Role of *K-ras* Mutation Status in Optimizing Selection of Colorectal Cancer Patients for Treatment with ERBITUX® (Cetuximab)

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a wholly-owned subsidiary of Eli Lilly and Company

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Objectives

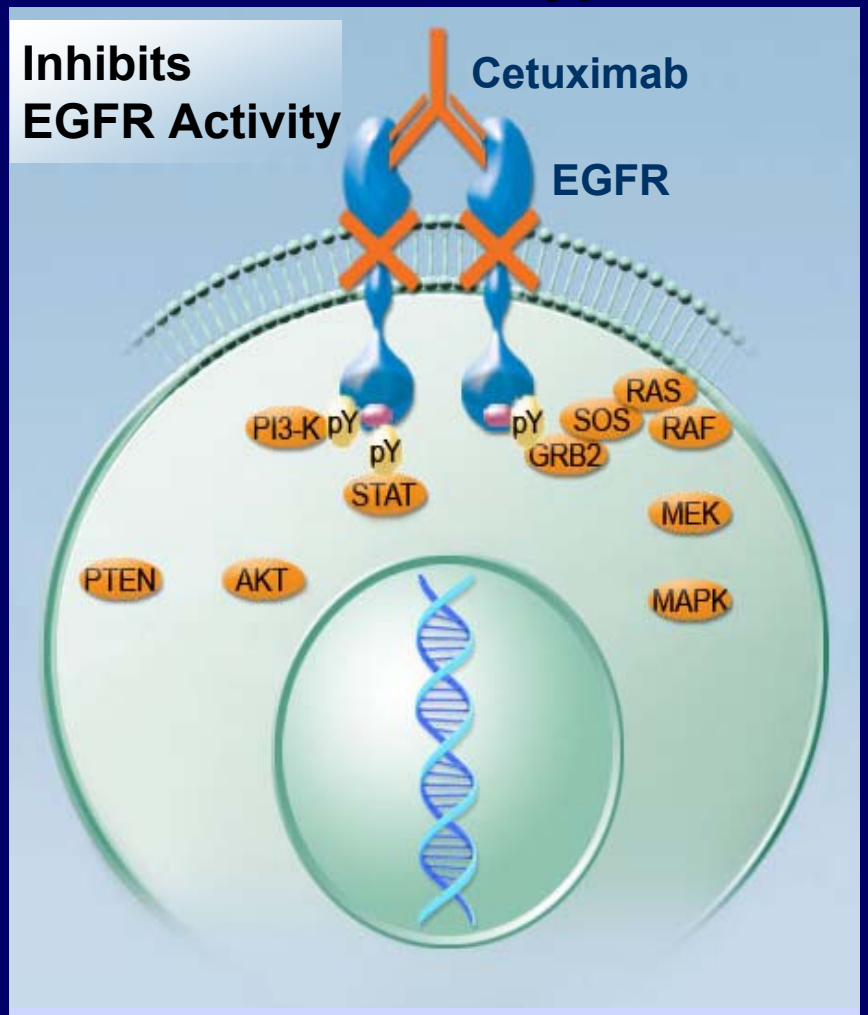
- Clinical data demonstrating the role of *K-ras* mutations as predictive of Erbitux efficacy in colorectal cancer
- Impact of *K-ras* testing on ongoing clinical investigations in colorectal cancer
- Rationale for modification of Erbitux labeling incorporating *K-ras* testing in colorectal cancer

Erbitux FDA Approved Indications

	Clinical Setting	Tumor Selection Criterion
Colorectal Cancer		
Erbitux with Irinotecan	Patients refractory to irinotecan containing therapy	EGFR-expressing
Erbitux as Single agent	Patients intolerant of irinotecan containing therapy	EGFR-expressing
Erbitux as Single agent	After failure of both irinotecan and oxaliplatin containing therapy	EGFR-expressing
Head & Neck Cancer		
Erbitux with Radiation Therapy	Locally or regionally advanced SCCHN	None
Erbitux as Single agent	Recurrent / metastatic SCCHN after failure of platinum based therapy	None

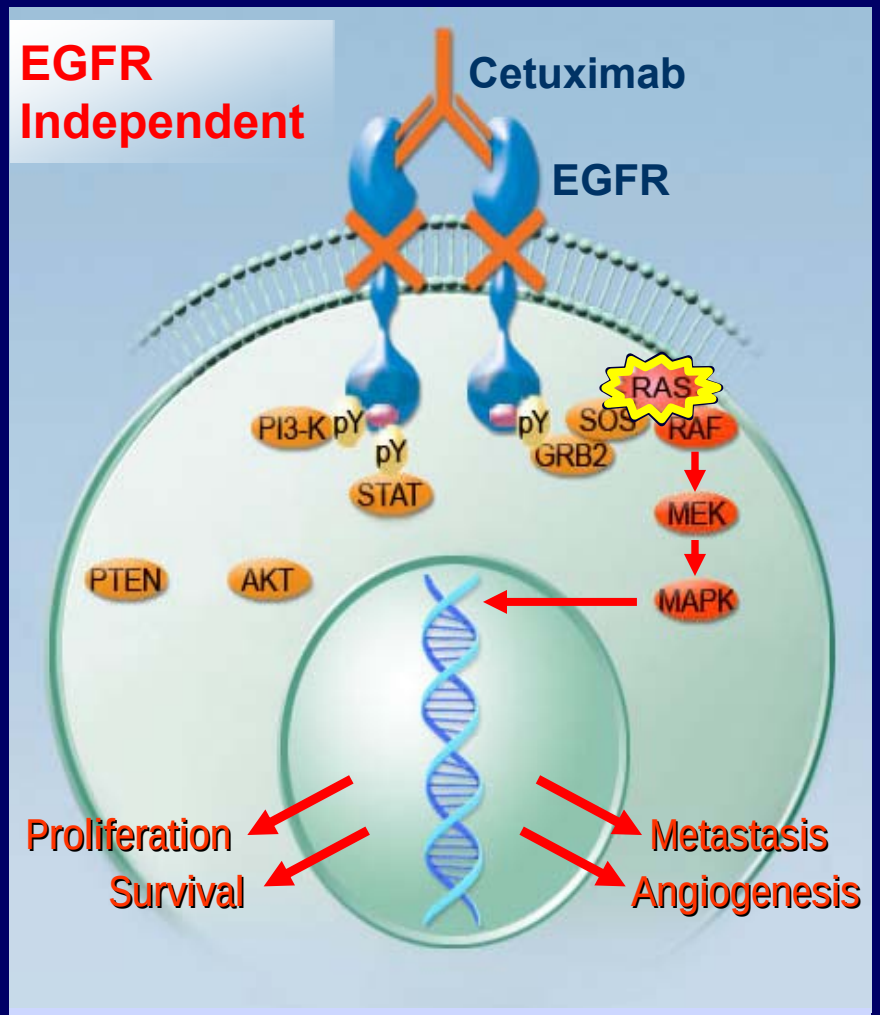
K-ras Status and Cetuximab Activity in CRC

K-ras wild type



No Downstream Signaling

K-ras mutant



Persistent Signaling

K-ras Status Consistently Predicts Response to Erbitux in Refractory mCRC

Study	Treatment	N (% WT)	Response Rate, %	
			WT	MUT
Liévre et al, 2006	Erbitux + Chemotherapy	30 (57)	65	0
Benvenuti et al, 2007	Erbitux ± Chemotherapy	23 (74)	41	0
De Roock et al, 2007*	Erbitux ± Chemotherapy	113 (59)	41	0
Capuzzo et al, 2007	Erbitux ± Chemotherapy	80 (48)	26	10
Di Fiore et al, 2007	Erbitux + Chemotherapy	59 (73)	28	0
Khambata-Ford et al, 2007	Erbitux	80 (62)	12	0
Liévre et al, 2008†	Erbitux ± Chemotherapy	89 (73)	40	0
Baker et al, 2008‡	Erbitux	226 (64)	22	1

* Patients from 4 clinical trials (EVEREST, BOND, SALVAGE, BABEL)
† Independent series of 89 patients
‡ Includes 80 patients from Khambata-Ford et al

Rapid Dissemination of *K-ras* Data

April	**Voluntary submission of *K-ras* data to FDA**
May	**Presentation of *K-ras* analyses at ASCO (CRYSTAL and OPUS trials)**
June	**Presentation of *K-ras* analysis at WCGIC (NCIC CO.17 phase 3 trial)**
	NCI / CTEP Action Letter suspends accrual of CRC patients with mutant *K-ras* tumors to ongoing phase 3 cooperative group trials of Erbitux
July	***K-ras* included in Erbitux European label**
October	**NEJM publication of *K-ras* analysis of NCIC CO.17**
	NCCN guidelines recommend *K-ras* testing for Erbitux treatment decisions

Company Sponsored Randomized Trials Analyzed for *K-ras*

	Trial Design	1° End Point	N (% *K-ras* Evaluable)	*K-ras* Assay Method
NCIC CO.17 Phase 3	Refractory CRC BSC ± Erbitux	OS	572 (69)	DNA sequencing
CRYSTAL Phase 3	1st line CRC FOLFIRI ± Erbitux	PFS	1198 (45)	Quantitative PCR
OPUS Phase 2	1st line CRC FOLFOX ± Erbitux	ORR	337 (69)	Quantitative PCR
EPIC Phase 3	2nd line CRC irinotecan ± Erbitux	OS	1298 (23)*	DNA sequencing

*Per protocol, only US patients had tissue samples available and were tested.

