

Immunotherapy with autologous tumor cell-BCG vaccine in patients with colon cancer: a prospective study of medical and economic benefits

C.A. Uyl-de Groot^a, J.B. Vermorcken^b, M.G. Hanna Jr.^{c,*}, P. Verboom^a, M.T. Groot^a,
G.J. Bonsel^d, C.J.L.M. Meijer^e, H.M. Pinedo^e

^a Department of Health Care Polity and Management, Institute for Medical Technology Assessment,
Erasmus Medical Center Rotterdam, The Netherlands

^b University Hospital, Antwerp, Belgium

^c Intracel, 93 Monocacy Blvd., Unit A-8, Frederick, MD 21701, USA

^d Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

^e Free University Hospital, Amsterdam, The Netherlands

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Abstract

We have completed a multicenter, randomized controlled phase III clinical trial in Stages II and III colon cancer patients with active specific immunotherapy (ASI) using autologous tumor cells with an immunomodulating adjuvant bacillus Callmette-Guérin (BCG) vaccine (OncoVAX®) in an adjuvant setting. In this study, patients were randomized to receive either OncoVAX® therapy or no therapy after surgical resection of the primary tumor and stratified by stage of disease. Since the biologic essence of the effective tumor immunotherapy is the presence in the vaccine of a minimum number of viable, metabolically active, autologous tumor cells, the processing of the vaccine product, occurred within 48 h after surgery.

Analysis of prognostic benefit in the pivotal phase III trial, with a 5.8 year median follow-up, showed that a beneficial effect of OncoVAX® is statistically significant for all endpoints including recurrence-free interval, overall survival, and recurrence-free survival in Stage II colon cancer patients. Surgery alone cures approximately 65% of Stage II (Dukes B₂, B₃) colon cancer patients. In the remaining patients, OncoVAX® in an adjuvant setting, significantly prolongs recurrence-free interval (57.1% relative risk reduction) and significantly improves 5-year overall survival and recurrence-free survival. No statistically significant prognostic benefits were achieved in Stage III (Duke's C₁–C₃) patients.

A health economics assessment was performed on these results in Stage II colon cancer patients using disease-free survival and overall survival (for the entire intent-to-treat population). Cost-effectiveness, cost-utility and sensitivity analysis were applied with, cost of life years, recurrence-free life years and quality adjusted life years (QALYs) as the primary endpoints to this analysis. The perspective of the economic analysis was the current direct medical cost established by the health care providers. The introduction of new technologies often leads to additional costs. This report verified that the use of OncoVAX® for patients with Stage II colon cancer not only has significant prognostic benefit and positive clinical outcomes, but also showed that OncoVAX® therapy yields impressive health economics benefits.

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1. Introduction

Colon cancer is a common malignancy in developed countries. In the United States, it is the second most common type of cancer in men and women. The American Cancer Society estimates that 106,370 cases will be reported in 2004

[1]. Among countries of the European Economic Community (EEC), the numbers are even greater. Approximately 6% of Americans develop the disease within their lifetime [2]. The risk of colon cancer increases after the age of 40 and rises exponentially from the ages of 50 to 55; the risk doubles with each succeeding decade.

Between 1985 and 1997, death rates of colon cancer in the United States declined slightly. The earlier detection of primary tumors, via stool blood tests, sigmoidoscopy,

* Corresponding author. Tel.: +1 301 668 8400x1007.

E-mail address: Michael.Hanna@intracel.com (M.G. Hanna Jr.).

colonoscopy, and screening tests for serum carcinoembryonic antigen concentration (CEA) levels have contributed to the reductions in mortality [3]. Finally, adjuvant chemotherapy with 5-fluorouracil combined with levamisole or leucovorin for Stage III disease has been linked to improved survival rates [4–6]. Preventive measures are still at their infancy while dietary measures likely will take decades to show benefits at the outcome levels.

Survival of colon cancer is related to the stage of disease at the time of the initial diagnosis. To date, surgery is the primary treatment modality for this disease [7]. However, by the time the patient presents with recurrent symptoms, the disease is rarely curable by surgery even when combined with other therapy. The 5-year survival rates for colon cancer patients is greater than 90% when tumors are detected at a localized early stage; after the cancer has spread regionally and involves adjacent organs or lymph nodes, the rate drops to 40–65%; survival is less than 10% for patients with distant metastases. Hence, there is still an urgent need to develop effective treatment strategies to reduce the morbidity and mortality from colon cancer.

