Impact of Nab-Paclitaxel Based Second-Line Chemotherapy in Metastatic Pancreatic Cancer

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Abstract..

Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with median survival of 20% at 1 year. We conducted a retrospective study to assess the efficacy and tolerability of nab-paclitaxel (NP)-based second-line chemotherapy in metastatic PDAC. Patients and Methods: Indiana University Simon Cancer Center pancreatic cancer program was used to identify patients with metastatic PDAC who received any second-line chemotherapy. Demographic, clinical and outcomes data were collected by manual chart abstraction. Patients were divided into two groups: a NP-based treatment group and a non- NP-based treatment group. Overall (OS) and progression-free (PFS) survival were estimated using Kaplan–Meier method. Cox proportional hazards regression was used for multivariate analyses. Results: A total of 120 patients received second-line chemotherapy. There were 47(39%) patients in the NP group and 73 (61%) in the non-NP group. As compared to the non-NP group, the NP group showed improved median PFS [2.8 *vs.* 2.1 months; hazard ratio (HR) = 0.62, 95% confidence interval (CI) = 0.38-1.02; *p*=0.06] and median OS (7.5 *vs.* 4.7 months; HR = 0.67, 95% CI = 0.45-1.00; *p*=0.05). Multivariate analyses adjusted for age showed a significantly improved PFS (adjusted HR = 0.60, 95% CI = 0.36-0.98; *p*=0.04) and a suggestion of improved OS (adjusted HR = 0.67, 95% CI = 0.44-1.01, *p*=0.05) in the NP group as compared to non-NP group. Serious adverse events were seen in 13.3% of patients in the non- NP group and 17.1% patients in the NP group. Conclusion: In a single-institution retrospective cohort study, we report a significant improvement in the PFS and suggestion of improvement in the OS with NP-based second-line chemotherapy with an acceptable toxicity rate.

Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer and is the fourth leading cause of cancer-related mortality in the United States (US) (1). In 2017 alone, 53,670 cases of PDAC are expected, resulting in approximately 43,090 deaths in the US (2). The median overall survival (OS) of patients with PDAC is 20% at 1 year and 8% at 5 years (3). Despite recent progress, there is a clear need to improve systemic treatments for PDAC. Recently, nab-paclitaxel (NP) in combination with gemcitabine was shown to lead to a clinically meaningful and significant improvement in the median OS and median progression-free survival (PFS) when compared with gemcitabine alone (4). This has led to the approval of gemcitabine as a first-line treatment for PDAC similar to FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin), the only other first-line treatment for patients with metastatic PDAC (5).

In clinical practice, many patients may receive FOLFIRINOX as first-line treatment and gemcitabine as the second-line treatment especially in the US (6). Many factors influence the decision to select between FOLFIRINOX and gemcitabine including age, performance status, associated comorbidities and potential toxicity (7). FOLFIRINOX is often chosen for patients with good performance status, age $\leq$75 years and lack of or controlled comorbidities (7, 8). Usually in this scenario, gemcitabine is the preferred second-line treatment after progression on FOLFIRINOX in the absence of prospective data. Alternatively, 5-fluorouracil based second-line therapy in combination with nanoparticle liposomal irinotecan (9) or oxaliplatin (10, 11) has shown overall survival (OS) benefit in second-line treatment. Interestingly, up to 50% of patients with PDAC may be eligible for second-line chemotherapy (12, 13).

There are no randomized data for the effectiveness of gemcitabine in the second-line treatment of PDAC. However, survival benefit with acceptable toxicity has been reported by several groups with gemcitabine in patients previously treated with FOLFIRINOX (14, 15). Notably, these are single-institution case series with small numbers of patients, resulting in selection bias. Additionally, there was no comparison group in these studies, which leads to poor internal validity (ability to draw causal conclusion between the exposure and outcome). Therefore, we conducted a retrospective cohort study with the primary aims of assessing: i) the efficacy of NP-based (as compared to non-NP-based) second-line treatment in PDAC; ii) assess the toxicity of NP-based (as compared to non-nab-paclitaxel based) second-line treatment in PDAC; and iii) reviewing the existing literature for the efficacy and toxicity of NP-based second-line chemotherapy in PDAC.

