# Pancreatic Cancer: Light at the End of the (Very Long) Tunnel

**Daniel Renouf**, MD, MPH, FRCPC
Medical Oncologist, BC Cancer Agency
University of British Columbia

BC Cancer Agency
CARE + RESEARCH
*An agency of the Provincial Health Services Authority*

PANCREAS CENTRE BC
CANCER RESEARCH
DIAGNOSIS TREATMENT.
EARLIER.

# Disclosures

*In compliance with accreditation, we require the following disclosures to the session audience:*

| | |
|---|---|
| Research Support/P.I. | Novartis; Bayer |
| Employee | N/A |
| Consultant | N/A |
| Major Stockholder | N/A |
| Speakers Bureau | N/A |
| Honoraria | Celgene |
| Scientific Advisory Board | Celgene, Shire |

# Audience Question:

Do you think we will make significant strides in the treatment of pancreatic cancer in next 10 years?

A) No
B) Yes improve overall survival by 5-10%
C) Yes improve overall survival by 10-20%
D) Yes improve overall survival by over 20%

# Optimism Disclosure

- I am very optimistic of the future of pancreatic cancer treatment

- But…I am a very optimistic person!

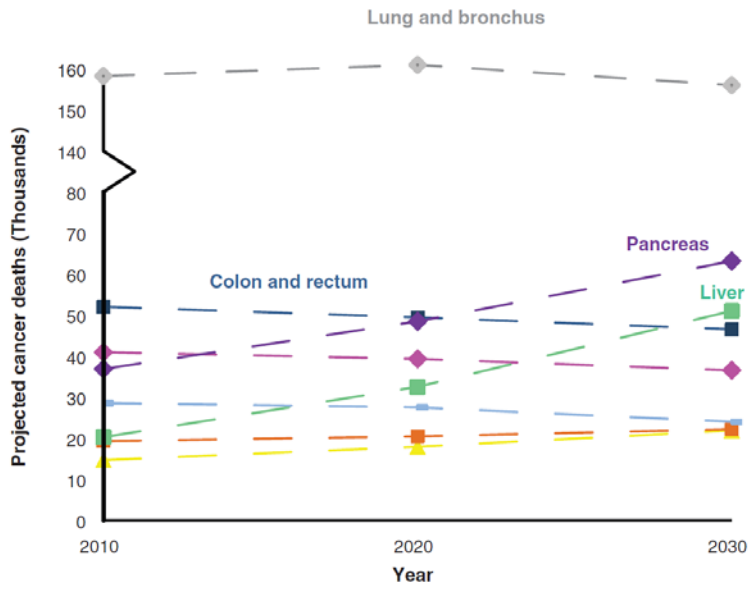
  - I'm a medical oncologist
  - I specialize in pancreatic cancer
  - I still think "holidays" will be "relaxing" despite having a 5 year old and 2 year old twins!

# Objectives

1. Discuss recent updates in systemic therapy options in the metastatic setting
2. Discuss the role of palliative radiation
3. Review genetic issues
4. Review adjuvant systemic and radiation therapy
5. Future directions

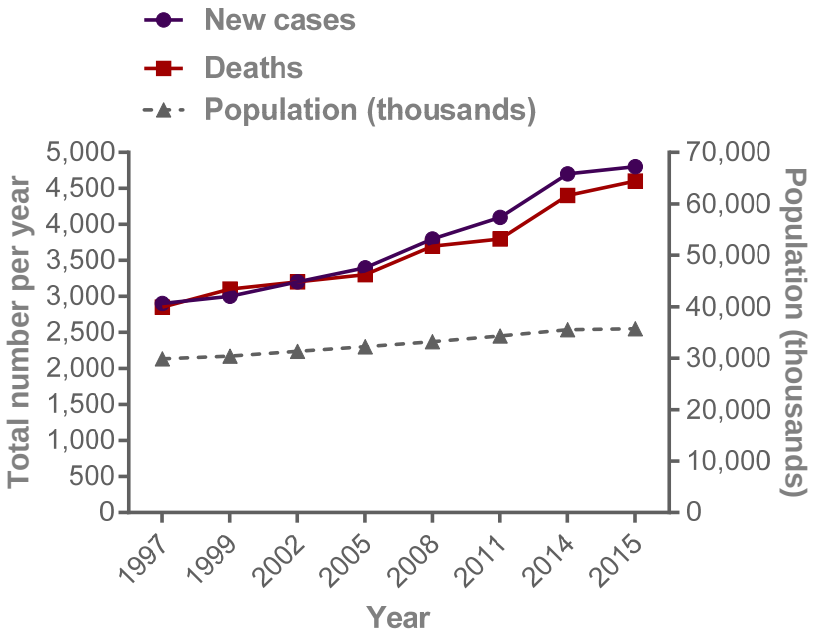
# Pancreatic cancer incidence and deaths are rising

**Pancreatic cancer will become 2nd most lethal cancer in the US by 2030**



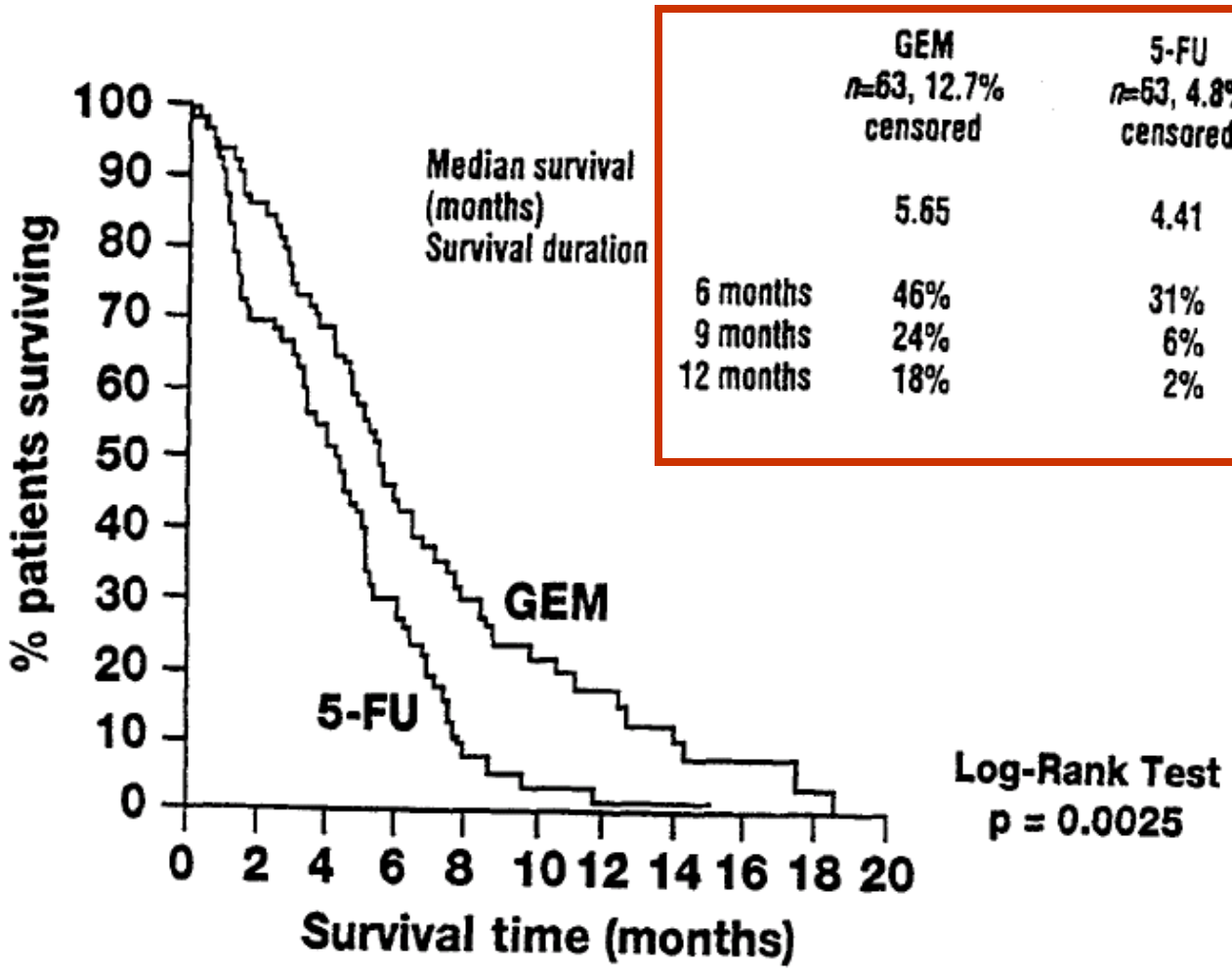

Rahib et al., *Cancer Res* (2014) 74:2913-2921

**Pancreatic cancer rates will double in Canada by 2030**




Based on annual reports from the *Canadian Cancer Society* and *Statistics Canada*.

