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Research Paper

Phase III Non-inferiority Study Evaluating Efficacy and Safety of Low Dose Gemcitabine Compared to Standard Dose Gemcitabine With Platinum in Advanced Squamous Lung Cancer

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ABSTRACT

Background: Prolonged infusion of low dose gemcitabine (PLDG) in combination with platinum has shown promising activity in terms of improved response rate and progression free survival (PFS); especially in squamous non-small cell lung cancer (NSCLC). Hence, we conducted a phase 3 randomized non-inferiority study with the primary objective of comparing the overall survival (OS) between PLDG and standard dose of gemcitabine with platinum.

Methodology: Adult subjects (age ≥ 18 years), with stages IIIB–IV, NSCLC (squamous) and ECOG performance status of ≤2 were randomized 1:1 into either carboplatin with standard dose gemcitabine (1000 mg/m^2 intravenous over 30 min, days 1 and 8) (STD-G arm) or carboplatin along with low dose gemcitabine (250 mg/m^2 intravenous over 6 h, days 1 and 8) (LOW-G arm) for a maximum of 6 cycles. Tumor response was assessed by RECIST criteria version 1.1 every 2 cycles till 6th cycle and thereafter at 2 monthly intervals till progression. The primary endpoint was overall survival. 308 patients were randomized, 155 in STD-G arm and 153 in LOW-G arm, respectively.

Results: The median overall survival in STD-G arm was 6.8 months (95%CI 5.3–8.5) versus 8.4 months (95%CI 7–10.3) in the LOW-G arm (HR-0.890 (90%CI 0.725–1.092). The results with per protocol analysis were in line with these results. There was no statistical difference in progression free survival (HR-0.949; 90%CI 0.867–1.280) and adverse event rate between the 2 arms.

Conclusion: This study suggests that PLDG is an alternative to the standard gemcitabine schedule in squamous NSCLC, and either of these can be selected subject to patient convenience.

1. Introduction

There has been a deluge of new targeted systemic therapies (Bevacizumab, Erlotinib, Gefitinib, Afatinib, Osimertinib, Crizotinib, Alectinib, etc.) approved in non-small cell lung cancer (NSCLC) over the last 2 decades [1]. However, to a large extent, these targeted therapies are mostly applicable in non-squamous histologies which exhibit relevant driver mutations. As opposed to this, platinum-based doublet chemotherapy has been the backbone of systemic treatment for squamous NSCLC in the last few decades [1–4]. Gemcitabine with a platinum (either cisplatin or carboplatin) is preferred in squamous cell histology [5–7].

Gemcitabine has been used in 3 distinct schedules depending on infusion rates. The standard schedule of 1000–1200 mg/m^2 administered

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Research in context

Evidence before this study

Gemcitabine and platinum chemotherapy (either cisplatin or carboplatin) is the standard of care and preferred regimen for the treatment of patients with advanced (stages III–IVB) squamous non-small cell lung cancer (NSCLC). Gemcitabine is delivered in the traditional schedule in this regimen of 1000 mg/m within 30 min. A PubMed search was performed using the terms (Lung Cancer) AND ((Prolonged low dose infusion) AND Gemcitabine in March 2019. Multiple small phase 2 studies and meta analysis in NSCLC had evaluated prolonged low dose gemcitabine of 250 mg/m^2 given over 6 h (PLDG) and it seemed that it had similar or better efficacy than the traditional schedule. Some reports also suggested that the regimen had lower rates of adverse events. However, the evidence was of low quality and at best was regarded as hypothesis generating. We found not a single phase 3 randomized study present comparing the traditional schedule with the PLDG in NSCLC and so we planned this study.

Added value of this study

We report the results of a phase 3 randomized study testing the above hypothesis with 1:1 randomization of patients between standard schedule of gemcitabine and low dose prolonged infusion schedule of gemcitabine, both with carboplatin. The primary endpoint was overall survival. The median overall survival was similar between both arms and the hazard ratio on intent to treat analysis was 0.89 (90%CI 0.725–1.092). The confidence interval was within the limit of non-inferiority. The results with per protocol analysis were in concordance with these results. In addition, there was no statistical difference between the 2 arms in terms of response rate or progression free survival.

