

## ONCOLYTIC ADENOVIRUS-BASED IMMUNOTHERAPY FOR MALIGNANT MESOTHELIOMA: PRECLINICAL ADVANCES AND FUTURE PERSPECTIVES

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**Abstract:** Malignant mesothelioma is a rare but highly aggressive cancer, with an incidence of approximately 1–2 cases per million per year in industrialized countries and a global annual mortality exceeding 30,000 cases. The disease is caused mainly by exposure to asbestos and is resistant to conventional treatment modalities, resulting in poor outcomes. Standard approaches include surgery, chemotherapy, and, more recently, immune checkpoint inhibitors. However, owing to the aggressive nature of cancer, the prognosis is poor, with limited treatment options. Globally, the disease accounts for more than 30,000 deaths annually. Current treatment efficacy remains suboptimal, particularly in advanced stages. Oncolytic virotherapy, especially adenovirus-based vectors, has emerged as a novel immunotherapeutic strategy with the potential to induce tumour lysis and stimulate antitumour immunity. This review summarizes the current treatment landscape for mesothelioma and highlights preclinical and early clinical findings on engineered oncolytic adenoviruses, particularly those expressing ICOSL, CD40L, and OX40L, and their promising synergistic effects with checkpoint blockade and chemotherapy. Furthermore, in this review, we present insights from clinical studies of the effects of adenovirus Ad5/3-D24-GM-CSF on mesothelioma and discuss promising avenues for future immunotherapy.

1. Introduction. 2. Oncolytic Adenoviruses and Their Therapeutic Potential. 3. Preclinical and Clinical Insights from Mesothelioma Models. 4. Immune Profiling and Tumor Microenvironment Modulation. 5. Perspectives on Adenoviral Vector Design and Combinations. 6. Future directions and clinical translation. 7. Challenges and Limitations of Oncolytic Adenovirus-Based Immunotherapy. 8. Conclusion.

**Keywords:** immunotherapy, mesothelioma, oncolytic adenovirus, cancer therapy, co-stimulatory molecules

### 1. Introduction

Malignant pleural mesothelioma (MPM) originates from mesothelial cells and is caused primarily by exposure to asbestos. The malignancy is usually diagnosed at an advanced stage, contributing to a median overall survival of only 9–12 months (Pisani et al. 2020). Current treatment strategies include surgery, chemotherapy, and immunotherapy, yet the outcomes remain unsatisfactory (Kuryk et al. 2022).

The standard of care for unresectable MPM is a combination of pemetrexed and cisplatin. Although this regimen modestly prolongs survival, the benefits are often transient due to chemoresistance and minimal immunologic activation (Kuryk et al. 2016). Mul-

timodal approaches involving extrapleural pneumonectomy or pleurectomy/decortication are considered in select operable patients but carry significant morbidity (Treasure et al. 2011).

In the immunotherapy era, immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. The CheckMate 743 trial demonstrated that the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) improved survival over chemotherapy, especially in patients with nonepithelioid subtypes. Nevertheless, the majority of cancer patients still fail to achieve long-term clinical benefit due to the immunosuppressive tumor microenvironment (TME) and low T-cell infiltration (Garofalo et al. 2022).

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To overcome these limitations, novel immune-based strategies, such as oncolytic virotherapy, have emerged as complementary approaches. Published meta-analyses have demonstrated that immune checkpoint inhibitors are more effective when combined with modalities that are able to modulate the TME, such as oncolytic viruses (Jones et al., 2021). Recent advancements suggest that combining ICIs with oncolytic virotherapy could increase antitumour responses and improve patient outcomes. The pathogenicity of MPM is complex and not only caused by asbestos but also by the complex molecular pathogenesis and intrinsic resistance mechanisms of the disease (Wadowski et al., 2020). This finding is supported by a broad analysis of immune checkpoint blockade in mesothelioma, which revealed limited responses unless immune checkpoint blockade was combined with other modalities (Boutin et al., 2021). One promising candidate, ONCOS-102, a chimeric Ad5/3-D24 oncolytic adenovirus expressing GM-CSF (ONCOS-102, Ad5/3-D24-GM-CSF), has shown encouraging signs of immune activation and prolonged survival when combined with chemotherapy in phase II studies (Ponce et al., 2023).

