A Phase 1 Study of AS1409, a Novel Antibody-Cytokine Fusion Protein, in Patients with Malignant Melanoma or Renal Cell Carcinoma

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Abstract

Purpose: AS1409 is a fusion protein comprising a humanized antibody BC1 linked to interleukin-12 (IL-12). It is designed to deliver IL-12 to tumor-associated vasculature using an antibody targeting the ED-B variant of fibronectin.

Experimental Design: We conducted a phase 1 trial of weekly infusional AS1409 in renal carcinoma and malignant melanoma patients. Safety, efficacy, markers of IL-12-mediated immune response, and pharmacokinetics were evaluated.

Results: A total of 11 melanoma and 2 renal cell carcinoma patients were treated. Doses of 15 and 25 mg/kg were studied. Most drug-related adverse events were grade 2 or less, and included pyrexia, fatigue, chills, headache, vomiting, and transient liver function abnormalities. Three dose limiting toxicities of grade 3 fatigue and transaminase elevation were seen at 25 mg/kg. IFN-γ and interferon-inducible protein-10 (IP-10) were elevated in all patients, indicating activation of cell-mediated immune response; this was attenuated at subsequent cycles. Antidrug antibody responses were seen in all patients, although bioassays indicate these do not neutralize AS1409 activity. Plasma half-life was 22 hours and not dose-dependent. Five patients received 6 cycles or more and a best response of at least stable disease was seen in 6 (46%) patients. Partial response was seen in a melanoma patient, and disease shrinkage associated with metabolic response was maintained beyond 12 months in another melanoma patient despite previous rapid progression.

Conclusions: The maximum tolerated dose was established at 15 mg/kg weekly. AS1409 is well tolerated at this dose. Evidence of efficacy assessed by RECIST, functional imaging, and biomarker response warrants the planned further investigation using this dose and schedule in malignant melanoma.

Introduction

AS1409 (huBC1-IL12) is a novel fusion protein comprising a humanized antibody BC1 and the cytokine interleukin 12 (IL-12). The antibody BC1 recognizes the extra-domain B (ED-B) fibronectin isoform, an oncofetal antigen that is expressed in fetal and tumor tissues, but has a restricted distribution in normal adult tissues (1, 2). ED-B fibronectin is produced by tumor cells and deposited in the subendothelial extracellular matrix in solid tumors, possibly playing a role in promoting angiogenesis to support tumor growth (1). The parental murine antibody BC1 has previously been administered to patients with primary brain tumors without major toxicities (3). We have used a hexameric fusion protein, AS1409 (molecular weight 300 kDa) linking the humanized BC1 antibody via the Fc domain to human IL-12 (Fig. 1).

IL-12 is a heterodimeric cytokine that mediates both innate and adaptive immunity. It stimulates the cellular cytotoxicity of natural killer (NK) cells and cytotoxic T lymphocytes, and induces the development of Th1 cells. This leads to macrophage activation via interferon gamma (IFN-γ) and interferon-inducible protein 10 (IP-10; ref. 4). The antitumor activities of IL-12 have been established in animal models (5, 6) and in a number of clinical trials in humans (7, 8). The systemic administration of interleukin 12 (IL-12) at doses of 500 ng/kg, 2 or 3 times weekly, was associated with a number of significant toxicities. These included fever, chills, fatigue, anorexia, nausea and vomiting, headache, myalgia, arthralgia, and reversible elevations in serum liver transaminase levels (7, 8). The severity of these toxicities has prevented further clinical development of single agent IL-12 as therapy for solid tumors.
One approach to improving the therapeutic ratio is to deliver IL-12 directly to the tumor site. The use of tumor-specific antibodies to target cytokines to the tumor microenvironment has been validated in mouse models (9) and other tumor types (prostate and colon). The efficacy of large antibody-based immunotherapies is potentially restricted by poor penetration of the tumor mass; targeting the extracellular matrix associated with tumor vasculature utilizes the proximity and accessibility of this antigen.

The affinity of AS1409 compared with the parental antibody BC1 for its antigen is not impaired and AS1409 retains IL-12 biological activity in both cell based assays and in vivo studies with Cynomolgus monkeys (unpublished observations, Antisoma Research Ltd). In addition, targeting of the antibody BC1 has been demonstrated preclinically in nude mice bearing human tumor xenografts (10). Human IL-12 is inactive in mice and as a result AS1409 could not be tested preclinically for antitumor activity in standard xenograft mouse models. A surrogate molecule (huBC1-muIL-12) containing mouse IL-12 demonstrated antitumor activity against a number of tumor cell types in animal models (11).