Implications of all the available evidence

On the basis of our report, PLDG (administered over 6 h) with carboplatin should be considered as an alternative to the standard of care schedule of 1000 mg/m^2 of gemcitabine administered within 30 min with carboplatin, as it leads to similar overall survival and progression free survival. In addition the PLDG has the advantage of decreasing requirement of gemcitabine and thus the cost of treatment by around 75%. The choice between the 2 schedules would depend upon the preferences of the patient and the treating physician as both regimens have equal efficacy and toxicity.

over 30 min (at a rate of 40 mg/m^2/min), moderately prolonged schedule of 1000 mg/m^2 over 100 min (at a rate of 10 mg/m^2/min) and the prolonged low dose schedule-gemcitabine (PLDG) of 250 mg/m^2 infused over 6 h (at a rate of 0.69 mg/m^2/min) [8]. The enzyme deoxycytidine kinase is the rate-limiting enzyme for gemcitabine activation. The pharmacological basis for using the prolonged low dose schedule is that this enzyme gets saturated at the low dose level [9,10]. PLDG has shown significant activity in several solid tumors including lung cancer [11]. In a phase 2 study by Zwitter et al., a response rate (RR) of 46%, with median progression free survival (PFS) of 6 months and 1 year overall survival (OS) of 40% was observed with PLDG [12]. In another study published by the same group, an apparent numerically superior activity and lower toxicity compared to the standard dose gemcitabine was reported [13]. Multiple phase 2 studies (at the time of planning this study) with PLDG echoed these findings of superior to similar activity in comparison with standard dose of gemcitabine [14,15].

In light of literature suggesting similar or better efficacy of PLDG and additional advantage of lowering the requirement of gemcitabine by approximately 75%, we decided to conduct a phase 3 randomized non-inferiority study with the primary objective of comparing the OS between low dose and standard dose gemcitabine, combined with platinum in advanced squamous NSCLC.

2. Methods

2.1. Study Conduct and Design

The study protocol was approved by the Institutional Ethics Committee and registered with the Clinical Trial Registry of India (CTRI/2013/02/003422). All patients provided written informed consent prior to participation in the study. The study was conducted in compliance with the Indian council of Medical research (ICMR) statement on human experimentation, the Declaration of Helsinki and the International Committee of Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP). The study was funded by grants from Indian Cooperative Oncology Network (ICON). This was a phase 3, randomized, parallel group, non-inferiority study. The study recruited patients between 3rd May 2013 to 12th March 2018 and the data was censored for analysis on 6th October 2018.

2.2. Participants

Patients included in the study were adults (≥18 years of age), stages IIIB–IV (according to the AJCC/UICC staging system-7th edition) [16], pathologically proven chemotherapy-naive NSCLC (squamous), planned for first-line palliative chemotherapy, Eastern Cooperative Oncology Group Performance status (ECOG PS) 0–2 and with adequate organ function. Patients with symptomatic brain metastasis, superior vena cava obstruction, uncontrolled comorbidities or any other malignancy within the last 5 years were excluded from the study.

2.3. Interventions

Patients were randomly allocated to gemcitabine–carboplatin doublet schedule of either standard dose gemcitabine–carboplatin (STD-G arm) or the low dose gemcitabine–carboplatin (LOW-G arm). The dose of gemcitabine in STD-G arm was 1000 mg/m^2 infused in 0.9% normal saline over 30 min on day 1 and day 8 of a 21 day cycle. The dose of gemcitabine in LOW-G arm was 250 mg/m^2 infused in 0.9% normal saline over 6 h on day 1 and day 8 of a 21 day cycle. Carboplatin was administered at area under the curve (AUC) of 5 mg per milliliter per minute in 5% dextrose (unless patient was diabetic, in which case it was administered in 0.9% normal saline) over 1 h on day 1 of the 21 day cycle. The creatinine clearance was calculated according to the Cockcroft–Gault (CG) formula, for calculation of carboplatin dose. Prior to chemotherapy, patients received moderate emetogenic antiemetic prophylaxis consisting of 5HT3 inhibitor and dexamethasone in both arms. Patients received a maximum of 6 cycles of chemotherapy in each arm if no progression was documented prior. Patients underwent contrast-enhanced computed tomography scan of the thorax and upper abdomen at baseline and after every 2 cycles of chemotherapy. Other imaging was also allowed, if indicated by patients' symptoms. Tumor response was assessed by RECIST criteria version 1.1 [17]. After completion of 6 cycles of treatment, scans were done every 2 months until progression. Patients were followed up till death. Adverse events were captured at each clinical visit and assessed according to NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 and managed accordingly. Dose reductions of chemotherapy according to adverse events were done in accordance with the study protocol.

