Study Protocol

Change in Body Weight During Treatment of Advanced Colorectal Cancer

PROTOCOL DATE: **January 1, 2019**

PROPOSED RESEARCH PROJECT

a) Title:

Change in Body Weight During Treatment of Advanced Colorectal Cancer

Abstract

Objectives: To evaluate whether change in body weight in advanced colorectal cancer patients occurring during systemic anti-cancer treatment influences treatment outcomes

Hypothesis to be tested: Weight loss during treatment is associated with adverse treatment outcomes in patients with advanced colorectal cancer, compared to patients without weight loss or with weight gain.

Design: A pilot, prospective, single-centered observational study of patients with advanced colorectal cancer having first line systemic anti-cancer treatment.

Setting: Outpatient Clinical Oncology clinic in Tuen Mun Hospital

Participants: Patients having histologically proven stage IV colorectal adenocarcinoma, requiring systemic anti-cancer treatment, which entail chemotherapy (5-fluouracil, capecitabine, oxaliplatin and irinotecan) with or without targeted therapy (cetuximab or bevacizumab) as first line treatment.

Main outcome measures: Primary outcomes: disease control rate, progression free survival. Secondary outcomes: Dose reduction of systemic chemotherapy.

b) Introduction:

Colorectal cancer (CRC) is a significant and growing health burden in Hong Kong. According to data from Hong Kong Cancer Registry, CRC ranked the first in incidence and the second in mortality, with around 5,000 new cases diagnosed and more than 2,000 cancer-related mortality in 2014.[1] Around one-fourth of CRC present as metastatic disease; it is also estimated that 50-60% of patients diagnosed with CRC eventually develop metastasis during their course of disease.[2] Among metastatic CRC (mCRC) patients, only few with limited metastases are potential long-term survivors after receiving locoregional treatment,[3] while the majority of them are incurable and the standard treatment is systemic therapy.

Over the past 15 years, the introduction of molecular targeted therapy into mCRC treatment armamentarium has dramatically improved the prognosis, with the median overall survival (OS) 14-16 months in the pre-targeted therapy era compared with around 30 months nowadays.[4] Systemic therapy with combination chemotherapy, Oxaliplatin-based or Irinotecan-based, plus targeted therapy, either anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAb) or anti-vascular endothelial growth factor (anti-VEGF) mAb becomes the current standard first-line treatment.

Studies have suggested that exposure to a greater number of chemotherapeutic agents is associated with better survival.[5] Therefore, the current principle of management of mCRC emphasizes on maximizing the exposure of various chemotherapeutic and molecular targeted agents in a stepwise manner.[6, 7]

However, these treatments have their peculiar side effects. Many chemotherapy treatments are dosed based on body weight or body surface area (BSA), with recommended milligrams (mg) per BSA (m^2) derived from studies testing for dose-limiting toxicities. Nevertheless, many patients still experience severe toxicity and subsequently experience reductions in dose or dose delays or discontinue treatment prematurely.[8, 9] Discontinuation, reductions, and delays in chemotherapy might adversely affect prognosis by reducing the exposure to therapeutic agents.[8, 10, 11] Great variability exists in patients' tolerance for cancer treatment that is not explained by age and comorbidities.[12, 13] Body composition, the amount and distribution of fat and lean soft tissue (the main compartment of which is skeletal muscle mass), is one factor influencing the pharmacokinetics and pharmacodynamics of many chemotherapeutic agents.[14]

Studies were conducted to evaluate the role of muscle mass and treatment tolerance and outcome in CRC patients.[8, 11] Computed tomography (CT) based cross-sectional measurement of muscle mass was shown to be highly correlated with total body muscle mass.[15] Based on this information, in a recent study by Feliciano et al.,[8] muscle mass was quantified using CT and was used to evaluate if body composition at diagnosis was associated with chemotherapy tolerance and overall survival in the adjuvant setting. The authors concluded that low muscle mass was associated with greater treatment toxicity and poorer chemotherapy adherence.[8] The evidence so far suggested muscle mass has prognostic value. However, the measurement required specialized software and staff training, making this resource draining and time-consuming. This produces practical difficulty especially for community oncology centers where budget and manpower is tight. It is likely that the measurement will be used mainly as research tool unless computer automation is available widely. Furthermore, other observational studies of muscle mass and treatment outcomes have been limited by modest sample size, and inadequate adjustment for confounding factors such as age, disease stage, race or comorbidities.[16, 17]

