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M.A. Socinski

Mansoor Saleh

D.F. Trent

T.W. Dobbs

L.M. Zehngebot

See next page for additional authors

Authors

M.A. Socinski, Mansoor Saleh, D.F. Trent, T.W. Dobbs, L.M. Zehngebot, M.A. Levine, R. Bordoni, and P.J. Stella

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A randomized, phase II trial of two dose schedules of carboplatin/paclitaxel/cetuximab in stage IIIB/IV non-small-cell lung cancer (NSCLC)

M. A. Socinski[1]*, M. N. Saleh[2], D. F. Trent[3], T. W. Dobbs[4], L. M. Zehngebot[5], M. A. Levine[6], R. Bordoni[2] & P. J. Stella[7]

[1]*Multidisciplinary Thoracic Oncology Program, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill;* [2]*Georgia Cancer Specialists, Marietta;* [3]*Virginia Cancer Institute, Richmond;* [4]*Tennessee Cancer Specialists, Knoxville;* [5]*Department of Hematology/Oncology, Florida Hospital Cancer Institute, Orlando;* [6]*Greater Baltimore Medical Center, Baltimore;* [7]*Ann Arbor Hematology Oncology, Ann Arbor; USA*

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Background: This trial investigated the efficacy and safety of weekly cetuximab combined with two different schedules of paclitaxel/carboplatin for stage IIIB/IV non-small-cell lung cancer (NSCLC).
Methods: A total of 168 patients with previously untreated stage IIIB/IV NSCLC were randomized to arm A, cetuximab (400 mg/m^2 day 1 followed by weekly 250 mg/m^2) + paclitaxel (Taxol) (225 mg/m^2)/carboplatin (AUC6) day 1 every 3 weeks or arm B, same cetuximab regimen plus paclitaxel (100 mg/m^2) days 1, 8, and 15 every 3 weeks and carboplatin (AUC6) day 1 every 4 weeks. Treatment continued for a four-cycle maximum. Patients with a complete response, partial response, or stable disease after four cycles could receive cetuximab 250 mg/m^2/week until disease progression or unacceptable toxicity. The primary end point was to evaluate progression-free survival (PFS).
Results: Median PFS was 4.7 and 4.3 months for arms A and B, respectively (6-month PFS, 27.3% versus 30.9%). Median overall survival was 11.4 versus 9.8 months for arms A and B, respectively; estimated 1-year survival, 47.7% versus 39.3%; and objective response rate, 29.6% versus 25%. The regimen was well tolerated with rash and hematologic toxicity being most common.
Conclusions: This study did not meet the prespecified benchmark of 35% 6-month PFS rate; both combination schedules of cetuximab plus paclitaxel/carboplatin were feasible and equivalent for treating advanced NSCLC.
Key words: biomarkers, cetuximab, combination therapy, EGFR, NSCLC

introduction

Despite therapeutic advances, lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for 1.4 million deaths [1]. For the ~40% of patients diagnosed with advanced non-small-cell lung cancer (NSCLC), the median survival remains between 8 and 12 months and 1-year survival rates range from 30% to 50% [2]. Clearly, new therapeutic targets are needed. One such target is the epidermal growth factor receptor (EGFR) pathway [3]. Cetuximab is a mAb that binds to the EGFR with greater affinity than its natural ligands, resulting in receptor internalization and downregulation of EGFR signaling. Cetuximab has shown synergism with several cytotoxics, including platinum and taxane agents, as well as radiotherapy [4, 5].

Cetuximab has been studied in NSCLC, both as a single agent and in combination with platinum doublets [6–10]. While the overall characterization of cetuximab activity in combination is important, elucidating how the administration schedule of a platinum-based doublet plus cetuximab can be optimized is also of interest. Standard administration of carboplatin/paclitaxel is based on an every 3-week schedule. An alternate schedule, however, has also been developed based on monthly carboplatin and weekly paclitaxel. Continuous low doses of paclitaxel show antitumor activity in preclinical models, and weekly low-dose paclitaxel may reach higher dose intensity that traditional every 3-week administration. Comparative studies have demonstrated that this schedule has comparable efficacy to the standard every 3 weeks and a seemingly different safety profile, which may be better suited for certain patients [11, 12]. The lower incidence of certain toxic effects, particularly neurotoxicity and arthralgia, observed with weekly paclitaxel may make it a preferable option for elderly patients (≥70 years) or those with compromised performance status. The present study investigated the efficacy/safety of weekly cetuximab in combination with the carboplatin + paclitaxel doublet, either in the traditional every 3-week schedule or using weekly

