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WORLD CONGRESS ON Gastrointestinal Cancer

The Phase 3 Study: Targeted Intra-Arterial Gemcitabine vs. Continuation of IV Gemcitabine plus Nab-Paclitaxel Following Induction with Sequential IV Gemcitabine plus Nab-Paclitaxel and Radiotherapy for Locally Advanced Pancreatic Cancer (TIGeR-PaC)

First Interim Analysis

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Disclosures (3 years)

Consultant/Advisory Board/Steering Committee:

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Travel, accommodations, and expenses support:

- Astellas, RenovoRx

Stock/Ownership:

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Research funding to my institution:

- Seattle Genetics, Tesaro, Arcus Bio, Ideaya, Repare Tx, Novartis, Pfizer, Merck, Tizonia, Takeda, RenovoRx, Biomed Valley Discoveries, Boerhinger Ingelheim, Astellas, Hutchinson Medipharma

Research funding to support CME:

- AstraZeneca, Exelixis, Caris, Incyte, Ipsen, Natera, Bayer, BMS, Eisai, Foundation Medicine, Pfizer, SeaGen, Taiho, Tempus, Merck, Novartis

Locally Advanced Pancreatic Cancer (LAPC)

- Pancreatic cancer is soon to be the second leading cause of cancer-related death in the United States
- 30% - 35% of pancreatic cancer patients present with locally advanced disease
- While 10-15% of patients with LAPC have their disease rendered surgically operable (with an R0 resection), the vast majority of patients have incurable disease
- The current standard of care therapies for patients with LAPC have led to a median overall survival of ~15 months

Rahib L, et al, Cancer Res. 2014 Jun 1;74(11):2913-2; Park W, Chawla A, O'Reilly EM, JAMA. 2021 Sep 7;326(9):851-862

Survival in Locally Advanced Pancreatic Cancer
Prospective Trials

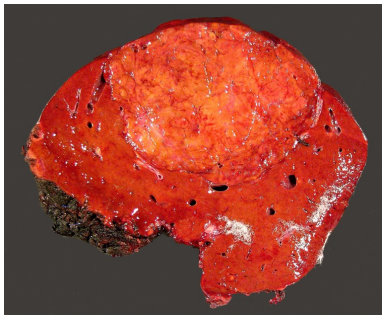
The current standard of care therapies for patients with LAPC have led to a median overall survival of 9.3 – 19.2 months

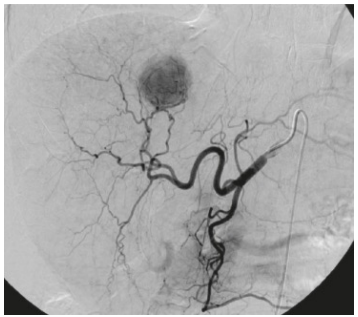
Prospective Trials				
2009	N=30	German LAPC Phase 2	RT-5FU	9.6 months
	N=32	German LAPC Phase 2	RT-Gem-cis	9.3 months
	N=31	German LAPC Phase 2	RT-Gem-cis → gem-cis	7.3 months
2011	N=69	MDACC Phase 2	Cetux-Gem-Cis → RT+cetux	19.2 months
2016	N=223	LAP 07 Phase 3	Gemcitabine	13.6 months
	N=219	LAP 07 Phase 3	Gemcitabine + erlotinib	11.9 months
2020	N=107	LAPACT Phase 2	Gemcitabine + nab-pac	18.8 months

Wilkowski R, Br J Cancer. 2009 Dec 1; 101(11): 1853–1859;Crane D, JCO. 2011 Aug 1; 29(22): 3037–3043;
Hammel P, JAMA. 2016;315(17):1844-1853; Philip PA, et al, Lancet Gastroenterol Hepatol. 2020 Mar;5(3):285-294

Chemotherapy is Not Effectively Delivered to Primary Pancreatic Tumors

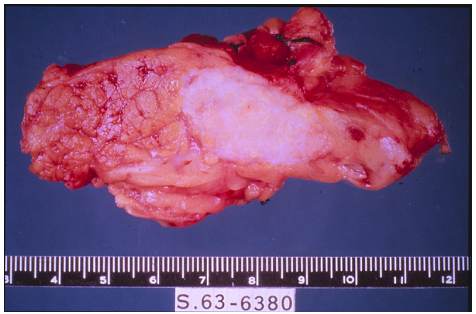
Dense fibrotic stroma | Sparse tumor cellularity | Hypovascular tumors

