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Progress in Oncolytic Virotherapy for Non-Small Cell Lung Cancer and Future Directions

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Abstract Oncolytic virotherapy (OV) represents an emerging therapeutic modality for non-small cell lung cancer (NSCLC), leveraging viruses to selectively target tumor cells and stimulate anti-tumor immunity. This review synthesizes evidence from key studies to evaluate the current landscape and future directions of OV in NSCLC. We systematically analyzed six pivotal studies investigating diverse oncolytic virus platforms, including Newcastle Disease Virus (NDV), pelareorep (reovirus), M1 virus, coxsackieviruses (CVA11 and CVB5) and engineered HSV-1 (RP2/RP3). The analysis encompassed both preclinical investigations and clinical trials to assess therapeutic efficacy, mechanisms of action and limitations. The evidence reveals a field marked by both promising breakthroughs and significant challenges. The most compelling clinical success comes from engineered HSV-1 (RP2/RP3) in combination with stereotactic body radiation therapy (SBRT) and pembrolizumab, demonstrating a 33.3% objective response rate and robust immune activation. In contrast, pelareorep combined with chemotherapy failed to show survival benefit, highlighting the critical importance of combination partner selection. Preclinical studies showed exceptional promise with coxsackieviruses achieving complete tumor regression and the M1 virus identifying MXRA8 as a predictive biomarker. However, these findings are tempered by translational challenges, including the gap between immunocompromised models and human trials and safety concerns regarding combination strategies that potentiate DNA damage. Oncolytic virotherapy demonstrates significant potential for NSCLC treatment, particularly as an immune-priming modality in rationally designed combinations. Future success requires strategic focus on immunologically congruent combinations, biomarker-driven patient selection and innovative trial designs to bridge the divide between preclinical promise and clinical application. The field must learn from both successes and failures to realize the full potential of these novel therapeutic agents.

Key Words Non-Small Cell Lung Cancer, Oncolytic Virotherapy, Oncolytic Viruses, Cancer Immunotherapy, Tumor-Targeting Viruses, Next-Generation Cancer Therapies

INTRODUCTION

Lung cancer is still a significant global health burden, accounting for approximately 1.8 million deaths annually and standing as the leading cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC), the predominant subtype comprising approximately 85% of cases, includes adenocarcinoma, squamous cell carcinoma and large cell carcinoma [2]. Despite advancements in standard treatments, such as surgery, chemotherapy, radiotherapy and targeted therapies, long-term survival rates remain poor for patients with advanced or metastatic disease [3]. This underscores the urgent need for innovative and effective therapeutic approaches. Oncolytic virotherapy (OV) has emerged as a promising therapeutic strategy that employs native or genetically modified viruses to selectively replicate in and lyse cancer cells, while sparing normal tissues. The efficacy of OV is understood to operate through a dual mechanism of action. The primary, direct effect is oncolysis, where the virus infects and replicates within tumor cells, leading to their direct destruction and the release of viral progeny to infect neighboring cancer cells. The secondary and potentially more critical, effect is immune activation. The immunogenic cell death triggered by oncolysis releases tumor-associated antigens, damage-associated