An alternative is to measure the weight change or body mass index (BMI). In patients with CRC weight loss is common at disease presentation.[9, 10] Weight loss is one of the diagnostic criteria for cancer cachexia, and is closely related to poor prognosis in cancer.[18] Weight loss is not only a problem at diagnosis, but is also encountered during treatment which might impair patients' tolerance to treatment, and treatment outcomes. In one retrospective study, 35% patients with mCRC already had weight loss on presentation, and it was shown that these patients received less systemic treatment on average, had significantly reduced tumor response, failure free survival, and OS.[10] In contrast, weight stabilization or reversal of weight loss during treatment was associated with longer failure free and OS in that study.[10] Similar relationship between serial body weight and outcome has been detected in advanced non-small cell lung cancer patients. Patel et al. reported weight gain of at least 5% was associated with higher response rate (odds ratio 2.55) and overall survival (OS) (HR 0.54), and progression-free survival (PFS) (HR 0.59).[19] Hypotheses include better nutritional status can improve the host's immunity and anti-cancer effects, and tumour control might inhibit or reverse the processes that promote cachexia and allow weight gain.[19, 20]

Multiple factors might affect body weight during treatment. Cancer-related symptoms can impair quality of life and appetite. Cachexia syndrome affects around 50% of colon cancer patients and is characterized by cancer-induced catabolism with involuntary weight loss (fat and muscle), patients have increased lipolysis and change in skeletal muscle metabolism, including increased energy expenditure at rest and protein degradation, and decreased protein synthesis.[21] Besides these disease factors, treatment related side effects are common causes of weight loss, such as inability to ingest or digest food effectively due to nausea, vomiting, and malaise. Based on these factors and the hypotheses between tumour control and weight gain, monitoring the serial weight change can have practical value. Body weight can be monitored readily in each clinical follow-up session. Increasing or maintained weight might indicate that the cancer is not worsening and the patient tolerates treatment well. In contrast, weight loss during treatment might alert clinicians to review for disease progression and patient's tolerance to treatment, with corresponding change in strategies initiated (including proactive symptom control, early stopping of ineffective treatment, change in treatment regimen, or earlier palliative care). Cost in healthcare may be saved by more efficient use of resource.[22]

As for dose reduction, toxicity, especially hematological, is the most common reason. In patients with metastatic disease, chemotherapy dose intensity is consistently associated with increased rates of complete and partial response, as well as PFS.[23]

Measurement of weight has the advantages of being cheaper, and easier, and the equipment is widely available in the clinic, whereas measurement of muscle mass needs CT or advanced techniques such as bio-impedance analysis. To the best of our knowledge, no prospective study has reported the impact of serial weight change during treatment for mCRC in terms of treatment tolerance and treatment outcomes. Studies have attempted to evaluate the value of measuring pre-treatment muscle mass or BMI in predicting patients' tolerance to systemic anti-cancer treatment, but most of them were for adjuvant setting and no serial measurement was made during the course of chemotherapy.[8, 11] These studies were not specifically conducted for mCRC patients undergoing first line palliative systemic treatment. We believe that body weight is strong clinical indicator of benefits related to tolerability and tumor response, in addition to tests such as liver and renal function tests or serum tumor markers during treatment. Besides, by establishing and quantifying the relationship between weight and patient outcomes, the potential value of nutritional interventions and what constitutes the cost-effective method to monitor patients during treatment can be evaluated in the future. Thus, for the potential benefits to both local and global healthcare system, we undertake this pilot study to assess the relationship between serial weight change and treatment tolerance (as reflected by dose reduction), tumor response (by disease control rate [DCR]) and survival outcomes (by PFS).

