NCIC CTG New Investigators Course Workshop 5: QoL Analysis

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Objectives

- Present NCIC CTG standard approach and some of its variations in the analysis of QoL data
- Provide examples of QoL analysis in NCIC CTG clinic trials

NCIC CTG Standard Approach of QoL Analysis

ELSEVIER

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Analysis and interpretation of health-related quality-of-life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group

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Step 1: Calculating Compliance rates

Calculate compliance (completion) rates as follows for each treatment group:

a. number of patients completing the baseline (pretreatment) assessment over the total number of eligible patients entered

b. number of patients completing assessments at designated time points over the total number of patients still on study and expected to complete at each time point (the "number expected" population)

Step 2 - Comparing baseline scores between groups

Calculate the mean baseline scores for each of the HRQOL components (domains and single items) within the questionnaire for each of the treatment groups, as follows:

a. number of patients providing responses,

b. mean score and standard deviation for each HRQOL component,

c. determine if there is an apparent difference between the mean or median scores between the treatment groups.

Step 3 – Comparing the change scores between treatment groups (Cross-Sectional Analysis)

Determine the change-from-baseline scores at a specific post-baseline assessment time for each HRQOL component of interest that was specified in the hypothesis, as follows:

a. calculate the means for the differences (the mean change score) +/- the standard error (SE) at each designated time point,

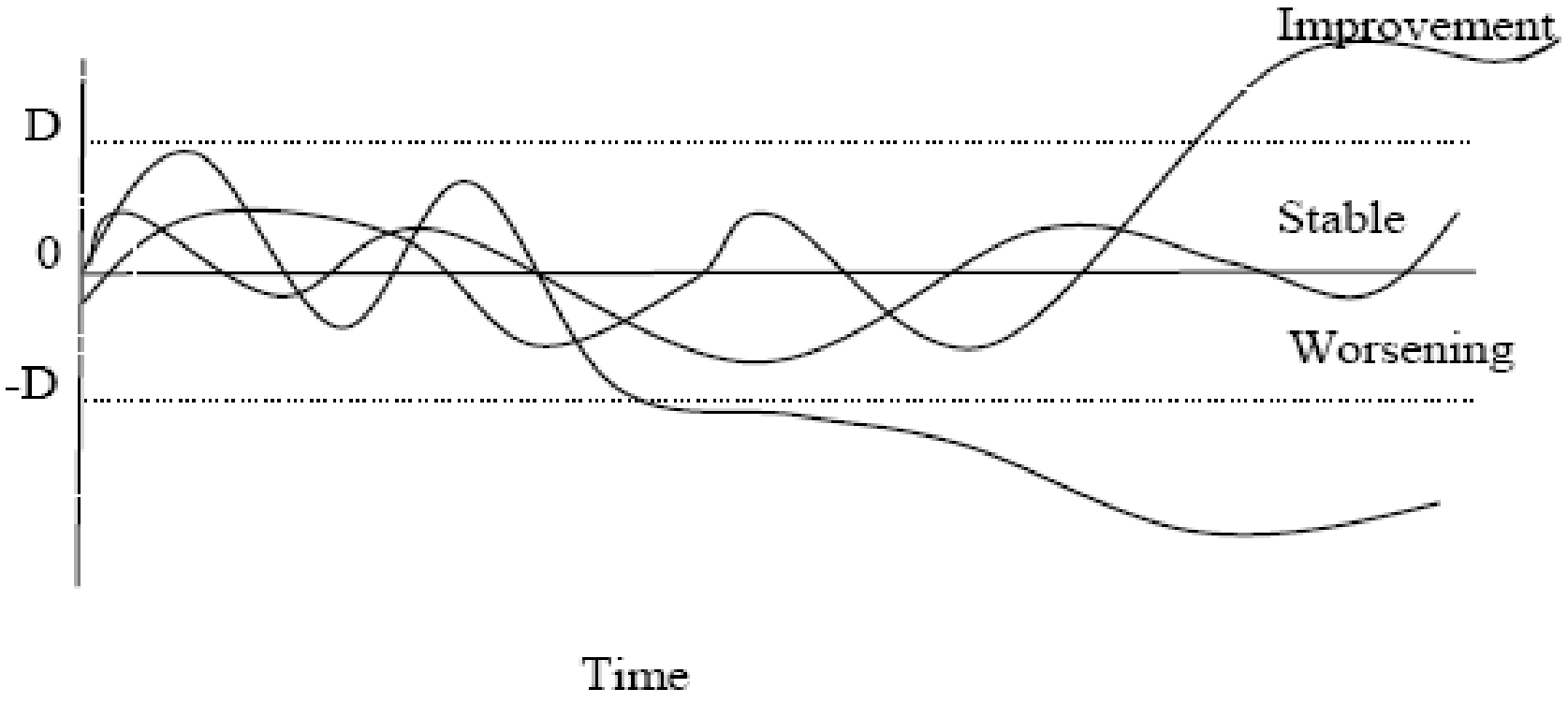
b. test for statistically significant differences in mean change scores between treatment groups

Step 4 – Determining the proportions of patients with improved, stable and worsened scores (QOL Response Analysis)

Decide, a priori, the magnitude of change (cut point) that will be considered to be a clinically meaningful change in HRQOL scores in order to consider the HRQOL response as being "improved", "worsened" and "stable".

Calculate the proportions of patients with clinically meaningful change and test for statistically significant differences among the three categories of responses between treatment groups.

Definition of QoL response



Examples

GEMVIN (NCIC CTG BR.14)

Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non–Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group

By Cesare Gridelli, Ciro Gallo, Frances A. Shepherd, Alfonso Illiano, Francovito Piantedosi, Sergio Federico Robbiati, Luigi Manzione, Santi Barbera, Luciano Frontini, Enzo Veltri, Brian Findlay, Silvio Cigolari, Robert Myers, Giovanni P. Ianniello, Vittorio Gebbia, Giampietro Gasparini, Sergio Fava, Vera Hirsh, Andrea Bezjak, Lesley Seymour, and Francesco Perrone

Purpose: **Platinum-containing chemotherapy regimens are the standard treatment for patients with advanced non–small-cell lung cancer (NSCLC), although toxicity is common and may significantly affect the patient's quality of life (QoL). This trial aimed to assess whether a combination of gemcitabine and vinorelbine had benefits in terms of QoL, without influencing negatively on survival, compared with cisplatin-containing regimens.**