Although the BC1 antibody is species-specific, nonhuman primates such as the Cynomolgus monkey are responsive to human IL-12. The Cynomolgus monkey was therefore selected as an informative species in which to test the safety of AS1409 before dosing to humans. A number of studies were performed using this species. AS1409 was well tolerated at all single dose levels tested (2–100 μg/kg), and in a repeat dose study (0–1,000 μg/kg intravenously weekly for 8 weeks) toxicities were not observed. Transient changes in laboratory values and reversible microscopic pathological tissue changes were however observed with twice weekly dosing at 5,000 μg/kg. The No Observable Adverse Event Level (NOAEL) was set at 500 μg/kg with a once weekly intravenous administration.

We chose to evaluate AS1409 in patients with malignant melanoma and renal cell carcinoma. Responses to human IL-12 have been demonstrated in these tumor types, albeit in association with significant toxicity (12, 13). ED-B fibronectin is consistently overexpressed in human tumors in the subendothelial extracellular matrix (1). This first-in-human phase 1 dose escalation study explored the safety, biological activity, clinical efficacy, and pharmacokinetics of the novel fusion protein in this patient population.

Materials and Methods

Study objectives

The primary objectives of this study were to determine the tolerability, safety, and maximum tolerated dose (MTD) of AS1409 in single and repeated doses. Further objectives were to determine the biological response to AS1409, including IFN-γ and IP-10 circulating concentrations, and in addition to define the pharmacokinetics and antitumor activity of AS1409.

Patients

Eligible patients were over 18 years of age with histopathologically confirmed malignant melanoma or renal cell carcinoma that was metastatic and not amenable to...
curative treatment. Malignant melanoma patients with unresectable stage III or IV disease and with metastases at any site were eligible. Renal cell carcinoma with clear cell, papillary or chromophobe histology was included. Patients were excluded if their only site of metastatic disease was a single bony lesion, although those with clinically stable CNS metastases not requiring steroid therapy were eligible. Patients may have had prior systemic treatment for their malignancy, although this must have been completed more than 4 weeks before study entry. In addition, patients who were ineligible for standard first line therapy were included. Patients were required to have adequate bone marrow, liver & kidney function. An ECOG performance status of 2 or less was required as well as either evaluable or measurable disease. Patients were excluded if they had a history of autoimmune or predominantly Th-1–driven clinical disorders (including rheumatoid arthritis, psoriasis, chronic inflammatory bowel disease), or were receiving systemic steroids or other immunosuppressive therapies. In addition, patients who were considered a poor medical risk as a result of nonmalignant systemic disease/active infection or those with diabetic retinopathy, substantive surgery within 4 weeks or a second malignancy other than nonmelanomatous skin cancer or cervical intraepithelial neoplasia were also excluded.

**Drug administration**

AS1409 was supplied as a 1 mg/mL solution in aqueous buffer at pH 6.0. It was administered to patients following a 1 to 1 dilution with 0.9% sodium chloride to a concentration of 0.5 mg/mL intravenous infusion over 30 minutes at weekly intervals for 6 cycles, or until disease progression. Patients were treated with paracetamol and an antihistamine as prophylaxis against fever, chills, and other potential systemic effects of the study drug. Where treatment-related toxicity was experienced, a maximum period of 3 weeks between doses was acceptable if necessary to allow recovery from treatment-related toxicities. Dose reductions were not permitted. Treatment was extended beyond 6 cycles at the investigators discretion for responding or nonprogressing patients. Sequential cohorts of patients were to receive increasing dosages of AS1409 starting at 15 mg/kg with a minimum of 1 week elapsing between first dosing of patients in each cohort. The starting dose of AS1409 was chosen on the basis of data available from comparative studies in Cynomolgus monkeys comparing

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>15 µg/kg (n = 7)</th>
<th>25 µg/kg (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>5/2</td>
<td>4/2</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>58 (51–77)</td>
<td>41 (22–57)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>2 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>5 (71%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>4 (57%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Prior surgery for cancer</td>
<td>7 (100%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>3 (43%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Completed ≥ 6 cycles AS1409</td>
<td>4 (57%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Median no. cycles (range)</td>
<td>6.0 (4–30)</td>
<td>4.5 (3–6)</td>
</tr>
</tbody>
</table>

