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STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

Industry's Giant Leap Into Cellular Therapy: Catalyzing Chimeric Antigen Receptor T Cell (CAR-T) Immunotherapy

Stacie Ittershagen[1] · Solveig Ericson[1] · Lamis Eldjerou[1] · Ali Shojaee[1] · Eric Bleickardt[1] · Manisha Patel[1] · Tetiana Taran[1] · Oezlem Anak[2] · Charlene Hall[1] · Mimi Leung[1] · Deborah Roccoberton[1] · Florence Salmon[2] · Miriam Fuchs[2] · Vadim Romanov[1] · David Lebwohl[1]

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Abstract

Purpose of Review We describe the significant technological leap from bench to bedside that was achieved through a strong academic-industry collaboration between dedicated clinicians and researchers at the University of Pennsylvania, the Children's Hospital of Philadelphia, and Novartis to commercialize the chimeric antigen receptor T cell (CAR-T) therapy tisagenlecleucel (CTL019; Kymriah®; Novartis Pharma AG, Basel, Switzerland).

Recent Findings Tisagenlecleucel was the first CAR-T therapy and the first gene therapy to receive US Food and Drug Administration approval in 2017, with an initial indication for pediatric and young adult patients with relapsed or refractory (r/r) acute lymphoblastic leukemia, followed by approval in May 2018 for a second indication in adult patients with r/r diffuse large B cell lymphoma. Subsequent approvals in the European Union, Switzerland, and Canada soon followed.

Summary The tisagenlecleucel success story represents the development and commercialization of a first-of-its-kind personalized cellular therapy with a manufacturing process that supports commercial production and ongoing global clinical trials in a growing number of countries.

Keywords Acute lymphoblastic leukemia (ALL) · Chimeric antigen receptor (CAR) · Chimeric antigen receptor T cell (CAR-T) · Chronic lymphoblastic leukemia (CLL) · Tisagenlecleucel · Diffuse large B cell lymphoma (DLBCL)

Introduction

Since August 2012, the Novartis chimeric antigen receptor T cell (CAR-T) therapy team has encountered many challenges during its development of the first-in-class, practice-changing, CAR-T therapy, Kymriah® (tisagenlecleucel, Novartis Pharma AG, Basel, Switzerland) The development of this innovative treatment required an entirely new approach for the integration of clinical development along with pioneering a revolutionary manufacturing process that ensured chain-of-identity (COId) for patient material while establishing the logistics of maintaining a global supply chain. For the CAR-T therapy team, many steps along the journey were fraught with uncertainty and risk, with the added pressure of converting an academic laboratory process into a scalable, good manufacturing process that was to provide a therapy for certain cancer patients who had few, if any, other treatment options available. The technical highlights and milestones of this giant leap into cellular therapy are presented here both as a historical account and as an example of academic-industry collaboration at the highest level.

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✉ Stacie Ittershagen
stacie.ittershagen@novartis.com

[1] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

[2] Novartis Pharma AG, Basel, Switzerland

CAR-T Technology

CAR-T technology is a new class of immunocellular therapy in which a patient's own T cells are genetically reprogrammed to target malignant cells in a type of "seek and destroy mission." To accomplish this task, the patient's white blood cells

are collected via leukapheresis at a local, Kymriah-certified (certification via specialized training in logistics and safety) leukapheresis center, cryopreserved, and shipped to a cell manufacturing facility. At the manufacturing facility, the patient's T cells are purified, activated, transduced with a vector to express the chimeric antigen receptor (CAR) and then expanded in vitro, cryopreserved, and shipped back to the treatment center as a single-dose suspension of CAR-positive viable T cells [1]. The manufacturing process is designed to generate a highly concentrated T cell population. Full product, quality-release testing is completed prior to release of the product. CAR-T manufacturing is done in line with current Good Manufacturing Practice. Throughout the process, a precise and reliable COId and chain of custody procedure ensures that the patient's reprogrammed T cells are tracked all along to guarantee the cells are received by the same patient from whom they were originally collected.

In most cancers, specific cell-surface antigens that can serve for targeted anti-cancer therapy are not well defined. However, CD19 is an attractive target for the treatment of B cell malignancies, as CD19 expression is restricted to normal B cells and their precursors and to malignant B cells but not expressed on pluripotent bone marrow stem cells or other tissues. Therefore, CD19-expressing B cell malignancies were the logical clinical path forward to develop CAR-T therapy, known as CART19 (referred to herein as tisagenlecleucel), at the University of Pennsylvania (Penn).

