A Phase III Trial Comparing mFOLFOX6 to mFOLFOX6 plus Bevacizumab in Stage II or III Carcinoma of the Colon: Results of NSABP Protocol C-08

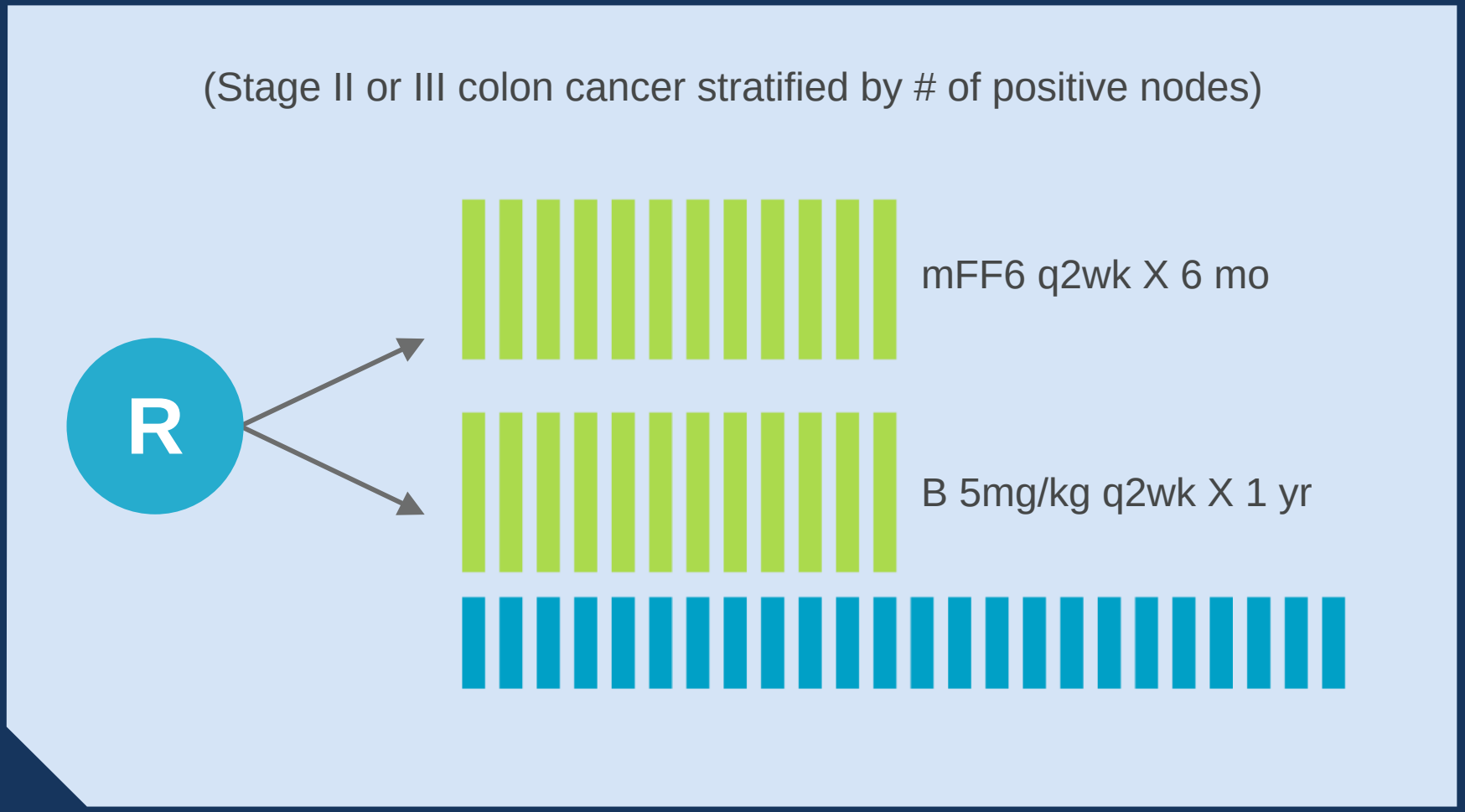
Wolmark N et al.
Proc ASCO 2009;Abstract LBA4.

Introduction

- Phase III trials have demonstrated that the addition of bevacizumab (B) to various chemotherapeutic agents (including oxaliplatin-based regimens) improves clinical outcomes for patients with advanced colorectal cancer (*NEJM* 2004;350:2335, *JCO* 2008;26:2013).
- Phase III trials MOSAIC[1] and NSABP C-07[2] demonstrated that the addition of oxaliplatin to 5-fluorouracil and leucovorin-containing regimens resulted in an increase in disease-free survival for patients with Stage II and III colon cancer ([1] *NEJM* 2004;350:2343, [2] *JCO* 2007;25:2198).
- Current study objective:
  - Assess the safety and efficacy of adding B to mFOLFOX6 for the treatment of Stage II or III colon cancer.

Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

NSABP C-08 Trial Design



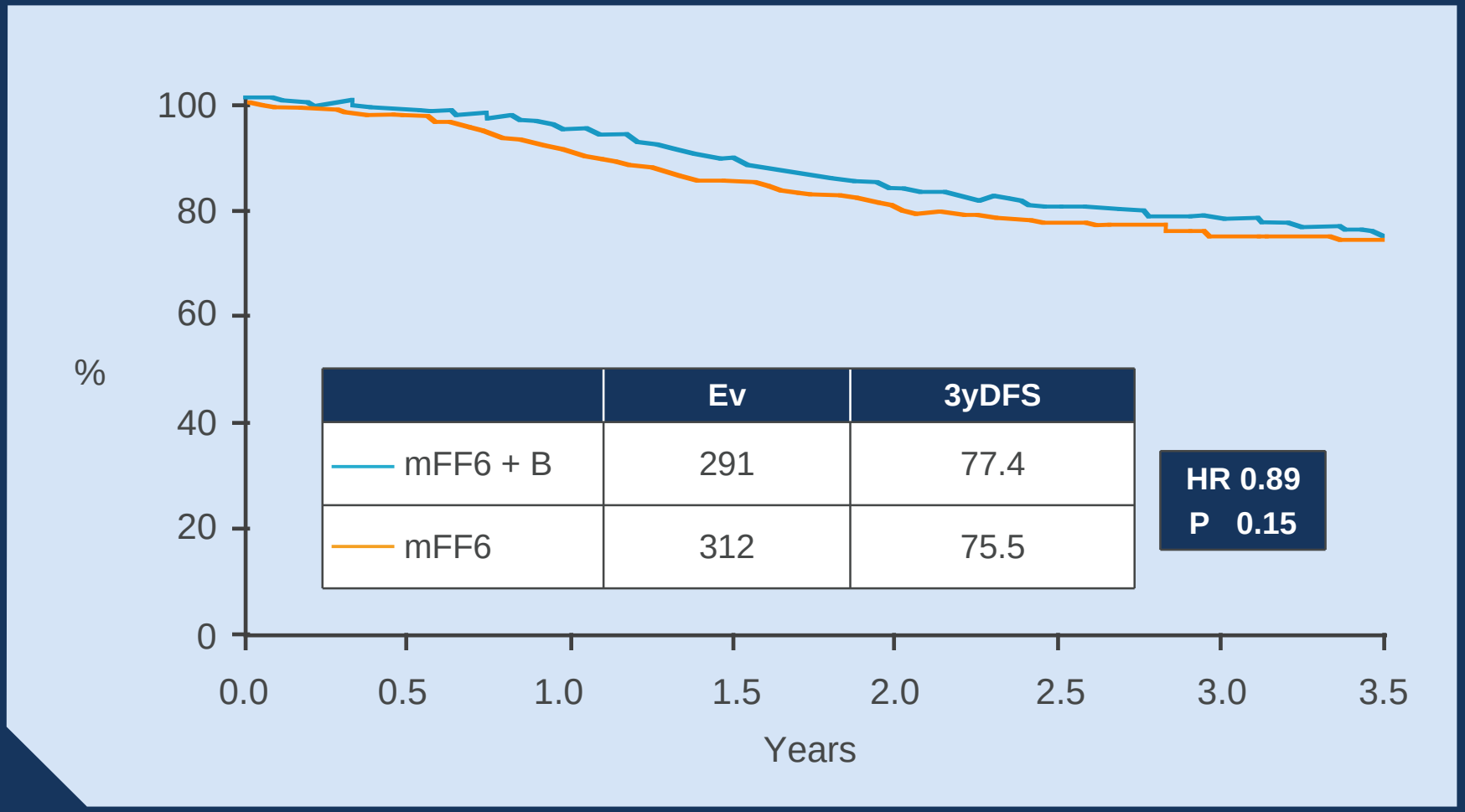
Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Methods

- Trial accrual:
  - Patients identified from 292 NSABP centers between September 2004 and October 2006.
  - Total patients randomized: 2,710
  - Stage II disease: 25%
  - Stage III disease, 1-3 positive nodes: 45%
  - Stage III disease, ≥4 positive nodes: 30%
- Median trial follow-up: 3 years
- Median duration of bevacizumab: 11.5 months
- Grade III+ toxicities significantly increased with bevacizumab included hypertension, pain, proteinuria and wound complications (*JCO* 2009;27:3385).

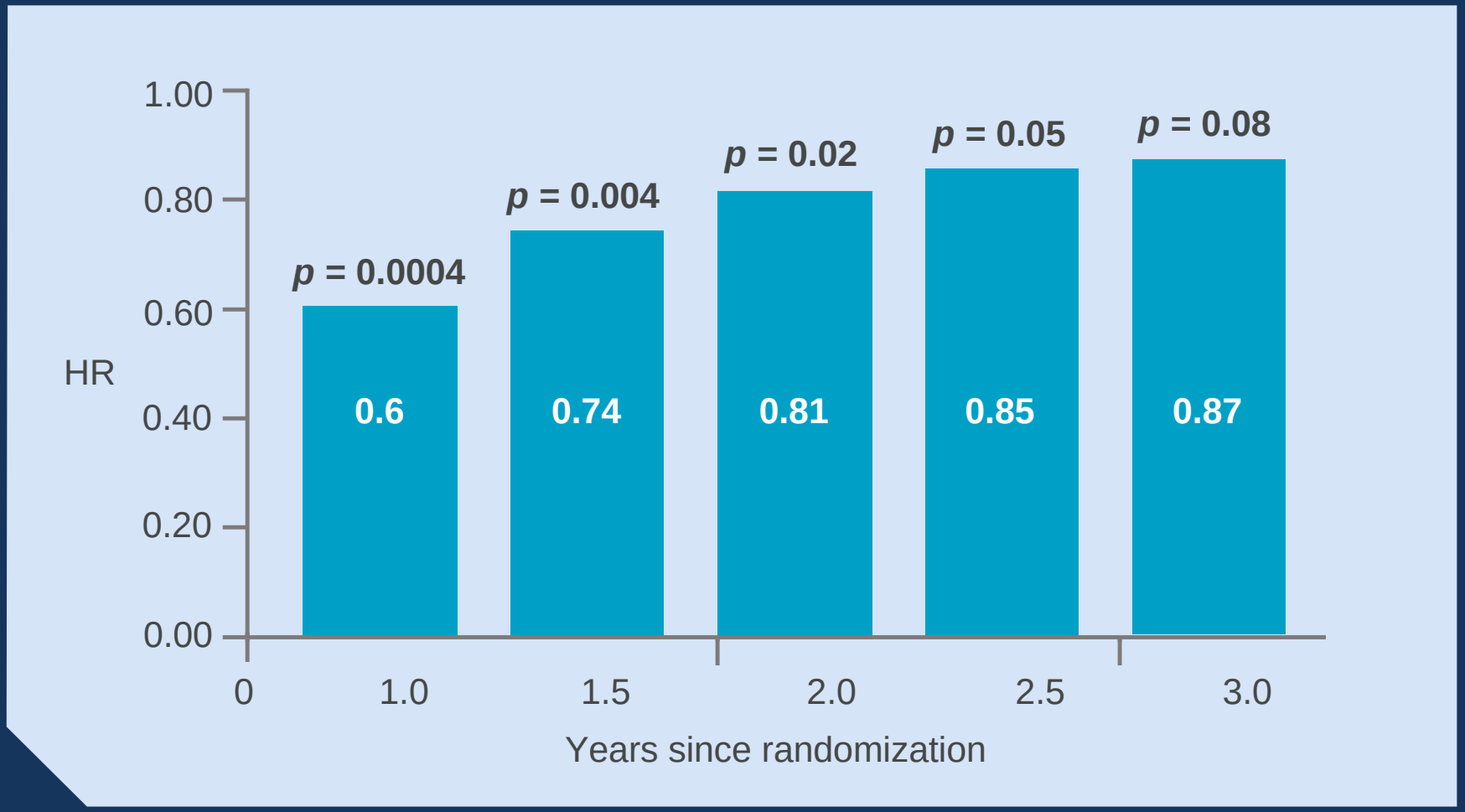
Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Results: 3-Year Disease-Free Survival (DFS)



