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

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

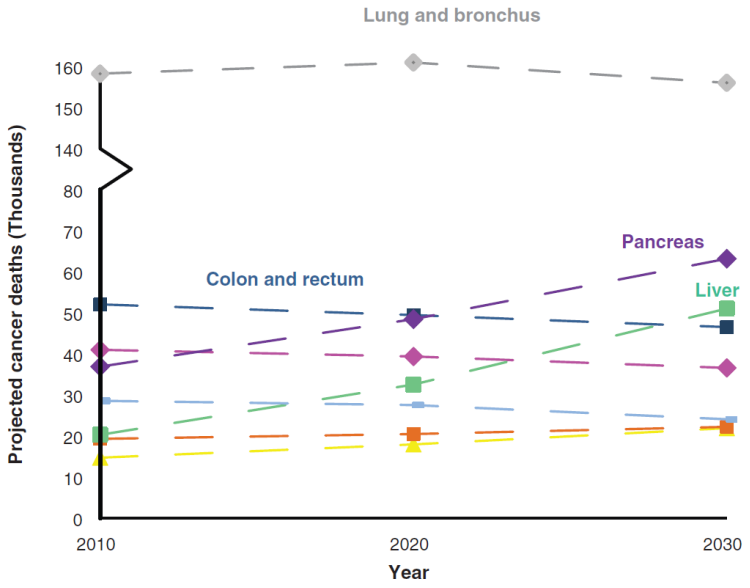
PANCREAS CENTRE BC
CANCER RESEARCH
DIAGNOSIS TREATMENT.
EARLIER.

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

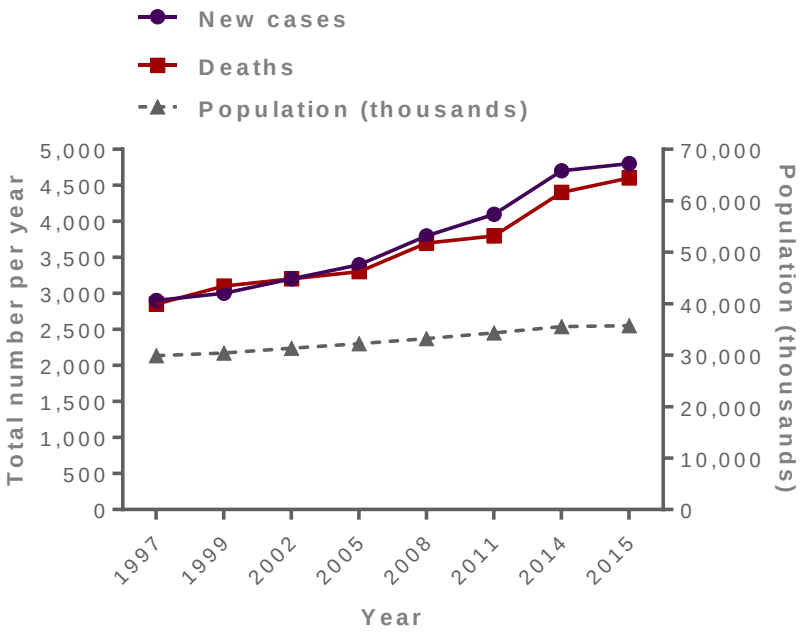
Pancreatic cancer incidence and deaths are rising

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



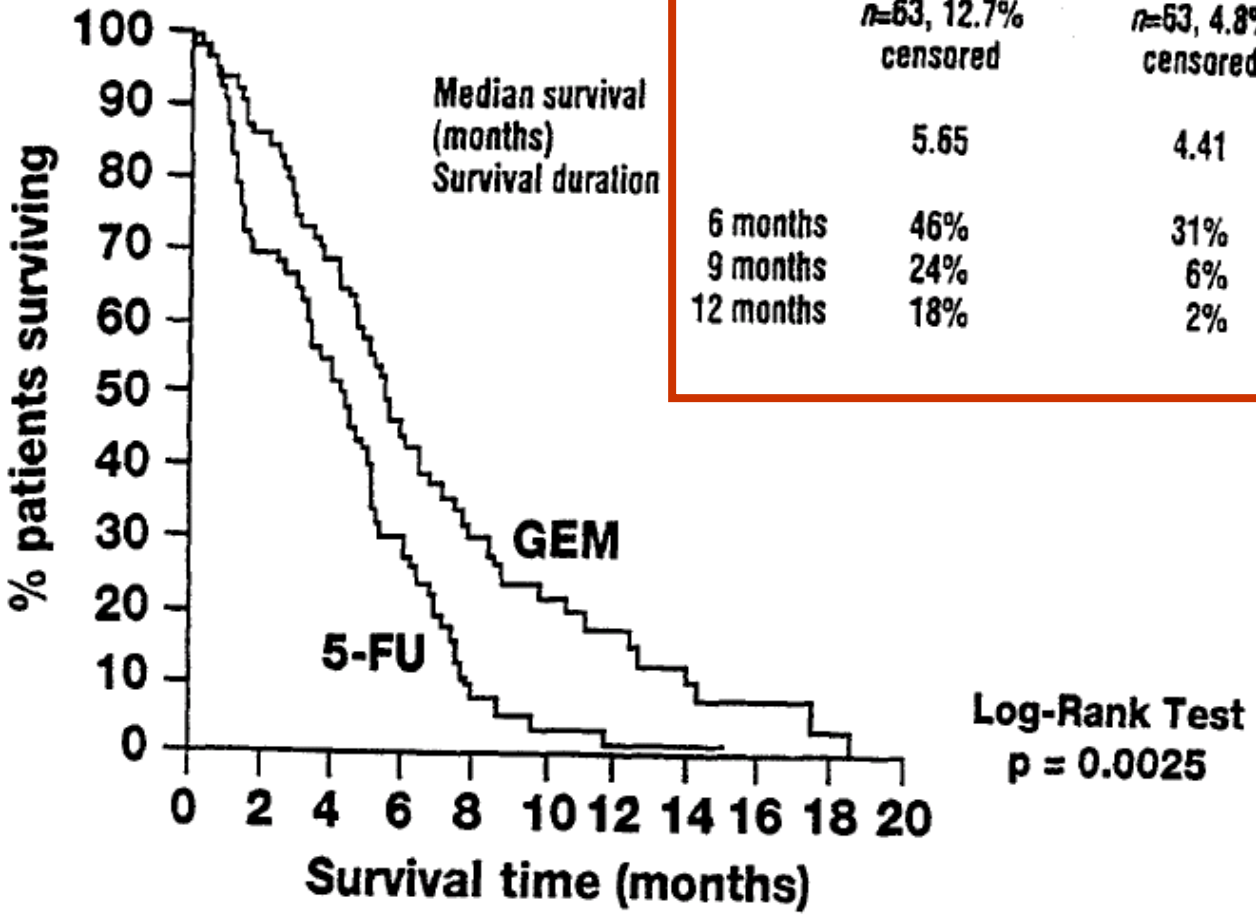
Rahib et al., *Cancer Res* (2014) 74:2913-2921