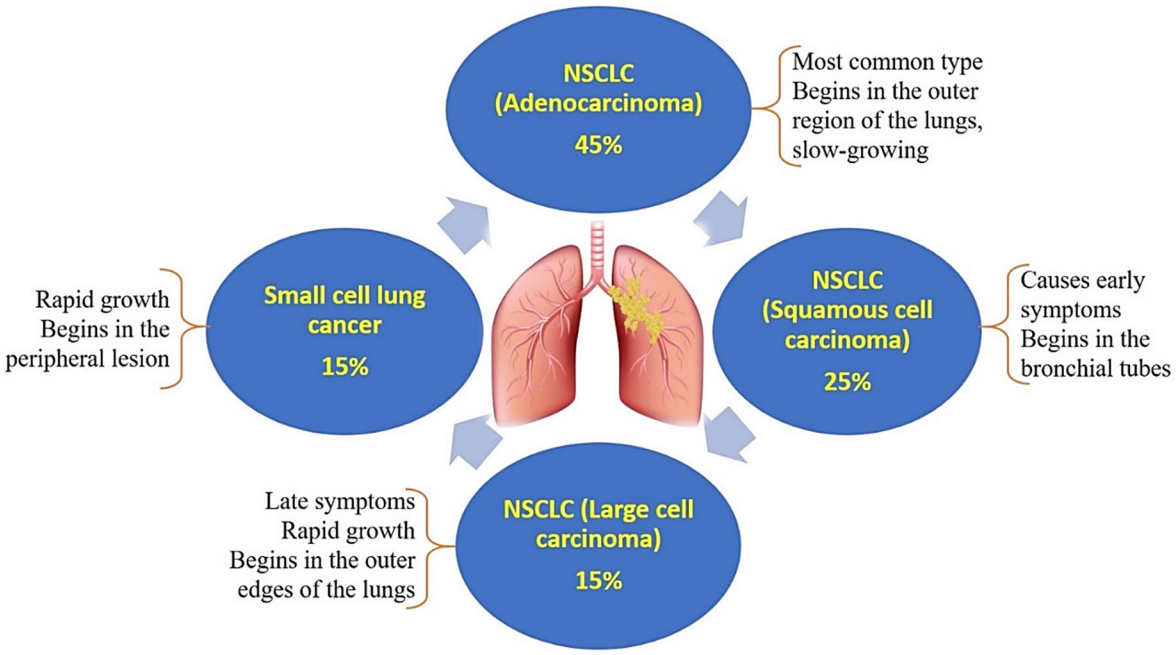

Figure 1: Representing lung cancer classification and each type's characteristics and origin

molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) into the tumor microenvironment (TME). This converts the traditionally immunosuppressive "cold" TME into an immunologically "hot" one, recruiting and activating dendritic cells and tumor-specific T-cells, thereby stimulating a systemic anti-tumor immune response [4,5]. The past decade has witnessed a surge in preclinical and clinical research exploring a diverse range of oncolytic viruses for NSCLC (Figure 1). Recent studies have highlighted the potential of various platforms, including coxsackieviruses (CVA21, V937, CVB5, A11) [6], the oncolytic M1 virus [7], modified adenoviruses [8], reovirus (pelareorep) [9] and Newcastle disease virus [10]. Crucially, the therapeutic potential of OVs appears to be significantly enhanced through rational combination strategies. Pre-clinical models demonstrate that combining OVs with JAK/STAT inhibitors can overcome viral resistance [11], while numerous clinical trials are now actively investigating OVs in combination with immune checkpoint inhibitors like pembrolizumab [9] and standard treatments like stereotactic body radiation therapy (SBRT) [12]. Despite the growth of this field and the progression of numerous oncolytic viruses into clinical trials, the available evidence remains fragmented. To our knowledge, been comprehensively synthesized in a systematic review covering the last decade of pre-clinical and clinical research on oncolytic virotherapy for non-small cell lung cancer. This gap hinders a clear assessment of the overall efficacy, safety and most promising future directions for this therapeutic class. This review aims to establish a consolidated evidence base to guide future research, inform the design of clinical trials and ultimately accelerate the development of effective oncolytic virotherapies for NSCLC patients.

METHODS

This review article provides a systematic evaluation of advancements in oncolytic virotherapy (OV) for non-small cell lung cancer (NSCLC). The following methodology was implemented to ensure rigor and reliability. This systematic review employed the PICO framework to investigate the following question.

- **Population (P)**: Preclinical models of NSCLC and human patients with NSCLC
- **Intervention (I)**: Treatment with oncolytic viruses, either as monotherapy or in combination with other agents
- **Comparison (C)**: Standard treatments, other anticancer therapies, placebo or no treatment
- **Outcome (O)**: Antitumor efficacy (e.g. tumor response, survival), safety and adverse events and immunomodulatory effects

Literature Search Strategy

A comprehensive search was conducted in PubMed, databases to identify relevant studies. The included keywords were “oncolytic virotherapy,” “NSCLC,” “viral therapy,” “immunotherapy,” and “tumor-selective virotherapy.” Boolean operators (AND, OR) and filters (e.g., study type, date range) were used to refine search results. Studies published between 2015 and 2025 were included to capture the latest developments. The methodological quality of the included studies was critically appraised using the Cochrane Risk of Bias (RoB 2) tool for randomized trials and overall confidence in the findings of this systematic review will be evaluated using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) checklist. A PRISMA flow diagram was employed to illustrate the search and selection process (Figure 2).

