European Journal of Cancer 109 (2019) 183–191

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

A randomised phase II clinical trial of *nab*-paclitaxel and carboplatin compared with gemcitabine and carboplatin as first-line therapy in advanced squamous cell lung carcinoma (C-TONG1002)

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Received 19 October 2018; received in revised form 14 December 2018; accepted 7 January 2019
Available online 7 February 2019

KEYWORDS
130-Nm albumin-bound paclitaxel;
Gemcitabine;
Carcinoma;
Squamous cell

Abstract ***Background:*** N*ab*-paclitaxel/carboplatin (*nab*-PC) and gemcitabine/carboplatin (GC) are the standard first-line chemotherapy in non–small cell lung carcinoma. Up to now, there is no head to head trial to compare *nab*-PC with GC in advanced squamous cell lung carcinoma.

Patients and methods: A multicentre randomised phase II trial was performed to compare the efficacy and safety for *nab*-PC with GC in previously untreated patients with advanced squamous cell lung carcinoma. The primary end-point was objective response rate (ORR). Progression-free survival (PFS), overall survival (OS), treatment-related adverse events and quality of life (QoL) were also analysed.

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https://doi.org/10.1016/j.ejca.2019.01.007

Results: Totally 127 participants were eligible for this study (62/65 *nab*-PC/GC). N*ab*-PC has higher ORR than GC without statistical significance (42% versus 27%, $P > 0.05$). After a median follow-up of 14.5 months, both PFS and OS had no difference between the two arms (6.7 versus 5.8 months, hazard ratio [HR] 0.75, $P = 0.143$; 11.6 versus 14.4 months, HR 0.92, $P = 0.846$). Both regimens were well tolerated; however, more dose reduction occurred after cycle 2 in GC (27%) than in *nab*-PC (12%) ($P < 0.05$). Significant QoL improvement measured by trial outcome index was seen in *nab*-PC than in GC ($P < 0.05$).
Conclusions: The first-line *nab*-PC and GC had the same response, PFS, and OS in patients with advanced squamous cell lung carcinoma. N*ab*-PCM has advantage over GC in QoL improvement.
Trial registration number: NCT01236716.

1. Introduction

For driver-gene mutation negative advanced non–small cell lung cancer (NSCLC), first-line chemotherapy is standard treatment in most developing and underdeveloped countries. In recent years, immunotherapy had been an alternative choice for those with PD-L1 expression on at least 50% of tumour cells [1]. However, immunotherapy combined with different chemotherapy regimens based on histology may become a new standard treatment in patients with PD-L1 negative or low expression [2–4]. In the era of the combination of chemotherapy and immunotherapy in lung cancer, the choice of histology-oriented chemotherapy regimen is still important.

Solvent-based paclitaxel plus carboplatin has already been most commonly used regimen for advanced NSCLC [5,6]. The 130-nm albumin-bound formulation of paclitaxel (*nab*-paclitaxel) was approved by the Food and Drug Administration in 2012, to be in combination with carboplatin in first-line setting in NSCLC as the result of a phase III trial showing superior efficacy to sb-PC [7]. N*ab*-paclitaxel/carboplatin (*nab*-PC) had less neurotoxicity and improved response rate (RR) when compared with paclitaxel/carboplatin [8]. Importantly, the lack of Cremophor EL in *nab*-paclitaxel makes it ideal for patients with diluent allergy or with steroid intolerance.

Another widely used regimen in squamous cell lung carcinoma is gemcitabine plus platinum. SQUIRE trial, which compared necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line therapy in patients with stage IV squamous non–small cell lung carcinoma, showed gemcitabine plus cisplatin had median overall survival (OS) of 9.9 months, median progression-free survival (PFS) of 5.5 months and RR of 29% [9]. There is no head to head trial to compare *nab*-PC with gemcitabine plus platinum in advanced squamous cell lung carcinoma.

This study is a multicentre, randomised, active controlled, open label phase II clinical trial to compare efficacy and safety of *nab*-PC with gemcitabine/carboplatin (GC) in first-line setting in advanced squamous cell lung carcinoma.

2. Methods

2.1. Patients

Eligible adults had histologically confirmed stage IV (7th Edition of TNM Staging Criteria) squamous cell lung carcinoma measurable by Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), and Eastern Cooperative Oncology Group performance status of 0–1 and life expectancy of at least 3 months. Smoking status was defined as smoker, non-smokers, who had smoked <100 cigarettes in their lifetime, and former smokers, who had not smoked any cigarettes within 12 months before entry.

