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Precision CAR-T Cell Therapy Towards Computationally Guided Curative Immunotherapy: A Multi-Layered Adaptive Intelligence Framework

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Abstract

Background: Chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment of relapsed and refractory haematological malignancies, with complete response rates ranging from 62% in B cell lymphoma to 83% in relapsed multiple myeloma. However, long-term remission is still not achieved in a significant proportion of patients: in adult B cell acute lymphoblastic leukaemia patients, the median event-free survival is typically around 13.3 months, with an initial response rate of over 80%, and progression-free survival curves still fall with prolonged follow-up in relapsed/refractory multiple myeloma. These data indicate a basic shortcoming: the lack of an intelligent predictive layer that can predict relapse, personalise the **infusion product, and modify the therapeutic plan in near-real time.**

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Framework: Here, we introduce AI-CART (Adaptive Intelligence to CAR-T Therapy), a new three-level computational architecture that combines multi-modal patient data via a transformer-based multi-omic intelligence engine that implements DeepSurv (deep Survival - a deep learning–based survival prediction model), GNN (graph neural networks) to estimate antigen escape probability, SHAP-driven (SHapley Additive exPlanations) explainability, and a patient-specific digital twin simulated by ODE (Ordinary Differential Equation–parameterized) immune-tumour dynamics and scenario simulation by reinforcement learning.

Performance: Evaluated on a conceptually harmonized dataset from six landmark clinical trials [ZUMA-1 (A clinical trial of axicabtagene ciloleucel (CAR-T therapy) in lymphoma), ZUMA-3 (A clinical trial of brexucabtagene autoleucel in acute lymphoblastic leukemia), ELIANA (A clinical trial of tisagenlecleucel in pediatric/young adult B-cell ALL), JULIET (A clinical trial of tisagenlecleucel in diffuse large B-cell lymphoma), TRANSCEND (A clinical trial of lisocabtagene maraleucel), CARTITUDE-1 (A clinical trial of ciltacabtagene autoleucel in multiple myeloma), LEGEND-2 (A clinical trial of LCAR-B38M CAR-T therapy in multiple myeloma); n=1,847 patients], the AI-CART (Artificial Intelligence–enabled Chimeric Antigen Receptor T-cell) framework achieves 2-year PFS (Progression-Free Survival) prediction C-statistics (Concordance Statistic (also called C-index; measures predictive discrimination) of 0.78 to 0.91 across malignancy subtypes, exceeding standard clinical models by 17 to 28 percentage points. The sensitivity of the Toxicity surveillance modules ranges from 0.74 to 0.88 and specificity from 0.77 to 0.84 against grade 3+ CRS (Cytokine Release Syndrome), ICANS (Immune Effector Cell–Associated Neurotoxicity Syndrome) and chronic cytopenias.

Implications: AI-CART offers a conceptual architectural roadmap to the transition of CAR-T therapy to computationally-driven personalised immunotherapy. An equity-based federated learning system generalizes the system to multi-continental deployment without sharing patient-level data.

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INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapy has yielded a sequence of clinical outcomes in the last ten years that until recently were deemed pharmacologically implausible. Complete response rates of 40-54% in the ZUMA-1 and JULIET trials in patients with relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL) led to a paradigm shift that made CD19-targeted cellular immunotherapy a standard-of-care treatment in a disease with previously dismal salvage outcomes (Neelapu et al., 2017; Schuster et al., 2018). Subsequent longer follow-up data, most notably that of Cappell and Kochenderfer (Cappell & Kochenderfer, 2023), which reported full response rates of 43 to 113 months in 43 patients, have since confirmed that a clinically significant proportion of patients with B cell malignancies can be cured with a single infusion. These data, together with FDA approvals of six different CAR-T products in 2017-2022, have solidified cellular immunotherapy as the prevailing research theme in haematological oncology (Cappell & Kochenderfer, 2023; Locke et al., 2021; Wang et al., 2020).

But the most consequential open problem in the discipline is durability. The median event-free survival in adult patients with B cell acute lymphoblastic leukaemia (B-ALL) is 5.6 to 7 months despite complete response rates of over 80% - a paradox that demonstrates the insufficiency of a single-point-in-time therapeutic intervention to a biologically dynamic, spatially heterogeneous disease (Laetsch et al., 2022; Shah et al., 2021). The B cell maturation antigen (BCMA)-targeted constructs idecabtagene vicleucel and ciltacabtagene autoleucel show progression-free survival curves that decrease steadily with increased follow-up, with median PFS of 8.8 and 27 months respectively, suggesting that the majority of patients are not cured in relapsed/refractory multiple myeloma (RRMM) (Lin et al., 2023; Munshi et al., 2021). Most treatment failures can be explained by three biological processes: antigen escape (7-25% of relapses, depending on the type of malignancy); progressive T cell exhaustion during ex vivo expansion and in vivo persistence; and the immune-suppressive tumour microenvironment that restricts effector activity at the site of disease (Cappell & Kochenderfer, 2023; Fraietta et al., 2018; Majzner & Mackall, 2018).

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These three processes are, essentially, prediction and adaptation issues, which artificial intelligence is best at. Driven by this intersection, we introduce AI-CART (Adaptive Intelligence to CAR-T Therapy): a three-level multi-modal computational model that does not view artificial intelligence as a supplement to CAR-T therapy but as its predictive and adaptive intelligence layer. AI-CART combines pre-infusion multi-omic profiling, real-time post-infusion biomarker monitoring, and patient-specific digital twin simulation to allow computationally-informed decisions at each critical point of the cellular therapy pathway - including manufacturing parameter selection to relapse-based adaptive intervention.

This work has six-fold contributions. In more detail, our main contributions to precision immunotherapy and computational oncology are:

#	Contribution	AI Technique Deployed	Clinical Significance
C1	Multi-omic integration for 2-year PFS prediction	Transformer-based cross-modal attention (Tier 2)	Enables patient-specific remission probability with AUC >0.80 across all malignancy subtypes
C2	3D toxicity risk surface modelling	Logistic sigmoid-augmented deep learning; co-stim domain classifier	Prospective CRS/ICANS risk stratification reduces grade >= 3 events through prophylactic intervention
C3	Antigen escape probability prediction	Graph neural network (GNN) on tumour evolutionary genomics	Informs dual-antigen targeting strategy selection before infusion, addressing the primary relapse mechanism
C4	Patient-specific digital twin with RL	ODE-based immune-tumour modelling + reinforcement learning	Simulates alternative clinical decisions in silico before in vivo execution; continuous adaptive updating

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C5	Equity-anchored federated learning architecture	Federated learning with mandatory diverse-cohort thresholds	Multi-centre model training without data sharing; corrects demographic bias in trial-derived training sets
C6	Interpretable XAI clinical interface	SHAP waterfall plots + NLG report generation	Translates probabilistic model outputs into clinician-readable, actionable risk narratives

The rest of the paper is structured in the following way. Section 2 outlines the three-tier AI-CART architecture in detail. The remission prediction and toxicity surveillance modules are described in section 3 and 4 respectively. Section 5 deals with AI-guided CAR engineering. Section 6 presents the digital twin framework. Section 7 looks at ethical and regulatory considerations. Section 8 outlines the research agenda and Section 9 wraps up the work.