Study NCIC CO.17

Phase 3

Refractory CRC

BSC ± Erbitux

NCIC CO.17

Best Supportive Care ± Erbitux in Refractory mCRC

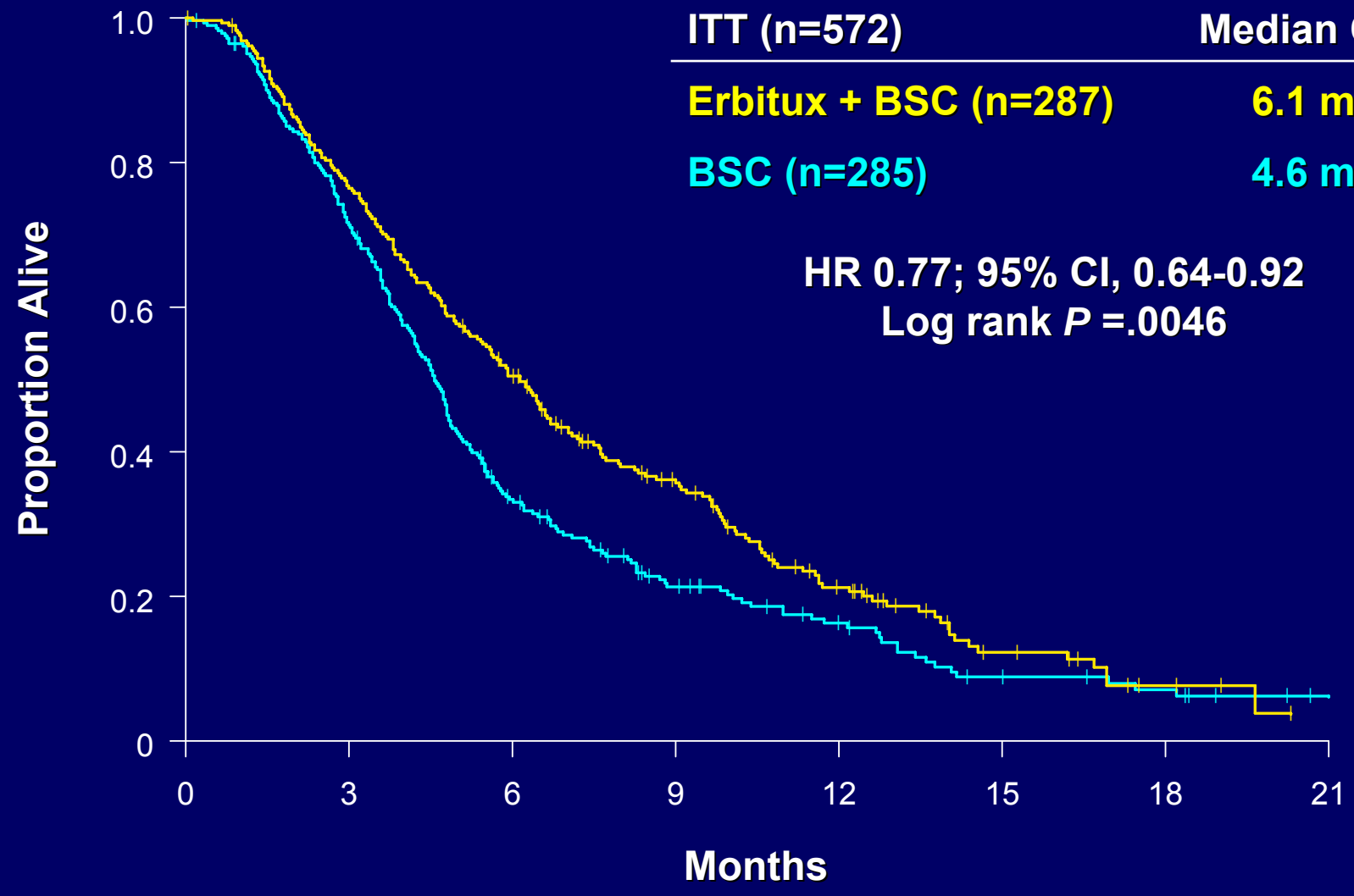
- EGFR-expressing (IHC) mCRC
- Failed or intolerant to all recommended therapies
- Stratification
  - Study site
  - ECOG PS 0,1 or 2