With permission from Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Hazard Ratio (HR) mFF6 + B versus mFF6



Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Summary and Conclusions

- The addition of B to mFOLFOX6 did not result in a statistically significant prolongation in 3-year DFS, but there was a transient benefit in DFS during the one year that bevacizumab was utilized.
- Grade III+ toxicities increased with the addition of B.
  - Hypertension (1.8% vs 12%)
  - Pain (6.3% vs 11.1%)
  - Proteinuria (0.8% vs 2.7%)
  - Wound complications (0.3% vs 1.7%)
- Consideration should be given to clinical trials assessing a longer duration of bevacizumab administration.
- AVANT trial is comparing FOLFOX4 to FOLFOX4 + B to XELOX + B in patients with Stage II and III colon cancer.

Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Faculty Comments

DR HOCHSTER: This was a key study and our best lead for making progress in the adjuvant treatment of colon cancer. It's disappointing that it was negative, but it wasn't completely negative. I agree with Dr Wolmark's perspective that there was a transient effect of bevacizumab, which is worth continuing to explore. We shouldn't "write off" bevacizumab in the adjuvant setting. The NSABP will likely go forward with another adjuvant study with a longer duration of bevacizumab if the AVANT trial yields similar results. Some models suggest that longer durations of bevacizumab may prevent more micrometastases from activating the angiogenic switch. If bevacizumab was a completely nontoxic, inexpensive drug that could be taken orally — like tamoxifen — people would be discussing five years of bevacizumab.

Preoperative Fluorouracil (FU)-Based Chemoradiation +/- Weekly Oxaliplatin in Locally Advanced Rectal Cancer. Pathologic Response Analysis of STAR-01

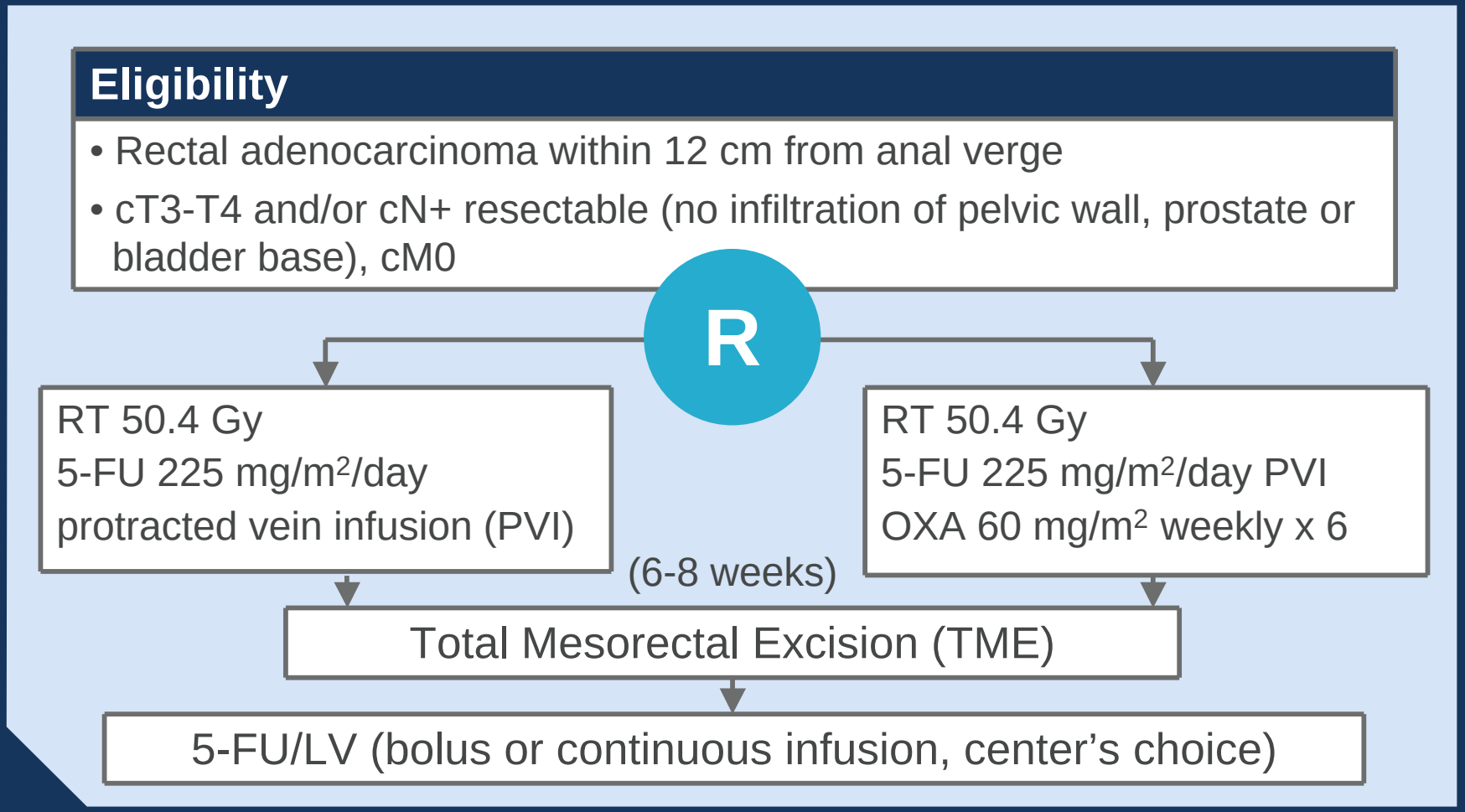
Aschele C et al.
Proc ASCO 2009;Abstract CRA4008.

Introduction

- Locally advanced rectal cancer (LARC) is associated with a high risk of distant metastases (30-35%) and a positive circumferential resection margin (CRM) in 10-30% of “resectable” tumors.
- Oxaliplatin (OXA) improves the efficacy of fluorouracil (FU)-based chemotherapy in the treatment of colon cancer, has radiosensitizing properties and shows promising activity when combined with preoperative radiation therapy (RT) and FU in Phase I/II studies.
- Current study objective:
  - Evaluate the impact of adding OXA to preoperative FU-based pelvic chemoradiation in patients with LARC.

Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

STAR Phase III Study Design (N = 747)



Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

Adverse Events

Adverse event	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 353)	*p*-value
Any Grade 3/4 event	8%	24%	<0.0001
Diarrhea (Grade 3/4)	4%	15%	<0.0001
Radiation dermatitis (Grade 3/4)	2%	5%	0.038
Sensory neuropathy			
Grade 2	0.5%	36%	
Grade 3	0%	1%	<0.0001
Treatment-related deaths	0.3%	0.6%	NR

Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

Pathologic Outcomes*

Pathologic complete response	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 368)
pT0N0* (95% CI)	16% (13-20%)	16% (13-20%)
Pathology (T)		
pT0	17%	18%
pT1-2	35%	35%
pT3-4	44%	42%
Median diameter	26 mm	24 mm
CRM-positive*	6%	4%

* No statistically significant differences between treatment arms

Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

Metastases at Surgery: Unplanned/Exploratory Analysis

	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 368)	*p*-value
pM1	11 (3%)	2 (0.5%)	0.014
Liver	6	1	—
Peritoneal	4	1	—
Nodes	1	0	—

Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

Summary and Conclusions

- These data do not support the addition of OXA to preoperative 5-FU/RT to maximize tumor shrinkage in LARC.
  - No improvement in local tumor response was observed.
  - Toxicity was significantly increased.
  - OXA-based regimens may not be the optimal backbone for incorporation of new radiosensitizing agents.
- The number of occult distant metastases at surgery lends support to the study's primary hypothesis that the addition of OXA will result in improvements in overall survival (confirmation with more mature data is required).
- Follow-up is ongoing to assess the impact on efficacy endpoints.

Aschele C et al. *Proc ASCO* 2009;Abstract CRA4008.

Faculty Comments

DR HOCHSTER: Unlike some of the rectal cancer clinical trials that have been done in Europe, STAR-01 at least used a conventional radiation therapy schedule and infusional 5-FU chemotherapy. The addition of weekly oxaliplatin added more toxicity, mainly neuropathy and diarrhea, but unfortunately did not have a major impact on the pathologic outcome. So these data suggest that oxaliplatin may not act as a radiosensitizer. However, the study does not inform us about the long-term benefit of oxaliplatin. Normally, we would use preoperative and postoperative therapy and look for a long-term survival benefit.

Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer: ACCORD 12/0405-Prodige 2

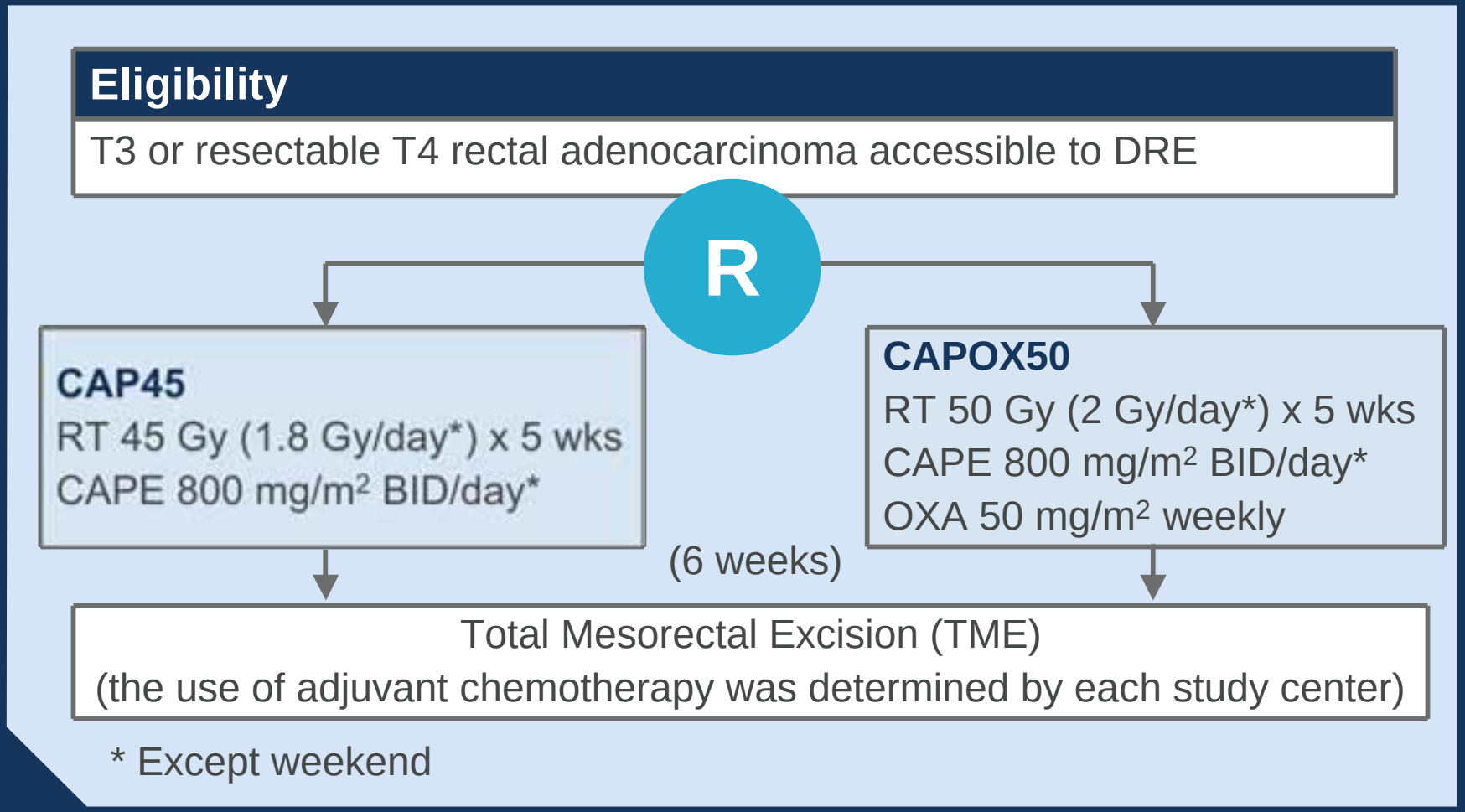
Gerard JP et al.
J Clin Oncol 2010;28(10):1638-44.

Introduction

- The German Rectal Cancer Study Group CAO/ARO Phase III trial established preoperative chemoradiation therapy (CRT) as the standard of care for T3/4 rectal cancer (*NEJM* 2004;351:1731).
  - Cumulative incidence of local relapse: 6% for preoperative CRT vs 13% for postoperative CRT
  - Reduced toxicity was observed.
  - No difference in overall survival was seen.
- Current study objective:
  - Evaluate the impact of radiation therapy (RT) dose increase from standard 45 Gy/5 weeks to 50 Gy/5 weeks and chemotherapy intensification with the addition of oxaliplatin to capecitabine (CAPOX50) on pathologic complete response in patients with T3/4 rectal cancer.

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Phase III Trial of Advanced Rectal Cancer: ACCORD 12/0405-Prodige 2



Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Dworak-Quirke Criteria for Grading of Operative Tumor Specimen

- Primary endpoint: Pathologic complete response (ypCR)
- Dworak-Quirke tumor grading criteria (*Int J Colorectal Dis* 1997;12:19, *J Clin Oncol* 2005;23:8688)
  - 0 = No or very little response
  - 1 = Partial response
  - 2 = Major response with few residual cancer cells
  - 3 = Complete response with no detectable cancer cells (ypCR)

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Pathologic Response and Circumferential Rectal Margin (CRM)

Endpoint	CAP45 (n = 282)	CAPOX50 (n = 283)	*p*-value
ypCR	**14%**	**19%**	**0.09**
ypCR or very few residual tumor cells	30%	39%	0.008
CRM	**CAP45 (n = 149)**	**CAPOX50 (n = 143)**	***p*-value**
R1 (≤1 mm)	13%	8%	0.17
R+ (≤2 mm)	19%	10%	0.022

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Adverse Events

Adverse event	CAP45 (n = 293)	CAPOX50 (n = 291)	*p*-value
All Grade 3/4 toxicity	11%	25%	<0.001
Diarrhea (Grade 3/4)	3%	13%	<0.001
Hematologic (Grade 3/4)	4%	5%	NS
Fatigue (Grade 3)	1%	5%	0.004
Hand-foot syndrome (Grade 2)	<1%	0%	NS
Peripheral neuropathy (Grade 2)	0.4%	5%	0.002

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Summary and Conclusions

- Escalation of RT dose and the addition of OXA to CAPOX50 did not significantly increase pCR or the rate of negative CRM compared to CAP45.
  - ypCR = 19% vs 14% (p = 0.11)
  - CRM-negative = 92% vs 87% (p = 0.17)
  - ypCR may not be a suitable surrogate endpoint for neoadjuvant chemoradiation trials in rectal cancer.
- The improved efficacy outcomes (19% ypCR) may be mainly attributable to radiotherapy dose intensification.
- Grade 3/4 toxicity was increased with CAPOX50.
- High-dose radiotherapy (ie, 50 Gy/25 fraction) plus CAPOX merits investigation for T3-4 rectal cancers.

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Faculty Comments

DR HOCHSTER: This is a prospective, randomized trial of neoadjuvant capecitabine with or without oxaliplatin in combination with radiation therapy for rectal cancer. The addition of oxaliplatin may have improved the pathologic response to a certain extent, with increased toxicity, but it was not a positive study and the use of oxaliplatin in this setting should not become a standard practice until additional data are available, particularly concerning longer-term outcome. Similar to STAR-01, this study informs us about the effect of oxaliplatin on the operative specimen, but it doesn't tell us about what happens in the long run. Oxaliplatin could still improve overall survival by reducing the rate of distant metastases.

Phase III Trial of Capecitabine + Oxaliplatin (XELOX) versus Bolus 5-FU/Leucovorin (LV) in Stage III Colon Cancer: Impact of Age on Disease-Free Survival

Haller DG et al.

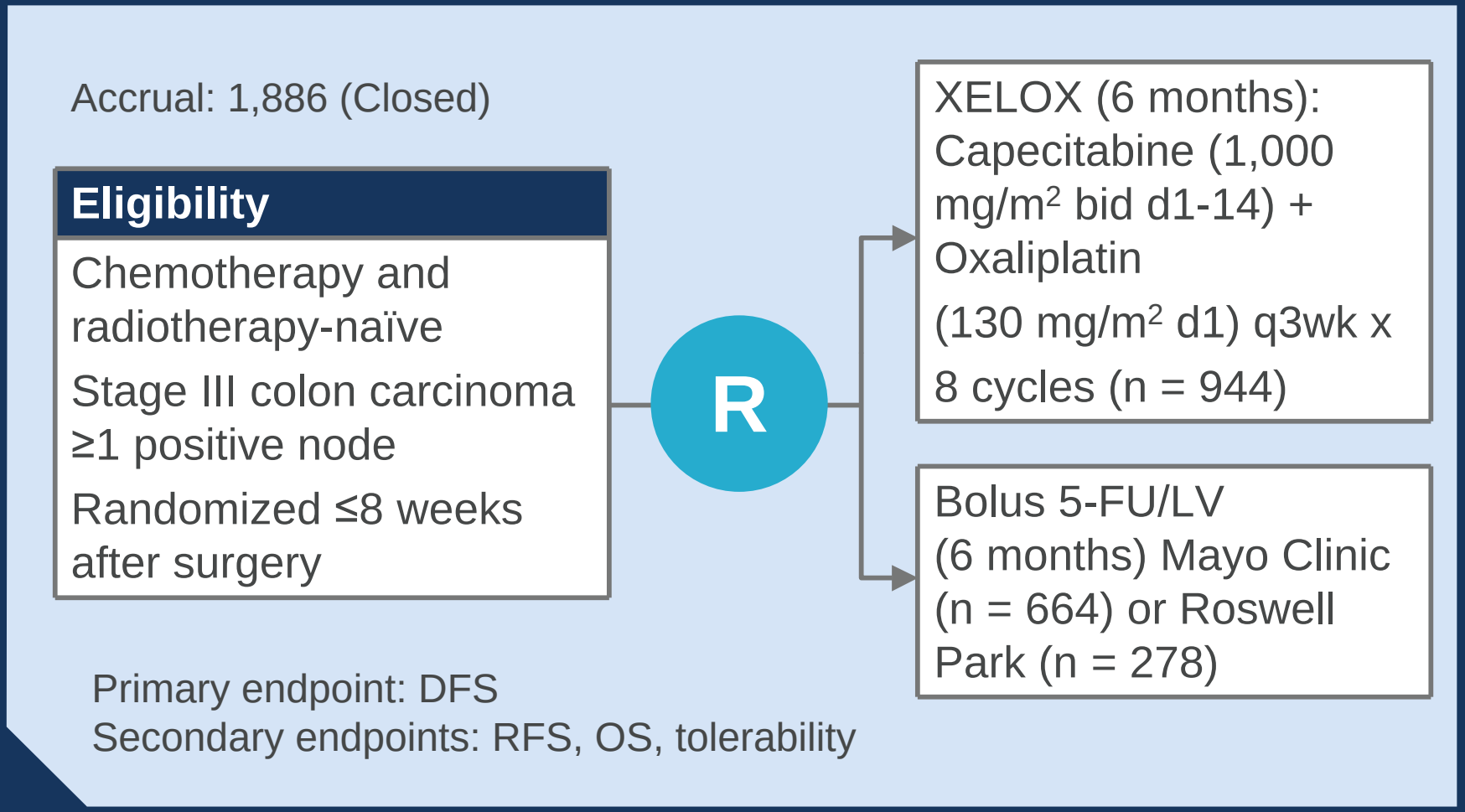
Gastrointestinal Cancers Symposium 2010;Abstract 284.

Introduction

- Capecitabine is noninferior to bolus 5-FU/LV in disease-free survival (DFS) and overall survival (OS) as adjuvant therapy in Stage III colon cancer (*NEJM* 2005;352:2696).
  - Patients ≥70 years showed improved outcome with capecitabine.
- ACCENT database concluded that newer adjuvant regimens (including oxaliplatin combinations) were not associated with significant efficacy benefits versus 5-FU/LV in patients ≥70 years, when compared with younger patients (ASCO 2009;Abstract 4010).
- Current study objective:
  - Examine DFS across age groups in NO16968, a Phase III trial comparing XELOX versus bolus 5-FU/LV in Stage III colon cancer.

