CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): Expanded ras analyses

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for the ALLIANCE and SWOG

Disclosures

- Advisory Board: Genentech/Roche, Merck KG, BMS
- Clinical Trial Support: Genentech/Roche, Merck KG, BMS
- Honorarium: Genentech/Roche, Merck KG
- NIH/NCI, SWOG Funding

Background

- In first-line treatment of *KRAS* codon 12/13 wild-type* mCRC, CALGB/SWOG 80405 showed no difference in OS or PFS between the addition of bevacizumab (BV) or cetuximab (CET) to chemotherapy with FOLFOX or FOLFIRI[1]

- Activating mutations at other codons within *KRAS* or *NRAS* have been associated with resistance to EGFR inhibitors [2]

- Current exploratory analysis investigated treatment effects in *RAS* wild-type patients as determined by expanded RAS testing using Beaming

*As assessed using a high-sensitivity locked nucleic acid-mediated PCR clamping and melting curve technique

[1].Venook, et. al., ASCO 2014
[2]Stintzing, WIGC 2014, Doulillard NEJM 2014

RAS mutation analysis: BEAMing

- **Tumor *RAS* mutation status was assessed* by BEAMing[1] (beads, emulsion, amplification, magnetics)**
  - **PCR amplification of single target DNA molecules on magnetic beads in the aqueous compartments of a water-in-oil microemulsion**
  - **Fluorescently tagged wild-type and mutant oligonucleotide probe pairs hybridized to bead-associated PCR products and beads typed by flow cytometry**
  - **Highly sensitive quantitative technology with the capacity to detect and enumerate mutant sequences down to a 1:10,000 ratio (mutant fraction 0.01%)[2]**

*Inostics GmbH, Hamburg, Germany

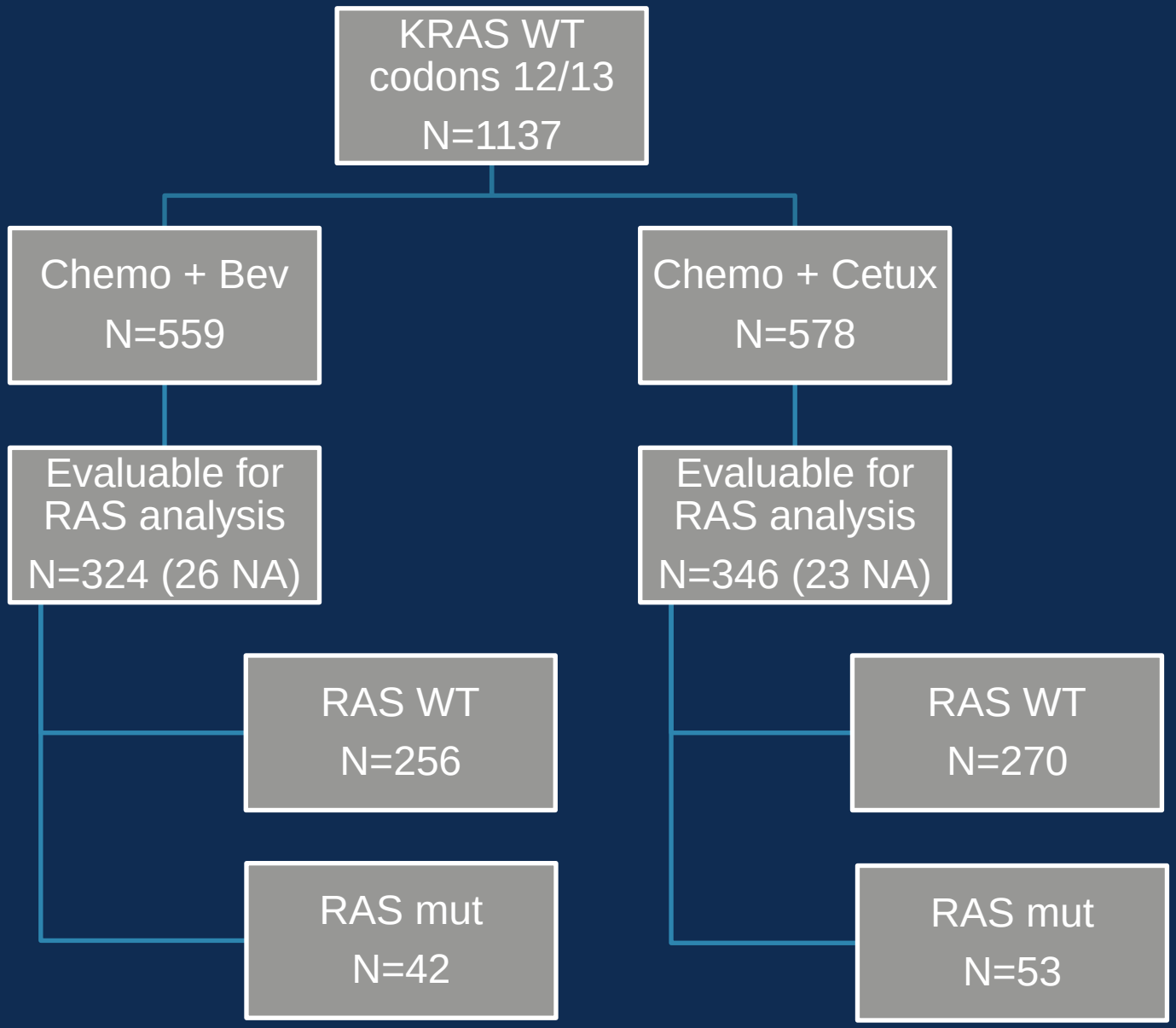
[1]Dressman D, et al. Proc Natl Acad Sci USA 2003;100:8817-22
[2]Diehl F, et al. Gastroenterology 2008;135:489-98

