfunction[3,4]
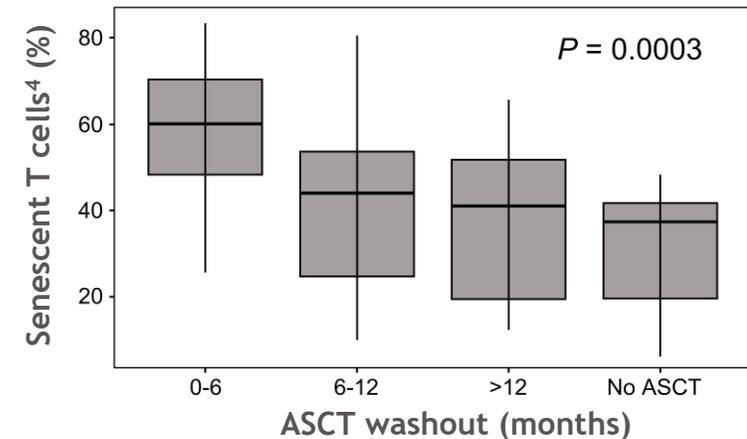

Response (%) — Patients who received ide-cel (n = 31)

- sCR: 58.1%
- CR: 22.6%
- VGPR: 3.2%
- PR: 3.2%
- MR: 6.5%
- SD: 6.5%

81% Complete response rate

74.1% 48-month event-free rate

Median follow-up: 55.4 months (51.4 – 59.5)

data cutoff: June 28, 2024

Senescent T cells[4] (%) vs ASCT washout (months): 0-6, 6-12, >12, No ASCT. *P* = 0.0003
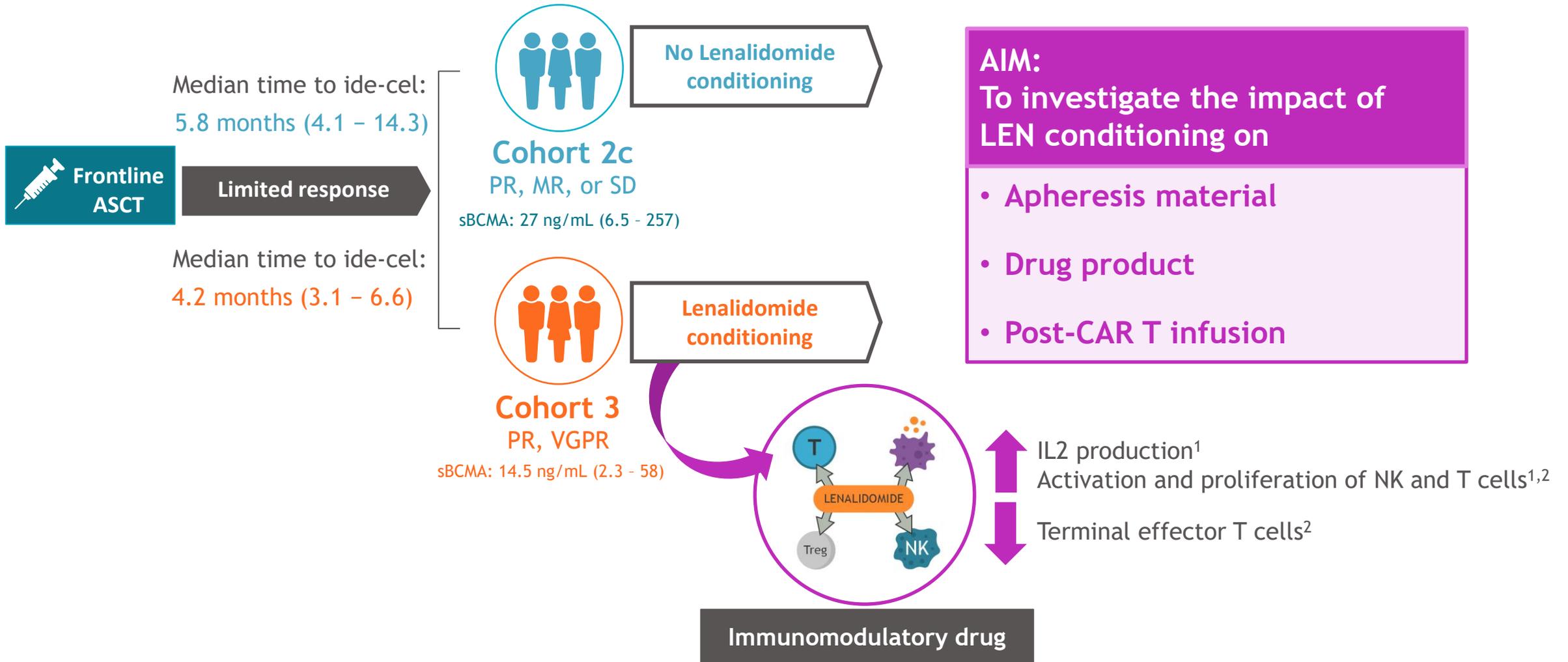
Can the quality of CAR T responses be improved for patients proximal to transplant?