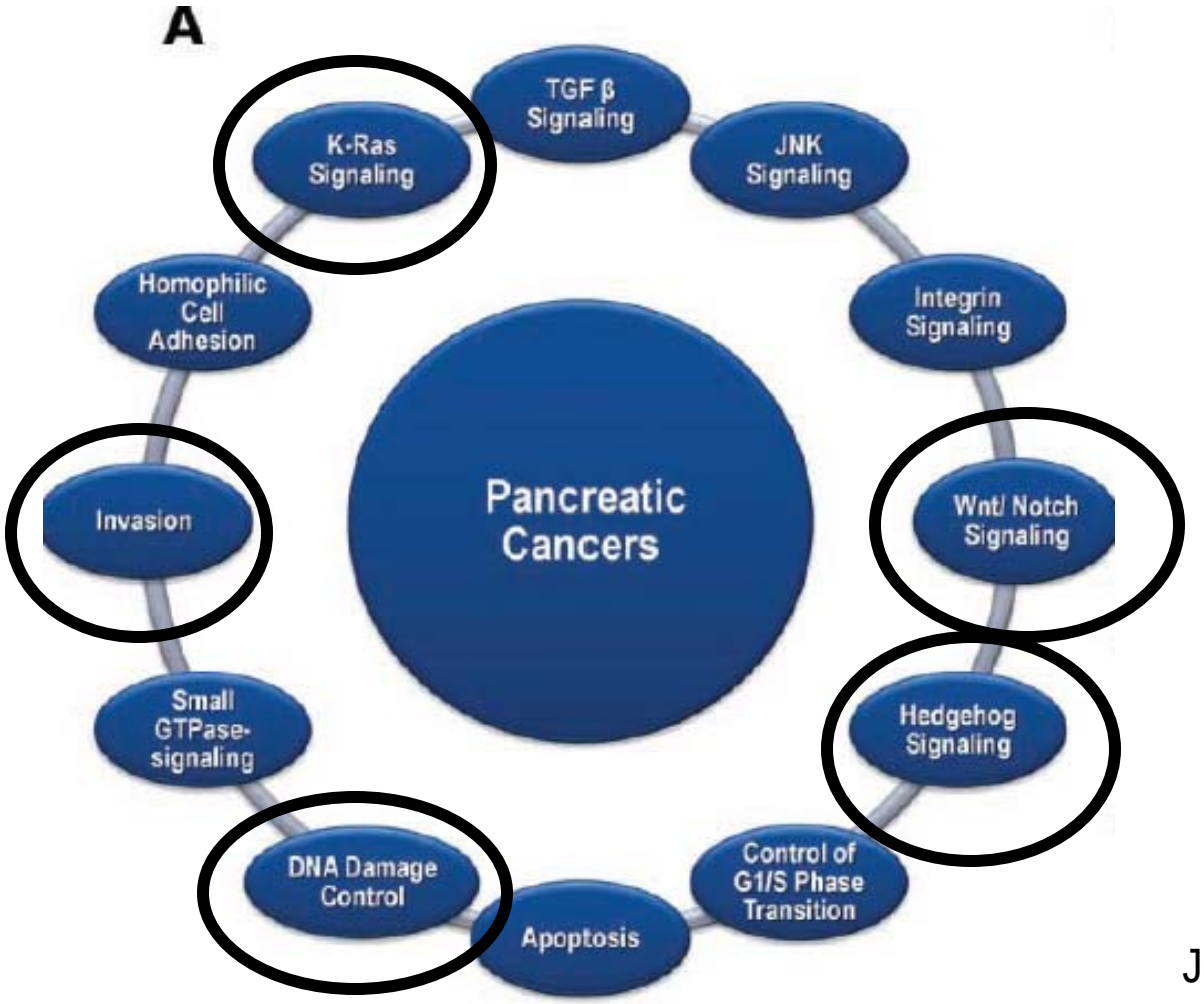
# Gemcitabine vs. 5-FU



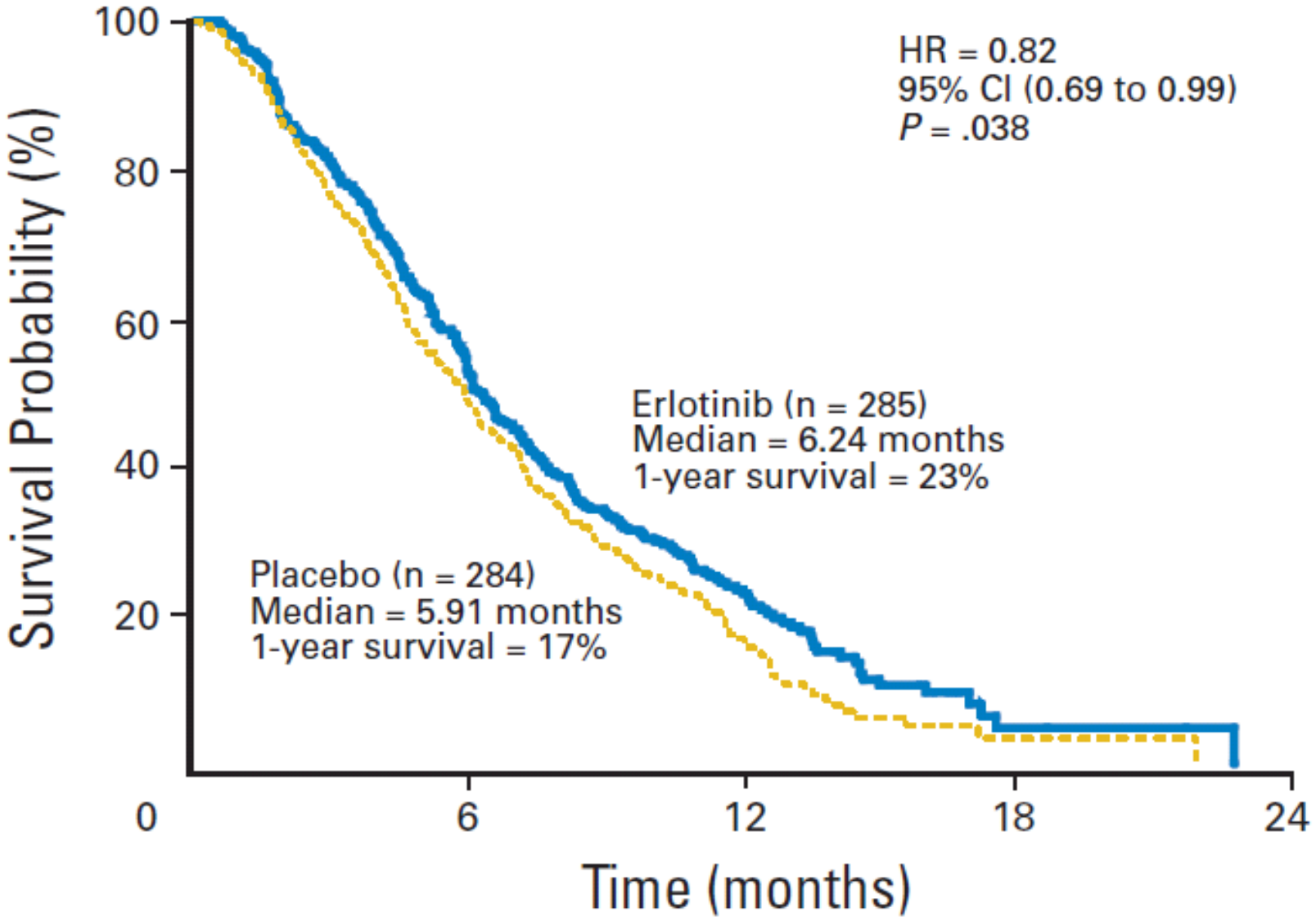

Burris et al, JCO, 1997

# Molecularly targeted therapy

- Preclinical studies have demonstrated several molecular pathways that may be important in pancreatic tumorigenesis




Jones et al, Science, 2008




1 year survival improved from 17-23% (p=0.023)

Moore et al, JCO, 2007

# Studies with biological therapy

| Treatment | Median survival (months) |
|---|---|
| Gemcitabine versus gemcitabine and erlotinib | 5.9 vs 6.2 (p = 0.038) |
| Gemcitabine versus gemcitabine and cetuximab | 6 vs 6.5 (p = NS) |
| Gemcitabine and cisplatin versus gemcitabine, cisplatin and cetuximab | 7.5 vs 7.8 (p = NS) |
| Gemcitabine versus gemcitabine and bevacizumab | 5.7 vs 6 (p = NS) |
| Gemcitabine, bevacizumab and erlotinib versus gemcitabine, bevacizumab and cetuximab | 7.2 vs 7.8 (p = NS) |
| Gemcitabine and erlotinib versus gemcitabine, erlotinib and bevacizumab | 6 vs 7.1 (p = NS) |
| Gemcitabine versus gemcitabine and tipifarnib | 6.1 vs 6.4 (p = NS) |
| Gemcitabine versus gemcitabine and marimastat | 5.5 vs 5.5 (p = NS) |
| Gemcitabine versus BAY 12-9566 | 6.7 vs 3.7 (p < 0.001) |

Renouf and Moore, Expert Rev. Anticancer Ther. 2010

# What are we doing wrong?

-Need for more active chemotherapy/combinations

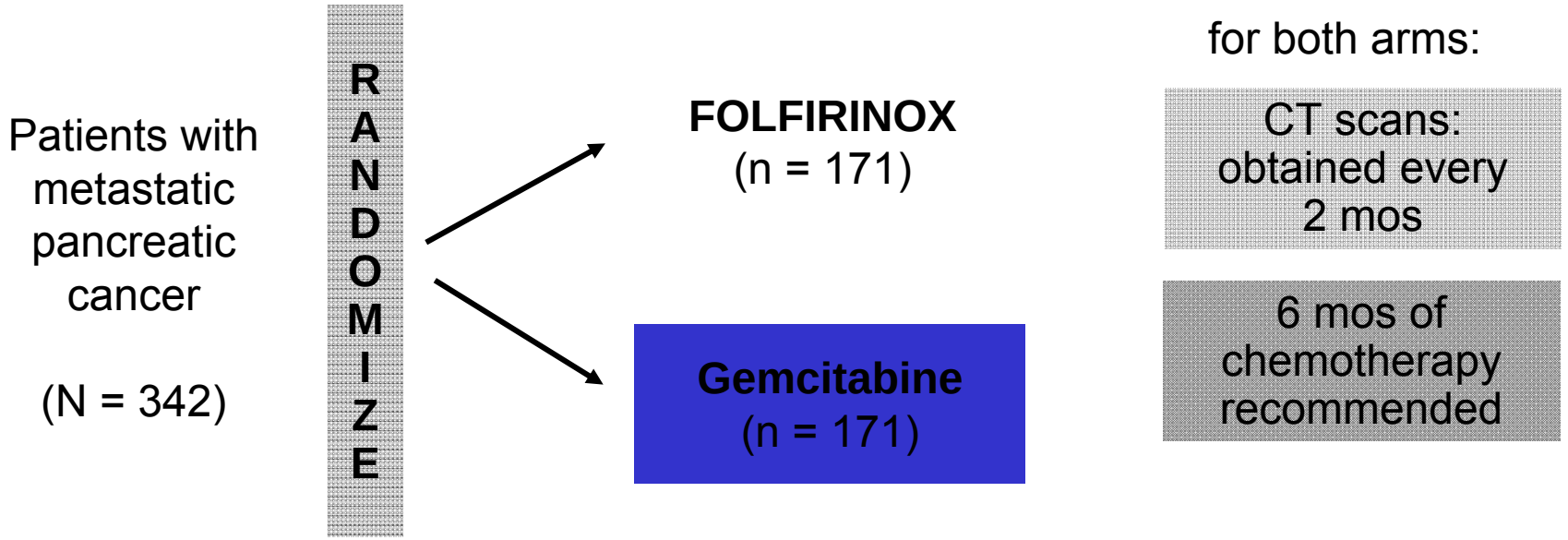
-Need for improved pre-clinical models

-Need for agents that target the microenvironment

Philip et al, JCO, 2009

# New Chemotherapy Combinations:

## PRODIGE 4/ACCORD 11 Trial

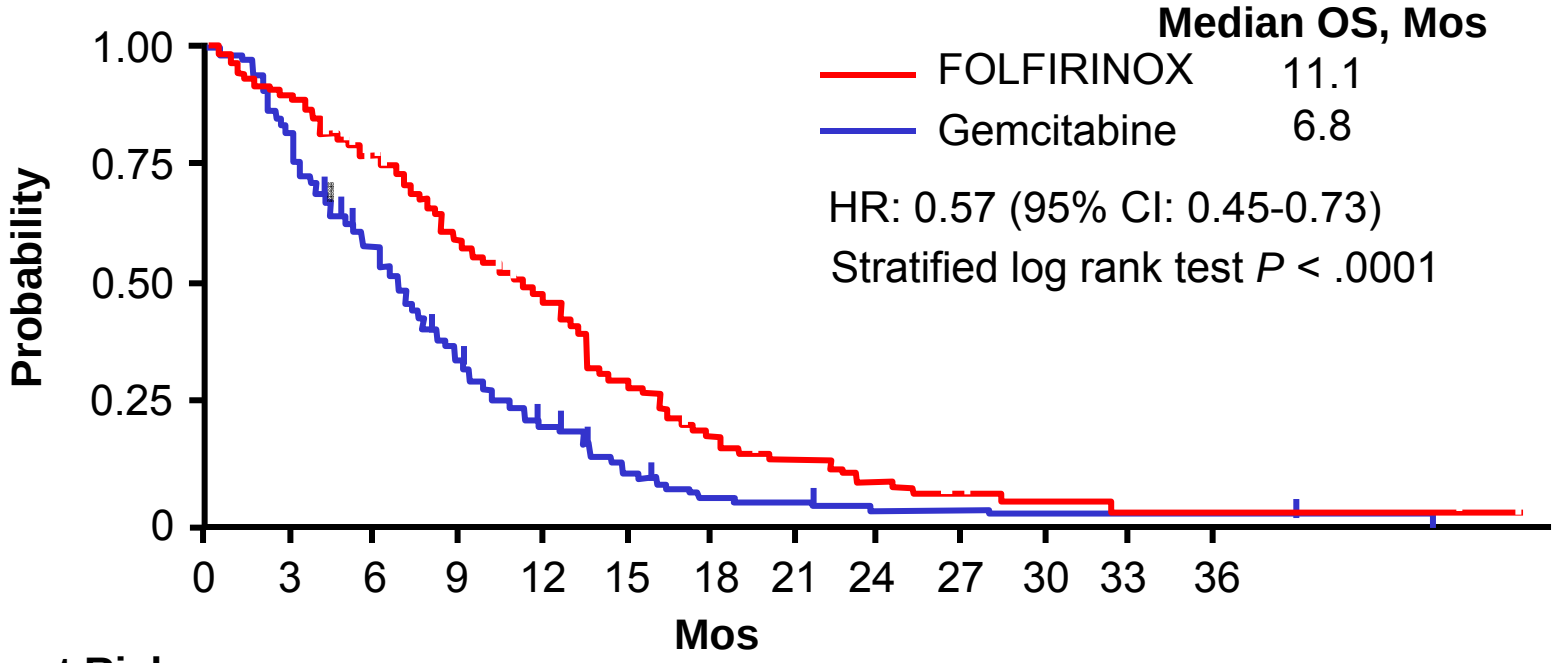



Stratified by

- Center
- Performance score 0 vs 1
- Location of the tumor: head vs other location of the primary

Conroy T, et al. ASCO 2010. Abstract 4010. Reprinted with permission
Conroy T, NEJM, 2011

# PRODIGE 4/ACCORD 11: Overall Survival



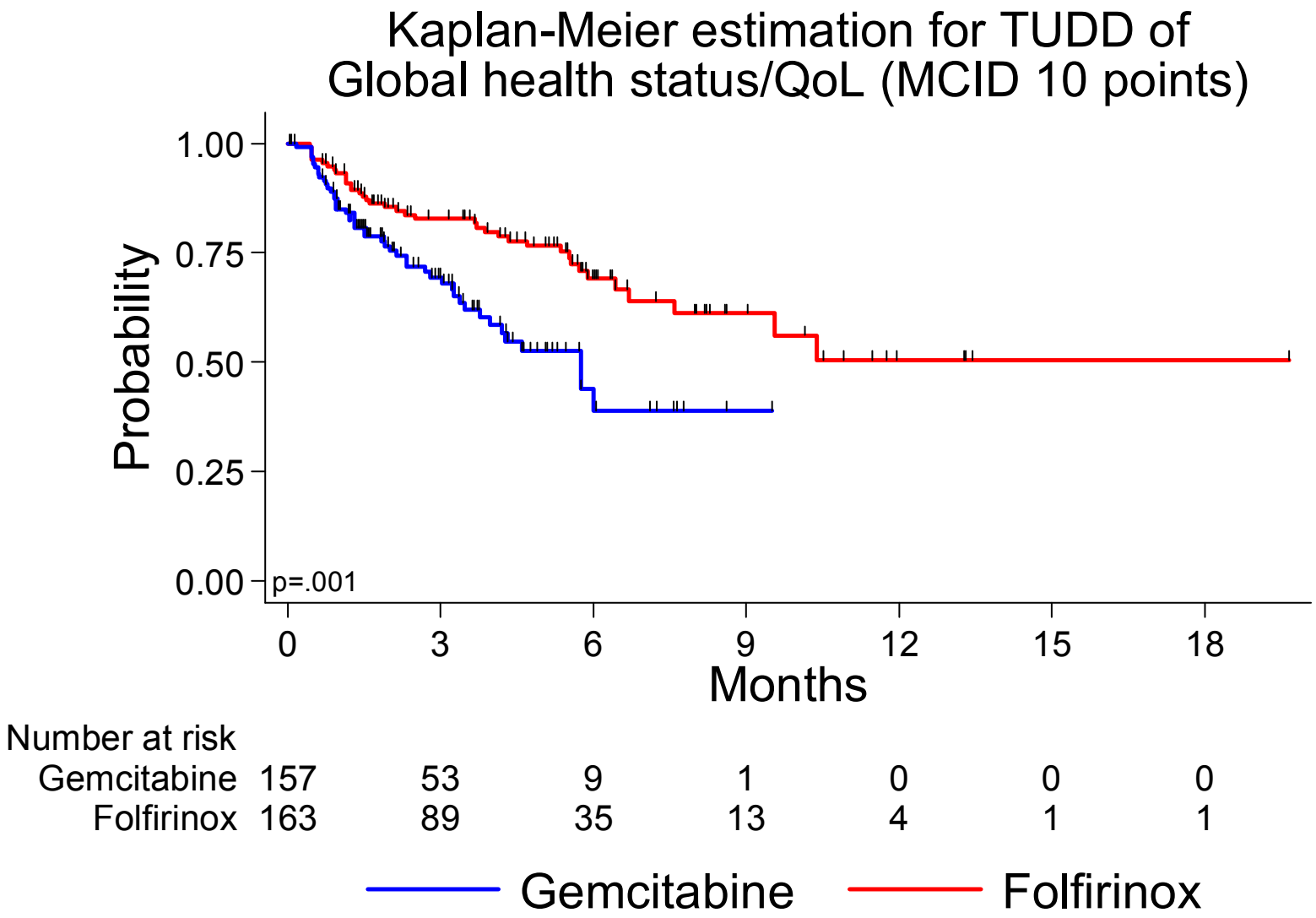

**Patients at Risk, n**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gemcitabine | 171 | 134 | 89 | 48 | 28 | 14 | 7 | 6 | 3 | 3 | 2 | 2 | 2 |
| FOLFIRINOX | 171 | 146 | 116 | 81 | 62 | 34 | 20 | 13 | 9 | 5 | 3 | 2 | 2 |

Conroy T, et al. ASCO 2010. Abstract 4010. Reprinted with permission.

