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A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer

G. Giaccone [a,*,1], L.A. Bazhenova [b,1], J. Nemunaitis [c], M. Tan [d], E. Juhász [e], R. Ramlau [f], M.M. van den Heuvel [g], R. Lal [h], G.H Kloecker [i], K.D. Eaton [j], Q. Chu [k], D.J. Dunlop [l], M. Jain [m], E.B. Garon [n], C.S. Davis [o], E. Carrier [p], S.C. Moses [p], D.L. Shawler [p], H. Fakhrai [p,2]

[a] *National Cancer Institute, Bethesda, MD, USA*
[b] *Moores Cancer Center, UC San Diego, La Jolla, CA, USA*
[c] *Mary Crowley Cancer Research Centers, Dallas, TX, USA*
[d] *Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA*
[e] *Korányi National Institute for TB and Pulmonology, Budapest, Hungary*
[f] *Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznań University of Medical Sciences, Poznan, Poland*
[g] *Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital, Thoracic Oncology, Amsterdam, Netherlands*
[h] *Guy's Hospital, King's Health Partners, London, England, United Kingdom*
[i] *James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA*
[j] *Seattle Cancer Care Alliance, University of Washington, Seattle, WA, USA*
[k] *Cross Cancer Institute, Edmonton, Alberta, Canada*
[l] *Royal Infirmary, Glasgow, Scotland, United Kingdom*
[m] *Noble Hospital, Pune, India*
[n] *University of California, Los Angeles, Los Angeles, CA, USA*
[o] *CSD Biostatistics, Tucson, AZ, USA*
[p] *NovaRx Corporation, San Diego, CA, USA*

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Abstract ***Background:*** Treatment options after first-line chemotherapy are limited in non-small cell lung cancer (NSCLC). Belagenpumatucel-L is a therapeutic vaccine comprised of 4 transforming growth factor (TGF)-β2-antisense gene-modified, irradiated, allogeneic NSCLC cell lines that may be useful for maintenance after initial treatment.

* *Corresponding author at:* Lombardi Comprehensive Cancer Center, Georgetown University, 3970 Reservoir Road, Washington, DC 20007, USA.
E-mail address: gg496@georgetown.edu (G. Giaccone).
[1] Drs. Giaccone and Bazhenova are co-first authors for this publication.
[2] Dr. Habib Fakhrai is the sponsor of the trial and inventor of NovaRx technology.

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Cancer immunotherapy
Cancer gene therapy
TGF-β

Methods: Stage III/IV NSCLC patients who did not progress after platinum-based chemotherapy were randomised 1:1 to receive maintenance belagenpumatucel-L or placebo. Patients were eligible for randomisation between one and four months from the end of induction chemotherapy. The primary endpoint was overall survival.

Results: This phase III trial enrolled 270 patients in the belagenpumatucel-L arm and 262 in the control arm. Belagenpumatucel-L was well tolerated with no serious safety concerns. There was no difference in survival between the arms (median survival 20.3 versus 17.8 months with belagenpumatucel-L versus placebo, respectively; hazard ratio (HR) 0.94, $p = 0.594$). There were also no differences in progression-free survival (4.3 months versus 4.0 for belagenpumatucel-L vs placebo, respectively; HR 0.99, $p = 0.947$). A prespecified Cox regression analysis demonstrated that the time elapsed between randomisation and the end of induction chemotherapy had a significant impact on survival ($p = 0.002$) and that prior radiation was a positive prognostic factor (median survival 28.4 months with belagenpumatucel-L versus 16.0 months with placebo; HR 0.61, $p = 0.032$).

Conclusions: Although the overall trial did not meet its survival endpoint, improved survival for belagenpumatucel-L is suggested in patients who were randomised within 12 weeks of completion of chemotherapy and in those who had received prior radiation. Further studies of belagenpumatucel-L in NSCLC are warranted.

1. Introduction

Lung cancer is the most prevalent cancer in the western world, with approximately 224,000 new cases and 159,000 deaths expected in the United States in 2014 [1], and 187,000 deaths in the European Union [2].

