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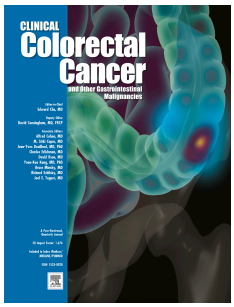

Outcomes of Older Patients (≥70 Years) Treated with Targeted Therapy in Metastatic Chemorefractory Colorectal Cancer: A Retrospective Analysis of NCIC CTG CO.17 and CO.20

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Abstract:

Background: The safety and efficacy of targeted therapy in older patients (≥70 years) with metastatic colorectal cancer is not well evaluated.

Patients and Materials: Outcomes of older patients (including overall survival (OS), progression-free survival (PFS), toxicity, and quality of life (QoL)) were compared to young patients using data from two large, previously reported, clinical trials—CO.17 (cetuximab vs best supportive care) and CO.20 (cetuximab plus placebo vs cetuximab plus brivanib). Only patients with wildtype KRAS tumours were included.

Results: 251/955 (26.3%) of patients were ≥70 years old. No significant differences in OS, PFS or grade 3/4 adverse events were observed between older and younger patients treated with cetuximab (or cetuximab with placebo) in either trial. Younger patients trended toward superior OS in both CO.17 (HR 1.80, p=0.16) and CO.20 (HR 1.34, p=0.07). QoL maintenance favoured younger patients in CO.17 (3.6 vs 5.7 months, p=0.046) but no difference of QoL maintenance was observed in the larger CO.20 trial (1.7 vs 1.8 months, p=0.64). Combination therapy of cetuximab and brivanib was significantly more toxic in older adults (87% vs 77%, p=0.03).

Conclusions: OS, PFS, and toxicities were similar between older and younger patients with wild type *KRAS* metastatic colorectal cancer when treated with cetuximab. Both age groups likely experience similar QoL maintenance with cetuximab. Dual targeted therapy was significantly more toxic in older patients.

Key Words:

Elderly, metastatic colorectal cancer, cetuximab, survival, quality of life

MicroAbstract:

Clinical trial data was used to evaluate cancer outcomes between older (n=251) and younger (n=704) patients with metastatic colorectal cancer who were treated with cetuximab. Overall survival trended towards favouring younger adults, but in general, outcomes, including quality of life benefit, were similar between age groups.

Background:

Colorectal cancer (CRC) is the third most prevalent type of cancer in North America, and is the second-leading cause of cancer-related death.[1] The median age of diagnosis in the United States and other developed nations is 70 years old.[2] The optimal treatment of older CRC patients is not well defined, as older patients have been underrepresented in clinical trials, resulting in a lapse of high-quality evidence.[3-5] This patient population is unique in that treatment decisions are significantly influenced by co-morbidities, risk aversion to treatment-related toxicities, and focus on maintenance of quality of life (QoL).[6,7]

The past decade has experienced a large expansion in the number of treatment options for metastatic CRC. Various combinations of chemotherapy, including fluropyrimidines, irinotecan, and oxaliplatin have improved overall survival (OS) in CRC patients, and these combinations appear to have similar benefits and toxicities in both young and fit older patients.[3,8-10] Numerous novel targeted therapies, including bevacizumab, cetuximab, panitumumab, aflibercept, ramucirumab, and regorafenib, have shown efficacy in CRC. Their use in older patients, as single agents or in combination with chemotherapy, is less well documented. The exception to this is bevacizumab, in

which several elderly-specific trials have been performed and are suggestive of efficacy and safety.[11,12]

Cetuximab is a monoclonal antibody that inhibits the epithelial growth factor receptor (EGFR), resulting in inhibition of cell growth and apoptosis.[13] Cetuximab significantly increases the OS and progression free survival (PFS) in metastatic CRC patients with wild-type *RAS* tumours.[14-16] No immediate toxicity concerns have been identified in several previous studies evaluating older patients treated with cetuximab with or without chemotherapy.[17-21] Fewer studies exist demonstrating the efficacy of cetuximab as a second-line or later agent in the elderly, and no studies have evaluated QoL in elderly patients treated with cetuximab.[14,21]

This study was designed to compare the efficacy, safety, and QoL of older (70+ years) versus younger patients with chemorefractory metastatic CRC receiving targeted therapy using data from two previously reported clinical trials.

Methods:

Clinical Trials and Patient Populations

This study analyzed CO.17 and CO.20, two previously reported phase III randomized controlled clinical trails conducted by the Canadian Cancer Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (NCT00079066 and NCT00640471, respectively).[14,22] In the CO.17 trial, 572 patients were randomized to receive either best supportive care (BSC) or BSC with cetuximab. Cetuximab demonstrated superior OS, PFS, and longer preserved QoL, as compared to BSC.[14] Subsequent studies found this benefit was limited to patients with wild-type *RAS* tumours.[14-16]

CO.20 randomized 750 patients to cetuximab plus placebo or to cetuximab plus brivanib alaninate, a dual inhibitor of vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor (FGFR). The CO.20 trial demonstrated that adding brivanib to cetuximab resulted in improved PFS but no difference in OS and an earlier deterioration in QOL.[22]

Eligibility criteria were similar between trials, and included the presence of advanced colorectal cancer, no response or intolerable to treatment with fluoropyrimidine, irinotecan, and oxaliplatin therapy, ECOG 0-2, and adequate bone marrow, renal, and hepatic function.

