

Myeloma Pipeline

MYELOMA PATIENTS EUROPE

CARAMBA clinical trial,
a HORIZON 2020
project



Edition: Myeloma Patients Europe (MPE)

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HORIZON 2020 CARAMBA

Myeloma pipeline

Myeloma Patients Europe (MPE) is involved in the CARAMBA project, supported by the European Union (EU) in the Research and Innovation Programme 'Horizon 2020'. The CARAMBA project is investigating an immunotherapy for the treatment of myeloma called Chimeric Antigen Receptor T-cell (CAR-T) therapy.

This publication explains:

- What is 'Horizon2020' and what projects are supported?
- How does CAR-T therapy work and how is it explored in CARAMBA?
- What is the Phase I/II clinical trial that will be run as part of CARAMBA?
- Who are the members of the project consortium and what is their role?
- What is the role of MPE in the project consortium?
- Where can you find further information on CARAMBA and CAR-T therapy?

Horizon 2020

Horizon 2020 is a large-scale European Union Research and Innovation programme over 7 years (2014-2020). It funds a wide range of different projects relating to science, innovation, and tackling societal challenges. To receive funding through the programme, multi-stakeholder consortiums work in partnership to develop a project proposal, which is reviewed by the European Commission. The CARAMBA project was approved by the European Commission and started in January 2018. Over 52 months, the CARAMBA project consortium will distribute the allocated funding to designated consortium members to allow them to carry out their assigned tasks.

The European Commission selected the CARAMBA project from a large number of highly competitive project proposals. The CARAMBA project was approved by the European Commission and started in January 2018. Over 52 months, the CARAMBA project consortium will distribute the allocated funding to designated consortium members to allow them to carry out their assigned tasks.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754658.

The CARAMBA project

The CARAMBA project is investigating an innovative immunotherapy for the treatment of myeloma called Chimeric Antigen Receptor T-cell (CAR-T) therapy.

Ten partners from six EU countries are collaborating in the CARAMBA project consortium. This includes four clinical centres of excellence in myeloma clinical care and research: University Hospital Würzburg (Germany), Ospedale San Raffaele (Italy), Universidad de Navarra (Spain) and the Centre Hospitalier Régional et Universitaire de Lille (France). These are the four sites that will run the CARAMBA clinical trial.

Further project partners include the patient organisation Myeloma Patients Europe (MPE), the GMP manufacturer DRK-Blutspendedienst Baden-Württemberg-Hessen (BSD-BRK), the German Federal Institute for Vaccines and Biomedicines (PEI), the biotech companies NBE-Therapeutics, based in Switzerland, and T-CURX, based in Germany, as well as the French project management provider ARTTIC S.A.S.

Although each of the four clinical trial sites may begin enrolment at different times, the opening of the CARAMBA clinical trial was in August of 2020. Patients enrolled in the study that received SLAMF7 CAR-T cell therapy will undergo short-term follow-up to assess safety and anti-myeloma effect of the treatment, and a long-term follow-up (up to 15 years according to national rules on advanced therapy medicinal products) to assess any potential delayed toxicity of SLAMF7 CAR T-cell and the persisting anti-myeloma effect.

SLAMF7 CAR-T

CARAMBA is studying CAR-T that targets a protein called SLAMF7 which is expressed on the surface of myeloma cells. The safety and efficacy of SLAMF7 specific CAR-T cells will be assessed in myeloma patients through a phase I/IIa clinical trial involving up to 38 eligible myeloma patients.

In preparation for treatment with SLAMF7 CAR-T, the patient's white blood cells, which make up part of the immune system, are collected through a process called leukapheresis. White blood cells consist of various cell types such as T-cells, which play an important role in the body's immune response.

The white blood cells, including the T-cells, are sent to a centralised manufacturing facility in Germany. Here, T-cells are separated to identify

the appropriate 'killer' and 'helper' T-cells which will be utilised for the manufacturing the SLAMF7 CAR-T product. The T-cells are equipped with the "Chimeric Antigen Receptor" (CAR), which instructs the T-cells to recognise the SLAMF7 protein and through this, enable them to seek and destroy myeloma cells in the patient's body. The modified T-cells are amplified (expanded) outside of the patient's body, a process that takes approximately two weeks to complete.

Prior to receiving the SLAMF7 CAR-T cells through an intravenous infusion, the patient will receive a lymphodepleting chemotherapy to reduce the amount of white blood cells in preparation for the CAR-T cell infusion. Once manufacturing has been completed, the SLAMF7 CAR-T cells are 'packaged' into an infusion bag (similar to a blood transfusion), shipped to the trial site with an overnight courier, and infused back into the patient. In the patient's body, the SLAMF7 CAR-T can multiply and seek and destroy the myeloma cells.

