Update on survival in a phase Ib/II study of DMXAA (AS1404) combined with carboplatin and paclitaxel in non-small cell lung cancer (NSCLC)

Joachim von Pawel[1], Martin Reck[2], Mark McKeage[3], AS1404-201 Study Group Investigators

[1]Asklepios Hospital, Gauting, Germany; [2]Hospital Grosshansdorf, Hamburg, Germany; [3]The University of Auckland, Auckland, New Zealand

Background

- Many patients with NSCLC have a late-stage presentation, where standard treatment is usually platinum-based chemotherapy, often in combination with the taxane paclitaxel
- None of the frequently used platinum-based regimens is more advantageous than the others,[1] indicating a need for new approaches to treatment
- 5,6-dimethylxanthenone-4-acetic acid (DMXAA [AS1404])[2] is a small-molecule vascular disrupting agent (VDA)[3]
- VDAs attack tumour blood vessels selectively, causing the rapid shutdown of tumour blood flow[4,5]
- In animal models DMXAA shows additive or supra-additive effects with cytotoxics, including taxanes and platinum compounds[6–8]
- Three randomised, controlled phase II trials have combined DMXAA with taxane or taxane plus platinum regimens in lung, prostate and ovarian cancers
- Initial data from the lung cancer study were reported at ASCO 2006; updated safety, time to tumour progression and survival data are now available

Objectives

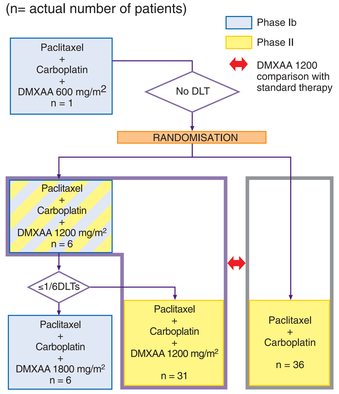
- Phase Ib: to test three incremental doses of DMXAA in combination with carboplatin and paclitaxel:
  - to confirm a suitable dose of DMXAA for this combination
  - to assess the potential for drug interactions
- Phase II: to determine the safety, tolerability and efficacy of DMXAA 1200 mg/m² in combination with carboplatin and paclitaxel in patients with locally advanced and metastatic NSCLC

Methods

Study design

- Men and women aged ≥ 18 yrs with histologically confirmed stage IIIb or IV NSCLC, previously untreated with chemotherapy
- Randomised, multicentre, open-label, integrated, phase Ib/II study (fig.1)
- One patient was treated with DMXAA 600 mg/m² plus standard therapy for initial assessment of safety before randomisation began; standard therapy was carboplatin AUC 6 mg/ml×min + paclitaxel 175 mg/m²; treatment was given every 21 days for up to 6 cycles
- Further patients were then randomised to receive DMXAA 1200 mg/m² (DMXAA 1200) plus standard therapy or standard therapy alone.
  - initial recruitment was staggered for safety monitoring
- A higher dose of DMXAA 1800 mg/m² was tested in six patients
- On day 1 of each 21-day treatment cycle, patients received:
  - paclitaxel as a 3-hour IV infusion, then
  - carboplatin as a 30-minute IV infusion, then (if allocated)
  - DMXAA as a 20-minute IV infusion
- Follow-up:
  - imaging assessment 6-weekly until disease progression
  - 3-monthly after progression confirmed

Figure 1: Study design flowchart
(n= actual number of patients)



Safety assessments

- Clinical examination
- Laboratory tests
- Adverse events
- 12-lead electrocardiograms (DMXAA arm only)
- Ophthalmic examination (DMXAA arm only)

Efficacy assessments

- Tumours measured using CT or MRI
- Radiological review by investigators and an independent, blinded reviewer
- Tumour response evaluated using Response Evaluation Criteria In Solid Tumours (RECIST)[9] and categorised as complete (CR), partial (PR), stable disease (SD) or progressive disease (PD)
- Response rate (RR) defined as % of patients in each group who achieved CR or PR
- Time to tumour progression (TTP) defined as time from initial treatment to first objective documentation of PD
- Survival defined as time from initial treatment to death