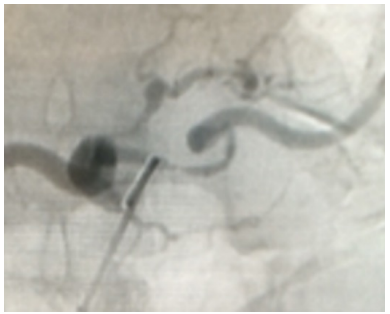




Liver tumors are vascularized

- Large tumor feeders – excellent targets for therapy
- Large branches within tumor - easily visualize tumor



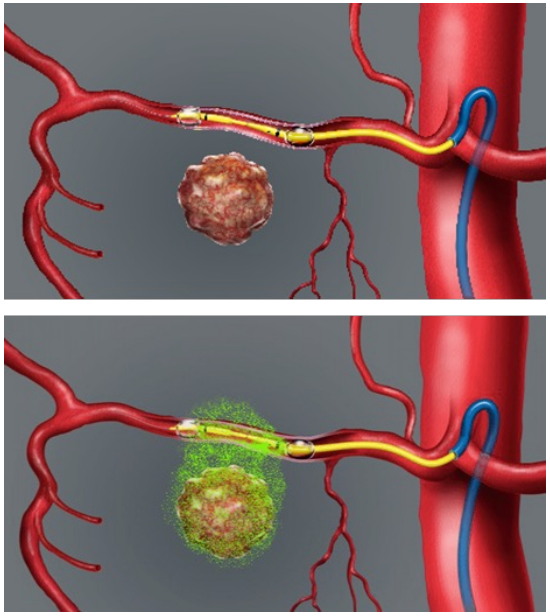


Pancreas tumors are hypovascular

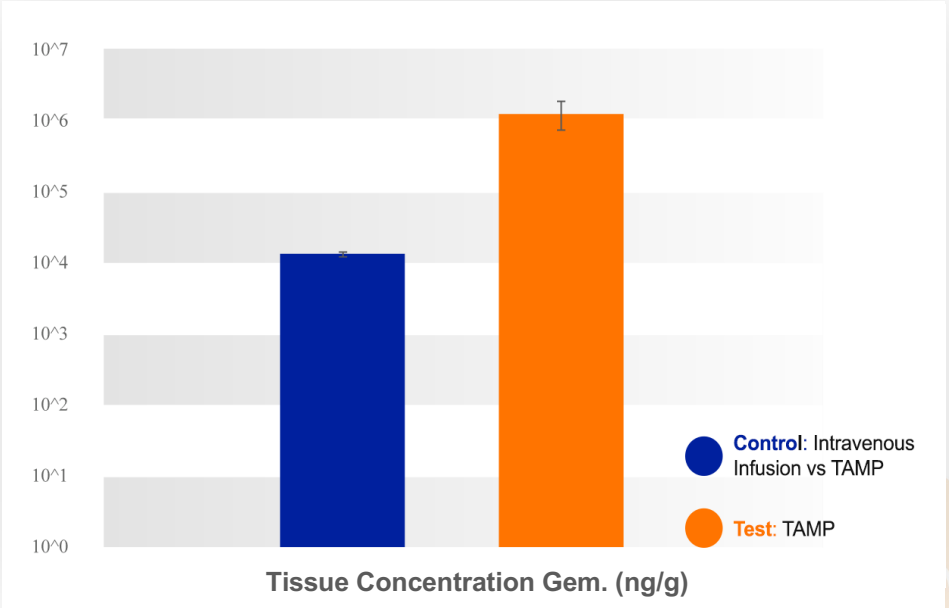
- Inability to identify tumor feeder vessels and penetrate drug into the tumor

Trans-Arterial Micro-Perfusion (TAMP)

Mechanism: after vessel isolation, increase in pressure forces drug across the artery wall into the micro-vasculature into tumor tissue



Increases Drug Concentration to Target Pathological Site by ~100X* Compared to IV Administration*

