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MRC COIN: Adding Cetuximab to Oxaliplatin-Based Chemotherapy Improves Response for Subset of Patients With Advanced CRC and Wild-Type *KRAS* Tumors

Posting Date: June 07, 2010

- MRC COIN: prospective subgroup analysis of randomized multicenter phase III trial

Summary of Key Conclusions

- No improvement in OS or PFS with addition of cetuximab to oxaliplatin-based chemotherapy for first-line treatment of advanced colorectal cancer (CRC)
  - Response rate improved among patients with wild-type *KRAS* tumors
  - Trend toward improved PFS among patients with wild-type *KRAS* and minimal metastatic disease
- Addition of cetuximab to chemotherapy associated with increased toxicity vs chemotherapy alone
- *KRAS*, *BRAF*, and *NRAS* mutation status strongly prognostic regardless of cetuximab treatment
  - Patients with mutated *BRAF* have poorest prognosis
  - Patients with wild-type *KRAS*, *BRAF*, and *NRAS* have the best prognosis

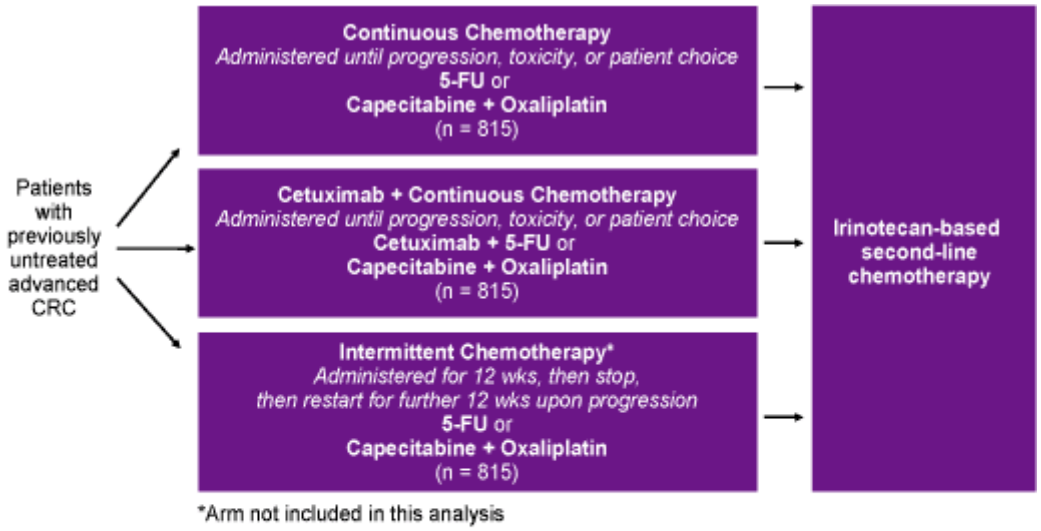
Background

- COIN trial

  Largest trial of epidermal growth factor receptor (EGFR)–targeted therapy for first-line treatment of advanced CRC

  Designed to evaluate benefit of addition of cetuximab to oxaliplatin-based chemotherapy for patients with previously untreated advanced CRC
- Current analysis sought to identify patient subsets from COIN with strongest responses to addition of cetuximab to chemotherapy

Schematic of Study Design



*Arm not included in this analysis

Regimens

OxFU administered q2w
l-folinic acid 175 mg
Oxaliplatin 85 mg/m^2
5-FU 400 mg/m^2 bolus, then 2400 mg/m^2 over 46 hrs

OxCap administered q3w
Oxaliplatin 130 mg/m^2
Capecitabine 1000 mg/m^2 BID for 2 wks

5-FU, 5-fluorouracil; OxCap, oxaliplatin plus capecitabine; OxFU, oxaliplatin plus 5-FU.