Patients and Methods

Study population. The Indiana University Simon Cancer Center (IUSCC) pancreatic cancer program was used to identify the patients with biopsy-proven diagnosis of PDAC between the years 2009-2015. Retrospective as well as prospective data collection was carried out on patients with PDAC who were new to IUSCC. Main inclusion criteria of the study were age >18 years, diagnosis of PDAC, receipt of second-line chemotherapy treatment and available demographic, clinical and outcomes data. Patients with diagnosis of neuroendocrine pancreatic cancer were excluded. The study was approved by the Institutional Review Board of Indiana University (IRB approval number 1409274071).

Data collection. Patients were divided into two groups, NP-based treatment group and non-NP-based treatment group. Manual chart abstraction was used in addition to IUSCC cancer registry to gather the demographic, clinical and outcomes data. Both paper and electronic medical records were reviewed to obtain patient's demographic (age, sex, race, family history of malignancy, history of diabetes, tobacco use, alcohol use, body mass index), clinical [comorbidities, histology of the tumor, carbohydrate antigen (CA-19-9) and bilirubin levels at presentation, location of the tumor, Eastern Cooperative Oncology Group performance status, number of metastatic sites, adjuvant chemotherapy, pathological staging (American Joint Committee on Cancer) of the tumor and whether the patient had undergone surgery or radiation therapy) and outcomes (best response, serious toxicity, OS and PFS) data. Data was collected and stored in OnCore® database (Forte Research Systems, Madison, Wisconsin, USA).

Statistical analyses. Baseline characteristics between the groups that received second-line NP-based *versus* non-NP-based treatment were compared using chi-square test for categorical variables and Student *t*-test for continuous variables.

Response evaluation and toxicity assessment. Response was categorized based on the best response documented by the treating physician and radiology report as partial response, complete response, stable disease or progressive disease. Note that the radiological scan interval was based on clinical care. Similarly, toxicity was assessed by retrospective chart review and considered serious (grade 3 or 4) if the adverse effect resulted in dose reduction, dose delay or holding off of scheduled

treatment. Individual toxicity assessment (type and grade) was not attempted due to the likelihood of incomplete data.

Survival and prognostic effect analyses. OS and PFS were estimated using the Kaplan–Meier method. OS was defined as the time from start of second-line treatment to death from any cause, whereas PFS was defined as the time from start of second-line treatment to either progression of PDAC or death from any cause. Survival was compared between the two groups using log-rank test. Censoring method was adopted for patients who were lost to follow-up or died. Cox proportional hazard regression model was used to estimate the simple and adjusted hazard ratios (HR) and 95% confidence interval (95% CI), adjusting for significant variables between the two groups. *p*-Values for differences were considered significant if 0.05 or less. All statistical analyses were performed using RStudio version 1.0.143 (16).

Results

Study participants. Between 2009-2015, a total of 120 patients with PDAC were treated with second-line chemotherapy, of which 47 (39%) were in the NP group and 73 (61%) patients were in the non-NP group. The univariate analyses showed that the patients in the NP group were significantly younger as compared to the non-NP treatment group (median age = 60.4 *vs.* 64 years respectively, *p*=0.02). Similarly, a lower percentage of patients in the NP group had diabetes mellitus at presentation as compared to the non-NP treatment group (26% *vs.* 49% respectively, *p*=0.10). However, none of the other demographic or clinical characteristics were significantly different between the two groups (Table I).

In the NP group, most patients received FOLFIRINOX in first-line chemotherapy (72%) and gemcitabine in the second-line setting (77%) (Table II). However, in the non-NP group, the most common first-line chemotherapy was gemcitabine (44%) and 5-FU or capecitabine based chemotherapy was the used in second-line treatment (54%).

Response evaluation and toxicity assessment. There were no complete responses. A total of eight patients had partial response, three (4.7%) in the non-NP group and five (11.5%) in the NP group, respectively. Seventeen and 11 patients had stable disease in the non-NP and NP groups resulting in a disease control rate (DCR) of 31.2% in the non-NP and 36.3% in the NP group. Overall serious adverse events were observed in 13.3% of patients of the non-NP group and 17.1% of patients in the NP group.

