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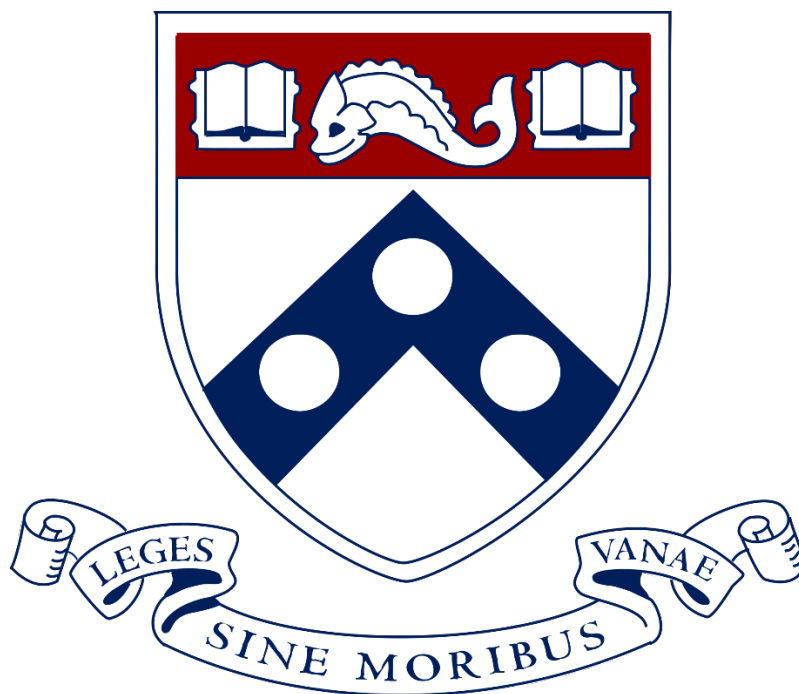
AN EXPLORATION OF THE CONTEMPORARY RESEARCH LANDSCAPE AND ITS IMPLICATIONS FOR MARKET INNOVATION PARADIGMS

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I. Introduction

1.1 Cellular Therapy Background

"We aren't made of drugs, we're made of cells. Harvested cells, or harvested cells in combination with pharmaceuticals, will be the future of medicine." [i] Here Cate Hildreth, president and chief executive officer of BioInformant, seems to echo the collective sentiments of many within the contemporary scientific community: cellular therapy will be perhaps the most essential and influential area within medical research within the coming decades. Once considered not much more than an overtly over-idealized postulate, cellular therapy has been one of the most rapidly expanding and vigorously pursued fields within the past few years. With extensive potential for implementation within substantially diverse use-cases, cellular therapy will only continue to grow and evolve given the continued research toward novel methodologies.

Fundamentally, cellular therapy is the practice of transplanting human cells for the purpose of replacing or repairing damaged tissues. With improving technologies and limitless imagination, a variety of different cell types could be employed for the treatment of many unique diseases. Currently, the predominant therapies target skin and chronic would patients, at forty percent of the total industry, musculoskeletal damage, at twenty-eight percent of the industry, and a variety of different cancers, at sixteen percent of the industry. [ii] These established areas within cellular therapy coupled with the promise for a multitude of future applications have driven tremendous growth within the industry over the past five years; rapid product innovation and increased treatment approvals by the Food and Drug Administration coupled with a considerable influx of funding for facility expansion and research and development has prefigured a compounded annual growth rate of 20.1 percent over the past five years. Ultimately given the continued rate of innovation within cell therapy research, it is quite possible that the industry will only continue to expand, allowing for positive feedback loops driving increasingly accelerated innovation.

1.2 CAR-T Therapy Background

As one of the most predominant areas of funding and research within cellular therapy, cancer has always been considered a pressing and well-aligned candidate for cellular therapy to target. While cell therapies for cancer treatment have been posited in many different forms, one of the most recent and perhaps most promising iterations has been Chimeric Antigen Receptor T-cell therapy, or CAR-T. In theory, CAR-T uses in-vitro cultured white blood cells, T-cells, to target and eliminate abnormal, cancerous cells. More specifically, the process begins by first harvesting the T-cells from a sample of the given patient's blood. Once extracted, an inactive virus is used to insert particular genes responsible for the production of chimeric antigen receptors into the sample T-cells. The modified T-cells possessing the chimeric antigen receptors, CAR-T cells, are then multiplied until a sufficiently large sample of the cells has been produced. Then once inserted back into the patient's body, these CAR-T cells target malignant tumor cells based on a specified cellular surface protein that is specific to the receptors within the CAR-T cells' membrane. Once bound to the target cell's surface antigen, the CAR-T cell triggers a cascade that results in tumor cell apoptosis. Moreover, CAR-T cells may remain within the local environment for an extended period of time following the tumor cell lysing.[iii] This allows the CAR-T cells to kill any tumor cells that may return, mitigating the potential for the cancer to resurface to some extent.

CAR-T has been repeatedly proven to work and testing data has been corroborated for its relative efficacy. However despite its many advantages and substantial promise, the treatment in its current iteration is still associated with significant side effects to consider. Perhaps the most concerning detriments is Cytokine Release Syndrome. Cytokines are essentially chemical messengers that aid T-cells function by facilitating communication between immune cells. With the transplantation of additional, specialized T-cells, cytokines are inherently released to levels that may potentially deviate from homeostatic levels within the patient body. In mild cases, the additional cytokine concentration can lead to fever, nausea, and headaches. However in more hazardous cases, severe cardiovascular complications including capillary leakage, hypoxia, hemophagocytic lymphohistiocytosis, and even cardiac arrest can be

induced.[iv] In essence, CAR-T therapies, although promising and quickly improving, must still be developed in order to achieve treatment outcomes similar to those of first-line therapies and what is currently the industry standard for oncological treatment.

1.3 CAR-T Discovery and Development

Given the intricately complex and deeply sophisticated processes involved with the CAR-T treatment in its current iteration, it is easy to see how contributions from many individuals specializing in distinct fields were required in order to piece together essential discoveries leading to CAR-T's development. The process was sparked with MIT's Dr. Michel Sadelain in 1992. With his employment of retroviral vectors, Dr. Sadelain was able to introduce pre-specified genes into T-cells to produce the first in-vitro engineered T-cells.[v] Shortly thereafter only one year later, Dr. Zelig Eshhar produced the first generation of CAR-T cells by introducing genes that would lead to the synthesis of an antibody fused to part of a T-cell receptor.[vi] While technologically innovative, these cells would not persist within the target in-vivo environment for any meaningful period of time. Subsequently in 1994, a team of scientists at Memorial Sloan Kettering Cancer Institute discovered how to isolate virus specific T-cells for use in stem cell transplants, mitigating post-transplant infection and virally caused cancers.[vii] Then finally in 2002, the first generation of effective CAR-T cells is developed by another research team from Memorial Sloan Kettering that targeted a prostate cancer antigen. This CAR-T iteration was proven to survive, proliferate, and eliminate prostate cancer cells in an in-vitro environment. Shortly following this development, Dr. Sadelain published a landmark paper in 2003 convincingly showing CAR-T cells targeting the CD19 antigen were effectively able to kill Leukemia cells in mice.[viii] Upon this discovery, Dr. Sadelain then provided a consistent and regimented manner in which to manufacture CD19 CAR-T cells with proven efficacy in treating patients with relapsed, chemorefractory leukemia. Ultimately it is the CD19 antigen that is most commonly targeted in current iterations of CAR-T treatment given its strong and uniform expression on particular malignant cancer cells. With this strong base of research, current scientists aim to apply the same CAR-T cells to novel biomarkers for the diversification of CAR-T applications.[ix]

II. CAR-T Positioning: Market Approval and Competitive Landscape

2.1 Transition from Laboratory to Marketplace

After Dr. Sadelain's discovery of CD19 as uniformly and strongly expressed antigens associated almost solely with malignant B cells, the development of a CAR-T therapy for treatment of particular blood cancers began to increase in pace and funding almost immediately. Shortly after Dr. Renier Brentjens of Memorial Sloan Kettering published convincing clinical trials conveying CAR-T therapy's efficacy in treating adults with acute lymphoblastic leukemia, the Food and Drug Administration granted CD19 directed CAR-T cells "breakthrough designation" in 2014.[x] With this initiative designed to minimize development costs and product lifetime within the approval timeline, many large industry players within the biotechnology industry were eager to pursue CAR-T therapy as a viable treatment paradigm for specific forms of leukemia. Once industry funding was injected into the development process for these therapies, the race to bring the first CAR-T therapy to market as a market first-mover was initiated and progress would only increase in pace.

