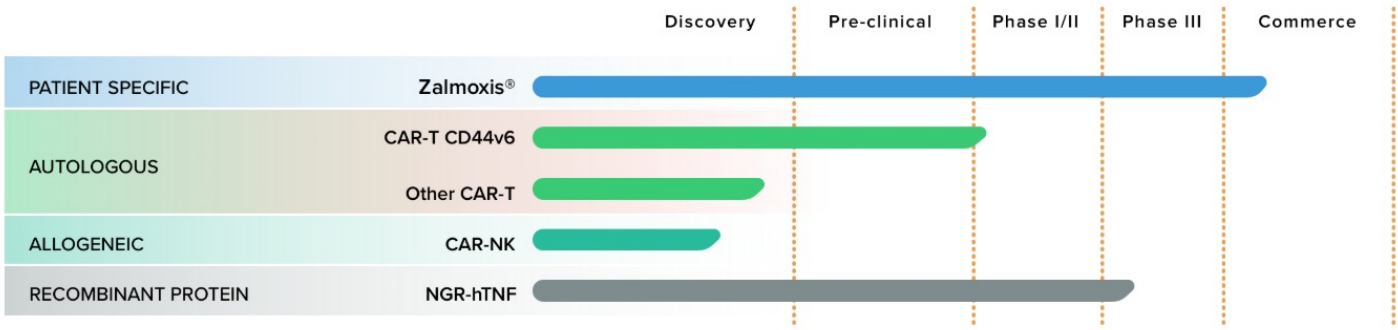
Pipeline

MolMed is a clinical biotech company focused on research, development, manufacturing and clinical validation of innovative therapies in oncology and immuno-oncology



Our proprietary pipeline includes products in clinical and preclinical stage: Zalmoxis® (TK), a cell therapy used in haploidentical transplants authorized for the EU market, the CAR-T CD44v6, targeting both liquid and solid tumors and a new CAR pipeline of autologus and allogeneic products.

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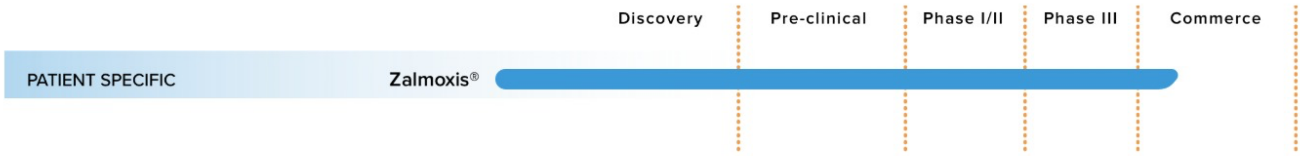
Zalmoxis®

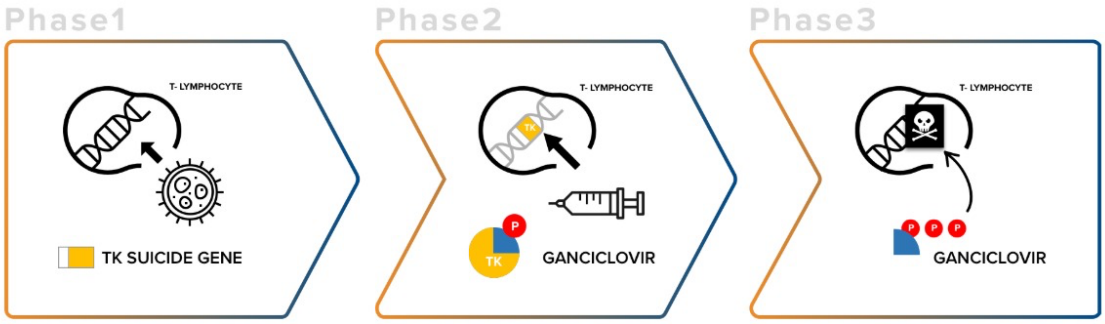
Pipeline



Zalmoxis®

Zalmoxis® is a patient-specific cell therapy based on the engineering of the immune system that, in association with haplo-identical hematopoietic stem cell transplantation, allows the treatment of adult patients with leukemia and other high-risk haematological malignancies.