Pancreatic cancer rates will double in Canada by 2030



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

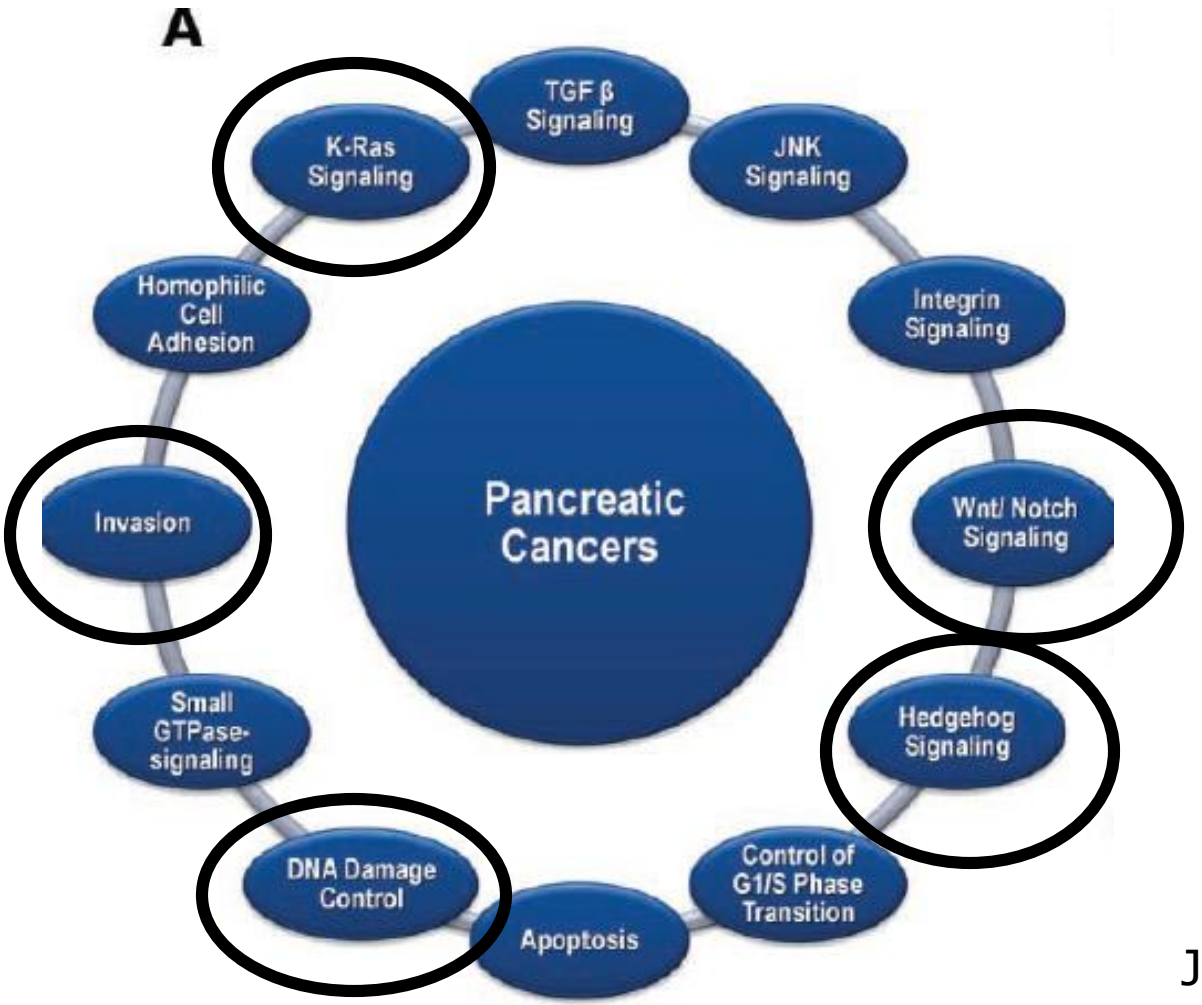
Gemcitabine vs. 5-FU



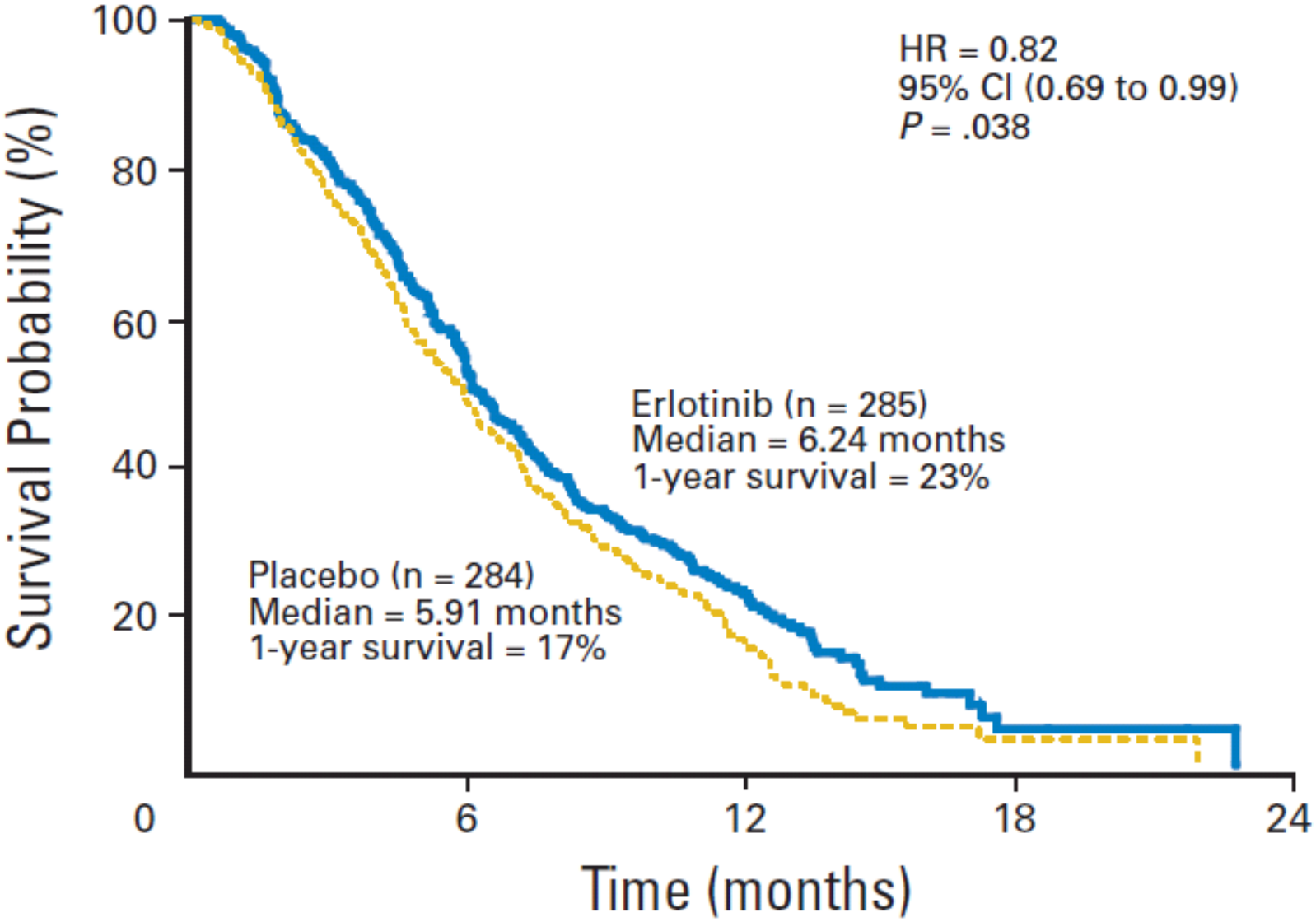
Burris et al, JCO, 1997

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

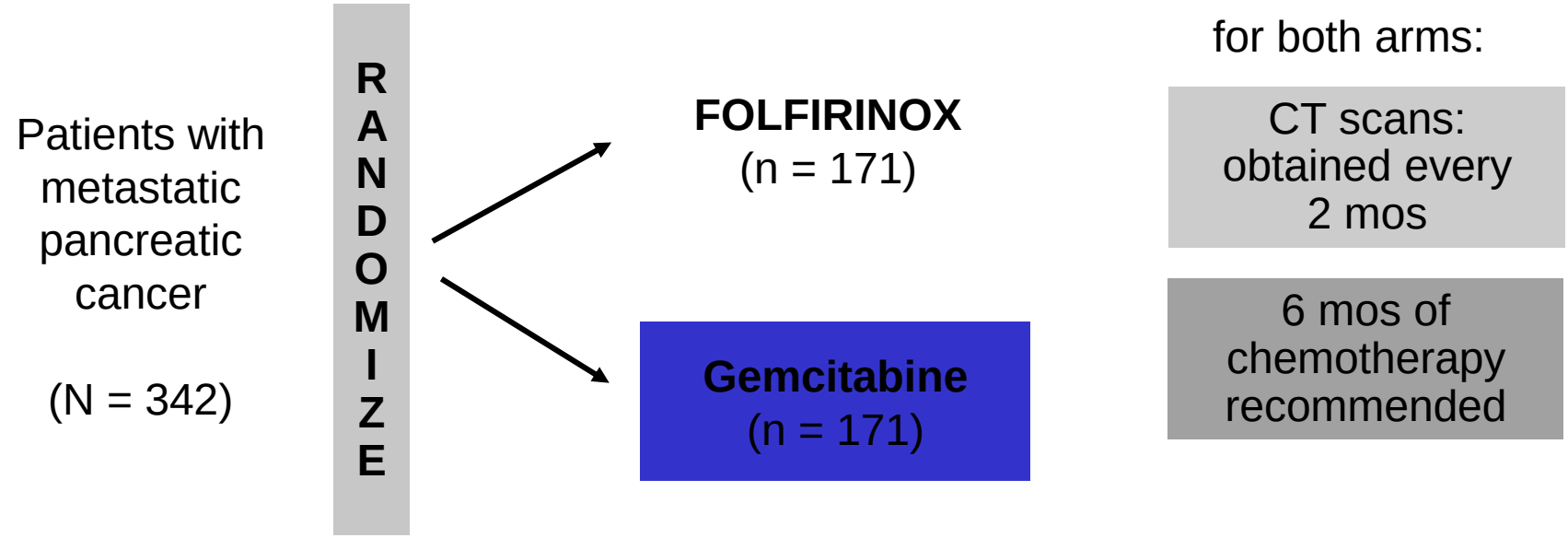
-Need for improved pre-clinical models

-Need for agents that target the microenvironment

Philip et al, JCO, 2009

New Chemotherapy Combinations:

