CARAMBA at the 5th EBMT-EHA European CAR T-cell meeting

The CARAMBA project presents its experiences, lessons learned and achievements in the development of an innovative CAR-T-cell therapy for Multiple Myeloma

Topics in this meeting report:

- CAR T-cell therapy
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- CARAMBA clinical trial
- CAR T-innovation pipeline
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- CARAMBA and beyond

Project Coordinator
Prof. Dr. Michael Hudecek
University Hospital Würzburg
www.caramba-cart.eu

Europe´s most important CAR T-cell therapy meeting

The European CAR T-cell meeting was initiated by the European Society for Blood and Marrow Transplantation (EBMT) and the European Haematology Association (EHA) in 2019 when the first CAR T-cell treatments were approved in Europe. To enhance the development of patient-ready therapies, the meeting offers a stage to discuss current treatments and clinical, regulatory and commercial challenges, bringing together leading European experts in academia, clinics and industry, global key opinion leaders and patient advocates, who share patients' perspectives and their latest experiences.

Since the beginning of the CAR T-cell meetings, CARAMBA was well represented, both in the programme planning team, chairing key sessions and presenting the project to Europe´s key stakeholders. Thereby, it was a special honour for Prof. Dr. Michael Hudecek, research group leader at the University Hospital Würzburg and coordinator of the EU CARAMBA CAR T-cell clinical trial, to chair the 4th and 5th EBMT-EHA CAR T meeting. This year´s event provided updates on the status of CAR T-cell therapy in general including deep science, translational, clinical and commercial development, offering the perfect platform to present important insights gained from the CARAMBA clinical trial.

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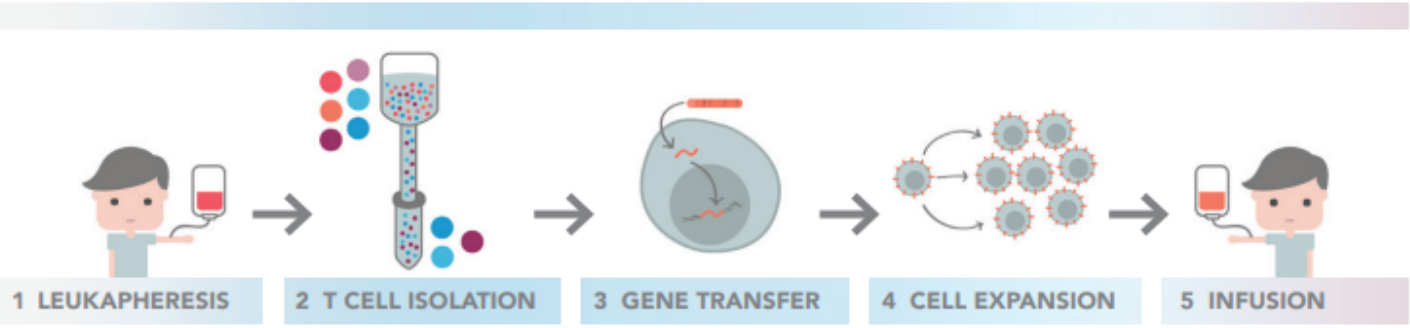
CAR T-cell therapy

CAR T-cells are a promising cancer therapy, in which patient-derived blood cells (T-cells) are engineered to carry a synthetic designer protein (chimeric antigen receptor; CAR) that binds to cancer cells, leading to their elimination. CAR T-cells are a "living drug" that self-amplifies and persists long-term in the body.
Since 2017, six CAR T-cell therapies have received FDA approval, all for the treatment of blood cancers, including lymphoma, leukemia. Recently, also two CAR T-cell therapies for multiple myeloma (Abecma and and Carvykti) have been approved. In both therapies, CAR T-cells bind to BCMA, a protein that is present on myeloma cells. Although CAR T-therapy appears to be effective, a challenge of current forms of CAR T-therapy is that the disease may return.

What is multiple myeloma?

