Toxicities of Chemotherapy: a focus on pancreatic cancer

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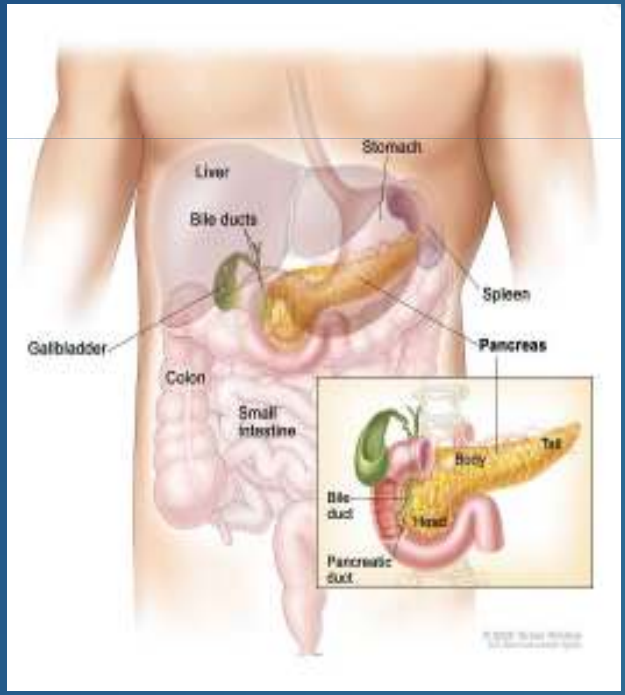
May 3 & 10, 2014



http://cancerlive.net/wp-content/uploads/2011/06/causes-of-pancreatic-cancer.jpg

Presenter Disclosure

- **Faculty:** Pat Trozzo

Relationships with commercial interests:

Grants/Research Support: Unrestricted educational grant for the pharmacy program from Sanofi Canada and Hoffmann-LaRoche

Speakers Bureau/Honoraria: Speaker's honorarium from Janssen

Consulting Fees:

Other:

- **Faculty:** Curtis Kellett

Relationships with commercial interests:

- **Advisory board with Sanofi-Aventis 2012**
- **Honoraria received for Amgen Presentations given**

Mitigating Potential Bias

Pat Trozzo

- Unrestricted educational grant was for the entire pharmacy department. Decisions on how to allocate funds are made by a committee.
- Speaker's slides were peer reviewed prior to my presentation to colleagues.

Curtis Kellett

- Interaction with Industry has been in the setting of Colorectal Cancer

Learning Objectives

At the end of this session, participants will be able to:

- Identify the expected side effects of the standard systemic therapy used to treat pancreatic cancer
- Outline the management of many of these side effects
- Identify appropriate clinical monitoring parameters for patients receiving these regimens

Patient Case

- R.F. is a 46 y.o. male who initially presented with severe epigastric pain in April 2012

  Began to notice other symptoms:
  - diarrhea with cramps approximately 4 - 5 episodes per day
  - steatorrhea
  - intermittent mid to low back pain
  - began losing a significant amount of weight
  - episodes of nausea, but denies vomiting

Patient Case (continued)

Concerned about his weight loss and other symptoms, he went to see his doctor

- had an MRI performed on 27 June 2012
  - septated cystic lesion in the head of the pancreas
  - 4 cm x 7 cm in diameter
- Numerous other investigations over next few months, including:
  - ERCP -> biliary stent placement
  - Endoscopic Ultrasound

Patient Case (continued)

Biopsy from EUS revealed adenocarcinoma cells

R.F. was determined to be a candidate for surgical resection

- performed on 7 September (Whipple procedure)

Patient Case (continued)

- Tumor was 3.6 x 3.1 x 5.1 cm
- pathology showed invasive adenocarcinoma mixed pattern from intraductal papillary mucinous neoplasm (Stage T3 N1, 9/12 lymph nodes positive)

Initial medical oncology visit (October 2012)

- doing very well and has no major concerns or complaints
- has lost approx 70 lbs since onset of symptoms in April (current weight 80.7 kg)

- ECOG is 0

What are we going to do for R.F.?

