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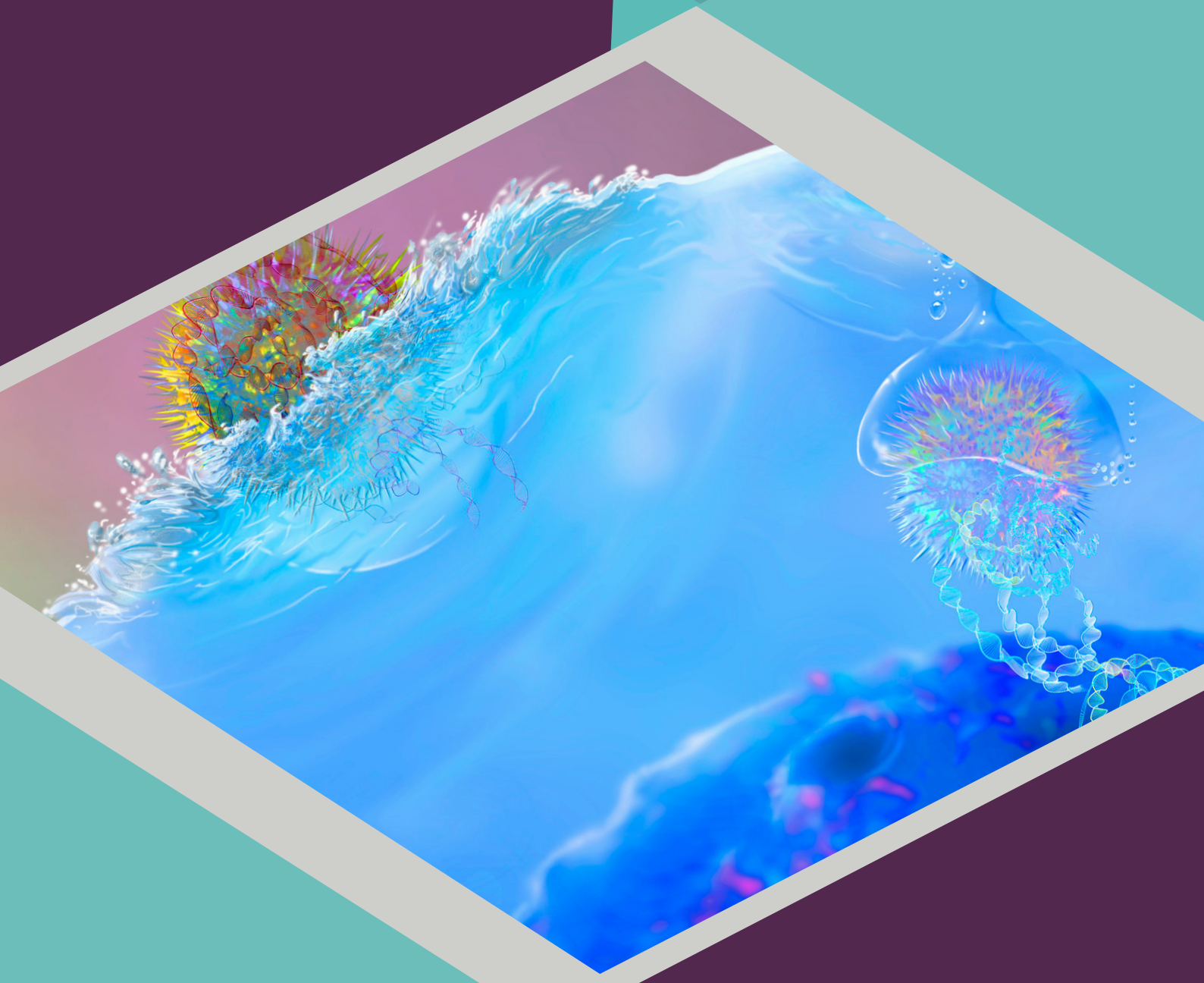

CAR-T therapy: preparing for clinical implementation

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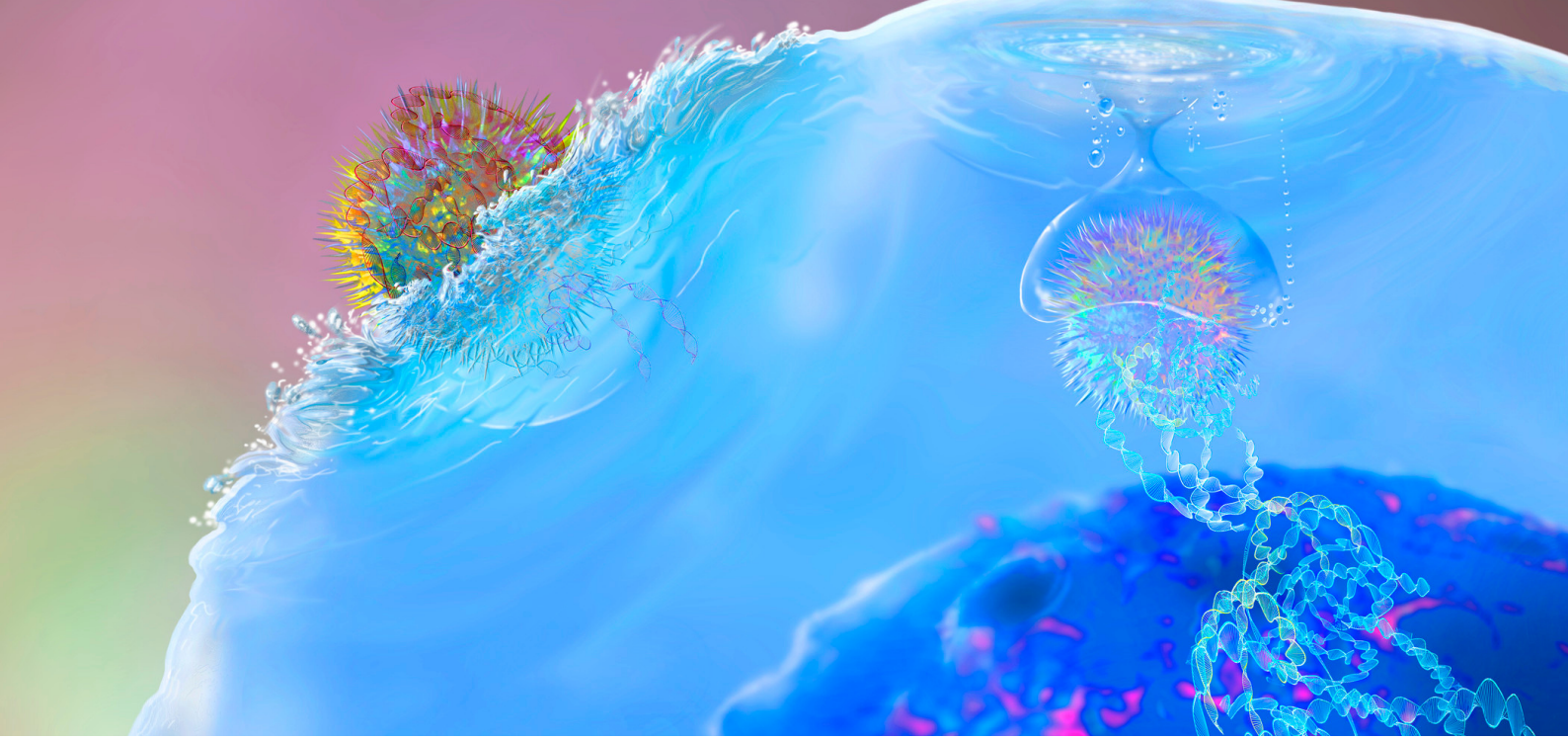

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ABOUT REGMEDNET

RegMedNet is a community site that unites the diverse regenerative medicine community. Through partnership with our sister journal, *Regenerative Medicine*, we seek to educate and inspire to help this exciting field move forward at an even faster rate.

On RegMedNet, you can find free educational webinars, expert opinion and insight, and exclusive peer-reviewed journal articles, as well as the latest news and advances. You can watch, listen and read about every step in the regenerative medicine and cell therapy pipeline, from development, clinical trial and manufacture to regulation and commercialization, all in one place.

International Women's Day

Women to Watch

Celebrating fantastic women in regenerative medicine

DR RAYNE ROUCE

Texas Children's Hospital (TX, USA)

RegMedNet

Women to Watch: translating CAR-T therapies from the lab to the clinic with Dr Rayne Rouce

As part of our 'Women to Watch' series on RegMedNet, we're putting Dr Rayne Rouce into the spotlight. Dr Rouce is a pediatric oncologist and physician–scientist at Baylor College of Medicine and Texas Children's Hospital (both TX, USA) focused on translating novel immunotherapies from the laboratory to the clinic. Specifically, she leads clinical trials of first-in-human genetically or otherwise modified T cells (CAR and virus-specific T cells) in patients with relapsed or refractory leukemia and lymphoma. In addition to translating novel therapies, she has worked in the laboratory and has partnered with other scientists to assist in the translation of these exciting therapies into the clinic.

1 Can you provide us with an overview of what your work involves?

My work is extremely satisfying, as I am truly involved in every aspect of bench-to-bedside development of these immune effector products: from preclinical conception and testing of these T-cell products, to optimization and validation in preparation for investigational new drug application submission, to protocol development and regulatory submission, to enrollment and day-to-day care of patients receiving these groundbreaking therapies.

2 What are the best aspects of your job? What are the most challenging parts?

The best part of my job is that I literally get to be a part of giving patients, particularly children suffering from these horrible cancers, a chance at life. The clinical trials that I lead are Phase I, thus typically reserved for patients who may have been told they have no further treatment options. I cannot express the gratitude I feel to each and every patient and family who has ever enrolled on a clinical trial I've led. It is an honor to walk with them through such a difficult time of their journey. Regardless of outcome, my colleagues and I, and the field of cellular and gene therapy, are forever grateful for the many sacrifices these patients and their families make, and their willingness to help us learn how to improve our therapies. Also, it should be obvious from the description of my work, that it is the epitome of 'team science'. On a daily basis, I get to work with and learn from countless scientists, lab personnel, regulatory professionals and healthcare professionals with various expertise. We work as a finely oiled machine with many moving parts, and only the occasional snag, which we work to troubleshoot together.

I would say the most challenging aspect is coming to grips with the current limitations of science and medicine, and how they affect my patients. I don't think in terms of scientific protocols or therapeutic products – I think in terms of patients. Little faces, big smiles, big dreams. When I can't offer a certain therapy because it has not been tested yet in children, or despite its promise, it remains in preclinical development… I feel defeated. However, it is this very sense of defeat that gives me the fiery resolve to not stop until I have a promising therapy to offer to every patient I encounter.

3 Have you faced any obstacles in your field due to your gender?

As a Black woman physician–scientist, I certainly have faced a number of obstacles. However, I have never encountered a barrier that was not surmountable, and I can honestly say that every challenge I've endured has added to my toolkit of negotiation and conflict resolution skills, and my general 'academic awareness'. In my field, I am usually the only person of color in the room, often the only one with a Southern drawl, and occasionally one of few women. Nevertheless, I have had amazing women mentors who have paved the way and shown me when to be gracious, and when to speak up.

4 In your opinion, what more could be done to promote gender equality in your field?

Women are promoted less often than men and are less likely to gain academic tenure. They are paid less, are less likely to be in leadership positions, and more likely to engage in work that, while meritorious at face value, is less likely to contribute to promotion. And yet, historically, we often don't ask for what we have earned. So, what can we do? Know our worth. Speak up. Ensure others understand that one token woman at the table is not enough. Then once we arrive, once we've made it, ensure we pay it forward, smoothly paving the pathway for women behind us.

5 What advice would you give to young women hoping to pursue a career in your field?

The sky is the limit. Never be intimidated. Replace that 'imposter syndrome' with 'superwoman syndrome'. Recognize that while you may be the first, you won't be the last. Identify leaders you strive to emulate and don't be shy about asking them to mentor you. Lastly, when people believe in you – believe them, and let that fuel your self-confidence.

6 Lastly, who is your female superhero?

Wow. Now THIS, is a hard one. I would say my female superhero is a combination of Michelle Obama, Rosa Parks, Katherine Johnson, Ruth Bader Ginsburg, Beyoncé and my mom and grandmother. While these women may seem like they have nothing in common – in my mind, they have everything in common. They broke down barriers and paved the way, all the while keeping their heads held high.

Acknowledgements

This interview was put together and conducted by our Senior Editor, Sharon Salt, with written responses provided to us by Dr Rayne Rouce.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of RegMedNet or Future Science Group.

Special Report

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Regenerative Medicine

Comparability: what we can learn from the review of advanced therapy medicinal products

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Publicly available summaries from Marketing Authorization Applications for gene and cell therapy products (advanced therapies) were evaluated to explore data expectations for product characteristics pre and post changes (comparability). Public assessment reports were used to analyze trends in information requests from regulators concerning comparability from current commercial advanced therapies. In the analysis, 12 products approved in the USA and EU were included. Inadequacies were highlighted for comparability data (six products); additional information requests (five products) and major objections were identified relating to comparability (two products, EU). Postapproval authorization obligations were imposed for six products. Comparability data are essential component for regulatory applications and public assessment reports provide a valuable source of insight into regulators' expectations.

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Keywords: advanced therapy medicinal product • Biologics License Application • cell therapy • comparability • European Public Assessment Report • gene therapy • Marketing Authorization Application • summary basis of regulatory action

Background

One of the most important challenges for obtaining and maintaining authorization for an advanced therapy medicinal product (ATMP) is assessment of the potential impact of changes made throughout development and beyond upon quality, safety and efficacy of the product. ATMPs are scientifically challenging, with their complexity and inherent variability making determination and quantitation of relevant properties difficult. Alterations in material source and quality, and/or processing conditions and facilities, can impart changes in biological properties that can be difficult to predict or to identify, making assurance of continued product quality an ongoing challenge during the product lifecycle.

Marketing authorization holders (MAH) and clinical trial sponsors have an obligation to evaluate changes made during development for their impact on biologically or clinically relevant product parameters. Similarly, regulators are responsible for assessing the impact of such changes and determining whether the data are sufficient to demonstrate that data generated on previous iterations of the product during clinical development are applicable to the product version intended for commercial marketing. The ultimate determinant of safety and efficacy is the conduct of clinical trials with medicinal product from the new process version, but clearly the costs and timelines associated with clinical trials make them a last resort in terms of assessing changes. There is thus great interest from sponsors and MAHs regarding the level of assurance and the types of data expected by regulators to demonstrate comparability.

With the rapid increase in marketing applications for gene therapy and cell therapy products, a potential wealth of information may be mined from the assessment of these applications. This includes the regulators' perceptions of the data provided by the applicant to demonstrate that after significant changes such as materials, processes and/or manufacturing site, the post-change medicinal product has not been detrimentally affected with respect to its clinical effects (efficacy and safety).

Future Medicine

Our research shows how publicly available information from the US FDA and the EMA reviews of US Biologics License Applications (BLAs) and EU Marketing Authorization Applications (MAA) can be used to understand the 'direction of travel' for a developer's own marketing application and therefore areas for potential focus during development. Some other regulatory authorities release public summaries of marketing application reviews but these tend to be limited in content and have not been included in this paper.

Public assessment documents from EMA and FDA were reviewed for 12 of the most recently approved gene and cell therapy products (at time of writing). We evaluated individual findings and comments identified during the initial assessment for these ATMPs, and have drawn out common themes which help to provide insight into the expectations and key concerns of regulators. Our focus in this article is the fundamental importance of a comparability strategy as illustrated by issues raised during marketing application review. Specifics of comparability study design, such as the evaluation of the potential impact of individual process steps, are not within scope of the analysis.

Comparable (highly similar) products & comparability assessments

Exhaustive characterization of a medicinal product to understand whether an original medicinal product, prior to changes, is 'the same' as a second iteration of that medicinal product after changes to the manufacturing process, is only feasible for the simplest biological products. Therefore, the established expectation for complex biological medicinal products such as ATMPs is the concept of 'comparable' which indicates that the two medicinal product versions are highly similar, but not necessarily identical. The assessment of similarity (comparability) uses an understanding of the specific characteristics (quality attributes) which are critical to desirable and undesirable clinical effects, specifically efficacy and clinical safety.

A critical quality attribute (CQA) is defined as a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality [1]. At its simplest, CQAs are characteristics which if impacted have the potential to affect efficacy and/or clinical safety.