Multiple Myeloma is the second most frequent blood cancer. In 2020, there were 35.842 new diagnoses and 23.275 people who died of Multiple Myeloma in Europe [1]. Multiple Myeloma is caused by a malformation in antibody-producing blood cells, producing a wide variety of symptoms, such as weakened immunity, fatigue, bone loss and pain. Although prognosis and outcome have improved in recent years due to the development of novel drugs, there is still no cure and in most cases, patients eventually die of the disease. Therefore, there is still a great need for new effective therapies.



The CARAMBA clinical trial

The researchers from the CARAMBA clinical trial have designed a new CAR T-cell treatment, which, instead of BCMA, targets a different surface-protein (SLAMF7), that is present on all myeloma cells in every patient (men and women). If the clinical trial is successful, this would increase the therapeutic options available for multiple myeloma patients as well as open the door for combined therapeutic approaches.
Next to a new therapeutic approach, CARAMBA also aims to pave the way for CAR T-cells becoming a standard treatment in Europe that can be manufactured more easily and at affordable costs.

1: https://ecis.jrc.ec.europa.eu/

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CAR T-innovation pipeline

There are currently two approved CAR T-cell products for treatment of relapsed/refractory MM (RRMM): ide-cel (Abecma) and cilta-cel (Carvykti). Both CAR T-cell products target BCMA, but they have a different mode-of-action. Clinical trials indicate that a significant number of patients with RRMM respond very well to CAR T-therapy, although further studies are necessary to see how this translates to the real world. An analysis of 108 patients with RRMM indicated that 73% had a response to ide-cel therapy and for most patients, disease did not progress for 9 months. An analysis of cilta-cel in 97 patients with RRMM revealed that 98% had a response and 60,5% remained disease-free for 24 months [2], However, in many cases the disease returned, meaning that CAR T-therapy needs to be further improved.

"Deeping the knowledge on the biological determinants of CAR T-cells activity will be crucial for improving their efficacy and safety profile and to widen their application to other disease indications including solid malignancies."

Dr. Monica Casucci
Group leader innovative immunotherapies
Ospedale San Raffaele

Challenges in CAR T-treatment and how the CARAMBA clinical trial aims to overcome these:

- **Disease recurrence** as it is experienced in BCMA CAR T-treatment is likely caused by different, patient-specific BCMA expression on different tumour cells, allowing cells without target molecule BCMA to escape and grow. For this reason, scientists are testing other potential targets in multiple myeloma. The CARAMBA clinical trial focuses on SLAMF7, a molecule that is expressed on all multiple myeloma tumour cells at high levels, which lowers the risk of escape. Thereby, combining SLAMF7 with BCMA CAR T-cell therapy may become a future strategy to prevent disease recurrence.

- Improving CAR T-cell **efficacy** is a major goal of CAR T-scientists. For this, it is important to establish quantitative tests to determine the efficacy of CAR T-cells, which despite years of research is not an easy task. Within the CARAMBA project, scientists are analysing CAR T-cells of established mouse models to determine indicators for cell effectiveness. One of the limiting factors is, that some CAR T-cells become dysfunctional over time (CAR T-cell exhaustion). To antagonise this process, CARAMBA scientists are continuously improving the treatment protocol, e.g. by reducing overactivation of CAR T-receptors. In addition, CARAMBA scientists could demonstrate that certain immunomodulatory agents may enhance the efficacy of CAR T-cells, which requires further investigation in the future. In general, it is very likely that CAR T-cell therapy is more effective if it is administered at an earlier stage of the disease. However, currently, patients are only eligible to receive CAR T-therapy after other therapies have failed. Therefore, safety and the effect of late treatment needs to be further elaborated in future clinical studies.

