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Symptom and quality of life results of an international randomised phase III study of adjuvant vaccination with Bec2/BCG in responding patients with limited disease small-cell lung cancer

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ABSTRACT

Aims: This study reports the symptom and HRQOL results in which standard treatment was compared to standard therapy plus Bec2, an anti-idiotypic antibody that mimics GD3, a ganglioside antigen.

Methods: Five hundred and fifteen LD SCLC patients were randomised to receive five vaccinations of Bec2 (2.5 mg)/BCG vaccine arm (VA) or an observational arm (OA) administered over a 10-week period. Survival was the primary end-point; HRQOL was a secondary end-point, assessed using the EORTC QLQ-C30/LC 13.

Results: There was no improvement in survival or progression-free survival in the vaccination arm. At baseline patients in both arms demonstrated significantly impaired scores on the global QOL scale, when compared to a normative population. However, HRQOL and symptom scores between the two treatment arms were not statistically different at any time point.

Conclusion: We found no benefits to patient HRQOL by additional vaccination with Bec2/BCG to LD SCLC for patients who have been undergoing standard therapy.

1. Introduction

Small-cell lung cancer (SCLC) is a fatal disease.[1] Approximately 30% SCLC patients present with limited disease (LD), that is the tumour is confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes.[1] In general, survival averages 18 months after diagnosis.[1] The single highest risk associated with the development of SCLC is cigarette smoking.

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Given the advanced nature of this disease, it is not surprising that LD SCLC patients may have impaired HRQOL. Patients with LD SCLC often present with symptoms that can include dyspnoea, coughing, chest pain, fatigue and weight loss.

The standard treatment for LD SCLC is a combination of chemotherapy and chest radiotherapy. However, research initially suggested that Bec2, an anti-idiotypic antibody that mimics GD3, may be an effective treatment, in the maintenance of a response obtained by initial chemoradiation. Based on this rationale, the EORTC Lung Cancer Group undertook a randomised phase III study to compare vaccination with Bec2/BCG versus observation in patients responding after combined modality therapy for LD SCLC. The clinical results of this study have been previously published.[2] This manuscript presents the symptom and HRQOL findings.

2. Methods

2.2. Study design and treatment

In this international, multi-centre, intergroup study (European Organisation for Research and Treatment of Cancer trial 08971-08971b; SILVA study), the primary outcome was overall survival. Secondary outcomes included progression-free survival, safety, tumour-humoural response and HRQOL symptoms. Patients were randomly assigned to the vaccination or the observation arm. Full details on the trial conduct and clinical outcome have been reported before.[2] In brief, patients had to have undergone adequate induction therapy of at least two drug regimes for 4–6 cycles, plus chest radiotherapy before being randomised to either the experimental arm of five vaccines or an observation arm.

The trial was conducted in accordance with the Helsinki declaration, and was approved by the EORTC protocol review committee and the ethics committee of each participating centre. All patients provided written informed consent before randomisation.

2.2. Procedures for HRQOL data collection

Two HRQOL measures were selected: the EORTC Quality of Life Questionnaire C30[3] and the EORTC Lung Cancer LC13 Module.[4] These tools have robust psychometric properties, and are the most frequently used HRQOL measures in lung cancer RCTs.[5] The EORTC QLQ-C30 is a core measure designed to be supplemented with disease-specific questionnaires.[6] The EORTC QLQ-LC13 focuses on symptoms and initially developed and validated specifically for lung cancer patients. Both instruments were available in the native language of all participating patients.

The EORTC QLQ-C30 measure comprises five functioning scales: physical, role, emotional, cognitive and social; three symptom scales: fatigue, nausea/vomiting and pain; six single item scales: dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact; and the overall health/global QOL scale.

The EORTC QLQ-LC13 was designed for use with a wide range of lung cancer patients undergoing chemotherapy or radiotherapy.[4] It includes 13 items addressing key lung cancer symptoms (cough, haemoptysis, dyspnoea and site specific pain), treatment related side-effect(s) (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The dysphagia scale is multi-item; the remainders are single items scales.

The items on both measures were scaled and scored using the recommended EORTC procedures,[7] excluding the financial impact of the treatment scale from the analysis given this has limited value in an international clinical trial. In addition, a health economic analysis was initially planned using the EORTC single item Health thermometer. The report only concerns the HRQOL symptom data; therefore, no report is made on this scale.