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CR, complete response; ide-cel, idecabtagene vicleucel; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; MR, minimal response; PR, partial response; sBCMA, soluble B cell maturation antigen; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

1. An Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma and in Subjects With High-Risk Multiple Myeloma (KarMMa-2). ClinicalTrials.gov identifier: NCT03601078. Updated July 10, 2025. Accessed November 18, 2025 2. Paul B, et al. Poster presentation at the 66th American Society of Hematology (ASH) Annual Meeting; December 7-10, 2024; San Diego, CA, USA & Online. Poster 3388. 3. Janakiram M, et al. *Transplant Cell Ther*. 2022 Feb;28(2):61–69. 4. Unpublished data from KarMMa-2.

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Aim: Investigate the effect of LEN conditioning before CAR T cell manufacturing on T cell fitness and pharmacodynamic biomarkers

Frontline ASCT
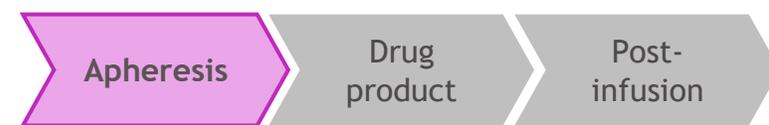
Limited response

Median time to ide-cel:
5.8 months (4.1 – 14.3)

Median time to ide-cel:
4.2 months (3.1 – 6.6)

Cohort 2c
PR, MR, or SD
sBCMA: 27 ng/mL (6.5 – 257)

No Lenalidomide conditioning

Cohort 3
PR, VGPR
sBCMA: 14.5 ng/mL (2.3 – 58)

Lenalidomide conditioning

AIM:
To investigate the impact of LEN conditioning on

- **Apheresis material**
- **Drug product**
- **Post-CAR T infusion**

T

LENALIDOMIDE

Treg   NK

Immunomodulatory drug

IL2 production[1]
Activation and proliferation of NK and T cells[1,2]

Terminal effector T cells[2]

