Advanced Therapies in Oncology: CAR-T Background, Supply Chain Considerations, and Recent FDA Insights

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FIRST PRINCIPLES
ADVISORY GROUP

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Introduction

Encouraging advances have been made in the field of oncology drug development over the past two decades. Exploitation of novel mechanisms of action and combination therapy opportunities, as well as a continuing drive towards personalized medicine through biomarkers and diagnostics, have significantly improved the standard of care in a number of indications. Nonetheless, novel therapeutic approaches – as opposed to molecular targets – have remained relatively infrequent.

The era of monoclonal antibody therapy began in oncology with the U.S. approval of Rituxan® (rituximab) in 1997. The first antibody-drug conjugate, Mylotarg™ (gentuzumab ozogamicin), followed in 2000.[1] Novel targets and biomarker-driven development characterized the trend of new product approvals during the first decade of the twenty-first century, and since 2011, the immune checkpoint inhibitors directed against CTLA-4 and PD-1/L1 in particular have dominated headlines and conference podium time. Nevertheless, the therapeutic modality most often remained monoclonal antibodies and small molecules. Contemporaneously, though, several new approaches have reached the market in oncology; the subset of Chimeric Antigen Receptor T-cell (CAR-T) therapies is the subject of this paper.

The two approved CAR-T therapies Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) represent the leading edge in the field of engineered adoptive cell transfer (ACT) therapies. These advanced therapies represent both the potential for step-function increases in clinical benefit for patients and a significant departure from the standard drug development, approval, and commercialization paradigm. As such, the category has broached previously uncharted territory for both FDA (from a US regulatory perspective) and the developers who must meet emerging hurdles and demands. This paper, the first in a series, provides an overview of what makes these therapies unique compared to legacy biologics and what FDA's actions to date on CAR-T therapies in particular suggest for future development. Our forthcoming second installment will examine progress with commercialization and pricing.

While we focus on CAR-T therapies here, readers should note that several other advanced therapeutic approaches will likely follow in oncology within the next decade. Figure 1 below provides a high-level, technology-based perspective on recent progress and likely near- to mid-term advances.

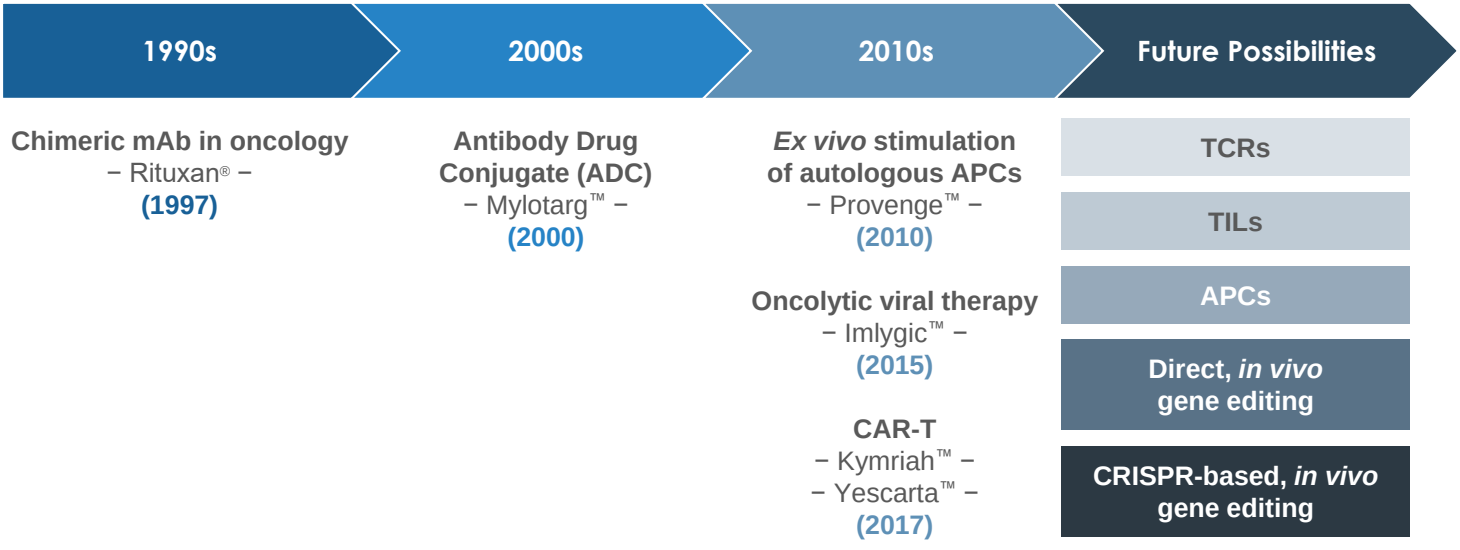

Figure 1: *A Timeline of Modality Advances in Oncology Therapeutics to "Advanced Therapies"*

[1] In a remarkable sequence of events, Mylotarg was withdrawn from the market in 2010 based on safety and efficacy considerations, then re-introduced in 2017. *See* Food and Drug Administration. "FDA approves Mylotarg for treatment of acute myeloid leukemia." News & Events. *Accessed on 9 May 2018*, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574507.htm.

FDA Premarket Review Jurisdiction

In contrast to the monoclonal antibodies, peptides, and small molecules that compose the majority of recent FDA drug approvals, the subject therapies of this paper are not reviewed by the Center for Drug Evaluation and Research (CDER). Instead, cellular therapy products fall under the jurisdiction of the Office of Tissues and Advanced Therapies (OTAT), which resides within the Center for Biologics Evaluation and Research (CBER). The OTAT also holds responsibility for approvals of gene therapies, vaccines, and blood-derived products, among others.