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968: A Phase III Trial of XELOX versus Bolus 5-FU/LV in Stage III Colon Cancer



Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968 Subgroup Analysis of 3-Year DFS by Age

<65 versus ≥65 years	XELOX	5-FU/LV	HR (95% CI)
<65 years (n = 1,142)	72%	69%	0.80 (0.65,0.98)
≥65 years (n = 744)	68%	62%	0.81 (0.64,1.03)
<70 versus ≥70 years	**XELOX**	**5-FU/LV**	**HR (95% CI)**
<70 years (n = 1,477)	72%	69%	0.79 (0.66,0.94)
≥70 years (n = 409)	66%	60%	0.87 (0.63,1.18)

HR = hazard ratio

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968 Subgroup Analysis of 5-Year OS by Age

<65 versus ≥65 years	XELOX	5-FU/LV	HR (95% CI)
<65 years (n = 1,142)	80%	77%	0.87 (0.67,1.13)
≥65 years (n = 744)	73%	70%	0.90 (0.68,1.19)
<70 versus ≥70 years	**XELOX**	**5-FU/LV**	**HR (95% CI)**
<70 years (n = 1,477)	80%	76%	0.86 (0.69,1.08)
≥70 years (n = 409)	69%	67%	0.94 (0.66,1.34)

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Select Grade III/IV Toxicities

Grade 3/4 adverse events	<70 years		≥70 years	
	XELOX (n = 748)	5-FU/LV (n = 711)	XELOX (n = 190)	5-FU/LV (n = 215)
Diarrhea	18%	19%	26%	25%
Nausea/Vomiting	8%	6%	11%	5%
Stomatitis	<1%	9%	1%	8%
Neutropenia (includes granulo-cytopenia)	9%	16%	10%	17%
Hand-foot syndrome	6%	<1%	4%	<1%
Neurosensory	11%	<1%	11%	0%

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Summary and Conclusions

- XELOX significantly improved DFS compared with bolus 5-FU/LV as adjuvant therapy for Stage III colon cancer.
- XELOX efficacy was observed in patients ≥65 and ≥70 years.
- Efficacy in the elderly subgroup eligible for trial was achieved despite decreased treatment duration and dose intensity.
- These findings differ from those of the MOSAIC study and the ACCENT analysis.
  - Reasons for this apparent difference are unknown.
- Current analysis supports consideration of XELOX for patients with Stage III colon cancer; age alone should not drive clinical decision-making.

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Faculty Comments

DR BENSON: This study builds upon the adjuvant data supporting oxaliplatin-containing combination regimens for patients with Stage III colon cancer. The original report demonstrated that capecitabine in combination with oxaliplatin was superior to bolus 5-FU. This presentation specifically attempted to determine whether age had an impact on disease-free survival. They concluded that CAPOX showed a similar advantage over 5-FU in patients younger than 70 and older than 70 years old. These data reinforce that age is not a determining factor in the selection of adjuvant therapy. Rather, other factors, such as patient comorbidities, are more important. The trial will require more mature follow-up until overall survival can be evaluated, but disease-free survival is an appropriate endpoint, so there can be some degree of comfort with these results.

Can Chemotherapy Be Discontinued in Unresectable Metastatic Colorectal Cancer? The GERCOR OPTIMOX2 Study

Chibaudel B et al.

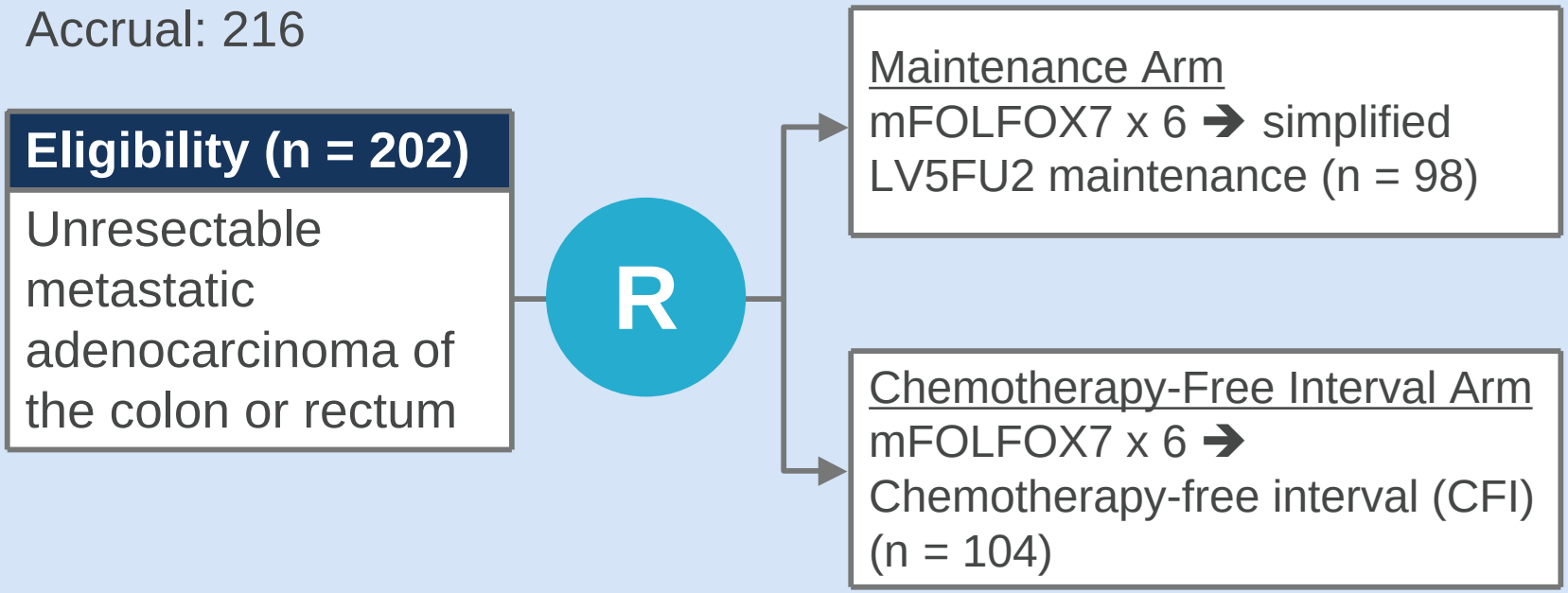
J Clin Oncol 2009;27(34):5727-33.

Introduction

- The OPTIMOX1 study demonstrated that using a stop-and-go strategy with oxaliplatin reduced toxicity without compromising efficacy in patients with advanced colorectal cancer (*JCO* 2006;24:394).
  - Oxaliplatin was stopped after six cycles of FOLFOX7 and maintenance therapy was continued with a simplified LV plus bolus and infusional FU (LV5FU2) regimen.
  - Efficacy of the stop-and-go strategy was comparable to that of continuing FOLFOX4 until progression or toxicity.
- Current study objective:
  - Compare the stop-and-go strategy evaluated in OPTIMOX1 and a novel strategy, OPTIMOX2, which involves the complete, but temporary, discontinuation of all chemotherapy.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

GERCOR OPTIMOX2 Phase III Trial Design



Reintroduction of modified FOLFOX7 (mFOLFOX7) for a further 6 cycles was planned at progression or in case of tumor-related symptoms in patients without residual sensory neuropathy Grade >1.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Efficacy Results (median follow-up 40.7 months)

	Maintenance (n = 98)	CFI (n = 104)	*p*-value
Median duration of disease control (DDC)	13.1 mo	9.2 mo	0.046
Median progression-free survival (PFS)	8.6 mo	6.6 mo	0.0017
Median overall survival (OS)	23.8 mo	19.5 mo	0.42
Median duration of maintenance therapy/CFI	4.8 mo	3.9 mo	—
Overall response rate Induction with mFOLFOX7 (n = 98, 104)	59.2%	59.6%	—

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

FOLFOX Reintroduction

	Maintenance (n = 54)	CFI (n = 66)	*p*-value
Reintroduction rate in eligible patients	81.8%	84.6%	NR
Median PFS of the first FOLFOX reintroduction	4.8 mo	3.9 mo	0.08
Overall response rates after first FOLFOX reintroduction[a]	20.4%	30.3%	NR
Control of tumor (partial response plus stable disease)	59.3%	57.6%	NR

[a] Ninety percent of patients who had a partial response at reintroduction previously had a partial response at initial chemotherapy.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Select Grade 3/4 Toxicities

Toxicity*	Maintenance Arm			CFI Arm	
	Cycles 1-6	Maint.	Reintro-duction	Cycles 1-6	Reintro-duction
Neutropenia	21.4%	9.8%	10.0%	11.7%	14.0%
Thrombocytopenia	8.2%	1.6%	6.7%	3.9%	2.0%
Neuropathy G3[a]	2.9%	4.9%	6.7%	4.9%	7.8%
Hand-foot syndrome	0%	4.9%	0%	0%	0%

* Toxicity per patient, using NCI-CTC criteria (v2.0)
[a] Defined by Lévi scale
Maint. = maintenance

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Summary and Conclusions

- Complete discontinuation of chemotherapy (OPTIMOX2) had a negative impact on DDC and PFS, but not OS, compared with the maintenance therapy strategy (OPTIMOX1).
  - DDC: 9.2 mos vs 13.1 mos ($p = 0.046$)
  - PFS: 6.6 mos vs 8.6 mos ($p = 0.0017$)
  - OS: 19.5 mos vs 23.8 mos ($p = 0.42$)
- Chemotherapy discontinuation cannot be prescheduled before therapy is initiated in patients with advanced colorectal cancer, since individual responses cannot be predicted.
- The ongoing DREAM GERCOR OPTIMOX3 study (NCT00265824) is evaluating maintenance therapy with targeted drugs alone after chemotherapy with bevacizumab.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Faculty Comments

DR BENSON: This is an important French study. We recognize that continuation of chemotherapy for patients with advanced disease has a price in terms of toxicity, particularly neurotoxicity with FOLFOX. The study demonstrated that patients who continued chemotherapy had significant improvement in disease control compared to those who had a chemotherapy-free interval. In addition, progression-free survival was significantly better for those individuals who continued therapy without a drug holiday. The authors concluded that a planned, complete discontinuation of chemotherapy is not an optimal strategy for many patients. So we cannot routinely recommend a chemotherapy-free interval as a standard of care for patients with metastatic disease who are responding to therapy because it does appear to negatively affect outcome.

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Van Cutsem E et al.