NK, natural killer cell; sBCMA, soluble B cell maturation antigen; Treg, regulatory T cell.
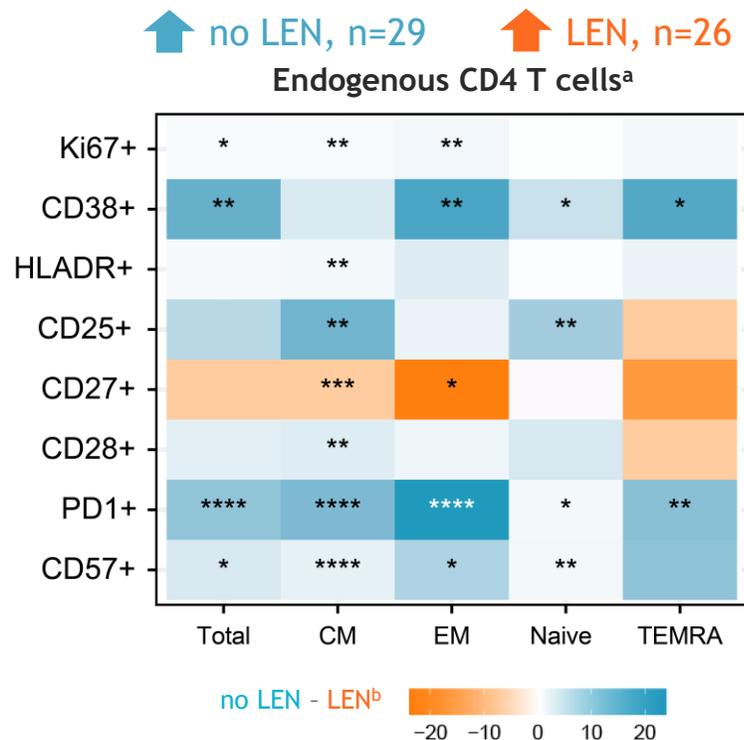
1. Kolta V, et al. *J Hematol Oncol*. 2009 Aug 12;2:36. **2.** Janakiram M, et al. *Transplant Cell Ther*. 2022 Feb;28(2):61–69.
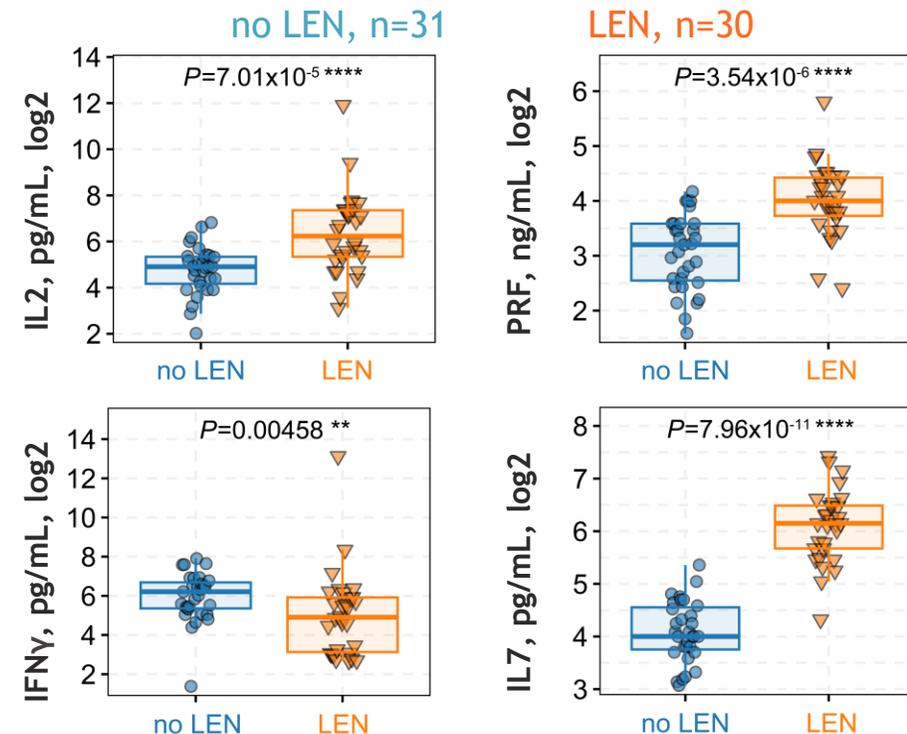
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Baseline T cell fitness is improved with LEN conditioning pre-apheresis

Activation and exhaustion markers

↑ no LEN, n=29   ↑ LEN, n=26

Endogenous CD4 T cells[a]

Heatmap rows: Ki67+, CD38+, HLADR+, CD25+, CD27+, CD28+, PD1+, CD57+
Columns: Total, CM, EM, Naive, TEMRA

no LEN – LEN[b] color scale: −20, −10, 0, 10, 20

Cytokine assessment at CAR T infusion

no LEN, n=31   LEN, n=30

$P=7.01 \times 10^{-5}$ **** (IL2, pg/mL, log2)
$P=3.54 \times 10^{-6}$ **** (PRF, ng/mL, log2)
$P=0.00458$ ** (IFNγ, pg/mL, log2)
$P=7.96 \times 10^{-11}$ **** (IL7, pg/mL, log2)

Impact of LEN conditioning

↓ **PD1, CD57, CD38** on CD4 and CD8 indicate **reduced T cell exhaustion**

↑ **Tem** CD8 T cells demonstrate **improved cytotoxic activity** (data not shown)