Correspondence to: Dr M. A. Socinski, Multidisciplinary Thoracic Oncology Program, Lineberger Comprehensive Cancer Center, CB 7305, University of North Carolina, Chapel Hill, NC 27599, USA. Tel: +1-919-966-4431; Fax: +1-919-966-6735; E-mail: socinski@med.unc.edu

coadministration of paclitaxel + cetuximab plus monthly carboplatin. The goal of this study was to determine whether both schedules were equivalent or potential differences may confer different clinical utility to either one.

methods

patients

Patients ≥18 years, with histologically or cytologically documented stage IIIB (supraclavicular lymph node or malignant pleural effusion) and IV NSCLC, were eligible. Disease had to be newly diagnosed or if recurrent, ≤1-year postadjuvant chemotherapy.

Other eligibility criteria included the following: presence of measurable disease, Eastern Cooperative Oncology Group performance status of zero or one, life expectancy ≥12 weeks, adequate hematologic (absolute neutrophil count [ANC] ≥1500/mm^3, white blood cell count ≥3000/mm^3, platelets ≥100 000/mm^3, and hemoglobin ≥9 g/dl), hepatic (bilirubin ≤1.5× upper normal limit [UNL], AST ≤2.5× UNL), and renal (serum creatinine ≤1.5 mg/dl or creatinine clearance ≥60 ml/min) function. Prior radiation therapy or major surgery was to be completed ≥2 weeks before enrollment, and patients were required to be completely recovered from all adverse effects. Patients who received prior cetuximab or other EGFR-targeted therapy were ineligible as were those with known peripheral neuropathy, active serious infection, or other serious underlying medical conditions.

The trial protocol was approved by Institutional Review Boards having jurisdiction over the sites that registered patients to the trial. All patients provided informed consent before enrollment.

treatment plan

Patients were randomized without stratification to either arm A (cetuximab 400 mg/m^2 day 1 followed 1 week later by cetuximab 250 mg/m^2 weekly + paclitaxel (Taxol, Bristol-Myer Squibb Company, Princeton, NJ) 225 mg/m^2 and carboplatin AUC6 day 1 of each 3-week cycle) or arm B (cetuximab 400 mg/m^2 day 1 followed 1 week later by cetuximab 250 mg/m^2 weekly + paclitaxel 100 mg/m^2 days 1, 8, and 15 and carboplatin AUC6 day 1 of each 4-week cycle).

Treatment was continued with a four-cycle maximum (arm A, 12 weeks; arm B, 16 weeks). Patients with a complete response [CR: the disappearance of all target lesions (those representative, by size and suitability of measurements, of all involved organs)], partial response [PR: at least a 30% decrease in the sum of the longest diameters (LD) of the target lesions taking as reference the baseline LD sum], or stable disease (SD: neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for progression, taking as reference the smallest LD sum since the treatment started) after four cycles in either arm could receive cetuximab 250 mg/m^2/week until disease progression (DP) or unacceptable toxicity.

Patients received premedication (diphenhydramine hydrochloride 50 mg i.v.) 30–60 min before the first cetuximab dose. Upon subsequent cetuximab administration, patients were to receive diphenhydramine but the dose could be reduced. Premedications for paclitaxel were given 30–60 min before first administration [dexamethasone 20 mg i.v., diphenhydramine 50 mg i.v., and a histamine receptor-2 blocker (e.g. cimetidine 300 mg or ranitidine 50 mg i.v.)] and could be altered thereafter at the investigator's discretion.

A maximum of two dose level (DL) reductions was permitted per patient for both paclitaxel and carboplatin. DL-1 and -2 reductions for paclitaxel were as follows: arm A, 200 mg/m^2 and 150 mg/m^2; arm B, 80 mg/m^2 and 60 mg/m^2. Carboplatin DL-1 and -2 reductions were AUC5 and AUC4, respectively, for both arms. Paclitaxel was reduced one DL if ANC was between 1000 and 1499/μl or platelet count between 50 000 and 74 999/μl. If ANC fell to <1000/μl or platelets fell to <50 000/μl, paclitaxel was held. For hematologic adverse events (AEs; e.g. febrile neutropenia), both paclitaxel and carboplatin were reduced 1DL. Paclitaxel and carboplatin were also reduced 1DL for grade 2 motor and/or sensory neuropathy; ≥grade 3 neuropathy patients were taken off study. Paclitaxel was withheld for grade 3 fatigue, arthralgias, or myalgias until resolution to ≤grade 2 and then resumed with a 1DL reduction. Paclitaxel was also decreased 1DL if bilirubin levels were between 1.5 and 2.0× UNL or withheld for >2.0× UNL until resolution to ≤2.0× UNL and then restarted 1DL lower. For all other grade 3/4 toxic effects, paclitaxel and carboplatin were withheld until resolution to ≤grade 2; treatment was then resumed with study medications reduced 1DL.

