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Research Article

Effect of NESEM™/S2013 in Indian Population undergoing Conventional Treatment for the Malignancies of the Head & Neck, GIT, Ovary, Breast and Lung as an Adjunct

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Abstract

Background: NESEM ™/S2013, 500mg capsules were prepared by NPP Ltd containing the extracted Secondary Plant Metabolites (eSPMs): S40, S54, S55. These eSPMs were identified to be biologically active using human cells expressing cancer specific monooxygenase enzymes. Extensive bioavailability assessments were carried out. An optimized blend was encapsulated in 500mg, size zero, two-piece, hard shell, vegetarian capsules (Vcaps). (Notes: NESEM™'s are produced through the shikimate pathway by natural elicitation mechanisms; NESEM™ is an acronym for Naturally Elicited Specifically Extracted Molecules).

It has been demonstrated in the past studies that NESEMTM/S2013s are phyto nutrients classified as phytoalexins that function through multiple mechanisms. One of the mechanisms is the intrinsic metabolism performed by CYP1B1, a universal cancer marker resulting in disturbances of cell cycling processes triggering apoptosis. There is limited availability of these phytonutrients in our diet due to modern day agricultural practices and food processing. Phytoalexins are produced as a way of defense mechanism, in response to infection or attack by predators. The purpose of this investigation is determining the effect of NESEM™/S2013 on Quality of Life (QoL) and survival in tandem to routine cancer therapy in malignancies of the Head & Neck, GIT, Ovary, Breast and Lung.

Patients and methods: This study was a two-arm randomized controlled trial with a cohort of 102 patients. The patients presented with malignancies of Head & Neck, Lung, Breast, GIT, and Ovary. The study subjects in the two groups were randomized to either receive chemotherapy, radiotherapy and surgery or a combination of two or more therapies. Both the groups were given Vitamin C and B complex. The test group

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along with the above received NESEM™/S2013 (three capsules of 500 mg each of NESEM™/S2013 500mg was given as leader/loading dose for a month followed by two capsules of 500 mg each of NESEM™/S2013 till discontinuation or death). Minus the NESEM™/S2013, the control group was treated same as the test group.

Results: In the Head & Neck Cancer patients, the mean overall survival (OS) was significant, p=0.0441. In the test arm, average OS was 15.91 ± 10.73 months compared to 8.0 ± 5.83 months in the control group. This represents a 99% increase in survivability for the NESEM™/S2013 arm. In subjects with lung cancer, the average OS in the test group was 8.708 ± 9.006 months compared to 2.292 ± 1.484 months in the control group. The average OS was significant, p=0.0234. This represents a 280% increase in survivability for the NESEM™/S2013 arm. In patients with cancer of GIT, the mean OS in the NESEM™/S2013 arm was 10.000 ± 10.317 months compared to was 3.550 ± 3.700 months in the control arm which was significant (p=0.0792). This represents a 182% increase in survivability for the NESEM™/S2013 arm. In patients with ovarian cancer, the average survival was 17.63 ± 7.19 months in the NESEM™/S2013 arm compared to 6.63 ± 7.56 in the control arm, that is statistically significant (p=0.0099), representing an increase of 166% in survivability for the NESEM™/S2013 arm. In patients with breast cancer, the mean survival in the test arm compared to control arm was statistically not significant, p=0.9073. The breast cancer patients exhibited the average survival in the test arm as 21.80 ± 6.96 months compared to 22.10 ± 4.01 months in the control group.

At completion of 24 months (3 months post-study), 9 subjects from the NESEM™/S2013 arm (90%) and 7 subjects from the control arm (70%) were alive representing a 29% increase in survivability for the NESEM™/S2013 arm. The overall survival (OS) was significant in the NESEM™/S2013 arm (14.480 ± 10.036 months) compared to the control arm (8.333 ± 8.507 months), p=0.0012, representing an increase in survival rate of 75%. The mean Eastern Cooperative Oncology Group (ECOG) Performance score was 1.12 ± 0.773 in the NESEM™/S2013 arm (n=51) compared to 1.58 ± 0.8593 in the control arm (n=51) which was statistically significant (p=.00591). The Hamilton Anxiety (HAM-A) scores in both arms was non-significant (p=0.97), 2.4314 ± 2.9138 in the NESEM™/S2013 arm (n=51) versus 3.0612 ± 3.4666 in the control arm (n=51). The mean The Patient-Generated Subjective Global Assessment (PG-SGA) scores was non-significant too (p=0.312209) were 6.4688 ± 2.8959 in the NESEM™/S2013 arm (n=51) versus 7.625 ± 5.7291 in the control arm (n=51).

Conclusion: The literature on the efficacy of NESEM™/S2013s as adjunct to cancer treatment is sparse. Only one case and a series case report have been reported thus far. No Randomized controlled clinical trials with NESEM™/S2013s as adjunct with conventional cancer treatment have been ever initiated. It, hence became almost critical to study the role of NESEM™/S2013 in a randomized controlled manner. The study was designed to compare the QoL and survival of 102 patients with cancers of the Head & Neck, Lung, Breast, GI, and Ovaries when NESEM™/S2013 were added to their prescribed treatment. The study showed to improve the OS in malignancies of the Head & Neck, Lung, GI, and Ovaries when NESEM™/S2013s were added to same TNM based treatment. NESEM™/S2013s impacted the ECOG scores positively but had no significant effect on HAM–A or PG-SGA. It can be concluded that NESEM™/S2013s may have played a role in improvement of OS and ECOG status. Both CYP1B1 pathway and NESEM™/S2013 were found to be encouraging findings for the improved treatment of cancer. It is also reassuring that these solutions pose no additional toxicities or side effects. Randomized trials in larger set-ups would further give insights and confirmation in the role of NESEM™/S2013s.

