Comparative outcomes of squamous and non-squamous non-small cell lung cancer (NSCLC) patients in phase II studies of ASA404 (DMXAA) – retrospective analysis of pooled data

Mark J McKeage,[1] Michael B Jameson,[2] AS1404-201 Study Group Investigators

[1]The University of Auckland, Auckland 1023, New Zealand; [2]Oncology Department, Waikato Hospital, Hamilton 3240, New Zealand

ABSTRACT

Background ASA404 (5,6-dimethylxanthenone-4-acetic acid) is a small-molecule, flavonoid tumor-vascular disrupting agent. Pooled data from phase II studies were analyzed retrospectively to compare safety and efficacy between squamous and non-squamous non-small cell lung cancer (NSCLC) patients.

Methods Data from previously untreated patients with stage IIIb/IV NSCLC who were randomized to receive up to six cycles of carboplatin (C; AUC 6 mg/ml•min) and paclitaxel (P; 175 mg/m^2) alone or with ASA404 (1200 mg/m^2), or enrolled in an extension study to receive CP and ASA404 (1800 mg/m^2), were analyzed. Differences between subgroups were calculated using Fisher's exact test.

Results Of the 108 enrolled patients, safety data from the 104 patients included in the safety population were pooled to compare results between histological subgroups (squamous *vs* non-squamous) and treatment (CP alone *vs* CP + ASA404). Addition of ASA404 to the standard chemotherapy regimen did not appear to substantially increase toxicity, and there were no serious adverse events associated with bleeding, pulmonary hemorrhage, or hemoptysis. Activity with CP + ASA404 appeared improved over CP alone, with median survival 10.2 *vs* 5.5 months in squamous, and 14.9 *vs* 11.0 months in non-squamous populations, respectively.

Conclusion This analysis is limited by its retrospective nature, and by the small size of the overall group, treatment and disease subgroups. However, as ASA404 appears to have a similar safety and activity profile in patients with squamous and non-squamous NSCLC, the findings support inclusion of both groups of patients in ongoing definitive phase III trials of ASA404 (NCT00832494).

Key Words: ASA404; non-small cell lung carcinoma; clinical trial; phase II; safety

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Introduction

Lung cancer is the leading cause of cancer death in the United States (1) and worldwide (2). Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers (2), and can be subclassified as squamous (~30%) or non-squamous (~70%; includes adenocarcinoma and large cell histologies) histological types (3).

Squamous NSCLC is a particularly aggressive form of lung cancer, for which there is a lack of effective and well-tolerated treatments available. New cytotoxic agents and targeted therapies have been evaluated, but many show little promise for first-line therapy of squamous NSCLC. For example, overall survival with the pemetrexed/cisplatin combination was inferior to gemcitabine/cisplatin in patients with squamous NSCLC histology, which was in contrast to the results seen in patients with some non-squamous forms of the disease (4). Furthermore, certain anti-angiogenic agents, such as bevacizumab, sorafenib and motesanib, have been associated with safety concerns in patients with squamous NSCLC, limiting their use to patients with non-squamous histology only (5-7).

ASA404 (vadimezan; DMXAA) is a novel, small molecule flavonoid tumor-vascular disrupting agent (Tumor-VDA) which targets the existing tumor vasculature, selectively inhibiting tumor blood flow and causing extensive necrosis of the tumor core (8). A phase II, multicentre, open-label study (9), and single-arm extension study (10) evaluated carboplatin and paclitaxel (CP) in combination with ASA404 (at doses of 1200

Conflict of interest was listed at the end of the text.

Corresponding author: Mark J. McKeage, MD. Department of Pharmacology and Clinical Pharmacology, The University of Auckland, 85 Park Road, Private Bag 92019, Grafton, Auckland 1023, New Zealand. Phone: +64-9-3737-599; Fax: +64-9-3737-556. E-mail: m.mckeage@auckland.ac.nz

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mg/m^2 and 1800 mg/m^2) as a first-line treatment for advanced NSCLC. Patients with both squamous and non-squamous NSCLC were enrolled. Addition of ASA404 to the standard chemotherapy regimen did not appear to substantially increase toxicity. Furthermore, in these two small phase II studies, ASA404 was associated with improved response rate, median time to progression (TTP) and median survival compared with the chemotherapy regimen alone.

