Phase II open label randomised trial of AS1409 compared to dacarbazine in the first line treatment of advanced malignant melanoma.

Introduction

AS 1409 is a fusion cytokine consisting of IL-12 conjugated to an antibody directed against EDB fibronectin. This is an oncofetal antigen preferentially expressed on a variety of malignant tissues, including that of melanomatous origin.

The management of advanced melanoma remains unsatisfactory and until very recently the only established agents were dacarbazine and temozolamide. Both produced only modest efficacy at best with response rates of about 15% and an improvement in progression free survival of only weeks. Alternatives such as carboplatin and fotemustine have failed to provide any additional benefit.

Recently however there have been a number of advances in the management of this condition, including immunotherapy approaches such as the CTLA-4 antagonist impilimumab and targeted agents such asvemurafenib directed against BRAF V600 mutant disease. Although advanced melanoma is now a very actively researched area, there remains a need for agents such as AS1409 with novel mechanisms of action in appropriately selected patient populations.

IL-12 by itself has been utilised previously in the treatment of advanced melanoma, when given by the intra-venous, subcutaneous and intra-muscular routes. It showed promising initial efficacy but more widespread use was limited by preclusive systemic toxicity. AS1409 represents a new and unique approach by combining this immunoactive agent with a targeted delivery mechanism.

Study Objectives:

1. To assess the comparative efficacy of AS1409 when compared to dacarbazine in the first line treatment of patients with advanced malignant melanoma
2. To assess the safety and tolerability of AS1409 in patients with advanced malignant melanoma
3. To assess pharmacodynamic effects of AS1409 on cytokine levels
4. To measure the pharmacokinetics of AS1409 and the level of anti-drug antibody production

Study Endpoints:

1. The primary endpoint is progression free survival (PFS).

2. Secondary endpoints include: Response rate (RR), Duration Of Response (DR) ,Time to Progression (TTP), Overall survival (OS)
3. Safety and tolerability as measured by CTCAE criteria
4. Effects on levels of gamma interferon and IP-10

Number of patients:	150 patients will be recruited, 100 in the AS1409 treatment arm and 50 in the dacarbazine arm
Number of Centres:	20
Number of Countries:	4
Duration of Recruitment:	12 months
Study Duration:	6 months
Total Study Duration:	18 months
Study Design:	Open label, 2:1 Randomised, Phase II. Patients will be followed up until disease progression or 6 months after randomisation, whichever occurs first

Main Inclusion Criteria:

1. Males or females aged over 18 years
2. ECOG Performance Status 0-2
3. Histologically confirmed diagnosis of melanoma
4. Surgically unresectable advanced malignant melanoma (AJCC Stage IIIC or Stage IV)
5. No previous chemotherapy or immunotherapy for melanoma (systemic or intra-lesional)
6. No radiotherapy within last four weeks
7. Measurable disease
8. Life expectancy of at least six months
9. Adequate organ function

Main Exclusion Criteria:

1. Active CNS metastases or cacinomatous meningitis
2. Previous treatment with dacarbazine (for any other unrelated malignancy)
3. Previous exposure to IL-12
4. Other malignancy within last two years
5. Uncontrolled or significant heart failure, myocardial infarction or pulmonary dysfunction
6. Patients receiving immunosuppressive therapy
7. Patients requiring oral corticosteroids
8. Autoimmune haemolytic disease
9. Clinically significant liver disease (baseline LFTs >3 x ULN)
10. Pregnant or nursing women

Study Drug Administration:

AS1409:	This will be given as a weekly 30 minute infusion, at a dose of 15 µg/kg, until disease progression or withdrawal due to toxicity.
Dacarbazine:	This will be administered intravenously at a dose of 250mg/m^2 for five days, every 3 weeks., until disease progression or withdrawal due to toxicity.

Study Schedule:

Screening Visit:	Within 14 days of randomisation
Study Day One:	Patients will be followed for 6 hours in the clinic after the first administration of study medication
Study Day 8 Onwards:	Weekly clinic attendance for administration of AS1409. Weekly clinic attendance every three weeks for administration of dacarbazine
Clinical Safety:	Day 8, and then every three weeks whilst on study medication
CT/MRI Imaging:	Baseline and then every six weeks, until progression
Clinical Tumor Assessment:	(Where possible) Baseline and then every six weeks, until progression

Lab Safety Testing:	Baseline, Day 8 and then every three weeks whilst on study medication
Cytokine Measurement:	Baseline, Day 1, Day 8 and then every six weeks whilst on study medication (AS1409 arm only).
Blood sampling for ADAs:	Baseline, Week 3, End of Study (AS1409 arm only).

Primary Endpoint:

The primary efficacy endpoint is Progression Free Survival. Kaplan Meier methods will be used to estimate PFS in each treatment group. Estimates of median survival will be provided along with 95% confidence intervals. Hazard ratio estimates will also be presented.

Sample Size:

The calculation of sample size is based on the comparison of the primary end point, PFS between the 2 treatment groups at a 2-sided significance level of 0.05%, assuming median PFS is 1.5 months in the dacarbazine group and 2.5 months in the AS1409 group.