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LATEST ADVANCES IN CAR-T CELL MANUFACTURE & CLINICAL DEVELOPMENTS

SPOTLIGHT

EXPERT INSIGHT

Ethical considerations in the translation of CAR-T cell therapies

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Despite the enormous promise of chimeric antigen receptor T (CAR-T) cell therapies, the translation and commercialization of these therapies raise a number of pressing ethical questions. These concerns include managing the toxicities associated with these powerful therapies both for research participants in clinical trials and patients receiving approved therapies. The safety concerns are a key issue for the field today but will become even more pressing as CAR-T cell therapies move from their current status as last-resort approaches closer to the therapeutic front-lines. They also include ensuring equitable access to these innovative therapies – along both financial and geographic lines – and managing expectations and patient demands for access to high potential but not yet proven interventions. The article aims to articulate these and other key ethical challenges for the field and suggest some strategies to help navigate these challenges and facilitate the successful translation and commercialization of CAR-T cell therapies.

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ETHICAL CONSIDERATIONS IN THE TRANSLATION OF CAR-T CELL THERAPIES

The recent approval of two new cancer therapies may herald a paradigm shift in the treatment of cancer. Both Kymriah (Novartis) and Yescarta (Gilead/Kite) are members of a new class of personalized cancer therapies that work by genetically manipulating a patient's own immune cells to attack their cancer. These novel treatments – called chimeric antigen receptor T cell therapies or CAR-T cell therapies for short – produced remarkable results in clinical trials [1–3] and have now gained market access for

the treatment of a subset of hard-to-treat blood malignancies.

As might be expected from the history of prior cell therapies [4], the initial rollout of approved CAR-T cell therapies has been somewhat rocky [5], with long waiting lists, concerns over reimbursement and a small number of locations offering the treatments [6]. Despite these initial challenges, excitement in the field remains high with numerous firms racing to develop more advanced CAR-T cell therapies to improve the treatment of blood cancers and modify the approach to target solid tumors. This scientific excitement has been reflected in investments in the CAR-T space in recent months, with Celgene agreeing to buy Juno for approximately $9 billion to gain access to JCAR017 – widely expected to be the third CAR-T cell product to gain market access in the USA – and Juno's broader pipeline of CAR-T cell products. This followed Gilead's $11.9 billion purchase of Kite Pharma in late 2017. Early 2018 has also seen activity in the allogeneic CAR-T therapy space with Pfizer partnering with Allogene to accelerate the development of 'off-the-shelf' CAR-T cell therapies.

Despite the clear scientific potential of these novel therapies, the path to successful translation and commercialization of CAR-T cell therapies is perilous and success is far from certain. Firms commercializing CAR-T cell therapies much overcome a series of scientific and technical challenges, including managing the serious side effects associated with CAR-T cell therapy and developing a process to reliably, efficiently and affordably manufacture the necessary cells. In addition to the scientific challenges, the translation and commercialization of CAR-T cell therapies raise a number of pressing ethical questions. Identifying these ethical considerations is the primary focus of this article. To orient this discussion, the paper begins with a brief review of the histories of the three most advanced CAR-T cell products – Novartis' Kymriah, Gilead/Kite's Yescarta and Celgene/Juno's JCAR017. These translational histories provide context to understanding the ethical considerations relevant to the development of the current generation of CAR-T cell therapies.

KYMRIAH (NOVARTIS)

Kymriah, manufactured and marketed by Novartis, received FDA approval in August 2017 for pediatric and young adult patients with relapsed or refractory acute lympoblastic leukemia (ALL) [7]. It is estimated that there are approximately 600 patients in the USA each year who are potential candidates for this treatment. The drug is priced at $475,000 for the one-time treatment. Novartis has introduced the product with an unusual pay-for-performance pricing model, in which patients who do not respond within the first month after treatment do not have to pay [8]. Kymriah's safety and efficacy were established in a multicenter clinical trial of 63 patients, in which 83% of patients entered remission within 3 months [7]. It was approved despite serious side effects and carries boxed warnings for both cytokine release syndrome (CRS), a short-term but serious inflammatory response, and neurological events, which can occur concurrently with CRS or independently.