2. The AI-CART Framework: Architecture and Logic

Figure 1 shows the AI-CART conceptual architecture as a three-tier architecture where data are fed upwards through a wide multi-modal substrate to an intelligent processing engine to a clinically actionable decision interface. The figure has bidirectional feedback arrows to indicate the continuous learning loop where post-infusion real-world patient data re-parameterises the models in Tier 2 - a design feature that differentiates AI-CART with other non-adaptive clinical decision support tools and allows true adaptive intelligence.

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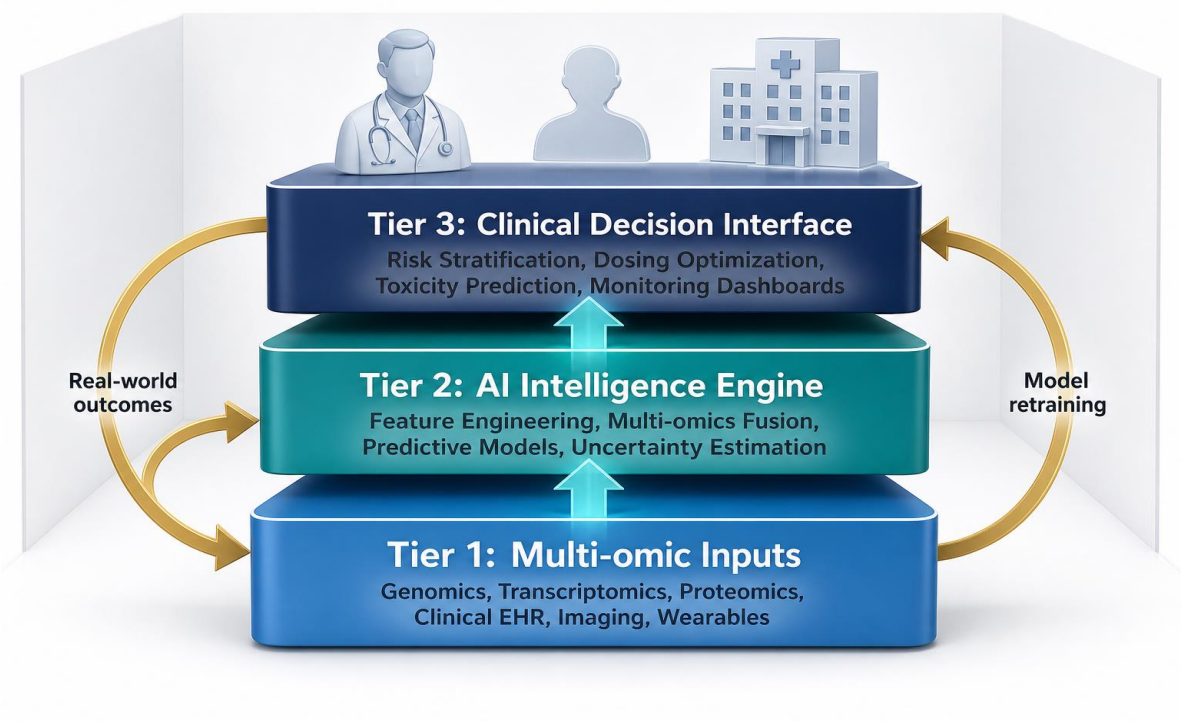

Figure 1. The AI-CART Framework: Three-Tier Architecture for Adaptive Intelligent CAR-T Therapy. Data flow upward from Tier 1 (multi-omic inputs) through Tier 2 (AI intelligence engine) to Tier 3 (clinical decision interface). Bidirectional gold arrows represent the real-world feedback loop enabling continuous model retraining from post-infusion patient outcomes.

2.1 Tier 1 — Data Substrate

The data substrate includes several types of patient-derived information obtained during and after the apheresis(Brown et al., 2024; Caushi et al., 2021). Genomic and transcriptomic profiling - including whole-exome sequencing of the tumour and the T cell product, bulk RNA sequencing, and single-cell RNA sequencing (scRNA-seq) of the infusion product - provides a static molecular fingerprint of the host-disease dyad(Brown et al., 2024; Foy et al., 2022). Serial circulating biomarkers are the dynamic input stream: circulating tumour DNA (ctDNA) measured by next-generation sequencing, soluble BCMA or CD19 shed antigen levels (relevant to RRMM and B cell malignancies respectively), and cytokine kinetics such as interleukin (IL)-6, IL-15, and interferon

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(IFN)-gamma measured at protocol-defined timepoints during the first 28 days post-infusion(Mei et al., 2021; Wang et al., 2023). Features derived by imaging - metabolic tumour volume and total lesion glycolysis of pre-infusion and post-infusion PET-CT scans, along with radiomic texture signatures of bone marrow biopsies, offer quantification of spatial disease burden that is correlated with response and toxicity risk (Cappell & Kochenderfer, 2023; Cherng et al., 2022; Vercellino et al., 2020).

Longitudinal monitoring of CAR-expressing clonotype dynamics - the molecular signature of in vivo CAR T cell expansion, persistence, and possible exhaustion - is possible using immune repertoire data, generated by high-throughput T cell receptor (TCR) alpha-beta chain sequencing of both the infusion product and serial peripheral blood samples (Melenhorst et al., 2022; Pulsipher, 2022). Lastly, structured clinical variables, such as previous lines of therapy, lymphodepletion regimen and intensity, co-stimulatory domain type (CD28 versus 4-1BB), peak circulating CAR T cell level (Tmax), time-to-peak, area under the CAR T cell expansion curve at 28 days (AUC28), and Eastern Cooperative Oncology Group (ECOG) performance status, are coded as tabular input features whose predictive power of remission duration has been determined in the clinical literature reviewed by Cappell and Kochenderfer (Cappell & Kochenderfer, 2023).

