Results: We found consistent hyperactivation of the PI3K–AKT pathway coupled to the activation of multiple RTKs such as HER2, HER3 and IGFR1 in resistant cells when compared to parental cells. Resistant clones exhibit an epithelial phenotype, more pronounced for mesenchymal-like parental cell lines of the CMS4 cluster (HCT116 and SW480). Either selective knockdown of these RTKs or treatment with the pan-HER inhibitor afatinib (BIBW2992) failed to revert the resistance phenotype in our cellular model, while treatment with pictilisib (GDC-0941, selective PI3Kα inhibitor) was able to restore the sensitivity to the drug combination. No new genetic alteration was detected.

Conclusions: Our in vitro preliminary data demonstrate that PI3K activation plays a central role in the acquired resistance to the combination of anti-EGFR and MEK-i in KRAS mutated colorectal cancer cell lines. PI3K activation is achieved through concurrent activation of multiple RTKs such as HER2, HER3 and IGFR1, suggesting a cooperative mechanism.

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