Preliminary evidence showed that active specific immunotherapy (ASI) of colon cancer using autologous tumor cell vaccines has potential as a valuable therapeutic option for improvement in recurrence-free interval and survival [8]. This therapeutic process assumes the presence of distinct tumor antigens on a patient's tumor cells that are either absent or in lower concentration on normal cells. This therapy attempts to activate the host defenses against tumor-associated antigens by enhancing the immunogenicity of the patient's own tumor cells (autologous tumor cells) with an immunomodulating adjuvant, such as bacillus Calmette-Guérin (BCG). The logistics and technical complications of manufacturing autologous tumor cell treatments for individual patients have resulted in a paucity of standardized, multicenter, randomized clinical trials.

We have completed a multicenter, randomized controlled phase III clinical trial in Stages II and III colon cancer patients with active specific immunotherapy (four vaccinations) using autologous tumor cells with an immunomodulating adjuvant bacillus Calmette-Guérin (BCG) vaccine (OncoVAX[®]) in an adjuvant setting [9]. In this clinical trial, patients were randomized to receive either surgery (control group) or OncoVAX[®] therapy, after surgical resection of the primary tumor. Stratification by disease stage was performed.

The presence of a significant delayed cutaneous hypersensitivity (DCH) response to tumor cells after the third and fourth OncoVAX[®] treatments (which lack BCG), is a measure of immunogenicity of the treatment and has been correlated with long-term survival [10]. This correlation may reflect the adequacy of the treatment (cell number and viability; correct intradermal placement of the injection), or some factor relating to the capacity of the patients to be immunized by their autologous treatments, or a combination of the two. In the earlier studies, patients received a three-treatment

regimen [8,11]. However, because the DCH response was found to wane at six months [10], this phase III study utilized a booster dose (fourth treatment) given 6 months after the surgical resection of the primary tumor [9]. The results from this study were used and analyzed to relate the long-term medical benefit to the positive health economics of OncoVAX[®].

2. Methods

2.1. Patients

This analysis is based on a Phase III, multicenter, randomized trial performed in The Netherlands, involving 254 patients with either Stage II (B₂ and B₃) or Stage III (C₁–C₃) colon cancer. The patients were randomly assigned after surgery to OncoVAX[®] treatment or no further treatment. Eligible patients had undergone curative resection for primary tumor. An adequate number of cells from the primary tumor and a performance status of 0 or 1 were also required. Patients with direct extension of tumor into the abdominal wall or an adjacent organ were eligible if en-bloc resection had achieved a tumor-free margin on microscopic examination. Patients who had intestinal obstruction that need a colostomy before definitive surgery for the primary tumor were eligible if they were able to enter the study within 28–35 days of resection. We excluded patients whose CEA concentrations did not return to normal within 21 days of resection; who had perforation or evidence of peritoneal seeding; a previous malignant disorder other than carcinoma of the skin; rectal cancer, defined as tumor below the peritoneal reflection; ulcerative colitis, Crohns disease, Gardners syndrome, or Turcott's syndrome; or who were receiving steroids, cytotoxic or immunosuppressive agents.

We stratified patients by the institution in which the surgery was done, location of the primary tumor and tumor pathological stage.

2.2. Vaccination schedule

OncoVAX[®] treatment involved the administration of four autologous tumor-cell vaccinations, started 28–35 days after tumor resection to allow sufficient recovery from immunological suppression that may have been induced by anesthesia and surgery. Treated patients received one intradermal vaccination per week for 2 weeks of about 10⁷ viable, irradiated autologous tumor cells and 10⁷ viable fresh-frozen BCG organisms (Organon Teknika, Durham, NC, USA). At 3 weeks and 6 months, patients received one vaccination of about 10⁷ irradiated tumor cells alone. The first and second vaccines were injected intradermally, one on each anterior thigh about 10 cm below the groin crease. The third and fourth vaccines were injected intradermally in the deltoid region of the upper arms.

2.3. Study design

The clinical study was done at 12 hospitals in The Netherlands, with a central vaccine preparation site at the University Hospital, Vrije Universiteit, Amsterdam. Eleven other hospitals within a 4 h radius of the University Hospital screened potential participants. Colon resections were done at one of the 12 sites, and the tumor sample was sent to the University Hospital's vaccine production laboratory for dissociation, cryopreservation, irradiation, and administration. Participating surgeons were experienced in colon resection. The protocol specified that the surgical procedure should involve wide removal of the involved bowel segment. Stratification of patients by institution keeps the influence of surgical technique on outcome to a minimum. All patient pathological diagnoses were reviewed by a referee pathologist. We obtained informed consent from all patients and ethical approval from all participating hospitals' medical boards.

