Global Immune Cell Therapy Drug Development: Current Status and Trends (Postprint)

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Date: 2018-07-31T00:00:00+00:00

Abstract

Objective: To analyze the current development status and future trends of immune cell therapy drugs from a product development perspective. Methods: Data from Clarivate Analytics' Cortellis database were retrieved, and the search results were analyzed using quantitative and comparative analysis methods. Results: Currently, 2 immune cell therapy drugs have been launched on the market, 1 is in the pre-registration stage, and 4 are in Phase III clinical trials; meanwhile, a large number of drugs in Phase II/I clinical trials indicate that more immune cell therapy drugs will be available on the market in the future. Regarding product transactions, commercial transactions for immune cell therapy drugs are also becoming increasingly frequent. Among the transactions that have occurred to date, this article enumerates and analyzes the top ten transactions by value, with drug development and commercialization licensing being the primary transaction model. Conclusion: The current market for immune cell therapy drugs is still in its infancy; however, with continuous technological development and improvement in the future, it is anticipated that more drugs will enter the commercial market, providing new opportunities for the treatment of cancer and other diseases.

Full Text

Preamble

Development Status and Trends of Global Immune Cell Therapy Drugs

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Abstract

Objective: To analyze the current development status and future trends of immune cell therapy drugs from a product development perspective.
Methods: Data from Clarivate Analytics' Cortellis database were retrieved and analyzed using quantitative and comparative analytical methods.
Results: Currently, two immune cell therapy drugs have been launched, one is in pre-registration, and four are in Phase III clinical trials, while a large number of drugs in Phase II/I trials indicate that more immune cell therapy products will enter the market in the future. In terms of product transactions, commercial deals related to immune cell therapy drugs are becoming increasingly frequent. Among the transactions that have occurred to date, this paper analyzes the top ten deals by value, revealing that drug development and commercialization licensing represents the predominant transaction model.
Conclusion: Although the immune cell therapy drug market is still in its infancy, continuous technological development and improvement will likely bring more drugs to the commercial market in the future, providing new opportunities for the treatment of cancer and other diseases.

Keywords: Immune cell therapy; Drug development; Market competition; Clinical R&D

Immune cell therapy, a cell-based therapeutic approach, refers to treatments that utilize autologous, allogeneic, or xenogeneic (non-human) immune cells such as T cells and B cells, which are manipulated ex vivo and then reinfused (or implanted) into patients. The infused cells can replace damaged cells or possess enhanced immune killing functions, thereby achieving therapeutic effects [**?**]. In December 2013, *Science* magazine named cancer immunotherapy as the top breakthrough among its annual top ten scientific achievements. Immune cell therapy again became a focal point at two major authoritative cancer conferences held in the United States in April and June 2015—the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). According to estimates by the internationally renowned consulting firm ResearchAndMarkets, the market for cell therapy applications in cancer treatment alone is expected to exceed $10 billion by 2022, further confirming the important position and development prospects of immune cell therapy in future disease treatment [**?**].

Given the relatively short history of immune cell therapy development, concentrated primarily in the last two years, the pharmaceutical industry has conducted limited systematic reviews of immune cell therapy drugs. Therefore, this paper focuses on immune cell therapy drugs as its primary research subject, examining the current state of product and market development to provide references for the development of related industries in China.

1. Data Sources and Methods

1.1 Data Sources

This study utilized Clarivate Analytics' Cortellis Competitive Intelligence database (formerly the IP & Science division of Thomson Reuters), which contains information on over 65,000 drugs and drug candidates, more than 80,000 drug transaction overviews, and 29,000 inter-institutional transaction contracts. Data were retrieved on April 17, 2018. Drug R&D and transaction data were searched through the "Drugs" and "Deals" portals in the advanced search function. Both searches employed the "Biotechnology concept" category under "Technologies," selecting "Immune system cell therapy" within "Cell therapy" as the search target.

