**Approved and emerging CAR-Ts in MM**

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**Unmet Medical Need:**

Poor outcomes in patients refractory to PI/IMiDs and CD38-mAbs

• 275 MM patients refractory to anti-CD38 mAbs

• mOS from refractoriness to CD38:

* all patients: 8.6 month
* "non-triple-refractory": 11.2 months
* "Triple- and quad-refractory": 9.2 months
* "penta-refractory": 5.6 months

• 249 patients received further treatment:

- mPFS: 3.4 months

- mOS: 9.3 months

Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6820050/)][[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/30858549)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Leukemia&title=Outcomes+of+patients+with+multiple+myeloma+refractory+to+CD38-targeted+monoclonal+antibody+therapy&author=UH+Gandhi&author=RF+Cornell&author=A+Lakshman&volume=33&issue=9&publication_year=2019&pages=2266-2275&pmid=30858549&)]

**BCMA CART Cell Therapy: KarMMa study: ldecabtagene vicleucel (ABECMA; ide-cel; bb2121) approved by FDA/EMA 2021 (**[**press release**](https://investor.bluebirdbio.com/news-releases/news-release-details/bristol-myers-squibb-and-bluebird-bio-announce-positive-top-line)**)**

• Open-label, single arm study: N=l40

• ≥ 3 prior therapies (including an IMiD, a Pl and an anti-CD38 antibody) median: 6

lines of prior therapy

• 94% of patients refractory to anti-CD38 antibody: 84% triple-refractory EMD 39%

• Median follow-up: 11.3 months

• Grade 2: 3 CRS: 5.5%

• Grade 2: 3 investigator identified neurotoxicity events: 3.1%

• in the subgroup of pts. achieving a CR: PFS > 20 m.

Cilta-cel: CART Cell Product targeting BCMA with 2 target domains

* At median FU 18 months: single infusion yielded deep, durable responses in all evaluated subgroups in CARTITUDE-1.
* ORR of 95%-100% across all subgroups, including those with high-risk cytogenetics, ISS stage III MM, baseline bone marrow cells ≥60%, and baseline plasmacytomas.
* In ISS stage III and with baseline plasmacytomas, median DOR appeared shorter and 18-mo PFS and OS rates lower.
* Cilta-cel safety profile across the subgroups consistent with the overall population,
* no new safety signals.
* [Efficacy outcomes in various subgroups of patients in CARTITUDE-1](https://ash.confex.com/ash/2021/webprogram/Paper146069.html)

**Updated Results from CARTITUDE-1:** Phase 1 b/2Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor Cell Therapy, in Patients With Relapsed Refractory Multiple Myeloma [Martin T. et al. Blood 2021;138 (Suppl 1):549](https://ashpublications.org/blood/article/138/Supplement%201/549/479381/Updated-Results-from-CARTITUDE-1-Phase-1b-2Study)

* ORR: 97.9%
* MRD negative: 92%

Anti-BCMA CART-cell therapy in multiple myeloma: can we do better?

Proposed mechanisms of resistance to anti-BCMA CART-cell therapy in MM

* CAR-T cell intrinsic
* MM cell intrinsic
* Microenvironment

More info in: [Anti-BCMA CAR T-cell therapy in multiple myeloma: can we do better?](10.1038/s41375-019-0669-4)

How to increase CAR T cell fitness / efficacy / persistence? Generate CAR T cells in earlier lines of therapy

More info in: [Clinical Predictors of T Cell Fitness for CAR T Cell Manufacturing and Efficacy in Multiple Myeloma](https://ashpublications.org/blood/article/132/Supplement%201/1886/273286/Clinical-Predictors-of-T-Cell-Fitness-for-CAR-T) (full text available)

[CARTITUDE-2:](https://ashpublications.org/blood/article/138/Supplement%201/2910/478907/CARTITUDE-2-Efficacy-and-Safety-of-Ciltacabtagene?searchresult=1) Efficacy and Safety of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor T-Cell Therapy, in Patients with Multiple Myeloma an Early Relapse after Initial Therapy.

* Early & deep responses in early clinical relapse/tx failure to initial therapy,
* manageable safety profile,
* MRD negativity achieved early.

How to improve Persistence of CART cells?

bb21217: next-generation anti-BCMA CAR T cell therapy product for multiple myeloma ([Berdeja et al 2019](https://ashpublications.org/blood/article/134/Supplement_1/927/427089/Updated-Results-from-an-Ongoing-Phase-1-Clinical?searchresult=1))

* bb21217 is cultured with Pl3 kinase inhibitor, bb007, to enrich for T cells displaying a

memory-like phenotype

* CAR T cells enriched for this phenotype may persist and function longer than non-

enriched CART cells

* Initial efficacy results with bb21217 CAR T therapy in heavily pretreated RRMM are encouraging, with 83% of patients demonstrating clinical response. Emerging data demonstrate long-term persistence of CAR T cells in long-term responders.

Updated Clinical and Correlative Results from the Phase 1 CRB-402 Study of the BCMA-Targeted CAR T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma ([Raje et al Blood 2021](https://ash.confex.com/ash/2021/webprogram/Paper146518.html))

* Adverse events are consistent with known toxicities of CAR T cell therapies.
* Efficacy results are encouraging with a median DOR estimate of 17months,
* CR rate continues to mature.
* Patients with higher levels of proliferative, less differentiated memory like CAR+ T cells at peak expansion more likely to experience prolonged DOR, continuing to support the hypothesis that the memory like T cell phenotype associated with bb21217 results in prolonged DOR.

