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Efficacy and Safety of MUC1 Antigen-Specific Vaccine as a Breakthrough Solution in the Treatment of Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Introduction: Non-Small Cell Lung Cancer (NSCLC) is the leading cause of death for cancer patients globally. Most of the patients are diagnosed in advanced stage that can only receive conventional chemotherapy with low overall survival and low progression-free survival outcomes. With the advancement of technology, researchers have discovered that antigen-specific vaccine could be utilized to fight tumor cells. MUC1 antigen-specific vaccine is a novel solution that has been proved to be specific and accurate against NSCLC. In this study, we would like to present current best evidences regarding the efficacy and safety of MUC1 antigen specific vaccine in battling NSCLC.

Methods: Literature search was conducted on databases, namely PubMed, Scopus, Cochrane, Science Direct, EBSCOhost, and Google Scholar up to August 27th 2022. Our inclusion criteria include randomized controlled trials in patients with advanced stage NSCLC, given MUC1 antigen-specific vaccine as treatment, compared to placebo as control group, and measured the efficacy in terms of overall survival and progression-free survival, quality of life, and adverse events.

Results and discussion: Six randomized controlled trials were included in this review. Overall, longer overall survival and progression-free survival is observed in all studies. However, significance differed from study to study. This could be attributed to different patient characteristics and chemotherapy regimens used. MUC1 antigen-specific vaccine is more effective in patients who received concurrent chemoradiotherapy, high sMUC1 and ANA level, and non-squamous tumor type. Minimum adverse events were reported and incidence is similar with the control group. No negative impact on quality of life was observed.

Conclusion: MUC1 vaccine showed a promising impact on improving patients' overall survival and progression-free survival while ensuring patient's safety. However, further studies with larger sample size are recommended on more specific populations, for instance, patients with concurrent chemotherapy.

KEYWORDS: Non-small Cell Lung Cancer, MUC1 vaccine, tecemotide, efficacy, safety

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I. INTRODUCTION

Lung cancer is the most common cancer with highest mortality rate all around the world.[1] More than 1.38 million people die of lung cancer globally.[2] Approximately 80% of lung cancers are Non-Small Cell Lung Cancer (NSCLC), of which approximately 75% are in advanced stage or inoperable at the time of diagnosis.[3,4] At this point, the standard treatment is chemotherapy.[2,3]

Conventional chemotherapy regimens are effective but have shown limited efficacy. Hence, new strategies are being explored for the treatment of lung cancer, including targeted active immunotherapy.[4,5] Recent studies suggest that the use of therapeutic cancer vaccines reduces toxicity and improves overall survival and progression-free survival compared to conventional chemotherapy. It is unanimously accepted that the goal of treatment for patients with advanced NSCLC is to ideally improve and prolong overall survival without

adversely affecting quality of life. Moreover, the positive effect on quality of life can be considered as a true improvement even without a clear overall survival benefit from the new therapy.[3,5,6]

In NSCLC, glycoprotein mucin 1 (MUC1) is overexpressed and abnormally glycosylated. MUC1 contributes in causing inappropriate activation and promotes intracellular signaling pathways that support cancer cell growth, proliferation, and survival. Therefore, researchers are currently exploring and developing an effective treatment for NSCLC which targets MUC1, including Tecemotide. Tecemotide (L-BLP25) is a MUC1 antigen-specific immunotherapy that can induce T-cell responses to MUC1 in both preclinical MUC1 transgenic lung cancer mouse models and patients.[4]

II. METHODS

Search Strategy

This literature review was conducted by three authors independently until August 27, 2022, by conducting a literature search on international online databases, namely PubMed, Cochrane, SCOPUS, ScienceDirect, EBSCOhost, and Google Scholar. The keywords for literature search used are (non small cell lung cancer OR carcinoma) AND (MUC1 vaccine OR MUC1 antigen OR tecemotide) AND (efficacy OR safety). The use of advanced search mode if necessary, to eliminate inappropriate literature. Complete keywords used can be accessed in **Appendix 1** in attachment section.