2.4. Endpoint

The primary endpoint was overall survival (OS), which was defined from date of randomization to date of death. Secondary endpoints were progression free survival (PFS), response rate (RR) and adverse event rate (AER). PFS was defined from date of randomization to date of progression or death, whichever was earlier. RR was defined as per RECIST version 1.1.

2.5. Sample Size

Non-inferiority was defined as an increase in the hazard of death (HR) <1.33 in the experimental arm (LOW-G arm), as compared with the standard arm (STD-G arm). One year survival of ≥33% [18] and 23% was assumed in the standard arm and experimental arm, respectively As the nature of treatment was palliative, a slight, non-marginal increase in the risk of death was considered clinically non-significant and could be offset by a decrease in toxicity or cost. Assuming a type 2 error of 20%, with a one sided type I error of 5%, equal allocation between both arms, accrual over 2 years and a study duration of 4 years, we required 220 events and sample size of 308 patients [19].

2.6. Randomization and Blinding

Simple randomization was done by a 3rd person (SK). The request for randomization was sent by the trial coordinator and the randomization arm was received online. The study was open label and hence both patients and treating physicians were aware of the study arms.

2.7. Statistical Methods

The final analysis was planned after the 220th event was observed. RStudio version 1.0.136 (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.

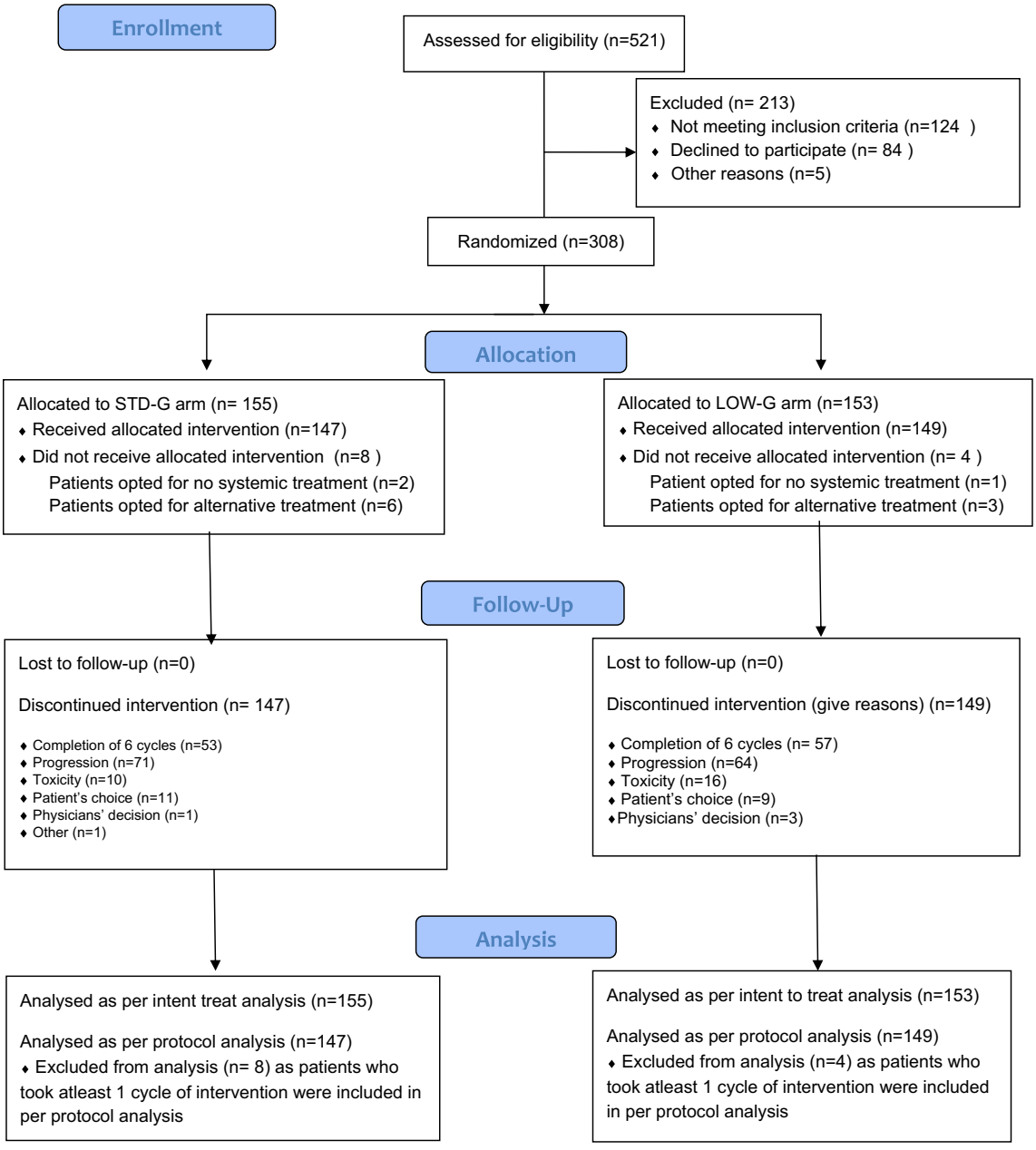

Fig. 1. Consort diagram. STD-G arm — standard dose gemcitabine with carboplatin arm. LOW-G arm — low dose gemcitabine with carboplatin arm.

com/) and SPSS version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) were used for analysis. Intention to treat analysis was performed. Kaplan–Meier method was used for the estimation of the probability of OS and PFS in each arm. The median estimates of OS and PFS in each arm with their respective 95% confidence interval (CI) were reported. Brookmeyer and