In this study, only patients with wild-type KRAS tumours were included; patient inclusion/exclusions for CO.17/20 are demonstrated in CONSORTlike diagrams in Figure 1 and Figure 2, respectively. Older patients were defined as those ≥70 years, consistent with a notion from the International Society of Geriatric Oncology stating “70 years is currently the most commonly used cut-off for defining patients as elderly”.

Outcome Measures

OS and PFS were measured from time of randomization. Severe toxicity was measured using the incidence of grade 2 and grade 3/4 adverse events using the National Cancer Institute Common Toxicity Criteria versions 2.0 (for CO.17) and 3.0 (for CO.20). QoL was measured the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) in each trial. All outcome measures are calculated and reported with similar methodology as the original CO.17 and CO.20 trials.[14,22]

Statistical Analysis

OS and PFS were compared between age groups using multivariate Cox models adjusting for potential prognostic factors included in the primary analyses of the trials. Specifically, the following baseline covariates were included in multivariate Cox models for CO.17: gender (male vs. female), ECOG performance status (2 vs. 0 and 1 vs. 0), body mass index (between 20 and 25 vs. less than 20 and higher than 25 vs. less than 20), site of primary (rectum only vs. colon only, and both rectum and colon vs. colon only), time from diagnosis to randomization (less than 2 years vs. 2 years or longer), baseline LDH level (above upper limit of normal (ULN) vs. equal to or less than ULN), alkaline phosphatase level (above ULN vs. equal to or less than ULN), anemia (grade 1 or higher vs. 0), serum creatinine (grade 1 or higher vs. 0), number of previous chemotherapy drug classes (more than 2 vs. 2 or less), side of primary tumor (right vs. left), Charlson co-morbidity score (0 vs. 1 or higher), and polypharmacy (five or more concurrent medications vs. four or less). [23,24] Cox models for CO.20 results included ECOG performance status, gender, baseline LDH level, alkaline phosphatase level, anemia, number of organ sites (2 or less vs. more than 2), number of chemotherapy classes received, previous VEGFR treatment (yes vs. no), liver metastases (yes vs. no), side of primary tumor, Charlson co-morbidity score, and polypharmacy.

A Charlson co-morbidity score was calculated after reviewing patient co-morbidities captured by the clinical trial intake screening forms; ICD codes were not available for classification.

Safety profiles were compared by Fisher's exact test between two age groups. QoL was measured with the EORTC QLQ-C30, using time to deterioration by ≥10 points of global health status as an endpoint.

Results:

Patient Characteristics

A total of 955 patients were included in the analysis of this study, of which 251 (26.3%) were 70 years or older at time of enrollment. In CO.17, 58/230 (25.3%) were aged 70 or older, while in CO. 20, 193/725 (26.6%) patients were over the age of 70. Baseline characteristics of patients in each trial are listed in Tables 1. In CO.17, baseline serum creatinine, presence of co-morbidities, and treatment arm were associated with age in univariate and multivariate analysis, while in CO.20, only liver metastases and presence of co-morbidities were associated with age in both univariate and multivariate analyses.

Overall Survival and Progression Free Survival

OS and PFS were statistically similar between older and younger patients treated with cetuximab in both CO.17 and CO.20. (Table 2) For cetuximab treated patients in CO.17, the median OS was 8.0 vs 9.7 months (HR 1.80, p=0.16) and the median PFS was 3.5 vs 3.8 months (HR 1.23, p=0.56) for older and younger patients, respectively. For cetuximab (plus placebo) treated patients in CO.20, the median OS was 8.3 vs 9.5 months (HR 1.34, p=0.07) and the median PFS was 2.8 vs 3.5 months (HR 1.25, p=0.16) for older and younger patients, respectively.

In CO.17, only younger patients treated with cetuximab had a significant improvement in both OS and PFS as compared to those receiving BSC (OS= 9.7 vs 4.8 months, p= 0.0006 and PFS= 3.8 vs 1.8 months, p<0.0001, for cetuximab vs BSC respectively). (Table 3) The OS and PFS did not reach statistical significance for older patients treated with cetuximab vs those receiving BSC. (Table 3)

Finally, in CO.20, both older and younger patients treated with cetuximab and brivanib had statistically similar OS (7.6 vs 9.1 months, respectively, p=0.62) and PFS (3.7 vs 5.3 months, respectively, p=0.16). (Table 4)

Toxicity and Quality of Life

Grade 3/4 adverse event rates are listed for CO.17 and CO.20 in tables 5 and 6, respectively. Older and younger patients receiving cetuximab experienced similar rates of grade 3/4 adverse rates in both CO.17 (81% vs 78%, p=0.71) and CO.20 (63% vs 52%, p=0.09). (Table 2). In CO.20, older patients treated with cetuximab experienced higher incidences of grade 3/4 abdominal pain (11% vs 4%, p=0.01), dehydration (4% vs 1%, p=0.04), and confusion (3% vs 0%, p=0.01) than younger patients. (Table 6) Rates of grade 3/4 adverse events were higher in patients treated with cetuximab as compared to those receiving BSC, but this was only significant in younger patients. (Table 3)

Grade 2 adverse events for CO.17 and CO.20 are listed in Supplemental Table 1. All patients treated with cetuximab in CO.17 experienced grade 2 adverse events, although grade 2 events were frequent in the BSC arm (93% in younger patients, 81% in older patients). Similarly, 95% of older and younger patients in CO.20 experienced grade 2 adverse events when treated with cetuximab and placebo. There were no significant differences between age groups for specific symptoms. The combination of cetuximab and brivanib was significantly more toxic in older patients (87%) than younger patients (77%, p=0.03). (Table 4 and 6) Grade 3/4 fatigue was the most common side effect more often seen in older patients (38% vs 22%, p=0.002, Table 6).