A maximum of 2DL reductions was also permitted per patient for cetuximab with the DL-1 and DL-2 reductions on each arm being 200 and 150 mg/m^2. Cetuximab was not reduced for hematologic toxicity. At the first occurrence of grade 3 acneiform rash, cetuximab infusion was delayed until recovery to ≤grade 2 and then resumed at the same dose. Upon second and third occurrences of grade 3 rash, the infusion was delayed until recovery to ≤grade 2 and then restarted 1DL lower. If a grade 3 rash occurred for a fourth time, the patient was removed from the study. Patients who experienced grade 1/2 infusion reactions to cetuximab had infusion rates reduced by 50% for subsequent doses. Cetuximab was discontinued for grade 3/4 infusion reactions.

assessment of efficacy and safety

Response was assessed by investigators using RECIST criteria every 8 weeks and confirmed within 4 weeks of initial response [13]. All patients were evaluated at completion of cycle 4 to determine eligibility for continuous weekly single-agent cetuximab. For patients continuing onto single-agent cetuximab, a chest computed tomography scan or magnetic resonance imaging was repeated every 8 weeks until 6 months from start of initial therapy. After 6 months, evaluations were repeated every 3 months until end of study therapy.

Non-hematologic toxic effects were continuously evaluated throughout the study by the investigators and were graded using the National Cancer Institute—Common Terminology Criteria for Adverse Events Version 3.0.

statistical analysis

Primary end points were median and 6-month progression-free survival (PFS). PFS was defined as the interval between the start of treatment and the occurrence of DP or death. PFS rate was defined as the number of patients with CR, PR, or SD at latest evaluation ≤6 months after start of treatment, divided by the number of randomized patients. Secondary end point was tumor response rate (RR).

Estimated median progression-free survival (MPFS), median overall survival (MOS), and 1-year survival were calculated using the Kaplan–Meier product-limit method, along with corresponding 95% confidence intervals (CIs), using the Brookmeyer–Crowley method [14]. This trial was designed to be noncomparative, therefore each arm was analyzed separately.

Estimated sample size was based on an expected (based on historic data) 6-month PFS rate of 35%. A total of 80 response-assessable subjects per arm were needed to produce a two-sided, exact 95% Clopper–Pearson CI extending a maximum width of 21% (lower limit ≥25%) for each arm.

Analyses of PFS, overall survival (OS), as well as time to and duration of response were carried out on all randomized patients; RR analyses were completed on the response-evaluable subset; safety analyses were based on treated subjects.

Patient demographics were summarized by treatment arm using descriptive statistics. All AEs were summarized both without regard to causal relationship and by causal relationship to study drugs, based on the investigator's opinion. Worst toxicity grades per subject were tabulated for selected AEs and laboratory measurements.

results

patient characteristics

From December 2004 to April 2007, a total of 168 patients were randomized across 20 sites (Table 1). The majority of patients discontinued the study because of DP or relapse. Patient baseline characteristics were well balanced between both arms (Table 2).

treatment administration

Fifty-eight percent of arm A and 53.6% of arm B received all four cycles of therapy. Seventy-four patients (44%) went on to receive single-agent cetuximab—arm A: $n = 41$ (49%); arm B: $n = 33$ (39%)—with the number of median infusions for arm A, 10 and for arm B, 9 (similar median cetuximab dose intensity, 248.0 mg/m^2/week for arm A and 245.8 mg/m^2/week for arm B). Dose reductions ≥1DL were required for 41 patients receiving carboplatin and 53 patients receiving paclitaxel. There were 19 patients (12.5%; arm A, $n = 7$; arm B, $n = 12$) who had ≥1 paclitaxel dose delay and 22 patients (14.7%; arm A, $n = 5$; arm B, $n = 17$) who had ≥1 carboplatin dose delay. Delayed hematologic recovery was the most common reported reason for delayed paclitaxel and carboplatin. Thirteen patients (7.9%) required reduction of cetuximab by 1DL, five (3.0%) patients required two dose reductions, and one (0.6%) patient required three dose reductions. Twenty-eight patients (17%) experienced ≥1 cetuximab dose delay, the most common reason being hypersensitivity reaction (arm A, $n = 7$; arm B, $n = 14$).

