Gemcitabine and Oxaliplatin versus Gemcitabine (Fixed-Dose Rate Infusion) Compared with Gemcitabine (30-Minute Infusion) in Pancreatic Carcinoma: E6201

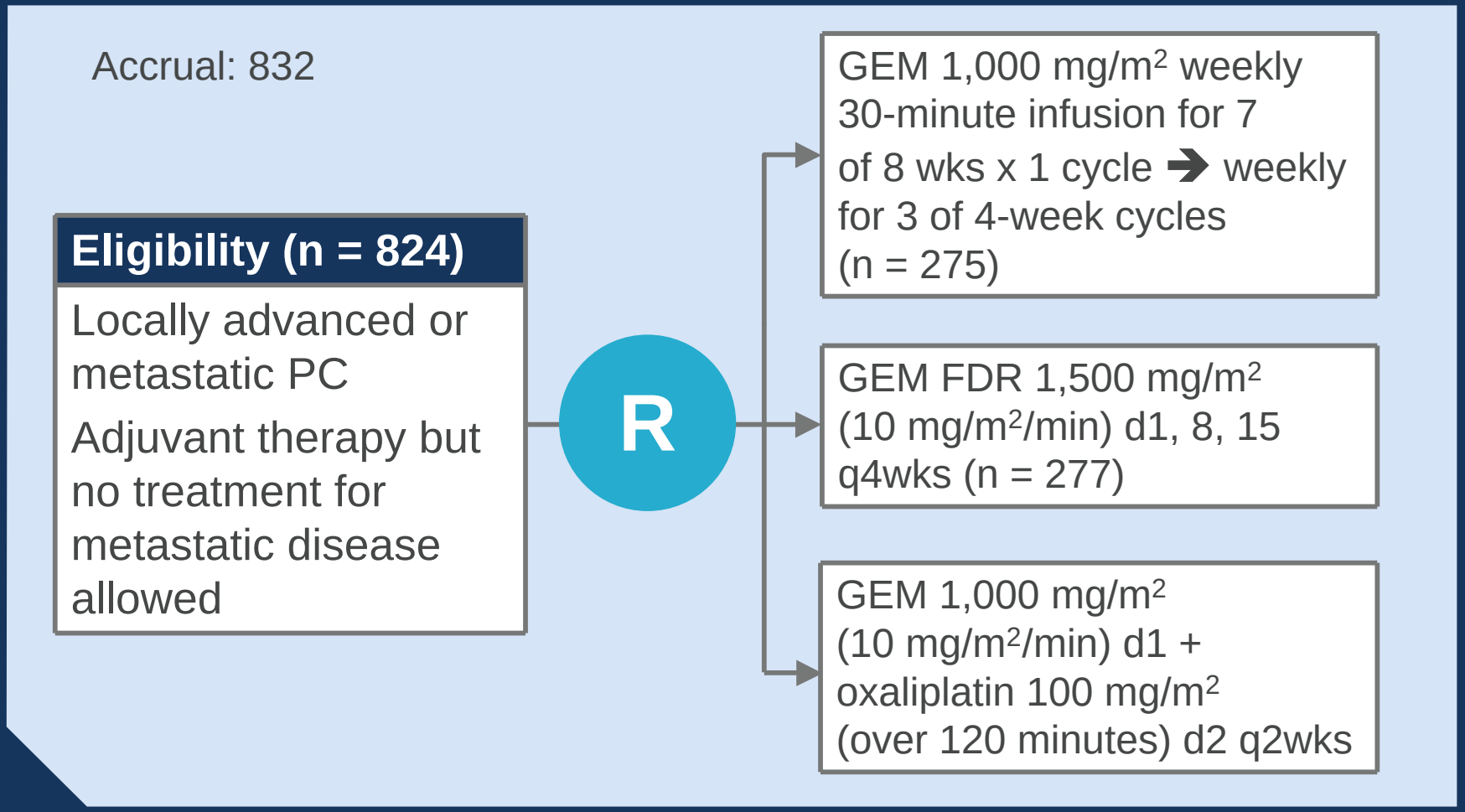
Poplin E et al.
J Clin Oncol 2009;27(23):3778-85.

Introduction

- Gemcitabine (GEM) is the currently accepted standard treatment for pancreatic cancer (PC), since no combination regimen has demonstrated an improvement in survival compared to GEM alone.
- Two recent studies suggested a benefit for the use of fixed-dose rate (FDR) GEM or GEM FDR plus oxaliplatin (GEMOX).
  - Phase II: Improvement in time to treatment failure for FDR GEM at 10 mg/m^2/min compared to GEM 30-minute infusion (*JCO* 2003;21:3402)
  - Phase III: GEMOX resulted in higher response rate and PFS compared to GEM (*JCO* 2005;23:3509)
- <u>Current study objective:</u>
  - Compare the effect of standard GEM, GEM FDR and GEMOX on overall survival in patients with locally advanced or metastatic PC.