2: Idecabtagene vicleucel versus ciltacabtagene autoleucel: a Sophie´s choice for patients with relapsed refractory multiple myeloma. Davis et al., Expert Review of Hematology, Volume 15, 2022 - Issue 6

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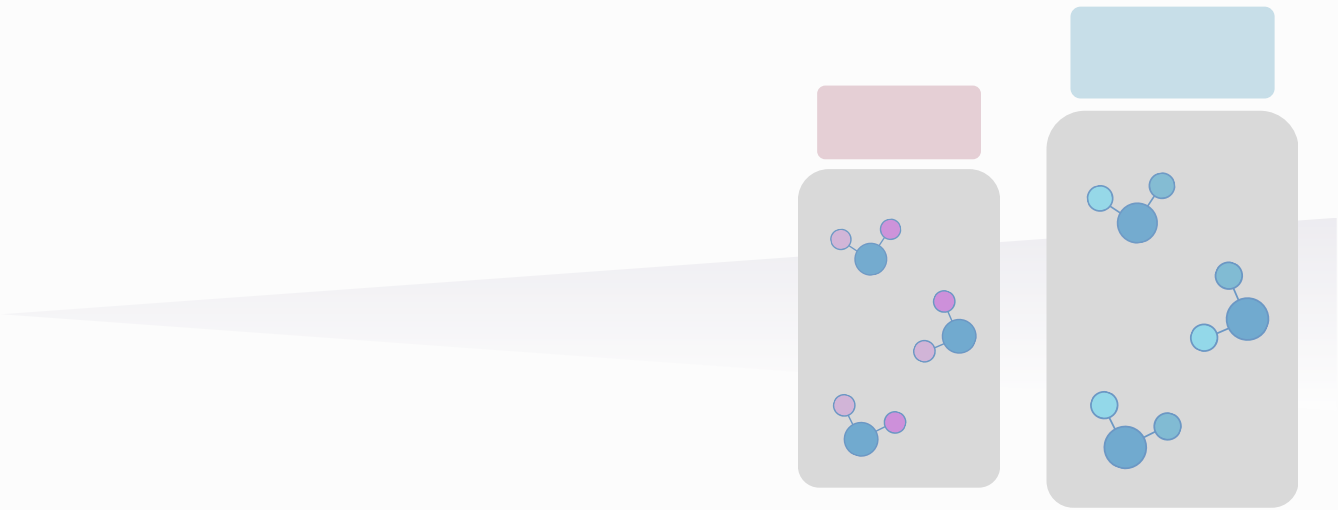
- The management of **short- and long-term toxicities** is one of the major challenges in CAR T-cell therapy. Toxicity may arise if non-tumour cells contain the specific CAR T-target molecules (See also Section on "**European guidelines for clinical trials and toxicity management**" below). To prevent this reaction, scientists are continuously improving the target selection process, for instance by identifying molecules that occur exclusively on tumour cells (neoantigens). Other toxicities may arise due to inflammatory reactions caused by the release of cytokines (Cytokine Release Syndrome, CRS). Hence, CAR T-cell dosage and close inpatient monitoring is vitally important. To decrease the CRS risks, CARAMBA scientists established safety mechanisms that can rapidly and temporarily switch-off the CAR T-cells. Moreover, it is known that the composition of the CAR T-product can trigger toxic effects. Therefore, CARAMBA researchers have tried to mix different kinds of T-cells resulting in lower toxicity in pre-clinical tests, although further confirmation studies are required.

- A serious challenge for the administration of CAR T-cell therapies are **manufactural and logistical issues** and limited **scalability** (see also Section "**CAR T-manufacturing concept**" below). Currently, CAR T-therapies have a very low availability in Europe (e.g. 12 doses BCMA CAR-T-cells per month in France), leading to long waiting lists. As first of its kind, the CARAMBA project is developing a virus-free CAR T-product, which is not only safer, but has also higher manufacturing rates and is more scalable than current CAR T-cell therapies. Thereby production costs can be significantly reduced, making the CARAMBA clinical product more accessible to more patients.

- **Costs:** The high costs of approved CAR T-cell therapies (ide-cel list price of 419,500$; cilta-cel 465.000$) are still prohibitive for standard therapies. Due to CARAMBA´s non-viral and highly-scalable sleeping beauty CAR T-cell manufacturing process, we anticipate the costs of the CARAMBA therapy to be 3x lower, which would significantly impact the accessibility.



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Clinical perspective: Clinical management and CAR T-failure

Since the start of the CARAMBA project in 2018, clinical management of CAR T-patients has changed and was adapted to patients´ needs. **Dr. Sophia Danhof** reports on her experiences in clinical management.

What were the major challenges in the clinical management of CAR T-patients?