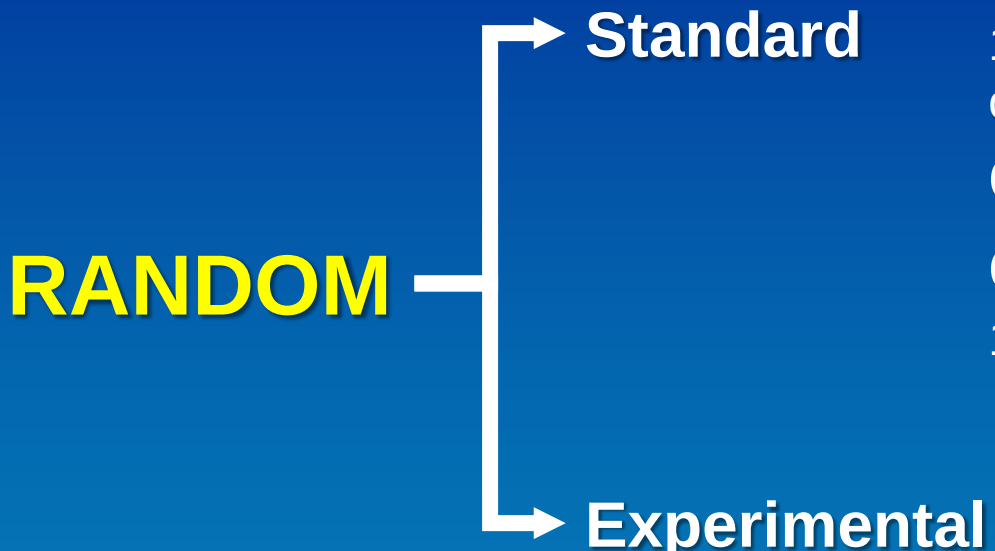
Patients and Methods: **Patients with stage IIIB (effusion and supraclavicular nodes) or IV documented NSCLC who were younger than 70 years of age were randomly assigned gemcitabine plus vinorelbine (GemVin) or either gemcitabine plus cisplatin or vinorelbine plus cisplatin (cisplatin-based). European Organization for Research and Treatment of Cancer scales were used for QoL analysis.**

Results: **Five hundred one patients were randomly assigned to treatment. The median age was 62 years. There were no significant differences in global QoL scores between the two arms after 2 months of treatment. However, worsening scores for appetite, vomiting, and alopecia were significantly more common in the cisplatin-based arm. Median survival was 38 *v* 32 weeks and median progression-free survival was 23 *v* 17 weeks in the cisplatin-based versus GemVin arms, respectively. For the GemVin arm the hazard ratio for death was 1.15 (90% confidence interval [CI], 0.96 to 1.37) and the hazard ratio for progression was 1.29 (90% CI, 1.10 to 1.52). Grade 3 or 4 myelosuppression, vomiting, alopecia, and ototoxicity were significantly more frequent with cisplatin-based treatment.**

Conclusion: **Global QoL is not improved with GemVin, although advantages in some components of QoL were apparent. GemVin is less toxic than standard cisplatin-based chemotherapy. There is a nonsignificant slight survival advantage with cisplatin-based chemotherapy. GemVin could be offered to advanced NSCLC patients who express concern about toxicity.**

J Clin Oncol 21:3025-3034.

GEMVIN (BR.14) – Study design



Cisplatin 80 mg/ /m², d 1
Vinorelbine 30 mg/m², dd 1&8

or (**at random**)

Cisplatin 80 mg/ /m², d 1
Gemcitabine 1200 mg/m², dd 1&8

Gemcitabine 1000 mg/m², dd 1&8
Vinorelbine 25 mg/m², dd 1&8

Stratified by center, PS, stage
All cycles given every 3 weeks, for a maximum of 6 times

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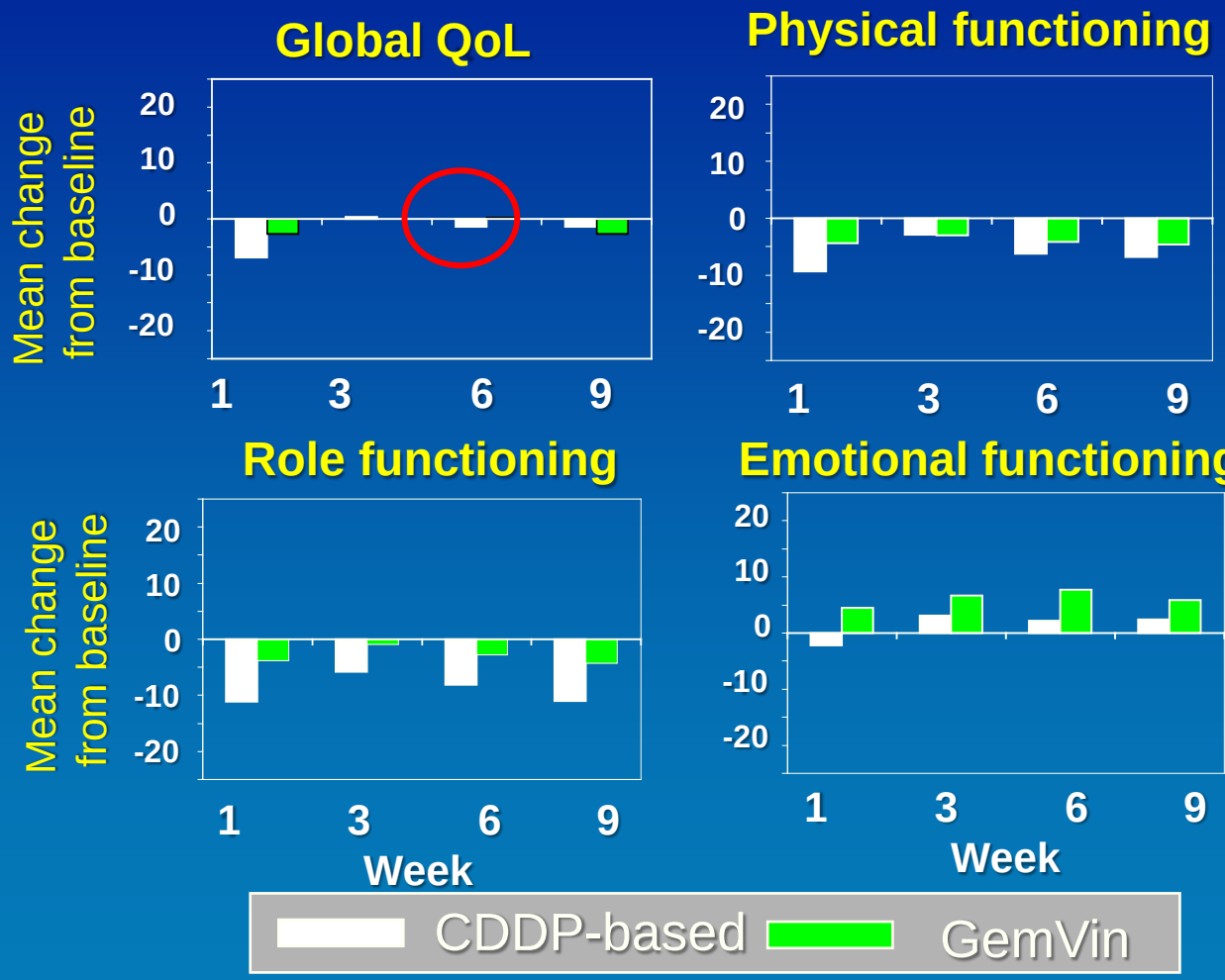
GEMVIN – Study end-points