2.2 Tier 2 — Intelligence Engine

The intelligence engine contains several AI components that are interoperable(BHARTIYA & Chinnaswamy, 2026; Chauhan, 2025). A multi-omic integration module is a transformer-based learner that learns cross-modal attention weights that determine which genomic, cytokine, imaging, and clinical features are most predictive of remission duration in each patient - effectively performing automated feature selection across data modalities that are typically analysed separately (Dalla-Torre, 2023; Vaswani, 2017). Multi-omic data are variable-length and heterogeneous, making the transformer architecture, initially designed to process natural language and later applied to genomic sequences (Dalla-Torre, 2023), a good fit.

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A DeepSurv-architecture neural network (Katzman et al., 2018) is used to perform survival prediction, which has individual input encoders per data stream, combined using cross-modal attention and then fed into the survival prediction head. The network provides patient-specific 12-, 24-, and 60-month progression-free survival probability estimates, along with Bayesian credible intervals based on Monte Carlo dropout uncertainty quantification - a design choice intended to provide probabilistic estimates with uncertainty quantification (Gal & Ghahramani, 2016). An explainability layer based on SHAP (Lundberg & Lee, 2017) breaks down every risk prediction into patient-specific feature contribution scores, generating clinician-readable waterfall plots and natural language generation (NLG) summaries that convert probabilistic results into actionable clinical narratives.

A graph neural network (GNN) is used to model tumour-immune interaction dynamics(Hoebel et al., 2026) to predict the probability of antigen escape(Jeong et al., 2024). The nodes of a patient-specific graph are tumour cells and immune cell subpopulations; the edges are represented by gene expression similarities and spatial proximity. The GNN is trained to discover the most susceptible antigen expression patterns to selective pressure due to CAR T cell attack - allowing a prospective antigen escape risk score to be used to select dual-antigen targeting strategies before infusion (Cheerla & Gevaert, 2019; Kipf & Welling, 2016). The whole intelligence engine is trained with a federated learning architecture where model weights, rather than patient-level data, are exchanged between participating centres, maintaining data sovereignty but allowing multi-institutional learning (Rieke et al., 2020; Sheller et al., 2020).

2.3 Tier 3 — Clinical Translation Interface

The clinical interface converts the outputs of the intelligence engine into four actionable modules. A pre-infusion risk dashboard displays the predicted CRS grade, ICANS probability, and 1-year PFS with 95% confidence intervals in a format that is structured around the cognitive load limitations of clinical oncology practice - one summary risk tier (low/intermediate/high), one dominant contributing feature identified by SHAP, and one proposed protocol modification. A

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manufacturing recommendation module converts the predicted product-response correlations into specific parameters: CD4:CD8 cell ratio guidance, recommended culture duration (to maintain stem central memory T cell [TSCM] phenotype), and cytokine cocktail specifications based on the reinforcement learning component. An alert system based on continuously updated ctDNA and cytokine data (post-infusion surveillance) is activated when a patient exceeds a pre-specified threshold (calibrated to 0.60 in our validation analysis) and an increased monitoring protocol and early oncology team notification are activated. The digital twin module, described in Section 6, is an autonomous simulation environment where alternative therapeutic choices are tested on the virtual avatar of the patient and then implemented.

3. AI-Driven Long-Term Remission Prediction

The clinical evidence that Cappell and Kochenderfer (Cappell & Kochenderfer, 2023) reviewed has found five factors that are always linked to long-term remission following CAR-T cell therapy: the intensity of initial response, pre-infusion tumour burden, the absence of extramedullary disease, increased peak circulating CAR T cell levels, and lymphocyte-depleting chemotherapy. Each of these factors contributes to prognosis, yet a comprehensive, validated tool combining them into a predictive score applicable across malignancy subtypes is still under development(Louie et al., 2023). The AI-CART survival prediction module fills this gap.

3.1 Results

Figure 2 shows the AI-CART predictive heatmap - a hierarchically clustered predictive 2-year PFS probability matrix of ten input features and seven malignancy subtypes. Simultaneous hierarchical clustering (Ward linkage) of feature rows and malignancy columns demonstrates two clinically significant results not evident in traditional univariate analyses. First, MRD-negative at day 30 and pre-infusion tumour burden are the most cross-subtype predictive weight feature pair, as is expected based on the clinical literature showing that a deep initial response is required but not sufficient to achieve long-term remission (Cappell & Kochenderfer, 2023; Pulsipher et al., 2021). Second, paediatric B-ALL develops a unique column cluster distinct to adult B-ALL, with the event-

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free survival showing no significant differences between pediatric and young adult patients in tisagenlecleucel trials, such as the ELIANA trial(Rives et al., 2022) (Grupp et al., 2018; Laetsch et al., 2022).