Table 1. Patient disposition

Patient disposition	Arm A, 3-week cycle, *n* (%)	Arm B, 4-week cycle, *n* (%)	Total, *N* (%)
Randomized	84 (100)	84 (100)	168 (100)
Treated with			
Cetuximab	81 (96.4)	84 (100)	165 (98.2)
Carboplatin	76 (90.5)	74 (88.1)	150 (89.3)
Paclitaxel	78 (92.9)	74 (88.1)	152 (90.5)
Response-evaluable population	81 (96.4)	84 (100)	165 (98.2)
Safety population	81 (96.4)	84 (100)	165 (98.2)
Subject status			
Discontinued from study	84 (100)	84 (100)	168 (100)
Reasons for discontinuation			
Disease progression/ relapse	45 (53.6)	46 (54.8)	91 (54.2)
Study drug toxicity	11 (31.1)	11 (31.1)	22 (13.1)
Subject request	4 (4.8)	3 (3.6)	7 (4.2)
Death	1 (1.2)	7 (8.3)	8 (4.8)
Patients noncompliance with protocol	1 (1.2)	0	1 (0.6)
Clinical deterioration without progression	10 (11.9)	9 (10.7)	19 (11.3)
Never treated	2[a] (2.4)	0	2 (1.2)
Other	10 (11.9)	8 (9.5)	18 (10.7)

[a]A third patient on arm A never received treatment and is included under 'other' reason for discontinuation.

Fifty-one (60.7%) patients on each arm received subsequent chemotherapy, most commonly: pemetrexed (arm A, 20.2%; arm B, 23.8%), carboplatin (arm A, 20.2%; arm B, 10.7%),

Table 2. Demographic and baseline characteristics—randomized population

Patient characteristic	Arm A, 3-week cycle, $n = 84$	Arm B, 4-week cycle, $n = 84$	Total, $N = 168$
Gender at birth			
Male	45 (53.6)	44 (52.4)	89 (53)
Female	39 (46.4)	40 (47.6)	79 (47)
Age (year)			
Mean	61.2	62.1	61.7
Median	62	61	61.5
Standard deviation	9.97	9.20	9.58
Minimum–maximum	37–80	42–86	37–86
n (%) < 65	48 (57.1)	53 (63.1)	101 (60.1)
n (%) ≥ 65	36 (42.9)	31 (36.9)	67 (39.9)
Race			
White	72 (85.7)	68 (81)	140 (83.3)
Black or African-American	9 (10.7)	13 (15.5)	22 (13.1)
Asian	3 (3.6)	1 (1.2)	4 (2.4)
Other	0	2 (2.4)	2 (1.2)
ECOG performance score			
0	43 (51.2)	49 (58.3)	92 (54.8)
1	39 (46.4)	32 (38.1)	71 (42.3)
Missing	2 (2.4)	3 (3.6)	5 (3)
Historical grade			
Well differentiated	8 (9.5)	4 (4.8)	12 (7.1)
Moderately differentiated	10 (11.9)	11 (13.1)	21 (12.5)
Poorly or undifferentiated	32 (38.1)	33 (39.3)	65 (38.7)
Unknown	34 (40.5)	36 (42.9)	70 (41.7)
Cell type			
Adenocarcinoma without BAC components	37 (44)	46 (54.8)	83 (49.4)
Adenocarcinoma with BAC components	4 (4.8)	6 (7.1)	10 (6)
Squamous cell carcinoma	18 (21.4)	14 (16.7)	32 (19)
Large cell carcinoma	5 (6)	6 (7.1)	11 (6.5)
BAC	0	1 (1.2)	1 (0.6)
Unknown	13 (15.5)	6 (7.1)	19 (11.3)
Other	7 (8.3)	5 (6)	12 (7.1)
Disease stage at entry			
Stage IIIB	9 (10.7)	14 (16.7)	23 (13.7)
Stage IV	75 (89.3)	70 (83.3)	145 (86.3)
Recurrent	10 (11.9)	5 (6)	15 (8.9)
Smoking history			
Never smoked	5 (6)	5 (6)	10 (6)
Ceased smoking	33 (39.3)	45 (53.6)	78 (46.4)
Current smoker	46 (54.8)	34 (40.5)	80 (47.6)
Prior radiotherapy			
Yes	20 (23.8)	21 (25)	41 (24.4)
No	64 (76.2)	63 (75)	127 (75.6)
Prior adjuvant chemotherapy for NSCLC			
Yes	5 (6)	0	5 (3)
No	79 (94)	84 (100)	163 (97)