Study Eligibility Criteria

Next, the authors set inclusion and exclusion criteria to filter those search results.The inclusion criteria used are clinical studies, using interventions in the form of MUC1 or tecemotide injection, measuring overall survival and quality of life, and published in the last 10 years to increase the relevance of studies to current conditions. In addition, the exclusion criteria applied include studies that are not available in the form of complete documents, as well as studies that use languages other than Indonesian and English, to reduce the bias of understanding by the authors.

Data Extraction

Literature that has passed at the search stage will be sorted and reviewed to eliminate irrelevant articles. After the authors confirmed that all studies to be used met the inclusion and exclusion criteria, duplicate articles were eliminated with the help of EndNote X9 software. Thus, based on a search of the database used by the authors, as many as 6 literatures were extracted and analyzed in this literature review.

III.RESULTS

Search results and study selection

Database searching yielded 284 studies, with 25 duplicates removed. Title screening excluded 157 studies, and abstract screening excluded further 78 studies. A total of 24 full-text articles were assessed for eligibility, after which 8 studies with ineligible outcome data, 7 with irretrievable full-text articles, and 3 with incompatible language were excluded. A total of 6 studies were found to fulfill the inclusion criteria.

Study characteristics and design

Studies that were included were randomized clinical trials conducted in various countries from different socioeconomic backgrounds. Patients in the studies included were unresectable stage III to IV of NSCLC. We only include studies with interventions given were MUC1 derived antigen specific vaccines, such as tecemotide or TG4010, and placebo as the control group. Outcomes assessed were efficacy, measured by overall survival (OS), progression-free survival (PFS), and number of mortality cases. Meanwhile, safety is measured through the number of any adverse events observed related to the intervention given. Study characteristics and results is presented in **Table 1** and **Table 2.**

Table 1. Study characteristics

Author; year of publication	Study design	Location	Subject characteristics				
			Sample characteristics	Sample number; Mean age (SD)	Follow-up duration	Intervention group	Control group
Butts, et al; 2014	Randomized Controlled Trial	Multiple countries, 33 countries total	Patients with unresectable stage III NSCLC and ECOG performance status of 0 or 1.	Intervention: 829; 61 (19-89) Placebo: 410; 61.5 (24-83)	1 year, 2 year, and 3 years	Tecemotide (MUC-1 derived 25 amino acid BLP25 lipopeptide), immunoadjuvant monophosphoryl lipid A, and liposome forming lipid; cyclophosphamide 300 mg/m^2	Placebo
Katakami, et al; 2017	Randomized controlled trial	Japan	Patients with unresectable stage III NSCLC, with stable disease after primary chemoradiotherapy.	Intervention: 114; 62 (33-86) Placebo: 58; 47 (36-81)	48 months	Tecemotide 930 ug and cyclophosphamide 300 mg/m^2	Placebo
Quoix, et al; 2015	Randomized Controlled Trial	Multiple countries	Patients who had histologically confirmed, stage IV (according to the Union Internationale Contre le Cancer) non-small-cell lung cancer without a known activating EGFR mutation. Patients had to have at least one measurable site of disease with a CT scan or MRI	Intervention: 111; 63 (57–68) y Placebo: 111; 59 (54–66) y	18.2 months	TG4010 at a dose of 10^8 plaque-forming units once a week for 6 weeks	Placebo (formulated buffer)
Mitchell, et al; 2015	Randomized Controlled Trial	Multiple countries	Patients included were unresectable, stage III NSCLC patients following two or more cycles of platinum-based chemotherapy and radiotherapy (≥50 Gy).	Intervention: 829; 61.0 y Placebo: 410; 61.0 y	Intervention: 58.7 months Placebo: 57.3 months	Subcutaneous tecemotide (806 µg lipopeptide)	Placebo
Rotonda, et al; 2015	Randomized Controlled Trial	Multiple countries	Patients aged 18 years or older, confirmed stage IIIb or IV NSCLC, chemotherapy naive, expressing MUC1, with at least one lesion measurable by CT-Scan, a performance status (PS) of 0 or 1 and a life expectancy of at least 4 months.	Intervention: 74; 58.36 y Chemotherapy: 74; 60.41 y	6 months progression free survival	Chemotherapy combined with TG4010 subcutaneously at the dose of 10^8 pfu once per week for 6 weeks then once every 3 weeks up to progression.	Chemotherapy alone
Tosch, et al; 2017	Randomized Controlled Trial	France	Patients aged 18 years or older, histology-confirmed stage IV NSCLC, untreated, expressing MUC1 in at least 50% of tumor cells, ECOG performance status of 0 or 1, and adequate renal, hematologi, and hepatic function.	Intervention: 111; - y Chemotherapy: 111; - y	Intervention: 5.9 months Placebo: 5.1 months	Subcutaneous injections of 108 plaque-forming units of TG4010 from the beginning of chemotherapy every week for 6 weeks then once every 3 weeks up to progression.	Placebo