RAS mutation analysis: BEAMing

- *KRAS* and *NRAS* genes were screened for particular missense* mutations:
  - *KRAS* exon 2; codons 12, 13
    exon 3: codon 59, 61
    exon 4; codons 117, 146
  - *NRAS* exon 2; codons 12, 13
    exon 3; codons 59, 61
    exon 4; codons 117, 146
- In line with other techniques which may be used clinically to determine *RAS* mutation status, a cutoff of **≥1% mutant** to wild-type alleles was used to discriminate patients
  - Tumors were scored as *RAS* mutant if mutant alleles were detected at a prevalence of ≥1% of total amplified sequences, regardless of whether all loci were evaluable
  - Tumors were scored as *RAS* wild-type only if all 26 mutation assays were evaluable and prevalence of mutant alleles was <1%

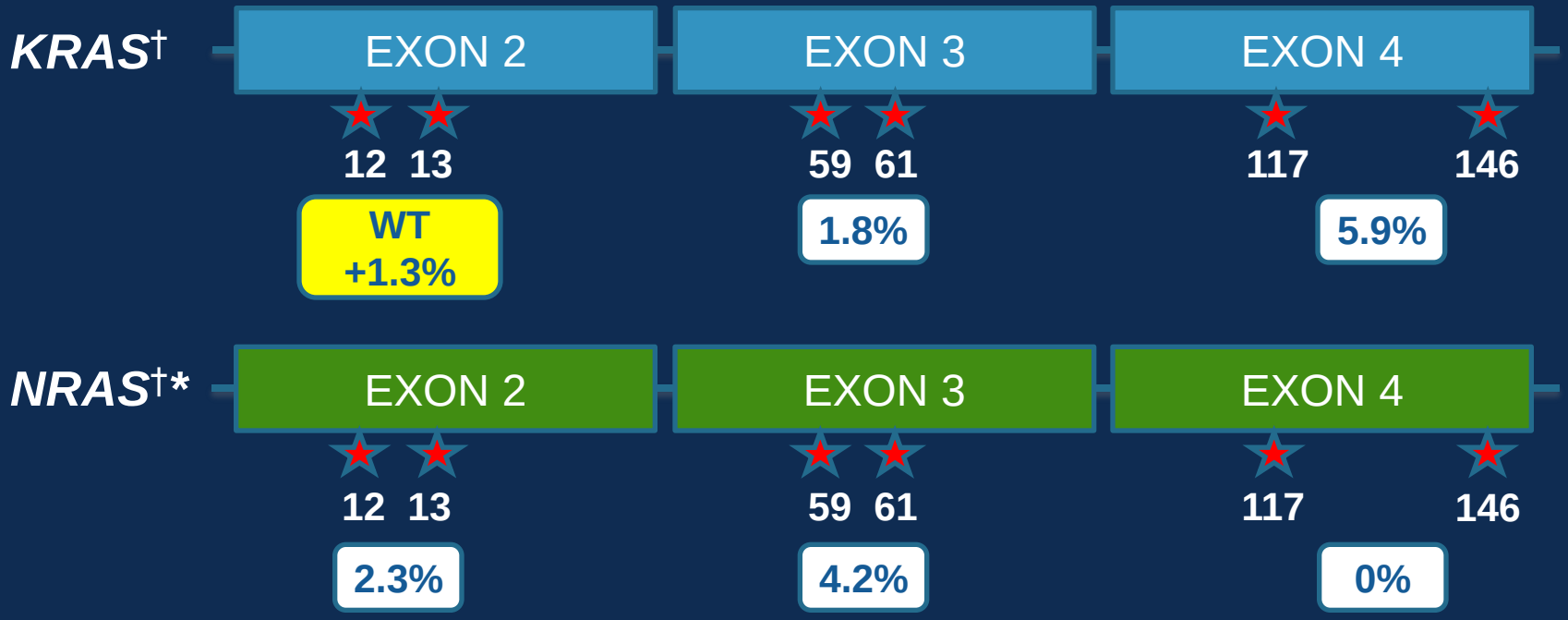
*Resulting in a change in the specified amino acid

Study profile



RAS mutations: CALGB/SWOG 80405

670/1137 patients (59%) with *KRAS* codon 12/13 WT tumors evaluable
621/1137 analyzed (55%) analyzed
95/621 (15.3%) patients new ras mutation identified



†Percentages relate to fraction of *RAS* evaluable patients with mutations in particular exons;

*One patient had a mutation at both NRAS Exon1 codon12 and NRAS Exon3 codon61

RAS mutation rates: first-line studies

Patients with *KRAS* codon 12/13 wild-type tumors

Study	Evaluable patients*	Method	Other *RAS* mutations, %
CALGB/SWOG 80405	670	BEAMing††	15.3
OPUS	118	BEAMing†	26.3
CRYSTAL	430	BEAMing†	14.7
FIRE-3‡	407	Pyrosequencing	16.0
PRIME §	620	Dideoxy sequencing/WAVE	17.4
PEAK	221	Dideoxy sequencing/WAVE	23.1

*For other tumor *RAS* mutations
†5% mutant/wild-type alleles diagnostic cutoff
† †1% mutant/wild-type alleles diagnostic cutoff
‡*KRAS* codons 59 and 117 not considered
§ *KRAS* and *NRAS* codon 59 not considered