Protocol specified that the primary scale would be the global HRQOL scale hypothesising there would be no difference in the global HRQOL scale between treatment arms over the treatment period. The remaining HRQOL and symptom variables were then examined on an exploratory basis to explore the side-effects and symptoms observed in the vaccination arm.

Given that statistical differences can occur when using large patient numbers and that these may not necessarily be clinically meaningful, a standard practice of interpretation of HRQOL scores, using the minimal important difference approach, was adopted. Differences of at least 10-points (on a 0–100 scale) were classified as the minimum clinically meaningful change in a HRQOL parameter.[8] Changes, equal to or more than 20 points were considered as large effects.

Assessments were performed at baseline, i.e. before start of therapy and not earlier than 14 d before randomisation; at weeks 6, 12 and 24 and thereafter every 6 months until progression. EORTC guidelines for administering questionnaires were provided, ensuring standardisation of HRQOL data by all personnel. Compliance levels were monitored using standard EORTC procedures and calculated as the number of forms received out of the number expected at each assessment point.

2.3. Statistical analysis

The sample size was based on the primary end-point (survival) with HRQOL a secondary study end-point. Randomisation was undertaken in Brussels, at the EORTC Data Centre, by telephone, using a minimisation technique, independent from the investigators. Treatment comparison and score changes between baselines were performed using statistical analysis software (SAS), based on the *intent-to-treat* principle. A mixed-model approach estimated the HRQOL differences with an unstructured covariance structure. All patients with at least one valid HRQOL form were included in the analysis ($n = 482$). In order to correct for multiple comparisons, and to avoid *type I* errors, the level of statistical significance was set at $p = 0.01$.

Given that missing data are a common problem in HRQOL studies, sensitivity analyses were performed investigating the reasons for *missingness* (by drop-out) for various clinical factors on the probability of a missing HRQOL observation. The number of missing observations (generalised linear model for Poisson process), the probability of any missing observations (logistic regression: completers versus non-completers) and time until drop-out (time-to-event analysis via Kaplan–Meier methodology, logrank test) were used. Analysis of com-

plete cases, last observation carried forward with missing observations (prior to death or progression), checked the robustness of the main results.

In addition, the best and worst reported changes from baseline per patient were considered appropriate summary statistics as an alternative methodology to the mixed modelling.

3. Results

Between March 1998 and October 2002, 515 patients were recruited into this trial from 120 institutions from 17 countries. Two hundred and fifty eight patients were allocated to the observation arm and 257 to the vaccination arm. The basic characteristics of those in each treatment group along with HRQOL assessments are presented in Table 1.

3.1. Clinical findings

The clinical results were reported previously.[2] Overall, the vaccination with Bec2/BCG had no significant impact on median survival compared to observations (16.4 and 14.3 month $p = .28$).

Table 1 – The basic characteristics of patients with HRQOL assessments in each treatment group

Characteristics at randomisation		
	Treatment	
	Observation (N = 258) N (%)	Vaccination (N = 257) N (%)
Age (years)		
Median	58.0	59.0
Range	33.0–81.0	35.0–89.0
Sex		
1. Male	158 (61.2)	162 (63.0)
2. Female	99 (38.4)	95 (37.0)
Missing	1 (0.4)	0 (0.0)
Race		
1. Ca-hisp	30 (11.6)	36 (14.0)
2. Ca-non hisp	219 (84.9)	213 (82.9)
3. African descent	3 (1.2)	2 (0.8)
5. Other	3 (1.2)	2 (0.8)
9. Not applicable	2 (0.8)	4 (1.6)
Missing	1 (0.4)	0 (0.0)
Relevant medical history		
0. No	82 (31.8)	71 (27.6)
1. Yes	175 (67.8)	186 (72.4)
Missing	1 (0.4)	0 (0.0)
Karnofsky at rando		
60–70	18 (7.0)	13 (5.1)
⩾80	240 (93.0)	244 (94.9)
PPD test		
Negative	201 (77.9)	206 (80.2)
Doubtful	27 (10.5)	25 (9.7)
Positive	30 (11.6)	25 (9.7)
Missing	0 (0.0)	1 (0.4)
Height		
Median	170.0	170.0
Range	140.0–193.0	145.0–196.0
At least 1 valid QoL form		
Yes	242 (93.8)	240 (93.4)
No	16 (6.2)	17 (6.6)

