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# Phase III Study of Adjuvant Vaccination With Bec2/Bacille Calmette-Guerin in Responding Patients With Limited-Disease Small-Cell Lung Cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study)

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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## ABSTRACT

### Purpose
Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside that is expressed on the surface of tumor cells and is of neuroectodermal origin. We assessed whether Bec2/bacille Calmette-Guerin (BCG) vaccination prolongs survival in patients with limited-disease small-cell lung cancer (SCLC) after a major response to chemotherapy and chest radiation.

### Patients and Methods
Patients were randomly assigned to receive five vaccinations of Bec2 (2.5 mg)/BCG vaccine or follow-up. Vaccination was given over a 10-week period. The sample size was targeted to detect an increase in median survival of 40% after random assignment, and stratification was by performance status, response, and institution. Quality of life was assessed by using the European Organisation for Research and Treatment of Cancer instrument. Humoral response was assessed in patients who received vaccination.

### Results
A total of 515 patients were randomly assigned. The primary toxicities of vaccination were transient skin ulcerations and mild flu-like symptoms. There was no improvement in survival, progression-free survival, or quality of life in the vaccination arm. Median survival from randomization was 16.4 and 14.3 months in the observation and vaccination arms ($P = .28$), respectively. Among vaccinated patients, a trend toward prolonged survival was observed in those (one third) who developed a humoral response ($P = .085$). Multivariate analysis showed a positive impact on survival by prior treatment with concomitant chemoradiotherapy, prophylactic cranial irradiation, female sex, low lactate dehydrogenase, and normal platelets.

### Conclusion
Vaccination with Bec2/BCG has no impact on outcome of patients with limited-disease SCLC responding to combined-modality treatment. Vaccination strategies in SCLC may still be warranted using vaccines that produce a better immunologic response.

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## INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States and many countries in the Western world. In 2005, 90,490 deaths resulting from lung cancer are expected in the United States.[1] Approximately 15% to 20% of lung cancers are small-cell lung cancer (SCLC). The outcome of SCLC is as poor as that of non-SCLC (NSCLC).

The median survival for patients with limited or extensive disease is approximately 18 and 10 months, respectively.

For patients with limited disease, a combination of chemotherapy and chest radiotherapy has become standard. One of the major problems with SCLC is that this disease, although sensitive to chemotherapy and radiotherapy, almost invariably recurs within 2 years and kills most patients. A well-recognized difficulty in the treatment of SCLC is the maintenance of response. Most studies using maintenance chemotherapy in an attempt to sustain response in responding patients failed to show an improved survival, and they often added substantial toxicity. Previous studies of biologic agents in this setting, including interferons and matrix metalloproteinase inhibitors, have been negative.[2]

Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside antigen. Gangliosides are complex glycolipid constituents of the cellular plasma membrane located in the outer leaflet of the cell surface. They are involved in numerous biologic functions including cell-cell recognition, cell matrix attachment, and differentiation.

Compared to normal lung, the concentrations of neutral glycosphingolipids were approximately twice as high in SCLC tissues.[3] GD3 was shown to be overexpressed in approximately 60% of the SCLC tissues examined,[4] similar to fucosyl-GM1. GD3 expression also is upregulated during neoplastic transformation of normal melanocytes to melanoma cells. Tumors of neuroectodermal differentiation, such as melanoma, SCLC, neuroblastoma, and soft tissue sarcoma, express high levels of GD3.[5] SCLC cell lines of the classic type (expressing neuroendocrine properties) express GD3,[6] whereas NSCLC cell lines do not. GD3 is also present in normal tissues such as brain, peripheral nerve, skin, thyroid, kidney, and pancreatic islets.[5]

Although GD3 is poorly immunogenic either alone or mixed with adjuvants,[7] the Bec2 anti-idiotypic monoclonal antibody was more effective in inducing anti-GD3 antibody responses in patients. Bec2, when given in combination with bacille Calmette-Guerin (BCG), produced detectable anti-GD3 antibodies in approximately 20% to 33% of patients.[8-10] Studies have been performed without and with several different adjuvants, and BCG was shown to be one of the best in combination with Bec2 in a number of studies. Bec2/BCG was demonstrated to be safe and to stimulate anti-GD3 responses in patients with melanoma.[11,12] A small pilot study in patients with SCLC was performed at Memorial Sloan-Kettering, where prolonged survival was observed in 15 patients vaccinated after induction therapy.[10] The median disease-free progression was not reached at over 5 years in seven patients with limited disease. These impressive results, together with the poor prognosis of SCLC patients, stimulated the start of this randomized phase III study, which compared vaccination with Bec2/BCG versus observation in patients who responded after combined-modality therapy for limited-disease SCLC.

