# If Wishes Were Horses…
# Well, Then We Would All Have Horses but Neoadjuvant Therapy Would Still Not Be Ready for Prime Time in Pancreas Cancer

Jordan Berlin, MD
Cornelius Abernathy Craig Professor of Medicine
Chair, Division of Hematology and Oncology, VUMC
Associate Director of Clinical Research, VICC
Director, Phase I Research
Chair, ECOG-ACRIN GI Committee

VANDERBILT-INGRAM CANCER CENTER

- Advisory Boards in last year
  - Mirati
  - Insmed
  - EMD Serono
  - Ipsen
  - Merck, Sharp, Dohme
  - Merus
  - Bms
  - Bexion (unpaid)
  - Mekanistic
  - Agenus (pending)
  - Astellas
  - Amplia
- Other
  - NCI (IDSC work, ECOG-ACRIN GI Chair)

- Current Research Support
  - Abbvie, Astellas, Atreca, Bayer, Dragonfly, I-Mab, Lilly, Incyte, EMD Serono, Pfizer, BMS, Tyra, Totus, Sumitomo Dainippon Pharma Oncology, 23 and me, parthenon/Incendia, hibercell, riboscience, NCI
- DSMB
  - Astra Zeneca
  - Novocure
  - Boehringer-Ingelheim
  - I-SPY

- Pancreas cancer is a systemic disease upon presentation
  - 10% of patients survive 10 years with surgery alone
  - Therefore 90% of resectable patients are metastatic upon presentation
- Highest response rates available are for chemotherapy
  - Still only 31% for FOLFIRINOX
  - 29% for gem-nab-paclitaxel
    - (investigator assessed)

- Goal of adjuvant and neoadjuvant therapy is to kill micrometastatic disease
  - Best “kill” is when it is smallest (This is technically post-op)
  - In a study of patients in Ontario, Canada only 75% of resected patients even received adjuvant gemcitabine*
    - But now our standard has moved past gemcitabine

*Kagedan, et al Curr Oncol 334-42, 2016 23:

# Does Preoperative Therapy Impact Operability? 3 Meta-Analyses

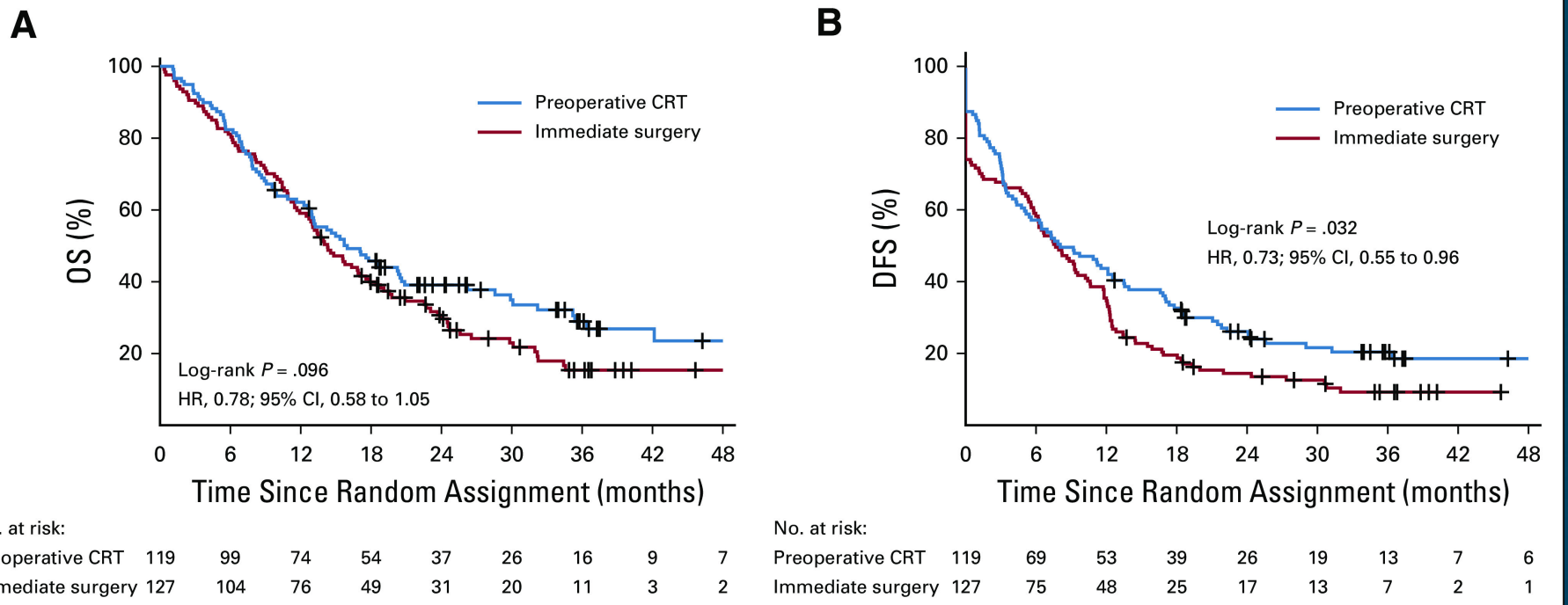
- 1. 11 studies including 56 phase I-II trials, 4,394 patients
  - Median OS was 23.3 months (most were before modern regimens)
  - **CONCLUSION:** We don't impact resectability negatively, even with weaker chemo, but we didn't impact it positively either
- 2. 38 studies, 3484 patients, 1738 had neoadjuvant therapy
  - OS for resected was 26.1 vs 15.0 months
  - **CONCLUSION:** OS improved, R0 and lymph node negativity improved
- 3. 6 randomized trials of neoadjuvant therapy (n, 411) vs surgery first (n, 439)
  - (4 included xrt, no modern chemo regimens) (including borderline resectable and resectable)
    - OS was improved with a hazard ratio of 0.73
    - Median 25.4 months vs 19.4 months , p <0.001
  - **CONCLUSION:** OS improved, resectability unchanged, but R0 and lymph node negativity improved

