BRAF^{V600E} Mutation in First-line Metastatic Colorectal Cancer: an Analysis of Individual Patient Data from the ARCAD Database

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Abstract

Background

First-line therapeutic strategies for patients with *BRAF*^{V600E}-mutated (*BRAF*mt) metastatic colorectal cancer (mCRC) mainly rely on subgroup analyses from randomized controlled trials (RCTs). We aimed at assessing the prognostic and predictive impact of *BRAF*mt for the efficacy of targeted therapies with first-line chemotherapy.

Methods

Individual patient data from first-line RCTs with *BRAF* and *KRAS* status data in the ARCAD database were pooled. Progression-free survival and overall survival (OS) were assessed using Kaplan-Meier and Cox models. Outcomes were compared between treatment groups that were concurrently randomized whenever possible.

Results

6391 patients from 10 RCTs were included: 573 *BRAF*mt (9.0%), 2059 *KRAS*mt (32.2%) and 3759 double wild-type (58.8%). *BRAF*mt mCRC patients experienced statistically significantly poorer OS than those with *KRAS*mt (adjusted hazard ratio [HRadj] =1.46, 95% confidence interval [95%CI] = 1.30-1.64) and patients with double wild-type tumors (HRadj =2.14, 95%CI = 1.94-2.36). Anti-EGFR agents did not improve progression-free survival or OS of *BRAF*mt mCRC patients, based on 4 RCTs testing chemotherapy ± anti-EGFR (HR_{adj} =0.96, 95%CI = 0.71-1.30 and HR_{adj} =0.85, 95%CI = 0.66-1.14, respectively).

Conclusion

Our data suggest that the addition of anti-EGFR agents to chemotherapy is ineffective as first-line treatment for *BRAF*mt mCRC patients.

Keywords

Colorectal cancer; BRAF; antiangiogenic; anti-EGFR; prognosis; survival

Therapeutic decisions for patients with metastatic colorectal cancer (mCRC) largely rely on biomarkers such as *KRAS*, *NRAS* and *BRAF* mutational status that are used as prognostic markers or predictors of treatment efficacy. Whereas the prognostic and predictive value of *RAS* mutations has been thoroughly analyzed, less data exists for outcomes in patients whose tumors harbor the *BRAF*^{V600E} mutation due to its relatively low frequency in mCRC (*i.e.* approximately 8-10%) [1].

Even though patients with *BRAF*^{V600E} mutated mCRC experience shorter survival compared to those with *BRAF* wild-type (*BRAF*wt) mCRC or non-*BRAF*^{V600E} mutated mCRC [1–5], there is increasing evidence that the population with *BRAF*^{V600E} mutation exhibit statistically significant prognostic heterogeneity. In a pooled analysis of the COIN, FOCUS and PICCOLO randomized controlled trials (RCTs), one-fourth of patients with *BRAF*^{V600E} mutation had favorable first-line PFS and post-progression survival (resulting a median OS = 24.0 months) whereas one-third progressed rapidly through first-line and later lines of chemotherapy, with a median OS of 4.7 months [4]. This observation was confirmed by Loupakis et al., who developed a prognostic scoring system based on two large retrospective series [6].

Therapeutic strategies in the first-line metastatic setting for patients with *BRAF*^{V600E} mutation in their tumors are mainly based on retrospective data with small sample sizes. In the phase III TRIBE study, the FOLFOXIRI-bevacizumab combination was associated with a non-statistically significant increase of PFS and OS compared to FOLFIRI-bevacizumab amongst the subgroup with *BRAF*^{V600E}-mutation [7]. Despite the small population sample of this subgroup analysis (N = 28), FOLFOXIRI-bevacizumab is now considered a valid option for patients with tumors that have *BRAF*^{V600E} mutation. A recent meta-analysis based on individual patient data from five RCTs did not confirm the superiority of FOLFOXIRI-bevacizumab versus doublets of chemotherapy plus

bevacizumab in the *BRAF*^{V600E} population (HR = 1.12, 95% confidence interval [95%CI] = 0.75-1.68) [8].

No randomized data evaluating the added value of antiangiogenic agents to standard first-line chemotherapy (*i.e.*, FOLFOX, FOLFIRI or FOLFOXIRI) are available for patients with *BRAF*^{V600E} mutation. However, underpowered *post hoc* analyses of RCTs have reported favorable trends for the addition of bevacizumab to first-line IFL or capecitabine, and for the addition of aflibercept to second-line FOLFIRI [9–11]. Considering anti-EGFR agents, the predictive impact of *BRAF*^{V600E} mutation for the efficacy of these compounds remains controversial. Although patients whose tumors have *BRAF*^{V600E} mutation don't seem to benefit from these compounds when used as single agents, data for first-line treatments combining chemotherapy plus anti-EGFR agents are less clear, and two meta-analyses have not been able to reach a definitive conclusion regarding whether or not a *BRAF*^{V600E} mutation is a biomarker of resistance to anti-EGFR agents [12–18]. Moreover, in both the FIRE-3 and CALGB 80405 RCTs, median PFS and OS for *BRAF*^{V600E} mCRC patients were similar whether the patients were treated with chemotherapy plus cetuximab or bevacizumab [2,19]. The observation that the choice of targeted therapy (anti-EGFR *vs* antiangiogenic) has no survival effect in patients with *BRAF*^{V600E} mutated tumors raises concerns about the optimal treatment of this population. Also, the positive results of the BEACON trial with encorafenib and cetuximab ± binimetinib as second-line treatment raises questions about the optimal therapeutic strategy in this population [20].

Here we assess the prognostic value of *BRAF*^{V600E} mutation and its predictive impact for the efficacy of antiangiogenic agents and anti-EGFR agents through the analysis of individual patient data from prospective RCTs in the Analysis and Research in CAncers of the Digestive System (ARCAD) database.

