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Treatment of recurrent and platinum-refractory stage IV non-small cell lung cancer with nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) as a single agent

Ashish Saxena, MD, PhD[a], **Bryan J. Schneider, MD**[a,1], **Paul J. Christos, Dr.PH, MS**[b], **Lauren Audibert, PA-C**[a,2], **Jennifer M. Cagney, NP**[a,3], and **Ronald J. Scheff, MD**[a]

[a]Weill Cornell Medicine, Department of Medicine, Division of Hematology & Medical Oncology, Weill Greenberg Center, 1305 York Avenue, 7th Floor, New York, NY 10021, USA

[b]Weill Cornell Medicine, Department of Healthcare Policy & Research, Division of Biostatistics & Epidemiology, 402 East 67th Street, New York, NY 10065, USA

Abstract

Background—The role of single-agent *nab*-paclitaxel in relapsed or platinum-refractory advanced non-small cell lung cancer (NSCLC) has not been well reported in Western populations. We reviewed our own institution's experience using *nab*-paclitaxel in these settings.

Patients and Methods—We analyzed the records of stage IV NSCLC patients with relapsed or platinum-refractory disease treated with single-agent *nab*-paclitaxel at Weill Cornell Medical College between October 2008 and December 2013. The primary endpoint of the study was treatment failure-free survival (TFFS), defined as the time from the start of *nab*-paclitaxel therapy to discontinuation of the drug for any reason. The best overall response was recorded for each patient and overall response and disease control rates were calculated.

Results—Thirty-one stage IV NSCLC patients received a median of 4 cycles (range 1-40) of *nab*-paclitaxel. Dose reduction or drug discontinuation due to toxicity occurred in 10 patients, mainly because of grade 2/3 fatigue or peripheral neuropathy. The overall response rate was 16.1% and the disease control rate was 64.5%. Median TFFS was 3.5 months (95% CI = 1.3-5.3 months). No statistically significant difference in TFFS based on line of therapy or prior taxane exposure

Corresponding Author Ashish Saxena, MD, PhD, 1305 York Ave, 7th Floor, Rm Y760, New York, NY 10021, USA, Phone: (646) 962-2066; Fax: (646) 962-1603, ahs9018@med.cornell.edu.

[1]**Present Addresses** University of Michigan Health System, Department of Internal Medicine, Division of Hematology/Oncology, Cancer Center Floor B1, Reception C, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA

[2]The Mt. Sinai Hospital, Pulmonary and Sleep Medicine, 5 East 98th St, 8th Floor, New York, NY 10029

[3]Memorial Sloan Kettering Cancer Center, Breast Cancer Medicine Service, Breast and Imaging Center, 300 East 66th St, New York, NY 10065, USA

Declaration of Competing Interests

Dr. Ashish Saxena declares that he has no competing interests.

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Dr. Paul J. Christos declares that he has no competing interests.

Lauren Audibert declares that she has no competing interests.

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was identified. There was a statistically significant decrease in TFFS for patients with non-adenocarcinoma histology, although there were only 5 patients in this group. There was a trend toward reduction in the risk of treatment failure with increasing age. One patient remained on *nab*-paclitaxel therapy for over 3 years.

Conclusions—Single-agent *nab*-paclitaxel was well tolerated and demonstrated efficacy in advanced NSCLC patients with relapsed or platinum-refractory disease. Further prospective clinical trials with *nab*-paclitaxel in these settings are warranted.

Keywords

Carcinoma; Non-Small-Cell Lung; Taxane; 130-nm albumin-bound paclitaxel; Neoplasm Recurrence; Treatment Failure

1. Background

Lung Cancer is the leading cause of cancer mortality worldwide, accounting for approximately 1.4 million deaths per year[1]. About 85% of cases are non-small cell lung cancer (NSCLC) and 40% of these patients will present with metastatic disease[2, 3]. In the front-line setting, the standard of care treatment is platinum-based doublet chemotherapy[4]. Standard 2nd/3rd line treatment typically involves the use of single agents given sequentially. Current options in this setting include pemetrexed, erlotinib, anti-PD-1 antibodies, and the taxane drug docetaxel with or without the VEGFR2 antibody ramucirumab[5].