Patients with stage IIIA and IIIB, who were not amenable to regional therapy according to decision by a tumour board including experienced surgeons, oncologists and radiologists, were also included. Patients had no previous malignant tumour history except cured cervical carcinoma *in situ*, basal cell carcinoma or superficial bladder cancer. They were previously untreated with chemotherapy such as gemcitabine, platinum and paclitaxel taxane. Patients, who have received chemotherapy for neoadjuvant or adjuvant treatment at least 12 months before the study treatment, were eligible.

Patients' blood test must meet the following requirements: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L and hemoglobin ≥ 90 g/L. Patients' clinical biochemistry examination must meet the following requirements: aspartate transaminase and alanine transaminase $\leq 2.5 \times$ upper limit of normal (ULN) without liver metastasis, aspartate transaminase and alanine transaminase $\leq 5 \times$ ULN with liver

metastases, serum creatinine ≤1.5 × ULN and total bilirubin ≤1.5 × ULN.

Patients were excluded from the study if they had brain metastasis, or any clinical laboratory findings gave reasonable suspicion of a disease or condition that contraindicates the use of any study medication or renders the subject at high risk from treatment.

2.2. Study design

This multicentre, 1:1 randomised, phase II study. The study evaluated the efficacy and safety of 135 mg/m^2 nab-paclitaxel on day 1 and 8 and followed by carboplatin area under the curve (AUC) 5 mg/mL/min (per Calvert formula) on day 1 every 3 weeks (group A) compared with 1250 mg/m^2 gemcitabine plus carboplatin at AUC 5 (group B) as first-line therapy in patients with advanced squamous cell lung carcinoma. Both groups receive up to six cycles of chemotherapy. History taking, physical examination, and haematological and biochemical testing were performed every 4 weeks, and radiologic investigations were performed every 6 weeks (Fig. 1).

The trial was done in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable local regulations. The study was approved by the ethics committees of all five centres, and all patients provided written informed consent form (ICF) before entry.

2.3. Efficacy and safety end-points

The primary objective was investigator-determined objective response rate (ORR), which was confirmed complete response (CR) and/or partial response (PR) rate. Spiral computed tomography scans were performed and evaluated per RECIST 1.1 [10] every 6 weeks from screening until progressive disease (PD) according to investigator assessment. The secondary objectives were PFS and OS. PFS was defined as the time from enrolment until the first radiographic documentation of objective progression or death from any cause. OS was defined as the time from enrolment to death from any cause.

All patients who received at least one dose of study drug (treated population) were evaluated for safety. The safety end-points were the incidence of treatment-related adverse events (TRAEs), graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) and serious adverse events (SAE).

2.4. Quality of life analysis

Patients' quality of life (QoL) and lung cancer–related symptoms were measured multidimensionally at randomisation and on day 1 of each cycle of subsequent chemotherapy by using self-report instruments Functional Assessment of Cancer Therapy–Lung (FACT-L), Lung Cancer Subscale (LCS) and Trial Outcome Index (TOI). Clinically relevant improvement of QoL was predefined as an improvement of six points or more in FACT-L and TOI scores or an improvement of two points or more in LCS scores, with the higher scores maintained for at least 21 days [11].

2.5. Statistical analysis

Inequality test using ratios of two independent proportions was used to calculate that 120 patients would give 80% power and a two-sided 5% significance level to detect a statistically significant difference of ORR with a calculated improvement in ORR from 19% for GC [12] to 40% for *nab*-PC [7].

The efficacy was assessed in the intent-to-treat population that included all randomly assigned patients. ORR was analysed by chi-square test. PFS and OS were evaluated by Kaplan–Meier method with a 95% confidence interval (CI), and the difference of survival between two arms was compared by using the log-rank test. OS was censored on the last known to be alive. We estimated hazard ratios and 95% CIs for *nab*-PC versus GC from stratified Cox proportional hazards models.

QoL scores in FACT-L, LCS and TOI were compared between two groups by using equally spaced repeated measures analysis of variance (ANOVA). Percentage of patients with QoL improvement in each group was compared by using Fisher's exact test and/or the Cocharan–Mantel–Haenszel test. *P* values of QoL odds ratios were calculated by using logistic regression.

Descriptive statistics were used to summarise the change from baseline to each visit on the CTCAE scale, assessed on day 1 of each cycle.