In only three years, Novartis would be the first to have its CAR-T therapy Kymriah approved to be sold commercially followed closely by Juno with its solution in Yescarta.[xi] Moreover, a variety of smaller competitors with improved therapies are at the brink of approval and threaten to steal market share from the current industry leaders. Here it entirely evident that competition is immensely vehement in pursuing iterative improvements to previously approved drugs within indications that have largely been proven to be highly responsive to CD19 CAR-T treatment. However, recent research within novel malignant cell antigen markers coupled with the economic impetus to provide therapies to a more expansive patient population have positioned an entirely new wave of CAR-T therapies quite well for eventual market approval. Ultimately, it is essential to more closely examine the development and product life cycle that each of the current, on-market CAR-T solutions have been associated with in order to more holistically understand what is required to bring novel treatments to market and to more accurately determine what the new wave of CAR-T therapies must contend with in order to reach approval.

2.2 Novartis: Market First Mover

As one of the largest biotechnology companies regardless of treatment area, Novartis would seem, at least viscerally, as an unlikely candidate to pursue the development, marketing, and sales of any substantially risky therapy, like CAR-T therapies. However given the stagnating sales of its top selling products at the time, Novartis was acutely aware of its need to emerge with novel therapeutic areas with strong promise for sustained growth. Given its firmly established core competency within oncology, CAR-T seemed like an optimal candidate to add within Novartis' immunotherapy portfolio. Ultimately with the assistance of Dr. Carl H. June's team at the University of Pennsylvania Perelman School of Medicine, Novartis resolutely forged ahead to provide the world with the first approved CAR-T solution: Kymriah.

2.2.1 Kymriah: Diversely Applicable and First of Its Kind

After being granted "breakthrough" designation by the Food and Drug Administration in 2014 for treatment of pediatric and adult patients with relapsed or refractory acute lymphoblastic leukemia, Novartis was able to more efficiently streamline its testing processes, solely targeting lymphoblastic leukemia to start.[xii] In its global Phase II study highlighting safety and efficacy, Novartis conveyed that out of fifty subjects eighty-two percent of infused patients achieved complete remission or complete remission with incomplete blood count recovery three months after initial treatment (Figure One).[xiii] Additionally, this test showed that the relapse-free rate among responders was sixty percent six months after infusion. Given these promising results, Kymriah was eventually unanimously voted by the Food and Drug Administration's board for approval, ultimately receiving approval in 2017 for treatment of certain pediatric and young adult patients with a form of acute lymphoblastic leukemia.

In addition to its development of Kymriah for lymphoblastic leukemia, Novartis was acutely aware of the therapy's potential application to other cancers with the expression of the CD19 antigen. Shortly after the approval of competing CAR-T therapies for treatment of large B cell lymphoma, Novartis aimed to reapply for an additional approval to cross-sell Kymriah for large B cell lymphoma as

well. In 2017, Novartis' global JULIET trial proved that Kymriah possessed an overall response rate of fifty-three percent, with forty percent of patients achieving complete response and fourteen percent achieving partial response, within adult patients with relapsed or refractory diffuse large B-cell lymphoma. After six months, the associated overall response rate was thirty-seven percent with a complete response rate of thirty percent (Figure Two).[xiv] With these results, Kymriah was granted a second approval to sell Kymriah for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. With an additional approval, Novartis expanded its target population and heightened its sales potential for Kymriah.

2.2.2 Risk Factors and Side Effects

While Kymriah has been approved multiple times for various treatments, it is not without considerable side-effects. Chief among the concerns associated with Kymriah is its tendency to trigger CAR-T therapy's most common unintended response: cytokine release syndrome. Within the ELIANA global trial for treatment of acute lymphoblastic leukemia, ninety percent of the sixty test subjects exhibited symptoms of CNS1, the mildest form of cytokine release syndrome. Moreover, seven percent of the subjects showed signs of CNS2 and three percent of patients suffered from CNS3, the most severe form of the complication (Figure Three).[xv] Moreover within the JULIET trial for treatment of large B-cell lymphoma, fifty-eight percent of all trial subjects experienced cytokine release syndrome with twenty-eight percent experiencing grade three symptoms.[xvi] Although cytokine release syndrome is currently an unavoidable side effect of all CAR-T treatments, Kymriah presents the most widespread and consistent development of the complication. Novartis has publically conveyed its insistence on improving Kymriah in order to minimize its inflammatory response. Without such improvements, Kymriah will leave itself vulnerable to competitors who have already achieved improved cytokine release syndrome rates.

2.3 Kite Pharmaceuticals: Leaders in Immunology

In diametric contrast to Novartis, Kite is perhaps the least surprising market player to have emerged with a novel CAR-T therapy. Founded with the fundamental dedication to developing innovative treatments to the most pressing clinical areas, Kite has cultivated one of the strongest core competencies within immunotherapies and has isolated its focus on oncology. After entering into a Cooperative Research and Development Agreement with the National Cancer Institute in 2012, Kite began developing what would eventually become its predominant portfolio therapy: Yescarta.

2.3.1 Yescarta: Improved Outcomes for Large B-Cell Lymphoma

As Novartis targeted Kymriah toward acute lymphoblastic leukemia, Kite determined to pursue a blue ocean treatment market by positioning its CAR-T therapy toward large B-cell lymphoma. In its primary analysis within the ZUMA-1 global trial, Yescarta was proven to meet the requisite clinical endpoint of objective response rate and rates of tumor response, both partial and complete, documented after a single infusion with an eighty-two percent response rate within patients with chemorefractory aggressive B-cell non-Hodgkin lymphoma. Moreover, this study examined stratified groups of patients with varying forms of aggressive non-Hodgkin lymphoma; patients with diffuse large B-cell lymphoma showed an eighty-two percent overall response rate with forty-nine percent having a complete response and patients with primary mediastinal B-cell lymphoma showed an eighty-three percent overall response rate with a seventy-one percent complete response rate (Figure Four).[xvii] Given these outcomes, Yescarta remains the industry leader in efficacy as a CAR-T solution targeting aggressive non-Hodgkins lymphoma, even after Kymriah was subsequently approved for the same indication. Provided with these promising results, the Food and Drug Administration soon approved Yescarta as the second on-market CAR-T therapy available overall, but the first to target large B-cell lymphoma in 2017. Yescarta has continued to examine Yescarta's clinical potential post-approval as well. To evaluate durability of the Yescarta patient responses from the ZUMA-1 global trial, data was collected one year subsequent to the initial treatment. Within the one hundred eight subjects, eighty-two percent had responded to Yescarta

with fifty-eight percent achieving complete remission. Additionally at a median of 15.4 months after the first infusion, forty-two percent of patients remained in response and forty percent within complete remission.[xviii] Here, Yescarta poses yet another advantage in its treatment of large B-cell lymphoma given its improved durability and tenured responses.

2.3.2 Risk Factors and Side Effects

Yescarta, like Kymriah before it, is inherently associated with considerable side-effects post-treatment. As is expected, the most concerning complication was the consistent observations of cytokine release syndrome. However with only eighteen percent of the tested population showing symptoms of grade three disruptions, it seems that Yescarta poses a significant advantage in comparison to Kymriah's twenty-eight percent. Moreover, the prevalence of cytokine release syndrome decreased to thirteen percent within the six month follow-up.[xix] The predominant grade three or higher adverse events to consider with Yescarta were anemia, at forty-three percent of tested subjects, neutropenia, at thirty-nine percent, neutrophil count, at thirty-one percent, diminished white blood cell count, at twenty-nine percent, thrombocytopenia, at twenty-four percent, encephalopathy, at twenty-one percent, and decreased lymphocyte count, at twenty percent.[xx] Although the substantive frequency with which these complications presented themselves within the patient population may be viscerally alarming, almost all of these instances were minor deviations from homeostasis that could be adjusted with post-treatment care. In essence, Yescarta, although more narrowly targeted to only one cancer indication, posits efficacy advantages as well as adverse effects benefits when compared to competition that is currently available.