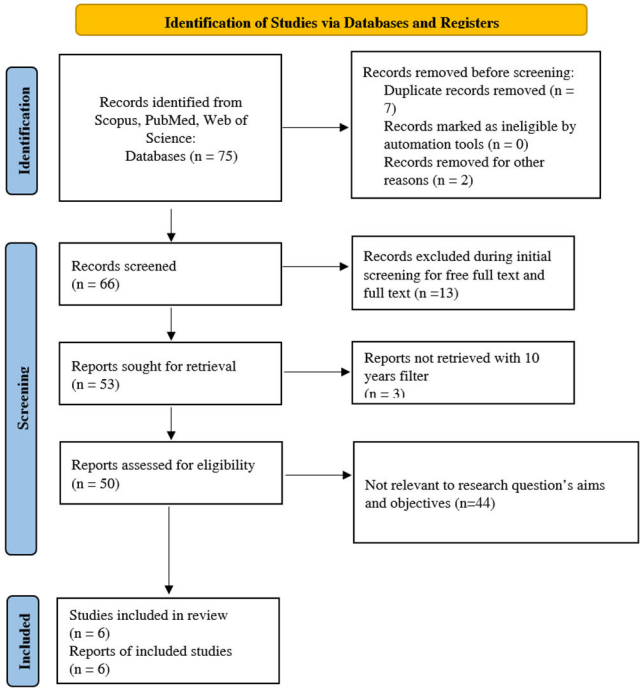

Figure 2: PRISMA flow diagram of the study selection process

RESULTS

The analysis of these six studies reveals a field marked by both exciting breakthroughs and sobering clinical realities (Table 1). While some platforms demonstrate significant potential, the results are inconsistent and notable failures highlight the critical challenges that remain.

Newcastle Disease Virus (NDV)

Hu *et al.* [10] demonstrated that NDV possesses intrinsic oncolytic activity against lung cancer cells grown in 3D spheroid models. A key finding was that the virus-induced cell death was significantly enhanced when combined with chloroquine, an autophagy inhibitor. This indicates that cancer cells activate autophagy as a protective survival mechanism in response to NDV infection and blocking this pathway potently augments the oncolytic effect. However, this study is limited by its preclinical nature, the absence of an intact immune system in the models and the potential toxicity of combining viral therapy with autophagy inhibition in clinical settings.

Pelareorep (Reovirus)

Bradbury *et al.* [9] conducted a randomized phase II trial of pelareorep, a reovirus, in combination with standard salvage chemotherapy for advanced NSCLC. The study concluded that the addition of pelareorep did not improve clinical outcomes, showing no significant difference in either progression-free survival or overall survival compared to chemotherapy alone. This suggests that this particular reovirus platform is not effective in this specific chemotherapeutic context for NSCLC. A key limitation is the potential mismatch between the virus's immunotherapeutic mechanism and the immunosuppressive nature of chemotherapy, highlighting a critical strategic failure in combination partner selection.