Chemotherapy is currently the main therapeutic strategy for patients with leukemia. Once subjected to chemotherapy cycles, the patient's hematopoietic and immune system is strongly debilitated. In order to favor its regeneration, we proceed to the transplantation of hematopoietic stem cells from a partially compatible donor. However, the transplant-borne stem cells need time to differentiate into the mature cells of a fully functional immune system. In this window, the patient is defenseless against both infections and possible leukemic relapses.



Editing of the Donor T-lymphocytes

The aplo-identical donor T lymphocytes are genetically modified to integrate the TK suicide gene in the genome

Ganciclovir administration

TK protein promotes the conversion of administered Ganciclovir in the active metabolite GCV-triphosphate

Apoptosis

GCV-triphosphate induces apoptosis in TK expressing cells, limiting the GvHD reaction

In the case of a perfectly compatible donor, the necessary immune defenses are provided by the donor's T lymphocytes. However, in the case in which the compatibility between patient and donor is only partial, the lymphocytes of the latter can not be used because they would involve a very high risk of developing the "graft versus host disease" (Graft versus Host Disease, GvHD), in which the cells transplanted from the donor attack the tissues of the transplanted patient, with often lethal results.

The therapeutic advantage introduced by Zalmoxis ® lies in the shelter of the protective action of the donor's T cells, even if the patient-donor therapy is only partial. Zalmoxis® is based on the use of genetically modified T lymphocytes in which a "suicide gene" (HSV-TK) has been inserted. These cells, once infused in patients undergoing non-compatible donor hematopoietic stem cell transplantation, facilitate the anti-leukemic and anti-viral effect. Furthermore, reimbursement to post-transplant immunosuppressive prophylaxis is no longer necessary and immunological reconstitution is faster. The insertion of the suicide gene allows to control the appearance of the first symptoms, because the lymphocytes in the rejection reactions can be selectively eliminated thanks to the administration of ganciclovir, a common antiviral drug that in combination with the suicide gene induces the death of the cells involved in the GvHD.

Thanks to this mechanism, Zalmoxis® therapy significantly increases long-term patient survival, making haplo-identical transplant safer and more effective, regardless of conditions at the time of transplantation.

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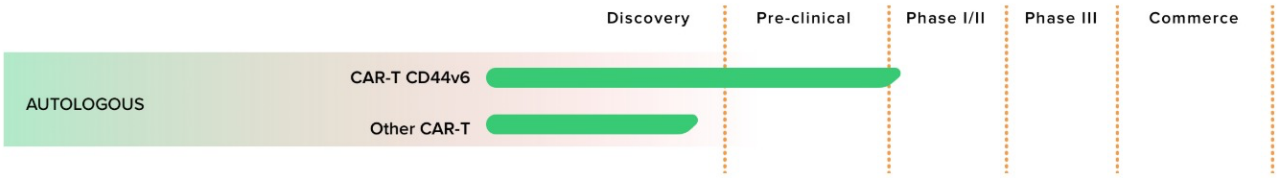
CAR-T CD44v6 and other CAR-Ts

Pipeline



CAR-T CD44v6

Chimeric receptors for the antigen (CAR), today represent a relevant therapeutic strategy in oncology and consist in the engineering of T lymphocytes with receptors directed against specific tumor antigens. The goal is to obtain T lymphocytes with the ability to selectively eliminate tumors, without attacking the patient's healthy tissues.

CAR CD44v6 has a wide therapeutic potential as it is based on the recognition of variant 6 (v6) of the CD44 antigen (CD44v6) which is expressed by many haematological neoplasms (acute myeloid leukemia, multiple myeloma) and by numerous solid tumors of epithelial origin. (breast, lung, colon, pancreas, and head / neck).

