bevacizumab and panitumumab in mCRC at ESMO

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Studies with bevacizumab and panitumumab

Impact of KRAS status on survival in patients (pts.) with metastatic colorectal cancer (mCRC) undergoing bevacizumab (bev) containing chemotherapy regimen– Analysis of the AIO Colorectal Cancer Study Group	584PD	CRC	A.C. Reinacher-Schick
Chemotherapy with or without Bevacizumab in advanced colorectal cancer: A Phase III trial	606P	CRC	G.P. Stathopoulos
Bevacizumab (BV) in combination with FOLFOXIRI compared with BV plus FOLFIRI as first-line treatment of metastatic colorectal cancer (MCRC): preliminary safety results of the TRIBE study by the Gruppo Oncologico Nord-Ovest (GONO)	608P	CRC	G. Masi
The role of perioperative Bevacizumab in the management of patients with colorectal cancer and liver metastases treated with liver metastasectomy	637P	CRC	A. Constantinidou
Efficacy and safety of second-line treatment with panitumumab plus irinotecan, both given every three weeks (Q3W), in patients (pts) with wild-type (WT) K-RAS metastatic colorectal cancer (mCRC): A study from the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)	583PD	CRC	A. Gomez

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Phase III trial mIFL +/- bevacizumab recently published

Clinical Study

Oncology

Oncology 2010;78:376–381
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Treatment of Colorectal Cancer with and without Bevacizumab: A Phase III Study

G.P. Stathopoulos C. Batziou D. Trafalis J. Koutantos S. Batzios
J. Stathopoulos J. Legakis A. Armakolas

First Oncology Clinic, Errikos Dunant Hospital, Athens, Greece

Bevacizumab did not improve RR nor OS in mCRC patients

Table 3. Survival time (months), Log-rank test p value = 0.1391

Treatment	Patients	Median
Arm A (chemotherapy with bevacizumab)	114	22.0
Arm B (chemotherapy without bevacizumab)	108	25.0

Table 2. Response rate

	Arm A	Arm B
Total number of patients	114 (100)	108 (100)
Complete response	–	–
Partial response	42 (36.8)	38 (35.2)

The NORDIC VII trial

Randomized phase III study of 5-fluorouracil/folinate/oxaliplatin given continuously or intermittently with or without cetuximab, as first-line treatment of metastatic colorectal cancer: The NORDIC VII study

K. Tveit et al. **ESMO LBA #4170**

What is the FLOX chemotherapy regimen that was used in NORDIC VII?

- FLOX, a combination of 5-fluorouracil, folinic acid and oxaliplatin, is not a chemotherapy that is used as standard in Europe.
- This regimen, like IFL, used 5-FU as a bolus therapy.

What do these new data from NORDIC VII show?

- In the NORDIC VII study, addition of Erbitux to the FLOX chemotherapy regimen did not significantly improve outcomes (RR, PFS or OS) for mCRC patients with KRAS wild-type tumors or for mCRC patients with KRAS mutant tumors.
- These findings were surprising for two key reasons:
  - In the ITT population, there was a trend towards benefit with Erbitux-based therapy.
  - And most surprising, the KRAS mutant patients treated with Erbitux-based therapy showed better outcomes than KRAS wild-type patients
- The latter findings are not consistent with the current scientific understanding *o*f the Erbitux MOA or the EGFR signaling pathway.
- The findings from NORDIC VII were not in line with those from all other studies in the 1st line setting (13 different trials), such as CRYSTAL and OPUS.

Could Erbitux just not be effective when used in combination with oxaliplatin-based chemotherapy regimens?

- Merck Serono's randomized Phase II OPUS study showed that the addition of Erbitux to the standard FOLFOX regimen significantly increased both PFS and tumor response. There was also a trend towards an increase in OS, although as this was a secondary endpoint the study was not powered to show a significant difference in this outcome measure.
- In other randomized trials (CELIM and CECOG), the combination of Erbitux with either FOLFIRI or FOLFOX showed comparable efficacy
- Additional analyses are ongoing to try to explain why the NORDIC VII findings were not in line with those from other studies, such as CRYSTAL and OPUS.

The CRYSTAL study

Early tumor shrinkage for the prediction of efficacy of cetuximab in metastatic colorectal cancer (MCRC): analysis from the CRYSTAL study

H. Piessevaux *et al.* **ESMO # 4777**

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The CRYSTAL trial

H. Piessevaux *et al.* **ESMO # 4777**

- Early tumor shrinkage may be a hallmark of efficacy of EGFR inhibition and could be used as an on treatment marker of efficacy. In contrast in the 1st - line trials objective response did not predict the outcome benefit from standard CT or the addition of bevacizumab

- Early tumor shrinkage was associated with a significantly better OS and PFS in KRAS wt pts receiving cetuximab plus FOLFIRI, but not for OS in FOLFIRI treated pts

- **Conclusions:** In the CRYSTAL study the presence of early tumor shrinkage in the KRAS wt population is predictive of optimal benefit for pts with mCRC treated 1st - line with cetuximab plus FOLFIRI.

