A Phase I study of the MEK1/2 inhibitor selumetinib in combination with first-line chemotherapy regimens for NSCLC

Emma Dean, Nicola Steele, Hendrik-Tobias Arkenau, Fiona Blackhall, Noor Md Haris, Colin R. Lindsay, Matilde Saggese, Raffaele Califano, Alastair Greystone, Mark Voskoboybin, Dana Ghorbhiu, Ian T. Dymond, Tam R. Plummer

The Christie Hospital NHS Foundation Trust, Manchester, UK; The Beatson West of Scotland Cancer Centre, Glasgow, UK; Sarah Cannon Research Institute UK, London, UK; Northern Centre for Cancer Care, Freeman hospital, Newcastle upon Tyne, UK; AstraZeneca, Alderley Park, Macclesfield, UK

Introduction

Selumetinib (AZD6244) is a selective MEK1/2 inhibitor entering phase II trials for the treatment of advanced cancers. This study evaluated selumetinib in combination with first-line chemotherapy regimens in patients with advanced NSCLC.

Methods

Patient eligibility criteria included patients with histologically confirmed NSCLC, no prior chemotherapy, ≤ 2 prior systemic therapies, and performance status (PS) 0–1. Chemotherapy regimens included: Sel50+gem+carb, sel50+gem+cis, sel75+pem+carb, and sel75+pem+gem.

Results

The study enrolled 21 patients to the four different chemotherapy regimens. The safety analysis set had 17 patients. Sel50+gem+carb was not tolerated. Safety and tolerability were assessed in patients enrolled in remaining regimens. Sel50+gem+cis and sel75+pem+carb were tolerated in phase 1 patients; sel75+pem+gem was not tolerated.

Conclusions

This phase 1 study demonstrated preliminary findings of the combination of chemotherapy + selumetinib, with acceptable tolerability and suitable dose levels for sel75+pem+carb and sel75+pem+gem. Further investigation of selumetinib in combination with chemotherapy is warranted.

Safety and Tolerability

Selumetinib

Adverse Event

Frequencies (%)

sel50+gem+carb

sel50+gem+cis

sel75+pem+carb

sel75+pem+gem

Grade 3–4

Grade 1–2

Grade 3–4

Grade 1–2

Grade 3–4

Grade 1–2

Grade 3–4

Grade 1–2

Selumetinib (50 mg bid)

Selumetinib (75 mg bid)

Grade 1

N=6 enrolled

N=5 enrolled

N=6 enrolled

N=3 enrolled

Female

Male

Total

Female

Male

Total

Female

Male

Total

Selumetinib (50 mg bid)

Selumetinib (75 mg bid)

Cohorts enrolled in parallel. Patients are still ongoing on treatment in the following cohorts: sel50+gem+carb, n=1; sel75+gem+cis, n=2; sel75+pem+carb, n=1 (partial response case).

Pharmacokinetics

Selumetinib plasma exposures, measured by plasma concentration (AUC) following daily oral administration (Figure 1). The plasma concentration-time (C-t) curves were generally flat, with a slight increase between cycles 1 and 2, and no difference between cycles 2 and 3.

Slopes were steeper in the dose escalation cohorts, indicating that dose escalation was tolerated.

Two patients died during the study due to AEs. One patient died due to sepsis post surgery; the second patient died due to myocardial infarction (left bundle branch block) during cycle 2 and was hospitalized for 3 days prior to death. The review of the ABM recordings indicated that no apparent changes were observed.

The mean steady state concentration (Cmax) of selumetinib was 29–113 ng/ml with a median of 61 ng/ml. The plasma exposure (AUC) was 87–384 ng·h/ml with a median of 169 ng·h/ml.

Conclusions

This phase 1 study demonstrated preliminary findings of the combination of chemotherapy + selumetinib, with acceptable tolerability and suitable dose levels for sel75+pem+carb and sel75+pem+gem. Further investigation of selumetinib in combination with chemotherapy is warranted.