Primary endpoint: Overall Survival

Secondary endpoints: PFS, ORR, safety, QoL

NCIC CO.17 Primary Endpoint Met

Erbitux Significantly Prolongs OS in *K-ras* Unselected Patients

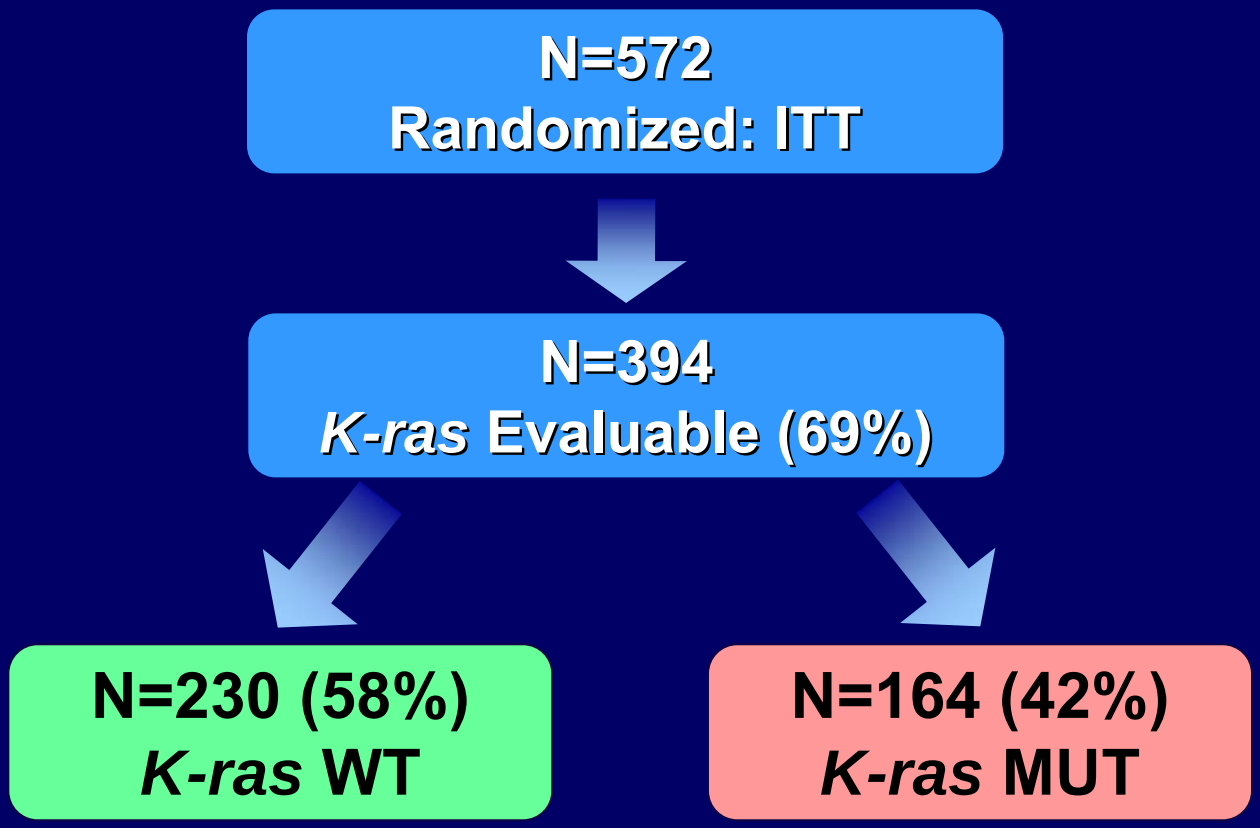


ITT (n=572)	Median OS
Erbitux + BSC (n=287)	6.1 m
BSC (n=285)	4.6 m

HR 0.77; 95% CI, 0.64-0.92
Log rank *P* =.0046

NCIC CO.17

K-ras Analysis



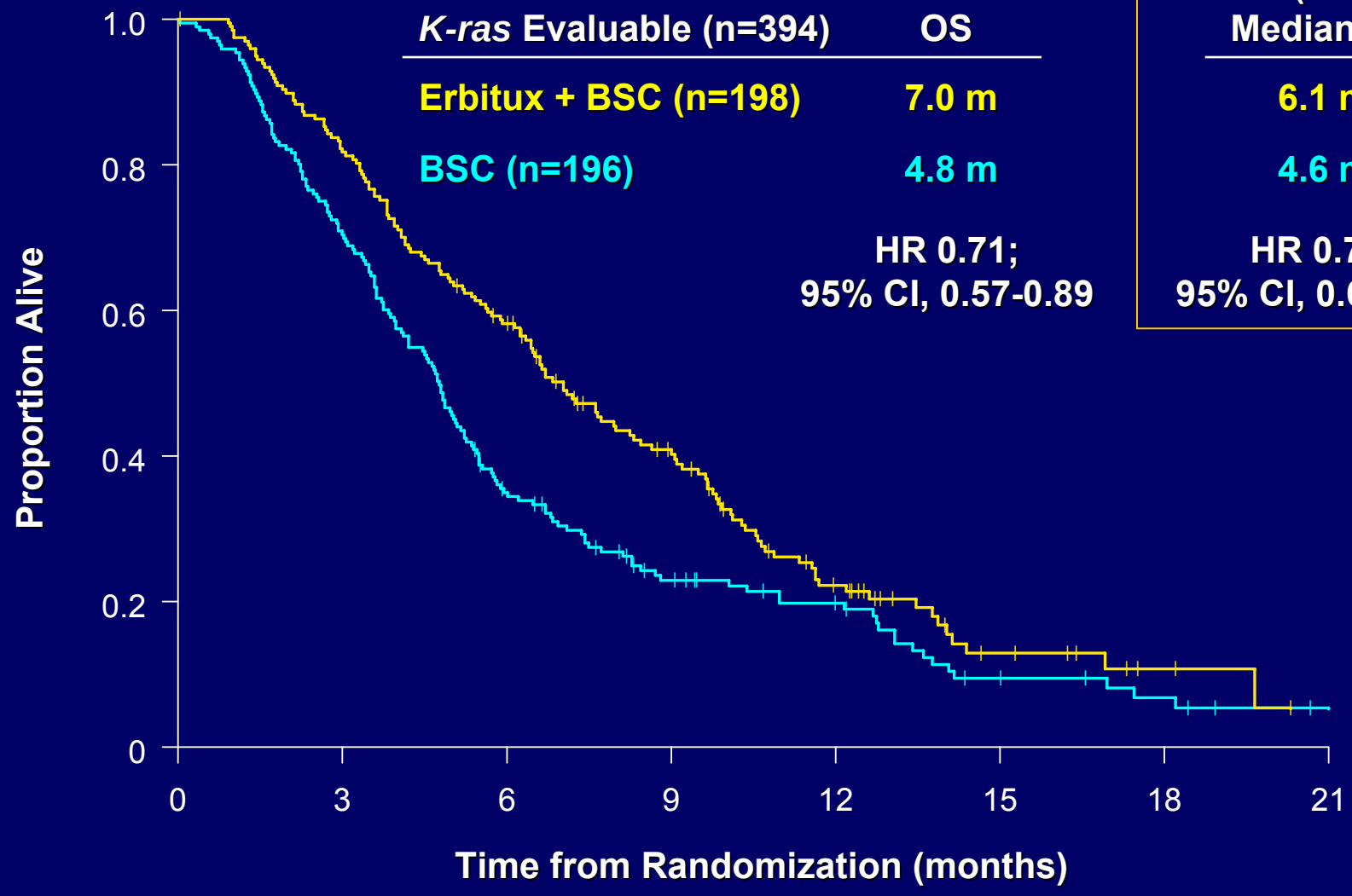
NCIC CO.17

Comparable Demographics in ITT and *K-ras* Evaluable

Parameter, %	ITT n=572	*K-ras* Evaluable n=394	*K-ras* WT n=230	*K-ras* MUT n=164
Age <65	59	59	58	60
Gender, male	64	65	68	62
ECOG PS 0/1	77	79	80	78
Prior adjuvant therapy	37	36	36	35
Involved disease sites ≤ 2	43	44	45	44

NCIC CO.17

Comparable OS in *K-ras* Evaluable and ITT



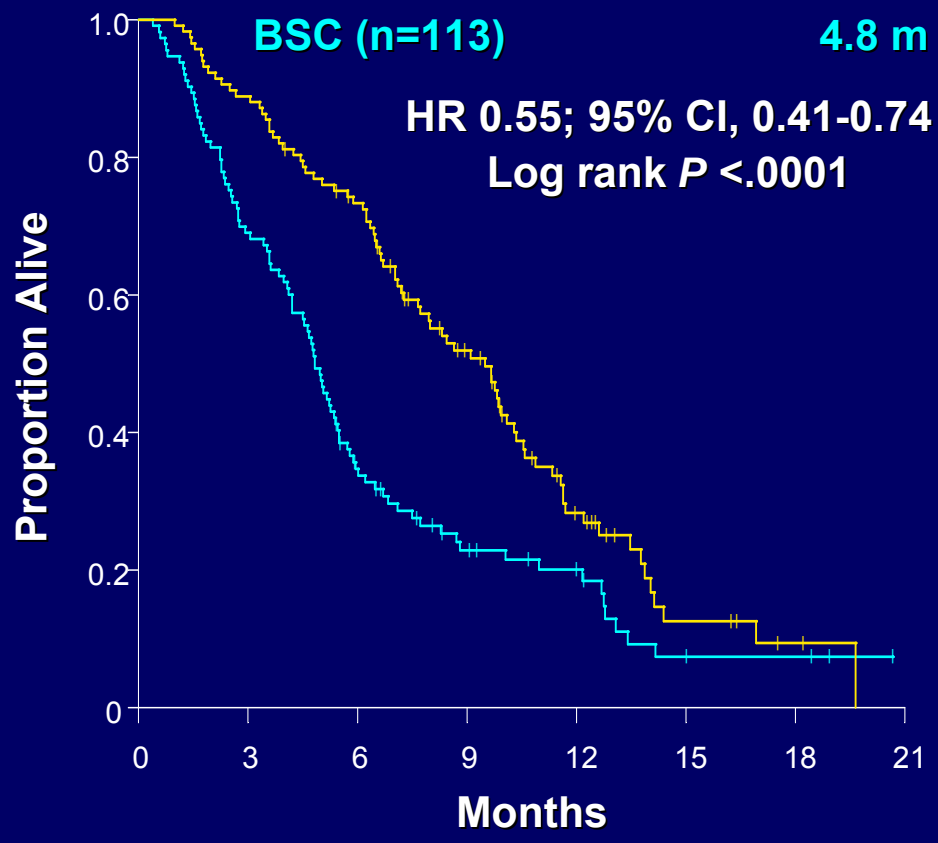
K-ras Evaluable (n=394)	Median OS
Erbitux + BSC (n=198)	7.0 m
BSC (n=196)	4.8 m
	HR 0.71; 95% CI, 0.57-0.89