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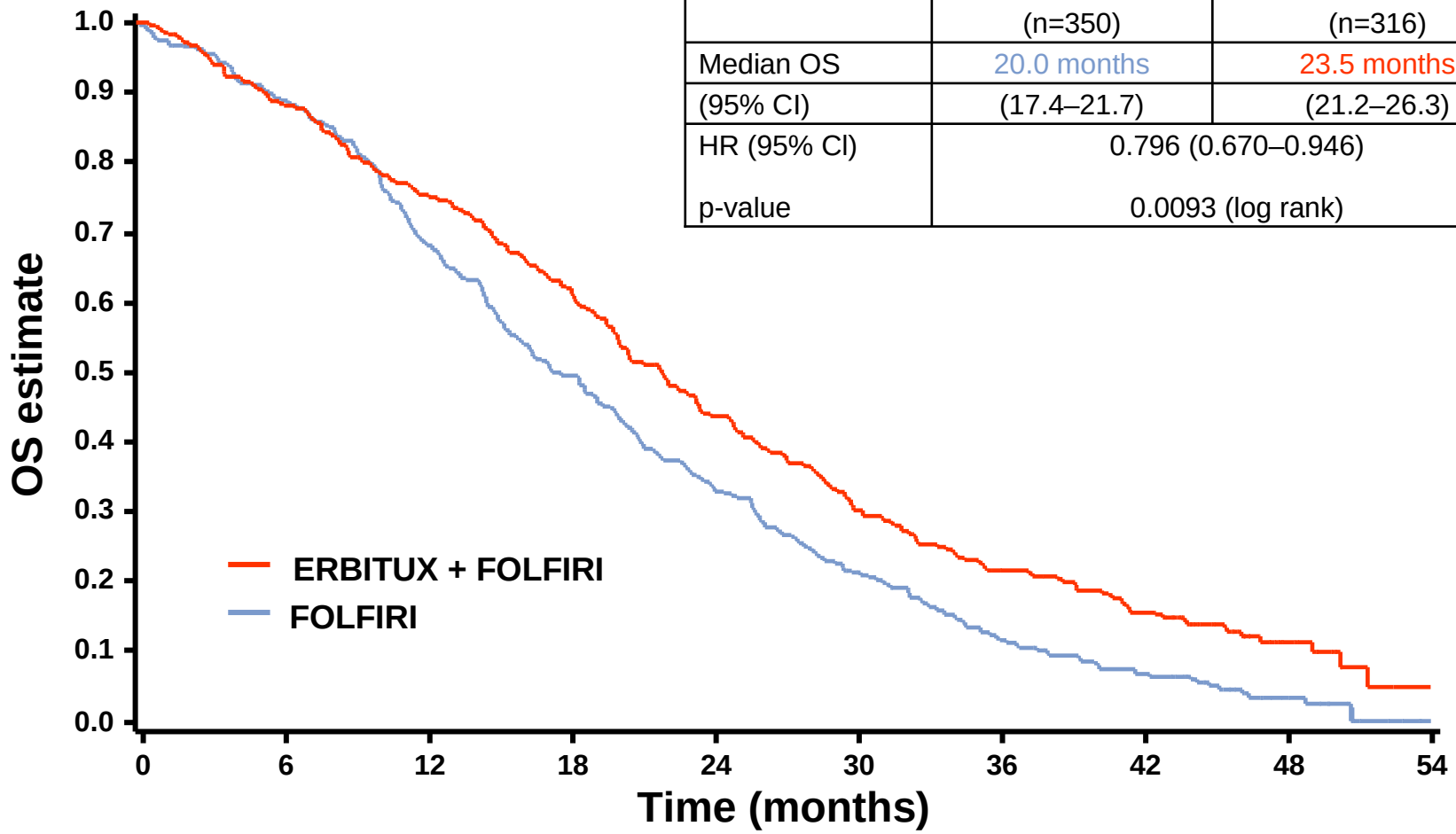
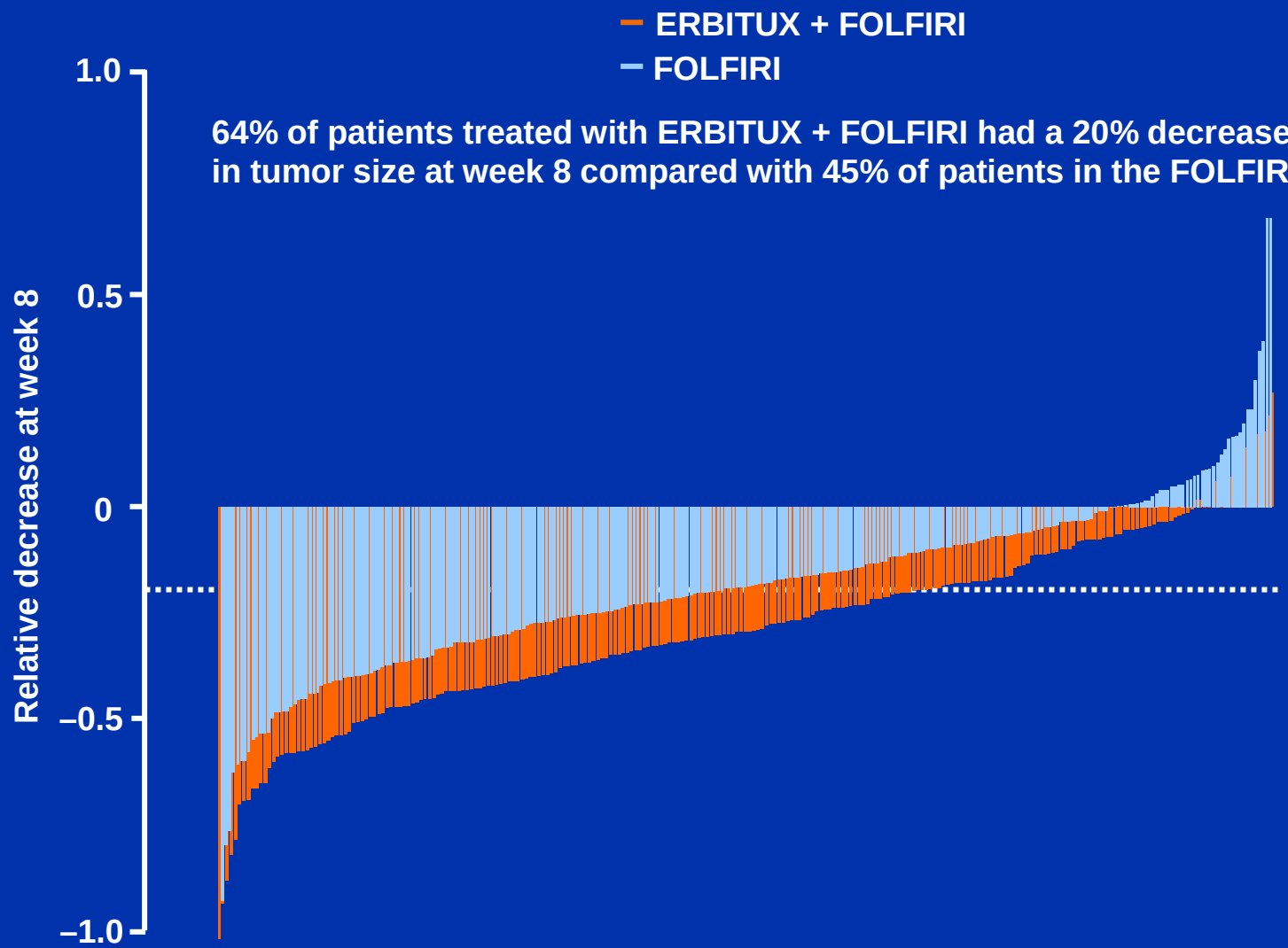
CRYSTAL: OS curves

	FOLFIRI (n=350)	ERBITUX + FOLFIRI (n=316)
Median OS	20.0 months	23.5 months
(95% CI)	(17.4–21.7)	(21.2–26.3)
HR (95% CI)	0.796 (0.670–0.946)	
p-value	0.0093 (log rank)	



CRYSTAL: 8-week tumor regression according to treatment in patients with KRAS wt tumors



Merck Serono, Data on file

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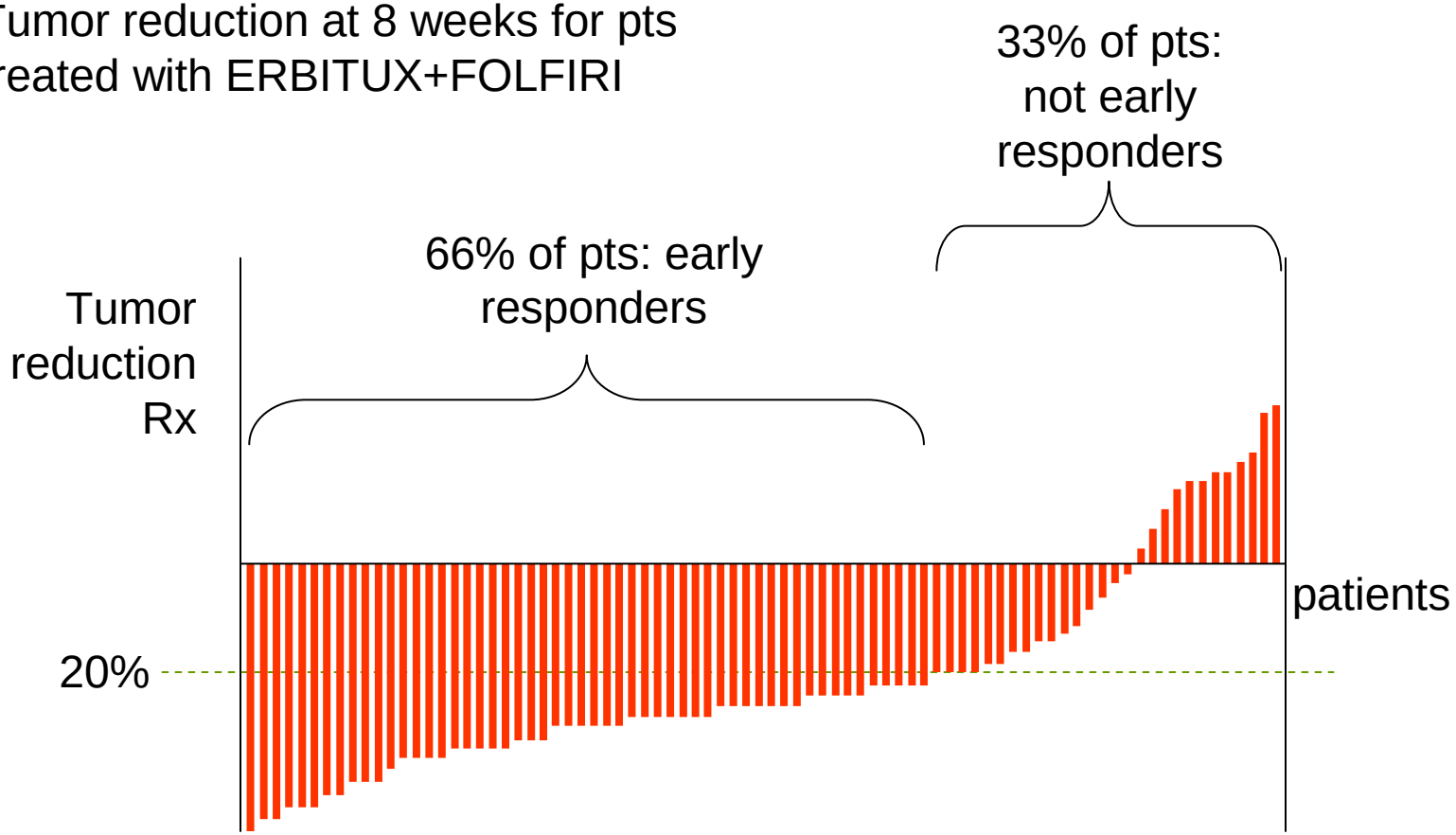
CRYSTAL: early shrinkage model