Keywords: NESEM™/S2013; CYP1B1; Polyphenol; Phytoalexin; Cytochrome P450; Diet and stress; Piceatannol; Chemotherapy; Surgery; Radiation.

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Introduction

NESEM™/S2013s are natural compounds that are cancer-specific when activated in cancer cells by the enzyme CYP1B1. This enzyme is a subfamily of monooxygenase enzymes called cytochrome P450's, designated as CYP1B1, first identified by Dan Burke in 1995 [1]. At the time of discovery Burke proposed to use CYP1B1 as a drug target. Work later showed this had promise as a rescue mechanism that depended on the metabolic activity of CYP1B1 [2-4]. Importantly, it was found that CYP1B1 was expressed in all malignancies regardless of oncogenic origin. This enzyme was not found in any healthy cells [5-7]. It is now widely regarded as a universal cancer marker [8]. When NESEM™/S2013s are metabolized by CYP1B1, they create metabolites that aid in apoptosis of the cancerous cell. In this way, NESEM™/S2013s operate as natural prodrugs that specifically target killing the malignant cells without any toxicity to normal cells. This CYP1B1 mechanism could operate prophylactically killing microscopic cancer cells after mutation or gross tumours in a therapeutic setting.

Each NESEM™/S2013 capsule (approximately 500 mg) is a proprietary extract blend of Citrus, Pumpkin (Cucurbita maxima), and Grape Seed (Vitis vinifera) and many other compounds in various proportions depending on availability. Unlike many drugs, NESEM™/S2013s represent multiple, unique molecular constituents and the formulation is developed to reflect their unique potencies [9]. NESEM™/S2013s are synthesized by plants as a part of a defense mechanism and are harmless to humans.

NESEM™/S2013s has two proposed modes of action that have been demonstrated in cell lines. The first of which is to function as natural prodrugs, confined to cancer cells, inducing apoptosis in those cells while causing no harm to normal cells [10-12]. The CYP1B1 enzyme, in turn, belongs to the cytochrome P450 family. P450s are known drug metabolizing enzymes. In addition, CYP1B1 is known to metabolise/detoxify chemotherapy agents. Therefore, it is postulated that NESEM™/S2013s second mode of action is to prevent the deactivation of chemotherapy agents by competing for the binding site of CYP1B1. This effect enhances the effectiveness of chemotherapy agents locally within the cancer cell. Both modes of action make NESEM™/S2013 an ideal adjunct to many if not all cancer treatments [2]. According to the analysis by the Institute for Health Metrics and Evaluation, Washington (Indian express Sunday 28th February 2021) India is ranked tenth at 106.6 new cancer cases in 2016 per 1,00,000. The study aimed to determine the positive effect of NESEM™/S2013; a nutritional adjunct to the already existing conventional treatment of cancer patients to see if NESEM™/S2013 could provide added benefits. Metabolites produced through the metabolism of NESEM™/S2013s by CYP1B1 are reported to be restricted to cancer cells and are disabled through cell destruction. This natural defence mechanism of NESEM™/S2013 could have beneficial effects on patients by being non-toxic. These substances can give new hope to cancer patients by initiating a cascade of events, which can have exceedingly beneficial effects on the human body.

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Patients and methods

The study was done in a regional cancer centre (MNJIO & RCC, Hyderabad-Telangana-India) where the patients presenting with locally advanced or metastatic malignancies were chosen as they formed the bulk of outpatients in our regional cancer centre (Head and Neck, GIT, Lung, Ovary and Breast). A cohort of 102 patients with biopsy-confirmed malignancies was selected for the study. Written consent and approval of the Institutional Ethics Committee was taken for all enrolled subjects. Most of the patients had either locally advanced or metastatic disease.

Inclusion criteria

1. Biopsy confirmed malignancies of the Head & Neck, Breast, Lungs, GIT, and Ovary.
2. Only recently diagnosed patients were included
3. Age group from 18-70 years
4. ECOG performance status of 0-2.
5. Patients must receive surgery, radiation, chemotherapy, or all as the standard management of cancer.
6. Having any stage of Cancer from I to IV.

Exclusion criteria

1. Patients who had received chemotherapy or radiotherapy prior.
2. Patients with prior malignancy
3. ECOG 3 and 4 were excluded.

Methods

The test medication contained NESEM™/S2013 weighing 280mg of extract (500mg filled weight). NESEM™/S2013 treatment commenced in the treatment arm with a lead dose of three 500mg capsules in three divided doses per day for the first month, followed by two 500mg capsules in two divided doses until study completion or death. The doses were administered on an empty stomach on waking and just before going to bed. Both cohorts were administered a single daily dose of 500mg of Vitamin C, biotin and cofactor Q10 which are required for better absorption of NESEM™/S2013s. The above three were supplemented with a standard formula of commercially available B-Complex containing the requisite RDA. The study commenced in November 2014 and ended in July 2016 (21 months). The control arm received a combination of surgery, radiotherapy and chemotherapy according to TNM status. The NESEM™/S2013 arm received the same above-mentioned treatment along with NESEM™/S2013. All patients had a complete staging workup including imaging, histological or cytological confirmation, tumour markers, biochemistry and haematological tests. The lesion sizes were recorded both clinically and radiologically, both initially and after 3 months of completion of treatment. The study endpoints were overall survival (OS), quality of life (QoL) and ECOG status. The ECOG status was recorded at the time of inclusion/randomization, end of treatment, every follow-up visits and end of the study. An overall ECOG score was created for every patient by averaging all the ECOG values hence making him or her comparable. The Quality of Life (QoL) was analyzed using the HAM-A scale and the PGSGA scale. These two parameters were also assessed at the time of inclusion/randomization, end of treatment

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and follow-up visits. Higher HAM-A and PGSDA scores indicated more stress and lesser scores indicating better QOL.