In patients treated with cetuximab (or cetuximab with placebo), QoL outcomes varied by trial. In CO.17, older patients treated with cetuximab had a less robust benefit to QoL as compared to younger patients (3.6 vs 5.7 months, p=0.046), whereas in the larger CO.20 trial, QoL maintenance was similar between older and young (1.8 vs 1.6 months, p=0.64, respectively). (Table 2)

When comparing cetuximab to BSC, neither older nor young patients had a statistically significant improvement in QoL with cetuximab treatment. (Table 3) In CO.20, the combination of cetuximab and brivanib resulted in a maintenance of QoL of 0.9 months for older patients vs 1.2 months for younger patients (p=0.02). (Table 4)

Discussion:

This study was designed to evaluate the outcomes of older patients with *KRAS* wild-type metastatic CRC undergoing targeted therapy. Our re-analysis of CO.17 and CO.20 suggest that both older and younger patients treated with cetuximab have statistically similar OS, PFS, and QoL maintenance, while experiencing similar rates of serious adverse events. However, this unplanned sub-analysis (and therefore underpowered) does trend towards improved OS for younger patients in both CO.17 (HR 1.80, p=0.16) and CO.20 (HR 1.34, p=0.07).

Several previous studies examining the outcomes of older patients treated with cetuximab have concluded there are no differences in outcomes between young and older patients. The original CO.17 trial included a planned sub-analysis of patients <65 and ≥ 65 years old, from which no differences were observed for OS, PFS, or overall response rates.[14] A subsequent analysis found no relationship between age (using a cutoff of <65), co-morbidities (measured by Charlson co-morbidity index), and OS.[19] In heavily pre-

treated patients, an observational study of 305 older patients (≥65 years old) saw no difference in adverse events or PFS as compared to younger patients.[20] A pooled analysis of the OPUS and CRYSTAL trials concluded that first-line cetuximab with chemotherapy was equally effective and had similar toxicities for older (≥70) and younger patients.[17]

The primary difference between our analysis and previous analyses of CO.17 is the higher age cutoff of ≥70, as this age is more consistent with current trends in geriatric oncology, and the complete exclusion of patients with mutant KRAS. This study also differs from other reports in that it uses phase III clinical trial data, includes only KRAS wildtype patients, and reports on all of OS, PFS, toxicity, and QoL. Additionally, the majority of other studies thus far have examined cetuximab in combination with chemotherapy. These differences may explain why our analysis showed a strong trend towards younger patients having more prolonged OS.

While OS and PFS outcomes are important, treatment toxicity and QoL maintenance are often more heavily weighted in treatment decisions for older patients.[25] To date, this is the first analysis to compare QoL outcomes between older and younger patients treated with cetuximab. Maintenance of QoL was significantly shorter in older patients than younger patients in the CO.17 trial; however, in the larger CO.20 trial the maintenance of QoL was similar between age groups. The reason for this discrepancy is not abundantly clear, as both trials followed similar protocols with the same QoL survey. This may be due to a type II error, as the older CO.17 QoL data included 17 patients whereas the CO.20 data included 84 patients.

Toxicity results from CO.17 intuitively demonstrate that cetuximab treatment is more toxic than BSC alone, and both trials show that cetuximab-related grade 2 and 3/4

toxicities are similar between age groups. Overall, treatment with cetuximab was associated with a 100% incidence of grade 2 adverse events but this must be contrasted against the fact that >80% of patients receiving BSC will also develop grade 2 adverse events. This shows that both treatment and non-treatment will be associated with burdensome symptoms.

Combination treatment with cetuximab and brivanib was significantly more toxic in older patients than younger patients. Various combinations of targeted therapies have been trialed in metastatic CRC, but thus far none have been approved. In the original CO.20 trial, the combination of cetuximab plus brivanib was found to be more toxic than cetuximab with placebo, and combination therapy did not prolong OS.[22] Several phase I and phase II studies have combined targeted therapies, including VEGF and EGFR inhibitors, with and without cytotoxic agents, and thus far the combinations appear to be reasonably tolerated, with predictable toxicities.[26-29] Unfortunately, the median age in these trials was <65 and the vast majority of patients had an ECOG status of 0-1, making it difficult to generalize these results. Nonetheless, our data suggest that greater baseline toxicities of these combinations may adversely impact older patients to a greater extent than in younger patients.

