FGFR selective inhibitor Debio 1347 induces tumor regressions in FGFR2-altered gastric cancer PDX models

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Summary

Potential of the threshold growth factor receptor (FGFR) signaling pathway due to receptor over-expression, gene amplification, point mutations or extracellular modifications is associated with cancer development and progression. This study was aiming at evaluating the impact of the FGFR signaling pathway on the activity of Debio 1347 (CH5183284), a novel selective FGFR inhibitor currently in clinical development.

A mouse trial was conducted in 39 different PDX models of various histotypes selected according to their FGFR1, 2 and 3 alteration status including gain expression, amplification and fusions. Debio 1347 was administered orally daily at a dose level as well as a total volume twice measured for 14 consecutive days.

In gastric cancer, Debio 1347 induced tumor regressions in models harboring the common FGFR2 amplification. Interestingly, Debio 1347 was also highly effective in a model with high FGFR expression but without FGFR amplification, indicating that not only gene amplification drives the activity of Debio 1347 in this indication, but also the FGFR2 expression level.

Debio 1347 induced high anti-tumoral efficacy in PDX models of different histotypes. Debio 1347 demonstrated high anti-tumoral efficacy in PDX models of different histotypes (Fig. 1). 39 PDX models of different histotypes representing the four following categories were selected and tested for efficacy: (a) increased copy number of an FGFR gene and expression of an FGFR, (b) increased copy number of an FGFR gene and overexpression of an FGFR, (c) overexpression of an FGFR gene but no amplification of an FGFR, and (d) expression of an FGFR fusion gene product.

Results

A total of 13 PDX models of gastric origin were investigated. Representative models with or without FGFR2 amplification (Fig. 3A), FGFR high mRNA expression but not amplification (Fig. 3C), low FGFR mRNA expression and amplification (Fig. 3E) showed differentially impacted profiles in Debio 1347 (Fig. 3B). Debio 1347 demonstrated high anti-tumoral efficacy in PDX models of different histotypes. Debio 1347 was administered orally daily at 60 mg/kg for 14 consecutive days. Debio 1347 was very well tolerated as measured by body weight, food intake, and debio 1347 caused no statistically significant reduction in mouse tumor volume when compared to the vehicle group (two-tailed t-test).

Conclusions

• Debio 1347 demonstrated high anti-tumoral efficacy in PDX models of different histotypes.

• In gastric cancer, Debio 1347 induced tumor regression in models harboring the commonly found FGFR2 amplification.

• Interestingly, Debio 1347 was highly effective in model with high FGFR expression but without FGFR2 amplification, indicating that not only gene amplification drives the activity of Debio 1347, but also gene expression.

• Debio 1347 is currently investigated in a Phase I trial in selected patients harboring FGFR alterations (NCT01948227).

Related Presentations

• AACR, Cancer Research and Conference (2014): Debio 1347 is a selective FGFR inhibitor. Sunday, Apr 19, 8:00 AM - 9:00 AM - Abstract #2729.

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