3. Results

3.1. Patients

A total of 127 patients were randomly assigned from Nov 29, 2010 through Jun 25, 2013, 62 to *nab*-PC and 65 to GC. Three patients withdrew without receiving study treatment after randomisation: one patient withdrew ICF (*nab*-PC), one patient withdrew due to delayed drug delivery (*nab*-PC) and one patient withdrew due to worsened performance status (PS) (GC). Five patients received at least one cycle of chemotherapy but did not undergo response evaluation; one patient withdrew due to nephritis after one cycle (*nab*-PC), one patient refused further chemotherapy after five cycles (GC), one patient underwent surgery due to pathological fracture after one cycle and refused

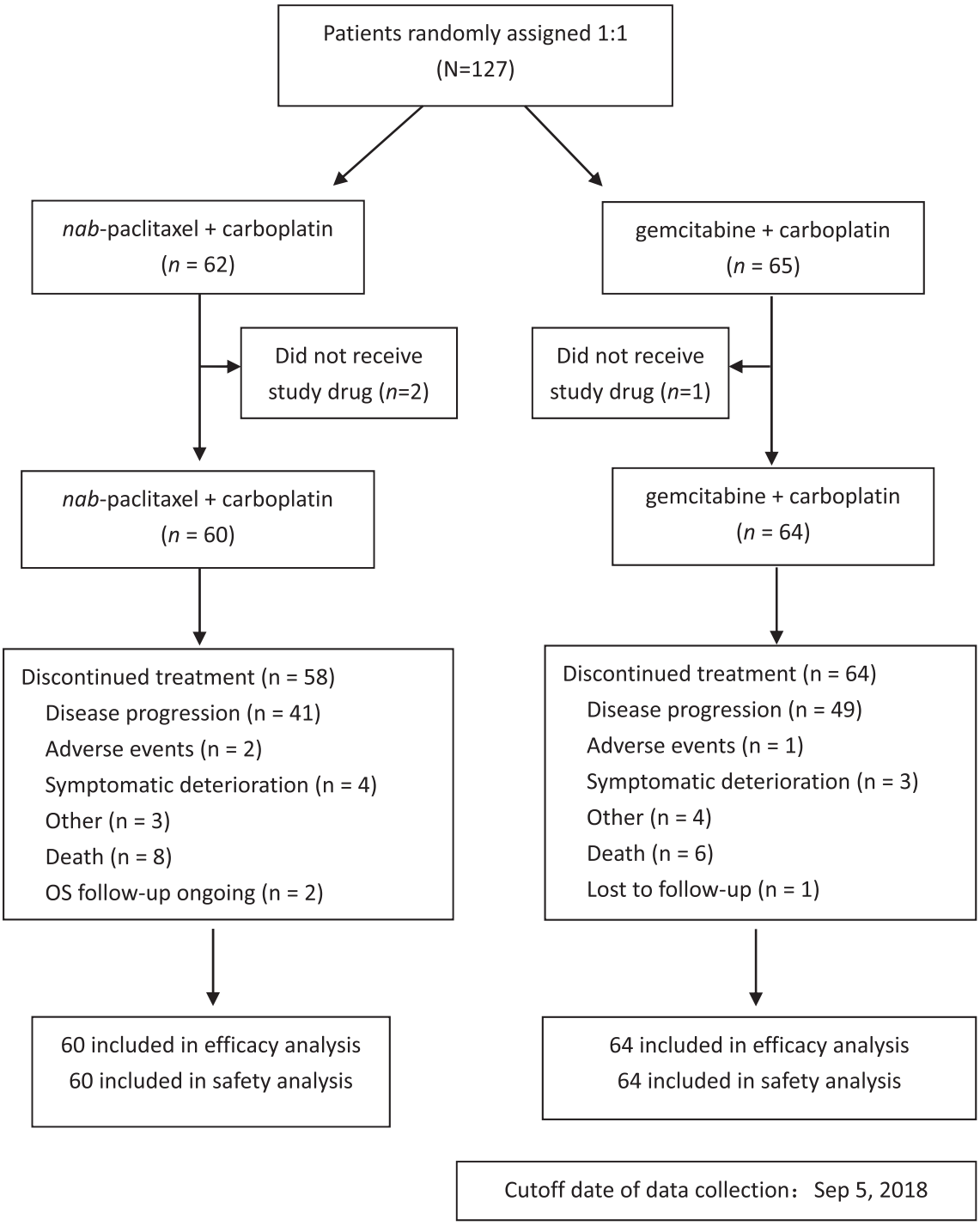

Fig. 1. Trial design. Chemotherapy for patients with NSCLC consisted of carboplatin (area under the concentration–time curve [AUC], 5), every 3 weeks for up to six cycles plus *nab*-paclitaxel (135 mg per square meter) on day1 and 8 each cycle or gemcitabine (1250 mg per square meter) on day 1 and 8 each cycle. NSCLC, non–small cell lung cancer.

further chemotherapy (GC), one patient withdrew for personal reason (GC) and one patient withdrew for SAE (*nab*-PC). Therefore, both safety and efficacy population comprised 124 patients (Fig. 1).