4. Compliance with HRQOL measures

Table 2 summarises compliance over the course of the study. Baseline questionnaires were available for 486 patients (93%) and all the subsequent analyses were based on this sample. There were no significant differences in clinical characteristics between those who completed a HRQOL form or those without (data not shown). Overall compliance for the 30 months 52% an 82%, with no significant differences between arms overall. Fisher exact-tests for compliance showed no significant difference from baseline over any treatment assessment time points at the $p = 0.007$ level (Bonferroni adjustment). Given the aggressive nature of LD SCLC, patient attrition due to drop-out or death (over treatment) led to a reduction in absolute numbers of patients available for inclusion in the analysis. For these reasons, the HRQOL analysis interpretation was restricted only on-treatment up to month 18 (Table 2) where compliance still remains acceptable at 62% and 66%.

5. HRQOL findings

Fig. 1 presents the mean baseline scores for both treatment groups. Using the EORTC reference-values manual[9] scores on the EORTC QOL C30 measures were compared. The manual also has reference scores of other patients with LD SCLC which we can compare. However, as expected, when compared to a normative reference population, on most, but not all scales, HRQOL was worse in both treatment groups. However, similar scores for the baseline EORTC reference data of

Table 2 – Compliance with HRQOL assessment over the course of the study

Table of compliance		
Received/expected compliance	Observation	Vaccination
Baseline	228/244	219/242
	93.44%	90.50%
Week 6	210/234	190/219
	89.74%	86.76%
Week 12	171/204	155/188
	83.82%	82.45%
Week 24	121/148	113/136
	81.76%	83.09%
Month 6	69/88	67/81
	78.41%	82.72%
Month 12	43/68	44/69
	63.24%	63.77%
Month 18	31/50	33/50
	62.00%	66.00%
Month 24	16/35	19/31
	45.71%	61.29%
Month 30	14/27	14/17
	51.85%	82.35%
Total	903/1098	854/1033
	82.24	82.67

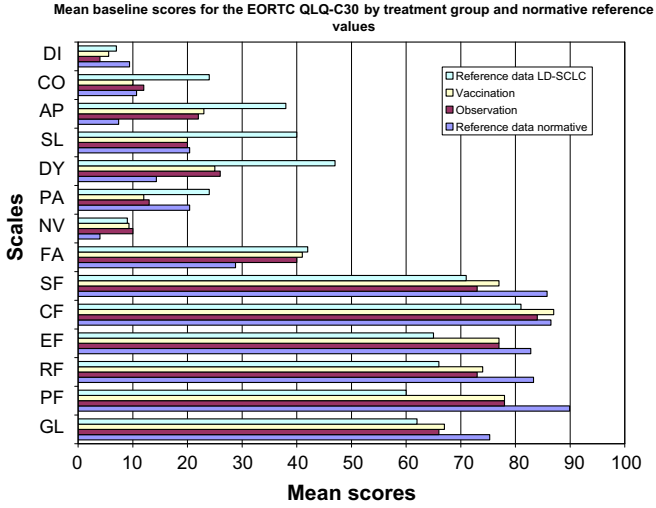

Fig. 1 – This figure presents the mean baseline scores for both treatment groups along with data from a reference sample of LD SCLC and a normative sample functional scales: physical (PF), role (RF), emotional (EF), cognitive (CF) and social (SF) and Global QOL (GL). Symptom scales/items: fatigue, (FA), nausea vomiting (NV) and pain (PA); six single item scales: dysponea (DY), sleep disturbance (SL), appetite loss (AP) constipation (CO) diarrhoea (DI) and global quality of life (GL) scale. A high score for a functional scale represents a high level of functioning, and a high score on global QOL represents high HRQOL, a high score on a symptom scale represents a high level of symptoms.