## PATIENTS AND METHODS

### Patients

To be eligible for the study, patients had to have limited disease (Veteran Administration classification[13]), histologically or cytologically proven SCLC, a major response (partial or complete) to adequate induction chemoradiotherapy, a Karnofsky performance status of 60% or more, adequate bone marrow, liver, renal, and heart functions, age over 18 years, and no known HIV or other active viral infections. Patients had to sign an informed consent form. Originally, patients with a positive purified protein derivative (PPD) test were excluded. This criterion then was relaxed in the fourth study amendment to exclude only patients with a history of tuberculosis or with a grade 3 skin toxicity to a PPD test of $\geq 5$ U. No surgical or second-line treatment given for SCLC was allowed, and no splenectomy or splenic radiotherapy or prior therapy with proteins of murine origin was permitted. Furthermore, patients with active infections or any prior active malignancies within 5 years or who were pregnant were excluded, as were patients requiring the chronic use of systemic antihistamines, nonsteroidal anti-inflammatory drugs, or corticosteroids.

### Therapy

Patients must have received adequate induction therapy, consisting of at least a two-drug regimen for four to six cycles and chest radiotherapy. Radiotherapy was given according to institutional policy. The timing of chest radiotherapy was left to the investigator, because at the time of the initiation of this study, it was unclear whether concomitant early chest radiotherapy was superior to sequential chemotherapy followed by radiotherapy. Prophylactic cranial irradiation (PCI) was recommended but not required for patients who achieved complete remission to induction therapy but had to be completed before vaccination.

In the initial part of the study, patients were registered before receiving induction therapy, but the protocol was later amended to simultaneously register and randomly assign patients after completing induction treatment. Before the start of induction therapy, patients had to have limited-disease SCLC verified by chest, upper abdomen, and brain computed tomography scans and adequate blood cell counts and chemistries and be able to receive induction therapy. At randomization the same tests were repeated and had to confirm a partial or complete response. At that time a PPD test and an ECG were performed.

Five vaccinations, each consisting of eight injections administered in a single limb, were planned, and vaccinations were rotated among upper arms and thighs at weeks 0, 2, 4, 6, and 10. The Bec2 dose was 2.5 mg. BCG was reconstituted in diluent, giving final solutions containing $2.0 \times 10^7$, $5.0 \times 10^6$, $1.0 \times 10^6$, $5.0 \times 10^5$, and $1.0 \times 10^5$ colony-forming units for vaccinations one through five, respectively.

Although initially patients with a positive PPD test were excluded from random assignment, when the accrual to the study was approximately halfway done, it was decided by the study's steering committee, on advice of an independent data-monitoring committee, that it was safe to vaccinate patients[14] with a positive PPD test (skin induration $\geq 10$ mm but National Cancer Institute of Canada Clinical Trials Group skin reaction $<$ grade 3) by using

attenuated vaccinations. For these attenuated vaccinations, BCG was reconstituted in diluent, giving final solutions containing $5.0 \times 10^6$, $1.0 \times 10^6$, $5.0 \times 10^5$, $1.0 \times 10^5$, and $5.0 \times 10^4$ colony-forming units for vaccinations one through five. Before each vaccination performance status, clinical symptoms and adverse effects were evaluated and blood sampling for humoral response was performed. Two weeks after the last vaccination (week 12), patients were reassessed with full blood counts and serum chemistry, chest x-ray, and ECG, and clinical signs of progressive disease were evaluated. Patients in the observation arm were treated according to best supportive care, but no cancer-specific therapy was allowed until documented progression of disease. First clinical assessment was performed 6 weeks after random assignment. At 12 weeks and thereafter, the assessments were the same as in the vaccination arm.

In both arms, a full radiological reassessment was performed at disease progression.

### *Quality of Life.*

Quality of life (QoL) was assessed in both arms by using the European Organisation for Research and Treatment of Cancer (EORTC) QOL-C30 version 3.0 complemented with the Lung Module (QLC-LC13) before random assignment, at weeks 6, 12, and 24 and every 6 months thereafter until progression.

### *Humoral Response*

Humoral response was assessed before each vaccination and at weeks 2, 6, and 12 after the last vaccination.

The serologic response to GD3 was assayed by an enzyme-linked immunosorbent assay (ELISA) using purified GD3. The GD3 ganglioside was dissolved in methanol (1 $\mu$g/mL) and adsorbed to ELISA plates (Corning-Costar, Corning, NY) by evaporation at 37°C. Plates were rehydrated in 300 $\mu$L of 4% human serum albumin (Calbiochem, San Diego, CA) in phosphate-buffered saline; then 100 $\mu$L of diluted serum was incubated overnight at 4°C. After several washes with high-salt phosphate-buffered saline plus 0.1% human serum albumin and Tween-20, 100 $\mu$L of polyclonal rabbit antihuman immunoglobulin (Ig)M or polyclonal rabbit antihuman IgG (Dako, Copenhagen, Denmark) appropriately diluted (1:700) in washing solution was incubated for 2 hours at 37°C. After several wash cycles, 100 $\mu$L of polyclonal goat antirabbit immunoglobulins alkaline phosphatase-labeled antibody (Dako) appropriately diluted (1:2,000) in washing solution was added to each well and incubated for 2 hours at 37°C. After several washing cycles, the reaction was developed with paranitrophenylphosphate (Calbiochem) and incubated for another 60 minutes at 37°C. The optical density of each well was read at 405 nm. The absorbance of the preimmune sera was subtracted from that of the immune sera to give the corrected absorbance. To eliminate the effect of nonspecific antibodies, the sera were also tested on ELISA plates, which were processed identically but to which no GD3 had been added. The background absorbance of this parallel assay was subtracted from the absorbance of each serum. Serologic titer in ELISA was defined as the biggest dilution yielding a corrected absorbance of 0.100 or greater.

