

Glutamine Strategy Shows Early Promise in Extending Survival for Pancreatic Cancer

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Cedars-Sinai's Phase I GlutaPanc trial challenges conventional thinking around glutamine metabolism, with L-glutamine plus standard chemotherapy demonstrating encouraging survival and tumour-response signals in advanced pancreatic cancer.



Pancreatic ductal adenocarcinoma (PDAC) remains one of the most difficult cancers to treat, creating an urgent need for therapeutic approaches that can improve outcomes without adding significant toxicity. The Phase I GlutaPanc trial at Cedars-Sinai is exploring an unconventional strategy: supplementing rather than depriving tumours of glutamine.

In an interview with **BioSpectrum Asia / MedTech Spectrum**, **Jun Gong, MD, Associate Professor of Medicine and Medical Director of Colorectal Cancer at Cedars-Sinai**, discusses the early findings from GlutaPanc, including a reported median overall survival of **22 months**, a **44% objective response rate**, and tumour shrinkage in **94% of patients** receiving oral L-glutamine alongside gemcitabine and nab-paclitaxel. He stresses that these findings come from a small, single-arm Phase I study and require confirmation in a larger randomised controlled trial.

Willis Lee, CEO of Emmaus Life Sciences, also discusses the company's plans to build on the Phase I findings and the potential for targeting cancer metabolism to create new therapeutic options for pancreatic cancer.

What is the most significant takeaway from the GlutaPanc Phase 1 results?

The key takeaways from the phase I GlutaPanc trial results are multiple. Firstly, it should be important to realize that glutamine deprivation, rather than supplementation, has been the historical approach to targeting glutamine metabolism in pancreatic ductal adenocarcinoma (PDAC). The glutamine dependency in PDAC is uniquely driven by the KRAS oncogene, which is highly prevalent in PDAC cases.

However, prior studies have proven that glutamine deprivation's antitumor effects in PDAC preclinical models are short-lived with translation to the clinical context challenging. The phase I GlutaPanc trial thus represents the first formal translation of glutamine supplementation using an FDA-approved, clinical-grade oral L-glutamine formulation as a therapeutic sensitizer to standard chemotherapy in advanced PDAC patients. It challenges the dogma that glutamine deprivation is the conventional therapeutic approach and supports that the pairing of high-dose glutamine is safe and feasible with gemcitabine/nab-paclitaxel chemotherapy. L-glutamine was very safe and the overwhelming majority of adverse events were from the chemotherapy backbone.

The study met its primary endpoint to establish the recommended phase II dose (RP2D) of the study combination, which was at maximum doses of oral L-glutamine daily plus full standard doses of gemcitabine/nab-paclitaxel. Secondary endpoints included preliminary signals of efficacy. Here, the combination of L-glutamine and gemcitabine/nab-paclitaxel resulted in a median OS of 22 months, which is near tripling of the median OS for gemcitabine/nab-paclitaxel itself (median 8.5 months) from the historical phase III registrational trial. The median PFS of the study combination was improved over the historical PFS of gemcitabine/nab-paclitaxel as well.

How might L-glutamine enhance the effectiveness of gemcitabine and nab-paclitaxel?

A strength of the GlutaPanc trial was the depth of correlative analyses that could shed light on the potential mechanisms of action for addition of L-glutamine to gemcitabine and nab-paclitaxel chemotherapy. In preplanned collected blood samples following a 1-week lead-in phase of oral L-glutamine alone, prior to the addition of chemotherapy, L-glutamine treatment resulted in increased plasma levels of glutamine and subsequent uptake into downstream intermediary metabolic pathways. Several of these metabolites were prognostic of OS to the study combination.

Next, in stool collected before and after L-glutamine administration during the 1-week lead in (absent of chemotherapy), we noted that L-glutamine administration did not significantly alter the gut microbiome composition. However, in recognition that L-glutamine is a central nutrient vital for gut bacterial growth, we performed shotgun metagenomics of stool and identified that L-glutamine treatment significantly impacted bacterial metabolism involved in multiple metabolic pathways important for bacterial growth and proliferation. We additionally identified that 50% of the patients experienced weight stability throughout the entire duration of study treatment, which is notable given that cachexia is highly prevalent in PDAC cases.