Challenges in the clinical management range from the optimal patient selection and incorporation of the CAR T-cells into existing treatment sequences to the management of (early and late) complications like viral infections. And especially the management of patients relapsing after CAR T-cell therapy remains a major challenge.

How did the clinical management change in the last 5 years and how did the CARAMBA experiences impact the patient management?

Luckily, over the last 5 years, CAR T-cell availability has dramatically improved, both in clinical studies and commercially. However, most CAR T-cells are still produced in the US, resulting in considerable production and shipping times that can delay treatment and make additional bridging therapy necessary. With a vein-to-vein time of 16 days, the CARAMBA study has demonstrated impressively that production in the EU is feasible and timely and that non-viral gene-transfer strategies can be applied. In this regard, CARAMBA provides a proof of principle that CAR T-cells can be made available quickly when required by the patient.

"Especially the management of patients relapsing after CAR T-cell therapy remains a major challenge."

Dr. Sophia Danhof
Treating Physician
University Hospital Würzburg

What are general experiences with CAR T-failure and in specific with SLAMF7 CAR T? Does the failure of other CAR T-treatments influence the SLAMF7 treatment?

CAR T-failure mainly results from insufficient persistence of the CAR T-cells or immune evasion of the tumor cells. If a relapse occurred due to loss of the CAR target antigen, targeting a different antigen has the potential to restore anti-myeloma efficacy. Today, we have different BCMA-directed immunotherapies available, unfortunately mostly with limited duration of response. Switching to a different target antigen, such as the SLAMF7, is rational in the setting of BCMA loss.

How will the experiences with CAR T-failure influence future CAR T-treatments?

One development that we are currently observing - and that is already reflected in the CARAMBA study protocol - is moving CAR T-cell therapy to earlier lines of treatment to achieve increased CAR T-fitness in the apheresis product. E.g. in the CARAMBA study, patients can be treated with CAR T-cells after 2 prior lines of therapy, whereas commercially, BCMA CAR T-cells are available for fourth or fifth line therapy only. Also, production protocols will be adapted to enrich for naïve and memory stem cell phenotype to improve expansion and persistence of the CAR T-cells. And, as multiple myeloma is a disease of clonal heterogeneity, combinatorial treatment strategies will be evaluated to increase therapeutic pressure and reduce the risk of clonal outgrowth of the disease.

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European guidelines for clinical trials and toxicity management

The CARAMBA clinical trial is a multicenter, first-in-human, phase I/IIa clinical trial. As the CAR T-cell therapy is new in Europe, there are strict European guidelines to ensure safety. CARAMBA investigators had to navigate through uncharted regulatory territory to obtain approval and in doing so, paved the way for future CAR T-cells studies.

The CARAMBA clinical trial is conducted in four European countries. Initially, the approval procedure was planned to be a pan-European process via the European Medicines Agency. However, for gene-modified cells, this procedure was not available, which meant that approval for the CARAMBA clinical trial had to be separately requested in each country. As each country has its own specific set of regulations for gene-modified cell therapy, this was a long and cumbersome process. By eventually obtaining the regulatory approval in Spain, France, Italy and Germany and continuous discussions with EMA, the CARAMBA clinical trial paved the way for more harmonised standards across Europe and a more harmonised approval process, which will accelerate the approval process of future multi-country CAR T-cell-based clinical trials. Next to challenges in the approval process, differences in clinical patient care between countries and even from centre to centre within the same country, challenge standardization and patient comparability. Therefore, standardisation of toxicity management is of central focus to guarantee patients´ safety across countries and centres.

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In the last years, CARAMBA investigator Prof. Dr. Ibrahim Yakoub-Agha (CHRU Lille) has launched an intiative with special emphasis on collecting and analysing clinical experiences. He summarised the current best practices in this new and rapidly evolving field, creating a book chapter on toxicity management for the EBMT/EHA CAR T-cell Handbook, which is regarded as the standard clinical practice guideline for all European clinicians and will support clinicians and other healthcare professionals to provide consistent, high-quality care.
In an interview with Myeloma Patients Europe, Prof. Dr. Ibrahim Yakoub-Agha gave an overview of the current European guidelines on the management of patients treated with CAR T-cells.

