



ACROSS  
RESEARCH  
PAPER

# CAR T-CELL THERAPY

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ACROSS GLOBAL™ ALLIANCE

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CO - AUTHORS: ENA ZUVIC & STEVEN BUKVIC



## ACROSS RESEARCH PAPER

# FOREWORD

Due to growing popularity, ACROSS Global has decided to devote time to the development of a CAR T-Cell Therapy ACROSS Research Paper. We plan to issue a bi-annual, open-access online paper covering CAR T-Cell Therapy, capturing the most interesting news, NDA approvals, data trends, changes in global regulations, as well as company profiles and pipelines in what is a rapidly growing therapy area.

CAR T-Cell Therapy holds great potential for the treatment of many diseases and the two approved therapies (i) Novartis - tisagenlecleucel (Kymriah) and (ii) Kite (a Gilead company) - axicabtagene ciloleucel (Yescarta) present an emerging new approach to cancer treatment. These two approvals represent an important milestone in the field of gene therapy.

# TABLE OF CONTENTS

1. CAR T-CELL THERAPY GENERAL OVERVIEW
2. 2017-2018 UPDATES
3. REGIONAL FOCUS USA - CLINICAL TRIAL DATA
4. FEATURED COMPANY PIPELINE
5. FEATURED COMPANY
6. CONFERENCES & EVENTS
7. GUIDELINES AND REGULATIONS
8. LIBRARY OF ARTICLES
9. REFERENCES



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# CAR T-CELL THERAPY

## General Overview

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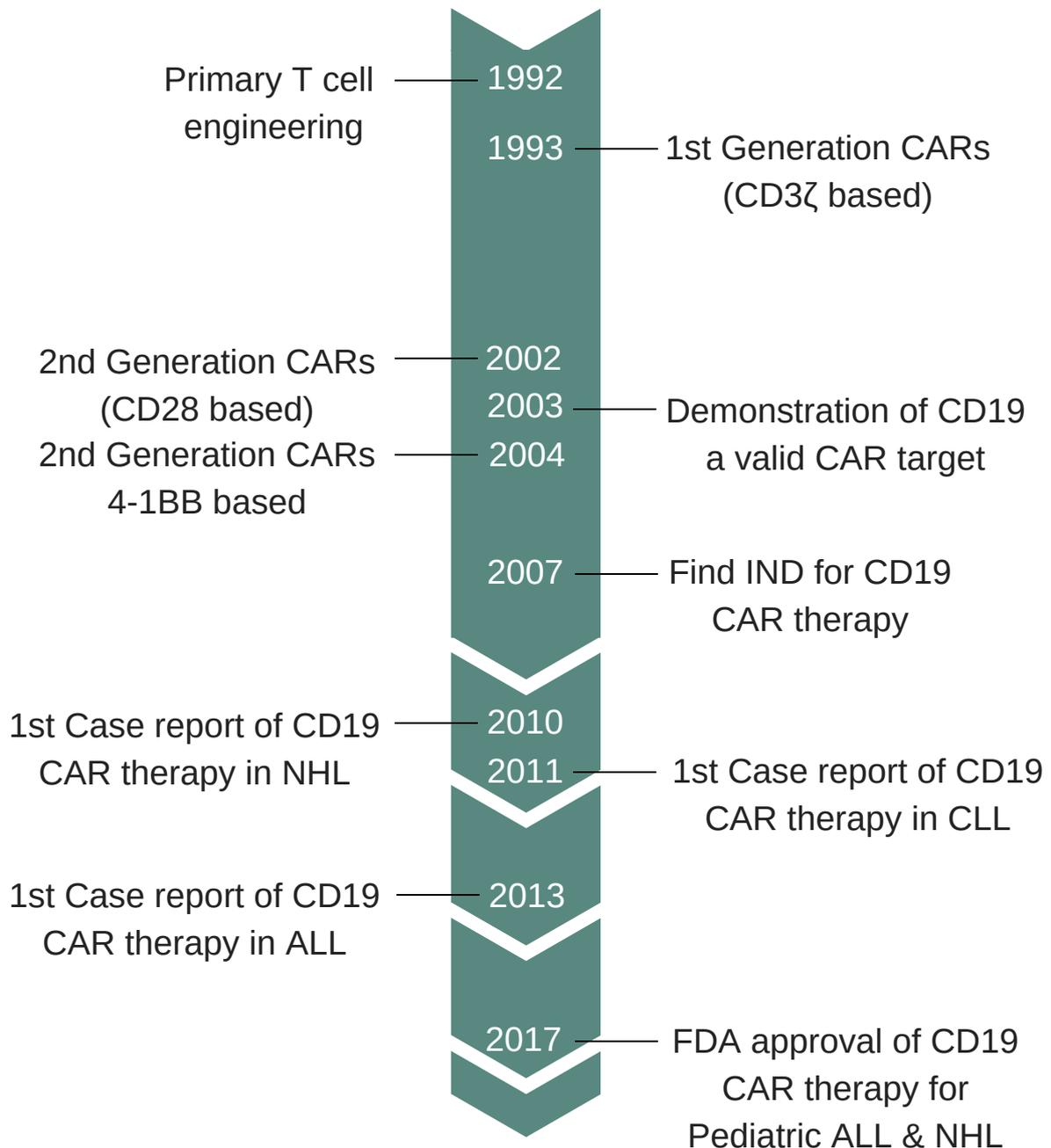
In recent years, immunotherapy has emerged as a promising approach in the battle against cancer. Discovering the therapeutic potential of monoclonal antibodies represented a major breakthrough in the treatment of cancer. Numerous studies have proved its effectiveness in the treatment of advanced cancers which had previously been considered untreatable.

