Tracking the CAR-T revolution: Analysis of clinical trials of CAR-T and TCR therapies for the treatment of cancer

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ABSTRACT

Chimeric antigen receptor and T-cell receptor (CAR-T/TCR) cellular immunotherapies have shown remarkable success in the treatment of some refractory B-cell malignancies, with potential to provide durable clinical response for other types of cancer. In this paper, we look at all available FDA CAR-T/TCR clinical trials for the treatment of cancer, and analyze them with respect to different indications, targeted antigens, products, and originator locations. We found that 448 of 679 registered are currently active and of those 195 (41%) originated in China and 198 (47%) in the US. Our analysis suggests that the rapid increase in the number of clinical trials is driven by the development of different CAR-T products that use a similar therapeutic approach. We coin the term bioparallels to describe such products. Our results suggest that one feature of the CAR-T/TCR industry may be a robust response to success and failure of competitor products.

Keywords: CAR-T, TCR, cancer immunotherapy, immunotherapy clinical trials

HIGHLIGHTS

• Rapid rise in initiated CAR-T/TCR clinical trials for the treatment of cancers
• CD19 CAR-T products are driving the overall number of clinical trials
• By the end of 2018, the number of active trials originated in China exceeded those in the US.

INTRODUCTION

Chimeric antigen receptor and T-cell receptor (CAR-T/TCR) immunotherapies are targeted cellular therapies that use the cytotoxic potential of T cells to eradicate cancer cells in an antigen-specific manner (June and Sadelain, 2018; Lim and June, 2018). The therapeutic approach involves genetic modification of isolated T cells from a patient in order to express the desired CAR or TCR gene on cells’ surface (Figure 1A). Genetically modified T cells are subsequently infused back into the patient, where they eventually come in direct contact with the cancer antigen, resulting in the killing of the cancer cell (Hartmann et al., 2017). In 2017, the Food and Drug Administration (FDA) approved two CAR-T therapies, tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), for the treatment of relapsed or refractory acute lymphocytic leukemia and large B-cell lymphoma respectively. Recent long-term follow-up studies for lymphoma (Schuster et al., 2019, Locke et al., 2019) showed overall response rates (ORR) >50% with complete response (CR) of 37% and 40% at 12 and 27 months respectively. These numbers represent a major improvement in treatment efficacy and response durability, especially for those patients who are refractory to chemotherapy.
In the light of the recent success and future potential of CAR-T/TCR therapies for the treatment of cancer, we aim to provide a comprehensive overview of the growth of the clinical trials space for these products, and to highlight some of the factors driving this growth. One such factor is the nature of CAR-T/TCR immunotherapies which makes it possible to develop many different products that use essentially the same therapeutic approach and achieve clinical efficacy (Huzair and Kale, 2015; Moore, 2017). Such CAR-T/TCR products that are currently in the clinical pipeline cannot be characterized as biosimilar products in the narrow sense of the term, so we propose that CAR-T/TCR products that use a parallel therapeutic approach be termed bioparallels. (In Appendix Figure 1B and 1C we depict several ways of developing bioparallel products.) We identified a total of 757 registered clinical trials related to CAR-T/TCR product development.

**MATERIAL AND METHODS**

Information related to CAR-T/TCR clinical trials was collected from the NIH’s ClinicalTrials.gov (CTgov). Only trials registered in CTgov are included in our sample (henceforth “CTgov” trials). The dataset is available as a supplementary material (Supplemental File 1). In total, we identified 757 NCT trials that involve CAR-T/TCR therapies or close analogs. Of these, 583 were CAR-Ts and 125 were TCRs. The remaining 49 trials comprised bispecific CAR CIK cells (cytokine induced killer cells), CAR NK cells (natural killer cells) and T cells engineered to have properties normally found in NK cells. Because the start date of a trial, as reported on CTgov, typically represents the starting point for patient enrollment, we used this date as the clinical trial initiation date in our analysis. Among the trials we found 35 that were flagged as “Not yet recruiting” – these were eliminated from our analysis, leaving a sample of 722 initiated trials. The first clinical trial in our database started in April 1998 (NCT0004178), with our sample including all identified CTgov trials starting between that date and December 31, 2019.

**RESULTS**

**Clinical trials for CAR-T/TCR and related therapies**

Of the 722 initiated clinical trials in our sample, 126 are no longer active (17.5%) and 86 have an “Unknown” status (11.9%). Of the 510 remaining active clinical trials, 441 trials (86.5%) are in Phase 1 or Phase 1/2, 49 trials (9.6%) are in Phase 2 or Phase 2/3, 5 are in Phase 3, and the rest of the trials are either long term follow ups (9) or trials with no self-reported phase (21) (Table 1).