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**Table 2. Drug-related adverse events (AE) by grade, excluding laboratory abnormalities**

<table>
<thead>
<tr>
<th>MedDRA preferred term</th>
<th>All grades</th>
<th>Grade 3,4</th>
<th>All grades</th>
<th>Grade 3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>7 (100)</td>
<td>0</td>
<td>4 (67)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (86)</td>
<td>1 (14)</td>
<td>6 (100)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (57)</td>
<td>0</td>
<td>4 (67)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (43)</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (43)</td>
<td>0</td>
<td>3 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (43)</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (43)</td>
<td>0</td>
<td>5 (83)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (57)</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (43)</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (29)</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (29)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pollakiuria (Urinary frequency)</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coombs Positive Haemolytic Anemia</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
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</table>
human IL-12 and AS1409. The Cynomolgus monkey is an appropriate species for in vivo exposure of AS1409 as it has an intact immune system and has been previously used for in vivo exposure of huIL-12. For AS1409 in Cynomolgus monkeys, the NOAEL was 500 mg/kg and the MTD was 2,500 mg/kg. By comparing the results seen for huIL-12 in nonhuman primates and human patients, it was possible to estimate a dose of AS1409 which may have activity and also be tolerable. This dose was estimated as 150 mg/kg. The starting dose for this study was therefore chosen as 10-fold lower than this estimated dose. The dosing schedule was determined as a result of observations made in nonhuman primate studies that weekly dosing was well tolerated and that bolus dosing resulted in elevated IFN-γ for at least a week.

Study design
The planned dose escalation in successive cohorts was 15, 30, 60, 120, and 200 µg/kg, with intermediate dose levels to be explored where appropriate. Dose escalations or cohort expansions occurred depending on dose limiting toxicities. A dose limiting toxicity (DLT) was defined as grade 3 nonhematological adverse events not improving to grade 2 or less within 24 hours (excluding nausea and vomiting), or any of 3 specific hematological toxicities—absolute neutrophil count of less than 0.5 x 10^9/L for more than 7 days; febrile neutropenia; or platelet count less than 25 x 10^9/L for more than 7 days, or with grade 3 to 4 hemorrhage at any time. The MTD was defined as the dose level below which 2 out of 6 patients experienced a DLT.

Safety assessments
Patients were admitted overnight following dosing at cycle 1 and 2 to facilitate safety monitoring procedures. This requirement for admission was waived after cycle 2 if there were no clinically relevant adverse events related to AS1409 encountered during the previous cycles. During the period of AS409 dosing patients attended the investigational units for safety evaluation at weekly intervals, and subsequently at 1, 4, and 12 weeks.

Efficacy assessments
Tumor assessments were performed (using conventional CT or MRI examination) every 6 weeks after initiating treatment until progressive disease as defined by RECIST criteria. Any patients who had not progressed after 6 months reverted to 12-weekly scanning frequency.

Pharmacodynamic assays
Plasma concentrations of the biomarkers IFN-γ and IP-10 were measured predose and 1, 2, 4, 6, 8, 12, and 24 hours postdose in cycles 1 and 2, and predose each subsequent cycle. Samples were also taken at weeks 1, 4, and 12 after the last dose of AS1409 was administered. Antidrug antibody (ADA) samples were drawn predose for each cycle (1–6) and for those patients receiving additional cycles of treatment at every 4th cycle, 1 hour after the dose. Additional samples were collected at 1, 4, and 12 weeks after the last dose of drug was administered. Plasma samples containing ADA were preincubated with AS1409 and incubated with NK92 cells in the presence of
ED-B fibronectin and the supernatant assayed for IFN-γ production.

**Pharmacokinetic sampling and assays**

Pharmacokinetic blood samples were drawn prior to the first dose and at 1, 2, 4, 6, 8, 12, and 24 hours postdose for cycles 1 and 2, and predose at each subsequent cycle. Plasma was separated from blood samples and stored frozen at −70°C, and the resulting cell pellet underwent red cell lysis. The isolated cells were also frozen at −70°C until analysis. Plasma samples were analyzed for unchanged AS1409 concentrations and the following pharmacokinetic parameters were evaluated from the plasma samples: the terminal half-life calculated from the terminal slope of the log concentration-time curve (t½), maximum concentration (Cmax), the time of peak plasma concentration (Tmax), and area under the curve (AUC).