Tumor reduction at 8 weeks for pts treated with ERBITUX+FOLFIRI



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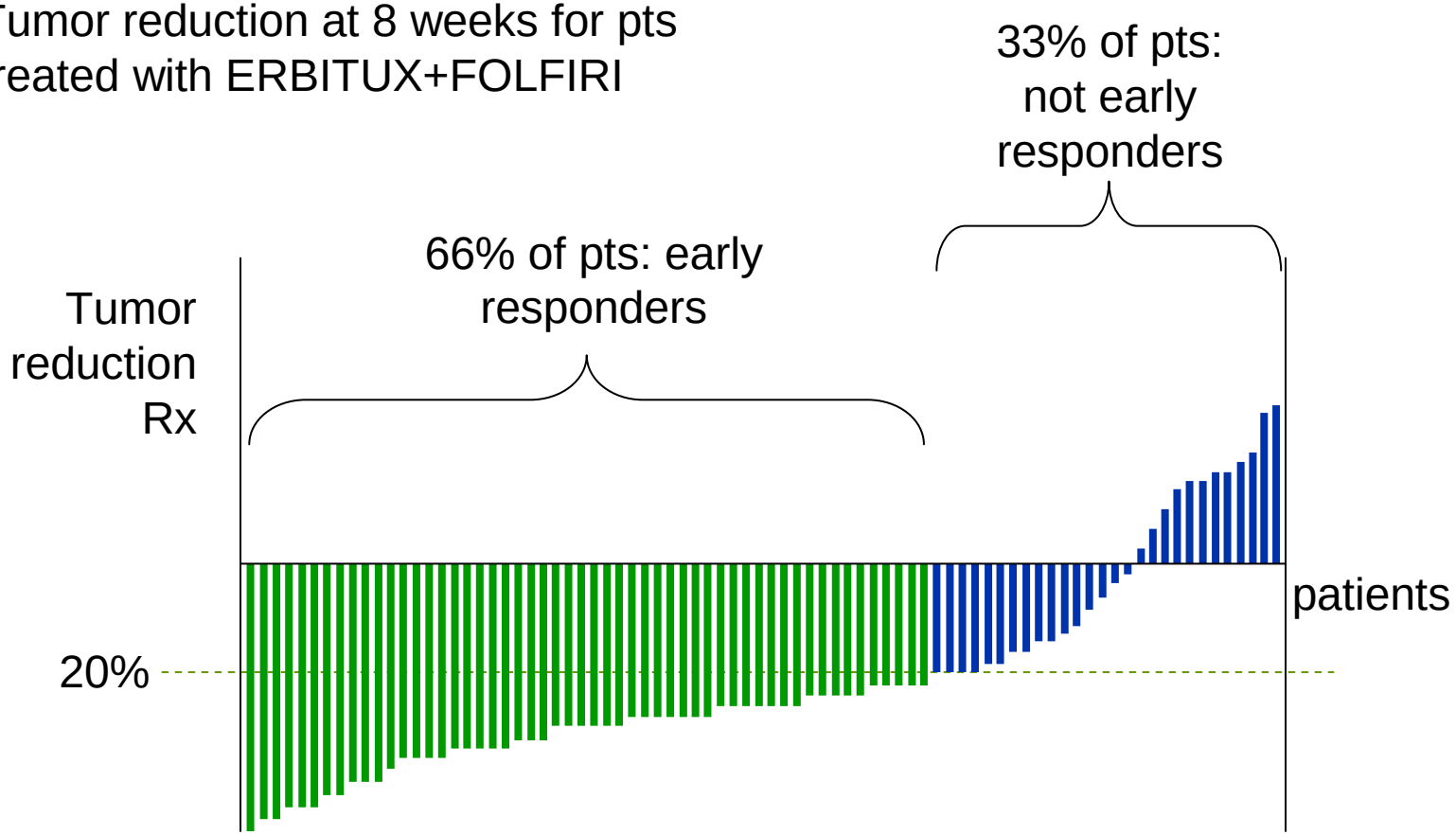
CRYSTAL: early shrinkage model

Tumor reduction at 8 weeks for pts treated with ERBITUX+FOLFIRI



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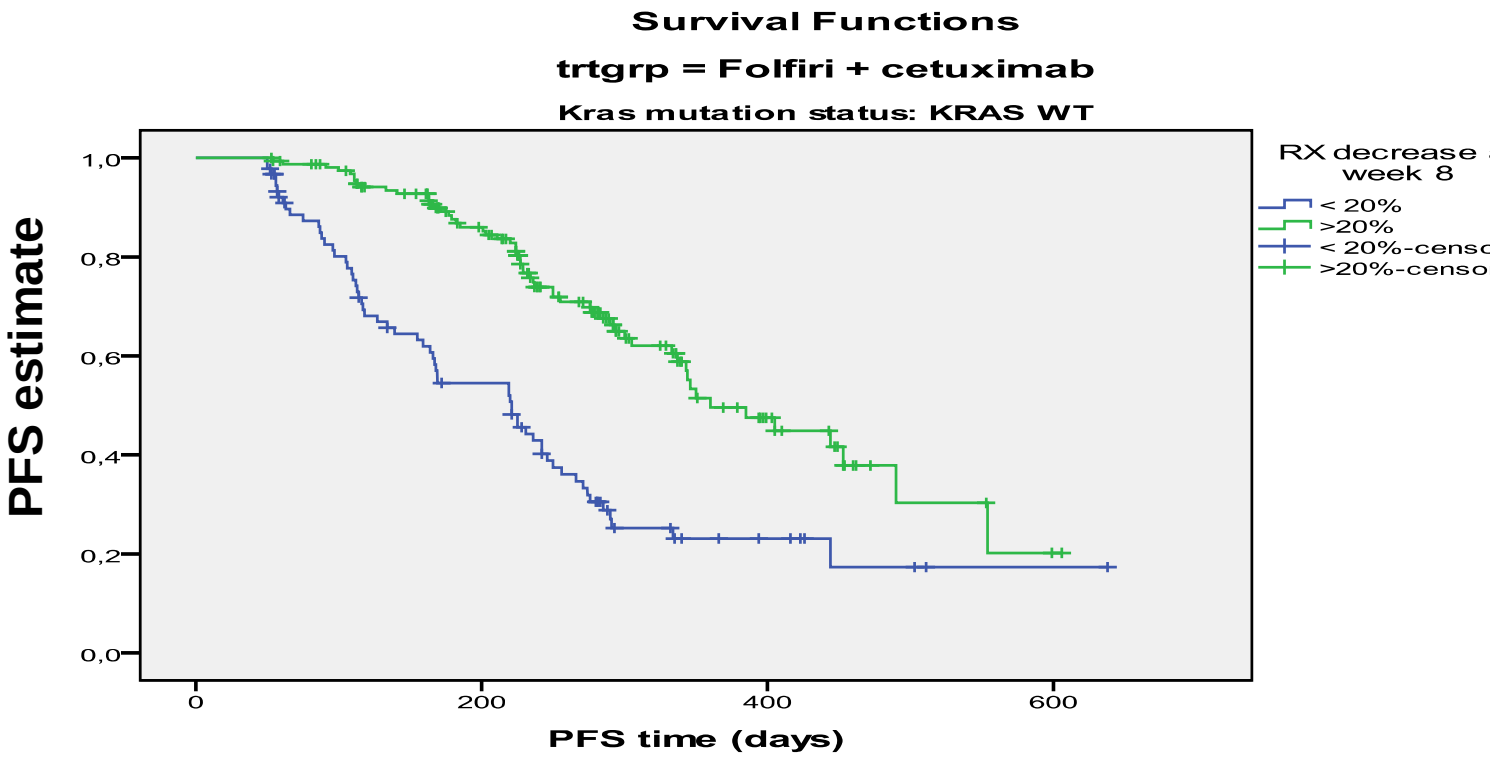
CRYSTAL: pts with KRAS wt tumors treated with ERBITUX+FOLFIRI



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CRYSTAL: pts with KRAS wt tumors treated with ERBITUX+FOLFIRI

