Exploring Mechanisms of Resistance to Elraglusib in Pancreatic Cancer PDX Models

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Abstract: #3857

ABSTRACT

Metastatic pancreatic cancer patients who previously progressed on nab-paclitaxel/gemcitabine (average of 3 previous lines if treatment) were treated with elraglusib 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 elraglusib response are unknown. In vitro screens of elraglusib on pancreatic PDX cell lines showed that some tumor cells possess modest intrinsic resistance to elraglusib 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 elraglusib. We then sequenced the transcriptome of the parental and resistant lines to identify potential mechanisms of elraglusib 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 AKR 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 elraglusib. 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 aldo-keto reductases as potentially associated with elraglusib resistance, but further investigation is warranted to establish a causal link between AKR and the resistant phenotype.

RESULTS

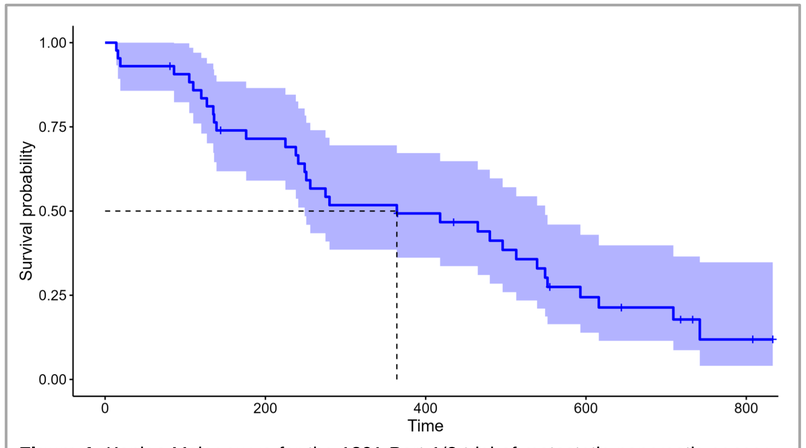

Figure 1. Kaplan Meier curve for the 1801 Part 1/2 trial of metastatic pancreatic cancer patients who failed an average of 3 previous lines of treatment

RESULTS

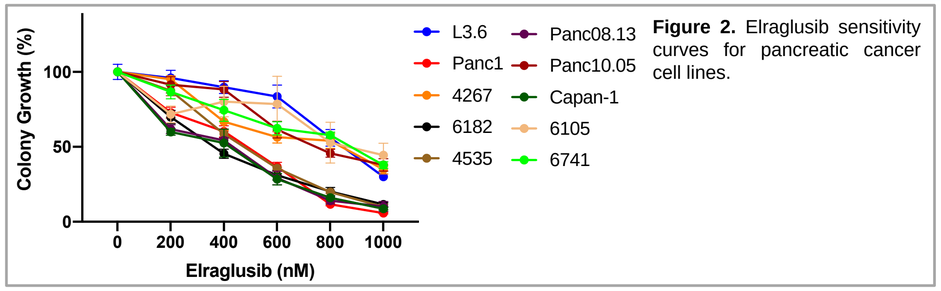

Figure 2. Elraglusib sensitivity curves for pancreatic cancer cell lines.

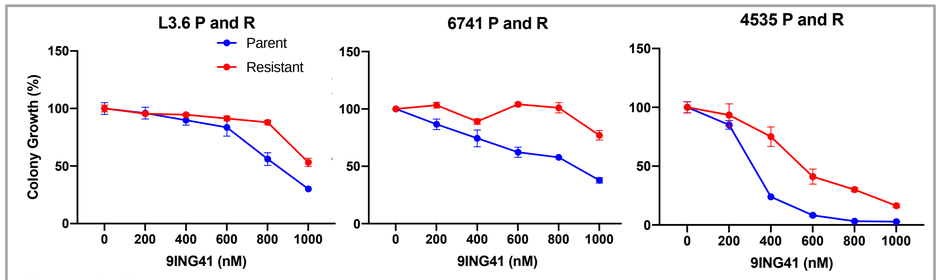

Figure 3. Elraglusib sensitivity curves for parental and induced resistance patient derived pancreatic cancer cell lines

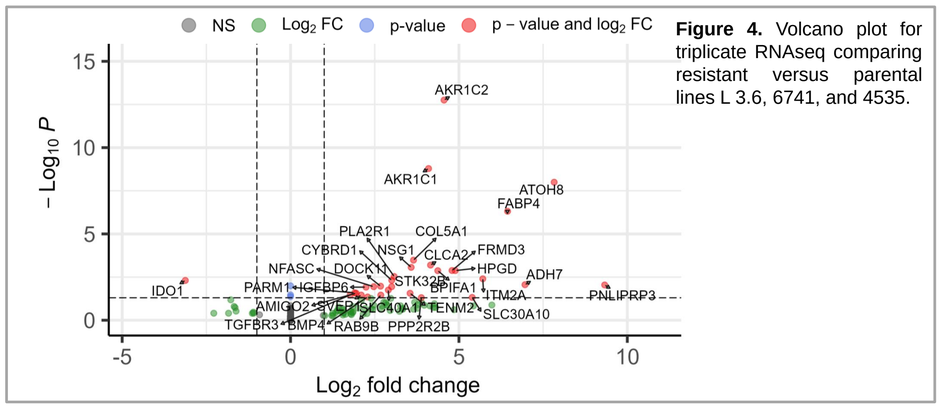

Figure 4. Volcano plot for triplicate RNAseq comparing resistant versus parental lines L 3.6, 6741, and 4535.

