

Early cancer trials in the era of personalised therapy

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September 21st 2011 Clinical Trial Showcase

Local Oncology Phase I expertise

- Group of oncology health professionals based at UoA and ADHB
- Over 20 years personal and institutional experience in oncology phase I trials
- Major contributions to
 - A broad range of phase I trials
 - first-in-man (IA), combination (IB) and late phase I trials
 - Development of novel anticancer agents originating from academia and industry
 - ACSRC, CRUK, Antisoma (UK), Novartis Oncology (Global), Proacta (USA), Oncomed (USA)
 - Single-centre and multicentre trials with other clinical groups through NZ and the globe



Dr Mark McKeage



Dr Peter Fong

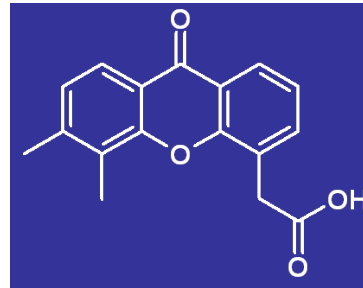


Dr Michael Jameson

ASA404: Tumour-Vascular Disrupting Agent (Tumour-VDA)

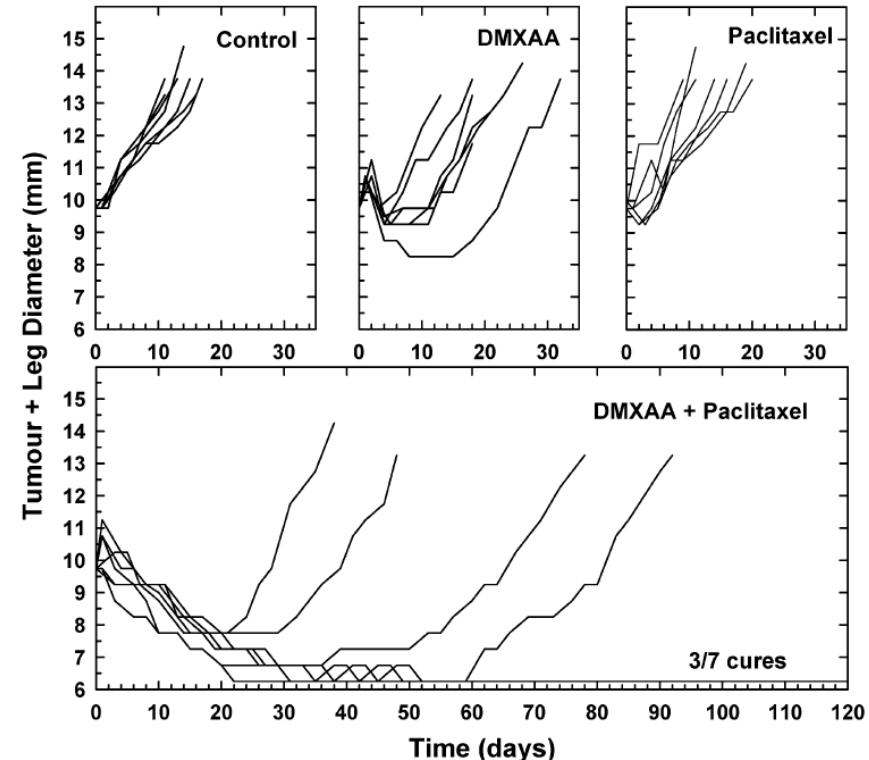


Auckland Cancer Society Research Centre



Pre-licensing	Discovery and early development at the Auckland Cancer Society Research Centre (ACSRC)
2002	Licensed to Antisoma, who initiated a programme of early-phase oncology trials
2007	Licensing deal with Novartis for \$890M US
2008	Novartis initiate phase III lung cancer (ATTRACT-1 and -2) and related trials

Marked antitumour activity in mice



Clinical development of ASA404 - our contribution

Phase	Trial	Sponsor	Our contribution Pt no. (total)
Early I	First-in-man	CRUK	63 (63)
Early I	DART	Antisoma	8 (15)
Late I	ADME	Novartis	7 (7)
Late I	Organ Impairment	Novartis	8 (8)
IB/II	NSCLC	Antisoma	27 (103)
III	ATTRACT-1 [PK sub-study]	Novartis	30 (1200)

ASA404 plus carboplatin and paclitaxel in advanced NSCLC
MJ McKeage et al Br J Cancer (2008) 99(12), 2006 – 2012