Study variables

- Primary safety outcomes: pharmacokinetic parameters (phase Ib), adverse events, laboratory abnormalities, effect on QTc interval (from 12-lead electrocardiograms) and ophthalmic toxicity
- Efficacy endpoints: objective RR, TTP, duration of response and stable disease, median and 1-year survival

Results

Patient characteristics

- In the randomised comparison of DMXAA 1200 and standard therapy:
  - 37 patients were included in the DMXAA 1200 safety population, 34 of whom were eligible for efficacy analysis
  - 36 patients were included in the standard therapy safety population, all of whom were eligible for efficacy analysis
  - the groups were well balanced for pre-treatment characteristics (Table 1)
- Additionally, in the phase Ib component:
  - One patient received DMXAA 600 mg/m² + standard therapy
  - Six patients received DMXAA 1800 mg/m² + standard therapy

Table 1: Baseline characteristics of patients

	DMXAA 1200 n = 37	Standard therapy n = 36
Male/female	23/14	24/12
Mean age (years)	59.4	61.0
Type of NSCLC		
Squamous	11	11
Adenocarcinoma	25	22
Other	1	3
Stage of NSCLC		
IIIb	11	13
IV	26	23
Karnofsky performance status		
70	1	3
80	9	9
90	17	14
100	10	10

Safety

- Phase Ib:
  - addition of DMXAA to standard therapy was well tolerated at all doses of DMXAA tested
  - no evidence for clinically relevant drug interactions between DMXAA and carboplatin and paclitaxel in combination (no change in AUC or C_{max} for carboplatin or paclitaxel)
- Phase II:
  - overall safety profiles similar in the DMXAA 1200 and standard therapy groups
  - 23 treatment-emergent serious adverse events in the DMXAA 1200 group compared with 24 in the standard therapy group (details in Table 2); 521 versus 396 treatment-emergent adverse events

Table 2: Treatment-emergent serious adverse events by number of patients

Category of SAE	DMXAA 1200 n = 37	Standard therapy n = 36
Blood and lymphatic system	1	3
Cardiac	4	1
Gastrointestinal	3	3
General disorders and adminstration site conditions	5	3
Immune system	0	2
Infections and infestations	7	2
Injury, poisoning and procedural complications	0	1
Metabolism and nutrition	1	1
Renal and urinary	0	2
Respiratory, thoracic and mediastinal	2	4
Vascular	0	1
Total no. of patients with one or more SAEs	16	17

- the addition of DMXAA to standard chemotherapy:
  - had no impact on the patients' ability to complete the standard chemotherapy schedule
  - did not increase heart rate-corrected QT (QTc) interval; cardiac SAEs were observed in some patients, all of which were transient, reversible and not deemed by the treating physician to be related to DMXAA
  - was not associated with clinically significant ophthalmic abnormalities
- There was no difference in safety findings between squamous and non-squamous patients

Efficacy – DMXAA 1200 vs standard therapy

Tumour response

- Figure 2 shows independently-assessed RECIST outcomes
  - RR was 31.2% in the DMXAA 1200 group and 22.2% in the standard therapy group
- Independent assessment of response in patients receiving DMXAA 1800 mg/m² showed 3PRs, 2SDs and 1PD

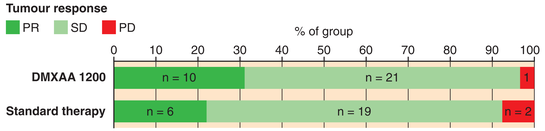
Time to tumour progression

- Figure 3 shows investigator-determined time to tumour progression after 12 months' follow-up of all patients:
  - median TTP was 5.4 months in the DMXAA 1200 group and 4.4 months in the standard therapy group (hazard ratio (95% CI) = 0.86 (0.5, 1.4))

