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Trajectories of body weight change and survival among mCRC patients treated with systemic therapy: Pooled analysis from ARCAD database

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Running head: Weight trajectory after mCRC diagnosis
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Abstract

Purpose: Higher body mass index is associated with a higher incidence of colorectal cancer, but also with improved survival in metastatic CRC (mCRC). Whether weight change after mCRC diagnosis is associated with survival remains largely unknown.

Patients and Methods: We analyzed individual patient data for previously untreated patients enrolled in five phase 3 randomized trials conducted between 1998 and 2006. Weight measurements were prospectively collected at baseline and up to 59.4 months after diagnosis. We used stratified multivariable Cox models to assess the prognostic associations of weight loss with overall and progression-free survival, adjusting for other factors. The primary endpoint was difference in overall survival between populations with weight loss and stable or increasing weight.

Results: Data were available for 3,504 patients. Median weight change at 3 months was -0.54% (IQR -3.9…+1.5%). We identified a linear trend of increasing risk of death associated with progressive weight loss. Unstratified median overall survival was 20.5, 18.0, 11.9 months (p<0.001) for stable weight or gain, <5% weight loss, and ≥5% weight loss, respectively. Weight loss was associated with a higher risk of death (<5% loss: aHR 1.18 [1.06-1.30], p<0.002; ≥5% loss: aHR 1.87 [1.67-2.1], p<0.001) as compared to stable or increasing weight at 3 months post baseline (reference), while adjusting for age, sex, performance score, liver and/or lung involvement, and number of metastatic sites.

Conclusion: Patients losing weight during systemic therapy for metastatic colorectal cancer have significantly shorter overall survival. Degree of weight loss is proportional to the observed increased risk of death and remains evident among underweight, normal weight and obese individuals. On-treatment weight change may be used as intermediate end-point.

Background

Prognostication of clinical course among patients with metastatic colorectal cancer (mCRC) remains challenging. Historically, most clinically useful mCRC prognostic markers are established at diagnosis (stage, resectability, molecular profile including RAS/RAF and MSI status) (NCCN 2021). Currently available dynamic markers of disease-course are either only fairly efficient (serial serum carcinoembryonic antigen (CEA) serum level), or lack widespread adoption (circulating tumor DNA) (Diehl, Schmidt et al. 2008, Loupakis, Sharma et al. 2021). The relationship between body weight and prognosis is complex, and appears to differ in cohorts with metastatic versus non-metastatic colorectal cancer (Poterucha, Burnette et al. 2012, Sinicrope, Foster et al. 2013, Renfro, Loupakis et al. 2016, Meyerhardt, Kroenke et al. 2017, Shahjehan, Merchea et al. 2018, Guercio, Zhang et al. 2020, Mello, Moura et al. 2020). Prior ARCAD work identified low body mass index (BMI) as a negative prognostic factor for overall survival among patients with mCRC and found no mortality risk increase among patients with BMI-defined obesity (Renfro, Loupakis et al. 2016, Renfro, Goldberg et al. 2017). In contrast, the ACCENT adjuvant treatment database-based research in patients with non-metastatic colorectal cancer suggested that both low and high BMI are associated with worse survival (Sinicrope, Foster et al. 2013).

While weight at diagnosis remains important, several smaller studies have established weight loss over time as a prognostic factor (Innominato, Giacchetti et al. 2013, Meyerhardt, Kroenke et al. 2017, Shahjehan, Merchea et al. 2018). In fact, models involving weight and skeletal muscle changes over time proved to be independently predictive of survival, even when eliminating the effects of traditional predictors (Martin, Birdsell et al. 2013, Kurk, Stellato et al. 2019).

The trajectory of weight change after diagnosis of mCRC, i.e. weight loss, stability or gain, may provide a practical, reproducible, and inexpensive dynamic prognostic factor, which would be easy to incorporate into clinical practice, perhaps even without the need for patients to visit a medical facility. Here we examined weight change gathered from individual patient data from randomized trials of systemic therapy for mCRC patients. We set out to describe weight trajectories after randomization and during systemic therapy and explore their association with overall survival. Additionally, we aimed to identify a weight loss threshold with clinical utility.

Methods

Description of the ARCAD Database and included studies

We analyzed individual patient data from 3504 patients with previously untreated mCRC enrolled in five phase III randomized trials (AVF2017g, AVF2192g, CRYSTAL, N9741, OPUS) conducted between 2000 and 2006. We selected these patients from the ARCAD foundation database (*the Aide et Recherche en Cancérologie Digestive*; www.fondationarcad.org). The ARCAD Foundation provided the database and is credited with its conception, development, and maintenance (Buyse, Sargent et al. 2012). This database integrates individual patient-level data from numerous phase 3 clinical trials (currently > 34,000 patients) and is intended to further explore potential prognostic markers and validate novel endpoints.

Inclusion criteria were: enrollment in one of the five phase III trials by a patient with previously untreated metastatic colorectal cancer (prior adjuvant therapy was allowed), who had at least two weight measurements recorded in the database after randomization.

We categorized patients into weight change categories by two methods and we report both analyses: (1) Per cent weight change at 3 months post baseline and (2) latent class modelling.

First, patients were categorized into three groups based on the per cent weight change at 3 months: stable or increasing weight (weight gain), weight loss up to 5% of baseline weight, and ≥5% weight loss. Second, the Latent Class Growth Modeling (LCGM) was used to identify distinct subgroups of individuals following different patterns of change in %weight-loss over time (not limited to the first 3 months). This model accounts for heterogeneity, and assumes that the association between time and the longitudinal outcome (in this case, %weight-change over time) are different for distinct subgroups. This allows us to model the association between time and the repeated measures of weight loss, as well as exploring subgroups within the data set. Cox models were used to assess the prognostic associations of weight change at 3 months with overall survival (OS) and progression-free survival (PFS), adjusting for baseline body mass index (BMI, kilogram/m^2), age, sex, World Health Organization performance score, number of metastatic sites (recorded as number of affected organs), presence versus absence of liver, lung and peritoneal metastases, chemotherapy backbone (5-fluorouracil vs. oxaliplatin vs. irinotecan), and targeted treatment type (antiangiogenic v anti-epidermal growth factor receptor). Sub-analyses included Cox models adjusted for additional clinical-pathological factors: primary tumor sidedness, baseline albumin, metastatic sites, and BRAF status. Resection status of primary tumor were not available.

Descriptive statistics for patient, disease, and treatment characteristics as well as mortality risk were computed, and rates of missing data reported. Missing baseline data were imputed and missing survival data were not.

Results

Five trials in the ARCAD database contained sufficient weight data at baseline and follow-up and were included in this analysis (Table 1, Appendix Table 1) yielding 3,504 evaluable patients

(Appendix Table 2, Appendix Table 3, Appendix Table 4). Of these 77% of subjects had ≥3

weight measurements beyond the initial weight (Appendix Figure 1, Appendix Figure 2).

Most patients lost weight at 3 months after baseline and randomization, and 375 (10.7%) patients

had no weight change (0% body weight change). The median weight change was -0.542%

(Interquartile range: -3.976%…+1.577%; largest weight loss -26.4%, and largest gain 26.7%;

Appendix Figure 3). On average, the entire cohort experienced a modest weight loss in the first 6

months, and some weight gain by 9 months among the surviving patients (Appendix Figure 2),

consistent with higher risk of earlier mortality among those with early weight loss.

Tumor BRAF status was available for 1,288 patients (36.7% out of total 3,504 patients). Per cent

weight change at 3 months did not differ among those with and without available BRAF status (-

1.406±5.161 versus -1.183±5.380%, p=0.736). Among those patients with available tumor

BRAF status 1,221 tumors were wild-type with weight change at 3 months post baseline -

1.402±5.146& versus -1.478±5.497% among 67 patients with mutated BRAF tumors (p=0.784).

Patients with peritoneal metastases (n=18) experienced a larger weight loss at 3 months post

baseline (-5.791±6.070%) as compared to those without peritoneal involvement (-1.584±5.165%;

p=0.002) among 336 patients with available data on peritoneal involvement.

Univariate analysis of overall and progression-free survival

We defined three clusters of weight change trajectories (gain, stable, loss) based on a non-

parametric machine learning model (Figure 1, Appendix Table 5). Observed median overall

survival was longest among 538 patients with "weight gain" trajectory (median OS [95% CI]:

24.41 [22.9-26.18] months) followed by those with "stable weight" trajectory (median OS [95%

CI]: 19.22 [18.46-19.98] months). Patients with "weight loss" trajectory experienced the shortest

overall survival (median OS [95% CI]: 14.49 [13.54-15.38] months; p< 0.0001, Figure 2).

Similar observations were made when the weight change was classified as stable or increasing weight, <5% weight loss, and ≥5% weight loss (respective median OS [95% CI] is 20.50 [19.38-21.39] months, 18.04 [17.18-19.38] months, and 11.86 [10.78-13.01] months; p < 0.0001, Appendix Figure 4). Progression-free survival analysis yielded corresponding findings when analyzed by latent classes (respective median PFS [95% CI] is 9.4 [9.1-10.51] months, 8.05 [7.62-8.34] months, and 7.33 [6.9-7.59] months for weight gain, weight stable, and weight loss cluster; p < 0.0001; Appendix Figure 5). Similar results for PFS were obtained when analyzed by weight gain/stable weight, <5% weight loss, and ≥5% weight loss (respective median PFS [95% CI] is 7.03 [6.67-7.49] months, 6.97 [6.44-7.52] months, and 5.29 [4.86-5.82] months; p < 0.0001).

Multivariate models of overall and progression-free survival (PFS)

Proportional negative prognostic impact of weight loss category was observed in the primary overall survival model using latent classification (Table 2), as well as the model using percent-based weight loss (Table 3). A corresponding effect was seen for PFS (Appendix Table 6). We performed exploratory models including patients with available data on primary tumor sidedness (n=1106 in total; Appendix Table 7), baseline albumin level and site of metastases (liver and/or lung involvement, n=972 patients in total, Appendix Table 8), and peritoneal metastases (n=291 patients in total, Appendix Table 9).

Optimal clinical cutoff for weight loss at 3 months and risk of death or progression

We used maximally selected log rank statistics to estimate an optimal cutoff value for weight loss in predicting death risk (optimal cut off = -6.435% weight change at 3 months, p=2.2x10^{-16}; Appendix Figure 6). An identical estimate value predicting risk of disease progression was obtained (optimal cut off = -6.435% weight change at 3 months, p=3.9x10^{-6}; Appendix Figure 7).

To account for analyses conducted by prior research groups and as a practical matter we chose a weight loss cutoff value of 5%. Interaction tests between weight cutoff categories (gain or stability, loss < 5%, loss ≥5%) and BMI were not significant for both overall (p=0.069) and PFS (p=0.104).

We plotted weight change against the log of relative risk of death (Figure 3). A consistent inflection point was seen at no weight change (0% weight change) in all analyses, including sensitivity analyses of weight change and PFS (data not shown). Therefore, we developed reported multivariate survival models utilizing clinically meaningful weight loss categories defined above and referenced previously in other settings (Fearon, Strasser et al. 2011).

Weight change at 3 months and disease response, stability, and progression

Patients with progressive disease experienced significant weight loss (-2.122±6.366%, [IQR: -5.672, 1.028]), compared to those who did not manifest progressive disease (-0.955±5.069%, [IQR: -3.537, 1.724]; p=0.0068]). Similarly, non-responders experienced greater weight loss at 3 months (-1.395 ± 5.497%, [IQR: -4.092, 1.437]) as compared to responders (-0.834 ± 4.997%, [IQR: -3.404, 1.896] for partial or complete responders; p = 0.0088). Multivariate models predicting progressive and responsive disease are available in the Appendix material online only (Appendix Table 10, Appendix Table 11).

Discussion

We have identified that weight loss among patients undergoing systemic therapy for mCRC is associated with shorter survival. Prior research has led to inconsistent findings regarding the effect of weight loss while receiving first-line chemotherapy for mCRC (Köhne, Cunningham et al. 2002, Poterucha, Burnette et al. 2012, Sanchez-Lara, Ugalde-Morales et al. 2013, Shahjehan,

Merchea et al. 2018, Kurk, Stellato et al. 2019, Guercio, Zhang et al. 2020). The effect size is significant, proportional to the degree of weight loss, and evident at 3 months after baseline (pre-randomization) measurement. Results remain robust after multiple adjustments, and comparable conclusions are drawn from complementary analyses of progression-free survival. While we examined weight loss after the diagnosis of mCRC in the present study, most prior studies classically focused on weight loss that predated the diagnosis. In these studies patients were commonly subdivided into cohorts with no, $\geq 5\%$, or $\geq 10\%$ unintentional body weight loss in 3 or 6 months preceding cancer diagnosis (Köhne, Cunningham et al. 2002, Innominato, Giacchetti et al. 2013, Sanchez-Lara, Ugalde-Morales et al. 2013, Meyerhardt, Kroenke et al. 2017, Shahjehan, Merchea et al. 2018, Guercio, Zhang et al. 2020).