The preparation of autologous tumor cell vaccine has been described previously [12]. The tumor samples were minced, dissociated with collagenase and DNASE into a single-cell suspension, and frozen in a controlled-rate freezer. Quality of the bulk vaccine was determined by cell number, viability, and sterility. About 60% of bulk vaccines contained microorganisms typically associated with normal gastrointestinal flora. No vaccines were deemed unsafe for administration because of microbial contents. On the day of vaccination, the cells were thawed, irradiated with 200 Gy, and, for the first two injections, 10^7 viable BCG organisms were admixed with the tumor cells and 0.2–0.4 mL vaccine was administered.

Patients were observed after each vaccination for erythema and induration at the site of injection, fever, lymphadenopathy, or any adverse reactions. Immunized and non-treated patients were scheduled for monitoring every 3 months for years 1 and 2, every 6 months until year 5, and once yearly thereafter. Carcinoembryonic antigen concentrations at each follow-up. Chest radiography was done every 3 months for year 1, every 6 months for year 2, and once yearly thereafter. Computed tomography and colonoscopy were performed annually. Documented histological diagnosis by percutaneous, colonoscopic biopsy, or surgical exploration was required to confirm recurrence of tumor, except in cases of lung or liver metastases, which were confirmed by unequivocal radiography or scan. The date of recurrence was recorded as the date of confirmation of disease recurrence.

2.4. Statistical analysis

Data management and statistical analyses were performed by an independent monitoring agency (IKA, Comprehensive Cancer Center, Amsterdam) using SAS software (version 6.11). Recurrence-free survival (free from any disease or cause of death) and overall survival (death of any cause) were the primary clinical endpoints. Recurrence-free interval (recurrences of any malignant disorder) was a secondary endpoint. All main analyses were by intention to treat (ITT). For

recurrence-free interval, recurrence-free survival and overall survival, Kaplan–Meier curves were generated and log–rank statistics were utilized. Cox's proportional hazards model was used to calculate ratios of recurrence and survival and for all multivariate analyses. The protocol prespecified separate analyses by pathological stage (Stages II and III). All statistical tests were two-sided.

The original protocol called for a sample size of 515 patients (377 Stage II and 138 Stage III) to be accrued over 5 years. Data on the degree of treatment effect were not available when the study started. During the course of the study, however, the final results of the clinical trial by Hoover et al. [8] became available. This study reported hazard ratios of 4.0 for overall survival and 2.67 for disease-free survival. Therefore, it was deemed appropriate to recalculate rates of 0.35 in Stage II and 0.50 in Stage III colon cancer. The weighting of these variables by 2:1, according to the observed accrual proportions and a hazard ratio of 2.67 by comparison of exponential parameters, implied a necessary number of at least 38 events to attain 80% power, type I error 0.05 for a two-sided test.

The results of this key study with a 5.3 year median follow-up were published in *The Lancet* [9]. A final audit of the data was performed by another independent monitoring agency (IMRO/Tramarko, Berghem, The Netherlands) with SAS software (version 6.11). The results with a 5.8 year median follow-up are used for this presentation.

The primary variables were 5-year significant difference in all endpoints and log–rank test using PROC LIFETEST in SAS Version 8.0. This same procedure was used to generate the data for the Kaplan–Meier survival plots. The primary analysis was a two-sided statistical test at the 0.05 level of significance. The hazard ratio, which is the overall event rate in the OncoVAX[®] group divided by that in the control group, and its two-sided 95% confidence interval were estimated by a Cox proportional hazards model using SAS PROC PHREG.

3. Design of the decision model

A decision analytic model using MS Excel was developed to model the course of the disease of patients with Stage II colon cancer. In the model, the following conditions were distinguished: recurrence-free survival, having a recurrence (of any kind) and death (of any cause). Transitions are allowed at 6 month intervals for the first and second years, and at once a year thereafter. The transition probabilities are assumed to be dependent on time since treatment, but not on other demographic factors such as gender. Transitions occur at half an interval. The base case analysis considered the results of the clinical study. Data on metastases are based on the study by Graham et al. [13]. Metastases are divided into several sites (namely liver, lung, colon, abdominal, mixed and other) and into operability (yes/no). Overall, approximately 77% of the patients who have metastases were not operable. In the model we have assumed that the

probabilities of developing metastases are the same for Dukes B₂, B₃, and C. Furthermore, we assumed that in the metastases group both operable and non-operable patients will receive chemotherapy consisting of 5-FU plus leucovorin.

4. Economic data

The economic evaluation focused on the direct health care costs. In this study, these costs consisted of the hospital costs, such as hospital days, outpatient visits, day care treatments, laboratory tests, medical procedures and medication, and costs of home care and terminal care.