In 2011, the FDA approved the first checkpoint inhibitor, ipilimumab for the treatment of the melanoma. Following the success of ipilimumab other checkpoints inhibitors have since found a place in the arsenal of cancer therapies.

Another clinical path of immunotherapy, adoptive cell transfer (using autologous tumor-infiltrating lymphocytes), has opened new possibilities in the treatment of a wide variety of cancer types, too.



# CAR T-CELL THERAPY TIMELINE



Data sourced from: <https://labiotech.eu/features/car-t-therapy-cancer-review/>



## General Overview

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Adoptive Cellular Therapy (ACT) includes several different therapies, however, one in particular, 'CAR T-cell therapy' has received significant attention lately since this type of therapy has advanced the furthest in clinical development.

CAR T-cell therapy uses a patient's own T-cells as a weapon against cancer. After the patient's T-cells have been removed from the patient they are genetically engineered to produce chimeric antigen receptors (CARs) on their surface. These genetically transformed T cells are now called CAR T-cells. Chimeric antigen receptors (CARs) equipped T cells have an improved ability to recognize and kill cancer cells that have the targeted antigen on their surface.

**Two crucial events have recently put CAR T-cell therapy at the forefront of cancer research activity.**

1. The first two CAR T-cell therapies approved by FDA (2017).<sup>1</sup>
2. In the annual ASCO report (January 30, 2018), CAR T-cell immunotherapy was named as the "advance of the year."<sup>2</sup>





# CAR T-CELL THERAPY

## 2017 - 2018 Updates

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In 2017 CAR T-cell therapy came into sharp focus with the first two CAR T-cell therapies having received FDA approval.

### **YESCARTA**(Gilead Sciences)

*"Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma."* <sup>3</sup>

### **KYMRIAH** (Novartis)

*"Indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse."* <sup>4</sup>

**June 29, 2018**, The first two CAR-T cell therapies were recommended for approval in the European Union.<sup>5</sup>

**August 27, 2018**, The European Commission (EC) approved Kymriah and Yescarta, the first approved CAR T-cell therapies in the European Union.<sup>6</sup>