Table 1: Summary of Clinical and Preclinical Evidence for Oncolytic Virotherapy in Non-Small Cell Lung Cancer (NSCLC)

Study (PMID) and Citation	Phase/ Type	Oncolytic Virus (Platform)	Key Combination Therapy	Sample Size (N)	Primary Therapeutic Outcomes	Key Immunological and Mechanistic Findings
Hu *et al.* [10]	Preclinical (*In Vitro* - 3D Models)	Newcastle Disease Virus (NDV)	Autophagy Inhibitors (Chloroquine)	N/A (Preclinical)	NDV induced cell death in lung cancer spheroids. Inhibition of autophagy enhanced the oncolytic effect.	NDV-induced cell death is enhanced by autophagy inhibition, suggesting autophagy is a pro-survival mechanism against NDV.
Bradbury *et al.* [9]	Phase 2 Clinical Trial (Randomized)	Pelareorep (Reovirus)	Standard Salvage Chemotherapy	85	No significant difference in PFS or OS between groups.	Well-tolerated but failed to demonstrate efficacy in combination with standard chemotherapy.
Song *et al.* [7]	Preclinical and Biomarker Analysis	M1 Virus (Alphavirus)	None (Monotherapy)	N/A	Efficacy correlated with MXRA8 receptor expression. Identified MXRA8 as a predictive biomarker.	MXRA8 expression levels predict oncolytic susceptibility. Virus selectively kills MXRA8-high cancer cells.
Sakamoto *et al.* [17]	Preclinical (*In Vitro* and *In Vivo*)	Coxsackievirus A11 (CVA11)	None (Monotherapy)	N/A (Preclinical)	Complete tumor regression in human NSCLC xenograft models.	Induced immunogenic cell death (ICD) and promoted strong anti-tumor T-cell responses.
Cui *et al.* [18]	Preclinical (*In Vitro* and *In Vivo*)	Coxsackievirus B5 (CVB5)	DNA-Damage Response Inhibitors	N/A (Preclinical)	Combination therapy induced complete tumor regression in mice.	Synergy mechanism: CVB5 induces DNA damage; DDR inhibitors prevent repair, leading to synergistic apoptosis.
Guan *et al.* [12]	Phase 2 Clinical Trial	RP2 and RP3 (HSV-1)	SBRT → Pembrolizumab	21	ORR: 33.3% DCR: 71.4% Median OS: 18.2 months	In-situ vaccination effect. Increased CD8+ T cells and pro-inflammatory cytokines post-treatment.

M1 Virus (Alphavirus)

Song *et al.* [7] identified the cellular receptor MXRA8 as a critical determinant of the oncolytic specificity of the M1 virus. Their research established that high expression of the MXRA8 protein predicts sensitivity to the virus across multiple solid tumors, including NSCLC. This finding

positions MXRA8 as a valuable predictive biomarker for selecting patients most likely to respond to M1 virus therapy. The major limitation is the purely preclinical nature of this evidence; the clinical prevalence of MXRA8 and the predictive power of this biomarker remain unvalidated in human trials, risking its utility in patient stratification.

Coxsackievirus A11 (CVA11)

Sakamoto *et al.* [17] reported that Coxsackievirus A11 exhibited potent oncolytic activity as a single agent. In human NSCLC xenograft models, CVA11 monotherapy was able to mediate complete tumor regression. The mechanism was associated with the induction of immunogenic cell death, which subsequently stimulated a potent anti-tumor T-cell immune response. The primary limitation is the significant translational gap, as these impressive results were observed in immunocompromised mouse models, leaving the efficacy and safety in humans completely unknown.

Coxsackievirus B5 (CVB5)

Cui *et al.* [18] found that Coxsackievirus B5 was not only oncolytic but also synergized powerfully with DNA-damage response (DDR) inhibitors. The study revealed that CVB5 infection itself induces DNA damage in cancer cells and when combined with an ATR inhibitor (which prevents DNA repair), it leads to catastrophic, irreparable DNA damage and results in complete tumor regression *In Vivo*. A critical limitation is the serious safety concern this synergy raises, as the potentiation of DNA damage could lead to genotoxicity in healthy, dividing cells, posing a significant potential risk for clinical application.

RP2 and RP3 (HSV-1)

Guan *et al.* [12] tested the genetically engineered herpes viruses RP2 and RP3 in a phase II trial with a multi-modal regimen of SBRT and pembrolizumab. The combination was clinically effective, achieving a 33.3% objective response rate. The treatment acted as an in-situ vaccine, evidenced by a significant increase in tumor-infiltrating CD8+ T cells and elevated systemic levels of pro-inflammatory cytokines, demonstrating successful immune activation. *The most notable limitations are the small sample size (N=21), which limits the statistical robustness and generalizability of the findings and the complexity of the regimen, which makes it impossible to discern the individual contribution of the oncolytic virus versus the radiotherapy or immunotherapy.