Randomization

The process of randomization was done in the outpatient department of MNJIO & RCC, Hyderabad. Suitable patients were selected from the outpatient population and randomized first to the NESEM™/S2013 arm. The controls were selected from the same outpatient population within one month. All were staged on TNM basis radiologically and clinically. The controls were matched for TNM stage age and ECOG status. Gender matching was not done. The process of randomization began in November 2014 and ended in February 2015. RECIST 1.1 analysis could not be attempted as all patients had advanced disease with short, expected survival. Both groups received similar treatment regimens. The duration and intensity of therapy varied according to tolerance and dropout rates.

Results

Head & neck group

Twenty-two patients with advanced and inoperable head and neck malignancies were randomized into 2 sets of 11 patients. All had squamous cell histopathology. These included: buccal mucosa (8/22-36.3%), tongue (8/22-36.3%), floor of mouth (1/22-4.5%), hypopharynx (4/22-18.1%) and hard palate (1/22-4.5%) matched anatomically and for TNM. Four patients underwent surgery followed by adjuvant radiotherapy without chemotherapy. Eighteen received radical chemoradiation for inoperable disease with concurrent chemotherapy @50mg/week. The prescribed dose of radiation was 66Gy@ 2Gy/day for all the patients. The mean dose of radiation received by the control group was 56Gy ± 13.89 and for the NESEM™/S2013 arm was 59.45Gy ± 17.09, which was not significant (P=0.6086). 2 patients in the control arm discontinued treatment due to toxicity. The mean dose of weekly cisplatin was 90.91 ± 86.08 mg in the NESEM™/S2013 arm versus 95.45 ± 108.29 mg in the control arm, which was not significant (P=0.9143).

The average age in the NESEM™/S2013 arm was 48.36 ± 16.39 years and in the control group 53.55 ± 8.81 years, which was not significant (P=0.3668).

The mean survival in the NESEM™/S2013 arm was 15.91 ± 10.73 months versus that in controls of 8.0 ± 5.83 months, which was significant (P=0.0441) (Figure 1a) (Table 1) (Represented by Kaplan Meier curve). This represents a 99% increase in survivability for the NESEM™/S2013 arm (see Appendix A). At the completion of the trial period 4 patients in the NESEM™/S2013 arm were still alive (36%). Follow on contact with these 4 patients was lost following months 24, 27, 28 and 30 respectively. All controls were dead by 19 months. The mean ECOG score for the NESEM™/S2013 arm was 1.318 ± 0.717 and in the control arm 1.182 ± 0.603 which was insignificant (P=0.6344). The mean HAM –A score for the NESEM™/S2013 arm was 1.91 ± 2.26 and in the control arm was 4.27 ± 3.13, which was not significant (p=0.0558). Similarly, the PG-SGA scale for the NESEM™/S2013 arm was 7.00 ± 2.90 and that in the control arm was 8.45 ± 3.62, which was also insignificant (p=0.3103).

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S. No.	Head and Neck		GI		Lung		Breast		Ovary	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
1	3	13	29	2	4	0.5	24	24	7	1
2	28	1	28	0.5	16	4	24	15	13	6
3	30	2	5	5	7	2	2	24	24	2
4	21	9	9	4	2	1	24	14	15	4
5	5	11	4	1	1	3	24	24	24	9
6	6	5	13	13	2	1	24	24	24	24
7	27	10	5	1	0.5	5	24	24	10	6
8	5	2	3	5	4	3	24	22	24	1
9	19	19	2	2	22	1	24	24		
10	7	13	2	2	2	1	24	24		
11	24	3			22	4				
12					22	2				
Total mean ± SD	175 15.9 ± 10.22	88 8 ± 5.55	100 10 ± 9.78	36 3.55 ± 3.51	104.5 8.7 ± 8.62	27.5 2.29 ± 1.42	218 21.8 ± 6.6	219 21.9 ± 3.75	141 17.62 ± 6.72	53 6.62 ± 7.06

Table 1: Overall Survival Data in months along with mean and standard deviation.

Lung group

This group constituted 24 subjects with inoperable stage IIIA/IIIB/IV lung cancer with 12 in each arm. 12/22 (54.6% had stage IV disease requiring palliative local radiation ± chemotherapy. Among them, 6/22 (27.2%) had bone metastasis, 6/22 (27.2%) had malignant effusion and 2/22 (9%) had brain metastasis. 10/22 (45.4%) had stage IIIA/IIIB lung cancer. All 24 patients were equally matched for stage and metastatic status. Those having brain and bone metastasis received palliative radiation of 30Gy/10#.

All stage 4 patients received chemotherapy with cisplatin @75mg/m^2 (D1) and etoposide 120mg/m2 (D1, D2, D3). Zoledronic acid 4mg was added for those who had bone metastasis. IIIA/IIIB were treated with radical radiation @66Gy/33# without chemotherapy. The mean cycles of chemotherapy received by the stage 4 patients in the NESEM™/S2013 arm was 2.167 ± 1.946 and that for the control arm was 2.292 ± 1.484, which was not statistically significant (p=0.8612). The mean age for the NESEM™/S2013 arm was 57.92 ± 12.36 and in the control, arm was 57.50 ± 10.10, which was not statistically significant (p=0.9288).