ITT (n=572)	Median OS
	6.1 m
	4.6 m
	HR 0.77; 95% CI, 0.64-0.92

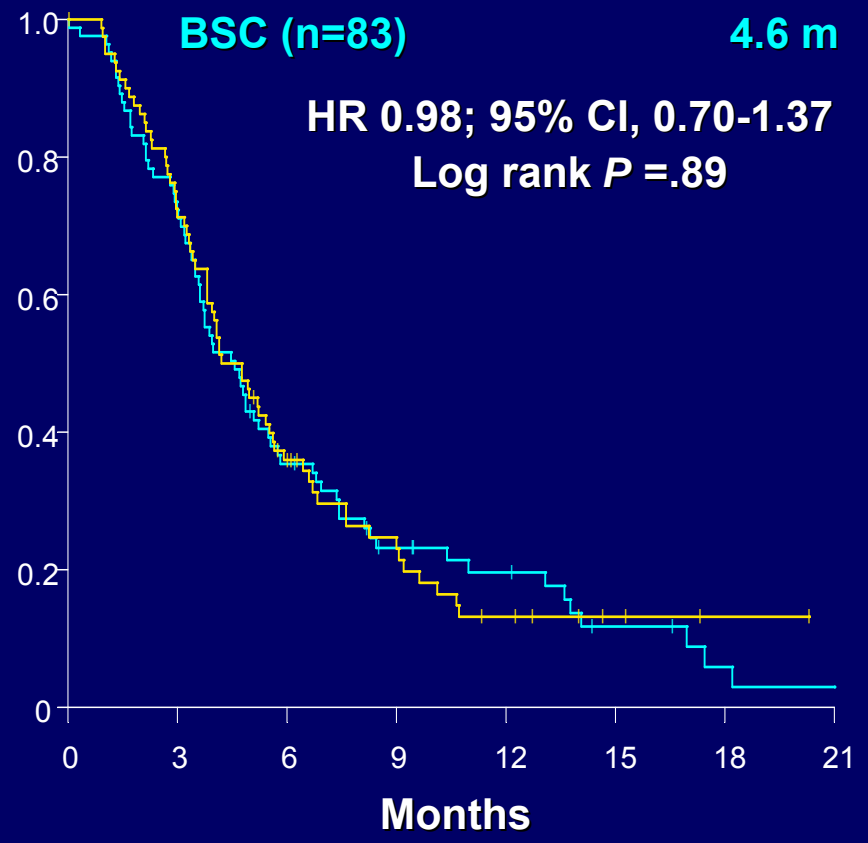
NCIC CO.17 Overall Survival

K-ras Status is a Significant Predictor of Efficacy with Erbitux

K-ras WT (n=230)	Median OS
Erbitux + BSC (n=117)	9.5 m
BSC (n=113)	4.8 m



K-ras MUT (n=164)	Median OS
Erbitux + BSC (n=81)	4.5 m
BSC (n=83)	4.6 m



P **=.01 for interaction between *K-ras* status and treatment**

NCIC CO.17 OS Sensitivity Analyses

K-ras Predictive of Efficacy Regardless of Missing Data Scenario

Scenario for Missing *K-ras* Data		*K-ras* WT		*K-ras* MUT		Interaction p-value
		Erbitux + BSC	BSC	Erbitux + BSC	BSC	
K-ras Evaluable Only	n	117	113	81	83	
	OS (m)	9.5	4.8	4.5	4.6	
	HR (95% CI)	0.55 (0.41, 0.74)		0.98 (0.70, 1.37)		0.01
Missing Assigned to MUT Group	n	117	113	170	172	
	OS (m)	9.5	4.8	4.6	4.4	
	HR (95% CI)	0.55 (0.41, 0.74)		0.96 (0.76, 1.21)		0.01
Missing Assigned to WT Group	n	206	202	81	83	
	OS (m)	6.6	4.6	4.5	4.6	
	HR (95% CI)	0.68 (0.55, 0.85)		0.98 (0.70, 1.37)		0.07

NCIC CO.17 OS Sensitivity Analyses

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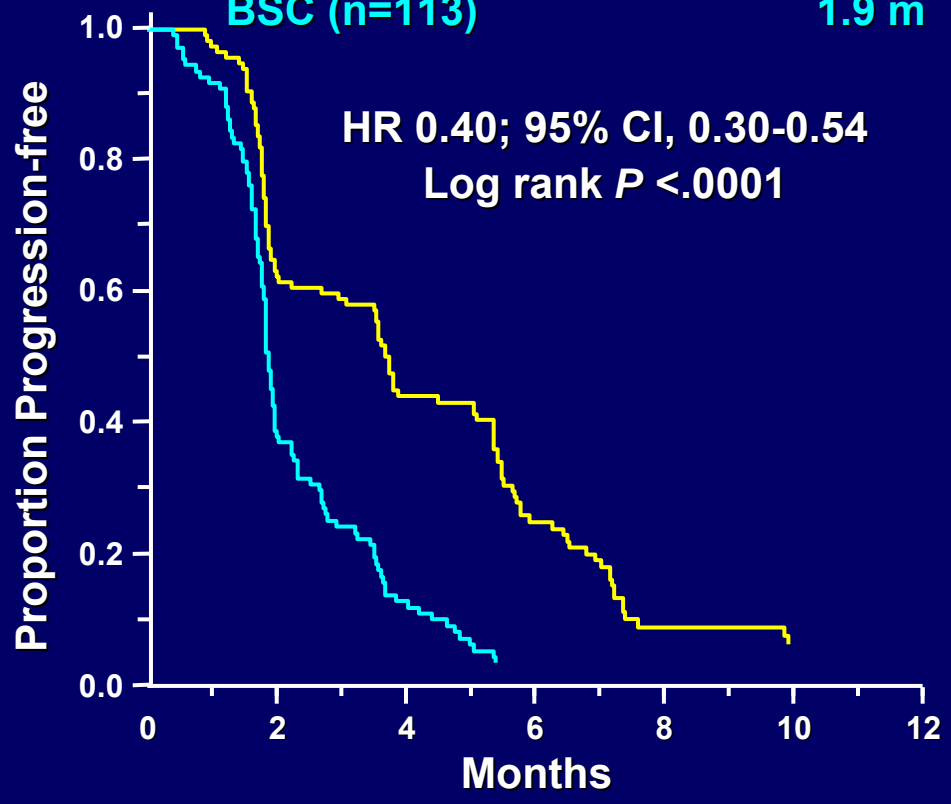
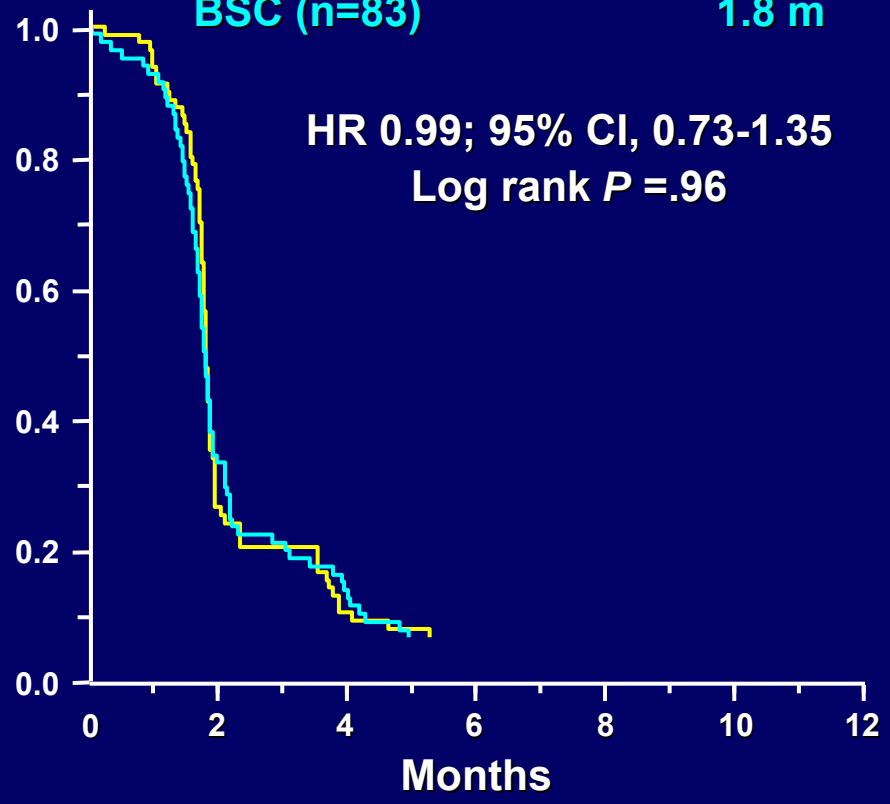
NCIC CO.17 Progression Free Survival

K-ras Status is a Significant Predictor of Efficacy with Erbitux

K-ras WT (n=230)	Median PFS
Erbitux + BSC (n=117)	3.8 m
BSC (n=113)	1.9 m



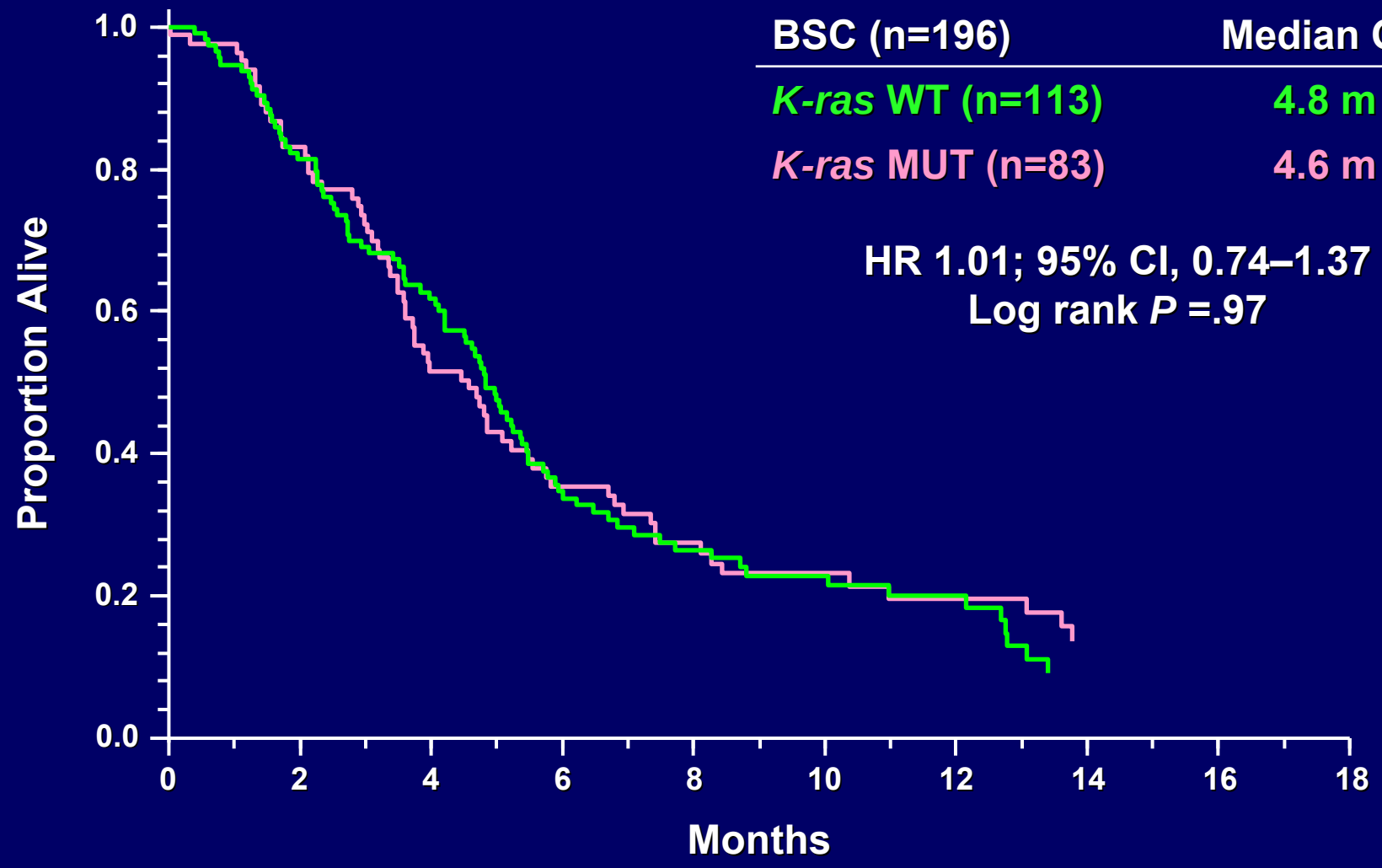
K-ras MUT (n=164)	Median PFS
Erbitux + BSC (n=81)	1.8 m
BSC (n=83)	1.8 m



