

A Multicenter Randomized Phase IIb Efficacy Study of Vx-001, a Peptide-Based Cancer Vaccine as Maintenance Treatment in Advanced Non–Small-Cell Lung Cancer: Treatment Rationale and Protocol Dynamics

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Abstract

We present the treatment rationale and study design of a multicenter, open-label, randomized, 2-arm, phase IIb study. Patients with stage IV or recurrent stage I to III non–small-cell lung cancer (NSCLC) whose disease does not progress after 4 cycles of first-line platinum-based chemotherapy will be randomized in a 1:1 ratio to 1 of 2 study arms. Patients will receive the cancer vaccine Vx-001 + Montanide ISA51 VG (Seppic, Paris, France) adjuvant subcutaneously, at a dose of 2 mg, or placebo + Montanide ISA51 VG adjuvant subcutaneously. The vaccination protocol comprises 2 injections with the TYR-Vx001 or placebo (1 at day 0 and another at week 3) and 4 injections with the ARG-Vx001 or placebo, at weeks 6, 9, 12, and 15. After the treatment assessment at week 18, patients will receive the ARG-Vx001 or placebo every 12 weeks starting from week 27 until disease progression, unacceptable toxicity, withdrawal of informed consent, or death. The primary end point of this study is the survival rate at 12 months. Secondary end points include time-to-event comparison of overall survival and comparison of time to treatment failure. Exploratory objectives include comparison of disease control rate after the end of subsequent second-line treatments, comparisons of vaccine immune responses, comparison of survival rate at 12 months in patients with vaccine-induced immune response detected after the second and sixth injections, identification of biomarkers on lymphocytes and on tumors, and comparison of safety and tolerability.

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Rationale

Non–small-cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, is the most common type of lung cancer, representing about 80% of lung cancer cases; it accounts for approximately 1.2 million new cases annually worldwide.¹ Because most patients have advanced disease at diagnosis, systemic therapy, including chemotherapy and new targeted agents, is the mainstay of management. The same approach is also reserved for distant recurrent stage I to stage III NSCLC, considering these populations of patients homogeneous in terms of recommended treatment and prognosis.² Platinum-based doublets are the standard of care in patients with newly diagnosed stage IV and dis-

tant recurrent stages I to III NSCLC with good performance status (PS). The median overall survival (OS) of these patients is approximately 10 months from diagnosis.³ The addition of bevacizumab to platinum-based doublets prolonged OS by 2 months in the Eastern Cooperative Oncology Group E4599 trial⁴ but failed to achieve a survival benefit in the AVAiL trial.⁵ The new maintenance approach after induction chemotherapy improved OS. When erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) was compared with placebo as switch maintenance therapy in patients with advanced NSCLC whose disease did not progress after platinum-based induction, significantly superior improved OS resulted for the whole population, with an absolute benefit of 1 month (median OS, 12 vs. 11 months, respectively; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.95; $P = .0088$).⁶ Pemetrexed was investigated vs. placebo as continuous maintenance in patients with advanced nonsquamous NSCLC whose disease did not progress after 4 cycles of cisplatin and pemetrexed. Pemetrexed statistically improved OS, with an absolute benefit of 2.9 months (median OS from induction, 16.9 vs. 14 months, respectively; HR, 0.78; 95% CI, 0.64-0.96; $P = .0191$).⁷ However, in patients with NSCLC harboring an endothelial growth factor receptor activating mutation, the specific inhibitor, gefitinib or erlotinib, is the standard of care. In this group of patients with NSCLC, both progression-free survival (PFS) and OS are longer.⁸