Whenever a change is made, there is a risk that the post-change medicinal product may present differences in characteristics which could impact and confound the validity of previously generated clinical data. Therefore, understanding that the product used throughout clinical development is highly similar despite multiple manufacturing and/or materials changes is fundamental to the validity of data. It is important to note that analyses performed will only permit the assessment of the characteristics investigated and this might not incorporate all critical elements. Specifically, developers should not rely on routine release specifications alone to assess comparability: this point is highlighted in EMA's Questions & Answers document on comparability for ATMPs [2]. This aspect contributes to the high degree of technical and regulatory challenge around comparability: process and material changes may have unanticipated consequences that could potentially remain undetected until the product is in general clinical use. As a result, regulators are mindful of this when assessing comparability data and this places a high burden of proof on the applicant. Formal scientific advice from regulators is both available and recommended [3].

One medicinal product type for which comparability studies have a different purpose is similar biological medicines (biosimilars). Developed in the 2000s as a regulatory concept to address the idea of generic medicinal products as the original patents for the first monoclonal antibodies expired, biosimilars are biological products with a high degree of similarity to a reference (original) medicinal product that present no clinically significant differences to the original biological product in regard to quality, safety and potency of the product [4]. Biosimilars are developed based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity) [5], allowing approval based on a reduced nonclinical and clinical dataset designed to identify any relevant differences in pharmacokinetics and immunogenicity [6]. Comparability as it applies to biosimilars is not included in the scope of this paper as it focuses on the degree of similarity between two medicinal products from different applicants. This concept is not applicable to ATMPs, which present issues of comparability between different process iterations during development of the same medicinal product.

Current guidance for comparability assessments

Over time the guidance available to gene and cell therapy product (advanced therapy) developers regarding the expectations for comparability assessments has expanded. Initially regulators, including the FDA, EMA and EU national regulatory authorities, typically cited ICH Q5E [7], an international guideline addressing comparability of

biological and biotechnological products. The scope of this guideline includes proteins, polypeptides and protein conjugates. These medicinal products can be produced via recombinant or nonrecombinant cell culture processes and can be highly purified and characterized by standard analytical methods. Although advanced therapies are not within scope of this guidance, regulators expect that the principles set out in this guideline will be applied [2].

More recently the FDA released a comprehensive guideline for investigational gene therapy products which indicates comparability expectations [8] and the EMA provided similar guidance in guidelines for Advanced Therapy Investigational Medicinal Products (ATiMPs; draft) [9], gene therapy products [10] and genetically modified cell-based products [11]. This was augmented with the EMA's Questions & Answers document dedicated to comparability assessments [2] (ATiMP is a term used to indicate an ATMP prior to approval of the marketing application).

Guidelines are also available for human cell-based medicinal products [12], for investigational somatic cell therapy products [13] and for both human somatic cell therapy and gene therapy products [14]. Japan's Pharmaceutical and Medical Devices Agency has also issued a guideline on the quality and safety of gene therapy products [15].

The general themes are consistent within guidelines, specifically requiring both an understanding of whether changes have detrimentally impacted product quality attributes and therefore could affect clinical effects, and a prospective study design which can facilitate an unambiguous conclusion. A stepwise approach consistent with ICH Q5E [7] is recommended, with the assessment of Chemistry, Manufacturing, and Controls (CMC) data as a minimum. Supplemental clinical/nonclinical data may be required if a conclusion cannot be made on CMC data alone.

Results

Summary of comments during marketing application review

A valuable source of information to gain an understanding of regulators' current expectations of comparability study data and design is the published assessment summaries from MAAs: the BLA in the USA and the MAA in the EU. The details of comparability assessments performed throughout clinical development should be included in Module 3 of the application dossier. Some of the information from US BLA and EU MAA reviews are made publicly available via the European Public Assessment Report and the US Summary Basis for Regulatory Action. These reports are an important source of intelligence to identify potential gaps and issues for a developer's own comparability assessments.

A brief summary of the comments from initial US BLA and EU MAA reviews is provided for 12 advanced therapy products: these include eight cell-based gene therapy products, two adeno-associated virus gene therapy products and two cell therapy products (Table 1, in reverse chronology of approval). Summary information from reviewers' comments is provided in Table 2.

Themes from reviewers' comments

A summary of some of the themes which emerged from the review information from the products listed is shown in Tables 3 & 4 and Figure 1 to indicate expectations and potential issues.

Changes made during development

Having identified regulators' expectations in relation to process changes and the comparability work necessary to evaluate them, it may be helpful to elucidate the flow of a typical comparability exercise. As outlined above, it is important that adequate knowledge, experience and data are gathered to support the changes made during development. A comparability assessment is intended to be a stepwise process: to build up a picture of the potential for impacts to product characteristics, to design studies to investigate these potential impacts, to gather pertinent data and to use accumulated experience to convert the information available into a conclusion of comparable or not comparable for the post-change medicinal product. An example of an approach to comparability assessment is provided in Figure 2.

To avoid bias to the outcome, the design of a comparability assessment should be prospective and consider all of the quality attributes which might be impacted. It should not be assumed that existing analytical methods, in other words, testing against the established release specification, will be sufficient. Although the conclusion of comparable or noncomparable relates to the final medicinal product as intended for administration, the data could be compiled using comparative data from different, relevant stages related to the production of the medicinal product. For example, comparing pre- and post-change drug substance could be sufficient if the changes relate to

Table 1. Recent marketing applications (approved) for gene and cell therapy product – US Biologics License Applications and EU Marketing Authorization Applications.

Proprietary name	Product type	Product description	Approvals		Ref.
			USA	EU	
Abecma	Cell-based gene therapy	CAR-T cell product for intravenous treatment of oncology indications	✓	†	[16]
Breyanzi	Cell-based gene therapy	CAR-T cell product for intravenous treatment of oncology indications	✓	†	[17]
Libmeldy	Cell-based gene therapy	Genetically modified CD34$^+$ cells for intravenous treatment of metachromatic leukodystrophy	†	✓	[18]
Tecartus	Cell-based gene therapy	CAR-T cell product for intravenous treatment of oncology indications	✓	✓	[19,20]
Zolgensma	AAV gene therapy	Adeno-associated virus product for intravenous treatment of spinal muscular atrophy	✓	✓	[21,22]
Zynteglo	Cell-based gene therapy	Genetically modified CD34$^+$ cells for intravenous treatment of beta thalassemia	†	✓	[23]
Luxturna	AAV gene therapy	Adeno-associated virus product injection into the eye for inherited retinal dystrophy	✓	✓	[24,25]
Yescarta	Cell-based gene therapy	CAR-T cell product for intravenous treatment of oncology indications	✓	✓	[26,27]
Kymriah	Cell-based gene therapy	CAR-T cell product for intravenous treatment of oncology indications	✓	✓	[28,29]
Alofisel	Cell therapy	Mesenchymal adult stem cells treatment by injection for rectal fistulas	†	✓	[30]
Spherox	Cell therapy	Matrix-associated chondrocytes for implantation for cartilage diseases	†	✓	[31]
Strimvelis	Cell-based gene therapy	Genetically modified CD34+ cells for severe combined immunodeficiency (ADA-SCID)	†	✓	[32]

†MA public review document not available: MA not submitted or review not completed.
AAV: Adeno-associated virus; ADA-SCID: Severe combined immunodeficiency; CAR: Chimeric antigen receptor; EU: EU Marketing Authorization Application; MA: Marketing application; US: US Biologics License Application.
The source of the information used was from the EMA website [33] and approved cellular and gene therapy products [34].

starting materials or early process alterations. The point at which samples are taken to study a CQA should ideally be that at which an impact on that quality attribute would have the greatest probability of detection.

Discussion

Comparability questions were raised during assessment of the majority of products, and further data were required on half of them before the application was approved. In the case of two products, comparability issues were raised as major objections in the EU procedures, meaning that if not resolved they would have been sufficient to cause rejection of the application. Over half of the products had to commit to post-approval activities directly or indirectly relating to comparability, such as a subsequent review of the suitability of the product specification. In this example, increased understanding of quality criteria should improve both routine quality control of the product and future comparability assessments. The requirement for additional actions post approval indicates that while not rendering the product non-approvable, the agencies required further assurance. A range of different concerns was identified, with common themes relating to the design of comparability studies, the use or inadequacy of non-clinical data to augment CMC findings, and the adequacy of potency assays used to underpin conclusions of comparability between product versions.

The purpose of comparability assessments is to allow the clear linking of data on early iterations of the product to the version intended for marketing, and to demonstrate the applicability of early clinical data in the MAA/BLA dossier. In conjunction with robust potency assays, which facilitate assessment of relevant biological functionality, the comparability strategy plays a key role in unifying the product development over the years of clinical development. Unfortunately, this aspect of development does not appear to be prioritized by applicants, and regulators have noted that inadequate comparability assessments, coupled with problematic potency assays, can undermine key clinical aspects such as the consistency of doses administered during clinical development [3]. It can therefore only be beneficial to ATMP developers to make full use of published intelligence on the issues highlighted by regulators and to seek to validate comparability strategies during scientific advice opportunities.

This issue is highlighted to further emphasize the importance of CMC (quality) data in supporting the conclusions of clinical trials: the quality and clinical sections of the dossier are as closely linked as the clinical and non-clinical sections. Issues within the quality module can have a profound impact upon acceptability of the clinical package and thus the overall approvability of the product itself. For example, the primary efficacy analysis was restricted

Table 2. Summary of comments from initial US Biologics License Application and EU Marketing Authorization Application reviews – comparability.

Product	US FDA (BLA)	EMA (EU MAA)	Ref.
Abecma	– Studies were conducted which demonstrated comparability of drug product manufactured with each process version used and comparability of LVV (anti-BCMA02 CAR LVV) manufactured at the clinical and commercial manufacturing facilities. Comparability assessments included comparison of lot release data, characterization studies, forced degradation studies and long-term stability studies	(Not applicable)	[16,35]
Breyanzi	– Studies to demonstrate comparability of products manufactured using process versions 2, 3 and 4 were performed during development and demonstrated that drug product batches manufactured with each process were comparable – Prospective comparability studies were used during product development and additionally, a retrospective comparability assessment of products was conducted using a subset of release testing data. Additionally, efficacy, safety and pharmacokinetics data were retrospectively compared to support the pooling of clinical data generated using products from the manufacturing processes	(Not applicable)	[17,36]
Libmeldy	(Not applicable)	– During development changes were made to the starting material source, $CD34^+$ enrichment system, container/closure and fill method and the vector manufacturing process. BM or mPB was proposed as the cell-starting material – A retrospective analysis was performed for batches manufactured using vector batches fractionated by the different product manufacturing processes – Batches were manufactured from BM and mPB derived from healthy donors and products analyzed before (fresh formulation) and after cryopreservation (cryopreserved formulation). Batch analysis data from clinical batches manufactured from BM as a fresh or cryopreserved formulation were also compared and a non-clinical study performed to compare engraftment. Data to support the use of healthy donor cells were provided and showed no differences in cell viability, % $CD34^+$ cells, vector copy number, clonogenic potential and transduction efficiency – A significant difference was observed in % $CD34^+$ cells and clonogenic potential between HD BM derived batches and HD mPB derived batches, with higher levels in the latter. A higher percentage of $CD34^+$ or clonogenic potential was not expected to have a negative impact on the clinical effect. Some differences in cellular composition were observed and the total amount of cells was higher for mPB. This difference was not expected to impact efficacy or safety and the dose is based on the % $CD34^+$ cells – Analytical results and adverse trends will be monitored as part of the ongoing process verification program and follow-up data gathered for patients treated with mPB derived batches	[18]
Tecartus	– Several manufacturing changes were implemented during clinical development and studies. Studies to demonstrate comparability of products manufactured at the applicant's clinical manufacturing site and the commercial manufacturing site were performed. These studies demonstrated that CD19 CAR-positive T cells manufactured at each site were comparable	Comparability was demonstrated between alternative manual and semi-automated processes used for the formulation and filling of medicinal product into bags – To avoid defects experienced during storage and handling of cryobags, foam inserts were introduced with the aluminum cassette used. Comparability data were provided for the cryopreservation process with and without the foam insert	[19,20,37]

For the products listed for the EMA (EU MAA), the source of the information used was EPARs. For the products listed for the US FDA (BLA) the source of the information used was publicly available review documentation for approved cellular and gene therapy products [34].

AS: Active substance; BLA: Biologics License Application; BM: Bone marrow; CAR: Chimeric antigen receptor; CHOP: Children's Hospital of Philadelphia; CQA: Critical quality attribute; DP: Drug product; EPAR: European Public Assessment Report; FH: Fraunhofer; HD: Healthy donor; IND: Investigational new drug application; LVV: Lentiviral vector; MAA: Marketing Authorization Application; MP: Morris Plains; mPB: Mobilized peripheral blood; PPQ: Process performance qualification; SMA: Spinal muscular atrophy; SMN: Survival motor neuron; VCN: Vector copy number.

Table 2. Summary of comments from initial US Biologics License Application and EU Marketing Authorization Application reviews – comparability (cont.).

Product	US FDA (BLA)	EMA (EU MAA)	Ref.
Zolgensma	– After Phase I clinical trial, the manufacturing process was changed considerably. Although the concentration of medicinal product declines over time during storage, the ratio of potency to vector genomes is comparable when lots from the current manufacturing process are compared directly to the initial clinical lot, including comparable ability to enhance survival in a mouse model of SMA. Medicinal product manufactured using the current manufacturing process has better purity – An *in vivo* assay had been used to assess potency. Mouse survival data from the old *in vivo* potency assay provided evidence for comparable biological activity between pre- and post-change batches with the caveat of limited sensitivity of the analysis – Together, all of these analyses of the survival data support the idea that differences between the manufacturing processes for the previous and current manufacturing sites likely do not cause any detectable differences in vector potency per unit of vector genome concentration in mice with selective deletion of SMN protein exon 7 (SMNΔ7 mice). And evaluation of comparability was difficult due to changes in assays, variable assays, manufacturing problems with early AveXis lots and the instability of DP over time.	– No conclusions could be drawn on comparability between the process A batch and process B batches. The assessment of the benefit risk of Zolgensma therefore needed to be based on the clinical data obtained with process B batches – Available batch analysis data of process B batches showed no obvious differences, to process A batches. However, the infectious titre per 10^{13} vg showed relatively large batch-to-batch variation, and comparison of the data was hampered by changes that were made to the test methods and not justified by data demonstrating that the revised methods yielded equivalent results. Also, stability data for the process A batch suggested that a shift in the measured titre may have occurred during development due to a change in method – Additional data were requested to address uncertainties and demonstrate assurance of comparability of the process B-batches with regard to vector titre and infectivity – Only a Phase I clinical batch was impacted by the shift in the measured titre due to a change in the analytical method. Phase III clinical batches and PPQ/commercial batches were tested using the revised test method and showed consistent genomic titre. Additional data were provided to demonstrate that batch-to-batch variation in infectious titre can be attributed to assay variability – Post-authorization measures included additional studies to characterize gradient centrifugation bands and demonstrate lot-to-lot consistency and comparability of batches manufactured according to process B-initial and process B-commercial at first conditional authorization renewal	[21,22,38]
Zynteglo	(Not applicable)	– Changes used in the commercial process aimed not only at improving process consistency but also to target VCN values to retain product efficacy while reducing theoretical risk of oncogenesis Re-evaluation of the specification with respect to other potency tests and clinical data was required. The applicant agreed to re-evaluate the acceptance criteria for attributes related to potency tests using batch release data and clinical results after 6 months follow-up of 20 patients treated with commercial batches Data were initially considered too limited to conclude on comparable product efficacy as it was insufficiently demonstrated that clinical data from batches could be considered representative of the commercial process – Tight control of potency attributes (i.e., within the range of prior process batches) was considered necessary but was not provided by the proposed specifications. This issue was raised as a major objection because subpotent batches were considerable risk to the patient in case of suboptimal efficacy (the treatment cannot be repeated)	[23]
Luxturna	– A comparability evaluation was conducted to demonstrate that the product manufactured by Spark Therapeutics (PA, USA) was comparable to the Phase III clinical material manufactured at CHOP. The drug substance process performance qualification lot manufactured at Spark was compared with the Phase III clinical material manufactured at CHOP by comparing the lot release testing data and side-by-side testing. A supplemental comparability evaluation of final filled DP to the Phase III clinical material was conducted under a separate protocol by side-by-side testing including all the tests for product potency	– Comparability of the proposed commercial medicinal product with the clinically qualified material was of concern, and underpinned a large number of the issues raised. A total of ten recommendations were aimed at providing further data on viral testing, effect of cell passage on CQAs, monitor performance of transfection solutions, ability to adequately discriminate between empty and full capsids, additional characterization and release test, refine analytical methods, and revaluation of specification once additional batch data becomes available – A comparability evaluation was performed to demonstrate the active substance produced at Spark was comparable to material used in the Phase III pivotal clinical study and that the change of manufacturing facility had no impact on the quality attributes of the active substance. The evaluation consisted of a combination of analytical release testing and side-by-side testing	[24,25]
Yescarta	– A site-to-site comparability study was conducted for each manufacturing facility producing clinical products under IND, including products used to make commercial products. Each of these studies demonstrated that CD19 CAR-positive T cells manufactured by all facilities were comparable	– Data from comparability studies to support changes introduced during development were considered acceptable – Non-clinical *in vitro* pharmacology studies were performed using two previous manufacturing processes which did not represent the proposed commercial process. Data from split apheresis studies were provided that compared product from the previous processes. Although these data revealed a lower transduction rate for products from one compared with the other previous process the specific activity against target cells was not impaired. Although the potential reason for the lack of correlation between transduction efficiency and IFN-γ release was not clarified for product from both processes, repeating the non-clinical *in vitro* data was not considered necessary since from a non-clinical point of view, comparability and/or equivalent performance has been sufficiently demonstrated between the products derived from the different processes	[26,27]

For the products listed for the EMA (EU MAA), the source of the information used was EPARs. For the products listed for the US FDA (BLA) the source of the information used was publicly available review documentation for approved cellular and gene therapy products [34].

