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PERSPECTIVE

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From monoclonal to polyfunctional immunotherapy: Reprogramming CAR-T-cell therapy with oncolytic viruses in B-cell malignancies

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The emergence of chimeric antigen receptor (CAR)-T-cell therapy has fundamentally transformed the therapeutic options for relapsed and refractory B-cell malignancies, establishing a new standard of care through unprecedented remission rates. Despite these clinical milestones, the long-term efficacy of CAR-T-cell therapy is frequently undermined by the adaptive nature of the tumor ecosystem.[1] We term this vulnerability therapeutic monoclonality, a unifying concept encompassing the well-recognized risks of antigen escape and microenvironmental immunosuppression that arise from the functional rigidity of a T-cell product fixed to a single target antigen. In this context, therapeutic monoclonality refers not only to restriction toward a single antigenic target but also to the broader inability of highly engineered cellular therapies to adapt to dynamic tumor ecosystems. Current strategies to address this, such as dual targeting or checkpoint inhibition, provide incremental rather than systemic solutions. We propose that oncolytic viruses (OVs) offer a unique solution by simultaneously remodeling the tumor microenvironment (TME), diversifying antigen presentation, and restoring the efficacy of exhausted CAR-T cells. While monoclonal antibodies and CAR-T cells have revolutionized hematology, the next therapeutic step may require a transition from monoclonal to polyfunctional immunotherapy.

To date, translational evidence specifically investigating OV–CAR-T-cell combinations in B-cell malignancy models remains remarkably limited, with only two primary studies relevant to B-cell malignancies. Wenthe et al. (2021) demonstrated that an oncolytic adenovirus (LOAd703) encoding CD40L and 4-1BBL could infect B-cell lymphoma cells via CD46, upregulating critical co-stimulatory and MHC molecules. This infection led to augmented CAR-T-cell effector function, reduced exhaustion markers, and enhanced chemokine secretion that promoted CAR-T-cell migration and improved tumor killing in vitro and in vivo.[2] Complementary research by Evgin et al. (2022) using vesicular stomatitis virus (VSV) and reovirus showed that the native TCR of human CD19 CAR-T cells could be stimulated by viral antigens to drive expansion, proliferation, and superior CAR-directed antitumor function.[3] While the in vivo efficacy of this latter approach was primarily established in solid tumor models, the CD19-specific expansion data provide a mechanistic proof-of-concept for hematologic applications.

Building upon these foundational insights, we suggest that extending OV-based strategies to B-cell cancers represents an underexplored but biologically plausible therapeutic opportunity, and outline a conceptual roadmap that illustrates how OVs could be integrated into the CAR-T-cell paradigm for B-cell malignancies.

Unlike solid tumors, B-cell malignancies develop within highly specialized immunologic niches, including lymph nodes, spleen, and bone marrow, where malignant cells remain in continuous bidirectional communication with stromal cells, macrophages, regulatory T cells, and cytokine networks. Thus, therapeutic resistance in hematologic malignancies reflects not only antigen escape but also ecosystem-level immune adaptation.

A CONCEPTUAL ROADMAP FOR POLYFUNCTIONAL CAR-T/OV CELL STRATEGIES

Given the limited but encouraging preclinical evidence, clinical translation remains exploratory. Rather than proposing a fixed development strategy, we outline a conceptual roadmap to organize key biological hypotheses and identify where OV–CAR-T-cell

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combinations may have the greatest impact. This framework is not exhaustive but is intended to guide prioritization and experimental design (Table 1). A graphical representation can be found in Figure 1. These strategies converge on a single principle: transforming CAR-T cells from static effectors into dynamic ecosystem modulators and, while direct evidence in B-cell malignancies remains limited, the consistency of mechanistic signals across available studies supports further exploration of this approach.