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Phase III Study Design



Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Progression-Free and Overall Survival

Patient Group	Progression-Free Survival		Overall Survival	
	Median	*p*-value	Median	*p*-value
All eligible patients (n = 824)	2.9 mo	—	5.6 mo	—
GEM (n = 275)	2.6 mo	0.09	4.9 mo	0.15
GEM FDR (n = 277)	3.5 mo		6.2 mo	
GEMOX (n = 272)	2.7 mo		5.7 mo	

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Progression-Free and Overall Survival: Univariate Analyses

Parameter	Progression-Free Survival		Overall Survival	
	Median	*p*-value	Median	*p*-value
Disease status				
Locally advanced	5.4 mo	<0.01	9.2 mo	<0.01
Metastatic	2.7 mo		5.4 mo	
Prior radiotherapy				
No	2.9 mo	0.53	5.5 mo	0.52
Yes	3.1 mo		6.9 mo	
Prior adjuvant chemotherapy				
No	3.0 mo	0.14	5.5 mo	0.10
Yes	2.9 mo		7.3 mo	

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Select Grade III/IV Toxicities

	GEM (n = 264)		GEM FDR (n = 275)		GEMOX (n = 263)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Leukocytes*	15%	1%	32%	7%	11%	1%
Neutrophils*	19%	14%	29%	30%	11%	11%
Platelets*	12%	1%	29%	4%	10%	1%
Fatigue	18%	1%	18%	1%	15%	2%
Anorexia	8%	—	6%	—	7%	<1%
Sensory neuropathy*	0%	—	1%	—	25%	—

* $P < 0.001$ among three treatment arms

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Summary and Conclusions

- Neither GEM FDR nor GEMOX significantly increased OS or PFS in patients with advanced PC compared to GEM 30-minute infusion.
- Grade 3/4 neutropenia and thrombocytopenia were highest with GEM FDR. GEMOX resulted in higher rates of nausea, vomiting and neuropathy.
- PC has a large number of genetic alterations, likely causing disregulation of multiple pathways. Additional data implicate the active role of PC stroma.
  - Future studies should include the coordinated use of multiple therapeutic agents or modalities that attack the most critical of these pathways.

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Faculty Comments

DR ILSON: This is an important, well-powered — albeit negative — study, so the conclusion that there was no difference in overall survival is meaningful and reinforces that a 30-minute infusion of gemcitabine does remain a standard of care.

DR HOCHSTER: I'm a big fan of fixed-dose rate gemcitabine. Of interest, the fixed-dose rate gemcitabine was as effective as fixed-dose rate gemcitabine in combination with oxaliplatin and was better than 30-minute infusion gemcitabine at the $p = 0.05$ level. However, because this was a three-arm study, a p-value of <0.025 was required for statistical significance. So, although Dr Poplin presented this as a negative study, I don't entirely agree with that conclusion, and I tend to accept that the fixed-dose rate is more effective than the standard 30-minute infusion.

Phase III Randomized Open-Label Comparison of Adjuvant 5-FU/FA versus GEM in Patients with Resected Pancreatic Ductal Adenocarcinoma: ESPAC-3 (v2)

Neoptolemos M et al.
Proc ASCO 2009;Abstract LBA4505.