Survival analyses. The PFS analysis included 104 patients, 42 in the NP group and 62 in the non-NP group. The median PFS was marginally improved in the NP group as compared to the non-NP group (2.8 *vs.* 2.1 months; HR = 0.62; 95% CI=0.38-1.02; *p*=0.06). Multivariate analysis adjusted for age showed significantly improved PFS in the NP group as compared to the non-NP group (adjusted HR = 0.60, 95% CI = 0.36-0.98, *p*=0.04).

The OS analysis included 104 patients, 47 in the NP group and 73 in the non-NP group. The median OS was significantly better in the NP group as compared to the non-NP group (7.5 *vs.* 4.7 months; HR = 0.67; 95% CI = 0.45-1.00; *p*=0.05). Multivariate analysis adjusted for age showed a suggestion of improved OS in the

NP group as compared to the non-NP group (adjusted HR = 0.67, 95% CI = 0.44-1.01, *p*=0.05).

Discussion

In this single-institution retrospective cohort study of 120 patients with metastatic, locally advanced or recurrent PDAC, we report a significant improvement in the PFS and suggestion of improvement in the OS with NP-based chemotherapy as compared with non-NP-based chemotherapy in the second-line treatment of PDAC. Our study is unique as we compared NP-based chemotherapy to non-NP based chemotherapy (mainly 5-FU-based) in the second-line treatment of PDAC. To our knowledge, this comparison has not been reported in any other study. Additionally, our study is the largest study examining the effect of NP-based second-line chemotherapy for PDAC in the existing literature.

In the past decade, significant progress has been made in the systemic therapy of PDAC, however, there is no current standard for the second-line treatment of PDAC. Recently, nanoliposomal irinotecan with fluorouracil and folinic acid was shown to confer a survival advantage over fluorouracil and folinic acid in patients with PDAC previously treated with gemcitabine-based therapy in a phase III, randomized controlled trial (NAPOLI-1) (9). This trial provides level 1 evidence for the use of nanoliposomal irinotecan with fluorouracil and folinic acid in patients treated with gemcitabine based chemotherapy in the first-line setting (9). However, in patients treated with first-line FOLFIRINOX, NP (in combination with gemcitabine) might be a better option as is suggested by our data and that of others (14, 15, 17-19).

Several case series from different countries (Table III) have reported their experience with second-line NP and gemcitabine therapy. Although 5-fluorouracil-based chemotherapy has been studied in second-line (9-11) (Table IV), there are no randomized trials of NP-based second-line chemotherapy. Therefore, we take the opportunity to summarize the existing studies of NP-based chemotherapy in the second-line treatment of PDAC and contrast our findings with the existing literature. The summarized data argues for a randomized trial to evaluate the sequence of the two best existing options of chemotherapy (FOLFIRINOX and gemcitabine) in the treatment of PDAC to standardize first- and second-line treatment in patients who are otherwise eligible for either therapy.

We conducted a thorough English literature search on PubMed and Google Scholar using the search terms ‘pancreatic cancer’, ‘pancreatic adenocarcinoma’ or ‘PDAC’, and ‘second-line NP’, ‘second-line Abraxane’ or ‘second-line chemotherapy’ until May 2017. We found a total of eight studies (Table III) reporting the experience with second-line NP in patients who were initially treated with FOLFIRINOX. Most of these studies are retrospective case series, except for the study by Portal and colleagues (14), in which they prospectively enrolled 57 patients to receive NP and gemcitabine after progressing on FOLFIRINOX (Table III).

Our efficacy and toxicity results are similar to those reported in these case series. For instance, the objective response rate in the NP group of our case series was 11.5% and the DCR was 36.3%, which is in line with the reported ranges of 7.1-30% and 24-80%, respectively. Similarly, the median PFS (2.8 months) and the median OS (7.5 months) in our study (NP group) was consistent with the reported median PFS (range = 2.5-5.1 months) and OS (range = 5-17 months), respectively.

Second-line NP-based chemotherapy has been generally well-tolerated, with some studies reporting up to 25% serious (grade 3/4) adverse event rate (18). The serious adverse events usually included neutropenia (up to 20%), anemia (in up to 25%), thrombocytopenia (in up to 25%), neurotoxicity (in up to 13%) and asthenia (in up to 9%). We had an overall serious adverse event rate of 17%, again consistent with existing literature. Notably, the adverse event rate was greater in the NP group as compared to the non-NP group (17.1% *vs.* 13.3%). Individual toxicity assessment could not be carried out in our case series due to lack of availability of such data.