**Results**

Thirteen patients were treated between January 2007 and January 2009, with median age 58 years (range 22–77 years). Patient characteristics are listed in Table 1. Eleven malignant melanoma and 2 renal cell carcinoma patients were treated. Most patients had received a prior systemic therapy. Some adverse events were observed at 15 μg/kg, the first dose level explored, and therefore the next cohort was treated at 25 μg/kg, at which DLTs occurred. The median number of cycles received was 6 for the 15-μg/kg cohort and 4.5 for the 25-μg/kg cohort.

**Safety**

No DLTs were seen at 15 μg/kg weekly. However, 3 patients experienced DLTs at the 25 μg/kg dose level: 1 patient developed grade 3 fatigue, and 2 patients developed grade 3 transaminase elevation which resolved on discontinuation of study drug. The MTD was therefore 15 μg/kg weekly, and 7 patients were treated at this dose.

In general AS1409 was well tolerated with the majority of adverse events being low grade (≤2). The most common events were pyrexia, fatigue, chills, headache, and vomiting (Tables 2 & 3). All patients in the first cohort and two-thirds in the second experienced mild pyrexia, fatigue and chills. Grade 3 to 4 fatigue was experienced by 3 patients and grade 3 to 4 vomiting, dehydration, urinary frequency, and loss of consciousness in 1 patient, not attributable to the study drug. Grade 3 to 4 elevation of transaminases was
observed in 3 patients (50%) treated at 25 μg/kg and in 1 patient this was also accompanied by hyperbilirubinemia. In all cases this was a transient elevation that resolved spontaneously. Grade 3 to 4 anemia was observed in a total of 5 patients (45%), and in addition 7/11 (63%) had a lymphopenia.

Pharmacokinetics

An exponential or biexponential decline of plasma concentrations was observed. The plasma AS1409 concentration versus time profiles are shown in Figure 2A. The pharmacokinetic parameters at cycle 1 are shown in Figure 2B, where the mean terminal elimination half-life was approximately 22 hours, and mean total body clearance approximately 700 mL/hour. No changes were observed in these parameters between the 15- and 25-μg/kg dose cohorts. Systemic exposure, as measured by $C_{\text{max}}$ and AUC$_{0-\infty}$, increased as expected with dose, although this increase was not dose proportional.

Pharmacodynamics

All patients showed an elevation of IFN-γ and IP-10 following the first dose, indicating activation of cell-mediated immune response (Fig. 3A and B); this was attenuated but clearly detectable at subsequent cycles.

Antidrug antibody responses

ADA responses were seen in all patients after administration of the first dose of AS1409. In vitro preincubation of AS1409 with ADA-containing patient plasma did not reduce IFN-γ stimulation on exposure to ED-B fibronectin, indicating that the binding of AS1409 to antigen is not blocked directly (data not shown). In vivo, binding of AS1409 by ADA may attenuate bioavailability as a result of clearance of resulting immune complexes. There was no correlation between ADA titre and clinical response.

Antitumor effects

One patient with melanoma achieved a partial response and remained on AS1409 at 15 μg/kg/week for 7 months (Fig. 4A). A best response of stable disease was seen in a further 5 patients (Fig. 4C). One patient with melanoma showed a 29% RECIST reduction accompanied by a metabolic response on FDG-PET maintained at 17 months after 6 weekly doses at 25 μg/kg/week (Fig. 4B). This patient’s metastatic nodal disease was progressing rapidly prior to enrolment despite the administration of dacarbazine chemotherapy. Another patient had stable disease for 4 months prior to progression with new disease. A patient with renal carcinoma had rapid involution of large subcutaneous metastases but progressed in the lungs.