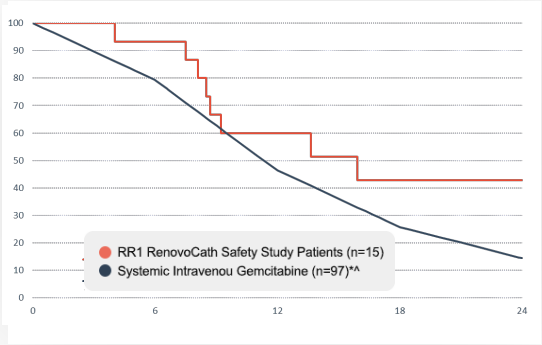


* K. Farsad, et al. Trans-pulmonary artery selective chemotherapy delivery to lung using a double balloon-occlusion catheter. JVIR. March 2019; 30 (3).

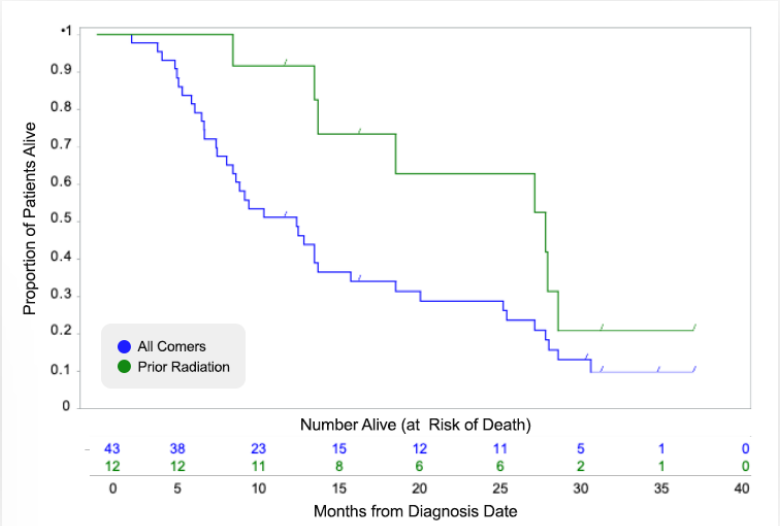
TAMP in Pancreatic Cancer: Registry Study to Explore Clinical Endpoints

RR1- Dose Escalation Safety Study*

- Primary Endpoint: Safety, MTD
- Secondary Endpoint: OS
- Completed July 2016
- Median OS = 13.6m *(inc. all patients w/ at least one cycle treatment)*



RR1 + RR2 Combined Data⁺



Group	Dead/N	Q1 (95% CI)	Median (95% CI)	Q3 (95% CI)
All Comers	37/43	6.6 (4.9, 8.6)	12.4 (8.0, 15.7)	25.4 (13.5, 30.6)
Prior Radiation	8/12	13.7 (8.4, 27.8)	27.8 (13.5, 28.6)	27.6 (27.1, NE)

Notes: Forward shales (/) indicate censored (alive) subjects. Month = Number of Days/30.44.

RR2 – Observational Registry

- Primary endpoints: survival, tumor response
- 6 centers Initiated Jan. 2016
- Limited to patients with prior radiation: March 2017
- Completed 2018
- Suggestion of increased benefit of TAMP in patients pre-treated with radiation (RR1 and RR2 combined data)

** Rosemurgy, et al, Journal of Pancreatic Cancer 2017; 3.1 : 58-65

⁺Internal Company data

TIGeR-PaC RCT

Trans(Intra)-arterial Gemcitabine vs. Continuation of IV Gemcitabine and Nab-Paclitaxel following Radiotherapy for Locally Advanced Pancreatic Cancer

TIGeR-PaC RCT– study to test the efficacy of TAMP approach as part of a phase III randomized clinical trial

Objectives

Primary Objective

- Overall Survival from the time of randomization

Secondary Objectives

- Overall survival for treatment received and non-surgical populations
- Progression Free Survival
- Objective response rate and duration of response
- Health Related Quality of Life assessed with the EORTC questionnaire
- Degree of peripheral neuropathy using FACT-NXT
- Frequency of neutropenia requiring the use of filgrastim or other medications for white blood cell stimulation
- Comparison of symptoms reported by subjects as measured by Quality-of-Life Questionnaire
- Tolerability and safety