Our study has some limitations. Firstly, response evaluation was performed using the best response categorized by the treating physician, therefore, this may not be as accurate as using Response Evaluation Criteria In Solid Tumors (20). However, our results are similar to those reported in other series and we have provided robust data for OS to complement the efficacy assessment. Secondly, we were unable to provide grading for serious adverse events as per Common Terminology Criteria for Adverse Events (21). mainly because this data was not available for all our patients. However, available prospective data suggest that NP (combined with gemcitabine) is well-tolerated in the second-line treatment of PDAC. Thirdly, our study is a retrospective comparison with inherent limitations such as confounding and possibly selection bias. However, we have tried to account for confounding by carrying out multivariate analysis. Similarly, selection bias was minimized by including all patients who received second-line chemotherapy in our cohort.

Conclusion

From a single-institution retrospective cohort study, we report that NP-based chemotherapy (in combination with gemcitabine) can extend PFS and possibly OS, with an acceptable toxicity rate. Our study is unique due to its large sample size, study design and presence of a comparison group. These results are hypothesis-generating and will help clinicians to counsel patients regarding the prognosis with NP-based and non-NP-based therapy in the second-line treatment of PDAC. Our results (and others) argue for a randomized trial to evaluate the best sequence of FOLFIRINOX and gemcitabine in patients who are eligible for both chemotherapies.

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Table I. Baseline characteristics of patients in nab-paclitaxel- and non-nab-paclitaxel-treated groups.

Variable	Nab-paclitaxel group (N=47)	Non-nab-paclitaxel group (N=73)	*p*-Value
Median age, (range), years	60.4 (37-75)	64 (37-89)	0.02
Median CA19-9 (range), U/ml	679 (1-88365)	211 (1-112840)	0.30
Gender, n (%)			
Male	29 (24)	41 (34)	0.60
Female	18 (15)	32 (27)	
Race, n (%)			
White	41 (34)	64 (53)	>0.999
Other	6 (5)	9 (8)	
Family history of any cancer, n (%)	43 (37)	22 (19)	0.40
ECOG performance status, n (%)			
0	8 (17)	8 (17)	0.64
1	19 (40)	10 (21)	
2	2 (4)	1 (2)	
History of diabetes mellitus, n (%)	31 (26)	59 (49)	0.10
Location of primary tumor, n (%)			
Head	28 (23)	47 (39)	0.66
Body	8 (7)	14 (12)	
Tail	11 (9)	12 (10)	
Tobacco use, n (%)	26 (22)	36 (31)	0.72
Alcohol use, n (%)	31 (27)	38 (33)	0.22
BMI, n (%)			
≤24.9 kg/m^2	23 (19)	46 (39)	0.21
24.9-29.9 kg/m^2	18(15)	17 (14)	
≥30 kg/m^2	6 (5)	9 (8)	
Jaundice at presentation, n (%)	21 (18)	31 (26)	0.96
Surgery, n (%)	25 (21)	41 (34)	0.89
Adjuvant gemcitabine, n (%)	21 (18)	29 (24)	0.73

CA19-9: Cancer antigen 19-9; ECOG: Eastern Cooperative Oncology Group; BMI: Body mass index.

Table II. Details of the first- and second-line chemotherapies in nab-paclitaxel- and non-nab-paclitaxel-treated groups.