Methods

Patient selection

The ARCAD database integrates individual patient data of mCRC patients treated with systemic treatment within prospective, randomized phase II and III RCTs. For the purpose of this study, we selected first-line RCTs of which data on tumor *BRAF*^{V600E} and *KRAS* mutational status were available. Studies with more than two-thirds of missing data for *BRAF*^{V600E} or *KRAS* status were excluded. Cases with concomitant *BRAF*^{V600E} and *KRAS* mutation were excluded from the analysis.

Statistical analysis

PFS was defined from randomization to first-documented disease progression or death from any cause, whichever occurred first. OS was defined from randomization to death from any cause. Distributions of PFS and OS curves were estimated with the Kaplan-Meier method. In the absence of confirmation of disease progression or death, PFS was censored at the last date of disease evaluation and survival time was censored at the date of last trial follow-up. The adjusted, stratified Cox models were used to evaluate the prognostic association between *KRAS/BRAF*^{V600E} mutational status and survival outcomes, with adjustment for gender and performance score, and stratification by treatment arm. Treatment arms combining chemotherapy plus both cetuximab and bevacizumab (CAIRO2, CALGB 80405), as well as chemotherapy triplet plus bevacizumab (TRIBE study), were not included for the analysis of *BRAF*^{V600E} mutation's predictive value.

The efficacy of anti-EGFR antibodies (cetuximab and panitumumab) was evaluated by pooling individual patient data from RCTs with head-to-head comparisons (*i.e.*, concurrent

randomization) of chemotherapy with or without anti-EGFR antibodies. Analyses were restricted to the population with *KRAS*wt tumors and stratified by chemotherapy backbone, adjusting for sex and performance status.

In the current ARCAD database, there are no trials with concurrently randomized patients with known *BRAF*^{V600E} mutational status who were assigned to chemotherapy ± bevacizumab. In order to minimize potential biases due to lack of randomization, the efficacy of bevacizumab was evaluated among matched patients with *BRAF*^{V600E} mutation in their tumors who were treated with chemotherapy alone or chemotherapy plus bevacizumab by propensity score matching methods after applying standard multiple imputations to missing covariates as detailed in the **Supplementary Methods**. Multivariable Cox proportional hazards model was then used to investigate the effect of bevacizumab. All tests were two-sided, a P-value less than .05 was considered statistically significant.

Results

Included trials

Ten first-line RCTs were included (**Table 1**; **Figure 1**): CAIRO2, CALGB 80405, COIN, COIN-B, CRYSTAL, FIRE II AIO-KRK-0104, FIRE III, OPUS PRIME and TRIBE [7,13,19,21–27]. Four RCTs directly compared chemotherapy versus chemotherapy plus cetuximab or panitumumab (COIN, CRYSTAL, OPUS and PRIME).

Demographics

Overall, 6391 patients were included: 573 had *BRAF*^{V600E} mutated tumors (9.0%), 2059 tumors were *KRAS*mt (32.2%) and 3759 double wild-type (58.8%). Patient and tumor

characteristics are summarized in **Table 2**. *NRAS* mutational status was missing for 48% of the population and therefore was not considered in the analyses. Primary tumor sidedness was available for 88.6% of the patients. *BRAF*^{V600E} mutation was more frequent in older women, with right-sided tumors and those with peritoneal and lymph node involvement while the mutation was less commonly seen in those with lung or liver metastases.

Survival

Prognostic importance of BRAF^{V600E} and KRAS mutated and double wild-type tumors. The overall median follow-up was 45.7 months (95%CI = 44.7-47.4). Patients with *BRAF*^{V600E} mutated tumors experienced statistically significantly poorer PFS (median PFS (mPFS) = 5.8 months) than those with *KRAS*mt (mPFS = 7.8 months; adjusted hazard ratio [HRadj] = 1.34, 95%CI = 1.19-1.50) or double wild-type tumors (mPFS = 9.2 months; HRadj = 1.92, 95%CI = 1.75-2.12) (**Figure 2**). Medians of OS were 11.1, 18.0, and 23.7 months, respectively (*BRAF*^{V600E} vs *KRAS*mt, HRadj = 1.46, 95%CI = 1.30-1.64; *BRAF*^{V600E} vs double wild-type pts, HRadj = 2.14, 95%CI = 1.94-2.36). *BRAF*^{V600E} mutation was associated with poorer survival in all subgroups (**Supplementary Figure 1**). The negative prognostic impact of *BRAF*^{V600E} was confirmed in multivariable analysis (**Supplementary Table 1**).

After stratification by treatment arm within studies, objective response rate and disease control rate of the cohort of patients with *BRAF*^{V600E} mutated tumors were statistically significantly lower than those with *KRAS*mt and double wild-type (respectively, 34.6% vs 45.8% vs 63.1%, P<.001 and 64.8% vs 75.9% vs 86.6%, P<.001).

Predictive value of *BRAF*^{V600E} mutation

Chemotherapy ± anti-EGFR monoclonal antibody. In the pooled population of COIN, CRYSTAL, OPUS and PRIME (*i.e.*, RCTs testing chemotherapy +/- cetuximab or panitumumab), the addition of an anti-EGFR monoclonal antibody was not associated with better outcomes in the population of patients with *BRAF*^{V600E} mutated tumors (HR_{adj} for PFS = 0.96, 95%CI = 0.71-1.30 and HR_{adj} for OS = 0.85, 95%CI = 0.66-1.14) (**Figure 3**; **Supplementary Table 2**). In the double wild-type population from these four RCTs, the combination of chemotherapy plus anti-EGFR agents was associated with a statistically significant PFS improvement (HR_{adj} = 0.70, 95%CI = 0.62-0.78), but the analysis for OS (HR_{adj} = 0.91, 95%CI = 0.82-1.02) did not show a statistically significant advantage.