Statistics and Major Inclusion/Exclusion Criteria

Statistical Design

- Primary endpoint: Overall Survival from the time of randomization
- Study designed to have a 80% power to detect a hazard ratio of 0.6 using the stratified Wilcoxin test at 2-sided α = 0.047
- Sample Size = 114 randomized patients

Interim Analysis	Percent of Final Analysis Events	Total Number of Observed Events (Deaths) to Trigger Analysis	Incremental Significance Level at time of Interim Analysis
First	30%	26	0.0001
Second	60%	52	0.011
Final	100%	86	0.047

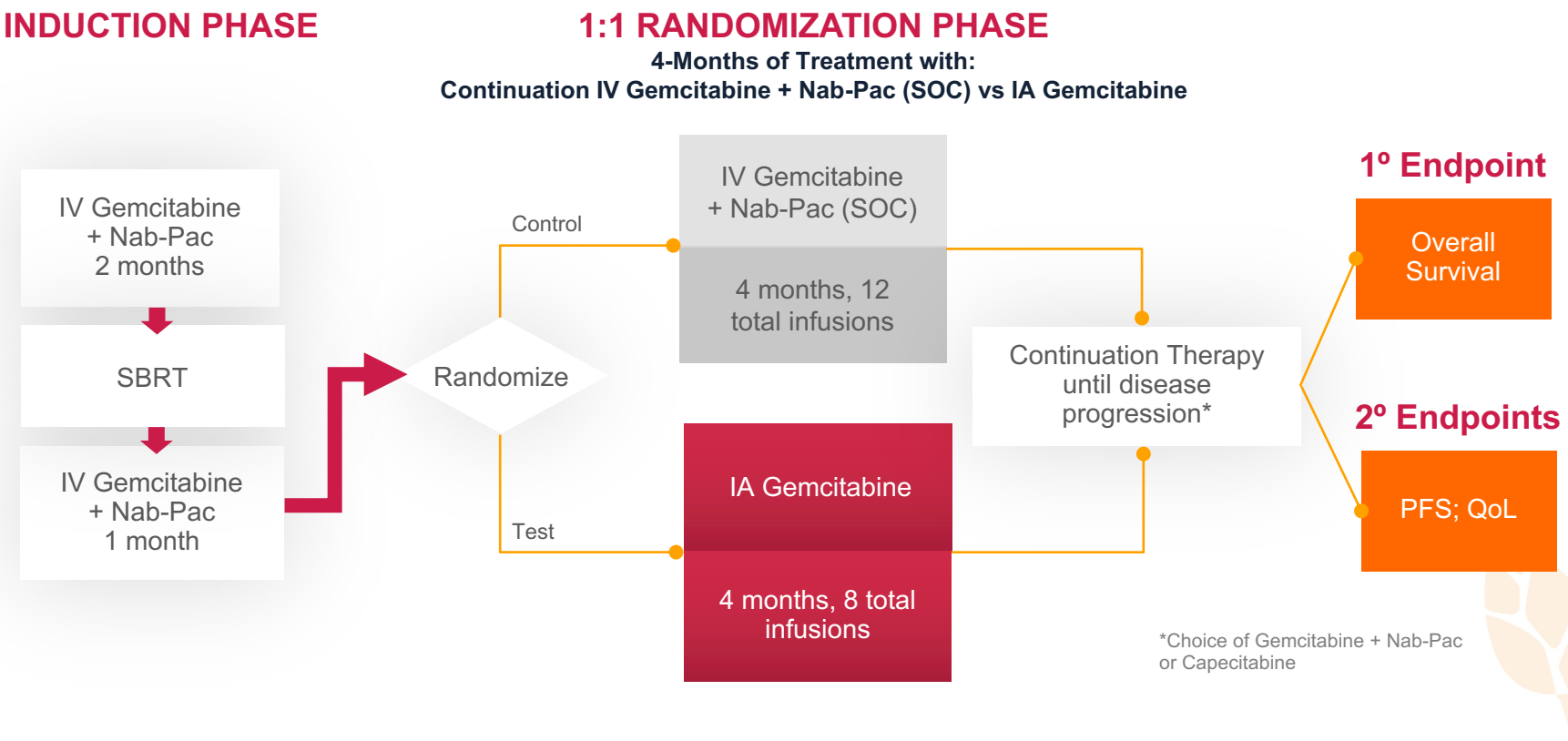
Inclusion

1. Histologically confirmed pancreatic adenocarcinoma with initial diagnosis within 6 weeks of consent
2. Locally advanced, unresectable disease, as defined by NCCN Guidelines
3. ECOG performance status 0-1