PRODIGE 4/ACCORD 11 Trial

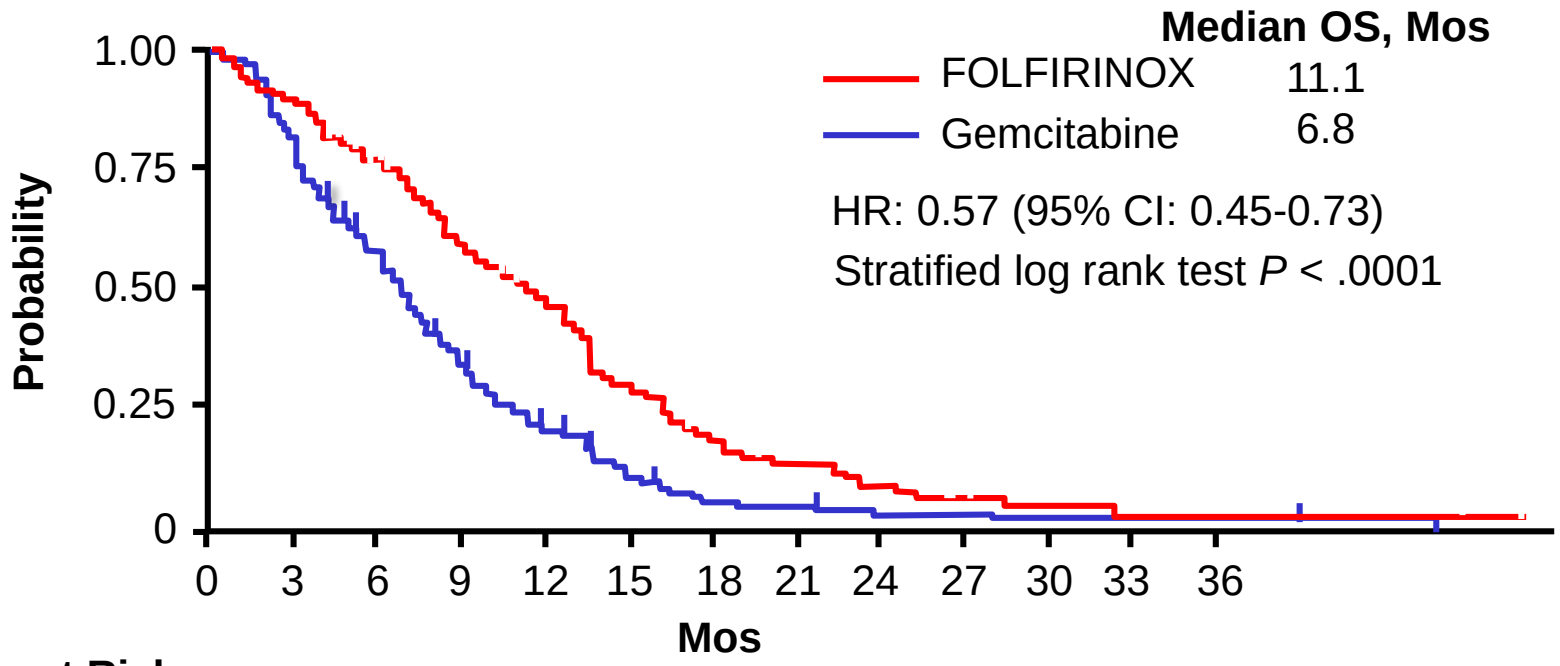


Stratified by

- 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



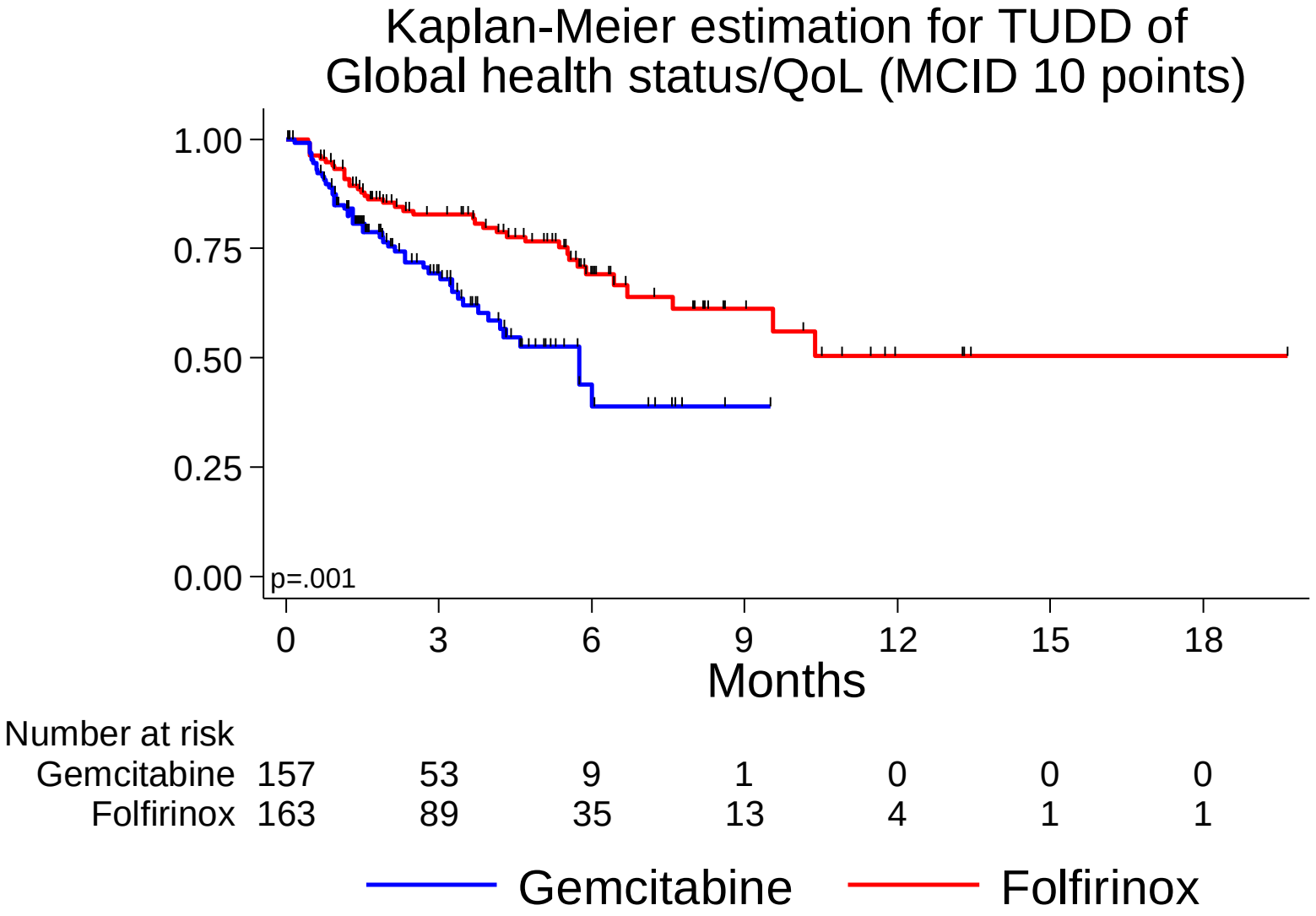
Patients at Risk, n

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

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

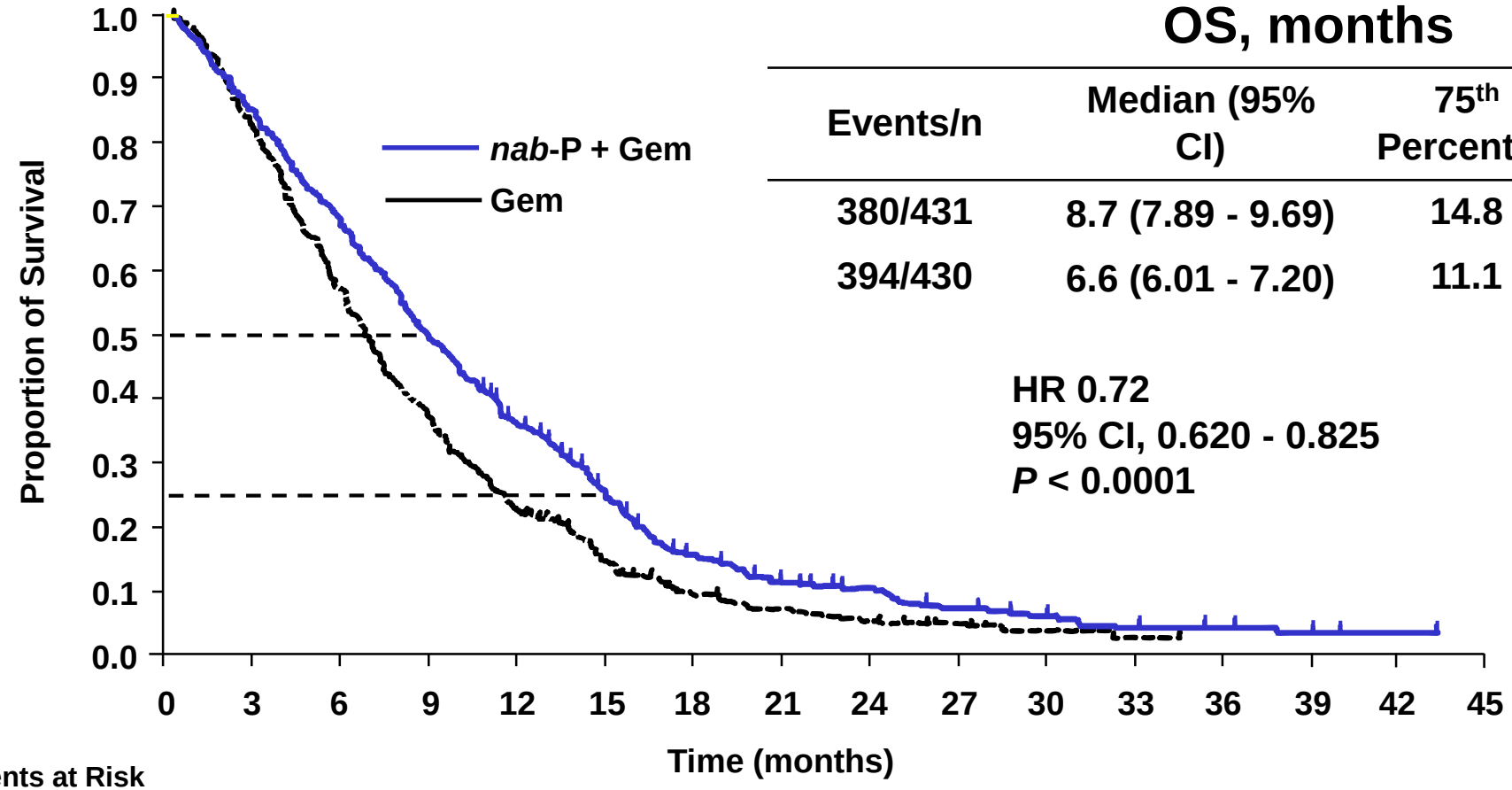
***nab*-Paclitaxel**
125 mg/m^2 IV qw 3/4 weeks
+
Gemcitabine
1000 mg/m^2 IV qw 3/4 weeks

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 α = 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

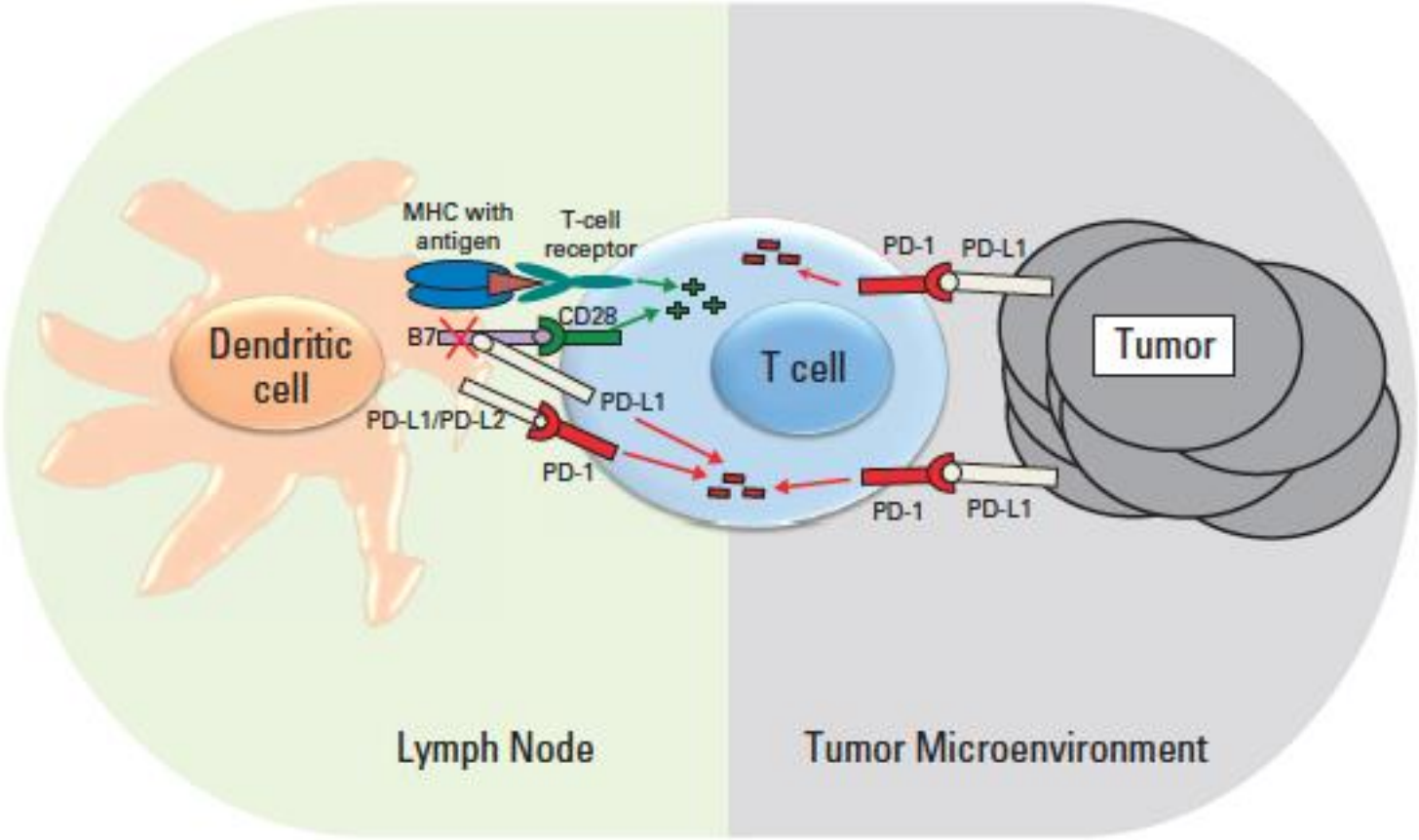
nab-P + Gem:	431	357	284	208	144	84	48	34	25	16	10	6	5	2	1	0
Gem:	430	340	231	149	90	47	27	19	14	8	4	2	0	0	0	0

