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Translating palbociclib to the clinic for DIPG - What is truly achievable?

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To the Editor,

Sun et al present a comprehensive analysis of the efficacy of the CDK4/6 inhibitor palbociclib in preclinical models of Diffuse Intrinsic Pontine Glioma (DIPG) [1]. DIPG remains an incurable disease and there is an urgent need to develop novel, active therapies. The authors conclude that palbociclib should be investigated in clinical trials of DIPG patients. However, we have concerns about the potential for their findings to be translated to the clinic. We note that the authors used an enteral dose of 150 mg/kg/day for 21 days in their *in vivo* DIPG models. The FDA approved adult dose of palbociclib is 125 mg orally once per day [2], based on a Phase 1 trial establishing 125 mg daily for 21 days as the maximum tolerated dose (MTD). Higher doses led to haematological dose limiting toxicity [3]. This dose is equivalent to 1.79 mg/kg for an average adult and converts of to a murine equivalent dose of 22 mg/kg [4]. Thus the dose used in this study of 150 mg/kg/day in mice is equivalent to a dose seven times higher than the MTD in humans, and equates to an adult human dose of 850 mg daily. The authors did not report on toxicity,but noted that doses were delayed in some animals due to weight loss. The majority of early phase trials are unsuccessful and one reason is the misinterpretation of preclinical data and translatability of research findings [5]. We are concerned that the doses used in this study are not clinically achievable and thus are not able to be effectively translated to the clinic.

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