RR 31.6 vs. 9.4%

# Time to definitive QoL degradation



# MPACT: Randomized Phase III Study

**Planned N = 842**

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

**_nab_-Paclitaxel**
125 mg/m$^2$ IV qw 3/4 weeks
+
**Gemcitabine**
1000 mg/m$^2$ IV qw 3/4 weeks

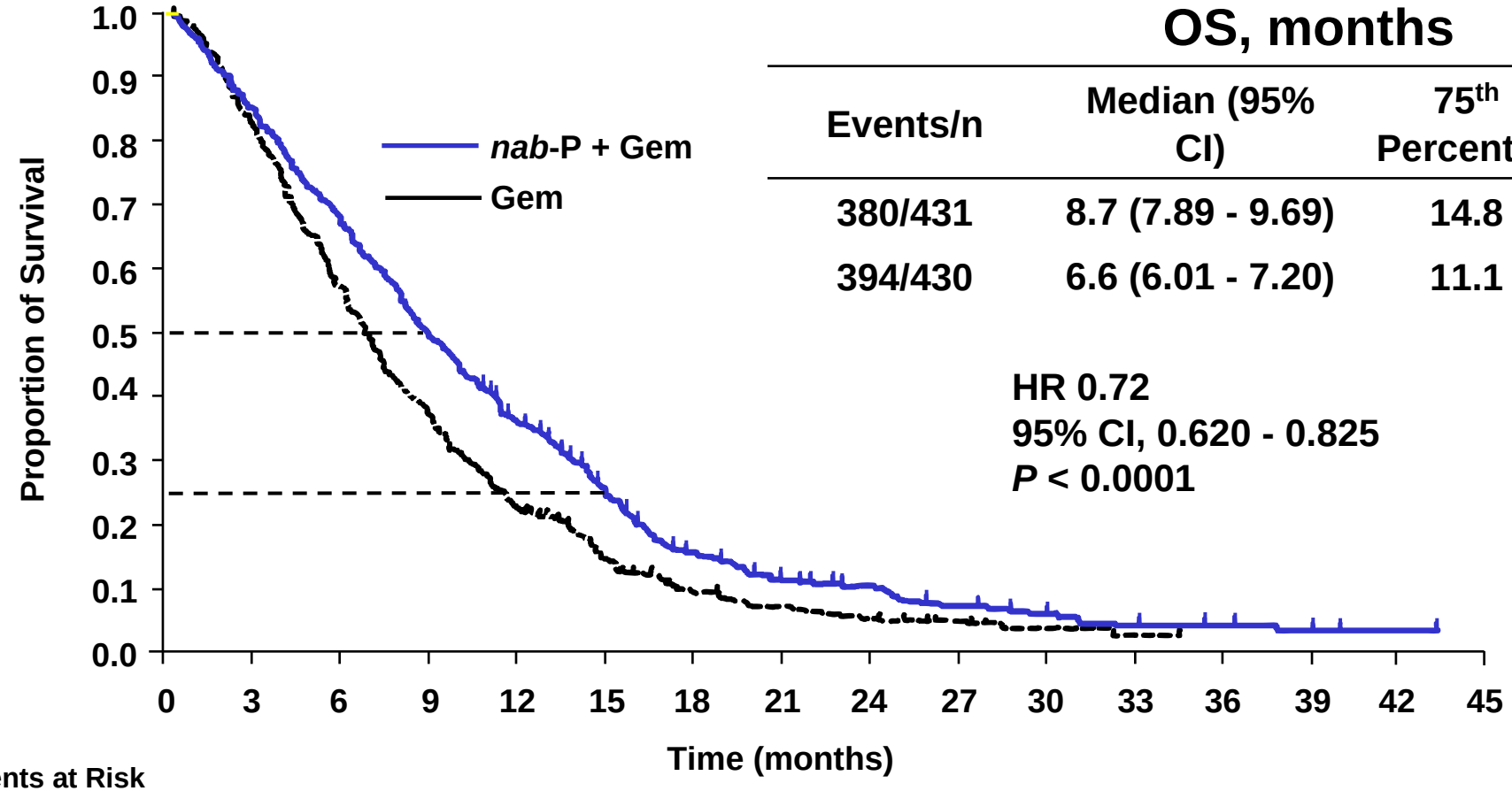
1:1, stratified by KPS, region, liver metastasis

**Gemcitabine**
1000 mg/m$^2$ IV qw for 7/8 weeks
then qw 3/4 weeks

- **Primary endpoint:**
  - OS
- **Secondary endpoints:**
  - PFS and ORR by independent review (RECIST)
- **Safety and tolerability**
  - by NCI CTCAE v3.0

- With 608 events, 90% power to detect OS HR = 0.769 (2-sided $\alpha$ = 0.049)
- One interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

# Gemcitabine and Nab-paclitaxel




| OS, months | | |
|---|---|---|
| Events/n | Median (95% CI) | 75th Percentile |
| 380/431 | 8.7 (7.89 - 9.69) | 14.8 |
| 394/430 | 6.6 (6.01 - 7.20) | 11.1 |

HR 0.72
95% CI, 0.620 - 0.825
*P* < 0.0001

Patients at Risk

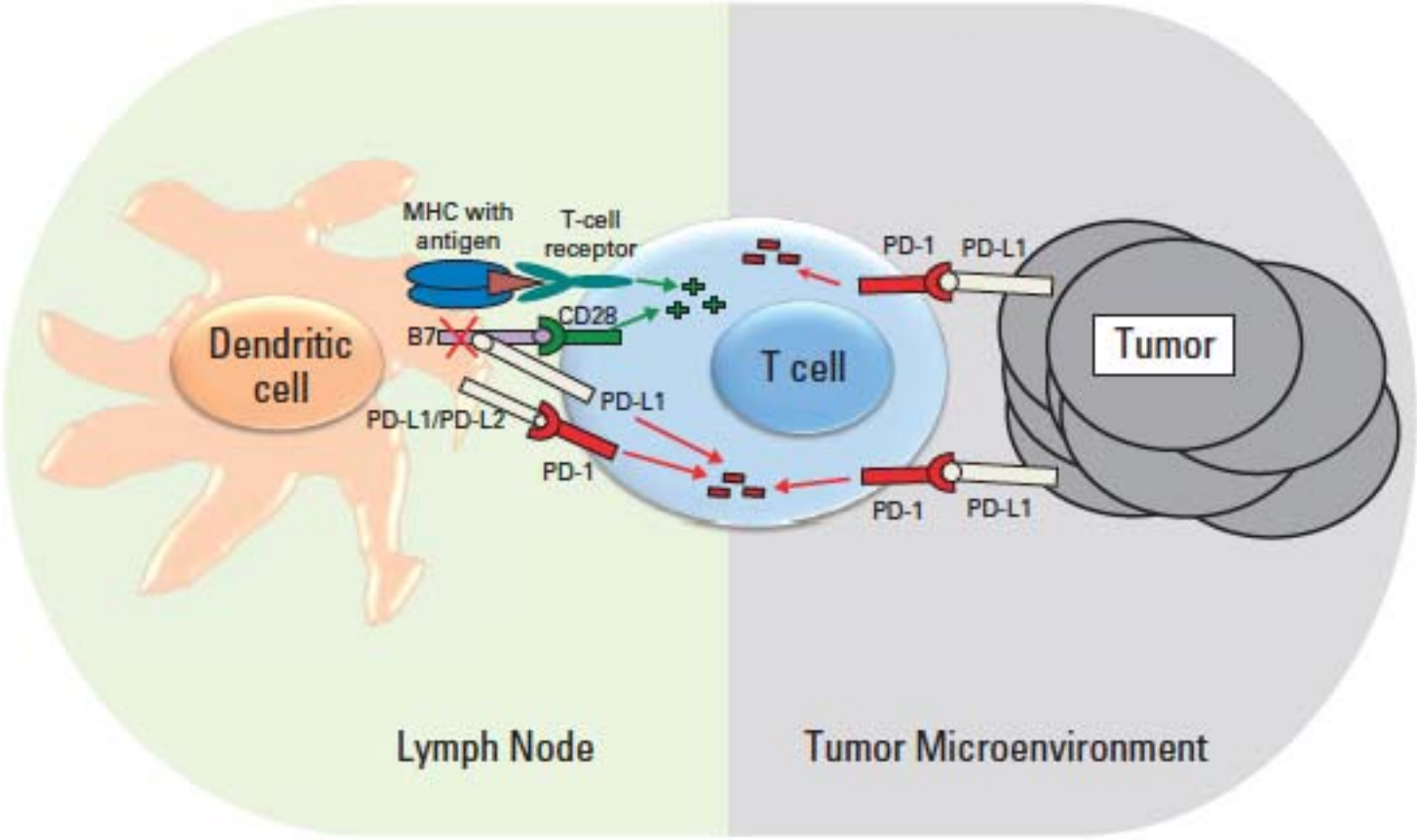
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *nab*-P + Gem: | 431 | 357 | 284 | 208 | 144 | 84 | 48 | 34 | 25 | 16 | 10 | 6 | 5 | 2 | 1 | 0 |
| Gem: | 430 | 340 | 231 | 149 | 90 | 47 | 27 | 19 | 14 | 8 | 4 | 2 | 0 | 0 | 0 | 0 |

# Gemcitabine + nab-Paclitaxel vs. FOLFIRINOX

| | **FOLFIRINOX** | ***nab*-P + Gem** |
|---|---|---|
| Number of patients | 342 | 861 |
| Sites of accrual | France | International |
| PS included | ECOG 0,1 | KPS 70-100 |
| Survival in Gem arm | 6.8 mos | 6.7 mos |
| Survival in experimental arm | 11.1 mos | 8.5 mos |
| HR for OS | 0.57 | 0.72 |
| HR for PFS | 0.47 | 0.69 |
| RR | 31.6 | 23 |

# Recent Updates:
# Any New Options?

# Immune Checkpoint



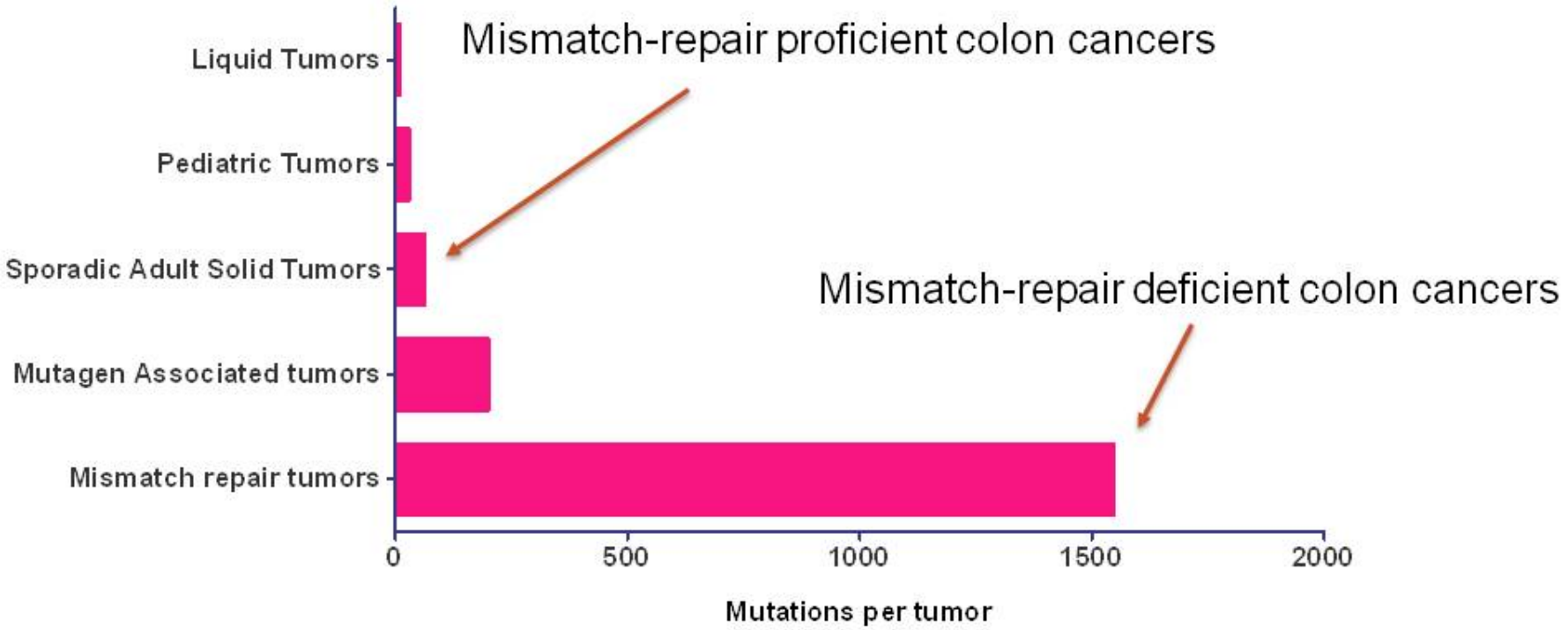

Postow et al, JCO, 2015

# Hypothesis

- Mutations have been shown to encode proteins that can be recognized and targeted by the immune system
- Average tumor has dozens of somatic mutations; Mismatch repair deficient tumors harbor thousands of mutations
- Immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

# Mutations per tumor




SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.