The mean survival in the NESEM™/S2013 arm was 8.708 ± 9.006 months and in for control arm was 2.292 ± 1.484 months which was statistically significant (p=0.0234) (Figure 1B) (Table 1) (Represented by Kaplan Meier curve). This represents a 280% increase in survivability for the NESEM™/S2013 arm (see Appendix A).

Three patients in the NESEM™/S2013 arm were alive after the trial period was completed (25%). Of these three, one patient died due to a choking incident in month 22. The second patient and the third patient were still alive at the time of writing this paper. It was decided that data collection for the lung cancer group

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would be concluded in month 22 as there were only two patients still alive. All patients in the control arm expired within the fifth month.

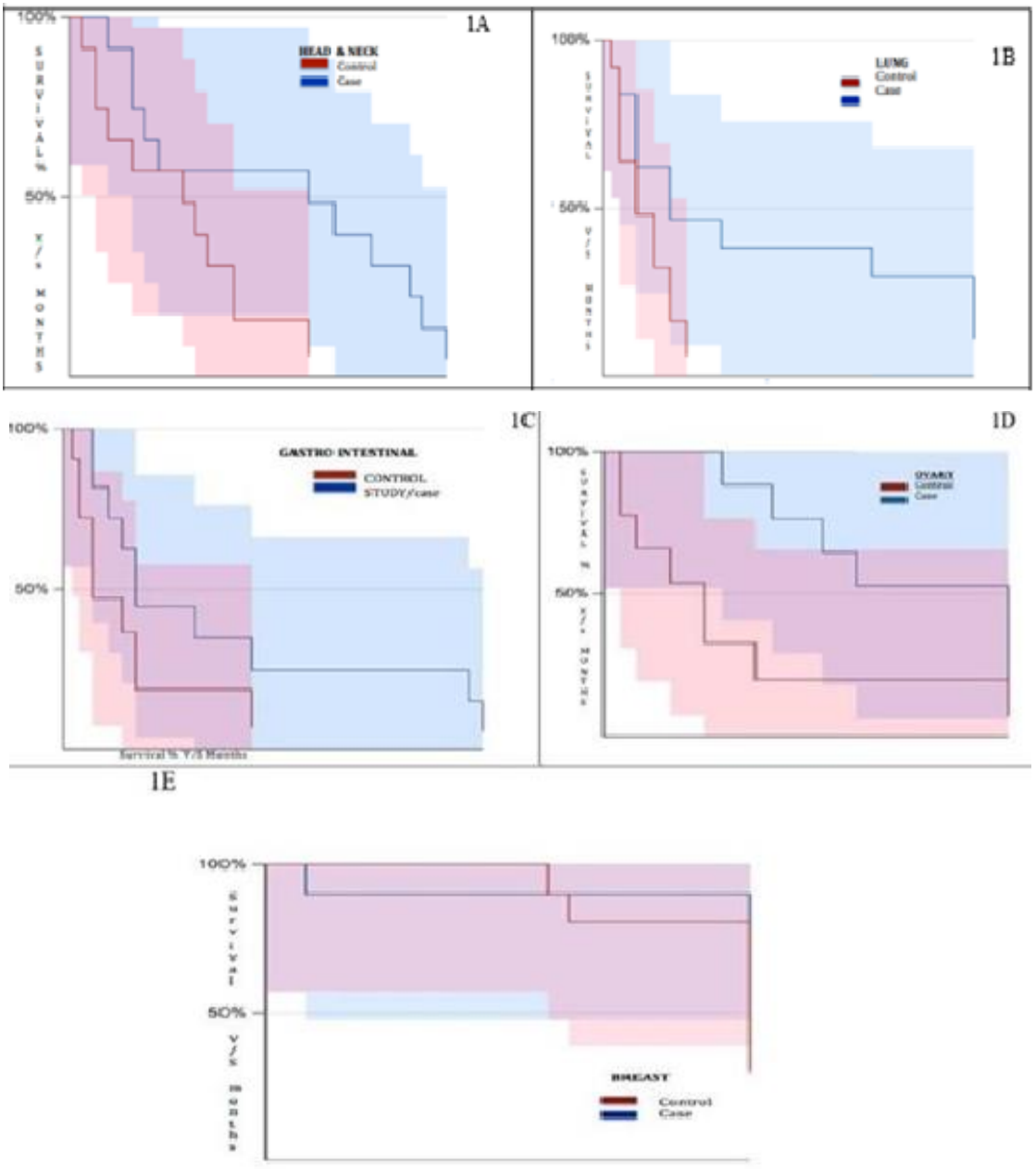

Figure 1: Represents survival data of various groups (1A: H&N, 1B: Lung, 1C: Gastrointestinal Tract, 1D: Ovary, 1E: Breast). (A) Survival data for the Head and Neck group in months. The hazard rates differ z=2.24, p=0.0252 (Confidence levels 95%). (B) Survival data for the Lung group in months. The hazard rates differ z=2.25, p=0.0242 (Confidence levels 95%). (C) Survival data for the Gastrointestinal Tract group in months. The hazard rates differ z=1.89, p=0.059 (Confidence levels 95%). (D) Survival data for the Ovary group in months. The hazard rates differ z=2.55, p=0.0106 (Confidence levels 95%). (E) Survival data for the Breast group in months. The hazard rates differ z=0.55, p=0.58 (Confidence levels 95%).

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GIT

A total 20 patients were recruited with 10 patients randomized to each arm (Table 1). 8 (40%) had Ca stomach, 8 (40%) had colorectal and 4 (20%) had oesophageal cancers.