We have used two different methods to define three groups based on weight trajectories after randomization. Latent-class categorization uses a machine-learning algorithm considering overall weight trajectory over the remaining life of patients. We obtained consistent results with percent-based weight change categorization at 3 months after randomization. Furthermore, we have validated 5% weight change as significant in concordance with the prior literature (Fearon, Strasser et al. 2011, Guercio, Zhang et al. 2020). We propose that evaluation of trajectory of weight gain or loss in mCRC patients is both simple and clinically useful. It may be measured economically, repeatedly, noninvasively, and may be automatically entered into electronic health records over networks. Thus, it may be considered as an important assessment tool in combination with serial serum carcinoembryonic antigen levels, circulating tumor DNA levels (Diehl, Schmidt et al. 2008, Loupakis, Sharma et al. 2021), and imaging assessments of response (NCCN 2021). Furthermore, because weight change trajectory does not require in-person clinical contact, it may prove more feasible to implement and maintain during pandemic-related

healthcare aberrations, as seen during contemporary COVID-19 pandemic (Chen, Haynes et al. 2021).

Weight change trajectories have major prognostic values in healthy populations (Zhang, Bauer et al. 2021). Weight loss is common among colorectal cancer patients (Fearon, Strasser et al. 2011, Poterucha, Burnette et al. 2012, Mello, Moura et al. 2020). Interestingly, the trajectory of skeletal muscle loss during palliative systemic therapy appears to be more accurate metric than crude weight loss (Martin, Birdsell et al. 2013, Kurk, Stellato et al. 2019), including assessments made during the 90 days prior to death (Prado, Sawyer et al. 2013). Weight changes are easy to obtain as compared to changes in skeletal muscle volume detected by serial computed tomography. Other well-supported intermediate correlates of survival, such as time to progression, duration of disease control, are useful but imperfect endpoints (Grothey and Sargent 2005). Both weight and muscle loss among mCRC patients may appear before radiologic evidence of cancer progression (Poterucha, Burnette et al. 2012),although others have not found weight not muscle loss over 4 month observation (Antoun, Bayar et al. 2019).

Unsurprisingly, BMI at diagnosis is a strong predictor of overall survival among patients with mCRC (Renfro, Loupakis et al. 2016). Subnormal BMI (defined as either ≤20 or ≤15) was associated with increased early mortality (at 30, 60 and 90 days after randomization) as well as a decrease in overall survival (Renfro, Goldberg et al. 2017). Additional plausible mechanisms driving weight loss among mCRC are catabolic activation (Lieffers, Mourtzakis et al. 2009, Prado, Sawyer et al. 2013), deficient nutrition, and poor symptom control due to subclinical partial bowel obstruction (Sanchez-Lara, Ugalde-Morales et al. 2013, Moran and Tzivanakis 2018) and therapy-induced side-effect (Poterucha, Burnette et al. 2012), all parameters that are oftentimes clinically inseparable (Franko, Graff et al. 2018). Here we have shown significantly

greater weight loss among patients with peritoneal metastases, who frequently suffer from intestinal obstruction (Sadeghi, Arvieux et al. 2000, Blair, Chu et al. 2001), thus offering insights in additional mechanisms contributing to cancer cachexia (Moran and Tzivanakis 2018, Antoun, Bayar et al. 2019). Prior studies suggest that there is a potential therapeutic window for treating cancer cachexia exist in period >90 days prior to death (Lieffers, Mourtzakis et al. 2009, Prado, Sawyer et al. 2013), that suggests patients may benefit from interventions spurred by tracking the weight trajectory and intervening when weight loss is manifested. The present report furthers the available objective measures for earlier identification of cachexia, which often is not apparent on the initial clinical exam (van der Werf, van Bokhorst et al. 2018).

Given the limitation of the dataset we were not able to examine potential reasons for weight loss. Interestingly, weight loss was associated not only with shorter overall survival, but also with shorter progression-free survival, suggesting a link between weight loss, cachexia, and cancer progression (NCCN 2021). Early-onset of weight loss has been associated with shorter time-to-progression and shorter overall survival among stage I-III colorectal cancer (Sinicrope, Foster et al. 2013, Meyerhardt, Kroenke et al. 2017) and to some degree among mCRC patients as well (Innominato, Giacchetti et al. 2013, Prado, Sawyer et al. 2013, Franko, Graff et al. 2018). Concepts of pre-diagnostic weight loss and cancer cachexia were outlined previously in a paper generated by consensus of an international investigator team (Fearon, Strasser et al. 2011). While weight is reproducibly and repeatedly measured, to our knowledge no prior studies of sufficient size and follow-up duration (Poterucha, Burnette et al. 2012, Shahjehan, Merchea et al. 2018, Kurk, Stellato et al. 2019) quantified weight change endpoints among mCRC patients with ongoing first-line systemic palliative therapy.

Limitations of this study include its retrospective character despite recognized robustness of prospectively collected individual patient data derived from the ARCAD project. We identified only 5 studies with 3,504 evaluable patients. We have no data on CEA trends, and limited data on tumor BRAF status. Furthermore, primary tumor status (resected or *in situ* at time of registration to study) was not known.

In summary, we identified that weight loss among mCRC patient strongly predicts progression-free and overall survival, and is associated with progressive disease. Weight loss over 5% at any time during mCRC management is associated with elevated risk of death, and we advise clinicians to search for correctable causes of weight loss when patients manifest it during first-line chemotherapy for mCRC.

Tables & Figures
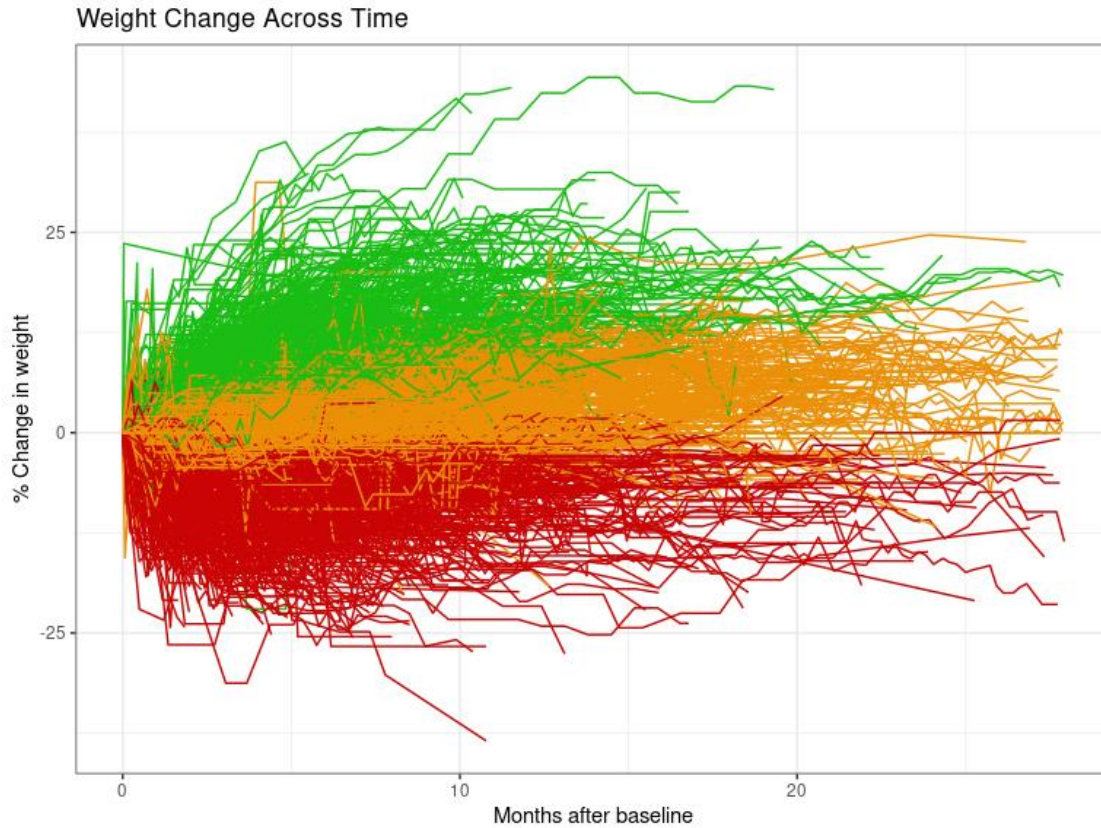
Figure 1. Three-group latent group classification plot. Weight loss group in blue, stable weight in green and weigh gain group in red. The thick red lines provide the smoothed means for the patients in each latent group.

Overall Survival by Latency Class
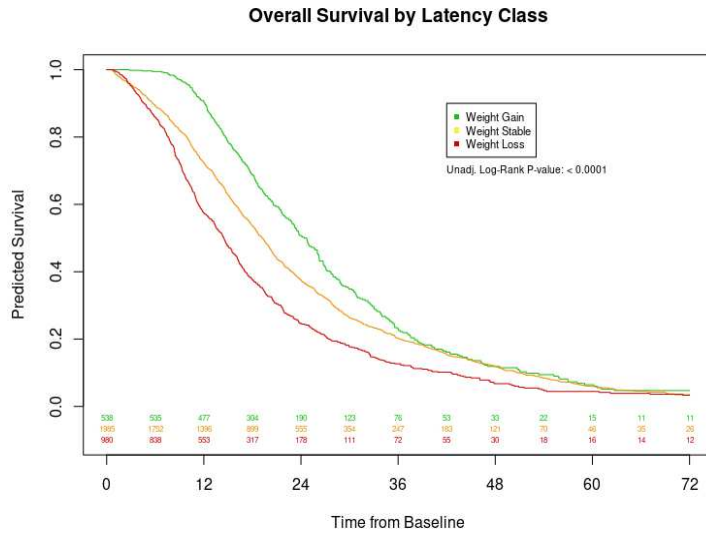
Latency Class	Events/N	Median (95% CI)	Log-Rank P-Value
Weight Gain	383/538	24.41 (22.9-26.18)	< 0.0001
Weight Stable	1544/1985	19.22 (18.46-19.98)	--
Weight Loss	821/980	14.49 (13.54-15.38)	--

Figure 2. Kaplan-Meier overall survival estimator among three latent groups.
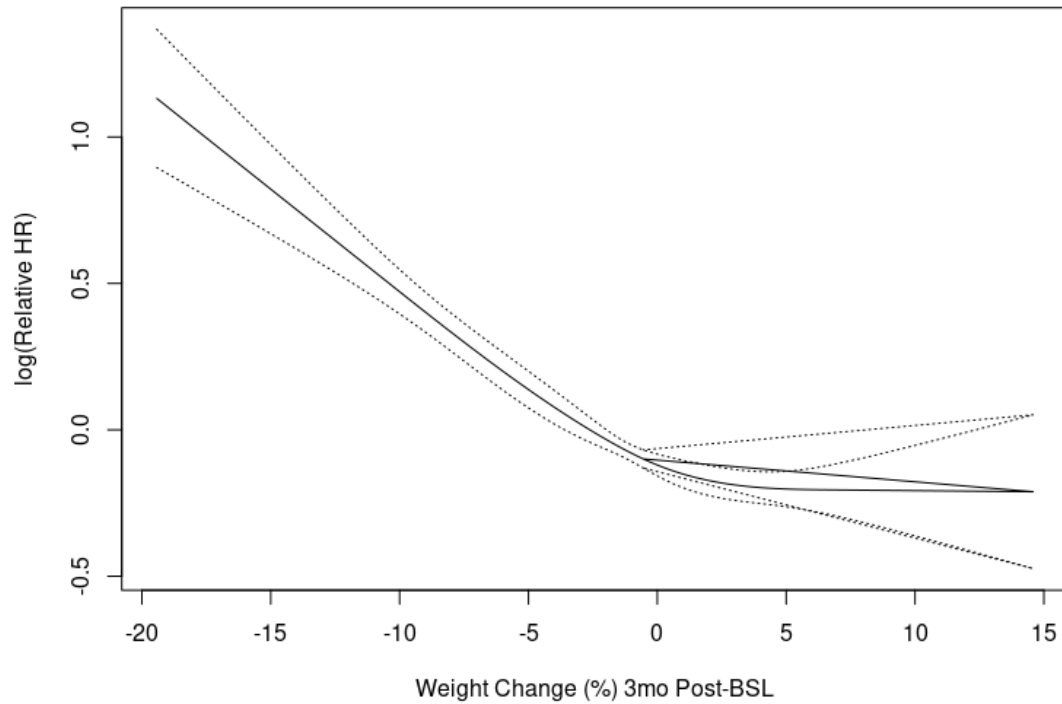
Figure 3. Relative risk of death and observed weight change 3 months after baseline. Inflection point exists at stable weight (0% weight change) with linear risk increase with weight loss (identified here with negative per cent weight change). Weight gain within first 3 months does not appear to have any prognostic impact. Dotted lines indicate 95% confidence bands for risk of outcomes as a function of weight change 3 months after baseline. HR, hazard ratio. Post-BSL, post-baseline (randomization/registration).