AS: Active substance; BLA: Biologics License Application; BM: Bone marrow; CAR: Chimeric antigen receptor; CHOP: Children's Hospital of Philadelphia; CQA: Critical quality attribute; DP: Drug product; EPAR: European Public Assessment Report; FH: Fraunhofer; HD: Healthy donor; IND: Investigational new drug application; LVV: Lentiviral vector; MAA: Marketing Authorization Application; MP: Morris Plains; mPB: Mobilized peripheral blood; PPQ: Process performance qualification; SMA: Spinal muscular atrophy; SMN: Survival motor neuron; VCN: Vector copy number.

Table 2. Summary of comments from initial US Biologics License Application and EU Marketing Authorization Application reviews – comparability (cont.).

Product	US FDA (BLA)	EMA (EU MAA)	Ref.
Kymriah	– The manufacturing process was significantly modified. The most significant changes were designed to improve the manufacturing process controls for product consistency and yield. These changes were designed to reduce non-T cells that negatively affect manufacturing ability, maximize the yield and improve the quality of the final cell product – A site-to-site comparability study was conducted at the Novartis and University of Pennsylvania facilities, and demonstrated that CD19 CAR-positive T cells manufactured by both facilities met all lot release specifications. However, the characterization of cell growth and transduction efficiency showed statistically significant differences. Thus, the products produced by the University of Pennsylvania and Novartis are not considered to be comparable – The modified manufacturing process at the Novartis Manufacturing Facility at Morris Plains can produce a more pure intermediate T-cell population before the transduction steps. This change was expected to improve the vector transduction efficiency and cell growth and reduce the chance of transduction of non-T cells (e.g., B-cell blast and residual levels of stem cells) that would pose a potential risk for the patients – A total of 68 subjects received Kymriah with products manufactured at MP, New Jersey (n = 63) and FH Institute, Germany (n = 5) and were included in the safety set. Since the comparability of the MP product with the FH product had not been completed, the efficacy set or primary efficacy analysis were restricted to the 63 subjects who were treated with Kymriah manufactured at the MP site	– Changes were introduced to plasmid design to increase the safety of the vector and generally considered conservative. A comparability exercise using healthy donor T cells was conducted vs an earlier version of the plasmid. This included data from originating batches used for clinical studies Comparability exercises were conducted for the introduction of a second vector substance and vector product manufacturing site – The most significant medicinal product changes were associated with options for starting material processing and site transfer of the process. Comparability was demonstrated for product manufactured at two manufacturing sites (MP and FH) on the basis of in-process controls, release testing results and additional characterization – For non-clinical data for the use of different vectors, the pharmacology studies were conducted with cells transduced with LVV made at the University of Pennsylvania, or at a further facility in the USA, whereas clinical studies were done with cells transduced with vector made by Oxford Biomedica (Oxford, UK). The two manufacturing sites used different plasmids to generate the LVV used – Commercial supply is from a site in Germany at the FH Institute, in Leipzig. Previous scientific advice on comparative *in vivo* pharmacology studies to support this change advised that such studies do not have the capacity to generate results that could be interpreted in the context of a comparability exercise. Absence of comparative *in vivo* preclinical experiments to support the use of product in Europe was therefore agreed	[28,29]
Alofisel	(Not applicable)	– A comprehensive prospective comparability exercise between batches produced pre and post change was included. The available data supported the prospective comparability exercise between batches produced for clinical trials and the commercial product	[30]
Spherox	(Not applicable)	– A comparison between clinical trial batches and batches in the process validation was provided which was considered to be acceptable to confirm the comparability between the clinical and commercial batches – A major objection was raised in relation to comparability between the proposed commercial process and earlier versions of the product. This was resolved during review by provision of a retrospective comparative analysis of batches including the updated tests for impurities, identity and potency. This showed that the process validation lots were comparable with lots from Phase II and III trials Process validation confirmed post marketing was required	[31]
Strimvelis	(Not applicable)	– A number of changes were introduced both for vector production and manufacture of the active substance and finished product in preparation for the commercial manufacture. These changes were intended to increase the quality of the product by reducing animal derived substance or the use of substances with reduced adventitious agent risk, improving sterility assurance and reducing process residuals in the finished product – For vector: a pairwise comparability assessment was conducted between each consecutive process development stage. Analysis focused on potency, identity, genetic stability and safety – A concern was raised in relation to the formation of viral aggregates with a commitment to develop an assay and monitor viral aggregates For drug substance (AS): a side-by-side analysis was used and compared commercial process AS prepared with commercial process vector to clinical process active substance prepared with clinical process vector – Medicinal product: the main dataset was based on product manufactured from the active substance comparability batches – Additional information was requested and provided during review and included new data on the transduction efficiency assay, which demonstrated that transduction efficiency observed during the clinical study is within the same range as that obtained for product from the proposed commercial manufacturing process	[32]

For the products listed for the EMA (EU MAA), the source of the information used was EPARs. For the products listed for the US FDA (BLA) the source of the information used was publicly available review documentation for approved cellular and gene therapy products [34].

AS: Active substance; BLA: Biologics License Application; BM: Bone marrow; CAR: Chimeric antigen receptor; CHOP: Children's Hospital of Philadelphia; CQA: Critical quality attribute; DP: Drug product; EPAR: European Public Assessment Report; FH: Fraunhofer; HD: Healthy donor; IND: Investigational new drug application; LVV: Lentiviral vector; MAA: Marketing Authorization Application; MP: Morris Plains; mPB: Mobilized peripheral blood; PPQ: Process performance qualification; SMA: Spinal muscular atrophy; SMN: Survival motor neuron; VCN: Vector copy number.

Table 3. Common expectations and/or advisable activities for comparability.

Type	Theme	Example
Scientific advice	Regulators promote the use of scientific advice procedures to gain an understanding of the expectations for comparability studies/data	Kymriah: advised that *in vivo* pharmacology (non-clinical) studies do not have the capacity to generate results that could be interpreted in the context of a comparability exercise
Comparability studies	Module 3 should contain details of studies/data to demonstrate comparability of product post changes	Alofisel: a comprehensive prospective comparability exercise between batches produced pre and post change was included Libmeldy: a retrospective analysis was performed for batches manufactured using vector batches fractionated by the different product manufacturing processes
Side-by-side design	Side-by-side comparability study design (with the intention to reduce potential variability and facilitate a clear conclusion)	Luxturna: release data and side-by-side testing of DS lots manufactured at Spark and CHOP were compared Yescarta: data from split apheresis studies were provided that compared product from the previous processes
Site change	Suitable comparability assessment conducted to support a change of site	Tecartus: comparability studies of products manufactured at clinical manufacturing site and commercial manufacturing site were performed. These demonstrated CD19 CAR-positive T cells manufactured at each site were comparable
Test method changes	Rationale and strategies for changing methods during development and assessing comparative method performance	Zolgensma: comparison of data was hampered by changes made to test methods and not justified by data demonstrating that the revised methods yielded equivalent results
Potency assay	Potency tests with adequate performance used for comparative analyses	Zolgensma: Mouse survival data from the old *in vivo* potency assay provided evidence for comparable biological activity between pre- and post-change batches with the caveat of limited sensitivity of the analysis
Non-clinical data	Use of non-clinical study to augment comparative assessment where a suitable quality method is not available/feasible	Libmeldy: non-clinical study performed to compare engraftment

The source of the information used was the European Public Assessment Reports [39] and publicly available review documentation for approved cellular and gene therapy products [34]. Refer to the references list for specific products.
CAR: Chimeric antigen receptor; CHOP: Children's Hospital of Philadelphia; DS: Drug substance.

Table 4. Comparability-related issues evident during initial review.

Type	Theme	Example
Site change	Inadequate comparability data provided for a change of manufacturing site	Kymriah
Surrogate material	Requirement to show that donated starting material used in lieu of patient material is suitably representative for CQAs studied	Libmeldy, Kymriah
Potency assay	Changes and variability in potency test resulting in difficulties for comparative analyses	Zolgensma
	Acceptance criteria not considered suitable for adequate control	Zynteglo
Efficacy data	In the absence of comparability data, some efficacy data was excluded from consideration (primary data)	Kymriah
Non-clinical data	Requirement to show suitable comparability for product used for non-clinical studies and intended for commercial supply	Yescarta
	Limited value of comparative *in vivo* pharmacology studies in the context of data to support a comparability assessment	Kymriah
Major objection[†]	Acceptance criteria for potency assay not adequate for mitigating risk of a treatment failure	Zynteglo
	Insufficient comparability information for medicinal product from proposed commercial process and earlier versions of product	Spherox
post-approval measures required	Continued monitoring (trending) of analytical results, e.g., as part of process verification	Libmeldy
	Requirement for additional analyses post-approval	Zolgensma
	Re-evaluate clinical data to understand whether release specification acceptance criteria can assure efficacy and safety	Zynteglo
	Develop an assay to monitor a vector impurity	Strimvelis

[†]For EU Marketing Authorization Applications: indicates that a positive opinion cannot be given unless the issue is adequately addressed.
The source of the information used was the European Public Assessment Reports [39] and publicly available review documentation for approved cellular and gene therapy products [34]. Refer to the references list for specific products.
CQA: Critical quality attribute.

to the 63 subjects who were treated with Kymriah manufactured at the US site due to insufficient comparability information supporting inclusion of data from patients treated with product manufactured in the German site [28].

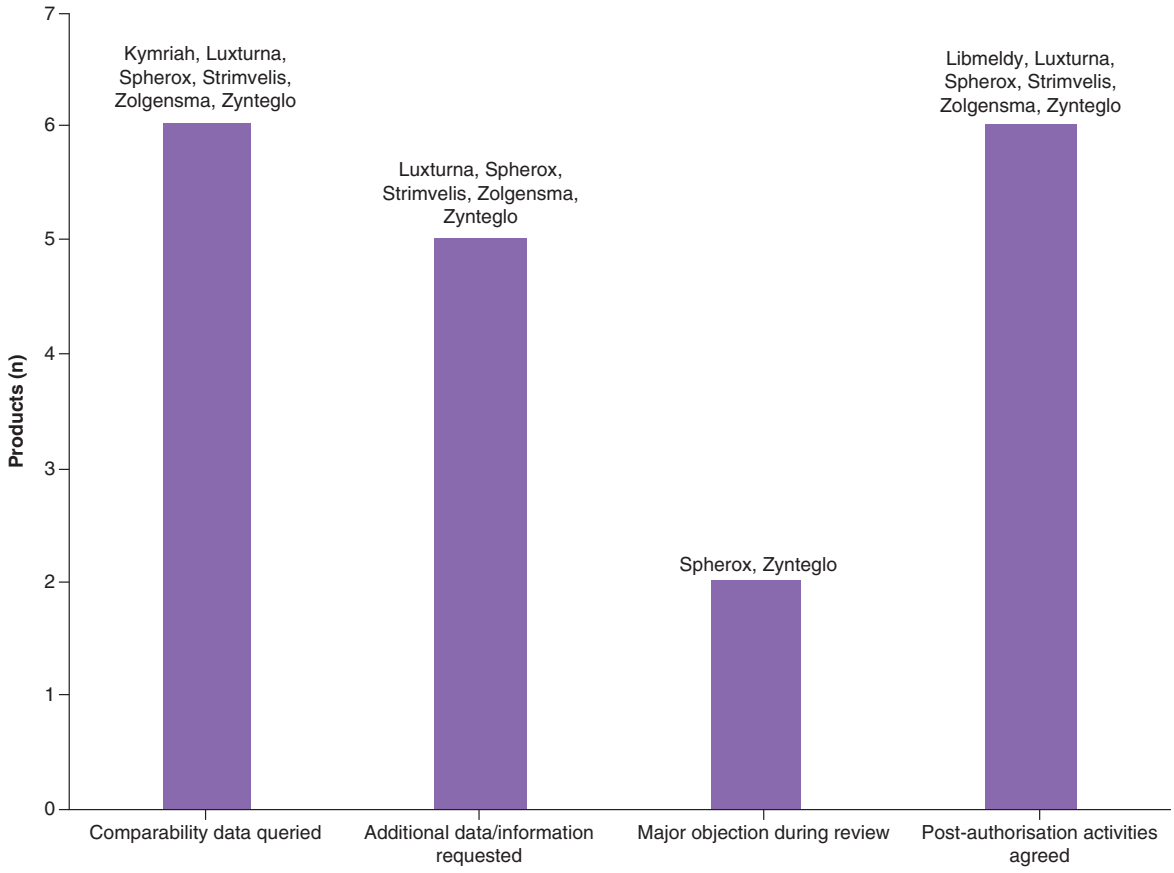

Figure 1. Extent of regulatory concerns identified in relation to comparability for 12 recently approved advanced therapy medicinal products. The source of the information used was the European Public Assessment Reports [39] and publicly available review documentation for approved cellular and gene therapy products [34] for the products listed. Refer to the references list for specific products.

Comparability of early versus late clinical trial product came under scrutiny following identification of data manipulation after the US approval of Zolgensma [40]. Data from an *in vivo* potency assay were disqualified, leading to additional comparability questions from the Japanese Pharmaceutical and Medical Devices Agency prior to its eventual approval in 2020. Although this was an exceptional case, the importance of comparability to underpin the clinical dataset was brought out in the assessment reports [41].

Regulators in both the USA and the EU have introduced options for faster development and approval of products for life-threatening or serious chronic diseases, and these routes are frequently relevant to indications being addressed by ATMPs. Our understanding and experience is that irrespective of the type of marketing license, such as accelerated approval in the USA and conditional marketing authorization and marketing authorization under exceptional circumstances in the EU, the requirement to demonstrate comparability and therefore the pertinence of the clinical data generated from product pre and post change is similar. In brief, the CMC requirements are not reduced for accelerated access routes, and arguably comparability takes on an even more crucial role in applications with limited clinical datasets.

The summary in Figure 1 is deliberately shown with respect to product rather than with respect to each review (where pertinent) since it is common for an organization to submit an application to one regulatory authority and subsequently to another with an update to the dossier between these two submissions. Therefore, this analysis should indicate a deficiency/issue with the content of the first application; applicants would have the opportunity to augment the second application if deficiencies were noted in the first submission.

Due to confidentiality obligations, regulatory authorities are not at liberty to release details of the assessment of clinical trial applications. Information on comparability challenges for products in clinical development is not publicly accessible until the European Public Assessment Report/Summary Basis for Regulatory Action is published.