↓ **IFNγ** indicate **low basal inflammation** and favorable TME

↑ **IL2, PRF and IL7** suggest **improved cytotoxic activity and homeostasis**

*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. [a]Label by FDR adjusted *P* values from Wilcox test. CD8 T cells showed same trend as CD4 T cells (data not shown). [b]Color by estimated median difference in no LEN - LEN. CM, central memory T cell; EM, effector memory T cell; FDR, false discovery rate; HLADR, human leukocyte antigen-DR isotype; IFN, interferon; IL, interleukin; Ki67, antigen Keil 67; PD1, programmed cell death 1; PRF, platelet-rich fibrin; Tem, effector memory T cell; TEMRA, terminally differentiated effector memory cell; TME, tumor microenvironment.
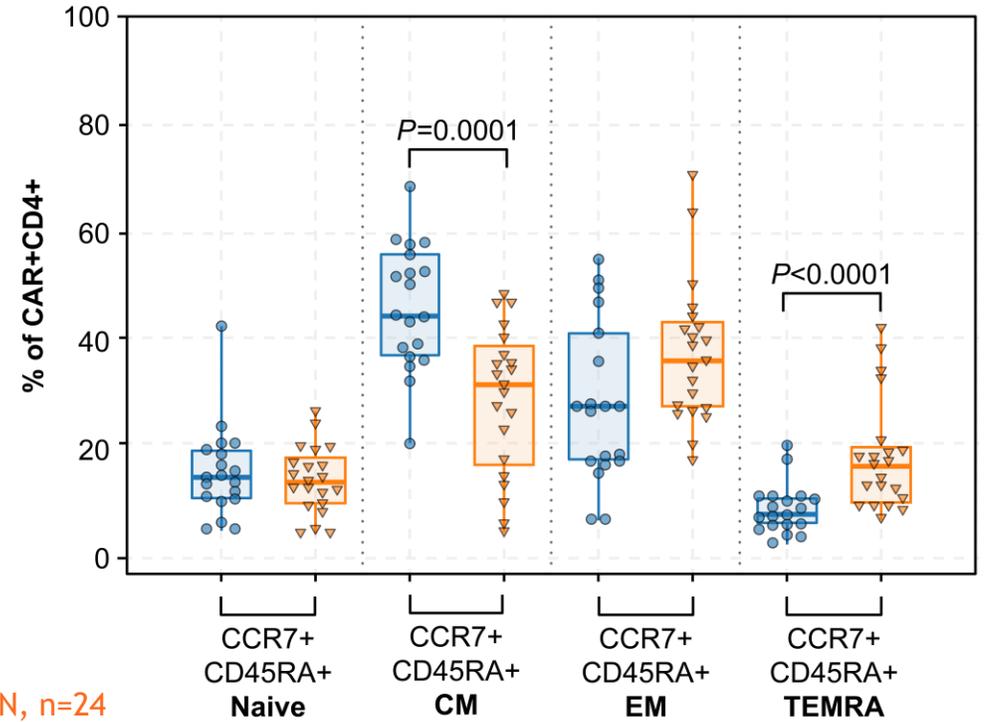
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LEN conditioning increased drug product potency
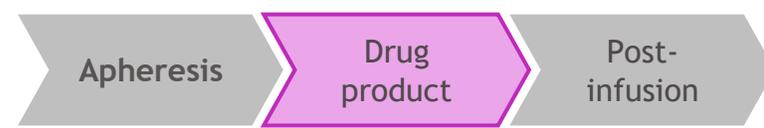
Drug product characterization
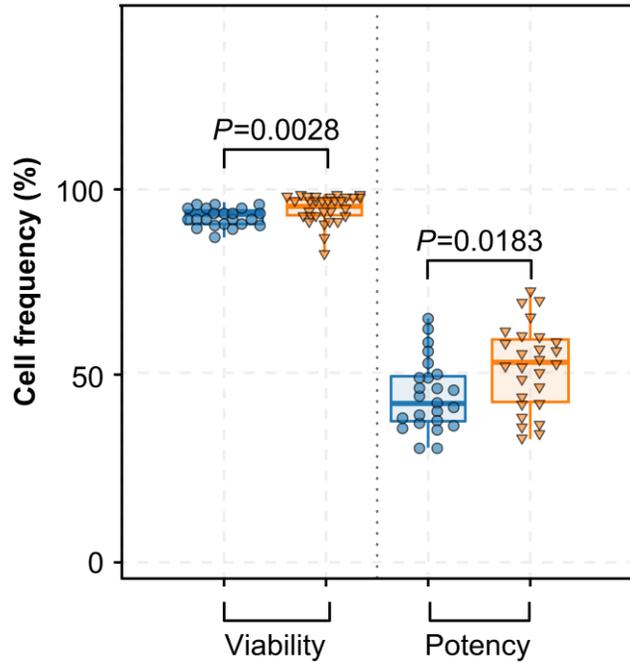
T cell memory subsets of drug product