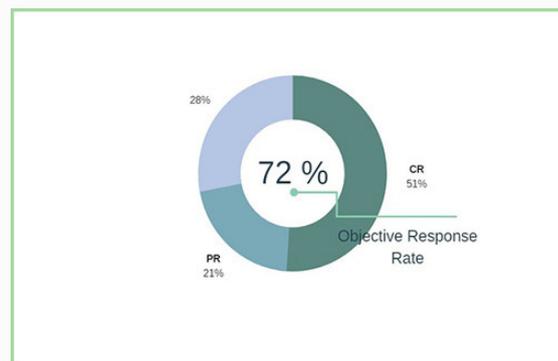




## 2017 - 2018 Updates

Despite the fact that both therapies had shown high remission rates, (Kymriah, 83% remission rate after three months in clinical trials with patients that do not respond to standard treatments, Yescarta induced remission in 72% of patients), side effects have been linked with CAR T-cell therapy and which may vary from mild to moderate in terms of severity and has even included life-threatening conditions like cerebral edema.<sup>7</sup>

Yescarta Results<sup>8</sup>



www.yescarta.com

*"In a clinical study of 101 patients with non-Hodgkin lymphoma who had failed other treatments, YESCARTA was shown to help 51% of the patients to (52 out of 101) achieve complete remission."<sup>9</sup>*





## 2017 - 2018 Updates

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Safety concerns remain one of the biggest challenges that the next generation of CAR T-cell therapies need to overcome. Decreasing the risk of cytokine release syndrome and neurotoxicity in patients which represent the most challenging of the serious side effects occurring in CAR T-cell therapy should therefore become a top priority.

In addition to the challenge of overcoming these serious side effects, proving the efficacy of CAR T-cell therapy in the treatment of solid tumours is another active field of research in cancer science and a major opportunity for biotech companies.

Research is developing simultaneously in multiple directions, including improving safety concerns, decreasing the toxicity of CAR T-cells, exploring their efficacy in solid tumours as well as limiting the costs of treatment and therefore this has contributed to the creation of a competitive landscape among biotech companies.

Apart from the competitors in the CD19 landscape such as Novartis, Gilead and Juno Therapeutics, other players are emerging in this exciting and rapidly developing field with promising new technologies from Bluebird Bio, Mustang Bio, Celgene etc. <sup>10</sup>





## 2017 - 2018 Updates

The predominant approach that leading companies are developing to treat B-cell malignancies is based on CAR T-cells targeting the CD19 antigen which is expressed on tumor cells and which include several forms of lymphoma and leukemia.

The next most popular targets after CD19 are CD22, BCMA and CD20 antigens, but most of the trials conducted to-date involving CD20 and CD22 have been performed in conjunction with CD19 (and/or/bispecific). <sup>11</sup>

### Share of CAR T-cell trials targeting CD19 <sup>12</sup>

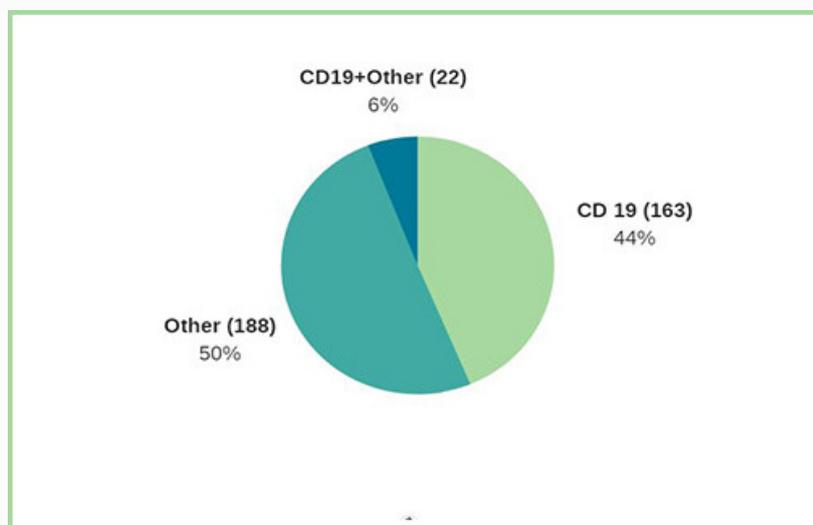


Diagram: [www.celltrials.org](http://www.celltrials.org)

*"50% of all registered CAR T-cell trials are targeting the CD19 Antigen. A small fraction of trials are CD19 with other targets (and/or/bispecific)."* <sup>13</sup>





## 2017 - 2018 Updates

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The two approved products currently present on the market from Novartis (Kymriah) and Gilead (Yescarta) have shown to be effective in a high percentage of patients that do not respond to other available treatments although severe side effects remain a big concern.