LD SCLC were noted, with the exception of the our sample of LC SCLC having worse scores on 4 of the 15 scales (appetite loss, greater dyspnoea, worse constipations and more sleep problems) than our sample. This may suggest the HRQOL impairment is not as representative as in other studies for these 4 of over 15 scales, or this is possibly due to the fact that patients had received prior treatment, which is not the case for the EORTC reference data.[9]

At baseline, both groups reflected clinically similar levels of HRQOL. No statistically (at $p = 0.01$ level) nor clinically (equal to or more than 10 points) significant differences were found at baseline between the two treatment arms, with the exception of pain in the chest score of the LC13 ($p = 0.05$). However, this was not a clinically meaningful difference, (e.g. less than 10 points).

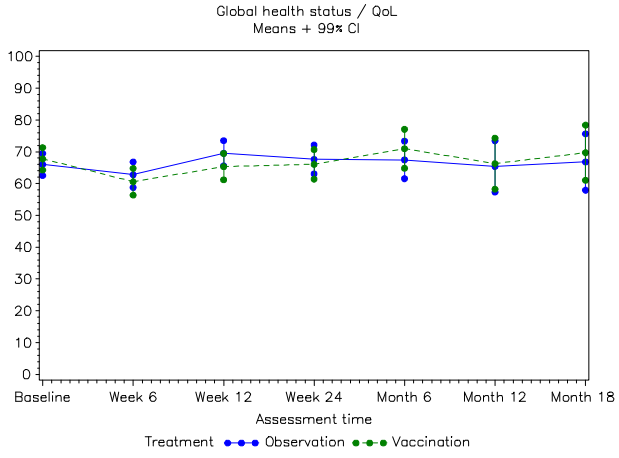

Fig. 2 – Primary HRQOL end-point scale.

5.1. *Primary HRQOL end-point*

Using the global HRQOL scale selected *a priori* in the protocol reveals a declining HRQOL for both treatment groups is hindered, yet comparable (Fig. 3). These differences (66 points in the observation arm and 67 in the vaccination arm) represent a considerable decline in global HRQOL when compared to a normative population (75 points). During the subsequent assessments there was no significant change in global HRQOL, suggesting that in both arms, whilst being considerably impaired, the vaccination had limited impact on patient wellbeing, and as expected, this was similar between both groups (see Fig. 2).

5.2. *Other HRQOL scale*

Fig. 3 presents *selected* remaining HRQOL scales.

The remaining scales of the EORTC QLQ- C30 and EORTC QLQ-LC13 suggest some HRQOL impairment at baseline: physical, role function, emotional function, cognitive functioning was consistent and yet stable over the treatment period (data not shown) and with no significant or clinically relevant difference between arms. However, fatigue, whilst showing no difference between arms (Fig. 3), showed a statistically significant improvement in both groups on-treatment compared to baseline ($p = 0.001$).

The nausea and vomiting scale showed only a small number of problems for patients at baseline, but this significantly decreased in both arms over time, although not to a clinically meaningful level. Levels of pain remained relatively stable in both arms, slightly increasing at week 6 in both arms, but were never significantly different at any time point. The dyspnoea scale of the EORTC QLQ-C30 showed both groups had some difficulties with breathing. In both arms this failed to