Chemotherapy ± bevacizumab. No RCT with head-to-head comparison of chemotherapy ± bevacizumab was available. In the entire dataset, 179 patients with *BRAF*^{V600E} mutated tumors from four RCTs received bevacizumab plus chemotherapy and 193 from a different set of four RCTs received chemotherapy alone (**Table 1**). Using IPTW after applying multiple imputations to compensate for missing baseline covariates, the addition of bevacizumab was associated with a significant improvement of PFS (HR_{adj} = 0.65, 95%CI = 0.49-0.87, P=.004) and OS (HR_{adj} = 0.64, 95%CI = 0.49-0.85, P=0.002) for patients whose tumors harbored a *BRAF*^{V600E} mutation (**Supplementary Table 2**). These findings were consistent using propensity score matching after multiple imputation (HR_{adj} = 0.65, 95%CI = 0.47-0.91, P= .01 and HR_{adj} = 0.61, 95%CI = 0.42-0.87, P=.007, respectively).

Discussion

We report here an analysis of the prognostic and predictive impact of *BRAF*^{V600E} mutation using individual patient data from ten RCTs testing first-line treatment options for patients with

mCRC. The majority of previously published studies investigated the prognosis among patients with *BRAF*^{V600E} mutation compared to those with *BRAF* wild-type tumors. We took into account the *KRAS* mutational status and confirm the poor outcomes of *BRAF*^{V600E} mutations in mCRC patients, compared to patients with either *KRAS*mt or double wild-type mCRC [1,3,4]. No survival improvement was detected with chemotherapy plus anti-EGFR versus chemotherapy alone for patients with *BRAF*^{V600E} mutated tumors in a pooled analysis of four RCTs.

Randomized trials dedicated to patients with *BRAF*^{V600E} mutated tumors are lacking to properly investigate the efficacy of anti-EGFR agents or antiangiogenics on patients with *BRAF*^{V600E} mutated mCRC. Given the acceleration of clinical research in this population (e.g., tyrosine kinase inhibitors, immunotherapy), it seems unlikely that investigators will conduct additional large prospective studies focused solely on the efficacy of chemotherapy and targeted therapies for patients with *BRAF*^{V600E} mutated mCRC. In the current ARCAD database, there were no randomized trials evaluating chemotherapy ± bevacizumab with available *BRAF*^{V600E} mutational data (in supplementary material) . The results based on matched populations showed that bevacizumab improved the outcomes of the population with *BRAF*^{V600E} mutated tumors after adjustment for important covariates. Our results reinforce the body of evidence supporting the efficacy of antiangiogenic agents in the management of *BRAF*^{V600E} mutated tumors in mCRC [9–11,28,29]. Nonetheless, caution should be taken in the interpretation of these results. While imperfect, the present work probably represent the highest level of evidence that will ever be obtained to address the question of bevacizumab effect for patients with *BRAF*^{V600E} mutated mCRC.

Post hoc analyses of CRYSTAL and OPUS, as well as PRIME, did show an improvement of survival and response rates with anti-EGFR monoclonal antibodies, but meta-analyses have not been able to conclusively delineate the efficacy or the inefficacy of these compounds in the

population with *BRAF*^{V600E} mutated tumors [12,13,17,18]. Here we provide results from the pooled analysis of individual patient data from four RCTs (COIN, CRYSTAL, OPUS and PRIME) testing first-line chemotherapy ± anti-EGFR antibodies with concurrent randomizations, showing no survival improvement in this population. Unfortunately, we were not able to evaluate the impact of primary tumor location on the predictive capacity of *BRAF*^{V600E}. It is noteworthy that the interaction tests did not reach statistical significance, meaning that, strictly speaking, we cannot affirm that the presence of a *BRAF*^{V600E} mutation predicts resistance to EGFR inhibitors. As highlighted by Rowland et al., it is the treatment effect interaction between subgroups, rather than the treatment effect of within an individual subgroup, that should primarily be interpreted when deriving a conclusion as to whether a potential predictive factor influences the treatment effect. However, this recommended approach is poorly powered to detect subgroup differences, especially for predictive biomarkers with low incidence and markers that predict partially attenuated response to therapy [18].

Our results should be put in perspective with the findings of the BEACON study [20]. This phase III RCT showed that the combination of cetuximab and the BRAF inhibitor encorafenib (with or without binimetinib, a MEK inhibitor) was superior to irinotecan plus cetuximab in the second- or third-line treatment setting for patients with anti-EGFR therapy-naïve *BRAF*^{V600E} mutated tumors.. Nevertheless, it is worthy to remember that only 33% to 66% of patients with *BRAF*^{V600E} mutated mCRC receiving first-line chemotherapy will eventually undergo second-line treatments [4,30].

Our work displays several limitations that need to be acknowledged. First, *BRAF*^{V600E} mutation is frequently associated with older age and peritoneal involvement, and many patients with *BRAF*^{V600E} mutated tumors are not fit enough to meet the criteria for clinical trial enrollment. Measurable disease was not required in the CALGB 80405 study, though [31]. Still, our results might

underestimate the incidence of *BRAF*^{V600E} mutations in mCRC but overestimate the true prognosis of this population [32]. Secondly, data were not available concerning the mismatch repair (MMR) status of the tumors. Approximately one-fourth of tumors with a *BRAF*^{V600E} mutation also exhibit deficient MMR [1], and controversies recently emerged concerning the potential prognostic impact of the MMR status in the metastatic setting [1,30,33]. Importantly, the prognosis for patients with MMR-deficient mCRC has been improved markedly by the administration of immune checkpoint inhibitors [34–37]. The population of MMR-deficient *BRAF*^{V600E} mutated mCRC patients should therefore be considered apart from patients with MMR-proficient *BRAF*^{V600E} mCRC, for whom the needs for effective therapeutic strategies are unmet. Last, even if the ARCAD database gathers individual patient data from prospective randomized trials, it is worthy to remind that our study was unplanned and therefore might be subject to uncontrolled biases. We aimed at taking into consideration these potential confounders with adjustments for main prognostic modifiers, stratification by study arm (for prognostic effect) or study comparison (for predictive effect).

