



an integrated
strategy
to cure cancer



PRODUCT

Cell-based therapy enabling transplant of stem cells derived from the bone marrow of partially compatible donors, without T cell depletion or immune-suppression

TK has Orphan Drug status in the European Union and in the US

CONCEPT

Donor T cells genetically engineered to keep their anti-infective and anti-leukaemia effects, while allowing control of GvHD

INDICATION

High-risk acute leukaemias (AML and ALL)

In perspective, might be applied to other haematological malignancies

CLINICAL STATUS

- Phase III in Italy
- Phase I in Japan (by partner Takara Bio Inc.)

MARKET

TK enables safe and effective bone marrow transplant for all patients who do not have a fully compatible donor (approximately 50% of candidates)

PARTNERSHIP

Co-development and out-licensing agreement with Takara Bio Inc. (Japan) for the Asian market

TK

A cell-based therapy opening the door of bone marrow transplant to all patients

PRODUCT PROFILE

TK is an *ex vivo* cell therapy, enabling safe haematopoietic stem cell transplant (HSCT) from partially compatible bone marrow donors, for the treatment of haematological malignancies and particularly high-risk acute leukaemias. Following HSCT, TK promotes early and sustained reconstitution of the immune system, thereby reducing transplant-related mortality, and allows to keep the anti-leukaemia activity of the graft, thus preventing disease relapse and increasing patients' overall survival and quality of life.

The production of the clinical-grade cell product is achieved by a standard, reproducible process in a dedicated GMP facility.

BACKGROUND

The best treatment currently available for leukaemias and other haematological malignancies is the transplant of haematopoietic stem cells derived from the bone marrow of healthy donors, but fully compatible donors are available only for 50% of patients, whereas partially compatible transplants are hampered by severe drawbacks - the major of which is graft versus host disease (GvHD), a systemic immune reaction mediated by donor T cells against the recipient's organs and tissues.

The standard way to prevent GvHD is total or partial donor T cell depletion, and administration of immunosuppressive drugs before and after the transplant. But donor T cells are very important in promoting engraftment and fostering the patient's immune-reconstitution, thus preventing opportunistic infections. Also, donor T cells significantly contribute to the direct anti-tumour activity of the graft.

CONCEPT

TK represents a therapeutic strategy to overcome the limitations of haploidentical transplantation and to broaden its applications, because TK allows to keep the therapeutic properties (GvI and GvL) of donor T cells, while controlling GvHD at the same time.

TK is based on the genetic engineering of donor T cells to express a gene (HSV-TK) which makes these cells sensitive to the antiviral drug ganciclovir: this represents a selective elimination system, allowing to kill donor T cells involved in a GvHD through administration of the drug.

TK - A cell-based therapy opening the door of bone marrow transplant to all patients

The major advantages of TK therapy are:

- Feasibility of HSCT for all potential candidates to the cure
- Dramatic reduction of transplant-related mortality, and promotion of stem cell engraftment
- Preservation of the anti-tumour activity of the graft
- Improvement of patient survival and quality of life

CLINICAL DEVELOPMENT

Phase III trial TK008

A Phase III randomised trial in adult high-risk leukaemia patients undergoing haplo-transplant started in Italy in Spring 2008. In 2009, the Italian Drug Agency (AIFA) approved an amendment to the clinical protocol of trial TK008, involving a new randomisation ratio. Expansion of trial TK008 with the amended protocol to other clinical centres in Europe is underway, and will be implemented by the end of 2010. The Phase III trial TK008 is pivotal for the registration of TK therapy, that could become among the very first cell therapies using genetically engineered cells to obtain market approval.

Clearance to Phase III was allowed by the very positive outcome of a Phase I/II trial of TK (TK007). An important acknowledgement from the international scientific community of the scientific and therapeutic value of the TK therapy approach comes from the publication in the prestigious medical journal *The Lancet Oncology* of an article on the results of trial TK007 (*Lancet Oncol.* 2009 May;10(5):489-500). Long-term follow-up data of trial TK007 were presented at ASCO 2010 (*J Clin Oncol* 28: 7s, 2010- suppl.; abst. 6534).

Phase I trials in Japan (by partner Takara Bio Inc.)

MolMed's partner for the Asian markets, Takara Bio Inc., started two Phase I trials of TK in Japan. Both trials are conducted at the National Cancer Centre in Tokyo, for relapsed leukaemia patients receiving a transplant from fully compatible donors (allo-transplant) or from partially compatible donors (haplo-transplant).

MARKET

At present, TK is the only investigational therapy addressing the issue of enabling safe and effective haplo-transplants in adult recipients without immune-suppression or immune-depletion, thus fully preserving the immune protection and anti-leukaemia activity provided by donor T cells, and thereby opening the door of bone marrow transplant to all patients.

In the Western world (Europe and North America), incidence of all high risk leukaemias is represented by a total number of 40.000 patients. Of these, 50% (i.e. 20.000 per year) could have prompt access to a stem cell transplant thanks to safe and effective haplo-transplant, as enabled by TK.

ORPHAN DRUG STATUS

TK was granted Orphan Drug designation:

- In the European Union in October 2003, with the indication: "Adjunctive therapy to haematological cell transplantation" (Reference codes: EMEA/OD/041/03; EU/3/03/168)
- In the United States in January 2005, with the indication: "Immunotherapy for acceleration of T cells reconstitution in patients undergoing allogeneic haematopoietic stem cell transplantation" (Reference code: 04-1923)

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