SELECTED OPPORTUNITY IN ONCOLOGY

Use of Hedgehog inhibitors for the treatment of mastocytosis (BIO17083)

USE OF HEDGEHOG INHIBITORS FOR THE TREATMENT OF MASTOCYTOSIS (BIO17083)

Product factsheet

stage

- **Target:**
  - Hedgehog signaling pathway
- **Product:**
  - Tested: Hedgehog inhibitors (vismodegib or GANT61)
- **Application:**
  - Treatment of mastocytosis (systemic indolent mastocytosis)
- **Rational:**
  - The canonical Hedgehog (HH) signaling pathway is activated in normal and abnormal human mast cells
  - Inhibition of hedgehog signaling pathways inhibits mast cells proliferation and induces apoptosis.
- **POC:**
  - Inhibition of HH signaling pathway, via increasing doses of vismodegib or GANT61 prevented the proliferation of ROSA cell lines, in a dose-dependent manner. This inhibition was more spectacular in KIT mutated ROSA cell lines (ROSA KIT D816V and K417) than in ROSA KIT WT cell lines.
  - Combination of PKC412 (tyrosine kina inhibitor) with Vismodegib increases significantly the cell death of ROSA WT and ROSA 417 as compared to PKC412 alone or vismodegib alone.
- **Patent and publication:**
  - WO 2018/211007

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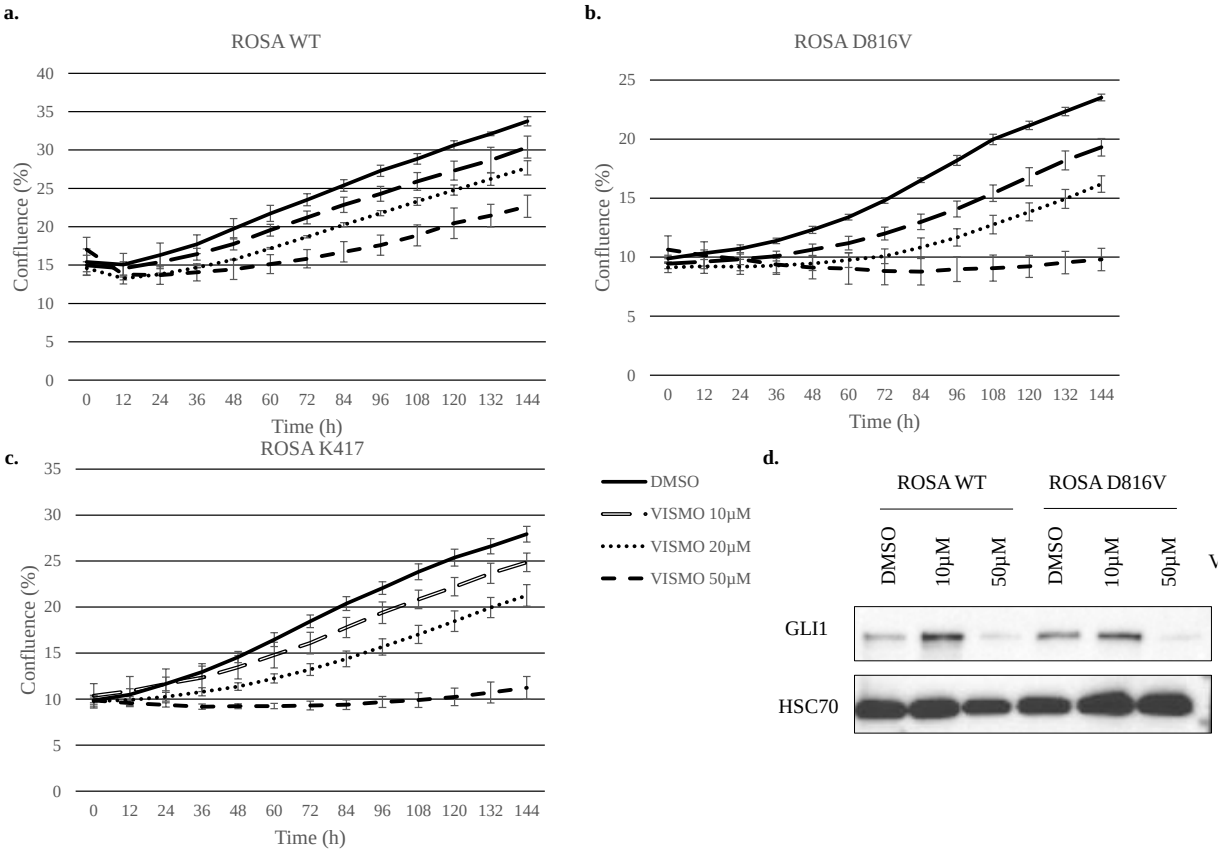
Proof of concept