Adjuvant therapy

- CONKO-001 was a phase III trial that randomized resected patients to adjuvant chemotherapy with gemcitabine versus observation
- Patients who received gemcitabine had significantly better median disease-free survival (13.4 months) versus those on observation (6.9 months)
- Overall survival was also statistically significantly improved in the gemcitabine arm versus observation (22.8 months vs. 20.2 months, p=0.005)

Ref: Neuhaus et al. J Clin Oncol 2008;26:LBA4504

Patient Case (continued)

- R.F. was initiated on adjuvant Gemcitabine with a plan for 6 months of treatment

Schedule:

  - Gemcitabine1000 mg/m2 IV Days 1,8, 15 q 28 days x 6 cycles

- R.F. tolerates the first 4 cycles very well

Patient Case (continued)

CT scans done at end of January 2013

- ordered by surgeon
- indicate the presence of numerous bilateral pulmonary nodules, measuring somewhere between 3 and 4 mm

Unfortunately, a wedge biopsy confirmed metastatic pancreatic adenocarcinoma

What can we offer him now?

Chemotherapy for metastatic pancreatic cancer: slow progress

- **1996-7: Gemcitabine is FDA approved**
- 1996-2005: Many drugs tested
  - no drug or drug combo is better than Gem
- 2005: Erlotinib + Gem is better than Gem.
  - **Erlotinib is FDA approved for pancreatic cancer**
- 2006: Oxaliplatin + Gem is not better than Gem
- 2006: Bevacizumab + Gem is not better than Gem
- 2007: Cetuximab + Gem is not better than Gem
- 2008: Bev + Gem-Erlotinib is not better than Gem-Erlotinib
- 2009: Axitinib + Gem is not better than Gem
- 2009: Capecitabine + Gem is better than Gem?

Gemcitabine Registration Trial

	Gemcitabine 1,000 mg/m^2 qwx7 →1 w rest, then qwx3 every 4w N=63	**5-FU** 600 mg/m^2 qw N=63	**p-value**
Clinical benefit response* (primary endpoint)	23.8%	4.8%	0.0022
Survival Median survival (months)	5.65	4.41	0.0025
1-year survival	18%	2%	-
Time to progression (weeks)	9	4	0.0002
Partial response**	5.4%	0%	NS
Stable disease**	39%	19%	NS

* Composite of measurements of pain (analgesic consumption and pain intensity), KPS and weight
**N=56 and N=57 with measurable disease at study entry for gemcitabine and 5-FU respectively
NS: not significant

Burris et al. *J Clin Oncol*. 1997;15(6):2403-13.

Would you offer him Gemcitabine alone?

Are there any newer / better options?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*

Conroy et al. *NEJM*. 2011;364:1817-25.

ACCORD 11: Gemcitabine vs FOLFIRINOX

Stratification :
- center
- PS: 0 vs 1
- head versus other location of the primary

Patients with metastatic pancreatic cancer
n=342

R

FOLFIRINOX
Oxaliplatin 85mg/m^2
Folinic acid 400mg/m^2
Irinotecan 180 mg/m^2
5-FU 400mg/m^2 bolus and 2.4g/m^2 on 46-h infusion
(chemotherapy regimen administered each 2 weeks)

Gemcitabine
1000 mg/m^2 over 30 minutes
given weekly for 7 out of 8 weeks
and then weekly for 3 out of 4 weeks

Primary : overall survival
Secondary:
- objective response rate (RECIST)
- toxicity (NCI-CTC version 3.0 grading)
- progression-free survival (PFS)
- quality of life (EORTC QLQ-C30 v 3.0)

Conroy et al. *NEJM*. 2011;364:1817-25.