Phase I: Backbone selection and safety engineering

The selection of a viral backbone is dictated by genome size, payload capacity, and replication kinetics. Large double-stranded DNA viruses, such as herpes simplex virus (HSV), vaccinia, and adenoviruses, provide substantial payload capacity, strong immunogenicity, and flexible engineering potential, making them attractive platforms for combinatorial immunotherapy strategies.[4]

Safety considerations are likely to be particularly important in immunocompromised patients. Two complementary strategies are microRNA (miRNA)-detargeting, which suppresses replication in normal tissues,[5] and suicide-gene systems. For example, HSV thymidine kinase allows for selective ablation of the therapeutic platform using ganciclovir if toxicity emerges. Precision control of replication may be essential to enable repeat dosing and minimize systemic toxicity.

Phase II: Microenvironment priming

Tumor-associated immunosuppression reflects the inability of monoclonal therapies to reshape hostile ecosystems.

- Cytokine-armed OVs: Unlike systemic cytokine administration, which is limited by neurotoxicity and cytokine release syndrome (CRS), OV-mediated expression enables spatially restricted release that enhances CAR-T-cell expansion.[6]
- Stromal targeting: OV-mediated stromal remodeling strategies may help overcome microenvironment-associated barriers that limit CAR-T-cell infiltration and persistence. Strategies developed for solid tumors may require adaptation for B-cell malignancies, where the TME is characterized more by immune-stromal signaling networks than by dense extracellular matrix barriers.[7]
- Chemokine secretion: OVs engineered to secrete chemokines (e.g., CCL5, CXCL9) can restore local chemotactic signals,[6] potentially guiding CAR-T cells into sanctuary sites like the bone marrow.

The success of microenvironment priming may depend on disease-specific anatomical constraints. In multiple myeloma, the marrow-infiltrative nature of the disease is driven by complex bidirectional interaction between malignant plasma cells and the bone marrow stromal niche. OVs engineered to disrupt these signals, perhaps through the local expression of stroma-degrading enzymes or CXCR4 antagonists, may contribute to "unmasking" the tumor both physically and immunologically, allowing infused CAR-T cells to penetrate deeper into the marrow niche than is currently possible with monoclonal approaches.

Phase III: Expanding antigen coverage and advanced platforms

A potential advantage of OV integration is the induction of epitope spreading, though its significance in B-cell malignancies, which often exhibit low mutational burdens, remains uncertain. While CAR-T cells are confined to the recognition of a single pre-defined antigen, OV-mediated oncolysis facilitates the release of a broad spectrum of neoantigens and damage-associated molecular patterns (DAMPs).[14] This process may function as a form of intratumoral in situ vaccination capable of broadening endogenous immune recognition beyond the primary CAR target. By diversifying the immune pressure, this approach may mitigate the selective advantage of antigen-negative clones, moving the therapy from a static intervention to a dynamic immune ecosystem. Whether virus-mediated tumor lysis can generate sufficient antigen diversity to recruit endogenous T-cell responses in low-tumour mutational burden (TMB) B-cell malignancies is an open empirical question.

Recent work shows that OV-mediated neoantigen presentation can be enhanced in low-TMB tumors through engineered expression of shared tumor-associated antigens rather than relying on endogenous neoantigen release[15]; this represents a more realistic path to antigen diversification. Other engineering strategies include the following:

- Tumor tagging: OVs can express CAR-targeted antigens (e.g., CD19) on antigen-negative tumor cells to restore therapeutic susceptibility.[8]
- Bispecific T-cell engagers: OVs can function as intratumoral factories for bispecifics, redirecting CAR-T and endogenous T cells toward heterogeneous tumor populations while avoiding systemic exposure.[9]
- Multipayload OVs: HSV platforms enable the co-expression of tumor-tagging antigens, cytokines, chemokines, and checkpoint inhibitors, potentially enabling a more integrated therapeutic effect against multiple resistance mechanisms.[10]

By diversifying immune pressure, OV-mediated antigen spreading may also reduce the evolutionary bottleneck imposed by single-antigen targeting, potentially limiting immunologic escape through clonal selection.