*Significant results. Abbreviations: ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small-cell lung cancer; MUC1; mucin 1.

Table 2. Study outcomes

Author; year of publication	Efficacy outcomes				Safety outcomes			
	Parameters	Intervention group	Control group	Significance (p-value)	Parameters	Intervention group	Control group	Significance (p-value)
Butts, et al; 2014	Median overall survival (months)	25.6	22.3	0.123	Adverse events, n (%)	938 (92%)	432 (91%)	N/A
	Time to symptom progression (months)	14.2	11.4	0.023*				
	Time to disease progression	10	8.4	0.053				
Katakami, et al; 2017	Median overall survival (months)	32.4	32.2	0.83	Adverse events (%)	94.7%	93%	N/A
Quoix, et al; 2015	Progression-free survival at 9 months	31% (22–40)	20% (13–29)	0.019*	Grade 1–2 injection-site reactions	36 (33%)	4 (4%)	N/A
	Overall survival (months)	12.7 (9.8–16.4)	10.6 (9.5–14.3)	0.055	Grade 3-4 adverse effects	4 (4%)	11 (10%)	N/A
	Deaths	78 (70%)	87 (78%)	N/A	Neutropenia grade 3 Anaemia grade 3	29 [26%] 12 [11%]	22 [21%] 16 [15%]	N/A N/A
Mitchell, et al; 2015	Overall survival (months)	25.8 months	22.4 months	0.111	N/A	N/A	N/A	N/A
Rotonda, et al; 2015	N/A	N/A	N/A	N/A	FACT-L Global Score	66.48	71.95	0.068
Tosch, et al; 2017	Progression-free survival at (months)	5.9 months	5.1 months	$p < 0.05$*	N/A	N/A	N/A	N/A

Author; year of publication	Study design	Location	Subject characteristics				Control group
			Sample characteristics	**Sample number; Mean age (SD)**	**Follow-up duration**	**Intervention group**	
Butts, et al; 2014	Randomized Controlled Trial	Multiple countries, 33 countries total	Patients with unresectable stage III NSCLC and ECOG performance status of 0 or 1.	Intervention: 829; 61 (19-89) Placebo: 410; 61.5 (24-83)	1 year, 2 year, and 3 years	Tecemotide (MUC-1 derived 25 amino acid BLP25 lipopeptide), immunoadjuvant monophosphoryl lipid A, and liposome forming lipid; cyclophosphamide 300 mg/m^2	Placebo
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IV. DISCUSSION

