Advances in Haploidentical Stem Cell Transplantation and Post Transplant Immunotherapy

Chair:
Prof. Hermann Einsele
(Julius-Maximilians University Hospital Würzburg, Germany)
Kiadis Pharma company profile

Kiadis Pharma is a clinical stage biopharmaceutical company focused on research, development and future commercialisation of innovative cell-based immunotherapy products that provide for a safer and more efficacious treatment of hematologic malignancies and inherited blood disorders, improving survival and quality of life and addressing significant unmet medical needs.

The Company believes that its products address current risks and limitations of allogeneic hematopoietic stem cell transplantation (HSCT). HSCT is considered to be the most effective curative approach to some hematologic malignancies and certain inherited blood disorders and Kiadis Pharma expects that HSCT will become a treatment option for many more patients by addressing its current risks and limitations.

ATIR™ (Allodepleted T-cell ImmunotheRapeutic) is an innovative cell-based therapeutic (Donor Lymphocyte Infusion - DLI) that addresses the key risks and limitations of current HSCT treatments in some hematologic malignancies, such as Acute Leukemias and Myelodysplastic Syndromes, and in inherited blood disorders. These key risks and limitations are opportunistic infections, graft-versus-host-disease (GVHD), hematologic malignancy relapse and limited donor availability. Using Kiadis Pharma’s Theralux platform, donor lymphocytes are depleted ex-vivo of alloreactive cells, associated with GVHD, whereas the full immune repertoire of donor immune cells, including immunological memory, is retained in the final product to fight opportunistic infections and bridge the time until the immune system has fully re-grown from the stem cells in the transplanted graft. ATIR101 also contains T-cells from the donor associated with the Graft versus Leukemia effect (GVL) that could mitigate the risk of relapse. ATIR™ is manufactured for each individual patient from a healthy, haploidentical family member’s donation and has the potential to make curative HSCT a viable option to many more patients who do not find a matched unrelated donor or a matched sibling donor.
### Program

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Prof. Arnon Nagler, MD, MSc, is Professor of Medicine at the Tel Aviv University, Israel, and visiting Professor at the Pierre and Marie Curie University, Paris, France. Prof. Nagler is Chair of the Acute Leukemia Working Party (ALWP) of the European Society of Bone Marrow Transplantation (EBMT), and co-Chair of the Scientific Council. He is Director of the Division of Hematology, Chaim Sheba Medical Center, Israel, Director of Bone Marrow transplantation and Cord Blood Bank, Chaim Sheba Medical Center, Israel. He also serves on the Board of Directors of Netcord organization of cord blood banks. Prof. Nagler has received several awards including the best scientific abstract award of the ASBMT/CIBMR Tandem meeting (2004) and the best clinical abstract award of the NMDP Council Meeting (2004).

Prof. Hermann Einsele, MD, is Professor of Internal Medicine and Director of the Department of Internal Medicine of the Julius Maximilian University, Würzburg, Germany. He is a Visiting Professor at the Fred-Hutchinson-Cancer-Research-Center in Seattle, USA and the City of Hope Hospital, Duarte, USA.

Prof. Einsele received the van Bekkum Award, the highest annual European award for research in the field of stem cell transplantation and was the 2012 Nobel Lecturer on Stem Cell Biology/Transplantation at the Nobel Forum, Karolinska Institute (Sweden). He has published > 350 articles in peer-reviewed journals. His research interests include stem cell transplantation and adoptive immunotherapy.

Prof. Arnon Nagler

Prof. Hermann Einsele

Dr. Leo Luznik is physician-scientist with expertise in transplant immunobiology, human tumor immunology and clinical management of patients undergoing allogeneic bone marrow transplantation. Currently, he serves as Attending Physician at Johns Hopkins Hospital and an Associate Professor of Oncology and Faculty member of the Graduate Program in Immunology and Pathobiology at Johns Hopkins University.

Dr. Luznik received his MD from the University of Zagreb School of Medicine, followed by training in Molecular Biology at the UCSD, Internal Medicine Residency at the University of Arizona and Fellowship in Medical Oncology and Hematology at the Johns Hopkins University.