2.4 Emerging Competitors

Given the expedited approval timelines and limited on-market competition within the CAR-T therapy space, it is natural that numerous competitors are in the midst of developing novel, improved iterations of currently available therapies. Perhaps the most promising of these therapies is Celgene's Liso Cel, a CD19-directed 4-1BB CAR-T solution targeting heavily pretreated, high-risk patients with chronic lymphocytic leukemia. With an eighty-one percent objective response rate and 43.8 percent complete

response rate within its most recent Phase I trials, it seems that Liso Cel presents the same overall efficacy ratings of Yescarta. However, what differentiates Liso Cel from current therapies is its CD4 and CD8 T-cell surface molecule composition and 4-1BB costimulatory domain, allowing for the amelioration of previously observed CAR-T cell exhaustion. Not only would the addition of the costimulatory domain allow for longer CAR-T activation within the in-vivo environment, but the defined composition also allows for a more precise treatment dose to be administered.[xxi] Moreover, presented the lowest overall observance of grade three cytokine release syndrome at 6.3 percent.[xxii] Ultimately with first-in-class posited durability and the proven diminishment of the most predominant adverse effect, Liso Cel shows significant promise to emerge as a disruptive force within contemporary CAR-T treatment.

III. Contemporary Research: The Next Wave of CAR-T Therapies

3.1 Improving Current Therapies

Given the heavy up-front investment the predominant, current market players have made within CAR-T therapies targeting acute lymphoblastic leukemia and large B-cell lymphoma, it is expected that one of the most heavily funded and ardently pursued areas of current CAR-T research aims to improve the current therapies provided for these indications. More specifically, researchers aim to meet two primary endpoints for the currently available therapies: reducing the toxicity of these treatments and improving response rates. These two clinical endpoints ultimately require substantially different approaches and, consequently, are being pursued separately altogether. However, the ultimate goal is to provide improvements to both variables simultaneously within current therapies in order to achieve compounded advantages in the next iteration of CAR-T solutions for blood cancers.

3.1.1 Reducing Therapy Toxicity

While current CAR-T therapies have been associated with significant remission rates and durability over extended periods of time, the troubling common variable amongst all available CAR-T therapies are the instances of toxic adverse effects. Most prominent amongst these deleterious responses

is cytokine release syndrome, an expectation associated with all currently approved CAR-T therapies. One of the primary impetuses for continued research within therapies for blood cancers, particularly within industry, is to minimize the percentage of cytokine release syndrome instances within the treated population. Perhaps the most promising approach to achieving this endpoint is through the inhibition of granulocyte-macrophage-colony-stimulating factor, or GM-CSF.

After consistently corroborated studies examining the underlying reasons for why cytokine release syndrome is initiated and persists, the scientific conventional wisdom has trended toward the understanding that monocytes and macrophages are chiefly responsible for the complication; given that the monocytes and macrophages use cytokines as the means by which to communicate with one another, their proliferation is directly correlated to the increase in cytokine concentration as well. Given this relationship, researchers posited that the reduction in these immune cells would result in a reduction in cytokines as well, thereby reducing the risk of cytokine release syndrome.[xxiii]

In order to reduce macrophage release, it was essential to determine a manner in which to limit or eliminate the presence of the protein responsible for macrophage and monocyte release on the surface of traditional CAR-T cells: the GM-CSF protein. Researchers at the Mayo Clinic, the primary driving force behind this avenue for therapy improvement, first employed the use of a clinical-grade antibody, lenzilumab, to inhibit the activity of pre-existing GM-CSF proteins within the CAR-T cells. Then by splicing out the region within the synthesized CAR-T cell's DNA responsible for GM-CSF production through the use of CRISPR gene editing technology, the scientists enabled the rapid proliferation of CAR-T cells that would not secrete the GM-CSF protein at all.

Although its progression toward approval is still in its nascency, Phase I preclinical models convey significant promise for this strategy. Firstly, the GM-CSF neutralization in-vitro enhanced CAR-T cell proliferation in the presence of monocytes and does not impair the CAR-T cell functional capacity (Figure Five).[xxiv] Although this was not the intended purpose of the GM-CSF inhibition, it was a welcome positive externality expressing the ability to make CAR-T synthesis more efficient with now functional harm. More importantly, however, the GM-CSF neutralization was discovered to ameliorate cytokine

release syndrome after CD19 CAR-T therapy within a xenograft model. After treatment, the presence of cytokines associated with cytokine release syndrome most commonly found in human patients were significantly reduced in the subjects treated with GM-CSF inhibited CAR-T cells in comparison to traditional CAR-T cells Figure Six).[xxv] Additionally, the xenograft models treated with the modified CAR-T cells also conveyed lower levels of weight loss post-treatment, a common symptom associated with cytokine release syndrome; while models treated with the modified CAR-T cells hovered around zero percent change in mass, the models treated with traditional CAR-T cells were associated with a ten percent decrease in mass (Figure Seven).[xxvi] Given these conveyed correlations between the GM-CSF inhibition in limited cytokine release syndrome, the Mayo Clinic is ardently pursuing a planned Phase II trial. With continued persistence, it is quite possible that these modified CAR-T cells will soon approach as the industry standard in immunotherapy.

3.1.2 Improving Response Rates

Coupled with the reduction in the associated adverse effects of current therapies, the pursuit of improved patient response rates to the available treatments is the most logical manner in which to improve on-market solutions. More specifically, researchers aim to improve the response rates in treatment of lymphoma and chronic lymphocytic leukemia since these diseases are associated with the lowest durable responses around forty percent.[xxvii] Ultimately with a higher overall efficacy, the provided CAR-T therapies will improve patient population health and posit a substantial competitive advantage for whichever market player is able to achieve the endpoint first.

Dr. Denderian S. Saad and his colleagues seem to have provided the most promising manner in which to improve CAR-T response rates for treatment of large B-cell lymphoma. Through a coupled administration of the CAR-T cells with a drug labeled TP0903, Saad et al. showed that synergistic effects within overall response rates for the target lymphoma could be achieved. The TP0903 drug functions primarily as a means to inhibit the Axl-RTK tumor membrane protein. As a receptor tyrosine kinase, the Axl-RTK protein functions as an intermediary, G-protein coupled receptor responsible for signaling cascades within tumor cells and has been posited to be responsible for tumor aggressiveness.[xxviii] In

limiting the functional capacity of this signaling protein, TP0903 ultimately impedes tumor cell proliferation and indirectly triggers target cell apoptosis. When administered in tandem with CAR-T cells, the treatment was found to significantly reduce the number of tumor cells in comparison to traditional CAR-T cells as measured by percentage of cells containing PD-1 and LAG-3 proteins, cell surface proteins almost exclusively associated with large B-cell lymphoma; while traditional CAR-T therapy was associated with around a forty percent presence of PD-1 positive cells and sixty percent presence of LAG-3 positive cells, the CAR-T cells administered with sixty-five nanomolar TP0903 was associated with ten percent and twenty percent respectively (Figure Eight).[xxix] Ultimately this iteration of the current CAR-T treatment paradigm for lymphomas is undoubtedly far from complete approval; the Phase I pre-clinical trial proves correlation contingent upon in-vivo protein concentration and must still convey stronger relationships in more expansive and direct. In essence, pursuit of improved treatment through elevated response rates is trailing research focusing on reducing toxicity of the current Car-T therapies and faces a long, more arduous path to approval.

3.2 New Antigen Targets for New Indications

While the pre-established CAR-T market players drive innovation toward improving their offered, on-market therapies, research within academia supported by smaller, more nimble firms are instead determined to pursue novel biomarker targets for an entirely new wave of CAR-T therapies in order to address cancers that have yet to be treated with cellular therapy. This is an ideal strategy for new market entrants attempting to emerge within the CAR-T space as market followers since it enables them to target a patient population currently void of CAR-T competitors. In theory, researchers aim to identify cell biomarkers that are most strongly, consistently, and exclusively expressed on target tumor cells. In many instances, these identified biomarkers are additionally expressed on a variety of other cancer cells as well, providing the potential for treatment diversification and cross-application for the treatment of multiple cancer types. After identifying the biomarker of interest, scientists must determine and test which chimeric antigen receptors must be embedded within the in-vitro synthesized CAR-T cells in order to

appropriately bind to the target biomarker and subsequently trigger tumor cell apoptosis. Given the ample amount of tumor cell surface proteins that seem to serve as ideal substrates to be targeted, the types of biomarkers being examined currently vary substantially. Many of these biomarkers have only preliminarily been studied and must be pursued further before any meaningful consideration can be given to them. However, two CD19 alternative biomarkers in particular stand out from the rest: Human Epidermal Growth Factor Receptor Two, or Her2, and B cell maturation antigen, or BCMA.