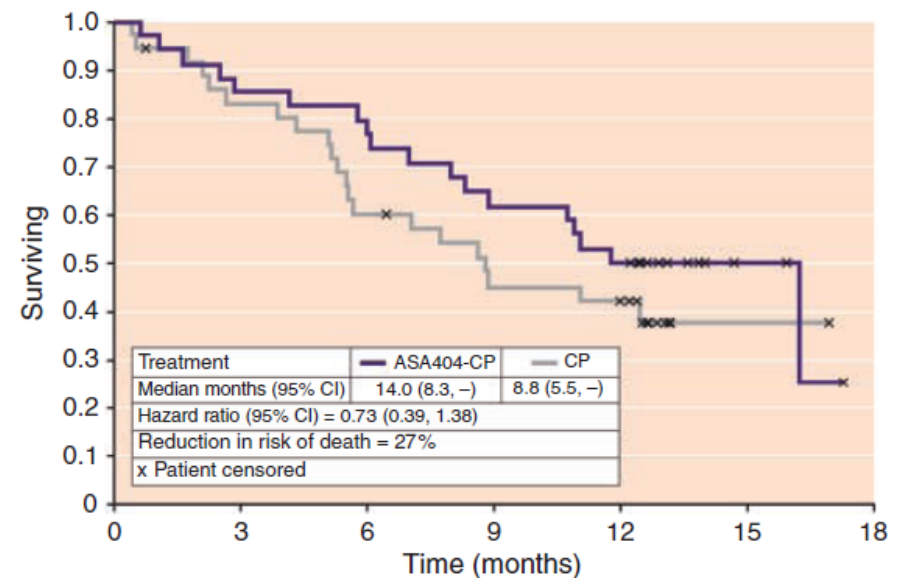
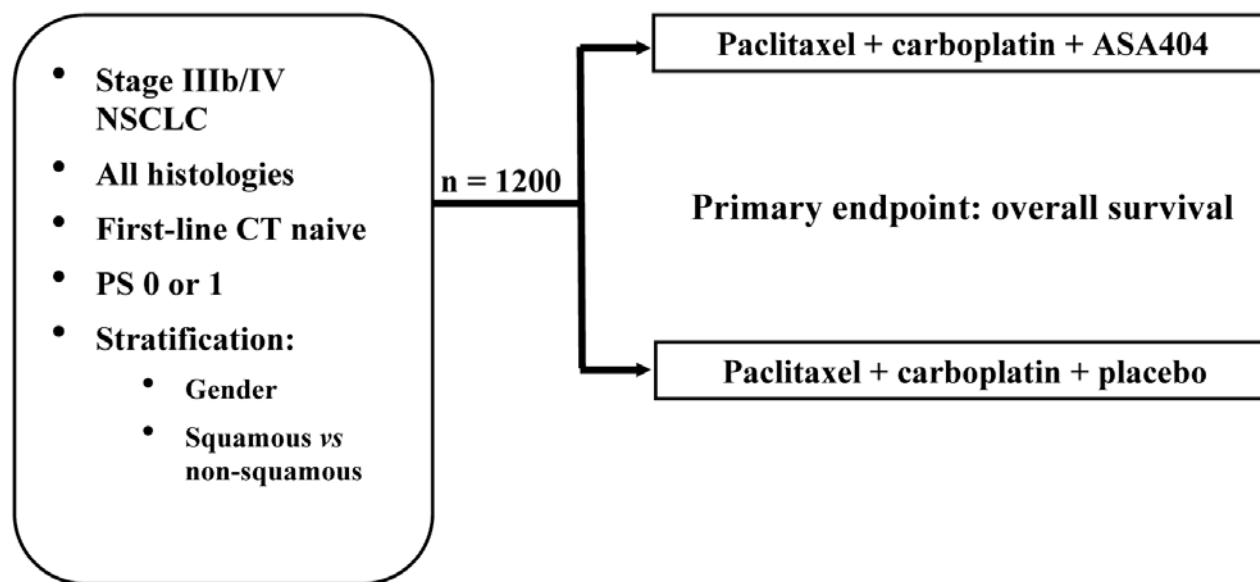


Figure 2 Kaplan–Meier estimate of the probability of survival; eligible population (ASA404-CP $n = 34$, CP $n = 36$).