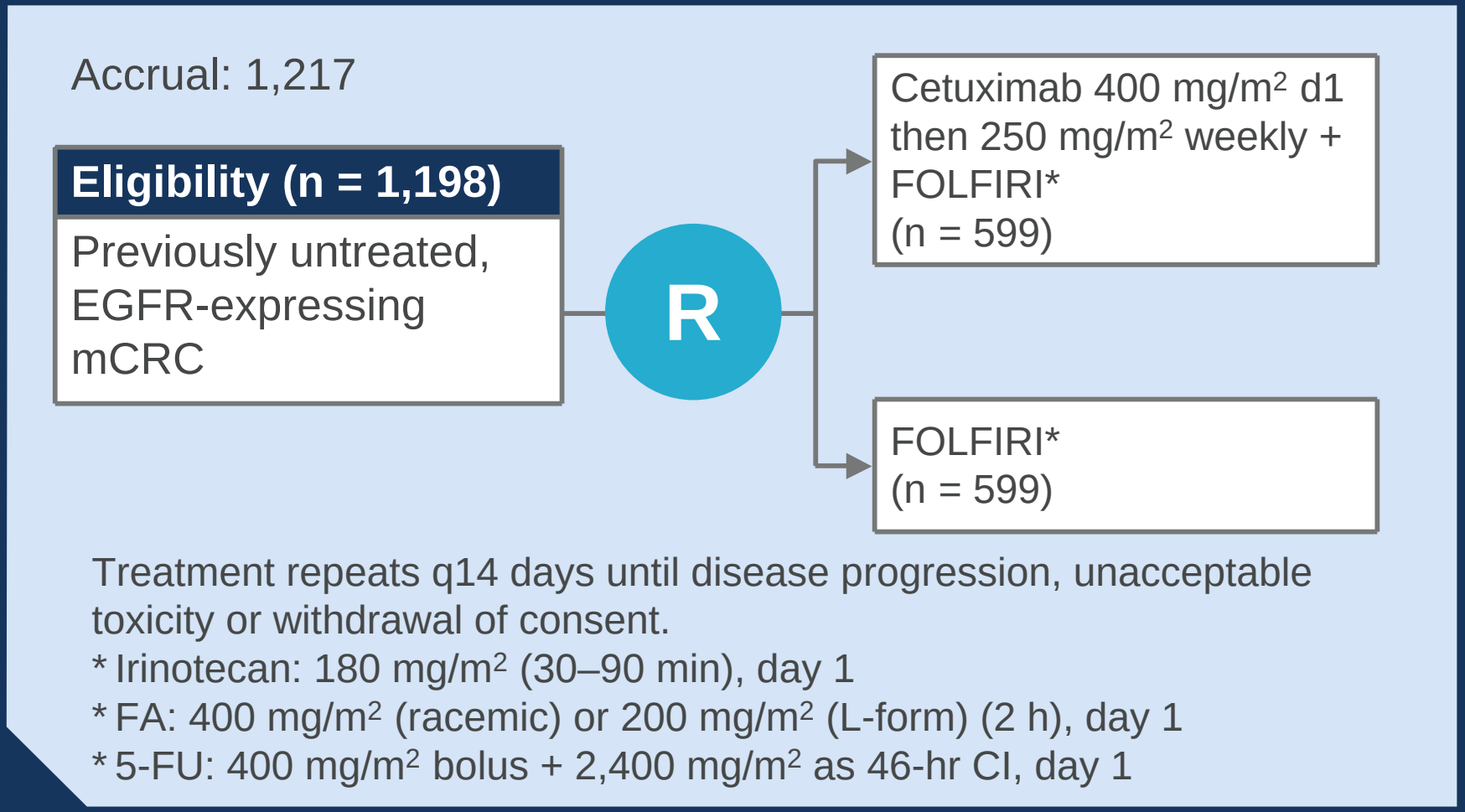
N Engl J Med 2009;360(14):1408-17.

Introduction

- Cetuximab is effective in combination with irinotecan or alone in irinotecan-refractory metastatic colorectal cancer (mCRC) (*NEJM* 2004;351:337, *JCO* 2006;24:4914).
- Cetuximab is active when added to irinotecan-based (*Ann Oncol* 2006;17:450, *JCO* 2004;22:Suppl:248s) or oxaliplatin-based (*JCO* 2007;25:5225, *Eur J Cancer Suppl* 2007;5:236, *Ann Oncol* 2008;19:1442) therapy as first-line treatment.
- No biomarkers reliably predict response to cetuximab but K-ras mutation status shows promise.
- Current study objectives:
  - Evaluate the safety and efficacy of first-line FOLFIRI with or without cetuximab.
  - Investigate the influence of K-ras mutation status on outcome.

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Study Design



Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Primary and Secondary Efficacy Analyses

	Cetuximab + FOLFIRI (N = 599)	FOLFIRI (N = 599)	Hazard or Odds Ratio	*p*-value
Progression-Free Survival (PFS)				
Progression event	49.7%	53.8%	0.85	0.048
Median PFS	8.9 mo	8.0 mo		
Overall Survival (OS)				
Deaths	68.8%	69.4%	0.93	0.31
Median OS	19.9 mo	18.6 mo		

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Efficacy Analysis According to K-ras Status

	Cetuximab + FOLFIRI	FOLFIRI	Hazard or Odds Ratio
Progression-Free Survival			
K-ras mutant (n = 105, 87)	7.6 mo	8.1 mo	1.07
K-ras wild-type (n = 172, 176)	9.9 mo	8.7 mo	**0.68**
Overall Survival			
K-ras mutant (n = 105, 87)	17.5 mo	17.7 mo	1.03
K-ras wild-type (n = 172, 176)	24.9 mo	21.0 mo	**0.84**

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Most Common Grade 3/4 Adverse Events and Special Adverse Events in the Safety Population

	Cetuximab + FOLFIRI (N = 600)	FOLFIRI (N = 602)	*p*-value
Neutropenia	28.2%	24.6%	0.16
Leukopenia	7.2%	5.1%	0.15
Diarrhea	15.7%	10.5%	0.008
Rash	8.2%	0%	<0.001
Dermatitis acneiform	5.3%	0%	<0.001
Special Adverse Events			
Skin reactions, all	19.7%	0.2%	<0.001
Acne-like rash	16.2%	0%	<0.001

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Summary and Conclusions

- The addition of cetuximab to first-line FOLFIRI reduced the risk of progression of mCRC.
  - Progression event: 49.7% vs 53.8%
  - Median PFS: 8.9 vs 8.0 months
- The benefit of cetuximab was limited to patients with K-ras wild-type tumors.
  - PFS: 9.9 vs 8.7 months, HR = 0.68
  - OS: 24.9 vs 21.0 months, HR = 0.84
- The overall incidence of Grade 3 or 4 adverse events was significantly higher with cetuximab plus FOLFIRI than with FOLFIRI alone (79.3% vs 61.0%), including increased diarrhea (15.7% vs 10.5%) and skin reactions (19.7% vs 0.2%).

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Faculty Comments

DR BENSON: This is an important study because it builds upon past cetuximab data showing benefits for patients who receive cetuximab with or without chemotherapy in the second- and third-line settings. This trial evaluated FOLFIRI with or without cetuximab in the first-line setting for patients with metastatic colorectal cancer. They looked at K-ras status and linked that to the clinical benefit of cetuximab. This study demonstrated an improvement in progression-free survival for the addition of cetuximab to FOLFIRI, which was limited to patients with K-ras wild-type tumors. So determination of K-ras status is important when considering the use of anti-EGFR therapy in patients with metastatic colorectal cancer.

Outcome of Primary Tumor in Synchronous Stage IV Colorectal Cancer Following Combination Chemotherapy without Surgery as Initial Treatment

Poultsides GA et al.
J Clin Oncol 2009;27(20):3379-84.

Introduction

- In the absence of symptoms, the role of surgical resection of a primary colorectal cancer and metastases is uncertain.
- With recent advances in systemic chemotherapy and improvement in survival of metastatic colorectal cancer (mCRC), the risks and benefits of a deferred surgical strategy have not been completely evaluated.
- Current study objective:
  - Describe the frequency of primary tumor-related complications requiring operative or nonoperative intervention in patients with synchronous mCRC who received initial treatment with modern, triple-drug, oxaliplatin- or irinotecan-based combination chemotherapy with or without bevacizumab, in the absence of prophylactic surgery.

Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Methods

- Inclusion criteria:
  - Patients presenting to MSKCC with synchronous mCRC and intact primary between 1/2000 and 12/2006
  - Asymptomatic with regard to primary tumor
  - No prior primary tumor-directed surgery, radiation therapy, endoscopic stenting or ablation
- Up-front, first-line therapies:
  - Bolus 5-FU/leucovorin and irinotecan
  - Infusional 5-FU/leucovorin and irinotecan
  - Infusional 5-FU/leucovorin and oxaliplatin
  - With or without bevacizumab

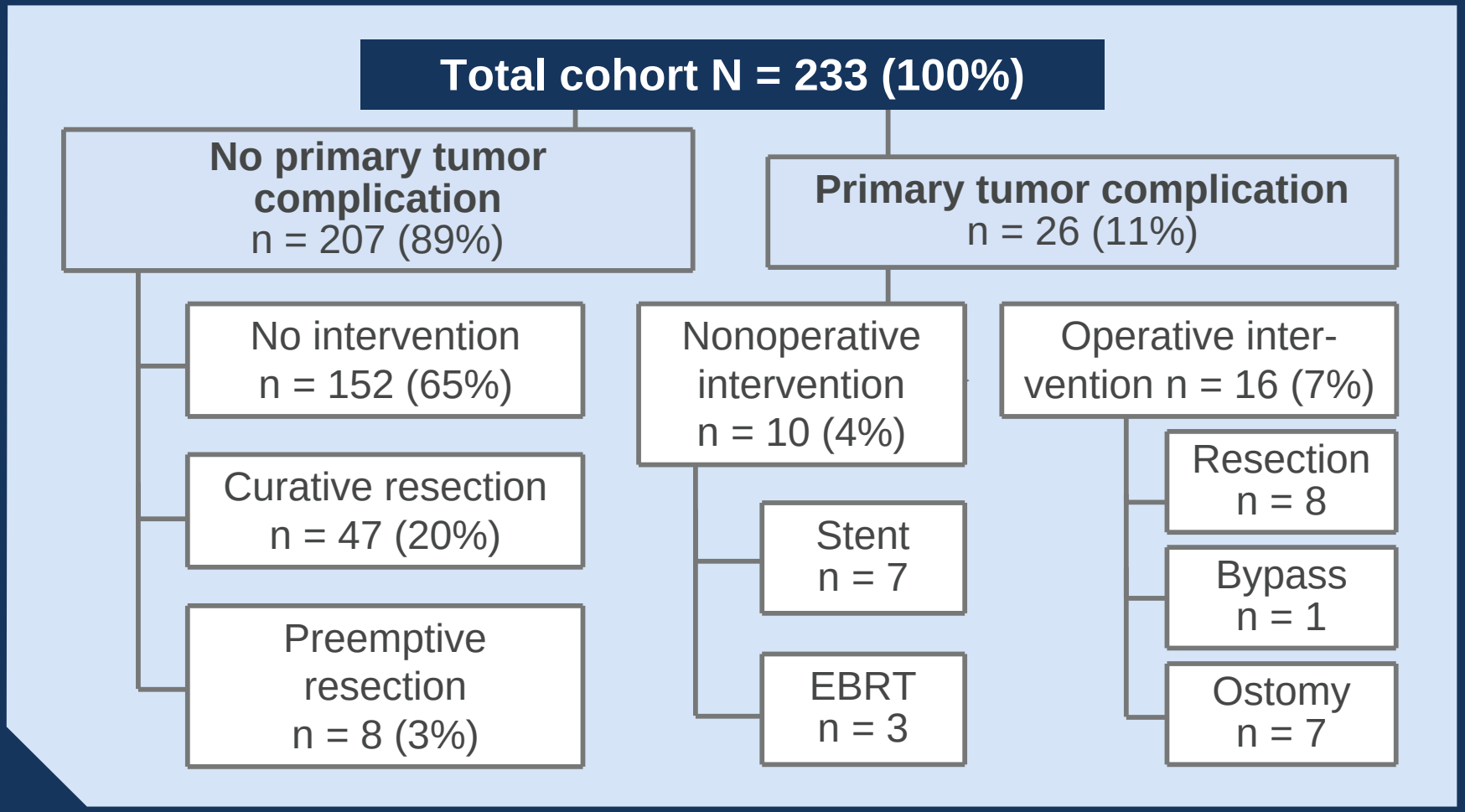
Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Patient Characteristics (n = 233)

Primary Tumor Location	
Right colon	37%
Left colon	29%
Rectum	34%
Major Site(s) of Metastatic Disease at Presentation	
Liver	95%
Retroperitoneal lymph nodes	39%
Lung	30%
Metastatic Sites Involved	
1 site/2 sites/3 or more sites	40%/45%/14%

Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Outcome of Unresected Primary Tumor



Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Median Time to Intervention and Subsequent Survival

Intervention or Resection, n (%)	Time from Initiation of Chemotherapy to Intervention	Survival After Intervention
Operative, 16 (7%)	7 mo	6 mo
Non-operative, 10 (4%)	12 mo	8 mo
Curative resection*, 47 (20%)	8 mo	44 mo
Preemptive resection, 8 (3%)	9 mo	15 mo
Median survival from initiation of chemotherapy for the 152 patients who never required an intervention was 13 months.		