○ no LEN, n=19   ▽ LEN, n=24

↑ **Potency** and **viability** indicate **better quality drug product**

⊜ **No impact** to **drug product doubling** or **T cell purity**

Impact of LEN conditioning

↑ CD4 and CD8[a] effector populations suggest **increased cytolytic potential**

↓ CD4 and CD8[a] CM

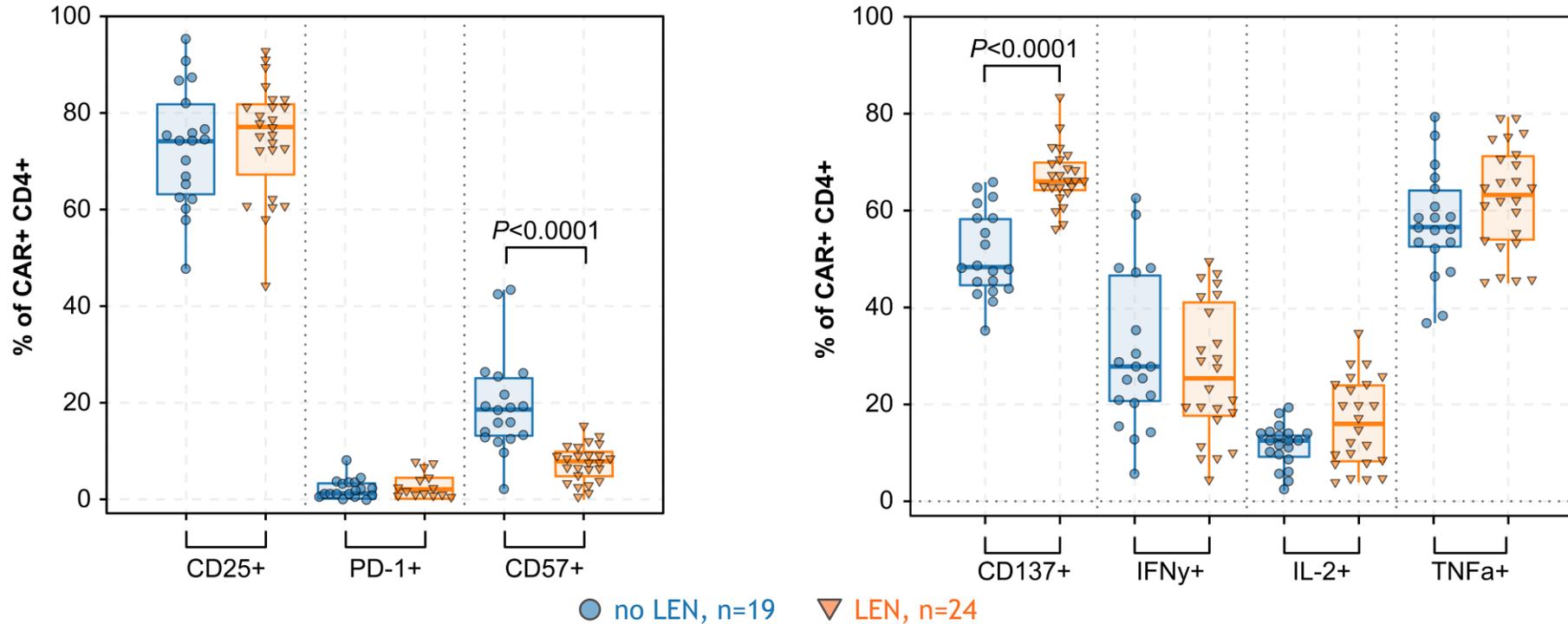[a]CD8 T cells showed same trend as CD4 T cells (data not shown).

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Decreased senescence and increased CAR-specific activation was observed with LEN conditioning

Expression of exhaustion and activation markers on CAR+ CD4 T cells

Left plot: % of CAR+ CD4+ for CD25+, PD-1+, CD57+ (P<0.0001 for CD57+)

