Case 1

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Case 1 – Medical History

- 71 year old female, retired language teacher
- Widow, husband died of bladder carcinoma,
- 2 sons, 1 daughter
- Father died of mesothelioma, mother in a nursing home
- Ex-Smoker (over 40py), drinks only at special occasions (2-3x a year)
- Multimorbid: Coronary artery disease, diabetes mellitus type II with complications (diabetic nephropathy CKD II, peripheral artery disease – stage I, peripheral neuropathy), hypertension, heart failure (NYHA II)
- List of medication: metformin and empagliflozin, application of insulin, dulagutide, enalapril, furosemide, nebivolol, spironolactone
- Patient obese: 90 kg, 160 cm

Case 1 - Symptoms

- Back pain (lower part) for several months, severe for two weeks
- Patient consulted GP → GP assumed lumbar disc herniation/ protrusion and recommended MRI of lumbar spine and prescribed analgetics
- MRI reveals a lumbar disc protrusion → GP suggested physical therapy
- However, pain persisted, patient developed jaundice → went to emergency → acute CT of abdomen revealed a tumor in head of pancreas

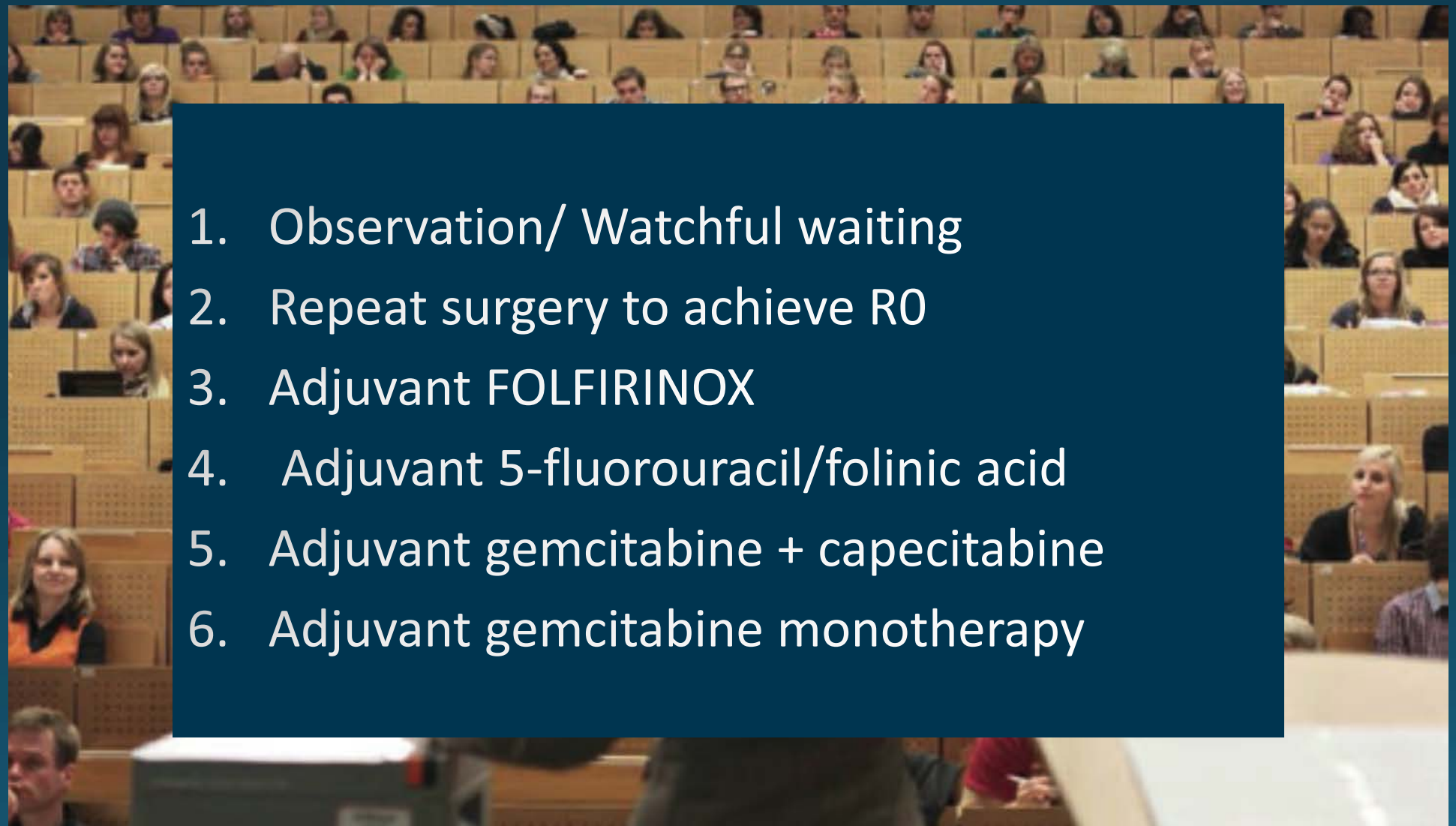
Case 1 – Medical findings

- MRI of abdomen ruled out hepatic metastasis
- Biopsy performed → Pancreatic Ductal Adenocarcinoma (PDAC) G3
- CEA: 28 ng/mL, CA19-9: 190 kU/L
- ECOG 1

Case 1 - Procedure

- Case discussion in multidisciplinary tumor board (MTB)
- PDAC is upfront resectable
- → patient underwent surgery
- TNM: pT3, pN1b, M0→ Staging IIB, Resection margin status: R1
- protracted recovery
- 10 weeks after surgery patient consulted oncologist

How would you proceed?



1. Observation/ Watchful waiting
2. Repeat surgery to achieve R0
