A Phase II Study of Perioperative Therapy For Patients With Resectable And Borderline Resectable Pancreatic Adenocarcinoma (with Gemcitabine, Docetaxel, Capecitabine, Oxaliplatin and Radiation Therapy)

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Background

- Surgical resection is the only potentially curative treatment for early stage pancreatic cancer, but cures only about 10%.
  - Most patients die of metastatic disease
  - A hallmark of pancreatic cancer is malignant cells spread early and the disease is systemic nearly from onset.
- Adjuvant chemotherapy improves survival compared to observation in randomized trials.
- Hypofractionated radiation can be incorporated while preserving systemically active chemotherapy dosing and may provide for an improvement in R0 resectability.
- Adjuvant therapy most commonly consists of gemcitabine with or without radiation therapy, historically:.
  - Median Disease Free Survival (mDFS) is 13.4 months
  - Median Overall Survival (mOS) is 22.8 months
- Systemic chemotherapy administered after surgery may be too little and too late.
- Multiagent chemotherapy in the metastatic setting improves DFS and OS compared to gemcitabine alone.

Objectives

Primary Objective

- To estimate the mOS of patients with adenocarcinoma of the pancreas treated with induction chemotherapy, neoadjuvant chemoradiotherapy, surgical resection and adjuvant chemotherapy.

Secondary Objectives

To determine

- The mDFS survival following surgical resection.
- The clinical response rate to neoadjuvant therapy
- The pathologic response rate to neoadjuvant therapy
- The surgical completion rate and complication rate following neoadjuvant therapy
- Adverse Events associated with this treatment regimen.

References

- CONKO -001: Oettle, JAMA 2007 and 2013
- GTX: Fine, J Cancer Chemother Pharmacol. 2008
- Resectability Criteria: NCCN Guidelines
- XRT: Katz, Sem Radiato Oncol 2014

Acknowledgements

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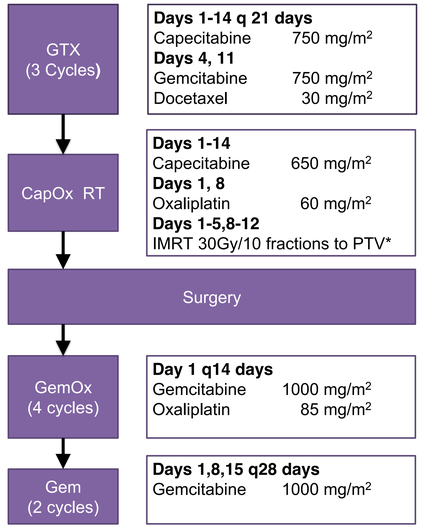
Methods

Eligibility

- Histologically or cytologically confirmed pancreatic ductal adenocarcinoma.
- Resectable or Borderline Resectable (T1-T3, N0-N1, M0)
- No prior therapy
- Age ≥ 18 years
- ECOG ≤ 2 / Karnofsky ≥ 60%
- Adequate Organ / Marrow Function including
  - Normal Bilirubin or < 6 and decreasing after stent placement
  - AST/ALT < 2.5x Upper Limits of Normal or Decreasing after stent placement

Study Schema



* = Radiation Planning Target Volume Definitions	
Gross Target Volume	= Primary Tumor and Enlarged Nodes
Clinical Target Volume	= GTV + 1.5 cm of uninvolved pancreas and regional nodes at risk
Planning **T**arget **V**olume	= CTV with an expansion of 0.5cm

Results

Demographics

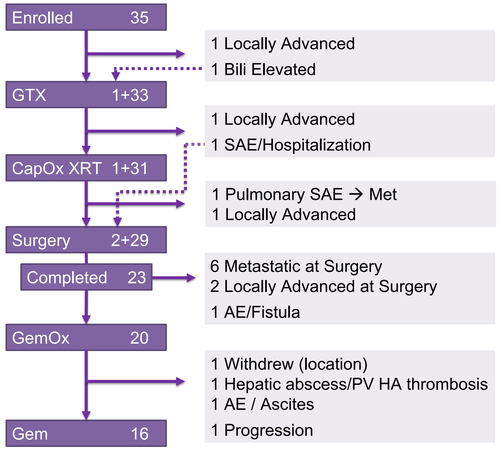
Characteristic	N	%
Median Age (Range)	62	(46-77)
Female/Male	16/19	46/54
ECOG		
0	19	54
1	14	40
2	2	6