1. PLoS Med 7:e1000267, 2010 2. Br J Surg 105:946-58, 20183. J Clin Med 9:1129, 2020

# “Best” of Neoadjuvant vs post-op

| Trial | Population | Treatment | # of Patients | OS (p value) |
|---|---|---|---|---|
| JSAP-05 | Resectable and borderline | Neo Gem +S1<br>Surgery then S1 | 182<br>180 | 36.7 months<br>26.2 (HR 0.72, p 0.015) |
| NEONAX | Resectable only | Neo Gem/nab-paclitaxel<br>Surgery then gem/nab-pac | 59<br>59 | 25.5 months<br>16.7 no stats |
| Preopanc-1 | Resectable and borderline | Gem-gem/xrt-surgery<br>Surgery then gem | 119<br>127 | HR 0.78 p, 0.096 |
| PANACHE-01<br>PRODIGE 48 | Resectable | Neoadj FOLFIRINOX<br>Neoadj FOLFOX<br>Surgery first | 70<br>50<br>26 | 30.6 months<br>31.3<br>>36 (No p) |
| NORPACT-1 | Resectable | Neoadj FOLFIRINOX<br>Surgery first (few options post-op) | 77<br>63 | 23 months<br>34.4 (HR 1.46, p 0.058) |

1. ASCO 2019 (No pub I could find) 2. Ann Oncol 34:91-100, 2023 3. JCO 40:1220-30, 2022
4. ASCO Abstract 4134, 2022 5. Lancet Gastroenterol Hepatol 9:205-17, 2024




- PREOPANC-1
  - Primary Endpoint OS was negative
  - Intriguing DFS but barely statistically significant
  - Ignore the bottom curves. Too many censored

Versteijne E, et al. JCO 2020 38:1763-73

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

Canadian Cancer Trials Group

Groupe canadien des essais sur le cancer

unicancer

LA LIGUE CONTRE LE CANCER

# PRODIGE 24/CCTG PA.6, an Unicancer GI trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J-L. Raoul, L. Choné, E. François, P. Artru, J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, C. Jouffroy, P. Rat, F. Castan, J-B. Bachet, for the CCTG and the UNICANCER-GI /PRODIGE Group

Institut de Cancérologie de Lorraine, Nancy; Hôpital Beaujon, Clichy; Hôpital Huriez, Lille; Centre Paul Strauss, Strasbourg; Princess Margaret Hospital, Toronto; Institut Paoli-Calmettes, Marseille; University hospital, Nancy; Centre Antoine-Lacassagne, Nice; Hôpital Jean-Mermoz, Lyon; Kingston General Hospital, Kingston; Hôpital Trousseau, Tours; University Hospital, Montpellier; CHD Vendée, La Roche-sur-Yon; Institut du Cancer de Montpellier, Montpellier; Centre Hospitalier Universitaire, Dijon; Hôpital Pitié-Salpétrière, Paris; Canadian Cancer Trials Group, Kingston, Canada; R&D UNICANCER, Paris; France