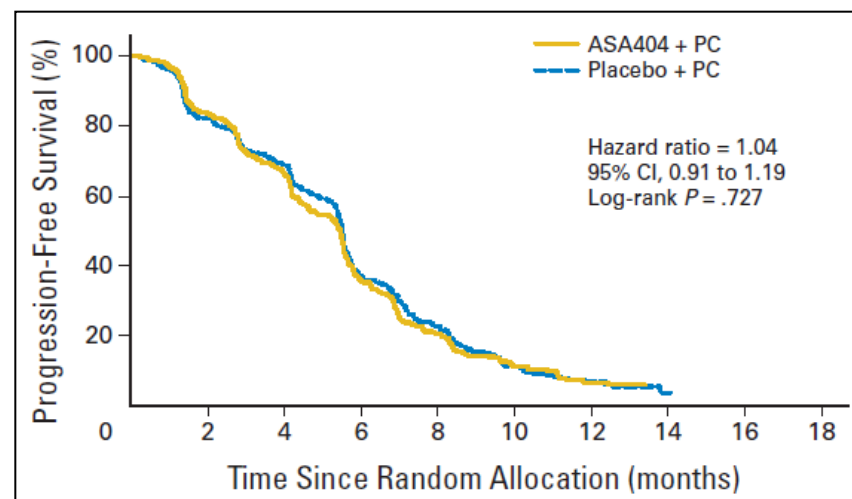
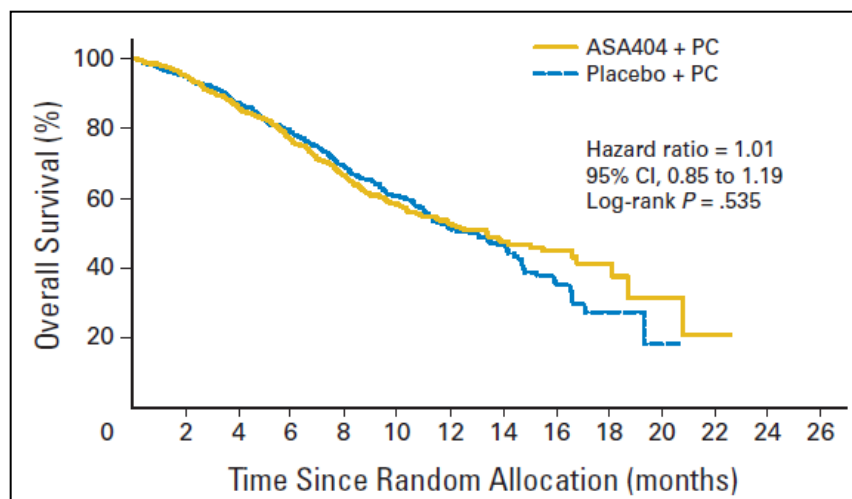
Randomized Phase III Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the Vascular Disrupting Agent Vadimezan (ASA404) in Advanced Non–Small-Cell Lung Cancer

Primo N. Lara Jr, Jean-Yves Douillard, Kazuhiko Nakagawa, Joachim von Pawel, Mark J. McKeage, Istvan Albert, György Losonczy, Martin Reck, Dae-Seog Heo, Xiaolin Fan, Abderrahim Fandi, and Giorgio Scagliotti



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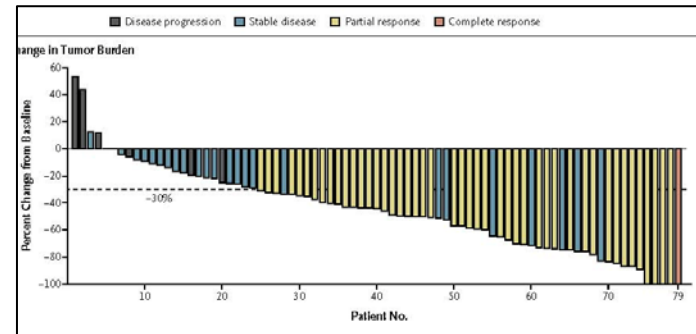


An Oncology Therapeutic Revolution

Concept: Detect the critical tumour mutation to match to a drug specifically targeting its encoded oncogenic protein