Ca oesophagus patients were inoperable and treated with radical radiation. Among the 4 patients, two received 40Gy, one received 60Gy and one received the best supportive care. The 8 patients with Ca stomach received palliative radiation @40Gy/20#, followed by chemotherapy with Mc Donald's regimen (Ca Leucovorin @20mg/m2 day 1 to 5 and 5FU@ 425mg/m2 day 1 to 5). 8 patients with Ca rectum received palliative radiation @50Gy/25# followed by chemotherapy with Mc Donald's regimen. The majority of the patients could not complete the entire course of prescribed radiation or chemotherapy due to deterioration of their ECOG status. The mean dose of radiation received by the NESEM™/S2013 group was 31.70 ± 23.92 Gy and that received by the control group was 24.80 ± 22.69 Gy and was not different (p=0.5164). The average number of cycles of Mc Donald's regime in the NESEM™/S2013 arm was 2.78 ± 1.86 and that received by the control arm was 2.80 ± 2.39 cycles, was not significant (p=0.9824).

The average age of the patients in the NESEM™/S2013 group was 63.00 ± 18.62 and that for the control group was 53.50 ± 18.46, was not significant (p=0.2669).

The average survival for NESEM™/S2013 oesophagus subgroup was 4 months and 3 months in the control group. The mean OS in the NESEM™/S2013 arm was 10.000 ± 10.317 months and in the control arm was 3.550 ± 3.700 months which was significant (p=0.0792) (Figure 1c) (Table 1) (Represented by Kaplan Meier curve). This represents a 182% increase in survivability for the NESEM™/S2013 arm (see Appendix A). At the conclusion of the trial 2 patients in the NESEM™/S2013 arm were still alive (20%). Follow on contact with these 2 patients was lost following months 28 and 29 respectively. All controls were dead by 13 months.

The mean ECOG score in the NESEM™/S2013 arm was 1.40 ± 1.17 and that in the control group was 2.10 ± 0.99 which was not significant (p=0.1673). The mean HAM–A scores for the NESEM™/S2013 arm was 0.50 ± 1.08 and that in the control arm was 1.30 ± 0.95, which was not significant (p=0.0954). The mean PGSGA scores for the NESEM™/S2013 arm were 6.50 ± 3.81 and that in the control arm was 11.00 ± 4.78, which was statistically significant (p=0.0318).

Ovary group

Among the16 patients in the ovary group 12 patients had stage IIIC disease, 2 had stage IIIA and 2 had stage IV disease (liver metastasis). All the patients were harmonized for stage, age and ECOG. As all the patients were inoperable, they were treated uniformly with neoadjuvant chemotherapy with paclitaxel @175mg/m^2 and Carboplatin @AUC 6 every 21 days for a total of 6 cycles. The mean number of chemotherapy cycles received by the NESEM™/S2013 arm was 5 ± 2.1 cycles and the control group was 4 ± 2.20, which was not significant (p=0.0867). All patients underwent CT scans of the abdomen after 3 cycles and 6 cycles to assess operability. Only 8 patients underwent cytoreductive surgery (4 from each arm). The average age in the NESEM™/S2013 group was 58.50 ± 10.23 years and the average age in the

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control group was 51.38 ± 11.76 years, which was not significant (p=0.2169).

The average survival in the NESEM™/S2013 arm was 17.63 ± 7.19 months and the mean survival in the control arm was 6.63 ± 7.56 months and this difference is considered to be quite significant (p=0.0099) (Figure 1d) (Table 1) (Represented by Kaplan Meier curve). This represents a 166% increase in survivability for the NESEM™/S2013 arm (see Appendix A). At the conclusion of the trial period 4 patients in the NESEM™/S2013 arm were still alive (50%). Follow on contact with three of these 4 patients was lost following month 24. The fourth patient was still alive in 2021 and has now died. One patient was still alive in the control arm at the conclusion of the trial period (12.5%). Follow on contact with this patient was also lost following month 24. It was decided that data collection for the ovarian cancer group would be concluded in month 24 due to the difficulties in maintaining contact with these patients.

The mean ECOG status score in the NESEM™/S2013 arm was 1.00 ± 0.53 and that in the control group was 1.75 ± 0.89 which is considered to be not quite significant (p=0.0596). The mean HAM-A score in the NESEM™/S2013 arm was 4.38 ± 3.02 and that of the control arm was 6.75 ± 5.39, which was not significant (p=0.2954). The mean PG-SGA score in the NESEM™/S2013 group was 5.63 ± 2.20 and that in the control group was 8.13 ± 2.90, which again was not significant (p=0.0725).

Breast

Patients with breast cancer that were randomized were 20. Each arm had 10 patients each. All the patients who were selected had already undergone a modified radial mastectomy (MRM) and post-operative staging. The patients were harmonized for their age and TNM status. All patients who were ER/PR positive received Tamoxifen in addition to their adjuvant chemotherapy. All patients received adjuvant chemotherapy with either the FAC regime (6 cycles) for low-risk patients or the AC-T regime (8 cycles) for node-positive patients except for one patient in the control arm due to refusal of chemotherapy. All patients received adjuvant radiation with 50 Gy/25# to the chest wall and drainage areas except for 2 patients in the control arm and 2 patients in that NESEM™/S2013 arm as they had T1/T2 node-negative lesions. The mean number of cycles of chemotherapy received by the NESEM™/S2013 arm was 7.40 ± 1.07 cycles and that received by the control group was 7.60 ± 3.47 cycles, which was statistically insignificant (p=0.8637).