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Thierry Conroy

Presented By Thierry Conroy at 2018 ASCO Annual Meeting
Publication Conroy T, et al NEJM 2018, 379:2395-2406

# PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

**Stratification:**
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

## mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
*Every 2 weeks; 12 cycles*
**Reduced to 150 mg/m² after patient 162*

## Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
*6 cycles*

**for both arms:**
- 6 months of chemotherapy
- CT scans: every 3 months

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

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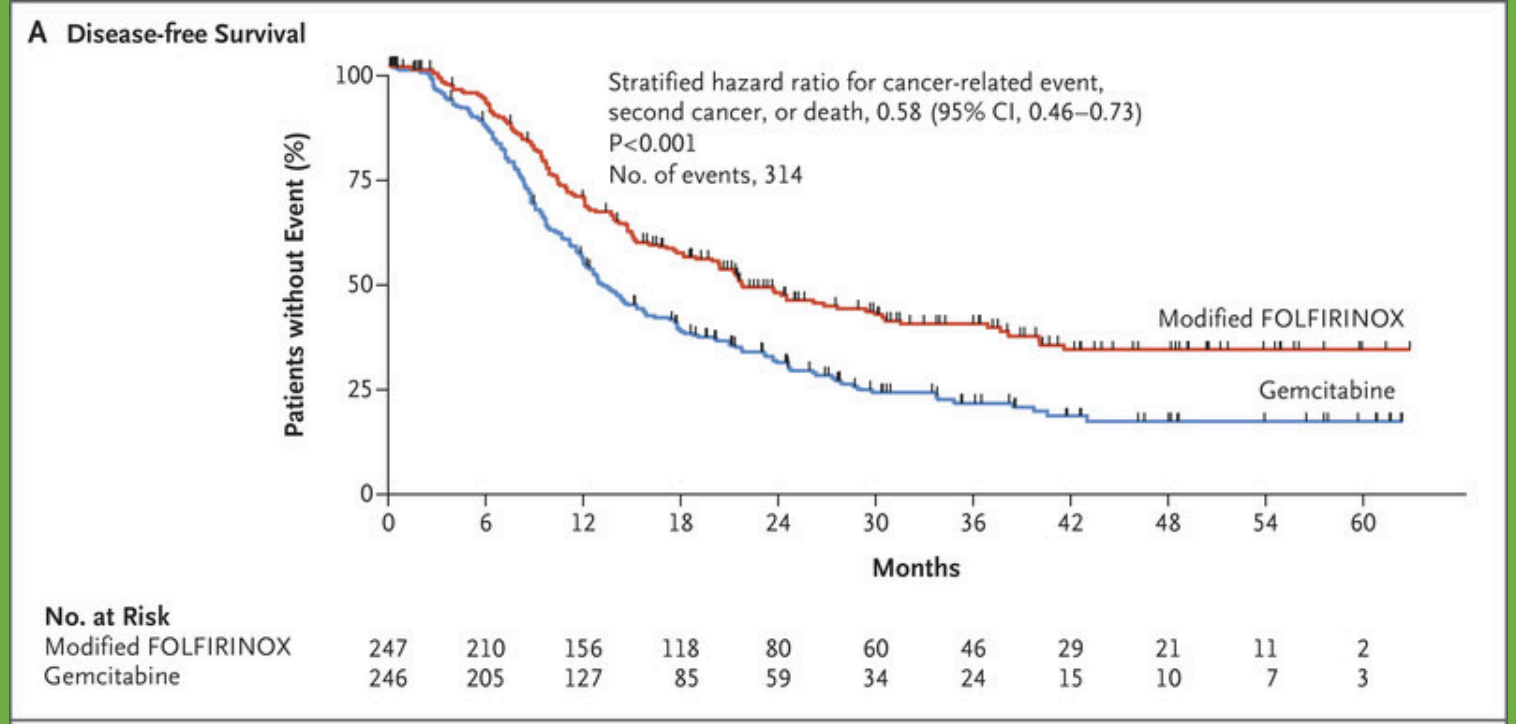
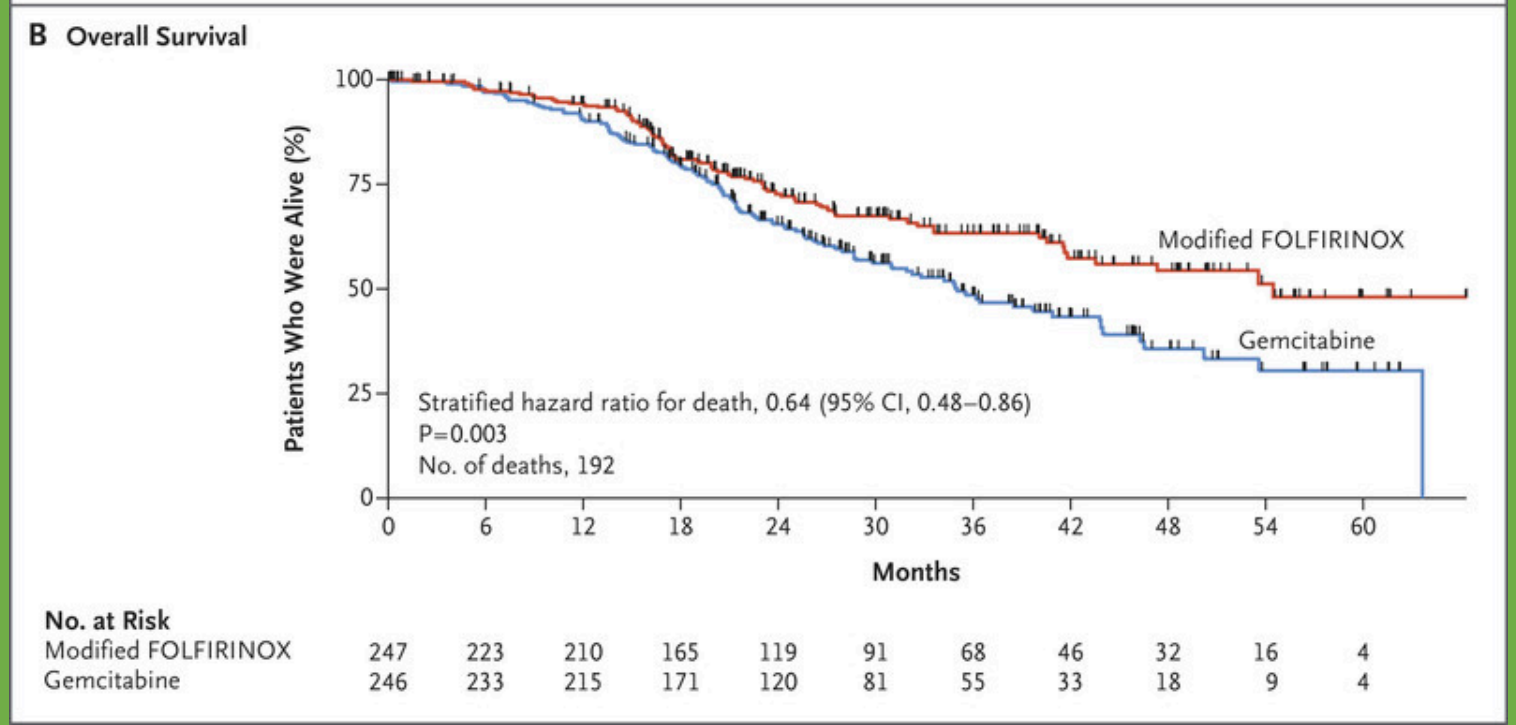



