

Phase 1 dose-escalation study of EBC-46 given by intratumoral injection to patients with refractory cutaneous and subcutaneous tumors.

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Background: EBC-46 is a novel protein kinase C (PKC) activator being developed for intratumoral treatment of cutaneous and subcutaneous tumors. Studies in syngeneic and xenograft mouse models showed that intratumoral injection of EBC-46 into subcutaneous tumors resulted in PKC-dependent hemorrhagic necrosis within 24 hours and complete loss of viable tumor cells. Immunostaining of tumor tissue for the endothelial marker CD31 showed marked vascular disruption at 24 hours after treatment (Boyle GM, et al. PLoS ONE 2014; 9: e108887). EBC-46 is also being studied in veterinary clinical trials in companion animals as an intratumoral treatment for spontaneous skin tumors. Notably, EBC-46 therapy leads to rapid healing at treated sites in animals and the mechanism of this is currently under investigation (Campbell J, et al. Proc ETRS 2014). **Methods:** This is a phase 1 first-in-human dose-escalation trial of intratumoral injection of EBC-46 in patients with cutaneous and subcutaneous tumors refractory to standard therapies. Other key eligibility criteria include an ECOG score of 0-2, adequate organ function, no involvement of major blood vessels by the tumor and no therapeutic anticoagulation or major abnormality of hemostasis. The starting dose of EBC-46 is 0.06 mg/m², which is prepared as a 0.25 mg/mL solution and infiltrated into a tumour volume 2-fold greater than the EBC-46 volume. Initial dose escalations are based on increasing the concentration of the EBC-46 solution until a maximum concentration is reached. Subsequent dose levels will inject higher volumes of EBC-46 solution into a correspondingly greater target tumour volume. Patients who tolerate the first dose, and who are deemed to be benefiting from treatment, will continue intratumoral injections in an extension protocol. Study endpoints include safety and tolerability parameters (local and systemic), pharmacokinetics of EBC-46 and preliminary efficacy assessments. Blood samples will be evaluated for biomarkers of vascular disruption and inflammation, and optional tumor biopsies will be performed pre- and post-treatment. Enrolment into the first dose level commenced in January 2015. [Clinical trial information: ACTRN12614000685617](https://www.anzctr.org.au/Trial/Registration/TrialRegistration.aspx?ACTRN12614000685617).