Juno Therapeutic's CD19: The safety profile of the JCAR017 program in DLBCL has the potential to change the competitive landscape in the CD19 space. Despite the negative efficacy trends, what could provide this programme with a potential advantage over the competition is the fact that the incidence of CRS (Cytokine release syndrome) is less compared to the other two products already on the market.<sup>14</sup>

Addressing some of the flaws of CD19 CAR T-cell technology as well as exploring the potential that CAR T-cells could show in the treatment of solid tumours are just two major trends that are ongoing in this area of research. In addition, numerous biotech companies are developing "off-the-shelf", or allogeneic, CAR T-cell therapies. Unlike the autologous treatments with Kymriah and Yescarta, where the T cells are derived from the individual patient's blood, then undergo genetic modification, in-vitro multiplication and then transferred back to the patients (which is a time-consuming and costly process) in the case of allogeneic CAR T cell therapies the 'off-the-shelf' CAR T-cells can be administered to multiple recipients, thus simplifying the overall process and therefore expanding access to this immunotherapy.





## 2017 - 2018 Updates

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The following table shows CAR T-cell therapy product lines that are currently being developed by a number of companies, to address toxicity issues as well as exploring the potential of CAR T-cells in the treatment of solid tumours.

Table of CAR T-Cell Therapy Product Lines

Company	Product Line	Challenges /Trends
Bellicum	<b>BPX-601</b> ( GoCAR-T ), <b>BPX 701</b> (CaspasCIDE safety switch)	Solid Tumors (PSCA), AML, Melanoma
Servier and Pfizer	<b>UCART19</b> (Universal Chimeric Antigen Receptor T cells)	CD19-Expressing hematological malignancies
Celyad	<b>CYAD - 01</b> (CAR-T NKG2D)	Solid Tumors
Bluebird Bio and Celgene	<b>bb2121</b> (BCMA CAR T )	MM (Phase 2/3)
Juno Therapeutics	<b>CD19: JCARO17</b>	Reducing toxicity
Collectis	<b>UCARTs</b> Programes	ALL, MM, NHL, AMHL, B-NHL, BPDCNL
Bluebird / TC Biopharm	<b>CAR-T Gamma Delta T Cell</b>	Safer versions, solid tumors
MustangBlo	<b>MB-101</b> (IL13R $\alpha$ 2-specific CAR)	Glioblastoma

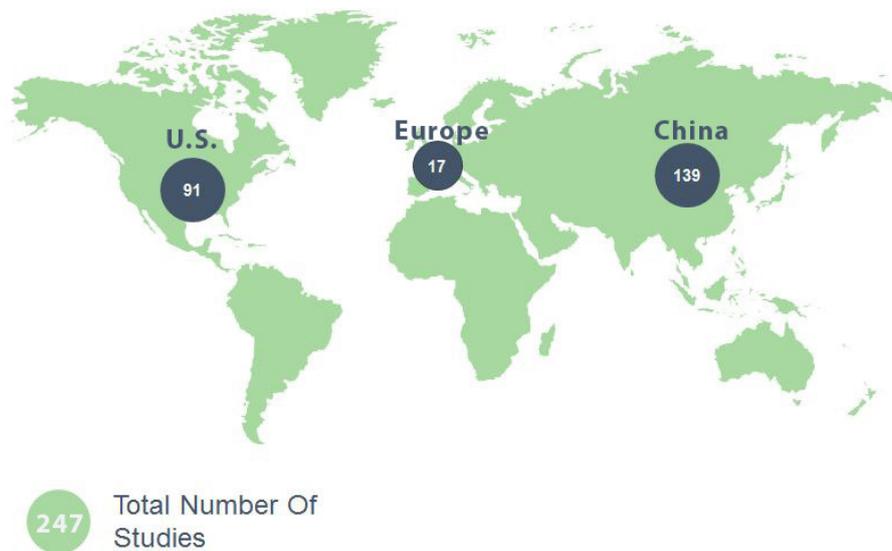
Table compiled by ACROSS based on the information sourced from the respected companies websites.