2. Oncolytic Adenoviruses and Their Therapeutic Potential

Oncolytic viruses (OVs) are engineered to selectively infect and lyse cancer cells while sparing normal tissues. This causes direct oncolysis and the induction of immunogenic cell death (ICD), which can trigger systemic antitumour responses. Adenovirus vectors have versatile applications in cancer therapy due to their genetic stability, large transgene capacity (Mura-

vyeva et al. 2024), immunogenicity and safety profile in humans (Biegert et al. 2021).

Early-generation vectors such as Ad5/3-D24-GM-CSF have shown promise in preclinical and early clinical trials when combined with chemotherapy (Kuryk et al. 2016; Ponce et al. 2023). More recently, oncolytic adenoviruses have been designed to express multiple immune-stimulating molecules, such as OX40L, CD40L, or GM-CSF, to increase antigen presentation and T-cell activation. The AdV5/3-D24-ICOSL-CD40L vector represents a novel generation of such constructs. It combines a tumor-selective E1A deletion (D24) with a chimeric Ad5/3 fibre for enhanced tumor targeting and is armed with ICOSL and CD40L to potentiate T-cell costimulation (Garofalo et al. 2021).

Interestingly, in a recent study, Chiaro et al. (2023) described a novel pipeline for identifying mesothelioma-specific MHC-I peptides via immunopeptidomics and incorporating them into a PeptiCRAd-based immunotherapy complex (adenovirus AdV5/3-D24-CD40L-OX40L-based platform). This novel strategy leverages the surface presentation of tumour antigens, allowing the selective coating of oncolytic adenoviruses with immunogenic peptides. The published results underscore the importance of direct MHC-I peptide selection and presentation in an immunological context. This allows the development of tumor-specific immunity and a more accurate representation of CD8<sup>+</sup> T-cell targets. PeptiCRAd-coated viruses induce potent antitumour immune responses in vivo, validating the concept of combining personalized antigen discovery with oncolytic virotherapy for mesothelioma (Chiaro et al. 2023). Table 1 lists the key characteristics of two oncolytic adenovirus vectors: AdV-D24-ICOSL-CD40L and Ad5/3-D24-GM-CSF.

Table 1. Summary of the key features of AdV-D24-ICOSL-CD40L and Ad5/3-D24-GM-CSF.

| Oncolytic Adenovirus         | Tumor Selectivity  | Transgenes                                        | Studies                                                     | Major results                                               |
|------------------------------|--------------------|---------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| AdV5/3-D24-ICOSL-CD40L       | Yes (E1A deletion) | ICOSL and CD40L for enhanced T-cell costimulation | Preclinical mesothelioma models (both in vitro and in vivo) | Safety profile, enhances efficacy, ICD, T-cell infiltration |
| Ad5/3-D24-GM-CSF (ONCOS-102) |                    | GM-CSF for improved antigen presentation          | Phase I/II in mesothelioma (NCT02963831)                    | T-cell infiltration, safety profile, improved efficacy      |

### 3. Preclinical and Clinical Insights from Mesothelioma Models

The AdV5/3-D24-ICOSL-CD40L vector has demonstrated promising preclinical efficacy in various *in vitro* and *in vivo* models of mesothelioma. In 2D and 3D spheroid cultures, the virus induced direct oncolysis and induced ICD. In immunodeficient and humanized mouse models bearing mesothelioma tumors, intratumoral injection of the vector resulted in significant tumor volume reduction—up to 60% in treated mice—especially when combined with anti-PD-1 therapy (Garofalo et al. 2023).