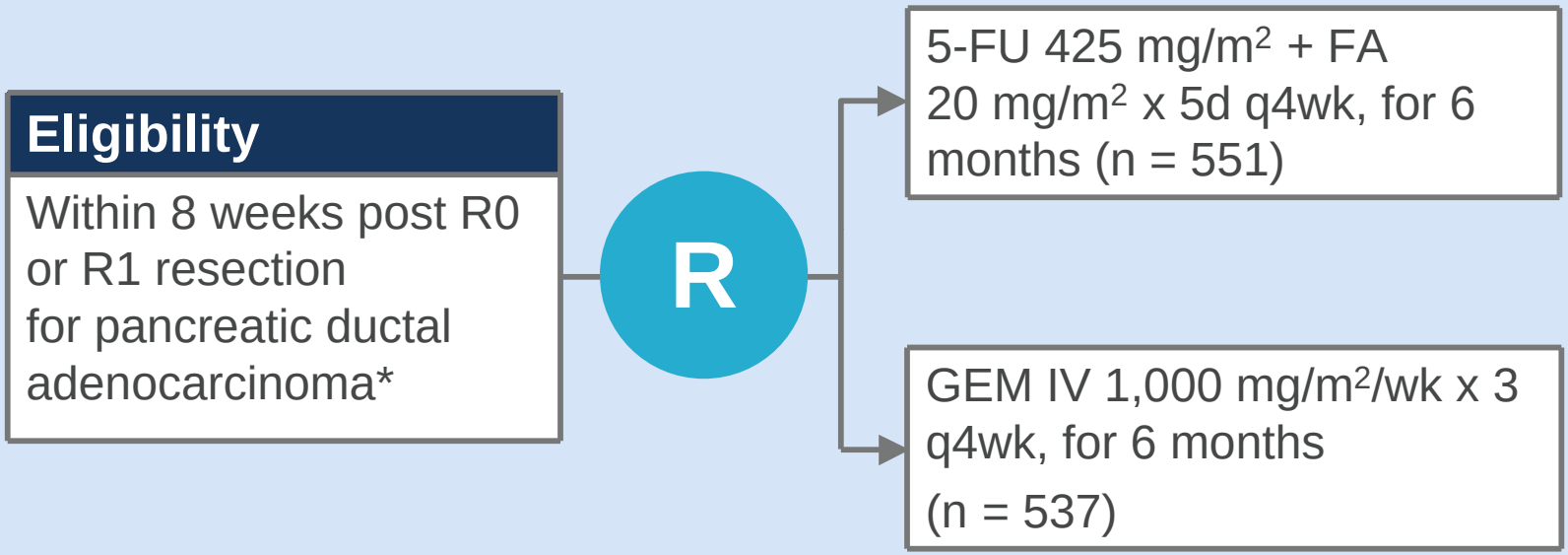
Introduction

- ESPAC-1 trial confirmed the clinical benefit of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) therapy for patients with resected pancreatic cancer compared to patients who received no chemotherapy (*NEJM* 2004;350:1200).
  - Hazard ratio for death (HR): 0.71 (p = 0.009)
- The CONKO-001 trial demonstrated that patients with resected pancreatic cancer experience improved survival when treated with adjuvant gemcitabine (GEM) compared with untreated patients (*JAMA* 2007;297:267).
- Current study objective:
  - Compare the survival benefit of adjuvant 5-FU/FA versus GEM in patients with resected pancreatic cancer.

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

ESPAC-3(v2): A Phase III Randomized Trial of 5-FU/FA versus GEM in Resected Pancreatic Cancer

Accrual: 1,088 (Closed)



* Stratified by resection margin status and country

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

Efficacy Results (Intent-to-Treat)

Median Survival	5-FU/FA (n = 551)	GEM (n = 537)	*p*-value
Progression-free survival (PFS)	14.1 mo	14.3 mo	0.44
Overall survival (OS)	23.0 mo	23.6 mo	0.39

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

Adjusted Treatment Effect

- Treatment effect was adjusted by the following stratification factors at randomization:
  - Country
  - Resection status

- Analysis of stratification factors by Frailty model:
  - Country, $p = 0.61$ (random effect)
  - Resection status, $p<0.001$ (fixed effect)
  - **Treatment, HR = 0.94 (95% CI: 0.81-1.08), $p = 0.36$**

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

Select Adverse Events

Grade 3/4 Toxicity	5-FU/FA (n = 551)	GEM (n = 537)
Leukopenia	6%	10%
Neutropenia	22%	22%
Thrombocytopenia*	0%	1.5%
Nausea	3.5%	2.5%
Vomiting	3%	2%
Stomatitis*	10%	0%
Tiredness	8%	6%
Diarrhea*	13%	2%

* $p<0.005$

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

Conclusions

- There were no differences in survival between the use of adjuvant 5-FU/FA vs GEM.
  - Median OS: 23.0 mo vs 23.6 mo, $p = 0.39$
  - Median PFS: 14.1 mo vs 14.3 mo, $p = 0.44$
- The safety profile of GEM was better than that of 5-FU/FA.
  - Stomatitis and diarrhea were significantly greater in the 5-FU/FA group, but thrombocytopenia was significantly greater in the GEM group.
  - Treatment-related serious adverse events were significantly greater in the 5-FU/FA group.
- These data reinforce the design of the ESPAC-4, comparing GEM versus GEM-capecitabine in a Phase III, international, randomized controlled trial of 1,080 patients with pancreatic ductal adenocarcinoma.

Neoptolemos M et al. *Proc ASCO* 2009;Abstract LBA4505.

Faculty Comments

DR ALBERTS: This was a noteworthy study in that it looked at a multicenter, international comparison of patients undergoing adjuvant therapy using 5-fluorouracil and leucovorin compared to gemcitabine alone. Given the size of the study and multicenter participation, it provided a fair comparison between the two approaches of adjuvant therapy and showed that there was no difference in the treatment across the groups that were evaluated. That is particularly important in looking at treatment options for patients for whom gemcitabine had been considered a standard for a long time. The use of 5-fluorouracil and leucovorin showed comparable outcomes, raising the possibility that future trials now can be done with 5-fluorouracil and leucovorin and not necessarily involve gemcitabine.

Preoperative Biliary Drainage for Cancer of the Head of the Pancreas

van der Gaag NA et al.

N Engl J Med 2010;362(2):129-37.