P =.0001 for interaction between *K-ras* status and treatment

NCIC CO.17

K-ras Status Not Prognostic for OS in Best Supportive Care Group



BSC (n=196)	Median OS
K-ras WT (n=113)	4.8 m
K-ras MUT (n=83)	4.6 m

HR 1.01; 95% CI, 0.74–1.37
Log rank *P* =.97

Additional Studies

CRYSTAL – Phase 3, 1st line CRC, FOLFIRI ± Erbitux

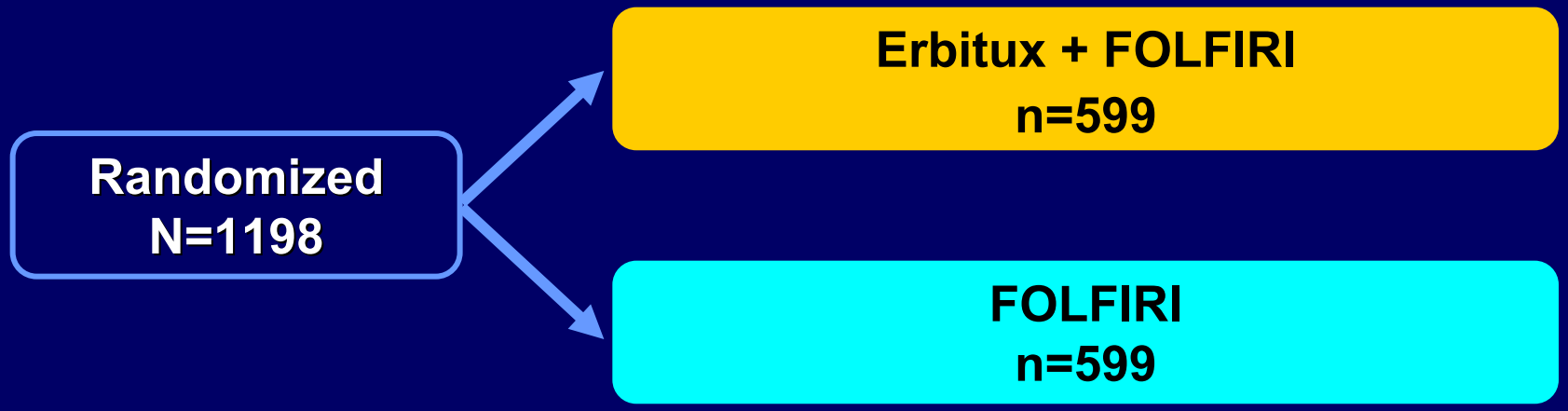
OPUS – Phase 2, 1st line CRC, FOLFOX ± Erbitux

EPIC – Phase 3, 2nd line CRC, irinotecan ± Erbitux

CRYSTAL

FOLFIRI ± Erbitux in 1st Line mCRC

- EGFR-expressing (IHC) mCRC
- No prior chemotherapy except adjuvant
- Stratification
  - Region
  - ECOG PS 0,1 or 2

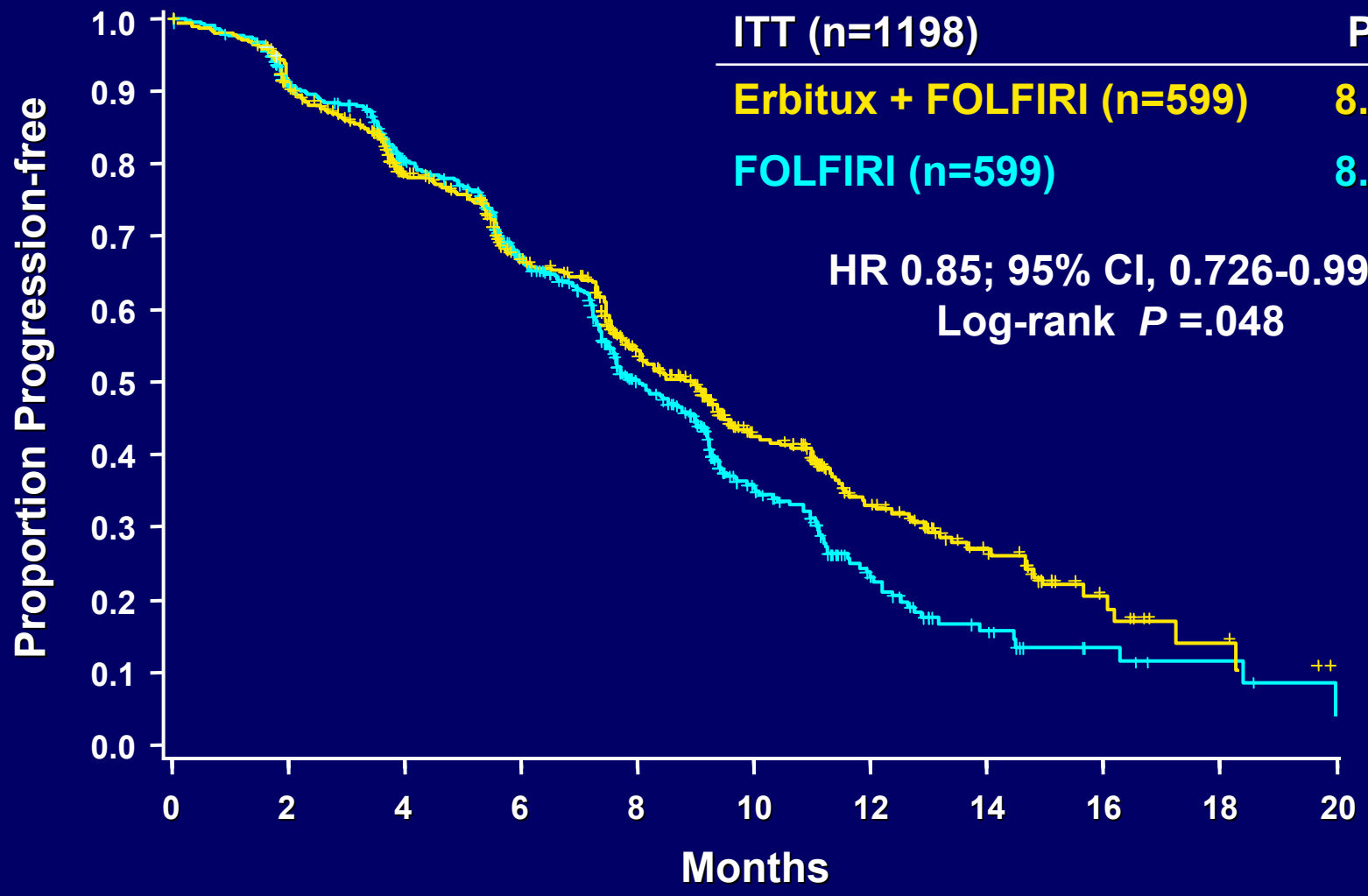


Primary endpoint: Progression Free Survival (independent review)