1.2 Analysis Methods

The study primarily employed quantitative analysis and comparative analysis. Quantitative analysis involved statistical examination of numerical characteristics, relationships, and changes to provide a foundation for comparative analysis. Comparative analysis identified differences between actual figures and baseline values to understand the current status and trends of the subjects under investigation.

2. Results

2.1 Overall R&D Status

As of the retrieval date, a total of 425 immune cell therapy drugs were identified in the Cortellis database. Excluding drugs that have been suspended, terminated, or have no R&D reports, 397 drugs are currently launched or in active development, with the vast majority still in R&D and clinical trial phases. Specifically, 213 products are in the drug discovery stage, accounting for 53.7% of the total; products in clinical and later stages represent 45.6% of the total, including 16 in unspecified clinical phases, 90 in Phase I, 71 in Phase II, 4 in Phase III, 1 in pre-registration, and 2 launched products (Note: The discovery stage includes discovery/exploration and preclinical phases involving pharmacological/toxicological evaluation in animals; the clinical stage refers to cases where clinical trials are mentioned but specific phases are not identified; pre-registration refers to the stage where marketing applications have been submitted and are awaiting approval).

[Figure 1: see original paper] Global R&D Status of Immune System Cell Therapies

2.2 Development Progress of Key Products

2.2.1 Launched Products To date, several cell therapy products have entered the market. The approval of new immune cell therapy products contin-

uously validates R&D investments in this field, clarifies market prospects, and further stimulates investment. In the short term, new immune cell therapy drugs will also expand their scope of application. Currently, two immune cell therapy drugs have received marketing approval globally: Kymriah, developed by Novartis, and Yescarta, developed by Kite Pharma, which were approved by the US FDA in August and October 2017, respectively (Table 1).

(1) Tisagenlecleucel-T/Kymriah

Tisagenlecleucel-T (formerly CTL019; trade name: Kymriah), launched by Novartis, is the first T-cell therapy product approved by the FDA using chimeric antigen receptor (CAR) technology, receiving US FDA approval in August 2017. Kymriah is a genetically modified autologous T-cell immunotherapy targeting CD19. Currently, its approved indication in the United States is for pediatric and young adult patients with acute B-cell lymphoblastic leukemia (ALL). Acute lymphoblastic leukemia is a neoplastic disease originating from B-lineage or T-lineage lymphoid progenitor cells and is the most common childhood cancer. Patients with relapsed or refractory B-cell ALL have a five-year survival rate generally below 10%-30%, with very limited treatment options. Kymriah provides a new option for these patients. According to information from Novartis, based on single-infusion Kymriah therapy, 63 pediatric or young patients with refractory or relapsed leukemia achieved an overall response rate of 83% within the short term (3 months) [**?**]. Previous clinical trial results showed that among 30 patients (including children and adults) receiving CTL019, the short-term complete remission rate was as high as 90%, with a 6-month event-free survival (EFS) rate of 67% (95% confidence interval [CI]) and an overall survival rate of 78% (95% CI) [**?**]. Kymriah is currently under review by the European Medicines Agency (EMA), having completed pre-registration in Europe, with expected approval in the first half of 2018.

(2) Axicabtagene ciloleucel/Yescarta

Axicabtagene ciloleucel (trade name: Yescarta), developed by Kite Pharma, received US FDA approval in October 2017, becoming the second CAR-T therapy approved by the FDA [**?**]. Yescarta is also a CD19-targeted CAR-T therapy product, formally approved by the FDA for the treatment of adult patients with specific types of large B-cell lymphoma who are unresponsive to or have relapsed after at least two other treatment regimens. Yescarta is also the first gene therapy approved for the treatment of specific types of non-Hodgkin lymphoma (NHL) [**?**].

In clinical trials, a total of 101 patients received a single infusion of Yescarta, with 72% showing response (overall response rate [ORR]) and a complete response rate of 51% [**?**]. Previous Phase II trial results showed an 18-month overall survival rate of 52% for patients with diffuse large B-cell lymphoma [**?**]. Yescarta is also currently under review by the EMA, having been granted PRIority MEdicines (PRIME) designation, with expected approval in the first half of 2018.