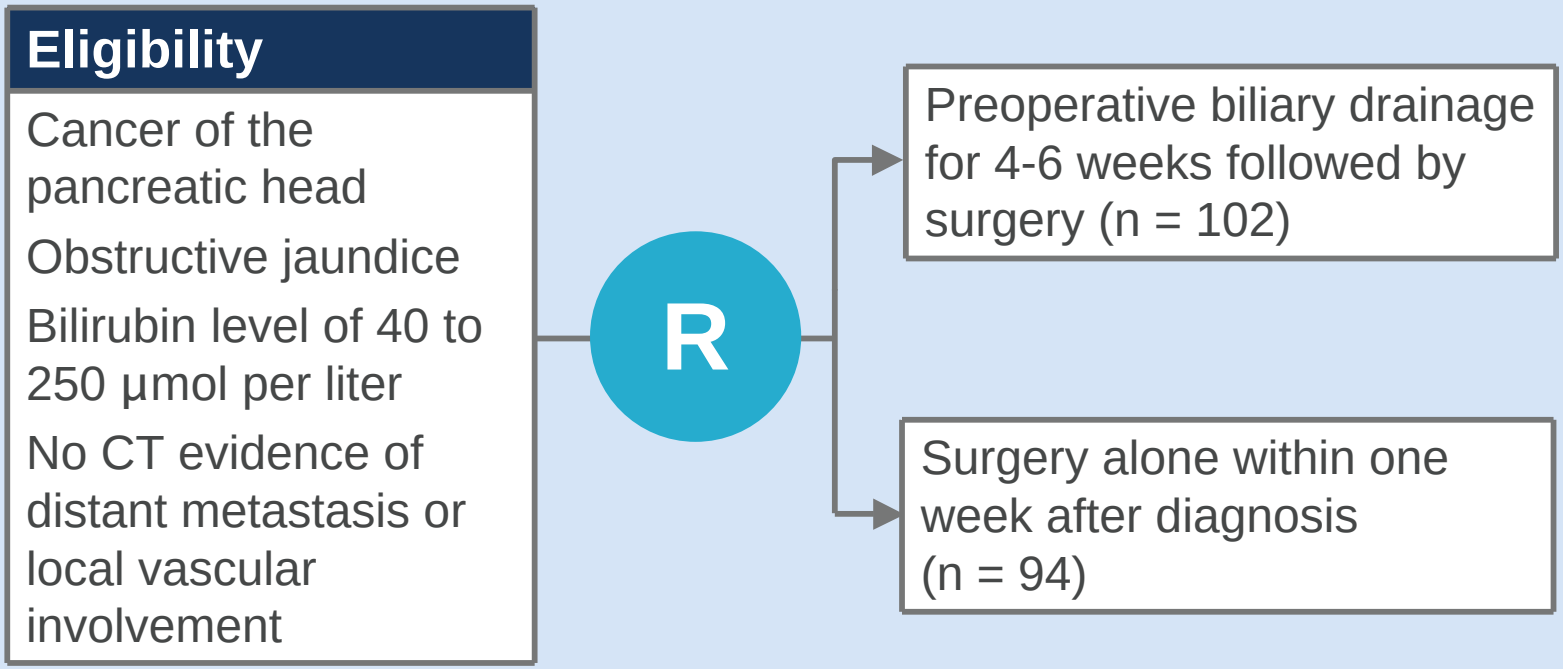
Introduction

- Preoperative biliary drainage (PBD) was introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head (*J Gastrointest Surg* 2009;13:814).
- Meta-analysis[a] and a systematic review[b] of the efficacy of PBD have shown that the overall complication rate was higher in patients undergoing PBD compared to patients who proceeded directly to surgery ([a] *Ann Surg* 2002;236:17, [b] *Cochrane Database Syst Rev* 2008;3:CD005444).
- Current study objective:
  - Assess the rates of serious complications and death and the length of hospital stay associated with PBD.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Multicenter, Randomized Trial of Preoperative Biliary Drainage

Accrual: 202 (Closed)



van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Serious Complications Related to PBD within 120 Days After Randomization[1]

Complication Related to PBD	Early Surgery (n = 94)	PBD (n = 102)
Any	2%	46%
Pancreatitis	0%	7%
Cholangitis[2]	2%	26%
Occlusion related to stent	1%	15%
Need for exchange related to stent	2%	30%

[1] The numbers refer to patients who had one or more complications.
[2] In two patients, cholecystitis occurred in connection with cholangitis, prompting antibiotic treatment without the need for cholecystectomy.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Serious Complications Related to Surgery within 120 Days After Randomization[1]

Complication Related to Surgery	Early Surgery (n = 94)	PBD (n = 102)
Any	37%	47%
Pancreaticojejunostomy leakage	12%	8%
Delayed gastric emptying	10%	18%
Wound infection	7%	13%
Pneumonia	5%	9%
Need for repeated laparotomy[2]	14%	12%

[1] The numbers refer to patients who had one or more complications.
[2] Refers to complications of preoperative biliary drainage or another surgical procedure.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Major Outcomes[1]

Variable	Early Surgery (n = 94)	PBD (n = 102)	Relative Risk[2]
Overall complications (protocol specified)	39%	74%	0.54
Death (protocol-specified complication)	4%	9%	0.48
Median hospital stay (protocol-specified treatment)	13 days	15 days	Not reported

[1] The numbers refer to patients who had one or more complications.
[2] Relative risk values are for early surgery versus PBD.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Conclusions

- Routine PBD in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications.
- The rates of serious complications were 39% in the early-surgery group and 74% in the PBD group.
  - Relative risk: 0.54 (95% CI 0.41-0.71, $p < 0.001$)
- Surgery-related complications occurred in 37% in the early-surgery group and 47% in the PBD group.
  - Relative risk: 0.79 (95% CI 0.57-1.11, $p = 0.14$)
- PBD was successful in 94% of patients, with complications in 46% of the patients (data not shown).
- Mortality and the length of hospital stay did not differ significantly between the two groups.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Faculty Comments

DR ALBERTS: The importance of this particular trial is in addressing what has often been regarded as the standard of care but hasn’t necessarily been questioned. To date, many have accepted that it’s appropriate, and probably better, to place a stent prior to surgery to reduce the bilirubin and help the patient go through surgery without additional complications. In this particular trial, however, the routine use of biliary drainage prior to surgery increased the rate of complications. It’s a level of complications that should make people aware that placing a drain prior to surgery is not necessarily in the patient’s best interest and may cause harm. So it’s a practice-changing study.