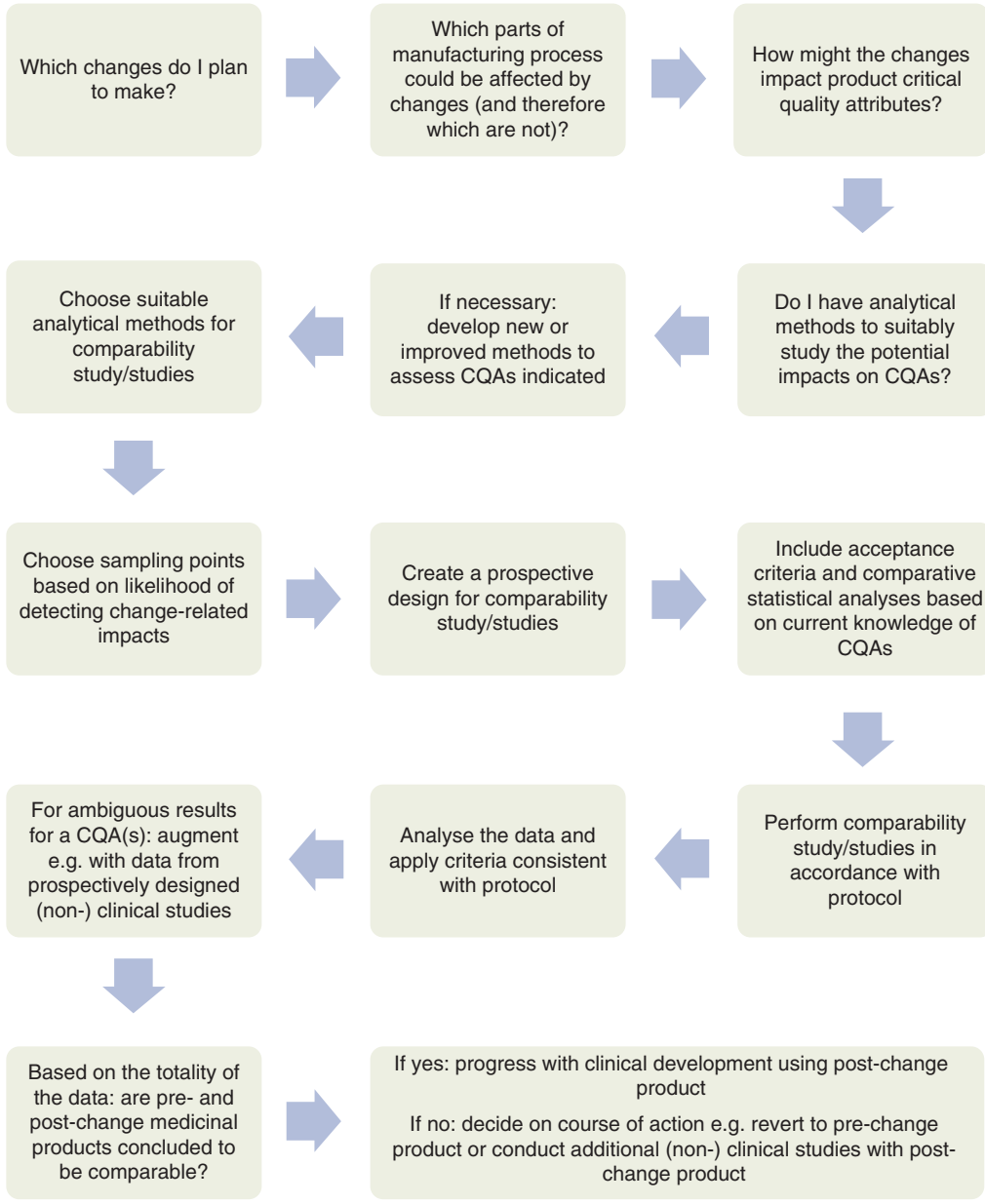

Figure 2. Example workflow for a typical comparability exercise.
CQA: Critical quality attribute.

Publicly accessible details for rejected and withdrawn applications are typically limited and often difficult to find. From the information reviewed, no additional comparability intelligence was gained. This raises the potential for bias in terms of identification of comparability issues: the issues raised were not sufficient to cause rejection of an application, although in 50% of assessments additional data were required. We can neither rule out the possibility, nor conclude, that comparability issues played a more significant role in rejected or withdrawn applications.

Conclusion

As part of the knowledge for comparability assessments, marketing application reviews can be used as a valuable source of intelligence. These can indicate expectations, potential issues, challenges and gaps and inform approaches to comparability studies during development of ATMPs. This can hopefully reduce the risk of significant delays, or worse, with developers' own marketing applications. Our discussion shows how the challenges of providing clear evidence of continuity of the use of 'the same' (highly similar) product batches throughout clinical development,

and therefore justification for the use of these batch data to support the measures in place to assure product quality can be confounded where the data are cast into doubt. Crucially, this may also impact the clinical data provided to support efficacy conclusions. Also of key importance is the integrity of the data which is central to the assessment of comparability. As can be seen for Zolgensma, data integrity is a concern for a regulatory authority's review of a marketing application: not only the integrity of the data concerned but its impact upon other areas of the dossier.

Regulators strongly advise that applicants should take scientific advice on the issue of comparability assessments during product development [3]. Our experience is that this issue is certainly one that can have significant impact on the overall approvability of an ATMP, and that developers of these complex products should take every opportunity to review the experience and insights that can be accessed via published approval summaries for marketing applications. The obligations of the MAH to consider comparability in relation to inevitable post-approval changes and maintenance of product lifecycle will be equally important, and regulatory agency reports addressing these changes will doubtless be of relevance as experience with these products continues to grow.

Future perspective

As ATMPs become ever more firmly established as first-line therapeutic options, the need for comprehensive comparability data will become increasingly critical to develop and maintain effective and commercially viable products. The owners of non-preserved autologous products will face the consequences of distribution challenges, which may require multiple manufacturing sites across different territories to meet demand for a successful therapy. Fundamental changes such as introduction of new donors in allogeneic product manufacture will necessitate extensive characterization and comparability evidence to support their introduction. As the ATMP industry expands and advanced therapies become more integrated into the therapeutic armamentarium, existing and new products will need to address the challenges of success, including changes in scale of production, introduction of more efficient vectors, and improvements in shelf life, preservation and transport logistics. The consequences of inadequate comparability may range from a request for further data to underpin the validity of clinical data submitted in the MAA/BLA, as seen in this discussion, through potentially challenging *in vivo* studies with uncertain outcomes, to, in the worst possible scenario a request for additional clinical data to support a post-change product. Developers of ATMPs will need to develop a detailed suite of tools to address the challenges of comparability, in combination with ongoing monitoring of the expectations of regulators in regard to this key issue.

Executive summary

- Comparable: for investigational advanced therapy medicinal products used in clinical trials, it is necessary to confirm that the product manufactured before and after changes are made are comparable (highly similar) with respect to the characteristics required for efficacy and safety.
- Comparability assessments: comparative studies are used to assess whether pre- and post-change medicinal products are highly similar and therefore can be concluded to be comparable.
- Assessment for commercial product registration: summaries for medicinal products from the review of marketing applications are publicly available and can be used as a valuable source of information, including insight into the comparability data provided.
- Comparability is a major challenge for organizations developing complex medicinal products as evidenced by the high proportion of requests for additional information during review.

Author contributions

The authors had full and equal involvement with the article.

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No writing assistance was utilized in the production of this manuscript.

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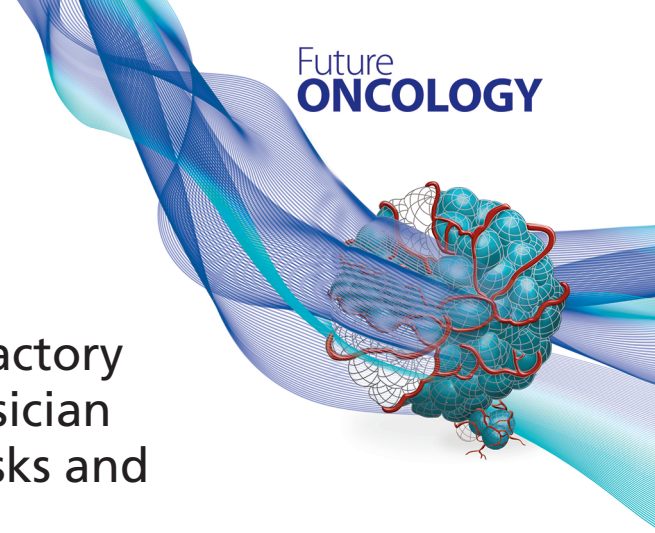

CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma: physician preferences trading off benefits, risks and time to infusion

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[‡]At the time this research was conducted

Aims: We evaluated physicians' willingness to trade-off benefits, risks and time to infusion for CAR T-cell therapy for relapsed or refractory diffuse large B-cell lymphoma. **Materials & methods:** In a discrete-choice experiment survey, 150 US oncologists/hematologists chose between two hypothetical CAR T-cell treatments defined by six attributes. **Results:** Decreasing time to infusion from 113 to 16 days yielded the greatest change in preference weight (1.91). Physicians were willing to accept a >20% increase in risk of severe cytokine release syndrome and 15% increase in risk of severe neurological events in exchange for an increase in the probability of overall survival at 24 months from 40 to 55%. **Conclusion:** Physicians value reducing time to infusion and will accept incremental increases in serious adverse event risks to gain survival improvements.

Lay abstract: CAR T-cell therapy is a treatment option for patients with diffuse large B-cell lymphoma that has not responded to at least two other kinds of treatments. CAR-T therapies are manufactured from a patient's white blood cells, modified to attack lymphoma cells. A CAR-T therapy takes time to manufacture after these cells are collected. CAR-T therapies can result in the reduction or disappearance of lymphoma tumors and can increase the chances of survival, but also cause serious side effects for a few patients. One of these is cytokine release syndrome (CRS), in which high levels of inflammation throughout the body may cause fever, heart problems or difficulty breathing. Another is the development of temporary but serious neurological problems such as confusion, seizures and memory problems. To understand how important physicians consider certain features of CAR-T therapies to be when deciding whether to recommend them, we asked physicians to choose between two treatment options resembling CAR-T therapies in a series of questions, with the CAR-T features varying in each question. Their answers indicated whether disappearance of tumors, a patient's chances of survival after 1 and 2 years of treatment, manufacturing time, or the risk of CRS or neurological problems was the most important factor. Physicians most wanted to reduce manufacturing time from 113 to 16 days, but also were willing to accept a >20% increase in risk of severe CRS and a 15% increase in risk of severe neurological events to increase a patient's chance of survival from 40 to 55% at 2 years.

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Keywords: CAR T • conjoint analysis • discrete choice • maximum acceptable risk

An estimated 81,560 Americans are expected to be diagnosed with non-Hodgkin lymphoma (NHL) in 2021 [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL among adults in the USA, repre-

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senting 33% of newly diagnosed NHL cases [2]. First-line treatment for DLBCL usually consists of rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP). Although the majority of patients with DLBCL will have long-term, disease-free survival after initial R-CHOP [3], overall 5-year relative survival among all newly diagnosed patients with NHL is still only an estimated 63.8% [4]. Those whose disease relapses or is refractory to initial therapy have historically had limited curative treatment options (e.g., high-dose chemotherapy followed by hematopoietic stem cell transplantation for responders).

At the time this study was designed, two autologous anti-CD19 CAR-T cell therapies were commercially available for the treatment of patients with relapsed or refractory large B-cell lymphoma with two or more prior systemic therapies: axicabtagene ciloleucel (Yescarta®; Kite, A Gilead Company [5]) and tisagenlecleucel (Kymriah®; Novartis Pharmaceuticals [6]). A third CAR-T therapy, lisocabtagene maraleucel, also was recently approved for relapsed or refractory DLBCL [7]. Although both axicabtagene ciloleucel and tisagenlecleucel are both CD19-directed, genetically modified, autologous T-cell products, in clinical trials these therapies differed in manufacturing time (time from leukapheresis to availability for infusion), overall survival (OS) and in the risk of important adverse reactions, including cytokine release syndrome (CRS) and neurological toxicities such as encephalopathy, headache, tremor, dizziness and aphasia [5,6]. Currently, there is little information available about how physicians make decisions when choosing between CAR-T treatments for patients with DLBCL.

This study aimed to explore physicians' preferences regarding CAR-T therapy for patients with relapsed or refractory DLBCL. The first study objective was to quantify physician preferences for efficacy, time from leukapheresis to infusion and risk of severe adverse reactions associated with CAR-T treatments for adult patients with relapsed or refractory DLBCL. The second objective was to quantify the trade-offs that physicians are willing to accept between risks, benefits and specific improvements in time from leukapheresis to infusion. The third objective was to determine whether physicians' treatment preferences varied systematically between a hypothetical patient with an average pace of disease progression for DLBCL and one with more rapid disease progression.

Materials & methods

Study design

The study employed a discrete-choice experiment (DCE) to elicit physicians' preferences for features or outcomes that differ between the available CAR-T treatments. DCE methods are based on the hedonic principle that products or services comprise multiple attributes and that an individual's choice of a product or service is a function of the utility of each attribute. Thus DCE methods can be used to elicit preferences for attributes of a good or service. DCEs have been used to elicit preferences for health and healthcare since before 1990 and for a wide range of healthcare topics, including physicians' cancer treatment decisions [7–11].

The DCE was developed and conducted according to good research practice guidelines published by the International Society for Pharmacoeconomics and Outcomes Research [12]. The study was reviewed by RTI International's institutional review board and deemed exempt from full review on 3 April 2019 (IRB ID: STUDY00020581). Oncologists or hematologists in the USA with experience treating patients with DLBCL were invited to complete the survey; all respondents provided electronic informed consent.

Survey instrument

The survey instrument included screening questions to confirm respondent eligibility, informed consent text, background questions on the respondent's experience treating patients with DLBCL and with CAR-T therapies, a series of DCE questions and background questions about the doctors and their practice.

In the DCE questions, physicians were asked to choose between pairs of unlabeled alternatives (hypothetical CAR-T treatments) for selected patient profiles. Figure 1 presents an example choice question. The hypothetical CAR-T treatments were defined by a set of treatment features or outcomes, called attributes. The attributes were chosen according to the best available information at the time the study was designed to represent those that reflected important differences between the existing CAR-T treatment options used to treat relapsed or refractory DLBCL after two or more prior systemic therapies. The attributes evaluated in the survey included probability of achieving a complete response (CR) at 6 months, probabilities of OS at 12 and 24 months, time from leukapheresis to infusion, risk of severe CRS and risk of a severe neurological event (Table 1). The efficacy attributes were constrained such that the level of CR at 6 months was always higher than the level of OS at 12 months, and the level of OS at 12 months was always higher than the level of OS at 24 months.

Treatment feature	CAR T-cell treatment A	CAR T-cell treatment B
Probability of complete response achieved at 6 months of treatment	52 out of 100 people (52%)	60 out of 100 people (60%)
Probability of OS at 12 months	52 out of 100 people (52%)	60 out of 100 people (60%)
Probability of OS at 24 months	48 out of 100 people (48%)	40 out of 100 people (40%)
Time from initial collection (leukapheresis) to infusion	16 days	47 days
Risk of severe cytokine release syndrome (CRS)	5 out of 100 people (5%)	5 out of 100 people (5%)
Risk of a severe neurological event	10 out of 100 people (10%)	10 out of 100 people (10%)
Which treatment would you prescribe for this patient?	☐	☐

Figure 1. Example of a discrete-choice experiment question.
OS: Overall survival.

Table 1. CAR T-cell treatment attributes and levels.

Attribute label	Attribute definitions	Levels
Probability of CR achieved at 6 months	Different CAR-T therapies result in different probabilities of achieving CR as assessed according to the International Working Group Response Criteria for Malignant Lymphoma In this survey, we will ask you to consider treatments with different rates of CR at 6 months ranging from 40 to 60%	40% 52% 60%
Probability of OS at 12 months	Different CAR-T treatments result in different probabilities of OS at 12 months In this survey, we will ask you to consider treatments with different rates of OS at 12 months ranging from 40 to 60%	40% 52% 60%
Probability of OS at 24 months	Different CAR-T treatments result in different rates of OS at 24 months In this survey, we will ask you to consider treatments with different rates of OS at 24 months ranging from 40 to 55%	40% 48% 55%
Time from initial collection (leukapheresis) to infusion	CAR-T therapy uses the patient's own immune cells to seek and destroy cancerous cells. After blood is taken from the patient, the T cells are removed from the sample, genetically modified to create CAR, and then infused back into the patient This process requires time from initial collection (leukapheresis) and manufacturing to reinfusing a patient's individual T cells In this survey, we will ask you to consider different treatments that take between 16 and 113 days to manufacture and get to the patient	16 days 24 days 47 days 73 days 113 days
Risk of severe CRS	Patients receiving CAR-T treatment are at risk for severe (grade 3 or 4) CRS. Symptoms of CRS may include pyrexia, hypotension, hypoxia, arrhythmia, chills and sinus tachycardia Please note that CRS is transient and that the median time to resolution is approximately 7–8 days; however, some patients will experience severe or life-threatening complications from CRS In this survey, we will ask you to consider treatments with a risk of severe CRS ranging from 5 to 25%	5% 10% 25%
Risk of a severe neurological event	Patients receiving CAR-T treatment are at risk of experiencing severe (grade 3 or 4) neurological events. These neurological events may include encephalopathy, confusion, tremor, aphasia, somnolence, agitation, memory impairment and mental status changes Please note that the severe neurological events described above are transient and that the median time to resolution is approximately 2 weeks In this survey, we will ask you to consider treatments with a risk of neurological events ranging from 10% to 32% of patients	10% 20% 32%

To ensure the presentation of efficacy in each hypothetical CAR-T treatment profile was realistic, the discrete-choice experimental design was constrained so that CR at 6 months was always greater than or equal to OS at 12 months and that OS at 12 months was always greater than or equal to OS at 24 months.
CR: Complete response; CRS: Cytokine release syndrome; OS: Overall survival.