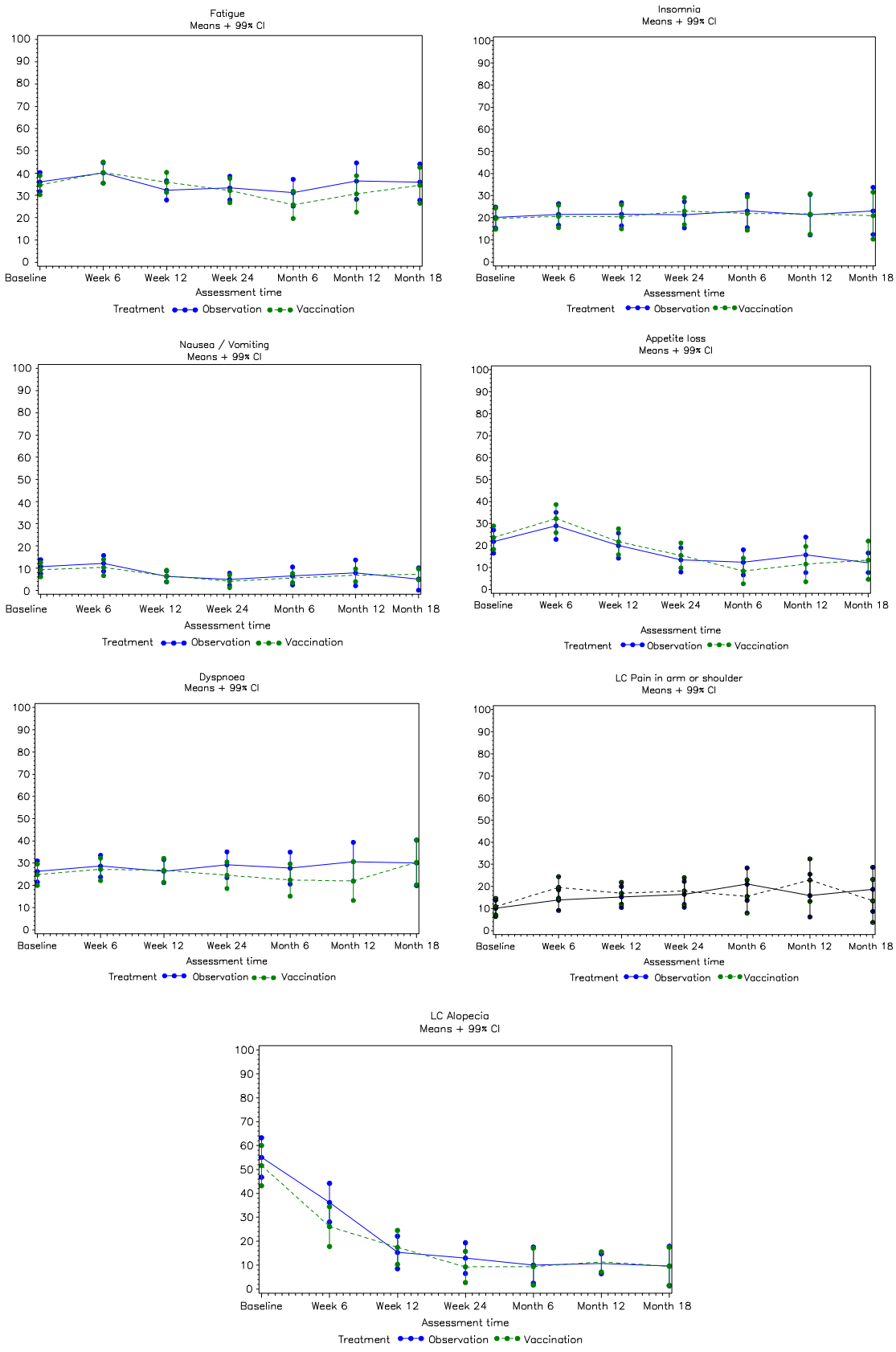

Fig. 3 – Primary HRQOL end-point scale.

improve over treatment time. A similar pattern was also seen for insomnia, a problem for patients, but remaining stable over the entire study. Appetite loss significantly improved in both arms over time, with statistically significant differences

($p \geqslant 0.001$) and clinically meaningful improvement in both arms from baseline. Alopecia changed significantly over time, and to a clinically meaningful event, in both arms, with less hair loss at the end of treatment. Pain in the arm or shoulder increased in both treatment groups, with worse scores later in the study. However, these were not statistically significant except at week 6 with more pain in the arm in the vaccination group (13.8 versus 19.5). However, this difference was not clinically significant. Nevertheless, this result is in concordance with some of the adverse events reported in the first clinical paper, with local skin toxicity with over one-third of those skin toxicities being grade 3.

Levels of insomnia, appetite loss, constipation, diarrhoea, lung cancer scale coughing, haemoptysis, sore mouth, dysphagia, pain in the chest, and pain in other parts were all stable and without treatment effects over time (data not shown).

5.3. *Missing data and missingness mechanism*

Modelling of the missing data mechanism revealed that the only variable to be consistently linked with missing HRQOL assessments was the time of the assessments. The longer patients were on the study, the more likely they were to forego a HRQOL assessment.

5.4. *Sensitivity analyses*

The sensitivity analysis using both complete case and last observation carried forward shows comparable results, supporting the main findings. The best and worst change from baseline revealed no differences in overall HRQOL at 5% significance level, nor in any of the secondary scales at the 1% level.