* Elective resection of primary metastases

Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Conclusions

- Of the total cohort of 233 patients, 93% never required surgery to palliate primary tumor-related complications.
- Postoperative mortality for those patients undergoing subsequent surgical intervention was 0.8% (data not shown).
  - Rate compares favorably with prophylactic colon resection in the metastatic setting.
  - The need for surgical intervention did not correlate with overall survival.
- These findings support the appropriateness of nonoperative systemic management as an initial treatment option for asymptomatic patients with intact primary CRC and synchronous mCRC in the absence of overt obstruction or severe acute bleeding.

Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Faculty Comments

DR BENSON: These patients with synchronous metastatic colorectal cancer and an unresected primary tumor received triple-drug therapy, with 5-FU/leucovorin in combination with oxaliplatin or irinotecan with or without bevacizumab as their initial treatment, and 93 percent of patients did not require surgical palliation of their primary tumor. Some patients underwent stent placement or surgery for primary tumor obstruction or perforation. These are practice-changing data. For many patients with colorectal cancer who present with synchronous metastatic disease, performing a prophylactic surgical resection of the primary is not routinely necessary. That is a practice-changing paradigm. Some patients require immediate surgical intervention, but for patients who are relatively asymptomatic, it is reasonable to proceed with chemotherapy as the initial intervention.

Phase IIIB Randomized Trial of Chemotherapy, Bevacizumab and Panitumumab versus Chemotherapy and Bevacizumab for Metastatic Colorectal Cancer

Hecht JR et al.
J Clin Oncol 2009;27(5):672-80.

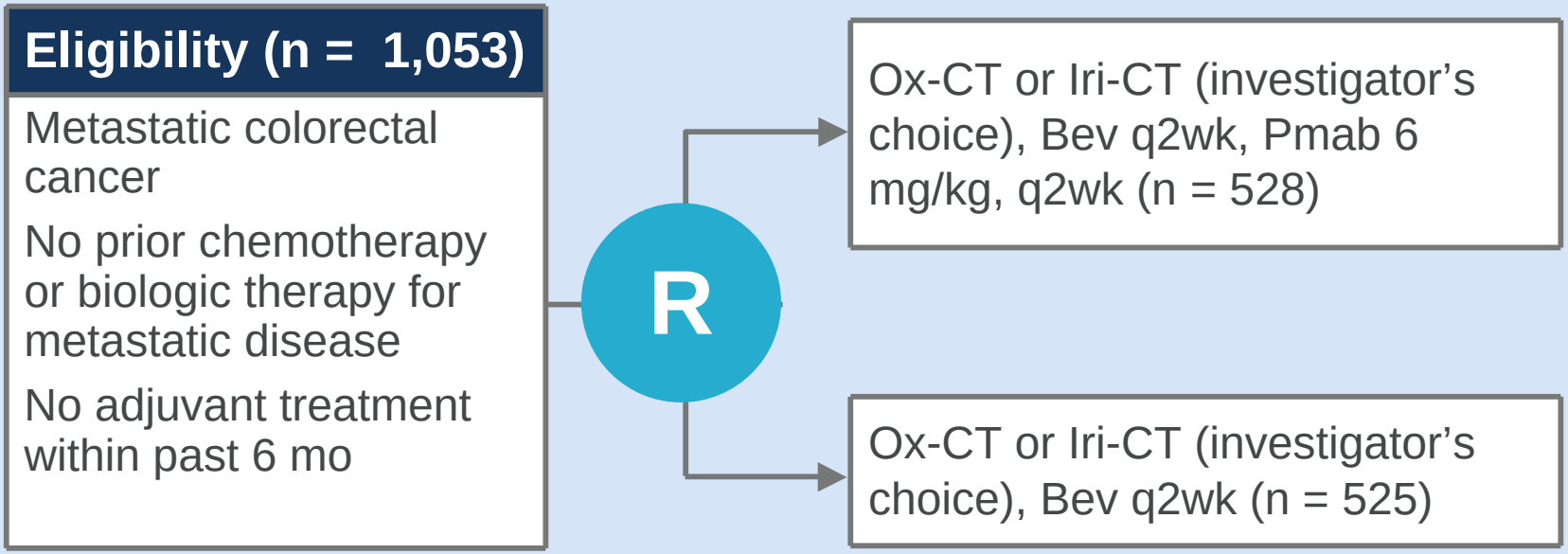
Introduction

- Within the past decade, important advances in the treatment of metastatic colorectal cancer have included the use of biologic agents and multiagent chemotherapy.
- When combined with chemotherapy (CT), bevacizumab (Bev) improves overall survival in first- and second-line settings (*NEJM* 2004;350:2335, *JCO* 2007;25:1539).
- Blocking both VEGF and EGFR pathways may increase antitumor activity (*JCO* 2007;25:4557).
- Current study objective:
  - Evaluate the efficacy and safety of Bev and oxaliplatin-based (Ox) or irinotecan-based (Iri) CT with or without panitumumab (Pmab), an antibody targeting EGFR, in previously untreated metastatic colorectal cancer.

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Phase IIIB Open-Label Trial of CT/Bev/Pmab versus CT/Bev in Metastatic Colorectal Cancer

Accrual: 1,240 (Closed)



Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Survival (Intent-to-Treat)

Median survival	Pmab + Bev Ox-CT (n = 413)	Bev Ox-CT (n = 410)	Pmab + Bev Iri-CT (n = 115)	Bev Iri-CT (n = 115)
Progression-free survival	10 mo	11.4 mo	10.1 mo	11.7 mo
Hazard ratio (95% CI)	1.27 (1.06 to 1.52)		1.19 (0.79 to 1.79)	
Overall survival	19.4 mo	24.5 mo	20.7 mo	20.5 mo
Hazard ratio (95% CI)	1.43 (1.11 to 1.83)		1.42 (0.77 to 2.62)	

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Objective Response Rate by Blinded Central Review (Intent-to-Treat)

Clinical response	Pmab + Bev Ox-CT (n = 413)	Bev Ox-CT (n = 410)	Pmab + Bev Iri-CT (n = 115)	Bev Iri-CT (n = 115)
Best overall RR Complete RR Partial RR	46% 0% 46%	48% <1% 47%	43% 0% 43%	40% 0% 40%
Stable disease	29%	33%	27%	37%
Progressive disease[1]	7%	4%	13%	3%

RR = response rate

[1] Central review unable to evaluate clinical disease progression or progressive disease after surgical resections

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Select Grade 3/4 Adverse Events

Toxicity	Pmab + Bev Ox-CT (n = 407)	Bev Ox-CT (n = 397)	Pmab + Bev Iri-CT (n = 111)	Bev Iri-CT (n = 113)
Skin toxicity	36%	1%	38%	0%
Diarrhea	24%	13%	28%	9%
Nausea/vomiting	13%	7%	13%	8%
Infections	18%	10%	14%	9%
Neutropenia	24%	24%	17%	21%
Deep vein thrombosis	7%	8%	13%	6%

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Conclusions

- The addition of Pmab to CT/Bev was associated with decreased progression-free survival.
  - Ox-CT PFS: 10 mo vs 11.4 mo
  - Iri-CT PFS: 10.1 mo vs 11.7 mo
- A trend toward worse survival was observed with Pmab in the wild-type K-ras group of the oxaliplatin cohort.
- The addition of Pmab to CT/Bev results in increased toxicity.
- The addition of Pmab to Bev and Ox- or Iri-CT is not recommended for the treatment of patients with metastatic colorectal cancer in clinical practice.

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Faculty Comments

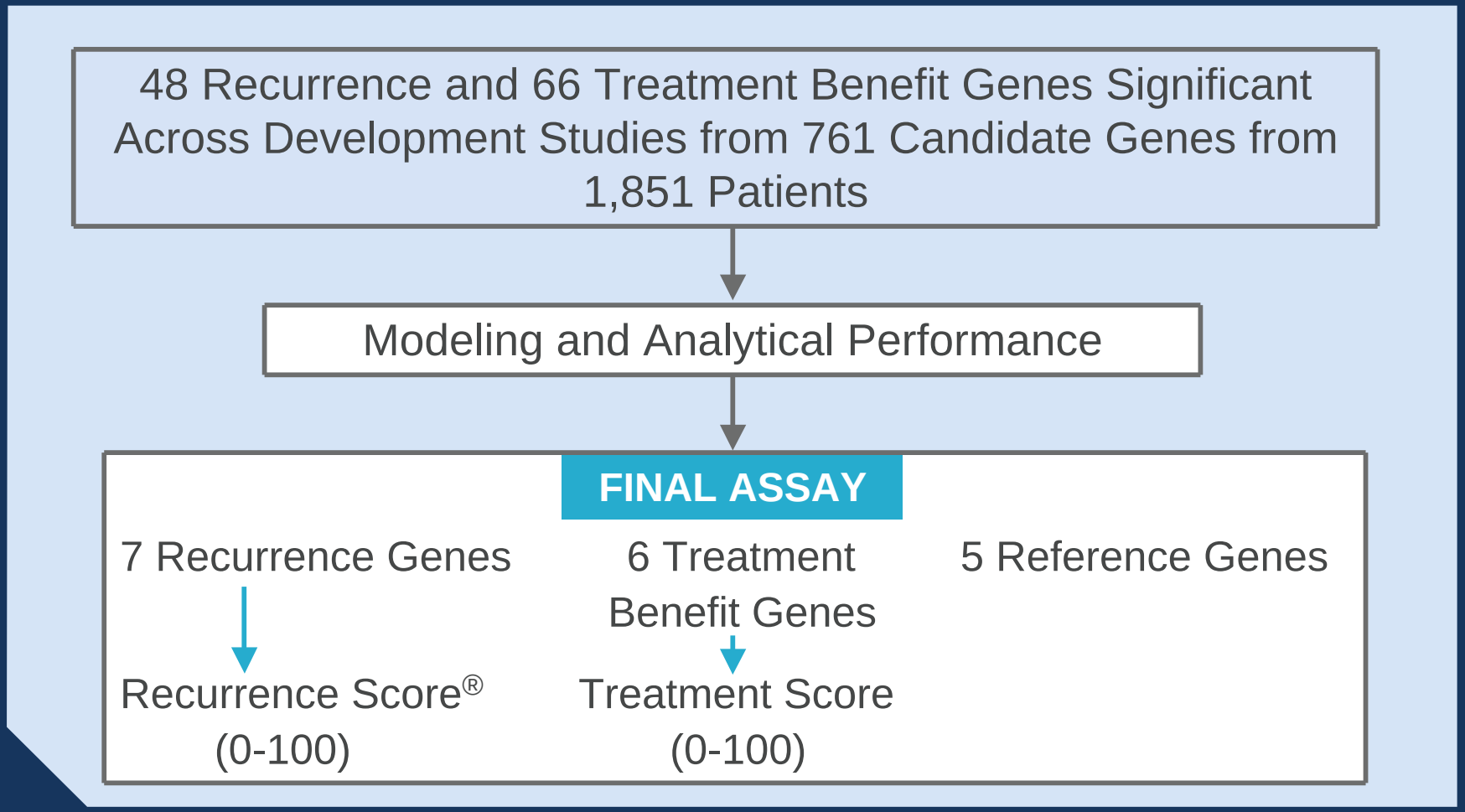
DR BENSON: This is an important study, with lessons to be learned. The rationale for dual biologic therapy in combination with chemotherapy in the first-line setting appeared reasonable, based upon previous data supporting the benefits of panitumumab and bevacizumab. These agents both partner well with chemotherapy and do not appear to have overlapping toxicities. The results were striking in that chemotherapy in combination with bevacizumab/panitumumab resulted in a worse outcome. Even patients with K-ras wild-type tumors who received panitumumab fared more poorly. This study represents a warning that we cannot assume that more is better or that we understand how these biologic agents interact together and with chemotherapy. We need more biologically driven studies to determine the best strategy to select biologic therapy combinations.