Fifty six percent of patients diagnosed with CRC are over the age of 65, yet the number of older adults enrolled in clinical trials remains disproportionately low; this will inevitably further cloud the optimal treatment of this patient group.[30] In this study, only 26.3% of patients were over the age of 70. As an example of up-and-coming therapies, the phase II trial of trastuzumab and lapatinib in treatment refractory metastatic colorectal cancer included only patients with an ECOG of 0-1 and no patients were over the age of

70.[31] For immune checkpoint therapy trials, including CheckMate 142 (nivolumab vs nivolumab with ipilimumab; NCT02060188) and KEYNOTE 177 (pembrolizumab vs investigator's choice; NCT02563002), it is not yet clear what proportion of patients will be older.

Future studies dedicated to the geriatric population that incorporate geriatric assessments are still needed. Several recent commentaries by the American Society of Clinical Oncology, Friends of Cancer Research, and the US Food and Drug Administration have published calls for the broadening of clinical trial eligibility criteria to be more representative of the general population.[32,33] Specifically, these groups advocate for inclusion of patients with clinically stable brain metastases, HIV-infected patients, patients with prior or concurrent malignancies, and a liberalization of renal function restrictions.[32] Lichtman et al. (2017) also suggest improved assessment of functional status to better stratify fit versus frail patients in clinical trial patietns.[33] The ASCO Guideline for Geriatric Oncology recommends inclusion of the geriatric assessment for patients >65 years old in clinical trials.[34] This tool includes an evaluation of functional status (activities of daily living, mobility), physical performance, comorbidities, depression, social support, nutritional status, and cognitive status.[35] Development and incorporation into trials will likely allow for more informed decision making when selecting treatments for older patients.

This study is limited by the fact that older patients in clinical trials rarely reflect the "true" older population, who may have more comorbidities and worse performance statuses. While our results are not generalizable to frail elderly patients, 20% of older patients in CO.17 had an ECOG of 2 and older patients were more likely to have multiple

comorbidities. Similarly, in CO.20 the older cohort had significantly more comorbidities, suggesting our older cohort was unique from the younger cohort. The calculation of Charlson co-morbidity index is limited by the lack of ICD-10 codes; there was also no manner to determine or adjust for the severity of each co-morbidity. Unfortunately, our limited sample size prevented a subset analysis by comorbidities or presence of polypharmacy. A sensitivity analysis of age was not feasible given the limited number of older patients >75; sample size also limited the usefulness of analyzing age as a continuous variable.

CO.17 and CO.20 were not originally designed to measure geriatric outcomes and as such no comprehensive geriatric assessments were performed, however, this is the first study to report QoL outcomes in older patients treated with cetuximab. Other limitations include the retrospective nature of this study, which was conducted using data from well-designed clinical trials, and only controlling for wild-type *KRAS* rather than extended *RAS*. Finally, it is important to recognize that age alone should not be used to dictate treatment, and that physiological age may vastly differ from chronological age.

Conclusions:

Age was not associated with statistically superior OS or PFS in patients with chemorefractory, *KRAS* wildtype metastatic CRC treated with cetuximab. However, a strong trend towards improved OS for younger patients treated with cetuximab was observed in both trials. Older patients likely experience similar QoL maintenance and similar toxicity rates as compared to younger patients, however, adverse event rates are high. The decision to initiate targeted therapy in older patients should balance modest improvements in cancer-specific outcomes with high incidence of toxicity. Dual targeted

therapy with cetuximab and brivanib was significantly more toxic in the older population. Further recruitment of older patients into clinical trials and elder-specific trials are necessary to better guide treatment decisions in this population.

Additional Information:

Disclosures: LS receives institutional clinical trials support from BMS. JS has received travel support from Amgen and Merck Serono. TP has served on advising boards for Merck (non-compensated), Amgen (compensated), and Takeda (compensated). NT has a consulting role for Merck Serono, BMS, and Amgen. CK has served on an advisory board for Amgen. GL has consulted for and received honoraria from AstraZeneca, Roche, Pfizer, Merck, Novartis, Abbvie, and Takeda. All remaining authors have declared no conflicts of interest.

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Availability of data and materials: Data is stored at the Canadian Cancer Trials Group in Kingston, Ontario.

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Table 1: Baseline Patient, Disease and Treatment Characteristics by Age in CO.17 and CO.20 Patients with Wild-type Kras