Chemotherapy regimen	Nab-paclitaxel group (N=47), N (%)		Non-nab-paclitaxel group (N=73), N (%)	
	First-line	Second-line	First-line	Second-line
FOLFIRINOX	34 (72)	0	15 (21)	6 (8)
FOLFOX/XELOX	7 (15)	0	6 (8)	17 (23)
FOLFIRI	1 (2)	0	0	5 (6.8)
Gemcitabine and nab-paclitaxel	2 (4)	40 (85)	32 (44)	0
Gemcitabine	2 (4)	0	7 (9)	17 (23)
Gemcitabine combinations[a]	0	0	6 (8)	9 (12)
5-Fluorouracil/ capecitabine	1 (2)	0	5 (7)	12 (16)
Other	0	7[b] (15)	2[c] (3)	7[d] (9)

FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; FOLFOX/XELOX: 5-fluorouracil, leucovorin and oxaliplatin/capecitabine and oxaliplatin; FOLFIRI: 5-fluorouracil, leucovorin and irinotecan. [a]Gemcitabine combinations included erlotinib, capecitabine, oxaliplatin or docetaxel combined with gemcitabine. [b]Included nab-paclitaxel alone (N=6) and nab-paclitaxel combined with pembrolizumab (N=1). [c]Included erlotinib and oxaliplatin (N=1), and cyber knife therapy (N=1). [d]Included erlotinib (N=1), irinotecan (N=1), cisplatin and capecitabine (N=1) and phase I clinical trials [enoticumab (REGN421), idelalisib, sacituzumab govitecan (IMMU-132) or AZD6244 hydrogen sulfate; N=4].

Table III. Case series of patients receiving gemcitabine plus nab-paclitaxel after FOLFIRINOX for metastatic pancreatic adenocarcinoma. None of these studies had a control or comparison group.

Study (Ref)	Country	Year	N	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)	Grade 3 or 4 toxicity
Salem *et al.* (abstract only) (22)	United States	2014	12	8	24	3.3	16.2	Fatigue (all grades) 54% and thrombocytopenia (all grades) 38%
Zhang *et al.* (15)	United States	2015	28	17.9	46.5	3	5.3	Neutropenia 17.9%, anemia 25.0%, thrombocytopenia 25%
Portal *et al.* (14)	France	2015	57	17.5	58	5.1	8.8	Neutropenia 12.5%, neurotoxicity 12.5%, asthenia 9%, thrombocytopenia 6.5%
Bertocchi *et al.* (18)	Italy	2015	23	17.4	43.5	2.7	5	Total 13%, thrombocytopenia 17.4%, neutropenia 8.7%, anemia 8.7% and neuropathy 13%
Vogl *et al.* (abstract only) (23)	Austria	2015	33	NR	NR	3	6.3	Neutropenia 13%, thrombocytopenia17%, polyneuropathy 7%
Caparello *et al.* (17)	Italy	2016	71	7.1	34.2	2.5	6.2	NR
Suzuki *et al.* (abstract only) (24)	Japan	2016	5	0	80	4.6	17	Neutropenia 20%
El Rassy *et al.* (19)	Lebanon	2017	12	30	60	4.9	NR	No grade 3/4 toxicity
Present study	United States	2017	120: NP: 47 *vs.* non-NP: 73	11.5 *vs.* 4.7	36.3 *vs.* 31.2	2.8 *vs.* 2.1*	7.5 *vs.* 4.7†	Total 17.1% *vs.* 13.3%

ORR, Objective response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival; NR, not reported. *Adjusted hazard ratio (95% confidence interval) = 0.60, (0.36-0.98), p=0.04; †adjusted hazard ratio (95% confidence interval) = 0.67 (0.44-1.01), p=0.05.

Table IV: Summary of phase III, randomized, controlled, studies in the second-line treatment of pancreatic ductal adenocarcinoma.