The current retrospective analysis explores the safety and activity of ASA404 in combination with standard CP chemotherapy in patients with squamous and non-squamous advanced NSCLC using pooled results from phase II evaluations of ASA404 (1200 and 1800 mg/m^2) (9,10). Although limited by the small sample size, the objective of this study was to provide a preliminary indication of the safety and efficacy of ASA404 in patients with squamous or non-squamous advanced NSCLC to inform the study design of phase III clinical trials.

Methods

Detailed methods for the randomized, phase II, multicenter, open-label study (CP + ASA404 1200 mg/m^2 *vs* CP alone) and extension study (CP + ASA404 1800 mg/m^2) have been published previously (9,10).

The core eligibility criteria for inclusion in the study were: age 18 years or older; histologically confirmed, locally advanced or metastatic NSCLC (stage IIIb/IV, not curable by surgery or radiotherapy); one or more unidimensionally measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST); and no previous chemotherapy (11). Other requirements included a Karnofsky performance status ≥70%; a life expectancy of ≥3 months; and adequate hematologic, renal and hepatic function. Exclusion criteria included major surgery or radiotherapy (unless palliative) within 4 weeks of enrollment, CNS metastases, small cell or mixed lung cancer, pregnancy, use of medication known to affect systemic serotonin levels or QTc interval, and QTc interval prolongation or cardiac arrhythmia. There were no restrictions relating specifically to prior history of hemoptysis, anticoagulant therapy, tumor cavitation or proximity to major blood vessels. Eligible patients could have either squamous or non-squamous histology. The studies were conducted according to the Declaration of Helsinki. Ethics committee approval and informed patient consent were obtained before the start of the trials. The trial was registered on ClinicalTrials.gov: NCT00832494.

Study subjects received carboplatin (area under the curve [AUC] = 6 mg/mL•min), paclitaxel (175 mg/m^2), and ASA404 (1200 mg/m^2 or 1800 mg/m^2) (CP + ASA404) or CP alone. For the purpose of this retrospective review, phase II data for activity and safety were pooled by histology and by treatment, with aggregation of the two ASA404 doses. Treatment-emergent adverse events (AEs) of grade ≥3 were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V.3). Safety and activity results were compared between groups of patients with squamous and non-squamous histology: (1) receiving the same treatment; and (2) receiving CP + ASA404 or CP alone. Treatment differences between groups were assessed by calculating the percentage difference (for response rates) and hazard ratio (for time-to-event endpoints) with the corresponding 95% confidence interval (CI). Differences in safety responses were calculated using Fisher's exact test. Statistically significant differences are indicated by $P<0.05$.

Results

A total of 108 patients were recruited, of whom 104 were included in the safety population (CP + ASA404, n=68; CP, n=36), and 100 were evaluable for activity (CP + ASA404, n=64; CP, n=36). Details on patients excluded from the analysis are published elsewhere (9,10). Characteristics of patients included in this analysis are shown in Table 1.

The treatment groups contained similar proportions of patients with squamous and non-squamous histology. Squamous histology was present in 31% of patients treated with CP alone and 32% of patients treated with CP + ASA404 in the pooled safety population, and in 31% of patients treated with CP alone and 33% of patients treated with CP + ASA404 in the pooled activity population (9,10).

Safety

Addition of ASA404 to standard doses of CP was generally well tolerated in patients with both squamous and non-squamous histology. There were no AEs of NCI-CTCAE grade ≥3 associated with the vascular effects of bleeding, pulmonary hemorrhage, hemoptysis, hypertension or proteinuria in patients (all histologies) treated with CP + ASA404.

In both histologic groups, blood and lymphatic disorders were the most frequently reported grade ≥3 AEs (Table 2). There was no significant difference in the proportion of patients receiving CP + ASA404 who experienced grade ≥3 anemia (13.6% *vs* 4.3%; $P=0.32$), neutropenia (13.6% *vs* 13.0%; $P=1.00$), and thrombocytopenia (13.6% *vs* 2.2%; $P=0.10$) in those with squamous compared with non-squamous histology, respectively. There were also no significant differences in the rates of grade 3/4 anemia, neutropenia or thrombocytopenia in patients with squamous *vs* non-squamous histology receiving CP alone ($P=1.00$ for each comparison). Comparison by treatment (all histologies) showed rates of grade 3/4 blood and lymphatic AEs of 13.9% and 20.6% ($P=0.59$) for CP alone and CP + ASA404, respectively. Similarly, rates of individual blood and lymphatic AEs were not statistically different when ASA404 was added to