Phase IV: Systemic and multisite delivery

Intratumoral administration is limited in disseminated disease. Engineering strategies designed to reduce antiviral neutralization may allow repeated OV dosing in disseminated disease settings. Cell-based carriers, including CAR-T cells themselves, may shield OVs from neutralizing antibodies and enhance delivery to metastatic niches. In this model, CAR-T cells are loaded with the oncolytic payload ex vivo during manufacturing. These cells act as carriers, utilizing their natural tumor-homing capacity to bypass neutralizing antibodies and deliver the virus directly into marrow and nodal sanctuary sites.[11] This approach could potentially streamline clinical implementation by merging two separate therapeutic components into a single delivery platform.

However, this approach faces a critical biological tension: OV replication within CAR-T cells may compromise T-cell viability and function before tumor delivery. While Zhang et al. demonstrated that CAR-T cells retained biological function after 3-day HSV loading,[11] other studies have shown that Type I interferon produced during viral infection can induce CAR-T-cell apoptosis, activation-induced exhaustion, and upregulation of inhibitory receptors.[12] The feasibility of this strategy will depend on precise control of viral replication kinetics to preserve CAR-T-cell fitness during transit. A recent study by Xing et al. demonstrated a novel approach where VSV was specifically loaded onto CAR moieties via engineered LDL receptor domains, which actually pre-activated CAR signaling and enhanced metabolic

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TABLE 1 Conceptual roadmap for oncolytic virus (OV) and chimeric antigen receptor (CAR)-T-cell-based therapies in B-cell malignancies.

No.	Phase and research direction	Mechanistic rationale	Suggested payloads/platforms	Potential translational relevance	Translational barrier	Ref.
	I. Backbone and safety					
1	Platform selection	Balancing viral genome capacity with replication kinetics, safety, and tropism for B-cell niches	All (HSV, Ad, Vaccinia, VSV)	Identify disease-specific optimal vectors	Limited tumor selectivity and antiviral immune clearance	[4]
2	Safety engineering	Utilizing miR-detargeting and suicide switches to prevent off-target replication; include CAR-T-cell therapy safety switch	miRNA cassettes; TK systems MV/HSV	Controlled ablation	Balancing viral attenuation with therapeutic efficacy	[5]
	II. Niche priming					
3	Cytokine arming	Localized expression of proliferative signals to reverse T-cell exhaustion	IL-12/15/7 HSV, Ad, VV	Sustained intratumoral CAR-T-cell therapy support	Excessive inflammatory signaling and CAR-T-cell therapy exhaustion	[6]
4	Chemokine arming	Restoring chemotactic gradients (e.g., CXCR3/CCR5 ligands) to guide trafficking	CCL5, CXCL9, CXCL10 HSV, Ad, VV	Enhanced CAR-T-cell therapy infiltration	Dysregulated immune-cell recruitment and off-target inflammation	[6]
5	Stroma remodeling	Enzymatic degradation of ECM (primarily relevant in solid tumors); in B-cell malignancies, targeting immune-stromal signaling	Hyaluronidase; FAP-targeted bispecifics HSV, Ad, VV	Modulation of immune-stromal interactions	Heterogeneity of immune-stromal interactions within marrow niches	[7]
	III. Antigen coverage					
6	Tumor tagging	Encoding OVs to express universal targets on antigen-negative tumor cells	Truncated CD19, BCMA Ad, VV	Mitigation of antigen-negative relapse	Heterogeneous antigen expression and antigen escape	[8]
7	Bispecific engagers	Directing CAR-T-cell therapy and bystander T cells toward heterogeneous populations	Bispecific T-cell engagers HSV, Ad, VV	Induction of polyclonal immune engagement	Increased manufacturing complexity and systemic immune activation	[9]
8	Multipayload HSV	Simultaneous delivery of cytokines, chemokines, and checkpoint blockade	Multiplexed HSV-1 constructs	Synergistic "ecosystem-level" therapeutic strike	Payload stability and regulatory complexity	[10]
	IV. Systemic delivery					
9	Cellular carrier platforms	Utilizing cell carriers or liposomes to bypass neutralizing antibodies	T-cell carriers; liposomal encapsulation	Effective colonization of disseminated disease	Variable viral loading efficacy and reproducibility	[11–13]
	V. Translation					
10	Sequencing optimization	Defining infusion intervals to maximize synergy and minimize overlapping CRS	All platforms	Safe, synchronized dosing	Lack of standardized treatment scheduling	-
11	Biomarker discovery	Real-time monitoring of viral kinetics and immune activation using ddPCR; longitudinal cytokines; ctDNA	All platforms	Adaptive, patient-stratified clinical dosing	Limited predictive biomarkers for OV–CAR-T-cell therapy responsiveness	-
12	Host conditioning	Refined lymphodepletion to suppress antiviral immunity, favor viral replication, and reduce CAR-T-cell therapy competition	Flu/Cy regimens	Predictable and durable viral expansion	Immunosuppression-associated toxicity and infection risk	-