For the model, the costs of the several interventions, disease stages and follow-up have been calculated by using literature, an 'in-house' cost database and using Dutch tariffs. The base year of the cost study was 2003. The costs of the various interventions, stages and follow-up are presented as costs of follow-up, costs of OncoVAX[®] therapy, operation and treatment costs in case of recurrence and costs of terminal care.

The statisticians then used these data in the calculation of the life years and recurrence-free life years. For the estimation of quality adjusted life years (QALYs) we used utilities as described by Stouthard et al. [14]. This study investigates the general and specific quality of life in patients with colorectal cancer. Utilities found for patients with diagnosis of colorectal cancer during primary therapy was on average 0.55. The utilities after curative primary therapy and therapy of metastatic carcinoma was approximately 0.83 and 0.15, respectively. We assumed that patients' quality of life was not influenced by the OncoVAX[®] therapy, based on the impressive safety profile of OncoVAX[®] treatments.

4.1. Primary and secondary endpoints

Recurrence-free survival and overall survival were the primary endpoints and recurrence-free interval was the secondary endpoint. In addition, this study documented and analyzed treatment cost, life years, recurrence-free life years QALYs, cost-effectiveness and cost-utility. Cost-effectiveness is defined as costs per life year gained and costs per recurrence-free life year gained. Cost-utility consist of costs per QALY gained. As both costs and QALYs are not expected to change after 8 years, we considered a follow-up period of 8 years. Both non-discounted and discounted ratios will be reported. The discount rate is 4%. The results were tested by varying the clinical outcome, the follow-up strategy after surgery, the recurrence-free survival and overall survival in the OncoVAX[®] treated patients, the unit prices and by varying the utilities of the several countries.

5. Results

In general, the characteristics of patients in the control and OncoVAX[®] groups were comparable and are presented in Table 1.

5.1. Recurrence-free survival (ITT) population

5.1.1. All patients

Patients in the control group had a higher incidence of disease progression (38.9%) than those treated with OncoVAX[®] (30.5%) (Table 2). The favorable 8.4% difference represents a 20.4% relative risk reduction of disease progression when

Table 1
Patient characteristics

Characteristic total number of patients	OncoVAX [®]		Control		Total	
	128	50.4%	126	49.6%	254	100.0%
Gender						
Male	67	52.3%	69	54.8%	136	53.5%
Female	61	47.7%	57	45.2%	118	46.5%
Age (years)						
Median	66		65		66	
Range	36.0–88.0		33.0–87.0		33.0–88	
Tumor location						
Right colon	54	42.2%	48	38.1%	102	40.2%
Transverse colon	6	4.7%	9	7.1%	15	5.9%
Left colon	68	53.1%	69	54.8%	137	53.9%
Stage at randomization ^a						
Stage I (Dukes' B ₁)	4	3.1%	9	7.1%	13	5.1%
Stage II (Dukes' B ₂ , B ₃)	80	62.5%	77	61.1%	157	61.8%
Stage III (Dukes' C ₁ , C ₂ , C ₃)	44	34.4%	40	31.7%	84	33.1%
Number of positive nodes (Stage III only)						
<3	34	26.6%	28	22.2%	62	24.4%
>3	10	7.8%	12	9.5%	22	8.6%

^a The only exception in patient characteristics in this audited update and the original publication (ref. [9]) was a shift of one Stage II patient from treated to control group.

Table 2
Summary of recurrence-free survival control vs. OncoVAX[®] (ITT) patients

Population	Control group	OncoVAX [®] group	5-year recurrence-free survival <i>p</i> -value	log-rank analyses	
				<i>p</i> -value	Relative risk ^a
ITT (all patients)	49 (38.9%) <i>N</i> = 126	39 (30.5%) <i>N</i> = 128	0.073	0.080	0.687 (0.451, 1.049)
ITT all patients randomized to TNM Stage II	32 (37.2%) <i>N</i> = 86	19 (22.6%) <i>N</i> = 84	0.005	0.015	0.496 (0.278, 0.884)
TNM Stage II (B ₂ , B ₃) ^b	29 (37.7%) <i>N</i> = 77	17 (21.3%) <i>N</i> = 80	0.009	0.018	0.493 (0.271, 0.897)
TNM Stage III	17 (42.5%) <i>N</i> = 40	20 (45.5%) <i>N</i> = 44	0.640	0.880	1.051 (0.550, 2.007)

^a HR (CI): hazard ratio (95% confidence interval).

^b Thirteen patients (nine control and four treatment) had disease stage TNM I and were not eligible for analysis.

treated with surgical resection plus OncoVAX[®] compared to the control group (5-year survival *p* = 0.073; log-rank analysis *p* = 0.080).