BAC, bronchoalveolar carcinoma; ECOG, Eastern Cooperative Oncology Group.

gemcitabine (arm A, 19.0%; arm B, 9.5%), and docetaxel (arm A, 11.9%; arm B, 7.1%).

efficacy

Survival and tumor response results are summarized in Table 3. PFS and OS curves are shown in Figures 1 and 2. MOS was 11.4 and 9.8 months for arms A and B, respectively (estimated 1-year survival: 47.7% and 39.3%). PFS was 4.7 and 4.3 months for arms A and B, respectively (6-month PFS: 27.3% and 30.9%). Objective response rates (ORRs) for arms A and B were 29.6% and 25%, respectively. Additionally, 66.7% of arm A and 63.1% of arm B achieved disease control, defined as CR + PR + SD. Median duration of response was 5.1 (arm A) and 4.4 months (arm B).

safety

Grade 3/4 study drug-related toxic effects with >2% incidence are shown in Table 4. Both neutropenia (arm A: 18.5% grade 3, 18.5% grade 4; arm B: 4.8% grade 3, 1.2% grade 4) and febrile neutropenia (arm A: 4.9% grade 3, 1.2% grade 4; arm B: 1.2% grade 3, 0% grade 4) occurred more often in the 3-week treatment arm A. Hypersensitivity reaction incidence was slightly higher for arm B: 4.8% grade 3, 1.2% grade 4 versus arm A: 2.5% grade 3 and 0% grade 4. Patients on both treatment arms reported a similar incidence of rash (arm A: 7.4% grade 3; arm B: 8.3% grade 3). No grade 4 rash was reported. Additionally, 6.2% in arm A reported grade 3 dermatitis acneiform compared with 8.3% in arm B.

Twenty-three patients (28%) in arm A experienced AEs leading to drug discontinuation. These events were grade 3/4 for 17 of those patients; the most common were fatigue ($n = 2$), hypersensitivity reactions ($n = 2$), pneumonia ($n = 2$), dehydration ($n = 1$), and rash ($n = 2$). In arm B, 27 patients (32%) discontinued treatment because of AEs, grade 3/4 for 24 of them. The most common were hypersensitivity reaction ($n = 3$), pneumonia ($n = 2$), dyspnea ($n = 2$), respiratory failure ($n = 2$), dehydration ($n = 2$), rash ($n = 1$), and acneiform dermatitis ($n = 2$). One death in arm B was

Table 3. Survival and tumor response

Patient accounting	Arm A, 3-week cycle	Arm B, 4-week cycle	Total
Overall and progression-free survival—randomized population			
Number of patients assessed	$n = 84$	$n = 84$	$N = 168$
Overall survival (month)			
Median	11.4	9.8	10.2
95% CI (median)	8.9–13.5	7.6–11.1	8.8–12.4
Survival at 1 year			
Estimated rate (%)	47.7	39.3	43.3
95% CI	36.5–58.8	28.7–49.8	35.6–51
Progression-free survival (month)			
Median	4.7	4.3	4.5
95% CI	3.7–5.6	3.8–5	3.9–5.2
Progression-free survival at 6 months			
Estimated rate (%)	27.3	30.9	29.1
95% CI	17.3–37.2	20.8–40.9	22–36.2
Response rate and time to/duration of response—response-evaluable population			
Number of patients assessed	$n = 81$	$n = 84$	$N = 165$
Objective response			
N (%)	24 (29.6)	21 (25)	45 (27.3)
95% CI	20–40.8	16.2–35.6	20.6–34.7
Disease control (CR + PR + SD)			
N (%)	54 (66.7)	53 (63.1)	107 (64.8)
95% CI	55.3–76.8	51.9–73.4	57–72.1
Time to response			
N	24	21	45
Median (month)	1.9	2	1.9
Standard deviation	2.29	1.54	1.96
Duration of response (CR + PR)			
N	23	19	42
Median (month)	5.1	4.4	4.5
95% CI (median)	3.7–6.5	3.6–10.1	3.7–6.7