Baseline characteristics

Characteristic	*KRAS* codon 12/13 wild-type			
	Overall n=1137		***RAS* evaluable** n=670	
	Chemo + BV n=559	Chemo + CET n=578	Chemo + BV n=324	Chemo + CET n=346
Age, years				
Median (range)	59 (21–85)	59 (20–89)	60 (23–84)	59 (21–90)
Male, %	62.3	60.4	64.0	62.1
Non-Caucasian, %	14.6	16.5	12.4	13.9
FOLFOX, %	73	74	75	74
Prior Radiation, %	8.9	9.0	9.0	9.0
Prior Adjuvant Chemotherapy, %	14.5	13.7	15.4	14.2
Palliative Intent, %	86.4	82.5	83.0	79.5
Primary in place, %	28	27	22	17
Liver Metastases Only, %	29.3	31.8	32.7	35.8

Comparability of *RAS* subgroups: Efficacy

Subgroup	Chemo + BV N	Chemo + CET N	Response Rate (%)* BV vs CET p-value	PFS time Hazard ratio 95% CI p-value	OS time Hazard ratio 95% CI p-value
***KRAS* codon 12/13 wild-type**	559	578	57.2 vs 65.6 p=0.02	10.8 vs 10.4† 1.04 0.91–1.17 p=0.55	29.0 vs 29.9† 0.92 0.78–1.09 p=0.34
***RAS* evaluable‡**	324	346	56.0 vs 68.8 p<0.01	11.4 vs 10.9† 1.10 0.90–1.30 p=0.31	30.3 vs 30.8† 0.90 0.70–1.10 p=0.40

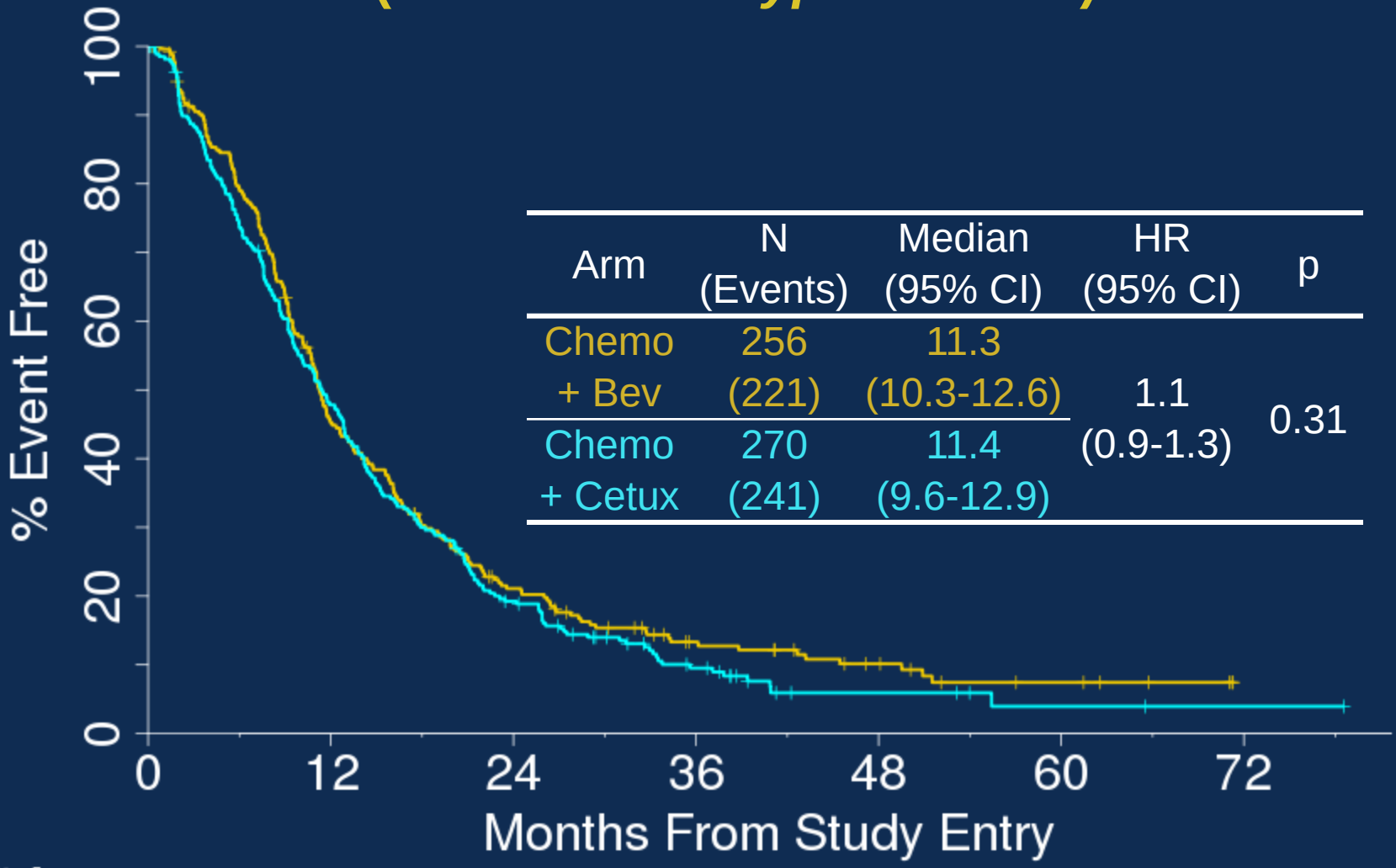
*733 KRAS codon 12/13 WT and 406 RAS evaluable patients are evaluable for response
†Median, months;
‡Patients with *KRAS* codon 12/13 wild-type tumors for which tumor DNA samples were evaluable for other *RAS* mutations