Patients' baseline characteristics were bell balanced between two groups (Table 1). Median age was 59 years, and 86% of patients were younger than 70 years. Patients comprised male (91%), smoker (83%) and stage IV disease (71%). No patient underwent prior systemic therapy except one, who was initially in early stage and relapsed to concurrent chemoradiotherapy after 5-years follow-up.

The median duration of follow-up was 14.5 months (0.2–94.6). At the time of data cutoff for the final

Table 1
Baseline patient demographic and clinical characteristics.

Characteristic	*nab*-PC (n = 60)	GC (n = 64)	All (n = 124)
	n (%)	n (%)	n (%)
Age, years			
Median	58	60	59
Range	41–79	39–76	39–79
< 70 years	51 (85)	55 (86)	106 (86)
≥ 70 years	9 (15)	9 (14)	18 (15)
Sex			
Male	56 (93)	57 (89)	113 (91)
Female	4 (7)	7 (11)	11 (9)
ECOG performance score			
0	17 (28)	16 (25)	33 (27)
1	43 (72)	48 (75)	91 (74)
Smoking status			
Non-smoker	9 (15)	12 (19)	21 (17)
Current smoker	51 (85)	52 (81)	103 (83)
Lung cancer family history			
No	57 (95)	62 (97)	119 (96)
Yes	3 (5)	2 (3)	5 (4)
Stage at random assignment			
IIIA	3 (5)	6 (9)	9 (7)
IIIB	16 (27)	11 (17)	27 (22)
IV	41 (68)	47 (73)	88 (71)

ECOG, Eastern Cooperative Oncology Group; *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin.

analysis on September 5, 2018, all but two patients had discontinued treatment. The common reasons for discontinuation were PD (73%) and adverse events (2%).

3.2. Efficacy results

On the basis of investigator-determined radiological assessment, ORR and disease control rate (DCR) for overall population were 34% and 63%, and *nab*-PC had higher ORR and DCR than GC without significant difference (Table 2). Median best percentage change from baseline in the sum of target lesions size was −28% (−78% to +33%) in *nab*-PC and −28% (−82% to +38%) in GC (Fig. 2).

Table 2
Response rates for the intent-to-treat population.

RR	*nab*-PC		GC		RR ratio*	*P***
	n (%)	95% CI	n (%)	95% CI	95% CI	
PR	25 (42)		17 (27)			
SD	17 (28)		19 (30)			
PD	13 (22)		19 (30)			
NE	5 (8)		9 (14)			
ORR	25 (42)	29.5–54.5	17 (27)	16.1–37.9	0.51 (0.24–1.08)	0.076
DCR	42 (70)	58.4–81.6	36 (56)	44.1–68.5	0.55 (0.26–1.16)	0.113

RR, response rate; *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin. PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; CI, confidence interval.
*95% CIs for RR ratios are calculated according to the asymptotic 95% CI of the relative risk of *nab*-PC to GC.
**P value are based on the Chi-square test.

3.3. Survival

Of 124 patients for efficacy analysis, 110 (89%) achieved PD or died. PFS had no difference between *nab*-PC and GC with 26% increase of PFS in *nab*-PC versus in GC (Fig. 3A). No difference of OS was found between two groups, although there was a 2.8 month decrease of OS in *nab*-PC versus in GC (Fig. 3B).

3.4. Safety results

The most common haematologic grade ≥3 TRAEs with *nab*-PC and GC were neutropenia (70% and 42%), leukopenia (42% and 17%), thrombocytopenia (35% and 44%) and anaemia (22% and 27%). The most common non-haematologic grade ≥3 TRAEs (all < 5%) were hyponatremia, hemoptysis, hypoalbuminemia, cerebral infarction, hypopotassaemia, liver injury, lymphopenia, proteinuria, nausea, fatigue and anorexia (Table 3). Sensory neuropathy (grade ≤ 2) occurred in 10% of *nab*-PC and in 2% of GC. No treatment-related death was documented.

Overall, 40% in *nab*-PC and 53% in GC experienced dose reduction ($P > 0.05$). More dose reduction occurred in GC (27%) than in *nab*-PC (12%) after cycle 2 ($P < 0.05$). Dose reduction had no difference between *nab*-PC and GC after cycle 1 (1.7% versus 4.7%, $P = 0.62$), cycle 3 (13.3% and 17.2%, $P = 0.55$), cycle 4 (18.3% and 20.3, $P = 0.78$) and cycle 5 (18.3% and 7.8%, $P > 0.08$). Reasons for dose reduction in *nab*-PC and GC were thrombocytopenia (71% and 94%), neutropenia (54% and 32%), weight loss (16.7% and 0) and fever (8% and 0). Notably, three (13%) patients in *nab*-PC had dose increase after cycle 2, cycle 3 and cycle 5 because of gaining weight. Dose delay had no difference between two arms (88% and 97%).

