

# INTRATUMORALLY ADMINISTERED STELFONTA® (tigilanol tiglate injection) 1 mg/mL CAUSES HEMORRHAGIC NECROSIS, RAPID TUMOR CELL DEATH AND LOCAL CURE OF TUMORS IN MOUSE MODELS

## OBJECTIVES

Describe the mode of action of intratumorally administered tigilanol tiglate (also known as EBC-46) in destruction of target tumors in syngeneic and xenograft mouse models.

## MATERIALS & METHODS

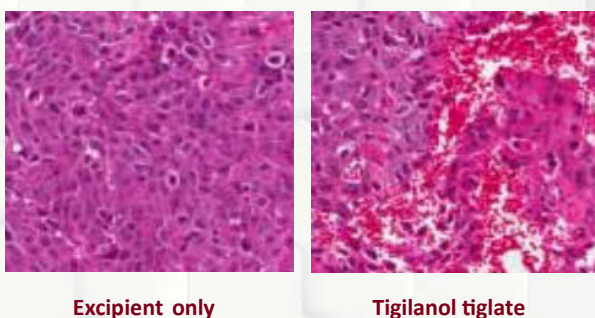
- Preclinical mouse models of melanoma and squamous cell carcinoma to assess tumor response, systemic exposure in serum, and effects on injection into healthy tissue.
- *Ex vivo* studies of viability of tumour cells after tigilanol tiglate treatment.
- *In vitro* studies of sensitivity of cancer cell-lines and protein kinase C (PKC) activation profiles.

## RESULTS

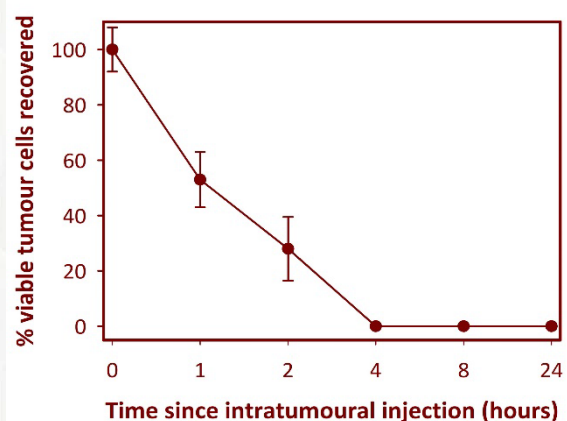
- The syngeneic and xenograft tumor mouse models showed that a single intratumoral injection of tigilanol tiglate caused:
  - Rapid localized inflammation and influx of white blood cells into the tumor and immediate surrounds;
  - Loss of integrity of tumor vasculature within 1 hour of treatment (Figure 1); and
  - Rapid death of cancer cells in the treated tumors (no viable cells recovered by *ex vivo* culture 4 hours after treatment – Figure 2).
- Activation of specific isoforms of protein kinase C (PKC) was shown to be responsible, at least in part, for the efficacy of tigilanol tiglate.

## CLINICAL INTEREST

A single intratumoral injection of tigilanol tiglate resulted in local cure of solid tumors in pre-clinical mouse models of cancer.



**Figure 1:** Vascular disruption and red cell extravasation is clearly evident in histopathology sections by 1 hour after treatment of squamous cell carcinoma xenografts on mice with tigilanol tiglate (right hand image) compared to tumors treated with excipient only (left hand image).



**Figure 2:** No viable tumor cells could be recovered in *ex vivo* culture from a xenograft mouse melanoma model by 4 hours after treatment with tigilanol tiglate.

## REFERENCES

Boyle GM, D'Souza MMA, Pierce CJ, Adams RA, Cantor AS, Johns JP, et al. Intra-lesional injection of the novel PKC activator EBC-46 rapidly ablates tumours in mouse models. PLoS One. 2014;9(10):1–12.