Exclusion

1. Any prior treatment for pancreatic cancer, except up to one-cycle of gemcitabine + nab-paclitaxel
2. Any evidence of metastatic disease or another active malignancy within the past two years except for cervical cancer in situ, in situ carcinoma of the bladder or non-melanoma carcinoma of the skin

Phase III TIGeR-PaC Study Design



TIGeR-PaC First Interim Analysis

First Interim analysis Feb 2023 – after 30% (26) of all events (deaths) occurred

At the first interim analysis:

- 45 patients randomized: 23 intra-arterial gemcitabine vs. 22 intravenous gemcitabine + nab-pac
- 13 events in each arm
- 19 patients alive and in the study, data censored as of date data lock*

Baseline Characteristics+	IA Gemcitabine (n = 23)	IV Gemcitabine + Nab-Pac (n = 22)
Gender (Male/Female)	10/13	10/12
Mean Age	65 (43-85)	70 (47-83)
Tumor size (sum diameters-cm)	6.5 (2.5,12.9)	6.95 (2.8, 15.0)
Race: Caucasian/Black/Other	75%/10%/15%	95%/5%/0%

Patients were stratified for ECOG Performance Status and Tumor Response (restaged) at time of randomization per protocol design.

*The 19 patients still alive at the time of interim analysis data lock, the last known survival date and CT scan was used for overall survival and PFS analysis respectively (all within 3 months of data lock)

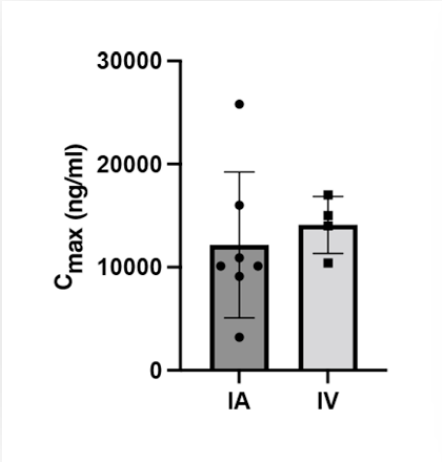
The PK analysis subset of TIGeR-PaC

Plasma levels of gemcitabine after intra-arterial (IA) gemcitabine vs. intravenous gemcitabine (IV) + nab-pac delivery

From the 15 patient substudy, results for 13 patients were available (7 IA, 6 IV)

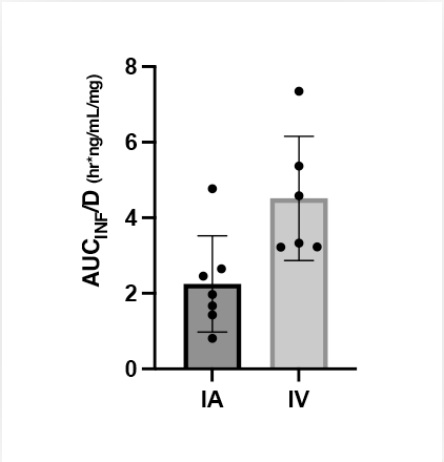
Delivery Rate	IA	IV
Gemcitabine Concentration	1000 mg/m^2	1000 mg/m^2
Gemcitabine Infusion Duration	20 min	30 min

Peak Plasma Levels



Peak plasma concentration of gemcitabine

Drug Exposure IA vs. IV Route



Impact of route of administration on drug exposure Area Under Curve-Normalized for Total Dose (hr*ng/mL/mg, p<0.015)