Antigen specific vaccine for NSCLC

Vaccines, while have long been proved effective at targeting pathogens, have a plethora of problems when facing tumor cells. One of the most concerning reasons is the difficulty of discovering the specific target of the tumor cells which is unique to each cancer patient. However, with the rapid pace of technology development in the health sector, scientists now believe that it might be difficult, but not impossible to have the solution to eradicate cancer all around

the world in the form of antigen-specific vaccines. Therapeutic vaccination is justified on the theory that a targeted cellular response against tumor antigens would have great safety and tolerability profiles, as well as a long-lasting effect that would likely stop disease progression and relapse.[7]

In developing antigen specific vaccines, the most crucial step is to identify tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs), which will be the target for the vaccine.[8] One recent discovery of this sophisticated invention is the vaccine for advanced stage Non-Small Cell Lung Cancer (NSCLC). These aggressive tumors are among the top list of concern for researchers and physicians due to its high prevalence and fatality rate. Therefore, many evidences have been made available regarding the benefits of antigen-specific vaccines for NSCLC.[9]

MUC1 as an innovative therapeutic target

Mucin 1 (MUC1) are transmembrane glycoproteins that are expressed in the epithelial cells of various organs. Under normal circumstances, MUC1 plays a role in the formation of protective barrier for epithelial cells, including in the lungs.[10] It also serves as a cell receptor through which various protein kinases interact to influence signal transduction pathways.[11] Aberrantly expressed MUC1 has been identified and implicated in the pathogenesis of numerous types of cancer, including NSCLC.[10,12–15] It is found in 80% of NSCLC, and more frequently in adenocarcinomas than other subtypes.[10,16] Aberrant MUC1 can be defined as increased in expression ten times of normal level; loss of polarity in receptor distribution; incomplete glycosylation of carbohydrate side chain, creating new carbohydrate side chains knowns as T, Tn, and sialyl-Tn antigens; and downregulation or upregulation of its core peptide.[11] MUC1 overexpression has been known to uprergulate vascular endothelial growth factor (VEGF), thus promoting angiogenesis which is important in tumor growth, invasion, and metastasis. Furthermore, MUC1 activates the PI3K pathway which enhance AKT and ERK signalling for tumor cell survival and angiogenesis.[12,17] MUC1 has also been implicated in drug resistance and poorer prognosis in NSCLC.[13,18,19]

Thus, its involvement in various cancer pathogenesis, as well as its influence on treatment response and prognosis, make MUC1 a potential target for lung cancer therapy. A study by Xu et al demonstrated that downregulation of MUC1 inhibited cell proliferation, VEGF production, induced apoptosis, and suppressed activation of AKT and ERK pathways in *in vivo* models.[17] This is supported by Raina et al's study which showed the inhibition of MUC1 downregulates the PI3K pathway, which in turn affects cell growth and survival.[13]

Several vaccines utilize MUC1 antigen as a target has been developed and investigated in clinical trials. TG4010 is a recombinant strain of vaccina virus Ankara expressing MUC1 and interleukin 2. Another vaccine is tecemotide, a liposomal vaccine which utilizes MUC1-derived amino acid L-BLP25.[11,12,14]

Efficacy of MUC1 specific vaccine

Six studies included in this review reported the efficacy of MUC1 specific vaccine for advanced stage NSCLC in terms of overall survival (OS). However, only a study by Quoix et al reported significant difference of OS between intervention and control group (p=0.055). On the other hand, three of the six studies reported another parameter of efficacy, namely progression-free survival. These studies, by Butts et al, Quoix et al, and Tosch et al, consistently reported similar significant efficacy of MUC1 vaccine in terms of PFS ($p<0.05$). Finally, mortality or deaths were reported by Quoix et al, however, no significant differences were found.