For humoral response, a responder was defined as a patient with prevaccine and postvaccine blood samples for whom the baseline corrected IgM and/or IgG anti-GD3 titers of at least two consecutive postvaccination samples were at least 1:50 within the same Ig subclass.

### *Study Design and Statistics*

The study initially was designed to register patients immediately after diagnosis and before starting induction therapy. The protocol also mandated specific types of chemotherapies, which was later amended to register and randomly assign patients only after the completion of all induction therapies and confirmation of a partial or complete response. The time frame for randomization had to be within 8 months from diagnosis, and randomization had to occur between 3 and 7 weeks after all induction therapy had been given.

The primary end point of the study was overall survival. Secondary end points were progression-free survival, safety, QoL, and humoral response. The study was coordinated by the EORTC Data Center in Brussels, which is where the randomization took place. The randomization was performed by using the minimization technique, stratifying for Karnofsky performance status (60% to 70% $v \geq$ 80%), complete versus partial remission to induction therapy, and institution. The study was approved by the Protocol Review Committee of the EORTC and the medical ethical committees of all participating institutions.

The study was powered to detect an increase in median survival of 40%, from 15 to 21 months from randomization, with a power of 90% and a two-sided type I error of 5%. The targeted number of events was 376; for that, 500 patients were to be accrued in 4 years and followed for 2 extra years. As foreseen by the study protocol, one interim analysis was performed after 108 deaths were reported. An $\alpha$ spending function with an O'Brien-Fleming boundary was used to determine the nominal significance level to be used. Results of this interim analysis were only declared to an independent data-monitoring committee, which recommended to pursue the trial to its final accrual.

All analyses were performed according to intent-to-treat principles. Overall survival and progression-free survival were estimated by using the Kaplan-Meier method; a two-sided log-rank test was used, and $P < .05$ was considered statistically significant. Univariate and multivariate analyses were performed on overall survival to study the impact of the following potential prognostic factors: age at random assignment ($>$ 59 $v \leq$ 59 years of age); continent (North America $v$ Europe $v$ Australasia); sex; Karnofsky performance status (60-80 $v$ 90-100); response to induction (complete $v$ partial response); sequential versus concomitant radiotherapy; no PCI versus PCI during induction; PPD test (negative/doubtful $v$ positive); baseline sodium level ($<$140 $v \geq$ 140 mmol/L); baseline calcium level ($<$2.4 $v \geq$ 2.4 mmol/L); baseline white blood cell level ($<5.2 \times 10^9$/L $v \geq 5.2 \times 10^9$/L); baseline platelets level ($<221 \times 10^9$/L $v \geq 221 \times 10^9$/L); and baseline lactate dehydrogenase level (grade 0 $v >$ 0). For the multivariate analysis, a Cox multivariate proportional-hazards model was used with a step-down (backward) variable-selection procedure (at the 5% $\alpha$ level). Both univariate and multivariate analyses were stratified for treatment arm.

A generalized linear mixed-model approach was used to analyze the QoL data, with treatment, time, and their interaction as fixed effects. The QoL analysis population was defined as all patients with a valid baseline questionnaire and at least one valid questionnaire during the first 24 weeks.

## RESULTS

Accrual to the study opened in March 1998 and closed in October 2002, with 515 patients from 120 institutions in 17

countries (1-34 patients were recruited per center) randomly assigned: 258 to the observation arm and 257 to the vaccination arm. This was an intergroup study to which several cooperative groups in Europe (EORTC Lung Cancer Group, Spanish Lung Cancer Group, Groupe Francais de Pneumo-Cancerologie, and Schweizerische Arbeitsgruppe für Klinische Krebsforschung), Veteran Administration centers in the United States, and centers in Australia and New Zealand participated. In addition, independent centers also participated in this study.

In the initial part of the study, when patients were registered before starting induction therapy, a total of 195 patients were registered, 89 of whom were randomly assigned after induction therapy. The major reasons for not being randomly assigned were lack of response or death (46%) or PPD-test positivity (21%). After this stage, the protocol was amended, and patients were no longer registered before the start of induction treatment, and eligible patients were directly assigned randomly after completion of induction. A total of six patients were found to be ineligible at randomization, with three in each arm: causes were insufficient induction treatment in two, outside the timeframe for randomization in two, splenectomy in one, and progression after induction in one.