Table 2. Patient profiles.

Patient profile 1	Patient profile 2
The patient is a 58-year-old female with histologically confirmed diffuse large B-cell lymphoma who has previously received two prior lines of treatment. The patient has refractory stable disease as the best response to the most recent chemotherapy regimen. The patient has no central nervous system involvement; no active infection; and adequate renal, hepatic, pulmonary and cardiac function. The patient has an ECOG performance status score of 1 (i.e., she is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework and office work). Currently, this patient has progressive, stage IV disease with an estimated survival of 6 months.	The patient is a 60-year-old male with histologically confirmed stage IV diffuse large B-cell lymphoma, which is *MYC* $^{+}$, *BCL2*$^{+}$ and *BCL6*$^{+}$ by FISH. He has rapidly progressed through three prior lines of treatment (R-CHOP, R-ICE and R-GDP). The patient has refractory progressive disease as the best response to the most recent chemotherapy regimen. He now presents with new-onset B-symptoms and elevated LDH. This patient has no central nervous system involvement; no active infection; and adequate renal, hepatic, pulmonary and cardiac function. The patient has an ECOG performance status score of 1 (i.e., he is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework and office work).

MYC is a gene whose expression may change in DLBCL; *BCL2* and *BCL6* are genes that may be mutated in DLBCL.
DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; R-CHOP: Rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone; R-GDP: Rituximab + gemcitabine, dexamethasone and cisplatin; R-ICE: Rituximab + ifosfamide, carboplatin and etoposide.

Each attribute was further defined by between three and five levels over which it could vary in each choice question in the DCE. The range of levels of each attribute was selected such that it encompassed the clinically relevant range of outcomes that has been seen or might be expected to be seen in clinical trials or clinical practice. The ranges also were selected to reflect the maximum range over which respondents are willing to accept trade-offs among attributes.

The survey instrument was pretested to assess the appropriateness of the descriptive information and the difficulty of the choice questions in telephone interviews with ten physicians in May 2019. The qualitative research company M3 was contracted to recruit the pretest participants from its existing panel of physicians. Board-certified or board-eligible US oncologists or hematologists who had treated at least ten patients with DLBCL in the past year were eligible to participate. Participants in the pretest interviews received a small compensation for their time.

During pretesting, physicians were able to complete the survey and choose between CAR-T treatment options presented in the DCE without difficulty. Pretesting also confirmed the appropriateness of the attributes and the clarity and accuracy of the descriptive information included in the survey. Based on suggestions made by physicians during the interviews, a few refinements were made to the survey. First, an Eastern Cooperative Oncology Group score of 1 was added to each patient profile, as physicians mentioned that having such a score in the patient profile was necessary for understanding the condition of the hypothetical patient and to decide between the CAR-T treatment options. In addition, while the survey initially presented four levels for time from leukapheresis to infusion (17, 45, 75 and 114 days), physicians stated during pretesting that the difference of even a few weeks was an important consideration, and some felt that waiting 45 days was too long. Treating a patient as quickly as possible was a major driver of choice during pretesting. Therefore, to encourage physicians to make trade-offs among the attributes and to reduce the possibility that respondents to the online survey would predominantly choose the time from leukapheresis to infusion as the most important attribute, the levels were revised during pretesting to be more realistic and in line with the clinical data available at the time. An additional level with a shorter time from leukapheresis to infusion also was included. The final levels chosen for the survey were 16, 24, 47, 73 and 113 days.

The market research firm Dynata was contracted to administer the final survey online to a subgroup of its online panel of physicians, following the same inclusion criteria defined for pretest interviews.

Experimental design

The hypothetical pair of treatment profiles in each choice question and full set of choice questions in the DCE were determined by an experimental design, constructed to have statistical properties that allowed estimation of the main-effect preference weights of interest using a random-parameters logit (RPL) model. The commonly employed D-optimal algorithm was used to construct a fractional factorial experimental design [13,14] developed in SAS 9.4 software (SAS Institute, Inc., NC, USA).

The experimental design comprised 60 DCE questions divided into five blocks of 12 questions. Each respondent was randomly assigned to one of the five blocks of questions. The order of the 12 experimentally designed choice questions was randomized for each respondent. Before being presented with the DCE questions, respondents were presented with two hypothetical patient profiles, one with average pace and one with a more rapid, predicted pace of disease progression (Table 2). Half of respondents were randomly asked to choose a CAR-T treatment for

the patient with an average pace of disease progression for DLBCL first, and the other half of respondents were presented with the patient with more rapid disease progression first. All respondents answered a total of 24 choice questions, 12 for each hypothetical patient profile.

Statistical analyses

Choice data were analyzed using RPL to generate preference weights for all attribute levels. The RPL model relates each respondent's choice to the attribute levels of each treatment profile in the choice questions. In addition, the model controls for variations among individual preferences not explicitly accounted for by the variables in the model by estimating a distribution of preferences (assumed to be normal in the analysis presented in this paper) around each model parameter [15,16].

To explore whether physician preferences varied systematically between the two patient types, we used a Wald test on an interacted RPL model to retrieve separate preference weights for each profile, and we also qualitatively compared those preferences. To further explore whether it was possible to combine the data from the two patient types in the analyses of physician preferences, we used the test proposed by Swait and Louviere [17].

The results from the final RPL specification were used to calculate maximum acceptable percentage-point increases in treatment-related risks as trade-offs for different improvements in treatment attributes. The maximum acceptable risk (MAR) increases were calculated as the negative of the ratio between the marginal utility for either the improvement in the CR and OS attributes or in time to infusion and the marginal disutility of each risk (i.e., severe CRS or severe neurological events) from the lowest level of that risk included in the DCE.

The analyses were performed in Stata 15 (StataCorp, TX, USA).

Results

Physician sample

Among the 150 physicians who completed the online survey, 79% were male and 47% worked in academic hospitals (Table 3). The respondent sample had considerable experience in treating DLBCL, and two-thirds (67%) of the sample had been involved in a transplantation procedure in the past year.

A majority of physicians (63%) worked at hospitals where one or both commercial CAR-T therapies (i.e., axicabtagene ciloleucel or tisagenlecleucel) are available. Among these physicians, 65% worked at institutions where both CAR-T treatments are used, 15% where only axicabtagene ciloleucel is used and 14% where only tisagenlecleucel is used; 6% did not know or were not sure which treatment(s) were available at their institution. Among the 94 physicians who worked at hospitals where a commercial CAR-T therapy was available, 84 (90%) had used commercial CAR-T therapy to treat patients with relapsed/refractory DLBCL during the past 12 months. More than 68% of them had used CAR-T therapy for six or more patients. In addition, 8% of physicians had been an investigator in a clinical trial for CAR-T treatment, and 33% of their institutions were currently running a clinical trial using CAR-T therapy. An additional 13 physicians had previously used CAR-T cell therapy (albeit not in the past 12 months), for a total of 97 physicians with any experience using CAR-T therapy.

Preference weights

The comparison between physicians' choices for the two patient profiles revealed that preferences did not vary systematically. Furthermore, the Swait and Louviere test [17] did not provide strong support for rejecting the null hypothesis that physicians had the same preference weights for the two patient profiles ($\lambda_{a.} = 5.07$; critical for 15 degrees of freedom = 22.31; $p = 0.99$). Therefore the data from both patient profiles were pooled for analysis.

Figure 2 shows the preference weight estimate for each attribute level. The preference weights indicate the ranking of levels within each attribute (i.e., a higher preference weight indicates that a level is more preferred). If the CIs for any pair of levels of the same attribute do not overlap, the mean estimates for those attribute levels are statistically significantly different from each other ($p < 0.05$). The preference weights were ordered as expected, with better outcomes being preferred to worse outcomes. On average, respondents preferred a greater probability of CR achieved at 6 months, a greater probability of OS at 12 and 24 months, and less time between leukapheresis and infusion. Furthermore, respondents preferred lower risks of severe CRS and neurological events compared with higher risks.

The change in utility associated with a change in any two levels of an attribute is represented by the difference between the preference weights for those levels of that attribute in Figure 2. Larger differences between preference weights indicate that respondents viewed the change as having a relatively greater effect on overall utility. For

Table 3. Respondent characteristics (n = 150).

Survey question	Respondents n (%)
Demographic characteristics	
What is your gender?	
– Female	29 (19.3)
– Male	118 (78.7)
– Prefer not to say	3 (2.0)
Which of the following best describes you?	
– n	149
– Medical oncologist	55 (36.9)
– Hematologist	2 (1.3)
– Hematologist/oncologist	92 (61.7)
– Missing	1
Which of the following best describes the geographic area in which you practice?	
– Urban	87 (58)
– Suburban	54 (36)
– Rural	9 (6.0)
US regions where you are licensed to practice medicine†	
– Northeast	39 (26.0)
– Midwest	28 (18.7)
– South	49 (32.7)
– West	39 (26.0)
Which of the following best describes the setting in which you treat your patients? (Please select all that apply)†	
– Academic hospital	71 (47.3)
– Community hospital directly affiliated with an academic medical institution	41 (27.3)
– Community hospital not directly affiliated with an academic medical institution	47 (31.3)
– Experience with DLBCL and CAR-T therapy	
Have you been involved in transplantation procedures in the past 12 months?	
– Yes, only autotransplantation	5 (3.3)
– Yes, only allotransplantation	1 (0.7)
– Yes, both	94 (62.7)
– No	50 (33.3)
Do you treat only hematologic malignancies?	
– Yes	32 (21.3)
– No	118 (78.7)
Approximately what percentage of your current patients has relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma?	
– 0–10%	27 (18.0)
– 11–20%	36 (24.0)
– 21–30%	27 (18.0)
– 31–40%	27 (18.0)
– 41– 50%	20 (13.3)
– 51–75%	12 (8.0)
– More than 75%	1 (0.7)
For how many years have you been treating adult patients with DLBCL?	
– 1–5 years	26 (17.3)
– 6–10 years	39 (26.0)
– 11–15 years	28 (18.7)
– More than 15 years	57 (38.0)

†Respondents could provide more than one answer to this question. For this reason, the sum of the responses may exceed the total number of respondents and the percentages may sum to more than 100%.
DLBCL: Diffuse large B-cell lymphoma.

Table 3. Respondent characteristics (n = 150) (cont.).

Survey question	Respondents n (%)
Approximately how many adult patients with DLBCL did you see in the past 3 months?	
– 2 or fewer patients	8 (5.5)
– 3–5 patients	25 (16.7)
– 6–10 patients	32 (21.3)
– 11–20 patients	25 (16.7)
– 21–50 patients	42 (28.0)
– More than 50 patients	18 (12.0)
Does your institution use commercial CAR-T to treat relapsed/refractory DLBCL patients?	
– Yes	94 (62.7)
– No	41 (27.3)
– Do not know or not sure	15 (10.0)
Among those whose institution uses commercial CAR-T therapy to treat relapsed/refractory DLBCL	
Which of the following commercial CAR-T therapies is used in your institution?	
– n	94
– Yescarta®	14 (14.9)
– Kymriah®	13 (13.8)
– Both	61 (64.9)
– Do not know or not sure	6 (6.4)
Have you used commercial CAR-T to treat relapsed/refractory DLBCL patients during the past 12 months?	
– n	94
– Yes	84 (89.4)
– No	10 (10.6)
Among those who have used commercial CAR-T therapy to treat relapsed/refractory DLBCL patients during the past 12 months	
How many times have you used commercial CAR-T to treat relapsed/refractory DLBCL patients in the past 12 months?	
– n	84
– 2 or fewer patients	9 (10.7)
– 3–5 patients	18 (21.4)
– 6–10 patients	31 (36.9)
– More than 10 patients	26 (31.0)
Among those whose institution does not use commercial CAR-T therapy	
Have you ever used commercial CAR-T to treat relapsed/refractory DLBCL patients?	
– n	41
– Yes	13 (31.7)
– No	28 (68.3)
Have you referred relapsed/refractory DLBCL patients to a hospital to be treated with commercial CAR-T during the past 12 months?	
– n	41
– Yes	31 (75.6)
– No	10 (24.4)
All participants	
Are you or your institution currently running a clinical trial using CAR-T therapy?	
– Yes	49 (32.7)
– No	101 (67.3)
Have you ever been an investigator in a clinical trial for a CAR-T treatment?	
– Yes	12 (8.0)
– No	138 (92.0)

†Respondents could provide more than one answer to this question. For this reason, the sum of the responses may exceed the total number of respondents and the percentages may sum to more than 100%.
DLBCL: Diffuse large B-cell lymphoma.

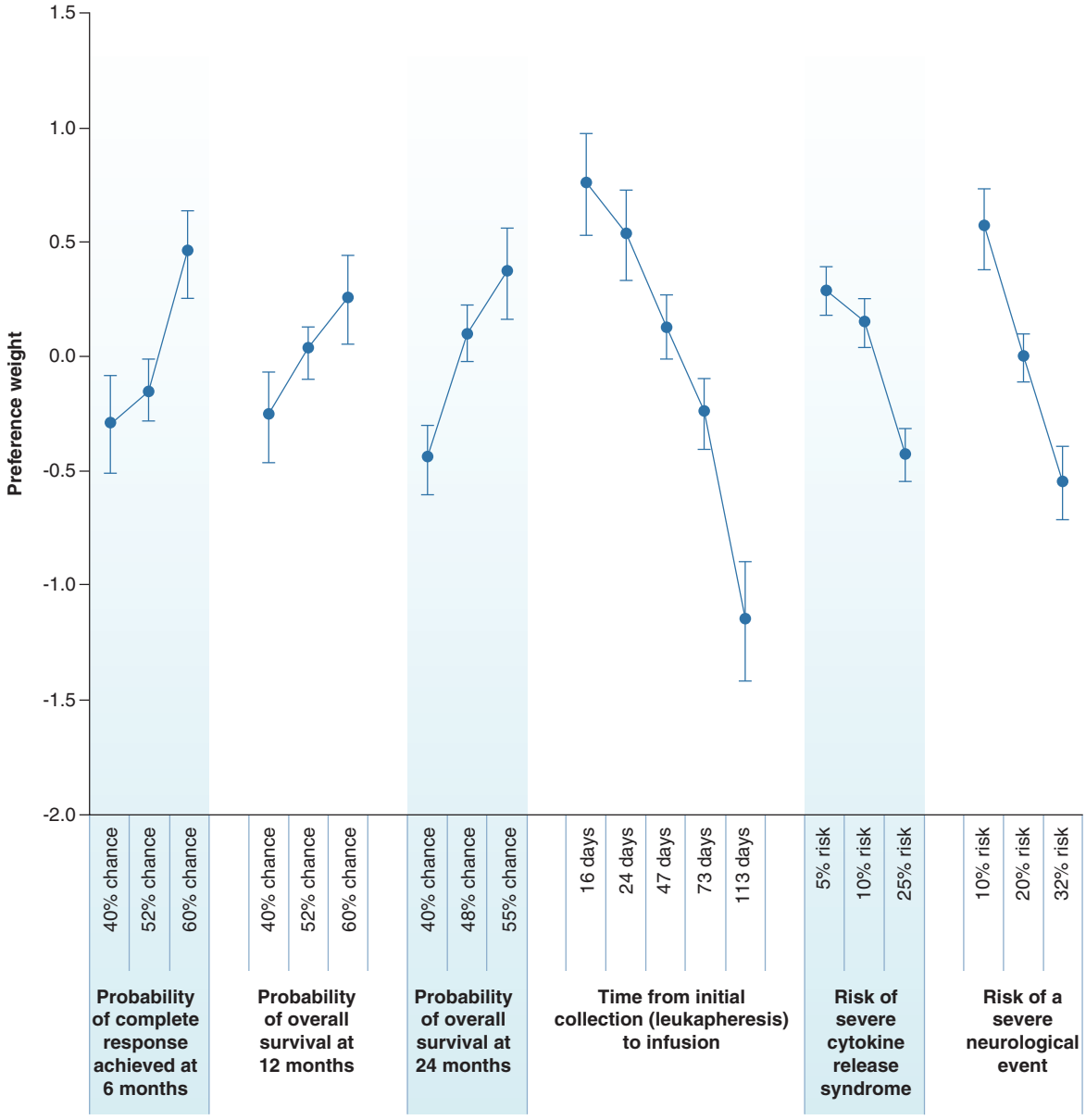

Figure 2. Preference weights (n = 150). Attributes are presented in the order in which they appeared in the discrete-choice experiment questions. The vertical bars around each mean preference weight represent the 95% CI around the point estimate. The change in utility associated with a change in the levels of each attribute is represented by the vertical distance between the preference weights for any two levels of that attribute. Larger differences between preference weights indicate that respondents viewed the change as having a relatively greater effect on overall utility.

example, decreasing the time to infusion from 113 to 16 days yields a change in utility of approximately 1.91 (1.16 + 0.75). Likewise, an improvement in the probability of OS at 12 months from 40 to 60% yields a utility of approximately 0.51 (0.26 + 0.25). Therefore reducing the time to infusion by 97 days is preferable to improving the probability of OS at 12 months by 20 percentage points because it has approximately 3.75 (1.91/0.51) times more impact on utility. Shifts from the least- to most-preferred levels of the other attributes yielded lower utility gains, with risk of severe neurological events generating slightly higher utility gains than the rest.