"With 9 patients enrolled in the CARAMBA study, the study appeared safe and no dose-limiting toxicity has been observed so far."

Prof. Dr. Ibrahim Yakoub Agha
Head of Hematopoietic Stem Cell Transplantation and Cellular Therapy
Lille University Hospital

What were the experiences with toxicity during the CARAMBA trial?

CARAMBA adheres to the highest standards to develop a safe and non-toxic product. Over the past few years, new insights in the safety of CAR T-cell therapies have emerged. One particular kind of CAR T-cell therapy (CD19-specific CAR T-cells generated by piggyback-mediated gene transfer) has been associated with new cases of therapy-related cancer. For that reason, the CARAMBA clinical trial has put additional safety mechanisms in place. CARAMBA employs a novel, virus-free gene transfer to modify T-cells and CARAMBA´s CAR T-cells are equipped with a safety switch that enables rapid and complete destruction if desired or indicated. Not only do these safety mechanisms lower the risk of CARAMBA CAR T-cells, they make CAR T-cell and gene therapy as a whole safer for humans. Of note, with 9 patients enrolled in the CARAMBA study, the study appeared safe and no dose-limiting toxicity has been observed so far.

How did COVID influence the CAR T-cell treatment in Europe?

The CARAMBA clinical trial like other clinical trials suffered delays because of the corona pandemic, which has dramatically reduced patient enrolment. The ability to treat and process study patients at the CARAMBA trial sites was limited as the requirement for intensive care unit beds and hospitalization of COVID patients was high and diminished the number of study physicians and study nurses. Furthermore, there were severe impacts on logistics to ensure temperature-controlled transport of the CAR T-cell products as the number of flights from GMP manufacturer to trial sites was drastically reduced, as well as limited availability of laboratory reagents, which made CAR T-cell production an unexpected challenge.

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Patient perspective and expectations

Giving patients a voice, is not only one of the key objectives within CARAMBA, but was also one of the major objectives of the CAR T-cell meeting organizers, especially for the CARAMBA coordinator and meeting chair Prof. Dr. Michael Hudecek. Patient representatives were involved right from the beginning in the planning of the programme and patients were represented in key lectures and podium discussions.

Dr. Solène Clavreul, CARAMBA partner and Head of Medical Education and Scientific Engagement at Myeloma Patients Europe, gave an overview on recent patient experiences and expectations.

In general, the experience with CAR T is very positive as it leads to good treatment responses and significant improve of quality of life. Patients often say they finally feel as good as they were before their myeloma diagnosis. This feedback should be taken cautiously, as patients who relapsed are less likely to share their experience. Patients have shared their need to hear other patients' stories, and efforts should be made to help those who are interested in hearing these stories with those who have already received CAR T-treatment.

They also point out that educational video clips such as physician interviews explaining the mechanisms of the illness and of the treatments, and patient organization websites are very valuable for them and that it is important that the medical team supports patients to find these resources.

"A major field for improvement is the management of patients` emotions; not only with CAR T but also with myeloma and its treatment."

Dr. Solène Clavreul
Head of Medical Education and Scientific Engagement
Myeloma Patients Europe

Regarding adverse events, patients who shared their experience found that the medical team managed the side effects they were experiencing quickly and efficiently, despite their high number. If CRS (Cytokine Release Syndrome) appears to be well managed, there is still some anxiety around ICANS (Immune-Effector-Cell-associated Neurotoxicity-Syndrome). In addition, patients would like to receive more information about complications which can happen after returning home, and in particular how vulnerable to infections they can be.

Patients are concerned about how the selection process for CAR T-treatment is done and ask for more transparency. There are most likely more eligible patients than available slots, and it is unclear how fitness, age, being treated in an excellence centre, play a role in the decision. Patients would like to know how the patient voice is included in these decisions.

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What is the major burden, next to side effects for patients?

A major field for improvement is the management of patients emotions; not only with CAR T but also with myeloma and its treatment. We should not forget that this is a chronic disease. Many patients have been living with myeloma for more than 10 years. Distress, anxiety, fear, overwhelming feelings, despair, worry but also hope and relief can be experienced at various moments of the journey.