Note: The strategies listed below are illustrative and hypothesis-generating, rather than comprehensive or immediately translatable.

Abbrevations: Ad, adenovirus; BCMA, B-cell maturation antigen; CCL, CC chemokine ligand; CD19, cluster of differentiation 19; CRS, cytokine release syndrome; ctDNA, circulating tumor DNA; CXCL, CXC chemokine ligand; ddPCR, Droplet digital polymerase chain reaction; ECM, extracellular matrix; FAP, fibroblast activation protein; Flu/Cy, fludarabine/cyclophosphamide; HSV, herpes simplex virus; IL, interleukin; miR/miRNA, microRNA; MV, measles virus; TK, thymidine kinase; VSV, vesicular stomatitis virus; VV, vaccinia virus.

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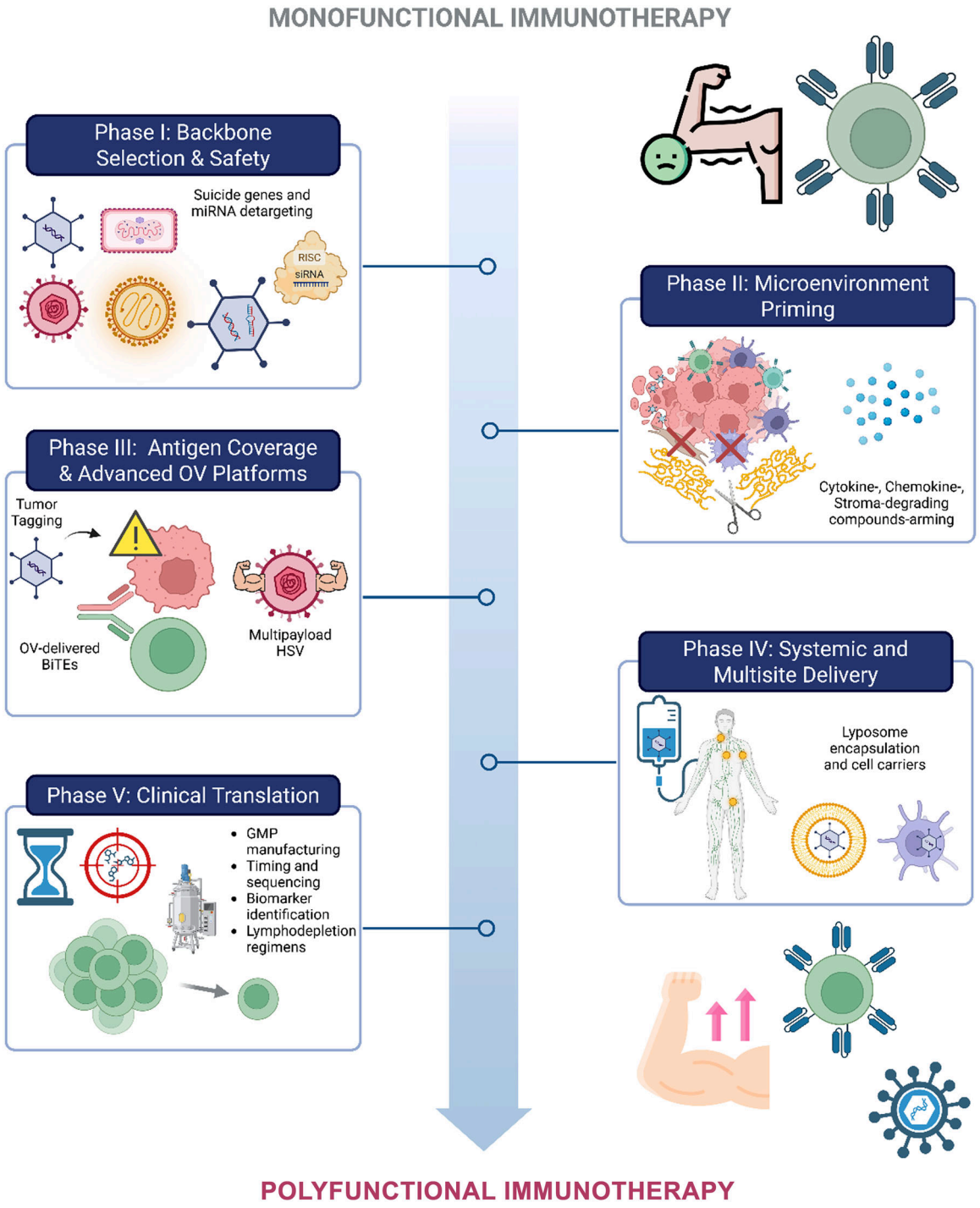