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

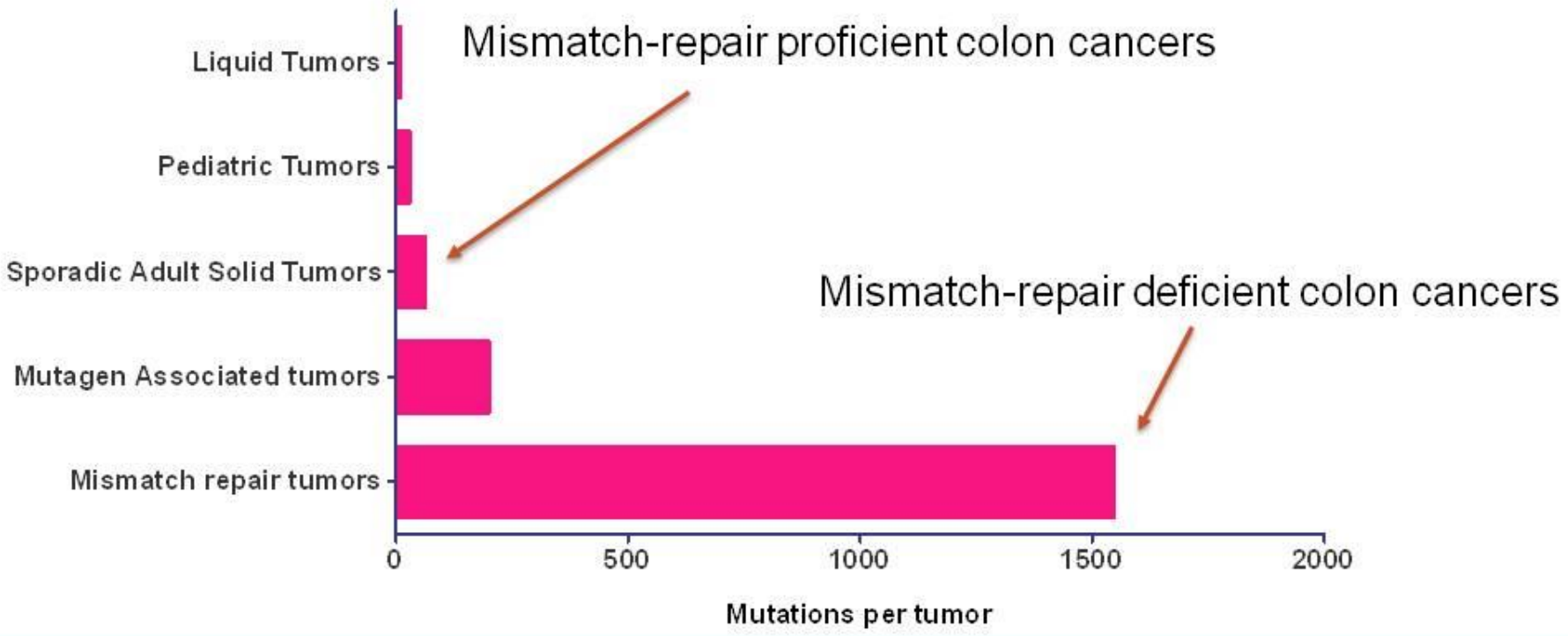


Postow et al, JCO, 2015

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

Mutations per tumor



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

PRESENTED AT 2016 Gastrointestinal Cancers Symposium

Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **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

Baseline Characteristics

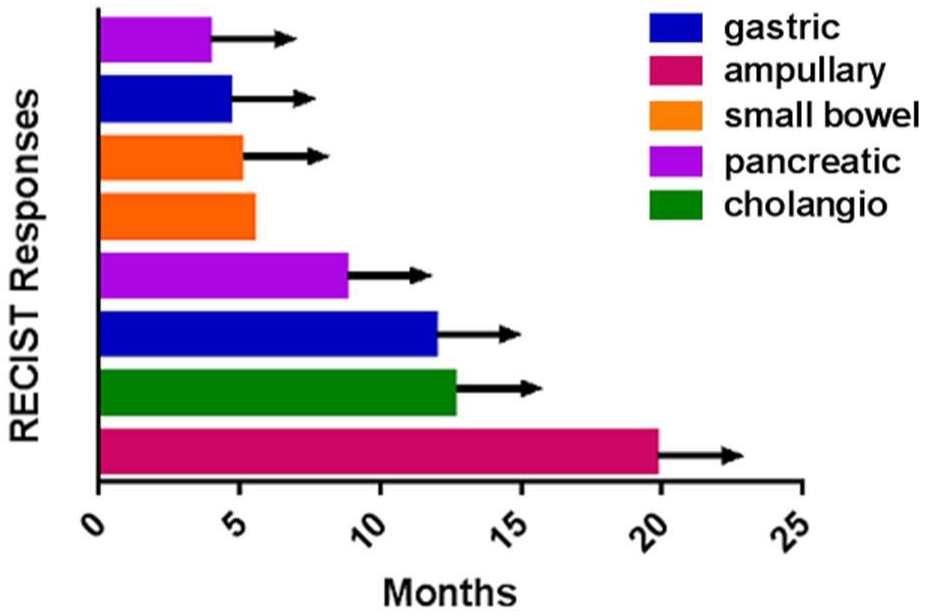
Characteristic	MMR-deficient GI non-CRC n=17 (%)
Median Age – years	60 (34-92)
Gender-female	5 (29)
ECOG PS-zero	5 (29)
Tumor Type	
Pancreas	4 (23)
Ampullary	4 (23)
Biliary	3 (18)
Small bowel	3 (18)
Gastric	3 (18)
Metastatic	17 (100)
Liver Mets	11 (65)
Median Prior Regimens	2

Objective Responses

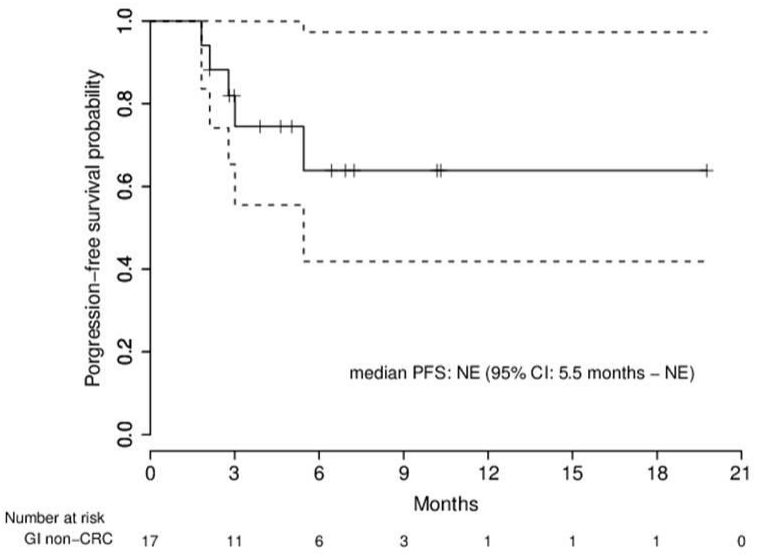
Type of Response-no (%)	MMR-deficient GI non-CRC n=17
Complete Response	4 (24)
Partial Response	4 (24)
Stable Disease (Week 12)	5 (29)
Progressive Disease	3 (18)
Not Evaluable[1]	1 (6)
Objective Response Rate (%)	47
95% CI	23-72
Disease Control Rate (%)	76
95% CI	50-93
Median Follow Up (mos)	5.3

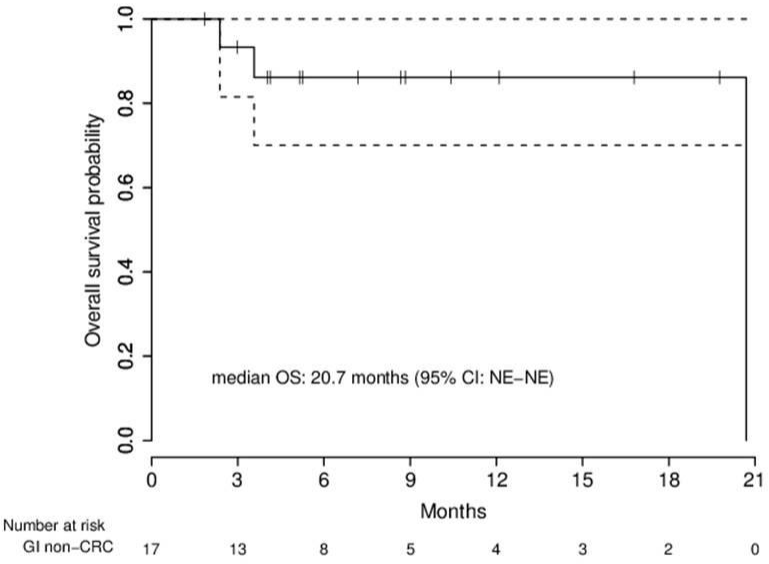
[1]Patients were considered not evaluable if they did not undergo a 12 week scan due to clinical progression.