A Quantitative Multi-Gene RT-PCR Assay for Prediction of Recurrence in Stage II Colon Cancer (CC): QUASAR Validation Study

Kerr D et al.

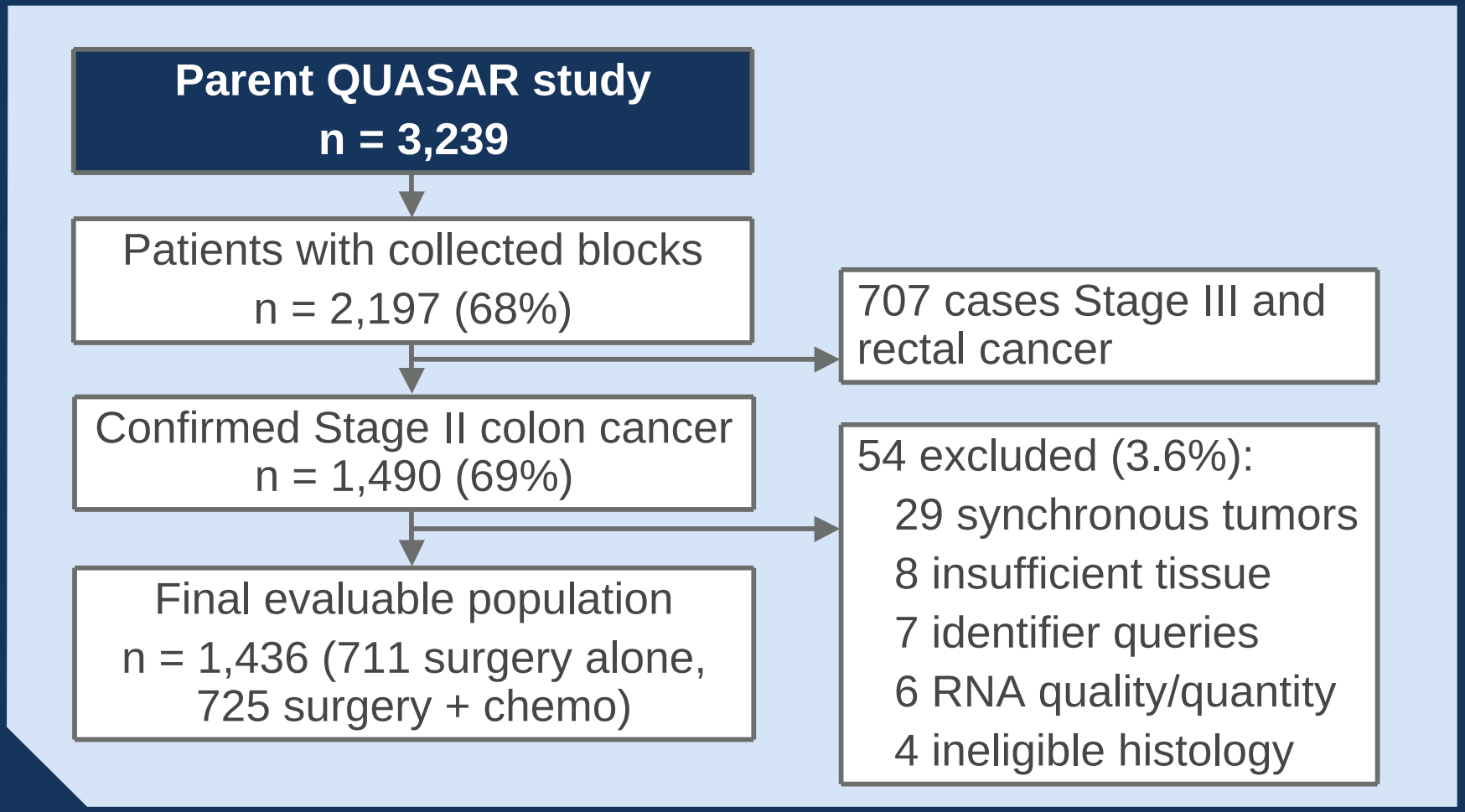
Proc ASCO 2009;Abstract 4000.

Final Assay for QUASAR Validation



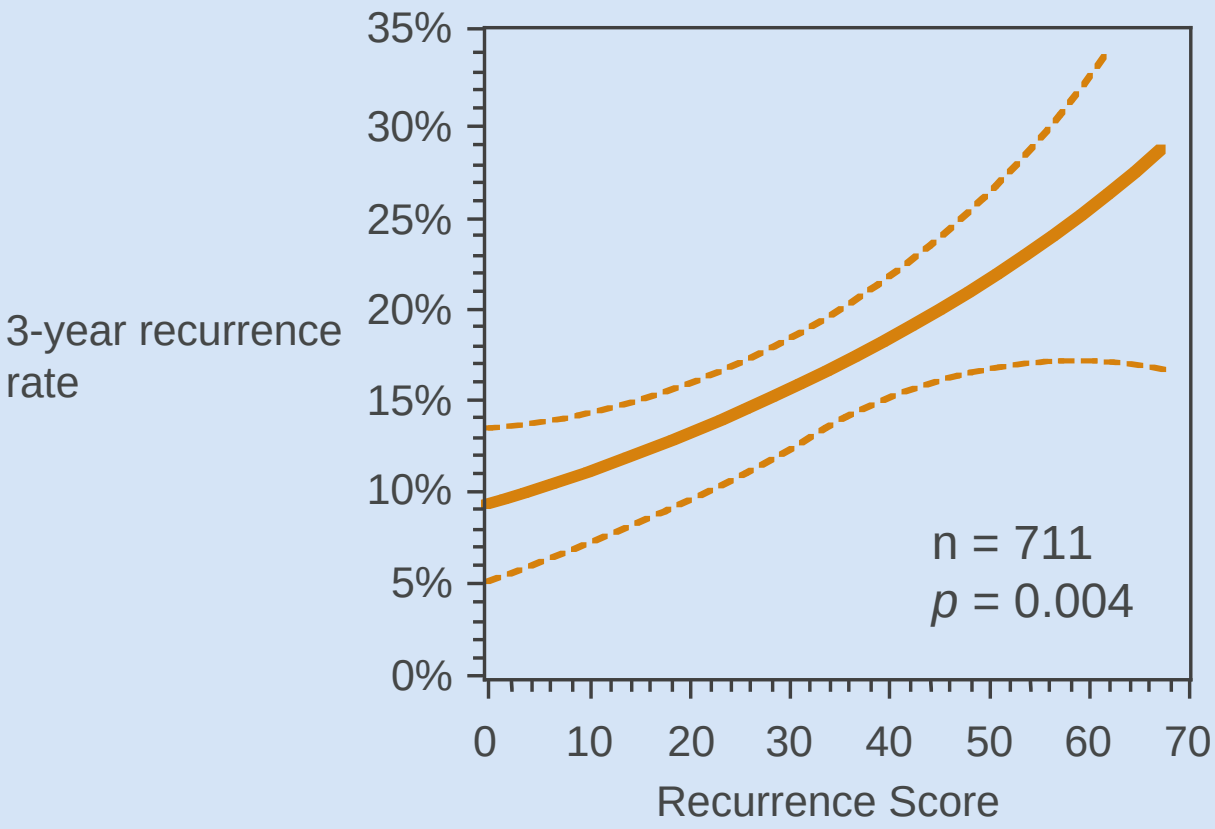
Kerr D et al. *Proc ASCO* 2009;Abstract 4000.

QUASAR: Evaluable Stage II Colon Cancer (CC) Patients



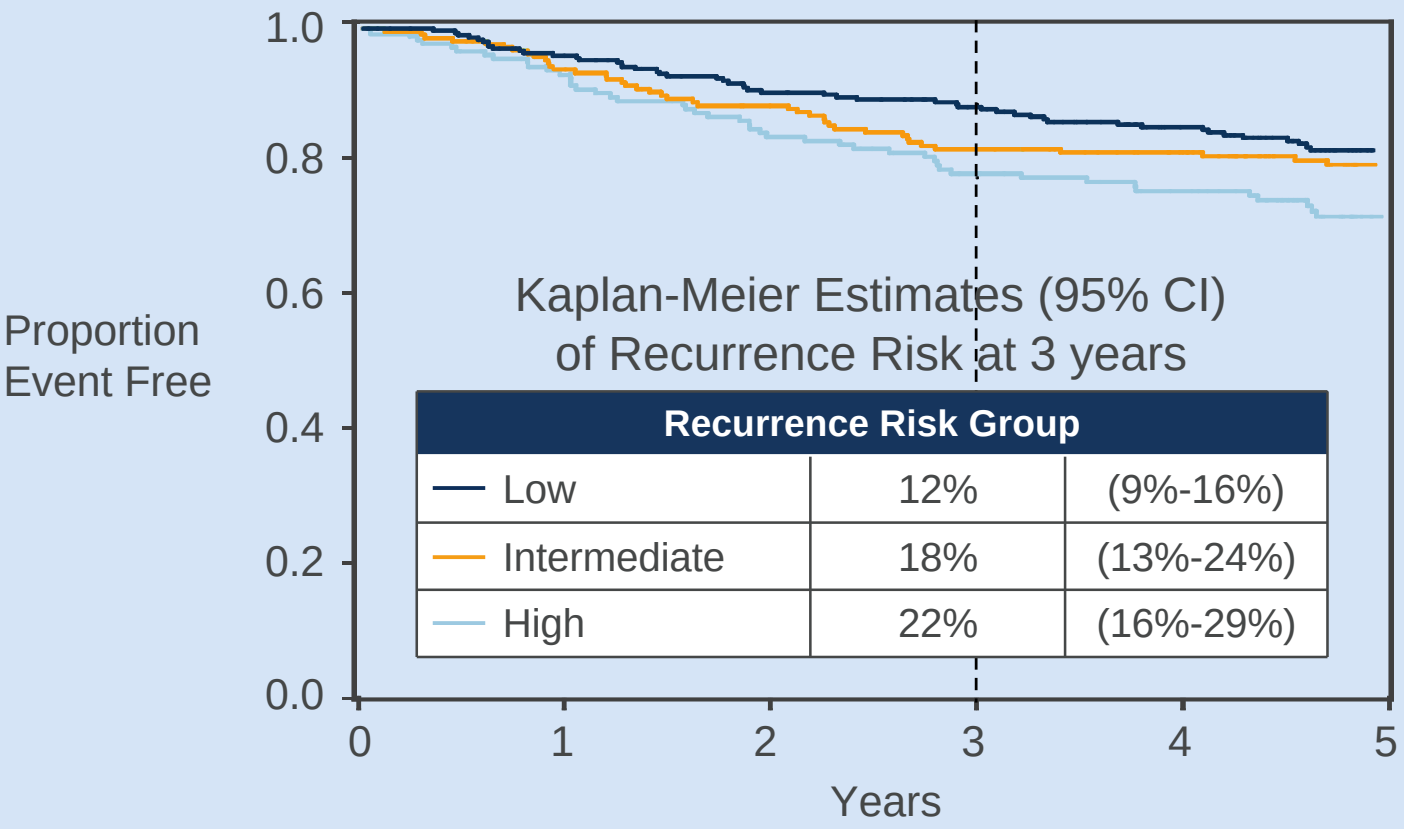
Kerr D et al. *Proc ASCO* 2009;Abstract 4000.