FIGURE 1 **Proposed roadmap for the clinical integration of oncolytic viruses (OVs) into chimeric antigen receptor (CAR)-T-cell therapy organized in five phases that could enable the transition from monofunctional to polyfunctional immunotherapy.** BiTEs, bispecific T-cell engagers; GMP, good manufacturing practice; HSV, herpes simplex virus; miRNA, microRNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA.

fitness rather than causing exhaustion.[13] This represents a potential engineering solution.

Phase V: Clinical translation and integrated monitoring

Several practical considerations will shape the clinical translation of OV–CAR-T-cell combinations:

- Conditioning and lymphodepletion: Fludarabine/cyclophosphamide, the standard lymphodepletion regimens before CAR-T-cell infusion, may transiently suppress antiviral immunity, favoring viral replication in marrow niches. Lymphodepletion thus serves both to promote CAR-T-cell engraftment and to suppress antiviral immunity.
- Timing and sequencing: Therapeutic timing is an unresolved variable; synchronizing CAR-T-cell delivery with viral kinetics is likely

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important to maximize efficacy while avoiding overlapping inflammatory toxicities.
- Integrated monitoring: Successful translation requires longitudinal monitoring of viral kinetics (via droplet digital polymerase chain reaction [PCR]) and immune activation. Translational readouts must include CAR-T-cell persistence markers and circulating tumor DNA as molecular indicators of remission.

By merging engineering precision with translational pragmatism, this phase may bridge the gap between mechanistic innovation and a clinically deployable standard of care.

KEY TRANSLATIONAL CHALLENGES AND OPPORTUNITIES

Beyond mechanistic synergy, OV–CAR-T-cell combinations raise broader translational questions regarding therapeutic sequencing, toxicity management, manufacturing complexity, and clinical positioning within existing hematologic treatment algorithms. These considerations may ultimately determine whether polyfunctional immunotherapy can evolve from a conceptual framework into a deployable clinical strategy.

Integration with existing therapeutic algorithms

A future clinical roadmap for B-cell malignancies will likely require OV–CAR-T-cell strategies to integrate with established targeted agents rather than replace them. In particular, BTK inhibitors such as Ibrutinib have been shown to improve T-cell fitness and reduce immunosuppressive signaling in chronic lymphocytic leukemia,[16] raising the possibility that targeted therapies may function not only as cytoreductive agents but also as immunologic primers for polyfunctional cellular therapies. Sequential strategies combining targeted agents, OVs, and CAR-T cells may therefore represent a biologically coherent framework for addressing both tumor burden and immune dysfunction.