Durability of Response



Progression-Free and Overall Survival



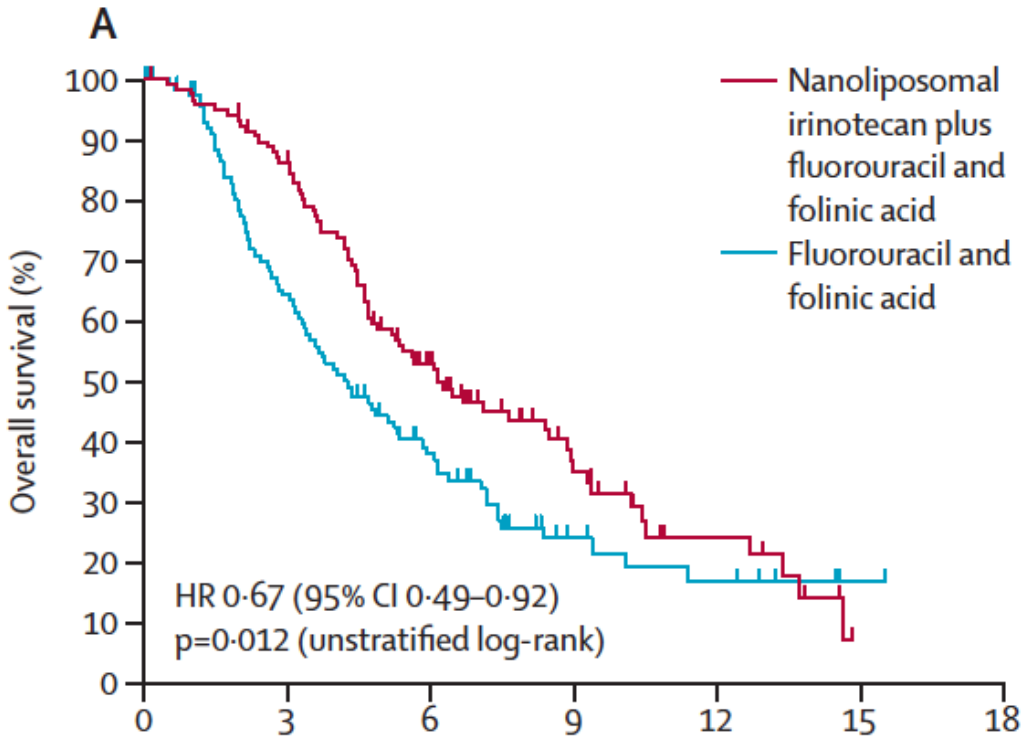


PFS = Non-estimable (NE)

OS = 21 Mos

Second Line Therapy: NAPOLI Trial

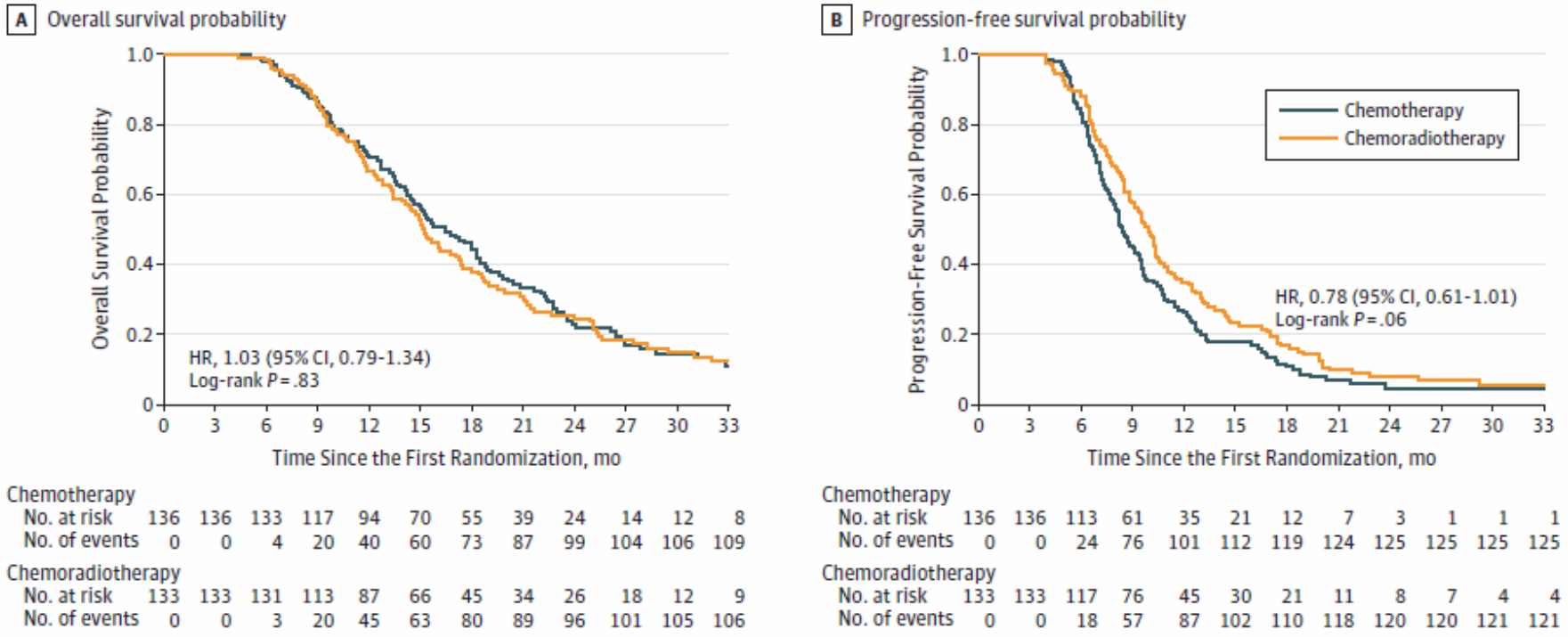
- Phase III trial of nanoliposomal irinotecan (MM-398/Onivide) alone vs. 5-fluorouracil alone vs. combination



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

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NCRI National Cancer Research Institute