Paclitaxel is a mitotic inhibitor that has poor solubility and is typically dissolved in Cremophor El as a delivery vehicle. However, Cremophor is associated with several toxicities such as hypersensitivity reactions, severe anaphylaxis, hyperlipidemia, and peripheral neuropathy[6]. Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane® [Celgene Corporation, Summit, NJ, USA]) is a formulation of paclitaxel which is not dissolved in Cremophor EL, reducing many of the toxicities associated with this solvent. This formulation also potentially increases the delivery of paclitaxel into tumor cells via the endogenous albumin pathways[7, 8].

Nab-paclitaxel was first approved in the United States for the treatment of metastatic breast cancer after failure of combination chemotherapy, based on the results of the phase III CA012 trial[9]. Efficacy has also been reported in the front-line treatment of advanced NSCLC, both as a single agent[8, 10] and in combination with other agents[11-13]. CA031 was a randomized phase III trial that compared carboplatin plus *nab*-paclitaxel with carboplatin plus solvent-based paclitaxel as frontline chemotherapy in patients with advanced stage NSCLC. The carboplatin plus *nab*-paclitaxel arm had a significantly higher overall response rate vs the carboplatin plus solvent-based paclitaxel arm (33% vs 25% respectively, $p = 0.005$), which was the primary endpoint of the trial. A trend towards improvement in both progression-free and overall survival was also identified in the *nab*-paclitaxel containing arm[13]. This trial lead to approval by the FDA of *nab*-paclitaxel for the first-line treatment of advanced NSCLC in combination with carboplatin.

While several studies have examined the efficacy of *nab*-paclitaxel for the initial management of advanced NSCLC, studies on the use of this drug as a single agent in the second-line setting and beyond have predominantly been done in East Asia[14-16]. Limited data therefore exists for *nab*-paclitaxel when used as a single agent in later lines of therapy in Western populations. Here we report our institution's experience using single-agent *nab*-paclitaxel in patients with relapsed or platinum-refractory advanced NSCLC.

2. Patients and Methods

2.1 Study Population

This study was approved by the Institutional Review Board of Weill Cornell Medical College (protocol number: 1112012070). After obtaining approval we analyzed the records of patients with Stage IV pathologically-confirmed NSCLC treated with single-agent *nab*-paclitaxel (Abraxane®) in the outpatient Thoracic Oncology Clinic at Weill Cornell Medical College between October 2008 and December 2013. Lung cancer staging was determined based on the American Joint Committee on Cancer Manual for Staging of Cancer[17]. Patients included in the analysis had received at least one line of systemic therapy (either platinum-based chemotherapy or erlotinib) for Stage IV NSCLC prior to receiving *nab*-paclitaxel and received at least one dose of *nab*-paclitaxel prior to censoring of the data. Patients were considered platinum-refractory if they demonstrated radiographic evidence of disease progression at the time of their first imaging scan while on platinum-based chemotherapy, which occurred after receiving 2-3 cycles and could be a CT or PET-CT scan. Patient data included age, sex, Karnofsky Performance Status (KPS), histology (as determined by pathological review at our institution), line of systemic therapy for stage IV disease, prior taxane exposure, number of cycles of *nab*-paclitaxel administered, dose adjustments, toxicity leading to dose adjustments, treatment response, and treatment failure-free survival (TFFS) estimated by Kaplan-Meier analysis.

2.2 Treatment and Follow-up Evaluations

Standard dosing of *nab*-paclitaxel was defined as 260 mg/m^2 IV every 21 days. However, some patients initiated therapy at reduced doses of 230mg/m^2 IV or 200mg/m^2 IV every 21 days, based on the clinical judgment of the treating oncologist. No pre-medications were given prior to administration of *nab*-paclitaxel and each dose was infused over 30 minutes. Dose and schedule reductions could be made at any point following the first cycle of therapy due to the development of toxicities. These adjustments involved either an increase to 28 days between doses or a 20-25% dose reduction of *nab*-paclitaxel in conjunction with an increase to a 28-day cycle.