Although it remains early days for cellular and gene therapy products, it is worth keeping in mind that management up to the director level differs compared to that which has been responsible for most oncology product approvals in recent years; this could conceivably impact Agency views on prospective products.

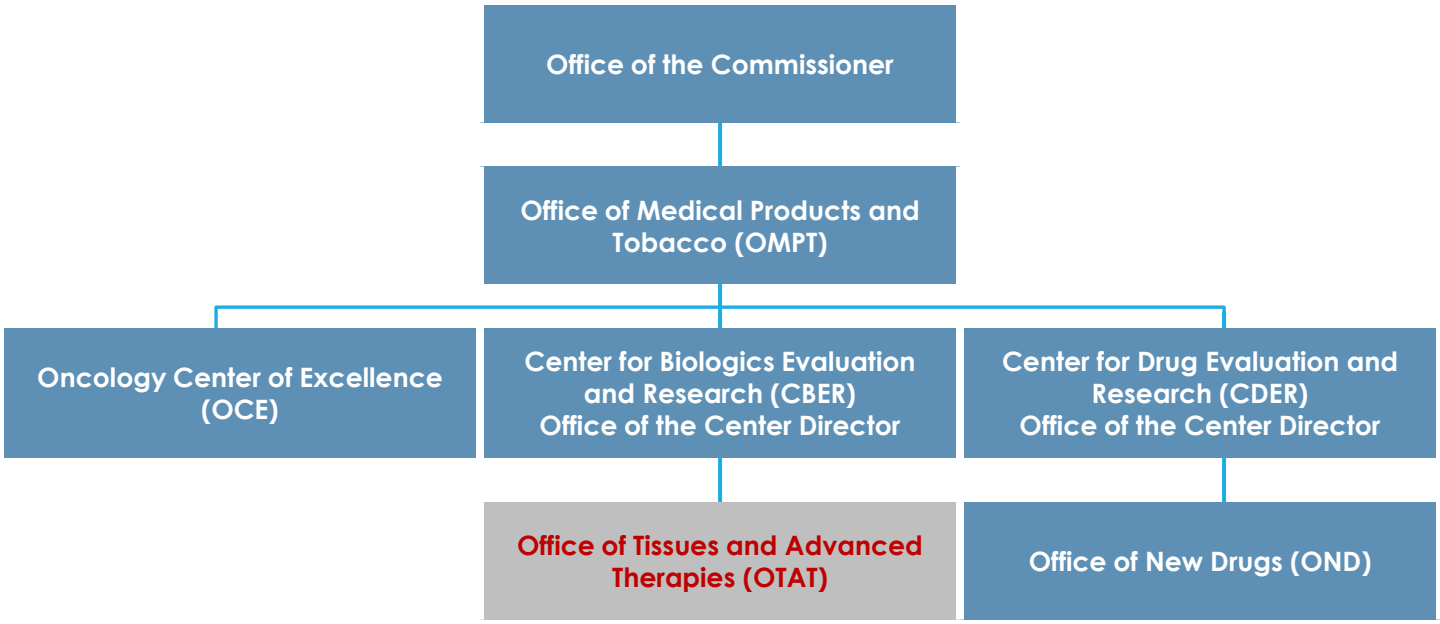

Figure 2: *A partial org chart showing how current FDA internal jurisdiction places cellular therapy products within the OTAT, whereas most other therapies full under the OND. The role of the OCE is a significant one for oncology products.*

Uniquely for the oncology disease area, however, the Oncology Center of Excellence (OCE) under the leadership of Dr. Richard Pazdur adds a pan-therapeutic perspective.

The role of the OCE includes "support[ing] an integrated approach in the clinical evaluation of drugs, biologics, and devices for the treatment of cancer" and industry veterans are familiar with the significant influence Dr. Pazdur has had on FDA thinking with respect to oncology therapeutics, for well over a decade.[2]

[2] Food and Drug Administration. "Oncology Center of Excellence." *Accessed on 9 May 2018,* https://www.fda.gov/AboutFDA/CentersOffices/ucm509057.htm; see also: Richard Pazdur. "The One-Year Anniversary of the Oncology Center of Excellence." FDA Voice. *Accessed on 9 May 2018,* https://blogs.fda.gov/fdavoice/index.php/2018/01/the-one-year-anniversary-of-the-oncology-center-of-excellence/.

Cellular Products Nomenclature

The FDA nomenclature of cellular and gene therapy products merits clarification, as it differs in some respects from other usages of terms of art such as "cellular therapy" and "gene therapy."

In the EU, regulation provides a definitional framework for modalities covered under the umbrella term of "advanced therapy medicinal products," including "gene therapy medicinal product," "somatic cell therapy medicinal product," and "tissue engineered product."[3] Under the US regulatory regime, the terminology is less straightforward.

Among the engineered autologous ACT approaches, it is the T-cell based chimeric antigen receptor (CAR-T) class that has reached the US market first with the approval of Novartis' Kymriah™ in August 2017, followed by Yescarta™ from Kite/Gilead less than two months later. In FDA nomenclature, this class represents a cell-based gene therapy,[4] since patient tissue (T-cells) is genetically modified and reintroduced.

In addition to being the first CAR-T to market in the US, FDA also cites Kymriah™ as its first gene therapy approval.[5]

In December 2017, FDA approved Luxturna (voretigene neparvovec-rzyl) from Spark Therapeutics, in what the Agency referred to as its first approval of a "*directly administered* gene therapy . . . that targets a disease caused by mutations in a specific gene."[6] [emphasis added]. Indicated for retinal dystrophy due to a specific monogenic mutation, the therapy utilizes an adeno-associated virus (AAV) as a vehicle for delivery of a corrective gene *in vivo*. Thus, it might be considered FDA's first approval of a "gene therapy" in a popularly understood sense.