3.2.1 Her2: Promising Target for Solid Tumor Treatment

One of the most compelling applications for CAR-T therapy is to solid tumors for the treatment of an entirely new array of cancers. Although such an application has proven to be quite challenging so far, the thought of diversifying CAR-T's use cases to include cancers outside of hematological tumors is driving the examination of seventeen unique biomarkers currently in clinical trials for solid tumors.

Chief among these biomarkers currently under examination is the Her2 protein. As a transmembrane tyrosine kinase within the ErbB family, Her2 has been proven to play essential roles in normal cell growth and differentiation through the activation of the RAS and MAPK as well as the PI3K and Akt signaling cascade pathways.[xxx] Moreover, the Her2 protein is of particular interest due to its crucial involvement within cancer cell growth. Previous literature has shown statistically significant overexpression, gene amplification, and mutation in a variety of diverse cancers, including breast, lung, colorectal, brain, ovarian, and pancreas.[xxxi] Additionally, the overexpression of this biomarker has been correlated to tumor cell proliferation and an increased resistance to apoptosis, further validating Her2's fortifying effect within tumor cells.[xxxii]

Given the strong evidence supporting solid tumor survival contingent upon Her2 function, it is logical to examine potential techniques to limit or eliminate the given protein's activity. Many preclinical trials have proven anti-tumor activity, subsequent persistence, and regimented application techniques. In one study conducted by Dr. Anandani Nellan and colleagues, anti-Her2 CAR-T cells were proven to influence durable regression of medulloblastoma when administered both locally and intravenously (Figure Nine).[xxxiii] In a separate study, Dr. Yali Han and colleagues prove that Her2 CAR-T cells promote

anti-tumor activity with persistence when applied to gastric cancer cells within xenograft models.[xxxiv] Another preclinical study conveys the potential for Her2 CAR-T cells to target and inhibit breast cancer metastasis to the brain after being directed to localized regions of Her2 overexpression.[xxxv] Her2 CAR-T cells' diversity in application and promise as a potential therapy have warranted the initiation of clinical trials as well; with an emphasis on biliary tract and pancreatic cancers as well as glioblastomas and sarcomas, these clinical studies aim to further corroborate Her2 as a legitimate and feasible biomarker target for the treatment of many different cancers.[xxxvi]

Her2 has also proven to be an effective target for combinatorial therapies designed to engage multiple protein targets simultaneously. In a study conducted by Dr. Adami Papi and colleagues, CAR-T cells were synthesized with the T1E28z chimeric antigen receptor allowing the produced cells to engage multiple ErbB signaling dimers, including the dimers associated with Her2. This CAR-T cell was additionally synthesized to be co-expressed with 4αβ, a chimeric cytokine receptor capable of amplifying stimulatory mitogenic input to improve target engagement.[xxxvii] Although the technique is early in its development and has only been proven to be safely administered to the localized tumor site within patients with advanced head and neck squamous cancer, the potential for a combinatorial use-case for Her2 CAR-T therapies poses as an advantage for Her2 targeted therapies to be cross-applied for the treatment of multiple cancers with one formulation.[xxxviii]

Despite all of its posited applications and proven anti-tumor associations with a variety of different solid tumor types, Her2 still remains within the nascency of its approval process. Even the most advanced studies currently being designed are simply within Phase I clinical trials. Moreover, even pre-clinical studies revealed cytotoxic adverse effects reminiscent of cytokine release syndrome relatively consistently. Even though few other posited biomarkers possess the extensive literature, diversity in potential use-cases, or strength and consistency in expression within target tumors, the significant uncertainty associated with Her2 CAR-T cells gives reason for skepticism. Until further, more sophisticated studies show similarly promising results, Her2 cannot be given the attention CD19 possesses as a biomarker.

3.2.2 BCMA: Expanding the CAR-T Applications within Hematological Cancers

Although researchers have been eager to expand the scope and diversity of the types of cancers CAR-T therapies can be applied to, many scientists prefer to slowly and more methodically explore novel applications for the technology. Given that CAR-T initially achieved success within particular blood cancers, large B-cell lymphomas and acute and lymphoblastic leukemia, researchers have intuitively began to explore the potential for CAR-T application within similar, hematological cancers. After extensive examination of the underlying mechanisms fundamental to proliferation and signaling within various blood cancer tumor cells, the scientific community seemed to collectively arrive at the discovery of one of the most promising target biomarkers: B-Cell Maturation Antigen, or BCMA.

BCMA is ultimately a tumor necrosis factor receptor responsible for binding B-cell activating factor, or BAFF. As a B-cell activating protein, the binding of the BAFF ligand to BCMA triggers a signaling cascade that progresses along classical and non-canonical NF-κB pathways, More specifically, the activation of this particular signaling pathway is responsible for B-cell formation and sustained B-cell proliferation.[xxxix] Given BCMA's crucial role in the growth and spread of B-cell tumor cells, researchers logically postulated its potential for treatment efficacy through targeted inhibition. Perhaps even more encouraging, however, was BCMA's universal expression on myeloma cell membranes compounded by its substantially sparse expression on major adult organs.[xl] If targeted appropriately, BCMA-inhibiting CAR-T therapies could theoretically promote high overall responses rates while limiting unintended damage to healthy, functioning tissue within the local area.

With such a promising framework for experimental exploration, researchers quickly continued with preclinical studies to quite assuring results. In one hallmark preclinical study, a BCMA CAR-T culture, labeled BI 836909, was synthesized as a bispecific single-chain variable fragment consisting of two linked single-chain variable fragments with monovalent binding to both BCMA and CD3ε, and additional cell surface protein consistently associated with T-cells. Ultimately, the BI 836909 was shown to induce the activation of T-cells, conveyed by the upregulation of CD25 and CD69 expression. Additionally, the BI 836909 proved to promote multiple myeloma cell lysis, as indicated by cytokine

release; employing the use of MM.1R cells and purified T-cells, the BI 836909-mediated lysis was determined at effector to target cell ratios of one-to-one hundred or higher with maximal tumor lysis was observed at ratios of one-to-one or higher (Figure Ten).[xli] In essence, BCMA CAR-T cells were substantially effective in targeting the appropriate tumor cells and mediating apoptosis as well as providing co-stimulatory effects in the upregulation of immune T-cells within the local physiology.

These preclinical studies were further corroborated with more sophisticated, Phase I clinical trial data. In Dr. Yarong Liu and colleagues' studies, a particular formulation of CAR-T cells with genetically modified T-cells comprised of an extracellular anti-BCMA human single-chain variable fragment and an intracellular 4-1BB costimulatory motif embedded within a CD3-zeta T-cell activation domain was synthesized in order to target multiple myeloma tumor cells with limited adverse events. This formulation, labeled CT053, induced a one hundred percent objective response rate within fourteen evaluated patients. CT053's complete response rate was 35.7 percent and its very good or better partial response rate was 42.9 percent. More importantly, however, was the twenty-nine percent observed rate of cytokine release syndrome, all low grade, and the absence of any neurotoxicity within any of the evaluated subjects.[xlii] In a separate Phase I clinical study, Dr. Yarong Liu and colleagues examine a simpler BCMA CAR-T cell-line comprised of a 4-1BB costimulatory domain and only the additional BCMA single-chain variable fragment transduced with a retroviral vector. This study targeted rescue patients with a median of five prior iterations of treatment, conveying the ineffectiveness of traditional treatment methods on their multiple myeloma. The objective response rate was eighty-five percent with a complete response of forty percent and a partial response of twenty-five percent. Moreover, forty-five percent of observed subjects remained in remission twenty-two months later with seventy-nine percent surviving despite the severity of their cancer prior to treatment. Additionally although cytokine release syndrome was present within forty-five percent of tested patients, only one patient exhibited grade three symptoms.[xliii] In essence, even the most severe cases of multiple myeloma were induced into remission with BCMA CAR-T treatment. Coupled with the therapy's lowered adverse event rate in comparison to on-market therapies, these results serve as substantial driving forces for continued studies.

One of the most interesting and creative applications of BCMA-specific CAR-T cells currently being explored is the combinatorial administration of traditional, CD19 CAR-T cells with BCMA CAR-T cells. More specifically, such a therapy has been administered to ten high-risk myeloma patients that is not refractory to treatment. After ninety days, one hundred percent of the tested patients achieved very good partial response or better. Fifty percent of these patients achieved stringent complete response as well. Additionally, sixty percent of the patients achieved minimal residual disease negativity. The responses observed were ongoing at the time of last collection, although the test was only run for three months before presentation.[xliv] Like the isolated clinical trials before it, the co-administration of BCMA CAR-T cells as well as CD19 CAR-T cells shows dually advantageous outcomes in substantial response rates to multiple myeloma treatment and reduced cytokine release syndrome symptoms. Given its application to severe myeloma cases, continued research may allow such a combination therapy to serve as an alternative to traditional treatments in circumstantial instances in the years to come.