The mean age of the patients in the NESEM™/S2013 arm was 52.50 ± 11.96 years and that of the control arm was 54.50 ± 7.23 years, which was statistically insignificant (p=0.6562). The mean survival in the NESEM™/S2013 arm was 21.80 ± 6.96 months and that of the control group was 22.10 ± 4.01 months, which was not significant (p=0.9073) (Figure 1a) (Table 1) (Represented by Kaplan Meier curve). In both the groups, the survival was not statistically different, as the duration of follow-up was not sufficient given the longer life expectancy for breast cancer patients compared with the other cancer groups. At the end of 24 months (3 months post-study), 9 patients from the NESEM™/S2013 arm (90%) and 7 from the control arm (70%) were still alive. This represents a 29% increase in survivability for the NESEM™/S2013 arm. During the trial

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period there was 1 death in the NESEM™/S2013 arm and 2 deaths in the control arm. During follow up one additional patient died in the control arm. Given the difficulties experienced in maintaining follow up with the other cancer groups it was decided to conclude data collection for the breast cancer patients at 24 months.

The mean ECOG performance scores in the NESEM™/S2013 group were 0.650 ± 0.580 and that in the control group was 1.350 ± 0.669, was significant (p=0.0223). The mean HAM-A score in the NESEM™/S2013 group was 1.40 ± 1.84 and that in the control group was 2.30 ± 2.31, was insignificant (p=0.3480). The mean PG-SGA scores in the NESEM™/S2013 group were 2.10 ± 2.18 and that in the control group was 3.70 ± 1.49 which was statistically insignificant (p=0.0719).

Overall Result (n=102)

The overall data for the 102 patients was analysed using ANOVA thereby accounting for the 5 diverse groups. The overall survival in the NESEM™/S2013 arm was 14.480 ± 10.036 months versus 8.333 ± 8.507 months in the control arm (Figure 2) (Table 1) (Representation by Kaplan Meier curve), which was statistically significant (p=0.0012). This represents a 75% increase in survivability for the NESEM™/S2013 arm (see Appendix A). In the NESEM™/S2013 arm 22 patients (43%) survived the trial period whilst in the control arm 9 patients (18%) survived the trial period.

The mean ECOG scores in the NESEM™/S2013 group were 1.12 ± 0.773 and that in the control group was 1.58 ± 0.8593 which was statistically significant (p=.00591) (Figure 3). The mean HAM-A scores in the NESEM™/S2013 group were 2.4314 ± 2.9138 and that in the control group was 3.0612 ± 3.4666 which was not statistically significant (p=0.97) (Figure 4). The mean PGSGA scores in the NESEM™/S2013 arm were 6.4688 ± 2.8959 and that in the control arm was 7.625 ± 5.7291 which was not statistically different (p=.312209) (Figure 5).

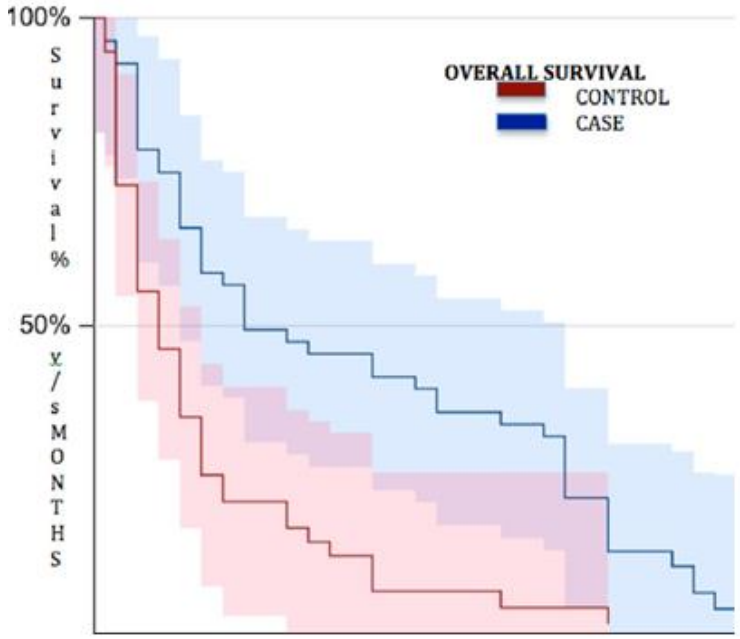

Figure 2: Overall survival data of all groups. Hazard rates differ z=4.88, p<0.001 (Confidence levels 95%).

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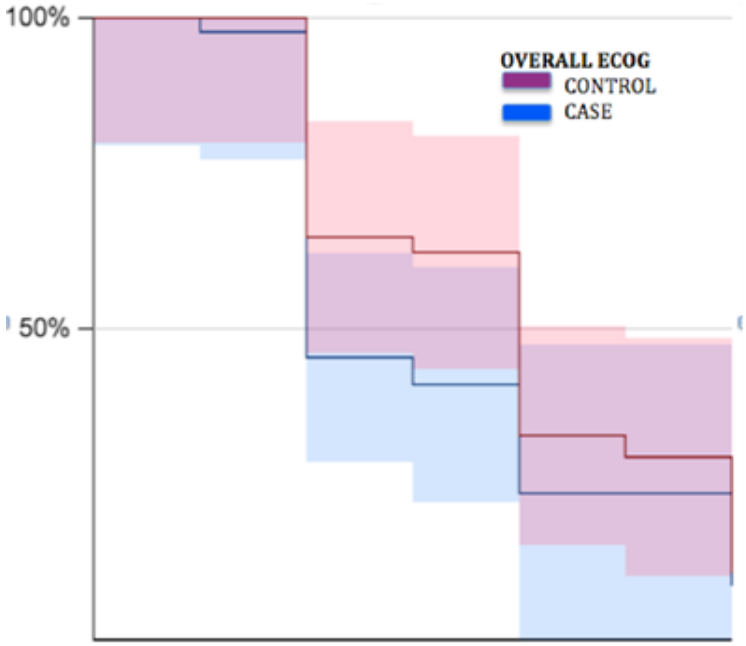

Figure 3: Overall ECOG data of all groups. Hazard rates differ z=2.67, p=0.00768.