Secondary endpoints: ORR (independent review), OS, QoL, safety

CRYSTAL Primary Endpoint Met

Erbitux Significantly Prolongs PFS in *K-ras* Unselected Patients

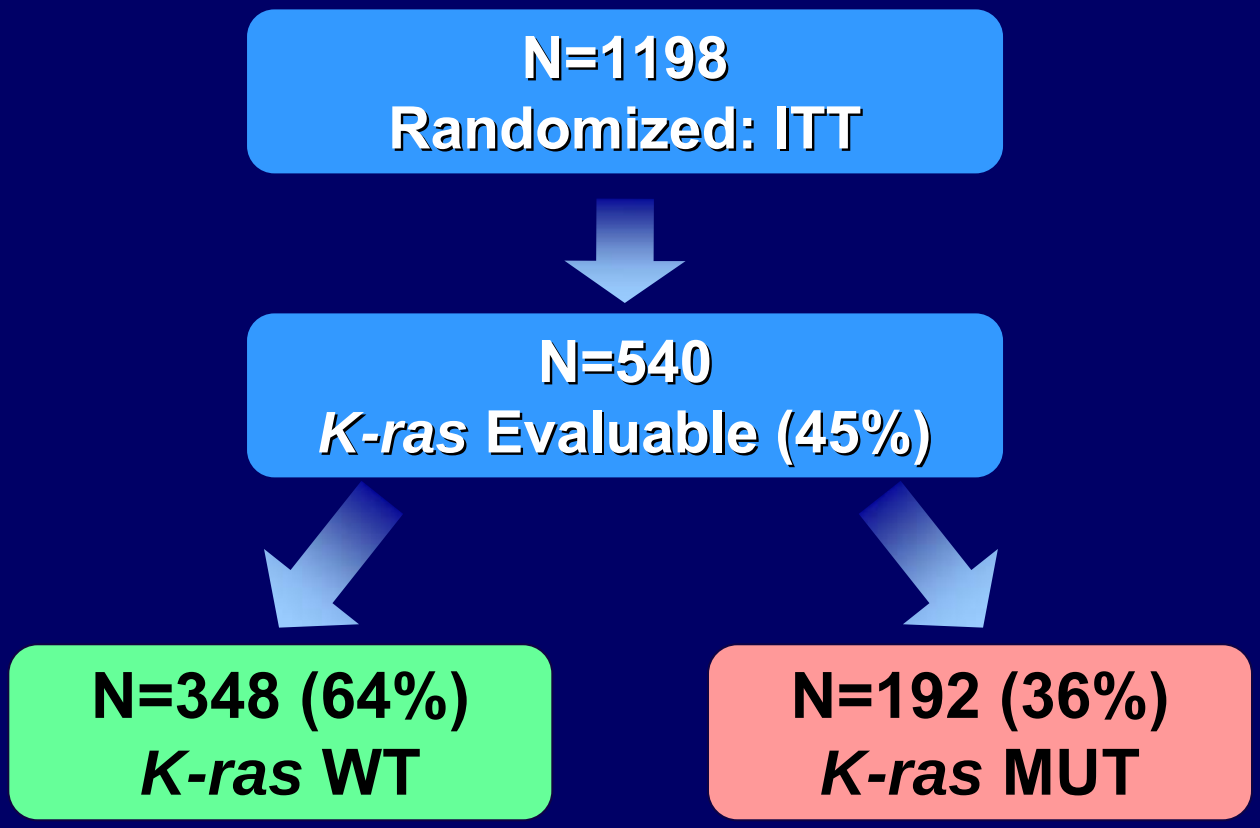


ITT (n=1198)	Median PFS
Erbitux + FOLFIRI (n=599)	8.9 m
FOLFIRI (n=599)	8.0 m

HR 0.85; 95% CI, 0.726-0.998
Log-rank *P* =.048

CRYSTAL

K-ras Analysis



CRYSTAL

Comparable Demographics in ITT and *K-ras* Evaluable

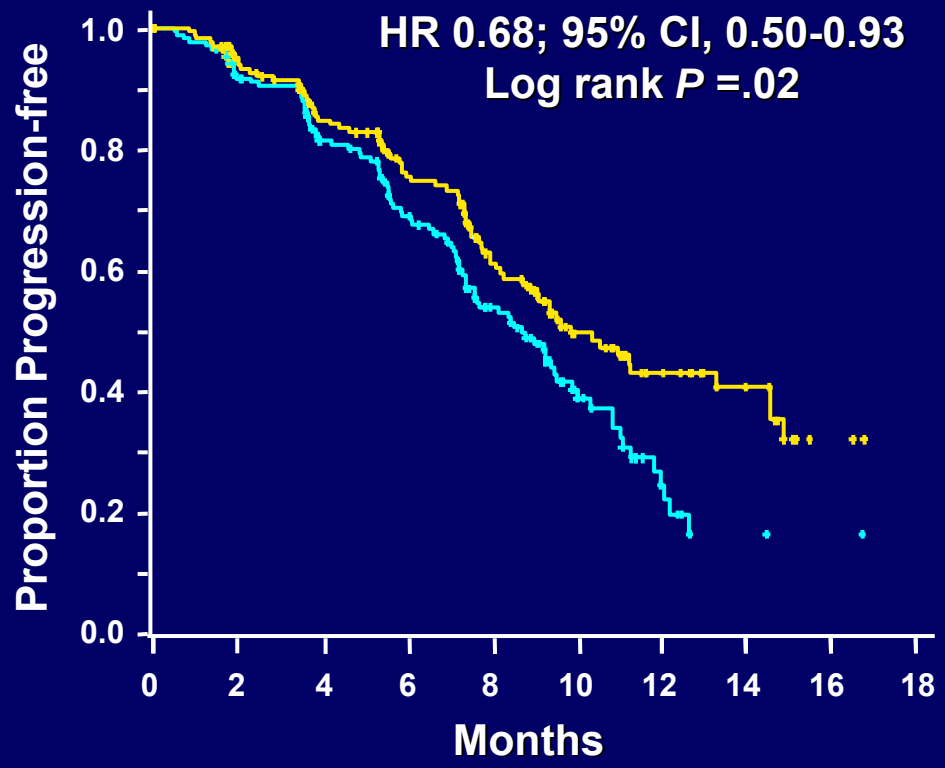
Parameter, %	ITT n=1198	*K-ras* Evaluable n=540	*K-ras* WT n=348	*K-ras* MUT n=192
Age < 65	63	64	66	60
Gender, male	61	58	58	58
ECOG PS 0/1	97	97	96	98
Prior adjuvant chemo	20	18	22	13
Involved disease sites ≤ 2	85	85	85	83
Liver-limited disease	21	20	19	22

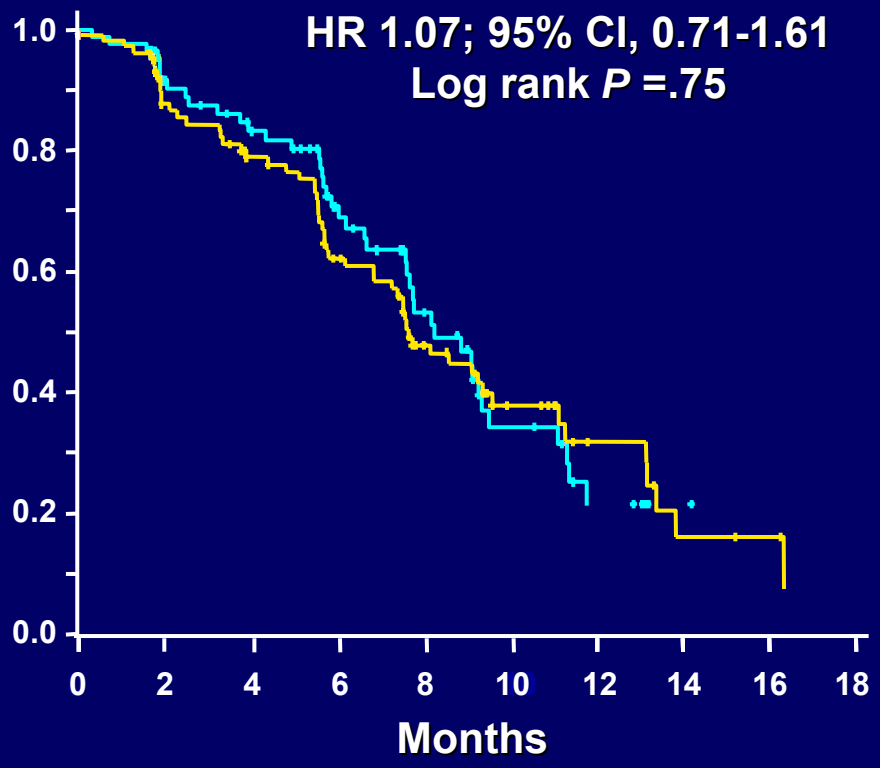
CRYSTAL Progression Free Survival

K-ras Status is a Predictor of Efficacy

K-ras WT (n=348)	Median PFS
Erbitux + FOLFIRI (n=172)	9.9 m
FOLFIRI (n=176)	8.7 m

K-ras MUT (n=192)	Median PFS
Erbitux + FOLFIRI (n=105)	7.6 m
FOLFIRI (n=87)	8.1 m