Patient characteristics are listed in Table 1. Major patient characteristics were well balanced between the two arms of the study. The majority of patients who were randomly assigned were men, had good performance status, and had a negative PPD test. In both arms, most patients (93%) received platinum-based chemotherapy (50% cisplatin-etoposide in both arms). Chest radiotherapy was mostly administered concomitantly with chemotherapy; PCI was delivered to 74% of the patients who had a complete response and to 49% of those who attained a partial response.

**Table 1.** Major Patient Characteristics at Randomization

| Variable | Observation (n = 258) | Vaccination (n = 257) |
|---|---|---|
| Age, years | | |
| Median | 58 | 59 |
| Range | 33-81 | 35-89 |
| Sex, % | | |
| Male | 62 | 63 |
| Female | 38 | 37 |
| KPS, % | | |
| 60-70 | 7 | 5 |
| ≥ 80 | 93 | 95 |
| PPD, % | | |
| Positive | 12 | 10 |
| Doubtful | 11 | 10 |
| Negative | 78 | 80 |
| Unknown | 0 | 0.4 |
| Chest radiotherapy, % | | |
| Concomitant | 58 | 58 |
| Sequential | 39 | 41 |
| Other | 3 | 1 |
| PCI, % | | |
| No | 38 | 38 |
| Yes | 62 | 62 |
| Response to chemotherapy, % | | |
| Complete response | 48 | 50 |
| Partial response | 51 | 50 |
| No response | 1* | 0 |

Abbreviations: KPS, Karnofsky performance status; PPD, purified protein derivative; PCI, prophylactic cranial irradiation.
*Ineligible.

### *Adverse Effects*

In the vaccination arm, a total of 1,104 vaccinations were given, with a median of five vaccinations (mean, four) per patient and 181 patients (70%) having received all five vaccinations. Fewer than four vaccinations were given to 18% of the patients. The reasons for giving fewer than the five prescribed vaccinations were progression in 54%, refusal in 28%, and toxicity in 16%. In total, 9.1% of the vaccinations were attenuated, mainly because of a positive PPD test. A total of 137 vaccinations were delayed for a variety of reasons, but only 17 delays were caused by toxicity. The main adverse effects caused by vaccination were local skin toxicity, flu-like symptoms, and lethargy. There were no grade 4 toxicities that were vaccination related. Toxicities are reported in Table 2. The typical skin toxicity, essentially related to the injection of BCG, was manifested by the development of induration then ulceration within the first 3 to 4 weeks, followed by slow healing and scarring in the several weeks after completion of the vaccinations. Just over one third of the skin toxicities were grade 3. These were the main adverse effects that resulted in certain patients refusing to continue treatment. Interestingly, the skin toxicity seems to be less impressive than in most BCG trials, in which 90% to 100% of patients have had grade 3 toxicity.[8-10,15] There were four toxic deaths in the observation arm

**Table 2.** Most Common Related Adverse Effects in the Vaccination Arm (n = 257)

| Adverse Effect | Grade 1 | | Grade 2 | | Grade 3 | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Skin (local) | 46 | 18 | 108 | 42 | 92 | 36 |
| Fever | 35 | 14 | 28 | 11 | | |
| Arthralgia | 20 | 8 | 15 | 6 | 3 | 1 |
| Lethargy | 47 | 18 | 40 | 16 | 9 | 4 |
| Myalgia | 20 | 8 | 17 | 7 | 1 | < 1 |
| Nausea | 17 | 7 | 12 | 5 | 3 | 1 |
| Diarrhea | 7 | 3 | 3 | 1 | | |
| Anorexia | 19 | 7 | 18 | 7 | 2 | 1 |
| Skin rash | 5 | 2 | 4 | 2 | | |
| Headache | 8 | 3 | 5 | 2 | 2 | 1 |
| Sensory | 5 | 2 | 1 | < 1 | 2 | 1 |
| Shortness of breath | 4 | 2 | 4 | 2 | 2 | 1 |
| Infection | 1 | < 1 | 10 | 4 | | |

and two in the vaccination arm: radiation pneumonitis caused three deaths (two in the vaccination arm), and three deaths were caused by pancytopenia after progression and administration of second-line chemotherapy (all in the observation arm).

### Survival and Progression-Free Survival

This analysis is based on a cutoff date of October 2004. The median follow-up was 35.6 months, and all patients were off protocol treatment at the time of the analysis. At the time of the analysis, 72% of patients had progressed in both arms. Most patients progressed at distant sites; 46% and 40% in the observation and vaccination arms, respectively, had distant progression only, and 25% and 29% experienced both local and distant progression. Overall, 71% and 76% of the patients were reported dead in the observation and vaccination arms, respectively. The major cause of death was tumor progression (88% and 86%, respectively). Table 3 reports the major survival results. Figures 1 and 2 depict the overall and progression-free survival curves, respectively. There were no statistically significant differences in outcome between the two arms for both overall survival and progression-free survival when all randomly assigned patients were taken into consideration. Similar results were obtained when the ineligible patients were excluded from the analysis.