2017 - 2018 Updates

## World Map of CAR T-Cell Therapy Clinical Trials



World map created by ACROSS Global based on data sourced from [www.clinicaltrials.gov](http://www.clinicaltrials.gov); (03-September-2018). Applied filters include the Other Terms (CAR T-Cell), Recruitment Categories ( Not yet recruiting, Recruiting, Enrolling by Invitation, Active not Recruiting), and Phases: Early Phase 1, Phase 1, Phase 2, 3 and 4.

In addition to the 247 clinical trials conducted in the US, EU and China a further (nn) clinical trials are being conducted elsewhere around the globe.

CAR T-cell therapy has opened the door to new possibilities in the treatment of other malignancies such as melanoma,<sup>15</sup> glioblastoma,<sup>16</sup> mesothelin expressed tumours ( Generally, mesothelin is commonly expressed and found among several cancers: mesothelioma, lung, pancreas, breast, and ovarian).<sup>17</sup>

*"Mesothelin-targeted chimeric antigen receptor (CAR) T-cell therapy has shown early evidence of efficacy in a phase I trial of patients with malignant pleural disease and mesothelioma, non-small cell lung cancer, or breast cancer (NCT02414269)."*<sup>18</sup>

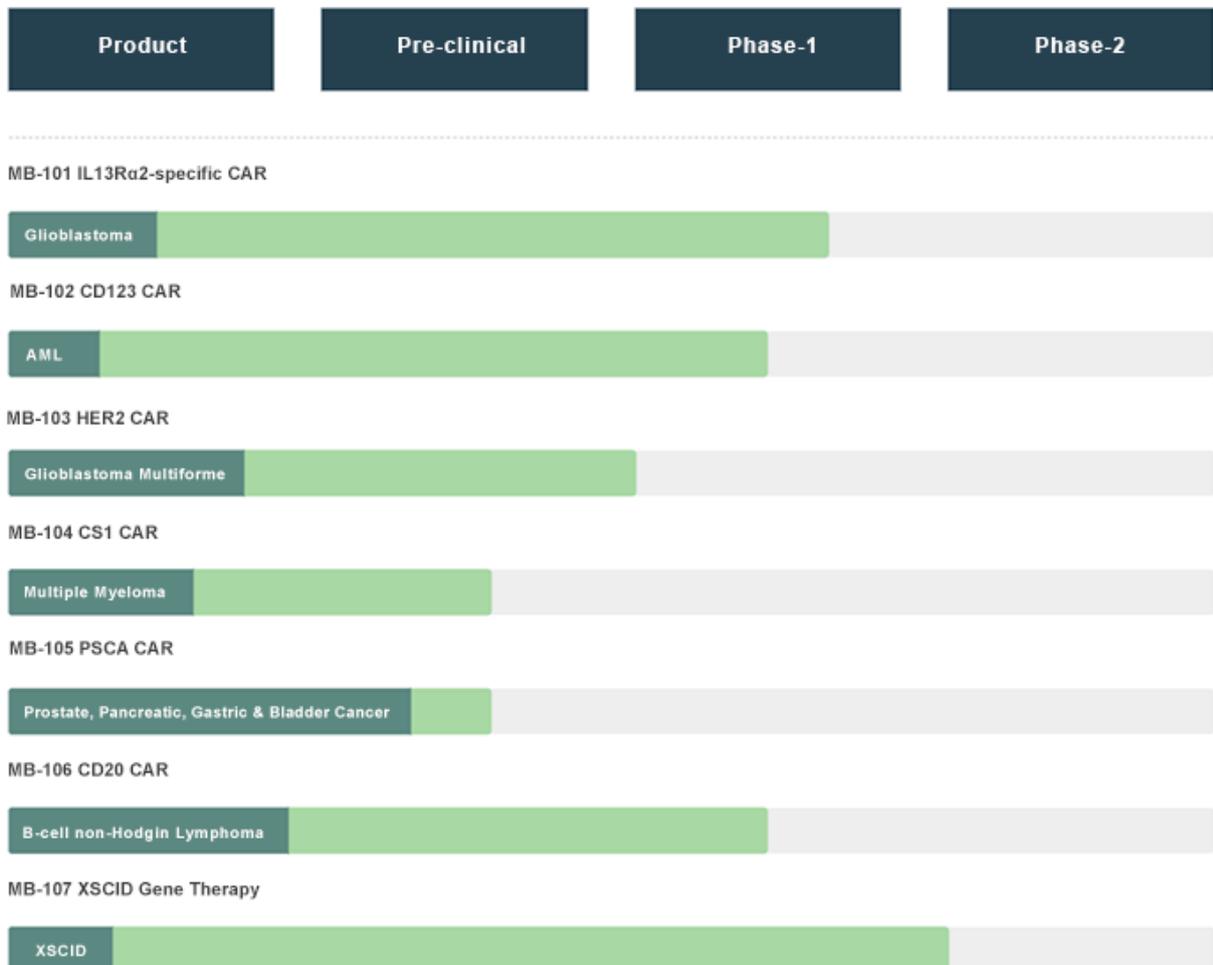




