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Fruquintinib Monotherapy Versus Fruquintinib Combined with Chemotherapy in Patients with Refractory Metastatic Colorectal Cancer: A Real-World Retrospective Cohort Study

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Fruquintinib Monotherapy Versus Fruquintinib Combined with Chemotherapy in Patients with Refractory Metastatic Colorectal Cancer: A Real-World Retrospective Cohort Study

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Abstract

Purpose: Fruquintinib is a selective vascular endothelial growth factor receptor (VEGFR)-1/2/3 inhibitor approved for refractory metastatic colorectal cancer (mCRC). Whether combining fruquintinib with chemotherapy improves outcomes over monotherapy in late-line clinical practice remains unknown.

Methods: We conducted a retrospective cohort study of patients with mCRC who received fruquintinib at a single institution. Patients were categorized as fruquintinib monotherapy (monotherapy group) or fruquintinib plus chemotherapy (combination group). Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox regression analysis was performed to evaluate risk factors for PFS and OS.

Results: Forty-seven patients were included (monotherapy group n = 11, combination group n = 36). The median number of lines of therapy at the time of fruquintinib initiation was 6. The combination group demonstrated significantly longer PFS (6.1 vs. 2.2 months; log-rank p = 0.001) and a numerically longer OS (not reached vs. 11.7 months; p = 0.14). On multivariable analysis, combination therapy was independently associated with improved PFS (hazard ratio [HR] 0.39, 95% CI 0.16–0.98; p = 0.045). Disease control rates were 60.7% in the combination group versus 18.2% in the monotherapy group.

Conclusions: Fruquintinib combined with chemotherapy was associated with significantly better PFS and a substantially higher disease control rate compared with monotherapy in this real-world cohort. These hypothesis-generating findings are consistent with emerging combination data and support prospective evaluation.

Keywords: fruquintinib; metastatic colorectal cancer; combination chemotherapy; progression-free survival; VEGFR inhibitor; real-world study

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1. Introduction

Colorectal cancer (CRC) is one of the most prevalent and lethal malignancies worldwide, with metastatic disease carrying a five-year survival rate below 15%[1]. Despite frontline chemotherapy combined with anti-VEGF (bevacizumab) or anti-EGFR (cetuximab, panitumumab) agents, patients with metastatic CRC (mCRC) often develop refractoriness requiring later-line treatment [2].

The later-line mCRC therapy is mainly composed of three oral agents: regorafenib, trifluridine/tipiracil (TAS-102), and fruquintinib. Regorafenib, a multi-kinase inhibitor, demonstrated a modest overall survival (OS) benefit over placebo in the CORRECT trial (HR 0.77; median OS 6.4 vs. 5.0 months) [3]. TAS-102, an oral fluoropyrimidine analogue, demonstrated superior OS versus placebo in the RECOURSE trial (HR 0.68; median OS 7.1 vs. 5.3 months) [4], with following SUNLIGHT trial significantly extended OS by combining bevacizumab over TAS-102 monotherapy (10.8 vs. 7.5 months; HR 0.61) [5]. Hence, it also validated that anti-angiogenic augmentation can substantially enhance the efficacy of a later-line backbone agent.

Fruquintinib is a highly selective oral VEGFR-1/2/3 inhibitor developed in China and globally approved. The phase III FRESCO trial demonstrated improved OS (9.3 vs. 6.6 months; HR 0.65) and progression-free survival (PFS) (3.7 vs. 1.8 months) versus placebo in previously treated Chinese patients with mCRC [6]. The global phase III FRESCO-2 trial subsequently

confirmed benefit in patients who had already progressed on or were intolerant to both TAS-102 and regorafenib (OS: 7.4 vs. 4.8 months; HR 0.66; PFS: 3.7 vs. 1.8 months; HR 0.32), leading to U.S. FDA approval in November 2023 [7]. Both the National Comprehensive Cancer Network (NCCN) 2026 guidelines and the ESMO 2026 Clinical Practice Guideline now list fruquintinib as a Category 1 recommendation for later-line mCRC, along with TAS-102 ± bevacizumab and regorafenib[8, 9].