Study	Years of Accrual	N Patients Enrolled	N Patients Eligible for Analysis (% of Enrolled Patients)	Study Arm	N Eligible Patients in Arm (% of Total Eligible Patients)
AVF2107g	2000-2002	923	866 (93.82%)	5FULV + Bevacizumab	107 (12.36%)
				IFL + Bevacizumab	380 (43.88%)
				IFL + Placebo	379 (43.76%)
AVF2192g	2000-2002	209	194 (92.82%)	5FULV + Bevacizumab	96 (49.48%)
				5FULV + Placebo	98 (50.52%)
N9741	1998-2004	1416	933 (65.89%)	FOLFOX	371 (39.76%)
				IFL	213 (22.83%)
				IROX	349 (37.41%)
CRYSTAL	2004-2005	1221	1175 (96.23%)	FOLFIRI	587 (49.96%)
				FOLFIRI + Cetuximab	588 (50.04%)
OPUS	2005-2006	344	336 (97.67%)	FOLFOX	167 (49.70%)
				FOLFOX + Cetuximab	169 (50.30%)
Total:		**4113**	**3504** (85.19%)		

Table 1. Reported first-line randomized trials of systemic therapy for mCRC included in this report. N –

number of cases from the original study included in this report;

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Latency Class					**<0.0001***
Weight Gain (reference)	154/515	ref	ref	ref	
Weight Stable	437/1900	0.359	1.43	(1.27-1.61)	<0.0001**
Weight Loss	159/938	0.737	2.09	(1.83-2.38)	<0.0001**
Baseline BMI Category					**<0.0001***
Underweight (<18.5)	12/100	ref	ref	ref	
Normal (18.5 to <25)	278/1386	-0.186	0.83	(0.67-1.03)	0.0941**
Overweight (25 to <30)	293/1203	-0.352	0.7	(0.56-0.88)	0.0018**
Obese (30 or Greater)	167/664	-0.392	0.68	(0.54-0.85)	8e-04**
Age Category					**0.2313***
< 65 years (reference)	474/2049	ref	ref	ref	
≥ 65 years	276/1304	-0.05	0.95	(0.88-1.03)	0.232**
Performance Score					**<0.0001***
0 (reference)	482/1756	ref	ref	ref	
1+	268/1597	0.529	1.7	(1.57-1.84)	<0.0001**
Gender					**0.4927***
Female (reference)	304/1369	ref	ref	ref	
Male	446/1984	-0.028	0.97	(0.9-1.05)	0.4924**
Chemotherapy Type					**0.0124***
5FU (reference)	103/301	ref	ref	ref	
OX Based	96/941	-0.219	0.8	(0.67-0.97)	0.0196**
IRI Based	551/2111	-0.103	0.9	(0.76-1.07)	0.2411**
Biologics Type					**<0.0001***
None (reference)	350/2015	ref	ref	ref	
Cetuximab	107/755	-0.214	0.81	(0.73-0.89)	<0.0001**
Bevacizumab	293/583	-0.276	0.76	(0.65-0.88)	2e-04**

Table 2. Multivariate prediction model for overall survival using latent class-based weight change over study duration. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio. *Type-III p-value. **Covariate-level p-value. C-value = 0.6512.

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Weight change at 3 months from Baseline					**<0.0001***
Weight Gain/Stable (reference)	1005/1347	ref	ref	ref	
weight loss < 5%	659/929	0.163	1.18	(1.06-1.3)	0.0017**
weight loss ≥ 5%	473/563	0.628	1.87	(1.67-2.1)	<0.0001**
Baseline BMI Category					**0.0067***
Underweight (<18.5) (reference)	72/84	ref	ref	ref	
Normal (18.5 to <25)	897/1159	-0.166	0.85	(0.67-1.08)	0.1796**
Overweight (25 to <30)	749/1021	-0.297	0.74	(0.58-0.95)	0.0177**
Obese (30 or Greater)	419/575	-0.306	0.74	(0.57-0.95)	0.0189**
Age Category					**0.2321***
< 65 years (reference)	1313/1761	ref	ref	ref	
≥ 65 years	824/1078	-0.055	0.95	(0.87-1.04)	0.233**
Performance Score					**<0.0001***
0 (reference)	1076/1534	ref	ref	ref	
1+	1061/1305	0.489	1.63	(1.5-1.78)	<0.0001**
Gender					**0.5739***
Female (reference)	866/1143	ref	ref	ref	
Male	1271/1696	-0.025	0.98	(0.89-1.06)	0.5736**
Chemotherapy Type					**0.0096***
5FU (reference)	159/255	ref	ref	ref	
OX Based	688/778	-0.264	0.77	(0.62-0.94)	0.0124**
IRI Based	1290/1806	-0.134	0.87	(0.72-1.06)	0.1704**
Biologics Type					**<0.0001***
None (reference)	1339/1662	ref	ref	ref	
Cetuximab	557/655	-0.214	0.81	(0.73-0.9)	<0.0001**
Bevacizumab	241/522	-0.236	0.79	(0.67-0.93)	0.0047**

Table 3. Multivariate prediction model for overall survival using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio. *Type-III p-value. **Covariate-level p-value. C-value = 0.6316. Optimism-corrected C value = 0.6277.

Supplemental Tables & Figures

Study Name	Years of Accrual	N Patients Enrolled	N Patients Elligible for Analysis (% of Enrolled Patients)	Study Arm	N Elligible Patients in Arm (% of Total Elligible Patients)
AVF2107g	Sep 2000-May 2002	923	866 (93.82%)	5FULV + Bevacizumab	107 (12.36%)
				IFL + Bevacizumab	380 (43.88%)
				IFL + Placebo	379 (43.76%)
AVF2192g	Aug 2000-Jul 2002	209	194 (92.82%)	5FULV + Bevacizumab	96 (49.48%)
				5FULV + Placebo	98 (50.52%)
N9741	Oct 1998-Oct 2004	1416	933 (65.89%)	FOLFOX	371 (39.76%)
				IFL	213 (22.83%)
				IROX	349 (37.41%)
CRYSTAL	Jul 2004-Nov 2005	1221	1175 (96.23%)	FOLFIRI	587 (49.96%)
				FOLFIRI + Cetuximab	588 (50.04%)
OPUS	Jul 2005-Mar 2006	344	336 (97.67%)	FOLFOX	167 (49.70%)
				FOLFOX + Cetuximab	169 (50.30%)
Total:		4113	3504 (85.19%)		

Appendix Table 1. Trial summary, enrollment, and eligibility for this study.

	Study Name						
	AVF2107g (N=866)	AVF2192g (N=194)	N9741 (N=933)	CRYSTAL (N=1175)	OPUS (N=336)	Total (N=3504)	P-value
Cutoff: Weight Loss 3 Month/s from Baseline							<.0001[1]
Weight Gain/Stable	315 (41.2%)	63 (39.4%)	365 (50.3%)	525 (51.6%)	143 (49.1%)	1411 (47.7%)	
0%-5%	292 (38.2%)	63 (39.4%)	234 (32.3%)	291 (28.6%)	84 (28.9%)	964 (32.6%)	
>=5%	157 (20.5%)	34 (21.3%)	126 (17.4%)	202 (19.8%)	64 (22.0%)	583 (19.7%)	
Missing	102	34	208	157	45	546	
Age Category							<.0001[1]
Younger than 65	576 (66.5%)	37 (19.1%)	594 (63.7%)	736 (62.7%)	206 (61.3%)	2149 (61.4%)	
65 or Older	290 (33.5%)	157 (80.9%)	338 (36.3%)	438 (37.3%)	130 (38.7%)	1353 (38.6%)	
Missing	0	0	1	1	0	2	
Gender							0.0608[1]
Female	346 (40.0%)	90 (46.4%)	371 (39.8%)	463 (39.4%)	157 (46.7%)	1427 (40.7%)	
Male	520 (60.0%)	104 (53.6%)	562 (60.2%)	712 (60.6%)	179 (53.3%)	2077 (59.3%)	
Performance Score							<.0001[1]
0	498 (57.5%)	57 (29.4%)	421 (53.6%)	641 (54.6%)	141 (42.0%)	1758 (52.4%)	
1+	368 (42.5%)	137 (70.6%)	364 (46.4%)	534 (45.4%)	195 (58.0%)	1598 (47.6%)	
Missing	0	0	148	0	0	148	
Baseline Weight (kg)							<.0001[2]
N (Missing)	866 (0)	194 (0)	933 (0)	1175 (0)	336 (0)	3504 (0)	
Mean (SD)	80.4 (19.92)	73.4 (15.85)	79.0 (18.37)	70.9 (14.89)	70.9 (14.77)	75.5 (17.76)	
Median (IQR)	78.0 (67.0, 91.8)	72.9 (61.5, 83.0)	77.1 (66.0, 88.6)	70.0 (60.0, 80.0)	68.6 (61.0, 80.0)	74.0 (63.0, 85.0)	
Range	36.0, 195.0	38.6, 151.0	39.5, 181.4	38.4, 130.5	39.0, 121.0	36.0, 195.0	

Baseline Height (m)							<.0001[2]
N (Missing)	866 (0)	194 (0)	933 (0)	1175 (0)	336 (0)	3504 (0)	
Mean (SD)	1.7 (0.10)	1.7 (0.11)	1.7 (0.10)	1.7 (0.09)	1.7 (0.09)	1.7 (0.10)	
Median (IQR)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.8)	
Range	1.4, 2.0	1.4, 2.0	1.3, 2.0	1.3, 2.0	1.4, 2.0	1.3, 2.0	
Baseline BMI							<.0001[2]
N (Missing)	866 (0)	194 (0)	933 (0)	1175 (0)	336 (0)	3504 (0)	
Mean (SD)	27.4 (5.99)	25.8 (4.95)	27.2 (5.56)	25.2 (4.50)	25.3 (4.55)	26.3 (5.32)	
Median (IQR)	26.5 (23.5, 30.4)	25.1 (22.5, 27.7)	26.3 (23.5, 29.9)	24.8 (22.2, 27.5)	24.8 (22.0, 27.8)	25.6 (22.8, 29.0)	
Range	13.2, 59.7	16.7, 47.8	15.4, 60.2	14.8, 45.9	16.0, 44.6	13.2, 60.2	
Baseline BMI Category							<.0001[1]
Underweight (<18.5)	20 (2.3%)	7 (3.6%)	14 (1.5%)	50 (4.3%)	11 (3.3%)	102 (2.9%)	
Normal (18.5 to <25)	297 (34.3%)	87 (44.8%)	339 (36.3%)	559 (47.6%)	163 (48.5%)	1445 (41.2%)	
Overweight (25 to <30)	316 (36.5%)	72 (37.1%)	349 (37.4%)	406 (34.6%)	111 (33.0%)	1254 (35.8%)	
Obese (30 or Greater)	233 (26.9%)	28 (14.4%)	231 (24.8%)	160 (13.6%)	51 (15.2%)	703 (20.1%)	
Baseline BMI Category							<.0001[1]
<25	317 (36.6%)	94 (48.5%)	353 (37.8%)	609 (51.8%)	174 (51.8%)	1547 (44.1%)	
>=25	549 (63.4%)	100 (51.5%)	580 (62.2%)	566 (48.2%)	162 (48.2%)	1957 (55.9%)	
Albumin Type 1 (g/L)							<.0001[2]
N (Missing)	824 (42)	190 (4)			96 (240)	1110 (2394)	
Mean (SD)	37.5 (5.20)	36.6 (4.62)			41.1 (5.35)	37.7 (5.23)	
Median (IQR)	38.0 (35.0, 41.0)	37.0 (34.0, 40.0)			42.0 (37.7, 45.0)	38.0 (35.0, 41.0)	
Range	19.0, 51.0	24.0, 48.0			28.0, 51.9	19.0, 51.9	
Tumor Sidedness							
Left Colon	0 (%)	0 (%)	0 (%)	859 (74.3%)	266 (79.6%)	1125 (75.5%)	
Right Colon	0 (%)	0 (%)	0 (%)	297 (25.7%)	68 (20.4%)	365 (24.5%)	

Missing	866	194	933	19	2	2014	
Metastatic Site: Liver							
No Involvement	184 (21.3%)	35 (18.0%)	166 (17.8%)	0 (%)	42 (12.5%)	427 (18.3%)	
Involvement	257 (29.7%)	58 (29.9%)	374 (40.1%)	0 (%)	129 (38.4%)	818 (35.1%)	
Involv. and >=1 Other Involv.	424 (49.0%)	101 (52.1%)	393 (42.1%)	0 (%)	165 (49.1%)	1083 (46.5%)	
Missing	1	0	0	1175	0	1176	
Metastatic Site: Lung							
No Involvement	455 (52.6%)	100 (51.5%)	651 (69.8%)	0 (%)	209 (62.2%)	1415 (60.8%)	
Involvement	48 (5.5%)	5 (2.6%)	48 (5.1%)	0 (%)	8 (2.4%)	109 (4.7%)	
Involv. and >=1 Other Involv.	362 (41.8%)	89 (45.9%)	234 (25.1%)	0 (%)	119 (35.4%)	804 (34.5%)	
Missing	1	0	0	1175	0	1176	
Metastatic Site: Peritoneal							
No Involvement	0 (%)	0 (%)	0 (%)	0 (%)	318 (94.6%)	318 (94.6%)	
Involvement	0 (%)	0 (%)	0 (%)	0 (%)	1 (0.3%)	1 (0.3%)	
Involv. and >=1 Other Involv.	0 (%)	0 (%)	0 (%)	0 (%)	17 (5.1%)	17 (5.1%)	
Missing	866	194	933	1175	0	3168	
N Metastatic Sites							
0-1	335 (38.7%)	68 (35.1%)	482 (51.7%)	0 (%)	152 (45.4%)	1037 (44.5%)	
2+	531 (61.3%)	126 (64.9%)	451 (48.3%)	0 (%)	183 (54.6%)	1291 (55.5%)	
Missing	0	0	0	1175	1	1176	
Chemotherapy Type							<.0001[1]
5FU Based	107 (12.4%)	194 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	301 (8.6%)	
OX Based	0 (0.0%)	0 (0.0%)	720 (77.2%)	0 (0.0%)	336 (100.0%)	1056 (30.1%)	
IRI Based	759 (87.6%)	0 (0.0%)	213 (22.8%)	1175 (100.0%)	0 (0.0%)	2147 (61.3%)	
BRAF Status							
WT	0 (%)	0 (%)	0 (%)	921 (94.2%)	300 (96.8%)	1221 (94.8%)	