Dr. Luznik’s research focuses on understanding basic mechanisms of allogeneic immune response with the overarching goal of improving the clinical application of allogeneic hematopoietic cell transplantation. An exciting outcome of this work has been the clinical development of post-transplantation Cy (PTCy) as GVHD prophylaxis in the human leukocyte antigen (HLA)-matched and HLA-mismatched (haploidentical) settings and the discovery that regulatory T cell resistance to Cy through expression of aldehyde...
Prof. Stephan Mielke

Professor at the Medical Faculty of the University of Würzburg (Germany), Prof. Mielke M.D. is director of the Adult Allogeneic Stem Cell Transplant Program, Chief Attending and Deputy Director of the Dept. of Int. Medicine II, Chief of the Interdisciplinary Outpatient Cancer Center (IOT), Chief of the Laboratory for Translational Tumor & Transplant Immunology of the Department of Internal Medicine II at the University Medical School of Würzburg.

Dr Mielke will soon be joining the Karolinska Institute in Stockholm (Sweden) as Professor of Hematology and Cell Therapy at the Department of Laboratory Medicine and the Department of Medicine, Huddinge as well as the Karolinska University Hospital as Head of the Center of Allogeneic Stem Cell Transplantation (CAST) and Director of Research & Development, Education and Innovation of the Cancer Center (Theme Cancer). Prof. Mielke has a strong research interest in tumor immunotherapy, and focuses on allogeneic hematopoietic stem cell transplantation from matched and mismatched donors.

Prof. Mielke has been serving as a principal investigator on several clinical trials investigating the role of advanced cellular therapy particularly in the field of haploidentical transplantation.

Prof. Denis-Claude Roy

Professor of Medicine at the University of Montreal, Québec, Canada, Denis Claude Roy is CEO of CellCAN, the Canadian Regenerative Medicine and Cell Therapy Network, and Director of Research at the CIUSSS-East-of-Montreal. He is Scientific Director of the Center of Excellence in Cell Therapy at the Hospital Maisonneuve-Rosemont in Montreal, He was trained in oncology-hematology at the Dana Farber Cancer Institute in Boston, USA.

Prof. Roy main domain of research is Immunobiology of leukemia and lymphoma, Graft engineering for stem cell transplantation and selective removal of alloreactive T-lymphocytes and Graft versus tumor reaction.

Prof Roy is a Principal Investigator in the multi-institutional Phase II clinical trial conducted in Europe and North America to assess the efficacy and tolerability of ATIR101, a Donor Lymphocyte Infusion investigational product enriched in T-cells and depleted ex-vivo of alloreactive cells via a Photodynamic process, for use as adjuvant therapy to haploidentical transplantation in acute leukemia patients.
Update on Haploidentical hematopoietic stem cell transplantation in Acute Leukemia:  
A report from the Acute Leukemia Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT)  

Prof. Arnon Nagler (Chaim Sheba Medical Center, Tel-Hashomer Israel)

Allogeneic stem cell transplantation (allo-SCT) represents the only possible cure for adult patients (pts) with high risk acute leukemia (AL). Haploidentical hematopoietic stem cell transplantation (Haplo-SCT) is being increasingly used as an alternative mode of transplantation in pts with intermediate and high risk Acute Leukemia with no HLA-matched sibling or 10/10 unrelated donor. The numbers of Haplo-SCT in Europe are constantly increasing with steep rising in recent years reaching 2,012 in 2015, a 291% increase since 2005 (Passweg J, BMT, 2017, in press). The growth of Haplo-SCT is seen more in pts with myeloid malignancies and mainly in AML. Notably, the increase is not only in pts with advanced disease but impressively similar increase is observed in pts with AML in CR1. We could not observed significant difference between outcome of Haplo-SCT in comparison to allo-SCT from 9/10 mismatch unrelated donor for pts with AML (Piemontese S, J Hematol Oncol, 2017;10:24; Versluis J, Blood Advances, in press, 2017).

Although results of T cell-depleted Haplo-SCT are improving (>2012) and T cell-depleted Haplo-SCT serve as an attractive platform for Treg/Tcon or other modes of post transplantation adoptive cellular immunotherapies, currently most of the Haplo-SCTs in Europe are performed with the T replete approach with either anti-thymocyteglobulin (ATG) or post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis (Piemontese S , Leukemia. 2015 ,29:1069-75). However, many questions are still open and most of the reports of Haplo-SCTs are from single centers and with rather short follow up in limited number of patients. We at the ALWP of the EBMT took advantage of our big registry data and performed several retrospective registry studies in last few years trying to address these open issues in the field. Specifically, we compared T replete Haplo-SCTs to Cord Blood Transplantation (CBT) addressing the topic of alternative donor transplants (Ruggeri A, Leukemia. 2015, 29:1891-900). Separate comparison was performed to Autologous transplantations (Gorin C, Haematologica,2015,100:558-564) and to transplantation from HLA matched siblings focusing on the question whether the broad HLA disparity involved in Haplo-SCT will result in stronger graft versus leukemia effect (GVL) (Ringden O, Leukemia 2016;30:447-55).