The success of the SUNLIGHT paradigm provoked a clinical question: can combining fruquintinib with chemotherapy similarly augment its monotherapy efficacy? A multicenter, single arm phase 2 trial (n = 100) evaluating fruquintinib plus investigator-choice chemotherapy as second-line therapy reported a median PFS of 6.9 months and OS of 20.1 months with a manageable safety profile [10]. Another updated single arm phase 2 trial of fruquintinib combined with TAS-102 as third-line therapy (n = 50) also reached a median PFS of 6.33 months and OS of 18.4 months [11]. Real-world data from a Chinese multicenter cohort (n = 520) identified combination therapy as an independent prognostic factor for both PFS and OS on multivariable analysis [12]. A recently-released multicentered, single arm phase 2 trial (n = 42) in at least second-line treatment of mCRC treated with fruquintinib plus either FOLFIRI or mFOLFOX6 also reached a median PFS of 8.1 months with median OS not reached [13]. In contrast, fruquintinib combined with immune checkpoint inhibitors (ICIs) in microsatellite-stable (pMMR/MSS) advanced CRC failed to demonstrate a clear PFS advantage over monotherapy in a recent retrospective study [14]. Similarly, the Phase III LEAP 017 trial of lenvatinib plus pembrolizumab failed to show superiority over standard of care in previously treated metastatic colorectal cancer [15], suggesting that the choice of combination partner for VEGFR inhibition may be critical. Therefore, our study aimed to compare the efficacy of fruquintinib monotherapy

with fruquintinib combined with chemotherapy in a real-world cohort of patients with refractory mCRC treated at our institution.

2. Materials and Methods

2.1 Study Design and Patient Population

This was a single-center, retrospective cohort study conducted at Taipei Veterans General Hospital, Taiwan. Patients with histologically confirmed mCRC who received systemic treatment in the hospital between January 1st, 2010 and December 31st, 2025 were identified from institutional records. Inclusion criteria were: (1) age ≥ 18 years at fruquintinib initiation; (2) confirmed metastatic CRC; (3) fruquintinib administered as any line of therapy; and (4) at least one post-treatment disease assessment or documented clinical event. Patients with incomplete treatment records were excluded.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital.

2.2 Treatment Groups

Treatment modalities were determined at the physicians' discretion. In accordance with the FRESCO-2 trial [7], fruquintinib was administered at the approved dose of 5 mg once daily for 21 consecutive days followed by a 7-day rest period. As emerging evidence from small-cohort studies supported the feasibility of fruquintinib-based combination regimens [10, 11], concurrent chemotherapy was incorporated from the outset for patients who subsequently initiated fruquintinib.

Therefore, according to the treatment strategies, patients were retrospectively categorized into two groups based on the treatment regimen:

- **Fruquintinib monotherapy (monotherapy group):** fruquintinib alone
- **Fruquintinib plus chemotherapy (combination group):** fruquintinib combined with any cytotoxic chemotherapy regimen, administered concurrently or in a planned combination schedule at the treating physician's discretion

2.3 Data Collection

The following baseline variables were collected: age; sex; primary tumor sidedness (right colon defined as cecum to splenic flexure); initial cancer stage at diagnosis; mismatch repair (MMR) status (assessed by immunohistochemistry or PCR-based microsatellite instability testing); RAS and BRAF mutation status (determined by next-generation sequencing or standard molecular assay); primary tumor resection status; primary tumor radiation status; treatment line at fruquintinib initiation; presence of lung, liver and brain metastases; and carcinoembryonic antigen (CEA) and Cancer Antigen 19-9 (CA 19-9) level at treatment initiation. Eastern Cooperative Oncology Group (ECOG) performance status was unavailable for analysis in this cohort and was therefore excluded from all models.

2.4 Endpoints and Definitions

The **primary endpoint** was PFS, defined as the time from fruquintinib initiation to documented disease progression per RECIST 1.1 criteria (increase in the length of measurable lesions for more than 20%) or death from any cause, whichever occurred first. Chest and abdominal CT were performed every two to four months by physicians' decision according to

the clinical situation after initiation of fruquintinib. Patients without a progression event were censored at last follow-up.