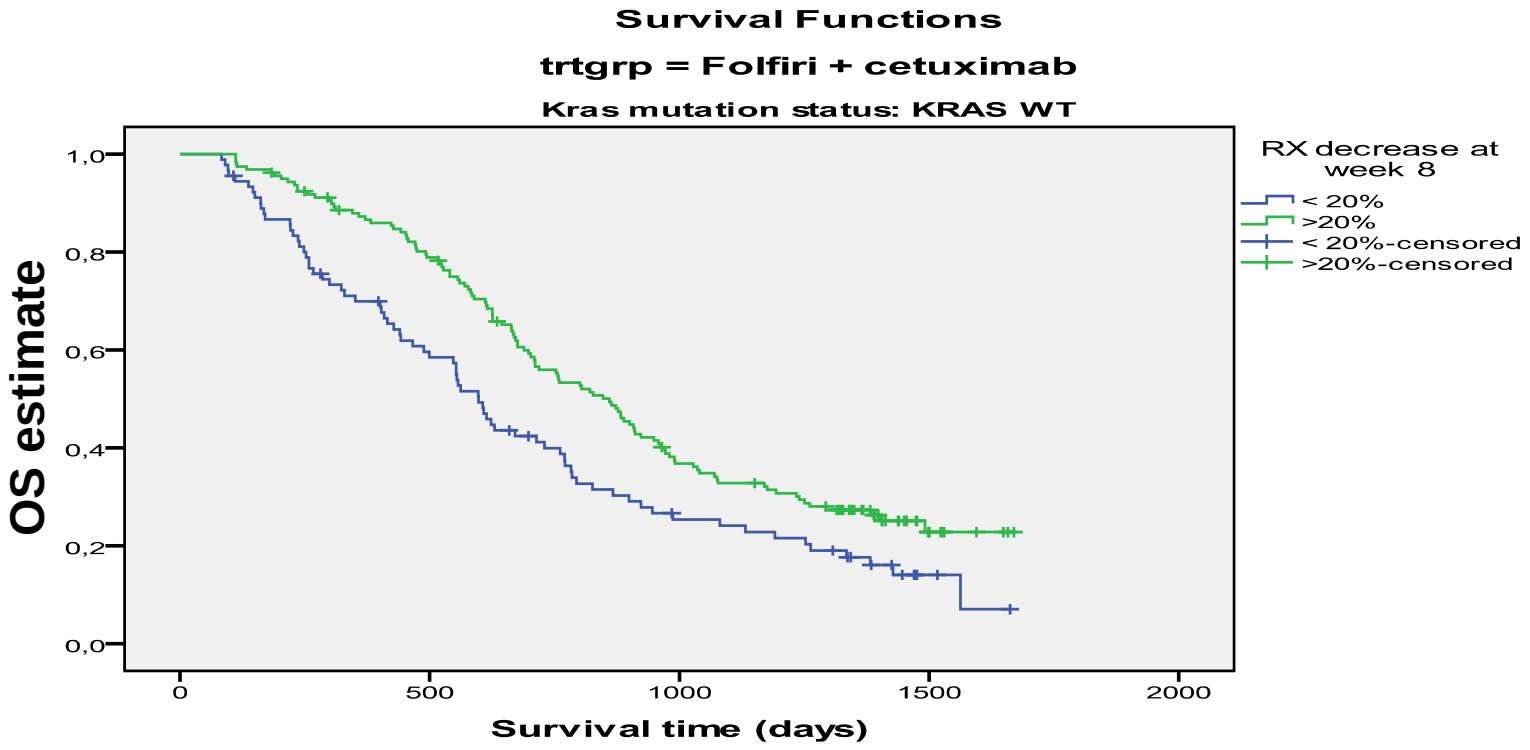

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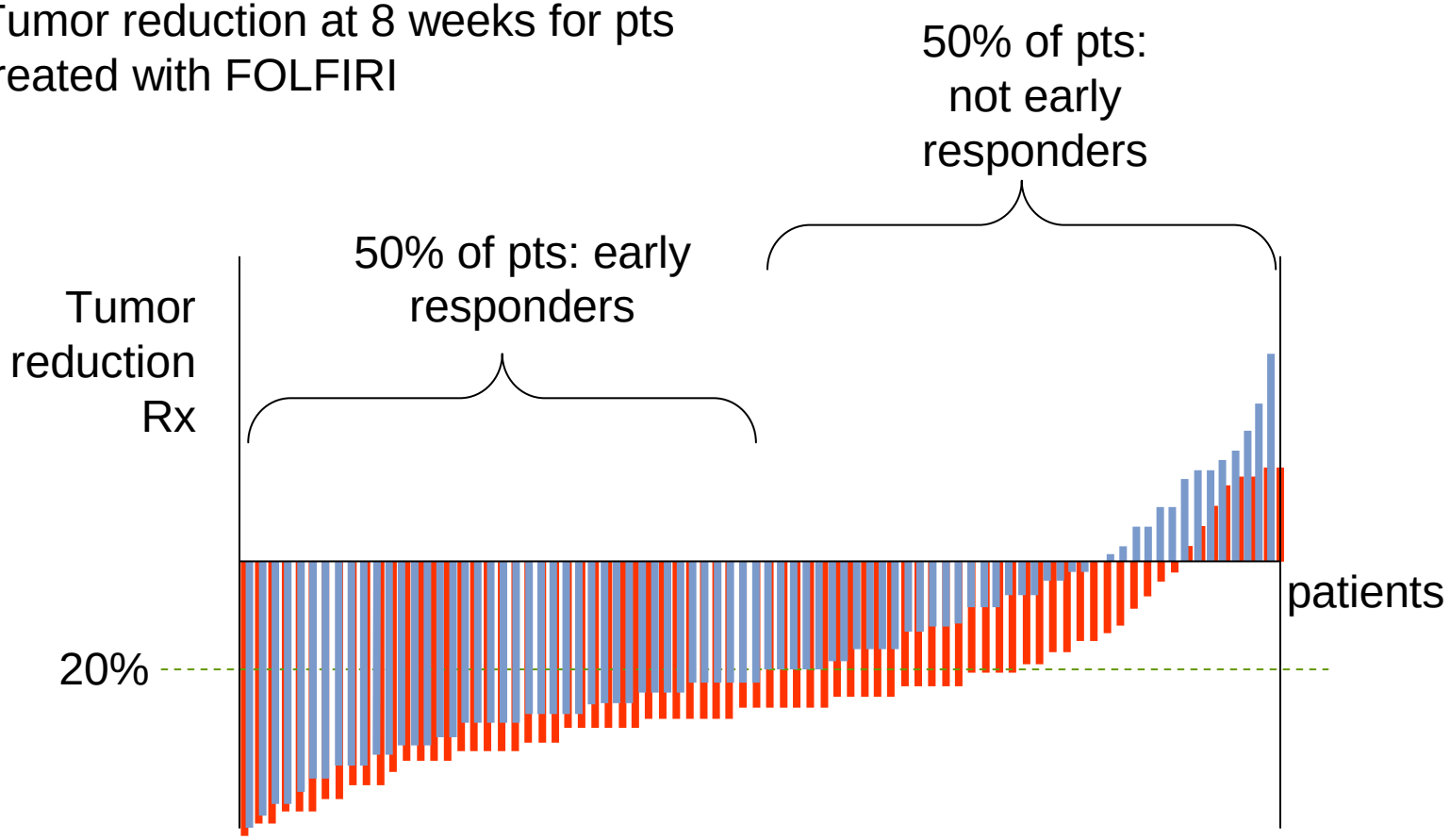
Table 2. Early tumor shrinkage and survival in *KRAS* wt patients treated with FOLFIRI +cetuximab		
	Early tumor shrinkage	
Characteristic	**<20% n=91**	**≥20% n=160**
PFS Median, months [95% CI]	7.3 [5.5–9.0]	11.8 [9.6–14.0]
Hazard ratio [95% CI] p-value*	0.368 [0.256–0.529] <0.0001	
OS Median, months [95% CI]	19.6 [17.3–22.0)	28.3 [24.6–31.9]
Hazard ratio [95% CI] p-value*	0.643 [0.480–0.862] 0.003	