6. Discussion

This study is one of a few large-scale randomised controlled trials investigating LD SCLC patient survival time and combining HRQOL and symptom outcomes with vaccination. The primary objectives were to evaluate survival benefits, along with the important secondary end-point of an evaluation of HRQOL and symptom impact, during treatment, when comparing the observation arm versus vaccination of Bec2/BCG in the experimental arm. The survival results unfortunately demonstrated no significant survival advantage of including Bec2/BCG and the HRQOL findings show no overall benefit of effects compared to the observation arm.

Examining the baseline HRQOL scores, similarities between the two groups were noted. However, whilst some statistical differences occurred on a few HRQOL scales between the baseline scores for each group, these were not of clinical significance. However, in comparison to the EORTC QLQ-C30 normative reference data with the study population some reductions were seen in HRQOL. However, when compared, the reference-values samples of LD SCLC baseline results are quite comparable, with the exception of 4 scales, but overall, suggesting the sample is representative of other LD SCLC patients.

Taking the global HRQOL scale as the primary HRQOL endpoint, it was observed that, over the study period, there were no differences between the two arms. However, it is clear that both groups had impairment of global HRQOL scores when compared to a normative general population. Importantly, in this disease population, this level did not deteriorate, remaining stable over the study period.

The remaining scales were reported on an exploratory basis. There were relatively few HRQOL differences between treatment arms over the course of treatment. However, appetite loss did reveal differences with statistically significant improvements over time in each arm; these are clinically meaningful. The cause may be suggested as the effect of patients stopping the more toxic therapies of standard care.

Pain in the arm or shoulder was a significant issue for some patients, at week six in the vaccination group (19.5) versus 13.8 in the observation group. However, this was not clinical significant as relatively similar scores at later assessments points.

Fatigue was seen at high levels in both groups at baseline (36 versus 34); this slightly decreased in both groups over the 18 months but was not a meaningful change. This demonstrates LD SCLC patients suffer considerable fatigue and ideally attention to alleviating fatigue in all LD SCLC patients is recommended.

Stabilisation of HRQOL and symptom scores was also seen for insomnia, constipation, diarrhoea, lung cancer scale coughing, haemoptysis, sore mouth, dysphagia and pain in the chest were also evident. All these HRQOL issues were constant with no deterioration over time. Cognitive functioning was unimpaired in the sample patients and comparable with a normative reference population, but over time both groups showed a significantly but not clinically meaningful decline in cognitive function.

Our study can be compared to a recent doubled blind placebo controlled trial in SCLC. This used a similar design to our study. The RCT was lead by Dr Shepard et al.,[10] and in brief, they examined the effects marimastat compared to placebo. The authors found a clinical significant negative effect on HRQOL and symptom results at both 3 and 6 months in the treatment arm. But longer terms results were unavailable, due to early closure of the trial, because of increased treatment toxicity in the marimastat arm, hence, it is difficult to compare to our study.

Certainly several limitations apply to our study. For example, whilst a high baseline compliance of 93% was obtained from a reasonable sample size ($n = 515$) due to rapid patient attrition, mainly patient death, the study was unable to focus on results after month 18. Patient numbers simply become too few to make conclusions from this point. Therefore, results are only representative of patients up to this point. However, a sensitivity analysis revealed no major bias in our analysis. Another concern may relate to the use of the measures, in particular the EORTC QLQ-LC13: whilst heavily symptom based, this measure is not specifically developed for assessing the symptoms of vaccines for use in LD SCLC patients, and there is the possibility that it would not be sensitive enough to detect the treatment effect of the vaccine.

In conclusion, this study suggests that there were no significant differences in the global HRQOL scale between groups over the course of the treatment. Given the unfortunate failure of Bec2/BCG to either improve survival, or indeed to have any positive effect on patient HRQOL or symptoms, this cannot be seen as a treatment option for future LD SCLC patients.

Conflict of interest statement

Giannicola D' Addario has received an honorarium from Merck Switzerland. All other authors declared no conflict of interest.

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Contributors

AB, GG, AA, CD, MM, contributed to the design of the study. GG, PZ, GA, LT, EF, MM and LR all recruited patients into this trial. Data analysis was conducted by CC and AB. All authors contributed to manuscript writing and preparation of the final report and agreed with the final version.

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