### Exploratory Analyses

In the small group of patients (n = 55) with PPD-positive reaction, those who received vaccination had a significantly shorter progression-free survival than those in the observation arm (median, 4.9 *v* 9.5 months; $P = .0377$), and a trend toward shorter survival was also observed (median, 13.3 *v* 23.8 months; $P = .0857$). In contrast, the progression-free and overall survival in patients with negative PPD tests were essentially similar to the results obtained in the whole population.

Progression-free survival and overall survival of patients with complete remission and partial remission were not significantly different between the two arms of the study.

By univariate analysis the following variables had a significant positive impact on survival at the 5% $\alpha$ level (Table 4): centers in North America versus rest of the world; complete versus partial response to induction; concomitant

**Table 3.** Overall Survival and Progression-Free Survival According to Treatment Arm, From Random Assignment (all patients assigned)

| | Observation (n = 258) | Vaccination (n = 257) | *P* |
|---|---|---|---|
| Overall survival | | | |
| Median survival, months | 16.4 | 14.3 | |
| 95% CI | 14.6 to 20.3 | 13.0 to 17.7 | |
| 1-year survival, % | 61.2 | 58.1 | |
| 95% CI | 55.3 to 67.2 | 52.0 to 64.1 | |
| 2-year survival, % | 37.5 | 35.5 | |
| 95% CI | 31.5 to 43.6 | 29.5 to 41.4 | |
| Hazard ratio | 1.12 | | .2834 |
| 95% CI | 0.91 to 1.37 | | |
| PFS | | | |
| Median PFS, months | 6.3 | 5.7 | |
| 95% CI | 5.6 to 7.7 | 5.3 to 6.6 | |
| 1-year PFS, % | 32.2 | 31.1 | |
| 95% CI | 25.5 to 37.9 | 25.4 to 36.7 | |
| 2-year PFS, % | 25.4 | 24.9 | |
| 95% CI | 20.1 to 30.7 | 19.5 to 30.2 | |
| Hazard ratio | 1.11 | | .2995 |
| 95% CI | 0.95 to 1.36 | | |

Abbreviation: PFS, progression-free survival.

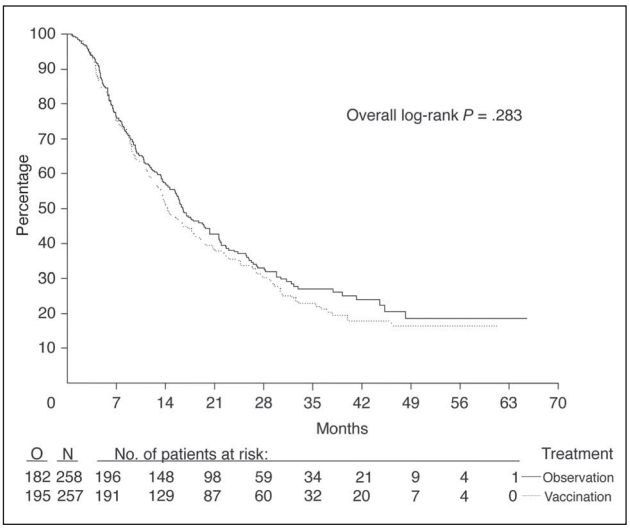


**Fig 1.** Kaplan-Meier overall survival curves. On the *y*-axis, the percentage of surviving is reported; on the *x*-axis, the time from randomization (months) is reported.

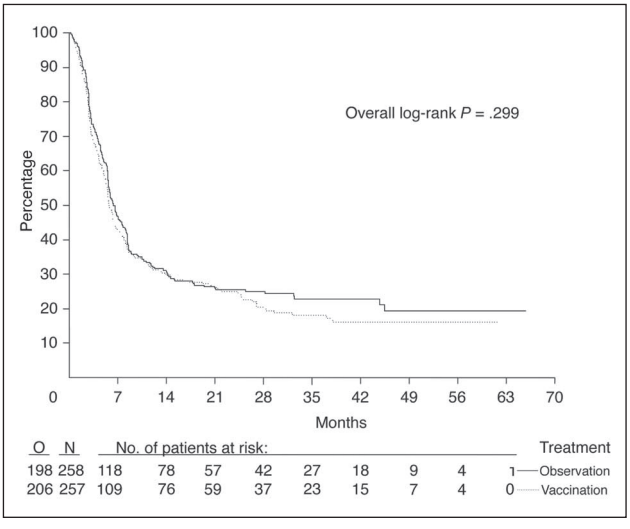


**Fig 2.** Kaplan-Meier progression-free survival curves. On the *y*-axis, the percentage of surviving without progression is reported; on the *x*-axis, the time from randomization (months) is reported.