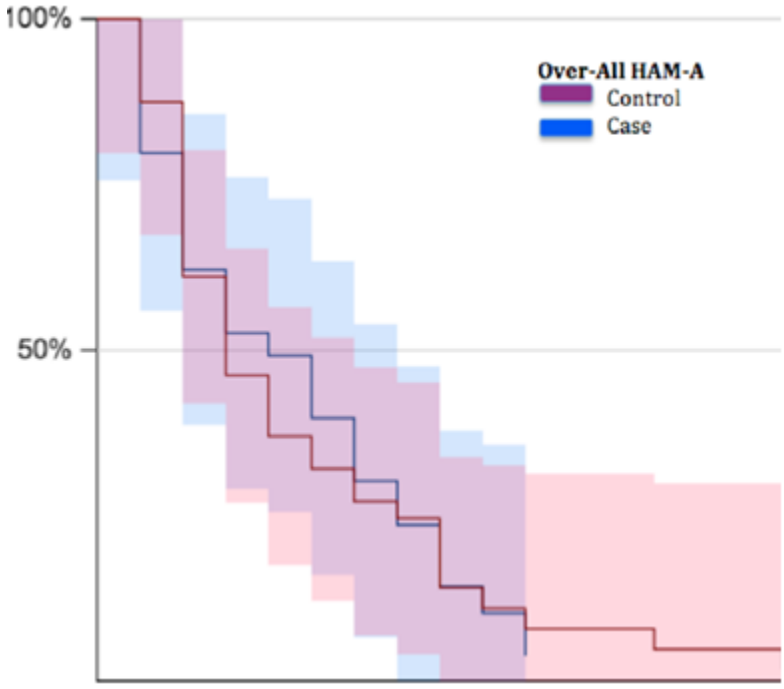

Figure 4: Overall HAM-A data of all groups. No Significant difference z=0.038, p=0.97.

Discussion

The discussion regarding NESEM™/S2013 as anti-cancer nutritional components can be disputed. The reason for this is that all studies published to date are studies of the molecular in vivo behaviour for this class of molecules, case studies or case series reports, showing some promising outcome in cancer patients

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[9,10, 14, 15]. However, to date, no randomized controlled study has been performed to assess more precise responses. In most of the case studies, conventional cancer medication and surgery were offered to make the benefit of NESEM™/S2013s unfathomable as there was no control group. These studies are insufficient to assess the effect or efficacy of NESEM™/S2013 in cancer. This study attempted to broaden the indication of a nutrition-based product, NESEM™/S2013 [16], which uses the unique metabolic properties of CYP1B1. This is probably the first randomized clinical trial that has been done on NESEM™/S2013 along with conventional treatment in regional cancer hospitals. The process of randomization and the selection of controls have added to the level of evidence and enabled a more precise assessment of the response of NESEM™/S2013 in a cancer setting.

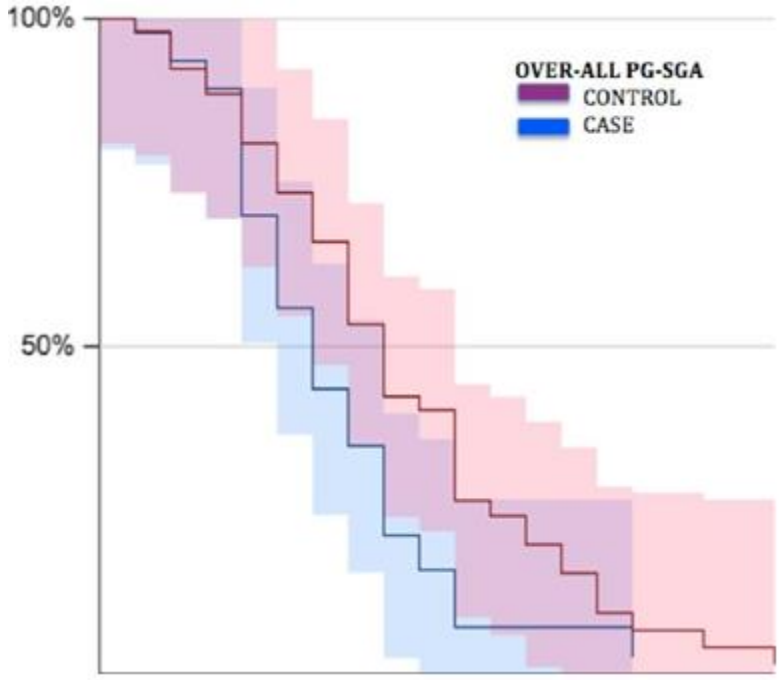

Figure 5: Overall PG-SGA data for all groups. Hazard rates differ z=3.03, p=0.00244.

In most of the previously reported case studies, the patient was either receiving conventional cancer therapy concurrently with NESEM™/S2013 or no mention whatsoever is made of any concurrent or past conventional cancer therapy, making any efficacy judgment difficult [9,10,14,15]. To shed some light on the combination of the CYP1B1 pathway and conventional cancer therapy, a randomized clinical trial was undertaken in a Regional Cancer Centre. Every patient received evidence-based treatment according to his/her TNM staging. The addition of NESEM™/S2013 in one arm was the only additional intervention. Most patients had advanced or terminal cancers; hence the study was completed in 21 months. Multi-modality treatment is the norm for most cancers. Hence, the addition of any intervention of possible benefit needs to be incorporated into the evidence-based treatment and patients duly randomized without bias.