DISCUSSION

The combined results of these six trials paint a convincing but complex picture of the changing function of oncolytic virotherapy (OV) in the treatment of non-small cell lung cancer (NSCLC). The findings show great promise, especially when viral platforms are carefully combined with contemporary immuno-oncology techniques, but they also highlight important issues that need to be resolved for effective clinical translation.

The Promise of Strategic Combinations

Learning from Success and Failure: The most compelling clinical evidence comes from the RP2/RP3 (HSV-1) trial by Guan *et al.* [12], where the triple-combination with SBRT and pembrolizumab achieved substantial clinical responses. This success exemplifies the modern paradigm of OVs as immunological primers rather than standalone cytolytic agents. The robust T-cell infiltration and cytokine induction observed align with the established mechanism that viral-mediated immunogenic cell death transforms the tumor microenvironment, creating optimal conditions for checkpoint inhibitor efficacy. This approach mirrors the success of talimogene laherparepvec (T-VEC) in melanoma, where the virus demonstrated the ability to convert immunologically "cold" tumors into "hot" microenvironments responsive to anti-PD-1 therapy [13]. Similarly, the ASPECT trial demonstrated that coxsackievirus A21 could modulate the tumor microenvironment in late-stage NSCLC patients, increasing CD8+ T-cell infiltration and PD-L1 expression [14]. However, the pelareorep (reovirus) trial by Bradbury *et al.* [9] presents a crucial counterpoint, demonstrating how improper combination strategies can lead to therapeutic failure. The lack of clinical benefit when combined with chemotherapy likely stems from multiple factors: chemotherapy-induced immunosuppression neutralizing the virus's immunogenic potential, timing issues in administration and potential direct antiviral effects of cytotoxic drugs. This challenge extends beyond NSCLC, as evidenced by the failed phase III MASTERPLAN trial of pelareorep in pancreatic cancer [15] and mixed results with ONYX-015 in combination with chemotherapy in head and neck cancers [16].

Preclinical Promise and Translational Challenges

The exceptional preclinical efficacy demonstrated by both coxsackievirus platforms highlights the ongoing innovation in viral vector development. The complete tumor regressions observed with CVA11 monotherapy [17] and CVB5-DDR inhibitor combinations [18] represent significant advances in viral engineering and combination strategy. However, these impressive results must be viewed in the context of known translational challenges. The field has repeatedly encountered the "efficacy gap" between immune-compromised mouse models and human trials, as seen with various adenovirus constructs that showed robust preclinical activity but limited clinical efficacy [19]. The DNA damage potentiation strategy employed with CVB5 represents a scientifically elegant but clinically risky approach. While the synthetic lethality achieved through viral-induced DNA damage combined with DDR inhibition is mechanistically sound, concerns about genotoxicity in normal tissues remain substantial. This challenge mirrors the development of PARP inhibitors, where initial enthusiasm was tempered by the recognition of hematological toxicities and the emergence of resistance mechanisms [20].

Biomarker Development towards Personalized Virotherapy

The identification of MXRA8 as a predictive biomarker for the M1 virus [7] represents a critical step toward personalized oncolytic virotherapy. This approach acknowledges that not all patients will respond equally to viral therapies and that biomarker-driven patient selection is essential for maximizing therapeutic index. The success of this strategy depends on several factors: establishing reliable assays for MXRA8 detection, determining clinically relevant expression thresholds and validating the biomarker's predictive power in prospective trials. Similar biomarker-driven approaches have revolutionized other cancer therapies, such as HER2-directed treatments in breast cancer [21] and EGFR mutation-guided therapy in NSCLC [22].