- **Primary: Quality of life (EORTC C30 & LC-13)**
  - **Global QoL/health status at the end of cycle 2**
- **Secondary:**
  - **Overall survival**
  - **Progression-free survival**
  - **Toxicity (WHO)**
  - **Response rate (WHO)**

QoL Analysis: Steps 1 and 2

- Between the two study arms there were no differences in any of the compliance parameters. The rate of completed questionnaires, out of those expected, slightly declined to 84%, 75%, 85%, 80% in the P-based and to 82%, 81%, 74% and 74% in the GemVin arm, at the 2nd, 3rd, 4th and 5th assessment, respectively.
- Baseline mean scores were comparable between the two arms for all of the QoL items

QoL Analysis: Step 3 – QLQ C30 functioning Domains and Global QoL



Negative is worse!

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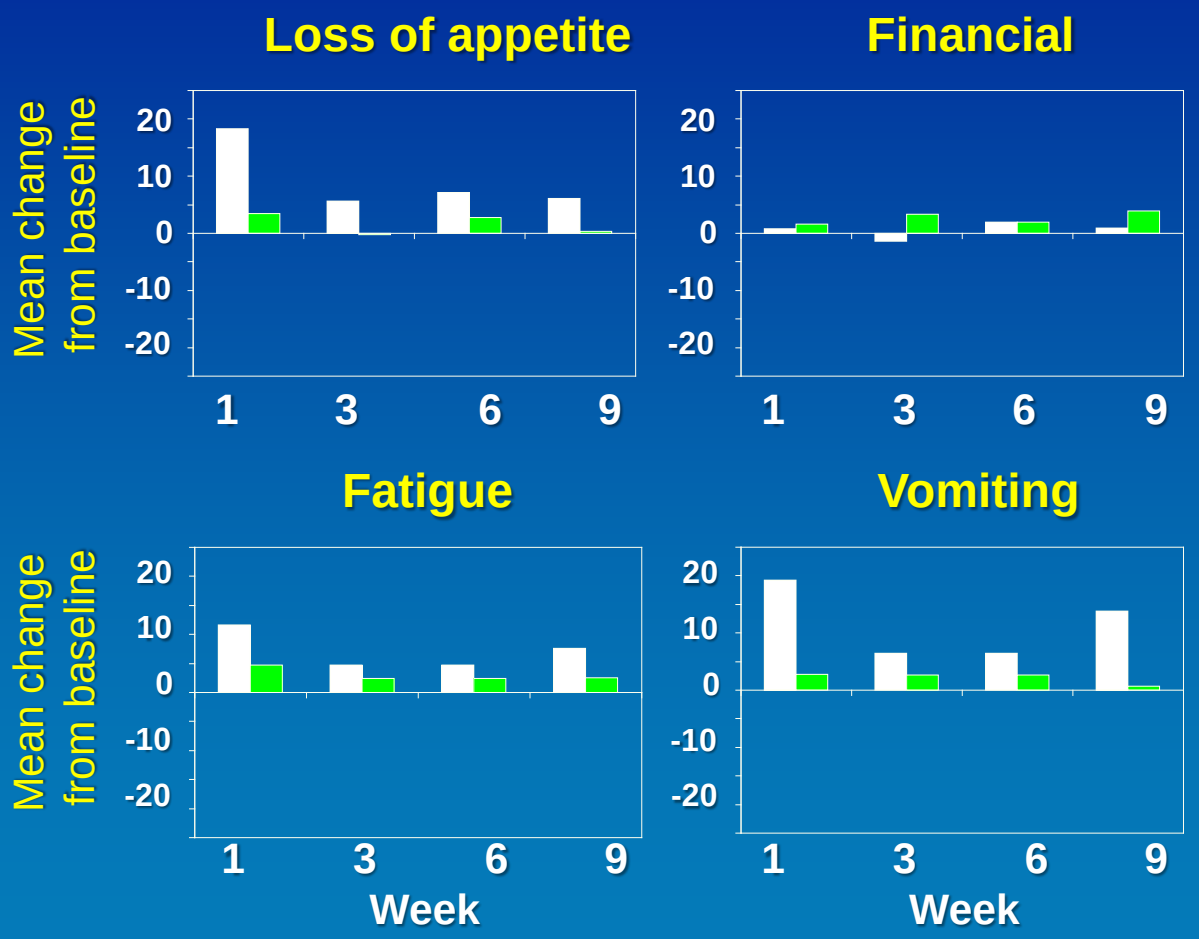
At the planned time point for primary QoL analysis (Global QoL/health status at the end of cycle 2) no difference was observed between arms (p = 0.94)

QoL Analysis: Step 3– QLQ-C30 symptoms



Positive is worse!

