**REDX04988, a novel dual B-RAF/C-RAF inhibitor and a potential therapeutic for BRAF-mutant colorectal cancer**

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### Background

- RAF kinases control signalling through the MAPK pathway and act as key regulators of cell proliferation and survival.
- BRAF\(^{\text{V600E}}\) is the most prevalent RAF kinase mutation in cancer and leads to constitutive activity and aberrant signalling via the MAPK pathway.

### Vemurafenib (Zelboraf\(®\)) and dabrafenib (Tafinlar\(®\)) are RAF inhibitors approved for the treatment of metastatic BRAF\(^{\text{V600E}}\)-mutant melanoma.

- However, they lack efficacy in other BRAF\(^{\text{V600E}}\) cancers such as colorectal cancer. This is partly due to EGFR-mediated reactivation of the MAPK pathway.\(^1\)
- In addition, RAF inhibitor treatment has been associated with the development of other skin cancers, such as cutaneous squamous cell carcinoma, due to MAPK pathway paradoxical activation.\(^4,5\)
- The MEK inhibitor trametinib (Mekinist\(™\)) has been approved for combinational use with dabrafenib for the treatment of BRAF\(^{\text{V600E}}\) metastatic melanoma, but has limited efficacy as a single agent in various cancers due to dose-limiting toxicity commonly seen with MEK inhibitors.
- There is therefore a clinical need for novel agents targeting the MAPK pathway that do not have these undesirable properties.

### REDX04988 binds to RAF kinases with high affinity

- Redx Oncology RAF inhibitors were screened for their ability to bind RAF and MEK kinases and EGFR using a TR-FRET Lanthascreen\(™\) binding assay.\(^6\)
- REDX04988 demonstrated sub-nanomolar binding IC\(_{50}\) values at BRAF\(^{\text{V600E}}\), BRAF\(^{\text{WT}}\) and CRAF, but did not bind MEK\(_{1}\) kinase or EGFR.

### References