A phase I/II clinical trial with adenovirus Ad5/3-D24-GM-CSF in combination with pemetrexed and platinum-based chemotherapy in patients with unresectable MPM further underscored the clinical potential of this strategy (NCT02963831). This study revealed that treatment with the vector was well tolerated and promoted robust tumor immune activation. In total, 31 patients were enrolled. Anaemia (15.0% and 27.3%) and neutropenia (40.0% and 45.5%) were the most frequent grade  $\geq 3$  adverse events (AEs) in the Ad5/3-D24-GM-CSF ( $n=20$ ) and chemotherapy-alone ( $n=11$ ) cohorts. No patients discontinued Ad5/3-D24-GM-CSF due to AEs. An improvement in overall survival (30-month OS rate 34.1% vs 0; median OS 20.3 vs 13.5 months) with Ad5/3-D24-GM-CSF versus chemotherapy alone has been reported. Therapy with Ad5/3-D24-GM-CSF was associated with increased T-cell infiltration and immune-related gene expression, which was not observed in the cohort receiving only chemotherapy. Importantly, immune activation in the TME was associated with survival in a cohort treated with a virus (Ponce et al. 2023). Notably, increased infiltration of CD4<sup>+</sup>, CD8<sup>+</sup>, and granzyme B<sup>+</sup> T cells and upregulation of cytotoxicity gene signatures were observed. In contrast, these findings were not observed in patients treated with chemotherapy alone (Ponce et al. 2023).

### 4. Immune Profiling and Tumor Microenvironment Modulation

The combination therapy of adenovirus AdV5/3-D24-ICOSL-CD40L with PD-1 inhibition in preclinical studies led to elevated levels of CD8<sup>+</sup> cytotoxic T cells, CD4<sup>+</sup> helper T cells, and granzyme B<sup>+</sup> effector cells, indicating active cytotoxic engagement. However, the number of regulatory FoxP3<sup>+</sup> T cells was reduced, suggesting a shift toward a proinflammatory TME (Garofalo et al. 2023).

Chiaro et al. confirmed that intratumoral injection of peptide-coated adenoviruses (PeptiCRAd) in mice

enhanced local immune responses, with significant increases in antigen-specific CD8<sup>+</sup> T cells and improved tumor control. Additionally, the study demonstrated that among strong MHC-binding peptides, only a subset is expressed on tumor cells, supporting the importance of immuno-peptidomics for peptide target validation, especially in cancer vaccine approaches. These results support the concept that specific peptides, when delivered via adenoviral platforms (PeptiCRAd), can reprogram the TME, elicit systemic immunity and enhance antitumor effects (Chiaro et al. 2023).

Similarly, multiplex immunofluorescence analyses in the Ad5/3-D24-GM-CSF clinical trial on mesothelioma revealed significant increases in the CD8<sup>+</sup>:Treg ratio and M1:M2 macrophage polarization. Transcriptomic analysis of tumor biopsies revealed elevated expression of T-cell markers (CD3E, CD4, and CD8A) and cytotoxicity-related genes in patients with the highest survival (Ponce et al. 2023).

Furthermore, gene expression analyses of the chemokines CXCL9 and CXCL10 revealed upregulation in tumours from combination-treated mice. In fact, these chemokines play critical roles in T-cell recruitment and retention, supporting the observation of increased numbers of tumor-infiltrating lymphocytes (TILs). The present findings underscore the role of the adenovirus vector as a potent immune primer capable of remodelling the TME toward an immune-permissive state (Garofalo et al. 2023).

### 5. Perspectives on Adenoviral Vector Design and Combinations

The shift toward armed oncolytic vectors expressing cytokines, chemokines, and costimulatory molecules reflects a broader effort to engage both innate and adaptive immunity, leading to increased anticancer effects. Recent studies with adenoviruses expressing TIMP2 and PADI1 have demonstrated antitumor efficacy in preclinical models of melanoma (Kuryk et al. 2023). TIMP2, a tissue inhibitor of metalloproteinases, disrupts tumour-stroma interactions and inhibits angiogenesis, whereas PADI1 expression induces immunogenic cell death through citrullination of histones, potentially increasing tumour antigenicity (Wu et al. 2023). Arming oncolytic adenoviruses with nonimmunostimulatory transgenes offers a complementary approach to enhancing their efficacy through various mechanisms, such as the TME and metabolic remodelling. This multimodal mode of action enhances immune T-cell infiltration and improves treatment responsiveness when combined with ICIs. Importantly, such strategies strengthen immunostimulatory approaches by disrupting stromal barriers, modulating

tumor metabolism, and promoting immune cell infiltration (Wu et al. 2024).