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QoL Analysis: Step 4

	Cisplatin Based								Gemcitabine + Vinorelbine									
	Baseline		Improved		Stable		Worse		Baseline		Improved		Stable		Worse			
Domain and Item	Mean	SD	N	%	N	%	N	%	Mean	SD	N	%	N	%	N	%	P*	P†
Global QoL	54	23	73	38	48	25	71	37	54	21	70	39	42	23	68	38	.97	.96
Physical	77	18	45	23	60	31	87	45	75	22	50	27	59	32	77	41	.38	.56
Role	69	29	52	27	47	25	92	48	66	31	61	33	52	28	73	39	.09	.17
Emotional	68	22	85	44	45	23	62	32	63	22	89	49	50	27	44	24	.17	.28
Cognitive	86	20	49	26	66	34	77	40	86	18	53	28	65	35	68	37	.43	.66
Social	78	25	60	32	51	27	78	41	78	25	58	32	61	33	65	35	.49	.35
Pain	32	28	96	50	41	21	55	29	34	28	95	51	39	21	52	28	.85	.87
Appetite	22	26	51	27	43	22	98	51	22	27	51	28	69	37	65	35	.03	.01
Constipation	16	27	39	20	66	35	86	45	14	23	34	18	76	41	76	41	.70	.42
Financial	13	24	32	17	116	62	39	21	13	23	29	16	112	61	43	23	.54	.73
Fatigue	35	24	72	38	26	14	93	49	36	24	76	41	35	19	74	40	.19	.16
Vomiting	8	15	30	16	37	19	124	65	8	17	30	16	88	48	67	36	< .0001	< .0001
Sleeping	29	30	55	29	69	36	66	35	30	32	53	29	78	42	54	29	.50	.41
Diarrhea	4	14	16	8	137	72	37	19	5	14	19	10	142	76	25	13	.13	.24
Dyspnea	29	20	71	37	69	36	52	27	26	22	50	27	66	36	68	37	.02	.16
Cough	40	24	85	45	73	38	33	17	37	25	68	38	61	34	52	29	.03	.13
Hemoptysis	6	16	22	11	157	82	13	7	9	18	32	18	134	74	16	9	.36	.68
Sore mouth	4	14	11	6	116	60	65	34	5	15	16	9	114	63	51	28	.15	.29
Swallowing	6	16	18	9	120	62	54	28	9	19	26	14	110	60	46	25	.24	.63
Neuropathy	7	17	25	13	103	54	64	33	8	18	27	15	107	58	49	27	.20	.30
Hair loss	2	8	5	3	95	50	91	48	2	13	4	2	117	64	63	34	.01	.01
Pain, chest	18	24	52	27	94	49	46	24	21	26	62	34	67	37	53	29	.78	.52
Pain, shoulder	26	30	61	32	85	45	44	23	26	28	66	36	68	37	49	27	.92	.69
Pain, elsewhere	24	30	61	33	72	39	54	29	22	29	52	29	78	43	50	28	.74	.76
Analgesic	61	49	50	26	112	59	29	15	55	50	29	16	128	71	24	13	.16	.75

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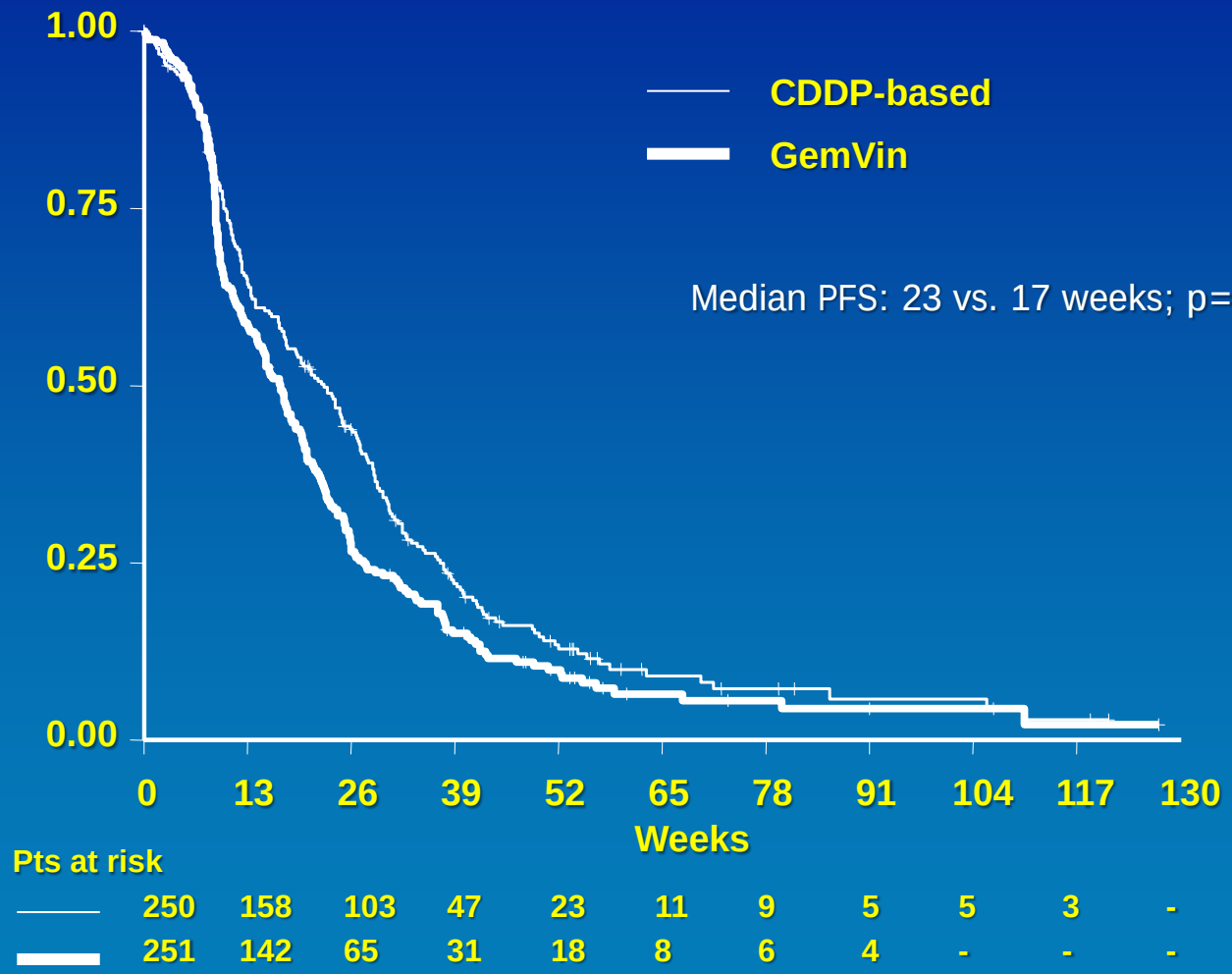
Journal of Clinical Oncology, Vol 21, No 16 (August 15), 2003: pp 3025-3034