5.1.2. Stage II patients

Forty-six TNM Stage II (B₂, B₃) patients (29 control, 17 treatment) were reported as having disease progression or having died during the study. Kaplan–Meier estimates of colon cancer rates show a statistically significant improvement of recurrence-free survival in the Stage II treated patients (Fig. 1). The percentages after 5 years of follow-up were 21.3 and 37.7% for the control and treatment groups, respectively. The favorable 16.4% difference represents a 41.4% relative risk reduction of disease progression (5-year survival *p* = 0.009; log-rank analysis *p* = 0.018).

A similar recurrence-free survival benefit was achieved in the ITT population of all patients randomized as TNM Stage II but having 13 B₁ patients (nine control and four treated).

5.1.3. Stage III patients

Recurrence-free survival for the ITT Stage III patients was 42.5% for the control group and 45.5% for the treatment group; the difference is not statistically significant (5-year survival *p* = 0.640; log-rank analysis *p* = 0.880).

5.2. Overall survival (ITT) population

5.2.1. All patients

The overall survival rate for the treated group was higher (75%) as compared to control (71.4%) (Table 3). The favorable 3.6% difference represents an 11.1% relative risk reduction when treated with surgical resection plus OncoVAX[®] when compared to the control group (5-year survival *p* = 0.100; log-rank analysis *p* = 0.252).

5.2.2. Stage II patients

Thirty-five TNM Stage II (B₂, B₃) patients (21 control, 14 treatment) died during the study. Overall survival showed a statistically significant improvement in the Stage II treated patients (17.5%) over those patients in the control group (27.3%) (Fig. 2). The favorable 9.8% difference represents a 33.3% relative risk reduction (5-year survival *p* = 0.010; log-rank analysis *p* = 0.074).

A similar overall survival benefit was achieved in the ITT population of all patients randomized as TNM Stage II but consisting of 13 B₁ patients (nine control and four treated).

5.2.3. Stage III patients

Overall survival for the ITT Stage III patients showed a higher incidence for the treatment group; however, the

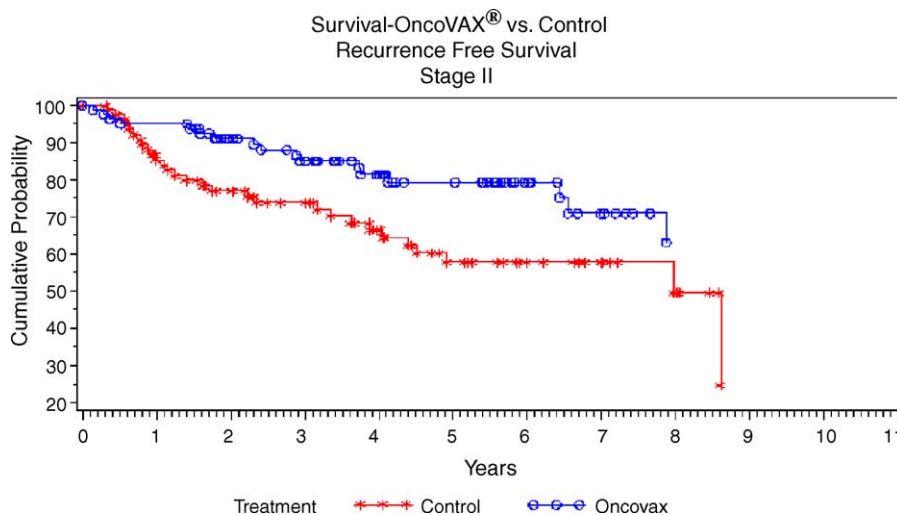


Fig. 1. Kaplan–Meier estimates of recurrence-free survival control vs. OncoVAX[®] (ITT) Stage II patients.

Table 3
Summary of overall survival control vs. OncoVAX® (ITT) patients

Population	Control group	OncoVAX® group	5-year overall survival <i>p</i> -value	log-rank analyses	
				<i>p</i> -value	Relative Risk ^a
ITT (all patients)	36 (28.6%) <i>N</i> = 126	32 (25.0%) <i>N</i> = 128	0.100	0.252	0.757 (0.469, 1.221)
All patients randomized to TNM Stage II	24 (27.9%) <i>N</i> = 86	16 (19.0%) <i>N</i> = 84	0.008	0.059	0.541 (0.284, 1.033)
TNM Stage II ^b	21 (27.3%) <i>N</i> = 77	14 (17.5%) <i>N</i> = 80	0.010	0.074	0.544 (0.276, 1.071)
TNM Stage III	12 (30.0%) <i>N</i> = 40	16 (36.4%) <i>N</i> = 44	0.694	0.685	1.168 (0.552, 2.469)

^a HR (CI): hazard ratio (95% confidence interval).