Phase III Randomized Comparison of Gemcitabine versus Gemcitabine plus Capecitabine in Patients with Advanced Pancreatic Cancer

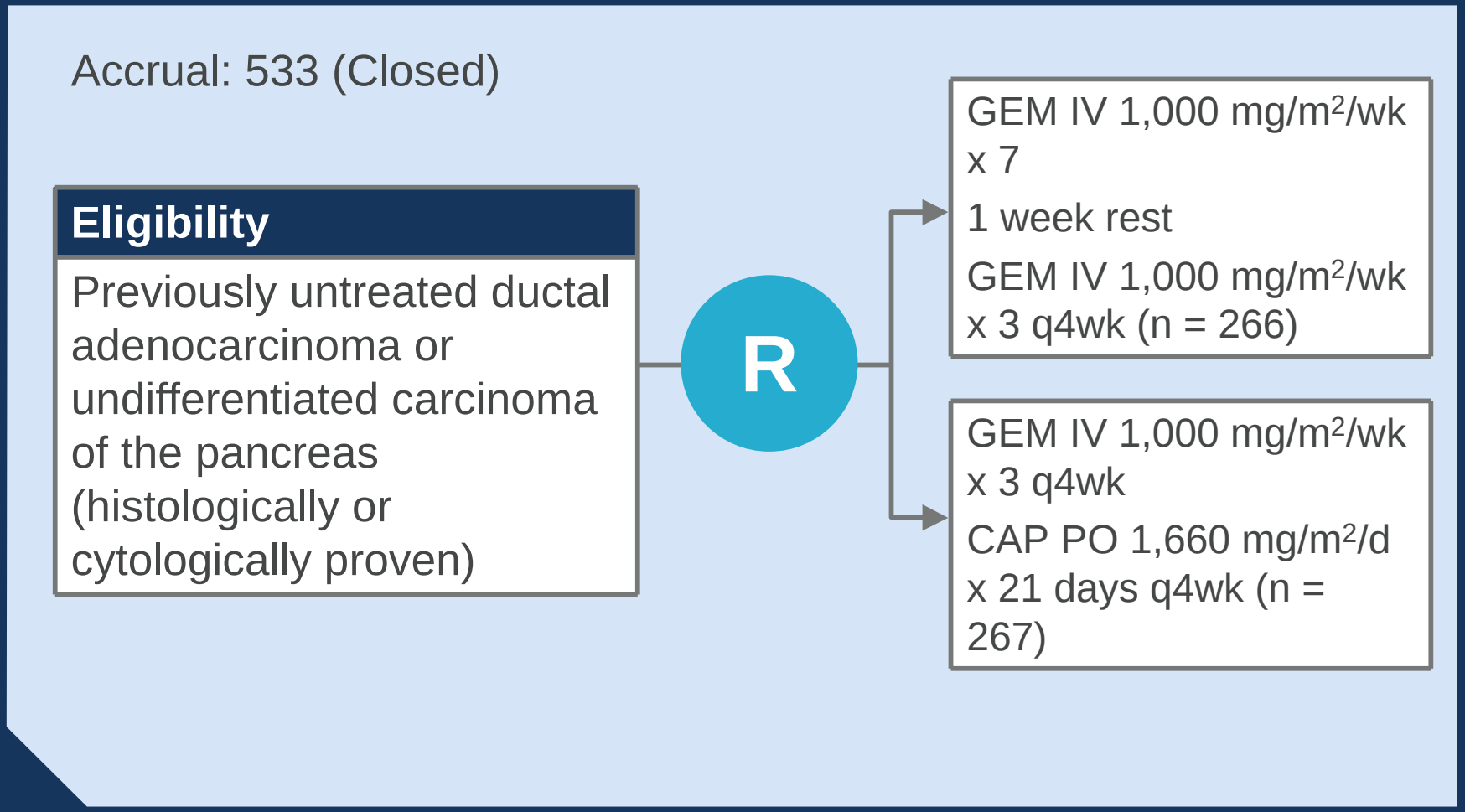
Cunningham D et al.
J Clin Oncol 2009;27(33):5513-8.

Introduction

- Gemcitabine (GEM) is considered the standard of care for untreated patients with advanced pancreatic cancer.
  - GEM has consistently resulted in a median survival of 5-7 months and a 1-yr survival rate of 20%.
- Phase I trial of capecitabine (CAP) combined with GEM established a dose schedule that allows for administration of standard-dose GEM with a modified dosing schedule of CAP.
  - Modified CAP dosing schedule (1,660 mg/m^2/d x 21 days) allows for similar dose intensity to the standard dose and schedule of CAP given alone (*JCO* 2002;20:582).
- Current study objective:
  - Assess if the addition of CAP to GEM would improve survival over GEM alone in patients with advanced pancreatic cancer.