Work done by us

Our team has previously carried out different kinds of oncology research, including in the field of

CRC. Tuen Mun Hospital is a tertiary referral oncology center with high clinical volume. Our team has extensive clinical experience on CRC and managed more than 1000 new cases of colorectal cancer per year; around 60% of them had metastatic disease either at the time of presentation or recurrence. More than 150 new patients start first line systemic treatment for mCRC each year.

c) Aims and Hypotheses to be Tested:

Aim:

To evaluate the association between serial weight change during first line treatment and outcomes in patients with mCRC.

Hypothesis to be tested: Weight loss during treatment is not associated with adverse treatment outcomes in patients with advanced colorectal cancer, compared to patients without weight loss or with weight gain during treatment.

Main outcome measures:

(1) Primary endpoint: DCR which includes stable disease, partial response and complete response as defined in RECIST 1.1; and PFS defined as the time from randomization until first evidence of objective tumour progression (as defined in RECIST 1.1) or death from any cause, with censoring of patients who are lost to follow-up.

(2) Secondary endpoints: Dose reduction is defined as <70% of relative dose intensity, which represents the ratio of dose intensity (dose given per unit body surface area per unit time i.e. mg/m^2/week) actually administered, to standard dose intensity.[8]

d) Plan of Investigation:

(i) Subjects

Sample size calculation:

We used power analysis program G*Power to calculate sample size.[24] Estimated proportion of subjects having significant weight loss is approximately 15%. Risk ratio of dose reduction was about 3.0 for patients with significant weight loss, according to a study in adjuvant setting. Prior study indicated that the failure rate among controls is 0.2. We will need to recruit 240 patients to be able to reject the null hypothesis that the primary endpoints (incidence of dose reduction) for patient with and without significant weight loss are equal with probability (power) 0.8. Assuming 10% loss to follow-up, total number of patients to require is 264. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use logistic regression to evaluate this null hypothesis.

Inclusion criteria for studies

We recruit male and female patients aged 18 years or older with stage IV, histologically

confirmed colorectal adenocarcinoma who will receive systemic treatment, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, an estimated life expectancy of greater than 3 months, and adequate organ function. We exclude patients who are pregnant, have human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and past medical history of another cancer.

(ii) Methods

This study is prospective observational cohort study, recruitment period is 24 months. We start to collect data once patient is recruited and individual data can be available before end of recruitment period. Baseline weight (in kilogram), height (in centimeter), and BMI (in kilogram per height in meters squared) are measured by medical assistants closest to the start of treatment as baseline, and at onset of every treatment cycle. Patients are weighed without shoes, in light clothes or hospital gowns, using a Seca digital scale with graduation 0.01 kg. Body height is measured to the nearest 0.1 cm with the same digital scale with graduation 0.1 cm.

Patients' demographics (age, sex, and ethnicity), and disease characteristics (left versus right colon cancer, RAS status) are collected. Other clinical variables considered to be important prognostic factors are collected and included in the analysis: TNM cancer stage, histological grade, peripheral blood neutrophil-lymphocyte ratio, serum carcinoembryonic antigen (CEA) level, ECOG performance status, Charlson comorbidity index.[25]

(iii) Study design

Disease is staged by CT from thorax to pelvis or positron emission tomography-computed tomography (PET-CT). Clinical assessment (history taking and physical examination) and routine laboratory tests (complete blood counts, liver and renal function tests) are performed at baseline and before every treatment cycle according to daily practice. Adverse events are assessed using clinical and laboratory data, and graded by using Common Terminology Criteria for Adverse Effects, version 4.02.

The treatment doses and administration dates are recorded at chemotherapy infusion tables. Any treatment delay and dose reduction is recorded.

Patient is followed up at each treatment cycle. Some patients opt for treatment interruption after four to six months of treatment to avoid cumulative toxicity and preserve a good quality of life, and are put on close monitoring, treatment can be reinitiated when progression is detected. Interval assessments of disease response are made with physical examination (every clinic visit), serum CEA level, and three to six monthly CT, PET-CT or X-ray.