CRYSTAL: early shrinkage model

Tumor reduction at 8 weeks for pts treated with FOLFIRI



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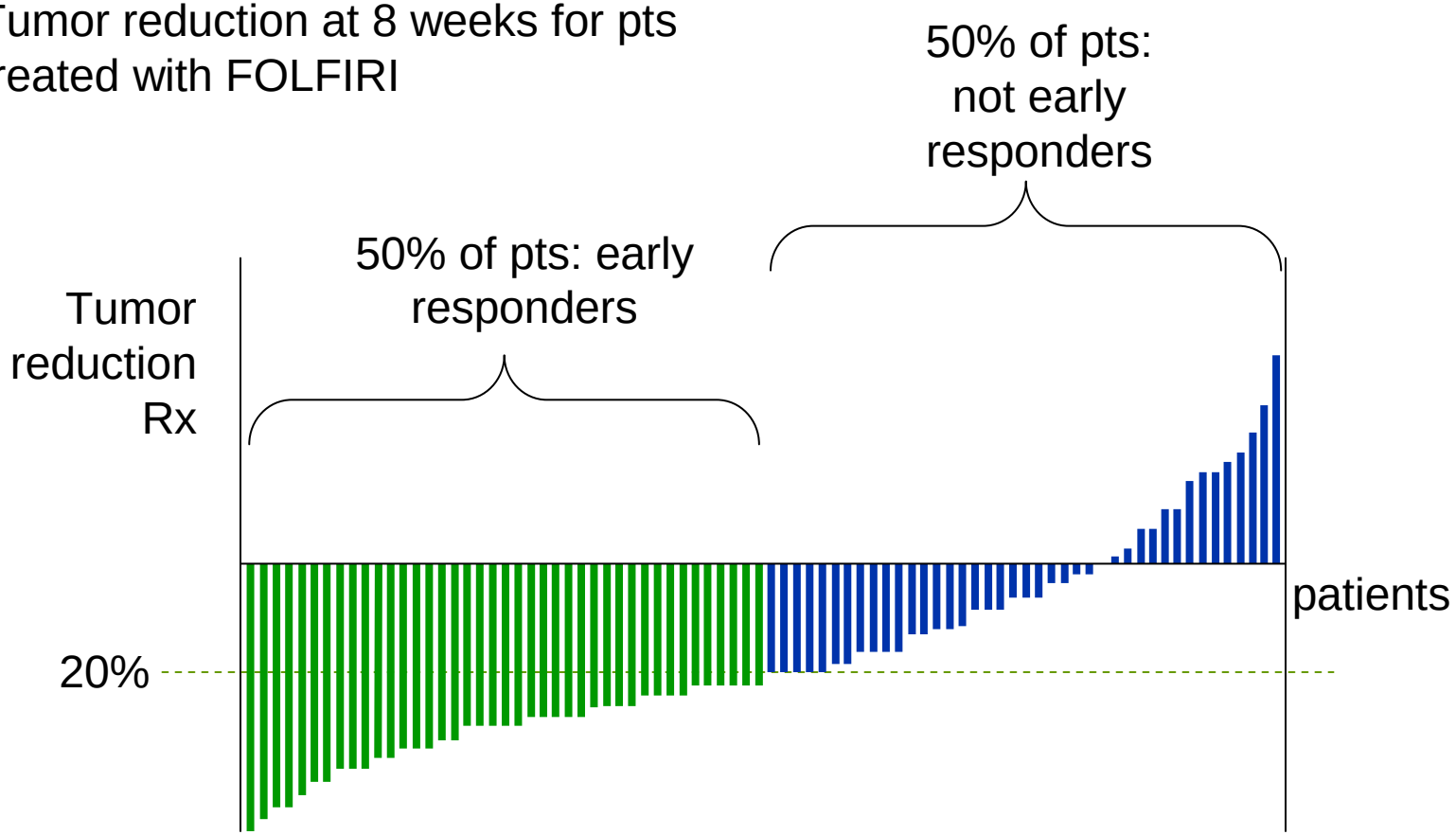
CRYSTAL: early shrinkage model

Tumor reduction at 8 weeks for pts treated with FOLFIRI



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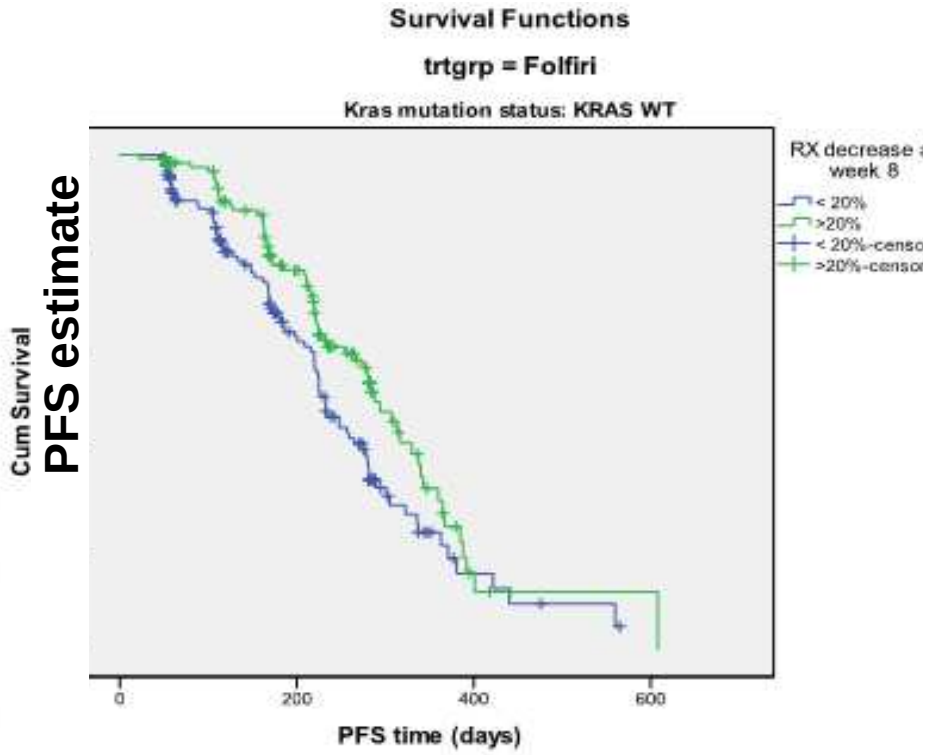
CRYSTAL: pts with KRAS wt tumors treated with FOLFIRI

PFS estimate



OS estimate

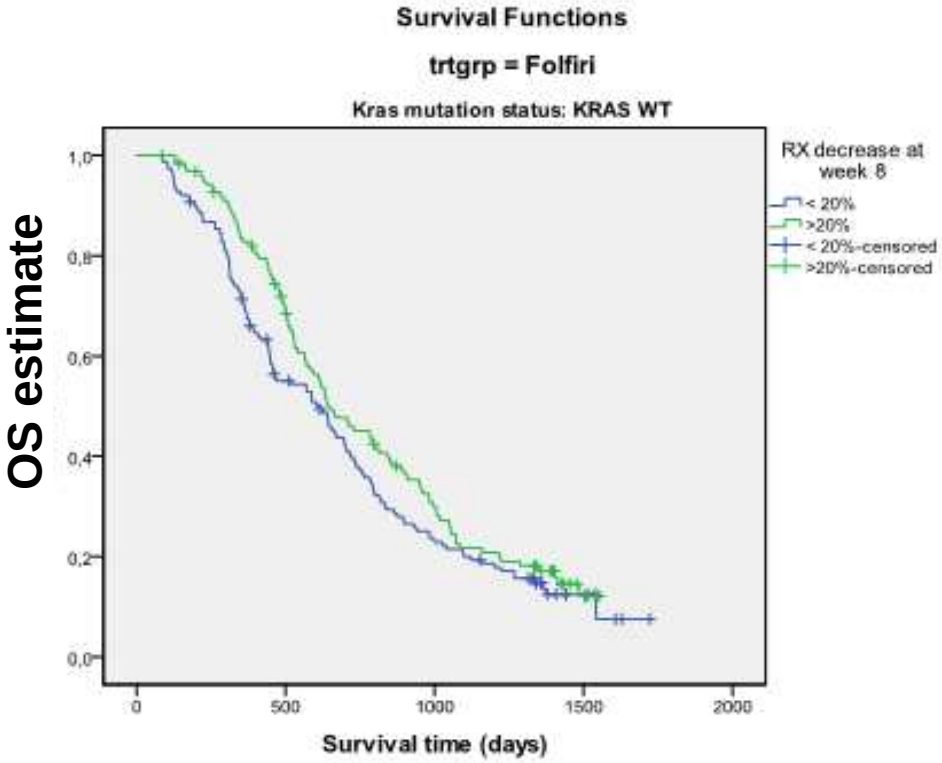


Table 3. Early tumor shrinkage and survival in *KRAS* wt patients treated with FOLFIRI

