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## Approved CAR T cell therapies: ice bucket challenges on glaring safety risks and long-term impacts

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Two autologous chimeric antigen receptor (CAR) T cell therapies (Kymriah<sup>TM</sup> and Yescarta<sup>TM</sup>) were recently approved by the FDA. Kymriah<sup>TM</sup> is for the treatment of pediatric patients and young adults with refractory or relapse (R/R) B cell precursor acute lymphoblastic leukemia and Yescarta<sup>TM</sup> is for the treatment of adult patients with R/R large B cell lymphoma. In common, both are CD19-specific CAR T cell therapies lysing CD19-positive targets. Their dramatic efficacy in the short term has been highlighted by many media reports. By contrast, their glaring safety gaps behind the miracles remain much less addressed. Here, we focus on addressing the crucial challenges in relation to the gaps.

### Introduction

Two chimeric antigen receptor (CAR) T cell therapies (Kymriah<sup>TM</sup> and Yescarta<sup>TM</sup>) were recently approved by the FDA [1,2]. Kymriah<sup>TM</sup> (tisagenlecleucel) is for the treatment of pediatric patients and young adults with refractory or relapse (R/R) B cell precursor acute lymphoblastic leukemia (ALL), whereas Yescarta<sup>TM</sup> (axicabtagene ciloleucel) is for the treatment of adult patients with R/R large B cell lymphoma. They are both genetically modified autologous T cells expressing a CD19-specific CAR, lysing CD19-positive targets (normal and malignant B lineage cells). A noted difference is shown in the vectors used for Kymriah<sup>TM</sup> (lentiviral vector) and Yescarta<sup>TM</sup> (γ-retroviral vector) [3]. The overall response rate (ORR) in the short term was very high (83%), solely based on a single infusion of Kymriah<sup>TM</sup> [1], where leukemia could not be cured by any other means,

and patients went into remission within 3 months of being treated with Kymriah<sup>TM</sup>. The recipients of Yescarta<sup>TM</sup> had 72% ORR [2]. Obviously, there is no doubt about the lifesaving potential of the treatments in these hopeless cases. Numerous media reports have dramatically highlighted the lifesaving potential of Kymriah<sup>TM</sup> and Yescarta<sup>TM</sup>, and they have been coined as ‘living drugs’.

Indeed, this is a history-rewriting progress in cancer medicine and a quintessentially modern paradigm of clinical oncology, which not only gives hope but also directly drives innovative cancer science to patient care and leads to a paradigm shift from protocol-based treatment to real-time personalized therapy unprecedentedly. However, in the real world, even though a drug has a greater potency or a medical technology provides dramatic benefits, distinct and even serious adverse health risks

can be associated either predictably or unpredictably [4]. It has been evident that many types of anticancer drugs or modalities including those modern ones with ‘breakthrough designation’ have induced life-threatening complications (e.g. cardiotoxicity) [5]. Kymriah<sup>TM</sup> and Yescarta<sup>TM</sup> remain therefore not only with serious patient safety events already noted in the short term but also with their long-term impacts (efficacy and safety) lacking. As all the stakeholders strive to understand the great successes, in the meantime, we should keep in mind the real-time challenges and realize gaps in the dramatic efficacy versus glaring safety concerns. Here, we analyze the crucial challenges regarding the gaps impacting quality-of-life (QOL) with the therapies, and provoke intensive debates especially regarding these potentially long-simmering problems that have not yet been fully explored.

## Efficacy versus resistance of Kymriah™ and Yescarta™

Overall, the efficacy versus toxicity and safety of a treatment manifests as short- and long-term effects. Despite the excellent clinical responses of the R/R B ALL patients to Kymriah™ [1] and R/R large B cell lymphoma patients to Yescarta™ [2], a significant number of patients treated by Kymriah™ have relapsed months later [6,7], and nearly 30% of patients had a partial response treated by Yescarta™ and the therapeutic effects tended to wane by the 6-month mark in many [8]. Thus, it remains unknown as to how long the benefits of Kymriah™ and Yescarta™ might last (i.e. there are concerns about long-term efficacy). Clinical relapse suggests that cancer cells develop resistance to the destruction unleashed by the cytotoxic T lymphocytes [9]. Many biological and biochemical factors could potentially impact the efficacy and safety of Kymriah™ and Yescarta™ (Table 1). However, the definite causes underlying the immune resistance or partial response are not fully understood. Some important factors possibly accounting for the efficacy, resistance or inefficiency are formulated here.