UKCRC Registered Clinical Trials Units

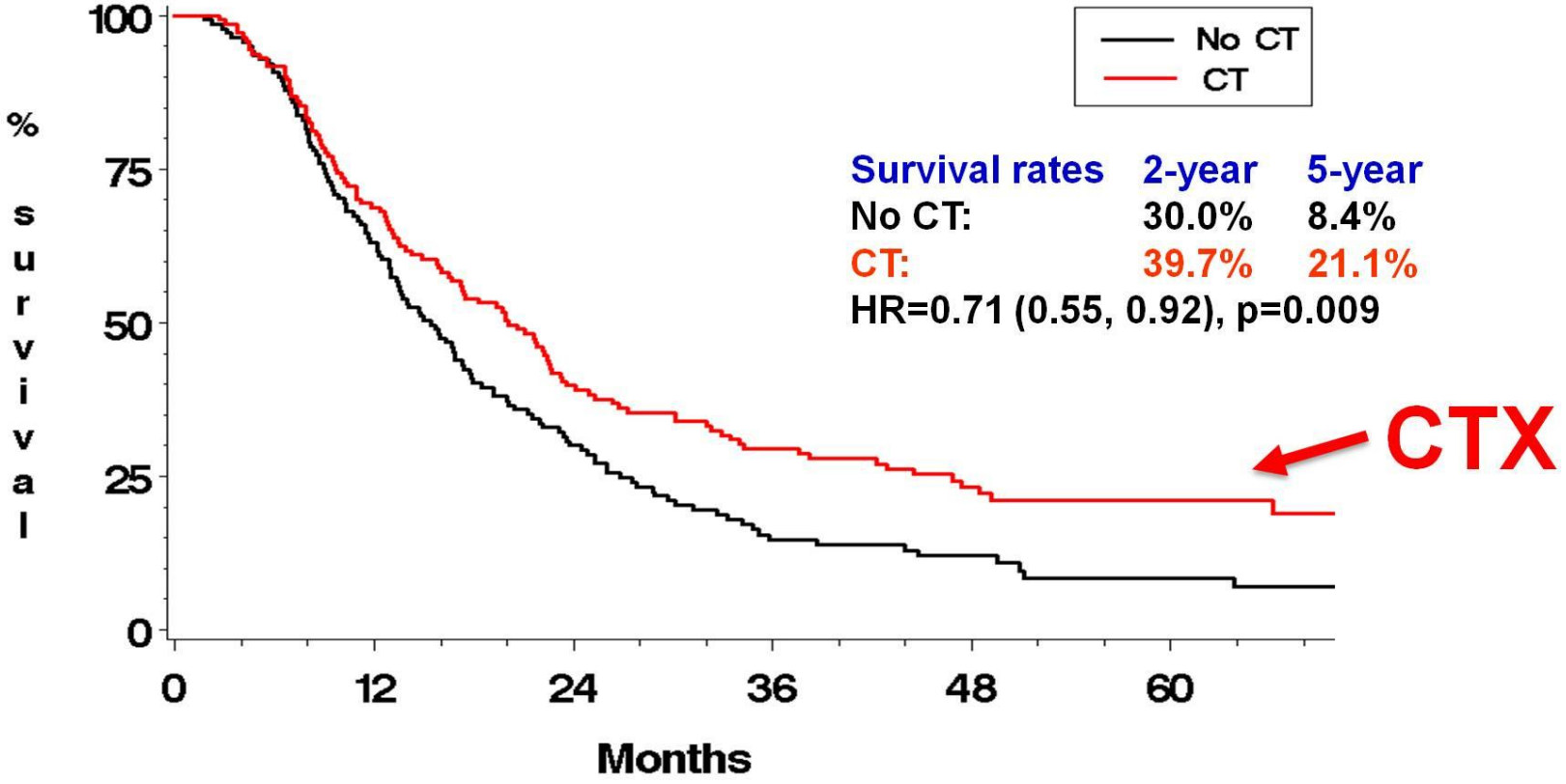
NWSTC

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

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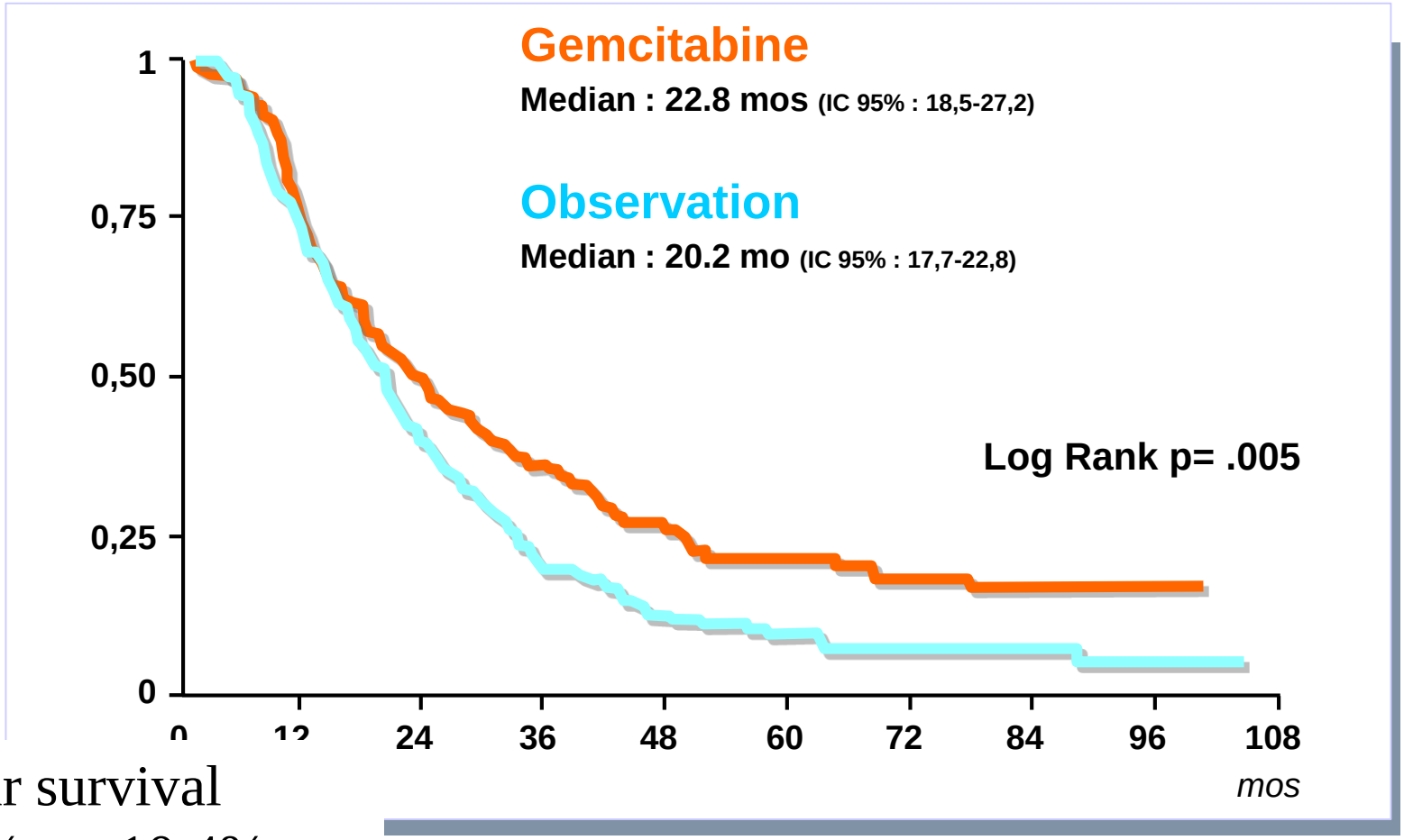
Presented By John Neoptolemos at 2016 ASCO Annual Meeting

CONKO-001: FINAL RESULTS

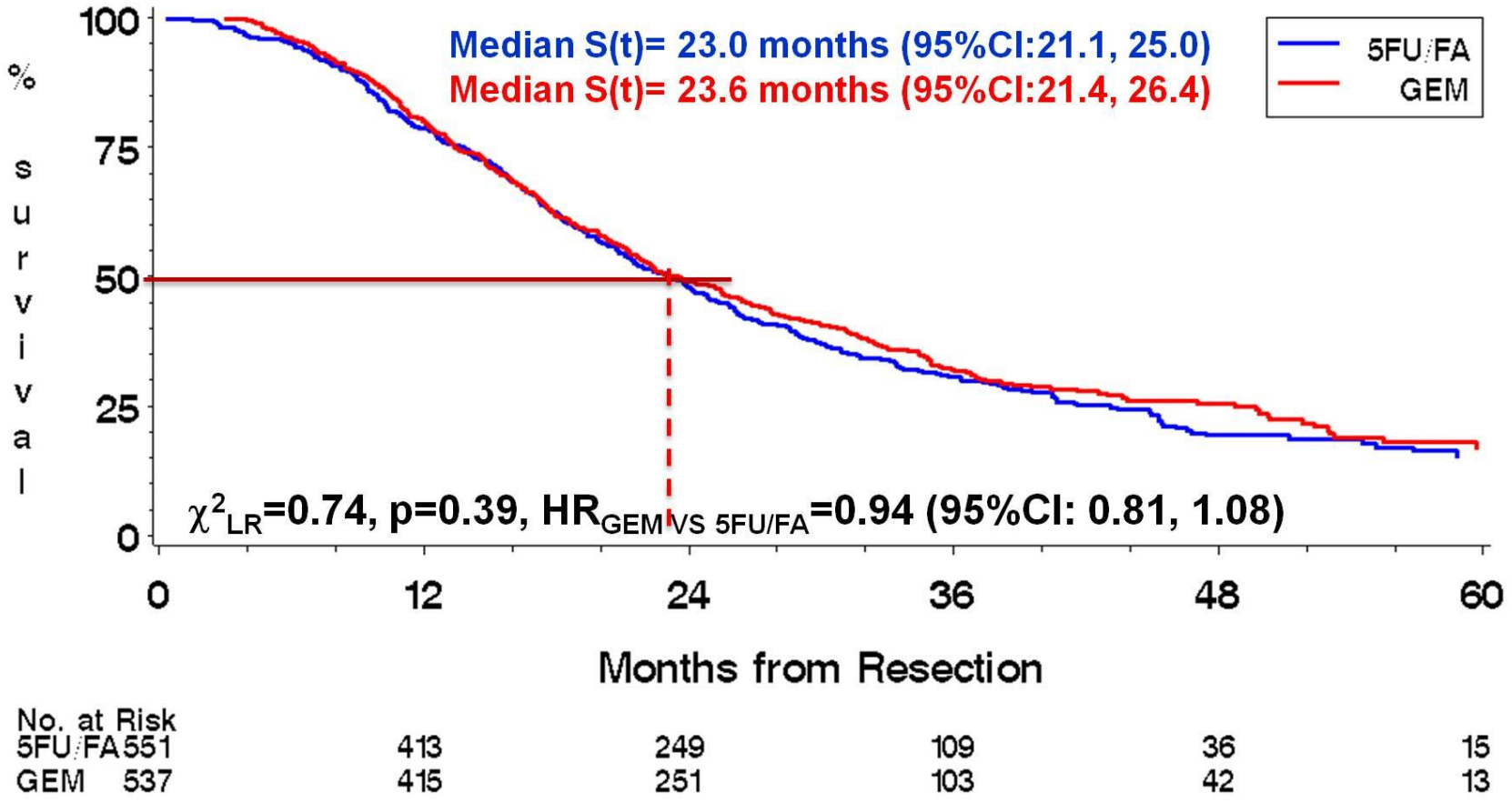
Overall Survival



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

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ESPAC - 4

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

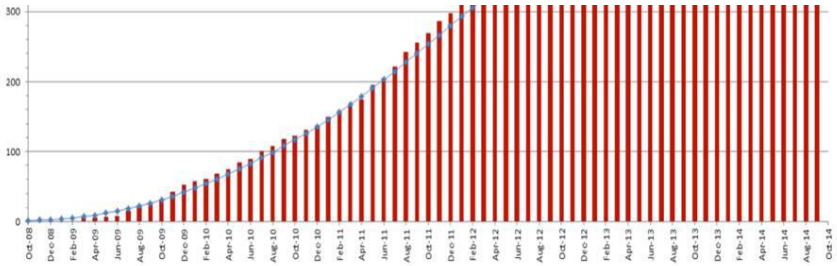
GEMCITABINE
1000mg/m² -Days 1,8 and
15 for 6 cycles
CAPECITABINE
1660mg/m²/day – 21/28d
i.e. 24 weeks

3-MONTHLY FOLLOW UP
FROM RANDOMISATION TO
DEATH

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

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 gro
- advanced setting demonstrated impr
- in PFS but not significant for OS (7
- months, p=0.08)



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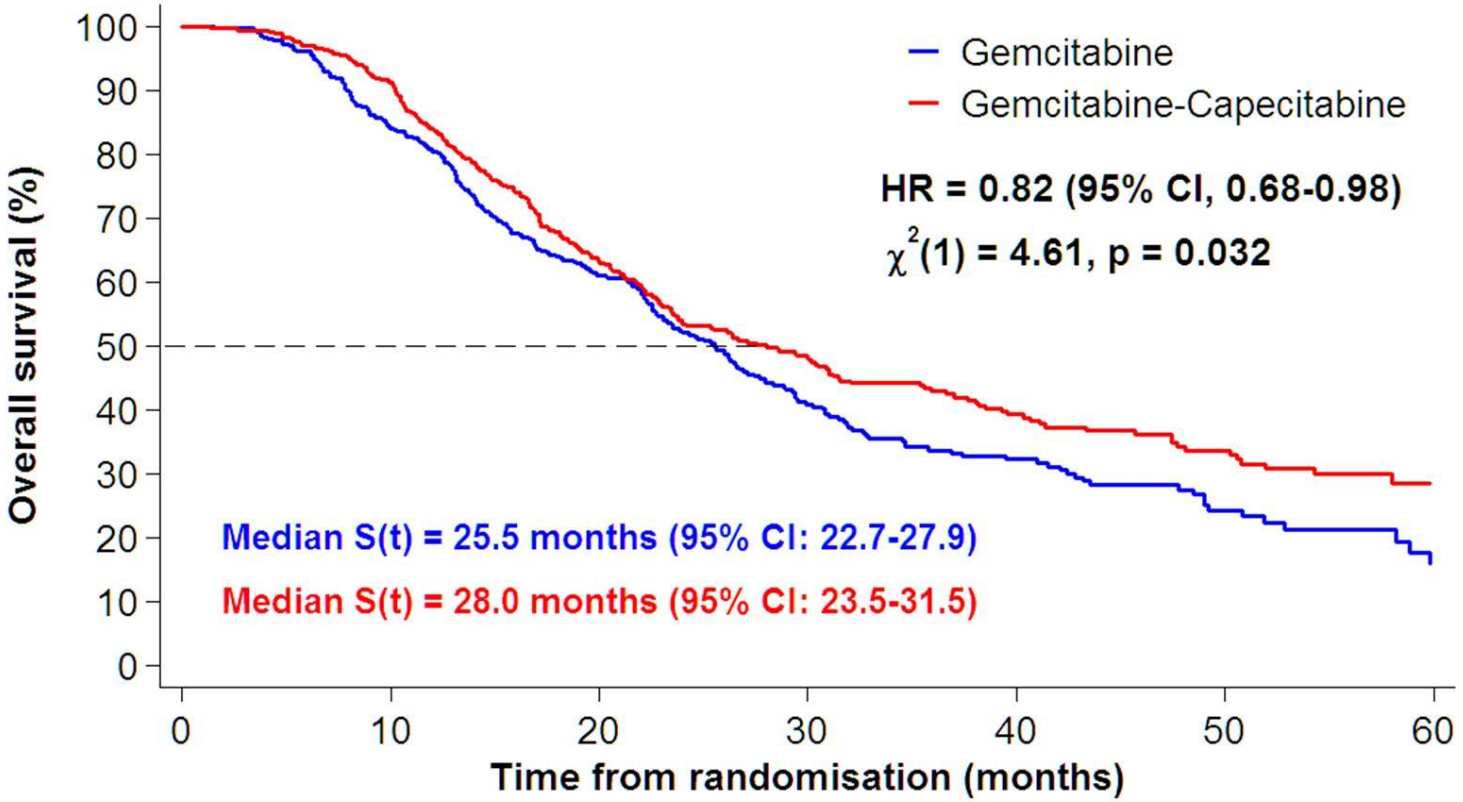
Survival by Treatment