Patients underwent imaging every 6-9 weeks (CT scan of the measurable disease or PET-CT). When the dosing interval was increased or the patient remained on *nab*-paclitaxel therapy for more than 6 months, scans were performed every 12 weeks. Toxicities were graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0[18].

Data were censored on December 31st, 2013, after 26 of the 31 patients discontinued treatment with *nab*-paclitaxel. TFFS was defined as the time between the start of *nab*-paclitaxel therapy and permanent discontinuation of the drug for any reason, including disease progression, symptom progression, reduced performance status, patient preference, treatment toxicity, or death resulting from any cause. The determination of overall response rate (ORR) and best overall response - complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) - were based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[19], except for one patient with symptomatic progression of disease at the time of first imaging scan who was classified as PD despite stable findings radiographically.

2.3 Statistical Analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) were calculated to characterize the study cohort. The primary endpoint of the study was TFFS as defined above. TFFS was expressed in months by dividing the value in days by 30.41. Univariate associations between treatment/prognostic variables and TFFS were assessed by the log-rank test. Univariate hazards ratios for the association between continuous prognostic variables (i.e., age) and TFFS were estimated by univariable Cox proportional hazards regression analysis. Ninety-five percent confidence intervals (95% CI) for hazard ratios and median treatment failure-free survival time estimates were calculated to assess the precision of the obtained estimates. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in Stata Version 13.0 (StataCorp, College Station, TX).

3. Results

3.1 Patient Characteristics

Thirty-one patients with Stage IV NSCLC received single-agent *nab*-paclitaxel between October 2008 and October 2013. All patients had previously received platinum-based doublet chemotherapy for Stage IV disease. Patient characteristics are summarized in Table 1. Median patient age was 69 years, range 48 to 83. The vast majority had a KPS of 70-80 and had adenocarcinoma histology. Five patients were platinum-refractory and for each of these patients *nab*-paclitaxel was the next line of therapy. Five of the 31 patients had EGFR activating mutation positive disease and 5 were treated with erlotinib as first-line therapy. Forty-two percent of the patients had received only one prior line of systemic therapy before starting *nab*-paclitaxel, while 35% had received 2 prior lines and 23% had received 3. Twenty-three percent of patients had received taxane therapy previously, and 77% were taxane-naïve.

3.2 Nab-Paclitaxel Treatment

Fifteen of the 31 patients initiated *nab*-paclitaxel therapy at a dose of 260mg/m^2 on day 1 of a 21-day cycle. Six started therapy with initial dosing of 230mg/m^2 and 10 started at a dose of 200mg/m^2 every 21 days. A total of 198 cycles of *nab*-paclitaxel were administered, with a median of 4 cycles (range 1-40) per patient (Table 2). No hypersensitivity reactions were seen amongst our patients.

Twenty-one patients discontinued *nab*-paclitaxel therapy because of disease progression identified on imaging. Two patients discontinued the drug after a single dose, one due to clinical deterioration and one due to grade 3 myalgias and arthralgias. One patient discontinued therapy after developing grade 3 peripheral sensory neuropathy after 4 cycles, and one discontinued therapy after being diagnosed with active tuberculosis. One patient was hospitalized with steroid-induced myopathy and died in the hospital. At the time of data censoring, 5 patients were alive and receiving *nab*-paclitaxel therapy, including one who had received 40 cycles.

3.3 Analysis of Outcomes

There were no complete responses observed. A partial response was identified in 5 patients (16.1%). Two of these 5 patients were platinum-refractory and one had known EGFR activating mutation positive disease. Fifteen patients (48.4%) demonstrated disease stability after at least one cycle of *nab*-paclitaxel and the remaining 11 patients (35.5%) had disease progression (Table 2). This translated into a disease control rate (PR + SD) of 64.5%. The seven patients with prior taxane exposure demonstrated an overall response rate (ORR) of 14.3% and a disease control rate (DCR) of 57.1%. Twenty-six patients with adenocarcinoma had an ORR of 15.4% and DCR of 65.4%. The ORR and DCR for the 3 patients with squamous cell carcinoma were 0% and 66.7%, respectively. Among the 5 patients with known EGFR activating mutations the DCR was 100%.