	CO. 17				*CO.20*			
Characteristic	**Age<70 (*N*=172)**	**Age>=70 (*N*=58)**	***P*-value* (Univariate)**	***P*-value** (Multivariate)**	**Age<70 (*N*=532)**	**Age>=70 (*N*=193)**	***P*-value* (Univariate)**	***P*-value** (Multivariate)**
Gender			0.75				0.11	
Female	54 (31.4)	20 (34.5)			198 (37.2)	59 (30.6)		
Male	118 (68.6)	38 (65.5)			334 (62.8)	134 (69.4)		
ECOG performance status			0.13				0.67	
0-1	136 (79.0)	47 (81.0)			482 (90.6)	173 (89.6)		
2	36 (21.0)	11 (19.0)			50 (9.4)	20 (10.4)		
BMI (kg/m^2)			0.44					
<20	14 (8.1)	3 (5.2)			--	--		
20-25	50 (29.1)	22 (37.9)			--	--		
>25	108 (62.8)	33 (56.9)			--	--		
Site of primary			0.83					
Colon only	104 (60.4)	33 (56.9)			--	--		
Rectum Only	32 (18.6)	11 (19.0)			--	--		
Colon and Rectum	36 (20.9)	14 (24.1)			--	--		
Number of metastatic organ sites							0.22	
≤ 2	--	--			423 (79.5)	145 (75.1)		
>2	--	--			109 (20.5)	48 (24.9)		
Presence of liver metastases							0.003	0.004
Yes	--	--			365 (68.6)	154 (79.8)		
No	--	--			167 (31.4)	39 (20.2)		
Prior VEGFR target therapy							0.35	
Yes	--	--			229 (43.0)	75 (38.9)		
No	--	--			303 (57.0)	118 (61.1)		
Time from initial diagnosis to randomization (year)			0.29					
>=2 years	91 (52.9)	36 (62.1)			--	--		
< 2 years	81 (47.1)	22 (37.9)			--	--		
LDH			0.30				0.85	
≤UNL	47 (29.4)	12 (21.4)			157 (29.5)	54 (28.0)		
>UNL	113 (70.6)	44 (78.6)			356 (66.9)	128 (66.3)		
Alkaline phosphatase			1.00				0.60	
≤UNL	47 (27.5)	16 (27.6)			192 (36.1)	74 (38.3)		
>UNL	124 (72.5)	42 (72.4)			335 (63.0)	117 (60.6)		
Hemoglobin			0.34	0.21			0.10	0.43
CTC grade 0	60 (34.9)	16 (27.6)			210 (39.5)	63 (32.6)		
CTC grade≥1	112 (65.1)	42 (72.4)			335 (60.5)	130 (67.4)		
Serum Creatinine			0.003	0.002				
CTC grade 0	163 (94.8)	47 (81.0)						
CTC grade≥1	9 (5.2)	11 (19.0)						
Number of previous chemo drug classes			0.22	0.11			1.00	
≤ 2	9 (5.2)	6 (10.3)			21 (3.9)	7 (3.6)		
>2	163 (94.8)	52 (89.7)			511 (96.1)	186 (96.4)		
Prior thymidylate synthase inhibitor			1.0				0.57	
Yes	172 (100)	58 (100)			529 (99.4)	193 (100)		
No	0 (0)	0 (0)			3 (0.6)	0 (0)		
Prior irnotecan			0.15				0.80	
Yes	166 (96.5)	53 (91.4)			518 (97.4)	187 (96.9)		
No	6 (3.5)	5 (8.6)			14 (2.6)	6 (3.1)		
Prior oxaliplatin			0.21				0.69	
Yes	168 (97.7)	54 (93.1)			525 (98.7)	192 (99.5)		

No	4 (2.3)	4 (6.9)			7 (1.3)	1 (0.5)		
Co-morbidity score			0.006	0.005			<0.001	<0.0001
0	134 (77.9)	34 (58.6)			449 (84.4)	134 (69.4)		
1	38 (22.1)	24 (41.4)			83 (15.6)	59 (30.6)		
Number of concomitant medications			0.35				0.06	0.43
<5	108 (62.8)	32 (55.2)			302 (56.8)	94 (48.7)		
≥5	64 (37.2)	26 (44.8)			230 (43.2)	99 (51.3)		
Side of primary tumor			0.70				0.67	
Left	80 (46.5)	25 (43.1)			227 (42.7)	91 (47.2)		
Right	41 (23.8)	15 (25.9)			110 (20.7)	49 (25.4)		
Treatment			0.006	0.008			0.45	
BSC only	75 (43.6)	38 (65.5)			--	--		
Cetuximab + BSC	97 (56.4)	20 (34.5)			--	--		
Brivanib + Cetuximab	--	--			263 (49.4)	102 (52.8)		
Placebo + Cetuximab	--	--			269 (50.6)	91 (47.2)		

* From Wilcoxon test for continuous variables and Fisher's exact test for categorical variables
** From logistic regression model including characteristics with p<0.1 in univariate analysis as covariates.
BMI= body mass index, LDH= lactate dehydrogenase, VEGFR= vascular endothelial growth factor receptor,
UNL= upper limit of normal, CTC= common terminology criteria, BSC= best supportive care, --= data not available/applicable

Table 2. Cancer specific outcomes of older (≥70 years) and younger patients treated with cetuximab (in CO.17) or cetuximab with placebo (in CO.20).

CO.17 Outcomes	N	Older (95% CI)	N	Younger (95% CI)	Hazard Ratio (95% CI)	P-Value
OS (months)	20	8.0 (5.7-10.3)	97	9.7 (7.2-10.6)	1.80 (0.80-4.09)	0.16
PFS (months)	20	3.5 (1.8-5.4)	97	3.8 (3.0-5.4)	1.23 (0.93-2.84)	0.56
Grade 3/4 Toxicity	53	81%	235	78%	n/a	0.71
QoL (months until deterioration)	17	3.6 (1.0-NA)	88	5.7 (5.7-5.7)	n/a	0.046
CO.20 Outcomes	N	Older (95% CI)	N	Younger (95% CI)	Hazard Ratio (95% CI)	P-Value
OS (months)	94	7.6 (5.6-9.2)	280	9.1 (8.5-11.4)	1.34 (0.98-1.83)	0.07
PFS (months)	94	2.8 (1.8-3.7)	280	3.5 (3.3-3.6)	1.25 (0.92-1.70)	0.16
Grade 3/4 Toxicity	94	63%	280	52%	n/a	0.09
QoL (months until deterioration)	84	1.8 (1.2-2.8)	264	1.6 (1.2-2.0)	n/a	0.64

Table 3. Comparisons of cancer specific outcomes between patients treated with cetuximab or best supportive care in CO.17, stratified by age.

