ON 123300, an Orally Administered Novel CDK4/6 + ARK5 Inhibitor, Exhibits Potent Antitumor Activity In Vivo: Comparative Studies with Palbociclib

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INTRODUCTION

• The overexpression of cyclin-dependent kinases 4/6 (CDK4/6) is known to cause cell cycle dysregulation in certain cancer types, making these cell cycle kinases attractive targets for pharmacological inhibition. The effectiveness of first-generation non-selective cyclin-dependent kinases, such as roscovitine and flavopiridol, was hampered by toxicities, leading to the development of second-generation compounds like IBRANCE®/Palbociclib that specifically inhibit CDK4 and 6.

• ON 123300 is a third-generation potent CDK4/6 inhibitor that also inhibits ARK5 with low nanomolar potency and has the potential to improve upon second-generation compounds. Previous studies have demonstrated the inhibitory effect of single-agent ON 123300 in various pre-clinical cancer models of MM and leukemia. [1 & 2]

• In this study, we investigated the comparative therapeutic potential of ON 123300 as an oral anticancer agent and a second-generation inhibitor, Palbociclib, in xenografted Rb+ve mouse models.

METHODS

• MDA-MB-435S xenografted mice were treated once a day for 21 days with ON 123300 (125mg/kg) or Palbociclib (125mg/kg). Tumor volumes were measured and peripheral blood was gathered to evaluate the effects on hematological parameters. Separately, Western blot analyses were performed to determine the effect of CDK4/6 inhibition on p-Rb following intra-tumoral treatment with ON 123300 (2.5µM) or Palbociclib (2.5µM).

• In addition, this study also suggests that ON 123300 may have the added advantage of reduced neutropenia when compared to Palbociclib.

• Prior preclinical data suggest that ON 123300 may be efficacious in Rb-ve tumors, where second-generation compounds have diminished single-agent activity, and our ongoing studies are aimed at further characterizing the in vivo activity of ON 123300 in this setting.

CONCLUSION

• Our in vitro and xenograft data indicates that ON 123300, a third-generation CDK4/6 inhibitor, is as effective as Palbociclib in an Rb+ve xenograft model.

• In addition, this study also suggests that ON 123300 may have the added advantage of reduced neutropenia when compared to Palbociclib.

• Prior preclinical data suggest that ON 123300 may be efficacious in Rb-ve tumors, where second-generation compounds have diminished single-agent activity, and our ongoing studies are aimed at further characterizing the in vivo activity of ON 123300 in this setting.

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REFERENCES


RESULTS

Figure 1. Chemical structure of ON 123300 and Palbociclib:

Figure 2: (A & B) The cell viability assay data indicate significant inhibition of MDA-MB-435S and HCC70 Rb+ve cancer cell lines after treatment with various concentrations of ON 123300 (0.15-0.30 µM) and Palbociclib (0.15-0.30 µM).

Figure 3: Treatment with ON 123300 or Palbociclib exhibits comparable anticancer activity in Rb+ve in vitro cancer models:

Figure 4: MDA-MB-435S xenografted mice were treated QD with ON 123300 (125 mg/kg) or Palbociclib (125 mg/kg) for 21 days. (A) The tumor volume data indicate comparable and significant anti-tumor activity that treatment with ON 123300 or Palbociclib. (B) Animal body weight does not show any significant change after treatment with ON 123300 or Palbociclib.

Figure 5: Treatment with ON 123300 exhibits reduced suppression of neutrophils in comparison to Palbociclib in mouse xenografts:

Figure 6: Intra-tumoral treatment with ON 123300 or Palbociclib significantly inhibits expression of pRb in tumor tissue: Veh - Vehicle and Palbo - Palbociclib.