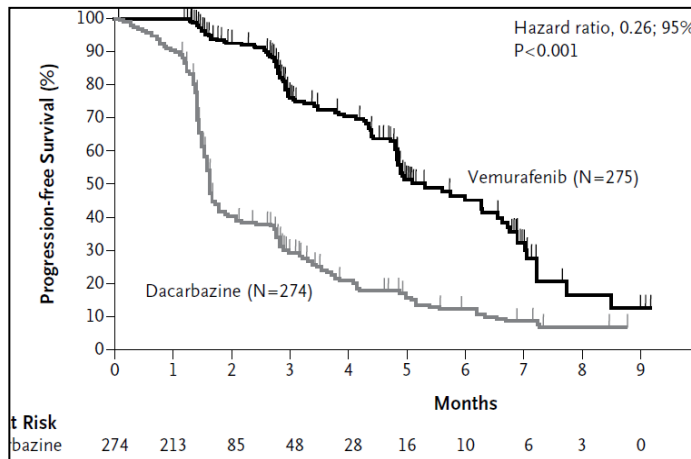
- Refining disease classification
- Unprecedented therapeutic efficacy
- Facilitating early approval and availability

ALK-mutant Lung Cancer: - crizotinib



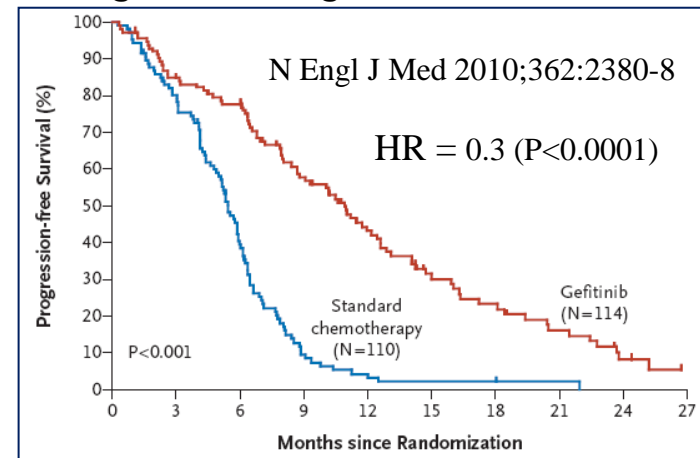
N Engl J Med 2010;363:1693-703

BRAF V600E-Mutant Melanoma - vemurafenib



N Engl J Med 2011;364:2507-16.

EGFR 19del or L858R-mutant Lung Cancer - gefitinib



New Challenges for early cancer trials

Genetic Screening



UoA Sequenom Mass-Array Platform

- 19 oncogenes and 250 somatic mutations in 1 run

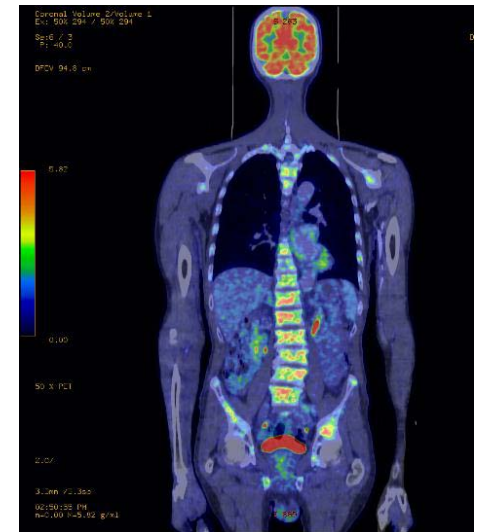
Molecular Stratification

- Broad portfolio of trials
- Collaborations with industry and academic drug development groups

Clinical Facility

- Patient access to oncology healthcare
- Dedicated space and staff
- Meets regulatory and sponsor requirements

Proof-of-Concept Trial Endpoints



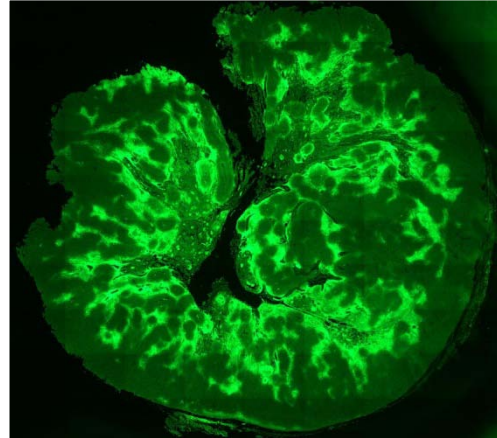
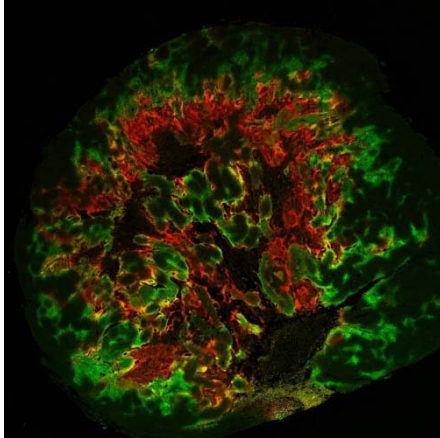
- PET-CT imaging and intervention radiology