	Early tumor shrinkage	
Characteristic	**<20% n=151**	**≥20% n=125**
PFS Median, months [95% CI]	7.7 [6.9–8.3]	9.7 [8.6–10.7]
Hazard ratio [95% CI] p-value*	0.689 [0.495–0.957] 0.026	
OS Median, months [95% CI]	20.2 [15.3–25.1)	21.2 [16.7–25.7]
Hazard ratio [95% CI] p-value*	0.814 [0.626–1.059] 0.125	

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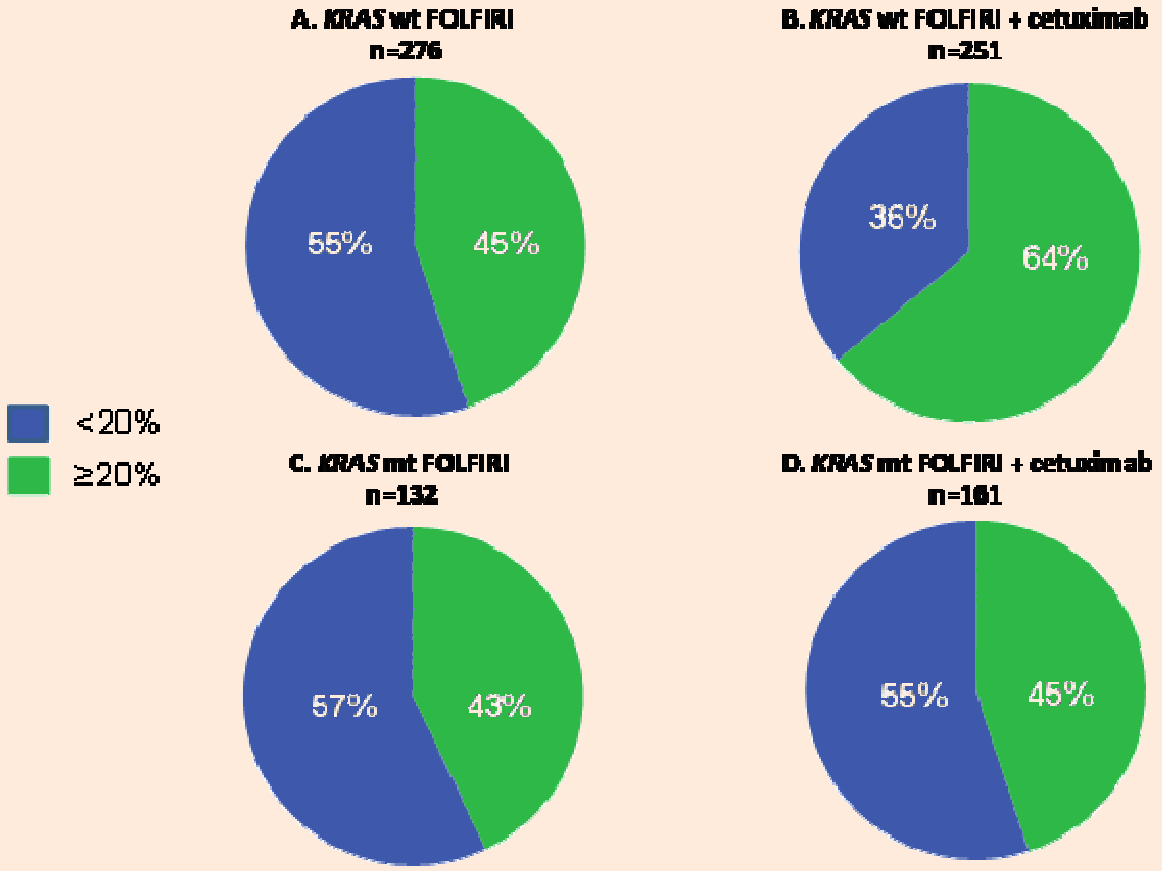
The effect of early tumor shrinkage on OS

Figure 2. Early tumor shrinkage by *KRAS* mutation status and treatment



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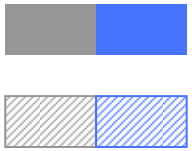
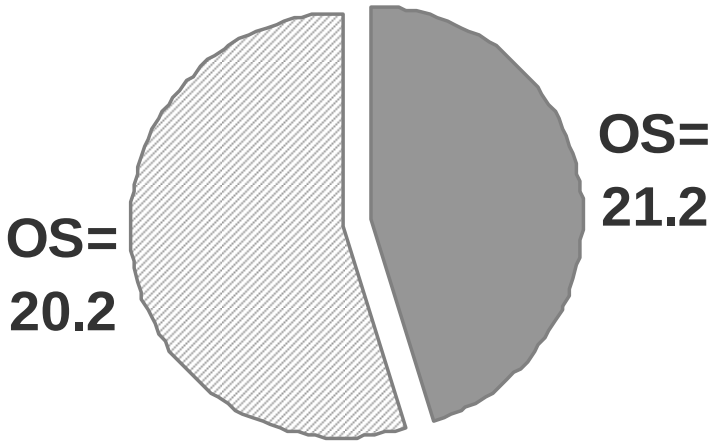
The effect of early tumor shrinkage on OS in patients with KRAS wt tumors