Clinical Stage	N	%
T1	1	3
T2	15	43
T3	18	51
T4	1	3
N0	19	54
N1	16	46

Site of Disease	N	%
Uncinate	2	6
Head	27	77
Neck	2	6
Body	6	17
Tail	3	9

Resectability	N	%
Resectable	18	51
Borderline	16	46
Unresectable	1	3

Patient Flow



Surgery Completed	N	%
Yes	23	66
No	12	34
Locally Advanced	5	14
Metastatic	7	20

Results continued

Dosing and AEs

	N	% Dosing	Missed	% Missed
Gemcitabine Docetaxel Capecitabine	33	90% 88% 86%	11 11 267	6% 6% 29%
Capecitabine Oxaliplatin	31	89% 98%	56 0	7% 0%
Gemcitabine Oxaliplatin	20	96% 95%	4 4	5% 5%
Gemcitabine	16	80%	8	9%

Grade 3/4 Treatment Related AEs (N > 1)	GTX (N=33)	CapOx (N=31)	GemOx (N=20)	Gem (N=16)
Hand Foot Syndrome	20	2	0	0
Neutropenia	16	1	1	11
Thrombocytopenia	6	1	1	5
Diarrhea	5	0	0	0
Anemia	4	0	0	2
Mucositis	4	0	1	0
Neutropenic Fever	3	0	0	0
Hyperbilirubinemia / Stent Occlusion	3	2	0	0
Nausea	3	0	0	0
Vomiting	2	0	0	0
Fatigue	2	0	0	0

Related Grade 3/4 AEs N=1:

Lower GI Bleed (1, GTX) Pneumonitis (1, GTX)
HUS (1, Gem) Anasarca* (1, Gem)
Liver Abscess / Sepsis (1 GTX, 1 post surgical)
* Unclear etiology and relatedness

Responses

RECIST	Pre Radiation	Pre Surgery
PR	9 (28%)	10 (31%)
SD	22 (68%)	19 (59%)
PD	1 (3%)	1 (3%)

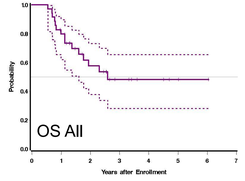
Pathologic Response	N	%
No Response	2	9
Partial Response	14	61
Near Complete Response	6	26
Complete Response	1	4

Results continued

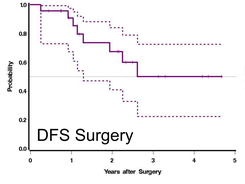
Responses continued

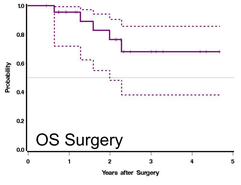
Pathology	Peri Operative Therapy		CONKO-001 (for comparison)
T1	8	35%	4%
T2	5	22%	10%
T3	10	43%	82%
T4	0	0%	4%
N0	20	87%	29%
N1	3	13%	71%
R0	17	74%	81%
R1	6	16%	19%

Survival



	Months
All Patients	
m Follow Up	30.6
mOS (all pts)	31.0
Surgery Group	
mDFS	31.3
mOS	Not Reached





The mDFS and mOS for the surgery group is calculated from time of surgery. Median time from enrollment to surgery for those who had surgery is 4.1 months (range, 3.4 - 6.3 months)

Conclusions

- Perioperative multiagent chemotherapy with chemoradiation was feasible with expected and described toxicities.
- The mDFS and mOS of the proposed therapy is promising compared to historical controls.
- These results are encouraging and warrant further evaluation in a randomized controlled trial versus standard therapy.