UniServices announce an investment to seed the development of an Oncology Early Phase Trial facility to be run jointly by UoA and ADHB

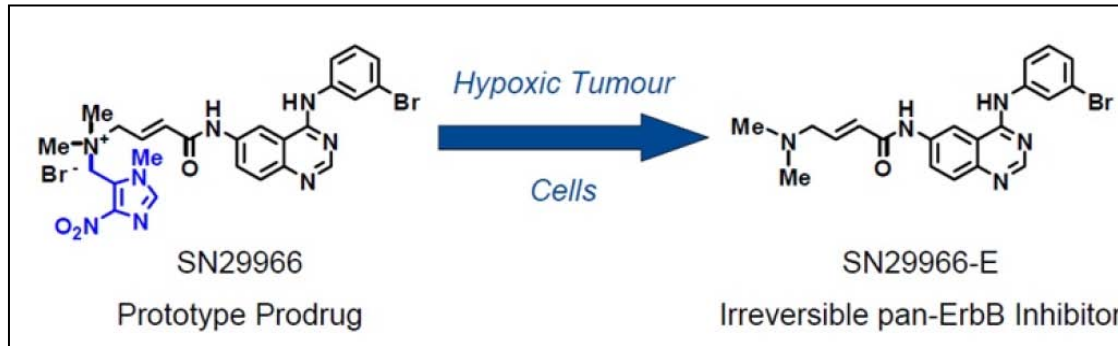
An Oncology Phase I Unit - Opportunities

- Cancer patients
 - Early access to novel therapies and diagnostics that may help them live longer and contribute to knowledge advancement
- Healthcare and Academic Institutions
 - Staff development and training, innovation, higher education and high quality research outputs
- Business collaborators
 - Advancement of research, development and financial objectives
- Clinicians
 - Contribute to improving therapies and patient outcomes

Hypoxia-selective multikinase inhibitors (HSMKI)



Human tumours stained for Hypoxic cells



Dr Adam Patterson



Dr Jeff Smail

First-in-man Phase I trial to start 2012

<http://tvnz.co.nz/ever-wondered/s2-e4-video-4363995>

Series 2, Episode 3: "Cancer" (August 24th)



TVNZ

On Demand

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

Sarah M. Rudman, Michael B. Jameson, Mark J. McKeage, et al.

Clin Cancer Res 2011;17:1998-2005. Published OnlineFirst March 29, 2011.