Secondary endpoints included: OS, defined as time from fruquintinib initiation to death from CRC (alive patients censored at last follow-up); objective response rate (ORR), defined as the proportion of response-evaluable patients achieving complete response (CR) or partial response (PR) per RECIST 1.1; and disease control rate (DCR), defined as the proportion achieving CR, PR, or stable disease (SD).

2.5 Statistical Analysis

Continuous variables are reported as median (range) and categorical variables as frequency (percentage). Between-group comparisons used the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Survival curves were estimated by the Kaplan–Meier method and compared by log-rank test. Median follow-up time was estimated by the reverse Kaplan-Meier method. Baseline characteristics and possible risk factors were put into the univariate Cox regression model. Data completeness was confirmed for all variables included in the analysis. No missing data were identified across the study cohort. Variables with $p < 0.1$ in the univariate analyses were entered into a multivariable model to assess the independent association of treatment group with PFS and OS, adjusting for age at initiation, sex, and RAS mutation count. Results are expressed as HR with 95% confidence intervals (CI). All analyses were performed in SPSS version 26.0.0.0. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Patient Characteristics

A total of 47 patients who received fruquintinib were included: 11 in the monotherapy group and 36 in the combination group. Baseline characteristics are summarized in **Table 1**. The median age was 60.0 years in the monotherapy group and 58 years in the combination group. Male patients comprised 36.4% and 33.3% of each group, respectively. Right-sided primary tumor was more frequent in the monotherapy group (54.5% vs. 27.8%). Nearly all patients had microsatellite-stable/proficient MMR (pMMR/MSS) disease; dMMR/MSI-H status was identified in one patient in combination group (2.8%). RAS mutation was more prevalent in the monotherapy group (81.8% vs. 52.8%). BRAF mutation was absent in the monotherapy group and present in 5.6% of the combination group. Median CEA and CA 19-9 at fruquintinib initiation were both higher in the monotherapy group (82.3 vs. 39.1 ng/mL in CEA; 58.2 vs. 210 ng/mL in CA 19-9). Combination chemotherapy was listed in Supplemental Table 1. No individual variable reached statistical significance between groups, and the imbalances in RAS mutation rate, primary tumor sidedness, and baseline CEA all showed no significant difference in either independent T tests, Fisher's Exact exam or Pearson Chisquare test, and were addressed in the multivariable analysis and limitations.

3.2 Tumor Response

The median follow-up time was 7.3 months (95% CI 5.7–8.9) for the entire cohort (8.9 months (95% CI 7.9–9.9) in monotherapy group; 6.4 months (95% CI 5.4–7.4) in the combination group). Tumor response was evaluable in 39 of 47 patients (monotherapy 11/11 [100%], combination 28/36 [77.8%]; **Table 2**). No patient in either group achieved CR. In the

monotherapy group, 0 of 11 patients achieved PR (ORR 0%) and 2 of 11 achieved SD (DCR 18.2%); progressive disease (PD) was reported in 9 of 11 patients (81.8%). In the combination group, 2 of 28 patients achieved PR (ORR 7.1%), 15 of 28 achieved SD, and 11 of 28 had PD, yielding a DCR of 60.7%. The DCR was substantially higher in the combination group (60.7% vs. 18.2%).

3.3 Progression-Free Survival

The PFS analysis included 47 patients (monotherapy n = 11; combination n = 36). Kaplan–Meier analysis demonstrated a significantly longer PFS in the combination group (**Figure 1**). Median PFS was 6.1 months (95% CI 4.9–7.3) in the combination group versus 2.2 months (95% CI 1.7–2.7) in the monotherapy group (log-rank $p = 0.001$).

On multivariable Cox regression adjusting for age, sex, and RAS mutation count, combination therapy remained an independent predictor of improved PFS (HR 0.39, 95% CI 0.16–0.98; $p = 0.045$; **Table 2**). No other covariate reached statistical significance: initial Stage IV (HR 2.07, 95% CI 0.74–5.80; $p = 0.167$; **Figure 2**), primary site undergoing operation (HR 0.45, 95% CI 0.18–1.09; $p = 0.077$; **Figure 2**), and RAS mutation count (HR 1.92, 95% CI 0.79–4.68; $p = 0.149$; **Figure 2**).