In conclusion, we report in this large study that patients with *BRAF*^{V600E} mCRC experience poorer survival outcomes and lower response rates than *KRAS*mt and double wild-type when treated with first-line therapies. Patients with *BRAF*^{V600E} mutated mCRC do not statistically significantly benefit from anti-EGFR therapy (*i.e.*, cetuximab or panitumumab) delivered in combination with chemotherapy in the first-line setting. The unplanned *post hoc* nature of the study implies that caution should be taken in the interpretation of these results.

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Data Availability

The data sharing of individual patient data from each participating trial will be subject to the policy and procedures of the institutions and groups who conducted the original study.

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Table 1: Trials included in the analysis

Study Name	Years of Accrual	No. of Patients in study	No. of Patients with known BRAF Status (% of Study Population)	No. of Patients with BRAFmt cancer (% of Patients with known BRAF status)	Arm Stratification	No. of Patients in Arm with known BRAF Status (% of Patients in Study with known BRAF Status)	No. of Patients with BRAFmt cancer (% of Patients in Arm with known BRAF Status)
CAIRO2 (NCT00208546)	Jun 2005-Dec 2006	755	514 (68.1)	45 (8.8)	CAPOX + Bevacizumab	258 (50.2)	17 (6.6)
					CAPOX + Bevacizumab + Cetuximab	256 (49.8)	28 (10.9)
CALGB-80405 (NCT00265850)	Jul 2007-Mar 2010	2326	851 (36.6)	120 (14.1)	Chemotherapy + Bevacizumab	320 (37.6)	54 (16.9)
					Chemotherapy + Bevacizumab + Cetuximab	211 (24.8)	29 (13.7)
					Chemotherapy + Cetuximab	320 (37.6)	37 (11.6)
COIN (NCT00182715)	Mar 2005-May 2008	2445	1931 (79.0)	171 (8.9)	Continuous CAPOX	427 (22.1)	35 (8.2)
					Continuous CAPOX + Cetuximab	439 (22.7)	31 (7.1)
					Continuous FOLFOX	201 (10.4)	22 (11.0)
					Continuous FOLFOX + Cetuximab	217 (11.2)	14 (6.5)
					Intermittent CAPOX	422 (21.9)	43 (10.2)
					Intermittent FOLFOX	225 (11.7)	26 (11.6)
COIN-B (NCT00640081)	Jul 2007-Mar 2010	226	151 (66.8)	24 (15.9)	Intermittent FOLFOX + Cetuximab maintenance	83 (55.0)	16 (19.3)
					Intermittent FOLFOX + Intermittent Cetuximab	68 (45.0)	8 (11.8)
CRYSTAL (NCT00154102)	Jul 2004-Nov 2005	1221	999 (81.8)	59 (5.9)	FOLFIRI	491 (49.2)	33 (6.7)
					FOLFIRI + Cetuximab	508 (50.9)	26 (5.1)
FIRE II (CIOX) (NCT00254137)	Sep 2004-Dec 2006	177	136 (76.8)	16 (11.8)	CAPIRI + Cetuximab	68 (50.0)	8 (11.8)
					CAPOX + Cetuximab	68 (50.0)	8 (11.8)
FIRE III (NCT00433927)	Jan 2007-Sep 2012	592	486 (82.1)	48 (9.9)	FOLFIRI + Bevacizumab	242 (49.8)	25 (10.3)

					FOLFIRI + Cetuximab	244 (50.2)	23 (9.4)
OPUS (NCT00125034)	Jul 2005-Mar 2006	344	315 (91.6)	11 (3.5)	FOLFOX	159 (50.5)	5 (3.1)
					FOLFOX + Cetuximab	156 (49.5)	6 (3.9)
PRIME (NCT00364013)	Aug 2006-Feb 2008	1183	619 (52.3)	53 (8.6)	FOLFOX4	309 (49.9)	29 (9.4)
					FOLFOX4 + Panitumumab	310 (50.1)	24 (7.7)
TRIBE (NCT00719797)	Jul 2008-May 2011	508	389 (76.6)	26 (6.7)	FOLFIRI + Bevacizumab	194 (49.9)	12 (6.2)
					FOLFOXIRI + Bevacizumab	195 (50.1)	14 (7.2)