3.5. QoL analysis

One hundred and nineteen (96.0%) patients (57 in *nab*-PC; 62 in GC) completed QoL questionnaires at randomisation, and questionnaires were also collected on day 1 of each subsequent chemotherapy. QoL scores measured by FACT-L, LCS and TOI had no difference between *nab*-PC and GC at baseline ($P > 0.05$). QoL scores at each time point after chemotherapy were comparted with baseline by using ANOVA to investigate QoL improvement. QoL improvement measured by FACT-L and LCS had no difference between *nab*-PC and GC. Improvement of TOI score in *nab*-PC was significantly higher than in GC (Table 4).

Percentage of patients with clinically relevant improvement of QoL in FACT-L and LCS had no

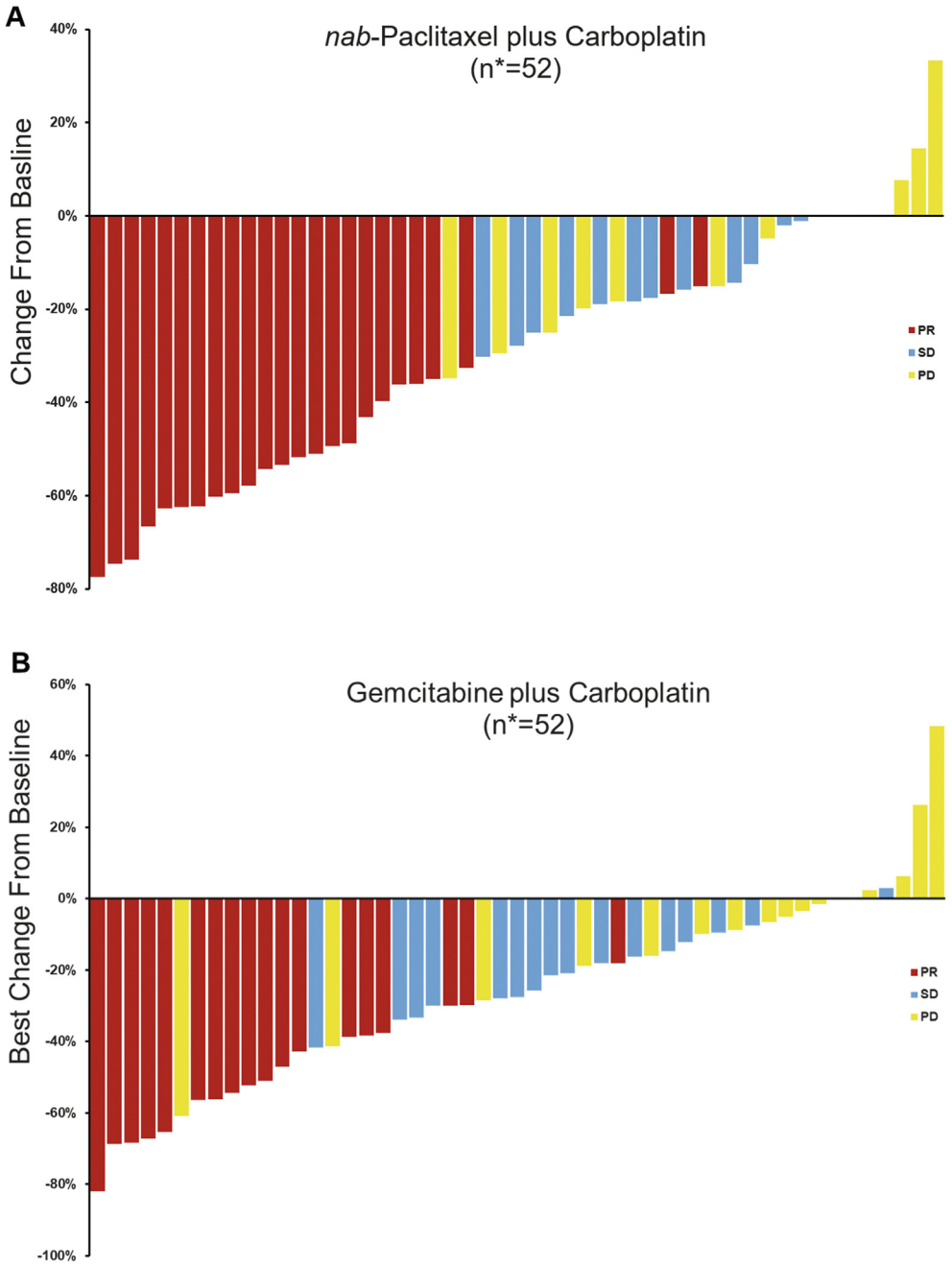

Fig. 2. Best percentage change from baseline in target lesion size for (A) *nab*-paclitaxel/carboplatin and (B) gemcitabine/carboplatin. Colours indicate patients' best overall responses per the Response Evaluation Criteria in Solid Tumour version 1.1 (RECIST 1.1) by investigator radiology review. Asterisks indicate that among the intention-to-treat population; data are shown only for patients whose tumour response was classified as partial response (PR), stable