GEMVIN – Progression-free survival



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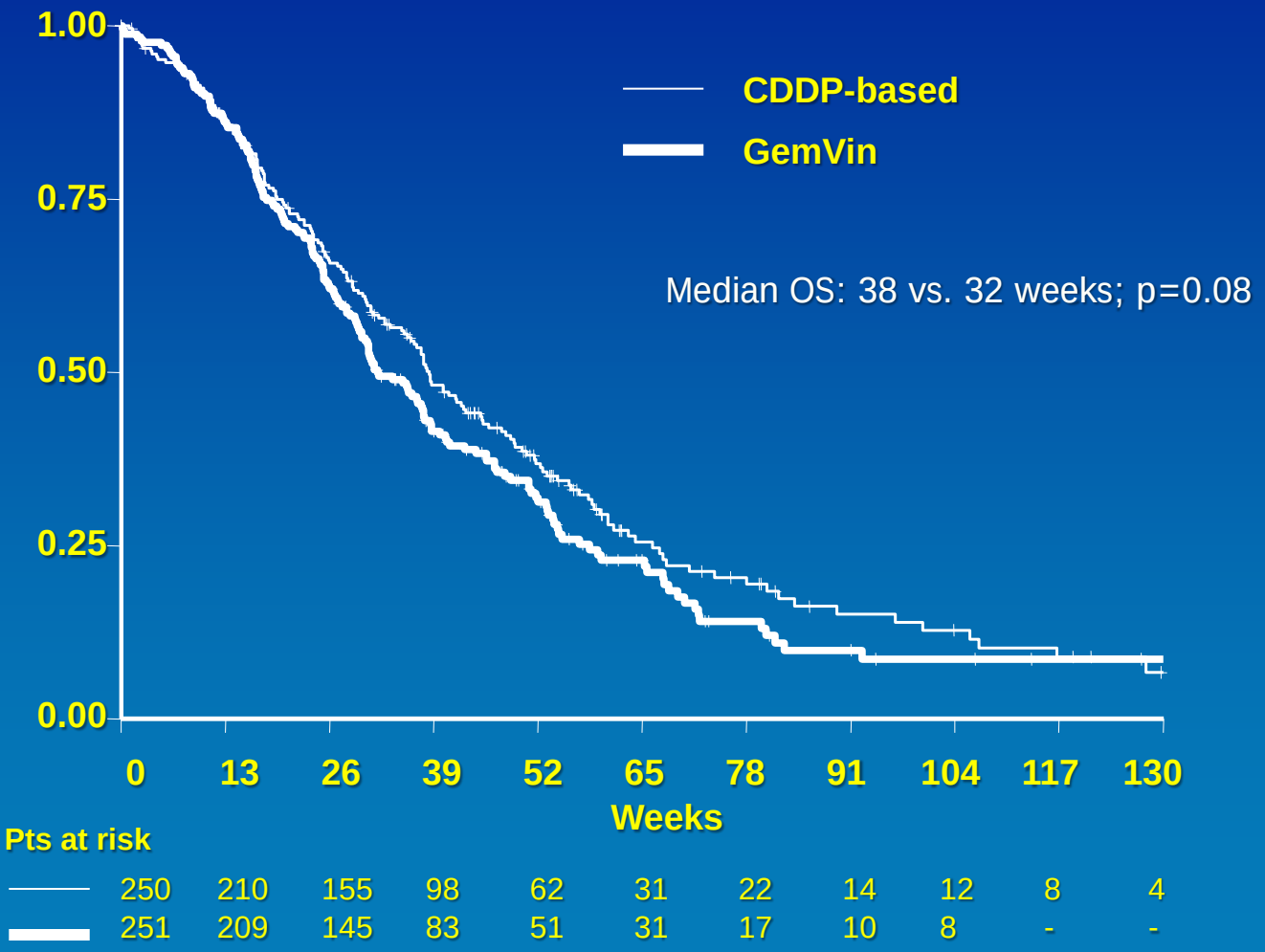
GEMVIN – Overall survival



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GEMVIN – Conclusions

- The non-platinum GemVin regimen, as compared to standard cisplatin-based chemotherapy, produces only short-term and sporadic advantages in some components of QoL, is less toxic, but with sligthly shorter overall and progression-free survival

- GemVin could be offered to advanced NSCLC patients who express concern for toxicity

NCIC CTG/AGITG CO.17

Health-Related Quality of Life in Patients With Advanced Colorectal Cancer Treated With Cetuximab: Overall and *KRAS*-Specific Results of the NCIC CTG and AGITG CO.17 Trial

Heather-Jane Au, Christos S. Karapetis, Chris J. O'Callaghan, Dongsheng Tu, Malcolm J. Moore, John R. Zalcberg, Hagen Kennecke, Jeremy D. Shapiro, Sheryl Koski, Nick Pavlakis, Danielle Charpentier, David Wyld, Michael Jefford, Gregory J. Knight, Nadine M. Magoski, Michael D. Brundage, and Derek J. Jonker

A B S T R A C T

Purpose
National Cancer Institute of Canada Clinical Trials Group CO.17 demonstrated the antiepidermal growth factor receptor (anti-EGFR) monoclonal antibody cetuximab improves overall and progression-free survival in patients with advanced, chemotherapy-refractory colorectal cancer (CRC), particularly in patients with wild-type *KRAS* tumors. This article reports the health-related quality-of-life (HRQL) outcomes from CO.17.