Vismodegib inhibits mast cells proliferation



a) Percentage of confluence of ROSA KIT WT treated with DMSO (control), vismodegib 10, 20 or 50µM during 144 hours.
b) Percentage of confluence of ROSA KIT D816V treated with DMSO (control), vismodegib 10, 20 or 50µM during 144 hours.
c) Percentage of confluence of ROSA KIT K417 treated with DMSO (control), vismodegib 10, 20 or 50µM during 144 hours.
d) Immunoblotting of GLI1 in ROSA KIT WT and D816V cell lines, treated with DMSO or vismodegib. Three independent experiments were performed in triplicate, using the IncuCyte® Live Cell Analysis system. Data are represented as the mean ± standard deviation.

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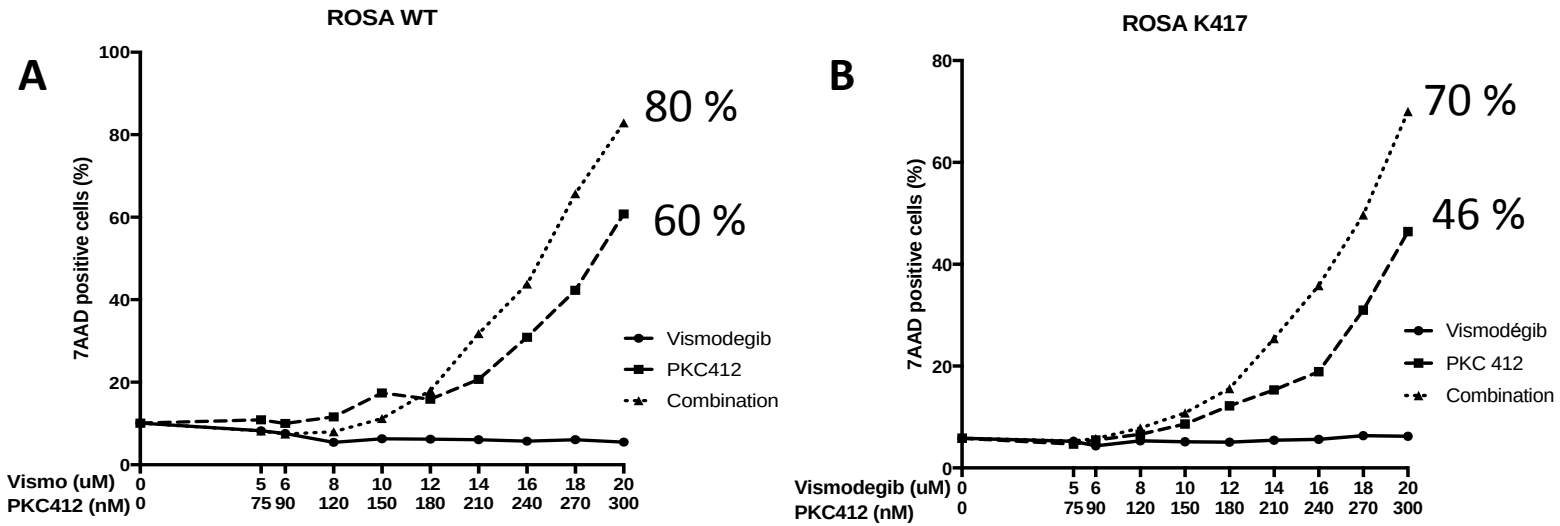
Proof of concept

- **Combination of PKC412 with Vismodegib increases significantly the cell death of ROSA WT and ROSA 417 as compared to PKC412 alone or vismodegib alone**



A- Combination of PKC412 300nM with Vismodegib 20uM induces 80% cell mortality in ROSA WT.

B- Combination of PKC412 300nM with Vismodegib 20uM induces 70% cell mortality in ROSA 417.

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