disease (SD) or progressive disease (PD); patients with no evaluable target lesion assessments are not shown. PR and SD were confirmed according to RECIST 1.1 regulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

difference between *nab*-PC and GC ($P > 0.05$), but in TOI, it was higher in *nab*-PC than in GC ($P < 0.05$) (Fig. 4).

3.6. Subsequent treatment

For all 124 patients in *nab*-PC and GC groups, there was no difference of distribution of subsequent treatment, which included 16.9% chemotherapy (8.3% versus 25.0%), 4.8% targeted therapy (3.3% versus 6.3%), 4.0% combination of chemotherapy and targeted therapy (5.0% versus 3.1%), 1.6% combination chemotherapy with local therapy (1.7% versus 1.6%), 1.6% combination chemotherapy and targeted therapy with local therapy (1.7% versus 1.6%) and 71.0% local therapy, Traditional Chinese Medicine or best support care (80.0% versus 62.5%).

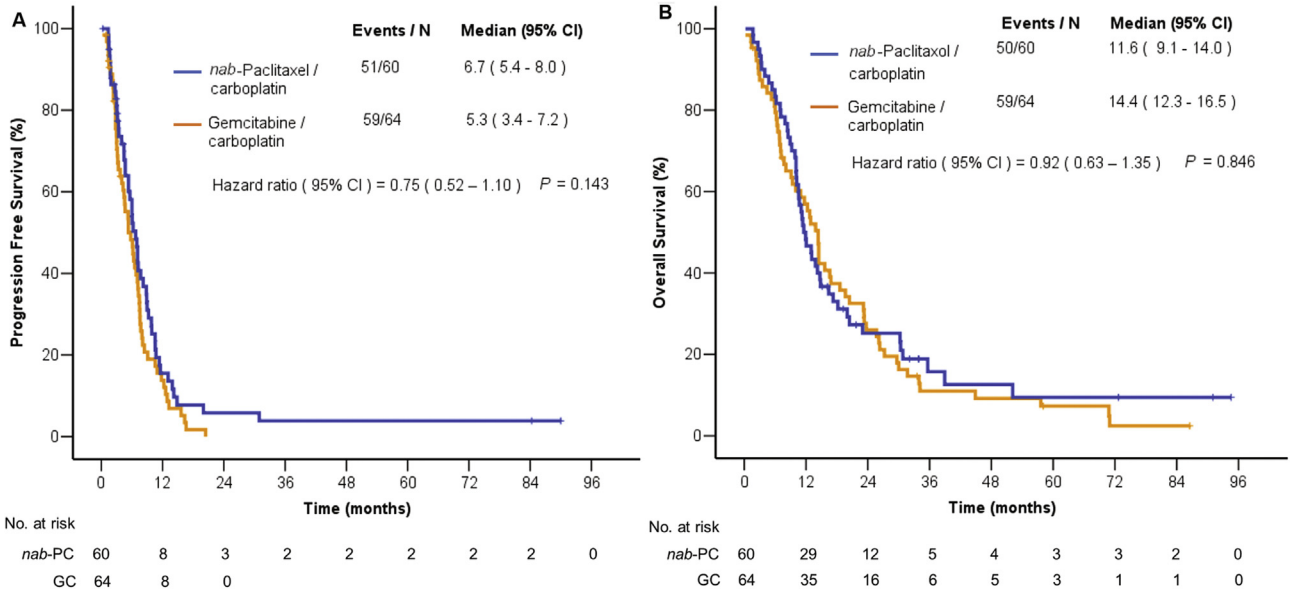

Fig. 3. Kaplan-Meier estimates of progression-free and overall survival (A) progression-free survival and (B) overall survival in the population. *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin; CI, confidence interval.

Table 3
Most common grade 3 or 4 TRAEs.