Efficacy: RAS Subgroups

Subgroup	Chemo + BV N	Chemo + CET N	Response Rate (%)* BV vs CET p-value	PFS time Hazard ratio 95% CI p-value	OS time Hazard ratio 95% CI p-value
RAS* evaluable*	324	346	56.0 vs 68.8 p<0.01	11.4 vs 10.9‡ 1.1 0.9-1.3 p=0.34	30.3 vs 30.8‡ 0.9 0.8-1.1 p=0.49
***RAS* wild-type**	256	270	53.8 vs 68.6 p<0.01	11.3 vs 11.4‡ 1.1 0.9–1.3 p=0.31	31.2 vs 32.0‡ 0.9 0.7–1.1 p=0.40

*406 RAS evaluable and 319 RAS WT patients evaluable for response
**Patients with *KRAS* codon 12/13 wild-type tumors for which tumor DNA samples were evaluable for other *RAS* mutations
‡Median, months

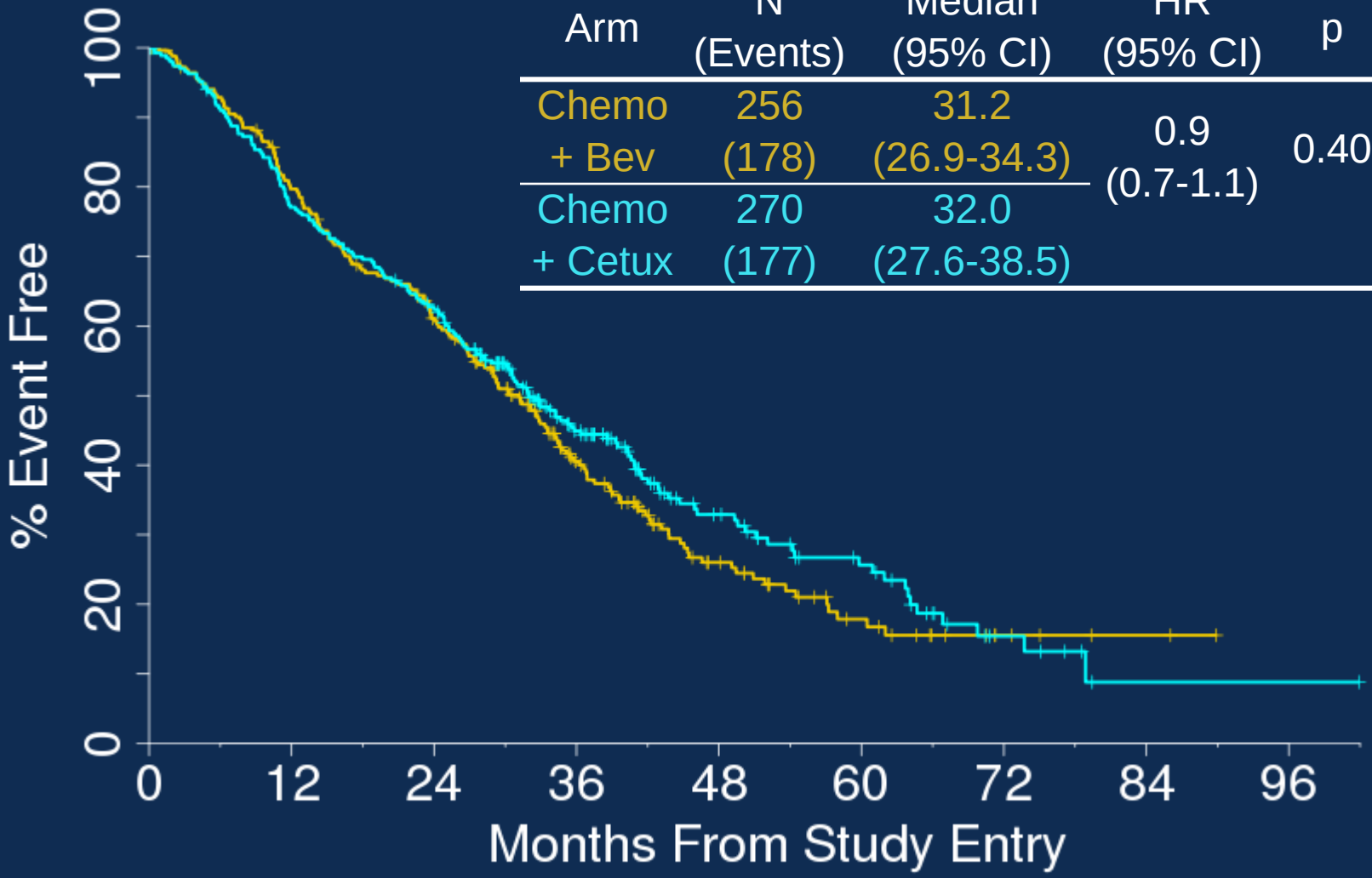
Progression Free Survival By Arm
(*All RAS Wild Type Patients*)



Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	256 (221)	11.3 (10.3-12.6)	1.1 (0.9-1.3)	0.31
Chemo + Cetux	270 (241)	11.4 (9.6-12.9)		

Overall Survival By Arm
(*All RAS Wild Type Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	256 (178)	31.2 (26.9-34.3)	0.9 (0.7-1.1)	0.40
Chemo + Cetux	270 (177)	32.0 (27.6-38.5)		