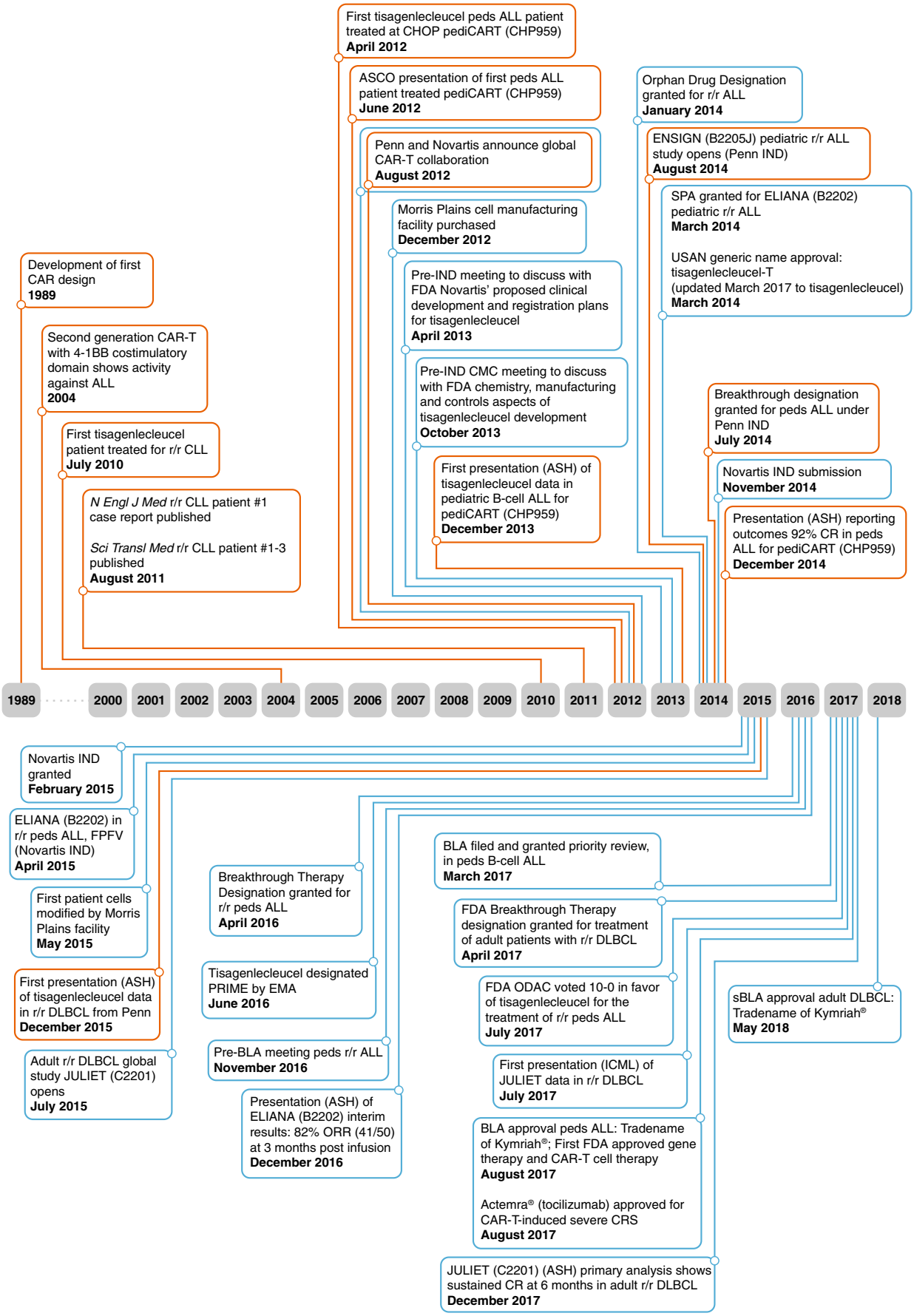
First-of-Its-Kind Academic and Industry Collaboration