No. at Risk

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

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ESPAC Trials: 5 Year Overall Survival

Trial	Treatment	No. of pts (N=2092)	5-Year OS (95% CI)	Stratified Log-Rank χ^2	p-value
ESPAC-1	5FU/FA	149	21 (14.6 – 28.5) %	7.03	0.030*
	No chemotherapy	143	8.0 (3.8 – 14.1) %		
	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

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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

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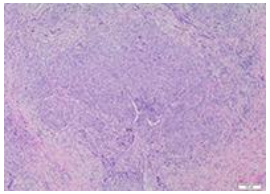
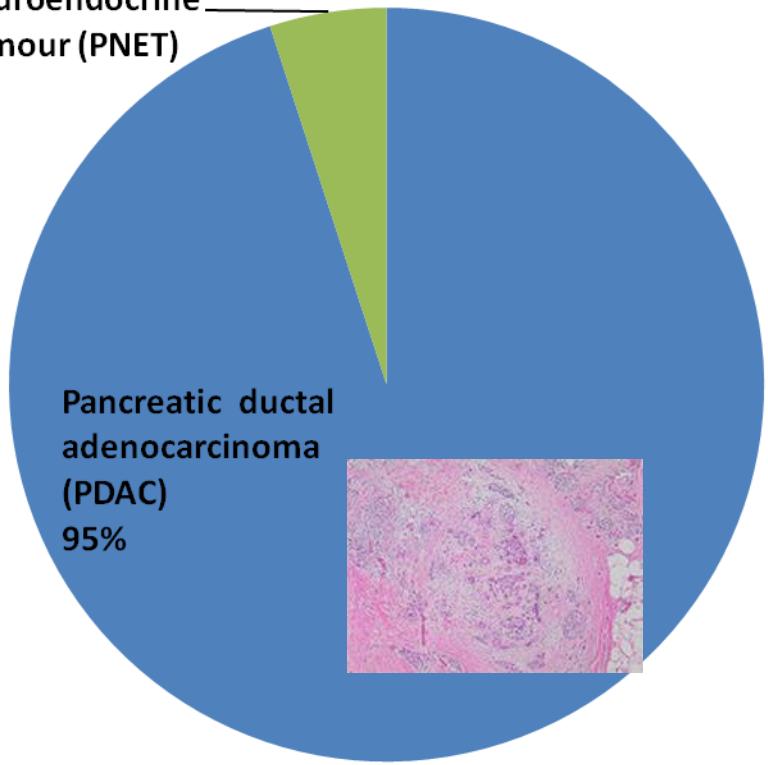
Pancreatic cancer subtypes (or lack thereof…)





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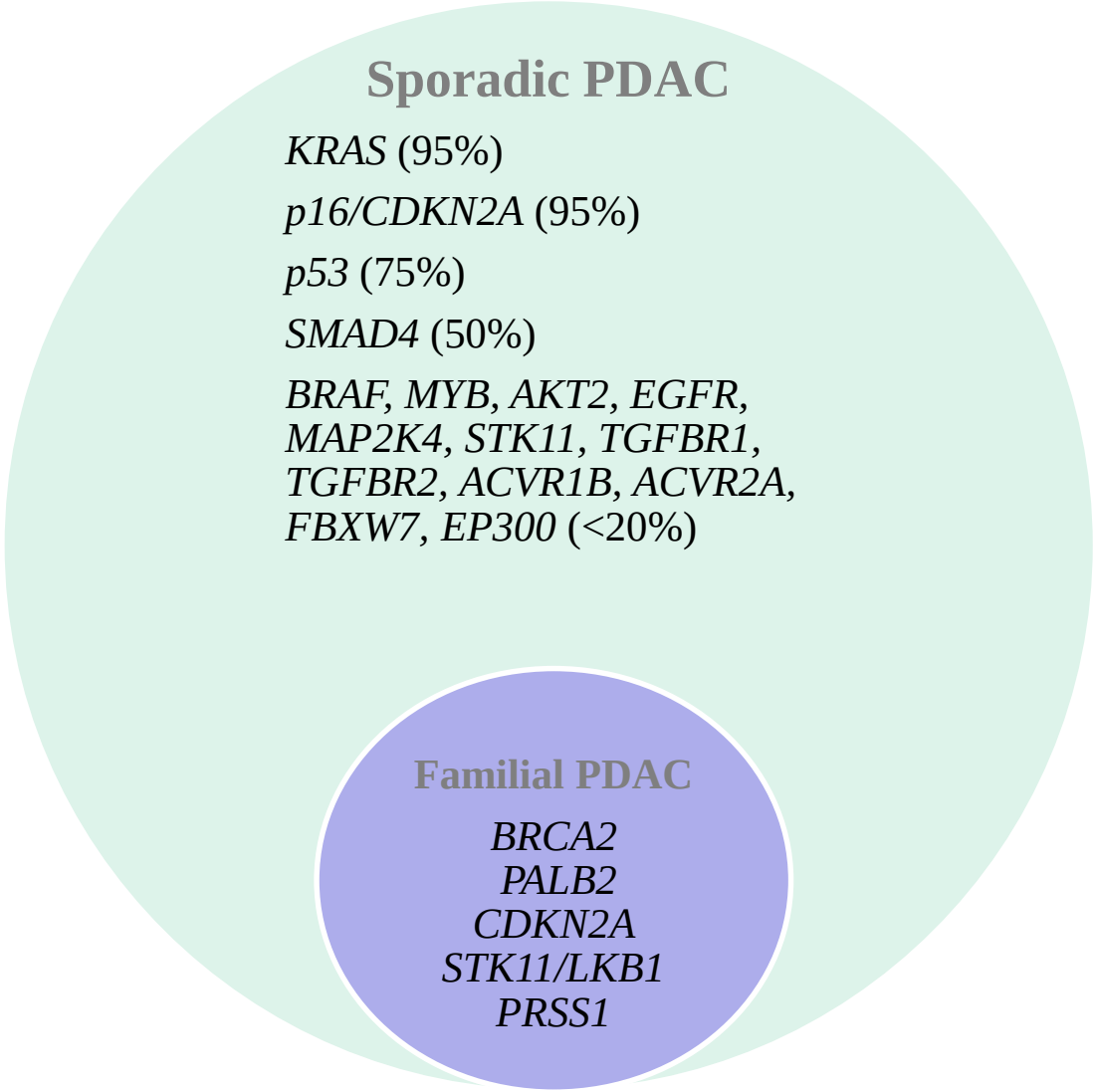
Inter-tumoral heterogeneity of pancreatic cancer: genetic mutations



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Critical focus areas in pancreatic cancer

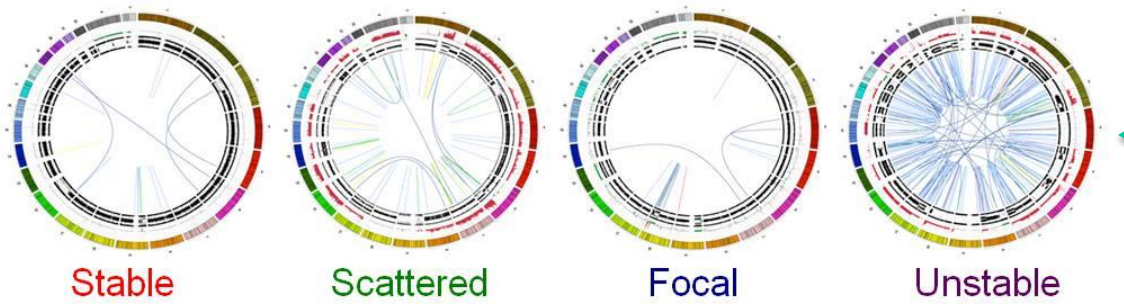
- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities

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**
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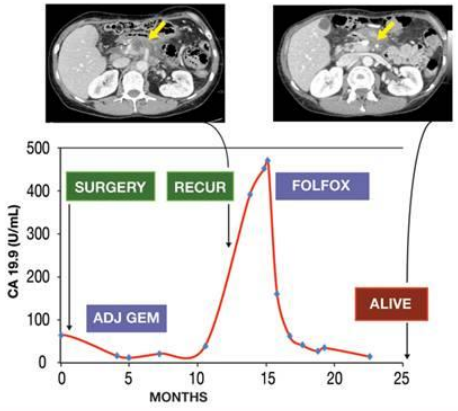
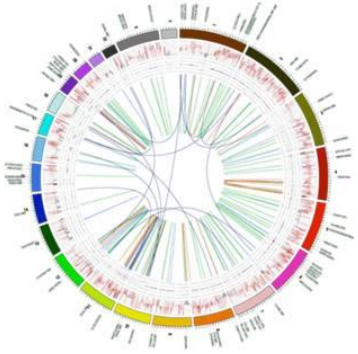
Unstables as Exceptional Responders