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

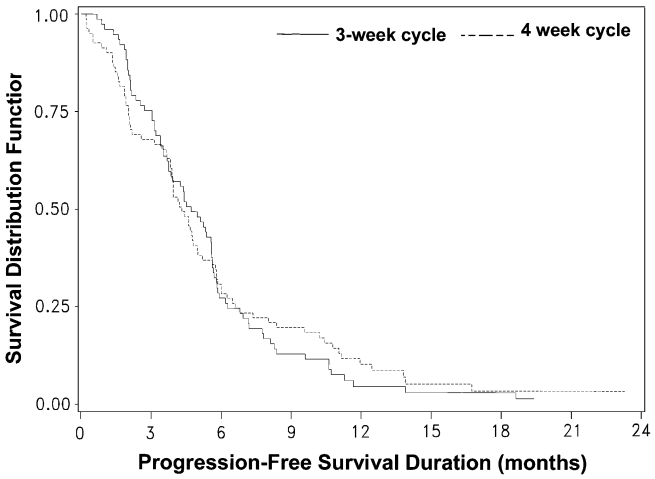

Figure 1. Kaplan–Meier plot of progression-free survival.

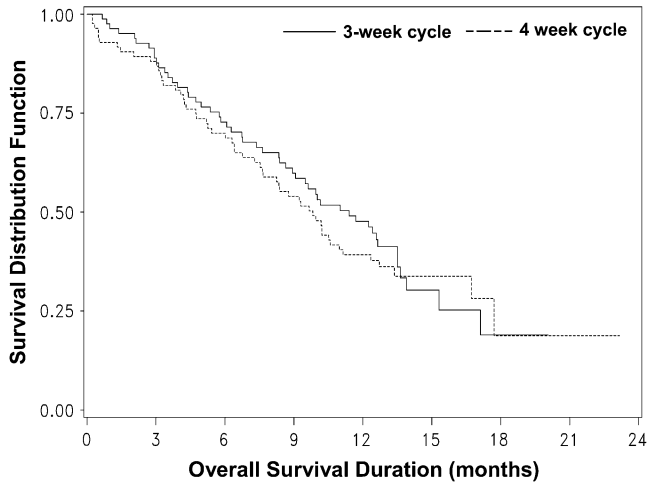

Figure 2. Kaplan–Meier plot of overall survival.

Table 4. Study drug-related National Cancer Institute grade 3–5 toxic effects (>2% incidence) for all treated patients

Event	Arm A, 3-week cycle ($n = 81$)		Arm B, 4-week cycle ($n = 84$)	
	Grade 3, %	Grade 4, %	Grade 3, %	Grade 4, %
Hematologic				
Neutropenia	18.5	18.5	20.2	3.6
Thrombocytopenia	3.7	1.2	0	0
Anemia	2.5	0	3.6	0
Febrile neutropenia	4.9	1.2	1.2	0
Non-hematologic				
Anorexia	4.9	0	4.8	0
Deep vein thrombosis	0	0	2.4	0
Dehydration	4.9	0	2.4	0
Dermatitis acneiform	6.2	0	8.3	0
Diarrhea	3.7	0	6.0	0
Dyspnea	0	0	1.2	2.4
Fatigue	6.2	1.2	3.6	0
Hypersensitivity	2.5	0	4.8	1.2
Hypokalemia	3.7	0	4.8	0
Hypomagnesemia	3.7	0	1.2	1.2
Muscular weakness	0	0	2.4	0
Pneumonia	0	1.2	2.4	0
Pruritis	3.7	0	1.2	0
Pulmonary embolism	0	0	0	2.4
Rash	7.4	0	8.3	0
Stomatitis	1.2	0	3.6	0

attributed to the study drug by the investigator: the patient died of interstitial pneumonia 12 days after receiving their first cetuximab dose, never having received paclitaxel or carboplatin.

discussion

In the present study, cetuximab added to two different schedules of a platinum doublet did not exceed the predefined 6-month PFS rate of 35% established as primary end point. ORR and disease control rates were similar with both schedules, while OS and PFS were longer with every 3-week paclitaxel + carboplatin (11.4 and 4.7 months, respectively) and comparable to that seen previously with platinum-based chemotherapy + cetuximab. Adding cetuximab did not greatly affect chemotherapy tolerability/safety, again comparable to prior studies. With the exception of rash, the majority of grade 3 AEs observed were hematologic in nature and likely attributable to the chemotherapy portion of the combination regimen.