Table 3 shows the median TFFS for all patients in the study as well as for different subsets of patients. Median TFFS for all patients was 3.5 months [95% CI = 1.3-5.3 months] (Figure 1). There was a trend toward shorter TFFS with prior taxane exposure [median TFFS of 3.5 months without prior taxane vs. 2.2 months with prior taxane; p=0.10] (Figure 2A). No statistically significant difference in TFFS was identified for patients who received *nab*-paclitaxel as 2nd line therapy compared to those who received the drug beyond the 2nd line [median TFFS of 2.2 months vs. 3.6 months; p=0.78] (Figure 2B). Patients with adenocarcinoma had a longer TFFS compared to those who had non-adenocarcinoma histologies [median TFFS of 3.6 months vs. 1.3 months; p=0.03] (Figure 2C). There was a trend toward reduction in the risk of treatment failure with increasing age [hazard ratio=0.96 for each 1-year increase in age (95% CI = 0.91-1.01); p=0.09].

Dose adjustments due to toxicity occurred in 8 patients (Table 4). The most common toxicities requiring dose adjustments were grade 2 or 3 fatigue and grade 2 peripheral sensory neuropathy. Other toxicities leading to dose adjustments included anemia and arthralgias/myalgias.

4. Discussion

Nab-paclitaxel is well tolerated and efficacious in the front-line treatment of advanced NSCLC, both as a single agent and in combination with carboplatin[8, 10, 13]. However, patients with this disease inevitably progress after initial therapy and subsequent treatment options are needed, especially as pemetrexed is more commonly used in the front-line setting. *Nab*-paclitaxel can add to the now growing armamentarium of agents effective in later lines of therapy.

In studies of single-agent *nab*-paclitaxel as initial therapy for metastatic NSCLC, a DCR of 50% was reported, with a median time to progression of 5-6 months[8, 10]. The DCR in our study was 64.5% for patients who received *nab*-paclitaxel in second-line therapy or later, with a median TFFS of 3.5 months. Although a direct comparison cannot be made, the TFFS of 3.5 months seen in our study is similar to the median progression free survival (PFS) of 2.9 months reported with use of pemetrexed or docetaxel as second-line treatment[20]. The median PFS for erlotinib as a single agent in the second or third line setting is 2.2 months[21] and the anti-PD-1 antibodies nivolumab and pembrolizumab have median progression-free survivals ranging from 2.3–3.7 months when used after font-line therapy in populations that include both PD-L1 positive and negative tumors[22-24]. The ORR of *nab*-paclitaxel in our study was 16%, comparable to the 7-9% response rates reported for docetaxel, pemetrexed, and erlotinib when used as monotherapy after front-line, platinum-based chemotherapy[20, 21]. Our data therefore suggest that *nab*-paclitaxel may have comparable activity to other single-agents used following progression on first-line therapy for NSCLC.

Our data is also consistent with that of similar single-institution studies from China which have also examined *nab*-paclitaxel as monotherapy for metastatic NSCLC following disease progression. A retrospective study by Xing et al of 21 patients treated with single-agent *nab*-paclitaxel for recurrent, advanced NSCLC found an ORR of 28.6% and a DCR of 76.2%. The PFS was 4 months, similar to the 3.5 month TFFS found in our group of US patients[14]. The results of a single-arm, prospective phase II trial of 56 patients in China with stage IIIB/IV NSCLC treated with single agent *nab*-paclitaxel as second-line therapy at 100mg/m^2 on days 1, 8, and 15 of a 28-day cycle was reported by Hu et al[15]. This trial showed an ORR of 16.1% and a median PFS of 3.5 months, again comparable to the results of our study. Finally, a phase II trial by Liu et al randomized 111 advanced NSCLC patients treated at the General Hospital of Chinese PLA to second-line therapy with either *nab*-paclitaxel at 150mg/m^2 on days 1 and 8 of a 21-day cycle or standard pemetrexed at 500mg/m^2 on day 1 of a 21-day cycle. The ORR in the nab-paclitaxel arm was 14.5% with a disease control rate of 65.5%. The median PFS was 5.1 months for nab-paclitaxel and 4.6 months for pemetrexed, with the difference not being statistically significant[16]. Together these data as well as those presented in our study provide evidence for the efficacy of *nab*-paclitaxel beyond front-line therapy in advanced NSCLC and suggest that Eastern and Western populations may respond similarly to the drug in this setting.

