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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Cellular Dynamics Following CAR T Cell Therapy Are Associated with Response, Resistance and Cytokine Release Syndrome in Relapsed/Refractory Multiple Myeloma

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Introduction
The introduction of B cell maturation antigen (BCMA)-targeting chimeric antigen receptor (CAR) T cells revolutionized the treatment of relapsed/refractory multiple myeloma (RRMM). While long-term follow-up of CD19 CAR T cells demonstrated a connection between CAR T cell expansion and persistence with outcome, very little is known about persistence and effects on bystander cells of BCMA-targeting CAR T cells.
Methods
We analyzed 27 RRMM patients (pts) treated with Idecabtagene vicleucel (Ide-cel) at our center. Pts were grouped based on their remission evaluated 100 days after infusion into responders (partial response or better, n=16) or non-responders (progressive disease, n=11). Peripheral blood (pb) was drawn at day of leukapheresis, at day of infusion/after lymphodepletion (LD, d0) and at several time points following Ide-cel infusion (d7, d14, d30 and d100). In order to reflect a comprehensive picture of the longitudinal dynamics of CAR and non-CAR T cells, we subjected pb mononuclear cells to advanced flow cytometry. Additionally, we assessed the impact of cellular dynamics on the occurrence of cytokine release syndrome (CRS), tocilizumab application and the incidence of cytopenia.
Results
The median number of infused CAR T cells was 430x10 ^{6} (range: 248.8 - 489.1x10 ^{6}) with one exception (25.7x10 ^{6}). There was no correlation between the median number of infused cells and *in vivo* expansion of CAR T cells after infusion as well as response or the development of CRS or cytopenia. Significant differences between responders and non-responders were already detected on day of leukapheresis: While non-responders showed similar numbers of CD4+ and CD8+ T cells, responders had significantly higher CD8+ T cell counts as compared to CD4+ T cells ($p<0.05$, Figure 1). Additionally, significantly reduced percentages of effector memory CD8+ T cells were detected in responders as compared to non-responders. The latter group showed significantly increased numbers of CD3+CD8+ T cells at the day of infusion indicating a less effective LD in non-responders. Following CAR T cell infusion, peak expansion occurred two weeks after infusion and was significantly higher in responders as compared to non-responders ($p<0.001$, Figure 2). CD3+ CAR T cell compartment predominantly comprised of CD8+ T cells regardless of response (median: 85%). Analysis of the distribution of CAR and non-CAR T cells after infusion revealed that the majority of CD4+ T cells in responders and non-responders were untransfected. Similar results were detected for CD8+ T cells in non-responders. However, in responders CD8+ CAR T cells approximated CD8+ non-CAR T cells with no significant differences on d7 and d14. With regard to T cell differentiation, almost the entire CD4+ T cells

exhibited either a central memory or effector memory phenotype after CAR T cell infusion. Shortly after CAR T cell infusion, effector memory CD8+ T cells outbalanced all other CD8+ T cell subtypes. Most pts had no detectable CAR T cells 100 days after infusion, regardless of remission. Overall, 22 pts (81%) developed CRS shortly after CAR T cell infusion and 7 of these (32%) required tocilizumab treatment. Whereas percentages of CD3+ CAR T cells were significantly elevated in both CRS positive groups ($p<0.05$) shortly after infusion, absolute numbers were significantly increased only in CRS positive pts without tocilizumab. Analysis of blood counts following CAR T cell infusion revealed that cytopenias persisted longer in CRS pts treated with tocilizumab, which was also reflected by significantly increased numbers of days below thresholds for all cell lines (anemia, thrombocytopenia and leukopenia, $p<0.01$). Even though the occurrence of CRS and especially the treatment with tocilizumab affected blood cell composition, it did not correlate to response.

Conclusion

We demonstrate that BCMA-targeting CAR T cells only transiently persist in pb after infusion. Still, initial CAR T cell expansion, predominantly caused by effector memory CD8+ CAR T cells, was linked to response and CRS in RRMM pts. A correlation between CRS and tocilizumab administration with prolonged cytopenias following CAR T cell infusion was also observed. Our data provide first evidence that responders and non-responders can early be distinguished by differential cellular composition in CAR and non-CAR T cell compartments with distinct features already present at day of apheresis.

Disclosures Fricke: *Novartis:* Consultancy, Honoraria; *Janssen-Cilag:* Consultancy, Honoraria; *Vertex Pharmaceuticals:* Consultancy, Honoraria; *Kite/Gilead Sciences:* Consultancy, Honoraria; *MSGO:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V.:* Patents & Royalties, Research Funding. **Kloetzer:** *Janssen:* Honoraria. **Heyn:** *Janssen:* Honoraria. **Ussmann:** *Sanofi:* Other: former travel support. **Herling:** *Abbvie, Beigene, Janssen, Stemline, Takeda:* Consultancy; *Mundipharma EDO, Janpix, Novartis, Roche:* Research Funding. **Jentzsch:** *JAZZ:* Honoraria; *Amgen:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Blueprint Medicine:* Honoraria; *BMS:* Honoraria. **Platzbecker:** *Novartis:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy; *Takeda:* Consultancy, Honoraria, Research Funding; *Celgene:* Honoraria; *Geron:* Consultancy, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *Curis:* Consultancy, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *Merck:* Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Fibrogen:* Research Funding; *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *Roche:* Research Funding; *BeiGene:* Research Funding; *BMS:* Research Funding. **Vucinic:** *MSD:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Sobi:* Honoraria, Other: Travel/Accommodations/Expenses; *Amgen:* Honoraria; *AstraZeneca:* Honoraria; *Janssen:* Honoraria; *Gilead/Kite:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria, Other: Travel/Accommodations/Expenses; *Novartis:* Consultancy, Honoraria; *Abbvie:* Honoraria. **Merz:** *AMGEN, TAKEDA, BMS, JANSSEN, STEMLINE, ROCHE:* Honoraria.