Despite the well-documented, often substantiated reason for optimism, however, BCMA must still be considered with essential caveats. Like Her2 and every other alternative biomarker studied for CAR-T therapies, BCMA is still very early within its development life cycle and has only advanced to few Phase I clinical trials. However, the concern extends beyond simply its position relative to market approval. Noticeably, the evaluated patient sample size within the most compelling clinical studies are substantially smaller than those even observed within the Her2 trials. More importantly, however, is that these studies may not increase in size for what may prove to be a prolonged period of time; the patients able to be recruited for BCMA clinical trials must have been provided with multiple rounds of attempted treatments due to the uncertainty associated with BCMA CAR-T therapy and the therapy's intention to target severe myeloma cases. In essence, the BCMA-mediated therapies target a small sub-population within a patient population that is already limited. Ultimately while BCMA CAR-T treatments will require many additional clinical studies, each expanding in size, ambition, and consequence, the time it takes to pursue these studies may inherently be much greater than in alternative biomarker studies.

3.3 Research Landscape

With the diverse and considerably broad array of the CAR-T framework's applications, it is not surprising in the least that scientists pursue unique and distinctly specific use-cases for the therapy. While the public sector predominantly focuses on the manner in which to iteratively improve on-market therapies, the rest of the research community is heavily stratified into particular niches. In this sense, it seems that CAR-T's coveted flexibility in application is both an advantage and detriment; the treatment framework promises to deliver countless alternative treatment paradigms for a variety of different cancers, but also inherently impedes development efficiency since the collective talents of the scientific community is spread across a variety of focus areas. This notion is particularly conveyed within the current research landscape; while CAR-T therapy for lymphomas and leukemia benefit from consistent and collective research driven by the public sector, the next wave of improved drugs are at the brink of updating the on-market CAR-T options, research toward novel biomarkers are progressing at a lethargic pace stagnating in the first clinical phase. This unfortunate circumstance is an inherent product of the biotechnology industry architecture; the largest amount of funding will always flow toward the research area showing greatest certainty for future returns. Ironically, however, it is this nature of the biotechnology industry that ultimately poses massive implications for future market competition.

IV. Market Strategy: Fortifying a CAR-T Competency

As an industry inherently contingent upon innovation, patent protection, and regulatory policy, the biotechnology space as a whole experiences volatile and often unexpected fluctuations within its competitive environment as the ebbs and flows of power structures prefigure evolving success determinants. Market players within the industry must consistently reconfigure their strategic positioning in anticipation of the innovation and potential deviations from current industry standards that may need to be contended with. Afraid of falling victim to incumbent inertia, even the largest firms cultivate an extensive product pipeline years in advance of any planned sales. Risky investment within nascent technologies is essential to maintaining competitive advantages. However for larger industry incumbents

in particular, the sustained success of on-market drugs is essential in driving retained earnings that can be recycled for use in the development of innovative products. Although the set of strategies involved with the development and management of proven technologies and the risky, anticipatory technologies are inherently diametric, the two must operate together cohesively and symbiotically in order to drive values within the company.

The investment and development of CAR-T therapies within the market, then, is complex and uniquely valuable given its capacity to be positioned on either end of the development spectrum. Contemporary research drives innovation iteratively within currently approved, on-market therapies as well as within unproven, but potentially disruptive indications. Competition within the space, even in CAR-T's developmental emergence, is fierce and will only continue to grow as novel treatment paradigms gain traction. Consequently, it is essential for firms of all sizes with the resources and competency to heavily consider its CAR-T strategy in the wake of its burgeoning progression.

4.1 Go-to-Market Strategy: Tailored Frameworks for Market Penetration

The industry players currently involved within the CAR-T space follow a simple and logical strategic mandate: fortify and iteratively improve upon the pre-existing CAR-T platform. These firms have already locked in sales for an approved therapy and are operating with the luxury of early-mover advantages within a sparsely competitive market. Given the high barriers to entry and the substantial gap in development time between the three prominent on-market players, Novartis, Kite, and Celgene, and other competitors, the current incumbents have little to worry about outside of maintaining market share through improved efficacy and toxicity rates. Accepting increased risk in pursuing unproven indications for CAR-T therapies, even if the company may possess the competency and resources to do so, is simply unwarranted; if a more nimble company does develop a more substantiated platform over time, these large incumbents could simply acquire the particular therapy of interest to immediately contend as a market power within the emerging space. Given this effective but rather arid strategy, there is not much to be gleaned from a more sophisticated analysis of these companies.

Much more insightful, however, is a more profound examination of how companies currently uninvolved should approach CAR-T therapies. More specifically, given the inherent resource and positioning differences of larger industry players and smaller, more nimble firms, examining the nuances in the go-to-market strategy for each type of company separately will allow for a more meaningful understanding and interpretation of the success determinants involved. Ultimately with a greater understanding of how new competitors can emerge within the space, a clearer depiction of industry involvement's implications for CAR-T development and innovation can be achieved.

4.1.1 Small, Nimble Competitors: Initiating the Market Innovation Cycle

The smaller firms emerging within the competitive landscape serve as an intriguing threat to the rest of the market. Given the limited available resources upon market entry and the reduced market clout upon the onset of competition, market penetration through substantial barriers to entry is quite difficult and unlikely for smaller players. With the odds counter to their positioning, small firms are inherently compelled to pursue solutions currently associated with minimal competition with the potential for massive market disruption. As expected, these posited technologies are fundamentally within the nascency of their development and, in turn, are associated with significant uncertainty and risk. However with no current sales from on-market drugs and with only one or perhaps two co-developed solutions within the pipeline, these smaller firms have the least pre-existing funding and tangible assets to lose and consequently are the most naturally positioned competitor to pursue such market strategies.

Although smaller players are naturally implored to pursue disruptive, innovative therapies, the founding of a company for such a pursuit is not necessarily expected and, in most instances, is never the intention of the provided research upon initiation. Most frequently, the most innovative research is first explored within academia, institutions without financially contingent impetus concerned with knowledge discovery and sharing rather than producing a solution to be sold. As the given research progresses and continues to accumulate corroborating data, manners in which the posited therapy could be more specifically tested for approval and eventual sales are then considered. It is only when the supporting data is aggregated to a level indicating significant potential and promise for a particular therapy that academic

research may transition to the marketplace. With a greater expected value for the given therapy driven by improved probabilities for success, academic research teams often incorporate and found startups around the basis of a therapy patent.

Given the personal, arduous journey these research and development teams trek to ultimately reach incorporation, it is often that these newly founded companies are fundamentally committed to the development of innovative therapies and the overarching disruption of the current industry standard for treatment. It is this founding principle that crystallizes perhaps the most essential role of smaller players within the market: bridging the gap between nascent research and market development.

4.1.2 Blue-Chip Incumbents: Leveraging Competencies and Aligning Resources

If not previously involved within the CAR-T space, the large biotechnology firms have the most to invest and, in turn, the most to lose in order to meaningfully emerge within the space as a legitimate competitive threat. Given the significant risk involved, it is essential for large industry players to determine what exactly they believe can be gained from cultivating a CAR-T platform. CAR-T has been consistently proven to show great capacity to treat a variety of cancers with substantial potential for cross-application to many cancer types at once. In essence if cultivated early enough, the establishment of competency for a CAR-T therapy within one indication can serve as the base for future innovation and treatment diversification. Consequently, the establishment of a CAR-T platform targeting new indications currently void of competition early should benefit every incumbent, provided research continues to support preliminary data.