The therapy with CAR-T CD44v6, involves isolating the patient&'s T cells and modifying them ex vivo with a viral vector. T cells are engineered to express the CAR and the HSV-TK suicide gene already used in Zalmoxis®. Thanks to the presence of CAR the lymphocytes recognize and kill the tumor cells, while the suicide gene allows to eliminate the T lymphocytes in case of toxic reaction against the patient's healthy tissues.

Once engineered, T cells expressing CAR are expanded in vitro until the required therapeutic dose is obtained and then infused into the patient. Before receiving the new cells, the patient undergoes a lymph-depleting chemotherapy, ie treatment with drugs that eliminate part of his T lymphocytes. This therapy favors the engraftment and permanence in the circulation of the T lymphocytes modified to express the CAR.

MolMed is also the coordinator of the EURE-CART project (EURopean Endeavor for Chimeric Antigen Receptor Therapies) which has obtained a European funding of 5,903,146 euros, as part of Horizon; aimed at demonstrating the safety and efficacy of immunotherapy based on CART-CD44v6 lymphocytes in acute myeloid leukemia and multiple myeloma.

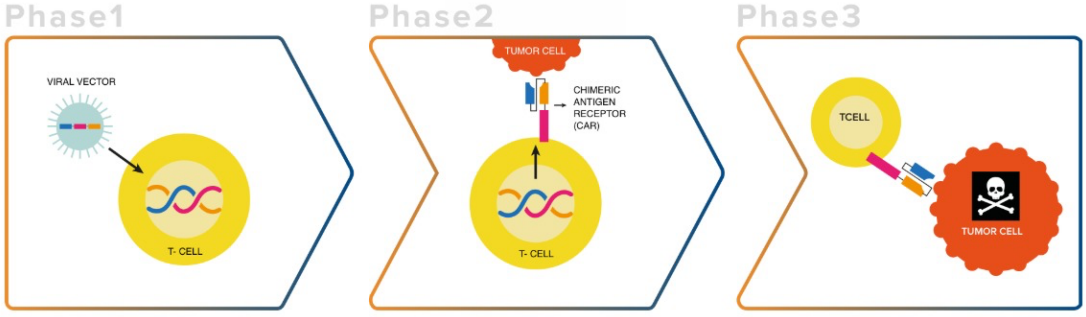
Altri CAR-T

Thanks to the experience gained in the development of autologous CD44v6 CAR-T, MolMed is developing autologous CAR-T products against different antigens selectively expressed by tumor cells.

The identification of the new tumor targets was based on a multidisciplinary approach coordinated by the members of the Scientific Advisory Board, in order to be potentially effective against a large number of neoplasms, both haematological and solid.

For the development of these products, MolMed will draw on one side of the experience acquired with the work done on the other proprietary products, on the other side MolMed has signed a Master Agreement with AbCheck sro, a subsidiary of Affimed GmbH and a European leader in identification and screening of antibodies.

On the basis of the agreement, AbCheck will use its proprietary platform for the research, selection, optimization and production of several human single-chain variable fragments (scFvs), able to specifically recognize each potential target chosen by MolMed. The scFvs are the portion of the CAR molecule dedicated to the specific recognition of the antigen expressed by the tumor cell.



Patient's T cells engineering

Patient's T Lymphocytes isolated from leukapheresis are engineered using viral vectors that insert the CAR sequence in the cell genome

CAR recognize the tumor antigen

CAR-T cells recognize the tumor cells that express the specific antigen. The ligand-receptor binding mediates the activation of the T Lymphocyte

Selective killing

Activated CAR-T lymphocyte has cytotoxic effect that induce selective killing of recognized tumoral cell