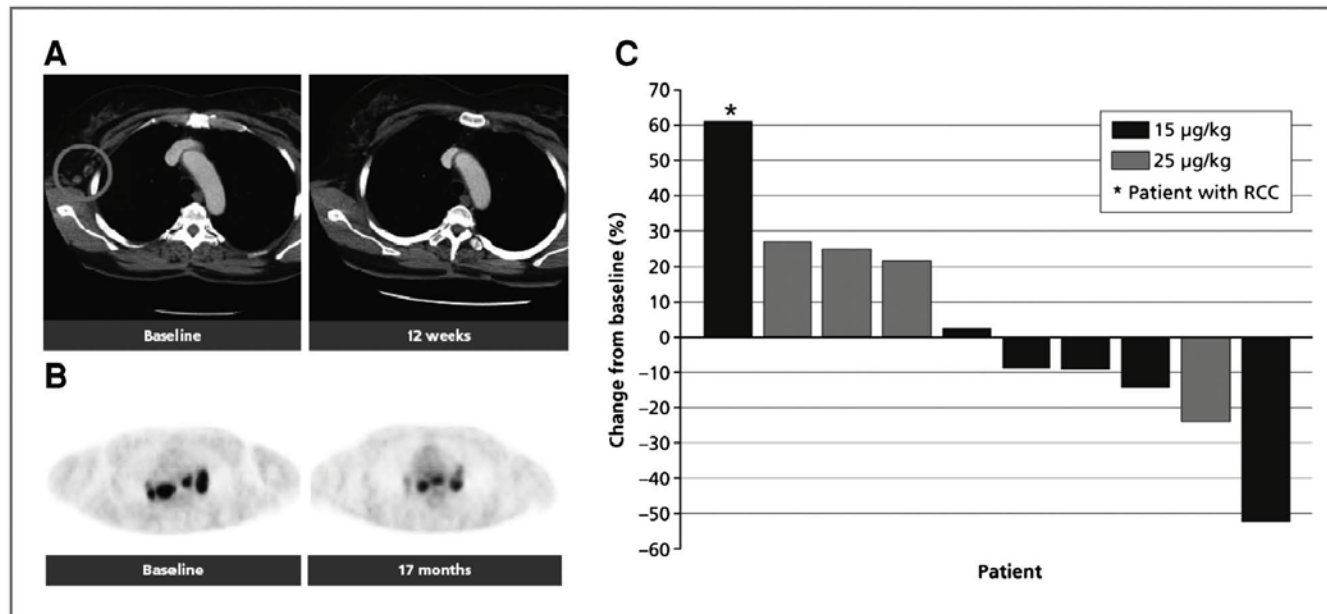
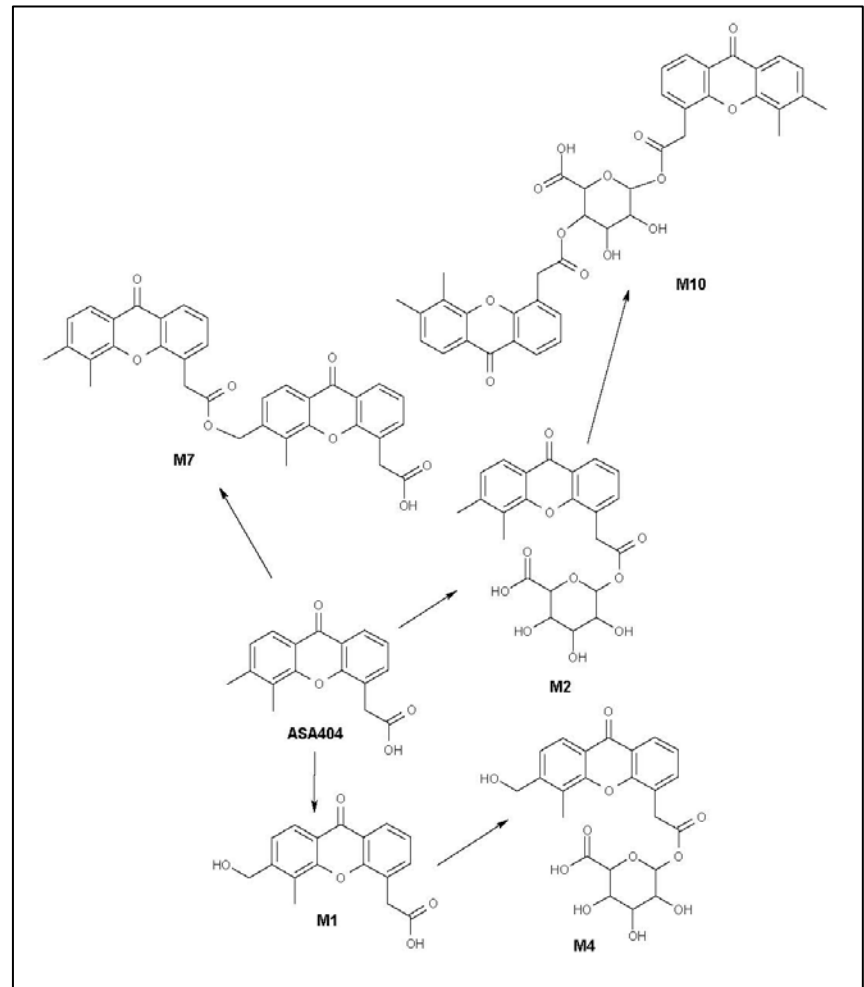
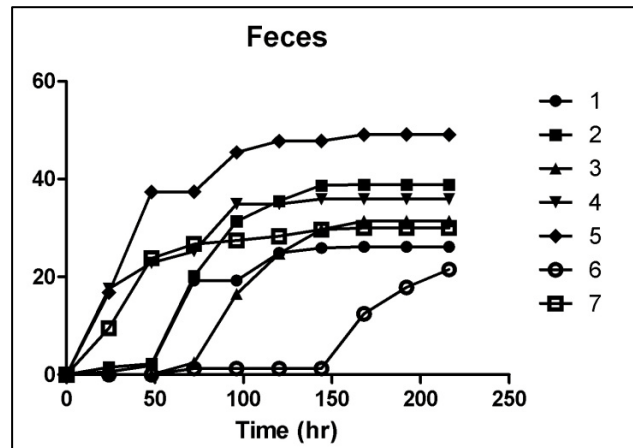
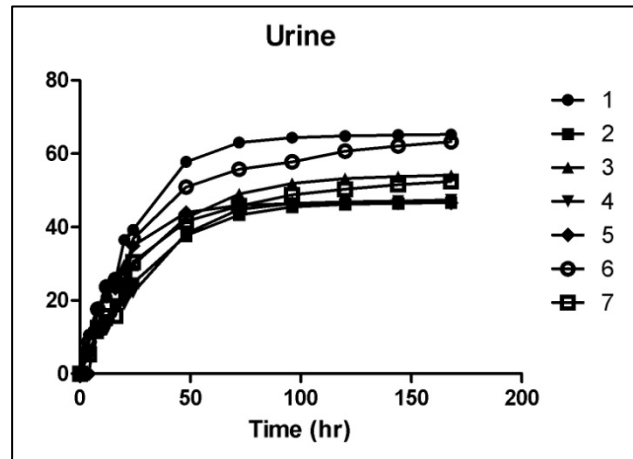