**Table 4.** Univariate Analysis of Potential Prognostic Factors for Overall Survival

| Variable | Median Survival (months) | 95% CI | *P* |
|---|---|---|---|
| Response to induction | | | |
| Complete response | 18.0 | 15.4 to 21.8 | .0084 |
| Partial response | 13.9 | 11.4 to 16.3 | |
| Chest radiotherapy | | | |
| Sequential | 12.5 | 10.7 to 15.4 | .0046 |
| Concomitant | 18.7 | 15.6 to 22.1 | |
| PCI | | | |
| No | 9.7 | 8.9 to 12.1 | < .0001 |
| Yes | 20.3 | 17.1 to 23.0 | |
| Lactate dehydrogenase | | | |
| Grade 0 | 17.3 | 15.6 to 20.8 | .0025 |
| > Grade 0 | 10.9 | 8.7 to 15.9 | |
| Platelets | | | |
| $< 221 \times 10^9$/L | 16.6 | 13.6 to 21.8 | .0243 |
| $\geq 221 \times 10^9$/L | 15.8 | 13.8 to 17.6 | |
| Continent | | | |
| North America | 20.7 | 16.0 to 26.5 | .0624* |
| Europe | 14.5 | 12.5 to 16.5 | |
| Australia/New Zealand | 13.6 | 9.5 to 29.11 | |
| Sex | | | |
| Male | 14.6 | 12.4 to 17.0 | .0580 |
| Female | 17.7 | 14.4 to 24.2 | |

Abbreviation: PCI, prophylactic cranial irradiation.
*Global Wald test for United States versus rest of the world: $P = .0235$.

**Table 5.** Multivariate Analysis for Survival

| Variable | Hazard Ratio | 95% CI | *P* |
|---|---|---|---|
| Sex | | | .0066 |
| Male | 1 | | |
| Female | 0.72 | 0.57 to 0.91 | |
| Chest radiotherapy | | | .0051 |
| Sequential | 1 | | |
| Concomittant | 0.72 | 0.57 to 0.91 | |
| PCI | | | < .0001 |
| No | 1 | | |
| Yes | 0.52 | 0.41 to 0.65 | |
| Lactate dehydrogenase | | | .0002 |
| Grade 0 | 1 | | |
| Grade > 0 | 1.71 | 1.30 to 2.26 | |
| Platelets | | | .0019 |
| $< 221\ 10^9$/L | 1 | | |
| $\geq 221\ 10^9$/L | 1.44 | 1.14 to 1.81 | |

Abbreviation: PCI, prophylactic cranial irradiation.

versus sequential chest radiotherapy, PCI versus no PCI; and normal versus abnormal levels of lactate dehydrogenase and platelets. Sex was borderline nonsignificant. Considering all the factors included in the univariate analysis, a Cox multivariate proportional-hazards model was fitted and stratified for treatment by using a stratified step-down (backward) variable-selection procedure (at the 5% $\alpha$ level). The factors listed in Table 5 are those that remained significant in the multivariate analysis model. Adjusting for these factors in a multivariate model, treatment effect on overall survival remained not statistically significant.

### *Humoral Response*

Humoral response could not be assessed in 44 vaccinated cases (17% of all patients enrolled in the vaccination arm), because samples were lost (50%), fewer than three samples were available (32%), no prevaccination sample was available (16%), or no data on humoral response were transferred to the EORTC (2%). Humoral response was negative in 142 cases and positive (responder) in 71 cases; therefore, the responders were one third of all patients for whom humoral response was assessable. The survival of responders was better than that of nonresponders, although this did not reach statistical significance (median survival, 19.2 *v* 13.9 months for responders *v* nonresponders; $P = .0851$; see Fig 3). However, looking at the distribution of patients in the two groups of this analysis, more patients received PCI in the responder group (70% *v* 58%); after stratifying or adjusting the comparison of survival for the presence or absence of PCI, the difference became not significant ($P = .1479$ and .1970, respectively). When considering only patients who received at least four vaccinations, 124 nonresponders and 65 responders were identified; a survival difference (albeit nonsignificant) was also visible in this comparison (median survival, 22.3 *v* 14.1 months in responders *v* nonresponders, respectively; $P = .0755$). After stratification or adjustment for PCI, the significance was reduced further in this comparison ($P = .1286$ and .1800, respectively).