### Challenges in synthetic immunobiology

Expansion and persistence of the CAR-modified T cells in the body are linked to many factors (Table 1). Any of these factors could collectively or individually influence the response in the patients treated by Kymriah™ and Yescarta™ [7,10–20].

### Formulation of T cell subsets

Each T cell subset has a unique cytokine profile, functional properties and presumed roles in pathogenesis [21] and holds a specific role in protective immunity [22]. Functionally, T cells can be identified as either beneficial tumor-specific T cells or deleterious counterparts [22]. Thus, controlling the T cell subsets with favorable function compositions of a CAR T cell product is one of the most important aspects for manufacturing more-effective clinical T cell products [10,22]. The strategy holds the potential to reduce product variability, improves the consistency of *in vivo* proliferation and provides reproducible potency [11,15,19,22,23]. Moreover, T cell maturation status is important as well, and it was found that less differentiated, stem-cell-like T cells possess greater therapeutic efficacy [24,25].

### Immunosuppressive tumor microenvironment

The immune system has a double-edged role, being involved in suppressing tumor growth by

destroying cancer cells and shaping the immunogenic phenotypes of tumors to promote tumor progression by escaping immunosurveillance [9,26]. These inhibitory and immunosuppressive stimuli can impede the function of CAR T cells [27] and ‘armored CARs’ could improve T cell function [28].

### CD19<sup>-</sup> variants (antigen-loss relapses)

CD19<sup>-</sup> ALL variants are being recognized with increasing frequency, rendering the CAR T cells ineffective against B cell tumors and thus representing a barrier to progress in CD19-directed immunotherapy [29,30]. Several novel mechanisms associated with CD19<sup>-</sup> ALL variants have been discovered [6,31–33] (e.g. alternative mRNA splicing, CD19 gene deletion or mutation, CD19-negative clonal evolution, induction of a myeloid switch). Allogeneic stem cell transplantation (allo-SCT) and co-targeting of multiple markers on leukemic cells could be the possible solutions [6]. But tumor-specific antigens are rare, and thus multiple targeting potentially increases off-tumor, on-target toxicities [5] including neoreactivities (allo-HLA and autoreactive activity) induced by mixed T cell receptor (TCR) dimers [34].

### CAR protein and RNA downregulation

CAR expression is decreased upon repeated stimulations [24,35,36] or when there is accelerated differentiation and exhaustion of the T cells [24,36]. These problems pose additional challenges of CAR in CAR T cell therapy. A possible solution for the problem is to direct a CD19-specific CAR to the TCR  $\alpha$  constant (TRAC) locus by CRISPR/Cas9 genome editing [35], which potentially yields some benefits (e.g. decreased T cell differentiation and exhaustion [22,37,38], minimizing the risks of insertional oncogenesis and TCR-induced autoimmunity and alloreactivity [35]).

### High dose of corticosteroids

It is unclear whether tocilizumab has any beneficial effects on neurotoxicities [39], because its size makes efficient blood–brain barrier (BBB) penetration unlikely [33,40]. Thus, the first-line agent to treat severe neurotoxicities is often with systemic corticosteroids rather than tocilizumab [33,39]. However, prolonged use of high-dose corticosteroids results in ablation of the CART cell population [20,41]. Moreover, inappropriate use of glucocorticoids is associated with risk for early relapse of primary disease [41].