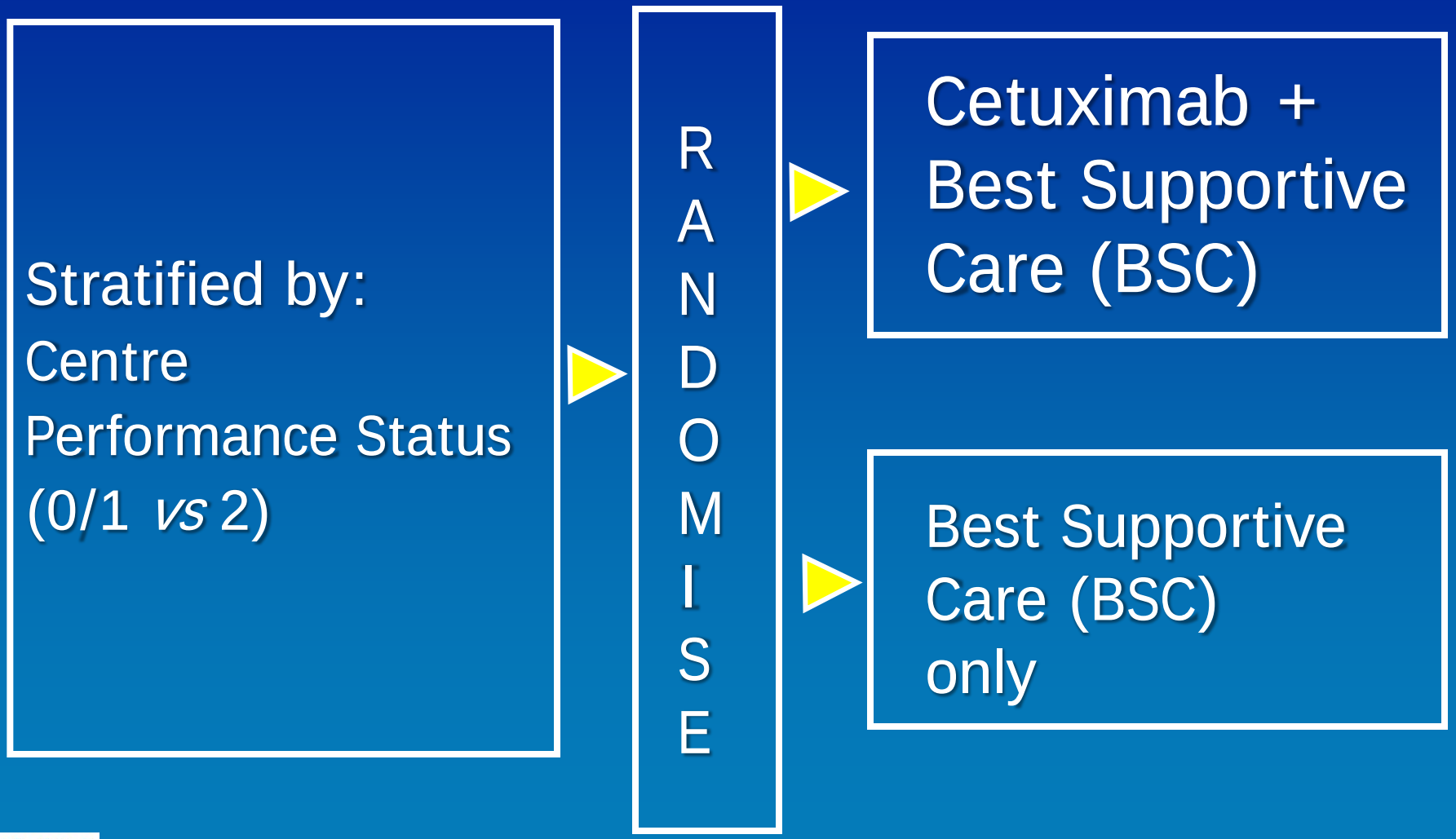
Patients and Methods
Patients (N = 572) with pretreated EGFR-detectable advanced CRC were randomly assigned to cetuximab and best supportive care (BSC) or to BSC alone. HRQL primary end points assessed by the EORTC QLQ-C30 were physical function (PF) and global health status (GHS); mean changes from baseline to 8 and 16 weeks were assessed. Post hoc analysis by *KRAS* mutation status was performed.

Results
Questionnaire compliance was 94% at baseline, but it declined differentially (67% *v* 47% for cetuximab *v* BSC at 16 weeks). PF change scores were −3.9 for cetuximab and −8.6 for BSC ($P = .046$) at 8 weeks and were −5.9 and −12.5 for cetuximab and BSC, respectively, ($P = .027$) at 16 weeks. GHS change scores were −0.5 and −7.1 ($P = .008$) at 8 weeks and were −3.6 and −15.2 ($P = .008$) at 16 weeks for cetuximab and BSC, respectively. In patients who had tumors with wild-type *KRAS* status, cetuximab resulted in less PF deterioration at 8 weeks (−0.7 *v* −7.2; $P = .11$) and 16 weeks (−3.4 *v* −13.8; $P = .008$) compared with BSC. Patients with wild-type status who received cetuximab experienced improved GHS at 8 weeks, whereas patients who received BSC alone deteriorated (3.2 *v* −7.7; $P = .002$). Cetuximab preserved GHS at 16 weeks (−0.2 *v* −18.1; $P < .001$). No significant differences were noted between study arms for patients with mutated *KRAS* tumors.

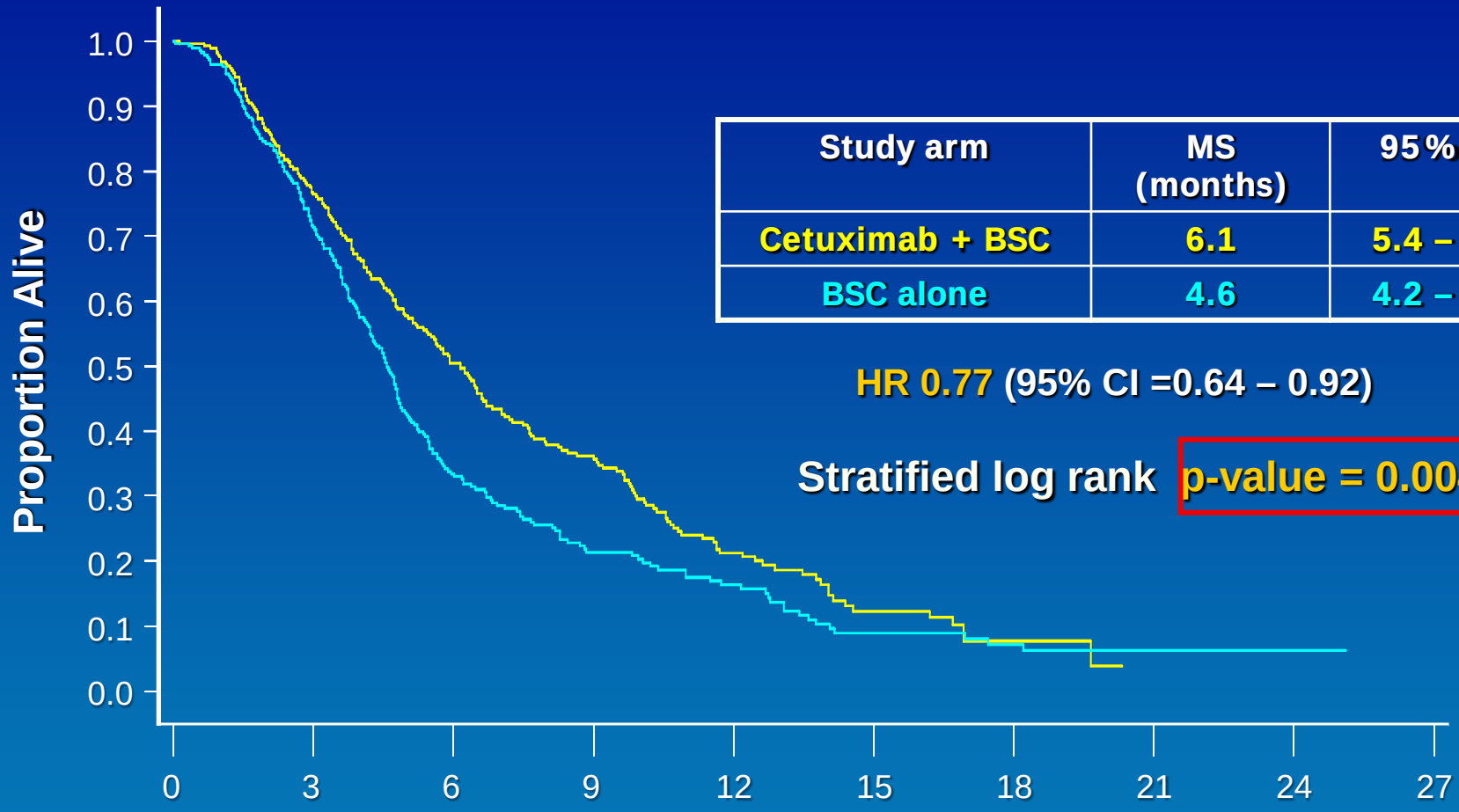
Conclusion
Cetuximab offers important HRQL and survival benefits for pretreated patients with advanced, wild-type *KRAS* CRC.