Single-arm studies of cetuximab in advanced NSCLC have shown activity. Hanna et al. [6] showed a 4.5% RR to single-agent cetuximab in refractory disease. In combination with first-line platinum therapy, the activity of cetuximab-based regimens has ranged from what was reported by Thienelt et al. [15] [26% RR, median time to progression (MTTP) of 5 months and MOS of 11 months] to the more recent study by Borghaei et al. [10] (57% RR; MTTP, 5.5 months; MOS, 13.8 months).

Randomized phase II studies have shown favorable efficacy by adding cetuximab to various platinum-based doublets, with RR of approximately 28–35% (versus 18–28% with chemotherapy alone) MPFS times reaching 5 months (versus 4 months with chemotherapy alone), and MOS ranging between 8 and 12 months (versus 7–9 months with chemotherapy alone) [7–9]. In the phase III study, BMS099 comparing carboplatin/taxane ± cetuximab as first-line therapy for patients ($N = 676$) with advanced NSCLC [16], independently determined MPFS (primary end point of the study) was 4.40 with chemotherapy + cetuximab versus 4.24 months with chemotherapy only [hazard ratio (HR) 0.902, 95% CI 0.761–1.069, $P = 0.2358$]. However, investigator-determined PFS was 4.30 versus 3.78 months (HR 0.766, 95% CI 0.649–0.903, $P = 0.0015$). The discrepancy in significance between the independent and investigator assessments remains unexplained. More conclusive was the FLEX trial (First-Line treatment for patients with epidermal growth factor inhibitor-EXpressing advanced NSCLC), a multinational study of vinorelbine + cisplatin ± cetuximab ($N = 1125$). Results indicate a significant increase in OS with cetuximab + platinum-based chemotherapy (HR 0.871, 95% CI 0.762–0.996, $P = 0.044$) [17].

While this trial did not reach the PFS benchmark prespecified based on historic controls, it is worth considering that PFS is a surrogate end point dependent on the individual judgment of the investigator that allows a limited evaluation of the effect of therapy in the time frame of the first line setting until progression. Furthermore, cetuximab plus the platinum doublet showed greater RRs than previously reported with paclitaxel/carboplatin alone [18]. These considerations, together with the collective results discussed above, including a significant improvement in OS in a phase III trial, suggest that there is a role for platinum-based chemotherapy + cetuximab in treating advanced NSCLC. It will be imperative, however, to identify reliable biomarkers that predict response and longer survival in order to improve upon the modest activity seen in unselected patients. Molecularly based patient selection has the potential to dramatically improve the clinical profile of cetuximab, much like selection based on human epidermal growth factor receptor 2 (HER2) positivity by FISH has allowed the identification of a target subpopulation in for trastuzumab [19], in which this agent is considered the cornerstone of treatment.

The identification of optimal markers for cetuximab patient selection is currently ongoing in multiple tumor settings and will hopefully provide similarly valuable information, allowing for the selection of patient populations with improved cetuximab responses. Patients for the positive FLEX study were selected, albeit not stringently, based on EGFR expression detected by immunohistochemistry [17], while in BMS099 and several phase II studies, including this one, there was no such selection. Whether this marker is relevant for the clinical activity of cetuximab is unclear at the moment. In the SWOG trial mentioned above [20], PFS and survival benefit with cetuximab seemed to be greater for EGFR–FISH+ patients. Mutational status of the *K-RAS* gene has emerged as an extremely robust biomarker for the use of cetuximab in metastatic colorectal cancer (CRC) [21], and its value in NSCLC is under study [16]. Well-designed, tissue-based clinical studies will be key in establishing the most appropriate use of cetuximab in the clinic.

In conclusion, the combination of cetuximab with paclitaxel/carboplatin did not reach the level of therapeutic activity prespecified as primary end point of this study. This trial indicates that cetuximab can be added to the standard every 3-week schedule of carboplatin + paclitaxel, as well as the monthly carboplatin + weekly paclitaxel alternate, and both schedules seem to have equivalent efficacy. The clinical profile of cetuximab in advanced NSCLC continues to be fully defined in larger trials, and future evaluation of cetuximab in selected patient populations will lead to better understanding of the role of this agent in NSCLC treatment.

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