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Session B. Melanoma and skin cancer

B01∗ **Negative influence of Melanocortin-1 receptor (MC1R) polymorphisms on clinical outcomes of metastatic melanoma (MM) patients (pts) harboring BRAF mutation and treated with BRAF inhibitors (BRAFi)**

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Background: In the pigmentation of hair and skin a key role is played by MC1R gene whose inherited variations encoding for a non-functional receptor are linked with melanoma risk. MC1R also mediates cell signals regulating DNA repair, survival and migration of melanoma. MC1R status does not seem to affect melanoma histology while its association with BRAF V600 mutation and pts survival are still debated. Our aim was to evaluate the effect of MC1R variants on outcomes of BRAF V600 pts treated with BRAFi considering that no data are available.

Patients and methods: Fifty-three pts treated with BRAFi (vemurafenib 46, dabrafenib 7) were studied. We divided pts in 2 groups according to MC1R status (wild type, 21 pts *vs* minor/major functional variants, 32 pts). BRAF and MC1R status was evaluated by sequencing methods on tumor tissue and peripheral blood samples, respectively. Baseline characteristics of pts and disease (age, sex, M stage, number and site of metastases, site of progression), overall survival (OS), overall response rate (ORR) and progression free survival (PFS) under BRAFi were compared between the 2 groups. MAPK pathway activation was also studied by measuring p/ERK and p/p38 levels in 2 representative BRAF V600 mutated melanoma cell lines (MBA72, Hmel-1) with different MC1R status (wt and presence of variants) in order to reproduce *in vitro* the features of the two pts groups.

Results: Baseline evaluation revealed a significant association between the presence of bone metastases and MC1R polymorphisms (p 0.0172). Moreover, the presence of MC1R variants was significantly associated with a worst outcomes under BRAFi in term of both ORR and median PFS (respectively 59% *vs* 95% [p 0.018 Ods Ratio 9.980] and 5 months *vs* 8 months [p 0.017Hazard Ratio 2.107] in MC1R variant *vs* wt). No significant difference was found in OS probably owing the influence of prior or subsequent treatments on this outcome. Data *in vitro* demonstrated high levels of p-Erk1/2 in both cell lines but significant higher levels in activation of p38 MAPK was found in MC1R variants.

Conclusions: These data demonstrated for the first time that MC1R variants have detrimental effects on clinical outcomes of pts treated with BRAFi by increasing the state of the hyperactivation of MAPK pathway. These evidences could shed further light on BRAFi resistance and suggest new therapeutic targets for MM.