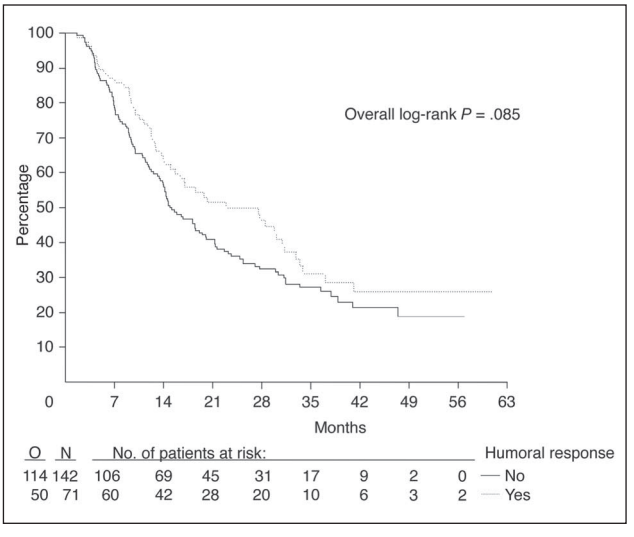


**Fig 3.** Kaplan-Meier survival curves of patients with and without humoral response. On the *y*-axis, the percentage of surviving is reported; on the *x*-axis, the time from randomization (months) is reported.

### QoL

A total of 2,271 (1,146 in the observation arm and 1,125 in the vaccination arm) QoL forms were collected, of which only 1,362 (723 in the observation arm and 639 in the vaccination arm) were used in the analyses. A total of 798 forms (388 in the observation arm and 410 in the vaccination arm) could not be assigned to a time window. An additional 181 (82 in the observation arm and 99 in the vaccination arm) forms belonged to patients who were not included in the analysis population. The clinical baseline characteristics of the 334 patients of the analysis population (176 observation and 158 vaccination) were comparable with the rest of the intent-to-treat population. The compliance for the analysis population was similar in the two arms up to approximately 1 year and was 80% or higher at the 6-month follow-up. QoL scores between the two treatment arms were not statistically different. There seems to have been a drop in global QoL in both arms at the 6-week time point, but this effect was of short duration; the scores returned to the baseline level at the next time point (Fig 4).

## DISCUSSION

Patients with limited disease display a high response to chemoradiotherapy, but only approximately 15% to 25% can be considered cured after combined-modality therapy.[16,17] Because SCLC is a disease that is sensitive to chemotherapy and radiotherapy, several approaches to try and reduce the relapse rate have been studied.[2] There is no clear evidence from reported data that maintenance chemotherapy improves survival duration,[18-21] although some studies have shown a prolonged time to progression.

A number of other approaches have been attempted to prolong tumor control in patients responding to initial standard treatment, including high-dose chemotherapy late intensification,[22,23] interferon alfa[24-27] and gamma,[28-30] and matrix metalloprotease inhibitors such as marimastat.[31] All these approaches failed to improve survival convincingly. A similar trial to the marimastat study, using the metalloproteinase BAY 12-9566, was closed early because a shorter survival was detected in the investigational arm. Other studies are ongoing with inhibitors of angiogenesis (ZD6474) in patients who responded to induction therapy.

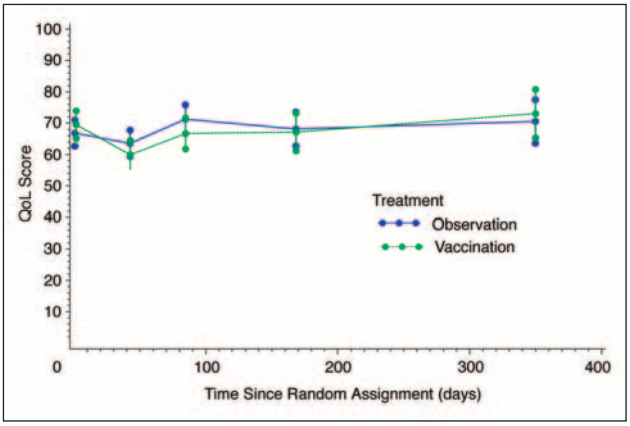


**Fig 4.** Means and standard deviations of overall health/quality of life QoL in both arms of the study.

A common characteristic of these studies is to attack minimal residual-disease SCLC after induction therapy to deal with the smallest tumor burden possible. The present study is a prototype of a vaccination strategy in patients with minimal residual-disease SCLC. Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside often expressed in tumors of neuroectodermal origin, including SCLC. In previous studies in melanoma patients, anti-GD3 antibody responses were detected in 20% to 33%[12,15]; however, the outcome did not seem to be improved by the treatment. In a pilot study of 15 SCLC patients, performed at Memorial Sloan-Kettering Cancer Center, promising results were observed,[10] which stimulated the initiation of this large phase III trial.

Unfortunately, none of the major end points of the present study were achieved, and no improvement in survival in patients who were vaccinated was observed overall or in any patient subgroups. QoL also was not improved in this study. Furthermore, substantial local toxicity and flu-like symptoms were accompanied by the administration of the vaccine, and some patients declined treatment because of these toxicities. Interestingly, the humoral response obtained in approximately one third of patients did seem to point in the direction of an improvement of survival. However, although a prospectively planned analysis, this comparison of nonrandomized groups of patients should be interpreted with caution, because imbalances of patient characteristics may be present; in fact, it seemed that a substantial number of patients in the responder group had received PCI, which in the multivariate analysis of the whole study imparted a significant positive influence on survival. In a study by Grant et al,[10] one third (five of 15) of patients also developed anti-GD3 antibodies. The exceptionally good results observed in this small pilot study probably can be explained by patient selection. Another interesting observation in our study is that patients with a PPD-positive skin reaction did significantly worse after vaccination. In the 1980s, intrapleurally administered adjuvant BCG was evaluated in patients with radically resected NSCLC. These studies not only failed to show a benefit,[32] but some of them suggested a worse outcome in patients receiving BCG.[33,34] Thus, it is conceivable that BCG might have had a negative impact in our study, at least in a subgroup of patients.