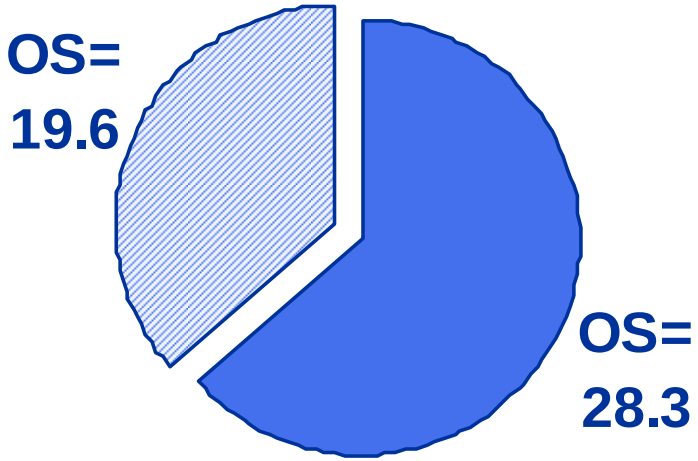


Early tumor shrinkage

Not early tumor shrinkage



FOLFIRI



FOLFIRI+ERBITUX

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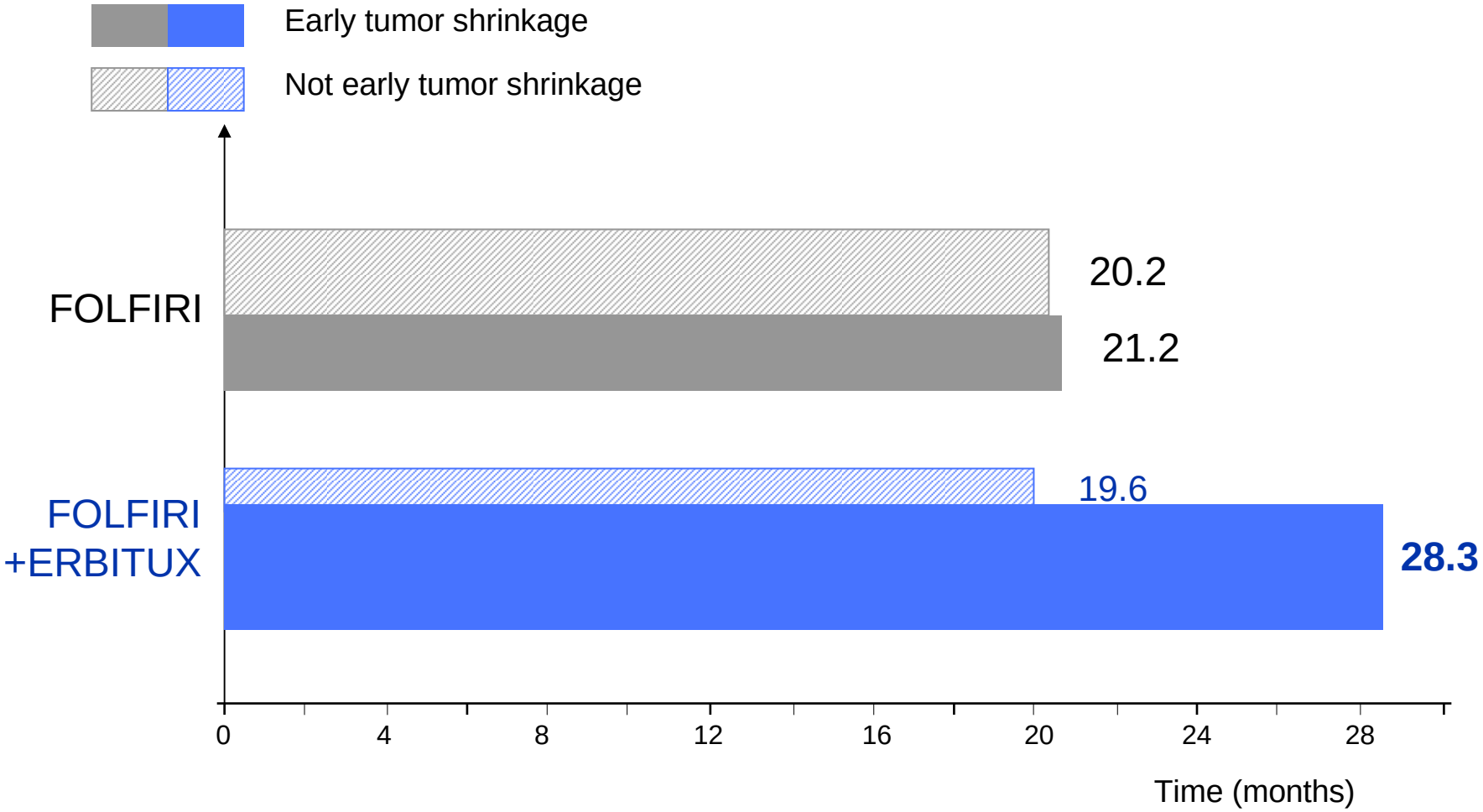
The effect of early tumor shrinkage on OS in patients with KRAS wt tumors



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Conclusions from the scientific poster

- In the CRYSTAL study early tumor shrinkage (≥20% at week 8) was experienced by 64% of *KRAS* wt patients treated with FOLFIRI + cetuximab in the 1st-line setting.
- In these patients this early tumor shrinkage translated to a long-term clinical benefit of 28.3 months median overall survival.
- No statistically significant benefit was found with early tumor shrinkage in patients treated with FOLFIRI alone.
- The association of early tumor shrinkage with long-term benefit seems to be specific to cetuximab therapy.

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Patient segmentation in 1st line KRAS wt mCRC and medical needs

Group 1

Patients with limited but initially unresectable metastases

(R0, RR, Tumor shrinkage, OS)

Group 2

Patients with never resectable metastases, high tumor burden or tumor-related symptoms

(RR, Tumor shrinkage, OS)

Group 3

Patients with never resectable metastases asymptomatic and with less aggressive disease

(OS, PFS)

Patient segmentation in 1st line KRAS wt mCRC and Erbitux results

ERBITUX mOS results:

- **converted to resectable and resected**
  → OS ~ 55 m

OS ~ 23.5 m

- **remained non-resectable**
  → OS ~ 23.5 m

Patient segmentation in 1st line KRAS wt mCRC and Erbitux promises

Potential for cure
OS = ∞

Potential for long-term survival
OS = 28.3 months

if

55 m

23.5 m

selling propositions

ERBITUX OS promises:

Erbitux offers high	Erbitux improves	Erbitux improves
potential for cure	symptom-free survival	overall survival

DOCTORS HAVE TO START TREATING ALL PATIENTS WITH ERBITUX IF THEY WANT TO REACH THESE RESULTS

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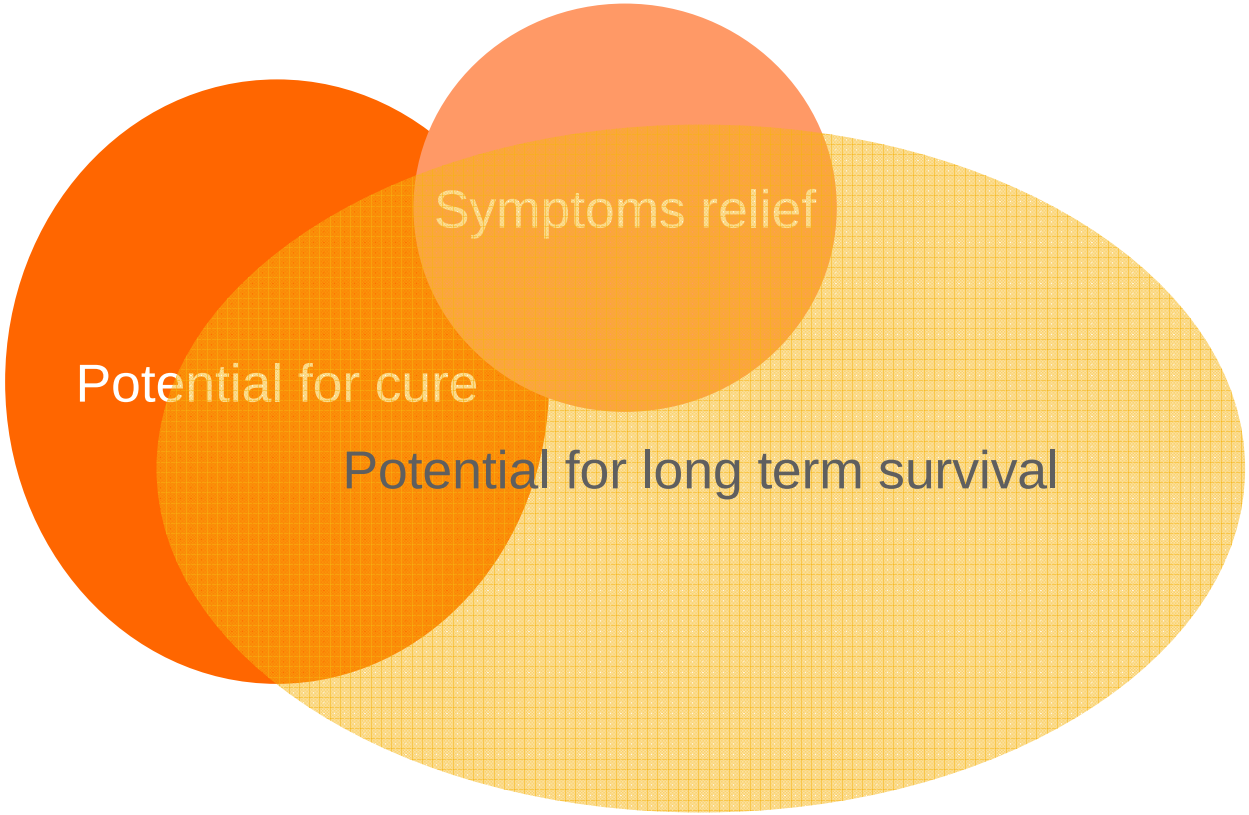
ERBITUX selling propositions

ERBITUX shrinks the tumors, therefore it provides:



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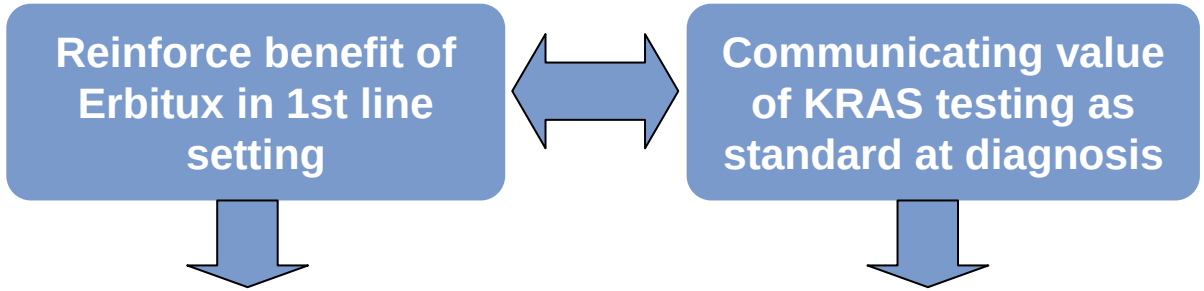
Communication flow (Early tumor shrinkage)