In contrast, the Agency refers to the earlier-approved immunotherapy Provenge® (sipuleucel-T, Dendreon Pharmaceuticals) as an "autologous cellular immunotherapy,"[7] because while the patient's cells (specifically, peripheral blood mononuclear cells) are activated by culturing them with a genetically engineered product, the patient cells themselves are not genetically engineered.

Further delineating the terminology of cellular and gene therapies is the genetically engineered oncolytic viral therapy Imlygic® (talimogene laherparepvec, Amgen). This modified herpes simplex virus type 1 (HSV-1) therapy for recurrent melanoma falls under the FDA categorization of cellular therapy[8] (and perhaps under OTAT mechanistically as a quasi-vaccine), but again is not a gene therapy, since the patient's genetic material remains unmodified. Thus, the class of "cellular therapy" in FDA usage comprises those modalities that involve the exposure of patient tissue (including blood and its components) to a cell or virus, while "gene therapy" requires the genetic manipulation of patient tissue, either *in vivo* or *ex vivo*.

[3] European Union. "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use." p.164-165. *Accessed on 9 May 2018,* https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. See also: European Union. "Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004." p.4-5. *Accessed on 9 May 2018,* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF.

[4] Food and Drug Administration. "FDA approval brings first gene therapy to the United States." News & Events. *Accessed on 9 May 2018,* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm; see also: Food and Drug Administration. "FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma." News & Events. *Accessed on 9 May 2018,* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm.

[5] Food and Drug Administration. "FDA approval brings first gene therapy to the United States." News & Events. *Accessed on 9 May 2018,* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm.

[6] Food and Drug Administration. "FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss." News & Events. *Accessed on 9 May 2018,* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm.

[7] National Cancer Institute. "FDA Approval for Sipuleucel-T." *Accessed on 9 May 2018,* https://www.cancer.gov/about-cancer/treatment/drugs/fda-sipuleucel-T.

[8] Food and Drug Administration. "Approved Cellular and Gene Therapy Products." Vaccines, Blood & Biologics. *Accessed on 9 May 2018,* https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm.

Approved Advanced Therapies: Modalities and Terminology

Drug Name	Company	FDA Terminology	Therapeutic Mechanism of Action	Indication	Approval Year
Provenge™ (sipuleucel-T)	Dendreon	Autologous Cellular Immunotherapy	Patient's APCs are cultured *ex vivo* with a recombinant antigen (PAP-GM-CSF) and the mature APCs are readministered to trigger T-cell response.	Prostate Cancer	2010
Imlygic™ (talimogene laherparepvec)	Amgen	Genetically Modified Oncolytic Viral Therapy	Intratumorally injected virus replicates and produces GM-CSF, leading to tumor cell lysis and promotion of immune response.	Melanoma	2015
Kymriah™ (tisagenlecleucel)	Novartis	Cell-based Gene Therapy	Patient's T-cells are genetically engineered *ex vivo* to express a chimeric antigen receptor that targets CD19-positive cells when readministered.	Acute Lymphoblastic Leukemia (ALL) Large B-cell Lymphoma	2017
Yescarta™ (axicabtagene ciloleucel)	Kite/Gilead			Large B-cell Lymphoma	2017
Luxturna™ (voretigene neparvovec-rzyl)	Spark Therapeutics	Directly Administered Gene Therapy	*In vivo* AAV2 transduction of retinal pigment epithelial cells with cDNA for the RPE65 gene, which provides functional protein product.	Retinal Dystrophy	2017

Figure 3: *The elements of cellular, gene, and immunotherapy in products reviewed by OTAT and approved by FDA highlight the complexities of nomenclature; no "directly administered gene therapy has yet been approved for an oncologic indication.*

This article focuses on FDA actions and commentary to date related to the approvals of Kymriah™ and Yescarta™. While FDA provides guidance for the development of cellular therapies for US approval,[9] the approval process in practice highlights its translation and application. The Agency's views may be applicable beyond autologous CAR-T therapies where other therapies share the same or similar considerations, for example, with autologous TCR therapies. And although currently further removed from market approval, allogeneic therapies and those that utilize tumor infiltrating lymphocytes (TILs) will face many of the same considerations and concerns. The FDA review of Luxturna™ provides additional insight for developers of viral vector-based gene therapies; while not covered here explicitly, many of the considerations related to viral vectors overlap with the discussion below.

[9] Food and Drug Administration. "Cellular & Gene Therapy Guidances." Vaccines, Blood & Biologics. *Accessed on 9 May 2018,* https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.

Insights from First Principles

- Notwithstanding the web of FDA terminology for advanced therapies, cellular and gene therapies will be reviewed by the OTAT within CBER, in contrast to most other recent therapies; developers may expect different "faces" compared to their CDER experiences
- For oncology products, Dr. Richard Pazdur and his leadership of the OCE merit particular attention; his aggressiveness with moving innovative therapies to market appears to have increased in recent years

CAR-T Manufacturing and Supply Chain Differences

Both of the CAR-T therapies approved by FDA to date fall into the category of engineered autologous adoptive cell therapies. As autologous therapies, they derive from the same patient who will receive the therapy; cells must be obtained from each patient, engineered, and returned to the same patient for administration. Allogeneic CAR-T therapies that (like most drugs historically) are not patient-specific are on the horizon, but a US approval is unlikely before 2020. Autologous engineered therapies require a more rigorous supply chain compared to traditional biologics, such as monoclonal antibody therapies, raising the bar in at least three ways:

1) **Coordination**: The manufacturing process must be coordinated with the extraction of the "raw material" of patient lymphocytes and delivery of the drug product back to the patient, creating new logistical demands from the manufacturer level to the clinic and patient. Moreover, this personalized manufacturing decreases supply chain slack, due to the heightened demands of transporting biological materials and the pressure to compact a manufacturing timeline that cannot begin until the therapy is prescribed.