Sleeping Beauty method

CARAMBA will be using SLAMF7 CAR-T cells that were created by the *Sleeping Beauty* transposon method, which is an innovative way to genetically reprogram T-cells to express the SLAMF7 CAR. The *Sleeping Beauty* method allows the reprogramming of the SLAMF7 CAR-T cells without the use of a virus. The *Sleeping Beauty* method is a breakthrough technology that makes CAR-T therapy faster, less expensive and safer. In addition to the SLAMF7 CAR, T-cells are also equipped with an "emergency off switch" which can be used in situations where patients experience severe side-effects.



Definition of a Phase I/IIa clinical trial

In a Phase I/IIa trial, researchers investigate the safety (i.e. side-effects) and efficacy (i.e. anti-myeloma effect) and determine the dose of a new treatment.

Phase I/IIa trials usually happen in two parts. The first part (Phase I) involves a small group of patients to assess safety and dose. The second part (Phase

IIa) assesses safety and efficacy of the best tolerated dose in a larger group of patients.

Phase I/IIa clinical trials are early phase, meaning that it may be the first time the specific intervention has been used in patients.

Phase I/II CARAMBA clinical trial

In the CARAMBA phase I/IIa clinical trial, the new intervention is a CAR-T cell treatment focused on a specific protein called SLAMF7.

In phase I, the clinical trial will assess the maximum tolerated dose of SLAMF7 CAR-T. There will be a "dose escalation", where patients receive pre-defined, increasing doses of SLAMF7 CAR-T. Patients will be treated sequentially, and a strict time interval will be observed between two consecutive patients. Each patient will only receive one dose of SLAMF7 CAR-T.

In phase II, the clinical trial is referred to as the "dose-expansion" part of the study. In this part, the maximum tolerated dose identified in phase I will be administered to patients and the anti-myeloma effect will be carefully analysed. Also, in the phase II part, the tolerability and safety of the treatment will be carefully monitored.

Eligibility for CARAMBA

CARAMBA will recruit up to 38 patients with multiple myeloma. The CARAMBA clinical trial will be available at specific sites in Germany, Spain, France and Italy and the logistics of travel to these countries may be difficult for some patients.

To participate in the trial, patients must have received at least two prior lines of treatment, including a proteasome inhibitor (such as bortezomib and carfilzomib), an immunomodulatory agent (such as lenalidomide or pomalidomide) and a monoclonal antibody (such as daratumumab).

Patients must have measurable disease markers of myeloma. Patients who have previously received treatment with elotuzumab, a monoclonal antibody targeting the same protein on the surface of the myeloma cells (SLAMF7), are eligible to take part in the CARAMBA clinical trial.

As CAR-T therapy can be a quite an intensive treatment, particularly given the potential side-effects, patients are also required to have a good performance status which is measured using the Karnofsky Performance Status. Patients must have a Karnofsky Performance Status $\geq 60\%$, implying a greater level of fitness, to participate in the trial. Patients are also expected to have adequate heart and lung, liver and kidney function as assessed by an heart ultrasound, breathing test and bloodwork prior to determining their eligibility for the clinical trial.

Patients who underwent a prior autologous and/or allogeneic stem cell transplantation are eligible for the CARAMBA trial. However, if the allogeneic stem cell transplantation is less than 12 months ago, and/or if patients suffer from Graft-versus-Host disease and are taking medications to suppress their immune system, patients are not eligible. Also, patients with an active infection including HIV, syphilis, hepatitis B and C, or SARS-CoV-2 are not eligible.

There are a number of inclusion and exclusion criteria for the CARAMBA clinical trial. Please speak to your consultant haematologist/doctor to understand your eligibility to participate. Patients may also go to <https://www.caramba-cart.eu> for further information on country specific CARAMBA contacts.

CARAMBA outcomes

In the CARAMBA clinical trial, researchers will be assessing the feasibility of using SLAMF7 CAR-T cells as treatment for myeloma patients. They will also be assessing the number and severity of adverse events (such as cytokine release syndrome and neurotoxicity, two common adverse events after CAR-T therapy).

Researchers will also be looking at how the SLAMF7 CAR-T cells behave over time and how patients' myeloma responds to the treatment.

Also, quality of life will be measured in the CARAMBA clinical trial. This will be done using questionnaires known as the EORTC QLQ-C30 and the EORTC QLQ-MY20. These questionnaires will ask about physical, cognitive, social and emotional well-being during the trial in addition to pain, fatigue and nausea/vomiting symptoms.