Most patients with advanced non-small cell lung cancer (NSCLC) are initially treated with four to six cycles of platinum-based doublet chemotherapy [3–5] but five-year survival of stage IIIB/IV patients is less than 10% [6]. Patients without progression following frontline chemotherapy may be placed on maintenance therapy. Patients with non-squamous cell carcinoma who receive maintenance pemetrexed show a moderate survival benefit [7]. Maintenance with erlotinib, a molecule targeting the epidermal growth factor receptor (EGFR), is approved for all NSCLC histologies [8], although it is most frequently used in EGFR mutant adenocarcinoma patients [3].

Immunotherapy trials performed in NSCLC have included whole tumour cell vaccines [9–12], single tumour-associated peptides such as MUC1, telomerase, epidermal growth factor, WT1 [13–16], multiple tumour-associated peptides [17] and dendritic cells pulsed with tumour cells [18].

Belagenpumatucel-L is an allogeneic whole tumour cell vaccine comprised of four NSCLC cell lines that were transfected with a human transforming growth factor (TGF)-β2-antisense vector designated pCHEK/HBA2 [9,10,19]. Two previous Phase II trials have demonstrated the safety and efficacy of belagenpumatucel-L in patients with NSCLC [9,10]. We report on the results of a randomised, placebo-controlled Phase III study to investigate the efficacy of belagenpumatucel-L as a maintenance therapy in patients not progressing following frontline platinum-based chemotherapy.

2. Patients and methods

2.1. Study design

Patients with advanced NSCLC were randomised to receive maintenance belagenpumatucel-L (2.5×10^7 cells per dose) or placebo in a 1:1 ratio in this international, double blind, intention to treat (ITT) study (NCT00676507).

Inclusion criteria included histologically confirmed diagnosis of stage IIIA (T3N2), IIIB or IV NSCLC [20]. Patients had stable disease or response following up to 6 cycles of a platinum-based frontline chemotherapy regimen, with or without radiation therapy. Patients had to be 18–75 years of age with an ECOG performance status of 0, 1 or 2 and an estimated life expectancy of at least 12 weeks. Other eligibility criteria were haemoglobin $\geqslant$ 9 g/dL, albumin levels $\geqslant$ 2.5 g/dL, bilirubin $\leqslant$ 1.5 times the upper limit of normal (ULN), aspartate transaminase and alanine transaminase $\leqslant 1.5 \times$ ULN, creatinine $\leqslant 1.5 \times$ ULN, alkaline phosphatase $\leqslant 5 \times$ ULN. Patients were eligible to be randomised between one and four months (4–17.4 weeks) following the completion of frontline chemotherapy. Patients must not have received other antitumour therapies within four weeks of randomisation.

Exclusion criteria included concurrent systemic steroids, bone metastases that required immediate therapy, uncontrolled pleural effusions, serious non-malignant disease and previous malignancies unless in remission for $\geqslant$2 years.

The protocol was approved by the Ethics Committee and the Institutional Biosafety Committee of each participating centre. Written informed consent was obtained from each patient. The study was undertaken in accordance with the ethics principles of the Declaration of Helsinki and the Belmont Report, in compliance with the obligations and requirements of clinical investigators, and with ICH Good Clinical Practices guidelines and all applicable laws and regulations. This trial was registered at www.ClinicalTrials.gov with the trial registration ID of NCT00676507.

2.2. Randomisation and stratification

An interactive voice-activated response system (IVRS) controlled patient randomisation and stratification. Patients, investigators, study team members and the sponsor were all blinded to the treatment assignment.

The Pocock and Simon minimisation method [21] was used to randomise patients into treatment and control arms while accounting for the different strata. The patients were stratified by stage (IIIA versus IIIB/IV), brain metastases, radiation during frontline chemotherapy and bevacizumab during frontline chemotherapy.

2.3. Procedures

Patients were eligible to receive up to 20 cycles of treatment; 18 cycles of monthly intradermal injections followed by two quarterly cycles of intradermal injections. Patients were removed from treatment upon disease progression or physician/patient decision to receive other treatments. Off-treatment patients were followed for survival.