3. Adjuvant FOLFIRINOX
4. Adjuvant 5-fluorouracil/folinic acid
5. Adjuvant gemcitabine + capecitabine
6. Adjuvant gemcitabine monotherapy

Case 1 - Treatment

- Adjuvant gemcitabine monotherapy once a week for three of every 4 weeks (one cycle)) for six cycles (24 weeks)

Safety profile of capecitabine precautions

Cardiotoxicity. Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris (see section 4.8).

Hypo- or hypercalcaemia. Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia (see section 4.8).

Central or peripheral nervous system disease. Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy (see section 4.8).

Diabetes mellitus or electrolyte disturbances. Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.

Coumarin-derivative anticoagulation. In an interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the

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ESPAC-4 trial

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

John P Neoptolemos, Daniel H Palmer, Paula Ghaneh, Eftychia E Psarelli, Juan W Valle, Christopher M Halloran, Olusola Faluyi, Derek A O'Reilly, David Cunningham, Jonathan Wadsley, Suzanne Darby, Tim Meyer, Roopinder Gillmore, Alan Anthoney, Pehr Lind, Bengt Glimelius, Stephen Falk, Jakob R Izbicki, Gary William Middleton, Sebastian Cummins, Paul J Ross, Harpreet Wasan, Alec McDonald, Tom Crosby, Yuk Ting Ma, Kinnari Patel, David Sherriff, Rubin Soomal, David Borg, Sharmila Sothi, Pascal Hammel, Thilo Hackert, Richard Jackson, Markus W Büchler, for the European Study Group for Pancreatic Cancer

ESPAC-4 trial

- OS gemcitabine + capecitabine 28.0 months versus gemcitabine mono 25.5 months (HR 0.82; p=0·032).
- No difference in R1 subgroup