There was a lot of anxiety before receiving the CAR T-infusion. At first around inclusion criteria, and also after enrolment in a trial, where patients would be on an emotional roller-coaster until the end, not knowing if their tests would come back good enough to go to the next step, if their disease would progress before the CAR T-cells are ready etc. The waiting time during the manufacturing is a big source of stress and anxiety. Will they make it to the infusion? Will they need bridging therapy? Finally, there is the anxiety and uncertainty around the response to the treatment and if it does not work, what comes next. Patients might need to be empowered and supported to manage all these emotions.

What are the patients' expectations and can we meet them?

There is a lot of attention for CAR T-cell therapy and therefore high expectations from the European patient community. The number of available slots for commercial products is extremely low (e.g. 12 per month in France), which is currently not sufficient to satisfy all myeloma patients' needs. Clinical trials offer more options but not everyone can be enrolled nor is eligible. This leads to frustration, knowing that this great treatment is out of reach, even more in countries where less expensive treatments are still not available. Negative reimbursement decisions at national levels and CAR T-manufacturing issues are aggravating factors.

Are patients as interested in CAR T-treatment as 5 years ago or do they hope for alternative treatments?

There are more and more patients aware about CAR T-cell therapies, even though most of them never discussed it with their doctor (MPE unpublished data). On the other hand, doctors are reluctant to talk about it when they know there is no access. Patients express more and more interest in CAR T-treatment as it gives the promise of long, treatment-free remission time. For patients who have been heavily pre-treated, after many lines of therapies, this is extremely valuable. It makes them feel that they are not sick anymore. Alternative treatments are generally considered only if there is no other choice. Let's not forget that CAR T is, according to current study results, still not a cure. At the very best, patients eventually relapse after 1 or 2 years. A cure is what we should aim for!

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CAR T-manufacturing concept

Increased accessibility of CAR T-cells strongly depends on efficient CAR T-cell manufacturing processes. For that reason, there is some debate on point-of-care CAR T-manufacturing vs. rapid CAR T-manufacturing at a central facility. **Prof. Dr. Halvard Bönig**, head of Department Cellular Therapeutics/Cell Processing at DRK-BSD and leading the manufacturing process in CARAMBA. reflects latest experiences:

"The CARAMBA manufacturing process is ideally suited to support rapid CAR T-cell manufacturing , since it is manufactured without the help of viral vectors."

Prof. Dr. Halvard Bönig
Head of Cellular Therapeutics/Cell processing
DRK-BSD

"Point-of-care CAR T-manufacturing (POCT) is proposed by some as the backbone of future CAR T-activities. The reasons given, lower costs and faster vein-to-vein times, can, however, not convince the discerning observer. Cost analysis of POCT does not account for the costs of the GMP facilities while they stand unused, the costs of registration, pharmacovigilance and ongoing inter-laboratory comparison.

Fresh-in-fresh-out is the preferred approach to POCT, although this invariable requires considerable vacant infrastructure reserves by the local GMP team, and significant compromises, also by the regulators, with regard to quality control, since many currently routinely performed quality assays delay the delivery of CAR T-cell products by approximately 3 weeks. True POCT programmes currently do not exist, although several academic manufacturers produce CAR T-cells in close proximity of their own patients, but transport products to patients in other cities.

Several commercial entities are pushing the development of multi-centric CAR T-cell manufacturing in physical proximity to the patient. Rapid manufacturing, harvesting shortly after transduction and thus skipping the in vitro expansion step, is currently mainly proposed by one commercial manufacturer. The promise to reduce vein-to-vein time from the current 6 weeks to 9 days, i.e. by 33 days, cannot, however, be explained by the shortened manufacturing of 3 vs. previously 12 days. Clearly, the cumulative effect of all other process improvements exceeds by almost three-fold that of process shortening. Rapid manufacturing may result in fitter CAR T-cells. Lower doses are infused, as expansion will occur in vivo and hence likely be more physiological. CAR T-toxicity is expected to be delayed, possibly spread out more, and thereby likely dampened in intensity. Clearly, rapid manufacturing is not compatible with vector copy number enumeration and evaluation of transduction efficiency as it is currently assessed for all CAR T-cell products, since a lot of vector remains non-integrated inside the cell and CAR is expressed off of extranuclear DNA at these early points in time.