CAR-T cell technology is a logistically challenging process that was decades in the making. The success story of tisagenlecleucel began with the work of Dr. Carl H. June and his colleagues at Penn. Over several decades, his team's research resulted in a pilot trial of a second-generation CD19-targeted CAR, containing 4-1BB and CD3-zeta costimulatory domains (CART19, tisagenlecleucel) in patients with relapsed or refractory B cell malignancies, such as chronic lymphoblastic leukemia (CLL) [2, 3] (Fig. 1). The first CART19 study enrolled 3 heavily pretreated CLL patients who had few if any further therapeutic options to consider. Dr. David Porter treated the first patient, a 65-year-old man, who achieved a complete remission at day 23 postinfusion of his CAR-T cells, and this result was published as a case report in *The New England Journal of Medicine* in 2011 [2]. Soon after that publication, a second report that detailed the outcomes of the first 3 patients enrolled in the Penn study was published in *Science Translational Medicine* (NCT01029366, [3]). The CAR-T cells rapidly expanded 1000 to 10,000-fold in vivo during the first month and 2 of the 3 patients experienced rapid and complete remission during the first 6 months [2, 3]. Because

Fig. 1 Kymriah (tisagenlecleucel) clinical development to FDA approval milestones. Orange boxes represent University of Pennsylvania milestones. Blue outlined boxes represent Novartis milestones. Abbreviations: ALL acute lymphoblastic leukemia; ASCO American Society of Clinical Oncology; ASH American Society of Hematology; CAR-T chimeric antigen receptor T cell; CLL chronic lymphocytic leukemia; CMC chemistry, manufacturing, and controls; CHOP Children's Hospital of Philadelphia; CR complete remission; CRS cytokine release syndrome; DLBCL diffuse large B-cell lymphoma; EMA European Medicines Agency; FPFV first patient first visit; ICER Institute for Clinical and Economic Review; ICML International Conference on Malignant Lymphoma; IND investigational new drug; ODAC Oncologic Drugs Advisory Committee; ORR overall remission rate; peds pediatric; PRIME priority medicines; r/r relapsed or refractory; sBLA supplemental biologics licensing application; SPA special protocol assessment; Penn University of Pennsylvania; USAN United States Adopted Names Council; US FDA United States Food and Drug Administration

of the impressive, sustained, complete remission achieved in those 2 patients treated with tisagenlecleucel, the promise of this therapy became tangible (as of the writing of this article, both patients remain in remission more than 8 years later). After the initial success with these CAR-T cells, Dr. June and colleagues at Penn had to determine if this product could be manufactured on a commercial scale. The team addressed significant logistical challenges, including the move from a single treatment site to multiple sites within the USA, and ultimately to global treatment sites. In addition, sufficient central manufacturing capabilities were needed to provide CAR-T cells for the initial clinical trials needed to generate data to support a filing for approval of tisagenlecleucel and in anticipation of the global supply chain needed to subsequently treat thousands of patients across the globe with CD19-positive malignancies. In parallel to the discussions that were ongoing at Penn about the future of CAR-T cell therapy, the first 2 Penn publications in August of 2011 [2, 3] caught the attention of many pharmaceutical and biotech companies, including Novartis Business Licensing and Development.