Belagenpumatucel-L is comprised of four NSCLC cell lines, SK-LU1/HBA2 (adenocarcinoma), H520/HBA2 (squamous cell carcinoma), RH2/HBA2 (squamous cell carcinoma) and H460/HBA/2 (large cell carcinoma). Each cell line was transfected by electroporation with TGF-β2 antisense as previously described [9,10]. The cells were grown in adherent cultures under cGMP conditions. The cultures were harvested, irradiated with 10,000 cGy and cryopreserved in Plasma-Lyte A (Baxter Healthcare, Marion, NC) containing 10% human serum albumin (Baxter Healthcare, Westlake Village, CA) and 10% dimethyl sulfoxide (DMSO; Bioniche Teo, Galway, Ireland). At the pharmacy the cells were thawed, mixed and 2.5×10^7 total cells were injected intradermally into the upper arm. Placebo consisted of 0.15% Intralipid® in solution composed of the cryopreservation formulation minus the DMSO.

The determination of tumour response to frontline chemotherapy was made by an independent radiology organisation (World Care Clinical, Boston, MA) by comparing pre-randomisation CT scans to end-of-chemotherapy scans. MRIs of the brain were also compared. If present, brain metastases must have been treated and remained stable for at least 2 months prior to study enrolment.

During the trial, patients were evaluated using standard blood panels and chemistries, physical examination and limited neurologic examinations. CT scans were performed every three months. For patients enrolled with stable brain metastases, MRI scans of the brain were performed every 3 months.

2.4. Statistical analyses

The primary efficacy endpoint of this clinical trial was overall survival (OS) of patients randomised to belagenpumatucel-L compared to patients randomised to placebo. OS was calculated from the date of randomisation to the date of death from any cause. Patients who were alive or lost-to-follow-up were censored at the last known date of contact. Survival distributions were estimated using Kaplan–Meier and the primary analysis was conducted using a two-sided log rank test. The trial was powered to detect a 3.5-month survival advantage for belagenpumatucel-L assuming a 10.5-month median OS for placebo [22]. Two interim analyses were performed. The first interim analysis was performed after 140 events and the second was performed after 210 events. The overall type-1 error rate was established at 0.0016 for the first interim analysis, 0.01 for the second interim analysis and 0.046 for the final analysis. The analyses were performed by an independent data safety monitoring committee.

Secondary efficacy endpoints included progression-free survival (PFS) and tumour response by RECIST. The Statistical Analysis Plan also prespecified additional analyses using the Cox proportional hazards regression model to assess the influence of time elapsed from the end of frontline chemotherapy to randomisation, histology, stage, prior radiation therapy, brain metastases, prior bevacizumab therapy, performance status, gender, age, clinical site, prior surgery, prior hormone therapy, prior immunotherapy and prior steroid therapy on OS. Based on two other maintenance studies [7,23] that limited enrolment to 6 and 12 weeks following the completion of frontline chemotherapy, time elapsed was categorised as less than or equal to 12 weeks (84 days) or greater than 12 weeks.

3. Results

3.1. Demographics

This international, randomised, double-blind, placebo controlled study enrolled 532 patients in 73 centres

in 8 countries between August 2008 and June 2012. The dataset was locked after the second interim analysis.

The belagenpumatucel-L and placebo arms were well balanced for baseline characteristics (Table 1). 220 patients (41.4%) were randomised in North America, 284 patients (53.4%) were randomised in Europe and 28 patients (5.3%) were randomised in India.

3.2. Overall survival (OS)

The study was terminated at the second interim analysis for futility. The median ITT OS was 20.3 months (95% CI, 16.8–23.7) for belagenpumatucel-L compared to 17.8 months (95% CI, 13.7–22.0) for placebo (hazard ratio (HR) 0.94, 95% CI, 0.73–1.20; $p = 0.594$) (Fig. 1A).

The OS and hazard ratios of the baseline characteristics, including the stratification criteria, are shown in Table 2. A prespecified Cox regression analysis showed a trend towards improved survival for patients who received belagenpumatucel-L within 12 weeks of the completion of frontline chemotherapy. No correlations with survival were seen with stage, presence of brain metastases, prior treatment with bevacizumab, age, gender, histology or racial/ethnic background.

Table 1
Demographics.