Eligibility

Inclusion criteria
- Advanced CRC
- No previous chemotherapy for metastatic disease
- No previous EGFR immunohistochemistry
- World Health Organization (WHO) performance score 0-2
- Good organ function

Baseline Characteristics

No significant differences in baseline characteristics
- Between treatment arms
- Between overall population and patients with wild-type *KRAS*

Characteristic	*All Patients (n = 2445)*	*Wild-Type KRAS (n = 1123)*
Male, %	65	68
Age		
Median age, yrs	63	64
75 yrs or older, %	9	8
WHO performance score 2, %	8	6
Adjuvant chemotherapy, %		
No	75	73
Yes for > 6 mos	16	18
Yes for 1-6 mos	4	4
Primary tumor site in rectum, %	31	31
Primary tumor status, %		

Characteristic	All Patients (n = 2445)	Wild-Type KRAS (n = 1123)
Resected	53	54
Unresected	42	39
Local recurrence	5	7
Metastases, %		
Synchronous	69	67
Liver only	22	24
Liver and others	53	51
Number of metastatic sites, %		
1	36	37
2	40	40
> 2	24	22

Description of Current Analysis

Prior to randomization, patients and their clinicians chose the type of chemotherapy they would receive

- OxCap: 66%
- OxFU: 34%

Primary endpoint

- OS
  - In patients with wild-type *KRAS* (defined as no *KRAS* mutation detected at codons 12, 13, and 61)

Secondary endpoints

- OS
  - In patients with mutated *KRAS*
  - In "all wild-type" patients (defined as wild-type *KRAS*, *NRAS*, and *BRAF*)
  - In patients with mutated *KRAS*, *NRAS*, or *BRAF*
  - In intent-to-treat population
- PFS
- Response
  - Investigator assessed, no confirmatory scans
- Quality of life
- Health economic evaluation

Main Findings

No significant difference in survival outcomes (OS, PFS) between treatment arms among patient subgroups

Survival Outcome, Mos	Cetuximab + Chemotherapy	Chemotherapy	HR (95% CI)	P Value
Wild-type *KRAS*				
Median OS	17.0	17.9	1.038 (0.90-1.20)	.68
Median PFS	8.6	8.6	0.959 (0.84-1.09)	.60
All wild-type patients				

Survival Outcome, Mos	Cetuximab + Chemotherapy	Chemotherapy	HR (95% CI)	P Value
Median OS	19.9	20.1	1.019 (0.86-1.20)	.86
Median PFS	9.2	8.8	0.922 (0.80-1.07)	.36
Patients with mutated *KRAS*, *NRAS*, or *BRAF*				
Median OS	12.7	14.4	1.004 (0.87-1.15)	.96
Median PFS	6.3	6.6	1.079 (0.95-1.23)	.33

- Improved response rate among patients with wild-type *KRAS* only
  - Overall and at 12 weeks

Response Outcome, %	Cetuximab + Chemotherapy	Chemotherapy	OR	P Value
All patients	n = 815	n = 815		
12-wk ORR	49	45	1.17	.124
Best ORR	53	51	1.08	.428
Wild-type *KRAS*	n = 362	n = 367		
12-wk ORR	59	50	1.44	.015
Best ORR	64	57	1.35	.049
Mutated *KRAS*	n = 297	n = 268		
12-wk ORR	40	41	0.97	.877
Best ORR	43	46	0.88	.449