2) **Identity**: Product identity must be tracked with patient-level precision, rather than in batches or lots that will supply distributors and multiple patients. Patient-specific therapies also mean that a manufacturing failure cannot be accommodated by shipping an alternative batch; product replacement requires re-starting from the beginning. For patients with rapidly progressive, life-threatening illnesses, a manufacturing do-over may have profound repercussions, not a just financial impact for the manufacturer.

3) **Speed**: The duration of the manufacturing process (lead time) and timing of extraction and delivery take on increased importance, as drug product can neither be manufactured in advance, nor stockpiled; thus, the supply chain must be nimble and able to absorb changes in product demand over time. Longer lead times also increase the risk that seriously ill patients will not receive drug in time. Particularly in oncology, where the development paradigm favors initial clinical trials in later stage patients, manufacturing lead time can cut significantly into the patient benefit offered by these therapies.

The heightened requirements for coordination, identity, and speed may be expected to impact the optimal manufacturing and supply chain structure compared to traditional small molecules and biologics. The next developer in line to reach the market with an autologous CAR-T therapy after Novartis and Kite/Gilead currently appears to be Juno Therapeutics (recently acquired by Celgene). Notably, all three have invested in single-site manufacturing facilities to supply near-term product demand based on US approvals.

The locations of these manufacturing facilities (Figure 4) suggest that proximity to a major airport is sufficient to ensure supply chain continuity and minimum shipping time, even to opposite coasts. In any event, transit time represents a minor portion of the total manufacturing lead time in current commercial-scale CAR-T manufacturing (though still in clinical stage implementation for Juno).

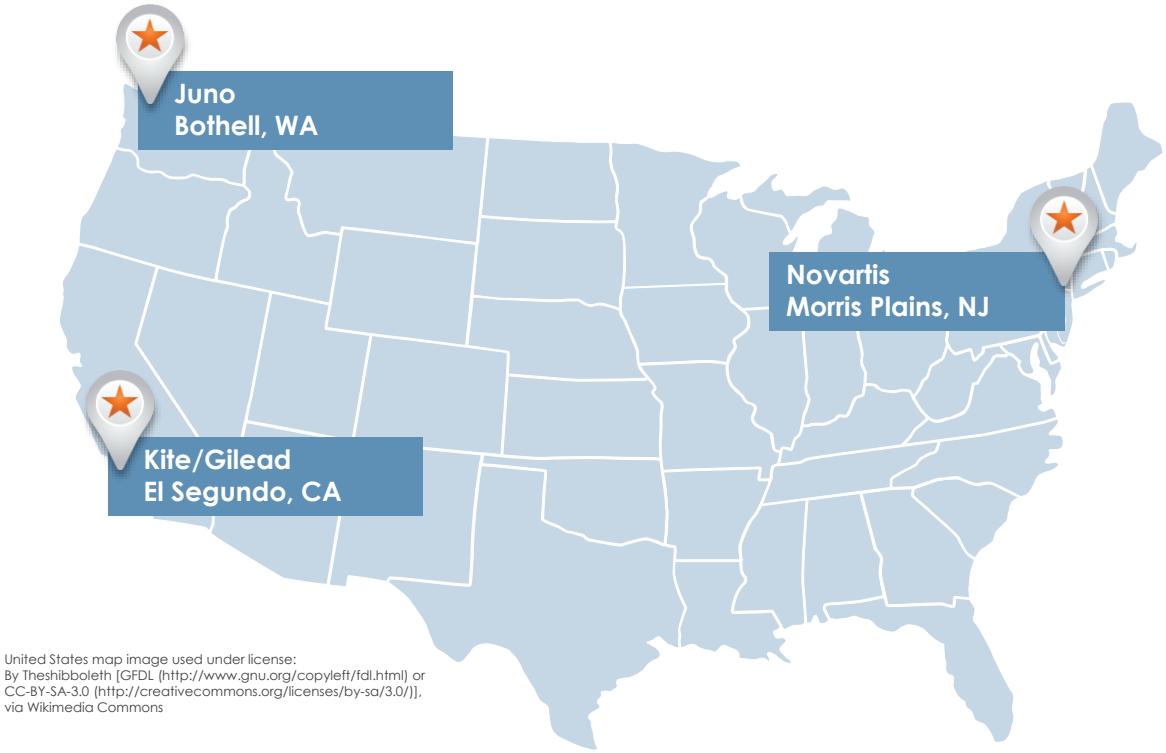

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Figure 4: *Centralized CAR-T manufacturing locations of Novartis, Kite/Gilead, and Juno.*