Overall Survival
RAS wt vs KRAS wt / all RAS mt *

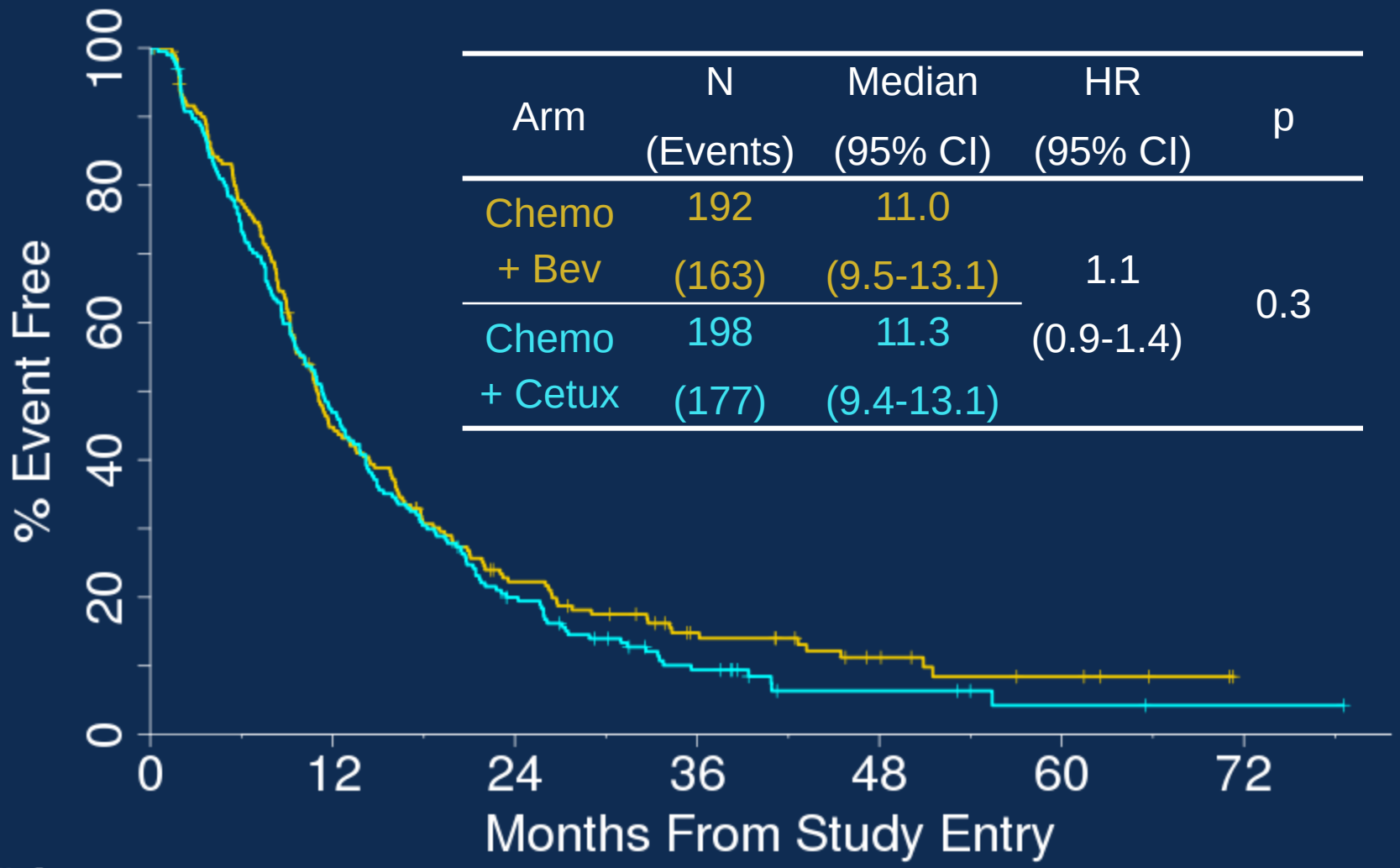
	RAS wt			KRAS wt exon 2 / all RAS mt		
Arm	N (Events)	Median† (95% CI)	HR (95% CI) p	N (Events)	Median† (95% CI)	HR (95% CI) p
Chemo + Bev	256 (178)	31.2 (26.9-34.3)	0.9 (0.7, 1.1)	42 (33)	22.3 (15.3, 29.0)	0.74 (0.4, 1.1)
Chemo + Cetux	270 (177)	32.0 (27.6-38.5)	p=0.40	53 (41)	28.7 (20.2, 34.7)	p=0.21

