High-grade pediatric gliomas (HGGs) remain devastating tumors, with the vast majority of afflicted patients succumbing to disease within 5-years. Conventional treatments such as surgery, radiation, and chemotherapy certainly have important roles in the management of these tumors, but are rarely curative by themselves. Indeed, it is humbling that the outcomes of pediatric patients afflicted by HGGs have not improved appreciably over the past several decades.

The manuscript by Mueller et al highlights the Wee-1 pathway as a critical mediator of radiation resistance in pediatric HGGs. Wee-1, when activated, promotes the inhibitory phosphorylation of cdc2, thereby preventing G2-M cell cycle progression (Fig. 1).1,2 In this study, MK-1775, which is a potent inhibitor of Wee-1, was demonstrated to enhance the therapeutic efficacy of radiation in preclinical models by down-regulating DNA repair capability of tumor cells irrespective of p53 status, and may provide valuable rationale for future clinical trials that combine radiation with MK-1775.3

Studies such as the present one serve to shed several valuable insights. First, the next great divide in improving outcomes of pediatric high-grade glioma patients may, indeed, emanate from targeting critical pro-survival pathways such as those mediated by Wee-1. Previous experience with targeted therapies for malignant HGGs dictates, however, that targeting one molecule and/or one pathway in isolation may prove futile unless redundant pathways are factored in. Second, to the extent possible, future treatments for pediatric HGG patients must be personalized towards the individual molecular characteristics of the tumor, rather than using a “one glove fits all approach.” The ultimate hope is that MK-1775 will enhance the effects of radiation for all pediatric HGG patients, but, our collective past experiences dictate that only subsets of patients will benefit while others will not; and response will likely be predicated upon underlying molecular profiles of the individual tumor. Future personalization of care with MK-1775 will require careful and systematic molecular profiling “piggy-backed” onto future clinical studies to identify which patients are likely to derive greatest benefit. The models and data presented in the current manuscript may prove to be valuable resources for future “reverse translational research studies” to this end. Third, as many of these targeted therapies are often evaluated as single agents alone in early phase clinical trials in the absence of radiation, these data alert us to the possibility that certain drugs such as MK-1775 may act additively and/or synergistically with radiation, although single agent activity may appear to be modest at best in initial Phase II studies with drug alone. It therefore follows that the preclinical data providing clear evidence of MK-1775’s ability to radiosensitize pediatric HGG’s, as presented by Mueller et al., should ideally be included in the body of evidence when evaluating the feasibility of future clinical trials of MK-1775 in combination with radiation in pediatric HGG patients.

References