MT	0 (%)	0 (%)	0 (%)	57 (5.8%)	10 (3.2%)	67 (5.2%)	
Missing	866	194	933	197	26	2216	
Regimen Includes Any Target Agents?							<.0001[1]
Regimen Includes Only non-Target Agents	379 (43.8%)	98 (50.5%)	933 (100.0%)	587 (50.0%)	167 (49.7%)	2164 (61.8%)	
Regimen Includes at Least One Targeted Agent	487 (56.2%)	96 (49.5%)	0 (0.0%)	588 (50.0%)	169 (50.3%)	1340 (38.2%)	
Biologics Type							<.0001[1]
None	379 (43.8%)	98 (50.5%)	933 (100.0%)	587 (50.0%)	167 (49.7%)	2164 (61.8%)	
Cetuximab	0 (0.0%)	0 (0.0%)	0 (0.0%)	588 (50.0%)	169 (50.3%)	757 (21.6%)	
Bevacizumab	487 (56.2%)	96 (49.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	583 (16.6%)	
Weight (kg) Measurement: 1Mo							<.0001[2]
N (Missing)	761 (105)	189 (5)	679 (254)	1164 (11)	336 (0)	3129 (375)	
Mean (SD)	80.7 (19.76)	73.0 (15.71)	77.9 (18.03)	69.7 (15.01)	69.9 (14.74)	74.4 (17.60)	
Median (IQR)	78.4 (67.0, 91.8)	72.5 (61.5, 81.8)	75.9 (65.9, 87.3)	69.5 (59.0, 79.0)	67.0 (59.0, 79.5)	72.5 (62.0, 84.0)	
Range	40.9, 195.0	38.6, 151.0	40.1, 182.8	36.9, 130.2	39.0, 120.0	36.9, 195.0	
Percentage Weight Change 1 Month/s from Baseline							<.0001[2]
N (Missing)	761 (105)	189 (5)	679 (254)	1164 (11)	336 (0)	3129 (375)	
Mean (SD)	-0.1 (0.86)	-0.1 (1.00)	-1.1 (3.11)	-1.6 (3.36)	-1.4 (3.15)	-1.0 (2.83)	
Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	-0.6 (-2.4, 0.5)	-0.6 (-3.1, 0.0)	0.0 (-2.8, 0.0)	0.0 (-1.7, 0.0)	
Range	-16.1, 0.0	-12.7, 0.0	-22.0, 17.9	-17.8, 16.1	-15.8, 6.4	-22.0, 17.9	
CTCAE Grade: Weight Loss 1 Month/s from Baseline							<.0001[1]
Weight Gain	0 (0.0%)	0 (0.0%)	201 (29.6%)	171 (14.7%)	48 (14.3%)	420 (13.4%)	
0	756 (99.3%)	187 (98.9%)	419 (61.7%)	844 (72.5%)	253 (75.3%)	2459 (78.6%)	

1	3 (0.4%)	1 (0.5%)	50 (7.4%)	119 (10.2%)	25 (7.4%)	198 (6.3%)
2	2 (0.3%)	1 (0.5%)	8 (1.2%)	30 (2.6%)	10 (3.0%)	51 (1.6%)
3	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Missing	105	5	254	11	0	375	
Weight (kg) Measurement: 2Mo							<.0001[2]
N (Missing)	804 (62)	164 (30)	852 (81)	1131 (44)	326 (10)	3277 (227)
Mean (SD)	79.4 (19.58)	72.4 (15.51)	78.3 (18.50)	69.5 (15.09)	69.6 (14.72)	74.4 (17.77)
Median (IQR)	77.2 (65.7, 90.8)	71.1 (61.0, 81.5)	76.3 (65.0, 88.7)	69.0 (58.5, 79.0)	67.0 (59.0, 79.0)	72.3 (62.0, 84.5)
Range	38.4, 195.0	40.7, 150.5	39.5, 186.9	36.3, 133.0	35.0, 120.0	35.0, 195.0
Percentage Weight Change 2 Month/s from Baseline							0.0001[2]
N (Missing)	804 (62)	164 (30)	852 (81)	1131 (44)	326 (10)	3277 (227)
Mean (SD)	-1.2 (4.22)	-2.0 (3.27)	-1.4 (4.45)	-2.2 (4.50)	-2.0 (4.09)	-1.7 (4.34)
Median (IQR)	-1.0 (-3.4, 0.8)	0.0 (-3.8, 0.0)	-0.7 (-3.8, 1.2)	-1.1 (-4.2, 0.0)	-0.8 (-4.1, 0.0)	-0.9 (-3.8, 0.2)
Range	-23.9, 23.5	-11.6, 9.0	-26.5, 16.0	-24.3, 16.1	-17.2, 9.8	-26.5, 23.5
CTCAE Grade: Weight Loss 2 Month/s from Baseline							<.0001[1]
Weight Gain	245 (30.5%)	9 (5.5%)	300 (35.2%)	227 (20.1%)	57 (17.5%)	838 (25.6%)
0	441 (54.9%)	127 (77.4%)	393 (46.1%)	672 (59.4%)	206 (63.2%)	1839 (56.1%)
1	98 (12.2%)	26 (15.9%)	127 (14.9%)	165 (14.6%)	45 (13.8%)	461 (14.1%)
2	19 (2.4%)	2 (1.2%)	30 (3.5%)	63 (5.6%)	18 (5.5%)	132 (4.0%)
3	1 (0.1%)	0 (0.0%)	2 (0.2%)	4 (0.4%)	0 (0.0%)	7 (0.2%)
Missing	62	30	81	44	10	227
Weight (kg) Measurement: 3Mo							<.0001[2]
N (Missing)	764 (102)	160 (34)	725 (208)	1018 (157)	291 (45)	2958 (546)
Mean (SD)	79.3 (19.29)	72.3 (14.70)	79.5 (18.84)	69.8 (15.09)	69.7 (14.96)	74.8 (17.80)
Median (IQR)	77.1 (65.5, 90.8)	72.8 (61.0, 81.2)	77.3 (66.8, 90.0)	69.4 (59.0, 79.0)	67.0 (59.0, 79.5)	73.0 (62.0, 85.0)

Range	38.4, 195.0	38.0, 118.0	39.1, 185.5	36.0, 134.4	35.0, 121.0	35.0, 195.0	
Percentage Weight Change 3 Month/s from Baseline							<.0001[2]
N (Missing)	764 (102)	160 (34)	725 (208)	1018 (157)	291 (45)	2958 (546)	
Mean (SD)	-1.6 (5.27)	-1.6 (4.70)	-0.5 (5.56)	-1.4 (5.16)	-1.8 (5.29)	-1.3 (5.30)	
Median (IQR)	-1.3 (-4.3, 1.4)	-1.7 (-4.4, 1.4)	0.0 (-3.3, 2.9)	0.0 (-3.8, 1.2)	-0.2 (-4.4, 0.0)	-0.5 (-4.0, 1.6)	
Range	-23.9, 21.1	-13.4, 12.2	-26.5, 26.7	-22.0, 17.7	-21.6, 12.2	-26.5, 26.7	
CTCAE Grade: Weight Loss 3 Month/s from Baseline							<.0001[1]
Weight Gain	265 (34.7%)	52 (32.5%)	321 (44.3%)	327 (32.1%)	71 (24.4%)	1036 (35.0%)	
0	342 (44.8%)	74 (46.3%)	278 (38.3%)	489 (48.0%)	156 (53.6%)	1339 (45.3%)	
1	109 (14.3%)	29 (18.1%)	87 (12.0%)	136 (13.4%)	42 (14.4%)	403 (13.6%)	
2	45 (5.9%)	5 (3.1%)	38 (5.2%)	63 (6.2%)	21 (7.2%)	172 (5.8%)	
3	3 (0.4%)	0 (0.0%)	1 (0.1%)	3 (0.3%)	1 (0.3%)	8 (0.3%)	
Missing	102	34	208	157	45	546	
Weight (kg) Measurement: 6Mo							<.0001[2]
N (Missing)	728 (138)	156 (38)	665 (268)	946 (229)	274 (62)	2769 (735)	
Mean (SD)	79.5 (19.30)	71.0 (14.89)	79.1 (18.98)	69.9 (15.14)	69.0 (14.80)	74.6 (17.86)	
Median (IQR)	77.9 (65.9, 90.9)	70.4 (59.1, 80.7)	76.6 (66.0, 89.3)	69.0 (59.0, 79.0)	67.0 (59.0, 79.0)	73.0 (61.8, 85.0)	
Range	40.0, 195.0	35.4, 110.3	38.2, 195.6	31.5, 138.3	35.0, 121.0	31.5, 195.6	
Percentage Weight Change 6 Month/s from Baseline							<.0001[2]
N (Missing)	728 (138)	156 (38)	665 (268)	946 (229)	274 (62)	2769 (735)	
Mean (SD)	-1.5 (6.91)	-2.9 (10.74)	-0.4 (6.96)	-1.4 (6.34)	-2.5 (6.51)	-1.4 (7.00)	
Median (IQR)	-1.2 (-5.3, 2.5)	-3.5 (-7.6, 0.0)	0.0 (-4.1, 3.6)	0.0 (-4.5, 1.8)	-1.2 (-6.3, 0.7)	-0.7 (-5.2, 2.3)	
Range	-31.3, 22.4	-17.5, 108.5	-22.2, 29.2	-25.5, 22.1	-26.5, 14.6	-31.3, 108.5	

CTCAE Grade: Weight Loss 6 Month/s from Baseline							<.0001[1]
Weight Gain	281 (38.6%)	37 (23.7%)	312 (46.9%)	316 (33.4%)	73 (26.6%)	1019 (36.8%)	
0	253 (34.8%)	59 (37.8%)	204 (30.7%)	406 (42.9%)	113 (41.2%)	1035 (37.4%)	
1	113 (15.5%)	36 (23.1%)	88 (13.2%)	141 (14.9%)	53 (19.3%)	431 (15.6%)	
2	71 (9.8%)	24 (15.4%)	59 (8.9%)	71 (7.5%)	31 (11.3%)	256 (9.2%)	
3	10 (1.4%)	0 (0.0%)	2 (0.3%)	12 (1.3%)	4 (1.5%)	28 (1.0%)	
Missing	138	38	268	229	62	735	
Weight (kg) Measurement: 9Mo							<.0001[2]
N (Missing)	553 (313)	108 (86)	361 (572)	629 (546)	167 (169)	1818 (1686)	
Mean (SD)	81.5 (20.02)	71.6 (15.07)	80.2 (19.03)	72.0 (15.60)	69.4 (14.41)	76.3 (18.26)	
Median (IQR)	80.0 (67.3, 93.0)	71.0 (60.4, 80.9)	78.2 (66.8, 91.8)	71.0 (60.0, 82.0)	68.0 (60.0, 77.6)	75.0 (63.5, 86.4)	
Range	36.0, 195.0	35.4, 112.0	39.3, 201.8	38.2, 140.0	35.0, 121.0	35.0, 201.8	
Percentage Weight Change 9 Month/s from Baseline							<.0001[2]
N (Missing)	553 (313)	108 (86)	361 (572)	629 (546)	167 (169)	1818 (1686)	
Mean (SD)	1.0 (9.64)	-2.2 (7.60)	1.4 (11.39)	1.0 (7.57)	-1.7 (7.29)	0.6 (9.12)	
Median (IQR)	1.1 (-4.2, 6.1)	-2.9 (-7.7, 4.7)	1.0 (-4.0, 6.0)	0.0 (-2.9, 5.2)	0.0 (-5.6, 2.4)	0.0 (-4.1, 5.3)	
Range	-30.2, 106.5	-17.5, 15.5	-23.8, 144.3	-25.6, 35.9	-26.7, 17.5	-30.2, 144.3	
CTCAE Grade: Weight Loss 9 Month/s from Baseline							<.0001[1]
Weight Gain	295 (53.3%)	38 (35.2%)	193 (53.5%)	313 (49.8%)	64 (38.3%)	903 (49.7%)	
0	135 (24.4%)	28 (25.9%)	96 (26.6%)	201 (32.0%)	57 (34.1%)	517 (28.4%)	
1	67 (12.1%)	26 (24.1%)	40 (11.1%)	78 (12.4%)	25 (15.0%)	236 (13.0%)	
2	47 (8.5%)	16 (14.8%)	28 (7.8%)	31 (4.9%)	16 (9.6%)	138 (7.6%)	
3	9 (1.6%)	0 (0.0%)	4 (1.1%)	6 (1.0%)	5 (3.0%)	24 (1.3%)	
Missing	313	86	572	546	169	1686	