2.2.2 Pre-registration According to the Cortellis database classification, the pre-registration stage (Pre-registered) indicates that a drug has submitted a marketing application and is awaiting approval. Currently, only one immune cell therapy drug has completed pre-registration globally: YYB-103, applied for by South Korea' s YooYoung Pharmaceuticals (Table 2).

YYB-103
According to the Cortellis database, YYB-103 is a new drug co-developed by South Korea' s YooYoung Pharmaceuticals Co., Ltd. and another company (name not disclosed). It is a CAR-T therapy product targeting interleukin-13 receptor alpha 2 (IL13R 2) (CART-IL13R 2). IL13R- -2 is a product expressed on the surface of most (50%-80%) glioblastomas but is almost absent in normal tissues. Therefore, YYB-103, which targets IL13R- -2, can effectively target glioblastoma, enabling precision therapy. In May 2015, YooYoung Pharmaceuticals submitted a new drug application to South Korea' s KFDA for YYB-103 for glioblastoma and motor neuron disease.

In May 2017, at the 20th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) held in Washington, D.C., YooYoung Pharmaceuticals presented preclinical data on YYB-103 for glioma treatment. The data showed that in a mouse xenograft glioma model, mice treated with YYB-103 demonstrated anti-tumor activity and a significant increase in survival rate [**?**].

2.2.3 Phase III Clinical Trials The success of immune cell therapy, represented by CAR-T cell therapy, has been primarily demonstrated in B-cell lymphoblastic leukemia patients with hematological malignancies. Currently, more clinical studies are underway to expand the indications for immune cell therapy drugs. According to the Cortellis database, four drugs have entered Phase III clinical trials globally (Table 3), with indications covering lymphoproliferative disorders, liver cancer, peripheral arterial occlusive disease, and diabetic complications, potentially providing treatment options for more diseases.

(1) Tabelecleucel
Tabelecleucel (formerly ATA129) is a T-cell immunotherapy product developed by Atara Biotherapeutics Inc. under license from Memorial Sloan-Kettering Cancer Center (MSKCC). Tabelecleucel is an allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T lymphocyte prepared by exposing donor T cells to EBV antigens. It is currently used to treat EBV-related post-transplant lymphoproliferative disease (EBV+PTLD) and other EBV-related hematological and solid tumors, including nasopharyngeal carcinoma (NPC), in patients who have previously failed rituximab treatment.

In November 2017, the company announced completed Phase II trial data showing an ORR of 80% in HCT-EBV-PTLD patients and 83% in SOT-EBV-PTLD patients, with a 1-year overall survival rate of 90.0%. No severe drug-related adverse reactions were observed, and safety and efficacy data were consistent with Phase II trial results [**?**]. In January 2018, the company announced

the initiation of two Phase III studies to evaluate Tabelecleucel for rituximab-treated EBV infection-induced PTLD (MATCH) and rituximab or rituximab plus chemotherapy-treated EBV infection-induced PTLD (ALLELE). Tabelecleucel has received FDA Breakthrough Therapy designation and Orphan Drug status. The drug will be submitted for clinical trial applications in multiple countries and will also explore combination therapy with Merck' s Keytruda for platinum-resistant or EBV infection-related nasopharyngeal carcinoma.

(2) Anti-CD19 CAR T-cell therapy
This drug is a CAR-T immunotherapy developed by Fujian Medical University, using genetically engineered T cells expressing anti-CD19 chimeric antigen receptors (CARs). Its primary indication is B-cell acute lymphoblastic leukemia.

In January 2018, Fujian Medical University initiated an open-label, single-arm Phase II/III trial in China (NCT03391739; CART-19-03) to evaluate the safety and toxicity of CART-19 cells in patients with refractory relapsed B-cell acute lymphoblastic leukemia (estimated enrollment n = 20), with completion expected in December 2019.