Among the new approaches and strategies to improve the disappointing results in the treatment of NSCLC, immunotherapy with vaccines is a renewed anticancer treatment. Although NSCLC was not felt to be immunogenic, it may provide an accessible target for the properly primed immune system. In fact, identifying lung tumor antigens and presenting them in the optimal context may enable the immune system to generate antitumor effector cells, which are usually absent.⁹ Maintenance treatment after induction chemotherapy fulfills the conditions necessary for tumor vaccination to be efficient. The Cancer Vaccine Consortium (recently named Cancer Immunotherapy Consortium) established and validated these conditions.¹⁰ Vaccines should be administered in patients with controlled or very slowly progressing disease. In fact, tumor vaccines do not act directly on tumors, as is the case with cytotoxic and biological agents, but they act through the stimulation of the immune system. Antitumor immune response needs several vaccinations and several weeks to be established and some additional weeks to be translated into clinical response. Progressing disease does not give the immune system enough time to mount an efficient vaccine-specific immune response and to translate this response into clinical benefit. Moreover, vaccines should be administered in patients with relatively low tumor burdens. The optimal indication for tumor vaccines is minimal residual disease. Small tumors are more easily accessible to vaccine-activated T lymphocytes, and their immunosuppressive microenvironment may be less efficiently organized.¹⁰ This explains why all 4 vaccines for NSCLC that are in late clinical development are administered either as maintenance treatment (Stimuvax [L-BLP25], Merck KGaA, Darmstadt, Germany) after chemoradiotherapy in stage IIIB NSCLC; Lucanix [NovaRx Corp, San Diego, CA] after chemotherapy in stage IIIB-IV NSCLC; racotumomab (plus best supportive treatment in stage III/IV NSCLC) or in the adjuvant setting (MAGE-A3 antigen-specific cancer immunotherapeutic

[ASCI] [GlaxoSmithKline, Brentford, Middlesex, UK] after surgery in patients with resectable NSCLC).⁹

Vx-001 is a vaccine that stimulates an HLA-A*0201-restricted cytotoxic T-lymphocyte (CTL) response against human telomerase reverse transcriptase (TERT). TERT is a universal tumor antigen expressed by approximately 80% of tumors of various histologic origins.^{11,12} TERT-specific CTLs stimulated by Vx-001 could therefore recognize and kill TERT-expressing tumor cells in HLA-A*0201-positive patients with NSCLC, especially those with high TERT expression who have the poorest prognosis.¹³ Vx-001 is composed of 2 peptides, each consisting of 9 amino acids. The cryptic peptide ARG-Vx001 (TERT572, RLFFYRKS^V) corresponds to an epitope naturally produced by intracellular processing of the TERT antigen and presented on the tumor cell surface in association with the HLA-A*0201 molecule. This peptide exhibits low affinity for HLA-A*0201 and is therefore not immunogenic. Its optimized counterpart TYR-Vx001 (TERT572Y, YLFFYRKS^V) differs from ARG-Vx001 at the first amino acid position, where arginine (R) is replaced by tyrosine (Y). It exhibits high affinity for HLA-A*0201 and is strongly immunogenic.¹⁴⁻¹⁶ The objective of Vx-001 vaccination is to induce CTLs specific for the cryptic TERT572 peptide that is naturally presented on the surface of tumor cells in association with the HLA-A*0201 molecule. The HLA-A*0201 restriction of the Vx-001-induced CTL response signifies that Vx-001 vaccination is suitable only for HLA-A*0201-expressing patients and that a vaccine-specific immune response cannot develop in patients who do not express HLA-A*0201. The immunogenic TYR-Vx001 peptide is administered first (first and second vaccine injections) to initiate an antitumor immune response. It is followed by vaccinations with the native cryptic ARG-Vx001 peptide to select among all CTLs stimulated by TYR-Vx001, ie, those with the highest specificity for the cryptic TERT572 peptide that is naturally presented by tumor cells.¹⁷

An exploratory phase I/II study involving 116 patients with different cancers—including NSCLC, breast cancer, prostate cancer, renal cell carcinoma, colorectal cancer, melanoma, pancreatic cancer, and cholangiocarcinoma—was conducted in 2 steps. The first step was a dose-escalation study with 19 patients. It aimed at defining the maximum tolerated dose and the optimal immunogenic dose. Patients were vaccinated 6 times at 3-week intervals. The TYR-Vx001 peptide was used for the first and second vaccinations and the native ARG-Vx001 peptide was used for the remaining 4 vaccinations. Patients received from 2 to 6 mg of the corresponding peptide per injection. The median follow-up of the 19 patients was 14.9 months (4.4-62.8 months).¹⁸ The second step of the study was done with the fixed peptide dose of 2 mg to evaluate the long-term safety and immunogenicity. A total of 97 patients were vaccinated 6 times at 3-week intervals. The TYR-Vx-001 peptide was used for the first and second vaccinations and the native ARG-Vx-001 peptide was used for the remaining 4 vaccinations. Patients who achieved disease control after the sixth vaccination received the ARG-Vx-001 until disease progression. The median follow-up of the 97 patients was 16.8 months (1-69.4 months). Peptide-specific immune responses were evaluated by enzyme-linked immunosorbent spot at baseline, and after the second and the sixth vaccinations. A TERT-specific T-cell immune response was observed in 37% and 70% of patients after the

