Rapid conversion to resistance, of a colon PDX with ret-fusion, by Ponatinib treatment could potentially be attributed to the introduction of the gate keeper mutation, V804M

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Abstract

We are interested in exploring the potential resistance development of Ponatinib treatment. We prolong treated both models and also observed that the resistant treatment rapidly drove CR2518 into resistance. (The resistant derivative is called CR2545). To investigate the underlying mechanism of the resistance, we performed RNAseq analysis of CR2545, which revealed retaining of the ret-fusion, but also the introduction of a previously described gate-keeper mutation, V804M, at ret kinase domain. V804M, a mutation frequently found in familial medullary thyroid carcinoma (FMTC), introduces a new V804M mutation.

Results

Ponatinib resistant CR2545 maintains ret-fusion, but introduces a new V804M mutation.

Conclusions

1. Treatment of a ret-fusion containing ponatinib sensitive a PDX-CRC model resulted in rapid development of resistance;
2. The resistant model still maintains the ret-fusion, but a new V804M gate-keeper mutation was found in the induced resistant model;
3. The resistant model seems to show less PD effects as compared to the sensitive parental model.

References

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