- DFS was 21.6 months vs 12.8 months
  - Gem arm had similar DFS to CONKO trial
- OS was 54.4 months vs 35.0 months, HR = 0.64

Conroy T, et al NEJM 2018, 379:2395-2406

# SWOG S1505: Results of Perioperative Chemotherapy with mFOLFIRINOX vs Gemcitabine/nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma

Davendra P. S. Sohal, Mai Duong, Syed A. Ahmad, Namita S. Gandhi, M. Shaalan Beg, Andrea Wang-Gillam, James L. Wade III, E. Gabriela Chiorean, Katherine A. Guthrie, Andrew M. Lowy, Philip A. Philip, Howard S. Hochster

*Presented By:* Davendra Sohal, MD, MPH
Associate Professor of Medicine
Director of Experimental Therapeutics, Clinic Medical Director
Hematology and Oncology, University of Cincinnati

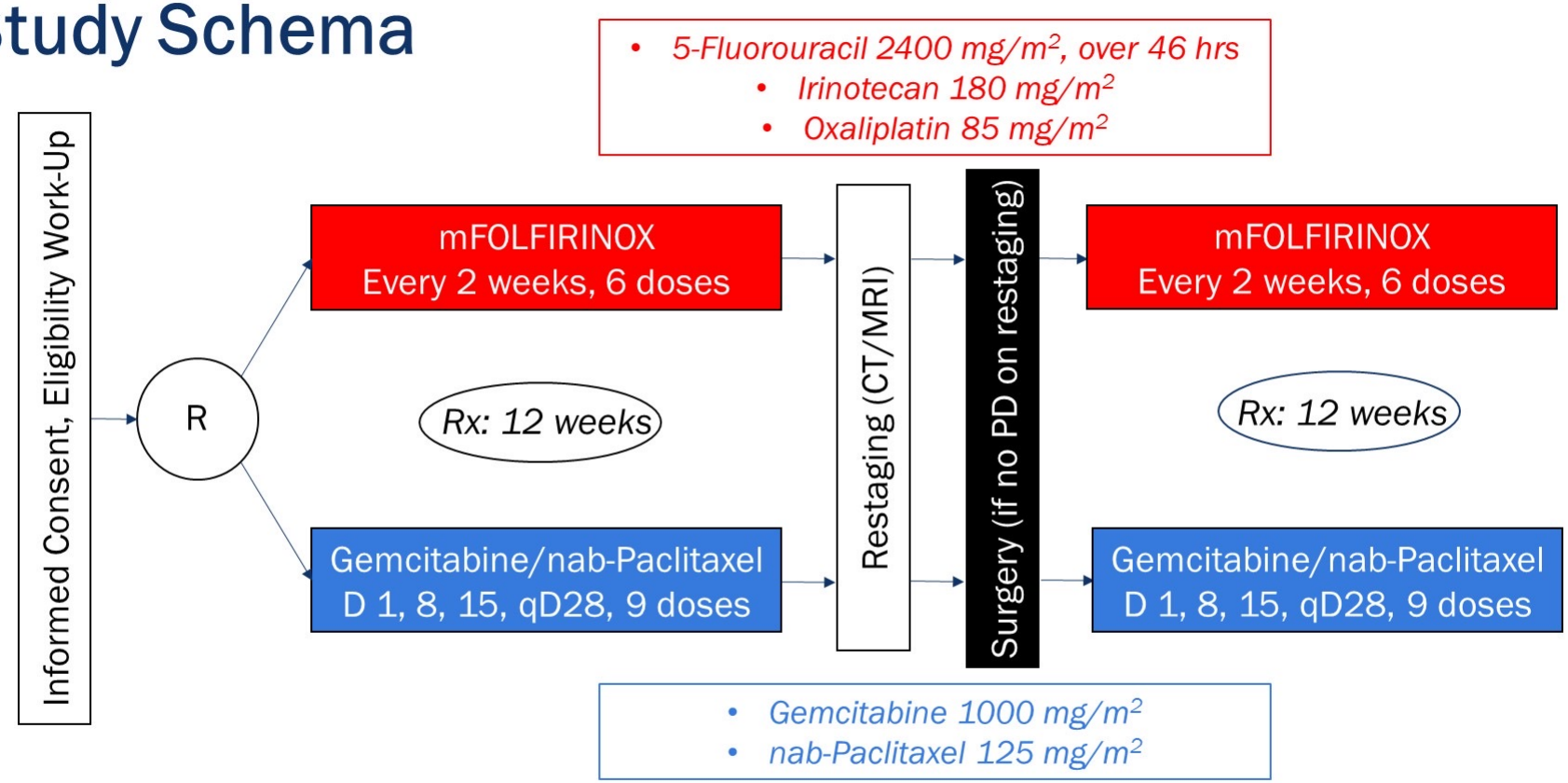
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Davendra Sohal, MD, MPH

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network, a National Cancer Institute program | NCI Community Oncology Research Program, A program of the National Cancer Institute of the National Institutes of Health