Supporting this benefit, we identified that L-glutamine treatment preserved gut barrier integrity and promoted anti-inflammatory responses which posits potential anti-cachexia effects with L-glutamine. All of these correlatives are hypothesis-generating and warrant further validation, but they altogether suggest that the possible mechanisms of action for L-glutamine addition to chemotherapy in PDAC could involve its effects on intermediary metabolism, gut bacterial metabolism, and anti-cachexia effects through preservation of gut barrier integrity and anti-inflammatory response.

How should the 94% tumour shrinkage and 44% objective response rate be interpreted at this early stage?

The tumor shrinkage rate and objective response rates are encouraging, considering that the ORR for gemcitabine/nab-paclitaxel was 23% from the earlier phase III trial of gemcitabine/nab-paclitaxel in first-line metastatic PDAC patients. However, given the small sample size these response rates should be considered preliminary and needs confirmation in a larger study.

What did the study reveal about the safety and tolerability of this combination?

Perhaps the most robust finding of the phase I GlutaPanc trial was the exquisite safety of L-glutamine. The grade ≥3 treatment-related adverse event rate was 66.7%, primarily from the gemcitabine/nab-paclitaxel chemotherapy backbone. There were a total of three dose-limiting toxicities (DLTs) that were encountered during the dose-finding portion, all deemed treatment-related to gemcitabine/nab-paclitaxel and not oral L-glutamine. The safety and tolerability is ultimately reflected in the determination of the RP2D, which showed that maximum proposed doses of oral L-glutamine was possible with full standard doses of gemcitabine/nab-paclitaxel.

What are the key questions that a larger randomised trial now needs to answer?

The phase I GlutaPanc trial was a single-arm trial with a relatively small sample size. The GlutaPanc results do not support that oral L-glutamine and gemcitabine/nab-paclitaxel is better than gemcitabine/nab-paclitaxel alone in the first-line treatment of metastatic PDAC. This question needs to be validated in the context of a larger, randomized controlled trial. A randomized controlled trial would also be important to validate the metabolic, microbiome, and inflammatory correlates as potential mechanisms and/or biomarkers to exploit L-glutamine's therapeutic potential in this setting.

Could targeting cancer metabolism open new treatment possibilities for pancreatic cancer?

Targeting cancer metabolism could open new treatment possibilities for pancreatic cancer. We do know that PDAC cells are heavily dependent on glutamine metabolism, a process that is driven by the KRAS oncogene.

Thus, targeting this KRAS-driven glutamine metabolism in PDAC could open a new avenue to exploit metabolic vulnerabilities as a novel therapeutic approach. With the advent of pan-RAS and allele-specific KRAS inhibitors in PDAC, the role of L-glutamine administration in enhancing the therapeutic benefit of these RAS inhibitors would be especially interesting.

The exquisite safety of oral L-glutamine daily demonstrated in our phase I trial would support that L-glutamine could reasonably pair well with RAS inhibitors and other systemic agents, in general, without much concern for additional toxicities with this pairing. The fact that there is a pharmaceutical grade, FDA-approved formulation available renders L-glutamine especially attractive to combine with systemic agents as it is primed for clinical translation.

For Willis Lee of Emmaus Life Sciences What is the company's perspective on the study and its potential implications?

Emmaus Life Sciences has closely monitored the research progress of Dr. Gong's team at Cedars Sinai. Despite the small sample size, a combination therapy with Endari, our FDA approved drug for sickle cell disease, and two chemotherapy drugs improved overall survival from 8.5 months to 22 months for advance stage pancreatic cancer patients. The company plans to take the positive Phase 1 data and start a larger scale Phase 2 data to validate efficacy. The collaboration of Cedars Sinai and Emmaus Life Sciences leverages the institution's premier oncological research capabilities alongside Emmaus's expertise in drug development. We hope to bring another treatment options to many patients, about 67,000 new PDAC cases per year in the U.S. alone.