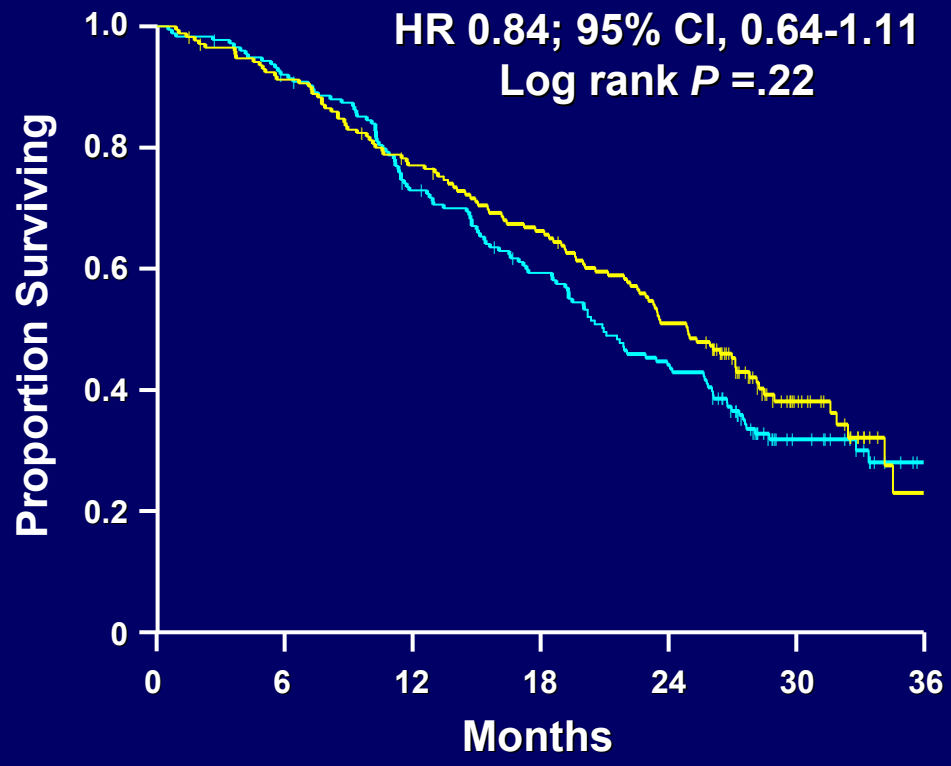
P =.07 for interaction between *K-ras* status and treatment

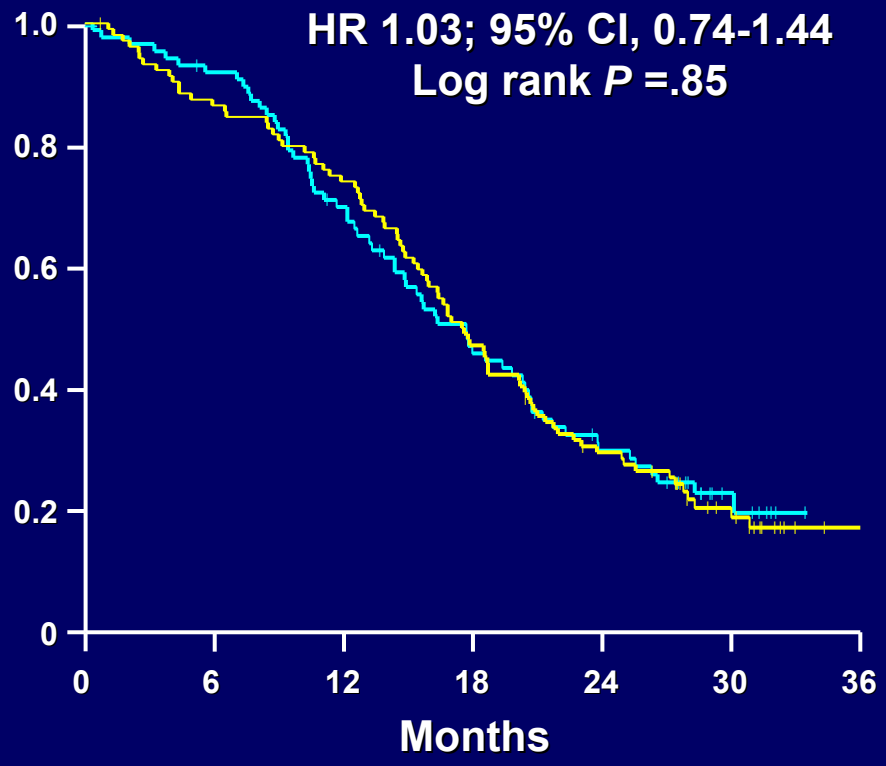
CRYSTAL Overall Survival

K-ras Status and Erbitux

K-ras WT (n=348)	Median OS
Erbitux + FOLFIRI (n=172)	24.9 m
FOLFIRI (n=176)	21.0 m

K-ras MUT (n=192)	Median OS
Erbitux + FOLFIRI (n=105)	17.5 m
FOLFIRI (n=87)	17.7 m





P =.44 for interaction between *K-ras* status and treatment

CRYSTAL Response Rate

K-ras Status is a Significant Predictor of Efficacy

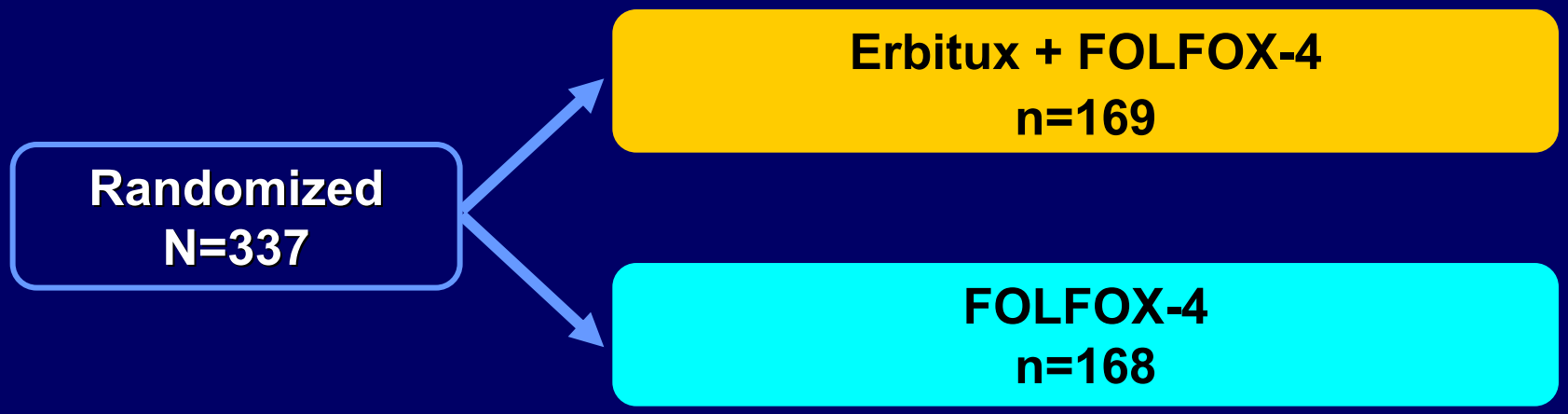
	ITT		*K-ras* WT		*K-ras* MUT	
	Erbitux + FOLFIRI n=599	FOLFIRI n=599	Erbitux + FOLFIRI n=176	FOLFIRI n=172	Erbitux + FOLFIRI n=87	FOLFIRI n=105
ORR, %	47	39	59	43	36	40
P	.0038		.0025		.46	

P **=.03 for interaction between *K-ras* status and treatment**

OPUS

FOLFOX-4 ± Erbitux in 1st Line mCRC

- EGFR-expressing (by IHC) mCRC
- No prior chemotherapy except adjuvant (no oxaliplatin)
- Stratification
  - ECOG PS 0,1 or 2