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The development of Kymriah can be traced back to work in Carl June's lab at the University of Pennsylvania (UPenn) in the 1980s and 1990s, but accelerated in the last decade with the focus on applying CAR-T cell technology to leukemia [9]. Promising clinical results in a handful of patients attracted interest from pharmaceutical firms and led to a partnership between Novartis and UPenn that launched in 2012 [10]. Recognizing the challenges of bringing cell therapies to market, Novartis created a special unit focusing on cell and gene therapies. They closed this unit in 2016, laying off 120 employees, and re-integrated CAR-T cell therapy development into the company's existing oncology unit [11,12]. At the time, Novartis indicated that development of the CTL019 (which eventually became Kymriah) would continue but the move raised questions about the firm's commitment to future CAR-T cell technology. Thus far, Novartis has applied for European market access for Kymriah to treat pediatric ALL and applied to the US FDA and European Medicines Agency (EMA) for approval to treat relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [13].

YESCARTA (KITE/GILEAD)

The US FDA approved Yescarta in October 2017, less than 2 months after Kymriah first gained market access, to treat patients with certain forms of non-Hodgkin lymphoma (NHL). Yescarta was developed primarily by Kite Pharma, which now operates as a distinct unit of Gilead Sciences, following Gilead's purchase of Kite in late 2017. Yescarta was the first CAR-T cell therapy approved for use in adult patients and is indicated for patients with several B-cell derived forms of NHL. These include diffuse large B-cell lymphoma (the most common form of NHL in adults), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma and diffuse large B-cell lymphoma arising from follicular lymphoma [14]. Safety and efficacy were established in a multi-center clinical trial of more than 100 patients, with a complete remission rate of 51% [14]. At the time of approval, it was estimated that approximately 3,500 people in the US would be candidates for Yescarta each year and the product was priced at $373,000 per treatment [15]. Like Kymriah, Yescarta was approved despite serious side effects and carries boxed warnings for both CRS and neurological events.

Although the mechanism of action for both Kymriah and Yescarta are similar, Yescarta grew primarily out of work in Steven Rosenburg's lab at the National Cancer Institute (NCI) as well as earlier insights from Israeli immunologist Zelig Eshhar [16].

JCAR017 (JUNO/CELGENE)

Celgene recently completed an acquisition of Juno Therapeutics, primarily to gain access to Juno's lead CAR-T cell product, JCAR017, which is currently in clinical trials for patients with Non-Hodgkin Lymphoma (NHL). Preliminary results for this product have been promising and some analysts expect it will be the third CAR-T cell therapy to gain market access in the USA, potentially in 2019 [17].

Despite the perceived promise of JCAR017, Juno has faced challenges

in its development of CAR-T cell therapies. Most notably, the company abandoned its previous lead candidate, JCAR015, after a series of patient deaths in clinical trials for adult patients with ALL [18]. Each of these patients died from neurological side effects, predominantly cerebral edema, associated with the CAR-T cell therapy. Three patients died in the summer of 2016, leading to a brief FDA hold and then another two patients died later in the year after the FDA had permitted the trial to restart [18]. Juno analyzed these deaths and shared their results publicly [19], although some analysts still question whether the cause of the deaths is fully understood and worry whether similar deaths will occur in other clinical trials or routine patient care [18].

KEY ETHICAL CONSIDERATIONS

Ethical issues can arise at any stage in the development and commercialization of a novel therapy, from the initial design of clinical research, well before a product gains market access, to post-market concerns, including difficulty accessing or affording novel treatments. Figure 1 highlights several ethical considerations relevant to the development of CAR-T cell therapies and breaks these down into issues that occur primarily in the pre-market phase, primarily in the post-market phase once approval for market access has been granted by the FDA or appropriate regulatory body, and issues that are cross-cutting through both the clinical development and approved product phases. The ensuing sections briefly examine each of these considerations, highlighting issues unique to or especially problematic in CAR-T cell therapy development and commercialization.

CROSS-CUTTING CHALLENGE: MINIMIZING HARM TO RESEARCH PARTICIPANTS & PATIENTS

Minimizing harm to research participants in CAR-T cell clinical trials and to patients receiving approved CAR-T cell therapies is a key ethical obligation that should be a focus of scientists and clinicians developing these innovative therapies. This ethical obligation does not imply that research participants can never be placed at risk nor harmed but rather that clinical research should be designed to minimize harms and maximize benefits and, further, that research participants should be fully informed of potential risks. Similarly, it is not the case that an approved treatment can never cause harm. Indeed side effects are a fact of life in modern medicine. Rather all treatment decisions, including those to utilize approved CAR-T cell therapies, should be made firstly, to avoid any intentional harm, and, secondly, with the aim of maximizing the net benefits to the patient, cognizant of the possibility of a variety of potential harms.