(3) Eltrapuldencel-T
Eltrapuldencel-T (product code: NBS20) is a dendritic cell therapeutic vaccine developed by NeoStem Oncology under license from Hoag Memorial Hospital Presbyterian. The product combines autologous dendritic cells with autologous tumor stem cell antigens to produce granulocyte-macrophage colony-stimulating factor (GM-CSF) for autologous immunotherapy of metastatic melanoma and potentially hepatocellular carcinoma.

In July 2014, at the 5th GTCBio Cancer Targets and Therapeutics Conference in Boston, Massachusetts, NeoStem Oncology presented randomized Phase II trial data from 42 patients, showing a two-year overall survival rate of 72% for melanoma patients after treatment (compared to 31% in the control group) [**?**]. NeoStem Oncology had received FDA approval in December 2013 to conduct Phase III trials for metastatic melanoma, and formally launched the Phase 3 clinical trial for eltrapuldencel-T in recurrent or Stage 4 metastatic melanoma in the United States in October 2014 [**?**]. The drug has received FDA Special Protocol Assessment, Fast Track Designation, Orphan Drug status, and EMA designation as an Advanced Therapy Medicinal Product. Additionally, in October 2012, its Chinese partner company, Cellular Biomedicine Group Inc., initiated a Phase I trial of eltrapuldencel-T for hepatocellular carcinoma. In March 2014, the company was planning Phase II safety and efficacy trials, though no results have been published to date.

(4) Rexmyelocel-T
Rexmyelocel-T (product code: REX-001) is an autologous bone marrow-derived mature mononuclear cell (BM-MNC) therapy for the treatment of critical limb ischemia (CLI) in both diabetic and non-diabetic patients. Previous clinical trials have shown that Rexmyelocel-T can stimulate new blood vessel growth, restore limb blood supply, alleviate symptoms, and improve quality of life in

CLI patients.

In May 2016, Rexgenero announced completion of Phase II clinical trials for Rexmyelocel-T in the United Kingdom, with the European Medicines Agency (EMA) confirming in writing that Rexmyelocel-T demonstrated strong efficacy in angiogenesis treatment for diabetic patients by reducing pain. In July 2016, Rexgenero announced the design of a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial in Europe for the treatment of CLI in diabetic patients based on EMA recommendations. The second stage of the Phase III trial began in April 2017.

2.2.4 Phase II Clinical Trials Due to the large market potential for immune cell therapy and encouraging results from early-stage basic research in clinical trials, developing immune cell therapy drugs has become a priority for numerous biotech and pharmaceutical companies. Currently, multiple products have entered Phase II clinical trials, including AUTO-3, a novel CAR-T therapy developed by UK-based biotech company Autolus that simultaneously targets CD19 and CD22 for the treatment of B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma. In June 2017, Autolus initiated a Phase II study in the UK for B-cell acute lymphoblastic leukemia.

Other examples include MG7-CART, developed by Shanghai GeneChem, for potential intratumoral treatment of liver metastases. MG7 is a novel gastric cancer target originally discovered by the State Key Laboratory of Cancer Biology led by Academician Fan Daiming at the Fourth Military Medical University. GeneChem then applied this target to cell therapy using its mature cell therapy platform. In June 2016, GeneChem initiated Phase II clinical trials in China and presented relevant clinical data at the 2017 American Association for Cancer Research (AACR) annual meeting [**?**].

Additionally, bb-2121, jointly developed by US biotech giant Celgene and partner Bluebird Bio, is a CAR-T therapy targeting B-cell maturation antigen (BCMA) for patients with relapsed/refractory multiple myeloma [**?**]. In December 2016, Bluebird Bio announced interim Phase I CRB-401 study data for its BCMA-targeted CAR-T therapy bb-2121 in multiple myeloma patients. In December 2017, Bluebird/Celgene jointly released final Phase I trial results for bb-2121 and announced the initiation of Phase II studies. Phase I clinical data showed that bb-2121 achieved a response rate of 94%, a very good partial response rate of 89%, and a complete response rate of 56%. In November 2017, bb-2121 received Breakthrough Therapy designation from the FDA and PRIME status from the EMA for the treatment of relapsed or refractory multiple myeloma.