# CAR T-CELL THERAPY

## Featured Company Pipeline - MustangBio

Mustang Bio is a biopharmaceutical company with a focus on the development of chimeric antigen receptor engineered T cell (CAR T) immunotherapies as well as gene therapies in areas of unmet need. Their impressive pipeline of products pictures the general trends in research involving the CAR T-Cells. MustangBio has several product lines targeting solid tumors, e.g. HER2 or MB-103: Immunotherapy for Glioblastoma Multiforme.



source: product pipeline:mustangbio.com





# CAR T-CELL THERAPY

## Regional Focus - U.S. Clinical Trial Data

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According to Clinicaltrials.gov database (3-September-2018), the current number of studies involving CAR T-cells is 142, the vast majority being in Phase 1 (119/142)

### Breakdown of CAR T-Cell Therapy by Clinical Trial Phase in U.S..

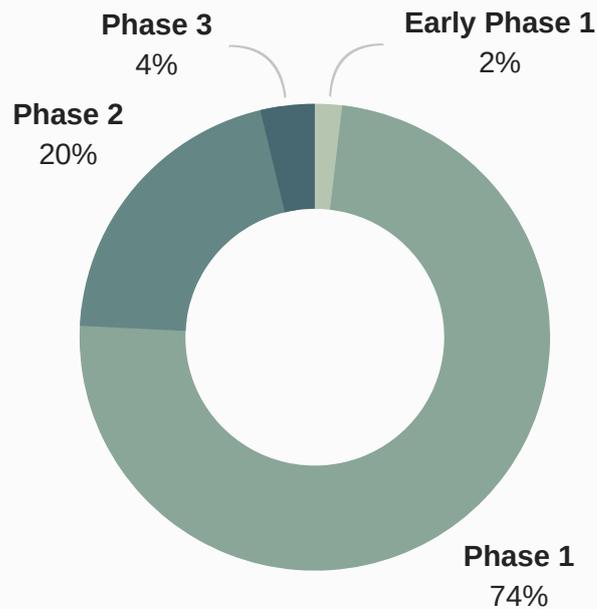


Diagram created by ACROSS Global based on data sourced from [www.clinicaltrials.gov](http://www.clinicaltrials.gov); 3-September-2018; Applied filters include the Country, Other Terms (CAR T-cell), Recruitment Categories ( Not yet recruiting, Recruiting, Enrolling by Invitation, Active not Recruiting), and Phases: Early Phase 1, Phase 1, Phase 2, Phase 3 and Phase 4.