ACCORD 11: Inclusion and Exclusion Criteria

Inclusion criteria

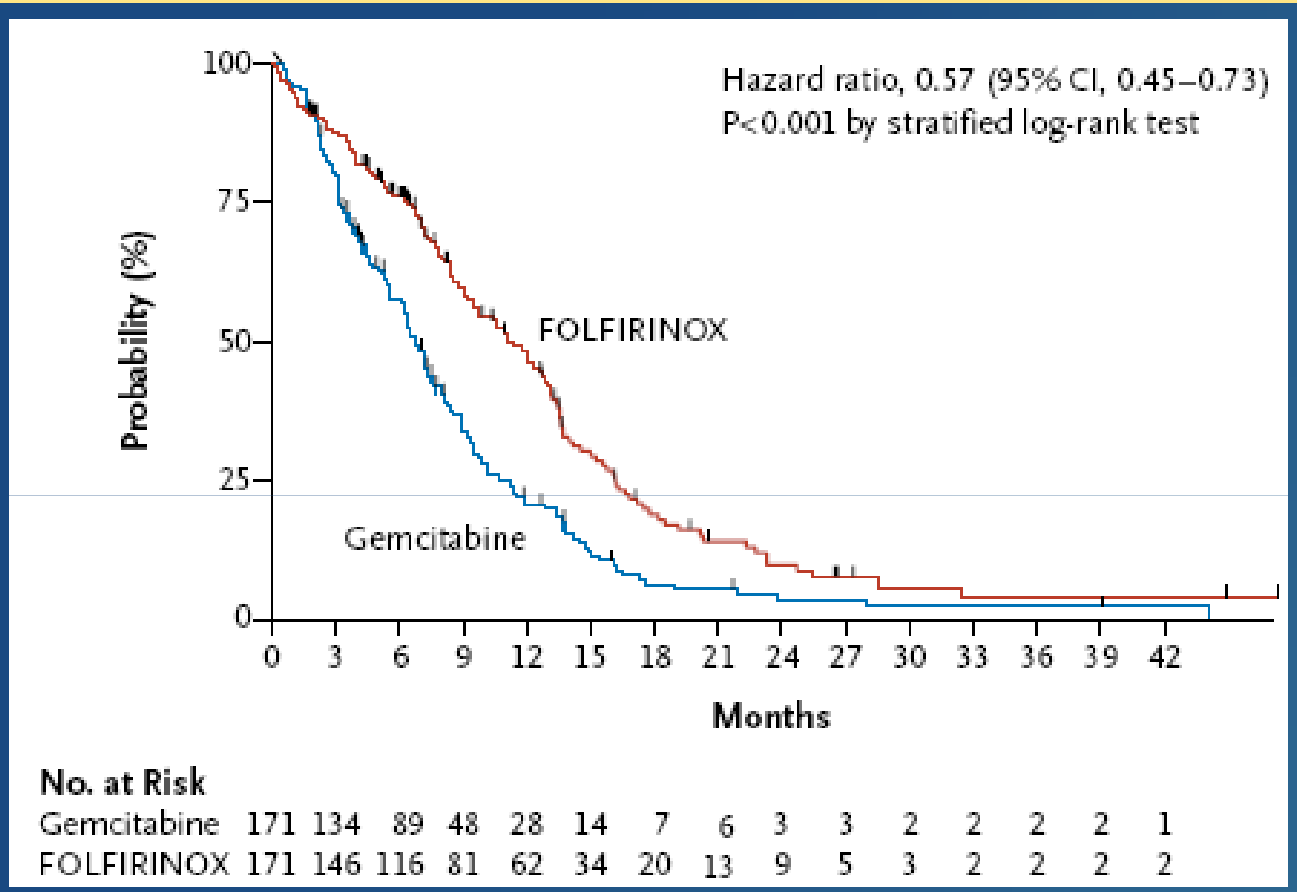
- Histologically/cytologically confirmed pancreatic adenocarcinoma
- ECOG performance status of 0 or 1
- Measurable metastases
- No prior cytotoxic chemotherapy
- No prior abdominal radiotherapy
- Age 18-75 years
- Adequate hematopoietic, hepatic and renal function
- Bilirubin ≤1.5 UNL
- No unstable angina or myocardial infarction within 12 months before entry
- Granulocyte count ≥1500 per cubic millimeter
- Platelet count ≥ 100 000 per cubic millimeter
- Written informed consent

Exclusion criteria

- Non ductal pancreatic cancer (endocrine, acinar cell…)
- Adenocarcinoma of the ampulla of Vater
- Unresectable locally advanced pancreatic cancer without distant metastases (stage III)
- Central Nervous System metastases
- Chronic diarrhea
- Clinally significant history of cardiac disease
- Other previous or concomitant malignant disease

Conroy et al. *NEJM*. 2011;364:1817-25.