Presented By Dung Le at 2015 ASCO Annual Meeting

# PD-1 Blockade in Mismatch Repair Deficient Non-Colorectal Gastrointestinal Cancers

Dung Le, Jennifer Uram, Hao Wang, Holly Kemberling, Aleksandra Eyring, Bjarne Bartlett, Richard Goldberg, Todd Crocenzi, George Fisher, James Lee, Tim Greten, Daniel Laheru, Nilo Azad, Ross Donehower, Brandon Luber, Minori Koshiji, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

*The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*
*Ohio State University Comprehensive Cancer Center, Columbus, OH*
*Providence Cancer Center, Portland, OR*
*Stanford University School of Medicine, Stanford, CA*
*University of Pittsburgh, Pittsburgh, PA*
*National Cancer Institute, Bethesda, MD*
*Merck & Co., Inc., Kenilworth, NJ*

2016 Gastrointestinal Cancers Symposium
Slides are the property of the author. Permission required for reuse.

Presented By Dung Le at TBD

# Study Design

| Colorectal Cancers | | Non-Colorectal Cancers |
|---|---|---|
| Cohort A<br>**Deficient in Mismatch Repair (n=25)** | Cohort B<br>**Proficient in Mismatch Repair (n=25)** | Cohort C<br>**Deficient in Mismatch Repair (n=21)** |

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability


Slides are the property of the author. Permission required for reuse.

# Baseline Characteristics

| Characteristic | MMR-deficient GI non-CRC n=17 (%) |
|---|---|
| **Median Age – years** | 60 (34-92) |
| **Gender-female** | 5 (29) |
| **ECOG PS-zero** | 5 (29) |
| **Tumor Type** | |
| Pancreas | 4 (23) |
| Ampullary | 4 (23) |
| Biliary | 3 (18) |
| Small bowel | 3 (18) |
| Gastric | 3 (18) |
| **Metastatic** | 17 (100) |
| **Liver Mets** | 11 (65) |
| **Median Prior Regimens** | 2 |


Slides are the property of the author. Permission required for reuse.

# Objective Responses

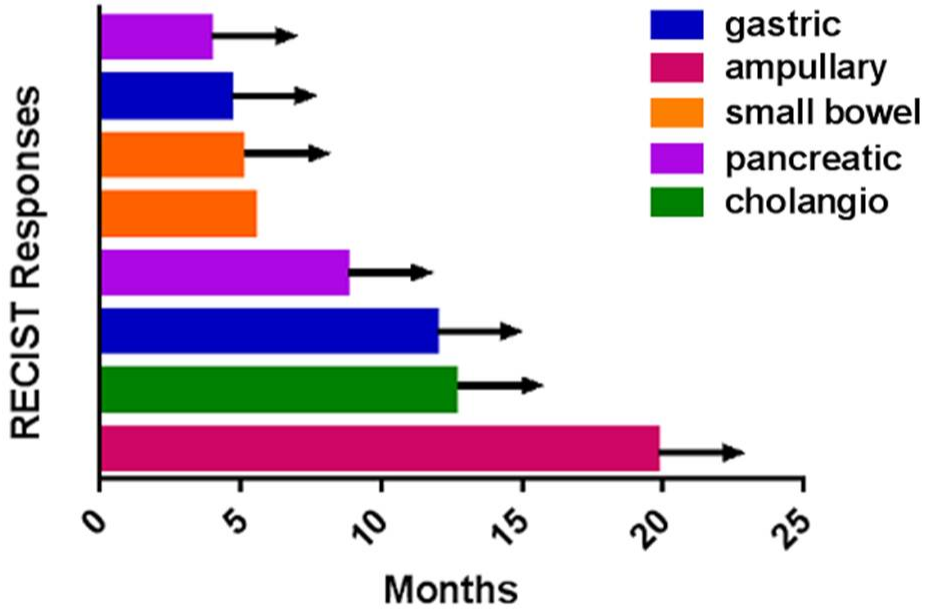
| *Type of Response-no (%)* | MMR-deficient GI non-CRC n=17 |
|---|---|
| *Complete Response* | 4 (24) |
| *Partial Response* | 4 (24) |
| *Stable Disease (Week 12)* | 5 (29) |
| *Progressive Disease* | 3 (18) |
| *Not Evaluable*[1] | 1 (6) |
| *Objective Response Rate (%)* | 47 |
| *95% CI* | 23-72 |
| *Disease Control Rate (%)* | 76 |
| *95% CI* | 50-93 |
| *Median Follow Up (mos)* | 5.3 |

[1]Patients were considered not evaluable if they did not undergo a 12 week scan due to clinical progression.



Slides are the property of the author. Permission required for reuse.

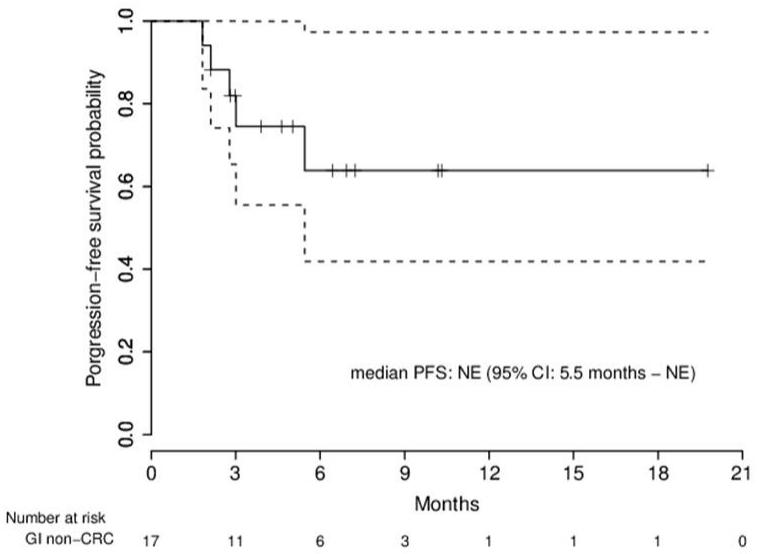
# Durability of Response

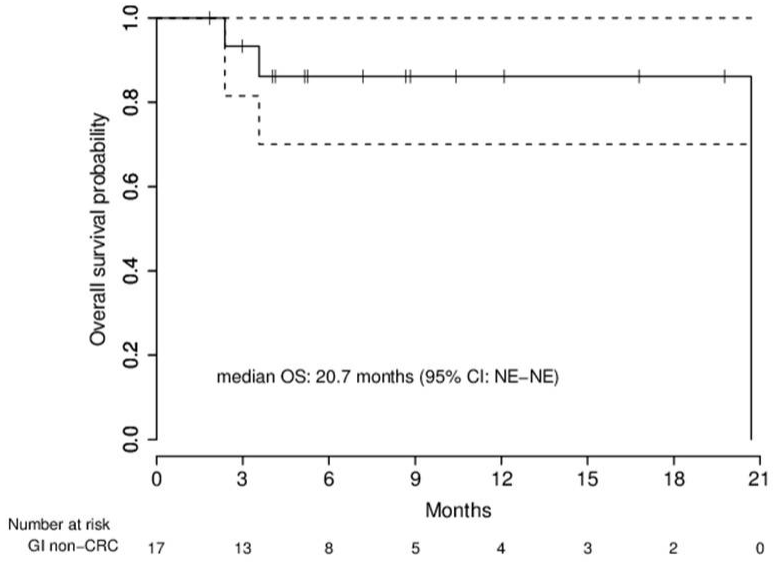




Slides are the property of the author. Permission required for reuse.

# Progression-Free and Overall Survival




**PFS = Non-estimable (NE)**

**OS = 21 Mos**

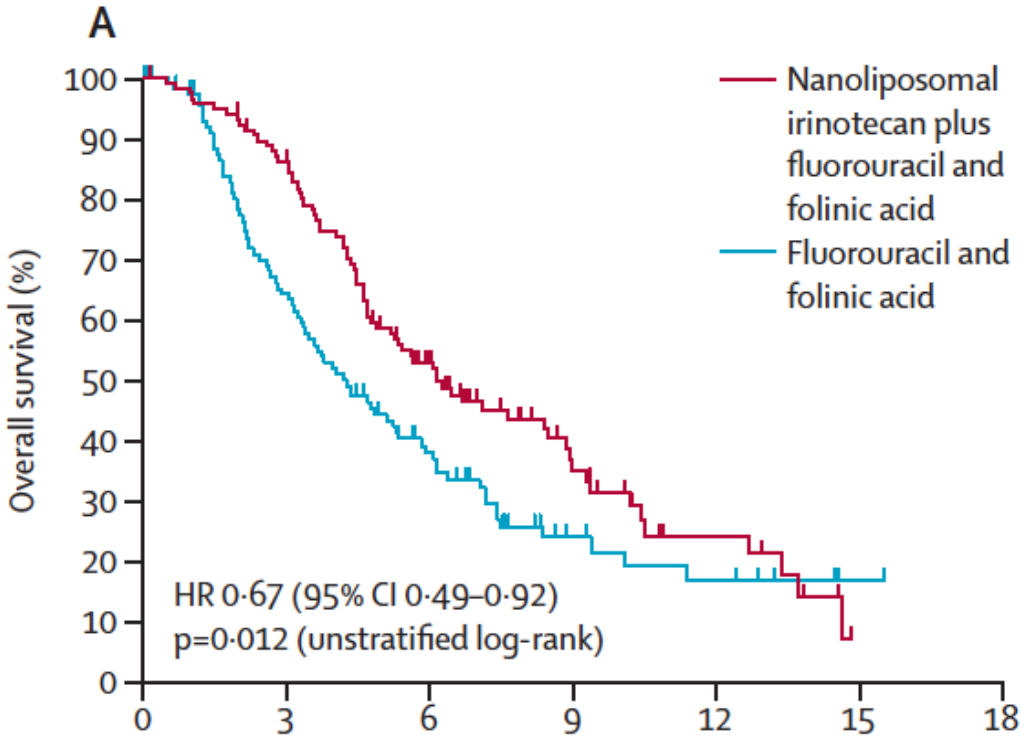



Slides are the property of the author. Permission required for reuse.