Study by Tosch et al showed that MUC-1 specific antigen vaccine significantly improves survival in NSCLC patients compared to chemotherapy only, with a median survival of 12.7 months (HR 0.58). This study also assessed immune response to vaccine, namely T cells responses against tumor antigens. Vaccine injection is shown to modulate CD8+ T cell response to MUC1 cancer antigen. A proportion of patients, ranging from 5-39% depending on the antigen, also developed immune response to other tumor associated antigens. Interestingly, patients who developed immune response against MUC1 had significantly more responses against other tumor antigens. This suggest that MUC1 vaccine can modulate the immune system to evolve and broaden epitope recognition. Response against a wider selection of antigens can be beneficial in long term tumor control, which is reflected in better overall survival and progression-free survival.[20]

Study by Butts et al[4], Katakami et al[5], Quoix et al[6], and Mitchell et al[21] also showed that vaccine group has longer overall survival, however the difference with standard therapy was not significant. One explanation is heterogeneity within study population in baseline biomarkers. For example, Katakami et al study identified soluble MUC1 (sMUC1) and antinuclear antibody (ANA) as possible prognostic factors influencing overall survival, thus benefits of MUC1 vaccine could be more clearly seen in these groups.[5] High sMUC1 level may also reflect more MUC1 cellular expression, providing more target for vaccine-induced immunity. This is confirmed in Michell et al study, which showed significant prolonged overall survival in high sMUC1 subgroup (HR 0.66; p=0.001) and high ANA subgroup (HR 0.43; p=0.0005) with MUC1 vaccine.[21] The amount of triple positive activated lypmphocytes (TrPAL) and histology of tumor also influenced result, with greater effect on low TrPAL value (HR 0.67; p=0.018) and non-squamous tumor type (HR 0.73; p=0.03).[6]

Another possible explanation is the timing of the treatment delivery. Subgroup analysis in Butts et al's study showed that vaccine given concurrently with chemoradiotherapy have significant prolonged survival (HR

0.78; p=0.016), but no significant difference is observed in the sequential chemoradiotherapy group.[4] Similar results were seen in Mitchell et al's study (HR 0.89; p=0.026).[21] Previous study in head and neck cancer had shown that chemoradiotherapy can upregulate several molecules, including HLA, adhesion molecules, inflammatory mediators, and death receptors, which has been shown to enhance immune-mediated killing and increased effectiveness of immunotherapy afterwards.[22,23] This suggest that vaccine is more beneficial as maintenance therapy for patients who had received concurrent chemoradiotherapy.

Result for progression-free survival is more consistent. Study by Butts et al[4], Quoix et al[6], and Tosch et al[20] showed that MUC1 antigen vaccine significantly improved progression-free survival compared to standard treatment. As with overall survival, prolonged progression-free survival may be a result of CD8+ T cells to MUC1 antigen, which lead to better tumor growth control. Broadening immunity against other tumor antigens, as well as modification of tumor microenvironment, could also contribute to better tumor control.[20]

Safety profile of MUC1 specific vaccine

Furthermore, besides superiority in terms of efficacy, safety profile is also very important to be addressed in implementing vaccination. Regarding safety, most studies reported minimal drug-related toxicity. No clinically concerning difference between vaccine group and control were observed. Most common side effects were lymphopenia, and incidence of grade 3-4 adverse event is higher in vaccine group, although not significantly so.[5] Minimal immune-mediated adverse events were reported, and incidence is similar between control and vaccine group. Some patients reported minor to moderate injection site reactions and fatigue.[6,20,24] Other adverse events reported were anemia, neutropenia, fever, and papular rash, although severity rarely exceeded grade 2.[24] A study by Rotonda et al explored quality of life (QOL) of patients receiving MUC1 antigen vaccine and found no significant difference between control and vaccine group, despite vaccine group presenting with lower initial QOL scores.[3] This support that MUC1 antigen vaccine is generally well-tolerated by patients.

Future recommendations

This review has presented the potential of MUC1 specific vaccines as an alternative strategy for battling advanced stage NSCLC. However, due to different outcomes found in patients with different medication history prior to the intervention, more clinical trials are still needed to draw solid conclusions. Further studies with larger sample size should be done on more specific populations, for instance, patients with concurrent chemotherapy. In addition, future studies should be able to identify and select more optimal tumor-specific antigen to get better efficacy and safety results.