Right plot: % of CAR+ CD4+ for CD137+ (P<0.0001), IFNγ+, IL-2+, TNFa+

● no LEN, n=19   ▽ LEN, n=24

CD57 in CD4 and CD8[a] CAR T compartment indicated **reduced senescence**
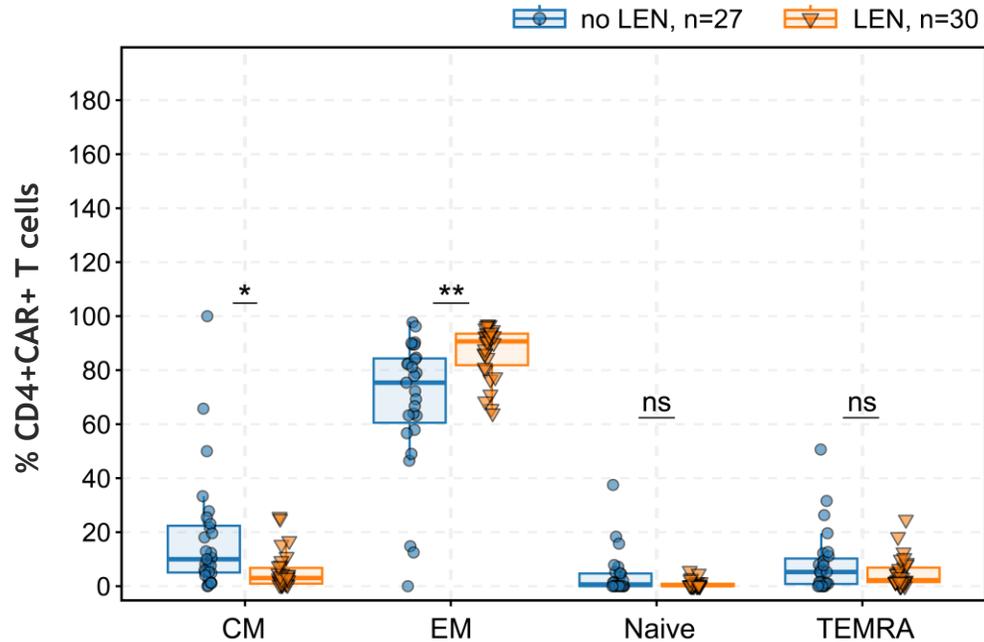
Impact of LEN conditioning

CD137 (4-1BB) CD4 and CD8[a] CAR T cells indicated **better activation**

[a]CD8 T cells showed same trend as CD4 T cells (data not shown).
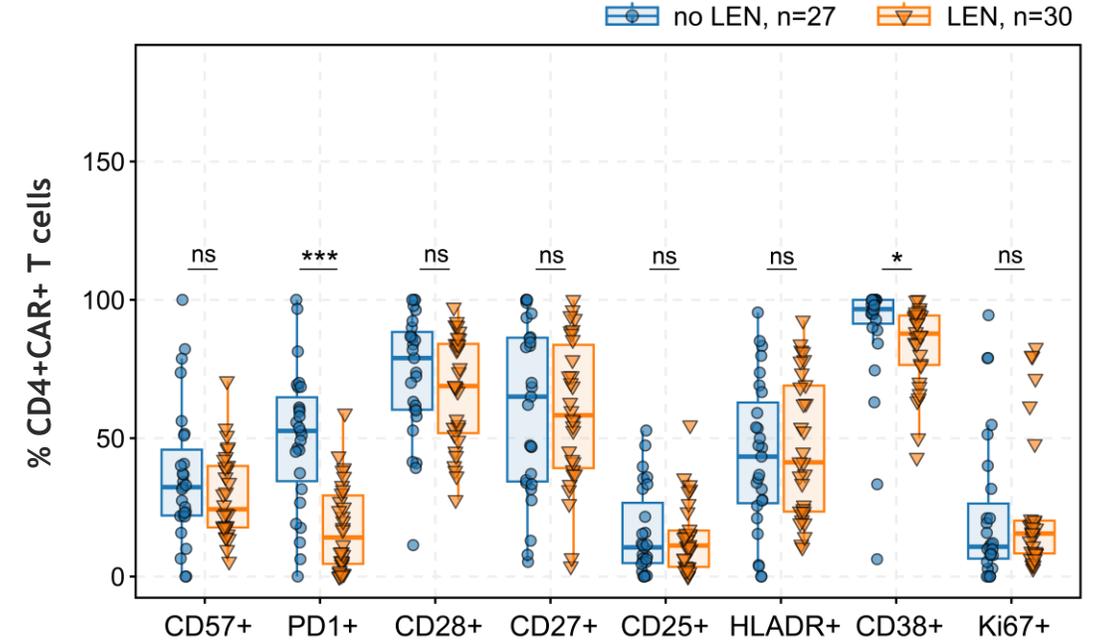
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Less exhausted T cell phenotypes were observed post-infusion with LEN conditioning
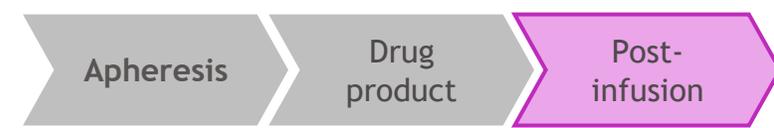
Distribution of CD4 CAR T cell subtypes at day15[a]
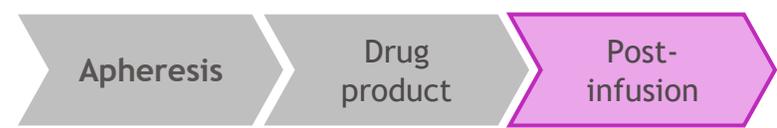
Expression of exhaustion and activation markers[a]

