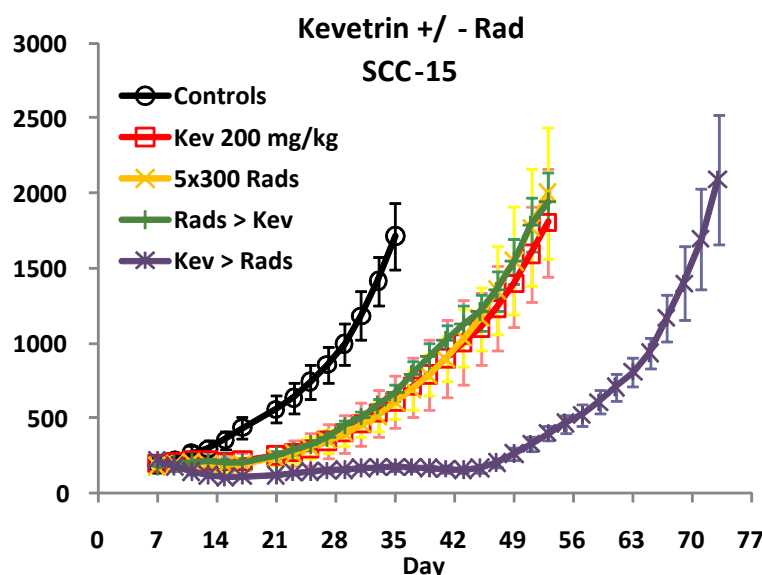


## Kevetrin synergistically enhanced the anti-tumor activity in combination with radiation therapy in a human head and neck cancer xenograft model

Combination therapy is commonly utilized as an effective strategy for cancer treatment. Radiation therapy may be enhanced by agents, such as Kevetrin, that target pathways involved in apoptosis. We discovered that combining Kevetrin and radiation greatly enhanced anti-tumor activity in a human head and neck cancer xenograft model significantly increasing the therapeutic index.

Kevetrin in combination with radiation therapy was evaluated in the SCC-15 squamous cell carcinoma of the head and neck xenograft tumor model. Mice with tumors treated with Kevetrin or local radiation alone significantly increased anti-tumor activity. Other groups of mice were with Kevetrin in combination with radiation given either 1 week prior to or following radiation treatment. Interestingly, the combination of Kevetrin treatment followed a week later by radiation significantly increased the anti-tumor activity compared to the reverse treatment: radiation followed by Kevetrin. Thus, Kevetrin appears to be acting as a radiosensitizer.

Since the sequence of Kevetrin followed by radiation was superior, Kevetrin may induce activity at the cellular level that sensitizes the tumor cells to radiation treatments. Agents, like Kevetrin, that activate p53 may play a role in sensitizing cells to radiation damage via chemosensitivity genes, e.g., Bid. Bid expression was induced in irradiated normal mouse epithelial cells (Sax et al., 2002). Therefore enhanced levels of proteins, such as Bid, can sensitize cells to irradiation by promoting apoptosis in a p53-dependent manner (Sax et al., 2002, Sax and El-Deiry, 2003). Radiation also activates ATM and Chk2 and phosphorylates serine on p53 (Dumaz et al., 1999; Hirao et al., 2002). In addition, following radiation, MDM2 becomes phosphorylated in an ATM-dependent manner which leads to reduced binding between p53 and MDM2 and therefore p53 protein stabilization (Maya et al., 2001). These findings may explain why the combination of Kevetrin followed by radiation produces such potent activity. Further, since radiation is given as local therapy, the combination with Kevetrin greatly increases its therapeutic index.



Details: Nude mice bearing established tumors were treated with either 200 mg/kg Kevetrin intraperitoneally (IP) every other day for 3 doses or 3 Gy of local radiation daily for 5 doses or in combination given sequentially 1 week prior to or following Kevetrin treatment. Treatment with Kevetrin alone, radiation alone, or radiation followed by Kevetrin resulted in similar TGDs ranging from 10 to 14 days (32 to 45%). However, Kevetrin treatment followed 1 week later by radiation significantly increased TGD to 36 days (116%) relative to controls and to each treatment alone.