	All		⩽12 weeks		>12 weeks	
Demographic	Vaccine	Control	Vaccine	Control	Vaccine	Control
Enrolled	270	262	169	149	100	109
Age						
Mean	61.5 ± 8.5	60.5 ± 8.5	61.2 ± 8.6	60.6 ± 9.2	60.2 ± 8.2	60.6 ± 7.6
Range	32–75	28–75	32–75	28–75	40–75	43–75
Sex						
Male	156 (58%)	151(58%)	102 (60%)	87 (58%)	54 (54%)	62 (57%)
Female	114 (42%)	111 (42%)	67 (40%)	62 (42%)	46 (46%)	47 (43%)
Race						
White	238 (88%)	235 (90%)	148 (88%)	134 (90%)	90 (90%)	97(89%)
Black	6 (2%)	4 (2%)	2 (1%)	0 (0%)	4 (4%)	4 (4%)
Asian	21 (8%)	20 (8%)	15 (9%)	14 (9%)	5 (5%)	6 (6%)
Not specified	5 (2%)	3 (1%)	4 (2%)	1 (1%)	1 (1%)	2 (2%)
Ethnicity						
Hispanic	5 (2%)	2 (1%)	3 (2%)	1 (1%)	2 (2%)	1 (1%)
Non-hispanic	265 (98%)	260 (99%)	166 (98%)	148 (99%)	98 (98%)	108 (99%)
Stage						
Stage IIIA	22 (8%)	20 (8%)	7 (4%)	6 (4%)	15 (15%)	12 (11%)
Stage IIIB/IV	248 (92%)	242 (92%)	162 (96%)	143 (96%)	85 (85%)	97 (89%)
Histology						
Adenocarcinoma	162 (60%)	141 (54%)	104 (62%)	72 (48%)	57 (57%)	66 (61%)
Squamous	65 (24%)	81 (31%)	36 (21%)	51 (34%)	29 (29%)	29 (27%)
Large Cell	16 (6%)	13 (5%)	12 (7%)	8 (5%)	5 (5%)	6 (6%)
Adenosquamous carcinoma	4 (2%)	4 (2%)	1 (1%)	3 (2%)	3 (3%)	1 (1%)
Undifferentiated	11 4(%)	6 (2%)	7 (4%)	3 (2%)	5 (5%)	3 (3%)
Other or not specified	12 (4%)	17 (3%)	9 (5%)	11 (7%)	1 (1%)	4 (4%)
Performance status						
ECOG 0	119 (44%)	130 (50%)	80 (47%)	84 (56%)	39 (39%)	46 (42%)
ECOG 1	139 (51%)	119 (45%)	82 (49%)	61 (41%)	56 (56%)	54 (50%)
ECOG 2	7 (3%)	6 (2%)	5 (3%)	2 (1%)	2 (2%)	4 (4%)
Brain metastases						
Positive	19 (7%)	18 (7%)	15 (9%)	12 (8%)	4 (4%)	5 (5%)
Negative	251 (93%)	244 (93%)	154 (91%)	137 (92%)	96 (96%)	104 (95%)
Pre-randomisation therapies						
Prior chemoRT	73 (29%)	63 (27%)	41 (27%)	29 (21%)	32 (34%)	34 (35%)
No prior chemoRT	177 (71%)	174 (73%)	114 (73%)	110 (79%)	63 (66%)	63 (65%)
Prior bevacizumab	30 (11%)	25 (10%)	19 (11%)	16 (11%)	11 (11%)	8 (7%)
No prior bevacizumab	240 (89%)	237 (90%)	150 (89%)	133 (89%)	89 (89%)	101 (93%)
Enrolment by region						
North America	113 (42%)	107 (41%)	76 (45%)	59 (40%)	37 (37%)	44 (40%)
Rest of the World	157 (58%)	155 (59%)	93 (55%)	90 (60%)	63 (63%)	65 (60%)