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Phase III Randomized Trial of GEM versus GEM Plus CAP in Advanced Pancreatic Cancer



Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Efficacy Results (Intent-to-Treat)

Clinical variable	GEM (n = 266)	GEM-CAP (n = 267)	*p*-value
Overall response rate (ORR)	12.4%	19.1%	0.03
Complete response	0.4%	3.0%	
Partial response	12.0%	16.1%	
Stable disease	29.3%	29.6%	—
Progressive disease	19.5%	15.7%	—
Median survival	**GEM (n = 266)**	**GEM+CAP (n = 267)**	***p*-value**
Progression-free survival (PFS)	3.8 mo	5.3 mo	0.004
Overall survival (OS)	6.2 mo	7.1 mo	0.08

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Meta-Analysis of Published Randomized Controlled Trials (Including Current Trial)

Study or subcategory	GEM, n	GEM-CAP, n	Hazard ratio* (95% CI)
Overall survival			
Cunningham 2009	266	267	0.86 (0.72 to 1.02)
Herrmann 2007	159	160	0.87 (0.69 to 1.10)
Schelthauer 2003	42	41	0.82 (0.50 to 1.34)
Subtotal (95% CI)	467	468	0.86 (0.75 to 0.98)

* Hazard ratio of <1 favors GEM-CAP

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Grade 3/4 Adverse Events

Toxicity*	GEM (n = 247)	GEM-CAP (n = 251)
Neutropenia	22%	35%
Lethargy	21%	21%
Nausea/vomiting	12%	13%
Thrombocytopenia	6%	11%
Anemia	6%	4%
Diarrhea	4%	5%
Hand-foot syndrome	0%	4%

*Toxicities observed in patients receiving at least one cycle of treatment

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Summary and Conclusions

- Addition of CAP to GEM significantly improved response rates and PFS in patients with advanced pancreatic carcinoma.
  - ORR: 19.1% vs 12.4%
  - Median PFS: 5.3 mo vs 3.8 mo
- A trend toward improved OS was seen with the addition of CAP to GEM.
- Increased clinical benefit was achieved without significant toxicity or detrimental effect on quality of life (data not shown).
- Based on these study results and those of the meta-analysis, GEM-CAP should be considered among the standard first-line options for the treatment of advanced pancreatic cancer.

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Faculty Comments

DR ILSON: This is a problematic, Phase III study in advanced pancreatic cancer, comparing gemcitabine to gemcitabine in combination with capecitabine in advanced pancreatic cancer, that failed to meet its overall survival endpoint. The hazard ratio of 0.86 was not statistically significant for overall survival, although there was a trend toward a better response and progression-free survival with the combination. At the end of the day, it’s a negative trial, but the authors did not accept that conclusion and performed a meta-analysis with other studies. Of note, the hazard ratio remained the same for overall survival, but it was significant for the combination with a larger pool of patients. This suggests that the gemcitabine/capecitabine may offer a benefit to some patients. In my practice, I reserve the combination for patients with a better performance status.

Phase III Trial of Bevacizumab in Combination with Gemcitabine and Erlotinib in Patients with Metastatic Pancreatic Cancer

Van Cutsem E et al.
J Clin Oncol 2009;27(13):2231-7.

Introduction

- In patients with advanced pancreatic cancer, the combination of erlotinib (ERL) plus gemcitabine (GEM) significantly improved survival (*JCO* 2007;25:1960).
- Phase II trials have shown promising results for bevacizumab (BEV) combinations in patients with advanced pancreatic cancer (*Proc ASCO* 2006;Abstract 4040, *Proc ASCO* 2007;Abstract 4553, Gastrointestinal Cancers Symposium 2008;Abstract 198).
  - Response rates from 11 to 24%
  - Overall survival from 8.1 to 9.8 months
  - Progression-free survival from 3.6 to 5.8 months
- Current study objective:
  - Assess the efficacy and safety of GEM-ERL-BEV therapy in patients with advanced pancreatic cancer.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Phase III Randomized Placebo-Controlled Trial of ERL, GEM, and BEV in Advanced Pancreatic Cancer

Accrual: 607 (Closed)

Eligibility

- Metastatic adeno-carcinoma of the pancreas
- Karnofsky PS ≥60%
- No prior adjuvant radiotherapy
- No prior adjuvant chemotherapy within 6 months

R

GEM 1000 mg/m^2 d1 x 7, q8wk followed by d1 x 3, q4wk
ERL 100 mg daily
BEV 5 mg/kg, d1,15, 29, 43 x 1 followed by d1,15 (n = 306)

GEM 1000 mg/m^2 d1 x 7, q8wk followed by d1 x 3, q4wk
ERL 100 mg daily
Placebo (PBO) 5 mg/kg, d1,15, 29, 43 x 1 followed by d1,15 (n = 301)

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Median Survival (Intent-to-Treat)