Weight (kg) Measurement: 12Mo							<.0001[2]
N (Missing)	368 (498)	69 (125)	156 (777)	385 (790)	80 (256)	1058 (2446)	
Mean (SD)	82.2 (19.87)	71.6 (14.08)	81.4 (18.95)	73.6 (14.97)	70.2 (15.06)	77.3 (17.96)	
Median (IQR)	80.8 (68.2, 93.5)	69.5 (60.9, 79.0)	79.1 (67.6, 95.6)	72.0 (63.0, 82.5)	68.5 (60.5, 76.0)	75.0 (64.4, 87.7)	
Range	36.0, 195.0	48.6, 106.4	37.5, 147.2	39.9, 124.6	38.0, 121.0	36.0, 195.0	
Percentage Weight Change 12 Month/s from Baseline							0.0024[2]
N (Missing)	368 (498)	69 (125)	156 (777)	385 (790)	80 (256)	1058 (2446)	
Mean (SD)	2.3 (9.75)	-1.2 (9.00)	1.7 (10.22)	2.3 (7.67)	-0.9 (8.26)	1.7 (9.01)	
Median (IQR)	2.1 (-4.1, 8.1)	-0.9 (-7.0, 4.4)	2.1 (-5.0, 8.3)	1.3 (-1.8, 6.3)	0.0 (-4.1, 2.8)	1.3 (-3.4, 7.0)	
Range	-44.6, 37.8	-21.6, 19.8	-27.3, 39.9	-18.8, 29.3	-26.7, 25.0	-44.6, 39.9	
CTCAE Grade: Weight Loss 12 Month/s from Baseline							<.0001[1]
Weight Gain	213 (57.9%)	31 (44.9%)	90 (57.7%)	210 (54.5%)	30 (37.5%)	574 (54.3%)	
0	74 (20.1%)	16 (23.2%)	27 (17.3%)	121 (31.4%)	32 (40.0%)	270 (25.5%)	
1	53 (14.4%)	12 (17.4%)	20 (12.8%)	32 (8.3%)	8 (10.0%)	125 (11.8%)	
2	25 (6.8%)	8 (11.6%)	17 (10.9%)	22 (5.7%)	9 (11.3%)	81 (7.7%)	
3	3 (0.8%)	2 (2.9%)	2 (1.3%)	0 (0.0%)	1 (1.3%)	8 (0.8%)	
Missing	498	125	777	790	256	2446	

Appendix Table 2. Analysis cohort by included prospective randomized trial. [1]Chi-Square p-value; [2]Kruskal-Wallis p-value.

Cutoff: Weight Loss 3 Months from Baseline

	Missing (N=546)	Weight Gain/Stable (N=1411)	Weight loss < 5% (N=964)	Weight loss ≥ 5% (N=583)	Total (N=2958)	P-value
Age Category						<.0001[1]
Younger than 65	308	975 (69.1%)	552 (57.3%)	314 (53.9%)	1841 (62.3%)	
65 or Older	238	435 (30.9%)	411 (42.7%)	269 (46.1%)	1115 (37.7%)	
Missing	0	1	1	0	2	
Gender						0.0041[1]
Female	239	523 (37.1%)	410 (42.5%)	255 (43.7%)	1188 (40.2%)	
Male	307	888 (62.9%)	554 (57.5%)	328 (56.3%)	1770 (59.8%)	
Performance Score						<.0001[1]
0	222	779 (57.8%)	514 (55.3%)	243 (43.2%)	1536 (54.1%)	
1+	293	569 (42.2%)	416 (44.7%)	320 (56.8%)	1305 (45.9%)	
Missing	31	63	34	20	117	
Baseline Weight (kg)						<.0001[2]
N (Missing)	546 (0)	1411 (0)	964 (0)	583 (0)	2958 (0)	
Mean (SD)	74.4 (18.02)	74.6 (17.75)	77.6 (17.56)	75.4 (17.64)	75.8 (17.71)	
Median (IQR)	72.0 (62.9, 82.3)	72.7 (62.1, 84.7)	76.0 (65.0, 88.0)	74.0 (62.7, 84.3)	74.0 (63.0, 85.6)	
Range	36.0, 180.3	38.4, 195.0	38.6, 141.5	39.0, 153.3	38.4, 195.0	
Baseline Height (m)						0.0075[2]
N (Missing)	546 (0)	1411 (0)	964 (0)	583 (0)	2958 (0)	
Mean (SD)	1.7 (0.10)	1.7 (0.10)	1.7 (0.10)	1.7 (0.10)	1.7 (0.10)	
Median (IQR)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)	
Range	1.3, 2.0	1.4, 2.0	1.3, 2.0	1.4, 2.0	1.3, 2.0	

Baseline BMI						<.0001[2]
N (Missing)	546 (0)	1411 (0)	964 (0)	583 (0)	2958 (0)	
Mean (SD)	26.1 (5.63)	25.8 (5.12)	27.2 (5.24)	26.6 (5.41)	26.4 (5.25)	
Median (IQR)	25.2 (22.3, 28.4)	25.2 (22.4, 28.3)	26.3 (23.6, 30.4)	25.8 (23.1, 29.1)	25.7 (22.9, 29.1)	
Range	15.0, 60.2	13.2, 53.0	14.8, 55.3	16.6, 59.7	13.2, 59.7	
Baseline BMI Category						<.0001[1]
Underweight (<18.5)	17	56 (4.0%)	16 (1.7%)	13 (2.2%)	85 (2.9%)	
Normal (18.5 to <25)	242	619 (43.9%)	355 (36.8%)	229 (39.3%)	1203 (40.7%)	
Overweight (25 to <30)	192	505 (35.8%)	336 (34.9%)	221 (37.9%)	1062 (35.9%)	
Obese (30 or Greater)	95	231 (16.4%)	257 (26.7%)	120 (20.6%)	608 (20.6%)	
Baseline BMI Category						<.0001[1]
<25	259	675 (47.8%)	371 (38.5%)	242 (41.5%)	1288 (43.5%)	
>=25	287	736 (52.2%)	593 (61.5%)	341 (58.5%)	1670 (56.5%)	
Albumin Type 1 (g/L)						0.0235[2]
N (Missing)	137 (409)	397 (1014)	368 (596)	208 (375)	973 (1985)	
Mean (SD)	35.4 (5.20)	38.2 (4.78)	38.4 (5.12)	37.0 (5.76)	38.0 (5.15)	
Median (IQR)	35.0 (31.0, 39.0)	38.0 (35.0, 41.0)	39.0 (35.0, 42.0)	38.0 (34.0, 41.0)	38.0 (35.0, 41.2)	
Range	24.0, 46.5	22.0, 51.9	20.0, 51.0	19.0, 49.0	19.0, 51.9	
Tumor Sidedness						0.0317[1]
Left Colon	142	504 (76.4%)	295 (79.5%)	184 (70.5%)	983 (76.1%)	
Right Colon	56	156 (23.6%)	76 (20.5%)	77 (29.5%)	309 (23.9%)	
Missing	348	751	593	322	1666	
Metastatic Site: Liver						0.0003[1]
No Involvement	71	139 (15.7%)	137 (20.4%)	80 (21.0%)	356 (18.4%)	
Involvement	127	358 (40.4%)	224 (33.3%)	109 (28.6%)	691 (35.6%)	
Involv. and >=1 Other Involv.	191	389 (43.9%)	311 (46.3%)	192 (50.4%)	892 (46.0%)	

Missing	157	525	292	202	1019	
Metastatic Site: Lung						0.0020[1]
No Involvement	254	574 (64.8%)	372 (55.4%)	215 (56.4%)	1161 (59.9%)	
Involvement	11	42 (4.7%)	35 (5.2%)	21 (5.5%)	98 (5.1%)	
Involv. and >=1 Other Involv.	124	270 (30.5%)	265 (39.4%)	145 (38.1%)	680 (35.1%)	
Missing	157	525	292	202	1019	
Metastatic Site: Peritoneal						0.0057[1]
No Involvement	42	140 (97.9%)	81 (96.4%)	55 (85.9%)	276 (94.8%)	
Involvement	0	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.3%)	
Involv. and >=1 Other Involv.	3	3 (2.1%)	3 (3.6%)	8 (12.5%)	14 (4.8%)	
Missing	501	1268	880	519	2667	
N Metastatic Sites						0.0002[1]
0-1	159	445 (50.3%)	284 (42.2%)	149 (39.1%)	878 (45.3%)	
2+	230	440 (49.7%)	389 (57.8%)	232 (60.9%)	1061 (54.7%)	
Missing	157	526	291	202	1019	
Chemotherapy Type						0.0115[1]
5FU Based	46	101 (7.2%)	107 (11.1%)	47 (8.1%)	255 (8.6%)	
OX Based	186	414 (29.3%)	289 (30.0%)	167 (28.6%)	870 (29.4%)	
IRI Based	314	896 (63.5%)	568 (58.9%)	369 (63.3%)	1833 (62.0%)	
BRAF Status						0.8539[1]
WT	155	556 (95.2%)	294 (95.8%)	216 (94.7%)	1066 (95.3%)	
MT	14	28 (4.8%)	13 (4.2%)	12 (5.3%)	53 (4.7%)	
Missing	377	827	657	355	1839	
Regimen Includes Any Target Agents?						<.0001[1]

Regimen Includes Only non-Target Agents	384	939 (66.5%)	539 (55.9%)	302 (51.8%)	1780 (60.2%)	
Regimen Includes at Least One Targeted Agent	162	472 (33.5%)	425 (44.1%)	281 (48.2%)	1178 (39.8%)	
Biologics Type						<.0001[1]
None	384	939 (66.5%)	539 (55.9%)	302 (51.8%)	1780 (60.2%)	
Cetuximab	101	274 (19.4%)	214 (22.2%)	168 (28.8%)	656 (22.2%)	
Bevacizumab	61	198 (14.0%)	211 (21.9%)	113 (19.4%)	522 (17.6%)	
Weight (kg) Measurement: 1Mo						<.0001[2]
N (Missing)	444 (102)	1272 (139)	892 (72)	521 (62)	2685 (273)	
Mean (SD)	72.6 (17.94)	74.0 (17.46)	76.7 (17.55)	72.7 (17.36)	74.7 (17.53)	
Median (IQR)	70.6 (60.2, 81.8)	72.0 (62.0, 83.4)	75.1 (64.4, 87.0)	72.0 (60.0, 81.9)	73.0 (62.3, 84.2)	
Range	39.0, 174.0	36.9, 195.0	37.0, 141.4	39.0, 153.0	36.9, 195.0	
Percentage Weight Change 1 Month/s from Baseline						<.0001[2]
N (Missing)	444 (102)	1272 (139)	892 (72)	521 (62)	2685 (273)	
Mean (SD)	-2.0 (3.84)	0.2 (1.91)	-1.1 (1.82)	-2.9 (3.67)	-0.9 (2.60)	
Median (IQR)	0.0 (-3.6, 0.0)	0.0 (0.0, 0.0)	0.0 (-2.1, 0.0)	-1.7 (-4.7, 0.0)	0.0 (-1.5, 0.0)	
Range	-17.8, 17.9	-12.1, 16.1	-9.4, 2.9	-22.0, 3.6	-22.0, 16.1	
CTCAE Grade: Weight Loss 1 Month/s from Baseline						<.0001[1]
Weight Gain	53	297 (23.3%)	56 (6.3%)	14 (2.7%)	367 (13.7%)	
0	315	958 (75.3%)	801 (89.8%)	385 (73.9%)	2144 (79.9%)	
1	55	15 (1.2%)	35 (3.9%)	93 (17.9%)	143 (5.3%)	
2	21	2 (0.2%)	0 (0.0%)	28 (5.4%)	30 (1.1%)	
3	0	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.0%)	
Missing	102	139	72	62	273	