^b Thirteen patients (nine control and four treatment) had disease stage TNM I and were not eligible for analysis.

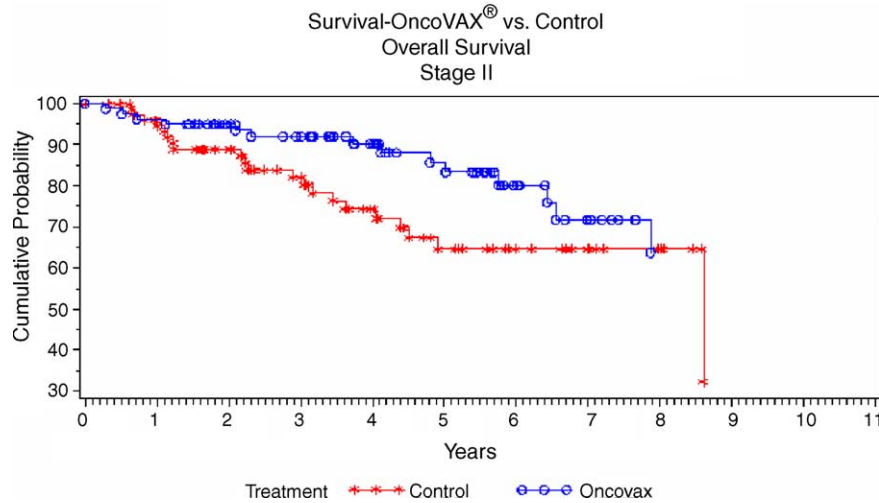


Fig. 2. Kaplan–Meier estimates of overall survival control vs. OncoVAX® (ITT) Stage II patients.

difference is not statistically significant (5-year survival *p* = 0.694; log-rank analysis *p* = 0.685).

5.3. Cost-effectiveness and cost-utility analysis

For the calculation of the life years and QALYs we used the overall survival and recurrence-free survival data of the clinical study. Concerning the QALY calculation, we distinguished patients who had a recurrence and patients who did not have a recurrence. The average time spent in a particular health state was averaged over all patients and QALYs were calculated by multiplying the average times spent in each health state weighted by their respective utility values and aggregating these weighed time periods per arm (Drummond et al. [15]).

The number of life years in the OncoVAX® group amounted to 6.96 and in the control group 6.25 (see Table 4). Thus, the number of life years gained are approximately 0.71. The number of recurrence-free life years gained is approximately 1.10. Moreover, in the OncoVAX® group, there were 5.51 QALYs and in the control group were 4.65 QALYs. The costs per life year, the costs per recurrence free life year and the costs per QALY for each group are also presented in Table 4.

The average costs per patient in the OncoVAX® group which includes cost of treatment plus follow-up

Table 4
Results of baseline model (costs in US\$)

	Control group	OncoVAX® group	Difference between groups
Number of life years	6.25	6.96	0.71
Number of recurrence-free life years	5.67	6.77	1.10
Number of quality adjusted life years	4.65	5.51	0.86
Average costs per patient	8784	28101	19317
Cost per life year	1405	4036	
Costs per recurrence free life year	1550	4151	
Costs per QALY	1888	5101	

costs amounted to US\$ 28,101. In the control group the costs were US\$ 8,784. The costs per life year gained amounted to US\$ 27,207, the costs per recurrence-free life year gained were US\$ 17,521 and the costs per QALY amounted to US\$ 22,561. The total discounted cost-effectiveness ratio of life years gained was US\$ 31,061 and the discounted cost-utility ratio amounted to US\$ 25,408 (Table 5).

Table 5
Cost-effectiveness and cost-utility ratios (costs in US\$)

	Cost-effectiveness ratio		Cost-utility ratio
	Costs per life year gained	Costs per recurrence-free life year gained	Costs per QALY gained
Base case scenario	27207	17521	22561
Base case scenario with discount rate of 4%	31061	19694	25408
Varying clinical outcome: using results of The Lancet 1999 publication [8]	24799	16084	20640
Decrease of recurrence-free and overall survival by 2%	34711	20367	26474
Increase of recurrence-free and overall survival by 2%	22685	15424	19752
Increasing unit prices with factor 1.5 (excluding cost OncoVAX [®])	26761	17234	22192
Varying utility: utility recurrence-free patients 0.90 and utility recurrence patient 0.75 (in both groups)	27207	17521	27873

5.4. Sensitivity analysis

In Table 5, the results of the sensitivity analyses are reported.