Early in the negotiations with Penn to establish a development and commercialization strategy for tisagenlecleucel, Novartis formed a multidisciplinary project team, and multiple sub teams, and held meetings at Penn to discuss an academic and industry alliance. A key focus at the time was the feasibility of developing a commercial manufacturing process and supply chain that could reliably deliver CAR-positive T cells back to patients worldwide. The multistep process would need to include lentiviral vector production required for the gene transfer, collection and purification of patient T cells, T cell transduction, cell expansion and processing, product release testing, and the logistics of cell transfer back to the treatment center—all while maintaining a secure, global COId program. Novartis made the decision to sign off on the collaboration with Penn based on the unprecedented success seen in the first pediatric patient with relapsed and refractory B cell acute lymphoblastic leukemia (ALL). This first pediatric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2018
Development of first CAR design
1989
Second generation CAR-T with 4-1BB costimulatory domain shows activity against ALL
2004
First tisagenlecleucel patient treated for r/r CLL
July 2010
N Engl J Med r/r CLL patient #1 case report published
Sci Transl Med r/r CLL patient #1-3 published
August 2011
First tisagenlecleucel peds ALL patient treated at CHOP pediCART (CHP959)
April 2012
ASCO presentation of first peds ALL patient treated pediCART (CHP959)
June 2012
Penn and Novartis announce global CAR-T collaboration
August 2012
Morris Plains cell manufacturing facility purchased
December 2012
Pre-IND meeting to discuss with FDA Novartis' proposed clinical development and registration plans for tisagenlecleucel
April 2013
Pre-IND CMC meeting to discuss with FDA chemistry, manufacturing and controls aspects of tisagenlecleucel development
October 2013
First presentation (ASH) of tisagenlecleucel data in pediatric B-cell ALL for pediCART (CHP959)
December 2013
Orphan Drug Designation granted for r/r ALL
January 2014
ENSIGN (B2205J) pediatric r/r ALL study opens (Penn IND)
August 2014
SPA granted for ELIANA (B2202) pediatric r/r ALL
March 2014
USAN generic name approval: tisagenlecleucel-T (updated March 2017 to tisagenlecleucel)
March 2014
Breakthrough designation granted for peds ALL under Penn IND
July 2014
Novartis IND submission
November 2014
Presentation (ASH) reporting outcomes 92% CR in peds ALL for pediCART (CHP959)
December 2014
Novartis IND granted
February 2015
ELIANA (B2202) in r/r peds ALL, FPFV (Novartis IND)
April 2015
First patient cells modified by Morris Plains facility
May 2015
First presentation (ASH) of tisagenlecleucel data in r/r DLBCL from Penn
December 2015
Adult r/r DLBCL global study JULIET (C2201) opens
July 2015
Breakthrough Therapy Designation granted for r/r peds ALL
April 2016
Tisagenlecleucel designated PRIME by EMA
June 2016
Pre-BLA meeting peds r/r ALL
November 2016
Presentation (ASH) of ELIANA (B2202) interim results: 82% ORR (41/50) at 3 months post infusion
December 2016
BLA filed and granted priority review, in peds B-cell ALL
March 2017
FDA Breakthrough Therapy designation granted for treatment of adult patients with r/r DLBCL
April 2017
FDA ODAC voted 10-0 in favor of tisagenlecleucel for the treatment of r/r peds ALL
July 2017
First presentation (ICML) of JULIET data in r/r DLBCL
July 2017
BLA approval peds ALL: Tradename of Kymriah®; First FDA approved gene therapy and CAR-T cell therapy
August 2017
Actemra® (tocilizumab) approved for CAR-T-induced severe CRS
August 2017
JULIET (C2201) (ASH) primary analysis shows sustained CR at 6 months in adult r/r DLBCL
December 2017
sBLA approval adult DLBCL: Tradename of Kymriah®
May 2018

patient was treated on study at Children's Hospital of Philadelphia (CHOP) with the CAR-T product, and the data were presented by Dr. June at the American Society of Clinical Oncology conference in June of 2012 [4]. After this success, the final deal between Novartis and Penn was set in motion. This first pediatric patient continues to be in remission more than 6 years at the time of this writing. It increasingly became clear that this technology had the potential to revolutionize the treatment of leukemia and other CD19-positive B cell malignancies, and Novartis was willing to pioneer large-scale manufacturing and to develop the therapy.

In August of 2012, Novartis entered into a global academic-industry collaboration with Penn [5]. The 27-million-dollar investment was aimed at accelerating the process of bringing novel cellular therapies to patients. Together, Penn and Novartis built the first-of-its-kind Center for Advanced Cellular Therapies (CACT), which was unveiled in 2016 [6]. The center is located on Penn Medicine's campus, and was devoted to the discovery, development, and manufacturing of adoptive T cell immunotherapies through a joint research and commercial development program led by scientists and clinicians from Penn, Novartis, and the Novartis Institutes for BioMedical Research (NIBR) [5, 6]. The first order of business for the new collaboration was the manufacture and clinical development of tisagenlecleucel (Novartis investigational code CTL019).

State-of-the-Art CAR-T Manufacturing Facility

In December 2012, Novartis purchased the former Provenge® cell manufacturing facility from Dendreon Pharmaceuticals in Morris Plains, New Jersey. With this deal, Novartis acquired a ~ 173,000-sq-ft state-of-the-art facility with Good Manufacturing Practice standards in place near Novartis' US headquarters in East Hanover, New Jersey. Novartis purchased this state-of-the-art cell manufacturing facility to produce tisagenlecleucel [7]. In addition, it was recognized very early on that a systematic logistic platform—with a focus on COId to reliably track a patient's cells and data from leukapheresis at a clinical trial site, through the manufacturing process, and delivery back to the same patient for infusion—was critical. One component of the full COId plan is the CellChain, a Novartis online portal that helps manage the CAR-T–patient treatment process and coordinates manufacturing and logistics. The manufacturing facility was sized to be able to grow operationally with the future demand of a clinical trial program across multiple indications and the eventual commercial demand worldwide.