2.3 Current Status of Product Transactions

As clinical research on immune cell therapy continues to advance, the global immune cell therapy market is developing rapidly. Immune cell therapy has be-

come internationally recognized as the fourth major cancer treatment method, with latest clinical trial results from Europe and the United States demonstrating promising application prospects. International pharmaceutical giants and biotech companies have identified immune cell therapy as a key focus for "betting on the future." Consequently, product transactions in this field are becoming increasingly frequent. Currently, transaction types in the immune cell therapy drug R&D field are mainly divided into two forms: drug development and commercialization licensing, and drug discovery and design. Among the top ten deals by value, drug development and commercialization licensing represents the predominant transaction model (accounting for 90% of the share) (Table 5). Details are as follows:

(1) Kite Pharma' s $3.16 Billion Alliance with Sangamo to Develop Next-Generation CAR-T Therapies

On February 20, 2018, Kite Pharma announced a global collaboration agreement with Sangamo Therapeutics to develop next-generation autologous and allogeneic cell therapies for different tumors based on Sangamo' s zinc finger nuclease (ZFN) technology platform. The total agreement value is approximately $3.16 billion. Under the agreement, Sangamo will receive an upfront payment of $150 million from Kite Pharma, with potential future milestone payments of up to $1.26 billion for R&D, regulatory, and commercial milestones (first sales milestone), plus $1.75 billion in sales milestone payments (when licensed product annual sales reach specific milestones), bringing the total transaction value to $3.15 billion. Additionally, Sangamo will receive tiered sales royalties from Kite. Kite will be responsible for product R&D, manufacturing, and commercial promotion.

(2) Pfizer' s Partnership with Cellectis to Jointly Develop CAR-T Cancer Immunotherapy

On June 18, 2014, Pfizer and French biotech company Cellectis jointly announced a global strategic collaboration to co-develop CAR-T immunotherapy for specific targets in oncology. Under the agreement, Pfizer has exclusive rights to select and develop CAR-T therapies for 15 specified targets in oncology. Both parties will collaborate on clinical research, with Pfizer responsible for developing and commercializing any CAR-T therapy for selected disease targets. The transaction involves a total value of $2.8903 billion, including an $80 million upfront payment from Pfizer to Cellectis, $2.775 billion in milestone payments, and $35.3 million for purchasing 10% of Cellectis' shares.

(3) Allogene' s Partnership with Pfizer and Cellectis to Co-develop UCART Programs

On April 3, 2018, cell therapy emerging company Allogene Therapeutics announced the acquisition and advancement of a series of experimental cell therapies previously controlled by Pfizer for universal CAR-T therapy treatment of solid tumors and blood cancers. The core technology for these cell therapies is provided by Cellectis, which will continue to benefit from the 2014 transaction with Pfizer, receiving up to $2.8 billion in milestone payments for 15 target

products at $185 million per product.

(4) Baxalta' s Partnership with Precision BioSciences, Focusing on Allogeneic CAR-T + Gene Editing

On February 25, 2016, gene editing company Precision BioSciences and biopharmaceutical company Baxalta reached a global strategic cooperation agreement to develop allogeneic CAR-T therapies using Precision BioSciences'ARCUS gene editing technology platform. Under the agreement, Baxalta will pay Precision BioSciences an upfront payment of $105 million, plus option fees, development, clinical, regulatory, and sales milestone payments totaling $1.6 billion, for a total transaction value of $1.705 billion.