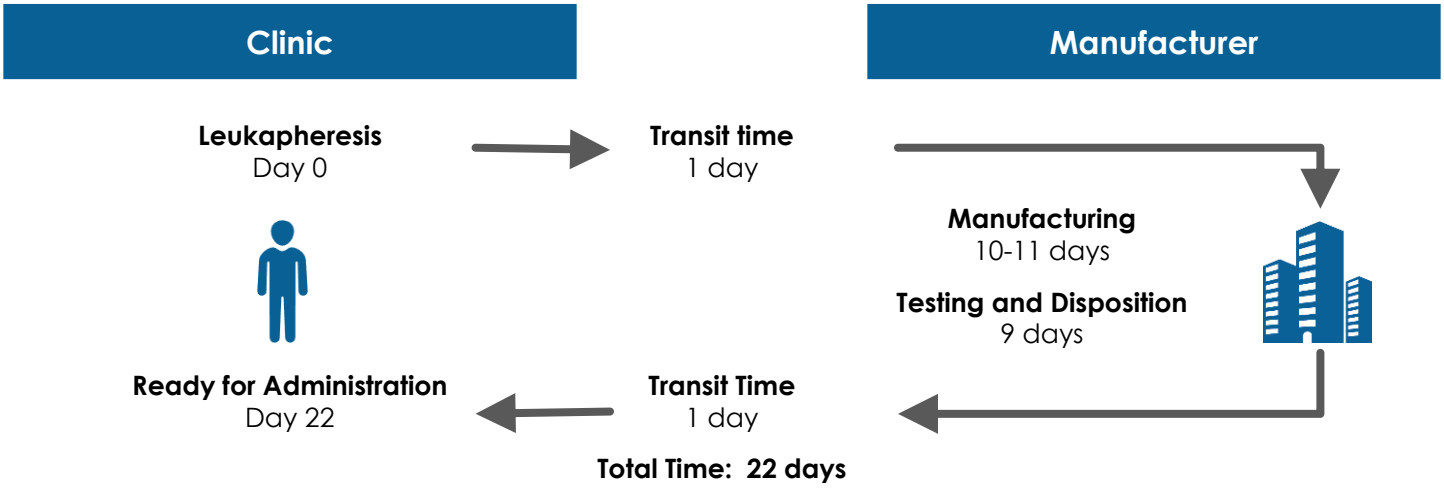

Figure 5: *Kymriah™ manufacturing timeline, adapted from Novartis comments at FDA advisory committee presentation on July 12, 2017.*

First-to-market Novartis detailed the activities that compose the 22-day duration from leukapheresis to return of the manufactured product to the clinical site (Figure 5) during its advisory committee presentation in July 2017.[10] In the company's October 2017 press release announcing its sBLA filing for Kymriah™ in DLBCL, Novartis reaffirmed the 22-day timeline,[11] which may be read as an implicit acknowledgment that it anticipates no further contraction of its current supply chain and manufacturing timeline.

Further reflecting the central importance of manufacturing to CAR-T therapies, Gilead remarked on its manufacturing in announcing FDA approval of Yescarta™ in October 2017. In addition to the customary and required language of product approval press releases, the company noted the 99-percent manufacturing success rate and 17-day *median* manufacturing turnaround time seen in its pivotal study.[12] It is unclear whether the choice of communicating a median time rather than a specific duration is indicative of outlier problems in the clinical study, a still-evolving supply chain at launch, a combination of these, or some other factor altogether.

Juno, though yet to submit a BLA for its current lead candidate JCAR017, has commented on both its near-term manufacturing supply chain, as well as longer-term prospects for significantly reduced manufacturing times. In the company's Q3'17 earnings call, CEO Hans Bishop communicated an expected commercial manufacturing turnaround time of "less than 21 days" for its upcoming pivotal trial.[13]

[10] Center for Drug Evaluation and Research. "Oncologic Drugs Advisory Committee (ODAC)." Food and Drug Administration. pp. 82-83. *Accessed on 9 May 2018,* https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM573720.pdf.

[11] Novartis. "Novartis submits application to FDA for Kymriah™ (tisagenlecleucel) in adult patients with r/r DLBCL, seeking second indication for first-ever FDA approved CAR-T therapy." *Accessed on 9 May 2018*, https://www.novartis.com/news/media-releases/novartis-submits-application-fda-kymriahtm-tisagenlecleucel-adult-patients-rr.

[12] Gilead. "Kite's Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA for the Treatment of Adult Patients With Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy." *Accessed on 9 May 2018*, http://www.gilead.com/news/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refractory-large-bcell-lymphoma-after-two-or-more-lines-of-systemic-therapy.

[13] Seeking Alpha. "Juno Therapeutics' (JUNO) CEO Hans Bishop on Q3 2017 Results - Earnings Call Transcript." *Accessed on 9 May 2018*, https://seekingalpha.com/article/4119379-juno-therapeutics-juno-ceo-hans-bishop-q3-2017-results-earnings-call-transcript.

While this is similar to Novartis's Kymriah™ timeline, Juno's timeline applies to a defined cell composition candidate. Apparently, Juno is able to accommodate the additional complexity of manufacturing to a specific profile of CD4 and CD8 T-cells in a competitive turnaround time. Moreover, in Juno's earlier Q1'17 earnings call, Bishop remarked that work on new technologies involving both instruments and reagents could potentially reduce manufacturing times to "around 2 days."[14] If realized, such a timeline would significantly mitigate one of the advantages of an allogeneic, or "off-the-shelf," CAR-T therapy.

However, even if the time-to-patient advantage of an allogeneic therapy over current autologous therapies is successfully narrowed, reduced supply chain complexity and total manufacturing cost would still likely favor an off-the-shelf solution. It is important to note for context, though, that the most advanced among these remain early in development and the recent clinical hold and subsequent protocol revisions for Cellectis's candidate UCART123 further clouds the timeline and near-term potential for an allogeneic CAR-T therapy.[15]

Manufacturing failure rate represents another key factor for the success of autologous cell therapies, for both manufacturer and patient. With current manufacturing processes, a failure inevitably delays delivery of the therapy to the patient. Novartis experienced clinical failure rates of nine percent and seven percent in the ALL and DLBCL trials for Kymriah™, respectively.[16] Kite/Gilead held manufacturing failures to just under one percent in its pivotal Yescarta™ study.[17] The labels for both drugs note that a second manufacturing may be attempted in cases of failure.