CAR-T side-effects

There are many potential side-effects that have been observed in the context of CAR-T therapy and each patient may respond differently to this treatment. The most common side-effects known to be associated with CAR T cell therapy are cytokine release syndrome (CRS) and neurotoxicity. These two side-effects typically appear within two weeks of administration of the CAR-T cell therapy and patients will be monitored closely in the hospital for symptoms.

CRS is a systemic inflammatory condition which appears as a flu-like illness and may include symptoms such as fever, fatigue, nausea, difficulty breathing and/or high heart rate. Neurotoxicity may appear as confusion, lethargy, headache, altered mental state, difficulty speaking and, in rare but severe cases, seizures.

Side-effects may differ for each patient and can be severe with long-term consequences and can even be fatal. The trial sites for the CARAMBA clinical trial have been carefully selected and do have experience in using CAR-T therapy – e.g. CD19 CAR-T therapy to treat leukaemia and lymphoma, and BCMA CAR-T

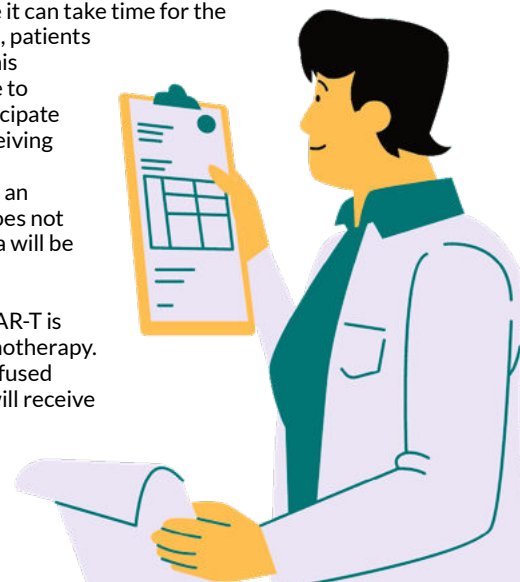
therapy to treat multiple myeloma. The physicians and nurses at each trial site are experienced and have been specifically trained and educated in how to best manage the potential side-effects of CAR-T therapy.

Considerations for patients

Because SLAMF7 CAR-T therapy is a new treatment, and due to the potential severity of side-effects that may occur after CAR-T treatment, patients will require hospitalisation for about three weeks to receive preparation, treatment and close observation. For some patients, hospital stays may be shorter or longer depending on how well they tolerate the treatment. Some patients who experience severe or concerning symptoms may also require intensive care unit admission. Because of the need for close monitoring patients should be aware that frequent hospital and/or office visits, potentially daily visits, will be required after discharge from the hospital, and these visits are very frequent within the first month after treatment (daily), frequent in the first three months (bi-weekly/monthly) and regular in the first two years after treatment (quarterly/semi-annually).

Enrolment in CARAMBA will likely be difficult for patients who do not live in countries with specific trial sites and patients must note that only a small number of patients can participate in phase I/II clinical trials like CARAMBA (up to 38 patients will be enrolled into the CARAMBA study). Patients should also be aware that enrolment in the CARAMBA clinical trial does not guarantee that they will receive treatment with SLAMF7 CAR-T (e.g. if the inclusion and exclusion criteria are not met or if manufacturing of the SLAMF7 CAR-T product fails). Also, because it can take time for the CAR-T cells to be processed, patients may lose eligibility during this time and will then be unable to receive the infusion or participate in the clinical trial. Also, receiving SLAMF7 CAR-T does not guarantee that there will be an anti-myeloma effect, and does not guarantee that the myeloma will be cured.

Treatment with SLAMF7 CAR-T is not completely free of chemotherapy. Prior to the patient being infused with the CAR-T cells, they will receive chemotherapy (also known as lymphodepleting therapy) to reduce the level of white blood cells and help the body accept the CAR-T cells.



Considerations for caregivers

Caregivers should be aware of the possibility of, and seriousness of, the side-effects of CAR-T therapy and when to seek help. Caregivers should also be aware of the potential burden of long hospital stays, frequent office visits, the need for frequent monitoring at home and the possibility that their loved ones may be admitted to the intensive care unit.

More information

Patients may also go to www.caramba-cart.eu for more information. Myeloma Patients Europe has also recorded a video with Prof Dr Michael Hudecek of Universitätsklinikum Würzburg and project coordinator, which can be found here: www.mpeurope.org/what-we-do/projects/european-commission-projects-horizon-2020/caramba/





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MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries and helps inform and raise awareness on a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor. If there is anything that is not clear to you, please always ask your clinical team.



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