Combined Inhibition of CHK1 and WEE1 As a New therapeutic Strategy for High risk MM Patients

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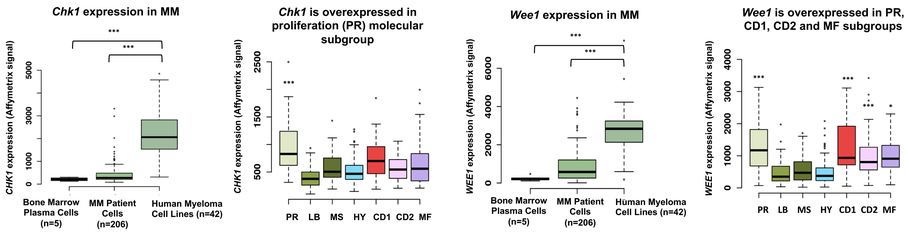
INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy characterized by an abnormal clonal proliferation of malignant plasma cells. Despite introduction of novels agents that have significantly improved clinical outcomes, most patients relapse and develop drug resistance. Therefore, novel therapeutic strategies to overcome chemotherapy resistance are needed in clinical settings.

MM is characterized by **genomic instability** and high level of replicative stress that arise during the disease's pathogenesis. In response to replicative and DNA damage stress, MM cells activate various DNA damage signaling pathways that include the kinases **ATR, Chk1 and Wee1.**
Chk1 is activated by ATR after DNA damage or replicative stress and promote cell cycle arrest through the regulation of S and G2 checkpoints**. Wee1 kinase** plays a central role in the proper timing of cell division cycle controlling entry into mitosis and DNA replication during S phase. Interestingly, experimental studies have identified that Chk1 inhibitors are strongly synergistic with Wee1 inhibitors in various cancer models. Furthermore, Chk1 and Wee1 inhibitors are currently under clinical investigation.

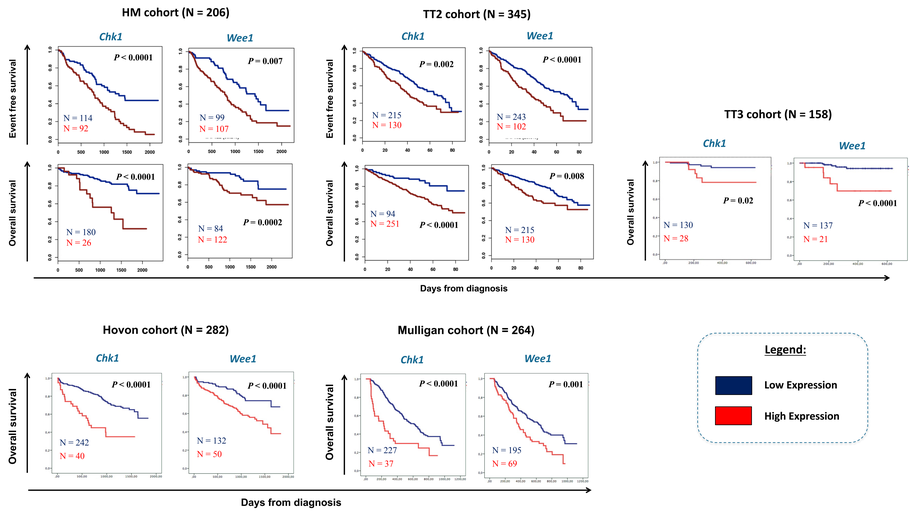
Here, we investigated the therapeutic interest of Chk1 and Wee1 in MM.