Weight (kg) Measurement: 2Mo						<.0001[2]
N (Missing)	361 (185)	1402 (9)	950 (14)	564 (19)	2916 (42)	
Mean (SD)	72.2 (17.82)	75.5 (18.10)	75.9 (17.28)	70.3 (17.02)	74.6 (17.75)	
Median (IQR)	69.9 (60.0, 82.2)	73.6 (63.1, 85.0)	74.0 (63.5, 86.6)	68.2 (58.3, 79.0)	72.8 (62.0, 85.0)	
Range	38.0, 150.5	38.0, 195.0	37.0, 143.4	35.0, 155.0	35.0, 195.0	
Percentage Weight Change 2 Month/s from Baseline						<.0001[2]
N (Missing)	361 (185)	1402 (9)	950 (14)	564 (19)	2916 (42)	
Mean (SD)	-3.7 (5.52)	1.2 (2.70)	-2.3 (1.96)	-6.7 (4.08)	-1.4 (4.11)	
Median (IQR)	-3.1 (-7.0, 0.0)	0.3 (0.0, 2.4)	-2.1 (-3.5, -1.0)	-6.3 (-8.6, -4.4)	-0.7 (-3.5, 0.4)	
Range	-24.3, 11.7	-11.4, 23.5	-11.5, 5.5	-26.5, 9.3	-26.5, 23.5	
CTCAE Grade: Weight Loss 2 Month/s from Baseline						<.0001[1]
Weight Gain	58	718 (51.2%)	50 (5.3%)	12 (2.1%)	780 (26.7%)	
0	172	673 (48.0%)	835 (87.9%)	159 (28.2%)	1667 (57.2%)	
1	92	10 (0.7%)	63 (6.6%)	296 (52.5%)	369 (12.7%)	
2	35	1 (0.1%)	2 (0.2%)	94 (16.7%)	97 (3.3%)	
3	4	0 (0.0%)	0 (0.0%)	3 (0.5%)	3 (0.1%)	
Missing	185	9	14	19	42	
Weight (kg) Measurement: 3Mo						<.0001[2]
N (Missing)		1411 (0)	964 (0)	583 (0)	2958 (0)	
Mean (SD)		76.6 (18.25)	75.8 (17.15)	68.6 (16.37)	74.8 (17.80)	
Median (IQR)		75.0 (64.2, 87.0)	74.0 (63.0, 86.0)	67.0 (57.0, 77.5)	73.0 (62.0, 85.0)	
Range		38.8, 195.0	37.5, 140.0	35.0, 142.0	35.0, 195.0	
Percentage Weight Change 3 Month/s from Baseline						<.0001[2]

N (Missing)		1411 (0)	964 (0)	583 (0)	2958 (0)	
Mean (SD)		2.7 (3.17)	-2.4 (1.32)	-9.1 (3.69)	-1.3 (5.30)	
Median (IQR)		1.7 (0.0, 4.1)	-2.3 (-3.5, -1.3)	-8.0 (-10.9, -6.3)	-0.5 (-4.0, 1.6)	
Range		0.0, 26.7	-5.0, -0.1	-26.5, -5.0	-26.5, 26.7	
CTCAE Grade: Weight Loss 3 Month/s from Baseline						<.0001[1]
Weight Gain	0	1036 (73.4%)	0 (0.0%)	0 (0.0%)	1036 (35.0%)	
0	0	375 (26.6%)	964 (100.0%)	0 (0.0%)	1339 (45.3%)	
1	0	0 (0.0%)	0 (0.0%)	403 (69.1%)	403 (13.6%)	
2	0	0 (0.0%)	0 (0.0%)	172 (29.5%)	172 (5.8%)	
3	0	0 (0.0%)	0 (0.0%)	8 (1.4%)	8 (0.3%)	
Weight (kg) Measurement: 6Mo						<.0001[2]
N (Missing)	64 (482)	1304 (107)	900 (64)	501 (82)	2705 (253)	
Mean (SD)	72.3 (16.54)	76.8 (18.41)	75.4 (17.19)	67.7 (16.02)	74.7 (17.89)	
Median (IQR)	70.6 (61.3, 82.7)	75.0 (63.7, 87.0)	74.0 (63.0, 86.0)	66.8 (56.4, 76.2)	73.0 (61.9, 85.0)	
Range	46.0, 125.0	38.1, 195.6	35.4, 140.0	31.5, 137.0	31.5, 195.6	
Percentage Weight Change 6 Month/s from Baseline						<.0001[2]
N (Missing)	64 (482)	1304 (107)	900 (64)	501 (82)	2705 (253)	
Mean (SD)	-2.7 (7.12)	3.0 (4.92)	-2.8 (5.17)	-9.9 (5.28)	-1.3 (7.00)	
Median (IQR)	-2.4 (-7.4, 2.1)	2.0 (0.0, 5.5)	-2.5 (-4.7, -0.9)	-9.1 (-12.9, -6.3)	-0.7 (-5.1, 2.3)	
Range	-16.7, 14.7	-25.5, 29.2	-23.9, 108.5	-31.3, 11.8	-31.3, 108.5	
CTCAE Grade: Weight Loss 6 Month/s from Baseline						<.0001[1]
Weight Gain	19	882 (67.6%)	114 (12.7%)	4 (0.8%)	1000 (37.0%)	

0	23	378 (29.0%)	580 (64.4%)	54 (10.8%)	1012 (37.4%)	
1	11	30 (2.3%)	168 (18.7%)	222 (44.3%)	420 (15.5%)	
2	11	11 (0.8%)	37 (4.1%)	197 (39.3%)	245 (9.1%)	
3	0	3 (0.2%)	1 (0.1%)	24 (4.8%)	28 (1.0%)	
Missing	482	107	64	82	253	
Weight (kg) Measurement: 9Mo						<.0001[2]
N (Missing)	26 (520)	889 (522)	616 (348)	287 (296)	1792 (1166)	
Mean (SD)	74.2 (17.11)	78.5 (18.98)	76.5 (17.26)	69.0 (16.27)	76.3 (18.27)	
Median (IQR)	73.8 (63.1, 82.6)	76.0 (65.0, 88.6)	75.5 (64.0, 86.8)	67.0 (58.0, 78.0)	75.0 (63.5, 86.4)	
Range	36.0, 125.0	41.0, 201.8	35.4, 139.5	35.0, 138.5	35.0, 201.8	
Percentage Weight Change 9 Month/s from Baseline						<.0001[2]
N (Missing)	26 (520)	889 (522)	616 (348)	287 (296)	1792 (1166)	
Mean (SD)	0.6 (7.26)	5.1 (8.17)	-1.7 (7.18)	-8.3 (7.17)	0.6 (9.14)	
Median (IQR)	0.1 (-3.0, 3.7)	4.4 (0.0, 8.3)	-1.7 (-5.2, 1.5)	-8.0 (-12.4, -4.0)	0.0 (-4.1, 5.3)	
Range	-13.9, 16.2	-26.7, 144.3	-20.3, 106.5	-30.2, 20.9	-30.2, 144.3	
CTCAE Grade: Weight Loss 9 Month/s from Baseline						<.0001[1]
Weight Gain	13	656 (73.8%)	203 (33.0%)	31 (10.8%)	890 (49.7%)	
0	9	202 (22.7%)	248 (40.3%)	58 (20.2%)	508 (28.3%)	
1	2	19 (2.1%)	124 (20.1%)	91 (31.7%)	234 (13.1%)	
2	2	8 (0.9%)	40 (6.5%)	88 (30.7%)	136 (7.6%)	
3	0	4 (0.4%)	1 (0.2%)	19 (6.6%)	24 (1.3%)	
Missing	520	522	348	296	1166	
Weight (kg) Measurement: 12Mo						<.0001[2]
N (Missing)	12 (534)	529 (882)	365 (599)	152 (431)	1046 (1912)	

|						
Mean (SD)	75.6 (15.78)	79.3 (18.88)	77.4 (16.62)	70.6 (16.36)	77.4 (17.99)	
Median (IQR)	77.9 (69.0, 86.6)	76.7 (66.0, 90.3)	75.6 (65.0, 88.0)	68.4 (60.0, 79.1)	75.0 (64.2, 87.7)	
Range	36.0, 96.0	44.0, 195.0	37.5, 132.3	38.0, 141.8	37.5, 195.0	
Percentage Weight Change 12 Month/s from Baseline						<.0001[2]
N (Missing)	12 (534)	529 (882)	365 (599)	152 (431)	1046 (1912)	
Mean (SD)	2.4 (6.18)	6.1 (7.87)	-0.8 (7.11)	-7.3 (7.97)	1.7 (9.04)	
Median (IQR)	0.3 (-1.9, 5.3)	5.3 (0.5, 10.5)	-0.8 (-5.4, 3.4)	-7.1 (-12.1, -2.9)	1.3 (-3.4, 7.0)	
Range	-4.1, 16.2	-44.6, 39.9	-21.6, 25.4	-38.4, 24.0	-44.6, 39.9	
CTCAE Grade: Weight Loss 12 Month/s from Baseline						<.0001[1]
Weight Gain	7	402 (76.0%)	144 (39.5%)	21 (13.8%)	567 (54.2%)	
0	5	105 (19.8%)	127 (34.8%)	33 (21.7%)	265 (25.3%)	
1	0	15 (2.8%)	65 (17.8%)	45 (29.6%)	125 (12.0%)	
2	0	5 (0.9%)	27 (7.4%)	49 (32.2%)	81 (7.7%)	
3	0	2 (0.4%)	2 (0.5%)	4 (2.6%)	8 (0.8%)	
Missing	534	882	599	431	1912	

Appendix Table 3. Analysis cohort by weight change category. [1]Chi-Square p-value; [2]Kruskal-Wallis p-value.

Weight Meas. Availability	1 month	2 months	3 months	6 months	9 months	12 months
Meas. Available, N (%):	3129 (89.30%)	3277 (93.52%)	2958 (84.42%)	2769 (79.02%)	1818 (51.88%)	1058 (30.19%)
Meas. Unavailable, N (%):	375 (10.70%)	227 (6.48%)	546 (15.58%)	735 (20.98%)	1686 (48.12%)	2446 (69.81%)
Off Treatment, N (%):		55 (1.57%)	156 (4.45%)	199 (5.68%)	469 (13.38%)	610 (17.41%)
Progression, N (%):		53 (1.51%)	185 (5.28%)	245 (6.99%)	602 (17.18%)	838 (23.92%)
Death, N (%):		54 (1.54%)	128 (3.65%)	285 (8.13%)	590 (16.84%)	986 (28.14%)
Reason Unknown, N (%):	375 (10.70%)	65 (1.86%)	77 (2.20%)	6 (0.17%)	25 (0.71%)	12 (0.34%)