Patients in our study tolerated *nab*-paclitaxel well as salvage therapy, consistent with other reports showing a favorable toxicity profile for the drug as a single agent[8, 14-16, 25]. A phase I/II trial by Rizvi et al of *nab*-paclitaxel given weekly at 125mg/m^2 for the front-line treatment of advanced NSCLC reported neutropenia, leukopenia, sensory neuropathy, and fatigue as the most common grade 3/4 toxicities[10]. A study by Green et al using 260mg/m^2 of *nab*-paclitaxel every 21 days also reported similar grade 3 toxicities, as well as a small percentage of grade 3 arthralgias[8]. The main grade 3 or 4 toxicities reported in the retrospective study by Xing et al also included neutropenia, peripheral neuropathy, myalgias/arthralgias, and fatigue[14], while the prospective trials done in China reported dizziness, fatigue, pulmonary embolism, nausea, fever, anemia, and thrombocytopenia as the most commonly seen grade 3 or 4 adverse events[15, 16]. Twenty-six percent of the patients in

our study required dose adjustment because of toxicity, mostly grade 2/3 fatigue and grade 2 peripheral sensory neuropathy. Interestingly, dose adjustments in our study were not more frequent in patients who initiated therapy with the standard dose and schedule of 260mg/m^2 every 21 days. Four patients in our study (13%) had *nab*-paclitaxel either dose adjusted or discontinued because of peripheral neuropathy, a common toxicity in many studies with *nab*-paclitaxel[26]. There is evidence from other studies, however, that *nab*-paclitaxel is associated with less peripheral neuropathy than solvent-based paclitaxel. In an analysis of patient- and physician-reported neuropathy symptoms in the CA031 phase III trial of first-line therapy for NSCLC, solvent-based paclitaxel plus carboplatin appeared to be more neurotoxic compared to *nab*-paclitaxel plus carboplatin[27].

In a phase I study of single-agent *nab*-paclitaxel for the treatment of several different advanced solid tumors in a population of Japanese patients who were refractory to or ineligible for standard treatment, 50% of patients with NSCLC had a partial response to the drug and two-thirds of those that responded had received prior taxane therapy[25]. In our study there was a trend toward shorter TFFS with prior taxane therapy that did not meet statistical significance. We also found no statistically significant difference in TFFS when nab-paclitaxel was used as second-line treatment vs third or fourth-line therapy. Together, these data suggest that *nab*-paclitaxel may be an appropriate single-agent therapy in advanced recurrent or platinum-refractory NSCLC regardless of prior taxane exposure or number of prior lines of therapy received.

Our study also showed a trend toward reduction in the risk of treatment failure with increasing age. An exploratory analysis of patients in the CA031 trial who were above age 70 demonstrated a near doubling of median overall survival with carboplatin plus *nab*-paclitaxel versus carboplatin plus solvent-based paclitaxel. There was no difference in overall survival between these two arms in the subset of patients less than 70 years old and there was no statistically significant difference in PFS between the two arms in either age group[28]. Both retrospective and prospective studies done in East Asia which specifically involved patients 65 years old or greater who were treated with single-agent *nab*-paclitaxel beyond the front-line setting have shown this drug to be safe and efficacious in this elderly patient population[29, 30].