Figure 1: T cell counts in peripheral blood at day of leukapheresis

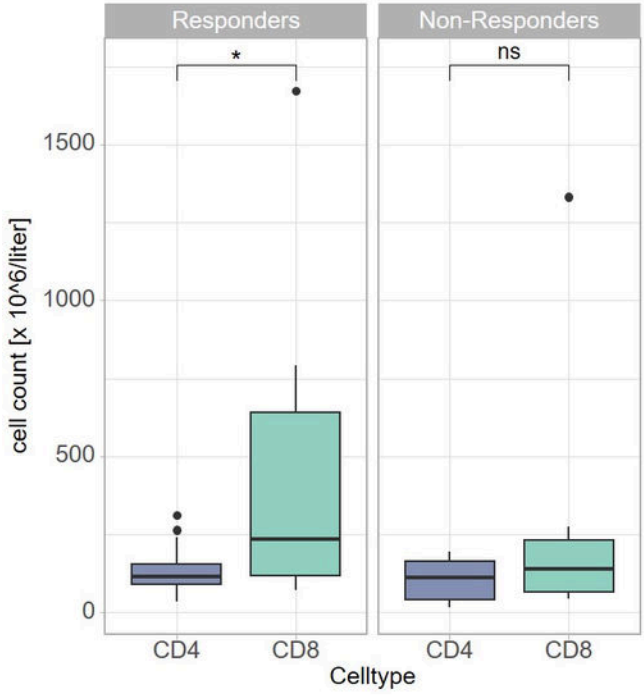

Figure 2: CAR T cell dynamics post infusion

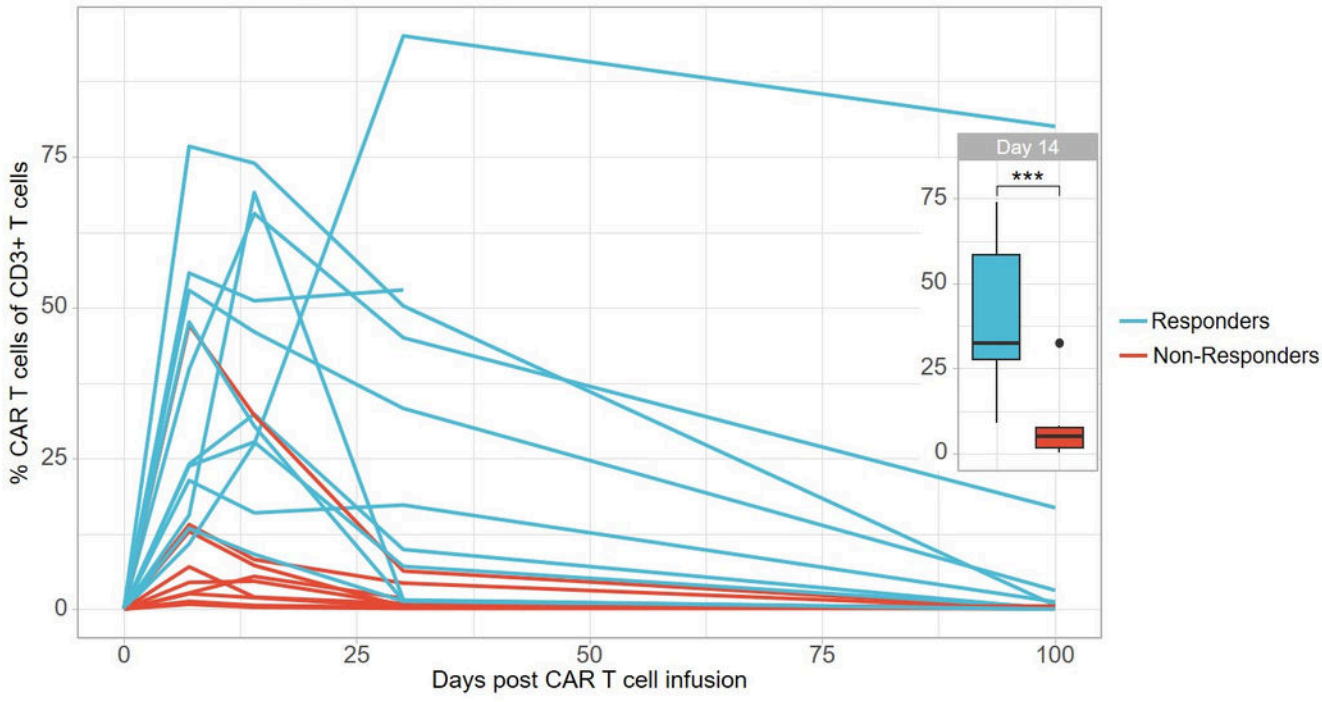

Figure 1

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