ACCORD 11: Overall Survival



- Patients in the FOLFIRINOX arm achieved significantly longer overall survival compared to patients in the gemcitabine arm (11.1 months vs. 6.8 months, respectively, p<0.001)

Conroy et al. *NEJM, 2011*:364;1817-1825

ACCORD 11: Overall Survival

	FOLFIRINOX N=171	Gemcitabine N=171	p	HR
Median Survival [CI 95%]	**11.1 mo.** [9.0 - 13.1]	**6.8 mo.** [5.5 - 7.6]	**<0.001**	**0.57**
6-Month Survival	75.9%	57.6%		
12-Month Survival	48.4%	20.6%		
18-Month Survival	18.6%	6.0%		

Median follow-up: 26.6 months [95% CI: 20.5 – 44.9]

Conroy *et al. NEJM,* 2011:364;1817-1825

QoL of PRODIGE 4/ ACCORD 11

- Quality of life was measured using the EORTC-QLQ-C30 instrument at baseline and then every two weeks.
- At baseline, no significant differences were observed between QoL completers in the 2 groups.
- Quality of life improved in both groups as assessed by the EORTC-QLQ-C30 instrument.
- No significant differences in change from baseline were noted between the groups at all times for all the domains of the EORTC QLQ –C30, except for diarrhea that was higher in the FOLFIRINOX group during the first 8 cycles (first 2 months of treatment).

Conroy et al. NEJM. 2011;364:1817-25.;
Gourgou Bourgade et al. J Clin Oncol. 2013;31(1):23-29;
Ko AH, J Clin Oncol; 2013:31(1):3-4
Conroy et al. Curr Oncol Rep . Jan 23. [Epub ahead of print]

Common or Clinically Significant Adverse Events

- Treatment-related grade 3 or 4 adverse events occurring in more than 5% of patients receiving FOLFIRINOX in the study by Conroy et al

Hematologic

- Neutropenia (45.7%)
- Febrile Neutropenia (5.4%)
- Thrombocytopenia (9.1%)
- Anemia (7.8%)

Common or Clinically Significant Adverse Events (Continued)

Non-Hematologic

- Fatigue (23.6%)
- Vomiting (14.5%)
- Diarrhea (12.7%)
- Sensory Neuropathy (9.0%)
- Elevated level of alanine aminotransferase (7.3%)
- Thromboemobolism (6.6%)

FOLFIRINOX Treatment

- Median number of cycles
  - 10 (1 - 47) in FOLFIRINOX group vs. 6 (1 - 26) in the gemcitabine group ($p<0.001$)
- Of note, supportive filgrastim treatment was administered as secondary prophylaxis in 42.5% of patients who received FOLFIRINOX
- Median relative dose intensities
  - Fluorouracil 82%
  - Irinotecan 81%
  - Oxaliplatin 78%
  - Gemcitabine 100%

Conroy *et al. NEJM,* 2011:364;1817-1825

When should dose adjustments be made or considered for FOLFIRINOX?

See CCMB Systemic Therapy Summary

- Neuropathy - Calcium and Magnesium?
- Febrile Neutropenia
- Myelosuppression
  - Thrombocytopenia
  - Neutropenia
- Diarrhea
- Stomatitis

Clinical Monitoring and Follow-up

- Baseline CBC and differential, Serum Creatinine, LFTs (Bilirubin, AST, Alkaline Phosphatase)
- Appropriate imaging study and tumour markers
- Patients to be seen by physician at every cycle (every 2 weeks)
- **At the beginning of each cycle**: CBC and differential, BUN, Serum Creatinine, LFT's (Bilirubin, AST, ALT, GGT, LDH, Alkaline Phosphatase), Electrolytes
- Quantitative evaluation of disease response status every eight weeks (4 cycles)
- Discontinue therapy if any progression of disease