A successful Penn-Novartis collaboration was the key to moving into a commercial-scale CAR-T production. Dr. Bruce Levine of Penn, who pioneered the CAR-T cell process for the Penn studies, worked closely with the Novartis team in the transfer of technology to the new Novartis manufacturing facility for producing tisagenlecleucel. Two vital aspects of the knowledge transfer between the multidisciplinary Penn and Novartis teams were (1) to ensure that training of operators and analytical staff was conducted and (2) to implement changes that improved aseptic processing [8]. A team of Novartis cell-processing experts leveraged the manufacturing process already in place at Penn, and through process mapping, risk assessment, and data mining, they designed a manufacturing process that could be scaled to meet the needs of multiple tisagenlecleucel clinical trials. Scaling the manufacturing process at the Novartis manufacturing facility involved numerous test runs, training of manufacturing and quality control staff, and comparative manufacturing runs in Penn and Novartis facilities to confirm the consistent quality of the products manufactured at both sites. Once the process transfer was complete and validated, clinical manufacturing began at the Novartis facility and the first tisagenlecleucel product was shipped. Additional manufacturing sites have been established at the Fraunhofer Institute, Germany, and at the Foundation for Biomedical Research and Innovation (FBRI) in Kobe, Japan, with additional plans to add the Contract Manufacturing Organization Cell for Cure (Les Ulis, France) and build a new Novartis facility in Stein, Switzerland, in 2019.

Optimized CAR Vector Production

A key aspect of the CAR-T cell manufacturing process is the use of a viral vector to transfer the CAR gene into the genome of the patient's T cells. The original CART19 vector, sourced from small-scale research institutions, could meet the demand for only the local early clinical trials. Appropriate facilities, financing, development, and expertise were needed to scale up vector production to meet the expanding clinical trial program and the eventual commercial demand on a global scale. Novartis identified Oxford BioMedica (Oxford, UK), where the vector was developed and manufactured according Good Manufacturing Practice standards at larger scale. Today, Kymriah (tisagenlecleucel) is manufactured using the Oxford BioMedica lentiviral vector that is produced in large quantities [9] to meet demand in a controlled way and to minimize any variability related to the vector manufacturing process. An overview of key steps in the tisagenlecleucel manufacturing process is shown in Fig. 2.

First CAR-T Manufacturing for Global Clinical Development

CD19 is a type I transmembrane glycoprotein that is only expressed on normal B cells, B cell precursors, and malignant