Adverse events	*nab*-PC n (%)	GC n (%)
Haematologic AEs		
Neutropenia	42 (70)	27 (42)
Thrombocytopenia	21 (35)	28 (44)
Anaemia	13 (22)	17 (27)
Non-haematologic AEs		
Hyponatremia	2 (3)	0 (0)
Hemoptysis	1 (2)	1 (2)
Hypoalbuminemia	1 (2)	1 (2)
Cerebral infarction	1 (2)	1 (2)
Hypopotassaemia	1 (2)	0 (0)
Liver injury	1 (2)	0 (0)
Lymphopenia	1 (2)	0 (0)
Proteinuria	1 (2)	0 (0)
Nausea	0 (0)	2 (3)
Fatigue	0 (0)	1 (2)
Anorexia	0 (0)	1 (2)

TRAE, treatment-related adverse events; *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin; AE, adverse event.

4. Discussion

To our knowledge, this is the first study to compare first-line *nab*-PC and GC regimens in advanced squamous cell lung carcinoma, and both of them showed anti-tumour activity. As previously reported, weekly *nab*-PC to had improvement in ORR compared with sb-PC (41% versus 24%, $P < 0.001$) in advanced squamous cell lung carcinoma [7]. N*ab*-PC had improvement in ORR compared with GC regimen in our study with no statistical significance reached. As reported in previous [7] and current study, the improvement of ORR was not translated into benefit of PFS or OS compared with other standard chemotherapy. However, 26% improvement for PFS in *nab*-PC is still intriguing for advanced squamous cell lung carcinoma since therapeutic options are limited. It is reasonable to extend sample size and carry out further study.

Table 4
QoL scores in *nab*-PC and GC (mean ± SD).

Time point	N	*Nab*-PC			n	GC		
		FACT-L*	LCS**	TOI***		FACT-L*	LCS**	TOI***
Baseline	57	89.7 ± 17.0	13.2 ± 4.2	53.1 ± 11.1	62	93.3 ± 10.0	13.4 ± 3.5	55.7 ± 7.8
Cycle 2	51	97.4 ± 11.3	16.0 ± 3.6	58.9 ± 7.7	52	95.9 ± 8.4	15.3 ± 1.5	55.0 ± 5.8
Cycle 3	46	95.7 ± 15.7	16.0 ± 4.0	60.4 ± 9.9	43	94.8 ± 12.5	15.1 ± 2.2	54.3 ± 9.1
Cycle 4	42	98.8 ± 11.2	16.9 ± 4.3	63.9 ± 7.5	32	94.4 ± 10.5	15.8 ± 2.0	54.7 ± 9.5
Cycle 5	31	97.1 ± 13.8	16.6 ± 3.7	61.2 ± 9.3	22	93.0 ± 13.4	15.5 ± 2.6	52.9 ± 9.4
Cycle 6	27	93.7 ± 13.0	16.0 ± 3.9	57.7 ± 10.2	16	95.1 ± 14.8	15.1 ± 2.0	53.1 ± 8.9

QoL improvement in FACT-L and LCS had no differences between nab-PC and GC (*, $P = 0.70$; **, $P = 0.30$). QoL improvement measured by TOI was higher in *nab*-PC than in GC (***, $P = 0.039$).
QoL, quality of life; *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin; SD, standard deviation; FACT-L, functional assessment of cancer therapy–lung; LCS, lung cancer subscale; TOI, trial outcome index.