Tem subset indicating **robust activation/expansion**
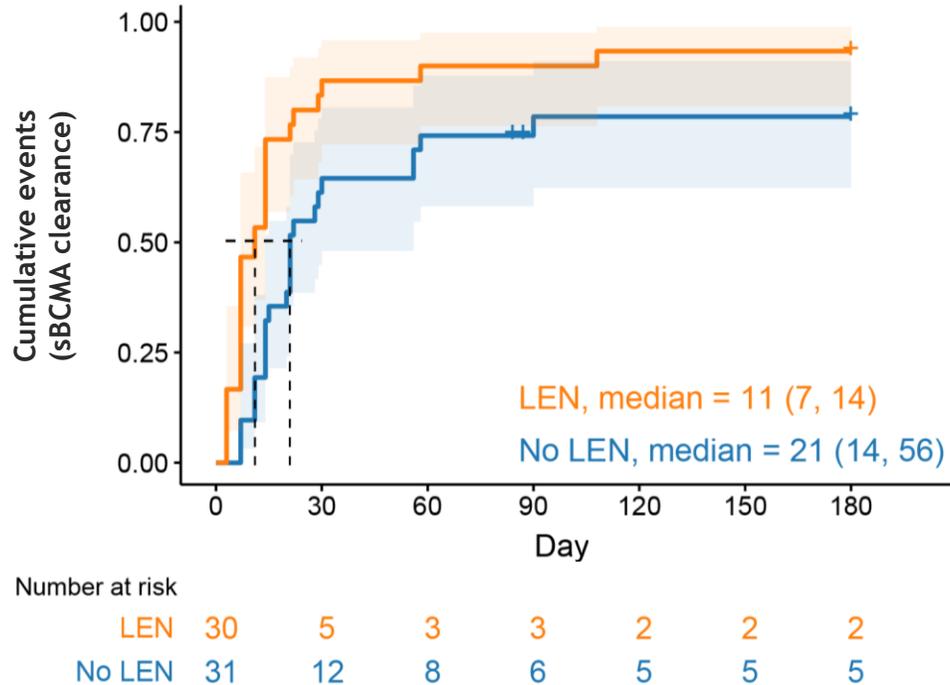
Impact of LEN conditioning

Expression of markers consistent with **exhaustion** (PD1 and CD38)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. FDR adjusted P values from Wilcox test.
[a]CD8 T cells showed same trend as CD4 T cells (data not shown).

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Administration of LEN conditioning provided promising early indication of deep tumor clearance

Assessment of sBCMA clearance

LEN, median = 11 (7, 14)
No LEN, median = 21 (14, 56)

Number at risk

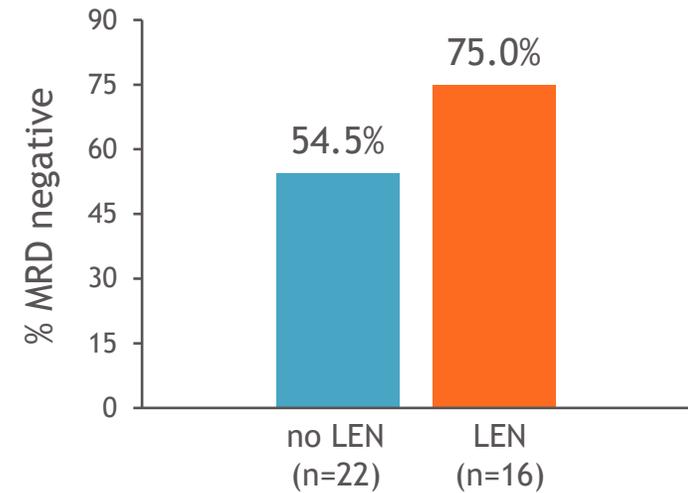|							
LEN	30	5	3	3	2	2	2
No LEN	31	12	8	6	5	5	5

Minimal residual disease (MRD) assessment[a]

Patients in whom disease was below the limit of detection (10^{-5}) for at least 2 consecutive readouts after ide-cel infusion