While these safety concerns cut across therapeutic approaches, they are especially pressing for CAR-T cell therapies. This reflects the range of severe adverse events and side effects observed in CAR-T cell clinical research to date, the intensity of patients' responses to these treatments and the personalized nature of these therapies, which may increase variability from dose to dose and patient to patient. Systematic

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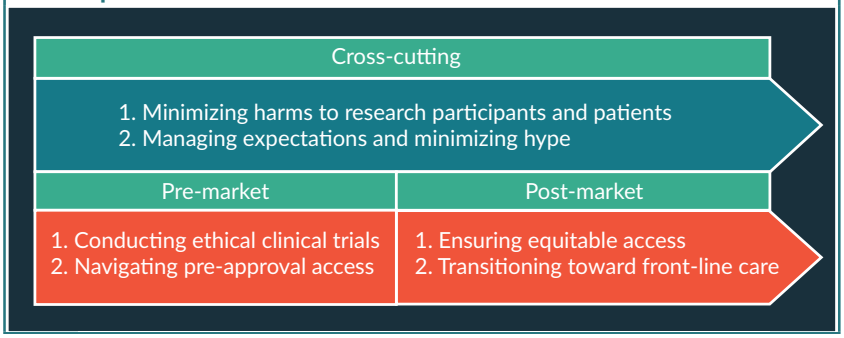
FIGURE 1

Key ethical considerations relevant to CAR-T cell therapy development and commercialization.



data on the adverse events associated with Kymriah and Yescarta are available from the FDA as part of the basis for approval [20,21]. All 68 patients who received Kymriah in the clinical trial supporting its approval experienced at least one adverse event and 57 (84%) experienced at least one grade 3 (severe) or higher adverse event. These adverse events included two deaths that the FDA concluded were attributable to the product. Results were generally similar for the 108 patients who received Yescarta in the clinical trials supporting its approval. All patients experienced at least one adverse event and 102 (94%) experienced at least one grade 3 or higher adverse event. Four deaths were judged by the FDA to be attributable to the product and are included among these adverse events. Summary data from the FDA on adverse events associated with both Kymriah and Yescarta are shown in Table 1.

CRS is among the most common complications of CAR-T cell therapy. It is a systemic inflammatory response to the activation of CAR-T cells in which patients experience high fevers, hypoxia, hypotension and malaise. The first clinical sign of CRS is typically fever, but the condition can rapidly progress and pose life-threatening risks including vasodilatory shock, capillary leak, respiratory failure or organ dysfunction [22]. Notably, both deaths attributed by the FDA to Kymriah and a portion of the four deaths attributed by the FDA to Yescarta were categorized as resulting from CRS [20,21]. Despite the frequency and seriousness of CRS, it is sometimes self-limiting and, if not, can often be managed by the use of tocilizumab, an antibody against the IL-6 receptor. This antibody has become standard practice in treating the effects of CRS [22] and, indeed, the FDA approvals for both Kymriah and Yescarta required that they only be administered in healthcare settings where doses of tocilizumab were available.

CAR-T cell therapies have also been associated with a broad range of neurologic toxicities ranging from headache, tremor and dizziness to delirium, aphasia, encephalopathy, seizures and cerebral edema. Although severe neurotoxicity is less common than CRS, it is perhaps more troubling as its cause(s) remain uncertain and management remains difficult. Mild cases of neurotoxicity are often self-limiting or managed with corticosteroids, but some cases progress rapidly and have led to patient deaths, including the deaths

TABLE 1

Adverse events in Kymriah and Yescarta clinical trials.

	Kymriah (n = 68)		Yescarta (n = 108)	
	All grades N (%)	Grades ≥3 N (%)	All grades N (%)	Grades ≥3 N (%)
Cytokine release syndrome	54 (79%)	35 (51%)	101 (94%)	14 (13%)
Neurologic toxicities	44 (65%)	12 (18%)	94 (87%)	34 (31%)
Febrile neutropenia	26 (38%)	26 (38%)	39 (36%)	35 (32%)
Infections	40 (59%)	19 (27%)	41 (38%)	25 (23%)

that derailed Juno's JCAR015 clinical program [23].

Better ability to predict and manage both CRS and neurotoxicity associated with CAR-T cell therapies are critical for the field to advance. In the meantime, clinical researchers and physicians have the obligation to be open and honest to research participants and patients about these risks and ensure these individuals have full understanding of the risks they are undertaking, the other options they may have, and the nature of the research or care they are receiving. They also have the obligation to be prepared to manage these and other toxicities aggressively.