The variability in the risk associated with cultivating such a platform between larger companies then comes from the capacity for such firms to leverage existing competencies and aligning available resources with what is required to develop these therapies. Depending on the amount of overlap between the given company's current positioning and what is required to build the target CAR-T platform, companies will determine to pursue the process immediately, at another period in time when the use-case is further substantiated, or perhaps never at all. The key factors to consider and determination framework is outlined below:

Investment Considerations

Synergies	Market Potential	Corporate Positioning
• How effectively can resources involved with other products within the current portfolio be employed for use within the CAR-T platform • Does the company possess established expertise within oncology or, more specifically, within the indication targeted • How robust is the current oncology offering and how effectively could those treatments be co-administered with the posited CAR-T therapy • How robust is the current cellular therapy platform within the overarching portfolio and how easily could expertise within this therapeutic area aid in building out the CAR-T therapy	• How large is the current patient population associated with the predominant target indication; what is the incidence rate of the given cancer considered • How saturated is the competition in treatment types for the targeted cancer type; what is the efficacy of these on-market alternative treatments and what is the associated purchase price • How promising is competing research examining alternative treatment paradigms for the target cancer • How strongly and diversely is the target tumor antigen expressed in varying cancer cell types	• How have other developing drugs been progressing within the pipeline; how many anticipatory drugs are currently being developed and how close are they to market • How have current on-market drugs been performing; have sales been consistent, stagnant, or improving • How much capital expenditure has already been allocated to the development of novel drugs within other areas • What does competition look like for currently sold or developing drugs • Does the company possess the upstream or downstream supply-chain partnerships required

After weighing the feasibility of building-out a CAR-T platform in composite with the expected

value of what is targeted to be gained, the interested firms must consider how to most effectively pursue

the development of a competency within the pre-specified CAR-T therapy. As a large, incumbent

company, corporate hierarchies implemented to streamline operations often inherently impede pure

research and development innovation and progression due to additional layers of management oversight

checkpoints that smaller, more nimble firms have the luxury of avoiding. Additionally if without an

established competency within the space, developing a CAR-T platform purely in-house would be

gradual, leaving the firm vulnerable to competitive threats. Given the impracticality of pursuing the CAR-

T platform in-house, larger companies must consider alternative, more creative methods to pursue the

development of such a platform. The alternative considerations are provided below:

CAR-T Development Mechanisms

	Advantages	Disadvantages
Strategic Acquisition	• Immediate emergence as a competitive threat within the target space • Eliminate competitive threat to potential market share • Inheritance of established expertise and competency • Avoid research, development, and production risk • Can leverage synergies to cross-sell products through integrated supply-chain networks for improved profit • Conglomeration allows for market share consolidation and increased overall market power	• Often expensive simply for the addition of one asset, particularly within the bloated mergers and acquisition market associated with the biotechnology space • Corporate integration frictions, particularly those associated with technology infrastructure and organizational restructuring, may impede workflow optimization • Loss of autonomy in cultivating platform tailored to unique corporate positioning • Subject to regulatory review, especially within the United States
Corporate Partnership	• Allows for the exchange of resources from the larger corporation for the expertise provided by the innovating firm; balanced leveraging of respective strengths and assets • Provides the means for knowledge sharing, enabling the larger firm to pursue a CAR-T platform in-house in the future post-partnership • Efficient emergence within the market as a competitive threat without integrative concerns • Enables larger corporations to observe and quantify the potential returns of the CAR-T therapy without full exposure or an overzealous investment	• Not a sustainable strategy in terms of long-term emergence within a market; one partnership with associated knowledge sharing does not necessarily ensure competency post-partnership • Asset profits not realized entirely due to the partnership tethering the involved parties for revenue splitting • Inconsistencies within corporate vision or strategic impetuses may hinder development efficiency and limit partnership potential • Patent considerations difficult to negotiate and may cause asymmetric cost to profit for one of the parties
Academic Partnership	• Most effective manner in which large players can pursue innovation within its earliest stages • Often times associated with technologies not considered by competitors	• Knowledge sharing more difficult to achieve optimally • Only a one-way exchange of resources • Greater associated risk given nascency of posited innovation
Platform Purchase	• Immediate emergence within space as a legitimate competitor • Avoid research, development, and production risk • Provided base upon which to more easily innovate	• Without included acquisition of provided workforce, knowledge sharing for continual improvement non-existent • May be difficult to access the requisite supply-chain channels

Although each of these mechanisms provide respective advantages and disadvantages, each individual method is specifically designed for a particular purpose. Corporate partnerships and platform purchases are optimal for companies looking to generate immediate revenue by selecting particularly promising drug candidates for immediate gain without much interest in cultivating a competency for sustained growth within the area. This strategy is most effectively applied within mature treatment areas with little promise for growth or innovation. Consequently when considering CAR-T, corporations would be least likely to pursue such strategies. In contrast, a strategic acquisition and academic partnership would be optimally applied within the CAR-T therapy space given its emphasis on establishing a platform of competency upon which to build and continually innovate. In fact, the history of CD19 CAR-T's approval substantiates the strategic theory; Novartis developed Kymriah in collaboration with Dr. Carl June's team at the University of Pennsylvania as CAR-T therapy was just emerging within the market and large acquisitions by Celgene for Juno's CAR-T platform and subsequently Bristol Meyer Squibb for Celgene occurred as the assets neared approval. This same pattern is expected to repeat as the CAR-T technologies still early in their exploration of novel biomarkers continue to develop.

4.2 Market Innovation Symbiosis

As acquisition prices for CAR-T therapy companies continue to soar, it is evident that incumbents are increasingly getting involved as prominent competitors vying for an early position within an industry ripe for explosion attempt to find a competitive edge. Now that CD19 CAR-T therapies have reached approval and are associated with greatly reduced risk, the large incumbents are committed to emerging within the space and driving continued innovation. The technology development inflection point at which the rate of development and increases dramatically is quickly approaching for the CD19 CAR-T therapies as the incumbents invest more heavily. Moreover as improvement within one area of CAR-T rapidly accelerates, attention will then shift toward monitoring the progression of CAR-T therapies for new cancers. Ultimately it is only when the incumbent collectively determine that these new CAR-T treatment iterations show sufficient upside that the positive feedback loop will repeat, inducing the true emergence

of the next wave of CAR-T therapies in the process. Here, market action and innovation seem to recursively iterate through a symbiotic pattern feeding off of one another; as new therapies continue their progression throughout the approval life-cycle, increasing industry funding will accelerate innovation rates, enabling the given technology to pursue an exponential development rate as it inches closer to market approval.

V. Conclusion

As a whole, the healthcare and life sciences industry is perhaps the principal target for the most impassioned political castigation and scrupulous regulatory scrutiny. Examining the biotechnology space from an overarching perspective, it is ultimately easy to see the source of such severe criticism. The inherent architecture of the industry and its relation to the source of innovation provides the basis for an incentive structure that is strikingly misaligned and conspicuously flawed. More specifically, the system fallaciously operates under the folly of rewarding A but expecting and, for patients in particular, requiring B. The purpose of the healthcare and biotechnology space is to provide patients with the affordable opportunity to optimal treatments without any hindrance in accessing these treatments. A substantial portion of this mandate requires the unencumbered pursuit of novel innovations for improved, potentially disruptive treatment paradigms. However importantly, there exists a substantial rift between the source of innovation, within academia and government funded agencies, and the market development of such innovation to be offered to the target patient population. While the impetus for innovation at the ground level pursuing potential solutions in their nascency is to examine new treatment pathways for discovery, as intended, the industry players with the resources, competency, and clout to effectively develop such posited therapies are inherently uninvolved. The entities with the ability to substantially accelerate the rate of innovation only get involved when expected returns are more promising as the research accumulates more supportive data. As an inherent bottleneck to optimal innovation rates, the incentive structures involved within the biotechnology marketplace limit the rate at which potentially beneficial treatments reach the market and can be applied for the benefit of the patient population.

The manner in which the development of CAR-T therapies has progressed, then, serves as a unique foil to the broader biopharmaceutical space. Unlike other treatment mechanisms, CAR-T therapies are ardently pursued by a variety of market incumbents currently for indications still only in preclinical or Phase I clinical trials. Here, the forces involved with impeding innovation in other branches of the biotechnology space are not at play.

Ultimately what seems to differentiate CAR-T therapies in particular from more traditional treatments are both its flexibility in diverse applications as well as the unique position the therapy finds itself in as both an on-market approved therapy and an early-stage, preclinical asset with the potential to serve as a platform to cultivate a competency addressing an entire market subsection. Since most drug solutions undergo one round of disruptive innovation and subsequent iterative improvements, often times one early-mover corporation is the first to build out a competency within the particular disease area, create substantial barriers to market entry for competitors, and ultimately operate as a monopoly within the space. However, CAR-T therapies in contrast are associated with multiple cycles for disruptive innovation; while the initial cycle for disruption has been achieved for treatment of certain hematological cancers, many other cancer types require effective development of CAR-T therapies. With its diverse applicability to unique biomarkers, CAR-T therapies constantly undergo repeated stages of intense innovation and development. Most importantly, however, is that incumbents are eager to get involved with the development of these therapies at the onset of their discovery since each indication is associated with the potential to build a first-mover competency within a deep-ocean market void of competition. In essence, the rift between powerful market developers and source therapy innovation is nonexistent and the innovation cycle flows through a unique positive feedback loop continually accelerating innovation.