Appendix Table 4. Weight measurement availability across time after baseline and randomization.
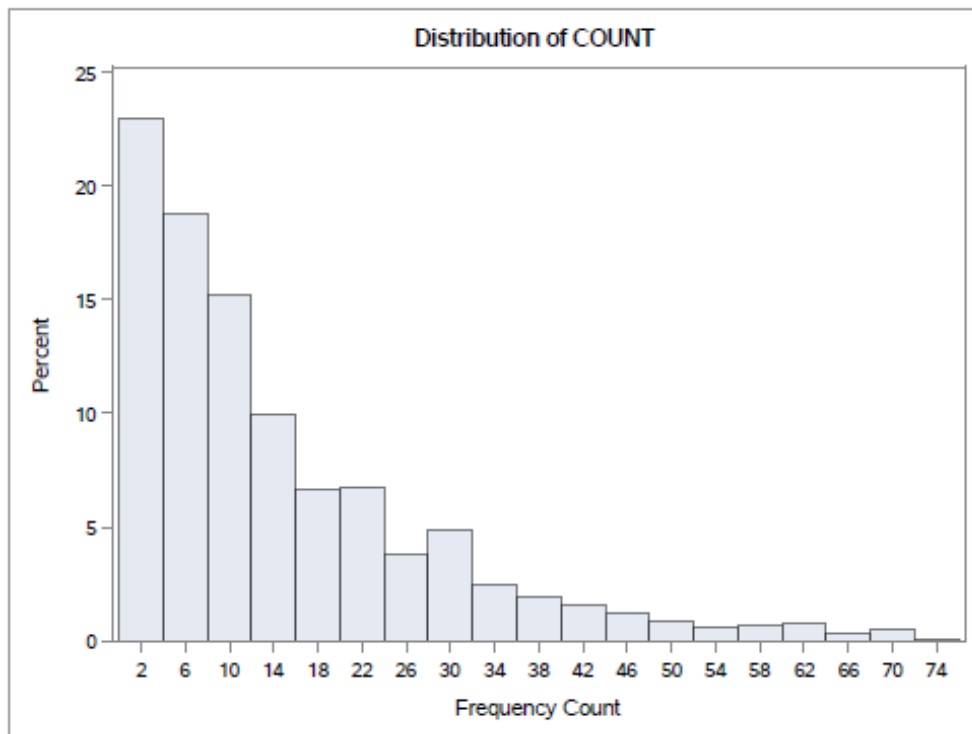
Appendix Figure 1. Distribution of number of weight measures post baseline
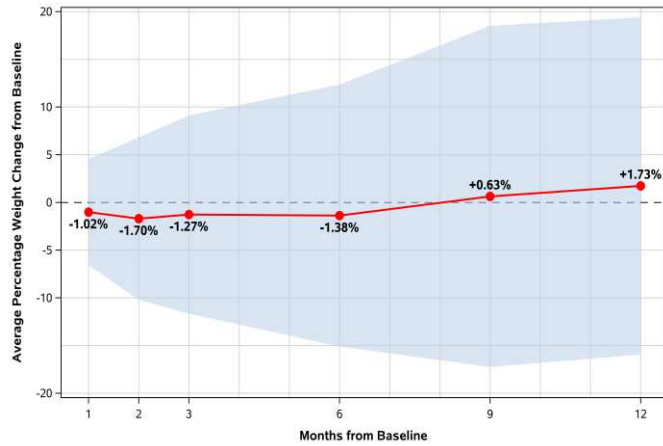
Appendix Figure 2. Average weight change plotted against time for the entire cohort.
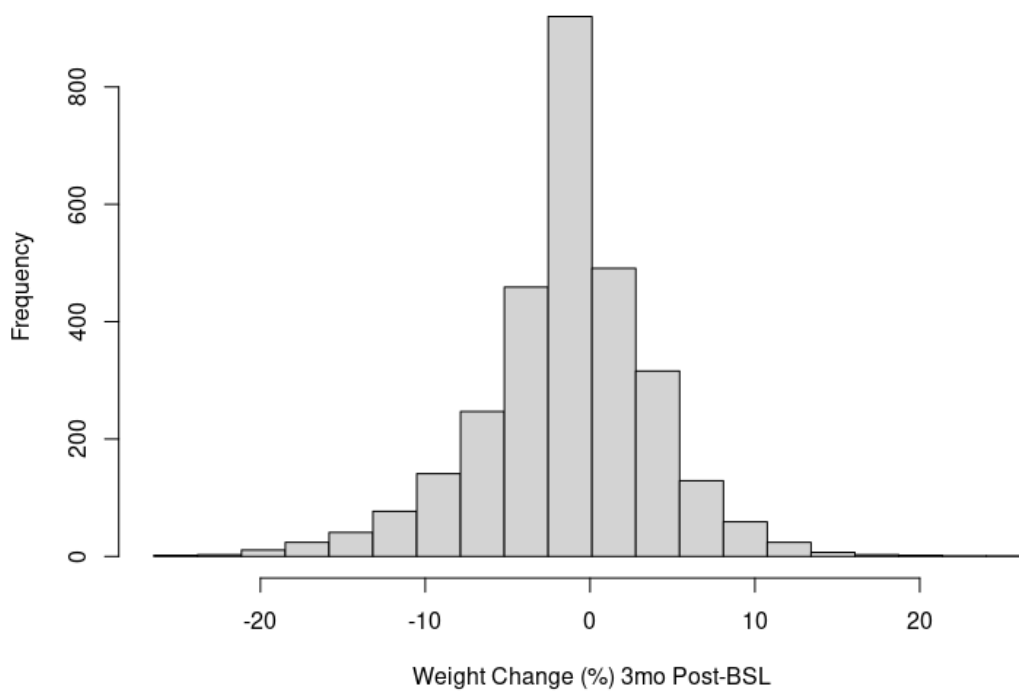
Appendix Figure 3. Distribution of weight change after baseline among evaluable patients. Interquartile range: -3.976%…1.577%, median -0.542%. Largest weight loss -26.4%, and largest gain 26.7%.
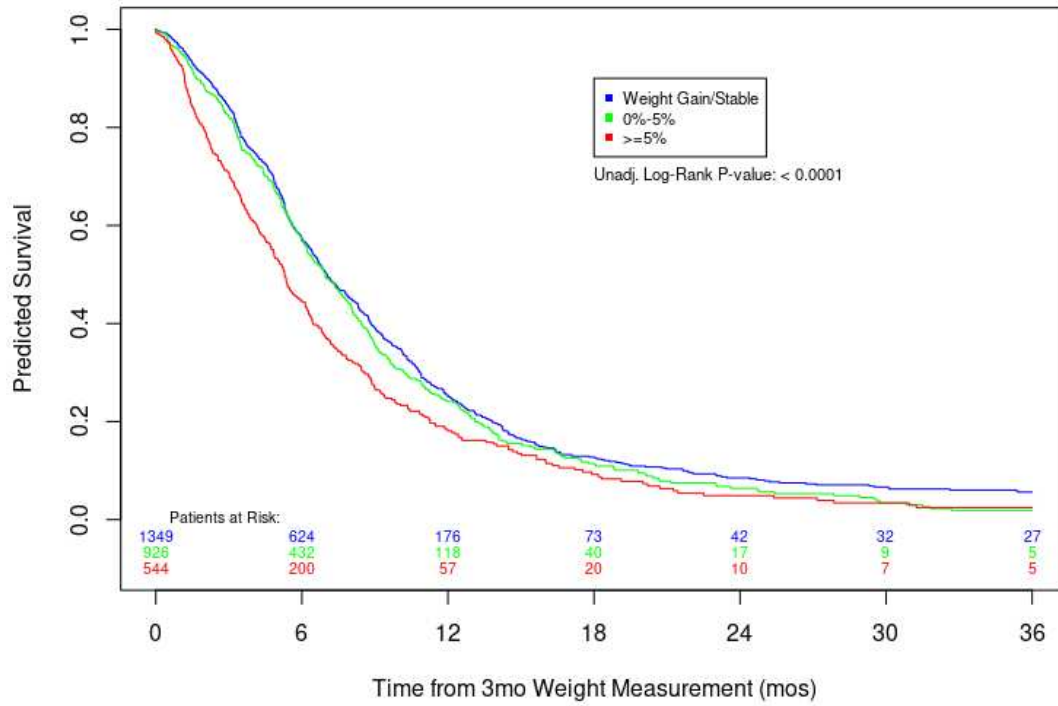
Overall Survival by Weight Loss at 3mos
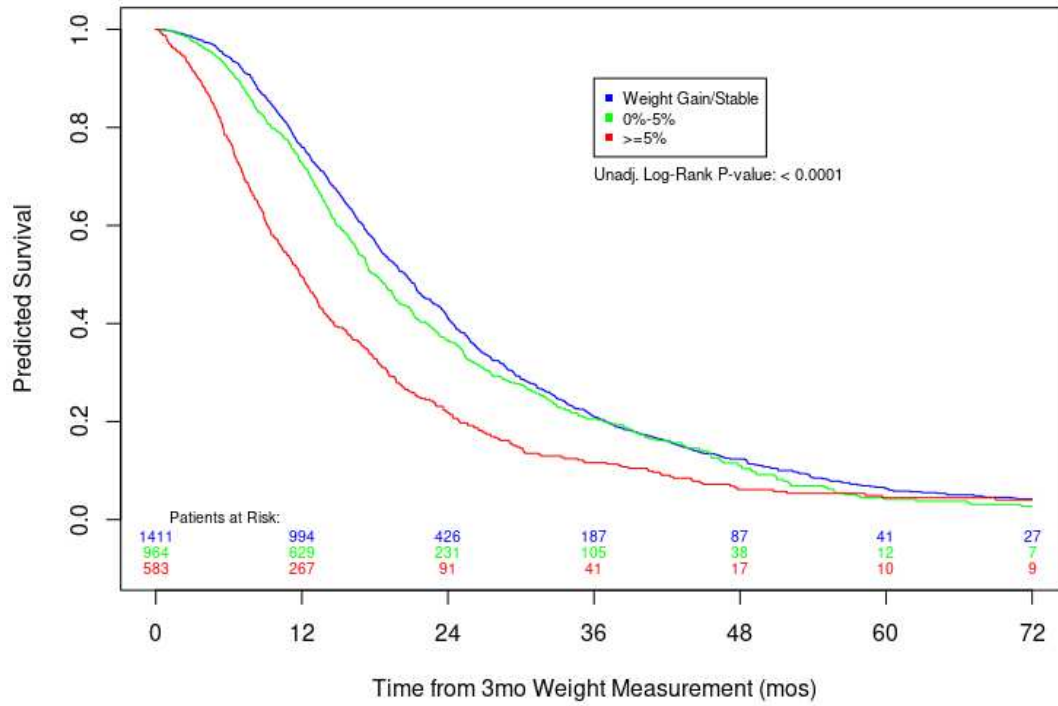
| Weight Change 3mo	Events/N	Median (95% CI)	Log-Rank P-Value
Weight Gain/Stable	1068/1411	20.5 (19.38-21.39)	< 0.0001
0%-5%	692/964	18.04 (17.18-19.38)	--
>=5%	493/583	11.86 (10.78-13.01)	--

Appendix Figure 4. Kaplan-Meier estimator for overall survival categorized by weight stable or gain as compared to <5% weight loss and ≥5% weight loss at 3 months post baseline.

Progression-Free Survival by Weight Loss at 3mos

Weight Change 3mo	Events/N	Median (95% CI)	Log-Rank P-Value
Weight Gain/Stable	941/1349	7.03 (6.67-7.49)	< 0.0001
0%-5%	660/926	6.97 (6.44-7.52)	--
>=5%	420/544	5.29 (4.86-5.82)	--

Appendix Figure 5. Kaplan-Meier estimator for progression-free survival categorized by weight stable or gain as compared to <5% weight loss and ≥5% weight loss at 3 months post baseline.
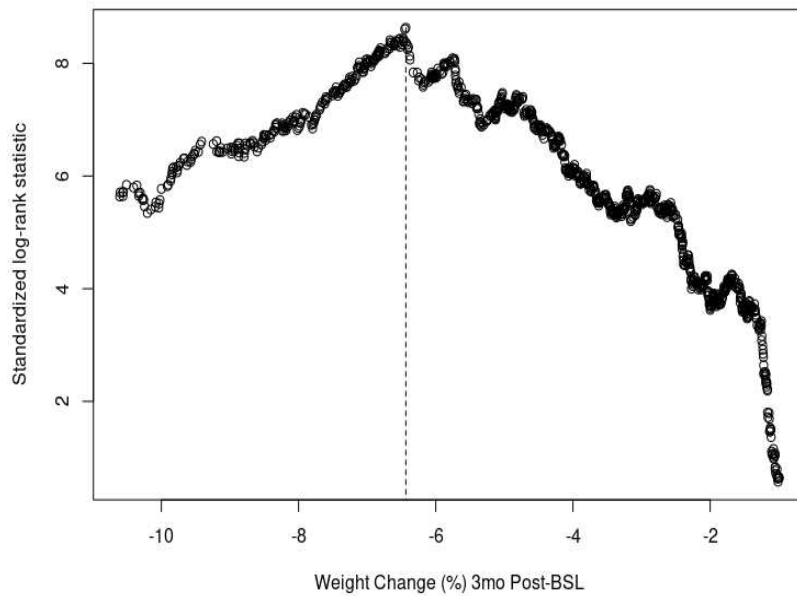
Appendix Figure 6. Estimation plot for optimal cutoff value of weight loss in predicting death risk. Observed weight change 3 months after baseline is plotted against log rank statistics (vertical axis). HR, hazard ratio. Post-BSL, post-baseline (randomization/registration). Optimal cut off = -6.435% weight change at 3 months, $p=2.2 \times 10^{-16}$.
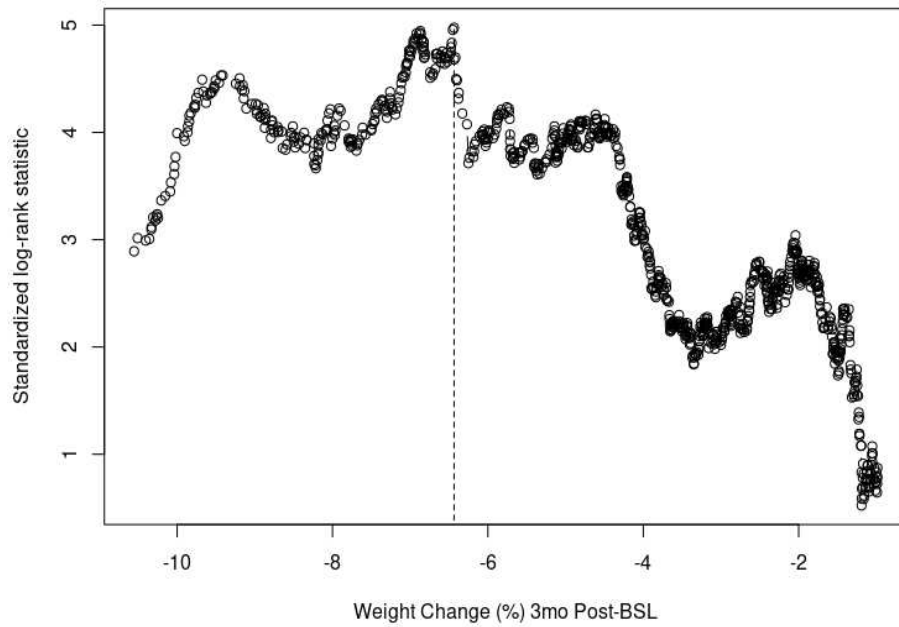
Appendix Figure 7. Estimation plot for optimal cutoff value of weight loss in predicting risk of disease progression. Observed weight change 3 months after baseline is plotted against log rank statistics (vertical axis) of progression-free survival. HR, hazard ratio. Post-BSL, post-baseline (randomization/registration). Optimal cut off = -6.435% weight change at 3 months, p=3.9x10^{-6}.