	GEM-ERL-BEV n = 306	GEM-ERL-PBO n = 301	*p*-value
Overall survival			
All patients	7.1 mo	6.0 mo	0.2087
Tumors in tail of pancreas	9.0 mo	5.5 mo	0.0025
CRP >1.4 mg/L	4.8 mo	3.6 mo	0.0009
Baseline LDH >ULN	4.7 mo	3.6 mo	0.0013
Progression-free survival	4.6 mo	3.6 mo	0.0002

CRP = C-reactive protein

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Best Overall Response (Intent-to-Treat)

	GEM-ERL-BEV n = 306	GEM-ERL-PBO n = 301	*p*-value
Overall response	13.5%	8.6%	0.0574
Complete response	0.7%	—	—
Partial response	12.8%	8.6%	—
Stable disease	49.2%	45.2%	—
Progressive disease	19.9%	24.3%	—

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Grade III/V Adverse Events

Adverse Event	GEM-ERL-BEV (n = 296)	GEM-ERL-PBO (n = 287)
Neutropenia	21%	17%
Thrombocytopenia	8%	6%
Rash	8%	3%
Anemia	7%	9%
Vomiting	5%	3%
Fatigue	5%	7%
Diarrhea	4%	6%*

* One patient experienced a Grade V adverse event.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Conclusions

- Combination of GEM-ERL-BEV did not significantly improve overall survival, although progression-free survival was significantly increased.
  - Overall survival: 7.1 mo vs 6.0 mo ($p = 0.2087$)
  - Progression-free survival: 4.6 mo vs 3.6 mo ($p = 0.0002$)
- There were no unexpected side effects associated with the treatments, and the incidence of Grade 3-5 toxicities was similar between the two study arms.
- It is possible that subgroups of patients with more aggressive disease (ie, elevated CRP or LDH) might benefit more from the GEM-ERL-BEV combination — further trials are needed to explore this possibility.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Faculty Comments

DR ILSON: I did not have positive expectations for this study because the preceding CALGB trial of gemcitabine with or without bevacizumab was a negative study. The addition of bevacizumab to gemcitabine in advanced pancreatic cancer did not improve any endpoint. In this study, the addition of bevacizumab did not result in an improvement in overall survival, although there was a trend for a progression-free survival benefit. This study validates that bevacizumab does not add benefit to gemcitabine-based chemotherapy in the treatment of metastatic pancreatic cancer.

DR ALBERTS: The addition of bevacizumab to gemcitabine and erlotinib did not add any additional benefit, so there is no reason to move this forward either as a standard of care or into a future clinical trial.

A Prospective, Randomized Trial of Chemotherapy with or without the Low Molecular Weight Heparin Enoxaparin in Advanced Pancreatic Cancer: CONKO 004

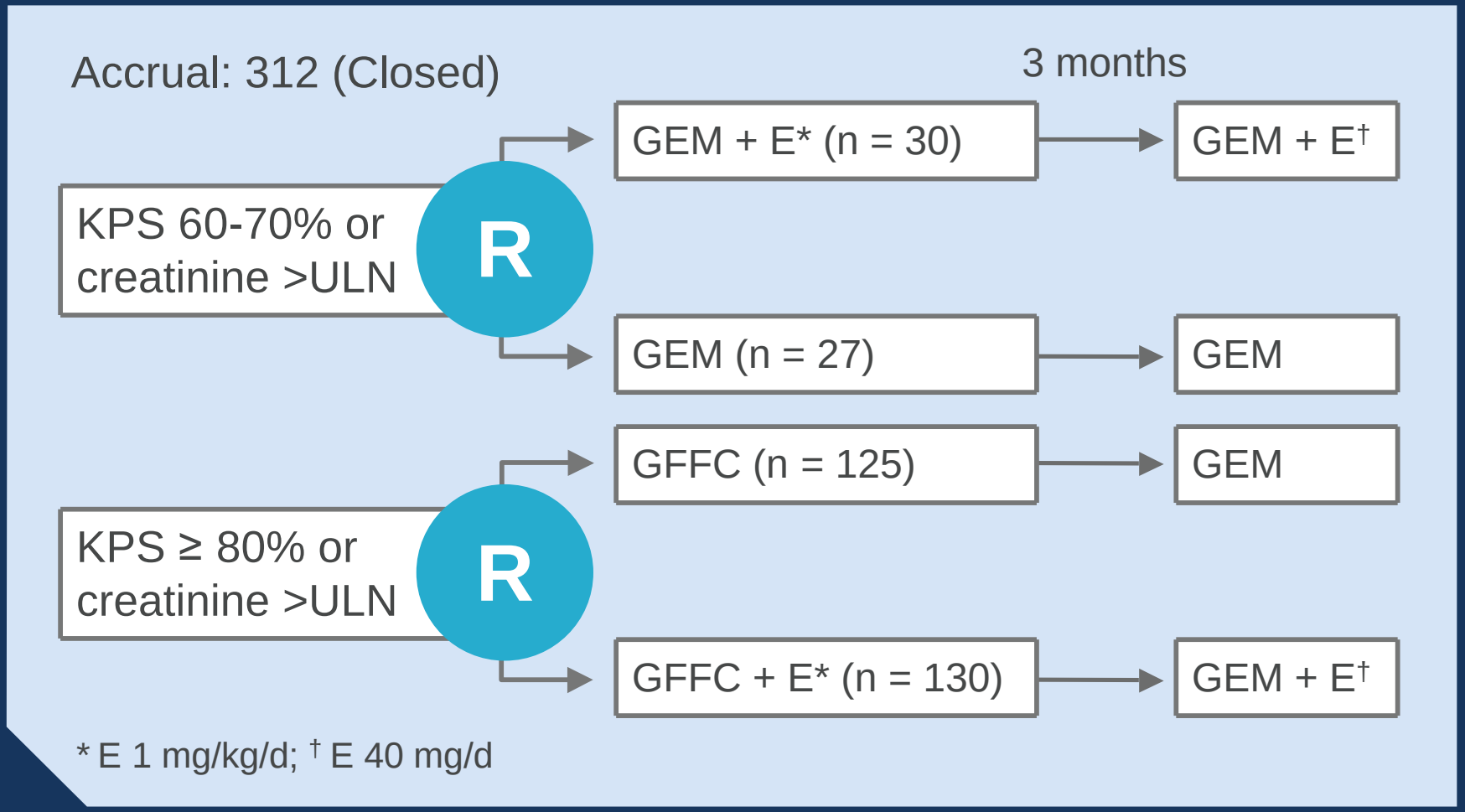
Riess H et al.
Proc ASCO 2009;LBA4506.