second and the sixth vaccinations, respectively. The long-lasting (> 6 months) disease control rate (DCR) was 30%, including 1 complete response and 3 partial responses. Patients who responded immunologically had a better clinical outcome than did nonresponders (DCR, 44% vs. 14%; $P = .047$; PFS, 5.2 vs. 2.2 months, $P = .0001$; and OS 20 vs. 10 months; $P = .041$). Multivariate analysis revealed that the immunologic response was an independent variable associated with increased PFS (HR, 3.35; 95% CI, 1.7-6.7).¹⁷ The most common adverse events were mild or moderate and included skin reaction, edema, and pruritus observed at the site of vaccine injections. These skin reactions, related to the vaccine, were caused by the adjuvant (Montanide ISA51 VG) used and were expected.

Thirty-three patients with NSCLC were enrolled in the earlier mentioned phase I/II trial. Almost 50% had progressive disease (PD) and 50% had metastatic disease. All 33 patients had previously received at least 1 line of treatment, mainly first-line chemotherapy. The median follow-up of these patients was 18.4 months. Fifteen (45%) patients achieved disease control (including 2 partial responses) for more than 6 months. Immune responders had longer survival than did nonresponders (24.8 vs. 6.9 months; $P = .053$).¹⁹⁻²¹

Based on these considerations, the current, randomized phase IIb trial was designed to evaluate whether Vx-001 will be able to prevent or delay tumor progression by inducing CTL to kill tumor cells that survive chemotherapy and are later responsible for PD. Administration of Vx-001 in this patient population is in full agreement with the current consensus of immunotherapy specialists, namely, that the efficacy of tumor vaccination is expected to be stronger in patients with low tumor burden and no progressive disease.¹⁰

Objectives

The primary end point of the present study is to compare survival rates at 12-months in Vx-001-treated and placebo-treated patients. The secondary end points include time-to-event comparison of OS and comparison of time to treatment failure in Vx-001-treated and placebo-treated patients. The exploratory objectives are comparison of DCR after the end of subsequent second-line treatments and comparison of vaccine-induced immune responses in terms of frequency of TERT-specific interferon- γ and granzyme B-producing T cells in the blood of patients in Vx-001 vs. placebo-treated patients. Immune response will be evaluated before treatment, after the second and sixth injections, and after every 2 injections from week 39. Other exploratory end points include (1) comparison of survival rate at 12 months in patients with a vaccine-induced immune response detected after the second and sixth injections vs. patients who received at least 2 and 6 injections of placebo, (2) patients randomized to Vx-001 who did not achieve a vaccine-specific immune response after the second and sixth injections of Vx-001, and (3) comparison of survival rate at 12 months in patients who had a vaccine-specific immune response before Vx-001 or placebo injection or high levels of TERT expression or low levels of TERT expression in their primary tumors. Moreover, identification of biomarkers on lymphocytes that could predict the generation of immune response in Vx-001-vaccinated patients and of biomarkers on tumors that could predict the clinical response of Vx-001-vaccinated patients will be

also evaluated. The safety objective is to compare the safety and tolerability in Vx-001-treated patients vs. placebo-treated patients.

Eligibility Criteria

Study entry is limited to patients aged ≥ 18 years of age with histologically or cytologically confirmed stage IV NSCLC as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project (seventh edition)²² or distant recurrent stage I to III disease at least 6 months after resection, after the end of adjuvant chemotherapy, or after standard locoregional treatment as defined by the American College of Chest Physicians.² Other requirements include patients treated with 4 cycles of first-line platinum-based treatment with no PD, PS 0 to 1, documented HLA-A*0201 positivity as determined by a local laboratory, and TERT-positive NSCLC as assessed by a central laboratory. For this, availability of adequate biopsy tissue from the primary tumor, lymph nodes, or distant metastases is a prerequisite. Additional eligibility criteria are adequate bone marrow, renal, and liver function. Patients with brain metastases are not eligible for trial participation.