Table 4. Maximum acceptable increase in percentage point risk of adverse events (n = 150)[†].

Attribute	From level	To level	Severe CRS			Severe neurological event		
			Mean[‡]	95% CI		Mean[§]	95% CI	
Time from initial collection (leukapheresis) to infusion	113 days	16 days	>20.00	33.45	68.19	>22.00	24.93	54.62
	113 days	24 days	>20.00	29.99	60.52	>22.00	21.87	48.08
	113 days	47 days	>20.00	22.92	46.41	>22.00	15.71	36.00
	113 days	73 days	>20.00	15.55	34.54	17.57	8.80	26.34
	73 days	16 days	>20.00	17.35	37.47	19.61	10.74	28.48
	73 days	24 days	>20.00	13.35	30.34	14.81	7.20	22.43
	73 days	47 days	11.25	4.55	17.96	6.58	1.77	11.39
	47 days	24 days	17.79	9.38	26.20	11.32	3.27	19.38
	47 days	16 days	12.23	4.41	20.04	7.24	2.02	12.47
	24 days	16 days	7.20	-1.82	16.23	3.81	-2.00	9.61
Probability of complete response achieved at 6 months of treatment	40%	52%	5.59	-3.38	14.56	2.70	-2.69	8.10
	40%	60%	>20.00	10.36	31.75	14.13	4.53	23.73
	52%	60%	17.10	9.90	24.30	10.73	3.78	17.67
Probability of OS at 12 months	40%	52%	8.97	1.49	16.44	5.01	0.20	9.83
	40%	60%	14.80	4.34	25.26	9.00	1.23	16.78
	52%	60%	7.47	-0.07	15.01	3.99	-0.72	8.70
Probability of OS at 24 months	40%	48%	15.51	9.22	21.80	9.49	4.49	14.49
	40%	55%	>20.00	12.80	32.22	15.38	6.85	23.91
	48%	55%	8.63	0.58	16.69	4.79	-0.47	10.04

[†]The estimates are maximum acceptable increases in risk above the minimum level presented in the survey instrument (5% for severe CRS and 10% for severe neurological events).
[‡]The percentage point difference between the highest (25%) and lowest (5%) risk of CRS presented in the survey is 20%. Estimates of increases in risk of CRS greater than 20 percentage points in the calculations of the MAR increase require the strong assumption that the disutility of each unit increase in risk remains constant beyond 25% (5% baseline + 20-percentage point increase). Rather than making this strong assumption about disutility outside the levels of CRS included in the DCE experimental design, estimates greater than 20 percentage points are reported as simply greater than 20.
[§]The percentage point difference between the highest (32%) and lowest (10%) risk of a severe neurological event presented in the survey is 22%. Estimates of increases in risk of a severe neurological event greater than 22 percentage points in the calculations of the MAR increase require the strong assumption that the disutility of each unit increase in risk remains constant beyond 32% (10% baseline + 22-percentage point increase). Rather than making this strong assumption about disutility outside the levels of a severe neurological event included in the DCE experimental design, estimates greater than 22 percentage points are reported as simply greater than 22.
CRS: Cytokine release syndrome; DCE: Discrete-choice experiment; MAR: Maximum acceptable risk; OS: Overall survival.

MAR increases

The preference weights were used to calculate the maximum acceptable percentage-point risk increase of severe CRS from 5% and of a severe neurological event from 10% (the lowest levels included in the DCE) that physicians would be willing to accept for increases in the probability of a CR, increases in the probability of OS, and reductions in time from leukapheresis to CAR-T infusion (Table 4). Physicians in the sample were generally willing to accept increases in the risk of severe CRS and severe neurological events to reduce the time between leukapheresis and infusion or to gain improvements in CR at 6 months and OS at 12 months. To gain an improvement in CR from 40 to 60% or an improvement in OS at 24 months from 40 to 55%, physicians were willing to accept more than a 25% risk of CRS, which was the largest potential increase in risk of CRS included in the survey instrument (a 20-percentage point increase from 5%). Physicians were also willing, on average, to accept a 25% risk of severe neurological events (a 15.38-percentage point increase from 10%) to gain an improvement in OS at 24 months from 40 to 55%. To gain an improvement in CR from 40 to 60%, they were willing, on average, to accept a 24% risk of severe neurological events (a 14.13-percentage point increase from 10%). To reduce time to infusion from 113 to 47 days (or lower), physicians were willing to accept more than a 25% risk of CRS and more than 32% risk of severe neurological events, which was the largest variation in risk of neurological events included in the survey instrument (a 22-percentage point increase from 10%). Because the increases in MAR for some of the benefits generated by improving treatment efficacy were greater than the largest variation of risk included in the questionnaire (20- and 22-percentage point increase for CRS and neurological events, respectively), estimating a specific value for the MAR increases would have required the strong assumption that the disutility of each unit increase in risk remains constant beyond 20 or 22. Instead of making this strong assumption outside the levels included in the DCE experimental design, any MAR increases that exceeded these values were considered to be greater than 20 or 22.

Discussion

CAR-T therapy is a relatively new option for patients with relapsed/refractory DLBCL who have failed on two or more other therapies. To our knowledge, this is the first study to have evaluated physicians' preferences related to CAR-T therapy for DLBCL. While there are serious risks associated with CAR-T therapy – including severe CRS and neurological events – CAR-T therapy is a promising therapy for patients with an otherwise poor prognosis. Treatment requires waiting during the time it takes for a patient's individual treatment to be manufactured, which can be an added risk for a patient whose disease is progressing rapidly.

This study explored the willingness of physicians to make trade-offs among manufacturing time, serious risks and potential benefits of CAR-T therapy for two different types of patients with DLBCL: one with an average pace of expected disease and another with more rapid expected disease progression. When offered choices between hypothetical CAR-T treatment profiles, physicians' preferences did not vary between the two patient profiles, suggesting that they prioritize reductions in waiting time and improvements in efficacy over adverse event risks, even for patients without rapidly progressing disease.

In both pretest interviews and the online survey, physicians preferred to avoid the longest wait times and treat a patient as quickly as possible. Physicians were willing to accept increases in adverse event risk to gain reductions in time spent waiting for an infusion. They also demonstrated a strong preference for 60% CR at 6 months compared with a 52% CR at 6 months. Physicians were willing to accept considerable increases in the risks of CRS and neurological events for higher CR and survival rates. Specifically, they were willing to accept increases of >20 percentage points in the risk of CRS or 14 percentage points in the risk of a severe neurological event to gain the largest improvement in CR presented in the survey, a move from 40% chance to 60% chance of CR. For the largest improvement in OS at 24 months (moving from a 40% chance to a 55% chance), physicians were willing to accept increases of >20 percentage points in the risk of CRS or 15 percentage points in the risk of a severe neurological event.

The results of this study should be considered within the context of a complex and evolving evidence base. Differences in the design of clinical trials evaluating axicabtagene ciloleucel and tisagenlecleucel, including the use of different toxicity grading scales, make direct comparisons between these products challenging. Nonetheless, evidence on the comparative efficacy and safety of the two available CAR-T products is emerging [18–21]. In addition, the clinical practice of CAR-T therapy has improved since this DCE was designed; in particular, adverse event rates have improved with better adverse event management [22,23]. A third CAR-T therapy, lisocabtagene maraleucel, also has been approved for relapsed or refractory DLBCL since this study was conducted [24]. Additional evidence from head-to-head comparative clinical trials among the three available CAR-T therapies with clinically similar participants is needed to inform risk–benefit comparisons of these treatments. Nonetheless, information from this study provides insights into how physicians weigh treatment attributes and consider them in clinical decision-making.

A key strength of the study is the use of a well-established methodology for quantifying preferences between alternative therapies and weighing various attributes in decision-making. The methodology allowed for a finely calibrated evaluation of trade-offs among a relatively small (yet realistic) range of outcomes. In addition, because a majority of respondents worked at hospitals where CAR-T therapy is available, their responses were grounded in their own knowledge and attitudes gained through treating patients with CAR-T therapies for DLBCL. Thus the respondents constituted a group with high interest in and extensive experience with CAR-T therapies, providing a more realistic window into preferences of decision-makers than might have been possible with a random sample of hematologists/oncologists. Some limitations must also be acknowledged. While the choice questions and patient profiles were designed to represent real-world settings and be as realistic as was feasible, the survey presents hypothetical scenarios to respondents; thus decisions made in the survey may not fully predict decisions that would be made in a clinical setting. In addition, although the two survival attributes, OS at 12 and 24 months, are related, pretests of the survey instrument confirmed that physicians could choose between CAR-T treatment options presented in the survey questions and accepted the hypothetical questions where probability of survival at different time points varied independently. Physicians were asked to assume that the two patient profiles were eligible for and had access to the treatments presented. The patient profiles were designed to include the characteristics most likely to drive earlier or more aggressive treatment, but not all relevant clinical factors could be included. Moreover, as the focus of this study was eliciting trade-offs that physicians were willing to accept among attributes of CAR-T therapies, we did not include forgoing CAR-T therapy or selecting an alternative stem cell therapy as an option

in the choice questions. The sample of physicians were recruited through opt-in panels of individuals who choose to participate in research and therefore may not be representative of the broader population of physicians who treat patients with DLBCL. The sample was not of a sufficient size for an analysis of whether preferences differed between physicians with experience using CAR-T therapies and those with no such experience. Future research should explore the specific preferences of CAR-T-experienced physicians. Finally, the time needed to prepare CAR-T products may be shorter in the future than was reflected in the survey, and other characteristics of these treatments and the management of their serious adverse events may change as practice evolves with the commercially available products, which might make the study results less applicable than they are currently.

Although physician preferences are important to the understanding of choices between competing therapies for DLBCL, the preferences of patients, caregivers and payers would also be relevant. Therefore, to gain a more complete understanding of decision-making among available options for DLBCL treatment, future studies should also explore the preferences of other stakeholders for CAR-T therapy.

Conclusion

Reducing time from leukapheresis to infusion was an important driver of physicians' choices between specific therapies resembling currently available choices of CAR-T products and was no less important to physicians in considering a patient with an average expected time to DLBCL progression than for one with more rapid expected progression, emphasizing the value of timely product preparation for prescribers of CAR-T therapies. Moreover, physicians demonstrated a willingness to trade incremental increases in risks of serious adverse events to gain improvements in CR and OS rates.

Future perspective

CAR-T therapy is a treatment option for patients with relapsed/refractory DLBCL after two or more lines of systemic therapy. CAR-T therapy carries risks – some serious, including CRS, encephalopathy, headache, tremor, dizziness and aphasia – and requires manufacturing time between leukapheresis and infusion. This DCE evaluated 150 US oncologists' and hematologists' willingness to trade-off benefits, risks and time to infusion for CAR-T therapy. Physicians were willing to accept the risks associated with CAR-T therapy in exchange for treatment benefit. Reducing time from leukapheresis to infusion was the most important driver of physicians' choices. Physicians also accepted absolute increases of more than 20% for severe CRS and 15% for severe neurological events to increase the probability of OS at 24 months from 40 to 55%. CAR-T therapy is a relatively new option for patients with relapsed or refractory DLBCL for whom prior therapies are not successful. Understanding how physicians value and prioritize the attributes of CAR-T therapy provides important context as this treatment option is integrated into routine clinical practice. Future research should explore patients' and caregivers' preferences for the attributes of CAR-T therapy and compare them with the physician preferences identified in this study.

Summary points

- A discrete-choice experiment survey was administered to 150 US physicians who treat diffuse large B-cell lymphoma to evaluate their preferences for CAR T therapy.
- Decreasing time to infusion from 113 to 16 days yielded the greatest change in preference weight (1.91) among the included attributes.
- Among efficacy attributes, increasing probability of overall survival at 24 months from 40 to 55% yielded the greatest preference weight change (0.81).
- Physicians were willing to accept absolute increases of >20% for severe CRS and 15% for severe neurological events to gain this improvement.

Author contributions

All authors made a significant contribution to this research, including in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; and agree to be accountable for the work.

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Ethical conduct of research

This study was reviewed by RTI International's institutional review board and deemed exempt from full review on 3 April 2019 (IRB ID: STUDY00020581). All participants provided electronic informed consent.

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Review

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Anti-CD19 chimeric antigen receptor T-cell therapy in B-cell lymphomas: current status and future directions

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Aims: To review recent data and relevant of the role of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for B-cell non-Hodgkin lymphoma (NHL). **Methods:** Review and compilation of the most recent and relevant data published in full text and abstract forms of anti-CD19 CAR T-cell therapy for B-cell NHL. **Results:** Different anti-CD19 CAR T-cell therapy products have been tested and shown significant clinical activity across B-cell NHL patients. The objective responses in relapsed DLBCL, FL and MCL were 50–83%, 83–93% and 93%, respectively. **Conclusions:** Anti-CD19 CAR T-cell therapy is a viable option for poor risk refractory B-cell NHLs.

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Keywords: CAR T • CD19 • immunotherapy • non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) accounts for 4% of all neoplastic disorders [1]. An estimated 77,240 new cases of NHL were anticipated in 2020; unfortunately, 19,940 deaths would still occur [1]. NHLs encompass a heterogeneous spectrum of lymphoid malignancies, mostly (85%) arising from B lymphocytes [2,3].

Diffuse large B-cell lymphoma (DLBCL) is the most common type among B-cell lymphomas, accounting for one-third of cases [4]. It is characterized by a rapidly growing lymphadenopathy, typically presenting with advanced stages and extranodal disease [5,6], with one-third reporting B symptoms [4]. Relapsed DLBCL after standard front-line chemoimmunotherapy are generally offered salvage therapy followed by autologous hematopoietic cell transplantation (auto-HCT) if chemosensitive disease [7–9]. Outcomes of refractory DLBCL after second-line or auto-HCT are poor [10,11].

US FDA approval of anti-CD19 chimeric antigen receptor T (CAR T)-cell therapy for R/R DLBCL constituted a breakthrough in immunooncology. In the ZUMA-1 study, axicabtagene ciloleucel (axi-cel; Yescarta®, Kite A Gilead company, CA, USA), yielded remarkable objective response rate (ORR) of 82% and complete remission (CR) of 54% [12]. Axi-cel is approved for DLBCL after failure of two or more lines of systemic therapy, including DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma and transformed follicular lymphoma [13]. Similarly, tisagenlecleucel (tisa-cel; Kymriah®, Novartis, NJ, USA), another anti-CD19 CAR T-cell therapy, was FDA approved in May 2018 for all aforementioned indications except PMBCL [14].