Take Home Message

- FOLFIRINOX regimen should be reserved for those who have a very good performance status

AND

- It is a toxic regimen and close follow-up is required

The NEW ENGLAND JOURNAL of MEDICINE

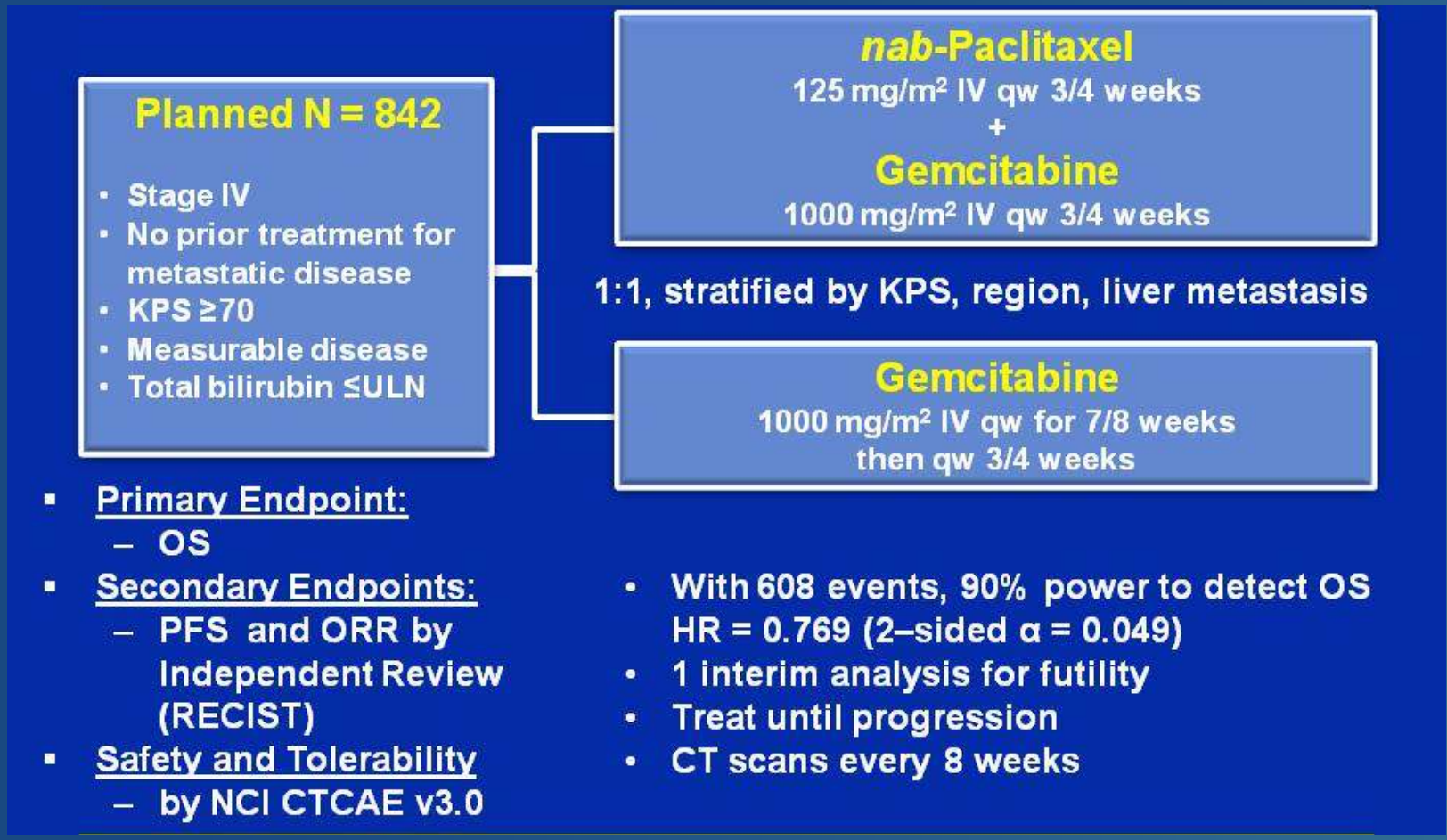
ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