### Extramedullary disease

The central nervous system (CNS) is a well-recognized reservoir wherein leukemia can escape

systemic cytotoxic therapy [42]. The CNS compartment is affected in roughly one-third of ALL relapses [43,44], whereas CNS involvement at relapse occurs mainly in patients who were CNS-negative at initial diagnosis [44,45]. Intriguingly, CD19 CAR T cells have been identified in the cerebrospinal fluid (CSF) of patients after infusion [46–48], even though many of the patients (80%) did not have a history of CNS leukemia [49], suggesting the ability of these cells to cross the BBB [47,50]. Thus, the therapy might be considered to replace multiple doses of either prophylactic or therapeutic, intrathecal chemotherapy and radiation in leukemia patients. Theoretically, the replacement could reduce cognitive impairment and developmental delay resulting from chemotherapy and radiation in the patient population, because ALL is most commonly diagnosed in children under 8 years of age, a crucial time in brain development [51]. However, a contradictory event in parallel consideration is neurotoxicity – one of the major complications of Kymriah™ and Yescarta™. As a result, caution should always be taken when considering the replacement. Furthermore, detection of CD19 expression in the brain parenchyma remains controversial [25], and thus the capacity for clearance of Extramedullary disease (EMD) by the therapy remains uncertain [22] and further research in this area is warranted.

### Common toxicities of Kymriah™, Yescarta™ and beyond

Given the extreme potency of the CAR-modified T cells and similar mode of action, the use of Kymriah™ and Yescarta™ harbors common fatal toxic potentials that can be as bad as or worse than the original condition and even lethal [1,2,10]. Some higher rates of serious adverse events manifested in acute or subacute forms have been demonstrated as immediately life-threatening [1,2,10] (Table 2). Because the cellular immune system has been artificially boosted for an enhanced activation, Kymriah™ and Yescarta™ act like ‘immuno-bombs’, reminiscent of the atomic bombing in Hiroshima and Nagasaki in 1945, and the immuno-bombs drop into the circulation system of the human body to nonspecifically destroy cancer cells and their innocent counterparts. Effective prevention of these acute and subacute toxicities (e.g. CRS: Cytokine-release syndrome and NT: neurotoxicity) remains unfeasible, because either the mechanisms of these toxicities remain poorly understood (e.g. NT) [22] or CAR T products have endogenously inherited features (e.g. CRS). To date, palliative supportive care (PSC) and immunosuppression remain the only approaches

TABLE 1

## Potential biological and biochemical factors impacting the efficacy and safety of Kymriah™ and Yescarta™

Potential factors	Potential mechanisms or causes	Major possible effects	Possible solutions and remarks	Refs
<b>Number of the transduced T cells</b>	Transduction efficiency	Impact the reproducible potency	Control vector copy and CAR expression	[7,20]
<b>Cell lineage and differentiation state</b>	Component variability of the product	Impact the reproducible potency	Improve production method	
[7,11,15,20,28,38]				
<b>Cell viability</b>	Nonviable cells	Impact the efficacy and safety profile	Improve production method	[7,10]
<b>Cellular impurities</b>	Non T cells (B lineage cells, blasts and others)	Impact the efficacy and safety profile	Improve production method	[7,10]
<b>Excipients (DMSO, dextran 40)</b>	Anaphylaxis	Impact the safety profile	Improve production method	[1,7,10]
<b>Manufacturing failures</b>	Poor starting autologous leukapheresis cells	Jeopardize disease control and survival	Use universal CAR19 T cells	[7,10,18]
<b>Specificity of the scFv domain</b>	Determinant for the CAR T cell safety profile	Off-target activity and B cell aplasia	Use therapeutic immunoglobulin, anti-Fc $\mu$ R CAR T, RNA CARs	[7,14,20]
<b>Affinity of scFv binding</b>	CAR T cell activation and effector functions	Impact the safety and activity	Not restricted by MHC (applicable to any MHC haplotype)	[7]
<b>Functional T cell subsets and ratios</b>	Component variability of the product	Impact the reproducible potency	Improve production method	
[7,11,20,22]				
<b>IFN-<math>\gamma</math> production</b>	A prerequisite for CAR T cell activity	An indicator of T cell activation	<i>In vitro</i> data may not correlate to <i>in vivo</i> efficacy, technical advances	[7]
<b>CAR signaling domains and spacer variants</b>	Off-target T cell activation	Impact the safety and activity (CD19-independent toxicities)	Biological optimization	
[7,12,13,16,17,20]				
<b>Decreased CAR expression</b>	Repeated stimulations, accelerated diff/ex	Reduced efficacy	TRAC-CAR to decrease differentiation of T cells, other approaches	[24,35,36]
<b>T cell dose versus tumor burden</b>	An inverse correlation	Impact the expansion and persistence	Bridging therapy to reduce tumor burden before Kymriah™	[11,28]
<b>Immunosuppressive environment</b>	Inhibitory and immunosuppressive stimuli	Impede the function of CAR T cells	'Armored' CAR T cells to enhance IS, risk of cumulative toxicities	[22,30]
<b>CD19-negative variants</b>	CD19 del/mut, CD19 <sup>-</sup> clonal evolution, lineage switch	Inefficacy	Target multiple antigens, allo-HSCT, risk of cumulative toxicities	[23,30–34,55]
<b>Anti-mCAR19 antibodies</b>	Immunogenicity	Immunity anaphylaxis, impact the efficacy and safety profile	Use human anti-CD19 CAR (HuCAR-19)	[1,7]
<b>Extramedullary disease (EMD)</b>	Sanctuary site relapse (e.g. CNS)	Uncertain capacity for clearance of EMD	Further studies for confirmation	[22,25]
<b>Lymphodepletion chemotherapy</b>	Conditioning regimen to reduce tumor burden	Augment the antitumor effects	Risk of cumulative toxicities	[7,11,28]
<b>High dose of corticosteroids</b>	Impede CAR T cell function	Diminished efficacy owing to immunosuppression	Tocilizumab, uncertain effects for neurotoxicities	[20]