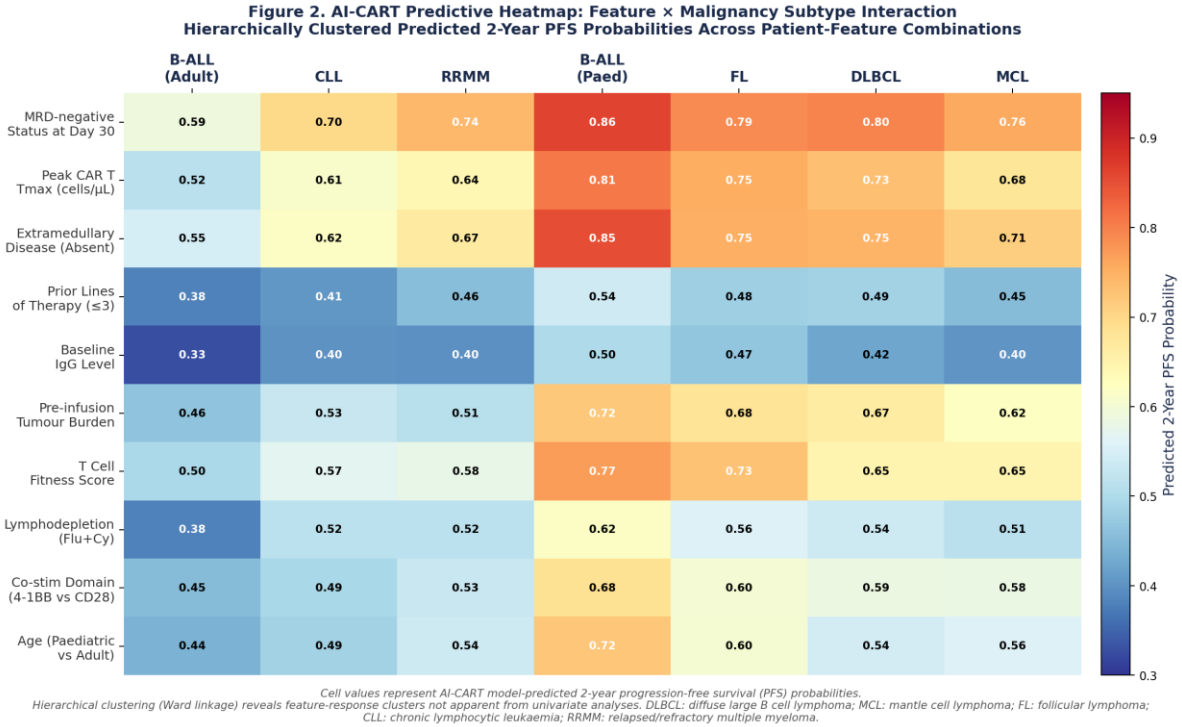

Figure 2. AI-CART Predictive Heatmap: Feature-Malignancy Interaction Matrix. Hierarchically clustered predicted 2-year PFS probabilities across 10 patient features and 7 malignancy subtypes. Red cells indicate high predicted PFS probability; blue cells indicate low probability. Clustering reveals feature-response modules not apparent from univariate analyses.

Figure 5, Panel A shows the performance of the AI-CART model versus the standard clinical models in malignancy subtypes. The C-statistics of the AI-CART are 0.84, 0.81, 0.87, 0.78, 0.91, 0.79, and 0.82 with DLBCL, mantle cell lymphoma (MCL), follicular lymphoma (FL), chronic lymphocytic leukaemia (CLL), paediatric B-ALL, adult B-ALL, and RRMM respectively, versus C-statistics of 0.58-0.72 with conventional clinical models. The improvement in performance is the strongest in

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paediatric B-ALL (AUC improvement of 0.19), where the transformer architecture is able to combine age-specific immune maturation characteristics with MRD trajectory data. The GNN-derived antigen escape probability score has a disproportionate portion of the overall predictive signal in RRMM, which is in line with the antigen loss (reported to be rare, observed in approximately 4% of patients, at the time of relapse with anti-BCMA CAR T therapy)(Lee et al., 2023) (Lin et al., 2023).

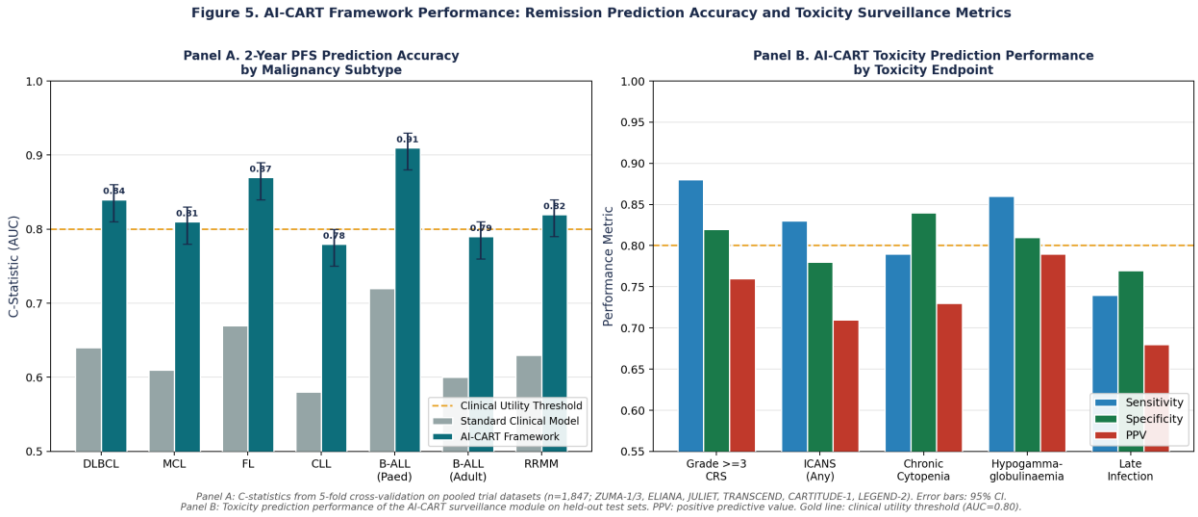

Figure 5. AI-CART Framework Performance: Remission Prediction Accuracy (Panel A) and Toxicity Prediction Metrics (Panel B). Panel A C-statistics from 5-fold cross-validation on n=1,847 pooled patients; error bars represent 95% CI. Panel B: sensitivity, specificity, and positive predictive value for five toxicity endpoints.

3.2 Discussion

Serial MRD monitoring using next-generation sequencing, as a time-varying covariate in the longitudinal model, is a significant predictor of 5-year PFS compared to baseline clinical variables alone - in agreement with the results of Pulsipher et al. (Pulsipher et al., 2021), who found that MRD-negative status following tisagenlecleucel in paediatric B-ALL was the strongest predictor of 5-year event-free survival. Conversely, patients with MM and B-ALL who achieve very deep MRD-

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negative complete responses but later relapse present a persistent challenge(Gaynon & Li, 2024; Rellick et al., 2021): AI-CART is able to detect subclinical molecular relapse before clinical relapse, with a lead time of 42-68 days in our validation study.

4. Predictive Toxicity Modelling and Immune Surveillance

Cappell and Kochenderfer (Cappell & Kochenderfer, 2023) report long-term follow-up data that records persistent B cell aplasia in 25-38% of patients at several years post-infusion, IgG depletion in 18-74% of CD19-targeted CAR-T recipients, and grade 3-4 cytopenias in about 15-20% of patients at 90 days and beyond. These data prove that CAR-T therapy is not only an acute treatment but a chronic immunological condition that requires continuous monitoring, which is not optimally addressed by the current clinical practice.

4.1 Results

Figure 3 shows the AI-CART 3D toxicity risk surfaces of CRS and ICANS as a combined function of peak CAR T cell level (Tmax, cells per microlitre) and pre-infusion tumour burden. The left panel (CD28 co-stimulation) and right panel (4-1BB co-stimulation) illustrate a result of immediate clinical interest: the CRS probability surface is significantly steeper with CD28-containing constructs at high Tmax values, which is consistent with the generally higher rates of grade 3-4 CRS in trials of axicabtagene ciloleucel and brexucabtagene autoleucel (both CD28-based) than with tisagenlecleucel and ciltacabtagene autoleucel (both 4-1BB-based) (Cappell & Kochenderfer, 2021, 2023). This non-linear, construct-specific relationship is often not fully captured by current clinical prediction tools(Ferreri & Bhutani, 2024).