Discussion

AS1409 is a novel fusion protein joining IL-12 with a humanized antibody BC1 specific for the extra-domain B (ED-B) isoform of fibronectin. IL-12 alone has been studied in both animal and human subjects, with antitumor activity but significant toxicities in clinical trials (7, 8). The rationale for the evaluation of AS1409 is to target the delivery of IL-12 to the tumor and thereby minimize systemic toxicity. In this first-in-human phase 1 clinical trial toxicity of AS1409 was manageable and predictable at 15 μg/kg, consisting primarily of pyrexia, fatigue, chills, and transient transaminase elevation. DLT was observed at 25 μg/kg, and the maximum tolerated dose was therefore established at 15 μg/kg. The DLTs observed were those consistent with known toxicities of IL-12, although less prominent than seen with the single agent cytokine in previous clinical trials. The tolerated dose of AS1409 is equivalent to an IL-12 dose significantly greater than that previously administered as a single agent (7, 8). This supports the hypothesis that linking of IL-12 to an antibody in AS1409 improves the therapeutic ratio of this cytokine. In addition, the reduced toxicity profile of AS1409 compared with IL-12 alone supports relatively successful specific delivery of IL-12 directly to the tumor, as previously demonstrated in animal models (10).
This phase 1 study treated 13 patients in total, 11 with malignant melanoma and 2 with renal cell carcinoma. Marked tumor shrinkage was seen in 2 melanoma patients. One patient with malignant melanoma achieved a sustained partial response, and a further melanoma patient achieved a 29% reduction in the size of measurable target lesions as best response, maintained 17 months later and associated with a metabolic response on FDG-PET. These observations in patients treated with AS1409 are consistent with induction and then maintenance of a host antitumor immune response.

IL-12 is known to mediate both innate and adaptive immunity by a number of mechanisms. It stimulates NK and T-cell effector function, and promotes MHC class I processing and presentation (4). In this study, IFN-γ and the chemokine IP-10 were measured to assess activation of a cell-mediated immune response. Evidence of stimulation of both IFN-γ and IP-10 was demonstrated in patients at both dose levels tested. These pharmacodynamic observations suggest that the expected immune response does occur following AS1409 administration. In general an attenuation of IFN-γ and IP-10 levels was seen between the initial and subsequent doses of AS1409. The development of ADA was observed in all patients after administration of the first dose of AS1409. The epitope for these antibodies has not been fully characterised, although it is clear from our in vitro studies that their presence does not interfere with binding of AS1409 to the antigen ED-B fibronectin, and there is no association between the presence of ADA and clinical response. In addition, IFN-γ and IP-10 stimulation continued to be observed despite the production of ADA. Despite the frequency of ADA responses observed, biomarker changes, clinical responses, and in vitro assays strongly suggest that immunogenicity of AS1409 does not severely compromise efficacy.

Pharmacodynamic and clinical evidence of AS1409 efficacy were seen at the starting dose of 15 μg/kg, and indeed this is the recommended dose for investigation in phase 2. Evidence of activity was obtained at the starting dose, and intolerable toxicity at the second dose level explored. This highlights the challenge in selecting starting doses for clinical studies of species-specific immunotherapies even where nonhuman primate data are available.

A number of other antibody-based therapies have been studied delivering therapeutically active molecules including toxins, radioisotopes, and cytokines. EMD273063, a humanized anti-GD2 monoclonal antibody linked to IL-2, has shown both immune activation and safety in a phase 1 trial in melanoma patients. Of particular relevance to the results seen with AS1409, 4 patients who received only 2 cycles (6 doses) of EMD273063 had disease stabilization for 26 to 60 months posttreatment without evidence of disease progression. The immunological changes observed in these patients included an increase in antibody-dependent, cell-mediated cytotoxicity, an increase in NK cell lysis, and an increase in serum CRP (14).

A potential limitation associated with the use of fusion proteins with a high molecular weight is poor
tissue penetration, risking limited delivery to tumor compared with smaller molecules. However the target chosen for AS1409 is an epitope on the extracellular matrix, which is likely to be accessible from the endothelial lumen even to a bulky antibody conjugate. We have not directly confirmed targeting of AS1409 to tumor, but the approach of targeting the ED-B domain of fibronectin has been explored in a clinical trial in Hodgkin’s lymphoma. Here an antibody against ED-B radiolabelled with $^{131}$I-iodine was administered to patients, and imaging studies using SPECT-CT and FDG-PET showed selective targeting to known sites of disease. Sustained partial responses were observed, and this agent is now being evaluated in patients with renal and pancreatic carcinomas (15). Clinical imaging studies of radiolabeled AS1409 may further confirm targeting of tumor by AS1409, and the parent BC1 antibody is known to target tumor in vivo (10).

Intravenous AS1409 is well tolerated at the recommended phase 2 dose of 15 μg/kg/week. Terminal half-life was compatible with the weekly dosing schedule used in this study. Molecular evidence for the expected biological activity of this agent, together with CT and PET evidence of efficacy, supports the planned further phase 2 development of AS1409 in malignant melanoma.

References

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