Ethical consideration: Our study adds no additional procedure or risk to the daily management of patients. Only medical personnel involving in care and the study can access the data, and sufficient protection of patient privacy is ensured. Data are entered and stored in the department computer for research purpose only. Data are protected by password. No personal identifier will be included in the data processing. All data will be destroyed 3 years after completion of study. The Clinical and Research Ethics Committee of New Territories West Cluster is reviewing the ethical aspects including the waiving of written informed consent.

Choices of systemic treatment regimens are available in appendix 1. Dose modifications details of the regimens are available in appendix 2.

(iv) Data processing and analysis

We present descriptive statistics (mean +/- standard deviation, median [range] and percentages) of weight change. Weight change is defined as maximum weight change during treatment. Besides being a continuous variable, the data on weight are divided into three groups: weight gain is >5% body weight increase, weight loss is >5% weight loss, the rest is stable weight. 5% is used as a cut-off to account for daily fluctuation in weight and standard error in measurement.

Unadjusted logistic regression is used to explore the association between baseline covariates and weight change during treatment.

For primary outcomes:

Time to death (PFS) as a function of weight change is evaluated by Kaplan Meier estimates, log-rank tests. Joint modelling approach that can model longitudinal and time-to-event data components jointly is used to assess the association between weight change and PFS. Fisher's exact test is used to compare the DCR between weight change groups as univariate analysis. Then adjusted logistic regression is used to assess the association between weight change and DCR. The models will be adjusted for age, sex, targeted therapies. Other variables, such as Charlson's comorbidity index, and BMI may be selected as covariables. Likelihood ratio test will be used to compare models for selecting the final model.

For secondary outcomes:

We use Chi squared test to explore the association between weight change and dichotomous outcomes (dose reduction in treatment). Then separate regression models are used to further estimate the association as multivariate analyses. Weight change will be analysed as continuous variable, and ordinal variable (coding continuously 0, 1 and 2 for weight loss, stable weight and weight gain respectively). Dose reduction is analysed as dichotomous variable. The models will be adjusted for age, sex, targeted therapies. Other variables, such as Charlson's comorbidity index, and BMI can be included as covariables. Likelihood ratio test

will be used to compare models for selecting the final model. BMI has been found to be correlated positively with muscle mass, and is associated with treatment outcomes and side effects in different cancers.

Stata is used for all analyses. All significance tests are two-sided.

e) Existing Facilities:

The Department of Clinical Oncology at Tuen Mun Hospital will be the primary center for the conduct and analytic work in this study. We have an experienced team of researchers of performing cancer research.

f) Justification of Requirements:

Travel costs: We have included in our budget travelling costs for one trip to attend international conferences ($10,000) in year 3. This is to reflect the need to present results at leading international conferences. This travel is mainly intended for international conference attendance.

Publication costs: These will cover the fee to publish the results in high-profile impact Open Access journals estimated at $20,000 each. We will promote Open Access publications, according to the 2003 Berlin Declaration, as an additional mean to disseminate research effectively to large audiences. Publications will be uploaded to the open access repository “Dryad” and official site of Tuen Mun Hospital.

Other goods: scientific software: i) Stata-SE 15 one-core statistical software license for 1 computer (USD$1,695 ~ HKD$13,302). English editing services for research articles estimated at $5,000 each. We further prepare $3,000 for reference materials. We budget $1,000 each year for stationeries and other expenses (e.g. printing and postage) because we expect printing and photocopying of a large amount of literature as well as miscellaneous office expenses relate mostly to the data collection, analysis, reporting and writing phase of the study.

g) Purpose and Potential:

CRC ranks the first in cancer incidence and second in cancer-related mortality in Hong Kong; and around 60% of CRC patients develop metastasis during their course of illness. This study will quantify the impact of weight change on the tolerability of treatment, as reflected by the need of dose reduction, and prognosis. Weight is easy and cheap to measure, which is suitable for resource-tight healthcare system such as that in Hong Kong. These are clinically important end-points which potentially impact the treatment strategies of stage IV colorectal cancer, including the nutritional intervention, and early stop or reducing dose of chemotherapy in case of weight loss.