†Median, months

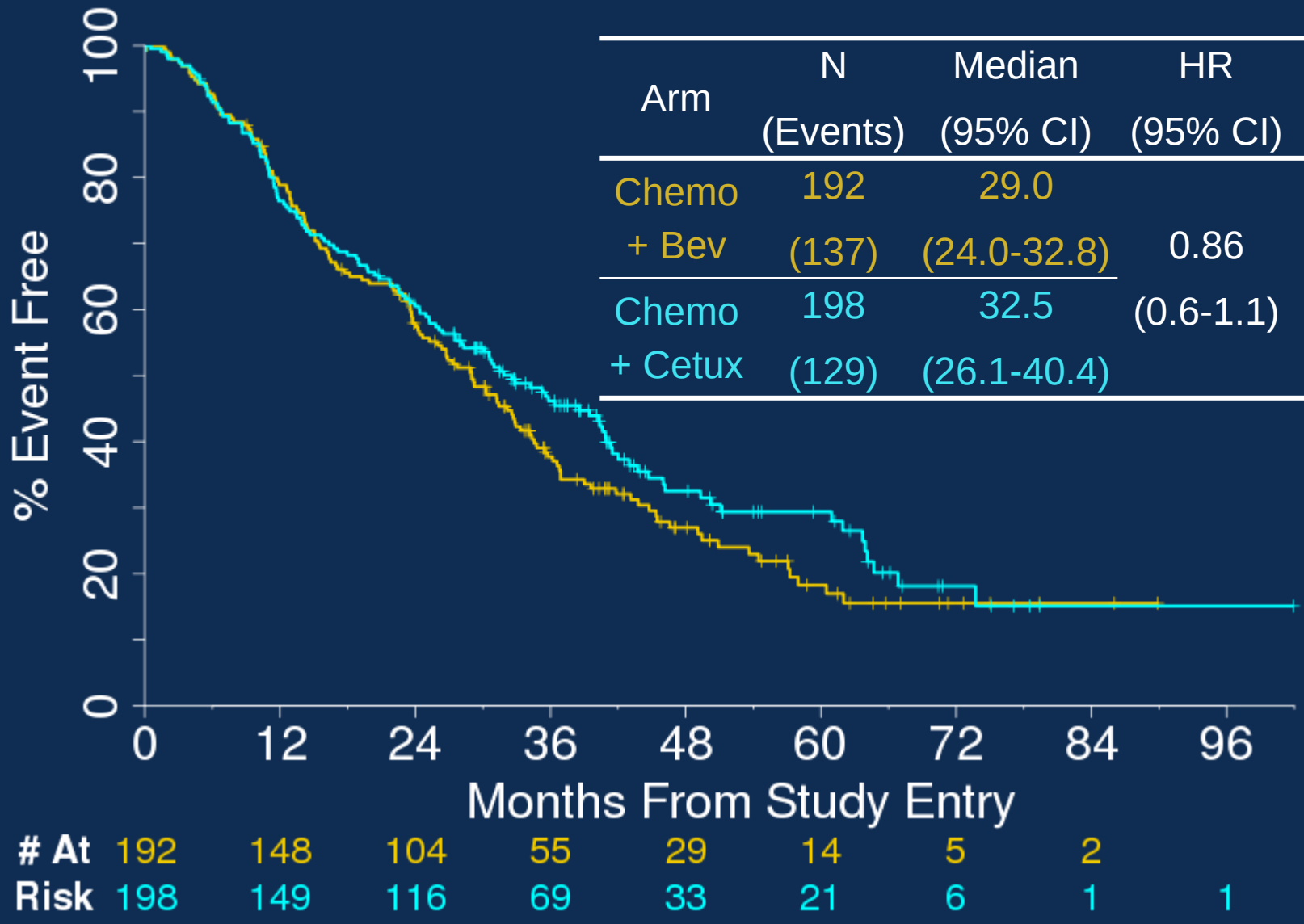
*these findings may not apply to KRAS mutations codons 12 and 13

Progression Free Survival By Arm (*All RAS Wild Type FOLFOX Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	192 (163)	11.0 (9.5-13.1)	1.1 (0.9-1.4)	0.3
Chemo + Cetux	198 (177)	11.3 (9.4-13.1)		