Ultimately it seems rather poetic that it is a cellular therapy that has been the first biotechnology solution that possesses this unique and fortunate quality; just as CAR-T autologous cells are administered to treat and heal the self, the CAR-T therapies are able to self-regulate their own innovation cycles in a stimulatory, positive feedback loop, benefiting the target patient population in a manner policy is seemingly incapable of.
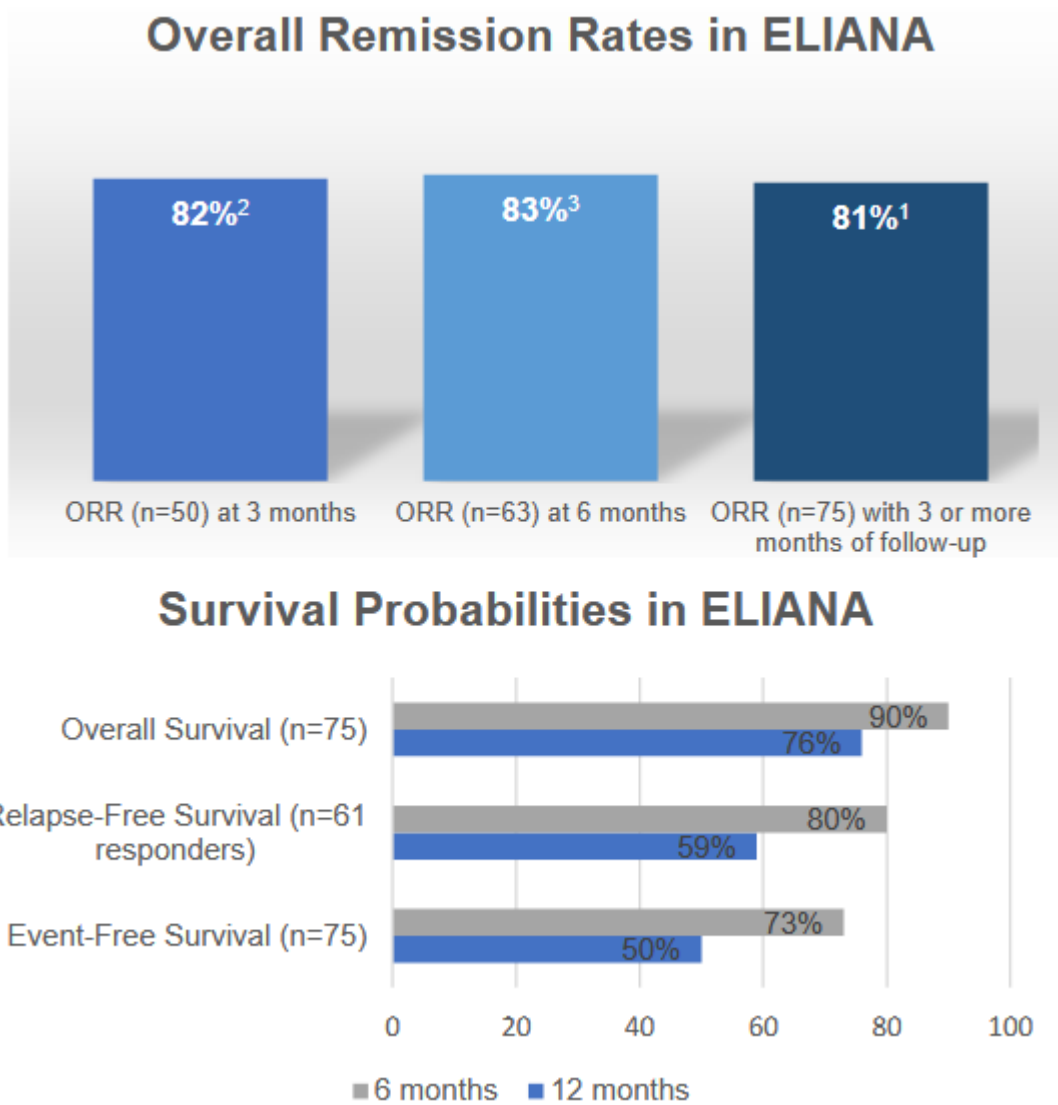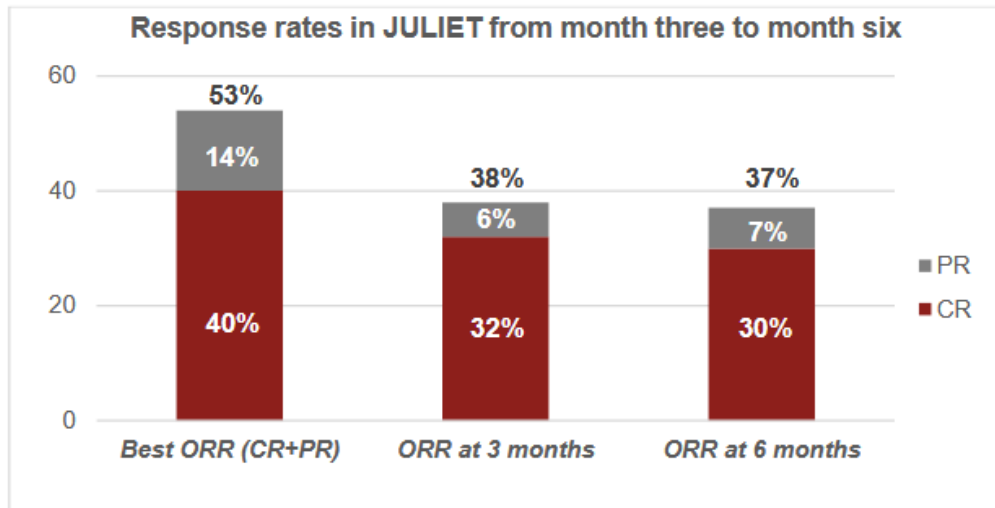
Appendix

Figure One

Overall Remission Rates in ELIANA

82%[2]   ORR (n=50) at 3 months

83%[3]   ORR (n=63) at 6 months

81%[1]   ORR (n=75) with 3 or more months of follow-up

Survival Probabilities in ELIANA

	6 months	12 months
Overall Survival (n=75)	90%	76%
Relapse-Free Survival (n=61 responders)	80%	59%
Event-Free Survival (n=75)	73%	50%

Figure Two

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Trial Results

Response rates in JULIET from month three to month six

- At month three, the CR rate was **32%** and the PR rate was **6%**, which remained consistent to month six (**30% CR, 7% PR**)
- The median duration of response was not reached. The relapse-free probability at six months was **74% (95% CI, 52%-87%)**
- The median overall survival was not reached. The median time from infusion to data cutoff was 5.6 months

Figure Three

CNS INVOLVEMENT (N=60)[11]

CNS status at infusion	Patients, n (%)
CNS1	54 (90)
CNS2[§§]	4 (7)
CNS3[‖‖]	2 (3)
CNS3[‖‖] within 12 months of infusion	16 (27)

Remission Rates[11]

- 83% of patients with CNS2 or CNS3 status at infusion (n=5/6) achieved CNS remission
- 73% of evaluable patients with prior CNS disease (n=11/15) achieved continuous remission as long as 2.5 years
- No CNS relapses in entire cohort (N=60), with 4 bone marrow relapses in CNS cohort (n=15) at time of analysis
- Experience with KYMRIAH in patients with active CNS leukemia is limited and these data should be interpreted with caution

Persistence Based on Pharmacokinetics[11]