3.4 Overall Survival

The median OS was 11.7 months (95% CI 5.0–18.4) in the monotherapy group, and the combination group median OS was not reached (**Figure 3**). OS events occurred in 7 of 11 (63.6%) mono patients versus 6 of 35 (17.1%) combination patients, indicating substantially immature OS data in the combination group (log-rank $p = 0.139$).

On standard multivariable Cox regression, combination therapy was associated with a numerically lower hazard of death (HR 0.41, 95% CI 0.11–1.48; $p = 0.2$), which did not reach statistical significance, consistent with the limited number of events in the combination group (**Table 3**). BRAF mutation is the only significant risk factor of mortality (HR 10.41, 95% CI 1.04–104.50; $p = 0.046$).

3.5 Adverse Effects

Since progressive disease may interfere with laboratory data as obstructive uropathy, obstructive jaundice and liver enzymes elevation, retrospective data within one month after fruquintinib initiation were analyzed. Adverse effects occurring within one month of fruquintinib was summarized in Supplemental Table 2. In the monotherapy group (n = 11), the most common toxicities were hypertension (45.5% Grade 1–2; 9.1% Grade 3–4), thrombocytopenia (36.4% Grade 1–2), and anemia (27.3% Grade 1–2). Notably, ALT elevation was observed in 18.2% of monotherapy patients at Grade 3–4 severity. In the combination chemotherapy group (n = 36), anemia (38.9% Grade 1–2) and hypertension (33.3% Grade 1–2; 16.7% Grade 3–4) were the predominant adverse effects, followed by ALT elevation (30.6% Grade 1–2) and thrombocytopenia (33.3% Grade 1–2). Skin rashes and hand-foot skin reactions were reported in 27.3% and 19.4% of patients in the monotherapy and combination groups, respectively. No statistically significant between-group differences were observed for any adverse effect (all $p > 0.05$), indicating a comparable safety profile between the two treatment regimens.

4. Discussion

This real-world retrospective cohort study demonstrated that fruquintinib combined with chemotherapy was associated with a significantly longer PFS (6.1 vs. 2.2 months; $p = 0.001$) and a markedly higher DCR (60.7% vs. 18.2%) compared with fruquintinib monotherapy in patients with refractory mCRC. OS data remain immature but trend toward benefit in the combination group (median OS not reached vs. 11.7 months).

Role of combination therapy

The PFS of 2.2 months observed in our monotherapy group is broadly consistent with published monotherapy benchmarks. Although direct cross-trial comparisons must be interpreted with caution, the median PFS of 2.2 months observed in our monotherapy group compares reasonably with the 3.7-month median PFS reported in the fruquintinib arm of FRESCO-2 [7], particularly given that our monotherapy cohort was enriched for adverse prognostic features: a later median treatment line (6th vs. 3rd or later in FRESCO-2), a higher prevalence of RAS mutations (81.8% vs. 63%), and a greater proportion of right-sided primary tumors (54.5% vs. 21%) — all established negative prognostic factors in mCRC [12]. By contrast, the combination group PFS of 6.1 months in later lines of therapy (median 7th line) aligns favorably with the phase II fruquintinib-plus-chemotherapy in second-line setting (PFS 6.9 months) [10] and with the updated fruquintinib-plus-FOLFIRI or mFOLOX6 second-line phase II result (PFS 8.1 months; n = 42) [13]. In our analysis of the choice of combination therapy, the choice of doublet/triplet therapy also showed significant superior PFS comparing to single-chemo group (Figure 4), supporting the generalizability of the combination benefit across settings and the

importance in selection of combination partners. The comparison of each clinical trial was listed on Table 4.