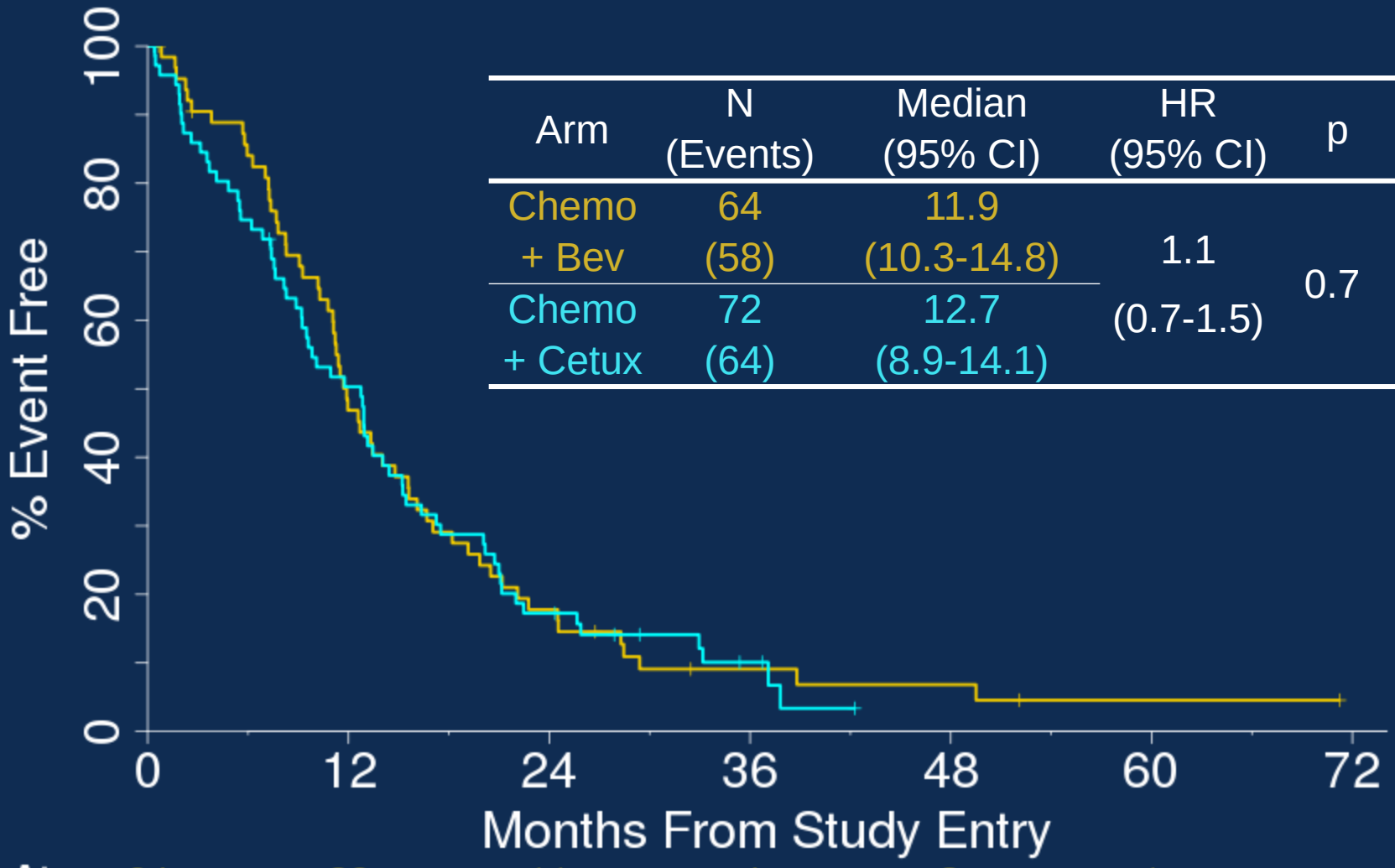


Overall Survival by Arm
(*All RAS Wild Type FOLFOX Patients*)



Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	192 (137)	29.0 (24.0-32.8)	0.86 (0.6-1.1)	0.2
Chemo + Cetux	198 (129)	32.5 (26.1-40.4)		

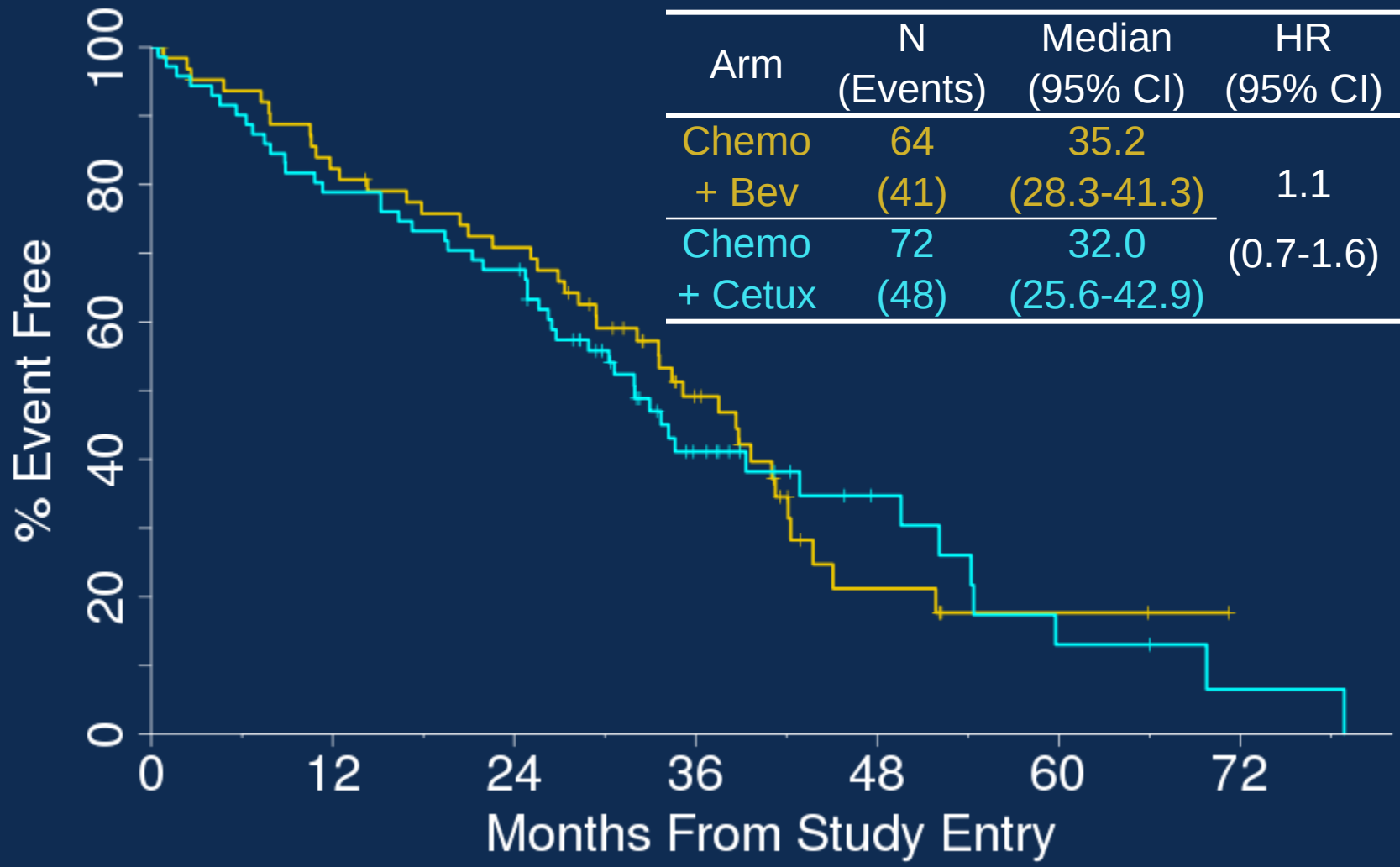
Progression Free Survival By Arm (*All RAS Wild Type FOLFIRI Patients*)



Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	64 (58)	11.9 (10.3-14.8)	1.1 (0.7-1.5)	0.7
Chemo + Cetux	72 (64)	12.7 (8.9-14.1)		

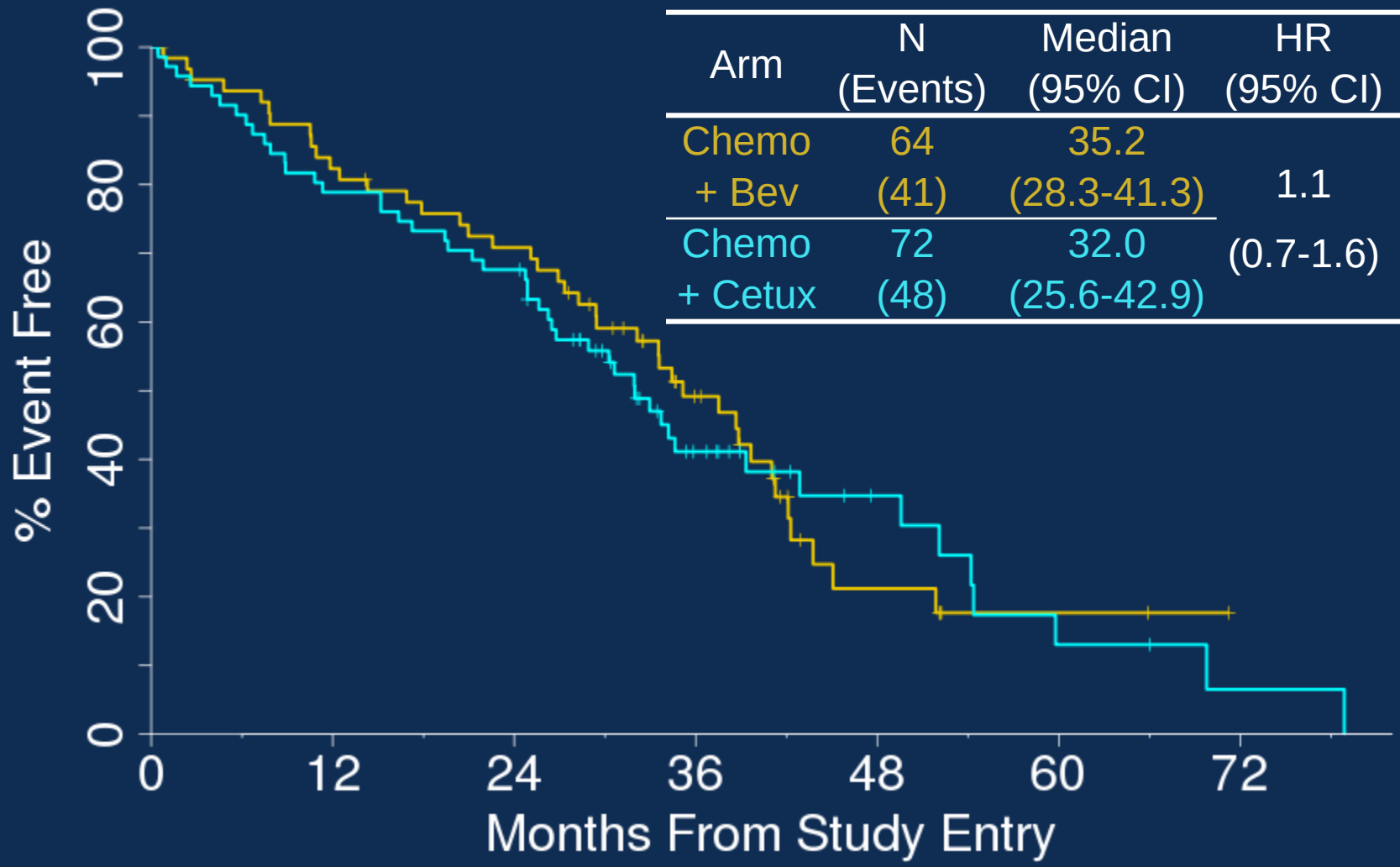
Overall Survival by Arm
(*All RAS Wild Type FOLFIRI Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	64 (41)	35.2 (28.3-41.3)	1.1 (0.7-1.6)	0.7
Chemo + Cetux	72 (48)	32.0 (25.6-42.9)		



Overall Survival by Arm
(*All RAS Wild Type FOLFIRI Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	64 (41)	35.2 (28.3-41.3)	1.1 (0.7-1.6)	0.7
Chemo + Cetux	72 (48)	32.0 (25.6-42.9)		



80405: Work in Progress

- Identifying and collecting additional tumor blocks from patients enrolled in 80405
- Confirmed response rate / Depth of response
- Duration of therapy / dose intensity
- Analysis special subsets:
  - Patients rendered NED
  - Patients recur after adjuvant therapy
- Further details 2nd and later treatments

Conclusions

- All patients with newly diagnosed mCRC should be tested for ras
- Overall Survival > 30 months in both arms sets a new benchmark for patients with mCRC which was achieved across a broad clinical trials network and suggests that the results apply in a variety of practice settings.
- First line therapy should reflect treatment goal and concern for potential side effects.
- With additional data such as dose intensity, treatment duration, location, tumor shrinkage, second line therapies and additional biomarker for anti-EGFR and anti VEGF therapies we might understand better the differences between FIRE3 and 80405

ACKNOWLEDGEMENT / THANK YOU

- We thank all our patients. We are humbled by their courage and by the confidence and trust they place in us by participating in clinical trials.
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- Special Thanks for Donna Niedzwiecki, Wendy Frankel, Alan Venook

By working together we can find the answers