Table 2: Demographic and disease characteristics

Patients' characteristics	BRAF/KRAS wild-type (n=3759)	KRAS mutated (n=2059)	$BRAF^{V600E}$ mutated (n=573)	Total (N=6391)	*P*
Age at enrollment					0.002[1]
No.	3758	2056	573	6387	
Mean (SD), y	60.9 (10.20)	61.5 (10.14)	62.2 (10.55)	61.2 (10.22)	
Median (range), y	62.0 (19.0, 87.0)	63.0 (22.0, 84.0)	64.0 (22.0, 83.0)	62.0 (19.0, 87.0)	
Age Category, No. (%)					0.02[2]
< 65 y	2224 (59.2)	1168 (56.8)	308 (53.8)	3700 (57.9)	
≥ 65 y	1534 (40.8)	888 (43.2)	265 (46.2)	2687 (42.1)	
Missing	1	3	0	4	
Sex, No. (%)					<.001[2]
Female	1282 (34.1)	823 (40.0)	283 (49.4)	2388 (37.4)	
Male	2477 (65.9)	1236 (60.0)	290 (50.6)	4003 (62.6)	
Performance Score, No. (%)					0.08[2]
0	2116 (56.4)	1150 (55.9)	294 (51.3)	3560 (55.7)	
1+	1639 (43.6)	909 (44.1)	279 (48.7)	2827 (44.3)	
Missing	4	0	0	4	
Primary Tumor Sidedness, No. (%)					<.001[2]
Left Colon	2681 (82.3)	1279 (66.6)	186 (38.5)	4146 (73.2)	
Right Colon	577 (17.7)	642 (33.4)	297 (61.5)	1516 (26.8)	
Missing	501	138	90	729	
Primary Tumor Resection, No. (%)					<0.001[2]
No	529 (23.3)	356 (28.2)	70 (20.0)	955 (24.6)	
Yes	1741 (76.7)	908 (71.8)	280 (80.0)	2929 (75.4)	
Missing	1489	795	223	2507	
Prior Chemotherapy, No. (%)					<.001[2]
No	2374 (77.6)	1653 (80.4)	421 (84.9)	4448 (79.2)	
Yes	687 (22.4)	404 (19.6)	75 (15.1)	1166 (20.8)	
Missing	698	2	77	777	
Prior Metastatic Surgery, No. (%)					<.001[2]
No	1791 (91.3)	1185 (93.8)	314 (96.3)	3290 (92.6)	
Yes	171 (8.7)	79 (6.3)	12 (3.7)	262 (7.4)	
Missing	1797	795	247	2839	
Metastatic Site: No. (%)					<.001[2]
Liver					
No Involvement	573 (22.0)	374 (22.4)	146 (31.9)	1093 (23.1)	
Liver Involvement Only	834 (32.0)	421 (25.3)	105 (22.9)	1360 (28.8)	
Liver and ≥ 1 non-Liver Involvement	1198 (46.0)	871 (52.3)	207 (45.2)	2276 (48.1)	
Missing	1154	393	115	1662	
Lung					<.001[2]
No Involvement	1675 (64.6)	930 (56.1)	337 (74.1)	2942 (62.5)	
Involvement	919 (35.4)	729 (43.9)	118 (25.9)	1766 (37.5)	
Missing	1165	400	118	1683	
Lymph Nodes					0.001[2]
No Involvement	1268 (58.8)	821 (59.4)	159 (47.2)	2248 (58.0)	
Involvement	889 (41.2)	560 (40.6)	178 (52.8)	1627 (42.0)	
Missing	1602	678	236	2516	
Peritoneum					<.001
No Involvement	1812 (90.3)	1041 (86.8)	251 (80.2)	3104 (88.2)	

Involvement	194 (9.7)	158 (13.2)	62 (19.8)	414 (11.8)	
Missing	1753	860	260	2873	
No. of Metastatic Sites, No. (%)					<.001[2]
1	948 (44.1)	633 (38.1)	174 (42.8)	1755 (41.6)	
2+	1204 (55.9)	1029 (61.9)	233 (57.2)	2466 (58.4)	
Missing	1607	397	166	2170	
Chemotherapy Backbone, No. (%)					<.001[2]
Oxaliplatin-based	2519 (67.0)	1499 (72.8)	421 (73.5)	4439 (69.5)	
Irinotecan-based	1240 (33.0)	560 (27.2)	152 (26.5)	1952 (30.5)	
Targeted Agents, No. (%)					0.23[2]
No	1291 (34.3)	750 (36.4)	193 (33.7)	2234 (35.0)	
Yes	2468 (65.7)	1309 (63.6)	380 (66.3)	4157 (65.0)	
Bevacizumab, No. (%)					<.001[2]
No	2859 (76.1)	1462 (71.0)	394 (68.8)	4715 (73.8)	
Yes	900 (23.9)	597 (29.0)	179 (31.2)	1676 (26.2)	
Cetuximab or panitumumab, No. (%)					0.02[2]
No	1970 (52.4)	1158 (56.2)	315 (55.0)	3443 (53.9)	
Yes	1789 (47.6)	901 (43.8)	258 (45.0)	2948 (46.1)	

[1] Two-sided Kruskal-Wallis test. SD: standard deviation

[2] Two-sided Chi-Square test..