New Platform CAR-NK

Pipeline

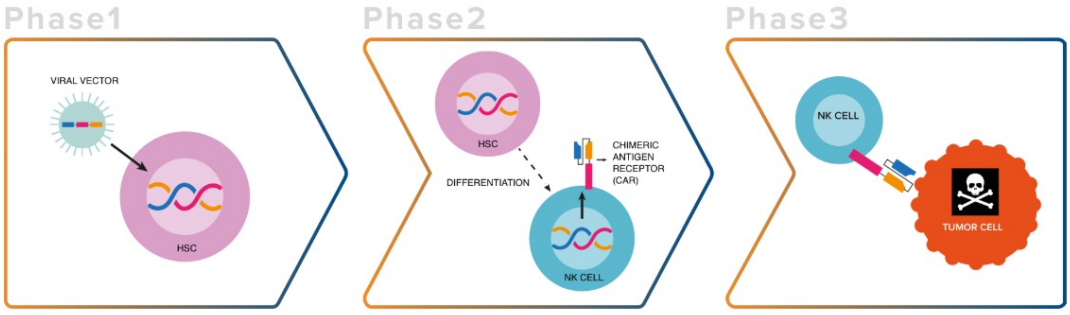
	Discovery	Pre-clinical	Phase I/II	Phase III	Commerce
ALLOGENEIC CAR-NK					

New Platform CAR-NK

In addition to autologous CAR-T products, MolMed is carrying out in parallel the development of a new platform based on NK cells (Natural Killer) genetically modified with lentiviral vectors, in order to obtain CAR-NK allogeneic products.

Genetically modified NK cells are today considered one of the most interesting and innovative candidates of pre-clinical research in cellular immunotherapy. These cells belong to the innate immune system and are able to mediate the anti-tumor effect without the risk of developing the transplantation disease against the host (GvHD). NK cells are therefore suitable for allogeneic therapy, allowing to treat a large number of individuals affected by cancer starting from a single lot resulting from a healthy donor. This allows to overcome the limits related to personalized autologous therapies, with significant benefits both from a technical and economic point of view.

MolMed has finalized an agreement with Glycostem Therapeutics, a Dutch company that uses a proprietary process of differentiation of CD34 + stem cells into NK cells. Glycostem and MolMed will collaborate synergistically in the development and production of new products made up of CAR-NK cells to recognize different tumor antigens.



Donor's HSC engineering

HSC (CD34+) from an healthy donor are engineered using viral vectors that insert the CAR sequence in the cell genome

NK Differentiation

The CAR-HSCs differentiate in NK cells, resulting in a population of CAR-NKs that can be used for multiple patients

Tumor recognition and killing

The CAR-NK infused in the patient selectively recognize the tumor cells expressing the antigen and mediate the killing

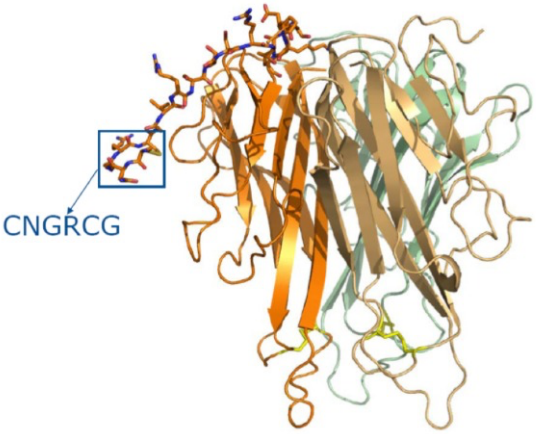
NGR-hTNF

Pipeline

NGR-hTNF

NGR-hTNF is a therapeutic agent that acts selectively on tumor blood vessels. It is a recombinant protein formed by combining the antitumor cytokine hTNF (Tumor Necrosis Factor) with a peptide (NGR) that binds a particular CD13 receptor complex located exclusively on the surface of endothelial cells that form the walls of tumor blood vessels. NGR-hTNF can be used in combination with other chemotherapy regimens, allowing them to be more effectively conveyed and enhanced.

For malignant mesothelioma and liver carcinoma, NGR-hTNF has received an orphan drug designation in both the United States and the European Union.



Crystal structure of an NGR-hTNF monomer. NGR-hTNF is a recombinant protein, genetically engineered by coupling the N-terminus of human TNF-α with the peptide Cys-Asn-Gly-Arg-Cys-Gly (CNGRCG). This peptide contains the NGR motif that is a ligand of CD13 antigen and targets the binding to tumor vessels. In parallel, the TNF peptide mediates tumoral toxicities.

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