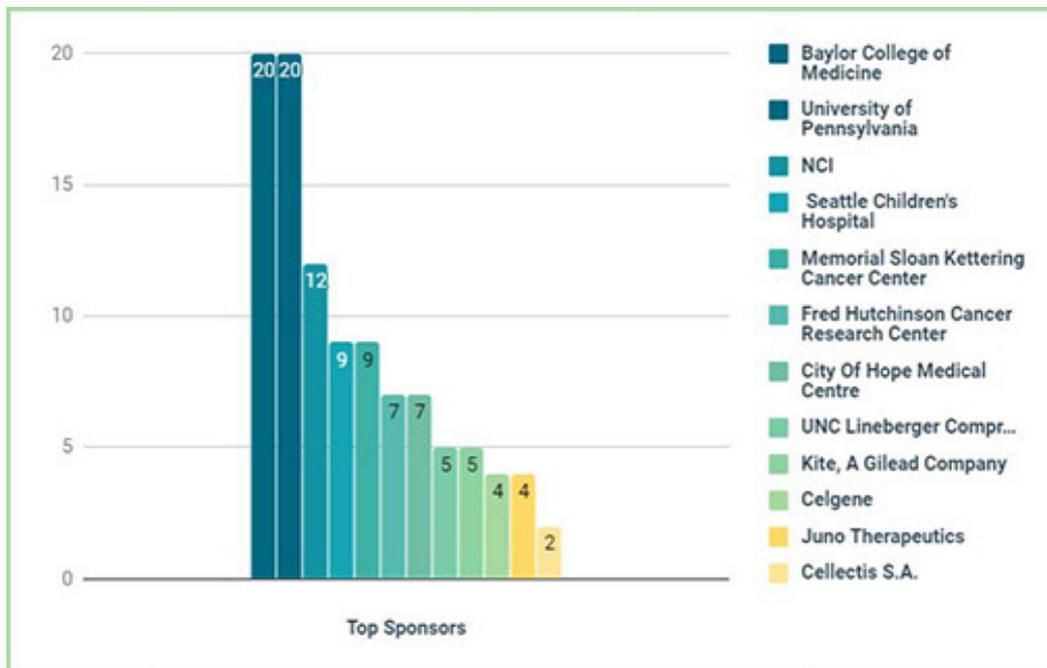




## Regional Focus - U.S. Clinical Trial Data



### Top Sponsors in U.S.



Graph created by ACROSS Global based on data sourced from [www.clinicaltrials.gov](http://www.clinicaltrials.gov); 3-September-2018; Applied filters include; Other Terms (CAR T-cell), Country, Recruitment Categories ( Not yet recruiting, Recruiting, Enrolling by Invitation, Active not Recruiting), and Phases: Early Phase 1, Phase 1, Phase 2, Phase 3 and Phase 4.