Crowley method was used for the construction of the 95%CI for the median. A non-inferiority p-value of 0.05 was considered as significant. The hazard ratio (HR) with its 90%CI interval was calculated using the COX regression analysis with Efron's method of tie handling, with STD-G arm being considered as reference. The assumptions of proportional hazard model were checked using Schoenfeld residuals and assumptions were met. Per protocol analysis was also performed using above methodology to confirm the robustness of the results. To determine non-inferiority, the upper boundary of 90%CI of HR had to be below or equal to 1.33.

3. Results

3.1. Patients

Of the 308 patients randomized, 155 and 153 patients were randomized in STD-G arm and LOW-G arm respectively (Fig. 1, Consort diagram). Baseline characteristics were matched between both the arms (Table 1). The median follow-up was 20.6 months.

Table 1
Baseline characteristics.

Characteristics	Standard dose gemcitabine–carboplatin arm (n = 155)	Low dose gemcitabine–carboplatin arm (n = 153)
Median age (interquartile range)—years	61 (55–66)	59 (54–64)
Age—no. (%)		
Elderly (≥65 years)	51 (32.9)	37 (24.2)
Non elderly (<65 years)	104 (67.1)	116 (75.8)
Gender—no. (%)		
Male	135 (87.1)	133 (86.9)
Female	20 (12.9%)	20 (13.1)
ECOG PS—no. (%)		
0	9 (5.8)	6 (3.9)
1	137 (88.4)	138 (90.2)
2	9 (5.8)	9 (5.9)
Smoking—no. (%)		
Yes	124 (80.0)	118 (77.1)
No	31 (20.0)	35 (22.9)
Histology—no. (%)		
Squamous	141 (91.0)	147 (96.1)
Squamous admixed with adenocarcinoma	14 (9.0)	6 (3.9)
Stage—no. (%)		
IIIB	37 (23.9)	28 (18.3)
IV	118 (76.1)	125 (81.7)
Driver mutation status—no. (%)		
Absent or unknown	150 (96.8)	142 (92.8)
EGFR sensitizing mutation	4 (2.6)	8 (5.2)
ALK translocation	1 (0.6)	3 (2.0)
Brain metastasis—no. (%)		
Yes	9 (5.8)	14 (9.2)
No	146 (94.2)	139 (90.8)
Radiation for brain metastasis—no. (%)[a]		
Yes	8 (5.2)	12 (7.8)
No	147 (94.8)	141 (92.2)
Radiation for bone metastasis—no. (%)[a]		
Yes	20 (12.9)	16 (10.5)
No	135 (87.1)	137 (89.5)

[a] 27 patients in each arm had received palliative radiation prior to enrollment.

