Combination of EGFR inhibitor and MET inhibitor– a new targeted therapeutic strategy for melanoma
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Conclusion
- A synergistic or additive apoptotic effect was observed by combining EGFR/ERBB2 inhibitor with MET/ALK inhibitor compared to either drug used alone in melanoma.
- The effect is independent of BRAF/NRAS mutational status.
- The combination treatment also reduces cell invasion.
- Few overlaps of differentially expressed proteins were observed between the cell lines after the combination treatment.

Introduction
Novel therapies targeting mutated BRAF and MEK have improved overall survival for 50% of the patients with BRAF mutated cutaneous melanoma. However, only a subgroup of the patients have long-term survival due to development of acquired therapy resistance. It is therefore essential to find new therapeutic strategies for patients with resistance as well as for patients with BRAF wildtype cutaneous melanoma. Overexpression of ERBB and MET receptor tyrosine kinases have previously been recognized as resistance factors to BRAF inhibitors.

Purpose
The aim of this study is to investigate if targeting the ERBB family receptors and the MET receptor in combination, could be an alternative treatment for BRAF inhibitor sensitive and resistant CMM as well as for NRAS mutant and BRAF/NRAS wildtype CMM.

Results

Figure 1. MET and HER3/ERBB3 expression in metastases from three melanoma patients. MET and HER3/ERBB3 have been suggested to contribute to poor clinical outcome in cutaneous melanoma.

Figure 2. Combination treatment enhances cell death by apoptosis compared to either drug used alone. Melanoma cell lines were treated with either 2µM EGFR/HER2) afatinib, 2µM MET/ALK) crizotinib or the combination for 72h and then analyzed by FACS. *P< 0.05, **P<0.01, ***P<0.001, ****P<0.0001 (Student’s t-test).

Figure 3. Melanoma cells show reduction in cell invasion after combination treatment. Melanoma cell lines grown as 3D spheroids were treated with either 2µM afatinib, 2µM crizotinib or combination for 72h, stained with phallolidin and imaged using fluorescent microscope.

Figure 4. Overlap of differentially expressed proteins after combination treatment is demonstrated by Venn diagram. Melanoma cell lines were treated with either afatinib, crizotinib or the combination for 3h or 24h and then analysed by RPPA in collaboration with M Davies, MD Anderson.

Future perspective
- Confirm combination effect in in vivo model
- Further explore the molecular underlying mechanisms of the combination treatment effects

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This study has been funded by