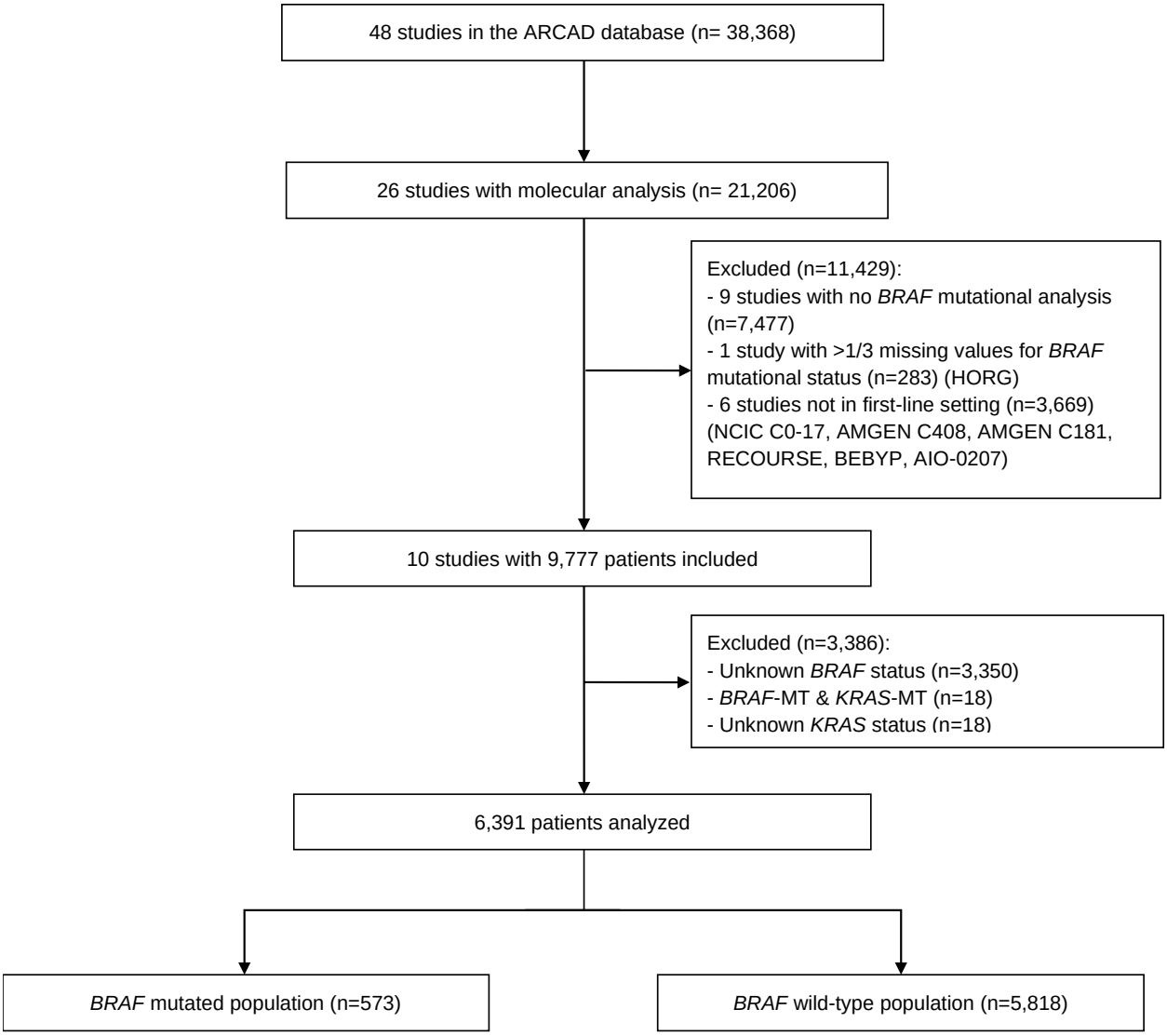
Figure legends

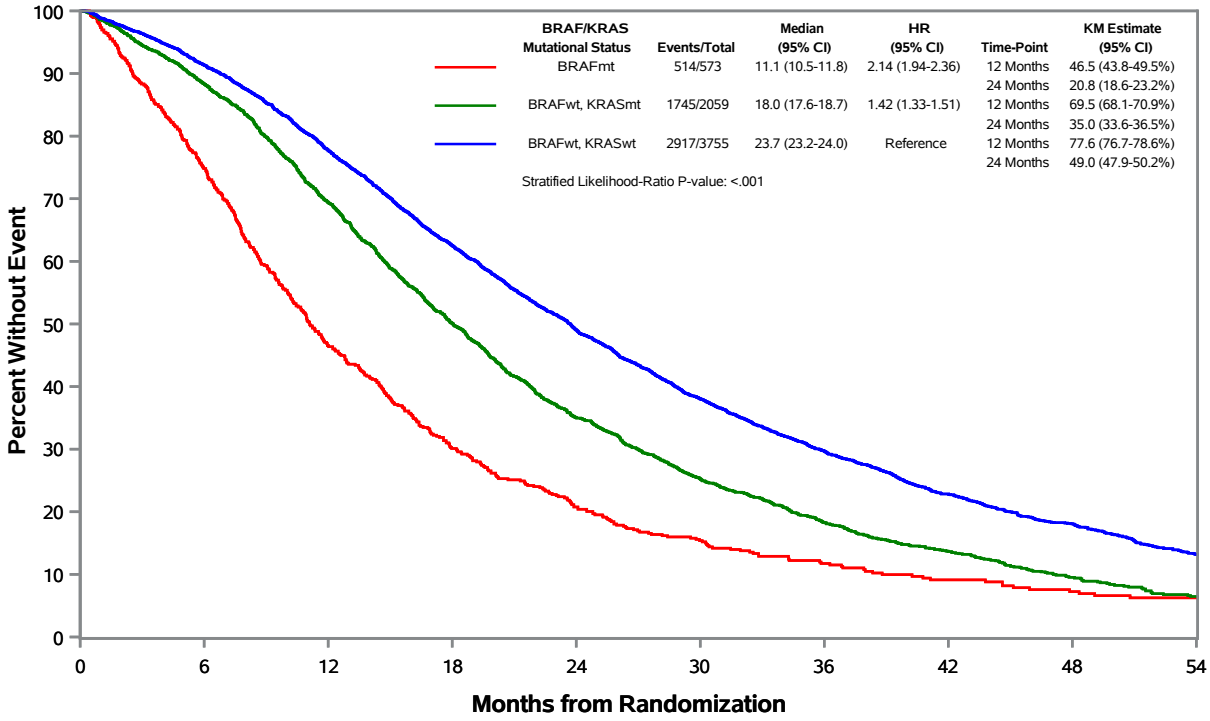
Figure 1: Flow Chart.