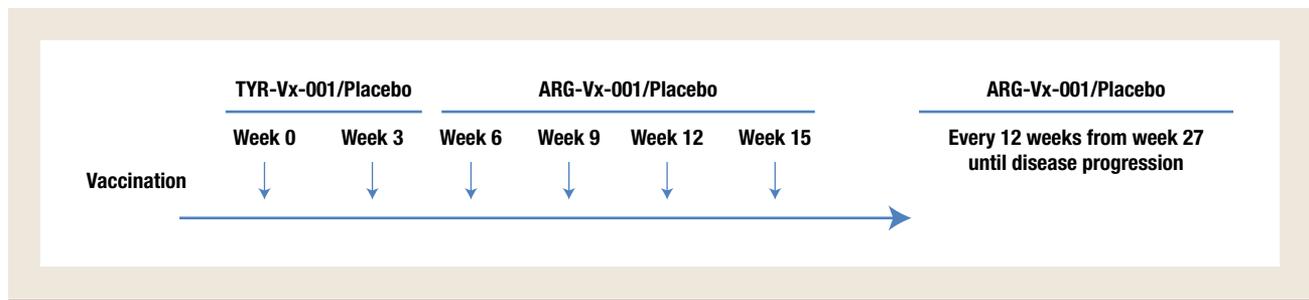
Exclusions include mixed small cell and NSCLC histologic types; autoimmune or immunodeficiency disease that in the opinion of the investigator may compromise the safety of the patient in the study; any preexisting medical condition requiring concomitant systemic corticosteroid or immunosuppressive therapy; known hepatitis B and/or C infection or HIV positivity; uncontrolled congestive heart failure or hypertension, unstable heart disease (coronary artery disease with unstable angina or myocardial infarction within 6 months of randomization) or uncontrolled ventricular arrhythmias at the time of enrollment in the study (atrial fibrillation or flutter is acceptable); splenectomy or splenic irradiation; another malignant tumor before randomization except for curatively treated nonmelanoma skin cancer or in situ carcinoma of the cervix, or other cancers curatively treated with no evidence of disease for at least 5 years.

One written informed consent with 2 agreements (1 to take part in the screening procedures and 1 to take part in the study) must be obtained for every patient before initiation of any trial-specific procedure or treatment. The first agreement is to participate in the screening procedures and the second agreement will be obtained at the baseline visit for participation in the treatment. Only patients harboring the HLA-A*0201 haplotype with TERT-expressing tumor and who have documented controlled disease can be randomized.

Treatment Plan

This international multicenter phase II study will be conducted according to a double-blind placebo-controlled randomized (1:1 ratio) design (Figure 1). Patients who do not progress after 4 cycles of first-line platinum-based chemotherapy will be administered, at predefined visits, the Vx-001 + Montanide ISA51 VG adjuvant subcutaneously at a dose of 2 mg, or placebo + Montanide ISA51 VG adjuvant subcutaneously. The vaccination protocol comprises 2 injections with the TYR-Vx001 or placebo, 1 at day 0 and another at week 3, and 4 injections with the ARG-Vx-001 or placebo at weeks 6, 9, 12, and 15. After the treatment assessment at week 18, patients will receive the ARG-Vx001 or placebo every 12 weeks starting from week 27 until disease progression, unacceptable toxicity, withdrawal of informed consent, or death.

Figure 1 Detailed Schedule of Vaccinations



A blood sample of 5 mL will be collected at the screening visit and sent to a local laboratory for HLA-A typing. In the presence of HLA-A*0201 positivity, ideally 8 slides (or a minimum of 4 slides) of 5 μ m from tumor biopsy tissue obtained from the primary tumor will be sent to a central laboratory for assessing TERT positivity. Patients who are TERT positive will undergo computed tomography of the thorax and upper and lower abdomen within 3 weeks after the last cycle of first-line platinum-based chemotherapy to document disease control before randomization. A bone scan is not mandatory at baseline for patients without known bone metastases at initiation of the first-line platinum-based chemotherapy and without any symptoms suggesting bone metastases. For patients with known bone metastases at initiation of first-line platinum-based chemotherapy or for patients with any new symptoms suggesting bone metastases, a bone scan should be obtained within 3 weeks after completion of first-line platinum-based chemotherapy treatment. A 12-lead electrocardiogram is requested at baseline, at week 18, and at the final visit. Further assessments will be performed as clinically indicated. Disease evaluations are based on investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

Blood samples to evaluate vaccine-induced immune response will be collected at baseline, before the third vaccination, and at week 18. Thereafter, from week 39 it will be evaluated every 24 weeks.