Table 1. Patient characteristics

%	ASA404 + CP		CP		All histologies	
	Squamous NSCLC (n=22)	Non-squamous NSCLC (n=46)	Squamous NSCLC (n=11)	Non-squamous NSCLC (n=25)	ASA404 + CP (n=68)	CP (n=36)
Female	32	39	18	40	37	33
Male	68	61	82	60	63	67
Mean age (years)	61	60	62	61	61	61
KPS 70,80	27	24	36	32	25	33
KPS 90,100	73	76	64	68	75	67
Stage III	41	30	46	32	34	36
Stage IV	59	70	55	68	66	64

ASA404: pooled data for 1200 mg/m^2 and 1800 mg/m^2; CP: carboplatin (AUC 6 mg/mL•min), paclitaxel (175 mg/m^2; KPS, Karnofsky performance status; NSCLC: non-small cell lung cancer.

CP: grade 3/4 anemia (2.8% and 7.4%; *P*=0.66), neutropenia (5.6% and 13.2%; *P*=0.32), and thrombocytopenia (2.8% and 5.9%; *P*=0.66) for CP alone and CP + ASA404, respectively. In patients with squamous histology, CP + ASA404 resulted in three reports (13.6%) each of grade 3/4 anemia, neutropenia and thrombocytopenia, which was not statistically different from the rates reported in patients treated with CP alone (*P*=0.53). The non-squamous subgroup also exhibited similar rates of grade 3/4 anemia (4.0% and 4.3%; *P*=1.00), neutropenia (8.0% and 13.0%; *P*=0.70), and thrombocytopenia (4.0% and 2.2%; *P*=1.00) for CP alone and CP + ASA404, respectively.

Five cardiac events of grade ≥3 were reported: two patients with squamous NSCLC receiving ASA404 1200 mg/m^2 (angina pectoris, tachyarrhythmia), two patients with non-squamous NSCLC receiving ASA404 1200 mg/m^2 (cardiomyopathy, myocardial ischemia), and one patient with squamous NSCLC receiving CP alone (tachycardia). No cardiac AEs occurred in the ASA404 1800 mg/m^2 dose cohort.

Anti-tumor activity

In patients with squamous histology, median survival was 10.2 months (95% CI: 6.0–NR [not reached]) for patients receiving CP + ASA404 compared with 5.5 months (95% CI: 2.1–12.5) for CP alone. In patients with non-squamous histology, median survival was 14.9 months (95% CI: 11.8–16.6) for patients receiving CP + ASA404 compared with 11.0 months (95% CI: 7.0–NR) for CP alone. Regardless of histology, the pooled median survival was 14.5 months (95% CI: 10.9–16.2) for patients receiving CP + ASA404 compared with 8.8 months (95% CI: 5.5–NR) for CP alone. RECIST response outcomes, TTP and median survival are shown in Table 3.

Discussion

In this retrospective, pooled analysis of a phase II, multicentre, open-label study (9), and single-arm extension study (10), the safety and activity of ASA404 in combination with standard CP chemotherapy were evaluated in patients with squamous and non-squamous stage IIIb/IV NSCLC. This analysis was limited by its retrospective nature, and by the small size of the overall group (n=104), treatment, and disease subgroups. Although strong conclusions cannot be made, these findings inform the design of definitive phase III studies of ASA404 by supporting inclusion of both squamous and non-squamous NSCLC patients.

In combination with CP, ASA404 was well tolerated in advanced NSCLC patients regardless of squamous or non-squamous histology. The profile of treatment-emergent AEs reported with ASA404 was similar to those typically associated with standard therapy. Although the incidence of thrombocytopenia and anemia was slightly higher in patients with squamous histology, it was generally manageable. The incidence of cardiac AEs was numerically higher in patients of all histologies receiving the ASA404 combination compared with CP alone (4 *vs* 1 patient). However, a casual relationship was not established to ASA404 as these events occurred in patients with pre-existing cardiovascular disorders. Cardiac safety of ASA404 should continue to be monitored in future studies.