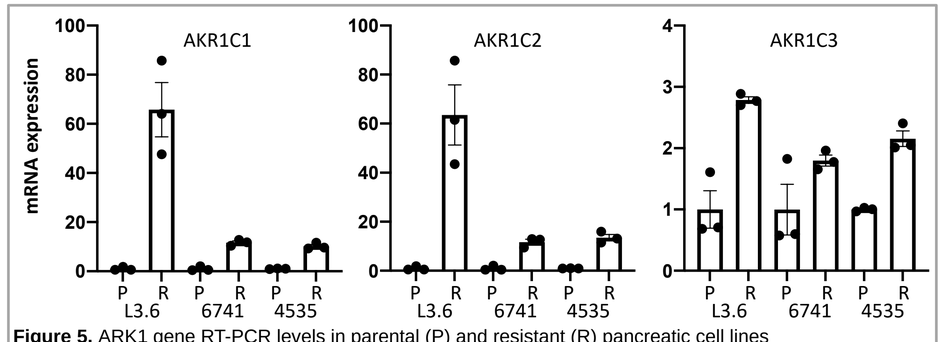

Figure 5. ARK1 gene RT-PCR levels in parental (P) and resistant (R) pancreatic cell lines

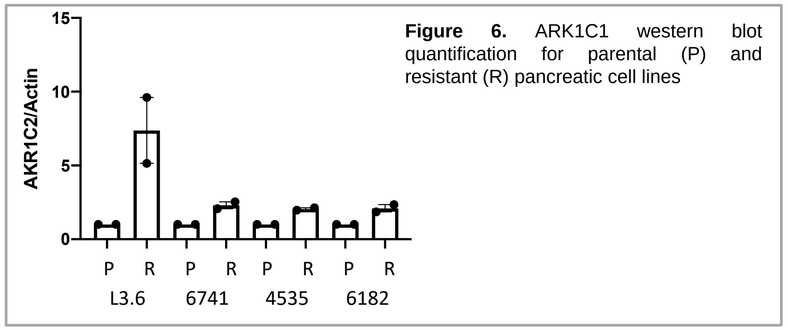

Figure 6. ARK1C1 western blot quantification for parental (P) and resistant (R) pancreatic cell lines

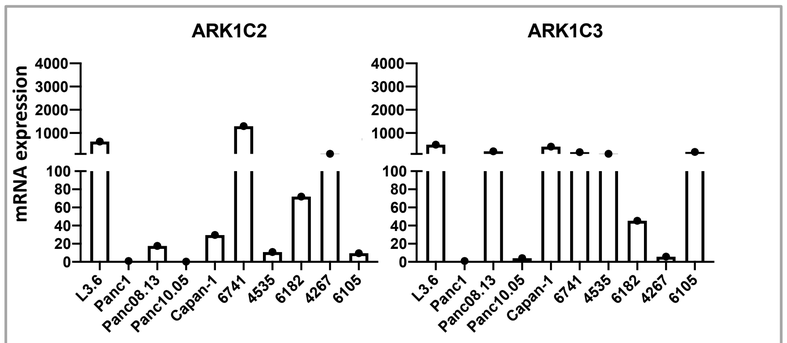

Figure 7. RT-PCR quantification of extended cell line panels

CONCLUSIONS

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

OTHER WORK FROM ACTUATE:

Immunomodulation in Elra Phase 1/2 Trials **Section 47 Poster 12 April 18th 9-12 AM**

Predicting Elra Response and Biomarkers using Machine Learning **Section 31 Poster 4 April 18th 1:30-5:00 PM**

- Huntington KE, Louie A, Zhou L, Carneiro BA, El-Deiry W. Abstract 4166: Small-molecule inhibition of glycogen synthase kinase-3 (GSK-3) increases the efficacy of anti-PD-L1 therapy in a murine model of microsatellite stable colorectal cancer (CRC); Therapeutic response correlates with T cell ratios and serum cytokine profiles in mice. *Cancer Research*.
- Carneiro BA, Cavalcante L, Bastos BR, Powell SF, Ma WW, Sahebjam S, et al. Phase I study of 9-ING-41, a small molecule selective glycogen synthase kinase-3 beta (GSK-3β) inhibitor, as a single agent and combined with chemotherapy, in patients with refractory tumors. J Clin Oncol 2020; 38 (suppl; abstr 3507).
- Ding, L., Madamsetty, V. S., Kiers, S., Alekhina, O., Ugolkov, A., Dube, J., Zhang, Y., Zhang, J.-S., Wang, E., Dutta, S. K., Schmitt, D. M., Giles, F. J., Kozikowski, A. P., Mazar, A. P., Mukhopadhyay, D., & Billadeau, D. D. (2019). Glycogen synthase kinase-3 inhibition sensitizes pancreatic cancer cells to chemotherapy by abrogating the TOPBP1/ATR-mediated DNA damage response. Clinical Cancer Research, 25(21), 6452–6462. https://doi.org/10.1158/1078-0432.ccr-19-0799
- Mahalingam, D., Carneiro, B. A., Safran, H., Powell, S. F., Coveler, A. L., Davis, E. J., Cervantes, A., Sahai, V., Steeghs, N., Huerta, M., Berlin, J., Mulcahy, M. F., Giles, F. J., Cavalcante, L., & Saeed, A. (2022). Phase 2 study of 9-ing-41, a small molecule selective glycogen synthase kinase-3 beta (gsk-3β) inhibitor, with Gemcitabine/NAB-paclitaxel (GNP) in first-line advanced pancreatic ductal adenocarcinoma (PDAC). Journal of Clinical Oncology, 40(4_suppl), 578–578. https://doi.org/10.1200/jco.2022.40.4_suppl.578