CO.17 Older	N	Cetuximab + BSC (95% CI)	N	BSC Alone (95% CI)	Hazard Ratio (95% CI)	P-Value
OS (months)	20	8.0 (5.7-10.3)	38	5.1 (2.7-8.3)	0.60 (0.32-1.14)	0.11
PFS (months)	20	3.5 (1.8-5.4)	38	2.3 (1.8-3.3)	0.67 (0.38-1.19)	0.17
Grade 3/4 Toxicity	53	76%	80	51%	n/a	0.09
QoL (months until deterioration)	17	3.6 (1.0-NA)	31	2.3 (1.81-NA)	n/a	0.94
CO.17 Young	N	Cetuximab + BSC (95% CI)	N	BSC Alone (95% CI)	Hazard Ratio	P-Value
OS (months)	97	9.7 (7.2-10.6)	75	4.8 (4.1-5.4)	0.55 (0.39-0.78)	0.0006
PFS (months)	97	3.8 (3.0-5.4)	75	1.8 (1.7-1.9)	0.31 (0.22-0.44)	<0.0001
Grade 3/4 Toxicity	235	78%	194	62%	n/a	0.03
QoL (months until deterioration)	88	5.7 (5.7-5.7)	51	3.7 (2.4-4.0)	n/a	0.06

Table 4. Comparison of cancer specific outcomes between older and younger patients treated with brivanib and cetuximab in CO.20.

CO.20 Brivanib plus Cetuximab Outcomes	N	Older (95% CI)	N	Younger (95% CI)	Hazard Ratio (95% CI)	P-Value
OS (months)	105	7.6 (5.2-8.8)	271	9.1 (8.0-10.1)	1.08 (0.78-1.50)	0.62
PFS (months)	105	3.7 (3.3-5.4)	271	5.3 (4.0-5.5)	1.25 (0.92-1.70)	0.16
Grade 3/4 Toxicity	105	87%	271	77%	n/a	0.03
QoL (months until deterioration)	87	0.9 (0.6-1.2)	244	1.2 (1.0-1.7)	n/a	0.02

Table 5: Number of Patients with Toxicities (Grade 3 or higher) in CO.17

Toxicity	Cetuximab + BSC			BSC		
	Age < 70	≥ Age 70	*P*	Age < 70	≥ Age 70	*P*
Number pts	96	21		73	37	
Any	75 (78)	16 (76)	1.0	45 (62)	19 (51)	0.31
Edema	4 (4)	2 (10)	0.59	6 (8)	3 (8)	1.0
Fatigue	29 (30)	6 (29)	1.0	18 (25)	9 (24)	1.0
Anorexia	5 (5)	3 (14)	0.15	2 (3)	1 (3)	1.0
Constipation	2 (2)	2 (10)	0.15	2 (3)	1 (3)	1.0
Nausea	6 (6)	0 (0)	0.37	6 (8)	1 (3)	0.42
Vomiting	6 (6)	0 (0)	0.37	4 (6)	0 (0)	0.30
Infection w/o neutropenia	8 (8)	2 (10)	1.0	5 (7)	0 (0)	0.17
Confusion	5 (5)	3 (14)	0.15	1 (1)	0 (0)	1.0
Abdominal pain	14 (15)	2 (10)	0.73	12 (16)	2 (5)	0.13
Other pain	17 (18)	2 (10)	0.52	6 (8)	1 (3)	0.42
Dyspnea	16 (17)	3 (14)	1.0	12 (16)	4 (11)	0.57
Rash	18 (19)	3 (14)	0.76	0 (0)	1 (3)	0.34

Table 6: Number of Patients with Toxicities (Grade 3 or higher) in CO.20

Toxicity	Cetuximab + Brivanib			Cetuximab + Placebo		
	Age<70	≥ Age 70	*P*	Age<70	≥ Age 70	*P*
Number pts	263	102		269	91	
Any	203 (77)	89 (87)	0.02	139 (52)	57 (63)	0.09
Fatigue	57 (22)	39 (38)	0.001	27 (10)	13 (14)	0.33
Hypertension	25 (10)	13 (13)	0.34	2 (1)	2 (2)	0.57
Rash	23 (9)	13 (13)	0.24	16 (6)	4 (4)	0.62
Abdominal pain	29 (11)	8 (8)	0.44	9 (3)	10 (11)	0.008
Dyspnea	22 (8)	13 (13)	0.23	15 (6)	5 (5)	1.0
Diarrhea	21 (8)	6 (6)	0.52	7 (3)	4 (4)	0.48
Dehydration	15 (6)	10 (10)	0.17	2 (1)	4 (4)	0.04
Confusion	6 (2)	9 (9)	0.008	0 (0)	3 (3)	0.01
Anorexia	10 (4)	8 (8)	0.17	4 (1)	1 (1)	1.0