5.4.1. Clinical outcome according to the Vermorken study [9]

Taking into account the clinical outcome of the Vermorken study, the cost-effectiveness ratio amounted to US\$ 24,799 (costs per life year) and in terms of costs per QALY the ratio would be US\$ 20,640.

5.4.2. Change in recurrence-free survival and overall survival

Decreasing the recurrence-free survival and overall survival of the OncoVAX[®] group by 2.0% resulted in higher cost-effectiveness ratios. If the recurrence-free survival and overall survival in the OncoVAX[®] group increased by 2.0%, the cost-effectiveness ratios would be more positive to OncoVAX[®].

5.4.3. Increasing prices for all cost items

Assuming variations of basic health care costs for different countries, we tested the impact on the medical economics. Changing the price of all cost items except for the price of OncoVAX[®] with a factor 1.5 had little impact on the cost-effectiveness and cost-utility ratios.

5.4.4. Quality of life/utility values

In the base case analysis utility values of the study of Stouthard et al. [14] were taken into account. We varied the utilities by using the results as described by Ramsey et al. [16]. This study investigates the general and specific quality of life of survivors of colorectal cancer. Utilities found for patients with diagnosis of Stage II colorectal cancer range between 0.85 and 0.91 depending on the time since diagnosis. The average utility was 0.86. For patients with recurrence, the utility score is assumed to be 0.65. As a result, the cost-utility ratio increased to US\$ 27,873.

6. Discussion

This study is additional proof of durable and long-term clinical benefits of OncoVAX[®] and the health economic rationale of this autologous tumor cell vaccine. The mechanism of action of this therapeutic process is distinctly different from conventional cytotoxic drugs to treat malignancies. Standard chemotherapy is directly cytotoxic to tumor cells and normal cells. Tumor vaccines are not directly cytotoxic, but mediate their effect through the induction of a cell-mediated immune response. Thus, while chemotherapy efficacy is closely related to the dose of the drug, the efficacy of a tumor vaccine is more complex, involving host-vaccine interaction. These interactions include: (1) immunogenicity of the vaccine with regard to tumor-associated as opposed to self antigen; (2) the status of the host immune response in terms of immune recognition and effector mechanisms; and (3) the ultimate development of host systemic cell-mediated immunity, including long-term immunologic memory, which exerts an influence over an extended period of time (3–5 years). Therefore, the potency of the vaccine is not determined by immunogenicity alone but by its ability to induce the host anti-tumor response; the induction of systemic, cell-mediated immunity.

An effective autologous tumor cell vaccine, through the use of adjuvants and the intradermal route of injection, transforms what is under normal circumstances a weak immunogen into an optimum cocktail of antigens that induces host recognition of the tumor-associated antigens, producing a functional immune response. Such is the ultimate potency test of any vaccine. This improvement in clinical outcome is a prognostic factor of general immune competence.

This novel, immunotherapeutic approach showed a statistically significant improvement in recurrence-free interval, recurrence-free survival and overall survival. The results were seen predominately for Stage II (B₂, B₃) colon cancer and this is particularly significant considering that the evidence supporting a benefit for treating Stage II patients with adjuvant chemotherapy is inconclusive [17–19].

Improvement in overall survival is generally accepted as the gold standard of a new therapeutic for cancer. OncoVAX[®] showed a statistically significant improvement in 5-year overall survival in Stage II but the log-rank analysis was only moderately significant ($p=0.07$). We speculate that this is due to two factors: (1) competing age related risk factors in this population (median age 66 years) for overall survival; and (2) the relatively good overall survival rate of Stage II colon cancer patients after tumor resection. Multivariate analysis using tumor stage, age, number of involved lymph nodes, tumor location, and gender as covariates in the regression model showed that age was a significant competing risk factor associated with overall survival. When considering overall survival, age 70 years or greater was associated with worst outcome in this study. This fact strengthens the use of 5-year overall survival benefits as a relevant clinical endpoint in colon carcinoma patients.

Thus OncoVAX[®] is a novel and innovative therapeutic approach to treating Stage II colon cancer and it is well known that the introduction of new technologies often leads to additional health care costs. In today's medical economic environment these costs are severely scrutinized. Clearly the acceptance of such additional costs must be offset by improved prognostic benefits and quality of life. This study shows that the application of an autologous tumor cell therapeutic process, in an adjuvant setting, in minimal disease colon cancer patients, is cost-effective, provides disease-free life years and improved quality of life.