Our study, represents the first large-scale phase III trial of an antiganglioside vaccine as adjuvant therapy in SCLC. It provides a large database of patients with limited-disease SCLC, which adds additional validation to currently

used therapeutic strategies in this disease. In particular, by univariate and multivariate analysis, it was shown that the use of concomitant chest radiation and chemotherapy was superior to sequential chemotherapy followed by radiotherapy in terms of survival; this may explain the longer survival in North American study subjects compared to those from the rest of the world, which was observed in univariate analysis, because concomitant chemoradiotherapy is more established in North America. Furthermore, patients who received PCI also had a significantly longer survival compared with those who were not treated prophylactically. This is likely the result of PCI in addition to the selection of better patients for this treatment. These results, however, are in line with studies comparing concomitant versus sequential chemoradiotherapy[35] and meta-analyses of PCI.[36] A meta-analysis of seven randomized trials evaluating the value of PCI in patients in complete remission reported improvement in brain metastasis recurrence, disease-free survival, and overall survival with the addition of PCI. The 3-year overall survival was improved from 15% to 21% with PCI.[36]

Why this study turned out to be negative is a matter of speculation. The fact that only one third of patients developed a humoral response is probably a major potential cause of failure, although this was the expected rate of immunologic response based on the previous study. The choice of adjuvant or the anti-idiotypic-vaccination approach may have contributed to this. Another potential explanation is the presence of GD3 in approximately only 60% of SCLC tissues.[4] This is less than 100%,[3,6] and in the present study patients were neither evaluated for nor stratified for GD3 expression; notwithstanding the difficulty in obtaining tissue to determine GD3 expression, this might have shed some light on the issue. In view of this possible reason of failure of the present study, a multivalent vaccine, perhaps including GD3, may be a better choice for future studies. In a recent study of a wide range of doses of Bec2 given in 50 patients with melanoma, doses lower than the 2.5 mg used in the present study seemed to be more immunogenic; however, prolonged booster response did not induce or maintain antibody responses.[15] Recently, chimeric monoclonal antibodies against GD3 have been developed[37]; in preclinical studies the monoclonal KM871 markedly suppressed tumor growth, and a phase I study with this antibody has been conducted.[38] In this study in 17 patients, there was dose-limiting toxicity; no human antichimeric antibody formation was detected; and interestingly, using 111In-KM871, a 15-fold uptake was seen compared to normal tissue in biopsies of tumors of at least 1.5-cm dimension. In this study, a major response was also documented.

Other gangliosides are highly expressed in SCLC, including GD2. An imaging study with labeled anti-GD2 antibody 3F8 confirmed tumor localization in all metastatic sites except the brain.[39] However, in a randomized phase III study of 334 patients with metastatic neuroblastoma, the chimeric antibody ch14.18 did not prolong survival.[40] GD2-lactone keyhole limpet hemocyanin (KLH), mixed with the adjuvant QS-21, induced antibodies against GD2 in most melanoma patients who were vaccinated.[41] EMD-273063 is a humanized antibody against GD2, coupled to two molecules of interleukin-2[42]; a phase I trial was performed in patients with melanoma that demonstrated that the dose-limiting toxicities were hypoxia, hypotension, and transient elevation of transaminases.[43] Fuc-GM1, also present on most SCLC cells, conjugated to the carrier protein KLH and mixed with the adjuvant QS-21, was administered to 10 patients with SCLC who responded to induction therapy.[44] All patients developed a serologic response, and the vaccine was well tolerated. Another study using synthetic Fuc-GM1 conjugated to KLH reported high antibody formation against GM1 as the bovine derivative.[45] Other vaccination approaches, using tumor cells genetically modified to produce granulocyte-macrophage colony-stimulating factor (GVAX), have been attempted with some success in NSCLC.[46]

In summary, this study of Bec2/BCG vaccination as maintenance therapy in responding patients with limited-disease SCLC is essentially negative. There could be other approaches to using gangliosides as targets for vaccination therapy in SCLC. However, higher titers of anti-GD3 antibodies in a larger proportion of patients may be needed to improve overall survival. Also, because no one single antigenic target is expressed on all SCLC tumors, additional antigens may be needed to form a multivalent vaccine.

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## Appendix

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## *Authors' Disclosures of Potential Conflicts of Interest*

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