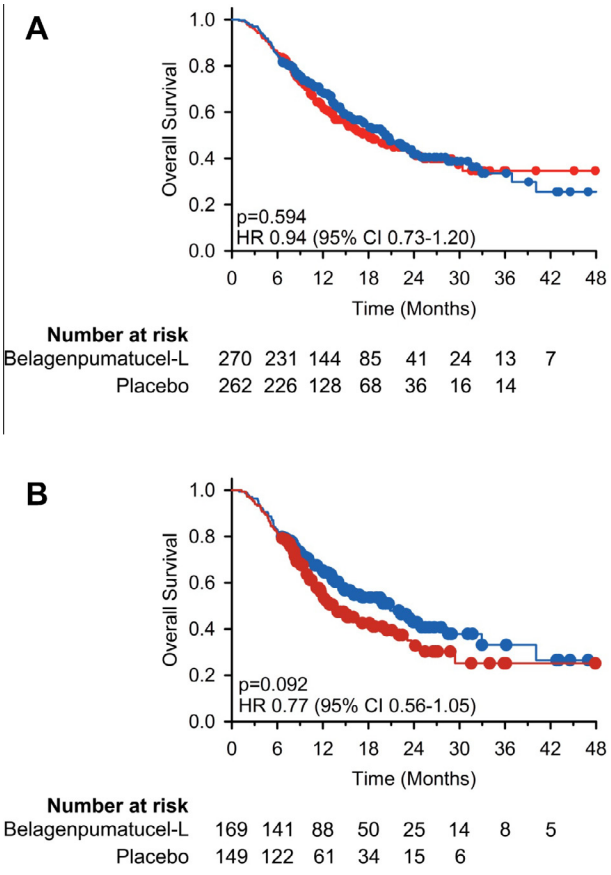

Fig. 1. Kaplan–Meier analyses of overall survival. A. Overall intention to treat (ITT) survival in all patients ($N = 532$). B. Overall survival of patients randomised within 12 weeks of the completion of frontline chemotherapy ($N = 318$). Survival in the Lucanix arm is shown in blue. Survival in the placebo arm is shown in red.

In the 318 patients who were randomised within 12 weeks of the completion of frontline chemotherapy (169 in the belagenpumatucel-L arm and 149 in the placebo arm) median OS for vaccine patients was 20.7 months (95% CI 14.6–26.9) and median OS for placebo patients was 13.4 months (95% CI 9.9–16.7) (HR 0.77, 95% CI 0.56–1.05; $p = 0.092$) (see Fig. 1B).

A prespecified analysis showed that patients who received chemoradiation therapy (chemoRT) prior to randomisation demonstrated better survival in the belagenpumatucel-L arm. There were 161 patients who received chemoRT prior to randomisation; 78 in the belagenpumatucel-L arm and 83 in the placebo arm. The main characteristics of these groups were well balanced. As shown in Fig. 2A, median OS for vaccine patients was 28.4 months (95% CI 14.1–42.7) versus 16.0 months (95% CI 8.9–23.1) for placebo (HR 0.61, 95% CI 0.38–0.96; $p = 0.032$). An exploratory analysis of survival in patients who received chemoRT prior to randomisation and were randomised within 12 weeks included 84 patients, 46 in the belagenpumatucel-L arm and 38 in the placebo arm. Median OS for vaccine patients was 28.4 months (95% CI 12.3–44.4) versus 10.3 months (95% CI 7.7–12.8) for placebo (HR 0.47, 95% CI 0.26–0.87; $p = 0.013$) (Fig. 2B). Patients who received RT less than or equal to 6 months prior to randomisation had better survival than patients who received RT more than 6 months prior, whereas in the placebo arm there was no difference between the two groups (Table 3).

3.3. Secondary end-points

There was no significant difference in PFS between the treatment arms. Median PFS was 4.3 months (95% CI, 3.4–5.2) for belagenpumatucel-L compared to 4.0 months (95% CI, 3.0–5.0) for placebo (HR 0.99, 0.82–1.20; $p = 0.947$).

In the belagenpumatucel-L arm there were 6 documented partial responses and one documented complete response for a response rate of 2.5%. In the placebo arm there was one documented partial response for a response rate of 0.4% ($p = 0.123$; Fisher's exact test).

3.4. Safety and toxicity

There were 81 Serious Adverse Events (SAEs) reported; 49 in the belagenpumatucel-L arm and 32 in the placebo arm. Seventy-six (93.8%) of these events were not drug-related as reported by the investigator. Five events were reported by the blinded investigator to be possibly or probably drug-related. One instance of cellulitis was reported in the control arm. Three instances of leptomeningeal carcinomatosis were reported, two in the belagenpumatucel-L arm and one in the control arm. Because these events occurred in both arms it is unclear that there was a relationship between the events and administration of belagenpumatucel-L.