CROSS-CUTTING CHALLENGE: MANAGING EXPECTATIONS & MINIMIZING HYPE

The impressive clinical results seen from CAR-T cell therapies in early clinical trials for last-resort patients with ALL and NHL have created substantial excitement in the field. This excitement has numerous benefits, including increased awareness of these technologies and increased funding for the field, yet they also pose challenges. Indeed, while the clinical successes have been dramatic, many questions and limitations remain. These include uncertainty about the long-term benefits and risks of approved CAR-T cell therapies, including how long patients are likely to remain in remission and how variable this is across patients. It also includes substantial uncertainly about how successful CAR-T cell therapy will be in the treatment of other blood cancers or solid tumors or whether the side effects of the treatments will ever be managed well enough for the treatment approach to move beyond its current status as a last resort therapy.

All stakeholders in the CAR-T cell therapy field, including scientists, biotech executives, patient advocates and others, should be careful to accurately communicate the status of clinical research or approved therapies and work to ensure that the successes, potential risks and uncertainties are accurately characterized.

Accurate communication can minimize hype and help address many of the other ethical considerations highlighted elsewhere in this article. Accurately understanding the potential benefits and limits of the evidence supporting CAR-T cell therapy promotes ethical recruitment into clinical trials, helps address some concerns associated with pre-approval access to promising treatments and may also help address the challenge of unscrupulous actors marketing unproven cell-based therapies and even encourage

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fair and responsible regulatory actions. Indeed one only need to look at the hype surrounding stem cell research over the last two decades [24,25] and the growth of the market for unproven stem cell therapies [26–29] to understand this risk. The rapid and, in retrospect, premature lifting of the clinical hold on Juno's clinical trial testing JCAR015 in adult ALL may reflect, at least in part, hype surrounding the development of CAR-T cell therapies and has caused some to question whether the FDA deserves a share of the blame for the patient deaths that followed the lifting of the clinical hold [30].

PRE-MARKET CHALLENGE: CONDUCTING ETHICAL CLINICAL TRIALS

Clinical trial design and implementation is a challenge for the development of almost any new therapy but is especially fraught for novel therapies that differ from existing paradigms, such as CAR-T cell therapies. Ethical considerations relevant to clinical trial design include identifying appropriate patient populations, developing appropriate recruitment and consent strategies, managing adverse events, identifying appropriate endpoints (or surrogate markers) to assess the success of the trial, and many others (e.g., [31] for a overview). Discussing the ethics of clinical research and clinical trials in general is beyond the scope of this article, but there are a few considerations specific to CAR-T cell therapy that merit attention.

The most notable of these concerns was articulated by Nancy Jecker and colleagues in a recent article that outlined a system of principles to govern recruitment into CAR-T cell clinical trials [32]. The ethical principle of justice is often used to argue for recruitment strategies that yield research participant populations broadly representative of the target population for the therapy to avoid disproportionately burdening specific populations. In the article, Jecker and colleagues argued that the combination of impressive early clinical results and small trial sizes (driven by cost, manufacturing complexity, risk, etc.) seen in CAR-T cell therapies as well, perhaps, as other breakthrough therapies, shifts the emphasis of justice concerns to ensuring fair access to the potential benefits rather than ensuring the fair distribution of burdens and risks [32]. A key realization critical to this argument is that for CAR-T cell therapy the demand for slots in clinical trials greatly exceeds capacity [33] and this runs the risk, without appropriate attention, of privileging some groups over others. This argument reflects the excitement surrounding CAR-T cell therapies and reflects the reality that, for some research participants, enrollment in a CAR-T clinical trial has saved, or at least added many years to their lives.

Still clinicians and scientists developing novel CAR-T cell therapies should remain cognizant of the concerns about hype. Indeed, while patients with relapsed or refractory ALL may quite rationally scramble to gain access to a CAR-T cell clinical trial, the potential benefit/risk profile will vary by patient and by indication. Clinical trial design should incorporate justice considerations both in regard to potential risks and benefits of participation. It should also include clear communication about the nature of the trial, the target population, and the likelihood of both risks and benefits.