Patients with squamous cell histology in the CA031 trial demonstrated a statistically significantly higher response rate in the arm containing *nab*-paclitaxel vs solvent-based paclitaxel. For patients with other histologies, the difference in response rate was not statistically significant. The authors concluded that first-line carboplatin plus *nab*-paclitaxel has a favorable risk-benefit profile in NSCLC patients regardless of tumor histology[31]. In our study, there were only 5 patients who did not have pure adenocarcinoma histology. We therefore cannot draw meaningful conclusions from our study regarding differential efficacy of *nab*-paclitaxel based on tumor histology.

5. Conclusion

Further treatment options for patients with advanced NSCLC who progress after or are refractory to standard platinum-doublet chemotherapy would be beneficial. Our data suggest

that single-agent *nab*-paclitaxel can be a good therapeutic option for these patients. This drug can be efficacious in these settings and is well tolerated. Our data also indicate that *nab*-paclitaxel may be an appropriate treatment option even in patients who have previously been exposed to taxanes or received multiple lines of therapy. The results of our study are in line with similar single-institution trials done in East Asian countries and suggest that *nab*-paclitaxel may be equally beneficial for Western populations. Further formal prospective phase II and phase III trials to evaluate this drug in the recurrent/refractory setting and compare it to other standard therapies are warranted. These studies may also better delineate whether specific subgroups, such as elderly patients or those with specific histologies or mutations, could derive particular benefit from *nab*-paclitaxel, as well as what the optimal dosing of the drug in this setting would be.

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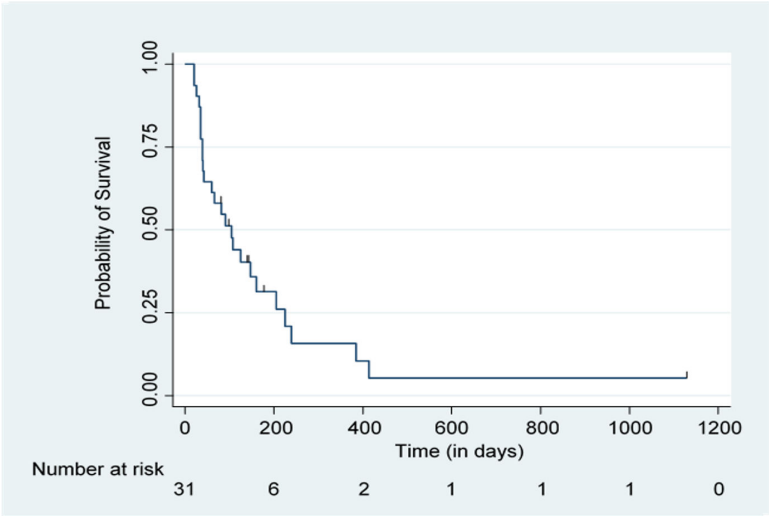

Figure 1. TFFS for All Patients

Kaplan-Meier Analysis of Treatment Failure-Free Survival (TFFS) for All 31 Patients Treated with *Nab*-Paclitaxel for Recurrent or Platinum-Refractory Stage IV Non-Small Cell Lung Cancer (NSCLC)

