Inhibition of angiogenesis contributes to enhanced radiation response in tumors following MDM2 inhibition by AMG 232

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**Introduction**

- AMG 232 is an effective p53 activator which acts by selectively inhibiting MDM2-p53 interaction.
- We previously elucidated the capacity of AMG 232 to augment radiation response across a spectrum of human tumors with wt p53.
- In the current study, we examine the capacity of AMG 232 to inhibit angiogenesis and the radiation response of human endothelial cells.

**Figure 1:** Combining AMG 232 and radiation exhibits anti-tumor and anti-angiogenic effects in H460 & SJSA-1 tumor xenografts

**Figures 2 & 3:** AMG 232 inhibits the proliferation and function of human endothelial cells

**Figures 4 & 5:** Combining AMG 232 with radiation causes cell cycle G2/M arrest in HUVEC cells

**Figure 6:** AMG 232 enhances tumor radiosensitivity under hypoxia

**Conclusions**

- AMG 232 augments radiation response by inhibiting tumor cell proliferation and by interfering with tumor-associated angiogenesis. (1).
- The anti-angiogenic impact of AMG 232 may result from the direct inhibition of the growth and function of endothelial cells.(2).
- AMG 232 enhances radiosensitivity of endothelial cells in part by inhibiting the repair of radiation-induced double strand breaks (3), which results in a significant increase of HUVEC cells in cell cycle G2/M arrest with unrepaired lethal DNA damage (4&5).
- Under hypoxic conditions, AMG 232 still demonstrates a significant capacity to augment radiation response in tumor cells (6). All together, our findings reveal the potential anti-angiogenic capacity of AMG 232 that may contribute to the augmentation of radiation response observed in xenograft studies.

*Poster is displayed in Harari lab web at https://www.humanc.wisc.edu*