Combination of MDM2 inhibition with milademetan and MEK inhibition leads to improved anti-tumor activity in cancer models harboring wild-type TP53

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#PB050

Background

- Loss of TP53 tumor suppressor function is critical for many cancers and is achieved by TP53 mutation in ~50% of tumors, but may occur through other mechanisms in tumors with wild-type (WT) TP53.
- MDM2 overexpression or - MDM2 regulator loss (p14ARF) encoded by CDKN2A.

The MDM2-TP53 pathway is dysregulated in a significant number of cancers due to upregulation of MYC or other alteration in components of this pathway leading to unchecked proliferation and anti-apoptotic signaling.

- p16-dependent activation of p53 may lead to tumor responses to both MDM2 inhibitors and MEK inhibitors.

Rationale for combined MDM2 and MEK inhibition

Synergistic activity of milademetan and trametinib combination in WT TP53 cell lines

Activity of milademetan and trametinib combination in CDKN2A loss

Activity of milademetan and trametinib combination in WT TP53

Activity of milademetan and trametinib combination in CDKN2A amplification

Summary

- Milademetan induced p16 activation in diverse cancer models with MDM2 amplification, CDKN2A loss or WT TP53, and also harboring oncogenic drivers such as RAS and RAF alterations.
- A combination of trxntx and milademetan induced sustained MDM2 inhibition.
- Synergistic anti-proliferative activity was observed using a combination of milademetan and trametinib in cell lines with MDM2 amplification, CDKN2A loss or WT TP53.
- A combination of milademetan and trametinib resulted in increased antitumor activity compared to single-agent treatment in MDM2 amplified, CDKN2A loss or WT TP53 xenograft models.

These data support clinical exploration of milademetan combination with MAPK pathway inhibitors in WT TP53 cancers with or without MDM2 amplification or CDKN2A loss.

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