This study was not powered for a statistical comparison of activity outcomes; however, the combination of CP and ASA404 showed a trend towards improved response rate, TTP and median survival in patients with both squamous and non-squamous NSCLC compared with those receiving CP alone. Notably, in patients with squamous histology, the addition of ASA404 to chemotherapy resulted in an improvement in

Table 2. Summary of treatment-emergent adverse events by histology: patients with ≥1 severe adverse event (grade ≥3)

n (%)	ASA404 + CP		CP		All histologies	
	Squamous NSCLC (n=22)	Non-squamous NSCLC (n=46)	Squamous NSCLC (n=11)	Non-squamous NSCLC (n=25)	ASA404 + CP (n=68)	CP (n=36)
Patients with any event grade ≥3[†]	15 (68.2)	28 (60.9)	8 (72.7)	16 (64.0)	43 (63.2)	24 (66.7)
Blood/lymphatic	4 (18.2)	10 (21.7)	0 (0.0)	5 (20.0)	14 (20.6)	5 (13.9)
o Anemia	3 (13.6)	2 (4.3)	0 (0.0)	1 (4.0)	5 (7.4)	1 (2.8)
o Neutropenia	3 (13.6)	6 (13.0)	0 (0.0)	2 (8.0)	9 (13.2)	2 (5.6)
o Thrombocytopenia	3 (13.6)	1 (2.2)	0 (0.0)	1 (4.0)	4 (5.9)	1 (2.8)
Nervous system	3 (13.6)	7 (15.2)	1 (9.1)	6 (24.0)	10 (14.7)	7 (19.4)
Skin/subcutaneous tissue	3 (13.6)	7 (15.2)	3 (27.3)	7 (28.0)	10 (14.7)	10 (27.8)
Infections/infestations	4 (18.2)	5 (10.9)	1 (9.1)	0 (0.0)	9 (13.2)	1 (2.8)
General/administration site	2 (9.1)	6 (13.0)	1 (9.1)	0 (0.0)	8 (11.8)	1 (2.8)
Respiratory/thoracic/mediastinal	3 (13.6)	3 (6.5)	1 (9.1)	0 (0.0)	6 (8.8)	1 (2.8)
Metabolism/nutrition	2 (9.1)	3 (6.5)	0 (0.0)	1 (4.0)	5 (7.4)	1 (2.8)
Cardiac	2 (9.1)	2 (4.3)	1 (9.1)	0 (0.0)	4 (5.9)	1 (2.8)
Gastrointestinal	3 (13.6)	1 (2.2)	0 (0.0)	1 (4.0)	4 (5.9)	1 (2.8)
Musculoskeletal/connective tissue	0 (0.0)	3 (6.5)	1 (9.1)	2 (8.0)	3 (4.4)	3 (8.3)
Psychiatric	1 (4.5)	2 (4.3)	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)
Investigations	2 (9.1)	0 (0.0)	0 (0.0)	1 (4.0)	2 (2.9)	1 (2.8)
Neoplasms benign/malignant/ unspecified	0 (0.0)	2 (4.3)	1 (9.1)	1 (8.0)	2 (2.9)	2 (5.6)
Immune system	0 (0.0)	1 (2.2)	2 (18.2)	0 (0.0)	1 (1.5)	2 (5.6)
Surgical/medical procedures	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Vascular	0 (0.0)	1 (2.2)	0 (0.0)	2 (8.0)	1 (1.5)	2 (5.6)
Hepatobiliary	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	1 (2.8)
Injury/poisoning/ procedural	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	1 (2.8)
Renal/urinary	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (2.8)
Reproductive/breast	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (2.8)

ASA404: pooled data for 1200 mg/m^2 and 1800 mg/m^2; CP: carboplatin (AUC 6 mg/mL•min), paclitaxel (175 mg/m^2; NSCLC: non-small cell lung cancer.

Values are the number of patients experiencing an event of grade ≥3; some patients may have experienced more than one event.

[†] Values are the total number of patients who experienced one or more event of grade ≥3.

median survival *vs* chemotherapy alone (10.2 *vs* 5.5 months, respectively). However, interpretation of these data is limited by the retrospective nature of the analysis and the small sample size.