In addition to these supply chain considerations, the manufacturing of patient-specific therapies introduces variables not seen with traditional biologics. In the next section, we summarize key issues for consideration in the development of these advanced therapies.

Insights from First Principles

- The strict supply chain control requirements of autologous engineered therapies elevate the importance of supply chain leadership for companies
- Current manufacturing lead times of around three weeks appear to be technology-limited, with little or no improvement expected in the near term; the ability to scale parallel-processing capacity may become important with increasing demand due to additional indication approvals
- However, the longer term potential to reduce manufacturing lead time to 2 days could mitigate one key advantage of allogeneic or "off-the-shelf" CAR-T therapies and focus competition more heavily on efficacy differences, cost of manufacturing, pricing, and access/reimbursement

[14] Seeking Alpha. "Juno Therapeutics' (JUNO) Hans Bishop on Q1 2017 Results - Earnings Call Transcript." *Accessed on 9 May 2018,* https://seekingalpha.com/article/4069480-juno-therapeutics-juno-hans-bishop-q1-2017-results-earnings-call-transcript?part=single?part=single.
[15] Cellectis. "Cellectis Reports Clinical Hold of UCART123 Studies." *Accessed on 9 May 2018,* http://www.cellectis.com/en/press/cellectis-reports-clinical-hold-of-ucart123-studies.
[16] Kymriah™ prescribing information, revised May 2018.
[17] Yescarta™ prescribing information, October 2017.

The Kymriah™ Approval

On July 12, 2017, FDA convened the Oncologic Drugs Advisory Committee (ODAC) to consider the BLA for CTL019 (tisagenlecleucel), as Kymriah™ was then known. While the committee ultimately voted unanimously in favor of approval, the discussion at this meeting and resulting Kymriah™ label language provide valuable guidance for developers of cellular therapies and autologous CAR-T therapies in particular. For those wishing to delve into the details of the ODAC discussion, FDA makes the meeting materials and transcript available,[18] however, we provide an overview of the salient points below.

When convening an advisory committee meeting, FDA provides guidance to the committee on the specific areas on which it would like input. This guidance takes the form of background information, commentary, and requests for committee consideration of specific topics or questions. Based on the demonstrated clinical efficacy of Kymriah™, the Agency took this subject off the table as a stand-alone consideration, stating early on in its briefing document that "[t]he overall effectiveness of this product is not the primary issue for consideration by this Committee."[19]

Instead, Agency reviewers made requests of the committee that we paraphrase as follows:

Chemistry, Manufacturing, and Controls (CMC)

- *Critique/improve* the plan for control of product quality
- *Discuss* the risks of replication-competent retrovirus (RCR) and insertional mutagenesis

Safety

- *Advise* on appropriate steps to protect patients in light of the Cytokine Release Syndrome (CRS) and neurotoxicities observed
- *Recommend* a Long Term Follow Up (LTFU) plan, considering a registry for 15-year data and follow up to track persistence of transduced cells

Benefit/Risk

- *Decide whether the benefits justify the risk in the defined population*

In the following section, we review the FDA concerns that underlie these requests.

High-level FDA Insights on CAR-T

- **Characterization and consistency of autologous cell therapies, and rigorous study of viral vector-based therapy risks including RCR and insertional mutagenesis, are significant concerns of FDA**
- **FDA approved substantially identical REMS plans for Kymriah™ and Yescarta™, which set a clear baseline expectation for CAR-T developers; similarly, FDA has outlined post-approval study requirements that include (minimum) 15-year follow up for safety**
- **In planning for the clinical study and commercialization of autologous cellular therapies, developers must carefully weigh the (dis)advantages of network size, including the necessity for staff training, enrollment speed, and site experience handling CRS and neurotoxicities**

[18] Food and Drug Administration. "2017 Meeting Materials, Oncologic Drugs Advisory Committee." Advisory Committees. *Accessed on 9 May 2018,* https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm547155.htm.

[19] Food and Drug Administration. "Oncologic Drugs Advisory Committee Meeting BLA 125646." FDA Briefing Document. *Accessed on 9 May 2018,* https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm566166.pdf.

Product Characterization and Quality

Compared to the manufacturing processes for small molecules, peptides, and monoclonal antibodies, CAR-T manufacturing as carried out today inherently involves greater variability and uncertainty; the FDA acknowledged this and left ODAC to discuss how much is too much.

The objective of leukapheresis in the context of CAR-T manufacturing is the isolation of autologous patient T-cells. However, the leukapheresis product will contain other leukocyte types, and potentially other blood components including erythrocytes and thrombocytes. Moreover, the constituent mix of lymphocytes and sub-populations of T-cells may differ significantly by patient and by the condition of the patient at the time of leukapheresis. All of these factors create variability in the starting material for an autologous CAR-T therapy. Novartis's data from its pivotal B2202 study showed that significant numbers of patient leukapheresis product consisted of high proportions of B-cells, monocytes, and NK cells. FDA acknowledged, nonetheless, that "their manufacturing process results in a final product that is consistently high in T-cell content . . . even when the starting material is quite variable . . ."[20]

The lentiviral vector containing the CAR transgene is the second of the two key starting materials. We cover manufacturing aspects here and potential concerns related more generally to the use of viral vectors below. The third-generation type lentiviral vector used in the production of Kymriah™ is designed for stable integration into the target genome and durable expression of the transgene at a low number of copies per cell. Novartis has contracted with Oxford Biomedica plc to supply the viral vector used for Kymriah™ manufacturing. Committee discussion of vector manufacturing touched on testing and release criteria, but otherwise was relatively muted – surprisingly so to at least one participant – but neither did this aspect of the Novartis CMC plan present any obvious red flags for the Agency.