MPACT: Study design



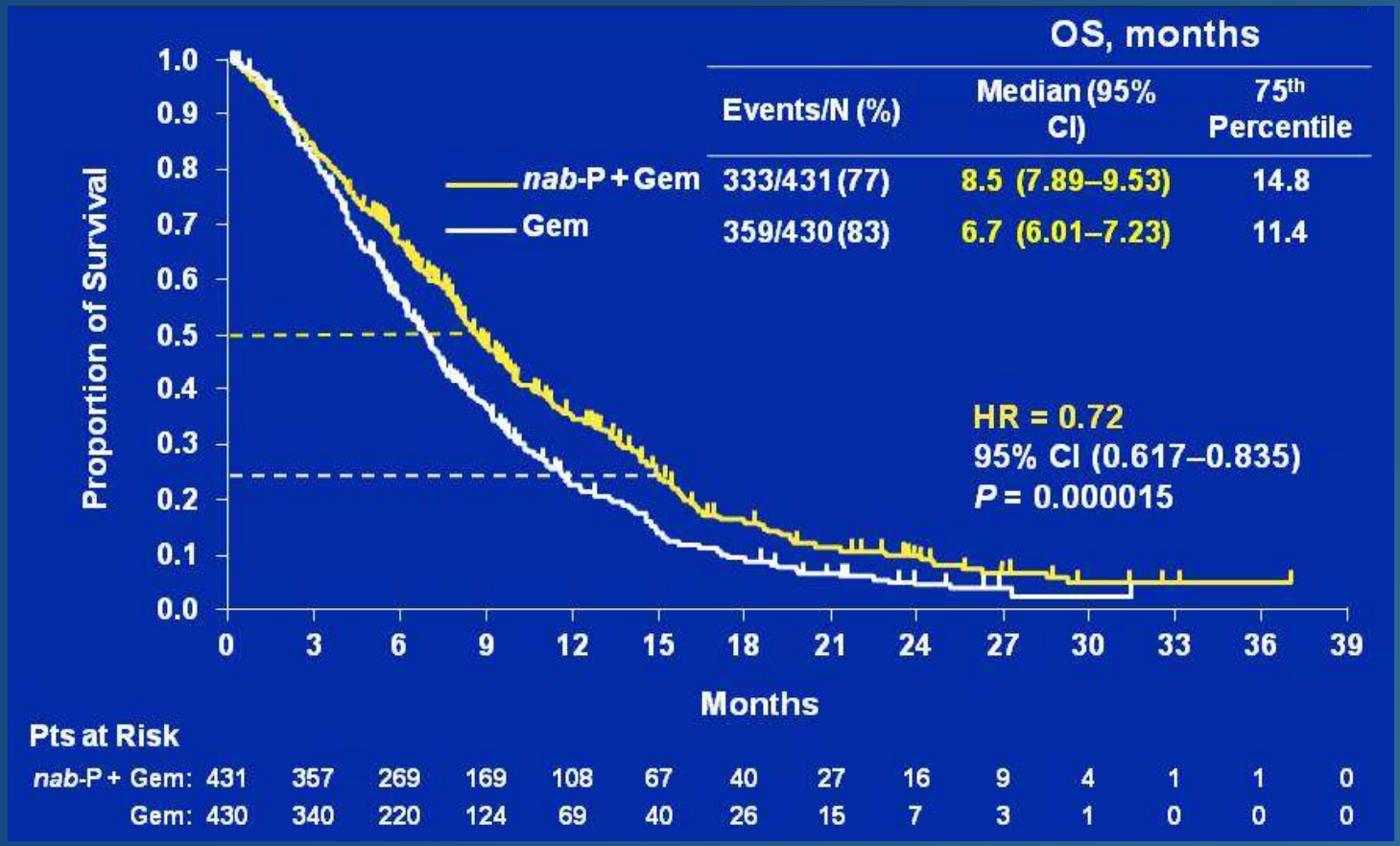
Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