Rapid manufacturing will significantly benefit manufacturers, since it increases the number of products that can be manufactured in a given facility and thus reduces costs. The CARAMBA manufacturing process is ideally suited to support rapid CAR T-cell manufacturing, since it is manufactured without the help of viral vectors, whereas other CAR T-cell products still contain relevant quantities of vector which are co-infused with the product and which may be dangerous for the patient."

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Young investigators in CARAMBA and at the CAR T-cell meeting

During the whole project period, all CARAMBA young scientists were strongly encouraged to present their CARAMBA and related CAR T work at the EBMT-EHA CAR T meetings to foster knowledge exchange. Also at this year´s event, several CARAMBA postdocs were present to discuss and exchange CARAMBA and CAR T-therapy results in various poster sessions.

As an example, the molecular mechanisms of CAR T-cell response in Multiple Myeloma were presented by **Dr. Juan R. Rodriguez-Madoz** under the lead of **Dr. Felipe Prosper**, University of Navarra, Pamplona, Spain.

Dr. Juan R. Rodriguez-Madoz
Young investigator
University of Navarra

CAR T-cell therapies, such as the recently approved BCMA CAR T-cell therapy, have revolutionized cancer immunotherapy. However, in a significant number of patients the cancer returns. To understand the reason behind, a team of CARAMBA investigators led by Felipe Prosper has investigated the individual CAR T-cell populations of differently responding patients on the molecular level, giving a first indication which pre-deposition may underlie the response level.

In another poster presentation, the research team highlighted that the myeloma disease stage of patients may affect the efficacy of BCMA CAR T-cell therapy.

Overall, both studies of the CARAMBA partner University of Navarra indicated that the individual CAR T-cell response depends on patient specific factors, which will impact the future design of CAR T-cell products.

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Further poster presentations were given by Prof. Dr. Hudecek´s team members, providing insights into CAR T development beyond CARAMBA.

Lukas Scheller, MD, a young medical researcher at the University Hospital Würzburg is working on deciphering the underlying mechanisms and identifying predictive models for adverse outcomes associated with CAR T-cell therapy.
He presented a case report of treatment options after relapse of BCMA CAR T-therapy: A treatment with chemotherapy, irradiation (DARA-VTD-PACE) and Teclistamab led to complete remission of the disease until today (5 months follow-up). More studies are necessary to investigate this treatment on a larger group of patients.

Lukas Scheller, MD
Resident for Hematology/Oncology, Clinician Scientist
University Hospital Würzburg

A team of researchers led by **Prof. Dr. Maik Luu** has studied the role of microbes in the gut on the efficacy of cancer immunotherapy.
Microbe-generated molecules and metabolites such as short-chain fatty acids (SCFA) may impact the immune system, but how this works is unclear. The team led by Maik Luu has identified the SCFA pentanoate as a metabolite that could enhance the cell-killing capacity of T-cells by generating epigenetic modifications and enhancing metabolic reprogramming of T-cells, which together can improve CAR T-cell function.

Dr. Maik Luu
Tenure Track W1 Professor for Translational Medicine
University Hospital Würzburg

Together, all CARAMBA researchers are highly committed to cultivate the EBMT-EHA CAR T meeting as the European key stakeholder event, transparently presenting and exchanging their latest experiences and results to enhance future CAR T-therapy designs for the benefit of European patients.

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caramba

University Hospital Würzburg
Würzburg, Germany

DRK-Blutspendedienst
Mannheim, Germany

Ospedale San Raffaelo
Milano, Italy

Myeloma Patients Europe
Brussels, Belgium

University of Navarra
Navarra, Spain

T-CURX
Würzburg, Germany

CHU Lille
Lille, France

ARTTIC SAS
Paris, France

Paul-Ehrlich-Institute
Langen, Germany

ARTTIC Innovation GmbH
München, Germany