Key CMC Parameters for CAR-T Manufacturing

- ***Vector copies per cell***, **as this this affects the likelihood of creating a CAR-T positive cell, but a higher value may also increase the risk of insertional mutagenesis**
- ***Transduction efficiency***, **or the proportion of T-cells that express the CAR-T construct after exposure to the lentiviral vector**
- ***Potency***, **as measured by response to antigen-specific stimulation of the CAR-T product; in the case of Kymriah™, interferon gamma production following exposure to CD-19 positive cells**

[20] Center for Drug Evaluation and Research. "Oncologic Drugs Advisory Committee (ODAC)." Food and Drug Administration. p. 72. *Accessed on 9 May 2018*, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/DrugsOncologicDrugsAdvisoryCommittee/UCM573720.pdf.

One notable aspect of the total CAR-T supply chain was provided by the Oxford Biomedica representative. CTO James Miskin confirmed that the manufacturing lead time is significant, commenting that "Vector manufacturing takes several weeks, but then coupled with the extensive testing panel that takes place, the entire process takes several months."[21]

Related to the final CAR-T product, both the Novartis and Agency presentations focused on three specific metrics: vector copies per cell, transduction efficiency, and potency, as defined and explained above. All three relate in a straightforward manner to the control of product characteristics and product release criteria. The number of vector copies present in each T-cell carries an additional safety consideration, in that a higher value may increase the probability of unintentional genetic disruption that leads to oncogenesis. This theoretical risk is one of the drivers for long-term patient follow up and is discussed in more detail below.

Cellular composition was also an area of several committee queries. The heterogeneity of the product and potential for differing efficacy and safety based on T-cell type was postulated as a reason for additional scrutiny of the product composition, as was the potential effect of on-target, off-tumor B-cell toxicity. The committee discussion leaned toward an interest in additional characterization studies and functional analyses, while stopping short of criticizing the Kymriah™ submission, in light of its demonstrated benefit/risk profile. These concerns do, however, set the stage for a positive reception of defined cellular composition products in the future.

In summary, a number of criteria are included in lot release specifications for a CAR-T product and were probed by the Kymriah™ Advisory Committee; its discussion carries several takeaways for observers. First, Novartis addressed concerns about the inherent variability of CAR-T manufacturing by showing that a relatively well-defined and characterized product resulted from its process. Second and relatedly, its clinical results tended to trump reasonable theoretical concerns. Finally, reassurance gained through experience with CAR-T therapies in the commercial setting will likely compete with a desire for additional characterization, as additional products reach the market and raise the bar for followers.

[21] Center for Drug Evaluation and Research. "Oncologic Drugs Advisory Committee (ODAC)." Food and Drug Administration. p. 53. *Accessed on 9 May 2018,* https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM573720.pdf.

Retroviral Vector-based Concerns and Considerations

The use of retroviral vectors carries two safety concerns rooted in their construction and mechanism of action: recombination leading to replication-competent virus and proviral gene insertion at a site that causes mutagenesis.

Unintended replication by a retroviral vector-based therapy can theoretically pose a serious threat to patient safety. A 1992 study involving retroviral-mediated gene transfer proved a catalyst for FDA action; the authors noted that several study animals (rhesus monkeys) with detectable replication-competent retrovirus (RCR) developed rapidly progressive T-cell lymphomas.[22] The Agency's 2006 edition of its guidance on testing for RCR continued to cite this study as background for its recommendations.[23] However, two notable developments suggest that the risk of RCR is low in light of current practice and precautions. First, the current third generation retroviral vector designs contain additional safeguards to reduce the likelihood of recombination that could lead to replication-competent virus. Second, encouraging clinical experience has been gained since the 1992 primate study: to date, RCR has not been detected in any clinical materials or in patients to whom those materials have been administered. In fact, recent commentary has argued for revisiting testing guidelines.[24] The high stakes of preventing the presence or formation of RCR in clinical therapies justify caution. However, the accumulated data suggest that the risk is low with current technology and may be further mitigated by continued advances in vector engineering and screening.

The risk that a viral vector will integrate in a way that disrupts normal gene function and cause malignant transformation, known as insertional mutagenesis, represents a second concern related to viral vector-based therapies. Leukemia due to insertional mutagenesis has been observed in clinical trials where gammaretroviral vectors were used as a therapy for X-linked severe combined immunodeficiency disease by correcting autologous CD34 bone marrow cells *ex vivo* and reintroducing the cells into patients.[25] Lentiviral vectors appear less prone to insertional mutagenesis, due to factors such as innate integration site preference and vector engineering. The screening that is carried out as part of the characterization process also ensures selection for viral vectors that are not prone to insertional mutagenesis. While no Kymriah™ patients to date have developed malignancies due to insertional mutagenesis, the potential for late onset AEs of this nature are a driver for the long-term follow up included in the post-approval commitments of the recently approved CAR-T therapies. Both Novartis and Kite/Gilead are required to complete large post-marketing studies with fifteen year follow up, in order to identify any risk of delayed secondary malignancies due to CAR-T treatment.