Finally, we assessed the impact of HLA disparities on the unshared haplotype (UH) and reported that HLA mismatches on the UH do not appear prominent for haplo-donor selection, however the GvHD prophylaxis modulates the influence of HLA mismatches on the UH on the outcomes after T-cell repleted Haplo-SCT (EBMT 2017). The results of the various studies will be discussed.
NOTES
Update on Post Haploidentical Transplant immune intervention with High dose Cyclophosphamid

Dr. Leo Luznik (Johns Hopkins University School of Medicine, Baltimore, USA)

We have developed the use of high-dose post-transplantation cyclophosphamide (PTCy) to selectively remove alloreactive T cells without compromising engraftment or the graft versus tumor effect. This strategy has allowed for successful transplantation of HLA-haploidentical (haplo) grafts, thus expanding the donor pool for the many patients who would not otherwise be a candidate for this life-saving procedure. Goals of the presentations are:

i) to describe novel insights into the mechanisms behind the activity of PTCy in preventing GVHD;

ii) discuss recent data on the immune reconstitution after the HLA-mismatched allografting using this strategy and iii) summarize clinical insights on the relapse after haploBMT with PTCy.

References:
T-cell immunotherapy and Haploidentical stem cell Transplantation: state-of-the-art and beyond.

Prof. Stephan Mielke (Würzburg University Medical Center, Germany)

The principle feasibility of mismatched/haploidentical stem cell transplantation has been proven in both mice and man almost two decades ago. The technical backbone of this groundbreaking procedure was a profound in vivo and in vitro T cell depletion allowing mismatched stem cells to escape rejection. Later the unique role of mismatched NK cells supporting the engraftment process was discovered. Unfortunately, the patients faced a tremendous risk of infectious complications and relapse reflecting delayed immune reconstitution. Since these early days both the process and the outcome after haploidentical stem cell transplantation have improved significantly. Nowadays improved stem cell selection or T cell depletion techniques such as magnet-based alpha-beta-depletion provide speed-up immune reconstitution beyond early NK cell recovery. Selective depletion techniques such as photodepletion offer accelerated and improved immune reconstitution protecting patients both from infection and relapse. These techniques act as immunotherapeutic platforms facilitating engraftment and basic immune reconstitution in an immunosuppression-free environment providing the ground for additional adoptive transfer of virus- and tumor-specific T cells, vaccination or use of immunomodulatory drugs thereby further improving the patients' overall outcome in the absence of clinically significant GvHD. In contrast, T-replete mismatched transplant strategies such as the post-cyclophosphamide approach have managed to overcome infectious complications. Nevertheless this approach still harbors respectable risks for both relapse and GvHD. Consequently, current clinical research focusses on comparative trials between T-replete and T-deplete transplant strategies in haploidentical transplantation such as the newly introduced HATCY study randomizing between photodepletion with ATIR101 and post-transplant cyclophosphamide.
Haploidentical-transplantation: how to conserve the GvL without GvHD and improve immune recovery: ATIR101

Prof. Denis-Claude Roy (Hôpital Maisonneuve-Rosemont, Montreal, Canada)

Haplo-identical stem cell transplantation can now be performed using a variety of approaches. Patients undergoing such transplants nevertheless frequently encounter infectious complications and disease relapse. This is primarily attributable to delayed immune reconstitution. However, the administration of untreated donor cells post-transplant causes lethal graft-versus-host disease (GVHD). Selective photodepletion (SPD) of alloreactive T cells present in the donor cell graft represents an appealing approach to eliminate GVHD-causing cells. Importantly, this SPD strategy preserves T cells with the ability to respond to infectious agents and leukemia cells. The T cell product photodepleted of anti-host reactive cells has been termed “ATIR”. A phase I dose-ranging study has confirmed the ability of ATIR to generate anti-infection activity and low relapse rates, suggesting promotion of the graft-versus-leukemia (GVL) effect. The most favorable results observed in a very high-risk patient category transplanted in this Phase I study have been confirmed in a Phase II clinical trial of 23 patients treated at a single ATIR cell dose of 2 million CD3+ cells/kg. In both studies, no patients encountered severe (Grade III-IV) GVHD although no GVHD immunoprophylaxis was given to any patient. These exciting results confirm the clinical potential of this novel immunotherapeutic strategy and prompted the development of a Phase III clinical trial. Laboratory and clinical results of these studies will be presented.