Follicular lymphoma (FL) is the second most common lymphoma in the USA and other Western countries. Although it is considered an indolent and incurable disease, its prognosis has improved in the rituximab era with a 10-year overall survival rate (OS) of 80% [15]. In symptomatic FL patients, the standard frontline therapies continues to evolve, from anti-CD20-based chemotherapy regimens to chemotherapy-free options [16,17]. Several scoring systems have been developed using clinical, laboratory and molecular/genomic variables that predict survival outcomes with high-risk subgroups having a %-year OS between 25 and 60% [18–20]. However, the strongest predictor of OS in FL is disease progression within 2 years of completing chemoimmunotherapy (POD24) with a OS of 50% at 5 years, independent of the FLIPI score [21]. The treatment landscape of relapsed FL has seen significant advances with the introduction of PI3K inhibitors (idelalisib, copanlisib and duvelisib) [22,23]. Tazemetostat is novel drug

that targets EZH2 is also FDA approved for R/R FL currently [24]. Despite these advances, FL continues to be considered an incurable disease and patients are expected to relapse.

Mantle cell lymphoma (MCL) is a rare subtype of NHL designated as an orphan disease, accounting for 5% of all lymphomas in the USA. Most patients present with advanced stages and extranodal disease [25]. Conventional chemotherapy yields a median survival of <3 years [26]. Despite front-line treatment intensification with auto-HCT in eligible cases (including rituximab maintenance), there is still and approximate 50% relapse rate [27–29]. There is no standard approach for R/R MCL, thus representing an unmet need. Bruton tyrosine kinase inhibitors (BTKi) are cornerstone therapy for R/R MCL with three BTKi agents currently FDA approved (ibrutinib, acalabrutinib and zanubrutinib) with significant response rates and durable [30–32]. Yet these agents are not expected to cure MCL, and outcomes of MCL progressing after BTKi are dismal [33].

A phase II study known as ZUMA-2 showed that KTE-X19 or brexucabtagene autoleucel (brexu-cel) induced high response rates (ORR of 93% and CR of 67%), leading to approval in the R/R setting [34].

As CAR T-cell therapy paves the way into a new era of cancer therapeutics, this review provides an in-depth outline of the current status and future directions of CAR T-cell therapy in DLBCL, MCL and other B-cell lymphomas.

Despite the various autologous CAR T products available, the manufacturing process is largely similar. The process starts with the harvesting of T cells through the collection of peripheral mononuclear cells (PMBCs) during leukapheresis. This product is shipped to the facility specialized in manufacture CAR T cells. Depending of the CAR T-cell product there will be a CD3+ T-cell separation followed by expansion and activation. For tisa-cel, activation occurs through anti-CD3 antibodies coated beads, whereas IL-2 is used for T-cell activation for axi-cel. The CAR gen is then inserted into the CD3+ T cells, mainly through a replication-deficient viral vector such as a retrovirus (axi-cel and brexu-cel or lentivirus (tisa-cel). The majority of CAR T cells share the scFv region (which functions as binding domain), FMC63. There are also differences in the costimulatory domain: CD28 (for axi-cel and brexu-cel) and 4–1BB (tisa-cel and lisocabtagene maraleucel) [35].

Diffuse large B-cell lymphoma

Efficacy

ZUMA-1 study was a multicenter trial evaluating axi-cel for R/R DLBCL. It consisted of phases I and II [12,36]. In the phase I, seven patients received low-dose conditioning chemotherapy, followed by axi-cel targeted at 2×10^6 CAR T-cells/kg. Five (71%) patients achieved an ORR within 1 month, including four (57%) of seven achieving a CR with some ongoing remission [36]. In the phase II, 101 patients with refractory DLBCL received axi-cel with resulting ORR (CR) rates of 82% (54%) [12]. These results highlight impressive CR rates vis-à-vis historical controls [11] Table 1.

JULIET was a multicenter global study evaluating tisa-cel in R/R DLBCL, transformed follicular or high-grade B-cell lymphoma. Similar to ZUMA-1, the primary endpoint was ORR and CR rates. In a single-center phase IIA of the trial, 28 patients with B-cell lymphoma received tisa-cel [37]. ORR was 64%, and CR occurred in 43% of 14 DLBCL patients, with 83% remaining in sustained remission. This led to the global phase II pivotal study of the JULIET trial, where 165 patients with R/R DLBCL were enrolled [38]. Among 93 evaluable patients, ORR was 52% (CR = 40%), with durable responses in poor-risk DLBCL Table 1.

Various studies have investigated the safety and efficacy of commercially available CAR T-cell therapies in the nontrial setting so called real-world experience (RWE). A post-marketing study on axi-cel by the Centefr for International Blood and Marrow Transplant Research (CIBMTR), the US CART Consortium (comprising 17 US academic centers) and another retrospective study led by the Dana Farber Cancer Institute with a ORR between 70 and 79% and CR rates around 50%, replicating what it was reported in the ZUMA-1. This efficacy was also seen in patients who would not have been otherwise eligible for the ZUMA-1 clinical trial [39–41]. The CIBMTR registry was also used to report the real-world outcomes of tisa-cel in R/R DLBCL in 70 treated patients with an ORR and CR rates were 59.6 and 38.3%, respectively; that were considered comparable to the JULIET trial [42]. Most recently and outside the USA, reports have emerged from French and UK cohorts [43,44]. The outcomes were quite different in the UK study, with lower response rates; however, prolonged time from patient review/selection to actual CAR T-cell infusion (median time of 63 days) might have contributed to these outcomes. Interestingly the EFS was 39% similar to what was reported in the long-term results of the ZUMA-1 [45]. These results are summarized in Table 1.

Table 1. Anti-CD19 chimeric antigen receptor T-cell therapy in large-cell B-cell lymphoma (selected clinical trials and real-world experience).

Trial/study	ZUMA-1 [43]	JULET [37]	TRANSCEND-NHL001 [42]	Nastoupil *et al.* [38]	Jacobson *et al.* [39]	CIBMTR [40]	CIBMTR	Sesques *et al.* [43]
CAR T product	Axi-cel	Tisa-cel	Liso-cel	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel/Tisa-cel
Patients apheresed (evaluable)	111 (101)	165 (93)	344 (269)	165†	65	453 (295)†	70 (70)	70 (61)
Bridging therapy (%)	0	90	59	53	40	NA	NA	97%
Median follow-up (months)	27.1	14	18.8	13.8	10.4	6.2	5.8	5.7
ORR (CR) %	83 (58)	52 (40)	73 (53)	82 (64)	70 (50)	70 (52)	60 (38)	63 (48)
Median PFS (months)	5.9	2.9	6.8	8.3	4.5	NA	NA	3.0
12-month PFS 24-month PFS	44% 39%	35% NA	44% NA	47% NA	NA NA	NA NA	NA NA	NA NA
12-month OS	60%	49%	57.9%	68%	67%	NA	NA	NA
CRS (any grade) CRS ≥3	93% 11%	58% 22%	42% 2%	92% 7%	96% 17%	83% 14%	NA 4.3%	85% 8%
NT (any grade) NT ≥3	64% 32%	21% 12%	30% 10%	69% 31%	76% 38%	61% NA	NA 4.3%	28% 10%

†Patients with adequate follow-up.
CAR T: Chimeric antigen receptor T cell; CIBMTR: Center for Blood and Marrow Transplant Research; CR: Complete response; CRS: Cytokine release syndrome; NA: Not available; NT: Neurotoxicity; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

Lisocabtagene maraleucel (liso-cel; JCAR017) is a CD19-directed CAR T-cell product incorporating a 4–1BB costimulatory domain and administered in a defined CD4:CD8 of CAR T cells. The multicenter study, TRANSCEND NHL 001, evaluated efficacy of liso-cel in R/R LBCL. The trial included DLBCL NOS, TFL and FL grade 3B. A total of 344 patients underwent leukapheresis, and 269 received liso-cel infusion. Outpatient CAR T-cell infusion was given to 25 patients, with 18 (72%) requiring admission for side effects related to CAR T-cell therapy. With a median follow-up of 18.8 months, the ORR and CR rates were 73 and 53%, respectively. The median PFS and OS were 6.8 and 17.5 months [46] Table 1.

Safety & toxicities

CAR T-cell therapy is associated with known toxicities such as cytokine release syndrome (CRS) and neurologic events (NEs), now termed immune effector cell-associated neurotoxicity syndrome (ICANS) [45,47–49]. CRS consists in a spectrum of signs and symptoms and laboratory abnormalities that are the result of the release and expansion of immune/inflammatory cytokines resulting from CAR T-cell interaction with the targeted antigen. Typical clinical findings are fevers, constitutional symptoms, hemodynamic instability and organ dysfunction, with different degrees of severity [50]. The typical presentation of ICANS consist in toxic encephalopathy with confusion and delirium as the most characteristic symptoms. However, patients can evolve to more serious concerns, such as expressive aphasia, seizures and, rarely, cerebral edema [51,52]. In the phase I portion of ZUMA-1 trial, the primary endpoint was dose-limiting toxicity (DLT). One (14%) of seven patients experienced DLT of grade 4 CRS and neurotoxicity and later died from an intracranial bleed, deemed not related to axi-cel. Grade ≥3 NEs were observed in four (57%) of seven patients. Because all CRS and ICANS events (except for DLT) were self-limiting and reversible, axi-cel was deemed safe for study in a phase II trial [36]. The phase II study of ZUMA-1 also reported all grades and grade ≥3 in 93 and 13%, respectively. For NEs, all grades and grade ≥3 occurred in 65 and 31%, respectively [12]. The 2-year follow-up from ZUMA-1 showed grade ≥3 CRS and NEs occurring in 11 and 32%, respectively [45]. Incidence of all grades CRS and CRS grade ≥3 in the JULIET study were 58% and 22%, respectively. As for NEs, the frequencies of neurologic events of all grades and grade ≥3 were 21% and 12%, respectively [38].

CIBMTR also assessed the safety of axi-cel in real-world practice. CRS (all grades) was observed in 83%, with two deaths attributed to CRS. ICANS (any grade) were reported in 61%, with one death from cerebral edema (of 181 with NEs). Approximately 34% were ≥65 years; however, they had comparable incidences of CRS and ICANS vis-à-vis patients <65 years of age. Toxicities reported by CIBMTR were comparable to ZUMA-1, despite differences in patient characteristics [41]. The multicenter study by Nastoupil *et al.* also evaluated safety of axi-cel in 163 patients. Grade ≥3 CRS and ICANS were reported in 7 and 31%, respectively [39]. Accordingly, the safety

profile of axi-cel appears comparable to ZUMA-1. Pertaining to tisa-cel, CIBMTR data showed rates of grade ≥3 CRS and ICANS of 4.3 and 4.3%, respectively [42].

In the DLBCL cohort of TRANSCEND NHL-001, all grade CRS and ICANS were observed in 21 (30%) and 14 (20%) patients, respectively, suggesting lower toxicity rates versus axi-cel or tisa-cel, with the caveats of a nonrandomized comparison and use of a different criteria to assess toxicities [53]. In the follow-up update of liso-cel study showed an incidence of CRS and ICANS of 42 and 30%, respectively, with relatively low rates of grade 3–4 CRS (2%) and NT (10%) [46].

Notwithstanding the unique toxicities, namely, CRS and NE, CD19 CAR T cells have revolutionized treatment of R/R DLBCL owing to impressive efficacy and durability of responses. Appropriate strategies and adequate expertise are needed to mitigate toxicities.

The rates of CRS and NE in DLBCL studies are summarized in Table 1.

Mantle cell lymphoma

Earlier studies from the Fred Hutchinson Research Cancer Center (FHRCC) using their anti-CD19 CAR T cells with 1:1 defined CD4:CD8 composition included four MCL patients and showed a modest activity with one of four achieving PR [54]. The follow-up study of the CD28/CD3 anti-CD19 CAR T cell from the NCI included one patient with relapsed MCL that achieved long-term remission [55]. This early experience led to further explore the role of CART in MCL patients in larger studies.

The FULL cohort of the TRANSCEND NHL 001 also included 17 R/R MCL patients [56]. The preliminary efficacy and safety were reported [57]. Patients received liso-cel at two dose levels (DL): DL-1: 50×10^6 (n = 6) and DL-2: 100×10^6 CAR T cells (n = 11) and included five with blastoid/pleomorphic histology, Ki-67 >30% (n = 13), prior ibrutinib failure (n = 16) and prior auto-HCT (n = 6). Any grade CRS occurred in seven patients with CRS ≥3 in one patient (6%). NT occurred in 2 patients (12%) [57,58].

The ZUMA-2 trial is the largest phase II trial in R/R MCL to date, which led to approval of KTE-X19 or brexucabtagene autoleucel. It evaluated KTE-X19 in 74 patients with high-risk MCL [34]. Bridging therapies (37%) were allowed. The intention-to-treat ORR and CR were 85% and 59%, respectively. After a median follow-up of 12.3 months, the 12-month PFS and OS were 61% and 83%, respectively. There were no differences in ORR (CR) rates, PFS and OS among key covariates such as age, MCL histology, TP53 status, Ki67% and BTKi refractoriness. CAR T-cell-related toxicities were CRS (all grades) in 91% (CRS ≥3 in 15%) and NE in 63% (grade ≥3 in 31%). The median onset of CRS and NE were 2 and 7 days, respectively. Tocilizumab and steroids were used in 26% and 38%, respectively. No grade 5 adverse events were reported. KTE-X19 has also been studied in R/R B-cell acute lymphoblastic leukemia [59]. As of August 2020, brexucabtagene autoleucel (KTE-X19) had been approved for the treatment of relapsed/refractory mantle cell lymphoma (Table 2).

Follicular lymphoma

The first reported case of efficacy of CAR T-cell therapy in NHL was in FL [60]. A subsequent National Cancer Institute (NCI) study showed long-term remissions in 2 cases [55]. The initial report of the University of Pennsylvania (UPenn) of CTL019 in refractory B-cell lymphomas included 14 with FL with high-risk features. ORR was 79% (CR = 71%). At a median follow-up of 28.6 months, 70% were disease-free [37]. The FHRCC also reported their experience of anti-CD19 CAR T that included eight patients with refractory FL [61]. With a median follow-up of 24 months, the study showed high and durable response rates, with seven of eight patients achieving CR and all remaining in remission at last follow-up.

ZUMA-5, the first and largest multicenter study to date of anti-19 CAR T-cell therapy (axi-cel) in refractory indolent lymphomas, included 140 patients (FL = 124 and marginal zone lymphoma = 16) enrolled and infused with axi-cel [62]. The efficacy analysis included 80 FL patients with ≥9 months follow-up, and the safety analysis included all axi-cel infused patients. It showed high response rates, with an ORR of 95% (CR = 81%). With a median follow-up on 15.3 months, 80% achieving CR had ongoing responses. The median PFS was 23.5 months. CAR T-related toxicities were: incidence of any grade (grade ≥3 CRS) CRS and any grade NT (grade ≥3 NT) of 77% (7%) and 55% (15%), respectively. Median time of onset of CRS and NT were 4 and 7 days, respectively. The ELARA is a global multicenter study trial evaluating the efficacy of tisagenlecleucel in follicular lymphoma has been presented recently with also encouraging results and tolerable side effects (Table 2).

Table 2. Anti-CD19 chimeric antigen receptor T cell studies in mantle cell lymphoma and follicular lymphoma.

Trial/study	ZUMA-2 [33]	TRANSCEND-NHL001 [54]	UPenn [36]	FHCRC [58]	ZUMA-5 [59]	ELARA
Disease	MCL	MCL	FL	FL	FL/MZL	FL
CAR T product	KTE-X19	Liso-cel	Tisa-cel	1:1 CD4+/CD8 4–1BB CART	Axi-cel	Tisa-cel
Patients apheresed (evaluable)	74 (68)	25 (17)	16 (14)	8	127 (80)	97 (52)
Median F/U (months)	12.3	8.4	28.6	24	15.3	NA
ORR (CR) %	93 (67)	71 (53)	79 (71)	100 (88)	93 (80)	82.7 (65.4)
Median PFS (months)	NR	5.8	NR	NR	23.5	NR
Median OS (months)	NR	11.1	NR	NR	NR	NR
CRS (any grade) CRS ≥3	91% 15%	41% 6%	57%† 18%†	59% 0	77% 7%	48.5% 0
Median onset CRS, days (range)	2 (1–13)	7 (2–10)	NA	NA	4 (1–15)	4 (1–14)
NT (any grade) NT ≥3	63% 31%	18% 12%	39%† 11%†	50% 0	55% 15%	9.3% 1%
Median onset NT, days (range)	7 (1–32)	9 (7–25)	NA	NA	7 (1–177)	8.5 (4–190)

†Data of CRS and NT available for the whole group (diffuse large B-cell lymphoma and FL).
CAR T: Chimeric antigen receptor T cell; CR: Complete response; CRS: Cytokine release syndrome; FHCRC: Fred Hutchinson Cancer Research Center; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; NA: Not available; NR: Not reached; NT: Neurotoxicity; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; UPenn: University of Pennsylvania.