- Strong OS prognostic effect of *KRAS*, *NRAS*, and *BRAF* mutation status evident regardless of cetuximab use
  - Patients with mutated *BRAF* have the poorest prognosis
  - Patients with wild-type *KRAS*, *NRAS*, and BRAF have the best prognosis
- Subgroup analysis suggests a benefit for cetuximab arm in patients with
  - Limited metastatic disease
    - 0 or 1 sites: HR 0.73 (95% CI: 0.55-0.97)
    - ≥ 2 sites: HR 1.07 (95% CI: 0.86-1.33)
    - *P* = .036
  - Usage of OxFU chemotherapy
    - OxFU: HR 0.72 (95% CI: 0.53-0.98)
    - OxCap: HR 1.02 (95% CI: 0.82-1.26)
    - *P* = .103
  - Subgroup of patients with wild-type *KRAS*, limited metastatic disease, and OxFU chemotherapy achieved best response with cetuximab
- Major differences between OxCap-treated and OxFU-treated patients
  - Patients in cetuximab arm treated with OxCap required a capecitabine dose reduction (from 1000 to 850 mg/m^2) due to high incidence of grade ≥ 3 diarrhea
  - Patients receiving OxFU went on to use significantly less second-line therapy compared with patients receiving OxCap

Other Outcomes

Patients in cetuximab arm experienced significantly more adverse events

Only neuropathy occurred more frequently in chemotherapy alone arm ($P < .01$)

Adverse Events Occurring More Frequently in Cetuximab Arm	*P Value*
Nail changes	< .001
Skin rash	< .001
Hand-foot syndrome	< .001
Nausea	NS
Vomiting	NS
Diarrhea	< .001
Stomatitis	< .001
Low magnesium	< .001
Anorexia	< .01
Lethargy	< .001
Others	< .01

NS, not significant.

Similar mortality among treatment arms and between patients with wild-type *KRAS* and overall population

Mortality Outcome, %	*All Patients*		*Wild-Type KRAS*	
	Cetuximab + Chemotherapy (n = 815)	*Chemotherapy (n = 815)*	*Cetuximab + Chemotherapy (n = 362)*	*Chemotherapy (n = 367)*
Deaths < 60 days from randomization	5.3	4.4	4.4	4.1
Deaths ≤ 30 days from start of last treatment cycle*	7.7	6.1	7.0	5.6
Treatment-related deaths ≤ 30 days from start of last treatment cycle*	1.1	1.3	0.8	1.4

*Calculated as a percentage of safety population.

Significantly fewer patients in the cetuximab arm went on to receive second-line therapy

Patients Undergoing Second-line Therapy, %	*All Patients*			*Wild-Type KRAS*		
	Cetuximab + Chemotherapy (n = 815)	*Chemotherapy (n = 815)*	*P Value*	*Cetuximab + Chemotherapy (n = 362)*	*Chemotherapy (n = 367)*	*P Value*
Any second-	56	62	.015	54	65	.006

Patients Undergoing Second-line Therapy, %	All Patients			Wild-Type KRAS		
	Cetuximab + Chemotherapy (n = 815)	Chemotherapy (n = 815)	P Value	Cetuximab + Chemotherapy (n = 362)	Chemotherapy (n = 367)	P Value
line therapy						
Irinotecan-based second-line therapy	44	50	.032	42	53	.008

KRAS, *NRAS*, and *BRAF* mutations evenly distributed among treatment arms

Population, n (%*)	Total Patients (n = 1630)	Cetuximab + Chemotherapy (n = 815)	Chemotherapy (n = 815)
Assessed for mutations	1316	668	648
Mutated *KRAS*	565 (43)	297 (44)	268 (41)
Mutated *NRAS*	50 (4)	32 (5)	18 (3)
Mutated *BRAF*	102 (8)	45 (7)	57 (9)
Wild-type *KRAS*	729 (55)	362 (54)	367 (57)
Wild-type *KRAS*, *NRAS*, and *BRAF*	581 (44)	292 (44)	289 (45)

*Percentage calculated as proportion of patients with that mutation out of the total number of patients assessed for mutations within that treatment arm.

References

Maughan TS, Adams R, Smith CG, et al. Identification of potentially responsive subsets when cetuximab is assed to oxaliplatin-fluoropyrimidine chemotherapy (CT) in first-line advanced colorectal cancer (aCRC): Mature results of the MRC COIN trial. Program and abstracts of the 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois. Abstract 3502.