3.2. Overall Survival

At data cutoff, 131 and 127 patients had died in STD-G and LOW-G arms, respectively. The median overall survival in STD-G arm was 6.8 months (95%CI 5.3–8.5) versus 8.4 days (95%CI 7–10.3) in LOW-G arm (Fig. 2). The hazard ratio for death was 0.890 (90%CI 0.725–1.092). The upper limit of 90%CI of hazard ratio was 1.092, which was below the acceptable non-inferiority margin of 1.33. The 1 year and 2 year overall survival in STD-G and LOW-G arm were 29.9% (95%CI 22.7–37.4) versus 33.1% (95%CI 25.6–40.8) and 7.8% (95%CI 3.5–14.4) versus 8.6% (95%CI 3.9–15.7). The p value for non-inferiority was 0.006.The results were consistent across all subgroups tested (Fig. 2).

The per protocol analysis for OS was performed in 296 patients (Fig. 1), 147 in STD-G arm and 149 in LOW-G arm. At the data cutoff, 124 patients had died in each of the arms. The results were in alignment with intention to treat analysis results (Fig. 3). The details of intent to treat, per protocol analysis and cause of death are shown in the Supplementary appendix (Tables 1S and 2S).

3.3. Progression Free Survival

At the data cutoff, 142 and 147 patients had progressed or died as first event in STD-G and LOW-G arms, respectively. The median progression free survival in STD-G arm was 3.1 months (95%CI 2.7–4.1) versus 4 months (95%CI 3.1–4.6) in LOW-G arm (Fig. 1S). The hazard ratio

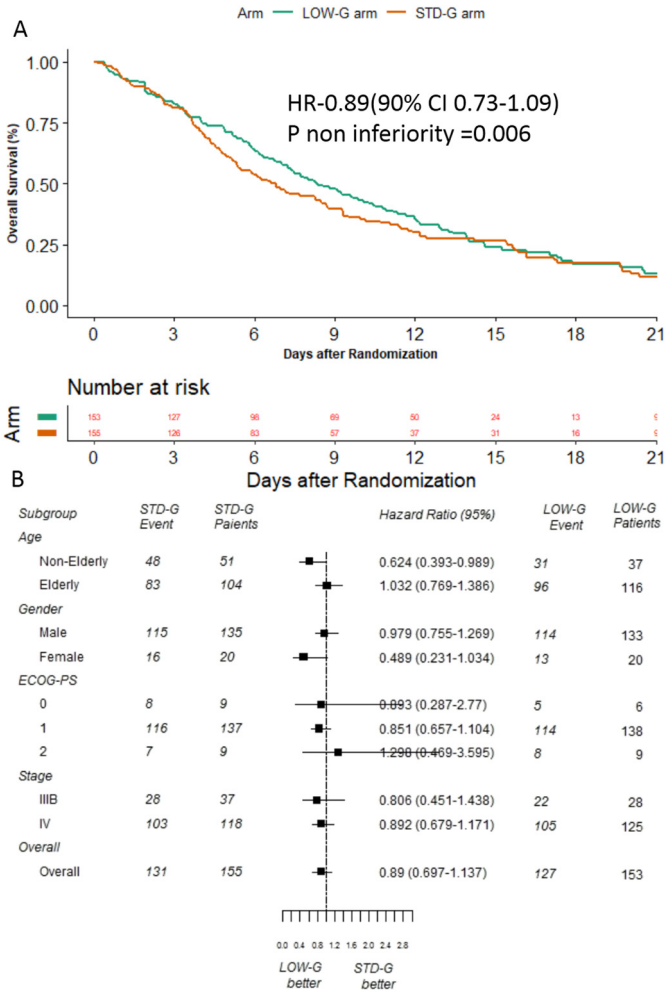

Fig. 2. Overall survival in the intent to treat population. Panel A shows the survival curves estimated by Kaplan–Meier method. Panel B shows the forest plot, depicting the impact of treatment on various subgroups. Data is as of 6th October 2018 (the date of data cutoff).

for progression was 0.949 (90%CI 0.867–1.280). The other details of intent to treat analysis and per protocol analysis for PFS are shown in the Supplementary appendix. The per protocol analysis for PFS was in concordance with the intent to treat analysis (Table 3S). The details of overall response rate in accordance with intention to treat and per protocol analysis are shown in Table 4S.