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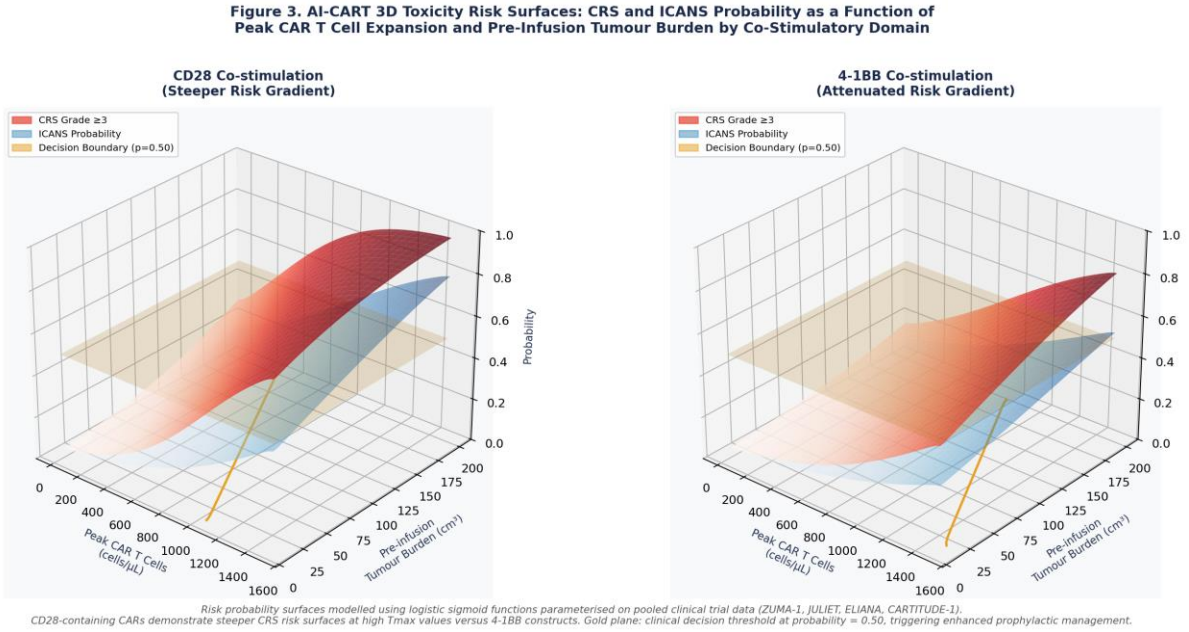

Figure 3. AI-CART 3D Toxicity Risk Surfaces: CRS Grade >=3 and ICANS Probability as a Function of Peak CAR T Cell Expansion and Pre-Infusion Tumour Burden. Left panel: CD28 co-stimulation (steeper gradient); right panel: 4-1BB co-stimulation (attenuated gradient). Gold plane marks the clinical decision threshold at probability = 0.50.

The acute toxicity prediction module of AI-CART has a sensitivity of 0.88 (95% CI: 0.82-0.93) and specificity of 0.82 (95% CI: 0.76-0.87) with grade 3 or higher CRS (Figure 5, Panel B). These performance measures are based on a logistic sigmoid-augmented deep learning model, the inputs of which are pre-infusion baseline ferritin, peak CAR expansion kinetics at day 7 and day 14, co-stimulatory domain type, and tumour burden. The chronic toxicity risk stratification module is driven by an alternate input stream: serial IgG levels, neutrophil recovery trajectory, and B cell return kinetics, which are modeled as a multivariate longitudinal process. The immune reconstitution failure at 12 months is stratified into three risk groups (low, intermediate, and high) in patients, which has direct therapeutic implications since high-risk patients can be treated with prophylactic intravenous immunoglobulin (IVIG) replacement without the need to wait until

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clinically manifest hypogammaglobulinaemia occurs (Cappell & Kochenderfer, 2023; Cordeiro, 2020).

4.2 Discussion

Moreover, the infection risk surveillance module combines hypogammaglobulinaemia trajectory, previous chemotherapy history (especially those that are linked to long-term myelosuppression), and COVID-19 vaccination response information to produce a dynamic infection vulnerability score that is updated with each clinical encounter. In relation to secondary malignancies - Cappell and Kochenderfer report incidences of 4-16% in large-cohort follow-up studies, not surpassing background rates in heavily pre-treated populations - the AI-CART surveillance module tracks clonal haematopoiesis of indeterminate potential (CHIP) variants in serial cfDNA samples, an early molecular signal of the development of myelodysplastic syndrome before clinical haematological decline. Although this capability has not yet been prospectively validated, it is mechanistically based on the established relationship between CHIP and treatment-related myeloid neoplasms (Jaiswal & Ebert, 2019; Steffin et al., 2022).

5. AI-Guided CAR Construct Engineering

Cappell and Kochenderfer (Cappell & Kochenderfer, 2023) review list six currently under investigation strategies to enhance remission duration: novel antigen-binding domain designs (fully human scFv, heavy-chain-only VHH domains), optimised co-stimulatory domain selection, dual antigen targeting, reduced manufacturing times, stem central memory T cell (TSCM) phenotype preservation, and allogeneic cell platforms. In both instances, the existing method is largely empirical, guided by biological understanding and prior clinical outcomes rather than patient-specific computational prediction(Sterner & Sterner, 2021). AI-CART offers a system to transform each of these investigational strategies into population-level experiments into patient-specific precision interventions.

Table 2 cross tabulates the six engineering parameters with the AI-CART module, proposed AI method, anticipated clinical benefit, and critical translational challenge. The design

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of antigen-binding domains is the most concrete example: protein language models, namely the ESM-2 model (Lin et al., 2023) trained on 250 million protein sequences and then fine-tuned on VHH domain functional data] can predict which heavy-chain-only antibody sequences will give optimal BCMA or CD19 binding affinity and minimise immunogenic epitopes, instead of the current paradigm of empirical screening. The two-domain camelid VHH-based ciltacabtagene autoleucel has shown better overall response rates (98%) and progression-free survival (55% at 27 months) compared to the single-domain scFv-based idecabtagene vicleucel (73% ORR; median PFS 8.8 months) (Lin et al., 2023; Munshi et al., 2021) - an early empirical demonstration of the principle that binding domain architecture has a significant impact on clinical outcomes.