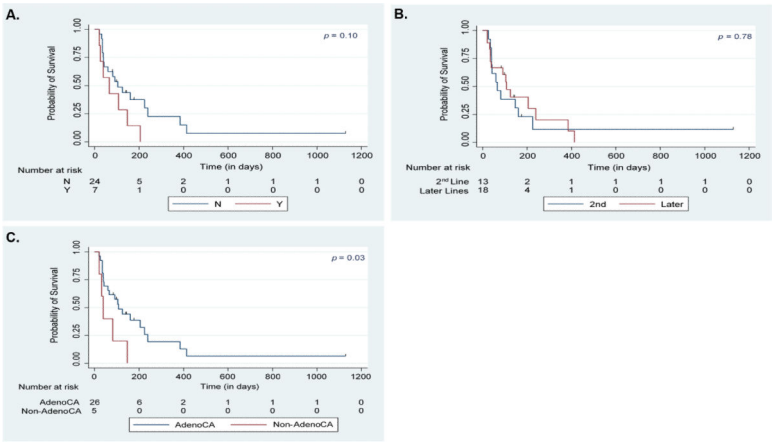

Figure 2. TFFS for Patient Subsets

Kaplan-Meier Analysis of Treatment Failure-Free Survival (TFFS) for Patients Treated with *Nab*-Paclitaxel for Recurrent or Platinum-Refractory Stage IV Non-Small Cell Lung Cancer (NSCLC) Based on **A.** Prior Taxane Exposure (N = No prior Taxane, Y = Prior Taxane); **B.** Line of Therapy; and **C.** Histology (AdenoCA = Pure Adenocarcinoma Histology)

Table 1

Characteristics of Patients Receiving Single-Agent *nab*-Paclitaxel

Characteristic	Number of Patients (%)
	N = 31
Age (Median Age = 69; Range = 48-83)	
<70	18 (58)
>/= 70	13 (42)
Sex	
Female	15 (48)
Male	16 (52)
Karnofsky Performance Status	
50	1 (3)
60	2 (6)
70	16 (52)
80	11 (35)
90	1 (3)
Histology	
Adenocarcinoma	26 (84)
Squamous Cell Carcinoma	3 (10)
Large Cell Carcinoma	1 (3)
Mixed Squamous Cell and Adenocarcinoma	1 (3)
EGFR Mutation	
Tested	13 (42)
Mutation Positive	5 (38)
Received Erlotinib First-Line	5 (16)
Refractory to Platinum-Based Chemotherapy	
Yes	5 (16)
No	26 (84)
Line of Systemic Therapy for Stage IV Disease	
$_{2}$nd	13 (42)
$_{3}$rd	11 (35)
$_{4}$th	7 (23)
Received Prior Taxane	
Yes	7 (23)
No	24 (77)
Received Chemotherapy for Earlier Stage Disease	
Yes	6 (19)
No	25 (81)

Table 2

Individual Data on Patients Receiving Single-Agent *nab*-Paclitaxel

Patient #	Age	Sex	Histology	KPS	Chemotherapy For Earlier Stage Disease	Platinum-Refractory	Prior Taxane	Line of Therapy	Started Standard Dose	Dose Reduced	# of Cycles Given	Best Overall Response
1	51	Male	AdenoCA	80	No	No	Yes	4th	No	No	3	PD
2	72	Male	AdenoCA	60	No	No	No	2nd	No	Yes	40	PR
3	75	Female	AdenoCA	70	No	No	No	3rd	No	No	19	SD
4	60	Female	AdenoCA	70	Yes	No	No	3rd	Yes	Yes	11	PR
5	71	Male	Mixed[a]	70	No	No	No	2nd	Yes	No	2	PD
6	67	Female	AdenoCA	80	No	No	No	3rd	Yes	No	18	SD
7	71	Female	AdenoCA	70	No	No	Yes	4th	No	No	9	SD
8	55	Female	AdenoCA	80	Yes	No	Yes	2nd	Yes	No	3	SD
9	78	Male	SCC	70	No	Yes	No	2nd	No	No	4	SD
10	82	Female	SCC	80	No	No	No	3rd	Yes	N/A	1	SD
11	59	Female	AdenoCA	70	Yes	No	Yes	4th	Yes	N/A	1	PD
12	70	Male	AdenoCA	70	No	No	No	2nd	Yes	No	2	PD
13	48	Male	AdenoCA	70	Yes	No	Yes	2nd	Yes	Yes	2	PD
14	61	Male	AdenoCA	80	Yes	No	Yes	4th	Yes	No	5	SD
15	58	Female	AdenoCA	70	No	No	No	4th	Yes	No	2	PD
16	79	Female	Large Cell	70	Yes	Yes	Yes	2nd	No	Yes	6	PR
17	69	Male	AdenoCA	70	No	No	No	3rd	No	No	6	SD
18	78	Male	AdenoCA	70	No	Yes	No	2nd	Yes	No	2	PD
19	60	Female	AdenoCA	80	No	No	No	4th	No	No	4	SD
20	57	Female	AdenoCA	70	No	No	No	3rd	Yes	No	2	PD
21	66	Female	AdenoCA	80	No	No	No	2nd	No	Yes	9	SD
22	65	Female	AdenoCA	90	No	No	No	3rd	Yes	No	5	SD
23	56	Female	AdenoCA	70	No	No	No	2nd	No	No	3	PD
24	81	Male	AdenoCA	80	No	No	No	2nd	No	No	8	SD
25	69	Male	SCC	70	No	No	No	3rd	No	No	2	PD
26	78	Male	AdenoCA	50	No	No	No	4th	No	Yes	6	SD
27	80	Male	AdenoCA	80	No	No	No	2nd	No	No	2	PD