PRE-MARKET CHALLENGE: NAVIGATING PRE-APPROVAL ACCESS

Developers of CAR-T cell therapies must be prepared to navigate the demands of patients clamoring for access to investigational but not yet proven interventions as well, perhaps, as requests for plausible, but off-label, uses of approved CAR-T cell therapies. In the USA, long-established policies exist for patients to request and for firms to provide access to drugs moving through the clinical trial process but not yet approved for general use. These expanded access policies (sometimes called 'compassionate use') offer the potential for patients with serious or immediately life-threatening conditions but who do not qualify to participate in a clinical trial to gain access to the investigational therapy. Although the FDA approves nearly all of the expanded access requests it receives, this approval does not mandate firms provide the investigational therapy and for a variety of reasons, they may be unwilling to do so [34]. The frequency and nature of these requests may be affected by right-to-try legislation currently pending in the US Congress [35,36].

In the context of CAR-T cell therapy development, the cost and time of manufacturing a single personalized dose of CAR-T cell therapy may discourage firms from providing treatments requested through FDA's expanded access policies. Indeed, with many manufacturing facilities for CAR-T cell clinical research running at maximum capacity [33], firms may justifiably refuse expanded access requests on these grounds. They should be aware that rejecting such requests may generate negative publicity, especially with increasing numbers of patients turning to social media to pressure firms to provide access to experimental therapies [37].

A similar dynamic could apply in the case of off-label requests for approved CAR-T cell therapies. In traditional mass-produced therapeutics, the firm has little control over the off-label use of their products should a physician choose to prescribe it. By contrast, because personalized CAR-T cell therapies are manufactured for a specific patient, firms can choose whether or not to accept a request and provide the therapy. Off-label requests could potentially come from patients outside the approved age group, with a rare variant of the underlying condition, or hoping to access CAR-T cell therapy without necessarily exhausting all other treatment options first. Having the ability to serve as a gatekeeper for these off-label requests will likely increase the pressure on CAR-T cell therapy firms to develop and publicize policies to address these requests, much like the 21st Century Cures Act requiring manufacturers or distributors of investigational drugs to make their policies for evaluating requests for expanded access publicly available. Having and posting such policies can help ensure that individual requests are treated fairly and consistently.

POST-MARKET CHALLENGE: ENSURING EQUITABLE ACCESS

Once a CAR-T cell therapy product gains market access, ethical concerns about equitable access come to the forefront. An extensive literature has examined health disparities

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among various groups of patients within the USA [38]. The causes of these disparities are complicated and varied but access to care is one contributor (e.g., [39]) and the risk certainly exists that the introduction of novel, expensive, personalized CAR-T cell therapies could exacerbate rather than mitigate these disparities. These concerns are driven by the high cost of the initial CAR-T cell therapies as well as the geographic constraints on where patients can receive treatment.

When Kymriah was approved, Novartis announced that it would cost $475,000 per treatment and that only patients who responded within the first month after treatment will be charged. When Yescarta was approved, it was priced at $373,000 per treatment. Health economics assessments by ICER in the USA [40] and NICE in the UK [41] suggest that, from a health system perspective, these prices are reasonable given the clinical outcomes. Still, in both cases, the price limits access primarily to the wealthy or well insured. Furthermore, the quoted cost includes only the product itself, not any associated care nor does it include handling the toxicities associated with CAR-T cell treatment, such as CRS, which can require extended stays in the intensive care unit and add substantially to the total cost of treatment. As a result, estimates suggest the total cost of CAR-T cell therapy could be closer to $1.5 million [42]. These high costs impose financial burdens on many CAR-T cell therapy patients. They may also, as was the case for previous autologous cell therapies [4], raise concerns among prescribing physicians about reimbursement and slow the rollout of these innovative therapies. These concerns are already visible in the initial roll-out of Yescarta [5]. The combination of high costs, both for the CAR-T cell treatment itself as well as associated care, along with uncertainty surrounding insurance coverage creates a possibility that access to CAR-T cell therapies could be unfairly stratified on socioeconomic lines. Firms should both be aware of this possibility and work actively to ensure that patient need and potential benefit rather than ability to pay determine who has access to these novel therapeutic options.

Limits on the number of sites that can administer CAR-T cell therapies further complicate access to these therapies [6]. Given the severity of the side effects associated with CAR-T cell therapy, ensuring that patients are treated in centers that are prepared to recognize and treat these side effects is a prudent strategy to minimize harm to patients. The downside of this approach, however, at least initially, is that these therapies will only be available at a limited number of facilities and some patients will need to travel long distances to access the therapy. This is further complicated by the requirement that patients remain close to the site of treatment for at least four weeks after treatment. For patients who live more than two hours from the nearest site that administers the CAR-T cell therapy, this requirement, although important for patient safety, imposes another burden and may limit access.