(5) Servier' s Partnership with Cellectis to Co-develop UCART19

On February 17, 2014, French pharmaceutical company Servier announced a global licensing agreement with French biotech company Cellectis to co-develop UCART19, a CAR-T cell therapy with significant therapeutic potential for hematological cancers. Under the agreement, Servier will be responsible for Phase II clinical development and subsequent trials, as well as registration and commercialization of the drug. The total transaction value reached $1.12 billion.

(6) Kite Pharma' s Collaboration with Amgen to Develop CAR-T Cell Therapy

On December 31, 2014, Amgen and Kite Pharma announced a strategic collaboration in cancer immunotherapy, integrating Amgen' s oncology targets with Kite' s innovative CAR-T platform. Under the agreement, the total collaboration value is $1.11 billion, with Kite receiving $60 million in upfront payments from Amgen and $525 million in milestone payments per project.

(7) Celgene' s Investment in Juno for Joint Development of Cancer Immunotherapy

On June 29, 2015, US biopharmaceutical company Celgene announced a $1 billion total investment in cancer immunotherapy innovator Juno Therapeutics and signed a global collaboration agreement. The $1 billion includes approximately $150.2 million in upfront payments and $849.8 million to purchase 10% of Juno' s shares. Both parties will collaborate in the field of cancer immunotherapy, focusing on the application of CAR-T therapy in cancer treatment.

(8) Merck' s $941 Million CAR-T Collaboration Agreement with Intrexon

On March 30, 2015, Merck announced a $941 million agreement with Intrexon to jointly develop CAR-T cell therapies for cancer. The agreement amount includes a $115 million upfront payment from Merck to Intrexon and $826 million in milestone payments for research funding, R&D, management, and sales. Under the agreement, Merck will exclusively obtain Intrexon' s CAR-T technology.

(9) Juno' s Alliance with Editas for R&D Partnership

On May 26, 2015, CAR-T newcomer Juno and gene editing company Editas Medicine reached an agreement to use the latter's CRISPR technology to jointly develop cancer immunotherapies CAR-T and TCR (high-affinity T cell recep-

tor), with a total agreement value of $747 million. Under the agreement, Juno will pay Editas $25 million in upfront payments and an additional $22 million in research investment to support three collaborative projects over the next five years. For each project, Juno will also pay $697.5 million in milestone payments and $2.5 million in option payments.

(10) Kite Pharma' s Partnership with Daiichi to Develop Cancer Treatments

On January 5, 2017, Kite Pharma Inc. announced a strategic cooperation agreement with Japan' s Daiichi Sankyo to co-develop CAR-T products and commercialize them in the Japanese market. Under the agreement terms, the total value is $450 million, with Kite receiving $50 million in upfront payments and up to $200 million in development dividends when commercial milestones are achieved. The agreement also stipulates that Daiichi Sankyo will have the opportunity to access other Kite candidate compounds within the next three years, with each candidate product eligible for up to $200 million in upfront and milestone payments, while Kite retains all development and commercialization rights outside Japan.

3. Summary and Outlook

In recent years, the immune cell therapy industry has been driven by two major forces: technological breakthroughs and advances in regulatory frameworks. On one hand, driven by growing patient demand and participation from major global research institutes and pharmaceutical giants, immune cell therapy technologies are becoming increasingly mature. On the other hand, governments including China have successively relaxed policy restrictions on immune cell therapy, and this policy warming will further promote industry development. With the milestone event of the FDA approving two CAR-T drugs in late 2017, the immune cell therapy industry will enter a period of rapid development in the future, with more products advancing to Phase II/III clinical trials and beyond.

Meanwhile, immune cell therapy faces numerous challenges ahead. The primary challenge currently facing the immune cell therapy market is the high cost of early-stage R&D and manufacturing. Taking tumor CAR-T therapy as an example, the world' s first approved CAR-T therapy is currently priced at $475,000, a cost prohibitively expensive for most people and in need of reduction. Subsequent CAR-T therapy development will prioritize cost reduction as a key objective.

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Note: Figure translations are in progress. See original paper for figures.