Patient #	Age	Sex	Histology	KPS	Chemotherapy For Earlier Stage Disease	Platinum-Refractory	Prior Taxane	Line of Therapy	Started Standard Dose	Dose Reduced	# of Cycles Given	Best Overall Response
28	61	Female	AdenoCA	80	No	No	No	2nd	Yes	No	8	PR
29	83	Male	AdenoCA	80	No	Yes	No	3rd	No	No	4	SD
30	69	Male	AdenoCA	60	No	No	No	3rd	No	Yes	3	SD
31	60	Male	AdenoCA	70	No	Yes	No	3rd	Yes	Yes	6	PR

Abbreviations: AdenoCA = Adenocarcinoma; SCC = Squamous Cell Carcinoma; KPS = Karnofsky Performance Status; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; N/A = Not Applicable

[a]Mixed = Mixed Adenocarcinoma and Squamous Cell Carcinoma

Table 3

Median Treatment Failure-Free Survival for Patients Treated with *nab*-Paclitaxel

Patient Characteristic	Number of Patients	Median Time to Treatment Failure (in Months)	p Value (by log-rank test)
All Patient	31	3.5 (95% CI = 1.3 – 5.3)	
Prior Taxane	7	2.2 (95% CI = 0.7 – 4.8)	0.10
No Prior Taxane	24	3.5 (95% CI = 1.3 – 7.9)	
Nab-Paclitaxel as 2nd Line	13	2.2 (95% CI = 1.3 – 5.3)	0.78
Nab-Paclitaxel beyond 2nd Line	18	3.6 (95% CI = 1.2 – 7.9)	
Adenocarcinoma	26	3.6 (95% CI = 1.4 – 7.4)	0.03
Non-Adenocarcinoma (Including Mixed Adenocarcinoma and Squamous Cell Carcinoma)	5	1.3 (95% CI = 0.7 – not estimated)	

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Table 4

Toxicities for which Dose Adjustment or Drug Discontinuation Occurred

Patient #	Starting Dose	Toxicities (Grade)	Dose Reduced To
2	200mg/m^2 every 21 days	Fatigue (Grade 2)	200mg/m^2 every 28 days
4	260mg/m^2 every 21 days	Facial Edema (Grade 2)	260mg/m^2 every 28 days
9	200mg/m^2 every 21 days	Peripheral Sensory Neuropathy (Grade 3)	Drug Discontinued
10	260mg/m^2 every 21 days	Arthralgias/Myalgias (Grade 3)	Drug Discontinued
13	260mg/m^2 every 21 days	Fatigue (Grade 3)	200mg/m^2 every 28 days
16	200mg/m^2 every 21 days	Fatigue (Grade 3) Arthralgias/Myalgias (Grade 2) Peripheral Sensory Neuropathy (Grade 2)	160mg/m^2 every 28 days
21	200mg/m^2 every 21 days	Peripheral Sensory Neuropathy (Grade 2)	200mg/m^2 every 28 days
26	200mg/m^2 every 21 days	Fatigue (Grade 2)	150mg/m^2 every 28 days
30	230mg/m^2 every 21 days	Anemia (Grade 2)	230mg/m^2 every 28 days
31	260mg/m^2 every 21 days	Fatigue (Grade 2) Peripheral Sensory Neuropathy (Grade 2)	200mg/m^2 every 28 days