Presented By Dung Le at TBD

# Second Line Therapy: NAPOLI Trial

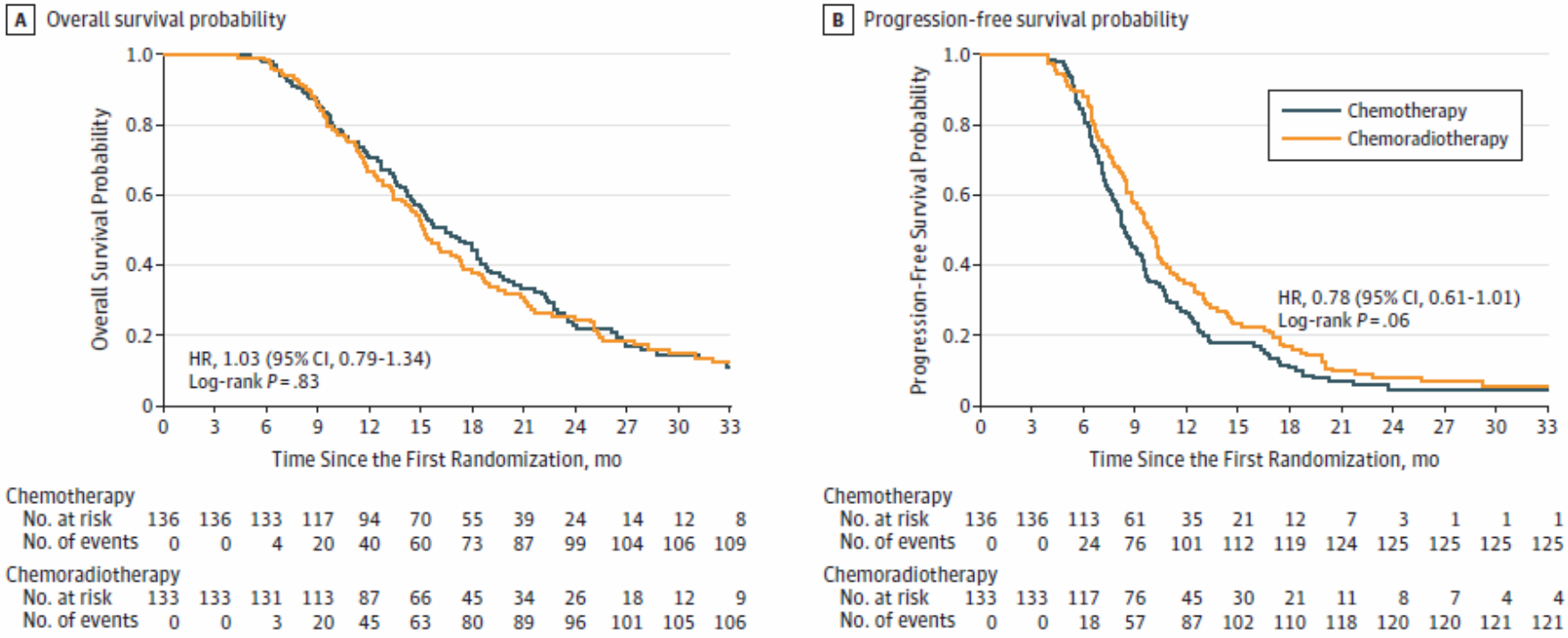
- Phase III trial of nanoliposomal irinotecan (MM-398/Onivide) alone vs. 5-fluorouracil alone vs. combination




**Median OS 6.1 vs. 4.2 months**

Wang-Gillam et al, Lancet 2016

# Radiation Therapy in Advanced Disease (LAP07 Trial)




JAMA, 2016

# Early Stage and Locally Advanced PDAC

- A number of trials ongoing
  - **Resectable**
    - Neoadjuvant FOLFIRINOX vs. Gem/Nab-Paclitaxel
    - Adjuvant FOLFIRINOX
    - Adjuvant Gem/Nab-Paclitaxel
  - **Borderline Resectable**
    - FOLFIRINOX +/- SBRT
  - **Locally Advanced**
    - Role of high dose radiation
- Multidisciplinary assessment is key

# ESPAC-4: A multicenter, international, open label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma

J. Neoptolemos , D. Palmer , P. Ghaneh , J. W. Valle , D. Cunningham , J. Wadsley , T. Meyer , A. Anthoney , B Glimelius , Pehr Lind, S. Falk , J. Izbicki , G. Middleton, P. Ross , H. Wasan, A. McDonald, T. Crosby, E. Psarelli, P. Hammel and M. Büchler for the European Study Group on Pancreatic Cancer (ESPAC)

NCRI Pancreatic Cancer Sub-Group

CRUK Liverpool Cancer Trials Unit

EudraCT#: 2007-004299-38

ISRCTN#: 43482138

CRUK#: C245/A8968/A20830

NCRN National Cancer Research Network

ASCO, Chicago 06/06/2016 8:00 AM - 11:00 AM LBA4006

LCTU Liverpool Clinical Trials Unit

NCRI National Cancer Research Institute

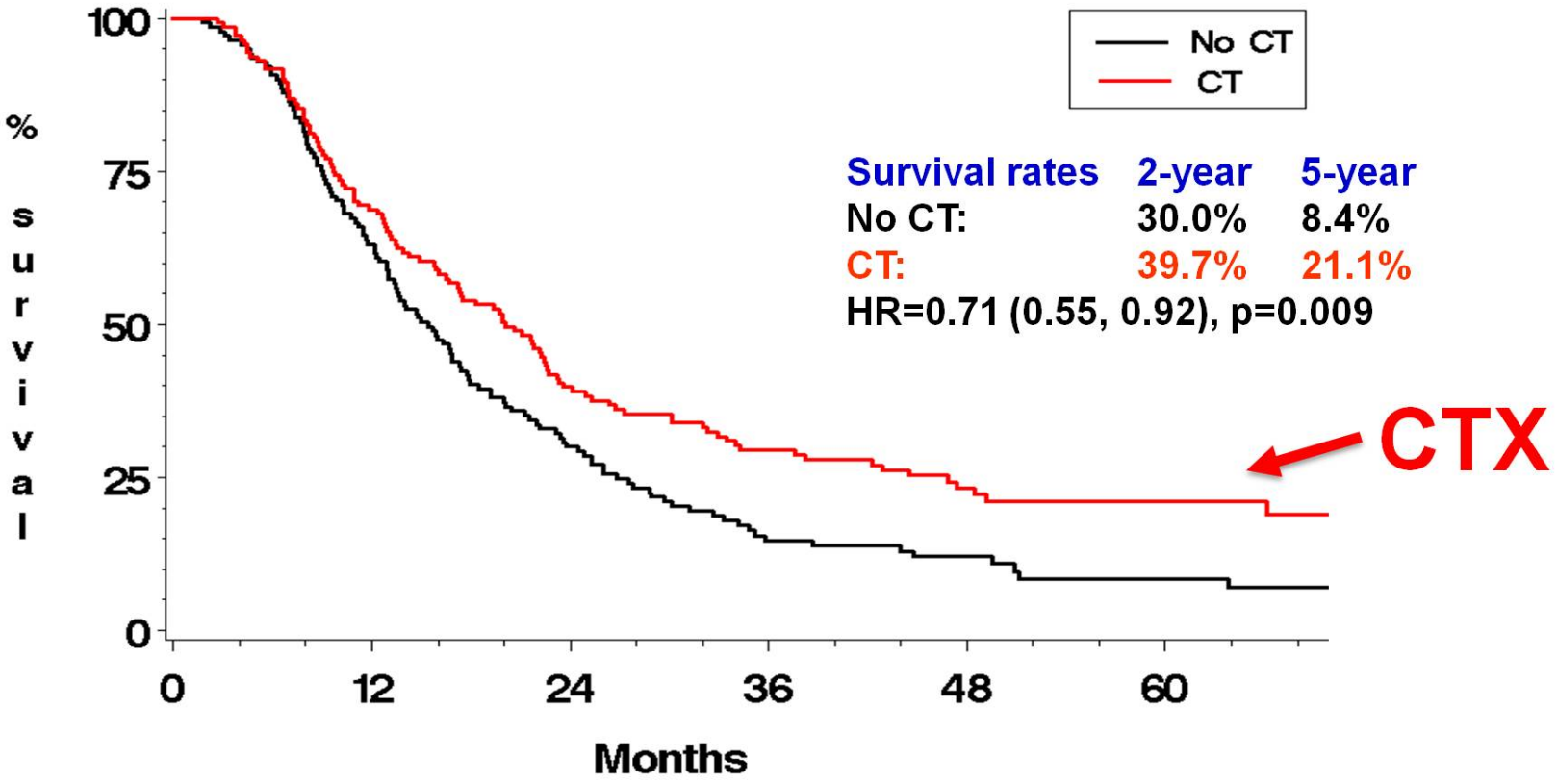
UKCRC Registered Clinical Trials Units

NHS National Institute for Health Research

CANCER RESEARCH UK

# ESPAC-1, N=289, NEJM 2004: Benefit for Chemotherapy

## 2x2 Factorial: Survival by Adjuvant Chemotherapy




| Survival rates | 2-year | 5-year |
|---|---|---|
| No CT: | 30.0% | 8.4% |
| CT: | 39.7% | 21.1% |

HR=0.71 (0.55, 0.92), p=0.009

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No CT | 142 | 89 | 41 | 18 | 11 | 7 |
| CT | 147 | 99 | 56 | 38 | 22 | 11 |

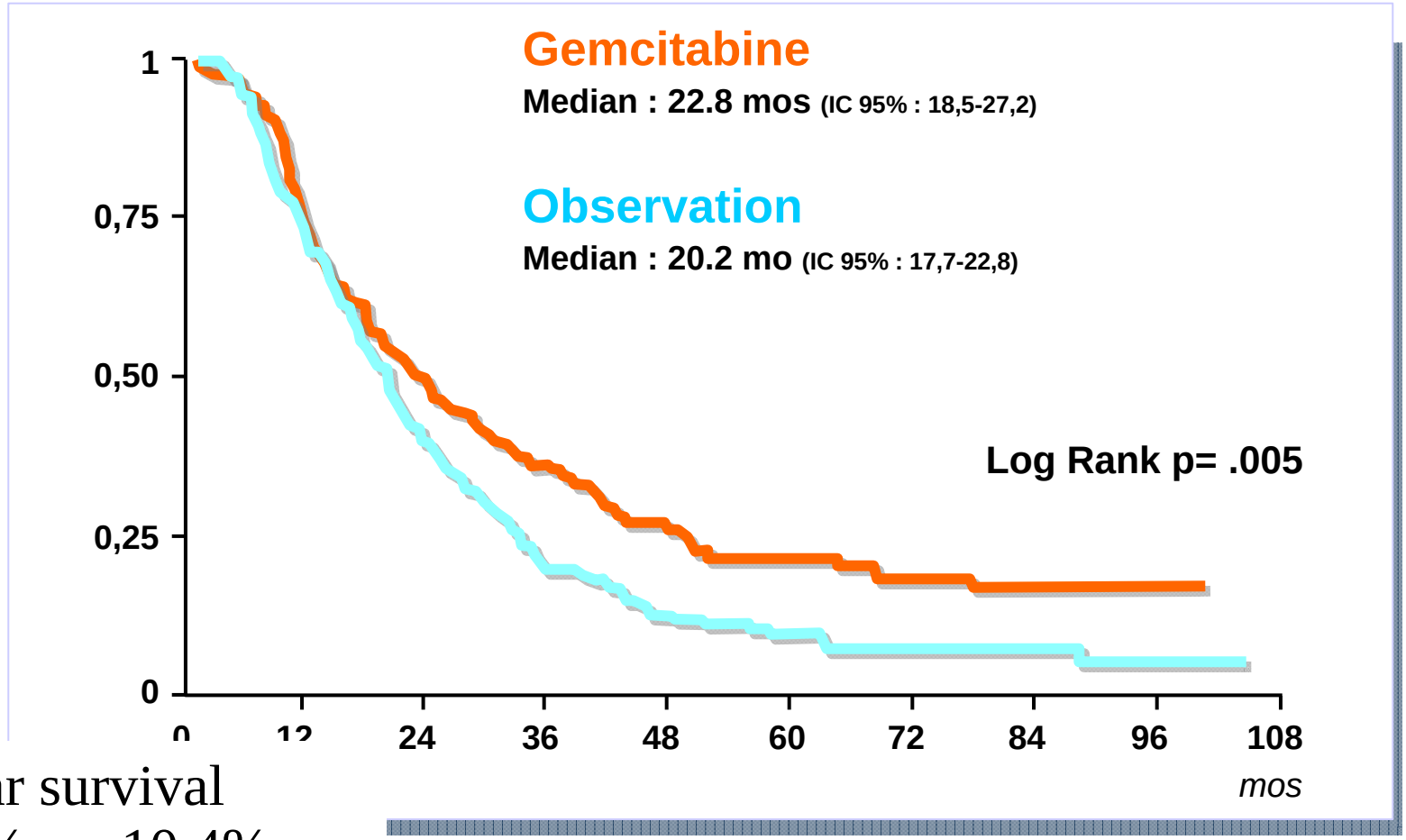
Neoptolemos JP et al
NEJM 2004; 350:1200-10

LCTU Liverpool Clinical Trials Unit | NCRI National Cancer Research Institute | UKCRC Registered Clinical Trials Units | NWSTC | NHS National Institute for Health Research | CANCER RESEARCH UK