The concept described by Chiaro et al. shows how immunopeptidomics analyses can be combined with PeptiCRAd, enhancing the specificity and potency of oncolytic immunotherapy vaccines (Chiaro et al. 2023). This opens new avenues for personalized multi-valent vaccine design. Future designs may include neoantigens alongside traditional immune costimulatory ligands, enzymes, inhibitors, cytokines, and chemokines to synergize with ICIs and other immunomodulators.

These advancements suggest that vector design can be tailored to tumour-specific features. For mesothelioma, combining oncolytic adenoviruses with chemotherapy, ICIs, or other immune modulators may enhance clinical efficacy and improve patient quality of life.

## 6. Future directions and clinical translation

The successful translation of novel oncolytic adenoviruses into the clinic will rely on optimizing multiple aspects, such as dosing frequency, route of administration, vector design, patient immune fitness and genetic background. Refined delivery strategies, such as repeated intratumoral dosing, systemic administration with tumour-targeting modifications, or shielding via carrier cells, are actively being explored to increase biodistribution and reduce antiviral neutralization.

Combination therapies that combine oncolytic viruses with ICIs, cancer vaccines, and TME modulators are expected to further increase antitumour efficacy. Importantly, predictive biomarkers such as baseline TIL, IFN-related gene signatures, or CXCL9/10 expression may guide patient selection and therapeutic personalization in the near future.

Clinical findings from the Ad5/3-D24-GM-CSF phase II study in patients with unresectable MPM support the viability of this strategy. In this trial, patients who received the adenovirus in combination with chemotherapy reached a median OS of 20.3 months versus 13.5 months in the group treated with chemotherapy only. Furthermore, profound infiltration of CD8<sup>+</sup> T cells and upregulation of interferon-stimulated and cytotoxic gene signatures were observed in the combination group (Ponce et al. 2023).

Although the intratumoral administration of adenoviruses remains a standard approach, novel intravenous delivery systems are more commonly and frequently utilized to target distant malignancies, thus broadening the therapeutic reach of adenovirus-based immunotherapy.

## 7. Challenges and Limitations of Oncolytic Adenovirus-Based Immunotherapy

Despite encouraging results, several challenges limit oncolytic adenovirus-based therapies in the treatment of malignant mesothelioma. One major barrier is the immunosuppressive TME, which affects the infiltration of TILs, the functionality of effector T cells and tumor recognition (Garofalo et al. 2023).

Additionally, preexisting immunity to adenoviruses may reduce viral spread and replication, thus potentially reducing therapeutic efficacy in patients previously exposed to the virus (Li et al. 2015). Nevertheless, various strategies, such as the use of chimeric fibres or shielding via carrier cells, are being developed to overcome this challenge (Bessis et al. 2004).

Another limitation is the heterogeneity of antigen presentation, as mesothelioma has a low mutational burden and limited neoantigen diversity, limiting the immunogenic potential of peptide-based vaccines (Chiaro et al. 2023).

Importantly, intratumoral injection of adenoviruses may not be feasible for patients with inaccessible tumors, stressing the need for improved systemic delivery systems (Zheng et al. 2019). Furthermore, there is an unmet need for validated predictive biomarkers that can be incorporated into clinical diagnostic routines. Currently, markers such as T-cell infiltration density or interferon-response gene signatures are essential for guiding therapeutic decisions and tailoring treatment strategies, highlighting the importance of clinical immune monitoring in clinical studies.

## 8. Conclusion

Adenovirus-based oncolytic immunotherapy serves as a promising approach to resolve the unmet clinical need in mesothelioma therapy. Through direct tumor lysis, immune activation, and ICD, these vectors can convert cold tumors into hot tumors. Engineered adenovirus vectors have shown potential in both pre-clinical and early clinical studies, particularly when combined with checkpoint blockade or chemotherapy. Continued improvements in the use of viral vectors in combination with standard and emerging therapies may significantly enhance outcomes for mesothelioma patients.



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### Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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