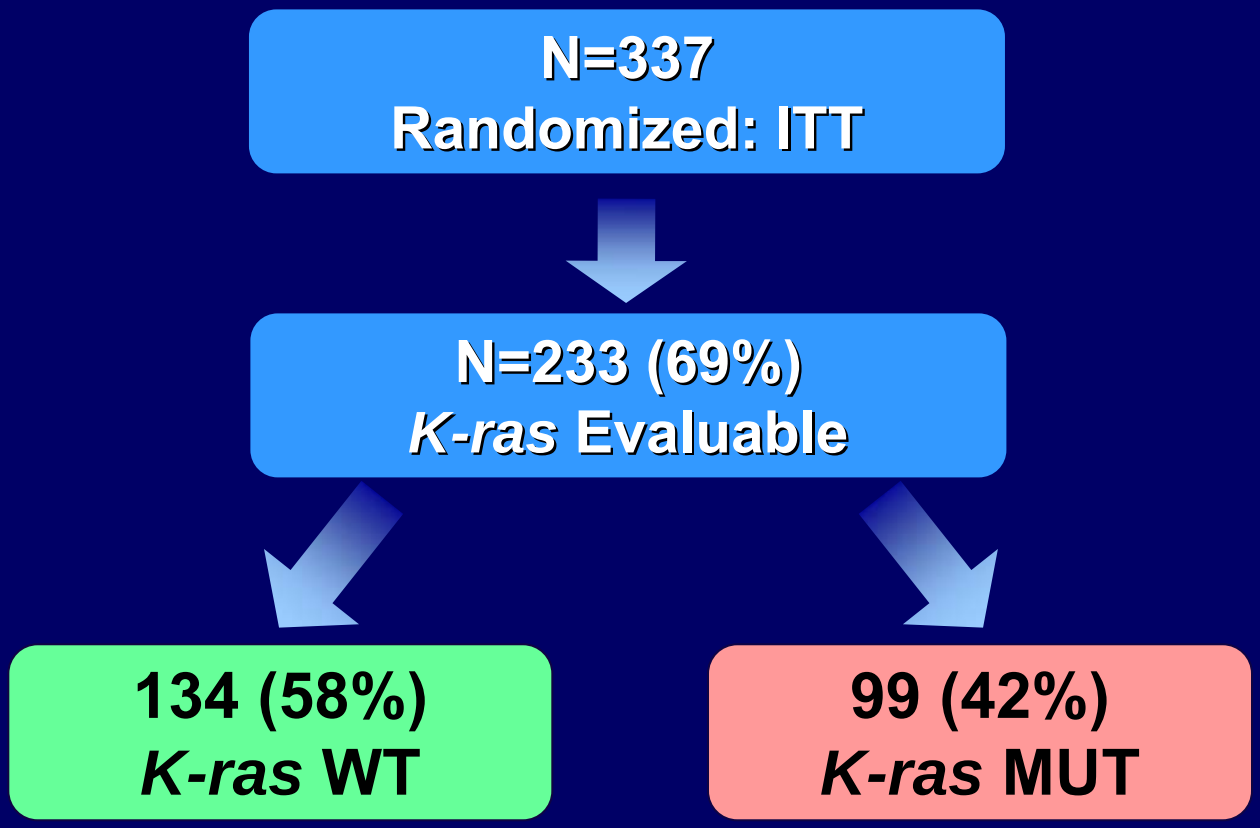


Primary endpoint: Overall Response Rate (independent review)

Secondary endpoints: PFS, OS, rate of curative resection

OPUS

K-ras Analysis



OPUS

Comparable Demographic Features in ITT and *K-ras* Evaluable

Parameter, %	ITT n=337	*K-ras* Evaluable n=233	*K-ras* WT n=134	*K-ras* MUT n=99
Age <65	61	63	63	63
Gender, male	54	53	55	50
ECOG PS 0/1	91	90	89	91
Prior adjuvant chemo	17	14	15	13
Involved disease sites ≤ 2	79	78	78	78
Liver-limited disease	26	27	28	25

OPUS

K-ras Status is a Significant Predictor of Efficacy

	ITT		*K-ras* Evaluable		*K-ras* WT		*K-ras* MUT	
	Erbitux + FOLFOX n=168	FOLFOX n=169	Erbitux + FOLFOX n=113	FOLFOX n=120	Erbitux + FOLFOX n=61	FOLFOX n=73	Erbitux + FOLFOX n=47	FOLFOX n=52
ORR, %	46	36	48	42	61	37	33	49
P	.064		.39		.011		.106	
PFS (m)	7.2	7.2	7.3	7.2	7.7	7.2	5.5	8.6
HR	0.931		0.928		0.57		1.83	
P	.617		.661		.016		.019	

P **=.003 for interaction between *K-ras* status and treatment for ORR**

P **=.0007 for interaction between *K-ras* status and treatment for PFS**

Summary

K-ras Status is a Predictor of Erbitux Efficacy

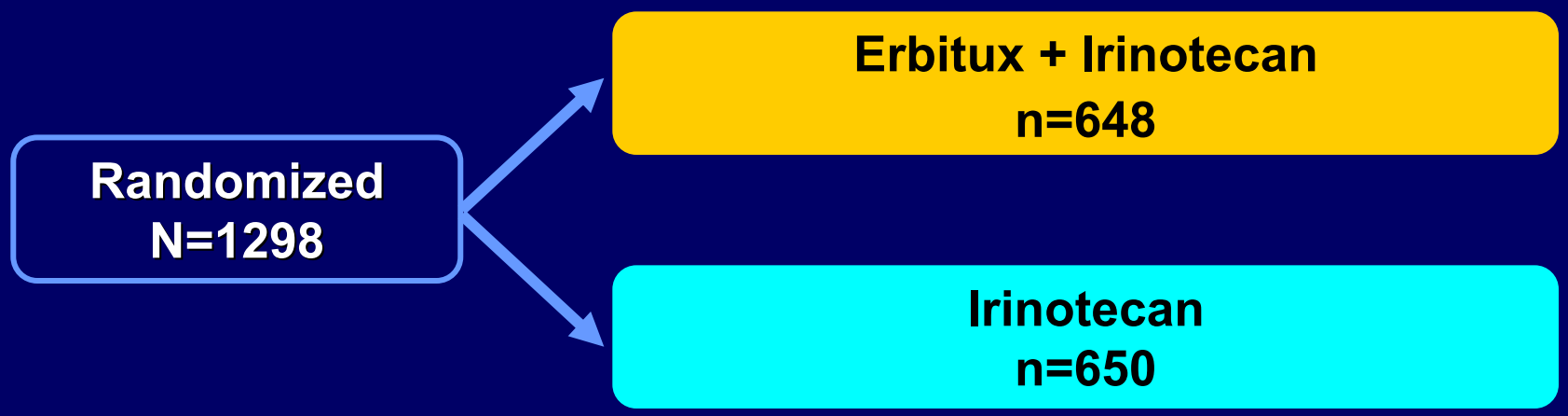
	N	*K-ras* Evaluable	Endpoint	*P* value interaction between *K-ras* status and treatment
NCIC CO.17	572	394	OS*	.01
			PFS	.0001
			RR	NR
CRYSTAL	1198	540	PFS*	.07
			OS	.44
			RR	.03
OPUS	337	233	RR**	.003
			PFS	.0007
			OS	NR

* Primary endpoint met; ** Primary endpoint not met; NR = Not reported

EPIC

Irinotecan ± Erbitux in 2nd Line mCRC

- EGFR-expressing (by IHC) mCRC
- Failure of prior oxaliplatin chemotherapy
- Stratification
  - Study site
  - ECOG PS 0,1 or 2
- Tissue collection limited by protocol to US patients



Primary endpoint: Overall Survival

Secondary endpoints: PFS, RR, QoL

EPIC

Efficacy in *K-ras* Evaluable Subset Differs from ITT Population

	ITT		*K-ras* Evaluable		*K-ras* WT		*K-ras* MUT	
	Erbitux + Irinotecan n=648	Irinotecan n=650	Erbitux + Irinotecan n=146	Irinotecan n=154	Erbitux + Irinotecan n=97	Irinotecan n=95	Erbitux + Irinotecan n=49	Irinotecan n=59
OS (m)	10.71	9.99	9.3	11.3	10.9	11.6	8.4	10.7
HR	0.98		1.25		1.29		1.28	
P	.71		–		.18		.29	
PFS (m)	4.0	2.6	3.5	2.8	4.0	2.8	2.6	2.7
HR	0.69		0.84		0.77		1.00	
P	<.0001		–		.095		.98	
ORR (%)	16.4	4.2	11	6.5	10.3	7.4	12.2	5.1
P	<.0001		–		.61		.29	

P **=.989 for interaction between *K-ras* status and treatment for OS**

Impact on Research and Clinical Practice

Ongoing Phase 3 Cooperative Group Trials

Revisions and Current Status of Trials

			Required Protocol Revisions		
	Clinical Setting	N (initial/ revised)	*K-ras* Testing Prior to Randomization	Randomize *K-ras* WT Only	1° Analysis *K-ras* WT Only
N0147* (NCCTG)	Adjuvant	2300 / 3768	√	√	√
PETACC 8	Adjuvant	2000 / 2549	√	√	√
C80405* (CALGB)	1st line	2300 / 3610	√	√	√
COIN † (MRC)	1st line	2421	NA	NA	√
S0600* (SWOG)	2nd line	1260 / TBD	√	√	√

* Accrual suspended as per 06-Jun-08 Action Letter issued by NCI / CTEP
† Accrual completed prior to amendment

NCCN Treatment Guidelines Incorporate *K-ras**

- NCCN revised guidelines recommend
  - *K-ras* testing in initial work-up for all patients with metastatic colorectal cancer
  - Treatment only for patients with tumors that express the wild-type *K-ras* gene:
    - Erbitux and Vectibix as single agents
    - Erbitux in combination with irinotecan

* NCCN Practice Guidelines in Oncology Version 3, 3-Nov-08

Support for *K-ras* as a Predictive Biomarker in CRC

- Multiple independent studies with similar conclusions
- Rigorous design of company sponsored randomized studies
  - Adequate, well-conducted and well-controlled, positive studies
  - Prospective focus on a specific biomarker
  - Prospectively defined analysis plans for *K-ras*
  - Blinded *K-ras* assessment
  - *K-ras* evaluable subset representative of ITT population
- Consistent results independent of test methodology
- Consistent results across Erbitux and Vectibix
- NCCN treatment guidelines, NCI and cooperative groups use *K-ras* guided patient selection
  - Prospective trials to confirm predictive value of *K-ras* no longer possible

Conclusions

- These observations, indicating that *K-ras* mutation status is predictive of Erbitux benefit in CRC, are clinically relevant and compelling
- *K-ras* mutation status should be used to optimize selection of patients for treatment with Erbitux in CRC
- ImClone and Bristol-Myers Squibb are pursuing discussions with FDA to revise current Erbitux labeling