Figure 2: Kaplan-Meier curves for overall survival and progression-free survival according to the *BRAF*/*KRAS* status. BRAFmt = *BRAF*^{V600E}-mutated; BRAFwt = *BRAF* wild-type; KRASmt = *KRAS*-mutated; KRASwt = *KRAS* wild-type

Figure 3: Pooled analysis of COIN, CRYSTAL, PRIME and OPUS trials. Stratified likelihood-ratio test was used to calculate P-values (two-sided), and it was two-sided test. anti-EGFR: cetuximab or panitumumab; CT = chemotherapy. BRAFmt = *BRAF*^{V600E}-mutated; BRAFwt = *BRAF* wild-type.

Figure 1

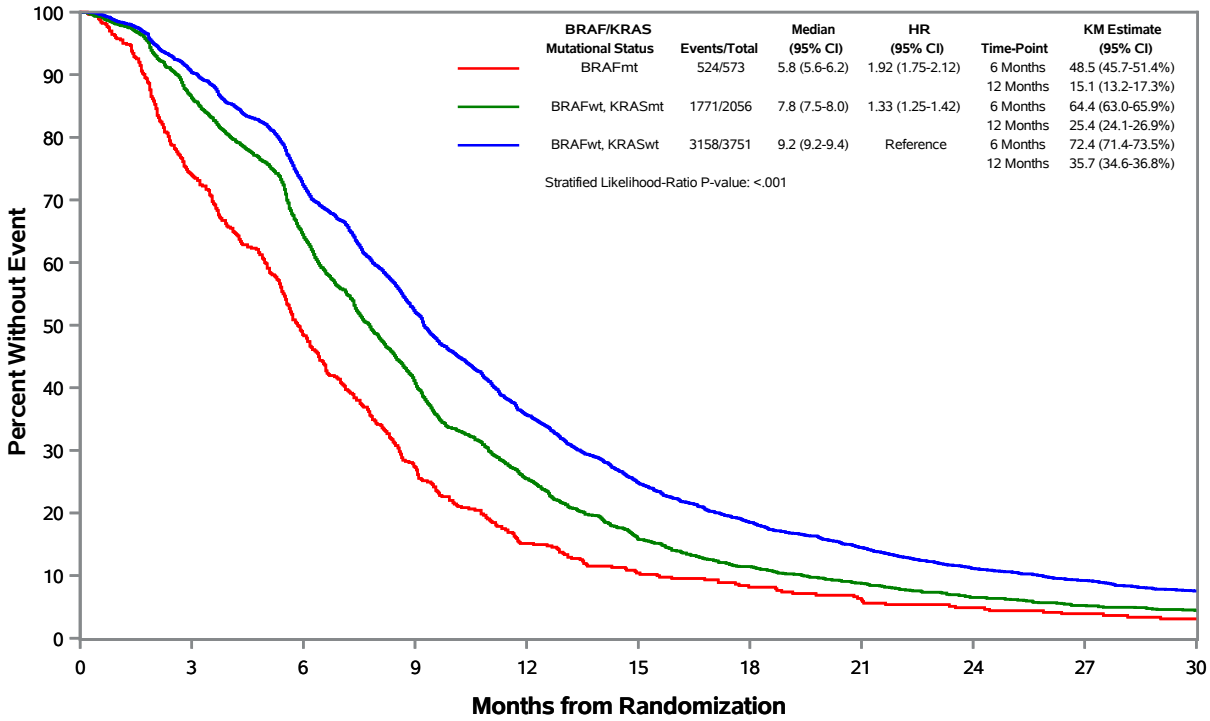




Patients-at-Risk

BRAFmt	573	426	267	169	113	79	51	35	26	18
BRAFwt, KRASmt	2059	1792	1393	984	641	412	244	152	81	47
BRAFwt, KRASwt	3755	3395	2859	2281	1739	1269	833	520	332	214

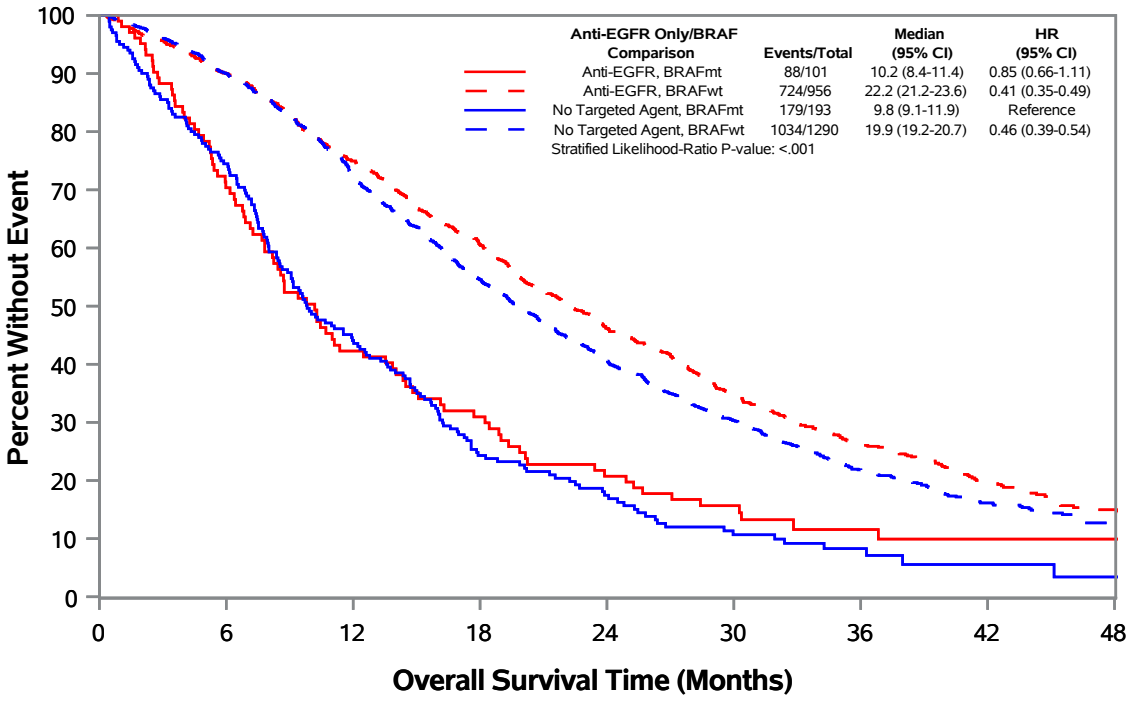
Adjusted for Gender and Performance Score;
Stratified by Combined Trial and Treatment;
KM-Kaplan Meier, HR-Hazard Ratio, CI-Confidence Interval;
BRAFmt-BRAF Mutated Type, BRAFwt-BRAF Wild Type, KRASmt-KRAS Mutated Type, KRASwt-KRAS Wild Type;