A conceptual tension exists in the proposed use of lymphodepletion: while it may transiently suppress antiviral neutralizing antibodies and favor viral replication, profound immunosuppression could simultaneously undermine the epitope spreading and endogenous T-cell recruitment that OVs are intended to stimulate. Recent evidence suggests that antiviral immune responses, rather than being purely detrimental, may contribute to antitumor immunity by cross-priming tumor-associated antigens released during virus-mediated oncolysis.[17] The optimal conditioning regimen will likely require calibrated immunosuppression that permits viral replication while preserving sufficient adaptive immune capacity for polyclonal T-cell engagement, a balance that remains empirically undefined.

A significant barrier to the clinical adoption of OV–CAR-T-cell combinations is the perceived high cost and logistical complexity of combining two separate Advanced Therapy Medicinal Products (ATMPs). Reviewers frequently highlight the potential for "doubling the cost" of therapy, yet this framing is often misleading.

The cost-effectiveness of CAR-T-cell therapy is exquisitely sensitive to durable complete response (CR) rates. Health economic analyses demonstrate that at a 40% 5-year progression-free survival (PFS), axicabtagene ciloleucel achieves an incremental cost-effectiveness ratio (ICER) of ~$129,000/QALY, but at 30% PFS, this rises to > $159,000/QALY.[18] If an OV–CAR-T-cell combination increases the durable CR rate by even 15%–20%, it could shift the ICER of the combined therapy below standard willingness-to-pay thresholds despite higher upfront costs. Post-CAR-T-cell relapse remains associated with poor outcomes and substantial healthcare burden, with median overall survival of only 5.2 months following treatment failure.[19] Within a value-based contracting framework where payment is tied to clinical response, a combination that increases durable CR rates directly improves the number of "payable events" while reducing payer exposure to costly treatment failures. Beyond cost alone, implementation will depend on institutional infrastructure capable of coordinating cellular manufacturing, viral handling, biosafety requirements, and real-time immune monitoring.

Manufacturing and clinical deployment

The regulatory classification of OV–CAR-T-cell combinations remains unresolved and may substantially impact clinical translation. In the EU, both components are classified as ATMPs, and their combination may fall under a combined ATMP framework requiring coordinated assessment by the EMA. In the United States, regulatory pathways are less defined; separately manufactured and sequentially administered products may be reviewed as distinct BLAs, whereas integrated manufacturing (e.g., ex vivo viral loading of CAR-T cells) could trigger classification as a single combination product with expanded CMC and potency requirements. These uncertainties underscore the need for early regulatory engagement to clarify development pathways and facilitate clinical entry.

The clinical implementation of OV–CAR-T-cell combinations will also require tighter integration between patient-specific cellular manufacturing and scalable, GMP-compliant viral production pipelines. This challenge extends beyond logistics alone and reflects a broader transition toward coordinated multi-platform immunotherapy systems.

Future therapeutic models may increasingly favor modular or partially unified manufacturing strategies capable of synchronizing viral preparation, lymphodepletion, and CAR-T-cell infusion within clinically relevant timelines. In parallel, approaches such as decentralized manufacturing or point-of-care production may become particularly important for rapidly progressing hematologic malignancies, where prolonged "vein-to-vein" intervals remain a major limitation of current CAR-T-cell workflows.