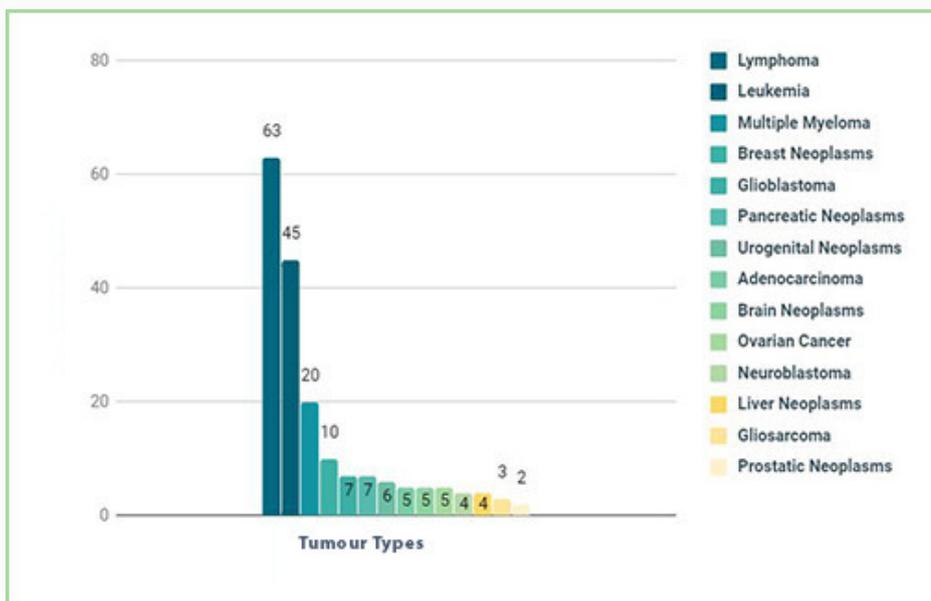
## Regional Focus - U.S. Clinical Trial Data

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The graph below shows the comparative trends in clinical trials targeting liquid tumours vs solid tumours. However, it's important to note that the number of CAR T-cell trials in solid malignancies is growing.

### CAR T-Cell Therapy Clinical Trials. Liquid vs Solid Tumours



Graph created by ACROSS Global based on data sourced from [www.clinicaltrials.gov](http://www.clinicaltrials.gov); 3-September-2018; Applied filters include; Other Terms (CAR T-Cell), Recruitment Categories ( Not yet recruiting, Recruiting, Enrolling by Invitation, Active not Recruiting), and Phases: Early Phase 1, Phase 1, Phase 2, Phase 3 and Phase 4.





# CAR T-CELL THERAPY

## Guidelines and Regulations

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- 1. FDA Perspective on the Regulation of TCR/CAR T-cell Products**
- 2. Regulatory Approval of Modern Gene-Based Cancer Immunotherapies – CAR T Cells**
- 3. Cellular & Gene Therapy Guidances**
- 4. European Medicine Agency - Guidelines relevant for advanced therapy medicinal products**





# CAR T-CELL THERAPY

## Conferences and Events

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18-20 June, 2019

San Francisco, U.S.

**Next Generation CAR & T Cell Therapies**

18-20 June, 2019

Shanghai, China

**CAR-TCR Summit Asia**

10-13 September, 2019

Boston, U.S.

**CAR-TCR Summit**





# CAR T-CELL THERAPY

## Library Of Articles

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1. Cancer Research Institute, Immunotherapy
2. National Cancer Institute
3. ASCO
4. Healio.com Hematology - Oncology
5. LABIOTECH.eu





# CAR T-CELL THERAPY

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6. MedScape, First CAR T Cells Approved in Europe
7. LABIOTECH.eu, A Cure for Cancer? How CAR-T Therapy is Revolutionizing Oncology
8. Yescarta.com, Results with Yescarta, diagram data
9. Yescarta.com, Yescarta is a one-time therapy that offers a chance for complete remission
10. Seeking Alpha, One Year Later: Lessons Learned In CAR T
11. Cell Trials, What is the hottest CAR cell therapy target beyond CD19?
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14. Nisarg Patel, Medium, Next-Generation CAR-T : The Race to Win the Future of Immuno-Oncology
15. Melanoma Research Alliance, Why so much excitement about CAR-T cells?
16. Neuro-Oncology, CAR T-cell therapy for glioblastoma: recent clinical advances and future challenges
17. Targeted Oncology, Early Signs of Efficacy Seen With Mesothelin CAR T-Cell Therapy
18. Targeted Oncology, Early Signs of Efficacy Seen With Mesothelin CAR T-Cell Therapy





## ACROSS RESEARCH PAPER

If you have any suggestions for improvement to future editions of our CAR T-Cell Therapy ACROSS Research Paper please contact me directly and I will welcome your thoughts.

Ena Zuvic

[zuvic@across.global](mailto:zuvic@across.global)

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