Study	Country	Year	Arms	N	ORR (%)	DCR (%)	Median PFS				Median OS				Grade
							Months	HR	CI	P	Months	HR	95% CI	P	
Pelzer et al CONKO-01 (11) *Terminated early	Germany, multicenter	2011	OFF *vs.* BSC	46	No responses	NR	NR	NR	NR	NR	4.8 *vs.* 2.3	0.45	0.24-0.83	0.008	None
Oettle et al CONKO-003 (10)	Germany, multicenter	2014	OFF *vs.* FF	168	- *1 patient in FF had CR	-	2.9 *vs.* 2.0	0.68	0.5-0.94	0.01	5.9 *vs.* 3.3	0.66	0.48 to 0.91	0.01	Anem Throm 1.3% Neuro
Wang-Gillam *et al.* NAPOLI-1 (9)	Global, multicenter	2016	Nal-iri + 5-FU + LLV *vs.* 5-FU + LLV	117 *vs.* 119	16 *vs.* 1	NR	2.3 *vs.* 1.4	0.68	0.45 to 0.78	0.0002	6.1 *vs.* 4.2	0·67	0·49–0·92	0·012	Nal-iri Neutr fatigu 13%, Anem 8%
			Nal-iri *vs.* 5-FU + LLV	151 *vs.* 149	6 *vs.* 1	NR	1.7 *vs.* 1.4	0.82	0.65-1.03	0.1	4.9 *vs.* 4.2	0·99	0·77–1·28	0·94	Nal-Ir 21%, appet neutro vomit hypok Anem
Ulrich-Pur *et al.* (25)	Austria, multicenter	2003	Raltitrexed + irinotecan *vs.* raltitrexed	38	16 *vs.* 0	NR	4 *vs.* 2.5	NR	NR	NR	6.5 *vs.* 4.3	NR	NR	NR	All 7.9 21.1 v Trans *vs.* 5. 10.5 v Naus *vs.* 5.

5-FU: 5-Fluorouracil; FF: 5-FU and folinic acid; HR: hazard ratio; OFF: oxaliplatin, folinic acid, and 5-FU 24 h; BSC: best supportive

care; LLV: L-leucovorin; Nal-iri, nanosomal irinotecan; OS: overall survival; NR, not reported; CR, complete response.

Figure 1. Kaplan–Meier survival analysis showing hazard ratio (HR) and 95% confidence interval (CI) for overall survival with nab-paclitaxel (NP) and non-NP groups.