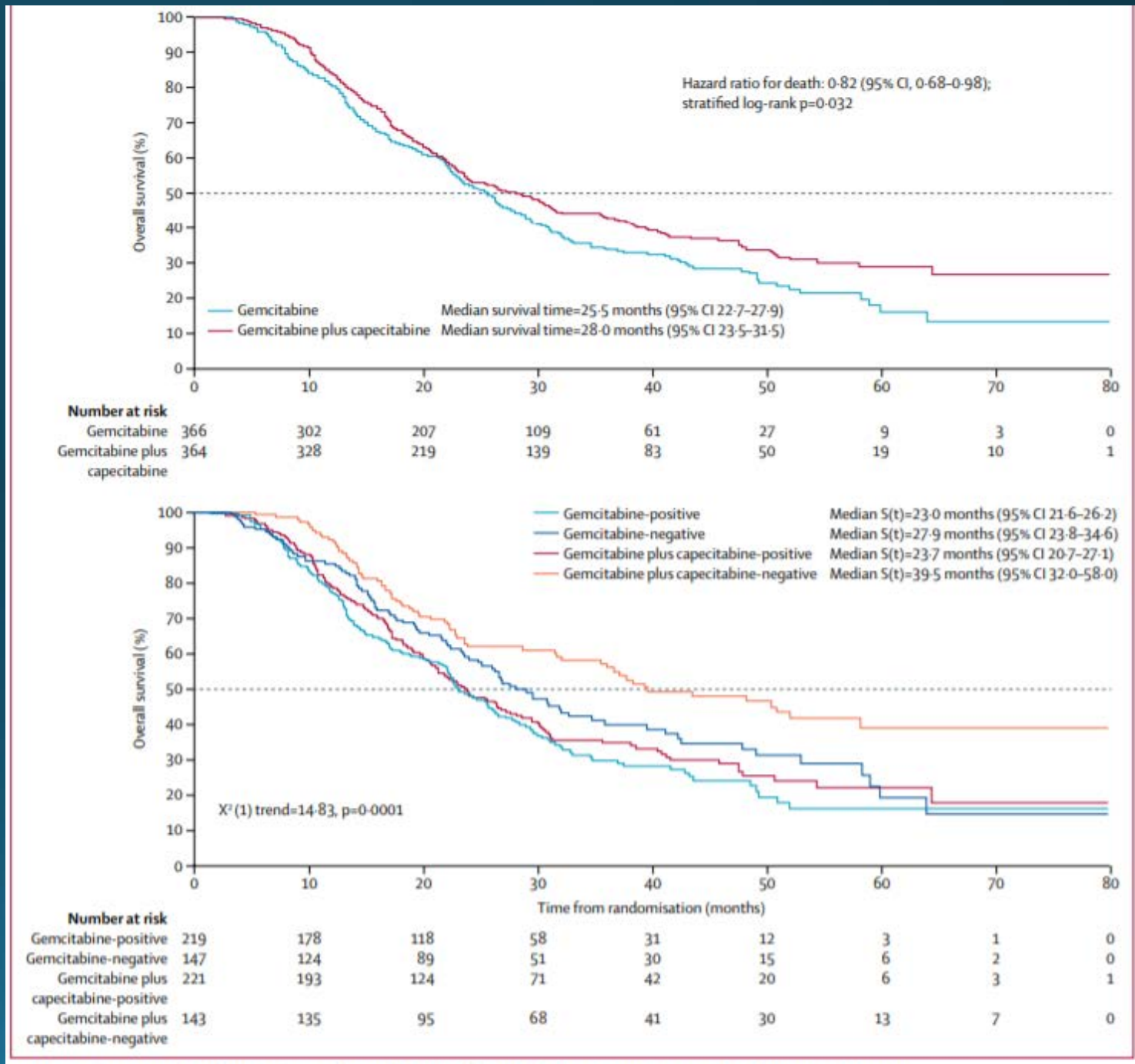
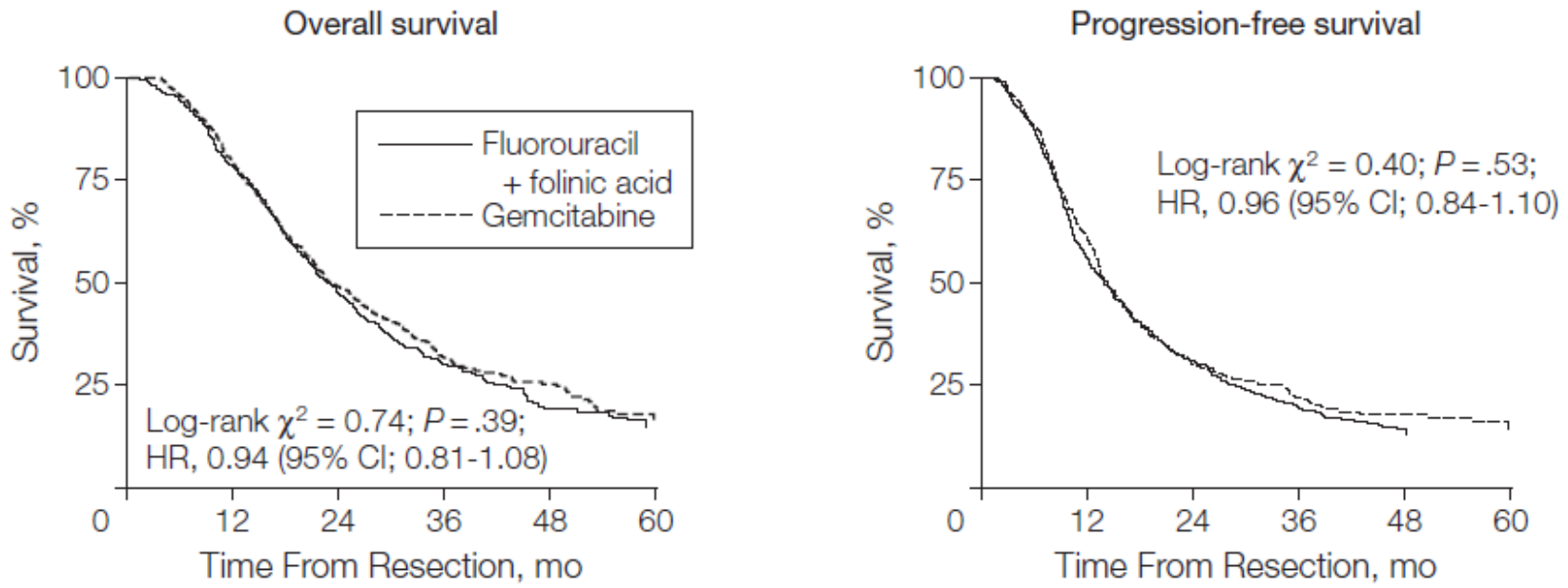


