Negative control experiments were conducted alongside single drug treatments for comparison and to demonstrate the specificity of the observed effects. The results of these experiments confirmed that the observed antitumor effects were indeed pathway-specific and not due to nonspecific cytotoxicity or off-target effects of the drug combinations.

**Results**

### Combinatorial drug treatment enhances the antitumor effects of Lerociclib

Combinatorial drug treatment was found to significantly enhance the antitumor effects of lerociclib compared to single-agent treatment. This was evident from the lower tumor burden and increased response rates observed in lerociclib-treated PDX models. The results suggest that lerociclib may be a promising agent for combination therapy in PDAC, especially when combined with other targeted agents such as ulixertinib.

### Gene signature enrichments associated with response or resistance to lerociclib-based combinations

Gene expression analysis using GSEA revealed several gene signatures associated with response or resistance to lerociclib-based combinations. These signatures were enriched in lerociclib-responsive PDX models, indicating that lerociclib may be able to preferentially target tumors with specific genetic profiles. Conversely, lerociclib-resistant tumors exhibited gene expression profiles that were distinct from responsive tumors, suggesting that these tumors may have developed resistance mechanisms.

**Conclusions**

1. **Cytotoxicity and antitumor effects:** Combination therapy with lerociclib and ulixertinib was found to have significant antitumor effects in lerociclib-responsive PDAC PDX models. This suggests that lerociclib can be a useful agent for combination therapy in PDAC.

2. **Gene expression signatures:** Gene expression analysis identified specific gene signatures associated with response or resistance to lerociclib-based combinations. These signatures could be used to identify potential biomarkers for predicting response to lerociclib therapy.

3. **Clinical relevance:** The results of this study support the need for further clinical trials to evaluate lerociclib in combination with ulixertinib in PDAC patients. The combination therapy may provide improved efficacy and reduced toxicity compared to single-agent therapy.

**References**


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