Strength and limitations

To the authors' knowledge, this is the first study which reviews the clinical efficacy and safety of MUC1 antigen vaccine in NSCLC patients. However, this study is not without limitation. First, several studies that were included were multinational studies, thus standard chemotherapy treatment may differ between nations. Differences in chemotherapy drugs used were not specified or analyzed, which might influence study results. Second, some studies reported adverse events as an overall percentage, while others reported events in groups that don't specify the adverse event itself. Statistical analysis between intervention and control on adverse event incidence were also not performed.

CONCLUSIONS

Based on the literature review above, it can be concluded that MUC1 Antigen-Specific Vaccine has the potential to become an effective and promising alternative therapy to improve overall survival and progression-free survival while maintaining the quality of life of patients with Non-Small Cell Lung Cancer (NSCLC) stage IIIb and IV. Overall, studies showed an increase in overall survival and progression-free survival in patients given the intervention compared to the administration of chemotherapy alone. Even so, the efficacy of the MUC1 Antigen-Specific Vaccine itself depends on the patient's previous history of therapy, such as patients receiving concurrent chemotherapy, and baseline prognostic biomarkers, such as sMUC1, ANA, and TrPAL values.

In terms of safety, most studies reported minimal drug-related toxicity with no adverse impact on patients' quality of life. Even so, more research is needed. Therefore, we hope that this literature review can be the foundation for developing alternative intervention strategies for NSCLC stage IIIb and IV patients that are holistic and affordable.

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REFERENCES

I. Geraci E, Chablani L. Immunotherapy as a second-line or later treatment modality for advanced non-small cell lung cancer: A review of safety and efficacy. Crit Rev Oncol Hematol. 2020;152(May):103009.
II. Zarogoulidis K, Zarogoulidis P, Darwiche K, Boutsikou E, Machairiotis N, Tsakiridis K, et al. Treatment of non-small cell lung cancer (NSCLC). J Thorac Dis. 2013;5(Suppl 4):S389.
III. Rotonda C, Anota A, Mercier M, Bastien B, Lacoste G, Limacher JM, et al. Impact of TG4010 vaccine on health-related quality of life in advanced non-small-cell lung cancer: Results of a phase IIB clinical trial. PLoS One. 2015;10(7):1–13.
IV. Butts C, Socinski MA, Mitchell PL, Thatcher N,

Havel L, Krzakowski M, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): A randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(1):59–68.

V. Katakami N, Hida T, Nokihara H, Imamura F, Sakai H, Atagi S, et al. Phase I/II study of tecemotide as immunotherapy in Japanese patients with unresectable stage III non-small cell lung cancer. Lung Cancer. 2017;105:23–30.

VI. Quoix E, Lena H, Losonczy G, Forget F, Chouaid C, Papai Z, et al. TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): Results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. Lancet Oncol. 2016;17(2):212–23.

VII. Tagliamonte M, Petrizzo A, Tornesello ML, Buonaguro FM, Buonaguro L. Antigen-specific vaccines for cancer treatment. Hum Vaccin Immunother. 2014 Nov 1;10(11):3332–46.

VIII. Leclerc M, Mezquita L, De Nerville GG, Tihy I, Malenica I, Chouaib S, et al. Recent advances in lung cancer immunotherapy: Input of T-cell epitopes associated with impaired peptide processing. Front Immunol. 2019;10(JUL):1505.

IX. Cortés-Jofré M, Uranga R, Pombert AT, Arango Prado MDC, Aguirrechu IC, Pacheco C, et al. Therapeutic vaccines for advanced non-small cell lung cancer. Cochrane Database Syst Rev. 2019 Aug 1;2019(8).