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<tr>
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<td>39</td>
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<td>3</td>
<td>10</td>
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<tr>
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<td>21</td>
<td>6</td>
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<td>2</td>
<td>3</td>
<td>55</td>
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<td>6</td>
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<td>75</td>
<td>6</td>
<td>5</td>
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Figure 2 shows the total number of initiated trials through 2019 both cumulatively and on a year-by-year basis. The overall picture is one of steadily accelerating growth although, from the year-by-year plot, a number of slowdowns can be seen before the start of near exponential growth in 2014. We note that slowdowns appear to have occurred at about the time of some widely reported failures including the failure of a TCR trial in colorectal cancer in 2009 and the failures of two TCRs targeting MAGE-A3 in solid tumors in 2011. There was no such slowdown coincident with the widely publicized termination of Juno’s JCAR015 in 2016. The remainder of this section provides a number of breakdowns of the overall picture of trials initiation.

**Figure 2.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 of CAR-T/TCR trials initiated under FDA guidelines.

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3 This is somewhat analogous to the development of monoclonal antibodies – particularly in the PD-1/PD-L1 space.

4 Kymriah and Yescarta are both CD19 targeted CAR-Ts and both use ScFv FMC63 but different promoters (EF1a vs MSCV), different costimulatory domains (4-1BBzeta vs CD28zeta) and different Hinge & TM (CD8alpha vs CD28).

5 Only trials with start dates before January 1, 2020 are included in this analysis.

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Footnotes:

1 This is somewhat analogous to the development of monoclonal antibodies – particularly in the PD-1/PD-L1 space.

2 Kymriah and Yescarta are both CD19 targeted CAR-Ts and both use ScFv FMC63 but different promoters (EF1a vs MSCV), different costimulatory domains (4-1BBzeta vs CD28zeta) and different Hinge & TM (CD8alpha vs CD28).

3 Only trials with start dates before January 1, 2020 are included in this analysis.

4 In earlier phases of our research some trials data was obtained from citeline’s Trialtrove® and Pharmaprojects® databases before being verified on CTgov.

5 “Unknown: A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.” 77 China-originated trials were reclassified from active to “Unknown” during 2019.
While the number of initiated trials has increased for all therapies, the number of CAR-T trials has increased significantly faster, especially since 2013 – CAR-T trials initiatives grew at a 40.8% compound annual growth rate vs. 27.4% for the other therapies in our sample from 2013 to the end of 2019 (Figure 3A).

**Figure 3A.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 - type of therapy.

That growth was largely fueled by CAR-Ts targeting CD19 (Appendix Figure 3B) – the antigen targeted by Kymriah and Yescarta. On a smaller scale, we can also observe the increase in trials targeting the antigen BCMA after 2016 (from a total of 7 initiated trials at that point to 19 in 2017 and 59 in 2019). This followed encouraging results in trials treating multiple myeloma. Overall, the result has been that, while the initiation of trials targeting solid tumors had kept pace with those for hematological cancers through 2015, 2016-2019 saw 237 trials initiated targeting hematological cancers (64%) vs. 193 targeting solid tumors. (Appendix Figure 3C). As we will see, one factor in the overall increase in hematological trials’ initiations was the increase in the number of trials initiated by China based originators.

Our sample includes trials originated by sponsors in 19 countries (Appendix Table 2). Originators based in the United States (333 trials) and China (298) dominate with the United Kingdom (37) a distant third. The other 14 countries originated 53 trials between them. The first CTgov trial from a China based originator was initiated in 2012. In the following two years a further 13 trials were initiated. Since that date a further 284 CTgov trials have been initiated by China based originators comprising almost 48% of all trials initiated over that period (Appendix Figure 3D). Breaking it down further, in 2016-2019, China based sponsors initiated 175 trials targeting hematological malignancies – 53.5% of such trials initiated in that period. Finally, we also note that China based originators have focused very strongly on CAR-T development (more than 90% of their initiated trials) in contrast to US based originators for whom TCRs and other related therapies made up more than 28% of trials initiated (Figure 4A and Appendix Figure 4B).

**Figure 4A.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – China based originators.

**Tissues and antigens targeted**

As previously noted, particularly in 2016-2019, trials initiated for hematological cancers far exceeded those for solid tumors with most of the hematological trials (93%) being CAR-Ts targeting either B-cell leukemias and lymphomas (299 trials of which 272 target CD19) or multiple myeloma (74 trials of which 59 target BCMA) (Figure 5A, Appendix Figures 5B and 5C).

