

## Combining radiation with a PI3K/MTOR inhibitor

Patients with HPV-negative head and neck cancer (HNSCC) carry a poor prognosis despite optimal treatment with chemoradiation, with a 5 year survival of less than 50%. The future for this disease must lie in further escalation of therapy which represents a difficult task given the fact that the current standard treatment of radiation and cisplatin already approaches the limit of tolerance. The emergence of a wide array of molecularly targeted agents over the last decade with the unique capacity of modulating cancer-specific cellular signaling and response to chemoradiation has garnered significant enthusiasm in the radiation oncology community based on the potential of these compounds to serve as radiation sensitizers. The Cancer Genome Atlas (TCGA) has uncovered a series of genes with common mutations in a large cohort of HNSCC patient samples. From these studies, common actionable mutations are present in HNSCC. One of these is *PI3KCA* which is a component of the *PI3K/AKT/MTOR/PTEN* signaling pathway involved in regulation of cell survival, growth, proliferation, metabolism and motility and an attractive drug target in cancer. The phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (MTOR) signaling pathways have been found to have an important role in the pathogenesis of HNSCC and there is evidence PI3K/MTOR antagonists are active against head and neck cancer cells. In this study we investigated whether a molecular targeted agent (PF-04691502) active against two components of the PI3K/AKT/MTOR survival pathway could enhance the effect of radiation treatment in two mouse xenograft models (UT-SCC-14 and UT-SCC-15) of HNSCC.

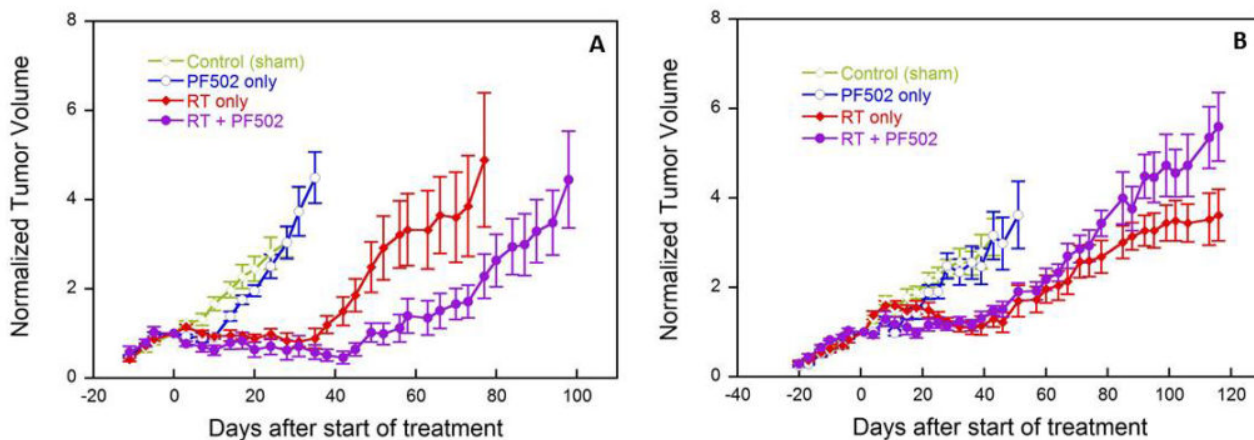


Fig. 1. The effect of PF-04691502 on tumor growth, in combination with radiation, in UT-SCC-14 (A) and UT-SCC-15 (B) xenografts. The data were normalized to the individual tumor volumes at the start of treatment.

The key findings from the study was that the drug was effective at inhibiting the growth of both cell lines in vitro but had no effect on growth of the cell lines as tumor models. The drug resulted in

increased radiosensitivity of the UT-SCC-14 cells but not the Ut-SCC-15 cell line. This was mirrored in vivo where the drug was very effective when combined with radiation in UT-SCC-14 (Fig. 1A) but this added effect was not seen in UT-SCC-15 (Fig. 1B). Interestingly, the drug alone was able to inhibit levels of phosphorylated proteins in PI3K/AKT/MTOR pathway in both tumor models but when combined with radiation, the inhibition was reduced in the UT-SCC-15 tumors. This highlights the complexity of combining radiation with pathway inhibiting drugs as radiation is known to cause an upregulation of these pathways as a cell survival mechanism. In addition we studied the mutation status of some key genes and observed that UT-SCC-15 harbors substantially more variants in PI3K/AKT/MTOR-associated genes as well as mutations in *HRAS* and *KRAS* and has a higher mutational burden than UT-SCC-14.

The data in this study showed that although one HNSCC xenograft model showed significant radiosensitization resulting from the combination with PF-04691502 another xenograft did not. The resistant model was a later-stage cancer and may have become resistant to the targeted therapy due to the more complex molecular dependencies that had developed which led to the activation of other survival pathways. It is clear that not every group of head and neck cancer patients will respond the same to therapy. Much research is still required to understand the contribution of mutations and deregulated pathways in HNSCC and to determine the effects of inhibitors that target molecules in these pathways. In some HNSCCs, a single targeted agent may be sufficient but others may require treatments that target several survival pathways.

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## Publication

[Antitumor activity of the dual PI3K/MTOR inhibitor, PF-04691502, in combination with radiation in head and neck cancer.](#)

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