Presented By John Neoptolemos at 2016 ASCO Annual Meeting

# CONKO-001: FINAL RESULTS

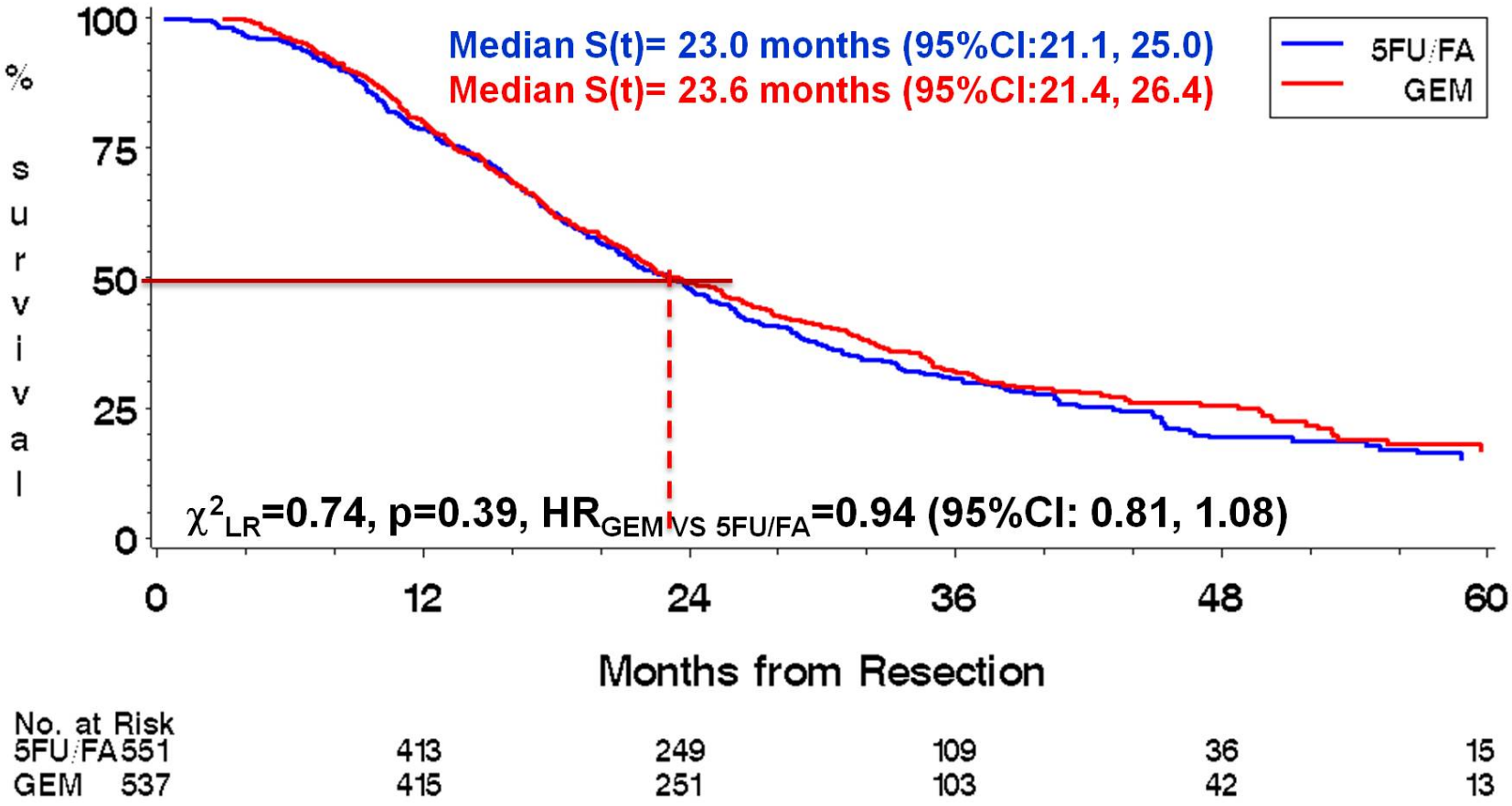
## Overall Survival




5-year survival
20.7% vs. 10.4%

*Oettle et al, JAMA, 2007*

# ESPAC-3, N=1,088: Gemcitabine not better than 5-FU/FA




Neoptolemos et al JAMA 2010; 304: 1073-81

LCTU Liverpool Clinical Trials Unit | NCRI National Cancer Research Institute | UKCRC Registered Clinical Trials Units | NWSTC | NHS National Institute for Health Research | CANCER RESEARCH UK

Presented By John Neoptolemos at 2016 ASCO Annual Meeting

# ESPAC - 4

**Stratified log-rank test with 5% 2-sided α, for a 10% difference in 2 year survival, 90% power = 480 events = 722 patients, 361 in @ arm**

722 patients
pancreatic ductal adenocarcinoma
'curative' resection ≤12 wks

↓

**RANDOMISATION at Liverpool Cancer Trials Unit**

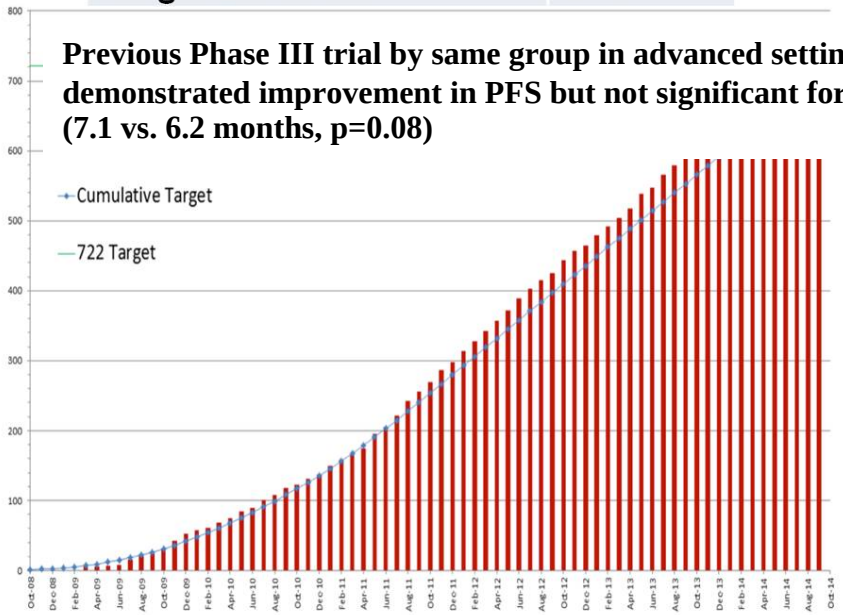
**GEMCITABINE**
1000mg/m² -Days 1,8 and 15 for 6 cycles

**GEMCITABINE**
1000mg/m² -Days 1,8 and 15 for 6 cycles
**CAPECITABINE**
1660mg/m²/day – 21/28d
i.e. 24 weeks

**3-MONTHLY FOLLOW UP FROM RANDOMISATION TO DEATH**

| Target number of patients | 722 |
|---|---|
| Start date | 13/01/08 |
| Number of sites opened | 106 |
| Planned close date | 01/11/14 |
| Target achieved | 31/07/14 |

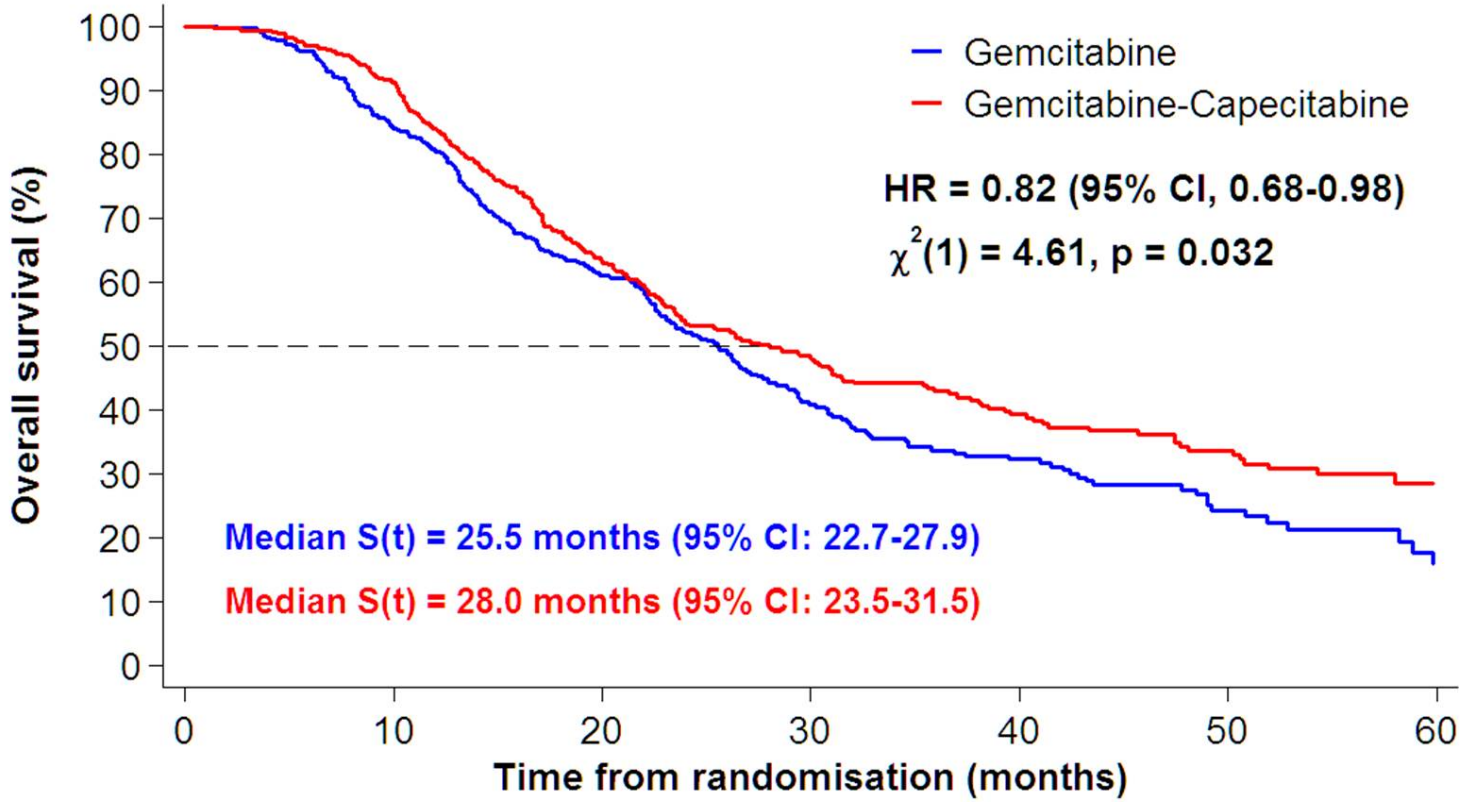
**Previous Phase III trial by same group in advanced setting demonstrated improvement in PFS but not significant for OS (7.1 vs. 6.2 months, p=0.08)**




LCTU Liverpool Clinical Trials Unit
NCRI National Cancer Research Institute
UKCRC Registered Clinical Trials Units
NIHR National Institute for Health Research
CANCER RESEARCH UK

Presented By John Neoptolemos at 2016 ASCO Annual Meeting

# Survival by Treatment




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gem | 366 | 302 | 207 | 109 | 61 | 27 | 9 |
| GemCap | 364 | 328 | 219 | 139 | 83 | 50 | 19 |

LCTU Liverpool Clinical Trials Unit | NCRI National Cancer Research Institute | UKCRC Registered Clinical Trials Units | NWSTC | NHS National Institute for Health Research | CANCER RESEARCH UK

Presented By John Neoptolemos at 2016 ASCO Annual Meeting

# ESPAC Trials: 5 Year Overall Survival

| Trial | Treatment | No. of pts (N=2092) | 5-Year OS (95% CI) | Stratified Log-Rank $\chi^2$ | p-value |
|---|---|---|---|---|---|
| ESPAC-1 | 5FU/FA | 149 | 21 (14.6 – 28.5) % | | |
| | No chemotherapy | 143 | 8.0 (3.8 – 14.1) % | 7.03 | 0.030* |
| | Chemoradiotherapy (5FU/Rad) | 145 | 10.8 (6.1 – 17.0) % | | |
| ESPAC-3 | GEM | 539 | 17.5 (14.0 – 21.2) % | 0.74 | 0.390* |
| | 5FU/FA | 551 | 15.9 (12.7 – 19.4) % | | |
| ESPAC-4 | GEM | 366 | 16.3 (10.2 – 23.7) % | 4.61 | 0.032† |
| | GEMCAP | 364 | 28.8 (22.9 – 35.2) % | | |

*Stratification factor: resection margin status; †stratification factors: resection margin status and country

# Adjuvant therapy for PDAC

- GEMCAP is now an option for resected PDAC
- Results of APACT and PA.6 will be eagerly awaited
- Role of neoadjuvant chemotherapy is being explored

# Exciting time in Oncology

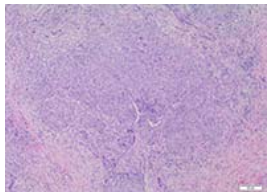
- Entering a new era
  - Chemotherapy for all (Up until 10 years ago)
  - Targeted therapy, basic molecular markers (KRAS) (10 years ago to present)
  - Mix of chemotherapy, targeted therapy, and immunotherapy
    - How can we get there in pancreatic cancer?

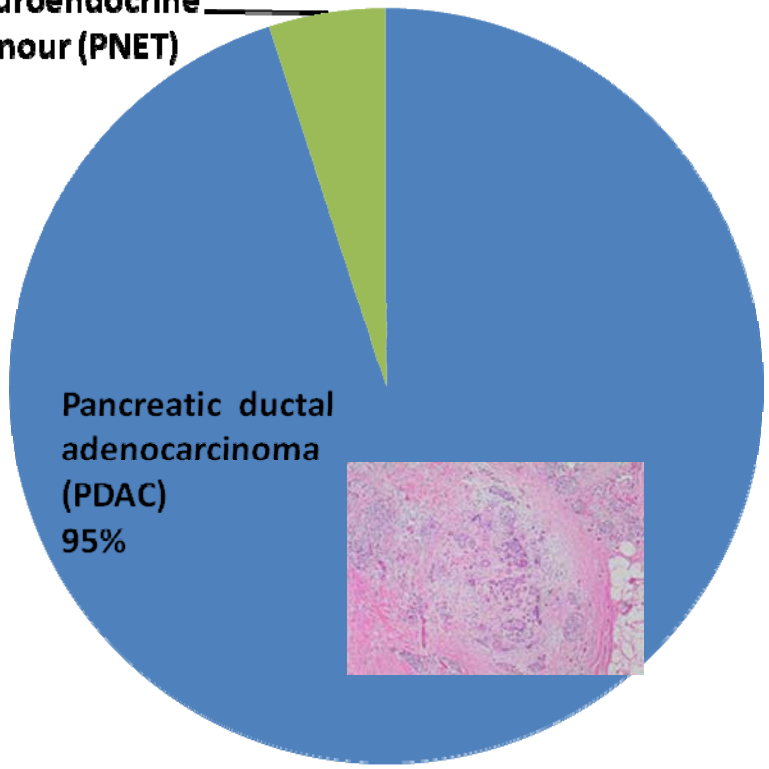
# Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities

PANCREAS CENTRE BC

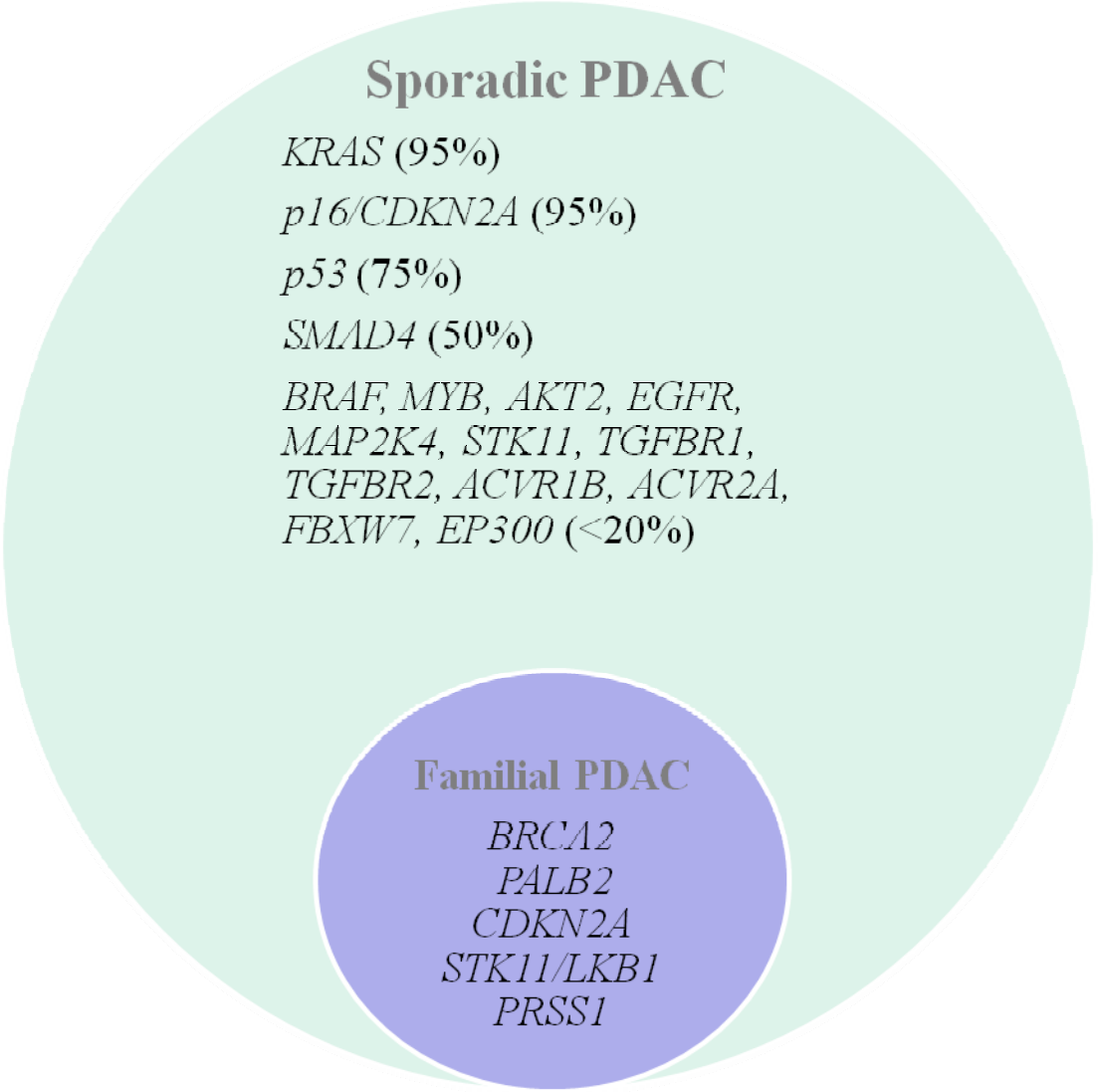
# Pancreatic cancer subtypes (or lack thereof…)






PANCREAS CENTRE BC

# Inter-tumoral heterogeneity of pancreatic cancer: genetic mutations



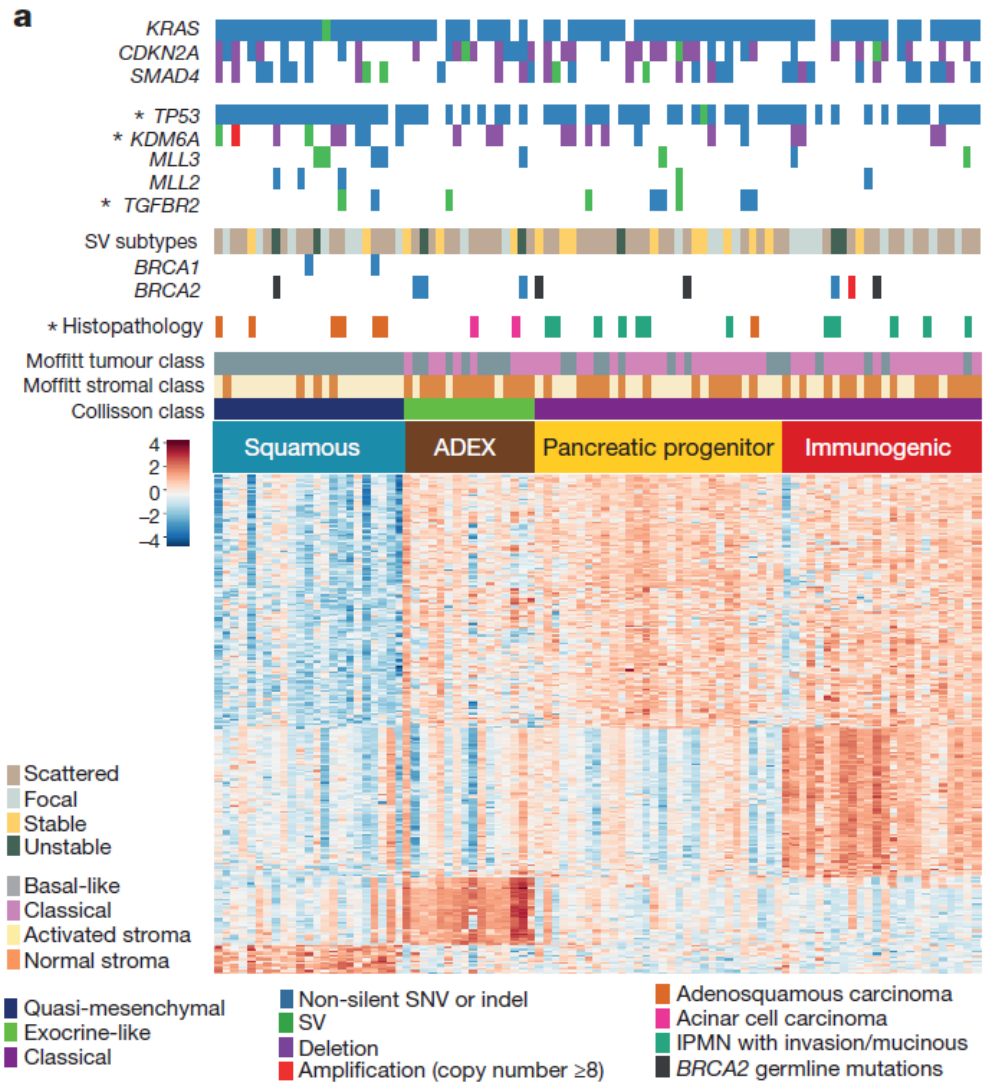

PANCREAS CENTRE BC

# Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities

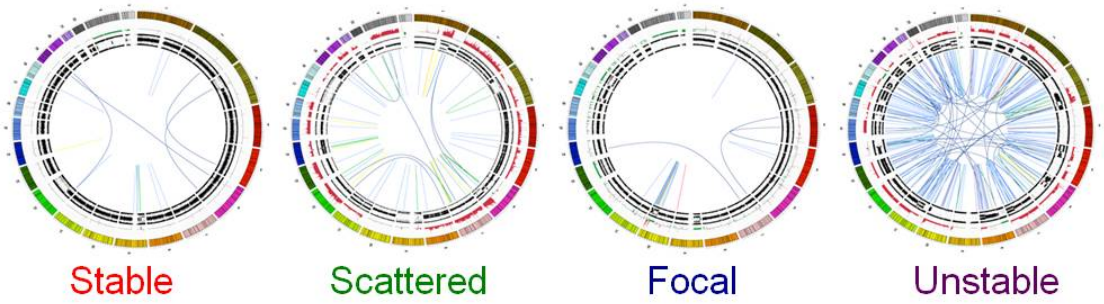
PANCREAS CENTRE BC

# Recently Proposed Subtypes




Bailey et al,
Nature, 2016

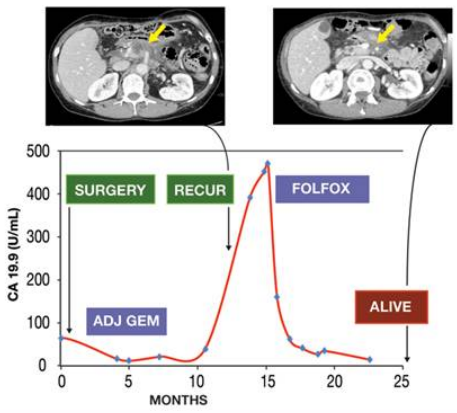
# BRCA mutant PDAC



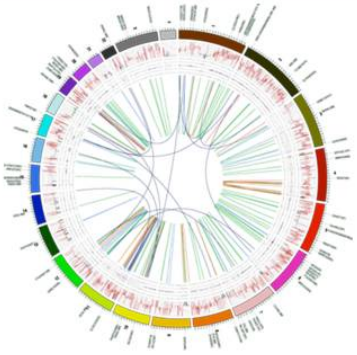

**"Unstable" subtype** (>200 structural variation events) is associated with **BRCA mutation signature**

Presented at the **Gastrointestinal Cancers Symposium**
*Slides are the property of the author. Permission required for reuse.*
Presented by: Sean M Grimmond

## Unstables as Exceptional Responders




**PHENOTYPE:**
GA / SOMATIC BRCA / DDR
Complete radiological & CA19.9 remission
OS: 25.2 mo
PFS: 14.0 mo



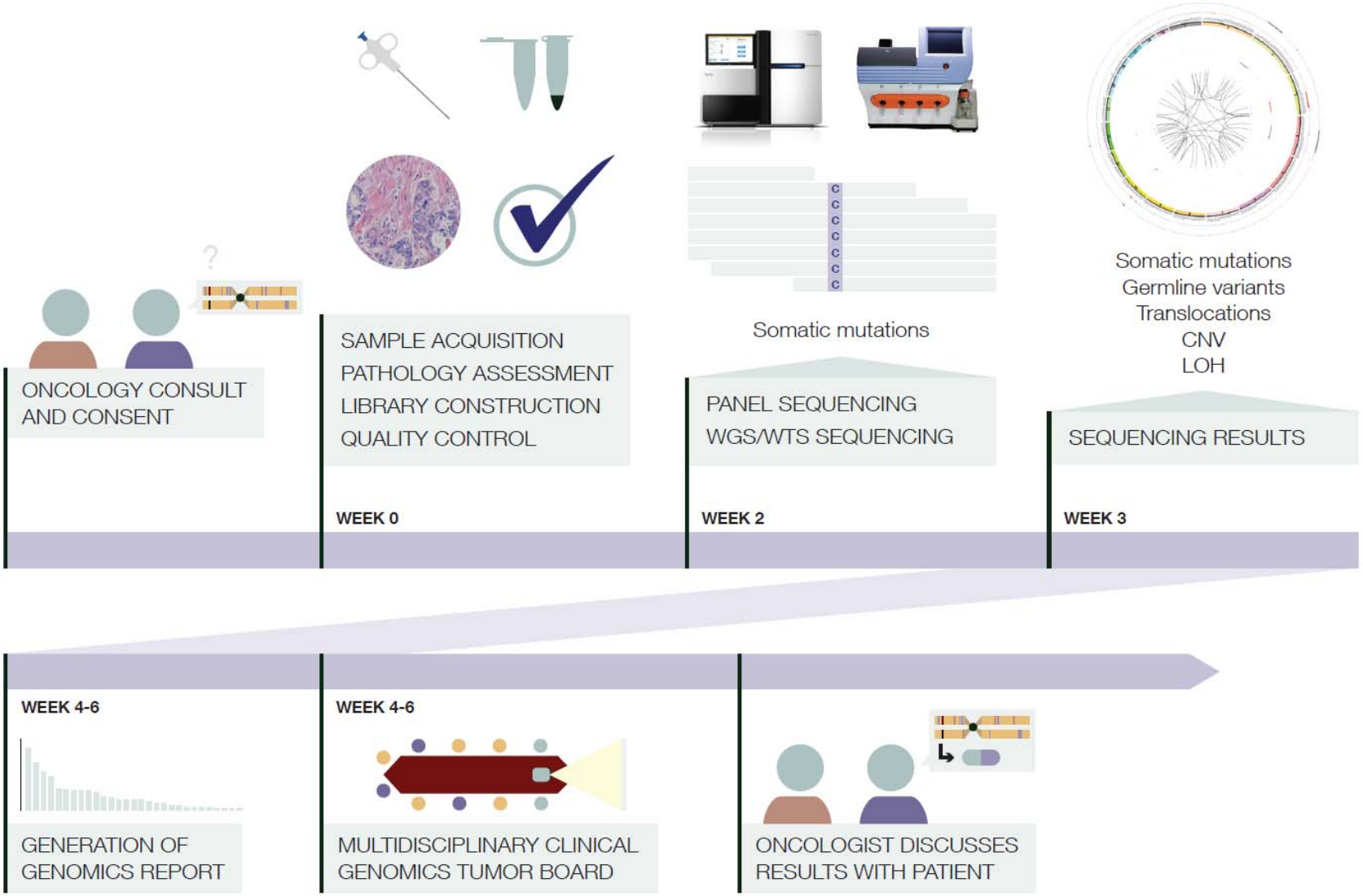
Somatic BRCA2 FS +LOH
Unstable genome

Presented at the **Gastrointestinal Cancers Symposium**
*Slides are the property of the author. Permission required for reuse.*
Presented by: Sean M Grimmond