Chk1 and *Wee1* are overexpressed in high risk MM patients

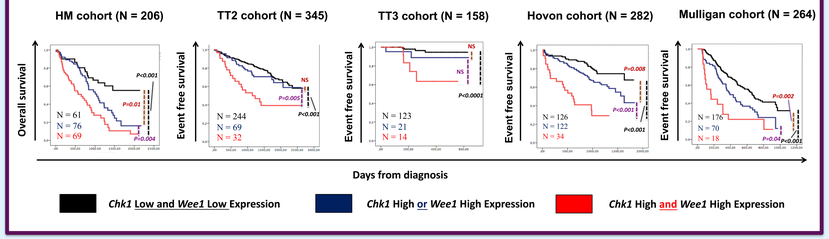


from www.genomicscape.com

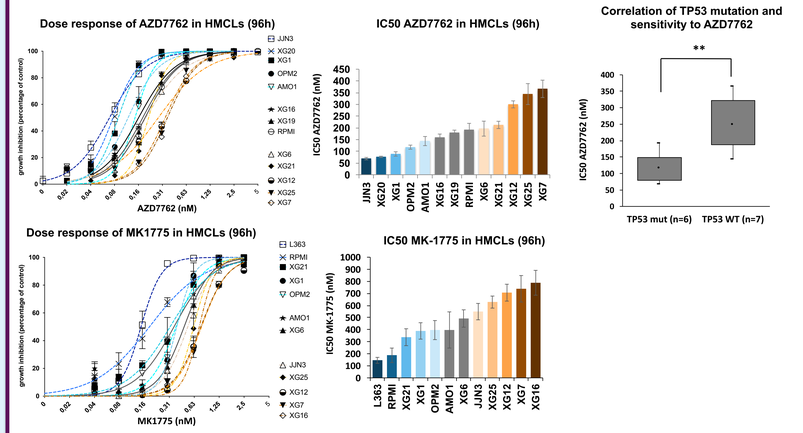
Chk1 and *Wee1* expression are associated with a poor prognosis in 5 cohorts of MM patients



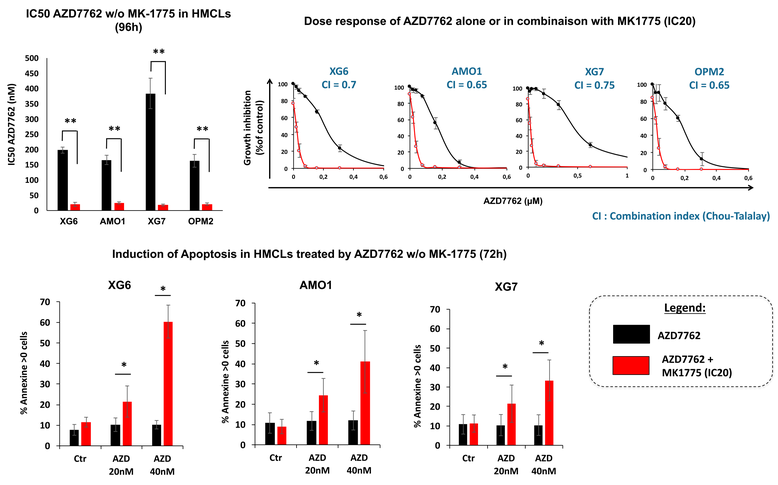
Combined high expression of *Chk1* and *Wee1* are associated to shorter survival in 5 cohorts of MM patients



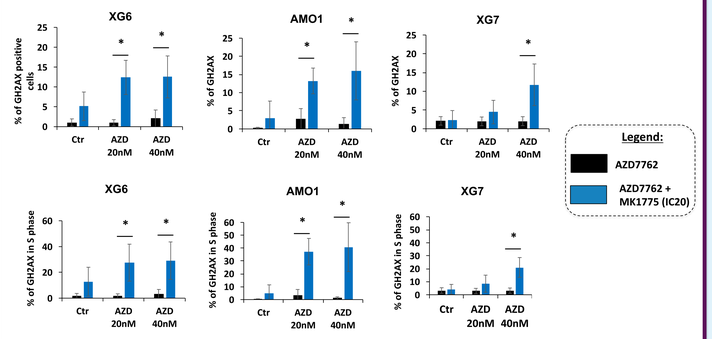
CHK1 inhibitor (AZD7762) and WEE1 inhibitor (MK-1775) affect HMCLs



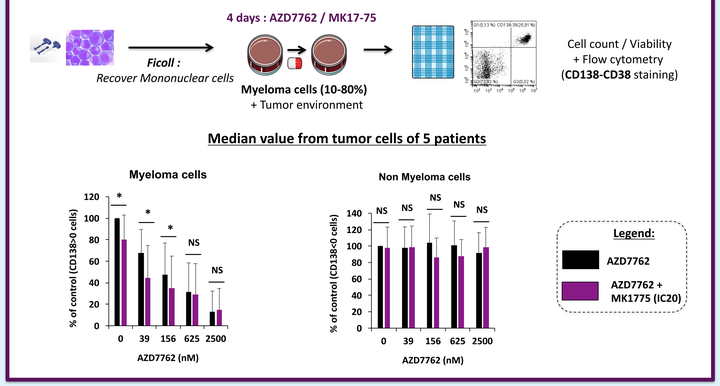
Combined inhibition of CHK1 and WEE1 shows a high synergy in HMLCs



AZD7762 and MK-1775 induce DNA damage in MM cells



CHK1 and WEE1 are critical for primary myeloma survival



CONCLUSION

Taken together, our results suggest that association of CHK1 and WEE1 inhibitors may represent a promising therapeutic approach in high-risk MM patients characterized by high *Chk1* and *Wee1* expression.

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