Patients-at-Risk

BRAFmt	573	415	264	141	71	46	34	24	19	15	11
BRAFwt, KRASmt	2056	1722	1215	737	429	263	186	137	97	76	61
BRAFwt, KRASwt	3751	3308	2568	1795	1141	772	565	427	317	255	196

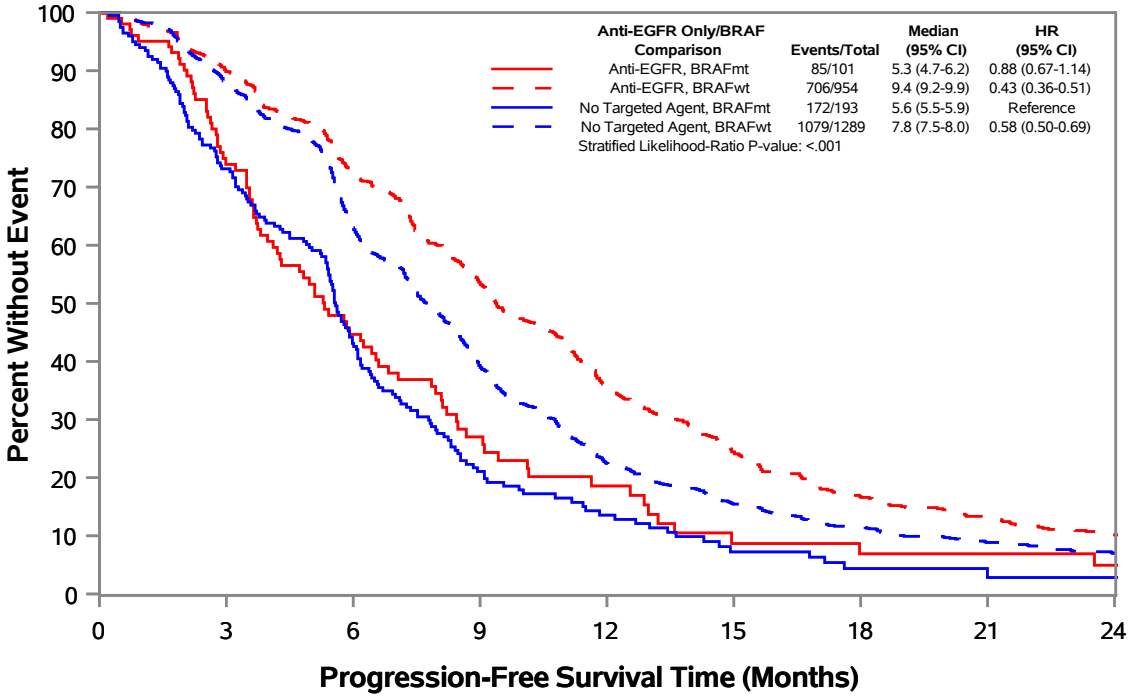
Adjusted for Gender and Performance Score;
Stratified by Combined Trial and Treatment;
KM-Kaplan Meier, HR-Hazard Ratio, CI-Confidence Interval;
BRAFmt-BRAF Mutated Type, BRAFwt-BRAF Wild Type, KRASmt-KRAS Mutated Type, KRASwt-KRAS Wild Type;



Patients-at-Risk

Anti-EGFR, BRAFmt	101	69	40	29	19	13	6	3	2
Anti-EGFR, BRAFwt	956	854	703	565	425	305	177	94	37
No Targeted Agent, BRAFmt	193	141	81	41	26	14	6	3	1
No Targeted Agent, BRAFwt	1290	1143	910	671	484	334	176	89	42

Adjusted for Gender, Performance Score, and Chemo Backbone;
Stratified by Arm Comparison;
HR-Hazard Ratio, CI-Confidence Interval, EGFR-Epidermal Growth Factor Receptor;
BRAFwt-BRAF Wild Type, BRAFmt-BRAF Mutated Type;



Patients-at-Risk

Anti-EGFR, BRAFmt	101	71	40	19	11	4	3	3	2
Anti-EGFR, BRAFwt	954	830	636	437	242	145	94	70	52
No Targeted Agent, BRAFmt	193	135	74	30	15	6	2	1	1
No Targeted Agent, BRAFwt	1289	1087	735	424	204	131	93	66	50

Adjusted for Gender, Performance Score, and Chemo Backbone;
Stratified by Arm Comparison;
HR-Hazard Ratio, CI-Confidence Interval, EGFR-Epidermal Growth Factor Receptor;
BRAFwt-BRAF Wild Type, BRAFmt-BRAF Mutated Type;