Presented By Davendra Sohal at TBD

# Study Schema





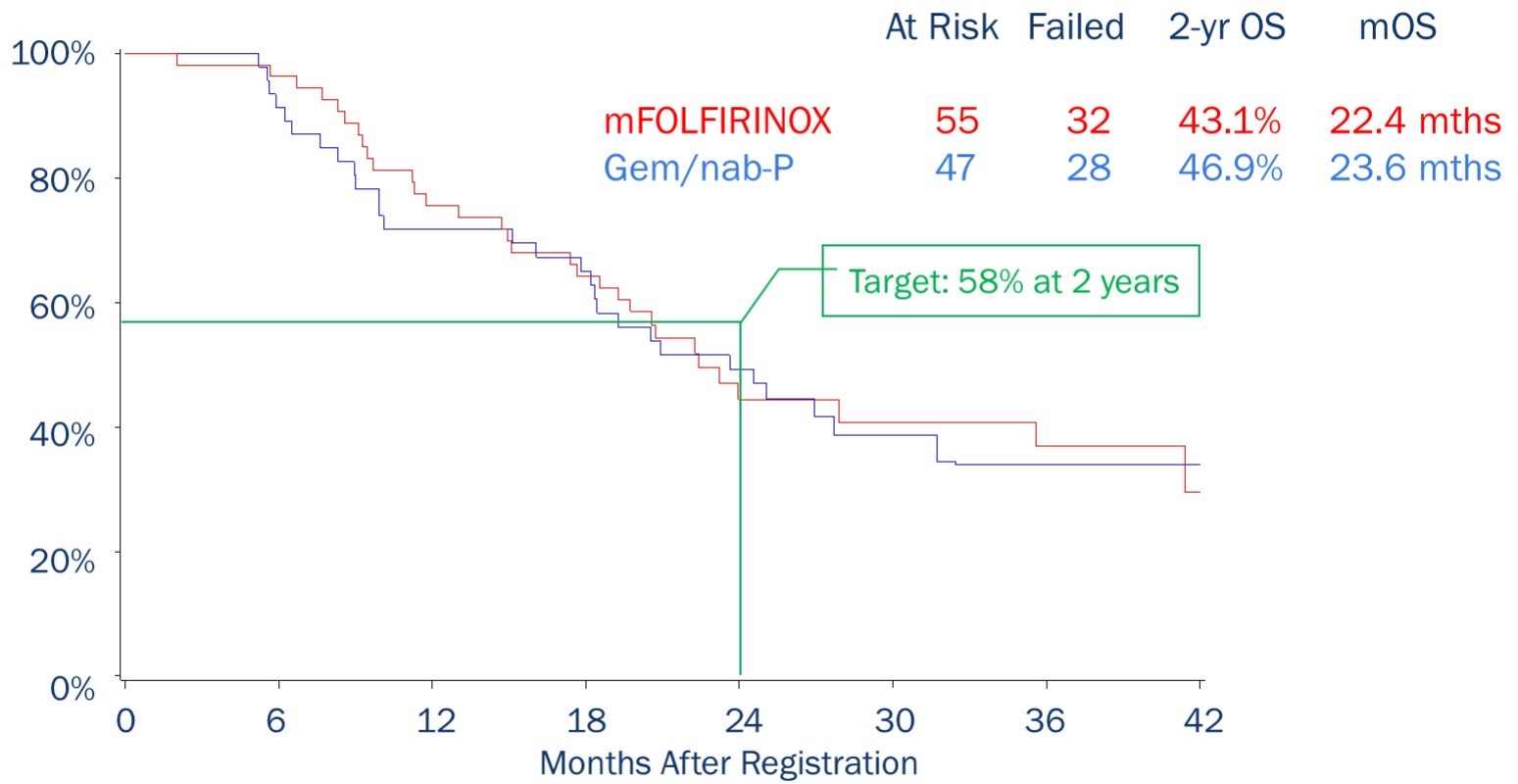



Presented By Davendra Sohal at TBD

# Surgery Results

| | mFOLFIRINOX (N=40) | Gem/nab-P (N=33) |
|---|---|---|
| R0 Resection | 34 (85%) | 28 (85%) |
| Complete or Major Pathologic Response | 10 (25%) | 14 (42%) |
| Total Nodes Resected, median (range) | 19 (1-56) | 18 (3-45) |
| Node Negative Resection | 16 (40%) | 15 (45%) |
| Disease-Free Survival after Resection | 10.9 mths | 14.2 mths |

# Primary Endpoint: Two-year OS



# Conclusions

- FOLFIRINOX is now our standard adjuvant therapy for healthy patients
  - PFS and OS exceed any prior adjuvant trial including the neoadjuvant trials
- Post-op FOLFIRINOX is proven
  - But ~25% of resected patients never get to adjuvant therapy, so investigation needs to be done to find ways to increase the percentage of patients who receive adjuvant therapy
- Pre-op FOLFIRINOX and gemcitabine + nab-paclitaxel are both safe
  - But pre-op therapy is still investigational for resectable pancreas cancer and should be reserved for clinical trials

# Cancer and Academic Research Excellence: *Most of all, we* **CARE**

**-VUMC Hematology and Oncology**