3.4. Compliance With Treatment

Out of the 155 patients allocated to STD-G arm, 147 patients (94.8%) took at least 1 cycle of treatment. The median number of cycles of gemcitabine and carboplatin received were 3 (IQR 2–6) and 3 (IQR 2–6), respectively. Six cycles of treatment were completed by 53 patients (34.2%). Progression of disease was the commonest reason for discontinuation of chemotherapy (n = 71 (45.8%)). The other reasons are shown in the Supplementary appendix in Table 5S. Number of patients who required gemcitabine and carboplatin dose reduction were 42 (27.1%) and 21 (13.5%), respectively. The median average relative dose intensity for the STD-G arm was 0.92 (0.77–1). The details of second line treatment are shown in Table 6S.

Out of the 153 patients allocated to LOW-G arm, 149 patients (97.4%) took at least 1 cycle of treatment. The median number of cycles of gemcitabine and carboplatin received were 4 (IQR 2–6) and 4 (IQR 2–6) respectively. Six cycles of treatment were completed by 57 patients (37.3%). Progression of disease was the commonest reason for not completing 6 cycles (n = 64 (41.8%)). The other reasons for incompletion are shown in the Supplementary appendix. Number of patients who required gemcitabine and carboplatin dose reduction were 40 (26.1%) and 19 (12.4%), respectively. The median average relative dose intensity for the LOW-G arm was 0.92 (0.8–1). There was no statistical difference in any of the compliance parameters between the 2 arms (Table 5S). Second line therapy was received by 81 patients, details are shown in Table 6S.

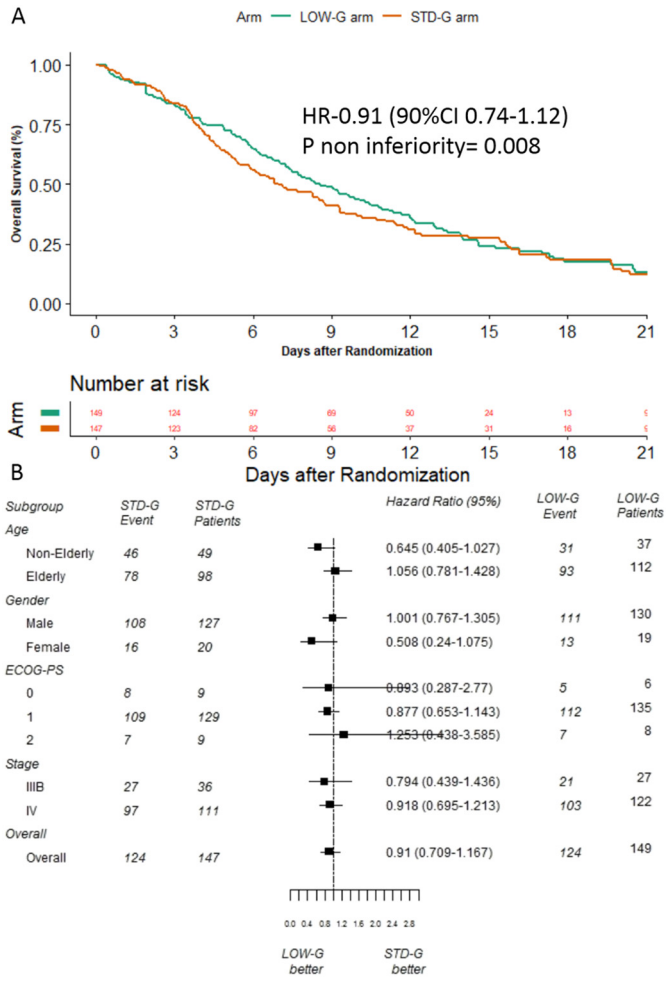

Fig. 3. Overall survival in the per protocol population. Panel A shows the survival curves estimated by Kaplan–Meier method. Panel B shows the forest plot, depicting the impact of treatment on various subgroups. Data is as of 6th October 2018 (the date of data cutoff).