MPACT: Baseline characteristics

		Nab-P + Gem (n=431)	Gem (N=430)
	Age (median, range)	62 (27-86)	63 (32-88)
	Age (% ≥65yr)	41	44
	Sex (% male)	57	60
Karnofsky performance score (%)	100 (ECOG 0)	16	16
	90 (ECOG 1)	42	46
	80 (ECOG 1)	35	30
	70 (ECOG 2)	7	8
	60 (ECOG 2)	<1	0
Tumor location (%)	Head	44	42
	Body	31	32
	Tail	24	26
Site of metastatic disease (%)	Liver	85	84
	Lung	35	43
	Peritoneum	4	2
Number of metastatic sites (%)	1	8	5
	2	47	48
	3	32	33
	>3	14	15

Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

MPACT: Overall survival



Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

MPACT: Toxicities

Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

* NA denotes not applicable, and NR not reached.
† Assessment of the event was made on the basis of laboratory values.
‡ Assessment of the event was made on the basis of investigator assessment of treatment-related adverse events.
§ Peripheral neuropathy was reported on the basis of groupings of preferred terms defined by standardized queries in the *Medical Dictionary for Regulatory Activities*.

Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

Is this treatment available?

- Currently under review nationally by pCODR
- Requires approval through CCMB P&T Committee
- No regimen reference order is currently available
- No information available through BC Cancer Agency or Ontario Cancer Care

Has been approved for use in a handful of patients in Manitoba

Some example dose modifications available online through Micromedex (approved in US through FDA)

When should dose adjustments be made or considered for Gem + Abraxane?

- Cutaneous Toxicity
- Febrile Neutropenia
- Myelosuppression
  - Thrombocytopenia
  - Neutropenia
- Mucositis
- Diarrhea
- Stomatitis
- Neuropathy
- Pneumonitis

What should we offer to R.F.?

Patient Case (continued)

- Due to patient's age and functional status, offered treatment with full dose FOLFIRINOX (April 2013)
- Tolerated quite well
  - Initial problems with nausea
    - managed with Dexamethasone, Ondansetron, and Metoclopramide
  - Some fatigue during 1st week of Cycle, but continued to golf 2 - 3x per week during 2nd week

Patient Case (continued)

August 2013

- treatment delayed x 2 due to Neutropenia
- Chemotherapy agents dose reduced by 10%

September 2013

- Pain is under fairly good control with current medications
  - using medicinal marijuana with good effect
- Significant neuropathy
  - Rx given for Duloxetine 30 mg OD
- Decision made to give chemo break x 2 months

Patient Case (continued)

CT scan done 22 November 2013

- Largely unchanged
- a few nodules that have increased in size (eg. from 3 mm to 5 mm)
- no new pulmonary nodularity, nor any lymphadenopathy

Still has residual neuropathies!

Patient Case (continued)

Decision to reinstitute chemotherapy without Oxaliplatin (ie. FOLFIRI) @ 90% dosing after Christmas 2013

- Concerned about nausea, so physician decided to add Aprepitant at this time

Today:

- R.F. continues to respond to dose modified FOLFIRINOX after 15 Cycles

What options are available to R.F. if he progresses?

Patient Case (continued)

- 2nd line Chemotherapy options, if well enough to receive them
  - Gemcitabine alone
  - Gemcitabine + NAB-Paclitaxel
    - Note: trial done in 1st line setting
    - Requires NF request
  - Gemcitabine + Erlotinib
- Clinical Trial
- Palliative Care

Take Home Message

- Recent, significant advances in the management of patients with metastatic pancreatic adenocarcinoma
- New therapies have the potential for increased survival and quality of life, but require appropriate management of toxicities
- Proper patient selection and dose reductions are vital

Take Home Message (2)

- All therapies, beyond single-agent gemcitabine, currently require special approval through CancerCare Manitoba
- Refer to Systemic Therapy Summaries, where available
- Do not hesitate to contact the CCMB Clinics for further directions

Questions?

http://www.acupunctureclinicvictoriabc.ca/wp-content/uploads/2011/01/pic_questions.jpg