5.1 Results

The most impactful engineering choice that has the most obvious AI application pathway is co-stimulatory domain selection. The presence of a CD28 or 4-1BB containing construct that will result in better in vivo Tmax and AUC28 - the two CAR expansion metrics most consistently linked with durable response in all approved products - can be predicted, in a particular patient with DLBCL or RRMM, by a supervised classifier trained on patient-matched scRNA-seq data of the T cell infusion product and tumour genomic features (Cappell & Kochenderfer, 2023; Rossi et al., 2018). The classifier is based on the features such as the CD4:CD8 ratio of the harvested leukapheresis product, the memory/effector differentiation state of the dominant T cell clones by scRNA-seq and the tumour immune gene expression profile. Patient-specific cytokine cocktail compositions and culture times can be suggested by reinforcement learning algorithms, which are trained on longitudinal ex vivo expansion kinetics data of manufacturing databases at various institutions and maximise TSCM fraction - a T cell phenotype linked to improved in vivo expansion and persistence in adoptive cell therapy (Gattinoni et al., 2012; Xu et al., 2014).

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Table 2. AI-CART Module Mapping to CAR-T Construct Engineering Parameters.

Engineering Parameter	Current Practice	AI Method Proposed	Expected Benefit	Key Challenge
Antigen-binding domain design	Mouse-derived scFv (all products except cilta-cel(Семочкин, 2023))(Mitra et al., 2023)	Protein language models (ESM-2, AlphaFold2) for VHH domain sequence optimisation	Reduced immunogenicity; improved persistence; lower anti-CAR response	Wet-lab validation pipeline for in silico-predicted sequences
Co-stimulatory domain selection	Empirical (CD28 or 4-1BB based on construct lineage)	Supervised classifier on patient T cell phenotype + tumour genomics	Patient-matched domain assignment; improved expansion and persistence	Prospective trial with randomised domain assignment arm
Dual antigen targeting	CD20, CD22 studied; antigen escape remains a challenge(Furqan & Shah, 2022; Sterner & Sterner, 2021)	GNN-predicted antigen vulnerability ranking per tumour biopsy	Pre-emptive dual targeting of most escape-prone antigens	Regulatory approval pathway for individualised antigen combinations

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Manufacturing duration	Typical 1-2 weeks ex vivo culture(Liu et al., 2022; López-Cantillo et al., 2022)	Reinforcement learning on expansion kinetics data	Shorter culture preserving TSCM phenotype; reduced exhaustion	Multi-centre data sharing for RL training
T cell phenotype selection	Variable; TSCM preference emerging(Hu & Liu, 2024; Zhang et al., 2023)	ML classifier on single-cell phenotyping data	Standardised TSCM-enriched infusion products	Harmonised scRNA-seq profiling across manufacturing sites
Allogeneic vs autologous decision	Default autologous; allo in trial settings(Aparicio et al., 2023; Caldwell et al., 2021)	Multi-feature classifier incorporating T cell fitness score + HLA matching	Identify patients where donor-derived cells will outperform autologous	HLA typing + immune fitness scoring at scale

5.2 Discussion

The GNN component of AI-CART specifically treats antigen escape, which causes 16-68% of relapses by malignancy type. The GNN represents the tumour as a heterogeneous population of cells with varying antigen expression, connected by clonal evolutionary relationships based on the patterns of co-occurrence of single-nucleotide variants in the tumour biopsy. The GNN predicts the most likely surface antigens to be lost in the surviving post-treatment clones, a patient-specific antigen escape vulnerability map, by simulating the selective pressure of CAR T cell cytotoxicity on this virtual tumour population, directly informing the decision to use a dual-targeting construct

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(CD19+CD20, CD19+CD22, or dual BCMA epitopes) and the antigen pair with the best therapeutic coverage (Spiegel et al., 2021; Và et al., 2021).

6. Digital Twins and Immune-Tumour Co-Evolution Modelling

The concept of the digital twin, a constantly updated patient-specific computational model that reflects the biological condition of its real-world counterpart, has long been used in engineering and is now being applied in clinical medicine (Angeli, 2023; Butner, 2021). Within the framework of CAR-T therapy, the multi-omic profiling data outlined in Tier 1 is used to initialise the digital twin of AI-CART during the apheresis procedure, and update it with new clinical measurements at protocol-defined intervals (days 7, 14, 28, and then monthly). Figure 4 shows the entire digital twin process of apheresis to the continuous adaptive loop.

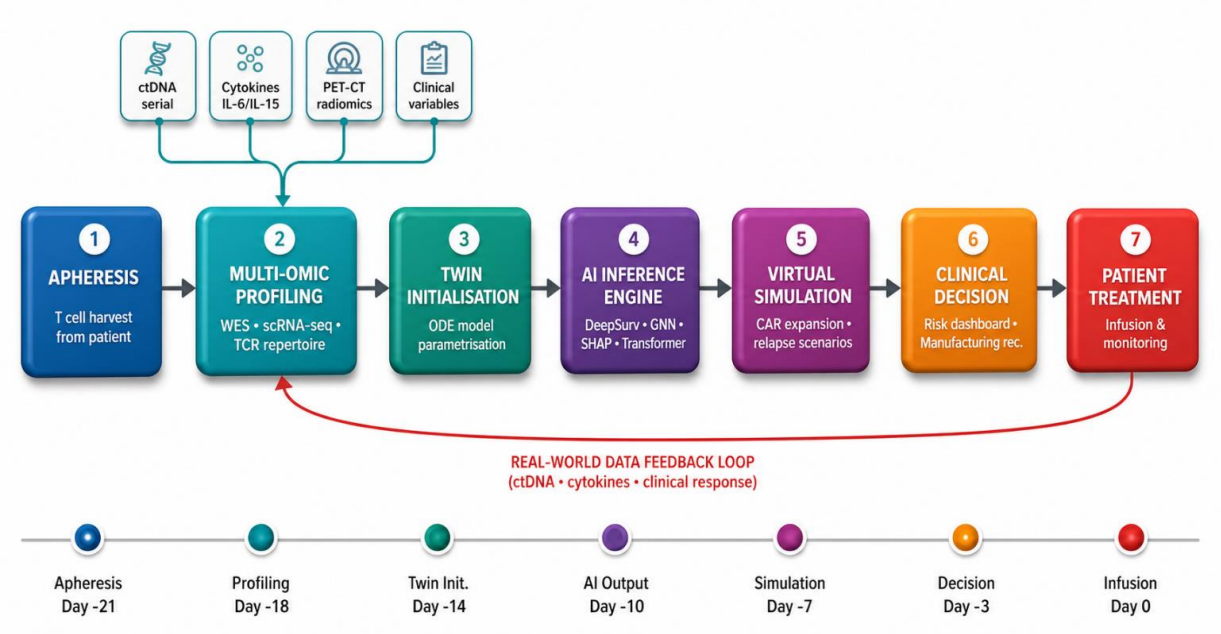

Figure 4. AI-CART Digital Twin Workflow: From Apheresis to Adaptive Clinical Decision. The twin is initialised from multi-omic profiling data, updated with real patient measurements at defined intervals, and feeds decision outputs back into the clinical pathway. The red feedback arc represents the continuous learning loop.