Graham et al. [13] determined the average costs of four tests in colon cancer follow-up: physical examination, CEA level measurement, chest X-ray, and colonoscopy. CEA measurement was the most cost-effective test in detecting potentially curable recurrent disease. Virgo et al. [20] estimated the costs of follow-up of colorectal cancer patients treated with curative intention. The study is based on a literature research and the articles contained specific follow-up recommendations. Nationwide average charges (base year 1992) for 11 follow-up strategies were computed for a 5-year, follow-up period. The Medicare charges varied from US\$ 561 per patient to US\$ 16,492 per patient. This study showed that the costs of follow-up can vary by a factor of 28. The problem is that there is no agreement on the appropriate follow-up and follow-up interval. So far, no one strategy has proven to increase survival and quality of life.

In this analysis, the cost-effectiveness ratio was calculated considering follow-up procedures in the ASCO guidelines [21]. The follow-up according to ASCO guidelines consisted of minimal tests and procedures. However, this has no impact on the cost-effectiveness ratio compared to the base case analysis. There is discussion about the extent of follow-up, because less intensive follow-up will miss recurrences.

Tumor recurrence in cancer patients who are apparently disease-free after tumor resection is a frequent event. Therefore, effective adjuvant therapy is needed. Cancer immunotherapeutics, such as OncoVAX[®], are receiving increased attention. A patient group where this is of relevance

is colon cancer. The majority of patients with recurrent colon cancer will die within 14–20 months. Therefore, improvements in recurrence-free survival rates are also of importance. In all of the OncoVAX[®] clinical studies significant improvement in recurrence-free episodes was found in patients with Stage II disease. This fact supports the basic tenant that immunotherapy works optimally in minimal residual disease [22].

Cost-effectiveness analyses are intended to support decision-making. They can provide essential information on the costs and benefits of each option and consequently, on the optimal policy mix, and thus support decision on the adoption and utilization of new treatment modalities. As more economic evaluations are performed, it becomes possible to make comparisons between health-care interventions in terms of their relative cost-effectiveness, in cost per life year gained, or cost per QALY gained. In our study, the cost per life year gained, per recurrence free life year gained and per QALY were US\$ 27,207, US\$ 17,521 and US\$ 22,561, respectively. Cost-effectiveness ratios among other effective or approved tests or therapies varied exceptionally; for example, considering the introduction of breast cancer screening the cost per QALY gained were US\$ 3706 and considering the administration of erythropoietin for anemia in dialysis patients the cost per QALY gained amounted to US\$ 100,529 [23]. In cancer treatment, there are many studies presenting cost-effectiveness or cost-utility ratios. For example, the cost per QALY of administering paclitaxel or docetaxel in patients with metastatic breast cancer amounted to US\$ 30,270 and US\$ 49,739 [24]. The cost-utility ratio (in terms of cost per QALY gained) of these treatments compared to mitomycin/vinblastine amounted to US \$99,547 and US\$ 256,304. Considering the height of the ratios, and the little impact on survival in this patient group, it is clear that the rationale of administering new treatment modalities are not always simply based on economic reasons.

Comparison of pharmacoeconomic data should be taken with care. Drummond et al. [15] found that there was considerable variation in methodology among studies. Important issues are the choice of comparison treatment strategy, the inclusion and exclusion of costs and consequences and the choice of discount rate. In our study, we focused on direct medical costs. Consequences considered were survival, recurrence-free survival, and quality of life. Recurrence-free survival was based on data of prospective randomized clinical trials. Quality of life data was based on literature. However, changing the utilities had little impact on the difference in QALYs. The comparator in our study was 'no additional treatment' as the standard therapy is surgery alone. Given the treatment costs in the beginning and the fact that gains in effectiveness occurred mainly in the long term, it will be clear that the discounting had a great impact on the results. Several authors argued whether cost-effectiveness decision rules are workable in practice and whether the adoption of a cost-effectiveness threshold is wise [25,26]. In the end, aseptic and immunologically effective control of the OncoVAX[®]

preparation and the quality assurance that the product meets specifications (viable tumor cells, identity and potency) are of the higher priority.

From a patient's perspective, the benefits of OncoVAX[®] appear to be substantial relative to average improvements reported in oncology. The time horizon of effect—onset at the second year, sustaining effect until at least 5 years—is pertinent to this group of patients. From the perspective of the clinic, this treatment poses few additional requirements apart from the procurement of tumor cells, the final formulation and intradermal treatments. Preparation of treatment entities from biological material of the patient, though uncommon, can also be observed in bone and skin grafting and autologous transfusions. Yet comparison in this domain appears to be inappropriate as the function is induction of an immunological response rather than supplementation. In the context of cytotoxic drug therapies OncoVAX[®] is better than implicit standards, with per case costs within accepted ranges.

In conclusion, OncoVAX[®] is a safe and highly effective treatment modality for patients with Stage II colon cancer with a favorable cost-effectiveness ratio, in the range of other oncological treatments.

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