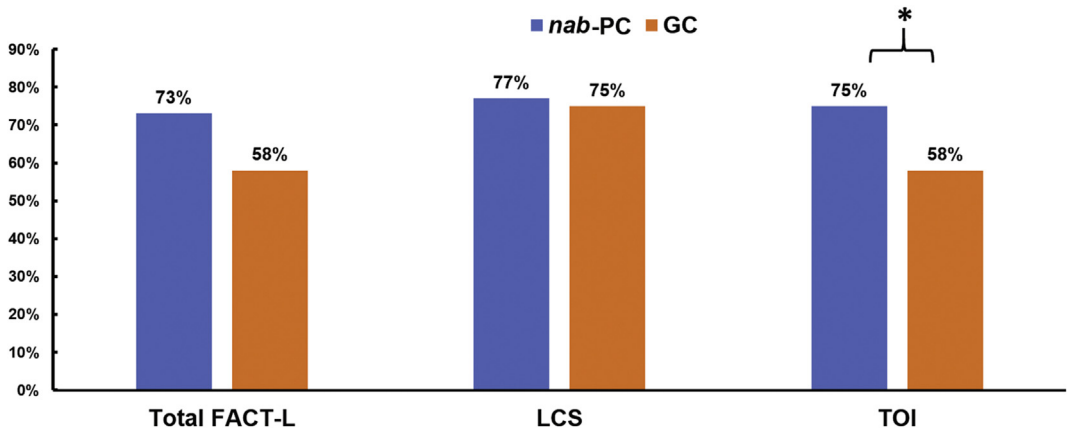

Fig. 4. Percentage of patients with clinical improvement of QoL. *Percentage of patients with QoL improvement in *nab*-PC was significantly higher than in GC under the measurement of TOI. No difference of QoL was found measured by FACT-L (73% versus 58%; OR, 0.52; 95%CI, 0.24–1.11; $P = 0.087$), LCS (77% versus 75%; OR, 0.91; 95%CI, 0.40–2.08; $P = 0.829$) and TOI (75% versus 58%; OR, 0.46; 95%CI, 0.21–0.98; $P = 0.043$) between two arms. *nab*-PC, 130-nm albumin-bound paclitaxel plus carboplatin; GC, gemcitabine plus carboplatin; QoL, quality of life; FACT-L, functional assessment of cancer therapy–lung; LCS, lung cancer subscale; TOI, trial outcome index; OR, odds ratio; CI, confidence interval.

Both *nab*-PC and GC regimens were well tolerated, with more neutropenia in *nab*-PC and more thrombocytopenia in GC. No difference of overall dose reduction between two arms was documented. Although more dose reduction occurred after cycle 2 in GC group, it did not impact the its effectiveness.

Since QoL improvement score and percentage of QoL improvement in TOI were significantly higher in *nab*-PC than in GC (both $P < 0.05$), nab-PC had significant improvement in TOI quantitatively and qualitatively compared with GC. TOI is derived by adding scores on the physical well-being and functional well-being subscales to the LCS [13]; *nab*-PC was therefore demonstrated to have advantage in improving physical functioning.

This trial excluded patients with brain metastases. It is known that patients with squamous cell lung carcinoma have low incidence of brain metastases [14,15], and patients with brain metastases usually have very poor prognosis. Making balance between two arms will be difficult if including patients with metastases in such small sample size trial with no stratification.

It is worth mentioning that there was a striking male predominance in both cohorts. This is resulted from the prevalence of squamous cell lung carcinoma in male population. Although the gender was well-balanced between two groups, we should be cautious when generalising our findings, which actually focused on male patients.

The combination of immunotherapy and chemotherapy will be standard therapy in the near future [2–4], and the choice of chemotherapy remains to be investigated. We believe that both *nab*-PC and GC regimens are suitable for combinatorial therapy. Actually, the efficacy of combination of *nab*-PC and immunotherapy such as pembrolizumab, atezolizumab and nivolumab in NSCLC had been demonstrated [2–4]. Pembrolizumab was also safely combined with gemcitabine or gemcitabine + *nab*-PC [16]. However, *nab*-PC has advantage over GC because of its QoL improvement.

The combination of *nab*-paclitaxel and gemcitabine approved to have antitumour synergy [17]. The interim analysis of an ongoing phase II trial, which designed for first-line combination of *nab*-paclitaxel and gemcitabine in patients with advanced squamous cell lung cancers, demonstrated promising efficacy (ORR 71% in dose-attenuated cohort) with favourable toxicity [18]. It is imaginable that clinical benefits of this combinatorial therapy might improve with the addition of platinum in future trial.

The limitation of this study is small sample size because of phase II design. The negative response results cannot affect the clinical decision-making and can only act as the reference for future study. The translation of ORR improvement in *nab*-PC into benefit of PFS or OS requires more patients in future study. It is still a question that if cisplatin is superior to carboplatin combined with third-generation of chemotherapy agents in advanced NSCLC [19].

5. Conclusion

This trial demonstrated that RR in *nab*-PC is higher in number but not significant in statistics than GC in patients with advanced squamous cell lung carcinoma. Non-significant improvement of PFS or OS was observed in *nab*-PC compared with GC. N*ab*-PCM has advantage over GC in QoL improvement.

Conflict of interest statement

None declared.

Funding

This work was supported by Celgene Corporation, Special Fund of Public Interest by National Health and Family Control Committee (Grant No. 201402031) and Key Lab System Project of Guangdong Science and Technology Department—Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2012A061400006/2017B030314120). Celgene Corporation was not involved in study design, the interpretation of data, the writing of the report or the decision of publication.

Acknowledgements

The authors owe thanks to all patients and their families, as well as the investigators, research nurses, study coordinators and site staff. All authors take full responsibility for this publication.

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