Abbreviations: IS, immune system; DMSO, dimethyl sulfoxide; MHC, major histocompatibility complex; IFN- $\gamma$ , interferon gamma; TRAC, T cell receptor  $\alpha$  constant locus; diff, differentiation; ex, exhaustion; del, deletion; mut, mutation; scFv, single-chain variable fragment; allo-HSCT, allogeneic stem cell transplantation; CNS, central nervous system.

**TABLE 2**  
**Common acute and subacute toxicities (incidences >50%, 20%, 10% and 2%) and long-term risks of Kymriah™ and Yescarta™**

Toxicities (T) and risks (R)	Category	≥50%	≥20%	≥10%	≥2%	Clinical form	Potential mechanisms/ causes	Management strategies and comments	Refs
<b>CRS</b>	T	+				Short term	Activated T cells produce high levels of cytokines	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Neurotoxicities</b>	T	+				Short term	Unknown	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Serious infection</b>	T	+				Short term	Acquired		
hypogammaglobulinemia	Familiar with FDA labels, REMS and ETASU	[1,2,7]							
<b>Prolonged cytopenias</b>	T		+			Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Acquired hypogammaglobulinemia</b>	T		+			Short term	On-target off-tumor toxicities (B cell aplasia)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Humoral immunogenicity</b>	T		+			Short term	Anti-mCAR19 antibodies	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Tachycardia</b>	T			+		Short term	Miscellaneous cause (e.g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Gastrointestinal disorders</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Acute kidney injury</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Acute respiratory distress</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Musculoskeletal disorders</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Hypotension</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Hypertension</b>	T			+		Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Cardiac failure or arrest</b>	T				+	Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>TLS</b>	T				+	Short term	Large amounts of tumor cells lysed	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>DIC</b>	T				+	Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>MAS</b>	T				+	Short term	Uncontrolled activation of macrophages and T cells	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Capillary leak syndrome (bleeding)</b>	T				+	Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]

TABLE 2 (Continued)