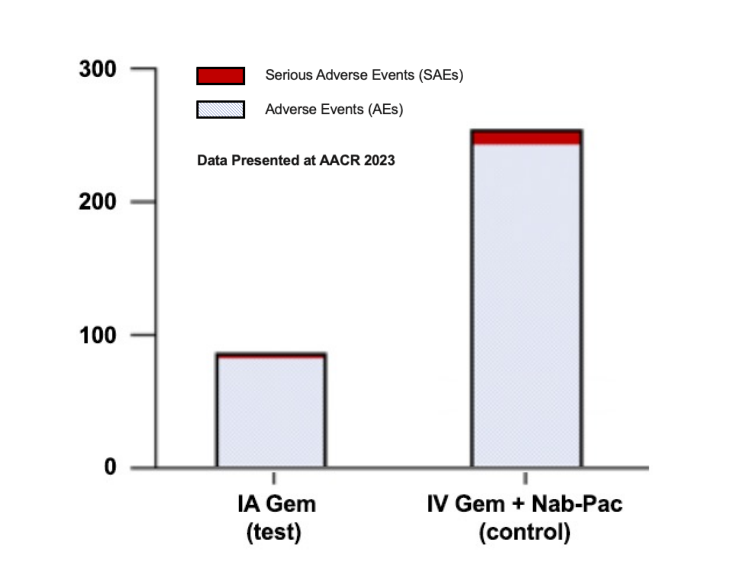
*Two patients in IV arm received a dose modified regimen at 80%: AUC/d analysis performed but the omitted for Cmax analysis

Tolerability and Safety of Treatment

Tolerability during active treatment:

- 61% of IA patients received all planned treatments at the pre-specified dose vs. 18% of IV (primarily due to AEs or SAEs)
- Patients receiving IA therapy had more nausea and abdominal pain events
- Patients receiving IV therapy had more myelosuppression, fatigue, dehydration, neuropathy, and metabolic derangements

65% fewer total AEs and SAEs in IA vs. IV arm

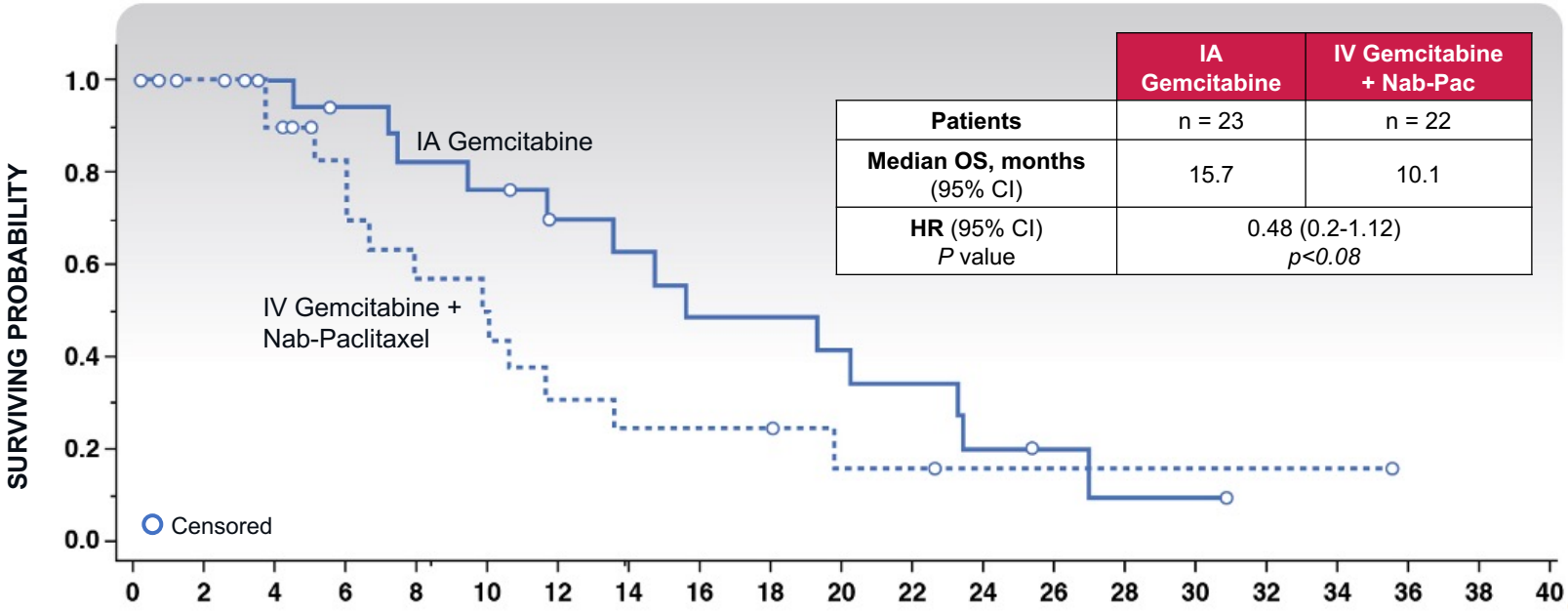


AEs with greater than 10% frequency in each arm (All Grades)