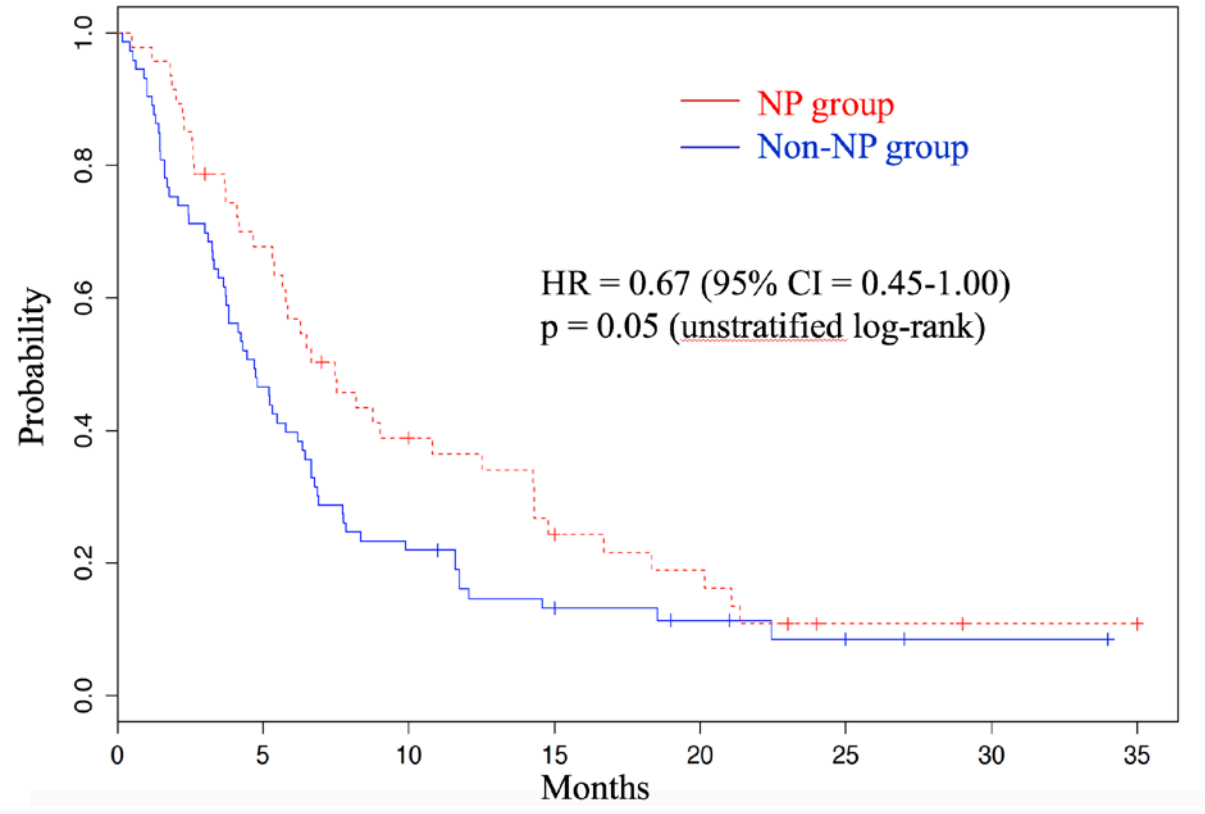
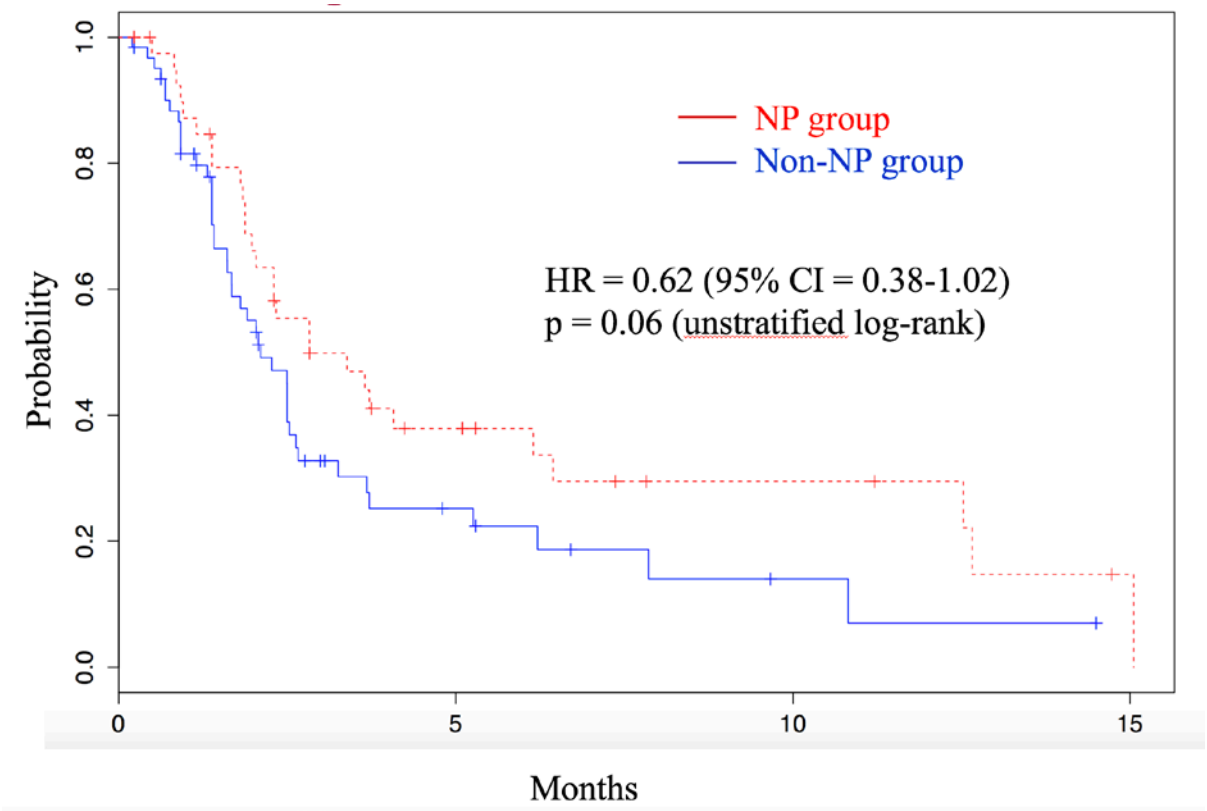


Figure 2. Kaplan–Meier survival analysis showing hazard ratio (HR) and 95% confidence interval (CI) for progression-free survival with nab-paclitaxel (NP) and non-NP groups.


NP group
Non-NP group
HR = 0.62 (95% CI = 0.38-1.02)
p = 0.06 (unstratified log-rank)
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
Months