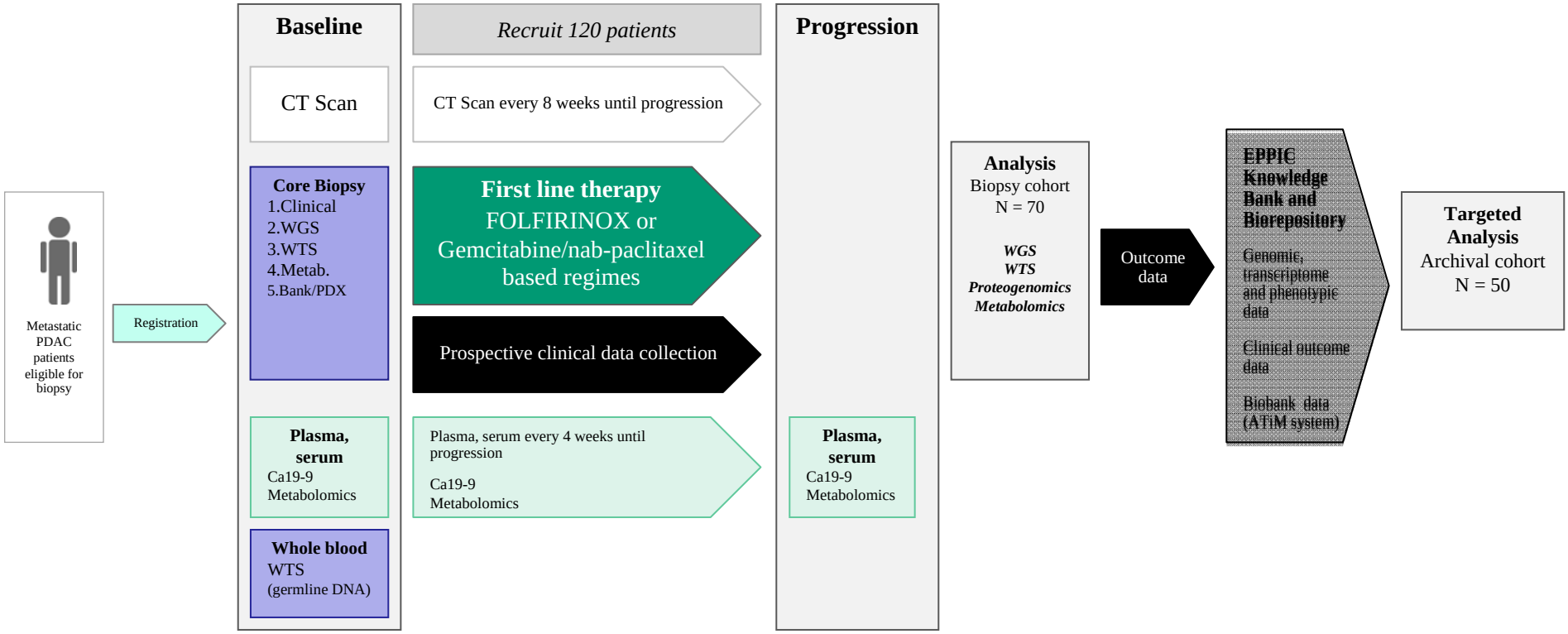
Patients with "unstable" PDAC subtype responded well to therapy

Waddell et al, Nature, 2015

# BCCA Personalized Oncogenomics



# PanGen study schema

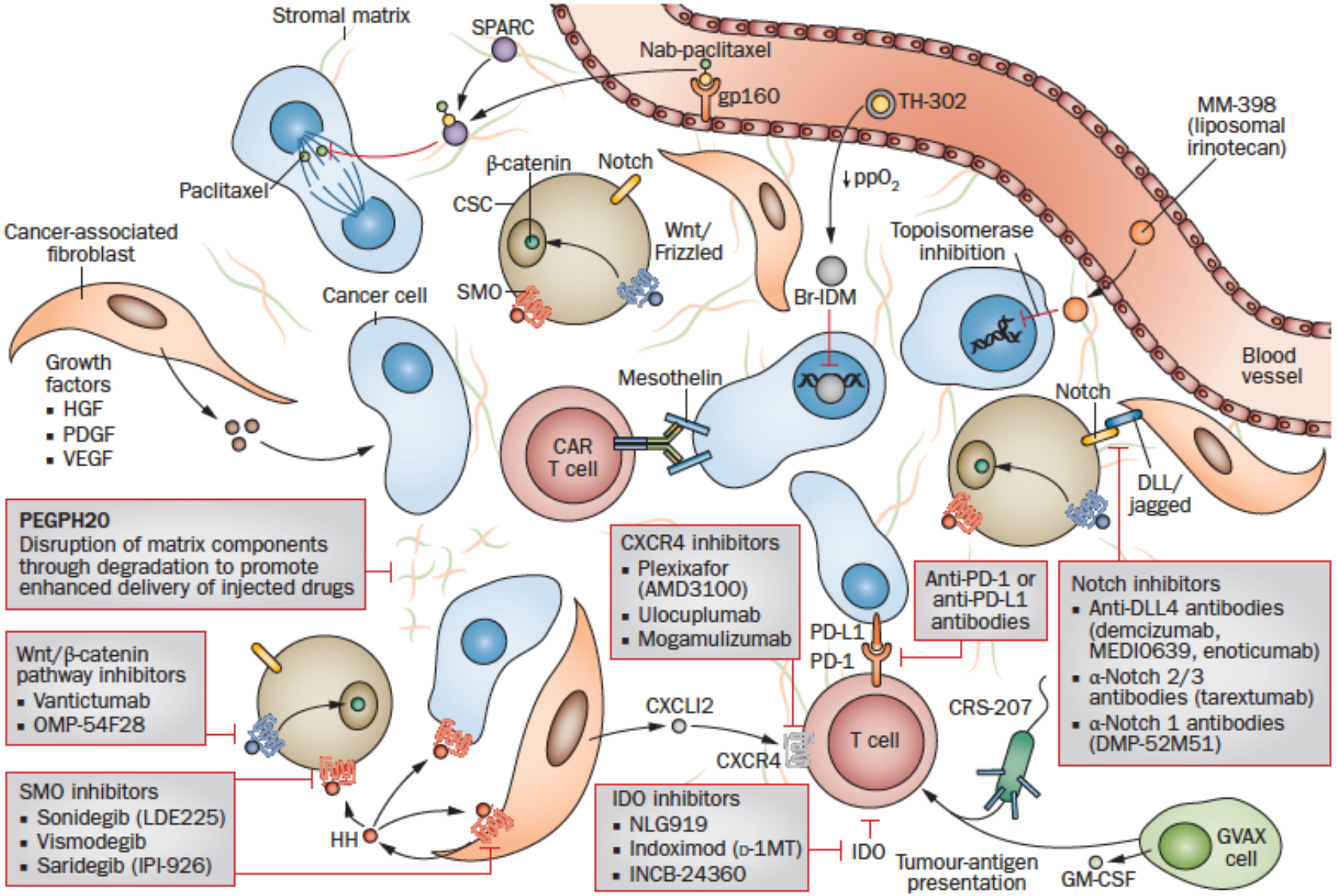


# Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities

PANCREAS CENTRE BC

# New Targets

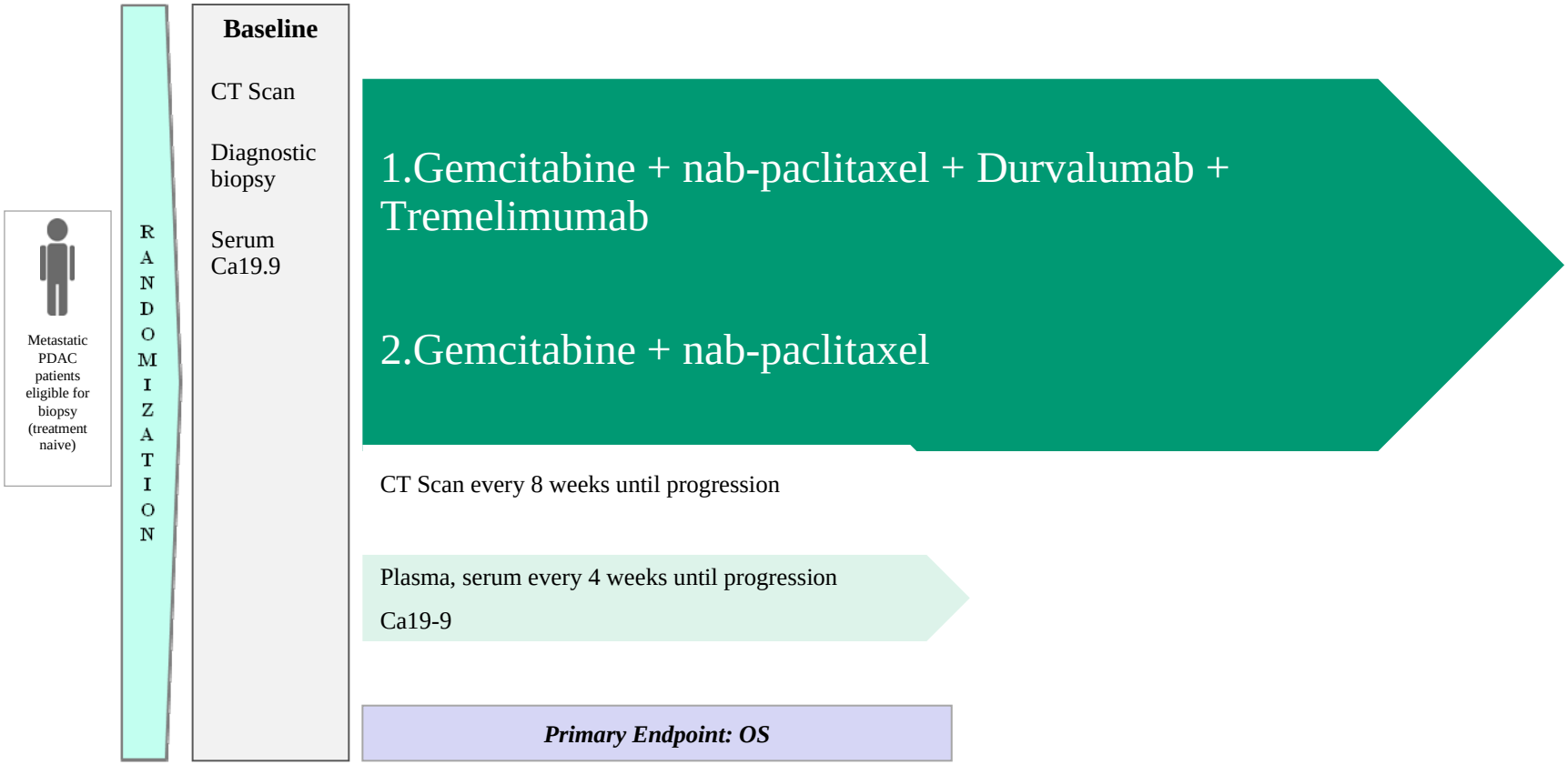



Garrido-Laguno and Hidalgo, Nature Review Clinical Oncology, 2015

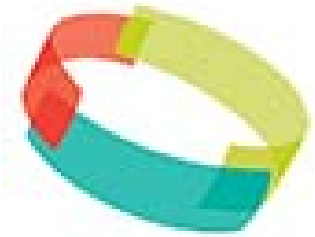
# Chemotherapy combined with Immunotherapy

- Limited activity of single agent PD-L1 inhibition in PDAC (MMR proficient)
- Mechanism of resistance may be related to cancer associated fibroblasts (CAF)
  - Depletion may induce sensitivity to PD-1/PD-L1 inhibition (Feig, C. *et al. 2013)*
- Nab-paclitaxel depletes CAFs
- Chemotherapy may induced neo-antigen release

# CCTG PA.7 study schema



# Multidisciplinary Team



PANCREAS
CENTRE BC

CANCER RESEARCH
DIAGNOSIS TREATMENT.
EARLIER.

# Summary

- Evolving biomarkers and therapeutic options for pancreatic cancer
- Entering era of increasing molecular sub-stratification (BRCA, MMR)
- Multidisciplinary assessment key
- Reason for Optimism!

# Acknowledgments


***Pancreas Centre BC***

Joanna Karasinska

Steve Kalloger

Candace Carter

Hui-li Wong

David Schaeffer

***Genome Sciences Centre***

Martin Jones

Marco Marra

Steven Jones

Alex Fok

Rob Holt


***Ontario Institute for Cancer Research***

Steven Gallinger

Julie Wilson

***McGill University***

George Zogolopolous

***Princess Margaret Cancer Centre***

Jennifer Knox

***Tom Baker Cancer Centre***

Oliver Bathe

***BC Cancer Agency***

Peter Eirew

Shoukat Dedhar

Janessa Laskin

Gregg Morin