J Clin Oncol 27:1822-1828. © 2009 by American Society of Clinical Oncology

NCIC CTG CO.17
Study Design



NCIC CTG CO.17: Overall Survival



Study arm	MS (months)	95% CI
Cetuximab + BSC	6.1	5.4 – 6.7
BSC alone	4.6	4.2 – 4.9

HR 0.77 (95% CI =0.64 – 0.92)

Stratified log rank p-value = 0.0046

SUBJECTS AT RISK										MONTHS
CET+BSC	287	217	136	78	37	14	4	0	0	0
BSC	285	197	85	44	26	12	8	2	1	0

CETUXIMAB + BSC
CENSORED

BSC
CENSORED

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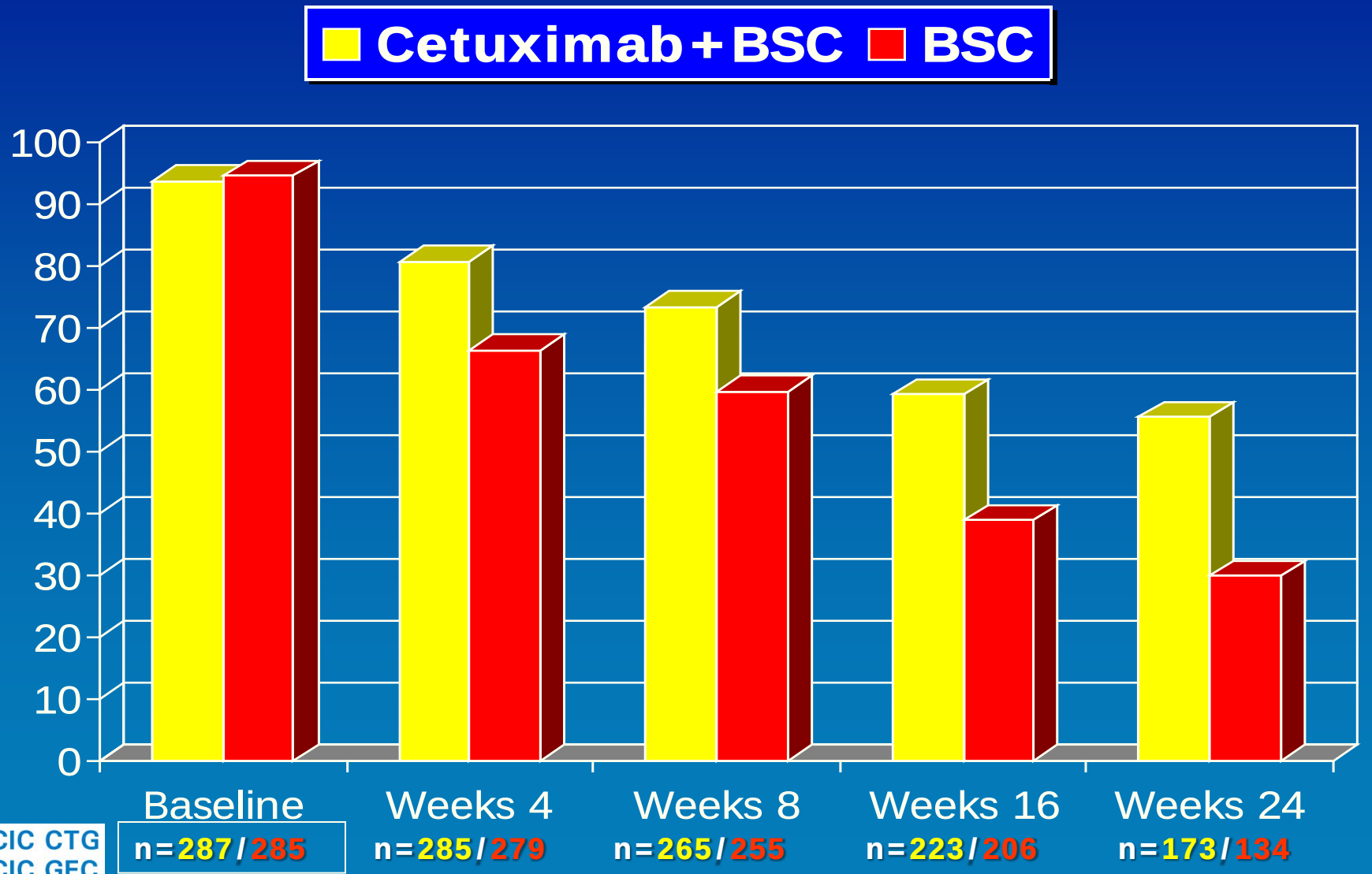
NCIC CTG CO.17 HRQoL Hypothesis

- In this population of heavily pre-treated advanced CRC patients, in whom all other treatments have failed and deterioration in HRQoL may be imminent, we hypothesized that pts may benefit from cetuximab with
  - A decrease in the magnitude & rate of decline in their HRQoL, particularly with regards to their physical functioning and overall wellbeing

Assessment of QoL in CO.17

- Primary QOL endpoints
  - Change scores of physical function and global Health status at 8 weeks and 16 weeks after randomization
- Tools
  - QLQ-C30
    - Global health status, Physical, Role, Emotional, Social, Cognitive functioning, Symptoms