Toxicities (T) and risks (R)	Category	≥50%	≥20%	≥10%	≥2%	Clinical form	Potential mechanisms/causes	Management strategies and comments	Refs
<b>Coagulopathy</b>	T				+	Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>Hypofibrinogenemia</b>	T				+	Short term	Miscellaneous causes (e. g. CRS)	Familiar with FDA labels, REMS and ETASU	[1,2,7]
<b>GVHD</b>	R				1%	Undefined	Residual donor lymphocytes from prior HSCT	Warning and intensive monitoring	[7]
<b>Anaphylaxis</b>	R					Undefined	Excipients (e.g. DMSO, dextran)	Warning and intensive monitoring	[1,2,7]
<b>Secondary malignancies</b>	R					Long term	Insertional oncogenesis and genotoxicity	Warning and lifelong monitoring	[1,2,7]
<b>Developmental and reproductive toxicity</b>	R					Long term	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warning and lifelong monitoring	[1,2,7]
<b>New incidence of neurologic disorders</b>	R					Long term	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warning and lifelong monitoring	[1,2,7]
<b>Exacerbation of pre-existing neurologic disorders</b>	R					Long term	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warning and lifelong monitoring	[1,2,7]
<b>New incidence of autoimmune disorders</b>	R					Long term	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warning and lifelong monitoring	[1,2,7]
<b>Exacerbation of prior autoimmune disorders</b>	R					Long term	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warning and lifelong monitoring	[1,2,7]
<b>Incidence and outcome of any pregnancy</b>	R					Undefined	Miscellaneous causes (e. g. DAMPs, prolonged CRS)	Warnings and monitoring during the pregnancy	[1,2,7]

*Abbreviations:* CRS, cytokine release syndrome; TLS, tumor lysis syndrome; DIC, disseminated intravascular coagulation; MAS, macrophage activation syndrome; GVHD, graft-versus-host disease; DAMPs, damage-associated molecular patterns; HSCT, hematopoietic stem cell transplantation; REMS, Risk Evaluation and Mitigation Strategy; ETASU, Elements to Assure Safe Use.



for treating these common complications [1,2], even considering the latest new guidelines [52]. Recently, a human study explored the mechanism of NT and suggested that an increased BBB permeability might explain NT [53]. The study could lead to further studies for development of novel treatment on the basis of mechanisms. B cell aplasia (acquired hypogammaglobulinemia) is an on-target off-tumor toxicity for CD19-targeted CAR [1,2] (i.e. a specific toxicity of CD19 CAR T) because CD19 is a cell-surface component of B cell lineage [3]. There are several possible solutions to potentially overcoming or minimizing B cell aplasia: (i) use of anti-Fc $\mu$ R CAR T [14]; (ii) use of RNA CARs [20]; (iii) infusion of pooled immunoglobulins [1,2]. Beyond this, additive side-effects (secondary or tertiary toxicities) derived from combining or bridging agents should not be overlooked (e.g. tocilizumab with an FDA warning and precaution labels [54], ibrutinib to prevent CRS after using anti-CD19 CART [55] with known cardiac concerns [5] and other serious complications [56,57]). Furthermore, the use of host lymphodepletion chemotherapy with immunosuppressive agents (e.g. cyclophosphamide) before a CAR T approach is a required step to augment the anti-tumor effects of this treatment [1,2,5,7]. However, such concomitant therapies can lead to clinical cardiotoxicity [5]. Consequently, these combining or bridging agents might increase some cumulative or synergistic toxicities for the patients.

### Uncertain long-term outcomes of Kymriah™ and Yescarta™

Data were fast-emerging on the early responses to Kymriah™ and Yescarta™, thus most of the patients participating in the trials have only been followed for a relatively short period of time [1,2], limiting the ability to assess the risk of long-term adverse events and rule them out. As a result, long-term sequelae and late toxic effects of Kymriah™ and Yescarta™ remain unknown although some are theoretically predictable (Table 2). Theoretically, the aftermath of the immuno-bombing in the human body can be just as deadly and far-reaching, because these cellular and molecular fallout from these damaged leukemia cells and their normal counterparts in the blood circulation reach as far as any systemic organs. Such damage to normal cells and tissues might be long-term and probably permanently toxic [7,58]. This is in-line with the rationale that the immune system not only responds to foreign substances (i.e. pathogens) but also responds to endogenously derived molecules that are