Resolving toxicity versus efficacy

Combining CAR-T cells with OVs raises a key toxicity question: both modalities trigger overlapping inflammatory cascades involving IL-6, IFN-γ, and TNF-α, yet their kinetics and mediator hierarchies likely differ. CAR-T-cell-associated CRS is driven by macrophage-derived IL-6 and IFN-γ and typically develops within days following infusion.[20] OV-induced inflammation, by contrast, appears IFN-dominant.[21] However, no direct comparative cytokine profiling between these two sources has been performed, and the degree of overlap in a combination setting remains undefined. No validated biomarker panel currently distinguishes these inflammatory etiologies in real time. Droplet digital polymerase chain reaction (ddPCR) for viral genome quantification and serial multiplex cytokine profiling (IL-6, IFN-γ, IL-18, and IL-1β) are candidate approaches but lack clinical validation. Safety switches (HSV-TK, inducible caspase-9) offer theoretical OV ablation capability, but their activation kinetics, typically hours to days, may be insufficient for fulminant CRS, which can progress rapidly. Prospective combination trials incorporating standardized cytokine sampling timepoints will be essential to define the kinetic signatures distinguishing these overlapping toxicities. These inflammatory pathways suggest that future OV–CAR-T-cell protocols may require kinetic rather than static toxicity monitoring approaches, integrating longitudinal cytokine signatures with viral replication dynamics.

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These challenges illustrate that OV–CAR-T-cell therapy should not be viewed simply as the addition of two independent modalities, but rather as the emergence of a more integrated and adaptive immunotherapeutic framework. The success of this approach will likely depend less on maximizing individual platform potency and more on coordinating immune activation, trafficking, persistence, and safety within a unified therapy.

LIMITATIONS

This framework is constrained by four key uncertainties. First, direct translational evidence in B-cell malignancies is limited to only two primary studies. Second, several mechanistic hypotheses rely on extrapolations from solid tumor models. Third, the "IFN paradox," where Type I interferons may concurrently stimulate CAR-T cells and promote functional exhaustion, remains unresolved. Finally, the clinical impact of epitope spreading remains speculative, as the low neoantigen availability characteristic of many B-cell cancers may limit the recruitment of an endogenous immune response.

Most importantly, no clinical trials have yet evaluated integrated OV–CAR-T-cell strategies in B-cell malignancies, limiting current conclusions to mechanistic extrapolation and early preclinical observations.

OUTLOOK AND CONCLUSION

CAR-T-cell therapy may be approaching a therapeutic inflection point where further advances may depend less on incremental optimization and more on conceptual shifts in how these therapies are deployed. In this context, OVs offer more than a complementary cytotoxic platform; they represent programmable immunologic amplifiers capable of reshaping antigen presentation, inflammatory signaling, immune trafficking, and therapeutic persistence simultaneously. While OV-CAR-T-cell combinations remain largely untested in B-cell malignancies, their complementary mechanisms suggest a potentially synergistic strategy to address antigen escape and microenvironmental resistance. The framework outlined here is intended to stimulate discussion and guide early translational efforts. A critical next step would be preclinical evaluation of armed OVs combined with anti-CD19 CAR-T cells in antigen-heterogeneous B-cell lymphoma models, with systematic assessment of epitope spreading, CAR-T-cell persistence, and toxicity kinetics. If successfully translated, such approaches may redefine cellular immunotherapy not as a static antigen-targeting intervention, but as a dynamic ecosystem-engineering strategy capable of overcoming the adaptive resistance mechanisms that currently limit durable remission.

AUTHOR CONTRIBUTIONS

Eduard Achim: Conceptualization; investigation; methodology; validation; writing—original draft; data curation. **Guy Ungerechts**: Conceptualization; investigation; methodology; supervision; writing—review and editing. **Ciprian Tomuleasa**: Conceptualization; investigation; funding acquisition; writing—review and editing; supervision. **Sabrina Friedel**: Conceptualization; investigation; supervision; writing—review and editing. **Michael Hudecek**: Conceptualization; investigation; writing—review and editing; supervision; visualization. **Cecilia Cristea**: Conceptualization; investigation; supervision; writing—review and editing; visualization. **Mihaela Tertis**: Conceptualization; investigation; methodology; visualization; supervision; writing—review and editing. **Hermann Einsele**: Conceptualization; investigation; visualization; writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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