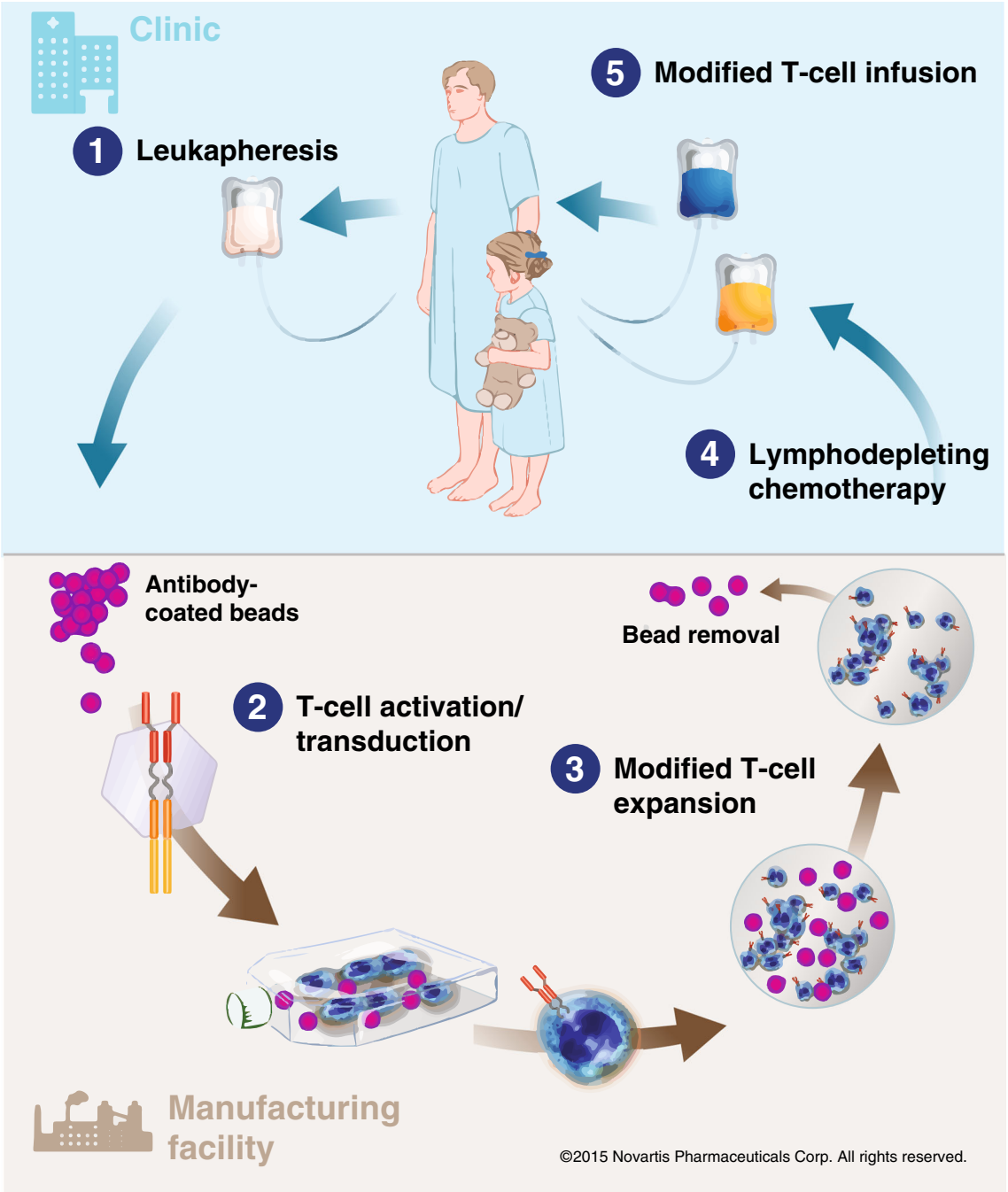

Fig. 2 Tisagenlecleucel manufacturing process. Key steps in the manufacturing process for tisagenlecleucel include: Cryopreservation of patient's leukapheresed mononuclear cells and shipment to the manufacturing facility; enrichment of T cells, activation, transduction with a lentiviral vector containing the anti-CD19 CAR transgene, cellular expansion and formulation; extensive testing of manufactured products to assess product quality; cryopreservation; shipment of the products to treatment facilities for administration to patients once all quality release requirements are satisfied. [32] Reproduced with permission from Novartis Pharmaceuticals. © 2015 Novartis Pharmaceuticals Corporation. All rights reserved

B cells, which makes it an ideal target for CD19-targeted tisagenlecleucel therapy [10]. Several B cell malignancies were being explored for potential treatment in the early development stage by Penn, prior to the Novartis-Penn Collaboration, including CLL, ALL, diffuse large B cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Shortly after the initiation of a CLL phase 1 study (NCT01029366) at Penn in July 2009 [2, 3, 11], Penn began a pilot phase 1 study in adult patients with r/r ALL (NCT01551043) [12], and in April 2012, CHOP began a pediatric ALL phase 1 study through the Penn development program (CHP959; NCT01626495) [13, 14]. Once the collaboration was

established in 2012, Novartis worked closely with Penn on the early phase 1 clinical studies. The focus of the clinical development plan was on disease states with high unmet medical need and promising long-term efficacy. Based on the remarkable CHOP data, which led to breakthrough therapy designation, pediatric ALL became the focus of Novartis' first global phase 2 CAR-T study (Fig. 1). The ENSIGN trial (NCT02228096) in pediatric and young adult patients with r/r B cell ALL was initiated by Penn/CHOP under the Penn investigational new drug application (IND), in partnership with Novartis in August 2014 [15]. This required the development of cell transport logistics and the transfer of clinical experience on tisagenlecleucel administration and management of potential adverse events (AEs) between a small number of highly specialized academic transplant centers in the USA and was instrumental in preparing for the Novartis pivotal global study in the same patient population. The following year, in April 2015, the pivotal ELIANA trial (NCT02435849) under the Novartis IND in pediatric and young adult patients with r/r B cell ALL enrolled its first patient [16]. A Penn study of tisagenlecleucel in patients with non-Hodgkin's lymphoma began in February 2014 [17]. This proof of concept study led to the initiation of the pivotal Novartis JULIET study (NCT02445248) in adult patients with r/r DLBCL [18]. (See Online Resource 1 for list of trial study sites, principal investigators, and steering committee members for the ELIANA and JULIET trials.)