Based on this study, further research can be conducted to evaluate the health economics on different treatment strategies which may affect the funding decision of health care payer and the future health care policy.

The results of this study will be submitted to international, peer-reviewed journals, and be presented in academic conferences.

h) Key References:

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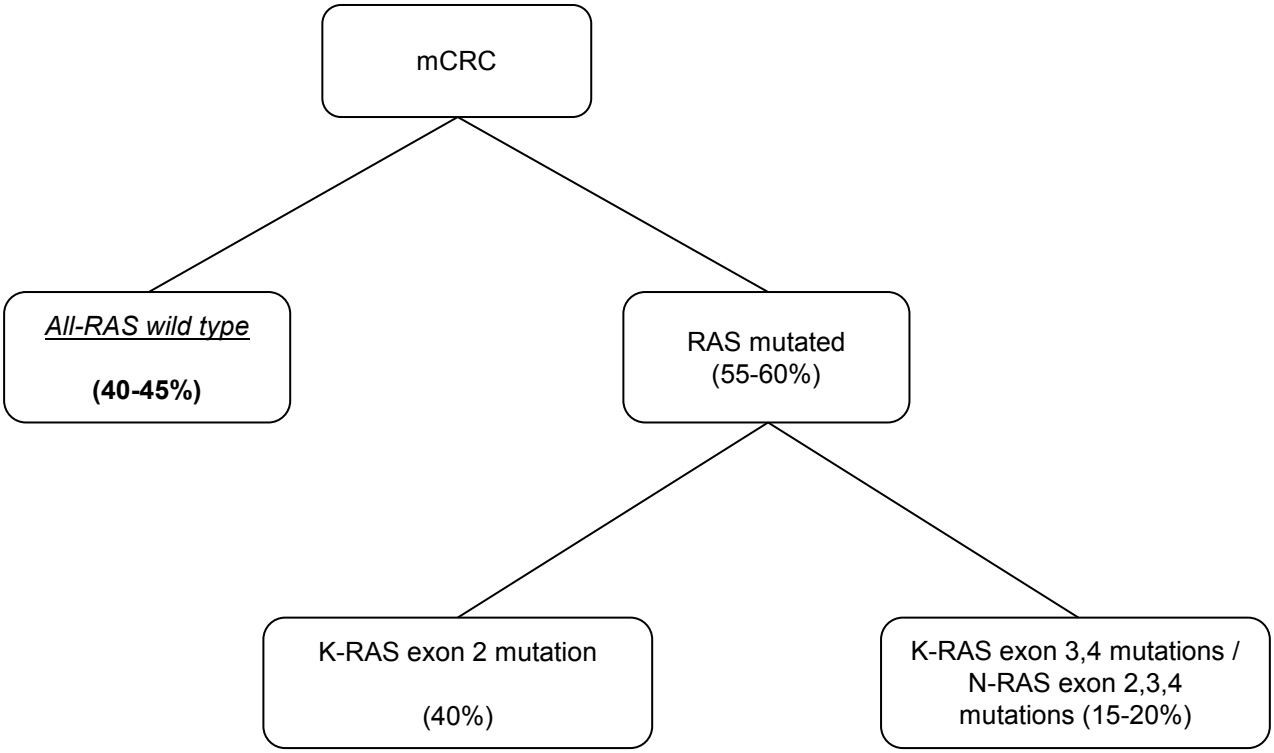
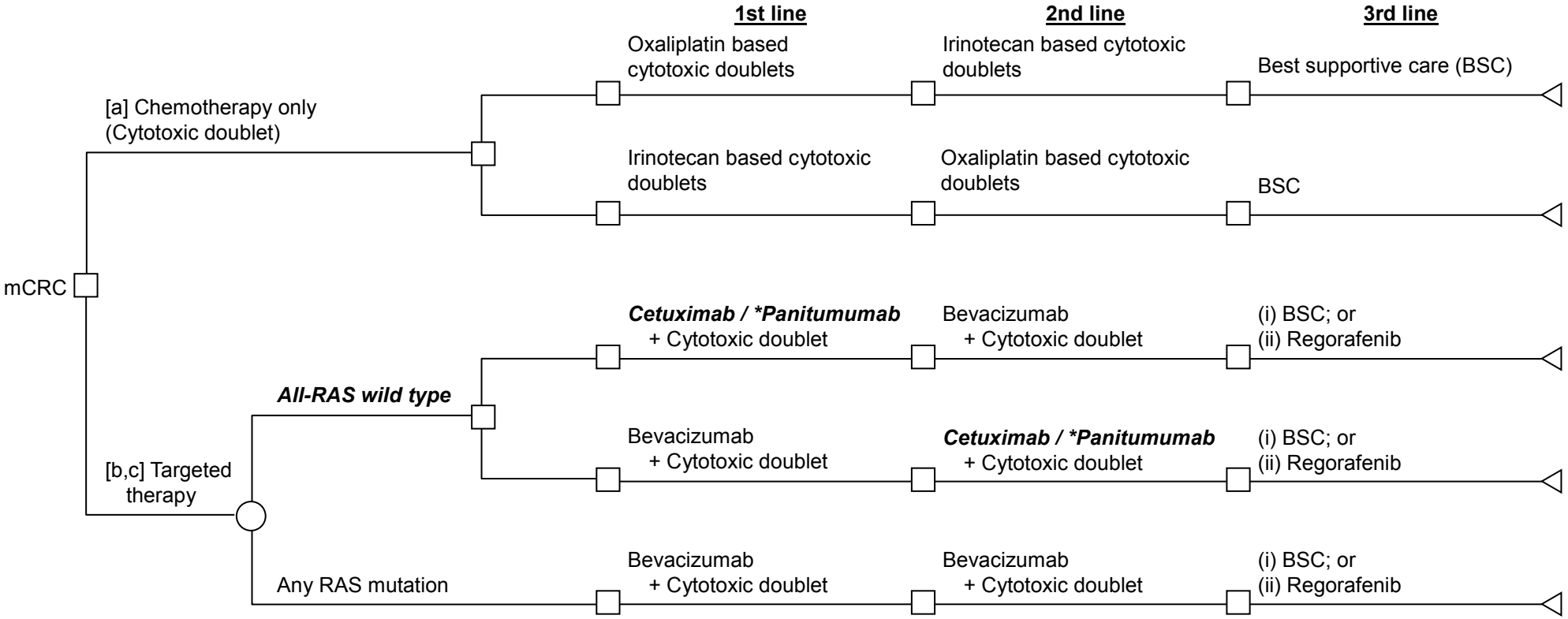
Figure 1. Grouping of mCRC tumors by KRAS exon 2 mutations and extended RAS mutations



Ref. [6, 7]

Figure 2. Simplified management algorithm in mCRC.



Abbreviations / remarks: BSC: best supportive care. *Panitumumab is not commonly used in our center, therefore it is not included in the study.

Notes: [a] In patients who cannot afford targeted therapy, only chemotherapy (cytotoxic doublet) will be available as the first- and second-line treatment and best supportive care (BSC) as the third-line treatment.

[b] In patients who can afford targeted therapy. Either anti-EGFR or anti-VGFR monoclonal antibodies (mAb) are indicated for all-RAS wild type; whereas only anti-VGFR mAb is applicable for RAS mutated patients.

[c] Using either (1) Oxaliplatin based cytotoxic doublets as the first-line and Irinotecan based cytotoxic doublets as the second-line, or (2) vice versa, as cytotoxic doublet chemotherapy regimens (i.e., the same paths as in [a] chemotherapy only).

Ref. [6, 7]