Exploring Mechanisms of Resistance to Elagliusib in Pancreatic Cancer PDX Models

Taylor Weiskittel, Li Ding, Lingling Han, Joseph McDermott, Benedito Carneiro, Hu Li, Daniel Billadeau, Andrew Mazar

ABSTRACT

Metastatic pancreatic cancer patients who previously progressed on nab-paclitaxel/gemcitabine (average of 3 previous lines if treatment) were treated with elagliusib in combination with a rechallenge of this combination. The majority of patients demonstrated a prolonged progression free survival. While this early clinical evidence is highly encouraging, the biological determinants of elagliusib response are unknown. In vitro screens of elagliusib on pancreatic PDX cell lines showed that some tumor cells possess modest intrinsic resistance to elagliusib as measured by LD50 which ranged from 316.9 nM to 1080 nM in a screen of 10 cell lines. To explore this phenomena further, we induced resistance in three cell line models by growing cells in the presence of increasing concentrations of elagliusib. We then sequenced the transcriptome of the parental and resistant lines to identify potential mechanisms of elagliusib resistance.

Comparison of RNA sequencing profiles identified upregulation of the Aldo-keto reductase (AKR) family of genes. This upregulation was confirmed by qRT-PCR and by immunoblot demonstrating that AKRs were upregulated at both the transcriptomic and protein level. We further quantified the AKRs levels in the remainder of the 10 cell lines and found that many of the more resistant lines had high expression of AKR1C2. However, not all of the resistant lines had high expression which could be because they have a separate mechanism of resistance to elagliusib.

A large body of literature has found that AKR genes provide resistance to many other small molecule inhibitors either by direct metabolism or by indirectly relieving oxidative stress. Given these results, we identify aldoketo reductases as potentially associated with elagliusib resistance, but further investigation is warranted to establish a causal link between AKR and the resistant phenotype.

RESULTS

Figure 1. Kaplan Meier curve for the 1801 Part 1/2 trial of metastatic pancreatic cancer patients who failed an average of 3 previous lines of treatment

Figure 2. Elagliusib sensitivity curves for pancreatic cancer cell lines

Figure 3. Elagliusib sensitivity curves for parental and induced resistance patient derived pancreatic cancer cell lines

Figure 4. Volcano plot for triplicate RNASeq comparing resistant versus parental lines L3.6, 6741, and 4535.

Figure 6. ARK1C1 western blot quantification for parental (P) and resistant (R) pancreatic cell lines

Figure 7. RT-PCR quantification of extended cell line panels

CONCLUSIONS

- Elagliusib provides significant treatment benefits to patients with late stage pancreatic cancer
- In vitro pancreatic cancer cell lines have a broad range of sensitivities to elagliusib
- RNASeq comparing parental vs resistant cell lines reveals upregulation of aldoketo reductases among other transcripts
- Aldo-keto reductase upregulation was confirmed at the transcriptomic level with RT-PCR and demonstrated at the protein level.

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