

A Phase II Study of FOLFIRINOX (FFX) Combined with the Glycogen Synthase Kinase-3 Beta (GSK-3β) Inhibitor Elraglusib (ELRA) and the Transforming Growth Factor-β (TGF-β) Inhibitor Losartan (LOS) in Patients with Untreated Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC).

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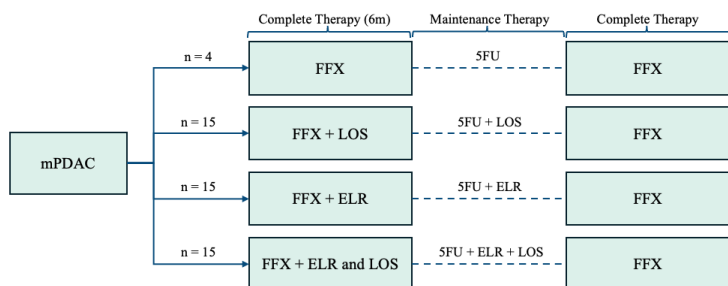
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Background

- mPDAC remains one of the most lethal malignancies with dismal long term survival outcomes despite therapeutic advances.
- GSK-3β promotes pancreatic cancer cell survival, chemotherapy resistance, and immune evasion through regulation of NF-κB signaling and tumor immune pathways.
- ELRA is a first-in-class, cell-permeable, ATP-competitive inhibitor of GSK-3β.
- LOS, via inhibition of TGF-β signaling, may modulate the TME, enhance immune activation and improve drug delivery by reducing stromal fibrosis and desmoplasia.

Methods

Multi-institutional, open-label, four-arm (non-comparator), randomized, phase II trial



Endpoints

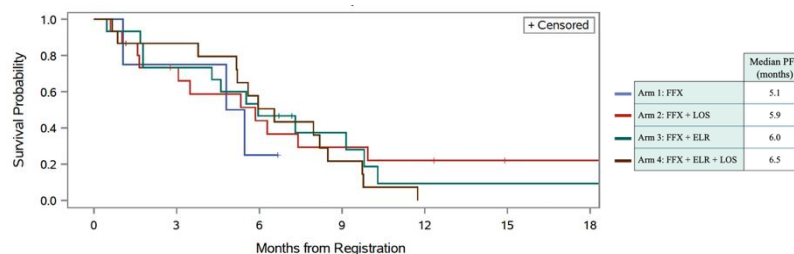
- Primary Endpoint:
 - Progression Free Survival
- Secondary Endpoints:
 - Overall Survival
 - Objective Response Rate
 - Time on maintenance therapy

Results

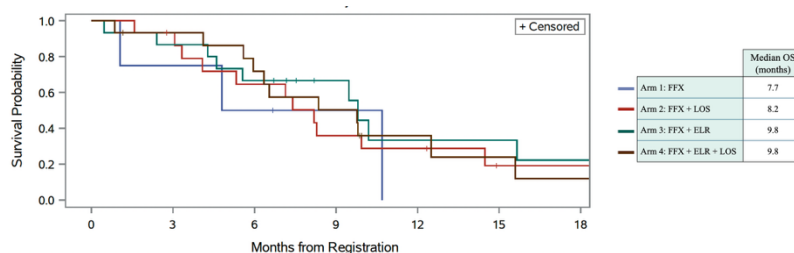
Baseline characteristics

| | | Total n=49 (%) | | | Total n=49 (%) |
|------------|------------------------|----------------|--------------------------------|-------------------------|----------------|
| Age, years | Median | 65 | ECOG PS | 0 | 36 (73) |
| Sex | Male | 24 (49) | 1 | 13 (27) | |
| | Female | 25 (51) | Metastatic Sites | 1 | 25 (51) |
| Race | White | 36 (73) | | 2 | 10 (20) |
| | Black/African American | 5 (10) | | ≥ 3 | 14 (29) |
| | Asian | 2 (4) | | Liver Metastases | 36 (73) |
| | >1 Race | 2 (4) | Main Pancreatic Tumor Location | Head / Uncinate Process | 24 (49) |
| | Other | 4 (8) | | Body / Tail | 29 (59) |
| Ethnicity | Hispanic or Latino | 2 (4) | Baseline CA 19-9 | < 37 U/ml | 5 (10) |
| | Not Hispanic or Latino | 46 (94) | ≥ 37 U/ml | 44 (90) | |
| | Ethnicity not known | 1 (2) | | | |

Progression Free Survival



Overall Survival



Objective Response Rate

| Best Response (overall) | n (%) |
|-------------------------|-----------|
| Partial Response | 12 (24.5) |
| Stable Disease | 22 (44.9) |
| Progressive disease | 7 (14.3) |

Time on maintenance therapy

| | n who received maintenance therapy | Median time on maintenance therapy (months) |
|------------------------|------------------------------------|---|
| Arm 1: FFX | 0 | - |
| Arm 2: FFX + LOS | 2 | 6.8 |
| Arm 3: FFX + ELR | 6 | 2.5 |
| Arm 4: FFX + ELR + LOS | 6 | 2.1 |

Treatment related toxicity

| Grade of toxicity (CTCAEV5.0) | n (%) | Common ≥ grade 3 TRAEs | n |
|-------------------------------|-----------|------------------------------------|---|
| ≥ grade 3 | 17 (34.7) | Diarrhea | 3 |
| ≥ grade 4 | 2 (4) | Fatigue | 3 |
| ≥ grade 5 | 1 (2) | Hypokalemia | 3 |
| | | Decreased platelet count | 3 |
| | | Alanine Aminotransferase increased | 3 |
| | | Alkaline phosphatase increased | 3 |
| | | Anorexia | 2 |
| | | Sepsis | 1 |

Treatment was generally well tolerated; one treatment-related death due to sepsis in Arm 3

Conclusion

- Although outcomes did not exceed historical standards, this phase II study demonstrated the feasibility and tolerability of combinatorial pathway inhibition in mPDAC.
- A subset of patients in Arms 3 and 4 demonstrated deep and durable responses, with ongoing biomarker analyses evaluating features associated with long-term benefit.
- This study established a robust platform for correlative analyses of EMT plasticity, stromal remodeling, immune escape, and mechanisms of therapeutic resistance in mPDAC.