expressed as a result of tissue damage or stressed cells, known as damage-associated molecular patterns (DAMPs) [59], which can cause various diseases (e.g. autoimmune diseases) [60,61]. Further, late onset of NT is another concern for cognitive dysfunction. Little is known about timing of the secondary and/or tertiary toxicities resulting from DAMPs. Referring to the pathogenesis and long-term course of many autoimmune diseases and neurocognitive disorders, a chronic, progressive disease process should be anticipated. Given the extreme importance to the young patient population uniquely targeted by Kymriah™, it is worth knowing that classical genotoxicity assays and carcinogenicity assessment *in vivo* (rodent models) were not performed for Kymriah™ [7,10]. Developmental and reproductive toxicity studies were not conducted in the nonclinical studies for Kymriah™ either [7,10]. Thus, detection of long-term problems as such will not only be dependent on a long-term follow-up but also enhanced clinical awareness and sensitive detection algorithms are required for a goal-oriented evaluation. Taken together, the safety profiles and the toxic potential of Kymriah™ and Yescarta™ cannot be assessed in isolation for short-term monitoring and management but need to be considered together with a long-term follow-up.

### Lifesaving versus QOL-preserving of Kymriah™ and Yescarta™

Immune-cell-based therapies open a new frontier for cancer treatments. But the changing landscape of medical benefits and risks creates new challenges for all the stakeholders in healthcare owing to potentially lethal side effects of the therapies and uncertain long-term impacts on QOL. Currently, because the data about the long-term impacts of Kymriah™ and Yescarta™ are not available yet, there is insufficient voice to claim much more benefits than medically acknowledged, instead of being increasingly aware of the short- and long-term risks [58]. Media reports often state disproportionately on risk by overstating benefits while understating the harms [4,58]. Nevertheless, the FDA plays a central part as an authoritative voice in communicating the benefits and risks of a drug [4]. It is important for all the stakeholders to become familiar with the FDA labels containing a Risk Evaluation and Mitigation Strategy (REMS) and an Elements to Assure Safe Use (ETASU) [1,2,7,10]. Lifesaving care and preserving patient QOL are the tasks of modern medicine, being especially important for the patient populations of children and young adults. As more infor-

mation about treatment options becomes available, patients, physicians, regulators and payers are reassessing how they balance the possible benefits and risks of therapeutic options [4]. Theoretically, no patients expect any treatment of procedure that is disproportionately costly, burdensome or painful [62]. However, practically, when doctors treat patients with life-threatening conditions (e.g. lethal cancers), the major focus would often be quickly directed toward instituting therapeutic measures to preserve life (lifesaving), and often they are unable to address the impact of medical care on QOL until after the lifesaving intervention [63]. Kymriah™ and Yescarta™ were regarded as a lifesaving treatment (a last-resort treatment) [1,2] and fall within the scope of a formal debate in this regard. Ironically, where advances in technology and knowledge have given doctors an increased capacity to preserve and prolong life, some fundamental ethical questions could be raised in parallel: should doctors be concerned only with curing disease (lifesaving)? Do they have a responsibility to give the patients the best possible QOL while being physically or fiscally reasonable [63]? These ethical dilemmas might have to be addressed at the clinic door that impacts individual patients by a participative management involving patients, doctors and other stakeholders. In this context, an ethical imperative requires classification of the medical significance of an intervention especially when the intervention remains controversial and underexamined, which will benefit from decreasing the uncertainty associated with the intervention.

### Concluding remarks and future perspectives

Kymriah™ and Yescarta™ gained ground as last-resort treatments for R/R pediatric ALL and R/R adult B cell lymphoma, respectively, owing to their lifesaving potentials. The broad applications remain challenging because of acute lethal toxicities and also uncertain long-term impacts. Post-approval pharmacovigilance is crucial as one of the first considerations for risk mitigation of these known short-term toxicities. Long-term follow-up for durable efficacy and safety concerns is pending further progress. Furthermore, advances in manufacturing processes could reveal the better version of T-cell-based therapies, even beyond cancer therapy, to extrapolate the approach to treatment of infectious and autoimmune diseases. To this end, all efforts should be channeled into turning the ice bucket challenges into solutions and opportunities.

## Conflicts of interest

The authors have no conflicts of interest to declare

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P.P.Z. conceived the ideas, organized the study and drafted the manuscript. All the authors reviewed and approved the submission.

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