Review of: "p16INK4A-deficiency predicts response to combined HER2 and CDK4/6 inhibition in HER2+ breast cancer brain metastases"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This paper describes the rationale of $p16^{INK4A}$ protein deficiency as a potential biomarker of resistance to HER2-targeted agents in patients with HER2 positive breast cancer with brain metastasis.

A tumour suppressor $p16^{INK4A}$ (CDKN2A) was shown to play a role in the inhibition of cell cycle through binding to CDK4/6.

This manuscript describes an important finding highlighting the role of CDKN2A through sequencing of multiple PDX models of TNBC, HER2+ and ER+ breast cancer which demonstrated that the over 50% of HER2+ patients with brain metastasis had low CDKN2A expression which primed using it as a potential biomarker.

The authors have also demonstrated a strong synergistic effect of abemaciclib with Tucatinib in the PDX models with *CDKN2A*-null and $p16^{INK4A}$-deficiency.

It was interesting to see that restoring CDKN2A expression replaced the need for the CDK4/6i inhibitor: once again emphasizing the important role of this tumours suppressor in cell cycle.

I think this paper has a high clinical importance and therefore, recommend it for publication