There was one allergic reaction related to the administration of belagenpumatucel-L, characterised by a grade 2 rash on the upper body and arms, which appeared after injection 5 and was exacerbated by injection 6 a month later. The patient was removed from treatment and the event resolved a month later.

The grade 1 and 2 Adverse Events (AEs) that were reported more than 20 times are shown in Table 4.

3.5. Post-study treatments

Table 5 shows a summary of the documented systemic anticancer therapies received after patients discontinued treatment on the study. 145 patients (54%) in the belagenpumatucel-L cohort and 138 (53%) in the control cohort received systemic anticancer therapy after

Table 2
Survival by baseline characteristics.

	Belagenpumatucel-L		Placebo		Hazard ratio	95% CI
	N	Median (months)	*N*	Median (months)		
Age group (years)						
<65	156	19.9	167	19.0	1.00	0.73–1.37
⩾65	114	20.5	95	13.3	0.83	0.56–1.22
Sex						
Male	156	17.3	151	16.4	0.94	0.68–1.28
Female	114	31.5	111	20.4	0.75	0.51–1.12
Time elapsed following frontline chemotherapy						
⩽12 weeks	169	20.7	149	13.3	0.77	0.56–1.05
>12 weeks	100	20.3	109	30.4	1.19	0.79–1.80
ECOG						
0	119	23.3	130	20.4	0.83	0.57–1.21
1	139	15.8	119	15.4	0.98	0.69–1.39
2	7	12.0	6	24.1	2.72	0.52–14.3
Histology						
Adenocarcinoma	162	22.5	141	20.4	0.92	0.66–1.29
Squamous cell carcinoma	65	17.7	81	15.2	0.92	0.58–1.46
Large cell carcinoma	16	16.1	13	13.3	0.69	0.26–1.79
Other	16	13.8	12	NR[1]	2.18	0.66–7.14
Stage						
IIIA	22	15.5	20	30.4	1.44	0.61–3.37
IIIB	67	36.9	68	17.9	0.88	0.52–1.48
IV	178	20.2	172	16.2	0.91	0.68–1.23
Brain metastases						
Positive	19	13.5	18	7.2	0.66	0.28–1.53
Negative	251	20.7	244	17.9	0.95	0.74–1.23
Pre-randomisation therapies						
Prior ChemoRT	73	23.5	63	15.1	0.83	0.51–1.33
No Prior ChemoRT	177	20.3	174	17.2	0.94	0.69–1.28
Prior bevacizumab	30	40.1	25	20.4	0.65	0.29–1.46
No prior bevacizumab	240	18.4	237	17.2	0.98	0.76–1.27

withdrawal from the study. The most frequent agents used were pemetrexed, erlotinib and docetaxel.

4. Discussion

This large double-blind randomised study failed to demonstrate a significant increase in survival of belagenpumatucel-L as a maintenance therapy in the overall patient population with stage III/IV NSCLC who had stable disease after frontline therapy.

A prespecified Cox regression analysis suggests the importance of the time elapsed between completion of chemotherapy and randomisation ($p = 0.002$). Patients randomised within 12 weeks of the completion of frontline chemotherapy had 20.7-month median survival in the belagenpumatucel-L arm compared to 13.3-month median survival for the placebo arm ($p = 0.092$). Of the 532 patients enrolled in the trial, 214 (40%) were randomised more than 12 weeks following the completion of frontline chemotherapy, raising the possibility that one reason why this trial did not meet the primary endpoint was due to late enrolment after induction therapy. These data do not control the inflated type I errors due to multiple testing and are therefore considered to be exploratory analyses.

Chemotherapy induces phenotypic changes in tumour cells, including upregulation of Fas, calreticulin and MHC class I, that make cells more sensitive to lysis by cytotoxic T-lymphocytes [24–28]. Enrolment of patients more than 12 weeks following induction may allow time for these effects to dissipate and for the tumour phenotype to revert to its less sensitive pre-chemotherapy condition [24–27].