Survival

- Figure 4 is a Kaplan-Meier plot for survival
  - median survival time was 14.0 months for the DMXAA 1200 group and 8.8 months for the standard therapy group (hazard ratio (95% CI) = 0.73 (0.39, 1.38))

Figure 2: Independently-assessed RECIST response outcomes



2 patients in the DMXAA group and 9 in the standard therapy group could not be evaluated in the independent assessment of response

Figure 3: Kaplan-Meier time to progression curves for DMXAA 1200 (n=34) and standard therapy (n=36) (investigators' assessment)

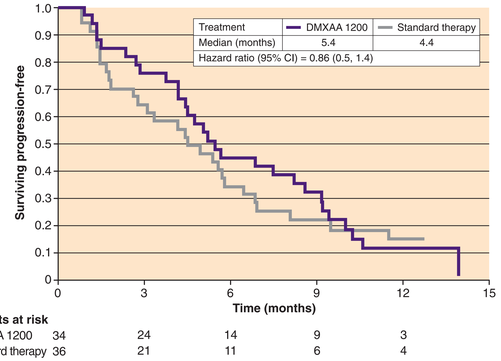
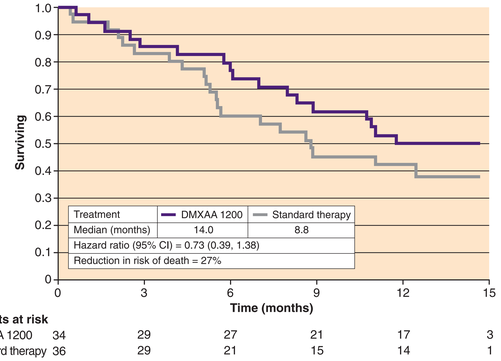


Figure 4: Kaplan-Meier survival curves for DMXAA 1200 (n=34) and standard therapy (n=36)



Conclusions

- **Addition of DMXAA to standard doses of carboplatin and paclitaxel in patients with locally advanced and metastatic NSCLC:**
  - **was well-tolerated, producing no substantial additional toxicity**
  - **improved a range of efficacy endpoints (response rate, TTP and survival) compared with carboplatin and paclitaxel alone**
  - **increased median survival by 5.2 months**
- **DMXAA is the first vascular disrupting agent to demonstrate proof of concept in a randomised controlled study**
- **These data are consistent with preliminary findings from other phase II studies, which show an increase in PSA response rate in hormone-refractory prostate cancer and an increase in tumour response rate in recurrent ovarian cancer when DMXAA is added to chemotherapy**
- **DMXAA combined with carboplatin and paclitaxel will now be evaluated in a phase III study in NSCLC**

References

1. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–8, 2002
2. Rewcastle GW, Atwell GJ, Li ZA, Baguley BC, Denny WA: Potential antitumor agents. 61. Structure-activity relationships for in vivo colon 38 activity among disubstituted 9-oxo-9H-xanthene-4acetic acids. J Med Chem 34:217–222, 1991
3. Siemann DW, Bibby MC, Dark GG, et al: Differentiation and definition of vascular-targeted therapies. Clin Cancer Res 11:416–20, 2005
4. Siemann DW, Chaplin DJ, Horsman MR: Vascular-targeting therapies for treatment of malignant disease. Cancer 100:2491–9, 2004
5. Kelland LR: Targeting established tumor vasculature: a novel approach to cancer treatment. Curr Cancer Ther Rev 1:1–9, 2005
6. Pruijn FB, van Daalen M, Holford NH, et al: Mechanisms of enhancement of the antitumour activity of melphalan by the tumour-blood-flow inhibitor 5,6-dimethylxanthenone-4-acetic acid. Cancer Chemother Pharmacol 39:541–6, 1997
7. Wilson WR, Baguley BC: Combination of the antivascular agent DMXAA with radiation and chemotherapy. Int J Radiat Oncol Biol Phys 46:706, 2000
8. Siim BG, Lee AE, Shalal-Zwain S, et al: Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA). Cancer Chemother Pharmacol 51:43–52, 2003
9. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–16, 2000