First for CAR-T: Multisite Global CAR-T Studies

The first multicenter pediatric study of CAR-T cell therapy conducted globally under Novartis-sponsorship for patients with pediatric B cell ALL (B2202/ELIANA) was led by Dr. Stephan Grupp at CHOP and enrolled the first patient in April 2015 (Fig. 1). At that time, many of the ELIANA investigators had never treated a patient with the novel CAR-T cell therapy. Clinical development in CAR-T cell therapy was complex and required non-standard clinical trial logistics, given the true individualized nature of this therapy. Additionally, management of postadministration AEs, which could be life-threatening, required close patient management. Due to the complexity of administering CAR-T cell therapy, physicians with expertise in stem cell transplant were chosen as investigators for the tisagenlecleucel phase 2 pivotal studies in pediatric patients with r/r ALL (ELIANA, Supplementary Table 1) and in adult patients with r/r DLBCL (JULIET, Supplementary Table 2) [19••, 20••]. Having physicians with stem cell transplant experience as the study leads allowed them to leverage existing relationships with the multidisciplinary teams involved in stem cell transplant, including cell labs, oncology nurses, and intensive care unit (ICU) staff. The involvement of the ICU team was especially important for managing the potentially severe and life-threatening AEs associated with CAR-T therapy. Centers that were involved in the Novartis pivotal phase 2 studies were required to be accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) or The Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) for allogeneic stem cell transplant or equivalent. This ensured that the centers where qualified to handle and infuse living cell therapies.

In addition to having experienced multidisciplinary teams at the treatment centers, investigators attended weekly calls with the Novartis team to share knowledge between treatment centers about their experience and to build best practices. These weekly calls between Novartis and investigators were particularly important for transferring knowledge on the management of potentially life-threatening AEs, such as cytokine release syndrome (CRS) and neurological AEs associated with CAR-T therapy. The investigators' understanding of the timing and management of these AEs was initially guided by the experience and know-how from Penn/CHOP physicians and evolved over time. The first 3 patients with CLL who were treated with tisagenlecleucel at Penn each exhibited clinical signs of CRS, including fever, transient hypotension, dyspnea, and elevated IL-6 levels, which in some cases required hospitalization and corticosteroid therapy [2, 3]. The first pediatric patient with r/r ALL enrolled on the CHP959 study at CHOP developed severe, life-threating CRS symptoms shortly after the tisagenlecleucel was infused [21]. The patient developed febrile neutropenia, hypotension, acute vascular leak syndrome, acute respiratory distress syndrome, and had significantly elevated IL-6 levels. Quick action by Dr. Grupp, Dr. June, and Dr. David Teachey resulted in the patient receiving a single dose of tocilizumab (anti-IL6 receptor antibody), which resulted in rapid resolution of the patient's fever within hours and improvement of hemodynamic instability. Tocilizumab was chosen because it is an anti-IL6 therapy available in a pediatric dose for juvenile arthritis. The decision to use tocilizumab perhaps not only saved the life of the first pediatric patient, but also enabled the CHP959 study to proceed, and allowed the further clinical development of what would ultimately become Kymriah.

Moving from the single-center CHP959 study to global clinical trials of tisagenlecleucel required precise coordination to account for country-specific customs clearance and regulatory requirements. Although the ELIANA trial protocol was designed to be compliant with local guidelines, the import of cells from patients located outside of the USA needed to be cleared by the US Food and Drug Administration (FDA). Similarly, shipping the manufactured tisagenlecleucel back to a patient outside of the USA needed custom clearance. Additionally, the transport to patients in the European Union required certification of the batch by a qualified person (QP) before the product can be released to the sites, which added some complexity.

Because of these technical and logistical challenges, the fact that the product is cryopreserved allows for global transport with no impact on the product quality despite the logistic challenges of cryogenic shipping. In the postapproval setting for pediatric and young adult patients with r/r ALL, other challenges are being worked out, such as manufacturing cells for very young patients (< 3 years of age) who had not been enrolled in the clinical trials.