The high costs and limited number of sites authorized to administer these novel treatments may be unavoidable, at least initially, but both

firms and regulators should keep access considerations in mind. They should strive, whenever possible, to reduce barriers to access and make it as easy as possible for patients to safely receive these promising therapies.

POST-MARKET CHALLENGE: TRANSITIONING TOWARD FRONT-LINE CARE

The initial CAR-T cell therapies were approved for last-resort patients with few, if any, remaining options, and life expectancies that were measured in days to months rather than years. Even in these populations, the high toxicities and side effects associated with CAR-T cell therapies are problematic. Anytime participation in a clinical trial leads to a patient dying sooner than if they had not participated, it is tragic. Yet it is not necessarily unethical to place research participants at such risk. Assuming that the trials were designed to maximize benefits and minimize risks and that patients were fully informed of the risks and the uncertainties associated with participating, these trials likely complied with relevant ethical norms. And, indeed, one can understand why an individual patient suffering from an untreatable cancer may well decide the potential benefit of CAR-T cell therapy is worth bearing the substantial risks.

This calculation will change, however, as CAR-T cell therapies are examined in patients with earlier-stage cancers and a wider variety of therapeutic options. This will be the case for many individuals making their own risk-benefit calculations. Importantly, it will also be the case from broader social perspective. Indeed, while adverse events, including the patient deaths in CAR-T cell clinical trials, have shaken the field, their impact has been mitigated to some extent because the research participants were very sick and had not responded to or relapsed following prior treatments. One need only look to the history of gene therapy, however, to see the potential risks – including loss of investor and regulator confidence – to the broader field posed by serious side effects (including deaths) among healthier patients with a wide array of treatment options [43].

Despite these risks, leading scientists are already discussing moving CAR-T cell therapy from a treatment of last resort closer to the therapeutic front lines (e.g., [44]) and clinical trials are starting to evaluate CAR-T cell therapies as first- or second-line treatments [45]. More generally, the financial interest and pressures in the field certainly suggest an expectation that CAR-T cell therapy will move fairly rapidly from its initial last resort indications to larger markets. Such a move may be necessary if CAR-T cells are to reach their full potential. However, scientists and firms should move slowly in this regard. From a societal perspective, it would be preferable for the use of CAR-T cell therapy to expand slowly but steadily, giving scientists and clinicians time to better predict and manage the associated side effects, than for the field to race forward and risk a series of adverse events that could jeopardize confidence in this still nascent technology and potentially set back the field for many years.

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A POTENTIAL PATH FORWARD

It is an exciting time for CAR-T cell therapy. The two approvals to date have validated the technology and opened the door for engineered cell therapies to emerge as a new paradigm in cancer care. Yet the future of the field is far from assured and a range of possible outcomes can be envisioned. A low projection might be for CAR-T cell therapy to remain a therapy of last resort for a handful for blood cancers with expansion beyond these indications hampered by persistent toxicities, high cost, and complicated manufacturing and business models. Even in this case, CAR-T cells would be an important advancement making a difference in the lives of many patients with few other options. With improvements in the safety profile of CAR-T cell therapy, more positive scenarios are possible. One could envision CAR-T cells moving from last resort to an earlier stage for multiple forms of leukemia and lymphoma, perhaps truly revolutionizing the treatment of blood cancer. Beyond this, the potential exists for CAR-T cell therapy to make inroads into the treatment of some solid tumors, potentially expanding the market and the health impact of this technology substantially. For a variety for reasons, tackling solid tumors with CAR-T cell technology is likely to prove challenging but improving CAR-T cell technology to address these challenges is a major focus in the field today and progress in this regard is certainly possible.

A variety of factors will shape the path forward for CAR-T cell therapy. Certainly advances in the science and technology of CAR-T cells, including an improved ability to predict, manage and ultimately avoid some of the key toxicities will be critical. Proactively addressing the ethical considerations affecting the field is also important to the field's long-term success. In too many cases, ethical concerns have been sidelined in the rush to bring new therapies to market. This risk exists for CAR-T cell therapy as well, but it is not inevitable. CAR-T cell therapy stakeholders, whether in academia, industry or other sectors would be well advised to consider and address to the extent possible the ethical challenges that arise during CAR-T cell therapy development. Doing so offers the potential both to avoid pitfalls that might hinder the development of the field and to shape the development of this promising and innovative technology in a manner that favors safe use and widespread access.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The authors have no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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