3.5. Safety

There was no statistical difference in adverse events between both arms. Grade 3 or above myelosuppression was seen in 73 patients (54.5%) in the STD-G arm versus 78 patients (56.9%) in the LOW-G arm (p = 0.7147). Grade 3 or above liver function derangement was seen in 5 patients (3.7%) in the STD-G arm versus 11 patients (8%) in the LOW-G arm (p = 0.1968). Death due to adverse events was seen in 3 patients and all three were in the LOW-G arm (p = 0.2473). The toxicity leading to death in these 3 patients was pneumonia leading to sepsis (n = 1), diarrhea leading to sepsis (n = 1) and non ST elevated myocardial infarction (n = 1). Out of the 3 deaths, only one death was attributable to the treatment but not related to trial participation. This patient had febrile neutropenia, diarrhea and sepsis on day eight of cycle 1 to which he succumbed (Table 2).

4. Discussion

To our knowledge this is the first phase 3 randomized study addressing the issue of dose schedule with gemcitabine. Our results clarify that low dose gemcitabine in combination with carboplatin is non-inferior to standard dose gemcitabine with carboplatin in squamous cell NSCLC as first line palliative therapy. The median OS, 1 year OS, 2 year OS, PFS and response rates were similar in both arms. In fact the results were numerically superior in favor of low dose gemcitabine though not

Table 2
Adverse events as per NCI-CTCAE version 3.0 till the date of data cutoff 6th October 2018. Adverse events which are occurred multiply are accounted as single and are represented by the highest grade of occurrence.

Adverse event	Standard dose gemcitabine–carboplatin arm (n = 134)		Low dose gemcitabine–carboplatin arm (n = 137)	
	Any grade	Grades 3–5	Any grade	Grades 3–5
Anemia	126 (94)	43 (32.1)	127 (92.7)	47 (34.3)
Neutropenia	71 (53)	38 (28.4)	75 (54.7)	48 (35)
Thrombocytopenia	64 (47.8)	34 (25.4)	61 (44.5)	27 (19.7)
SGOT increase	59 (44)	5 (3.7)	68 (49.6)	8 (5.8)
SGPT increase	69 (50.4)	3 (2.2)	61 (45.5)	11 (8)
Bilirubin increase	7 (5.2)	–	5 (3.6)	–
Creatinine increase	11 (8.2)	1 (0.7)	7 (5.1)	–
Hyponatremia	99 (73.9)	43 (32.1)	114 (83.2)	51 (37.2)
Hypernatremia	1 (0.7)	–	1 (0.7)	1 (0.7)
Hypokalemia	22 (16.4)	3 (2.2)	31 (22.6)	4 (2.9)
Hyperkalemia	30 (22.4)	1 (0.7)	30 (21.9)	3 (2.2)
Hypomagnesemia	50 (37.3)	1 (0.7)	62 (45.3)	–
Hypermagnesemia	4 (3)	–	3 (2.2)	1 (0.7)
Hypocalcemia	18 (13.4)	–	14 (10.2)	–
Hypercalcemia	14 (10.4)	–	15 (10.9)	1 (0.7)
Febrile neutropenia	–	6 (4.5)	–	12 (8.8)
Fatigue	75 (56)	13 (9.7)	91 (66.4)	19 (13.9)
Oral mucositis	9 (6.7)	–	14 (10.2)	2 (1.5)
Rash—maculopapular	11 (8.2)	–	8 (5.8)	–
Fever	48 (35.8)	1 (0.7)	65 (47.4)	3 (2.2)
Diarrhea	32 (23.9)	10 (7.5)	45 (32.8)	10 (7.3)
Vomiting	24 (17.9)	4 (3)	31 (22.6)	2 (1.5)
Pneumonia	11 (8.2)	8 (6)	15 (10.9)	14 (10.2)

statistically significant. These results were achieved without any apparent increase in adverse events.