**Figure 5A.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – Hematological cancers.

Other hematological cancer trials target myeloid leukemias and myelodysplasia (63 trials), as well as T-cell lymphomas and Hodgkin’s lymphoma (17 trials). While predominantly CAR-Ts, these also include TCRs and other related therapies.8

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6 In terms of active trials, excluding those with “Unknown” status, the US (240) led China (206) at the end of 2019.

7 CD20 and CD22 also figure significantly in B-cell leukemia and lymphoma trials.

8 Most frequently CAR-Ts targeting CD123 and TCRs targeting WT-1 although many other antigens are targeted.

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Trials addressing solid tumors comprise CAR-Ts (163), TCRs (99) and other related therapies (27) (Figure 6A).

**Figure 6A.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – Solid tumors.

They target over 60 antigens or oncoproteins expressed by tumors affecting 20 solid organs and tissues. The most frequently targeted antigens are NY-ESO-1 (whose 52 trials make up 47% of all solid tumor TCRs), mesothelin (30), EGFRvIII (30), GD2 (27), HER2 (20), and MUC1 (20) (Appendix Figure 6B). The most frequently targeted tissue types have been cancers of the brain and nerve tissue (35 trials) liver (24), female reproductive system (23) and lung (19) (Appendix Figure 6C). The number of multi-organ CAR-T/TCR clinical trials that recruit patients with different solid tumors has increased rapidly since 2013 (currently 57 trials), perhaps because it is a more efficient strategy to perform trials and recruit patients.

**DISCUSSION**

**Rapid rise in the number of CAR-T/TCR bioparallel products**

We define bioparallel products as different biological products that use a parallel therapeutic approach to achieve similar clinical efficacy. In the case of CAR-T/TCR therapies, bioparallel products can be designed in several ways. Appendix Figures 1B and 1C depict how several different CAR-T/TCR products can target the same antigen by recognizing a different epitope. For example, the two FDA approved CAR-T therapies, tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta), both target the same antigen, CD19. In the case of TCR therapies, JTCR016 (Juno Therapeutics) and CMD-602 (Cell Medica Ltd.) are examples of two different TCR products undergoing clinical trials that recognize the same antigen, Wilms tumor protein (WT-1), which is mutated in multiple types of cancer. Our clinical trials analysis suggests that the development of bioparallels may be driving the overall numbers of CAR-T/TCR trials as many companies are in the process of entering the market by developing their own variants of a therapeutic approach that has a lower risk of failure or has already proven successful. CAR-T products that target CD19 are the most obvious example - we have identified almost 80 bioparallel CD19 targeting products that are either in trials or are already approved (with around 20 more in multi-CAR-T trials). Another example is a CAR-T therapeutic approach that targets BCMA for the treatment of multiple myeloma. BCMA is a cancer antigen that is therapeutically similar to CD19 in several ways. It is highly expressed on all plasma cells and loss of BCMA does not have significant adverse influence on the overall homeostasis of B-cells or plasma cells, but it is critical for long-term survival of plasma cells (Tai and Anderson, 2015). This means that eradicating BCMA expressing cells using CAR-T/TCR approach is a sound therapeutic option. We have identified 42 clinical trials that target BCMA, and CAR-T clinical trials targeting this antigen are the fastest growing after CD19. Current clinical trial pipelines consist of over 20 different BCMA CAR-T programs.

In addition to targeting different epitopes, the highly modular nature of CAR-T therapeutics allows for even greater product diversification, as was evident in the development of several different generations of CAR-T designs (Hartmann et al., 2017). Some approaches target multiple epitopes with the same CAR-T product. For example, several clinical trials use bispecific CAR-T cells that simultaneously target CD19 and CD20 or CD22 (NCT03271515, NCT03241940). Expression of recombinant receptors, such as EGFRt, for antibody-mediated depletion of CAR-T cells from the patient, or the use of T cells with deleted PD-1 to avoid immunosuppression, are more recent CAR-T products (NCT03085173, NCT03298828). These and other variants of CAR-T/TCR products represent a platform for the development of an ever-growing number of bioparallels (Labanieh et al, 2017). Indeed, this behavior resembles to a large extent the “gold rush” of biosimilar monoclonal antibodies, which can be diversified to a similar extent (Ecker et al., 2015; Kaida-Yin et al., 2018).