Currently, first-line treatment of squamous NSCLC consists of standard chemotherapy-based regimens. New targeted therapies and chemotherapeutic agents have been evaluated in NSCLC, but many show little promise as first-line treatments in patients with squamous histology (4-7). For example, overall survival was less favorable with first-line pemetrexed plus cisplatin than with gemcitabine plus cisplatin in patients with squamous NSCLC (9.4 months *vs* 10.8 months, respectively; *P*=0.05) (4). In light of these findings, the use of pemetrexed is now limited to patients with non-squamous histology (4). Moreover, in a phase III trial of the multiple tyrosine kinase inhibitor (TKI) sorafenib in combination with CP, mortality rates in patients with squamous NSCLC receiving the sorafenib combination were higher than in those receiving CP alone (7). Similarly, in combination with CP, the TKI-based vascular endothelial growth factor inhibitor motesanib increased mortality over standard chemotherapy in patients with squamous NSCLC (5). This phase III study, MONET-1, was suspended by the Data Safety Monitoring Board, although it has recently been reopened for patients with

Table 3. Anti-tumor activity by histology

	Squamous NSCLC		Non-squamous NSCLC		All histologies	
	ASA404 + CP	CP	ASA404 + CP	CP	ASA404 + CP	CP
Response rate, % (95% CI)*	40.0 (19, 64) (n=8/20)	14.3 (0.4, 58) (n=1/7)	31.7 (18, 48) (n=13/41)	25.0 (8.6, 49) (n=5/20)	34.4 (23, 48) (n=21/61)	22.2 (8.6, 42) (n=6/27)
Median TTP, months (95% CI)	5.6 (4.1, 8.1) (n=21)	1.6 (1.3, 11.4) (n=11)	5.5 (4.6, 7.9) (n=43)	4.8 (3.2, 5.7) (n=25)	5.5 (4.6, 7.9) (n=64)	4.4 (2.7, 5.7) (n=36)
Median survival, months (95% CI)	10.2 (6.0, NR) (n=21)	5.5 (2.1, 12.5) (n=11)	14.9 (11.8, 16.6) (n=43)	11.0 (7.0, NR) (n=25)	14.5 (10.9, 16.2) (n=64)	8.8 (5.5, NR) (n=36)

ASA404: pooled data for 1200 mg/m^2 and1800 mg/m^2; CI: confidence interval; CP: carboplatin (AUC 6 mg/mL•min), paclitaxel (175 mg/m^2); NSCLC: non-small cell lung cancer; NR: not reached; TTP: time to progression.

*Twelve patients evaluable for other efficacy parameters were not evaluable for response.

non-squamous NSCLC only (5).

The anti-angiogenic agent, bevacizumab, was evaluated in a randomized phase II study in combination with standard CP chemotherapy in previously untreated patients with locally advanced or metastatic NSCLC. Six major life-threatening pulmonary hemorrhages occurred in patients receiving the bevacizumab-containing regimen (6). This outcome was more common in patients with squamous histology (4 of 13 patients, 30.8%) than in those with non-squamous histology (2 of 54 patients, 3.7%), and may be explained by the fact that squamous tumors are often central, large and grow in close proximity to major blood vessels. Despite these findings being described in only a small number of patients, this early signal resulted in limitation of the phase III clinical development program and subsequent registration of bevacizumab in NSCLC to patients with non-squamous histology only (12). In the present study, despite almost one-third of patients having squamous histology, no cases of major pulmonary hemorrhage were reported in patients treated with ASA404 in combination with CP. An apparent lack of severe adverse vascular effects may be unexpected for a drug causing tumor hemorrhagic necrosis, but could be attributed to the distinct anti-vascular action of ASA404 compared with anti-angiogenic agents such as bevacizumab.

Conclusions

Phase II evaluations suggest that ASA404 is a promising addition to standard chemotherapy for the first-line treatment of NSCLC, regardless of histology. This small analysis indicates that ASA404 has a similar safety and activity profile in patients with squamous and non-squamous NSCLC but this finding must be confirmed by larger prospective studies. The phase III study of ASA404 as a first-line treatment for NSCLC in combination with chemotherapy (ATTRACT-1) has been halted following interim data analysis showing futility (13). However, no safety concerns were identified and the phase III second-line study in combination with docetaxel (ATTRACT-2) is ongoing. The latter phase III study includes patients with both squamous and non-squamous histologies. The current retrospective analysis of pooled data from two small phase II studies has several limitations but informs the design of these subsequent larger definitive trials.

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