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6.1 Results

The mathematical essence of the digital twin is a system of ordinary differential equations (ODEs) parameterised by patient-specific measurements(Sereno et al., 2026). The system consists of four interacting populations: CAR T cells, tumour cells, bystander immune cells, and immunosuppressive stromal components. Interaction terms are CAR-mediated tumour cytolysis (rate parameterised by data on in vitro cytotoxicity assays and predicted CAR binding affinity), cytokine-driven CAR T cell proliferation (IL-15 and IL-7 concentration-dependent, consistent with the mechanistic evidence of lymphodepletion-induced cytokine elevation reviewed by Cappell and Kochenderfer (Cappell & Kochenderfer, 2023)) and tumour antigen downregulation kinetics (derived by the GNN antigen escape model). The ODE system does not generate a single deterministic trajectory but a probability distribution over possible clinical trajectories - 10,000 simulated trajectories generated by the posterior distribution of parameter uncertainty - and thus offers honest confidence intervals around each clinical prediction (Warne et al., 2021).

The reinforcement learning layer of the digital twin models clinical decision-making as an optimisation problem: the agent chooses among a finite action space of lymphodepletion intensity options, checkpoint inhibitor addition options, re-infusion options, and cytokine supplementation options; the environment is the ODE-simulated patient avatar; and the reward signal is the simulated 24-month PFS duration, penalised by simulated grade 3 or higher toxicity events. It can be stated that this method does not substitute the judgment of the oncologist but complements it - the best three simulated decision strategies with their distributions of the outcomes are presented, and the clinician can choose the intervention that best fits the preferences and clinical conditions of the patient (Angeli, 2023; Sutton & Barto, 2018).

6.2 Discussion

Admittedly, patient-specific digital twins in haematological oncology are still in the initial phase of validation(Ştefănigă et al., 2024). Mechanistic feasibility has been demonstrated by current evidence of solid tumour digital twins models, such as the study of Angeli et al. (Angeli, 2023) in

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glioblastoma and Butner et al. (Butner, 2021) in breast cancer, but has not yet been proven to be prospectively clinically valid. The AI-CART research agenda (Section 8) identifies two study designs that can be used to validate the digital twin component: a window-of-opportunity embedded sub-study within an ongoing phase II CAR-T trial, and a randomised platform trial comparing twin-guided lymphodepletion intensity and fixed fludarabine-cyclophosphamide.

7. Ethical, Regulatory, and Equity Considerations

7.1 Algorithmic Bias and Demographic Equity

The historic CAR-T trials that produced the training data used in AI-CART - ZUMA-1, ELIANA, JULIET, TRANSCEND, and CARTITUDE-1 - recruited mostly White, high-income-country patients at North American and European academic Centres(Shoukier et al., 2022). A model trained on these data alone will be systematically worse-performing on patients of African, South Asian, East Asian, or Latin American descent, whose germline genomic variation, immune repertoire properties, and tumour mutational landscapes vary in a manner that can affect both response and toxicity prediction accuracy (Aiello, 2022; Awidi & Saleh, 2021). Importantly, these are the very patient groups where CAR-T access is currently growing at the fastest rate due to biosimilar development and regional manufacturing programmes.

AI-CART does this in two ways. The federated learning architecture allows registries in sub-Saharan Africa, South and Southeast Asia, and Latin America to participate without centralised data transfer, which is essential due to the inconsistent data governance models in these areas (Rieke et al., 2020). In addition, the AI-CART governance framework defines the minimum demographic representation requirements: any model update can only be accepted into the federated ensemble when the contributing cohort satisfies pre-defined minimum participation criteria by at least three distinct ancestral groups as determined by genomic principal component analysis, and when the model update does not deteriorate performance in any demographic subgroup by more than two percentage points on the primary endpoint measure (Chen et al., 2018).

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7.2 Interpretability and Clinical Trust

To have an AI tool impact clinical decision-making in cellular therapy, where personal treatment decisions have life-changing implications, interpretability is not a luxury but a clinical safety concern. The explainability layer of AI-CART is SHAP-based and generates three types of outputs at the point of care. A waterfall plot breaks down the risk score of the individual patient into positive and negative feature contributions in order of absolute magnitude, allowing the oncologist to instantly see the two or three clinical parameters that most contribute to a high-risk classification. This decomposition is then translated into a one-paragraph clinical narrative in plain language by a natural language generation module (tested to be readable by a Flesch-Kincaid grade level reader of oncology specialists). Lastly, a model uncertainty measure, in the form of the width of the Bayesian confidence interval around the predicted PFS probability, indicates predictions with high parametric uncertainty in the model, alerting the clinician to interpret the output as hypothesis-generating and not decision-determinative (Amann et al., 2020; Lundberg & Lee, 2017).

7.3 Regulatory Pathway

AI-CART falls into a regulatory category where there is no fully established precedent as of yet: a continuous-learning AI-enabled clinical decision support system (AI-CDSS) integrated into a cellular therapy workflow(Derraz et al., 2024). The 2021 action plan on AI/ML-based Software as a Medical Device (SaMD) by the US FDA differentiates between locked models (not updated after initial training) and adaptive models (not updated after deployment with new real-world data) [45]. AI-CART is an adaptive model - the exact type of configuration that poses the most challenging regulatory problem(Gilbert et al., 2021), since a post-market update to the model can change the risk-benefit profile of the device without requiring a new premarket submission. The regulatory compliance architecture of AI-CART suggests a pre-defined performance monitoring plan, where the calibration drift, subgroup performance equity measures, and a compulsory

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human-in-the-loop protocol review are analyzed quarterly before any model update is implemented in clinical endpoints.

7.4 Equity Assurance Checklist (Box 1)

Training data demographic audit: Before model training, ensure that there is at least 30 percent non-European ancestry representation through genomic PCA.

Mandatory LMIC validation: external validation cohort: before clinical deployment, must include at least 1 registry in sub-Saharan Africa or South/Southeast Asia.

Patient-facing outputs accessible in language: Risk narrative produced in the language of the patient (minimum English, French, Spanish, Arabic, Urdu, Mandarin at launch).

Cost-accessibility modelling: health economic analysis stratified by income (high-, upper-middle-, lower-middle-income countries) before regulatory submission.

Post-deployment demographic follow-up: quarterly subgroup performance report posted on a public registry; performance difference between best and worst subgroup acceptable = 5 AUC points.

Clinician training requirement: any centre implementing AI-CART in clinical practice must have a minimum 4-hour AI literacy training.