Figure Four

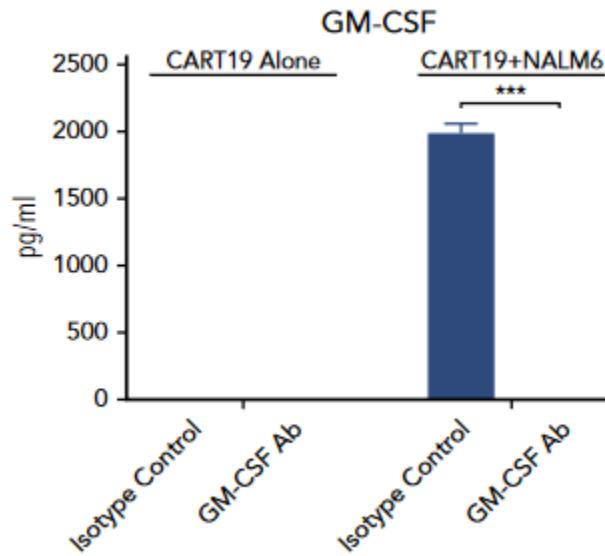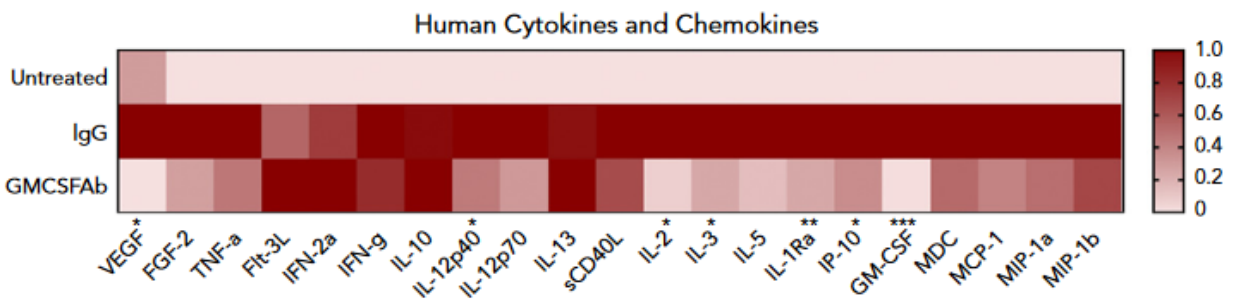|			DLBCL (n=77)					TFL/PMBCL (n=24)					Combined (n=101)			
			ORR (%)			CR (%)		ORR (%)			CR (%)		ORR (%)			CR (%)
ORR			82			49		83			71		82			54
Month 6			36			31		54			50		41			36

Figure Five
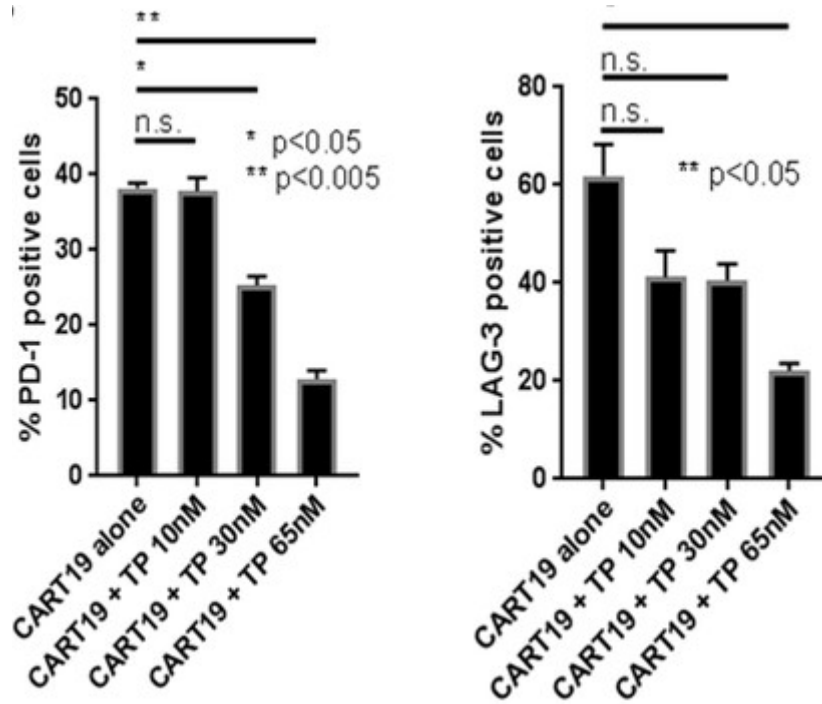

Figure Six

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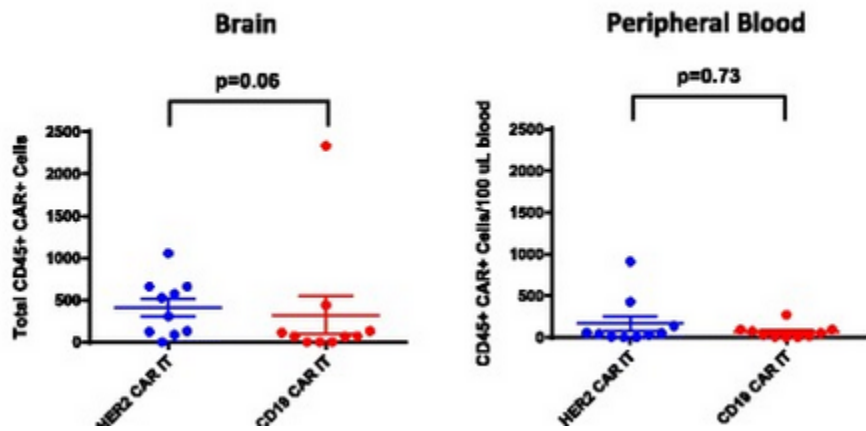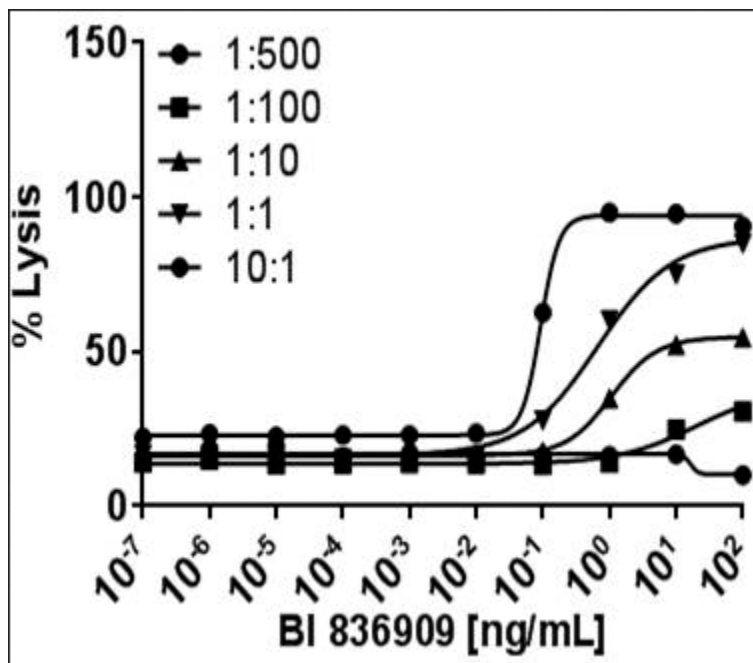Figure Seven
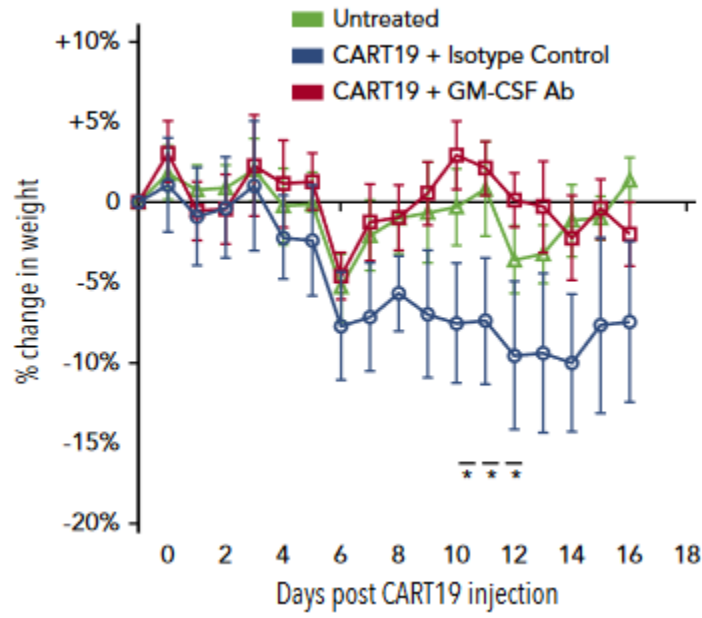
Figure Eight

Figure Nine

Figure Ten

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