Compliance with QOL data completion



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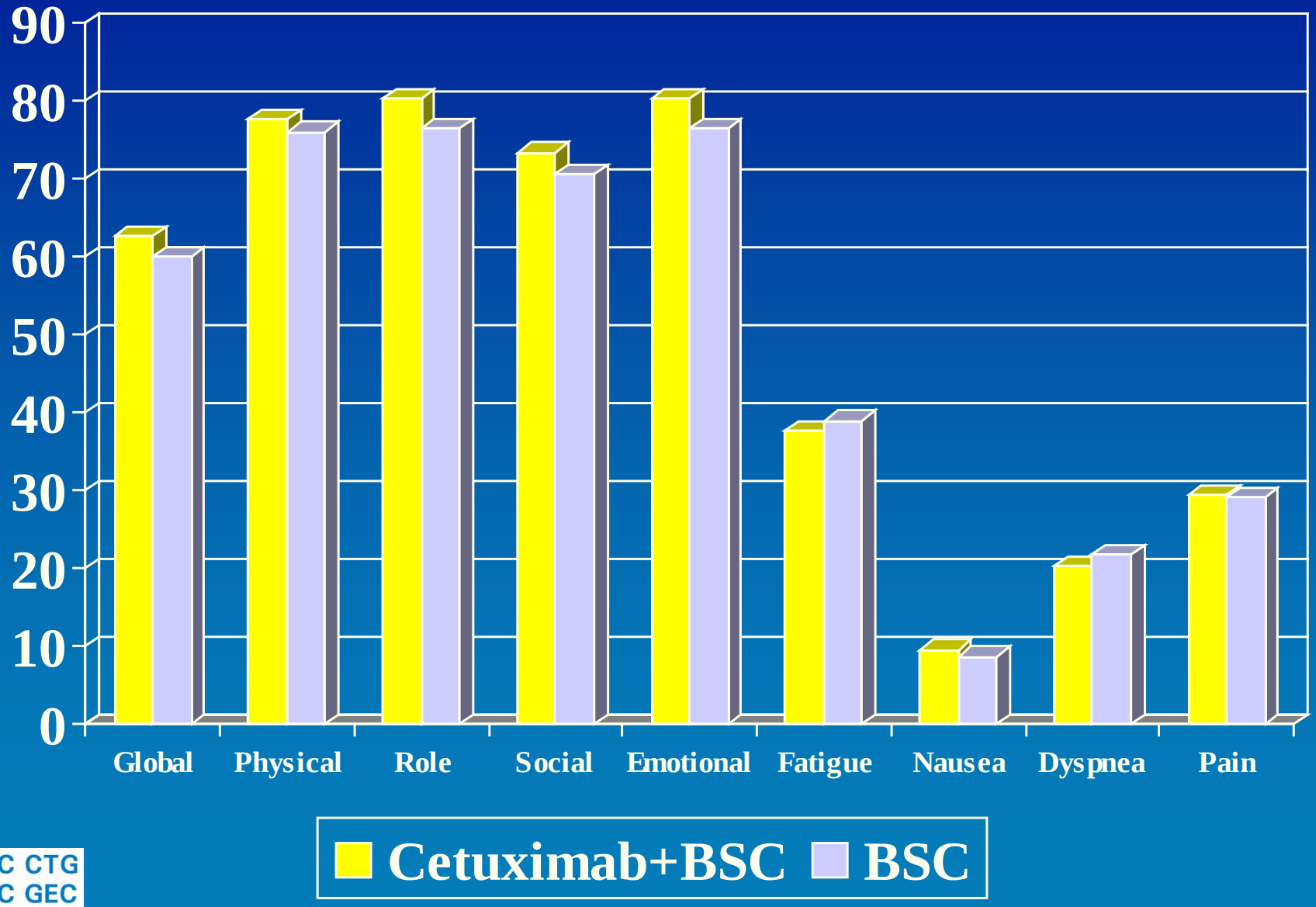
Mean QOL Scores at Baseline



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Mean Change Scores at 8 and 16 Weeks

Variable	Cetuximab +BSC	BSC	p-value
Week 8			
Physical Function	-3.9	-8.6	.046
Global Health Status	-0.5	-7.1	.008
Week 16			
Physical Function	-5.9	-12.5	.027
Global Health Status	-3.6	-15.2	.0008

Proportion of Patients Who Had Deterioration* at 8 and 16 Weeks

Variable	Cetuximab +BSC	BSC	p-value**
Week 8			
Physical Function	24.9%	34.7%	0.051
Global Health Status	23.2%	38.3%	0.004
Week 16			
Physical Function	30.4%	43.4%	0.069
Global Health Status	31.3%	49.3%	0.011

*change score from baseline ≦ -10

** from Fisher's exact test

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CO.17 Time to Deterioration in QoL Primary Endpoints

	Cetuximab+BSC		BSC		P*
	N	Median (95%CI)	N	Median (95%CI)	
Physical Function	235	5.4 m (3.8-5.7m)	202	3.7 m (2.0-3.9m)	0.02
Global Health Status	233	5.4 m (3.9-5.7m)	200	3.7 m (2.1-3.9m)	0.06

*log-rank test

CO.17 QOL Response

	Cetuximab+BSC			BSC			P-value
	Improve*	Stable	Worse**	Improve*	Stable	Worse**	Chi Square
QOL Domain and Items							
Pain	47	19	34	27	23	51	<0.0001
Fatigue	41	16	44	31	13	56	0.04
Nausea	22	49	29	16	41	44	0.01
Dyspnea	22	44	33	13	46	41	0.04
Financial	23	62	15	14	59	27	0.0003

*change score from baseline $\geq$ -10 at any time

** change score >-10 at all times with at least one $\geq$ 10

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NCIC CTG CO.17
HRQoL Summary & Conclusions

- This study met its primary endpoint demonstrating improved physical function and global health scores at 8 & 16 weeks with cetuximab compared to BSC.
- Cetuximab resulted in better HRQoL than BSC alone.
  - Patients on cetuximab experienced significantly less HRQoL deterioration and a longer time before this deterioration occurred.

NCIC CTG CO.17 demonstrates that cetuximab offers survival and HRQoL benefits for patients with advanced colorectal cancer.

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Missing Data

- Prevention is better than statistical cures
  - make attempt to reduce the magnitude in the design
- Sensitivity Analyses:
  - In CO17
    - All pts (either arm) with missing data assumed to have worsened HRQoL as per response analysis
    - Pattern Mixture models

Sensitivity Analysis† Proportion of Patients Who Had Deterioration* at 8 and 16 Weeks

Variable	Cetuximab +BSC	BSC	p-value**
Week 8			
Physical Function	48.3%	64.3%	<0.0001
Global Health Status	47.2%	65.8%	<0.0001
Week 16			
Physical Function	67.7%	84.0%	<0.0001
Global Health Status	67.3%	85.9%	<0.0001

† Pts with missing data assumed to have deteriorated
* Change score from baseline ≦ -10 at any time
** From Fisher's exact test

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