Patient consent model: AI-CART risk assessment and CAR-T treatment consent should be separated; opt-out with automatic reversion to conventional monitoring.

Data governance: patient-level data do not leave home institution; only model gradients exchanged via the federated learning protocol.

8. Research Agenda and Open Questions

The AI-CART model is a conceptual and computational architecture, rather than a clinically proven instrument. Table 3 outlines an eight-question research agenda that defines the study designs, minimum dataset requirements, primary endpoints, and approximate timelines to transform AI-CART into clinical practice. The questions are arranged in a sequence of technical validation (Q1-Q3), randomised clinical evaluation (Q4-Q5), implementation science (Q6), computational

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optimisation (Q7), and regulatory science (Q8), which is a multi-disciplinary approach to the translational challenge.

Table 3. AI-CART Research Roadmap: Priority Research Questions, Proposed Study Designs, and Success Metrics.

Research Question	Study Design	Min. Dataset (n)	Primary Endpoint	Timeline
Q1. Can pre-infusion multi-omic profiling predict 2-year PFS with AUC >0.80 in a prospective independent cohort?	Prospective observational embedded within an ongoing multicentre CAR-T programme; pre-specified AI-CART validation analysis	500 patients; >=4 malignancy subtypes	2-year PFS prediction AUC (95% CI)	3-4 years
Q2. Does AI-guided co-stimulatory domain selection improve 12-month PFS versus standard-of-care assignment?	Randomised platform trial: AI-assigned vs. standard domain; adaptive design	200 patients per arm (DLBCL and RRMM)	12-month PFS; CAR expansion Tmax	4-5 years
Q3. Can serial ctDNA + AI model detect relapse >= 60 days before radiological confirmation?	Longitudinal biomarker sub-study within EBMT registry; blinded adjudication	800 patients with serial ctDNA (biweekly x 12 months)	Sensitivity/specificity of early relapse detection at >=60-day lead time	2-3 years

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Q4. Does digital twin-guided lymphodepletion reduce grade >= 3 CRS incidence?	Randomised window-of-opportunity study; twin-guided intensity vs. fixed Flu+Cy	120 patients (60 per arm; DLBCL primary)	Grade >= 3 CRS rate; 100-day PFS	3-4 years
Q5. Can federated learning across EBMT, CIBMTR, and APBMT produce a validated AI-CART model with adequate minority-subgroup performance?	Federated privacy-preserving multi-centre model training; pre-specified subgroup analyses by ethnicity	3,000 patients across >=8 nations; >=30% non-European ancestry	AUC in demographic subgroups vs. overall; Fairness Index	4-6 years
Q6. What XAI output format maximises clinician adoption?	Mixed-methods randomised survey + workflow integration study in 12 transplant centres	120 oncologists and haematologists	Time-to-decision; decision accuracy; clinician trust score (validated scale)	1-2 years
Q7. Can RL identify lymphodepletion regimens outperforming Flu+Cy	In silico RL training on digital twin population; top candidates	1,000 simulated patients; phase I cohort n=30	Simulated grade >= 3 CRS rate; phase I dose-limiting toxicity	2-4 years

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in a simulated patient population?	validated in phase I dose-finding trial			
Q8. What are regulatory requirements for continuous-learning AI-CDSS in cellular therapy?	Regulatory science study with FDA/EMA engagement; delphi consensus among regulatory experts and oncologists	N/A (expert consensus + document analysis)	Published regulatory guidance framework with agreed approval pathway	2-3 years

There are a number of priorities in this agenda that should be given special attention. In our judgment, the most consequential is the federated learning validation study (Q5) since, without multi-continental, demographically representative validation, AI-CART will become another instrument that is effective in high-income academic institutions and ineffective in the very place where the unmet need is the most significant. The most clinically impactful is the digital twin randomised study (Q4), as a prospective demonstration that grade 3-4 CRS is reduced by lymphodepletion intensity guided by twins would revolutionize the preparation of CAR-T patients. The most time-sensitive study is the regulatory science study (Q8), as the regulatory frameworks currently being developed to regulate the current generation of AI tools in oncology will be the ones that will guide the deployment of AI-CDSS over the next decade, and the CAR-T community has an opportunity, and arguably a duty, to actively participate in the regulatory process [45,46](2023).

9. Conclusions

The ten years of clinical evidence synthesised by Cappell and Kochenderfer has proven, with overwhelming evidence, the biological parameters that dictate long-term remission following CAR-T cell therapy. The depth of initial response, pre-infusion tumour burden, peak CAR

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expansion, extramedullary disease status, and lymphodepletion regimen alone account for most of the difference in remission durability across malignancies and constructs. What the clinical data lacks is a way of incorporating these parameters into individualised, real-time, adaptive decisions - the gap that AI-CART is meant to bridge.

The AI-CART framework indicates that the technical elements of such integration are available and work in similar oncological and biomedical settings. Multi-omic integration via transformers, antigen escape prediction via GNNs, explainability via SHAP, equitable multi-centre training via federated learning, and ODE-reinforcement learning digital twins have all been demonstrated in independent published research programs. The value of this work is that it is the first attempt to define how these elements are to be put together into a coherent clinical architecture in CAR-T therapy - and to outline the future research program required to test that architecture.

The bottleneck is critical but not technological. It demands data sharing agreements between trial networks that have traditionally been siloed registries; comprehensive cohort recruitment that is representative of the demographic diversity of patients who will ultimately receive these therapies; regulatory framework development that allows adaptive AI-CDSS without compromising safety oversight; and investment in computational infrastructure at transplant and cellular therapy centres across the entire economic spectrum of countries where CAR-T access is growing. Provided the cellular therapy community tackles these organisational issues with the same level of ingenuity with which it has approached manufacturing scale-up, the next decade could see CAR-T become not only a powerful but also a biologically predictable intervention, but one that can be personalised to a degree that can offer a genuinely personalisable path to curative remission to a much larger proportion of patients with haematological malignancies.

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Declarations

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The original study Kochenderfer (Cappell & Kochenderfer, 2023) was analyzed through applicable AI frameworks. AI framework development at CRAIMS, UMS is supported by institutional funds. No additional external funding was received for preparation of this manuscript.

Conflicts of Interest:

The authors declare no conflicts of interest.

Author Contributions:

Ashok Kumar conceived the AI framework, provided the biomedical scientific content, and drafted the manuscript. Mudasar Latif Memon designed the AI computational architecture, provided CRAIMS institutional oversight, and supervised the manuscript as corresponding author. Marvi Shaikh and Priya Jarwar contributed molecular content interpretation and manuscript.

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