Continuous RS Predicts Recurrence in Stage II CC Following Surgery



With permission from Kerr D et al. *Proc ASCO* 2009;Abstract 4000.

Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)



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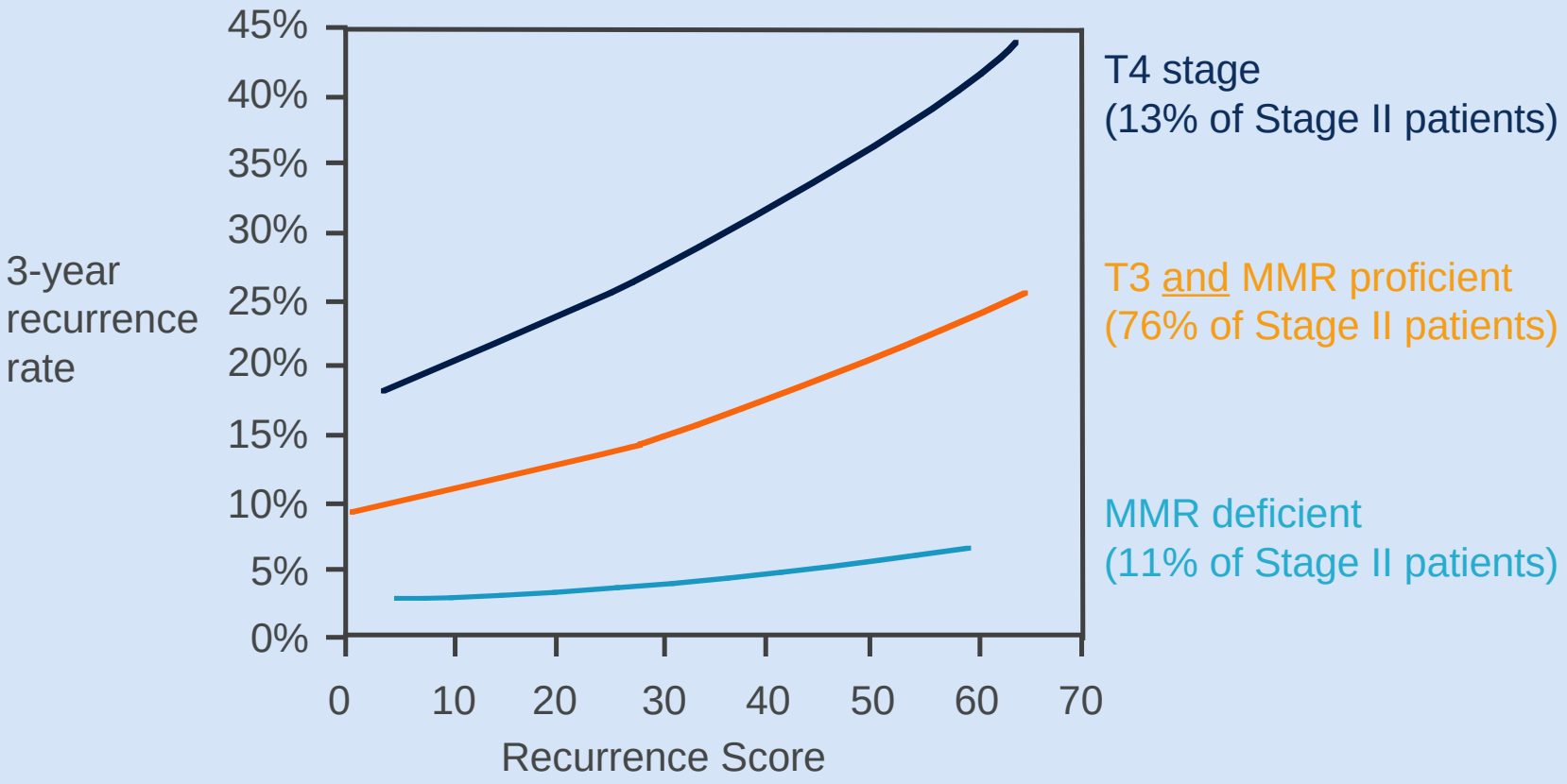
RS, T Stage and MMR Deficiency: Key Independent Predictors of Recurrence in Stage II CC



With permission from Kerr D et al. *Proc ASCO* 2009;Abstract 4000.

Conclusions

- First demonstration that a prospectively-defined gene expression assay can independently predict recurrence in Stage II CC following surgery.
  - Recurrence Score (RS) provides independent value beyond available prognostic factors.
- RS provides individualized assessment of recurrence risk.
  - Greatest clinical utility when used in conjunction with T stage and Mismatch Repair (MMR/MSI), particularly for the majority of patients for whom those markers are uninformative (~70% of patients)
- The continuous Treatment Score did not predict a differential benefit from 5FU/LV (data not shown).

Kerr D et al. *Proc ASCO* 2009;Abstract 4000.

Faculty Comments

DR HOCHSTER: The Oncot*ype* DX assay may be helpful in identifying patients with higher-risk, Stage II colon cancer. Approximately 18,000 patients per year in the United States have T3, non-MSI-high colon cancer that could benefit from a molecular determination of their risk for recurrence. I'm sure that the NSABP and other groups will attempt to validate Onco*type* DX in clinical trials, and this test could become part of our clinical practice. I tell patients that we currently estimate their risk of recurrence using nineteenth-century technology by looking at cells under a microscope, but perhaps we could do better using modern molecular biology techniques and determine who does and does not need adjuvant chemotherapy.

Prognostic Role of KRAS and BRAF in Stage II and III Resected Colon Cancer: Results of the Translational Study on PETACC-3, EORTC 40993, SAKK 60-00 Trial

Roth AD et al.
J Clin Oncol 2010;28(3):466-74.

Introduction

- Mutations within the K-ras proto-oncogene have predictive value but are of uncertain prognostic value in the treatment of advanced colorectal cancer.
- The PETACC-3 trial is a large Phase III trial comparing adjuvant fluorouracil/leucovorin with or without irinotecan in Stage II/III colon cancer in which patient tissue blocks (n = 1,404) have been prospectively collected.
  - Analysis of K-ras exon 2 and B-raf exon 15 mutations has been successfully performed in 1,321 cases (409 Stage II, 912 Stage III).
- Current study objective:
  - Examine the prognostic value of K-ras and B-raf tumor mutation status in patients with Stage II or III colon cancer enrolled in PETACC-3.

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

K-ras Tumor Mutation Interactions with Other Prognostic Markers

Patient Population/Prognostic Markers	Odds Ratio (95% CI)	*p*-value
Stage III vs II (n = 894, 405)	1.10 (0.85-1.43)	0.45
Tumor site right vs left (n = 516, 783)	1.43 (1.11-1.84)	0.0052
Female vs male (n = 550, 749)	0.88 (0.69-1.11)	0.28
>60 yo vs ≤60 yo (n = 655, 644)	1.07 (0.84-1.36)	0.57
Grade 3/4 vs 1/2 (n = 120, 1,170)	0.46 (0.28-0.73)	0.0016
MSI high vs low/stable (n = 188, 1,047)	0.72 (0.50-1.05)	0.091

MSI = microsatellite instability

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

B-raf Tumor Mutation Interactions with Other Prognostic Markers

Patient Population/Prognostic Markers	Odds Ratio (95% CI)	*p*-value
Stage III vs II (n = 900, 407)	1.18 (0.72-1.98)	0.52
Tumor site right vs left (n = 517, 790)	4.03 (2.39-7.02)	3.7×10^{-7}
Female vs male (n = 552, 755)	1.75 (1.11-2.77)	0.017
>60 yo vs ≤60 yo (n = 659, 648)	3.03 (1.86-5.06)	1.3×10^{-5}
Grade 3/4 vs 1/2 (n = 120, 1,179)	3.72 (2.04-6.70)	1.4×10^{-5}
MSI high vs low/stable (n = 188, 1,055)	3.59 (2.09-6.19)	3.8×10^{-6}

MSI = microsatellite instability

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Survival Analysis (RFS and OS) According to K-ras Status

Population/Stage	RFS		OS	
	HR	*p*-value	HR	*p*-value
Population by K-ras status				
Stages II and III (n = 1,299)	1.05	0.66	1.09	0.48
Stage II (n = 405)	1.09	0.74	1.16	0.63
Stage III (n = 894)	1.04	0.71	1.08	0.55
K-ras MSI-L/S patients only				
Stages II and III (n = 1,047)	1.14	0.24	1.15	0.29
Stage II (n = 305)	1.19	0.52	1.20	0.57
Stage III (n = 742)	1.13	0.32	1.14	0.36

RFS = recurrence-free survival; OS = overall survival; HR = hazard ratio; MSI-L/S = microsatellite instability low/stable

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Survival Analysis (RFS and OS) According to B-raf Status

Population/Stage	RFS		OS	
	HR	*p*-value	HR	*p*-value
Population by B-raf status				
Stages II and III (n = 1,307)	1.19	0.34	1.66	0.0069
Stage II (n = 407)	0.94	0.85	1.13	0.82
Stage III (n = 900)	1.23	0.28	1.76	0.0050
B-raf MSI-L/S patients only				
Stages II and III (n = 1,055)	1.49	0.067	2.19	0.00034
Stage II (n = 307)	1.84	0.24	2.81	0.05
Stage III (n = 748)	1.40	0.16	2.07	0.0025

RFS = recurrence-free survival; OS = overall survival; HR = hazard ratio; MSI-L/S = microsatellite instability low/stable

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Summary and Conclusions

- K-ras (37%) and B-raf (7.9%) tumor mutation rates were not significantly different according to tumor stage (data not shown).
- In a multivariate analysis, K-ras mutation was associated with grade ($p = 0.0016$).
- In a multivariate analysis, B-raf mutation was significantly associated with female sex ($p = 0.017$) and with right-sided tumors, older age, high grade and MSI-high tumors (all $p < 10^{-4}$).
- In univariate and multivariate analysis, K-ras mutations did not have a major prognostic value regarding RFS or OS.
- B-raf mutation was not prognostic for RFS, but was for OS, particularly in patients with MSI-low and stable tumors (HR = 2.2; $p = 0.0003$).

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Faculty Comments

DR AJANI: This is a new field and a lot of assumptions are being made. If one interrupts the proximal area of the pathway, such as the cell-surface receptor, the pathway can still be activated downstream. We have much more to learn, and increasingly molecular biologists believe that we need to interrupt pathways as distally as possible to yield the highest therapeutic advantage. B-raf is further downstream from K-ras, but it may not be enough. So this is a good exploratory study that will be advantageous for developing further therapeutic strategies, but I believe we don’t know enough yet to make sense of these results.