Adverse Events	IV Gem + Nab-Pac	IA Gemcitabine
Neutropenia	81%	21%
Anemia	48%	8%
Thrombocytopenia	38%	4%
Elevated AST	33%	4%
Elevated ALT	29%	13%
Fatigue	19%	8%
Neuropathy	19%	0%
Dehydration	19%	8%
Hypertension	14%	4%
Hypokalemia	14%	4%
Hypoalbunemia	14%	4%
Abdominal Pain	0%	21%
Nausea	10%	17%

Adverse event prevalence: IA IV

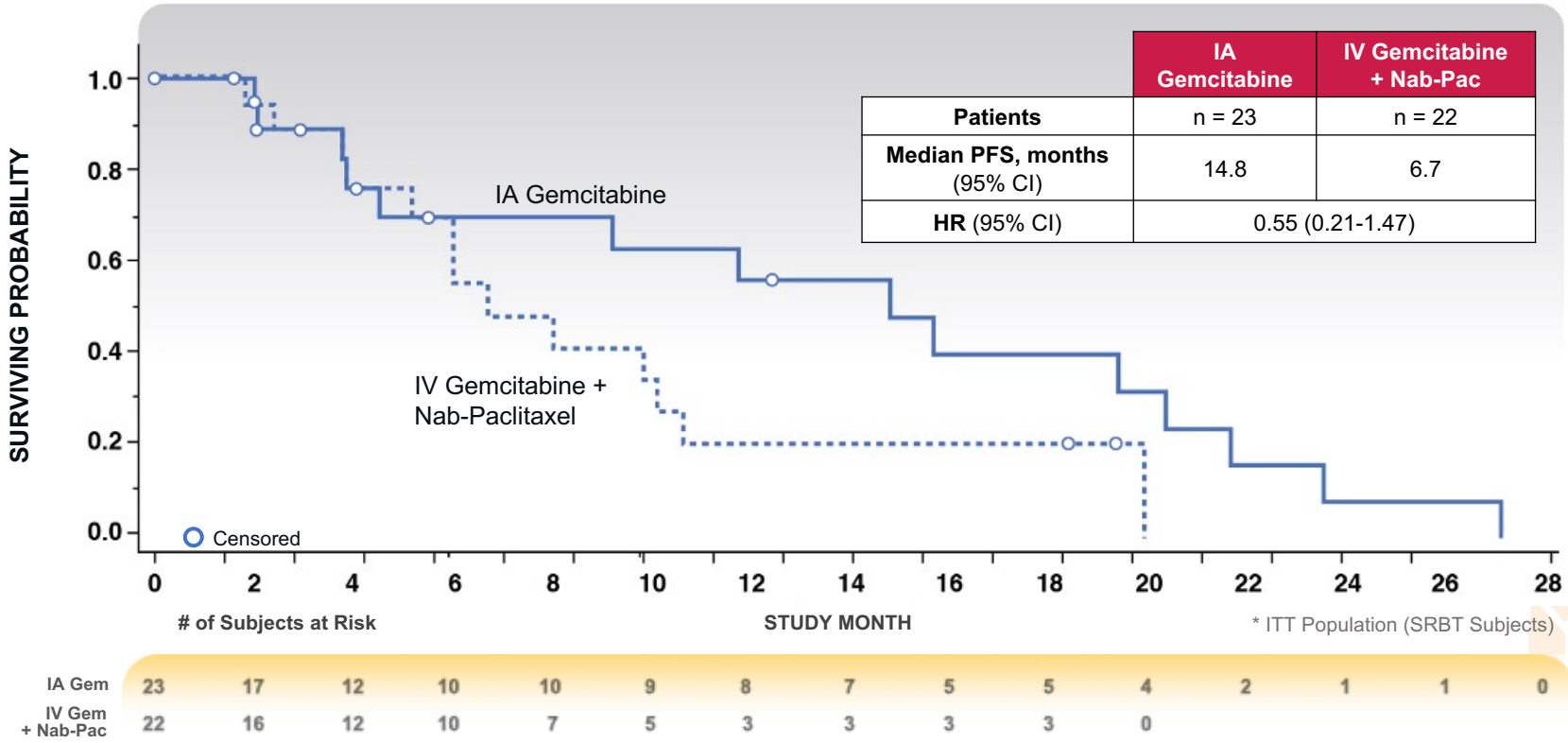
Primary Endpoint: Overall Survival



	IA Gemcitabine	IV Gemcitabine + Nab-Pac
Patients	n = 23	n = 22
Median OS, months (95% CI)	15.7	10.1
HR (95% CI) *P* value	0.48 (0.2-1.12) *p<0.08*	

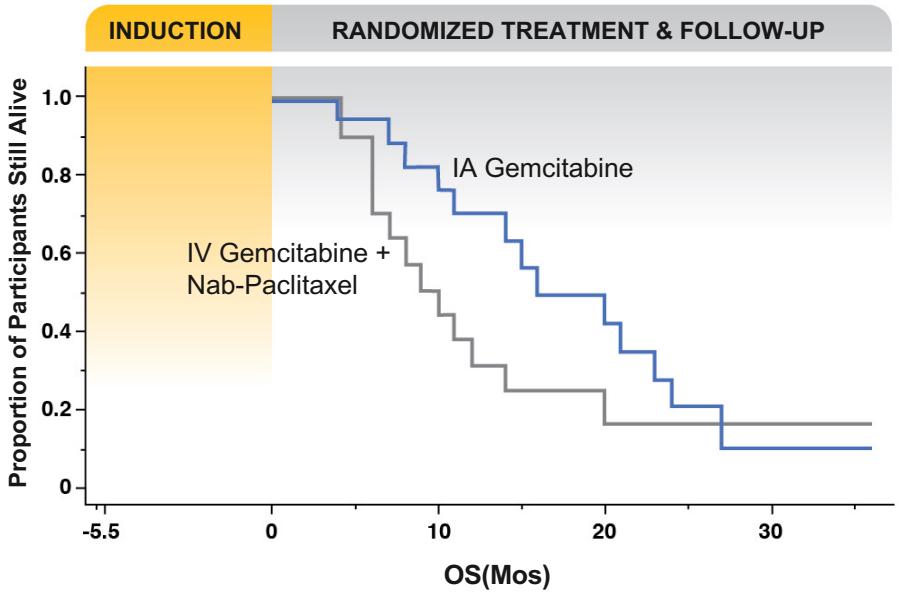
Secondary Endpoint: Progression-Free Survival*

	IA Gemcitabine	IV Gemcitabine + Nab-Pac
Patients	n = 23	n = 22
Median PFS, months (95% CI)	14.8	6.7
HR (95% CI)	0.55 (0.21-1.47)	



Data Presented at AACR 2023

Estimated Overall Survival from Diagnosis



Data on 45 patients randomized

- 23 randomized to IA gemcitabine
- 22 randomized to IV gem + nab-pac

Median Overall Survival (OS) Difference: 6-months

IV Gem + Nab-Pac (control arm)

Avg 5.5 mo dx to randomization | 10 mo from randomization

10 Months from randomization

~15.5 months from diagnosis

IA Gemcitabine (test arm)

Avg 5.5 mo dx to randomization | 16 mo from randomization

16 Months from randomization

~21.5 months from diagnosis

Conclusions

At the first interim analysis:

- Overall survival for patients treated with intra-arterial gemcitabine was 16 months from randomization compared to only 10 months for patients who continued intravenous gem + nab-pac
- Progression-free survival for patients treated with intra-arterial gemcitabine was 14.8 months from randomization compared to only 6.7 months for patients who continued intravenous gem + nab-pac
- During the randomization period, patients treated with intra-arterial gemcitabine had fewer adverse events and significant adverse events
- Study accrual is ongoing with the results of the second-interim analysis anticipated in 2024

Acknowledgements

- The patients and their families for making this trial possible
- The clinical study teams and their investigators for their work and contribution
- This study is supported by RenovoRx
- All authors contributed to and approved this presentation