Figure 4. A, evidence of tumor shrinkage on computed tomography scan in a patient with malignant melanoma. Computed tomography shows a maintained partial response in an axillary lymph node metastasis following 6 cycles of AS1409 at 15 µg/kg/week, maintained at 30 cycles. B, positron emission tomography showing metabolic response in another patient with mediastinal lymph node melanoma metastases, which were progressing rapidly prior to enrolment. This patient remains progression-free beyond 17 months. C, waterfall plot showing best response in patients with measurable disease (n = 10).

Disposition and metabolism of [¹⁴C]ASA404 in cancer patients

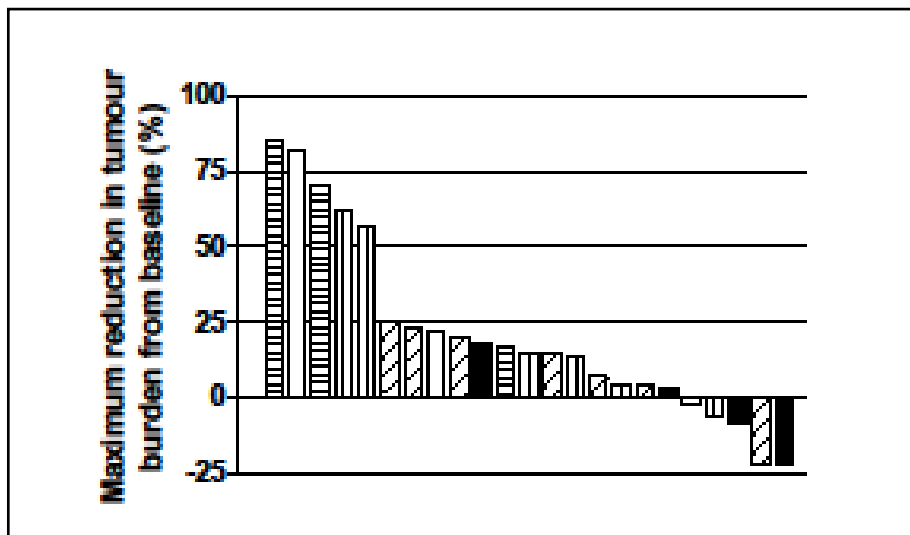
McKeage MJ, Fong PC, Hong X, Flarakos J, Mangold J, Du Y, Tanaka C, Schran, H



A phase I trial of PR-104, a pre-prodrug of the bioreductive prodrug PR-104A, given weekly to solid tumour patients

Mark J McKeage, Yongchuan Gu, William R Wilson, Andrew Hill, Karen Amies, Teresa J Melink, Michael B Jameson

Waterfall Plot



Thrombocytopenia