Leucopaenia induced by platinum-based chemotherapy regimens is one of the limiting toxicities for the treatment of NSCLC [29,30]. However, not all immune effector subsets are equally affected by chemotherapy and different subsets show different kinetics during and following chemotherapy [24,31–34]. Studies have shown a sustained depletion of the $Foxp3^{+}$ $CD127^{lo}$ regulatory T cell subset (Tregs) following platinum-based chemotherapy [24,28,33]. Chemotherapy induces decreases in the ratio of Tregs to both $CD4^{+}$ T cells [24,31,34] and $CD8^{+}$ T cells [31,33,34]. An increase in

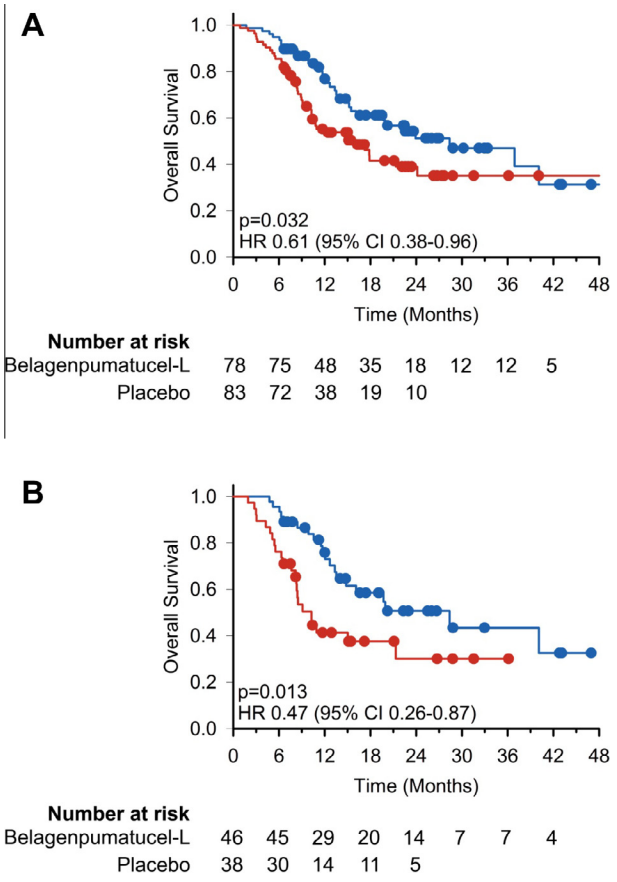

Fig. 2. A. Overall survival in patients who received chemoradiation therapy (chemoRT) during frontline chemotherapy ($N = 161$). B. Overall survival in patients randomised within 12 weeks of the completion of frontline chemotherapy who received chemoRT during frontline chemotherapy ($N = 84$). Survival in the Lucanix arm is shown in blue. Survival in the placebo arm is shown in red.

the Th1 subset of T cells has also been shown to coincide with the decrease in Tregs following platinum-based chemotherapy [31]. All of these result in a beneficial antitumour immune environment that is associated with better survival [33]. Randomising patients more than 12 weeks following the completion of chemotherapy gives the Tregs time to regenerate and allows the immune system to revert to the immunosuppressive pre-chemotherapy state. Thus, our further evaluation of the study population within 12 weeks following the completion of chemotherapy to define optimal activity

Table 4
Grade 1 and 2 Adverse Events.

AE	Vaccine	Placebo	Total	*p*-Value
Arthralgia	29	31	60	NS
Back pain	28	22	50	NS
Cough	71	65	136	NS
Decreased appetite	32	16	48	0.023
Erythema	35	7	42	<0.001
Extremity pain	21	15	36	NS
Fatigue	66	54	120	NS
Headache	48	28	76	0.025
Induration	22	4	26	<0.001
Injection site reaction	260	62	322	<0.001
Musculoskeletal pain	34	21	55	NS
Nasopharyngitis	26	11	37	0.017
Nausea	40	36	76	NS
Non-cardiac chest pain	23	9	32	0.017
Pyrexia	25	17	42	NS
Rash	23	10	33	0.030
Respiratory tract infection	33	28	61	NS

of belagenpumatucel-L is in line with other maintenance therapies [7,23].