A third consideration related to clinical benefit is the persistence of gene expression. Persistence of the CAR-T cells *in vivo* is necessary to optimize efficacy. However, extended side effect duration (such as B-cell aplasia) may accompany longer persistence and T-cell exhaustion may manifest with prolonged exposure to antigen, making the optimal persistence unclear.[26] The committee discussion of Kymriah™ persistence in patients generally reflected the view that greater persistence is generally a good thing. The Kymriah™ registry will indirectly track persistence, using B-cell depletion as a surrogate marker. Looking into the future, the ability to actively manage persistence will likely be an area of development for CAR-T therapies, through the engineering-in of mechanisms such as suicide switches and susceptibility to modulation by another administered molecule.

[22] Robert Donahue, et al. "Helper virus induced T cell lymphoma in nonhuman primates after retroviral mediated gene transfer." J. Exp. Med. 176:1125-1135. DOI: 10.1084/jem.176.4.1125.

[23] Food and Drug Administration. "Cellular and Gene Therapy Products." Vaccines, Blood & Biologics. *Accessed on 9 May 2018,* https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/%20Guidances/CellularandGeneTherapy/.

[24] Katherine Marcucci, et al. "Retroviral and lentiviral safety analysis of gene-modified T cell products and infused HIV and oncology patients" Molecular Therapy. 26:269-279 DOI: 10.1016/J.YMTHE.2017.10.012.

[25] Salima Hacein-Bey-Abina, et al. "Efficacy of gene therapy for X-linked severe combined immunodeficiency" N Engl J Med. 363: 355-364, DOI: 10.1056/NEJMoa1000164.

[26] For a review of considerations related to persistence, see Wendell Lim and Carl June. "The principles of engineering immune cells to treat cancer." Cell (Review). 168: 724-740.

Safety: SAEs and REMS Requirements

The benefit of CAR-T therapy is frequently accompanied by side effects directly related to the mechanism of action, including Cytokine Release Syndrome (CRS, "cytokine storm") and certain neurotoxicities. Because of the possibility of rapid onset and the necessity of expert management of these Serious Adverse Events (SAEs), as well as the overall side effect profile, FDA has applied heightened requirements to the administration of Kymriah™ and Yescarta™ in the commercial setting.

Since 2007, FDA has had the legal authority to require drug developers to design and implement a Risk Evaluation and Mitigation Strategy (REMS) as part of an initial approval and at any time subsequent, based on new information when "necessary to ensure that the benefits of the drug outweigh the risks. . . ."[27] This determination of necessity takes into consideration several enumerated factors, which we summarize as follows [28]:

- Size of the eligible population
- Seriousness of the disease/disorder
- Expected benefit of the drug
- Duration of treatment with drug
- Seriousness of any known or potential adverse events that may be related to the drug (taking into account background rates)
- Whether the drug is a new molecular entity (an NME, i.e., the active moiety has not been previously approved)

2016 FDA draft guidance provides some insight into its views on REMS and its application of the statutory factors above towards determining when a REMS is necessary.[29] The Agency also provides a list of approved REMS, which currently totals 74 entries.[30]

The approved REMS for Kymriah™ and Yescarta™, as outlined in the approval letter for each, are substantially equivalent.[31] Among the elements of the REMS are certification of hospitals and associated clinics, training of staff and adherence to defined protocols, and maintaining a minimum supply of tocilizumab (Actemra®, Roche) for each CAR-T patient, for use in treating CRS without delay. The REMS for each also includes requirements for record keeping, regular reporting related to AE experience, and assessment of program performance. Clearly, the mandate by FDA to implement a REMS represents a significant burden, since its requirements involve not only the developer, but also the hospital, clinic, and all staff involved in prescribing, dispensing, and administering the drug.

[27] 21 U.S.C. § 355-1 (2010).
[28] 21 U.S.C. § 355-1 (a)(1) (2010).
[29] Food and Drug Administration. "FDA's Application of Statutory Factors in Determining When a REMS Is Necessary." Guidance for Industry. *Accessed on 9 May 2018,* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM521504.pdf.
[30] Food and Drug Administration. "Approved Risk Evaluation and Mitigation Strategies (REMS)." REMS. *Accessed on 9 May 2018,* https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.
[31] *See*: Food and Drug Administration. "BL 125646/0 Approval Letter." *Accessed on 9 May 2018,* https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM574106.pdf and Food and Drug Administration. "BL 125643/0 Approval Letter." *Accessed on 9 May 2018,* https://www.fda.gov/downloads/BiologicsBloodVaccinesCellularGeneTherapyProducts/ApprovedProducts/UCM581259.pdf.

Insights from First Principles

- Though RCR screening may be an area where requirements are relaxed in the future, the overall trend will be towards greater characterization and comparison of cellular therapies, as new entrants raise the bar and advances such as humanized constructs are introduced
- FDA use of a REMS as a potent tool to shift the benefit-risk balance is more likely for advanced therapies that are less well understood as a class and carry serious side effects; the lack of a REMS requirement for Luxturna™ demonstrates that a REM can be avoided where safety is clean
- Because a REMS represents a significant additional burden for commercialization of a drug, developers should consider the likelihood of a REMS requirement and proactively scenario plan by the time of pivotal study

Conclusions

The second half of 2017 proved a watershed period for the progress of cellular and gene therapies, with FDA approving Kymriah™, Yescarta™, and Luxturna™ in rapid succession. The clinical promise of these therapies is accompanied by significant departures from the historical drug development paradigm. In this paper, we have probed some of the key development and commercialization considerations for autologous cell therapies and the CAR-T class in particular. We've given examples of how the unique challenges of these therapies raise the stakes for planning and execution by developers, particularly in the area of manufacturing, supply chain, and commercialization with a REMS.

The forthcoming second installment in this series on advanced therapies will focus on commercialization experience with CAR-T drugs and what may be in store for others, covering up-to-date experience with pricing and reimbursement.

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