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However, using the same principles it was observed that the NESEM™/S2013 group had a statistically significant overall survival (p=0.0012). NESEM™/S2013s have not been able to improve the quality of life as seen in the HAM-A and PGSGA scores. However, a significant improvement in the ECOG status may be attributed to the possible contribution of NESEM™/S2013 as the ECOG was matched at randomization. The results of the study were compelling to give these molecules a new look as an adjunct in the treatment of malignancies of the Head & Neck, Lung, GIT and Ovary. These results indicate that there may be a role for CYP1B1 induced pathways in several cancers [1,2, 15,16].

The addition of NESEM™/S2013 probably stimulates these pathways leading to an additional gain from surgery, radiotherapy and chemotherapy. A significant improvement in overall survival and ECOG status deserves a closer look at polyphenols like NESEM™/S2013s contributing as an adjunct to modern treatment or even as part of palliative care when no further cancer treatment can be offered. Hence there is a need for larger randomized trials that may shed light on the role of polyphenols, and NESEM™/S2013s in cancers.

Conclusion

The cases presented here were from a cross-section of cancers such as head & neck, lung, GIT, breast and ovary. The trial has highlighted the difficulties of monitoring patients beyond the treatment phase of the trial in a rural Indian setting. Follow up required more resources than could be mustered to try and maintain contact with all but a small number of patients. Given this, follow-up data collection was largely constrained to a 24 month period, including the treatment phase, for all but a handful of highly motivated patients. The data from the study makes one optimistic that regardless of the choice of treatment adding NESEM™/S2013 may prove to be beneficial for both the patients and the physicians. The study highlights, based on experience of the cancer patients, that the metabolic properties of CYP1B1 are beneficial to them, a few of the cases being in third and fourth stages. The cases also bring to light the valuable role NESEM™/S2013 can play in improving OS and QoL. Such cases instill confidence in the minds of patients and physicians to turn towards nutritional approaches prior to or in concurrence to conventional therapy to achieve better outcomes.

The use of NESEM™/S2013s in tandem to surgery, radiotherapy and chemotherapy in malignancies of the Head and Neck, Lungs, GIT, and Ovaries may improve OS and ECOG status. Both CYP1B1 pathway and NESEM™/S2013 were found to be promising solutions to improve cancer treatment with no added side effects or toxicity.

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Ethical approval letter

Given 21 January 2014.

Consent for publication

Consent letter available.

Conflict of interest

There is no conflict of interest.

Funding

The funding was given by Prayus Natural Products India Pvt. Ltd.

Trademark

NESEM is a trademark of Naturally Pure Products Ltd.

Authorship

Dr. Gayathri Bathoju (Medical Director of Prayus) designed the study, Patient studies and Data acquisition, Statistical analysis and Manuscript preparation. Dr. Raghu Raman selection of patients, Conventional treatment and Manuscript Preparation. Dr. Vijay Kumar Conventional treatment.

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Appendix A.

	Head & neck	GIT	Lung	Ovary	Breast	Overall
Case	175(99%)	100(182%)	104.5(280%)	141(166%)	218(NA)	738.5(75%)
Control	88	35.5	27.5	53	219	423

Table 2: Total months of survival by cancer group and percentage increase in survivability.

Year	Across all cancer groups	
	Case	Control
>6 months	33/51(65%)	19/51(37%)
>12 months	28/51(55%)	15/51(29%)
>18 months	24/51(47%)	10/51(20%)
>=24 months	19/51(37%)	8/51(16%)

Table 3: Overall number of patients alive and percentage alive at the end of months 6, 12, 18 and 24 in each trial arm.

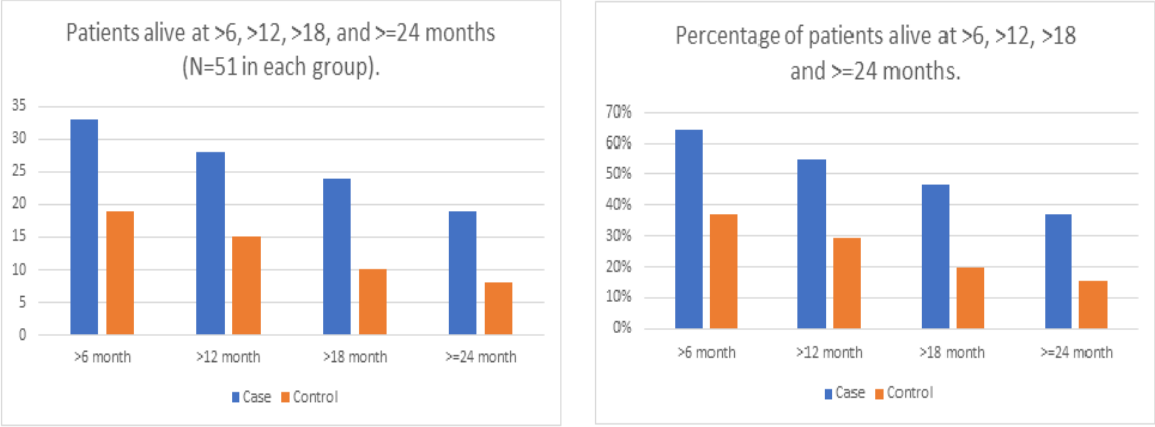

Figure 6: Overall number of patients alive and percentage alive at the end of months 6, 12, 18 and 24 in each trial arm.

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