Resistance Mechanisms and Safety Considerations

The NDV study [10] provides important insights into autophagy as a resistance mechanism while highlighting the challenges of targeting fundamental cellular processes. The enhanced oncolysis observed with the chloroquine combination, while mechanistically interesting, raises concerns about the therapeutic window. Clinical experience with hydroxychloroquine in cancer therapy has been mixed, with trials often showing limited efficacy and significant toxicity, particularly when combined with other agents [23]. Safety considerations extend beyond autophagy inhibition. The potential for viral pathogenicity, off-target tissue damage and immune-mediated toxicities must be carefully evaluated. The development of T-VEC established important safety precedents, demonstrating that engineered viruses can be administered with manageable toxicity profiles, though herpes-like symptoms and injection site reactions were common [24].

Future Directions and Clinical Implications

The future advancement of oncolytic virotherapy's clinical use in non-small cell lung cancer (NSCLC) depends on some essential strategies. Instead of using standard chemotherapy, success demands a purposeful move to logical combinations that enhance the immune system, like checkpoint inhibitors and radiotherapy. Early on in clinical studies, this transition needs to be steered by a method that utilizes biomarkers to find the patients with the highest likelihood of showing a positive reaction. Enhancing the ability of vectors to target tumors and their effectiveness necessitates ongoing engineering and adaptive clinical trial frameworks are going to be very important for testing these intricate treatment plans effectively. In the end, using the lessons learned from encouraging outcomes and difficult setbacks will be essential in guiding the advancement from laboratory potential to tangible clinical results, making certain these cutting-edge therapies can be safely and successfully added to the range of treatments available for NSCLC.

CONCLUSIONS

Oncolytic virotherapy shows significant promise for NSCLC treatment, particularly when used in strategic combinations. The engineered HSV-1 platform (RP2/RP3) combined with SBRT and pembrolizumab has demonstrated substantial clinical efficacy through robust immune activation. However, challenges remain, including variable efficacy across different viral platforms, safety concerns with combination therapies and significant translational gaps between preclinical and clinical results. Future success will require optimized combination strategies, improved patient selection through biomarker development and innovative clinical trial designs to fully realize the potential of this emerging therapeutic modality. The fundamental mismatch between OV's immunostimulatory mechanism and chemotherapy's immunosuppressive effects serves as a critical lesson for future trial design. Preclinical studies reveal substantial promise, particularly with coxsackievirus demonstrated remarkable efficacy with complete tumor regressions, while MXRA8 as a promising predictive biomarker. However, these encouraging findings are tempered by significant translational challenges, including the "efficacy gap" between immunocompromised models and human trials and legitimate safety concerns regarding combination strategies that potentiate DNA damage. The path forward requires a multifaceted strategy prioritizing immunologically congruent combinations, rigorous biomarker validation, innovative vector engineering and adaptive clinical trial designs. Future success will depend on learning from both breakthroughs and setbacks, maintaining realistic expectations about the translational process and systematically addressing the identified challenges of safety, efficacy and optimal patient selection. In summary, while oncolytic virotherapy has demonstrated its potential to meaningfully impact NSCLC treatment, particularly as an immune-priming modality, its full clinical integration will require disciplined, scientifically rigorous development that builds upon the valuable lessons captured in these foundational studies.

Abbreviations

NSCLC (Non-Small Cell Lung Cancer), OV (Oncolytic Virotherapy), TME (Tumor Microenvironment), DAMPs (Damage-Associated Molecular Patterns), PAMPs (Path-Associated Molecular Patterns), HSV-1 (Herpes Simplex Virus type 1), SBRT (Stereotactic Body Radiation Therapy), ORR (Objective Response Rate), DCR (Disease Control Rate), OS (Overall Survival), PFS (Progression-Free Survival), NDV (Newcastle Disease Virus), ICD (Immunogenic Cell Death), DDR (DNA-Damage Response), MXRA8 (Matrix Remodeling-Associated Protein 8), CVA11 (Coxsackievirus A11), CVB5 (Coxsackievirus B5) and T-VEC (Talimogene Laherparepvec). These abbreviations represent key concepts, therapeutic platforms and clinical parameters central to understanding the current landscape of oncolytic virotherapy in lung cancer treatment.

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