Distribution of % Weight Change for OS 12 Months
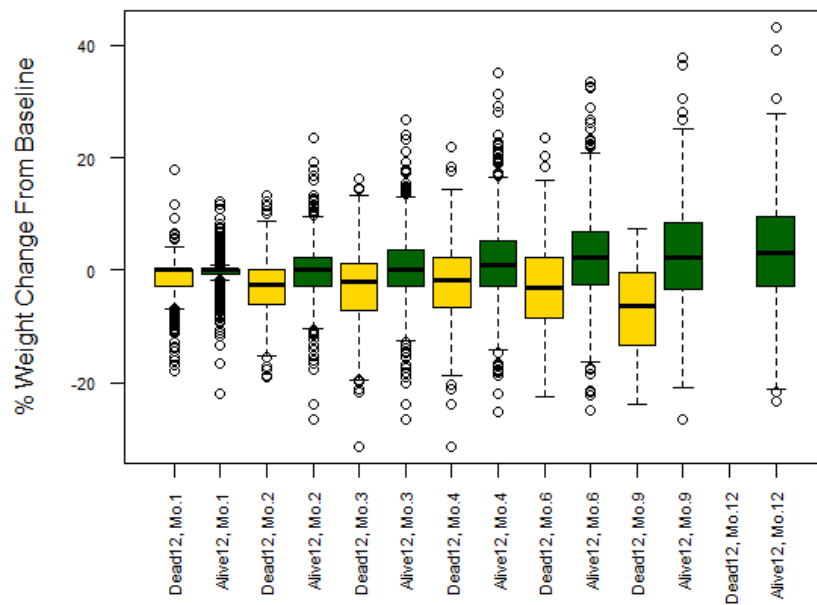
Appendix Figure 8. Distribution of relative change (in per cent of baseline) in body weight and survival status at 12-month post randomization.

3 months post baseline

Latency Class	Weight Gain (N=538)	Weight Stable (N=1985)	Weight Loss (N=980)	Total (N=3503)	p value
Percentage Weight Change					< 0.001
N-Miss	12	391	143	546	
Mean (SD)	4.795 (4.055)	-0.346 (2.664)	-6.828 (4.443)	-1.266 (5.299)	
Median (Range)	4.443 (-5.882, 26.698)	0.000 (-13.793, 9.386)	-6.029 (-26.465, 2.545)	-0.542 (-26.465, 26.698)	

6 months post baseline

Latency Class	Weight Gain (N=538)	Weight Stable (N=1985)	Weight Loss (N=980)	Total (N=3503)	p value
Percentage Weight Change					< 0.001
N-Miss	19	509	207	735	
Mean (SD)	6.934 (4.641)	-0.408 (4.143)	-8.807 (4.999)	-1.377 (7.002)	
Median (Range)	6.610 (-22.001, 29.184)	0.000 (-14.062, 108.511)	-7.657 (-31.250, 1.818)	-0.683 (-31.250, 108.511)	

12 months post baseline

Latency Class	Weight Gain (N=538)	Weight Stable (N=1985)	Weight Loss (N=980)	Total (N=3503)	p value
Percentage Weight Change					< 0.001
N-Miss	315	1397	734	2446	
Mean (SD)	13.037 (6.352)	1.874 (4.638)	-8.923 (5.582)	1.716 (9.006)	
Median (Range)	11.976 (-2.351, 39.857)	1.408 (-44.602, 13.368)	-7.825 (-38.449, 3.143)	1.286 (-44.602, 39.857)	

Appendix Table 5. Analysis cohort by weight change category classified by latency class at 3, 6, and 12 months post baseline/randomization.

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	877/1285				<0.0001*
0%-5%	627/891	0.132	1.14	(1.03-1.27)	0.0142**
>=5%	401/525	0.395	1.48	(1.31-1.68)	<0.0001**
Baseline BMI Category (Underweight (<18.5))	60/82				0.0053*
Normal (18.5 to <25)	760/1097	-0.159	0.85	(0.65-1.11)	0.2391**
Overweight (25 to <30)	664/972	-0.327	0.72	(0.55-0.94)	0.0165**
Obese (30 or Greater)	421/550	-0.236	0.79	(0.6-1.04)	0.0922**
Age Category (Younger than 65)	1190/1679				0.2563*
65 or Older	715/1022	-0.056	0.95	(0.86-1.04)	0.2572**
Performance Score (0)	985/1470				<0.0001*
1+	920/1231	0.318	1.37	(1.25-1.51)	<0.0001**
Gender (Female)	789/1078				0.1403*
Male	1116/1623	-0.07	0.93	(0.85-1.02)	0.1395**
Chemotherapy Type (5FU Based)	209/240				0.0066*
OX Based	626/755	-0.293	0.75	(0.62-0.9)	0.0022**
IRI Based	1070/1706	-0.171	0.84	(0.71-1)	0.0467**
Biologics Type (None)	1217/1579				<0.0001*
Cetuximab	313/620	-0.247	0.78	(0.69-0.89)	2e-04**
Bevacizumab	375/502	-0.356	0.7	(0.61-0.8)	<0.0001**

Appendix Table 6. Multivariate prediction model for progression-free survival using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio; *Type-III p-value. **Covariate-level p-value. C-value = 0.5900. Optimism-corrected C value = 0.5839.

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	489/578				<0.0001*
0%-5%	251/305	0.029	1.03	(0.88-1.21)	0.7191**
>=5%	200/223	0.558	1.75	(1.47-2.08)	<0.0001**
Baseline BMI Category (Underweight (<18.5))	32/35				0.1091*
Normal (18.5 to <25)	456/530	-0.206	0.81	(0.57-1.17)	0.2671**
Overweight (25 to <30)	318/380	-0.33	0.72	(0.5-1.04)	0.0816**
Obese (30 or Greater)	134/161	-0.367	0.69	(0.47-1.03)	0.0691**
Age Category (Younger than 65)	589/703				0.9236*
65 or Older	351/403	-0.007	0.99	(0.87-1.14)	0.9236**
Performance Score (0)	497/610				<0.0001*
1+	443/496	0.454	1.57	(1.38-1.8)	<0.0001**
Gender (Female)	385/458				0.1839*
Male	555/648	-0.092	0.91	(0.8-1.04)	0.1829**
Tumor Sidedness (Left Colon)	711/838				0.1432*
Right Colon	229/268	0.116	1.12	(0.96-1.31)	0.1395**
BRAF Status (WT)	893/1054				0.0014*
MT	47/52	0.533	1.7	(1.26-2.31)	6e-04**
Chemotherapy Type (5FU Based)	0/0				0.1413*
OX Based	210/266	0.12	1.13	(0.96-1.32)	0.1375**
IRI Based	730/840				
Biologics Type (None)	470/550				0.0244*
Cetuximab	470/556	-0.155	0.86	(0.75-0.98)	0.0244**
Bevacizumab	0/0				

Appendix Table 7. Multivariate prediction model for overall survival using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio. WT – wild type; MT – mutated; *Type-III p-value. **Covariate-level p-value. C-value = 0.6311. Optimism-corrected C value = 0.6229.

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	181/397				<0.0001*
0%-5%	167/367	0.233	1.26	(1.01-1.58)	0.0389**
>=5%	146/208	0.736	2.09	(1.65-2.64)	<0.0001**
Baseline BMI Category (Underweight (<18.5))	20/29				0.0321*
Normal (18.5 to <25)	193/360	-0.595	0.55	(0.34-0.89)	0.0151**
Overweight (25 to <30)	165/341	-0.711	0.49	(0.3-0.8)	0.0044**
Obese (30 or Greater)	116/242	-0.763	0.47	(0.28-0.77)	0.0028**
Age Category (Younger than 65)	289/585				0.0314*
65 or Older	205/387	-0.211	0.81	(0.67-0.98)	0.0322**
Performance Score (0)	207/514				<0.0001*
1+	287/458	0.424	1.53	(1.27-1.84)	<0.0001**
Gender (Female)	211/397				0.6588*
Male	283/575	0.041	1.04	(0.87-1.25)	0.6591**
Albumin Type 1 (g/L) (Step Size: 1)	494/972	-0.063	0.94	(0.92-0.96)	<0.0001**
N Metastatic Sites (0-1)	174/387				0.0789*
2+	320/585	0.472	1.6	(0.94-2.73)	0.0813**
Metastatic Site: Liver (No Involvement)	75/201				0.2715*
Involvement	151/302	0.179	1.2	(0.75-1.92)	0.4583**
Involv. and >=1 Other Involv.	268/469	0.227	1.25	(0.92-1.7)	0.1453**
Metastatic Site: Lung (No Involvement)	269/517				0.1259*
Involvement	9/47	-0.591	0.55	(0.25-1.23)	0.1454**
Involv. and >=1 Other Involv.	216/408	-0.177	0.84	(0.66-1.06)	0.1474**
Chemotherapy Type (5FU Based)	157/251				0.1382*
OX Based	60/87	-0.449	0.64	(0.4-1.01)	0.0571**
IRI Based	277/634	-0.099	0.91	(0.73-1.12)	0.3673**
Biologics Type (None)	226/419				2e-04*
Cetuximab	34/50	-0.328	0.72	(0.41-1.25)	0.2462**
Bevacizumab	234/503	-0.395	0.67	(0.55-0.82)	<0.0001**

Appendix Table 8. Multivariate prediction model for overall survival using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio. *Type-III p-value. **Covariate-level p-value. C-value = 0.7049. Optimism-corrected C value = 0.6969.

Param (Ref)	Events/N	Estimate	HR	95% HR CI	P-value
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	110/143				5e-04*
0%-5%	66/84	0.604	1.83	(1.33-2.52)	2e-04**
>=5%	54/64	0.463	1.59	(1.12-2.24)	0.0086**
Baseline BMI Category (Underweight (<18.5))	8/10				0.5531*
Normal (18.5 to <25)	112/141	-0.001	1	(0.48-2.09)	0.9973**
Overweight (25 to <30)	76/95	-0.071	0.93	(0.44-1.99)	0.8547**
Obese (30 or Greater)	34/45	-0.283	0.75	(0.34-1.68)	0.4898**
Age Category (Younger than 65)	139/181				0.4976*
65 or Older	91/110	-0.094	0.91	(0.69-1.2)	0.4988**
Performance Score (0)	90/128				<0.0001*
1+	140/163	0.698	2.01	(1.52-2.65)	<0.0001**
Gender (Female)	108/135				0.7405*
Male	122/156	-0.046	0.96	(0.73-1.25)	0.7404**
Metastatic Site: Peritoneal (No Involvement)	218/276				0.0442*
Involvement	12/15	0.682	1.98	(1.07-3.64)	0.0289**

Appendix Table 9. Multivariate prediction model for overall survival using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); HR – hazard ratio; 95% HR CI – 95% confidence interval for hazard ratio. *Type-III p-value. **Covariate-level p-value. C-value = 0.6512.

Param (Ref/Step Size)	Events/N	OR (95% CI)	P
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	89/1186		
0%-5%	71/800	1.24 (0.89-1.73)	0.2081
>=5%	66/444	2.18 (1.53-3.09)	<0.0001
Baseline BMI Category (Underweight (<18.5))	7/74		
Normal (18.5 to <25)	98/988	1.1 (0.49-2.5)	0.8181
Overweight (25 to <30)	77/875	1 (0.44-2.31)	0.9933
Obese (30 or Greater)	44/493	1.04 (0.44-2.46)	0.9238
Age Category (Younger than 65)	148/1525		
65 or Older	78/905	0.8 (0.59-1.08)	0.1400
Performance Score (0)	104/1310		
1+	122/1120	1.34 (1.01-1.77)	0.0428
Gender (Female)	99/976		
Male	127/1454	0.89 (0.67-1.18)	0.4233
Chemotherapy Type (5FU Based)	22/212		
OX Based	44/691	0.39 (0.21-0.72)	0.0028
IRI Based	160/1527	0.73 (0.42-1.26)	0.2612
Biologics Type (None)	130/1438		
Cetuximab	66/596	1.07 (0.78-1.49)	0.6705
Bevacizumab	30/396	0.56 (0.35-0.9)	0.0171

Appendix Table 10. Multivariate prediction model for identification of overall disease progression using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); OR – odds ratio; 95% OR CI – 95% confidence interval for hazard ratio. C-value = 0.6265.

Param (Ref/Step Size)	Events/N	OR (95% CI)	P
Cutoff: Weight Loss 3 Month/s from Baseline (Weight Gain/Stable)	730/1186		
0%-5%	481/800	0.94 (0.78-1.14)	0.5470
>=5%	232/444	0.66 (0.52-0.83)	0.0003
Baseline BMI Category (Underweight (<18.5))	52/74		
Normal (18.5 to <25)	585/988	0.6 (0.36-1.01)	0.0554
Overweight (25 to <30)	536/875	0.66 (0.39-1.12)	0.1250
Obese (30 or Greater)	270/493	0.51 (0.29-0.87)	0.0136
Age Category (Younger than 65)	891/1525		
65 or Older	552/905	1.21 (1.02-1.45)	0.0302
Performance Score (0)	819/1310		
1+	624/1120	0.76 (0.65-0.9)	0.0016
Gender (Female)	577/976		
Male	866/1454	0.98 (0.83-1.16)	0.8026
Chemotherapy Type (5FU Based)	106/212		
OX Based	424/691	1.85 (1.28-2.67)	0.0011
IRI Based	913/1527	1.57 (1.12-2.18)	0.0082
Biologics Type (None)	823/1438		
Cetuximab	391/596	1.49 (1.21-1.83)	0.0001
Bevacizumab	229/396	1.33 (1.02-1.73)	0.0358

Appendix Table 11. Multivariate prediction model for identification of overall disease response (partial or complete response status) using percent-based weight change at 3 months. BMI – body mass index (kilogram/m^2); OR – odds ratio; 95% OR CI – 95% confidence interval for hazard ratio. C-value = 0.5833.

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