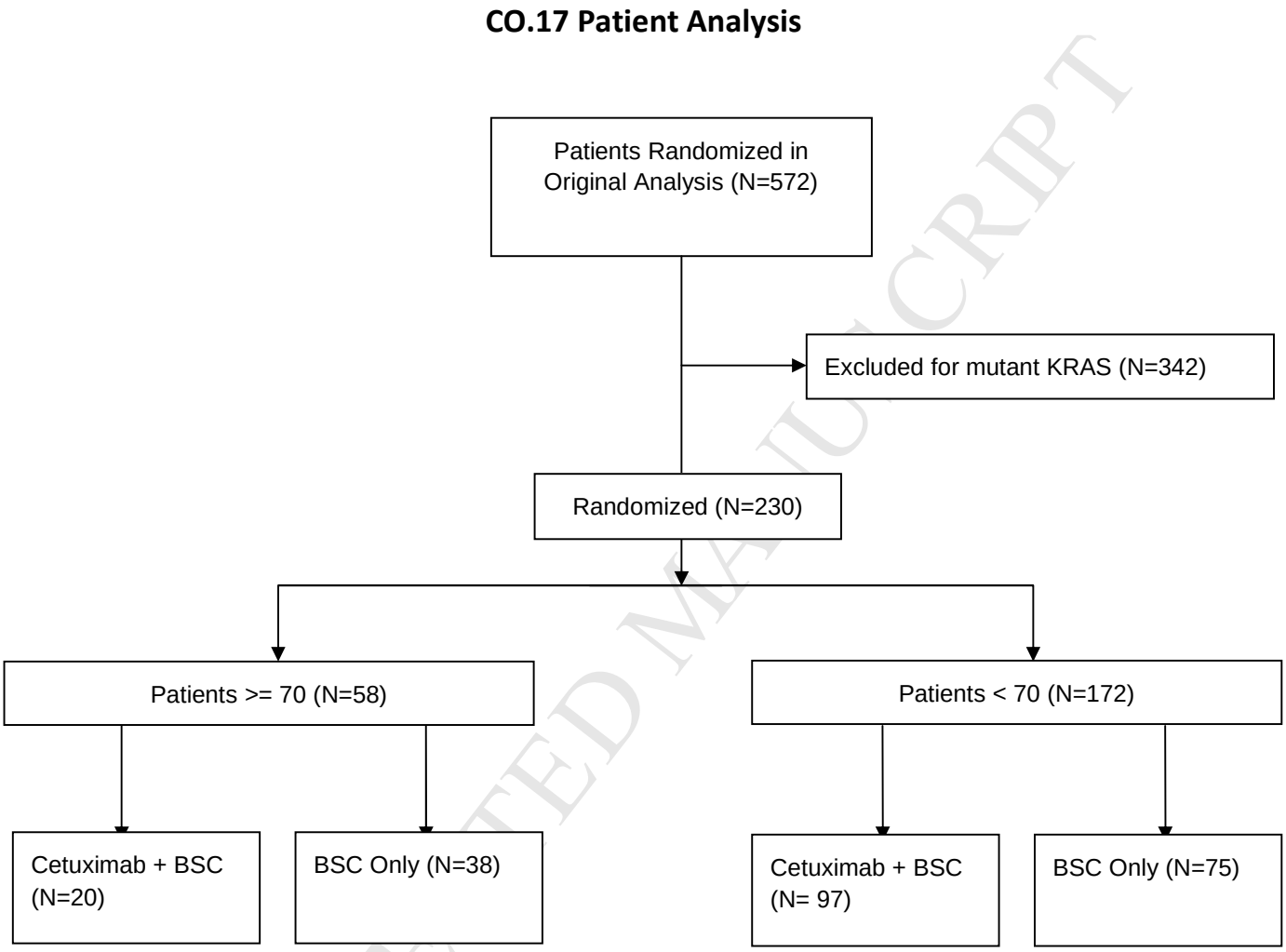

Figure 1: Flow diagram demonstrating the selection of patients from the original CO.20 trial and the division amongst age and treatment groups.