Figure 2: **Kaplan Meier plots for overall survival (A) and for overall survival by resection margin status and treatment group (B)**

ESPAC-3 trial

- Seventy-seven patients (14%) receiving fluorouracil plus folinic acid had 97 treatment-related serious adverse events, compared with 40 patients (7.5%) receiving gemcitabine, who had 52 events (*P*.001).
- Patients receiving fluorouracil plus folinic acid had significantly increased grade 3/4 stomatitis (P<001) and diarrhea (P<.001), whereas patients receiving gemcitabine reported significantly increased grade 3/4 hematologic toxicity

Figure 2. Survival Results by Randomized Treatment



No. at risk						
Fluorouracil + folinic acid	551	413	249	109	36	15
Gemcitabine	537	415	251	103	42	13

551	296	160	64	23	11
537	319	152	68	22	11

CI indicates confidence interval; HR, hazard ratio.

ESPAC-3 trial

Table 2. Reported Toxicity

Toxicity Variable	Reported NCI CTC Version 2 Toxicity[a]				
	Fluorouracil + Folinic Acid (n = 551)		Gemcitabine (n = 537)		
	Grade 1/2, No.	Grade 3/4, No. (%)	Grade 1/2, No.	Grade 3/4, No. (%)	*P* Value[b]
WBC count	154	32 (6)	262	53 (10)	.01
Neutrophils	180	121 (22)	270	119 (22)	.94
Platelets	57	0	170	8 (1.5)	.003
Nausea	292	19 (3.5)	282	13 (2.5)	.37
Vomiting	159	17 (3)	131	11 (2)	.34
Stomatitis	304	54 (10)	96	1 (0)	<.001
Alopecia	189	1 (0)	135	1 (0)	>.99
Tiredness	340	45 (8)	351	32 (6)	.16
Diarrhea	333	72 (13)	194	12 (2)	<.001
Other	262	67 (12)	290	43 (8)	.03

Abbreviations: CTC, Common Terminology Criteria; NCI, National Cancer Institute; WBC, white blood cell.

[a] Toxicity grades defined per CTC Version 2.0.[22]

[b] From Fisher exact test with significance level set to $P < .005$ and with Bonferroni adjustment to account for multiple testing.

PRODIGE 24 trial

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FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

PRODIGE 24 trial

The median overall survival was 54.4 months in the mFOLFIRINOX group and 35.0 months in the gemcitabir group (HR 0.64, P = 0.003).