A prespecified analysis showed a survival advantage for patients who received chemoRT prior to receiving belagenpumatucel-L (HR 0.61, $p = 0.032$). Tumour radiation exerts a number of effects that are beneficial for antitumour immunity [35]. Radiation upregulates MHC class I, increases the pool of peptides presented by the class I molecules [36] and alters the phenotype of Tregs, which significantly impairs their immunosuppressive function [37]. Although tumour radiation induces a significant reduction in both T and B cells, the reduction in Tregs is greater and more long lasting than in conventional T cells [38]. Based on these observations, the association between prior radiation and survival on belagenpumatucel-L, which are consistent with data reported by the tecemotide (MUC1) vaccine [23], generates an important hypothesis for the further study of tumour vaccines and should be considered in the design of future immunotherapy vaccine protocols.

While the overall trial did not meet its prespecified endpoint, additional analyses summarised in this paper indicate encouraging results in predefined subsets of patients. Most importantly, a clinically meaningful increase in overall survival was observed in the belagenpumatucel-L arm for patients who were randomised within 12 weeks of the completion of frontline chemotherapy. Furthermore, prolongation of survival

Table 3
Effect of time from prior radiation to randomisation.

Cohort	Radiation therapy	N	Median OS	*p*-Value	Hazard ratio
Vaccine	≤6 months before randomisation	34	40.1	0.040	0.41
	>6 months before randomisation	13	14.8		
Placebo	≤6 months before randomisation	32	9.1	0.972	0.98
	>6 months before randomisation	5	21.3		

Table 5
Post-study treatments.

Therapy	Belagenpumatucel-L	Control
Any systemic anticancer therapy	145 (54%)	138 (53%)
Any combination therapy	43 (16%)	51 (19%)
Carboplatin	24 (9%)	20 (8%)
Cisplatin	10 (4%)	12 (5%)
Pemetrexed	35 (13%)	37 (14%)
Erlotinib	32 (12%)	29 (11%)
Docetaxel	31 (11%)	25 (10%)
Paclitaxel	8 (3%)	7 (3%)
Gemcitabine	17 (6%)	16 (6%)
Gefitinib	6 (2%)	2 (1%)
Vinorelbine	5 (2%)	7 (3%)
Bevacizumab	6 (2%)	9 (3%)

was most notable in patients who received chemoRT prior to randomisation into this trial. Although the number of cases is small, a *post hoc* analysis showed that the effect or radiation was observed in the belagenpumatucel-L arm only, when radiation was given 6 months or less before randomisation. The toxicity profile of belagenpumatucel-L compares very favorably with that of the currently available maintenance therapies [7,8]. Based on the suggested survival benefits described above, a confirmatory study of belagenpumatucel-L in these patient populations is warranted. Exploratory studies of combination of belagenpumatucel-L and PD-1 or PDL-1 are also warranted.

Contributors

Concept and design: Giuseppe Giaccone, Ewa Carrier, Steven C. Moses, Daniel L. Shawler, and Habib Fakhrai.

Assembly of data: Steven C. Moses, Daniel L. Shawler, and Habib Fakhrai.

Enrolment of patients: Giuseppe Giaccone. Lyudmila Bazhenova, John Nemunaitis, Erzsébet Juhász, Rodrig Ramlau, Michel M. van den Heuvel, Rohit Lal, Goetz H Kloecker, Keith D. Eaton, Quincy Chu, David J. Dunlop, Minish Jain, and Edward B. Garon.

Data Analysis and interpretation: Giuseppe Giaccone, Lyudmila Bazhenova, John Nemunaitis, Ming Tan, Charles S. Davis, Steven C. Moses, Daniel L. Shawler, and Habib Fakhrai.

Manuscript writing: Giuseppe Giaccone, Lyudmila, Bazhenova, John Nemunaitis, Rohit Lal, Quincy Chu, Edward B. Garon, Charles S. Davis, Ewa Carrier, Steven C. Moses, Daniel L. Shawler, and Habib Fakhrai.

Final approval of manuscript: All authors.

Conflict of interest statement

S. Moses, D. Shawer, E. Carrier and H. Fakhrai are employees of NovaRx.

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