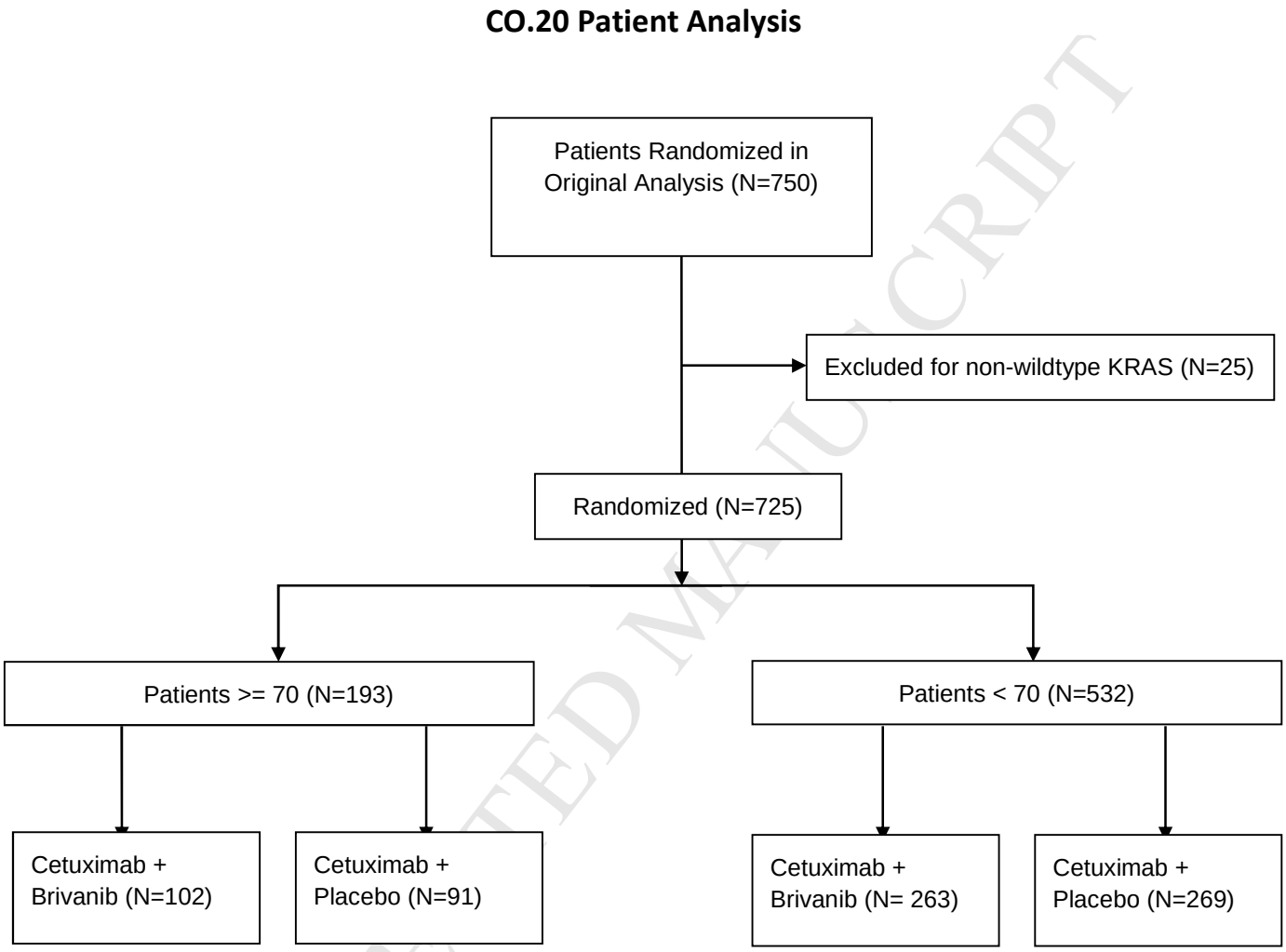

Figure 2: Flow diagram demonstrating the selection of patients from the original CO.20 trial and the division amongst age and treatment groups.

Supplemental Table 1: Number of Patients with Toxicities (Grade 2 or higher)

(1) CO.17 Treated Patients with Wild-type Kras

Toxicity	Cetuximab + BSC			BSC		
	Age < 70	≥ Age 70	p	Age < 70	≥ Age 70	p
Number pts	96	21		73	37	
Any	95 (99)	21 (100)	1.0	68 (93)	30 (81)	0.10
Edema	17 (18)	3 (14)	0.77	15 (21)	8 (22)	1.0
Fatigue	55 (57)	15 (71)	0.33	46 (63)	19 (51)	0.31
Anorexia	27 (26)	6 (29)	1.0	30 (41)	11 (30)	0.30
Constipation	22 (23)	9 (43)	0.10	13 (18)	6 (16)	1.0
Nausea	22 (23)	2 (10)	0.24	17 (23)	6 (16)	0.46
Vomiting	20 (21)	2 (10)	0.36	12 (16)	2 (5)	0.13
Infection w/o neutropenia	24 (25)	5 (24)	1.0	10 (14)	5 (14)	1.0
Confusion	9 (9)	5 (24)	0.13	2 (3)	0 (0)	0.55
Abdominal pain	38 (40)	9 (43)	0.81	26 (36)	12 (32)	0.83
Other pain	34 (35)	8 (38)	1.0	17 (23)	5 (14)	0.31
Dyspnea	46 (48)	10 (48)	1.0	31 (43)	18 (49)	0.55
Rash	58 (60)	10 (48)	0.33	3 (4)	2 (5)	1.0

(2) CO.20 Treated Patients with Wild-type Kras

Toxicity	Brivanib + Cetuximab			Placebo + Cetuximab		
	Age<70	≥ Age 70	P	Age<70	≥ Age 70	P
Number pts	263	102		269	91	
Any	262 (100)	101 (99)	1.0	255 (95)	86 (95)	1.0
Fatigue	160 (61)	71 (70)	0.18	103 (38)	40 (44)	0.39
Hypertension	59 (22)	30 (29)	0.22	13 (5)	6 (7)	0.59
Rash	116 (44)	48 (47)	0.73	111 (41)	27 (30)	0.06
Abdominal pain	73 (28)	22 (22)	0.23	53 (20)	25 (27)	0.14
Dyspnea	45 (17)	25 (25)	0.14	26 (10)	15 (16)	0.09
Diarrhea	81 (31)	30 (29)	0.80	26 (10)	16 (18)	0.06
Dehydration	26 (10)	18 (18)	0.05	6 (2)	5 (5)	0.15
Confusion	10 (4)	13 (13)	0.003	4 (1)	3 (3)	0.37
Anorexia	77 (29)	28 (27)	0.70	44 (16)	17 (19)	0.63