**Effects of clinical success and failure in the CAR-T/TCR market**

The rapid rise in the number of developing CD19 CAR-T products after reports of clinical success from tisagenlecleucel trials in 2012 is an indication of how the market responds to a successful therapeutic approach in the CAR-T/TCR space. Similarly, the recent increase in the number of BCMA CAR-T products for the treatment of multiple myeloma represents another example of how a successful clinical trial may influence development decisions at other companies. In 2016 two clinical trials of BCMA targeting CAR-Ts reported therapeutic tolerability and efficacy, with more than half of the patients achieving complete remission (NCT02658929, NCT03090659). In the subsequent two and a half years 35 BCMA trials were initiated.

Developers are not only connected because of the intrinsic biological similarity of their products, but there seems to exist a
complex network of CAR-T/TCR companies that are interacting via technology licensing, academic collaborations, and research support. Indeed, the cost of research and development of a new drug presents a risk for a pharmaceutical company, so leveraging the information from other similar trials can alleviate some of the costs (Krieger, 2017). Therefore, the reports of clinical success or failure of one product in development would have an effect on a more global scale. While this is not a novel behavior in drug development industry, different CAR-T/TCR therapies are so biologically similar that trends appear to be more robust.

Finally, the observation of relatively fewer different CAR-T/TCR products and clinical trials for solid tumors may be explained by the lack of clinical efficacy for current products and the previously noted failures of several earlier TCR trials. The greatest number of clinical trials has been initiated for cancers affecting brain and nerve tissue, for which CAR-T/TCR therapies have not yet demonstrated clinical success. Clinical trials have thus far focused on CAR-T products targeting the GD2, EGFVIII, and HER2 antigens and TCRs targeting NY-ESO-1, a cancer/testis antigen. GD2 is a complex glycosphingolipid, highly expressed on the surface of several solid tumors, especially neuroblastoma and melanoma, while EGFVIII and HER2$^*$ are surface protein receptors highly expressed on the surface of many solid tumors. These antigens were known from previous studies to be clinically suitable targets for monoclonal antibody therapy (Plössel et al. 2016; Razpotnik et al. 2017). In the context of CAR-T therapy, all 3 antigens have shown clinical tolerability, however none of the approaches have resulted in significant eradication of tumor cells (Morgan et al., 2012; Ahmed et al., 2015; Hecezy et al., 2017). The proposed reasons for poor performance of CAR-T/TCR therapies in solid tumors range from the highly immunosuppressive environment, to the lack of therapeutically effective cancer antigens (Newick et al., 2017; D’Aloia et al., 2018; Castellarin et al., 2018). Were these roadblocks to be effectively overcome, it would not be surprising to see a growth in the number of initiated trials similar to that experienced in trials targeting BCMA or, indeed, CD19.

CONCLUDING REMARKS

CAR-T and TCR therapies are revolutionary biotechnology products that have already shown long-term durable remission for the treatment of some types of refractory B-cell leukemias and lymphomas, with potential to provide durable remission for other types of cancers. Our analysis of all identified CTgov trials for CAR-T/TCR therapeutics suggests that there is a rapid rise in the number of bioparallel products, the term we coined to describe different products that use a parallel therapeutic approach. It will be interesting to see if this continues in the future as more CAR-T/TCR products get FDA approval, particularly if one is a CAR-T/TCR therapy for the treatment of a solid tumor.

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ABOUT FOCUS

The MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable and potentially curable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by these therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement in this endeavor.

*Both EGFR and HER2 are proven cancer targets for treatments involving monoclonal antibodies or tyrosine kinase inhibitors (TKIs) – each class providing examples of biosimilar products*


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APPENDIX

Figure 1B

Figure 1C
Table 2. Summary of number of trials by country of origin.

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<th>Country of origin</th>
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<th>Currently Inactive</th>
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Figure 3B. The cumulative number of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 for the 12 most frequently targeted antigens.

Figure 3C. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 - hematological cancers and solid tumors.

Figure 3D. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – country of the originator.

Figure 3E. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – hematological cancers and solid tumors.

Figure 4B. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – US based originators.

Figure 4C. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – hematological cancers and solid tumors.

Figure 5B. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – most frequently targeted antigens in hematological cancer therapies.

Figure 5C. The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – hematological cancers and solid tumors.
**Figure 5C.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – types of hematological cancers.

**Figure 6C.** The cumulative number of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – the most frequently targeted tissue types with solid tumors.

**Figure 6B.** The cumulative and yearly numbers of CAR-T/TCR trials registered on clinicaltrials.gov and initiated on or before 12/31/2019 – the most frequently targeted antigens in solid tumors.