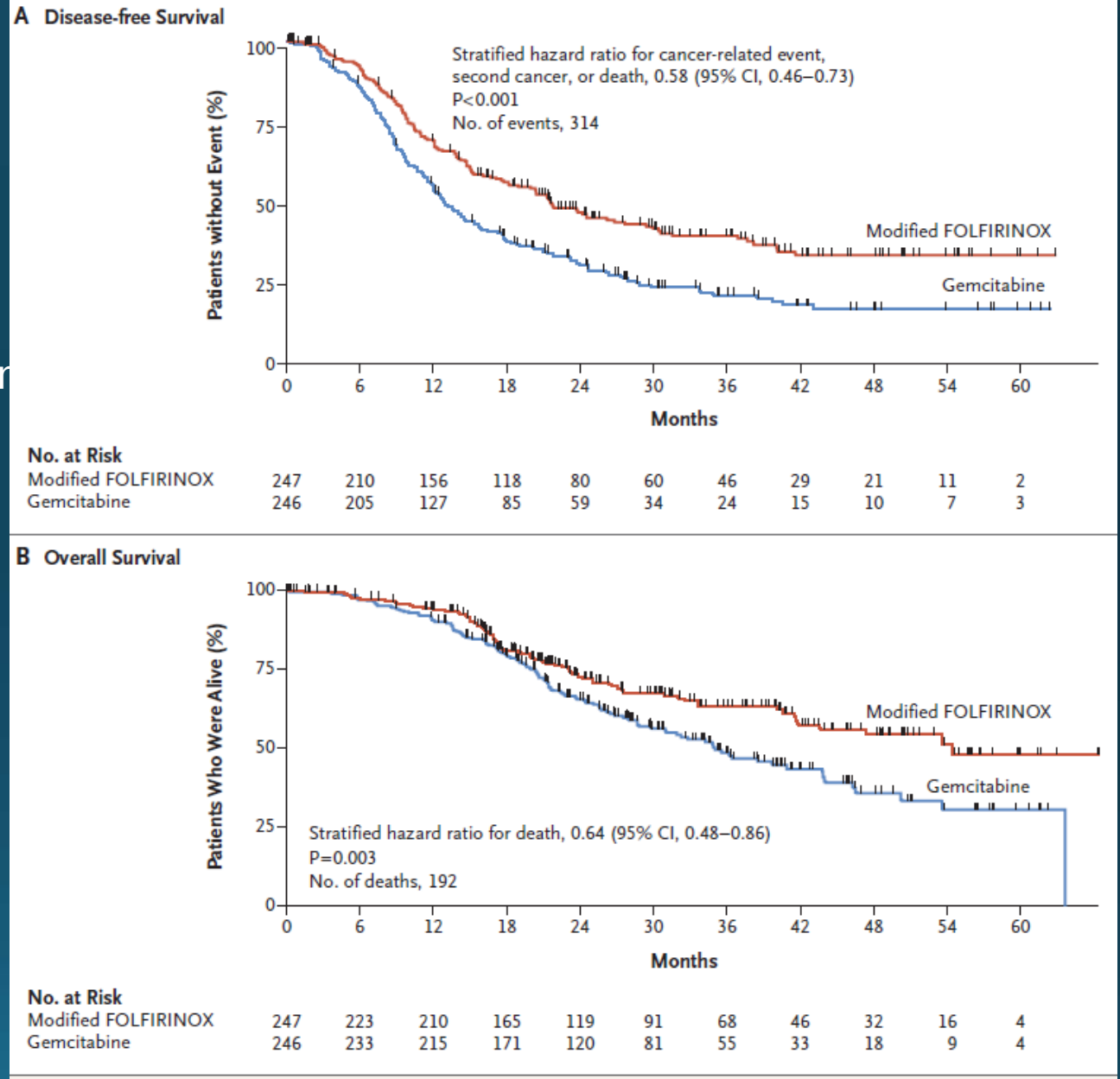

Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival in the Intention-to-Treat Population, According to Treatment Group.

The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group, as compared with 12.8 months in the gemcitabine group (Panel A). The median overall survival was 54.4 months in the modified-FOLFIRINOX group, as compared with 35.0 months in the gemcitabine group (Panel B). Tick marks indicate censored data.

PRODIGE 24 trial

- Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group.
- The incidence of grade 3 or 4 events of diarrhea, increase in the γ-glutamyltransferase level, paresthesia, fatigue, sensory peripheral neuropathy, nausea, vomiting, abdominal pain, and mucositis was significantly higher in the mFOLFIRINOX group, whereas thrombocytopenia of grade 3 or 4 was significantly more common in the gemcitabine group.
- Conclusion: This study regimen should be considered only for patients who are fit enough to tolerate it.

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—
Biochemical event¶							
Increased alanine aminotransferase level	151 (64.0)	10 (4.2)	0	178 (73.6)	12 (5.0)	0	0.71
Increased aspartate aminotransferase level	158 (66.9)	9 (3.8)	1 (0.4)	167 (69.0)	8 (3.3)	0	0.76
Increased alkaline phosphatase level	173 (73.6)	5 (2.1)	0	111 (45.9)	5 (2.1)	0	1.00
Increased γ-glutamyltransferase level	150 (65.2)	42 (18.3)	6 (2.6)	110 (46.0)	20 (8.4)	3 (1.3)	0.002
Hyperglycemia	59 (24.9)	7 (3.0)	0	59 (24.4)	5 (2.1)	0	0.53

Conclusion

- Always think of tumors/ carcinomas in case of persistent back pain particulary in patients >70 years
- Patients should undergo adjuvant chemotherapy
- In elderly frail patients gemcitabine monotherapy is a valid option in the adjuvant setting

Thank you!