**FP-CA4**

*Asia-Pacific Journal of Molecular Medicine 2017, 7 (SUPP 1)*

**Abstracts for 7th Regional Conference on Molecular Medicine (RCMM)**

 **in Conjunction with 3rd National Conference for Cancer Research 2017**

**10-12th November 2017, Auditorium UMBI, Kuala Lumpur**

**Maritoclax represses anti-apoptotic protein MCL-1 and sensitizes Nasopharyngeal carcinoma cell lines to BH3-mimetic ABT-263**

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**ABSTRACT**

Malaysia has one of the highest national incidences of Nasopharyngeal carcinoma (NPC) in Southeast Asia. Improved treatment strategies are needed for NPC as patients with recurrence and advance NPC develop resistance to radio- and chemotherapy. BCL-2 anti-apoptotic proteins (BCL-2, BCL-XL, MCL-1, BFL-1) are upregulated in many cancers and hence are attractive therapeutic targets. The interest to target them mounted with the emergence of BH3-mimetics namely ABT-263 which specifically inhibit BCL-2, BCL-XL, and BCL-w. Unfortunately, most solid cancers were resistant to this drug and MCL-1 was characterised as the resistance factor of ABT-263. Hence, drugs that can repress the level of MCL-1 are predicted to synergize with ABT-263. SyBr Green I assay was employed to access cell proliferation after drug treatment. Spheroids generated were subjected to the drug combination treatment over 10 days. Viability of spheroids were determined using the live-dead stain. Maritoclax repressed MCL-1 in a dose- and time-dependant manner. However, Maritoclax also transiently repressed BCL-XL and BCL-2 in the NPC cell lines. Combination of Maritoclax and ABT-263 exhibited synergistic effects on NPC cell lines HK-1 and C666-1. Furthermore, drug potentiation studies revealed that Maritoclax sensitized both NPC cell lines to ABT-263. Similar results were obtained when the combination was tested in the 3D cell culture model. More notably, both HK-1 spheroids and C666-1 loose aggregates did not develop resistance to the combination rapidly. Collectively, our results demonstrate that combination of Maritoclax and ABT-263 has potential to be translated into the clinic for NPC treatment. In the study conducted, we could not determine the effect of Maritoclax on BFL-1 which may confer resistance to ABT-263 treatment. Moving forward, CRISPR/Cas9 technology will be utilized to determine the role of BFL-1 for NPC survival. The ongoing work would rationalise the use of upcoming BFL-1 inhibitors for NPC management.