Off the shelf CAR T-cell therapy

Despite the success of autologous anti-CD19 CAR T-cell products, there are limitations. Availability of a CAR T-cell product is affected by manufacturing failure and prolonged manufacturing time [63]. Delays could be challenging in the face of a highly proliferative disease. For instance, in the JULIET study ~30% of enrolled patients did not receive infusion due to progressive disease, and ~7% patients had manufacturing failures. In ZUMA-1, 10 patients out of 111 did not receive CART infusion (one patient had manufacturing failure). In ZUMA-2 (MCL), of 74 patients enrolled, six did not receive CART infusion (three due to manufacturing failure, two due to PD). In ZUMA-5, 151 were enrolled and apheresed, 146 received CART infusion (there were no manufacture failures (three ineligible, one death and one with DLBCL transformation) [12,34,38,62]. Additionally, an autologous CAR T-cell product can be affected by T-cell dysfunction related to number of prior therapies, with consequent decrease in functional T cells available for manufacturing. Use of allogeneic CAR T cells ("off-the-shelf" CAR T) is promising to overcome the aforementioned factors. Encouraging activity with donor-derived anti-CD19 CAR T cells were seen in DLBCL, CLL, MCL and ALL without significant increased graft-versus-host disease (GVHD) rates [64,65]. A follow-up report by the NCI of anti-CD19 CAR T cells derived from patients' donors and who relapsed after allo-HCT, included 20 patients with various B-cell malignancies. Eight of 20 achieved either CR or PR with a 6-month PFS of 32%. Nine of 20 had grade ≥3 symptoms of possible CRS. No cases of acute GVHD were reported [65]. Although donor-derived allo-CAR T cells offered promising results, it is not practical due to the need of an HLA-matched donor, thus limited to patients who underwent or are planned for allo-HCT.

Using healthy, nonrelated donors is an alternative source for allogeneic CAR T-cell manufacturing. Strategies to minimize GVHD include T-cell receptor (TCR) gene editing by disrupting the alpha chain of the TCR (TRAC) that is responsible for alloreactivity. A common editing technology is the transcription activator-like effector endonuclease (TALEN). The first allogeneic anti-CD19 CAR T-cell trial using TALEN mediating TRAC editing (UCART19) was reported in B-cell ALL, with promising results and low GVHD rates [66].

At the 2020 ASCO meeting, results of the first in-human trial of anti-CD19 allogeneic CAR T-cell therapy with TALEN-mediated TRAC and CD52 gene editing (ALLO-501) was reported in refractory DLBCL and FL [67]. ALLO-501 was administered with the anti-CD52 antibody at three dose levels. Additionally, ALLO-501 had a safety switch that is activated by rituximab. Patients received lymphodepleting therapy with Flu/Cy. The study enrolled 12 patients (DLBCL = 5) with nine evaluable for efficacy. ORR was 78% with three CRs. The safety profile was manageable, with grade 1–2 CRS in 27% (grade 3 CRS in 5%), 1 developed NT. No patients developed GVHD. Although these results are encouraging, completion of the escalation/expansion phase and longer follow-up are needed.

Areas of unmet needs: post-CAR T-cell relapse management

Unfortunately, 50% or more patients experience relapse [68]. Outcomes post-CAR T-cell relapse are dismal, especially within 3 months post-infusion [69,70]. The mechanisms of relapse or lack of response to CAR T include several factors: product quality, efficacy of conditioning chemotherapy, antigen escape (CD19 loss), increased expression of T-cell exhaustion markers (PD-L1, TIM-3, etc), immunosuppressive tumor microenvironment (increased tumor associated macrophages, myeloid-derived suppressive cells and soluble immunosuppressive factors) [39,71–77]. The US CART consortium reported ORR with checkpoint inhibitors, lenalidomide-based regimens, and chemotherapy of 24%, 20% and 10%, respectively [70]. Radiation therapy seems effective, particularly in localized relapses [78].

Pembrolizumab demonstrated an ORR of 27% (CR = 1; PR = 2) in 12 post-CAR T B-NHL. The authors noted sustained CAR T-cell transgene peaks and expansion in responders [79]. ZUMA-6 investigated combining axi-cel with atezolizumab, a PDL-1 inhibitor, for four doses at different time points (n = 28), showing an ORR of 75% (CR = 46%). Grades ≥3 CRS and NT were similar to ZUMA-1 [80].

Bispecific antibodies (BsAbs) have emerged as an alternative approach to eliminate tumor cells by engaging cytotoxic T cells. Blinatumumab, a CD3/CD19 BsAb, first-in-class agent currently approved for R/R B-cell acute lymphoblastic leukemia [81]. It also showed activity in R/R DLBCL with CR rates of 22–36% (none were post-CAR T-cell relapses) [82,83]. Combination with lenalidomide appears to yield greater activity but longer follow-up is needed to confirm this observation [84]. Limitations are the logistics (continuous infusion administration for 2–4 weeks) and side effects (particularly neurotoxicity). Data on mosunetuzumab (a novel CD3/CD20 BsAbs) from a large study (n = 218) in R/R B-cell NHL (mainly DLBCL and FL) showed an ORR (CR) of 62.7% (43.3%) and 37.1% (19.4%) in FL and DLBCL, respectively [85]. The study included post-CAR T-cell failures (12 patients) with an ORR and CR of 43.5% an 25%, respectively. Similarly, another CD3/CD20 antibody (REGN1979) was evaluated in R/R NHL and included 3 DLBCL cases relapsing after CAR T-cell therapy with two resulting CRs [86]. Epcoritamab (GEN3013) a novel antiCD3/antiCD20 bispecific antibody (DuoBody) administered subcutaneously showed encouraging safety profile and activity in R/R B-cell NHL. This trial reported three objective responses in four post-CAR T-cell DLBCL relapsed cases [87].

Retreatment with CAR T-cell reinfusion was allowed in ZUMA-1 in patients who had initial response and post-biopsy relapse was still CD19 positive. The ORR was 54% with four CR and three PR (out of 13 retreated patients). The median duration of response was 81 days with two still in remission at last follow-up. A larger study and longer follow-up are needed to confirm these results [88].

Dual antigen targeting with CAR T cells is an option aimed at overcoming escape from CD19 loss. The escalation phase of the dual CD19-CD22 lentiviral transduced CAR T cell (41BB/CD3z LV20.19CAR T) was reported in 11 patients with B-cell NHL (DLBCL, MCL and CLL) with an ORR of 82%. There were no reported grade ≥3 CRS or NE [89]. AUTO3 is a CD22–CD19 dual-targeting CAR T cell that uses a retroviral vector and reported preliminary results in a phase I/II study in R/R DLBCL (n = 23) at different doses levels and with/without pembrolizumab. AUTO3 showed remarkably activity with ORR of 65% (CR = 48%) [90].

Discussion

CD19 is an attractive target for immunotherapy, specifically with CAR T cells. Initial success of anti-CD19 CAR T cells in poor-risk DLBCL led to its expansion to other CD19+ malignancies – namely, MCL and FL. Novel strategies are needed for post-CAR T-cell failure.

Combination therapies to improve CAR T-cell efficacy, currently under evaluation, include the addition of targeted, immunomodulatory and/or checkpoint blockade agents – namely utomilumab (4-1BB agonist) + axi-cel (ZUMA-11, NCT03704298), ibrutinib (BTK inhibitor) + tisa-cel (NCT03876028), lenalidomide + axi-cel (ZUMA-14, NCT04002401) and pembrolizumab + tisa-cel (NCT03630159). The PLATFORM trial is a multiarm study that combines liso-cel with an immunomodulatory imide drug (IMiD), PD-L1 inhibitor and BTKi. (NCT03310619; Table 3).

CAR T-cell therapy in the second-line setting may challenge the role of auto-HCT in DLBCL. There are currently three ongoing randomized clinical trials that compare anti-CD19 CAR T-cell versus salvage chemotherapy plus auto-HCT in DLBCL after relapse or lack of response to front-line chemoimmunotherapy: axi-cel (ZUMA-7, NCT03391466), tisa-cel (BELINDA, NCT03570892) and liso-cel (TRANSFORM, NCT03575351). CAR T-cell therapy is also being studied in the frontline setting in the ZUMA-12 trial in high-risk DLBCL (NCT03761056).

Other challenges besides CAR T-cell resistance/relapse include the cumbersome manufacturing process and overcoming T-cell dysfunction. Off-the-shelf or allogeneic CAR T cells are a promising alternative with proven

Table 3. Anti-CD19 chimeric antigen receptor T-cell therapy: combination studies in diffuse large B-cell lymphoma.

CAR T product	Indication	Agents	Phase	NCT N
Axi-cel (ZUMA-6)	R/R DLBCL	Atezolizumab	I/II	NCT02926833
Axi-cel (ZUMA-11)	R/R DLBCL	Utomilumab	I/Ib	NCT03704298
Axi-cel (ZUMA-14)	R/R DLBCL	Lenalidomide and rituximab	I/Ib	NCT04002401
Tisa-cel	R/R DLBCL	Ibrutinib	Ib	NCT03876028
Tisa-cel (PORTIA)	R/R DLBCL	Pembrolizumab	Ib	NCT03630159
Liso-cel (PLATFORM)	R/R DLBCL	CC-122, durvalumab, ibrutinib	I/II	NCT03310619

DLBCL: Diffuse large B-cell lymphoma.

activity and manageable toxicity profile. PBCAR0191 is another anti-CD19 allogeneic product in which the CD19 specific CAR is inserted into the TRAC locus in cells harvested from healthy donors. PBCAR0191 is currently enrolling patients with refractory B-cell NHL, acute lymphoblastic leukemia and chronic lymphocytic leukemia (NCT03666000) [91].

CAR T-cell therapy comes with a hefty price between US$373,000–475,000 for the product only. The price does not account for the cost of the pre-CAR-T workup, hospitalization and treatment of toxicities. The value of CART has been analyzed through cost–effectiveness studies using the quality adjusted life years method has been reported [92]. The impact on budget seems to be as significant as patient access/coverage [93]. Outpatient administration, in-house CAR T-cell manufacturing and improving the safety of the therapy may reduce the overall cost [92].

Conclusion

In conclusion, the role of anti-CD19 CAR T-cell therapy in B-cell NHL shows promise in beyond DLBCL. Evolving strategies such as combinatorial regimens with CAR T and earlier use (second-line setting in DLBCL) may change the treatment paradigm of B-cell NHL.

Future perspective

Current data show the activity and efficacy of anti-CD19 CAR T-cell therapy. It is likely that CD19 will continue to be the most attractive target for B-cell NHL patients. We hope that anti-CD19 CAR T-cell therapy will be approved for follicular lymphoma given the preliminary data of activity shown recently. It is possible that CAR T-cell therapy will be approved as second-line treatment for relapsed DLBCL if the randomized studies (ZUMA-7, BELINDA and TRANSFORM) show positive outcomes in comparison to standard of care.

We also discussed the poor outcomes of post CART relapses, particularly in DLBCL. Efforts in understanding the mechanism and potential strategies are underway, such as combination therapies with targeted agents that may improve the CAR T product (ibrutinib), improve CAR T-cell expansion and trafficking into the tumor (IMiDs and/or checkpoint inhibitors). We also hope that the manufacturing process and logistics will be optimized so that this therapy will be more accessible.

Executive summary

- B-cell non-Hodgkin lymphoma (NHL) is an heterogenous disease and treatable in general; however, a proportion of patients will have refractory disease and options will be limited.
- Targeting CD19 with CAR T-cell therapy is a viable and efficacious strategy to treat poor risk B-cell NHL.
- There are several products available such as axicabtagene ciloleucel, brexucabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel that has shown significant activity in poor risk diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma.
- Real-life experience data with FDA-approved products have confirmed the efficacy results in DLBCL.
- CAR T-cell therapy will likely move with new indications (i.e., in FL) and possibly in earlier lines (second-line in DLBCL).
- Challenges remain with CAR T-cell therapy in B-cell NHL, such as manufacturing time, access, cost and post-CAR-T relapses. Addressing these challenges may improve the general outcomes with CAR T cell therapy.

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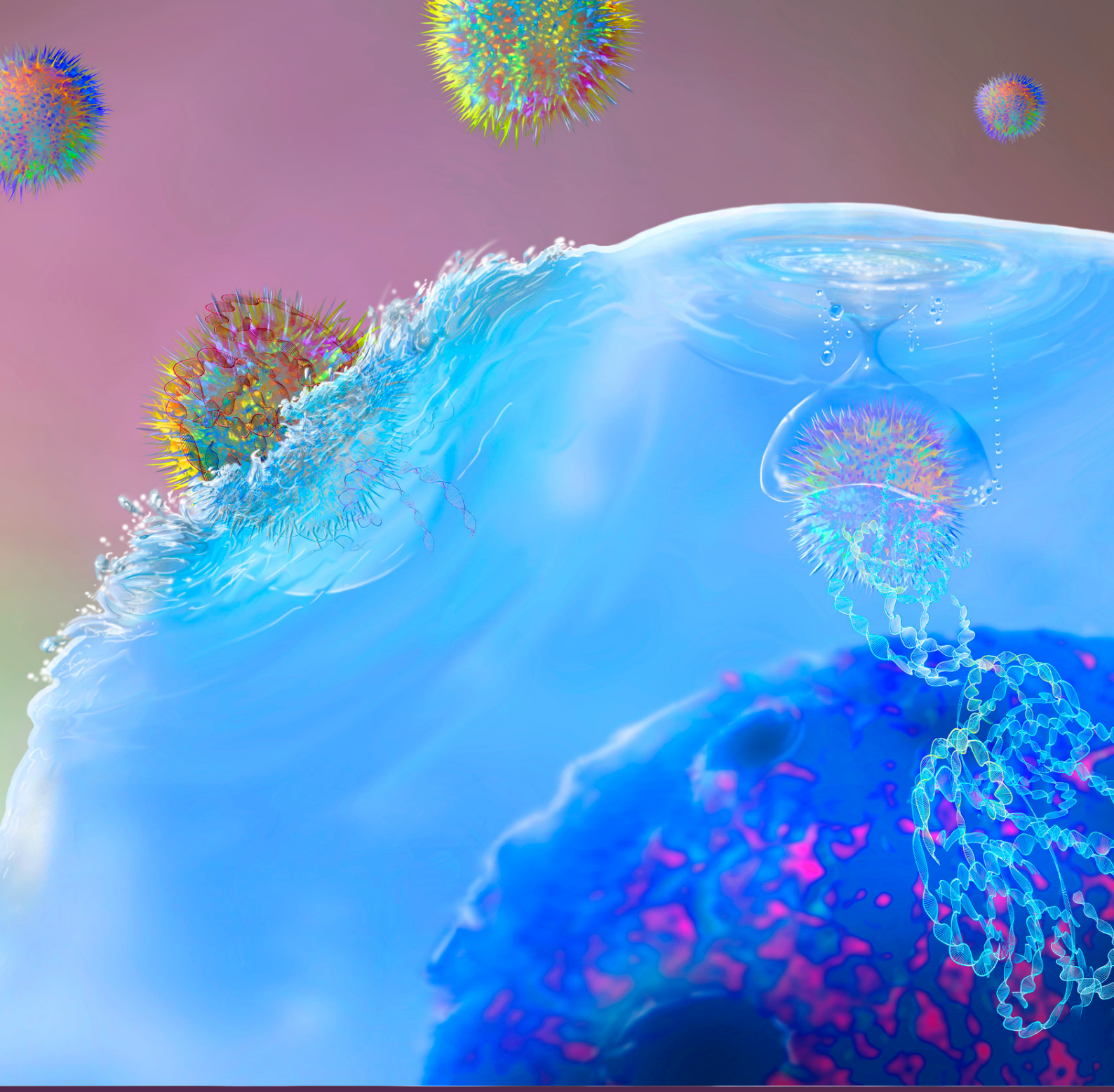

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