Introduction

- There is a high incidence of venous thromboembolic events (VTE) in patients with advanced pancreatic cancer (*Eur J Cancer* 2006;42:410).
- Gemcitabine (GEM) is considered the standard of therapy for pancreatic cancer and combinations of GEM/cisplatin or GEM/5-fluorouracil/folinic acid show favorable outcomes (*BMC Cancer* 2008;8:82).
- Low molecular weight heparin (LMWH) is an effective anticoagulant used to prevent VTE (*Chest* 2008;133:381S).
- Current study objective:
  - Assess the efficacy and safety of LMWH enoxaparin (E) with GEM or GEM/5-fluorouracil/folinic acid/cisplatin (GFFC) in patients with advanced pancreatic cancer.

Riess H et al. *Proc ASCO* 2009;LBA4506.

Open-Label Trial of Chemotherapy ± LMWH in Advanced Pancreatic Cancer



Riess H et al. *Proc ASCO* 2009;LBA4506.

Venous Thromboembolic Events (Intent-to-Treat)

Events	Observation n = 152	Enoxaparin n = 160
Pulmonary embolism	2	0
Deep vein thrombosis (DVT)		
Proximal leg	9	2
Distal leg	2	0
Upper extremity	3	0
Total events	16	2
Total patients (VTE rate)	15 (9.9%)	2 (1.3%)

Riess H et al. *Proc ASCO* 2009;LBA4506.

VTE — Risk Reduction (Intent-to-Treat)

Treatment	Absolute risk reduction	Relative risk reduction	*p*-value
All enoxaparin-containing	8.6%	87%	<0.01
GEM + enoxaparin	12.4%	79%	0.3
GFFC + enoxaparin	6.6%	90%	0.025

Riess H et al. *Proc ASCO* 2009;LBA4506.

VTE and Major Bleeding Rates (Median Follow-Up 30.4 Weeks)

Events	Observation n = 152	Enoxaparin n = 160	*p*-value
VTE	15.5%	5.0%	<0.05
Bleeding	9.9%*	6.3%	0.6

* Three lethal bleedings — two tumor-associated lethal GI-bleeding in GFCC-treated patients and one lethal esophageal hemorrhage in a GEM-treated patient

Riess H et al. *Proc ASCO* 2009;LBA4506.

Conclusions

- The addition of enoxaparin to chemotherapy was associated with a reduced number of patients with VTEs.
  - 15 patients (9.9%) in the observation group vs 2 (1.3%) in the enoxaparin group
- In the GFFC group, there was a 90% relative risk reduction ($p = 0.025$) in VTE among those treated with enoxaparin compared with those assigned to observation only.
- There were no significant differences between the observation arm and the enoxaparin arm regarding major bleeding events.
  - At 30 weeks, the rate of bleeding events was 9.9% vs 6.3% ($p = 0.6$).

Riess H et al. *Proc ASCO* 2009;LBA4506.

Faculty Comments

DR ILSON: In pancreatic cancer the risk of developing thrombophlebitis can be as high as 10 to 20 percent, and there has always been a debate about whether patients would benefit from prophylactic anticoagulation. This study did show a reduction in the rate of deep vein thrombosis (DVT) from 9 to 10 percent to 3 to 4 percent with enoxaparin, and only one pulmonary embolism was observed on the study. Treatment with enoxaparin did not appear to affect overall survival or quality of life. Essentially we would treat 90 patients who would receive no benefit to prevent a DVT in 6 to 7 percent of patients, so I believe it's difficult to argue that this study should change standard practice. I don't believe we should be subjecting patients to daily injections when they have a limited life span to prevent a nonlife-threatening complication and not improve quality of life or survival.