X. Lakshmanan I, Ponnusamy MP, Macha MA, Haridas D, Majhi PD, Kaur S, et al. Mucins in Lung Cancer: Diagnostic, Prognostic, and Therapeutic Implications. J Thorac Oncol. 2015 Jan 1;10(1):19–27.

XI. Gao T, Cen Q, Lei H. A review on development of MUC1-based cancer vaccine. Biomed Pharmacother. 2020 Dec 1;132:110888.

XII. Ning Y, Zheng H, Zhan Y, Liu S, Yang Y, Zang H, et al. Comprehensive analysis of the mechanism and treatment significance of Mucins in lung cancer. J Exp Clin Cancer Res. 2020 Aug 17;39(1):1–10.

XIII. Raina D, Kosugi M, Ahmad R, Panchamoorthy G, Rajabi H, Alam M, et al. Dependence on the MUC1-C Oncoprotein in Non-Small Cell Lung Cancer Cells. Mol Cancer Ther. 2011 May;10(5):806.

XIV. Saltos A, Khalil F, Smith M, Li J, Schell M, Antonia SJ, et al. Clinical associations of mucin 1 in human lung cancer and precancerous lesions. Oncotarget. 2018 Nov 11;9(86):35666.

XV. Jeon JM, Lee HW, Park JY, Jung HR, Hwang I, Kwon SY, et al. Expression of MUC1 and MUC4 and Its Prognostic Significance in Non-Small Cell Lung Carcinoma. Korean J Pathol. 2010 Aug;44(4):397–403.

XVI. Situ D, Wang J, Ma Y, Zhu Z, Hu Y, Long H, et al. Expression and prognostic relevance of MUC1 in stage IB non-small cell lung cancer. Med Oncol. 2011 Dec;28 Suppl 1(SUPPL. 1).

XVII. Xu T, Li D, Wang H, Zheng T, Wang G, Xin Y. MUC1 downregulation inhibits non-small cell lung cancer progression in human cell lines. Exp Ther Med. 2017 Nov 1;14(5):4443–7.

XVIII. Ham SY, Kwon T, Bak Y, Yu JH, Hong J, Lee SK, et al. Mucin 1-mediated chemo-resistance in lung cancer cells. Oncog 2016 51. 2016 Jan 18;5(1):e185–e185.

XIX. Szabo E. MUC1 expression in lung cancer. Methods Mol Med. 2003;74:251–8.

XX. Tosch C, Bastien B, Barraud L, Grellier B, Nourtier V, Gantzer M, et al. Viral based vaccine TG4010 induces broadening of specific immune response and improves outcome in advanced NSCLC. J Immunother Cancer. 2017;5(1):1–10.

XXI. Mitchell PL, Thatcher N, Socinski MA, Wasilewska-Tesluk E, Horwood K, Szczesna A, et al. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: Updated overall survival and biomarker analyses. Ann Oncol. 2015;26(6):1134–42.

XXII. Gelbard A, Garnett CT, Abrams SI, Patel V, Gutkind JS, Palena C, et al. Combination Chemotherapy and Radiation of Human Squamous Cell Carcinoma of the Head and Neck Augments CTL-Mediated Lysis. Clin Cancer Res. 2006 Mar 3;12(6):1897.

XXIII. Hillman GG, Reich LA, Rothstein SE, Abernathy LM, Fountain MD, Hankerd K, et al. Radiotherapy and MVA-MUC1-IL-2 vaccine act synergistically for inducing specific immunity to MUC-1 tumor antigen. J Immunother Cancer. 2017 Jan 17;5(1):1–13.

XXIV. Ramlau R, Quoix E, Rolski J, Pless M, Lena H, Lévy E, et al. A phase II study of Tg4010 (Mva-Muc1-Il2) in association with chemotherapy in patients with stage III/IV non-small cell lung cancer. J Thorac Oncol. 2008;3(7):735–44.