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



Somatic BRCA2 FS +LOH
Unstable genome

Patients with "unstable" PDAC subtype responded well to therapy

Waddell et al, Nature, 2015

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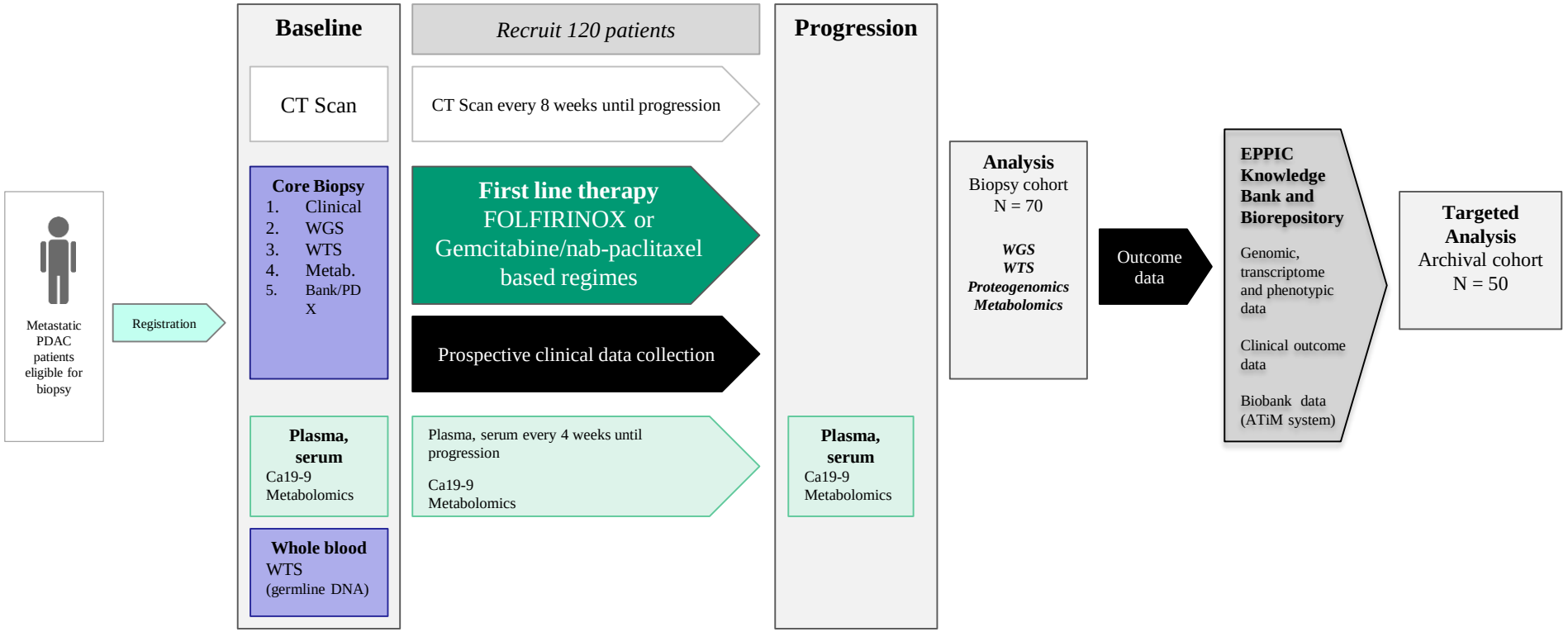
PanGen study schema

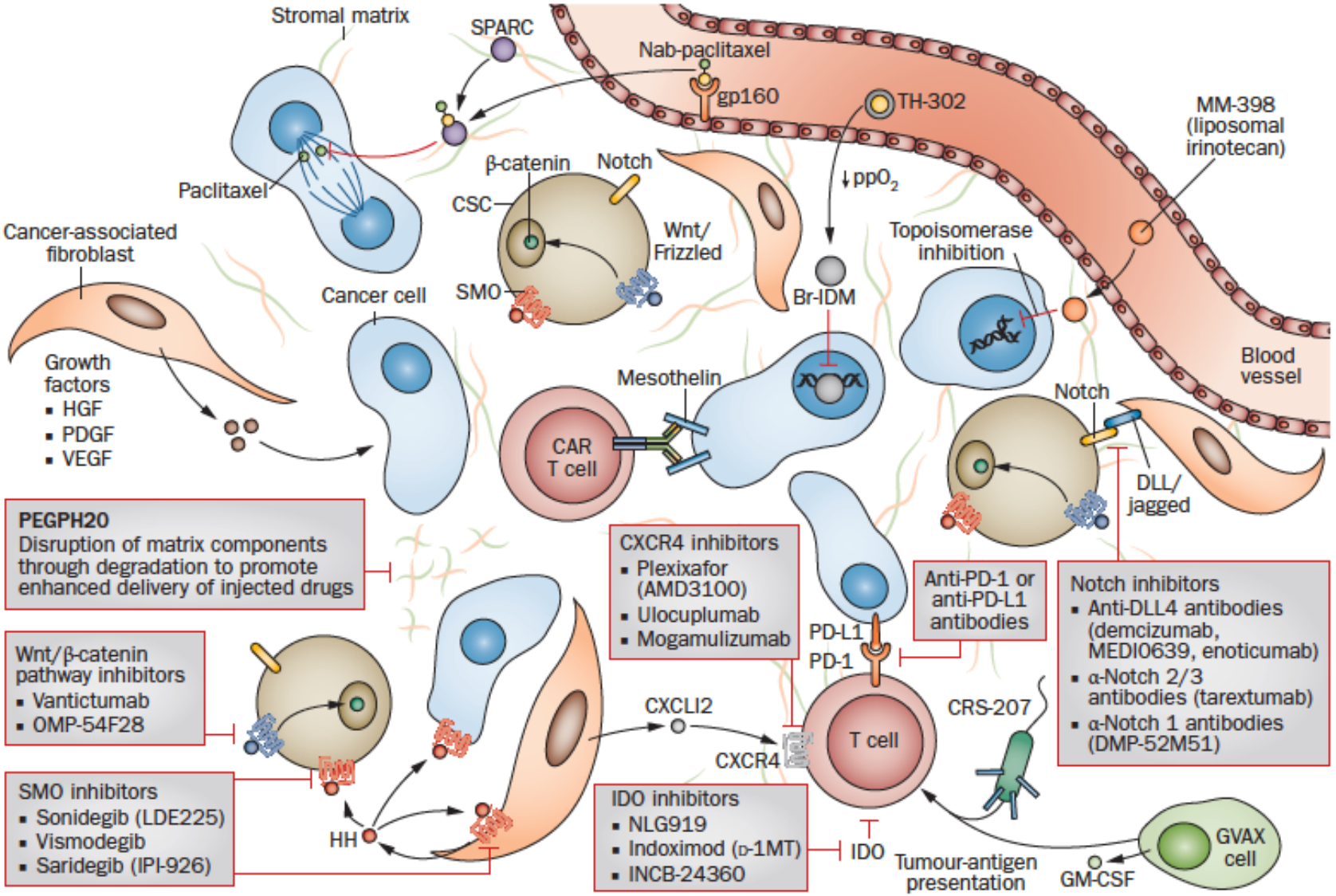


Critical focus areas in pancreatic cancer

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

PANCREAS CENTRE BC

New Targets

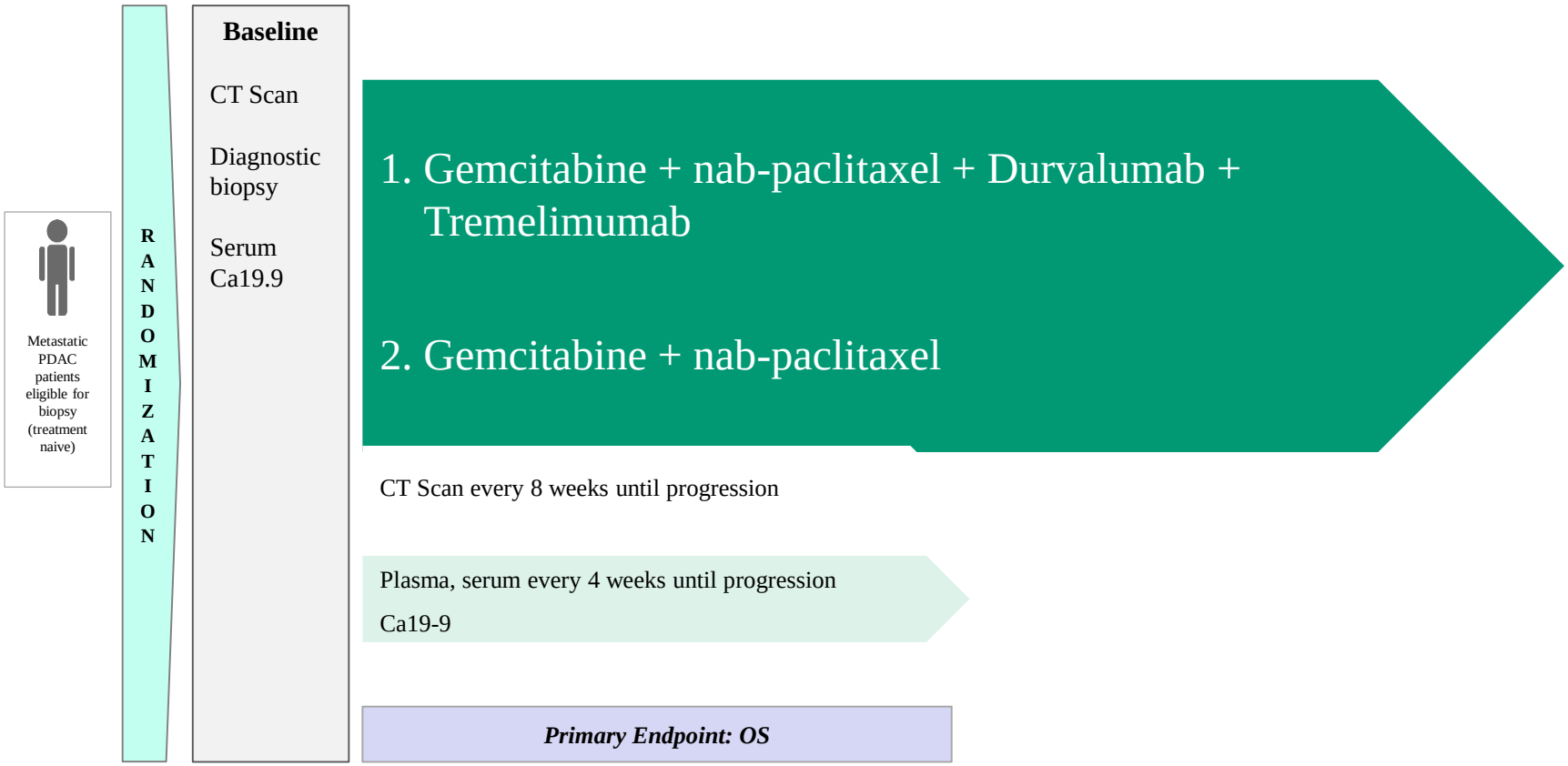


Garrido-Laguno and Hidalgo, Nature Review Clinical Oncology, 2015

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!

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Pancreas Centre BC

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