Expected Results and Toxicities

The sample size calculation for this trial is based on an 18-month recruitment period and minimum follow-up of 12 months. There will be no interim analysis for efficacy. Assuming that 70% of screened patients will experience DCR after first-line chemotherapy and 43% of screened patients will be HLA-A*0201 positive, of whom 80% will be TERT positive in their primary tumors, approximately 920 patients will be screened to enroll 220 patients (110 on the Vx-001 arm and 110 on the placebo arm), as calculated using SAS, version 9.2 software (SAS Institute, Cary, NC). The number of patients to enroll is estimated based on the following hypotheses: (H0) the proportion of patients with OS after 12 months of treatment in the Vx-001 group is less than or equal to that of the placebo group and (H1) the proportion of patients with OS after 12 months of treatment in the Vx-001 group is greater than that of the placebo group. The primary analysis will be performed after all patients have been followed up for at least 12 months. Based on the preceding assumptions for OS at 12 months and 200 evaluable patients (100 on the Vx-001 arm and 100 on the placebo arm), the primary efficacy

analysis would have an overall power of approximately 80% to detect a difference in treatment effect at the 0.1 1-sided significance level. The study design is based on comparison of proportions in 2 treatment arms using a 1-sided Pearson χ^2 test. Eligible patients will be randomized through an interactive web response system through a central stratified block randomization process using the following stratification factors: response to first-line chemotherapy (complete response/partial response vs. stable disease (SD)); histologic type (squamous vs. nonsquamous); NSCLC stage (IV vs. recurrent stage I to III).

Analytical Methods

The primary analysis (full analysis set [FAS]) will be performed by a 1-sided Pearson χ^2 test of proportions to compare the survival rate of the Vx-001-treated group with the placebo-treated group at 12 months. A patient with OS (success) at 12 months is defined as a patient who is alive as confirmed by the visit at week 52. If the patient misses the visit or has been lost to follow-up, every effort will be made by the investigator to ascertain whether the patient was alive on the theoretical date of his or her week 52 visit. If no information is available, the patient will be analyzed as a failure in the FAS.

Sensitivity analyses will include analyses of the primary end point using the per protocol dataset and logistic regression of the primary endpoint (FAS and per protocol analysis set). The logistic regression models will be adjusted for the stratification factors. Similar conclusions to those drawn from the primary analysis should be drawn from all sensitivity analyses for robustness.

Secondary efficacy analyses will be based on time to treatment failure based on investigator opinion and defined as the time from the day of randomization to the day of the treatment discontinuation resulting from PD, unacceptable adverse events, death, major protocol violation, withdrawal of consent, the date of the initiation of other antitumor treatment, or other reason for study closure, whichever came first. OS is defined as the time from randomization to death for patients who were alive at the time of analysis (OS will be censored at the time of the last survival data). Exploratory efficacy analyses will be based on disease control of subsequent second-line treatments and on correlation between survival rate at 12 months and immune response.

Safety analyses will be based on adverse events, clinical laboratory evaluations, physical examinations, vital signs, electrocardiography, PS, and local site reactions. All adverse events will be coded using Medical Dictionary for Regulatory Activities down to the lower level term and analyzed by preferred term and system organ class.

Conclusion

The present trial is designed to examine the efficacy and safety of Vx-001 vaccination vs. placebo in patients with stage IV or recurrent stage I to III NSCLC whose disease does not progress after 4 cycles of platinum-based induction chemotherapy. Patients will be randomized to receive either Vx-001 or placebo as maintenance treatment. Patients will be monitored and assessed throughout the duration of the study as described earlier. The primary end point of this study is survival rate at 12 months; a number of secondary and exploratory objectives will also be obtained.

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Disclosure

Dr Vassilis Georgoulis, Dr Jean-Yves Douillard, Dr David Khayat, Dr Christian Manegold, Dr Rafael Rosell, and Dr Cesare Gridelli serve as consultants for Vaxon-Biotech. Dr Jeanne Menez-Jamet is an employee of Vaxon-Biotech and owns stock in Vaxon-Biotech. Dr Marina Ichè and Dr Kostas Kosmatopoulos own stock in Vaxon-Biotech. All other authors have stated that they have no conflicts of interest.

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