Schema



Messages

- **For mCRC KRAS wt p'ts with initially unresectable LLD, they have high chance to achieve "Potential for cure"**
- **For mCRC KRAS wt p'ts with never resectable metastases, they have high chance to achieve "long-term survival: 28 months" by experiencing early tumor response**

Objectives

KRAS testing should be implemented at the time of disease diagnosis

ERBITUX should be integrated into the most upfront treatment in mCRC patients with KRAS wt tumors

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ESMO Abstract Numbers: 596P

	Your Contact
News Release	Dr. Raphaela Farrenkopf Phone +49 6151-72 2274

Early Tumor Shrinkage with 1st Line Erbitux Therapy Leads to Longest-Ever Median Survival in KRAS Wild-Type mCRC

- **Further analysis of the CRYSTAL trial shows unprecedented median overall survival of 28.3 months for patients who experienced early tumor shrinkage**
- **This finding further demonstrates the value of Erbitux as the first-choice, 1st line therapy**

- **The correlation between tumor shrinkage and long-term survival seems to be Erbitux-specific as it has not been reported with any other mCRC therapies**

The OPUS and CRYSTAL studies

CETUXIMAB AND 1ST-LINE CHEMOTHERAPY IN ELDERLY AND YOUNGER PATIENTS WITH METATASTIC COLORECTAL CANCER (MCRC): A POOLED ANALYSIS OF THE CRYSTAL AND OPUS STUDIES

G.Folprecht *et al.* **ESMO # 597P**

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The OPUS and CRYSTAL studies

G.Folprecht *et al.* **ESMO # 597P**

- Individual data from *KRAS* wild-type pts treated in the CRYSTAL (FOLFIRI +/- cetuximab) and OPUS (FOLFOX +/- cetuximab) trials were analyzed for OS, PFS and safety in elderly (≥70 years) and younger (<70 years) pts.

- In younger pts with or without cetuximab, the median PFS was 10.0 vs. 7.7 months and median OS was 23.6 vs 20.2 months. Similar differences were observed in elderly pts with or without cetuximab: PFS was 8.9 vs 7.2 months and OS was 23.3 vs. 15.1 months

- **Conclusions:** With a cut-off of 70 years, no major interference between age and efficacy of cetuximab in combination with standard chemotherapy or on the differences for toxicity was shown.

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Table Efficacy and safety in pts pooled from the CRYSTAL and OPUS studies				
	Younger (<70 years) pts		Elderly (≥70 years) pts	
	Cet + CT n=320	**CT n=380**	**Cet + CT n=78**	**CT n=67**
Efficacy				
Median PFS (months) [95% CI]	10 [9.0–11.5]	7.7 [7.4–8.9]	8.9 [7.2–16.1]	7.2 [6.0–9.3]
Median OS (months) [95% CI]	23.6 [20.7–26.8]	20.2 [18.6–22.0]	23.3 [16.8–25.7]	15.1 [12.6–18.8]
Safety, n (%)	**n=321**	**n=380**	**n=78**	**n=67**
Grade 3/4 toxicity				
Neutropenia	100 (31.2)	90 (23.7)	26 (33.3)	24 (35.8)
Diarrhea	41 (12.8)	30 (7.9)	18 (23.1)	10 (14.9)
Fatigue	13 (4.0)	18 (4.7)	2 (2.6)	5 (7.5)
All skin toxicity	81 (25.2)	3 (0.8)	18 (23.1)	1 (1.5)
60-day mortality	7 (2.2)	8 (2.1)	1 (1.3)	2 (3.0)
Cet =cetuximab; CT= chemotherapy (FOLFIRI or FOLFOX)				

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COIN in one slide

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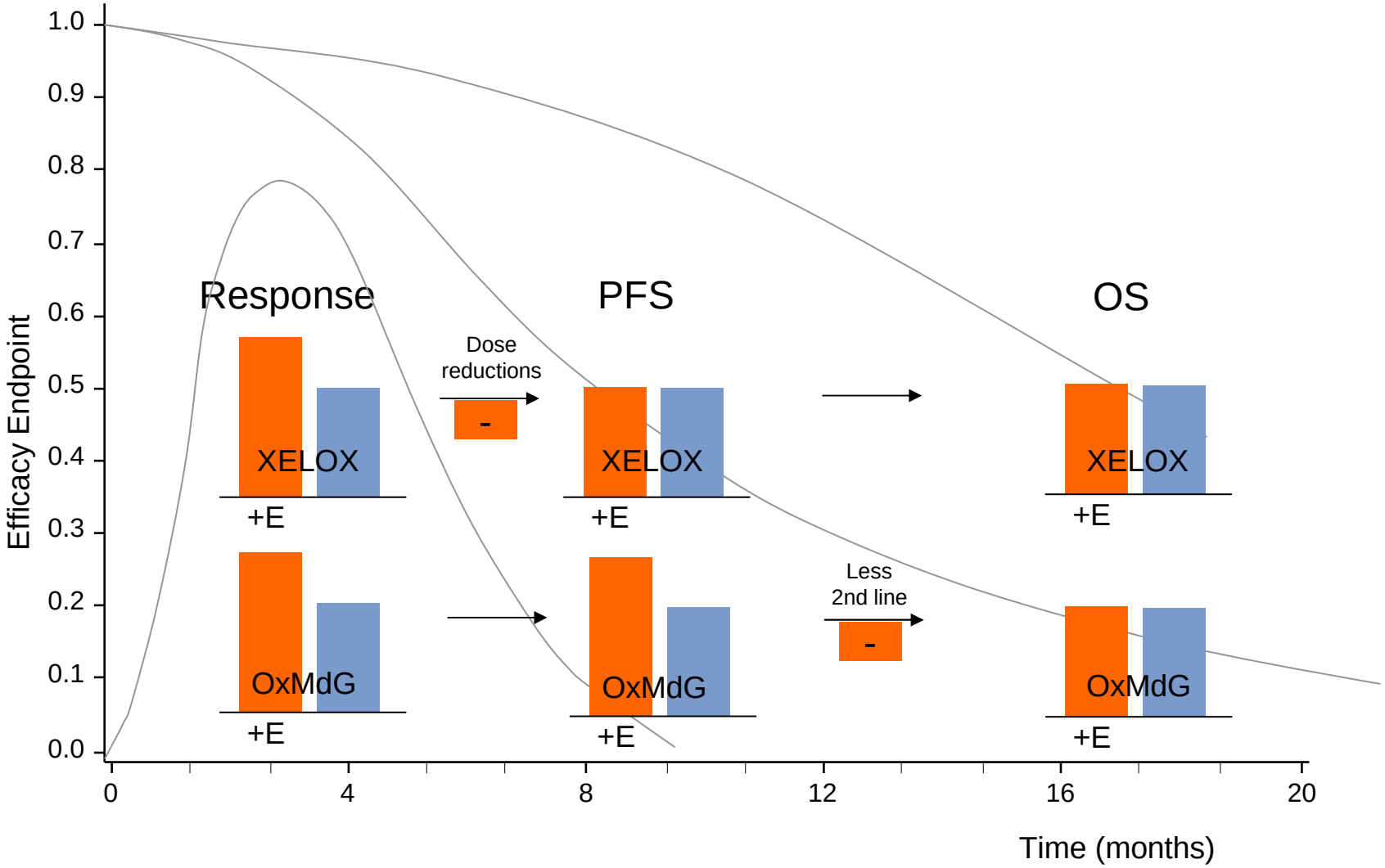
The COIN trial



MERCK SERONO SYMPOSIUM

Personalized treatment –
A new standard for prolonging overall survival in mCRC

15:00–16:30 on Friday October 8th, 2010

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MERCK SERONO SYMPOSIUM

15:00–16:30 on Friday October 8th, 2010

Agenda

ERBITUX® CETUXIMAB

Chairs:	**Alberto Sobrero** **Eric Van Cutsem**	
15:00 – 15:10	Welcome Introduction	A Sobrero
15:10 – 15:35	Prolonging survival through a personalized approach in mCRC	C Bokemeyer
15:35 – 15:55	Tumor shrinkage impacts long-term outcomes in mCRC	S Tejpar
15:55 – 16:15	Perspectives on resection in mCRC	W O Bechstein
16:15 – 16:30	Summary	E V Cutsem