Multiple small underpowered studies prior to ours have tried to address this question and a recent meta analysis of these studies suggested that low dose gemcitabine with prolonged infusion leads to a similar 1 year OS and has a lower rate of leukopenia and thrombocytopenia [12–14,20–23]. However, the authors had cautioned that the evidence was of low quality and a high quality large trial was required to answer this question and to test the validity of their results. Our study confirms and validates the results of the meta analysis. Majority of the studies with low dose prolonged infusion of gemcitabine have been found to have either milder or similar adverse rate as compared to standard dose gemcitabine. However, concerns have been raised in occasional report where higher rates of thrombocytopenia were seen with prolonged low dose infusion of gemcitabine [24]. However our results suggest that there is no statistically significant difference in adverse event rates between both the infusion schedules. This was surprising as nearly 1/4th of the dose of gemcitabine was administered. Gemcitabine (which is a prodrug) is phosphorylated by deoxycytidine kinase, to gemcitabine monophosphate, then to gemcitabine diphosphate and finally to gemcitabine triphosphate, which is the active compound [9,10]. It seems that the same mechanism of saturation of deoxycytidine kinase, which led to a similar efficacy between PLDG and STD gemcitabine schedule might be responsible for similar adverse event rates.

The current NCCN guidelines recommend treatment with systemic chemotherapy if driver mutation status (EGFR, ALK, ROS-1, BRAF) is negative or unknown and PDL1 expression is below 50% in squamous cell NSCLC requiring palliative systemic therapy [1]. The cumulative incidence of presence of these mutations status is in the range of 10–15% [25,26] and PDL1 expression above 50% is seen in 18% of patients [27–32]. Hence, despite recent advances in the treatment of NSCLC, majority of the patients (>50%) are only eligible for systemic chemotherapy. Further, the access to targeted therapies and immunotherapy in low and middle income countries is limited [33,34]. Thus, these results have implications in such economically underprivileged countries. In the current study too, approved immunotherapy agents where received by less than 5% of eligible patients (Table 6S) and thus lowering the OS.

These results also have financial implications. On crude calculation itself, a decrement in dose from 1000 mg/m^2 to 250 mg/m^2 will decrease the cost of treatment with gemcitabine by 75% per dosing. As of March 2019, cost of 1 g of Gemzar was 782.05 USD and 200 mg was 163.21 USD [35]. Assuming a body surface area of 1.8, this would amount to a cost difference 945.26 USD per dosing and per cycle cost difference of 1890.52 USD for gemcitabine. However, the cost of administration for longer duration needs to be accounted in this calculation, especially in those countries where longer duration of administration of chemotherapy is charged higher. However, in the PI's institute and in the majority of low and middle income countries the cost of chemotherapy is far larger than its administration [36]. A detailed financial analysis, however, was not performed in the study and hence the lowered costs of chemotherapy need to be balanced against the inconvenience and cost of administration of PLDG. PLDG requires 6 h of gemcitabine infusion against 30 min in the standard schedule which might necessitate the use of a central line.

Our study is not without its limitations. The study randomization was not stratified and it was a single centre study. However, there was no apparent difference in baseline characteristics of the 2 arms. Being a single centre study, the quality checks and uniformity was easily maintained during the study. The chemotherapy and supportive care protocols used were standard and thus generalizable. Another important limitation was the lack of prespecified cost effective analysis.

However, despite these limitations, the results of this large phase 3 randomized study suggest that low dose prolonged gemcitabine infusion is an alternative to the standard gemcitabine schedule. It produces similar OS, PFS and ORR without an increase in the adverse event rate.

Conflict of Interest

None declared.

Author Contributions

1. Dr. Vijay Patil — literature search, figures, study design, study implementation, data collection, data analysis, data interpretation, writing, final approval.
2. Dr. Vanita Noronha — literature search, study design, study implementation, data interpretation, writing, final approval.
3. Dr. Amit Joshi — study design, study implementation, data interpretation, writing, final approval.
4. Dr. Anuradha Chougule — study implementation, data interpretation, final approval.
5. Mrs. Sadhana Kanan — study implementation, data interpretation, final approval.
6. Dr. Atanu Bhattacharjee — data analysis, data interpretation, writing, final approval.
7. Dr. Supriya Goud — study implementation, data interpretation, final approval.
8. Dr. Sucheta More — study implementation, data interpretation, final approval.
9. Dr. Arun Chandrasekharan — study implementation, data collection, final approval.
10. Dr. Nandini Menon — study implementation, data collection, final approval.
11. Dr. Sujay Srinivas — study implementation, data collection, final approval.
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23. Mrs. Vichitra Behel — study implementation, data interpretation, final approval.
24. Dr. Abhishek Mahajan — study implementation, data interpretation, final approval.
25. Dr. Amit Janu — study implementation, data interpretation, final approval.
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Appendix A. Supplementary data

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