Increase Target Antigen Expression to improve efficacy of CAR T cells ([Cowan et al, Blood 2021](https://ashpublications.org/blood/article/138/Supplement%201/551/479409/Safety-and-Efficacy-of-Fully-Human-BCMA-CAR-T)):

* Gamma-Secretase-Inhibitors (GSI) increase the BCMA-Antigen expression on MM cells, reduce the level of soluble BCMA and increase the efficacy of BC MA-CART cells in a mouse model
* Here: Dose-Escalation Study of BCMA-CART cells+ GSI (3x/week) in patients with r/r MM
* Combination safe and tolerable.
* GSI administration routinely increased BCMA surface density on plasma cells.
* Durable, rapid responses in a heavily pretreated refractory population of MM patients, of whom a significant proportion had prior treatment with BCMA targeted therapy and CAR T therapy.
* The combination of BCMA CAR T and GSI may augment anti-tumor activity, even when very low doses of BCMA CAR T cells are administered.

Irreversible Loss of BCMA Expression ([Yan Asmann, ASH 2021](https://ash.confex.com/ash/2021/webprogram/Paper153254.html))

scRNAseq analysis of myeloma cells suggest:

* Different tumor transcriptome profile may be identified in myeloma cells that could relapse early after CAR-T therapy
* In addition, host immune profile both in the BM microenvironment and in systemic PB circulation could be associated with durable clinical response.
* Antigen escape is a common mechanism of escape after CART19 in particular in ALL (40-75%), but also in DLBCL (~30%)

**Genomic aberrations in genes encoding for immunotherapy targets (**[**Truger, 2021**](https://ashpublications.org/bloodadvances/article/5/19/3794/476760/Single-and-double-hit-events-in-genes-encoding)**, full text):**

Monoallelic deletion of Targets for immunotherapy as a first step to biallelic deletions and thus complete irreversible Target Antigen Loss

► Heterozygous deletions in GPRC50 (15%), CD38 (10%). TNFRSF17 (4%) (BCMA)

► Clear trend for more deletions in pretreated patients

1590 -16p Deletion Involving BCMA Locus Is Frequent and Predominantly Observed with del17p ([Mehmet K. Samur et al., ASH 2021A](https://ash.confex.com/ash/2021/webprogram/Paper152286.html))

* monoallelic BCMA deletions are frequent events,
* patients with these events show increased aneuploidy, mostly deletions, potentially making these cells vulnerable for biallelic loss of genes, especially under the pressure of targeted therapy,
* BCMA expressions in bulk sample may not detect the presence or absence of cells with target loss,
* therefore, combining strategies at bulk and single cell level are necessary to understand the disease status.

Results suggest the need to study del16p in patients being targeted for BCMA-directed therapy and its association with other risk factors in MM.

**Irreversible and Complete BCMA loss - How to proceed with CART Therapy?**

**SLAMF7 CART Therapy**:

SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7+ normal lymphocytes ([Gogishvili 2017](https://ashpublications.org/blood/article/130/26/2838/36597/SLAMF7-CAR-T-cells-eliminate-myeloma-and-confer))

• Tailored spacer design ([Hudecek 2015](https://aacrjournals.org/cancerimmunolres/article/3/2/125/467742/The-Nonsignaling-Extracellular-Spacer-Domain-of))

• Virus-free Sleeping Beauty CAR gene transfer ([Munjezi 2017](https://pubmed.ncbi.nlm.nih.gov/27491640/))

• Defined composition of CD8+ and CD4+ CAR-T cells ([Sommermeyer 2016](https://www.nature.com/articles/leu2015247))

• EGFRt marker (detection & safety switch) ([Paszkiewicz 2016](https://www.jci.org/articles/view/84813))

• Humanized targeting domain huLuc63

**Phase I First-in-Class Trial of MCARHJ09, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Patients with Relapsed or Refractory Multiple Myeloma** ([Mailankody 2021](https://ashpublications.org/blood/article/138/Supplement%201/827/480249/Phase-I-First-in-Class-Trial-of-MCARH109-a-G)):

* MCARH109 has a very manageable safety profile with no serious or unexpected toxicities,
* Efficacy is promising in heavily pre-treated RRMM, reflected in high rates of clinical response as well as MRD-negativity, including at doses as low as 25x10 6 CAR T cells,
* All 6 patients who relapsed after BCMA CAR T therapy responded to GPRC5D targeted CAR T therapy, including 2 patients who achieved sCR.

Anti-BCMA CART-cell therapy in multiple myeloma: can we do better?

* Anti-PD1 mAbs as salvage therapy in patients progressing after BCMA CAR T therapy
* Modulation of the expression of oncogenes and oncogenic signaling to prevent immune evasion

**Conclusions**

* The first CART cell product targeting BCMA was approved in the US/EU /Abecma
  + ide-cel) in 2021 and a second BCMA CART cell product (cilta-cel) will be approved for r/r MM probably in 2022
* CART cell therapy can induce ORR up to 100% and a CR beyond 80% in patients with r/r MM (with a median of 6 lines of prior therapy) and a PFS of > 2 years

**In The Future:**

* CART therapy will potentially become a part of the first-line therapy for ultra/high risk patients
* CART therapy will challenge ASCT in TE NDMM
* CART therapy for earlier lines of therapy also in non-transplant eligible patients

(low rate of grade >3 CRS/ICANS)