Discussion/Future of CAR-T

The emergence of engineered T cells as a form of cancer therapy represents the start of a new era in medicine, providing a transformative therapy for the complexities of cancer. Engineered T cells, such as CAR-T, provide a new chapter in the rapidly emerging field of immunooncology. The innovative aspect of these therapies is the concept of utilizing living cells as a therapeutic platform [22]. Living cells provide the capacity to sense and respond to the environment, setting them apart from inanimate platforms such as small molecules or antibodies. The manufacturing and administration of this new therapy add a new dimension to treatment. CAR-T therapy integrates diverse fields of medicine and basic science into a formidable cell-therapy platform. The fields of engineered antibodies, vaccinations, and stem cell transplantation combine to deliver a synthetic biology embodied by CAR-T therapy. CAR-T therapies, such as tisagenlecleucel, link the heavy and light chains from an antibody to the signaling machinery of a T cell, thus creating a persistent "living drug."

The Kymriah CAR-T has raced from the first patient infused at Penn to a commercially approved new therapy given to more than 500 patients with advanced leukemia and lymphoma in 8 years, which is remarkable for a first-of-its-kind therapy. After thorough review of the efficacy, safety, and manufacturing data, the FDA Oncologic Drugs Advisory Committee in July 2017 voted unanimously 10 to 0 in favor of tisagenlecleucel for pediatric and young adult patients with r/r/ B cell ALL [23]. The approved tisagenlecleucel represents a first version of such therapies and delivers impressive results for patients who failed most other modern treatments. The next frontier for tisagenlecleucel is clinical research designed to determine whether the therapy is safe and effective as earlier-line therapy in the near future. As a result of the painstaking pioneering efforts of the early researchers in this field and recent improvements in the understanding of how these therapies work in patients, the number of academic centers and industry partners joining the efforts have greatly expanded and the field is rapidly developing and testing the next generation of CAR-T therapies. The versions of a CAR-T therapy that follow may demonstrate greater efficacy, broader application among hematological malignancies, improvements to safety, faster manufacturing, and, importantly, the potential to drastically improve outcomes for patients with the most common solid tumors. Another key aspect of delivering CAR-T therapy that needs to be more clearly defined is the health economics of this potentially life-saving therapy [24]. However, a recent cost-effectiveness analyses of tisagenlecleucel demonstrated it to be cost-effective for pediatric and young adult patients with r/r ALL compared with other non-CAR-T therapies that could be therapeutic options for these patients (e.g., second stem cell transplant, clofarabine chemotherapy, blinatumomab) [25].

Emerging solutions for engineering CAR-T therapies in the future focus on four general aspects, including (1) malignant cell recognition, (2) proliferation/persistence, (3) the microenvironment, and (4) preventing AEs or reducing their severity. New and potential targets of CAR-T include B cell maturation antigen (BCMA) for multiple myeloma, CD22 for leukemia, and potential combinations of dual CAR-T cells to improve malignant cell recognition [26–28]. Combinatorial recognition circuits as with synNotch receptors or affinity-attuned receptors may improve discrimination between malignant and normal cells [29]. Proliferation/persistence may be optimized with the selection of less senescent T cells from the leukapheresed material, combination with immunomodulatory agents such as Bruton's Tyrosine Kinase (BTK) and IL-2 Inducible T cell Kinase (ITK) inhibitors, or different costimulatory domains in the CAR construct [30]. The microenvironment may be altered with a combination of CAR-T cells with PD-1 inhibition or fourth-generation CAR-Ts (armored CARs) [30], which secrete pro-inflammatory cytokines such as interleukein-12 [31]. Control of future CAR-T therapies may include "on or off switches" or combinations of anticytokine therapy to minimize CRS without reducing efficacy. Some researchers have envisioned engineering synthetic down-regulatory feedback circuits into the CAR-T cells, thereby allowing them to autonomously control proliferation based on IL-6 levels in the blood.

As CAR-T therapies accelerate in an iterative and rational way, "version 10.0" of this therapy may represent the end of the road for the emperor of all maladies. Finally, CAR-T therapy may drive new treatments for other diseases beyond hematology and oncology targets, including but not limited to infections, autoimmune and inflammatory diseases, fibrosis, and degeneration.

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Conflict of Interest Stacie Ittershagen, Lamis Eldjerou, Eric Bleickardt, Manisha Patel, Oezlem Anak, Charlene Hall, Mimi Leung, Ali Shojaee, Deborah Roccoberton, Miriam Fuchs, and Florence Salmon declare that they are employees of Novartis Pharmaceuticals Corporation.

Solveig Ericson, Tetiana Taran, Vadim Romanov, and David Lebwohl declare that they are employees and shareholders of Novartis Pharmaceuticals Corporation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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