% MRD negative

no LEN (n=22): 54.5%
LEN (n=16): 75.0%

Rapid clearance of tumor was observed

⬆ Higher number of subjects **achieved deep tumor clearance**
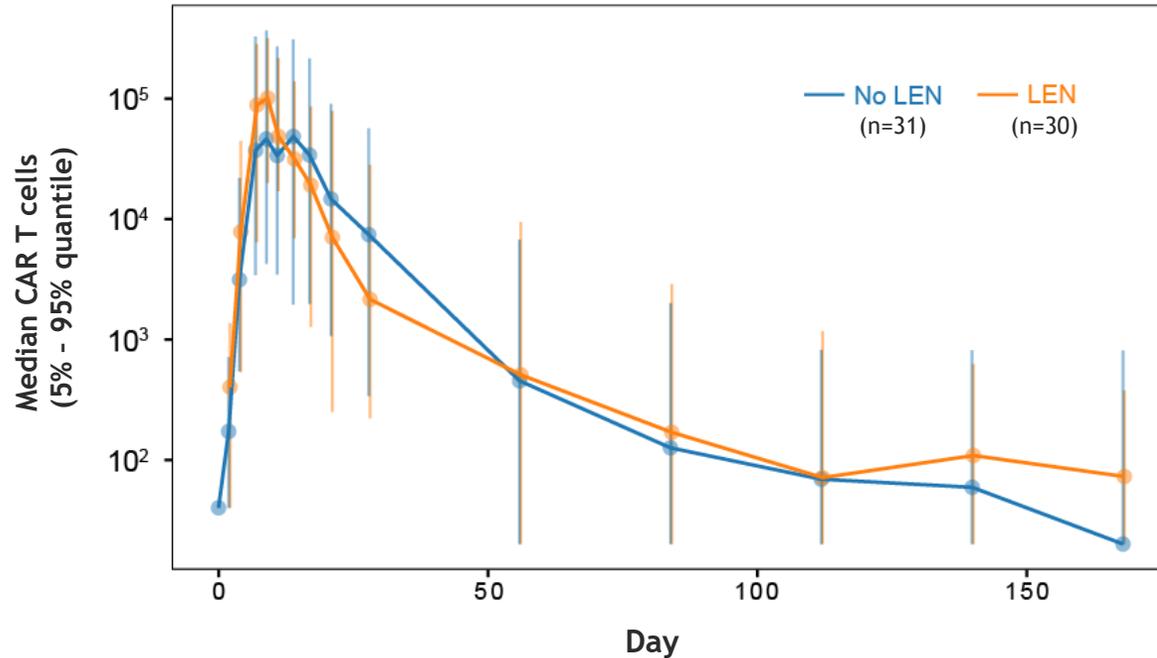LEN (93%, 28/30), no LEN (77%, 24/31)

Impact of LEN conditioning

⬆ **Higher MRD-negativity** was observed indicating deep tumor clearance

[a]Calibration rate in LEN and no LEN cohorts was 53% and 71%, respectively (Sept 2025). Analysis performed for the MRD evaluable population.

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CAR T cell expansion was similar between cohorts

CAR T cell expansion by cohort in PK–evaluable patients

Median CAR T cells (5% - 95% quantile) vs Day. No LEN (n=31), LEN (n=30).

Characterization of pharmacokinetic parameters

Clinical characteristics, median (range)	no LEN (n=31)	LEN (n=30)
C_{MAX} Max conc, gag copies/µg	158112.7 (5945.0 - 549995.4)	141155.1 (27527.9 - 424336.8)
T_{MAX} Time of C_{MAX}, day	9 (7 - 21)	9 (7 - 14)
AUC_{0-28} AUC_{0-28}, day*gag copies/µg	1205280.7 (75659.7 - 3841095.9)	815216.2 (196900.4 - 5495077.7)

- Robust cell expansion was observed in PK-evaluable patients for both cohorts
- PK-evaluable patients had measurable ide-cel levels at 6 months and 12 months post-infusion

AUC, area under the curve; PK, pharmacokinetic.

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CONCLUSIONS: LEN conditioning enhances T cell quality with positive impacts on CAR T drug product potency and anti-tumor performance

Pre-apheresis immune profile

Improved quality and characteristics of T cell and immune function

- Less differentiated T cells and fewer terminally exhausted cells
- Improvements in T cell fitness and inflammation

CAR T Drug Product

Increased potency and viability

- Less senescence and exhaustion

Post-CAR T infusion

More efficient tumor clearance and reduced signatures of exhaustion

- Similar levels of CAR T cell expansion
- Rapid and deep tumor clearance
- Higher rate of sustained MRD negativity

IMPACT: Lenalidomide conditioning has potential for broad utility to improve CAR T responses in MM and may warrant safety and efficacy evaluation for use prior to other T cell redirecting modalities

MM, multiple myeloma.

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Acknowledgments

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- The cross functional team within BMS

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