The mechanistic rationale for combining fruquintinib with chemotherapy parallels the VEGFR inhibition-plus-chemotherapy paradigm validated in the SUNLIGHT trial, which demonstrated that adding bevacizumab to TAS-102 approximately doubles PFS and extends OS by 3.3 months in refractory mCRC (PFS HR 0.44; OS HR 0.61) [5]. The choice of combination partner appears to influence outcome. In a recent retrospective study by Huang et al., fruquintinib combined with ICIs did not significantly improve PFS versus monotherapy in pMMR/MSS advanced CRC [14], and the phase III LEAP-017 trial of lenvatinib plus pembrolizumab similarly failed to outperform standard of care in unselected previously treated mCRC [15]. A salvage lenvatinib-based regimen in heavily treated patients also showed limited but selective benefit [16]. These negative ICI combination results contrast with the PFS benefit observed in chemotherapy-based combinations in our cohort and in phase II trials [10, 13], suggesting that cytotoxic chemotherapy—rather than immunotherapy—may be the more effective backbone for VEGFR inhibitor combination in the predominantly MSS mCRC population.

According to a previous discussion about fruquintinib's mechanism, highly selective VEGFR-1/2/3 inhibition may normalize tumor vasculature and thereby enhance chemotherapy delivery—the vascular normalization hypothesis—leading to additive or synergistic cytotoxicity [17, 18] The multivariable-adjusted HR of 0.39 for PFS in our cohort is consistent in magnitude with findings from the 520-patient Chinese real-world multicenter study, in which combination therapy was identified as an independent prognostic factor for both PFS (6.2 vs. 4.2 months) and OS (13.3 vs.11.0 months) [12]. According to this retrospective study, 76% received fruquintinib

as third-line treatment, and 25.6% patients received combination therapy with 53.4% of these patients receiving immunotherapy combination and 42.1% receiving chemotherapy combination. The mean PFS were 6.13 months and 5.8 months respectively, though whether there is significant difference between combination choice still requires further investigation [12].

Limitations

Several limitations of this study warrant emphasis. First, the retrospective, single-center design with a small monotherapy group (n = 11) limits statistical power and generalizability. Second, the non-randomized allocation introduces selection bias: the combination group had a more favorable baseline profile (lower RAS-mutant rate [52.8% vs. 81.8%], lower CEA, less right-sided primary tumor), all of which are associated with better prognosis in mCRC, and might be selected into combination group due to better performance status. Although multivariable Cox regression was applied to address these imbalances, residual confounding from unmeasured variables—particularly ECOG performance status (unavailable) and treatment line distribution—cannot be excluded. Third, OS data are immature, with only 6 events in the combination group, precluding definitive OS conclusions.

Moreover, further treatment choices after progression as expertise experience and crossover from monotherapy group to combination group may also interfere the OS result. Fourth, the combination regimen was not standardized across patients, representing heterogeneous chemotherapy backbones. Hence, the subgroup progression free survival was estimated via Kaplan-Meier method by log-rank test. Fifth, 6 patients in the combination group lacked PFS data, which may introduce further bias. Last but not least, combination with immunocheckpoint inhibitors was not conducted in this cohort, lacking multi-dimensional comparison. These limitations collectively restrict the current findings to hypothesis-generating

level evidence. Larger, prospective, preferably randomized studies with standardized combination regimens and longer follow-up are needed to confirm and extend these observations.

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5. Conclusions

In this real-world retrospective cohort of 47 patients with refractory mCRC, fruquintinib combined with chemotherapy was associated with significantly longer PFS (6.1 vs. 2.2 months; adjusted HR 0.39, 95% CI 0.16–0.98; p = 0.045) and substantially higher DCR (60.7% vs. 18.2%) compared with fruquintinib monotherapy. Consistent with the anti-angiogenic-plus-chemotherapy paradigm established by SUNLIGHT and with emerging phase 2 combination data, these findings support further prospective evaluation of fruquintinib-based combination strategies in the refractory mCRC setting.

Ethics approval and Informed Consent

This retrospective study was conducted based on population-based data from Taipei Veterans General Hospital, Taiwan. This study followed the guidelines of the Declaration of Helsinki and was approved by the ethics committee and institutional review board of Taipei Veterans General Hospital, Taiwan (No. 2026-06-006CC). The requirement for informed consent was waived due to the retrospective nature of the study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Competing Interest

The authors declare no conflicts of interest.

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Figure Legends

Figure 1. Kaplan–Meier Curves for Progression-Free Survival by Treatment Group

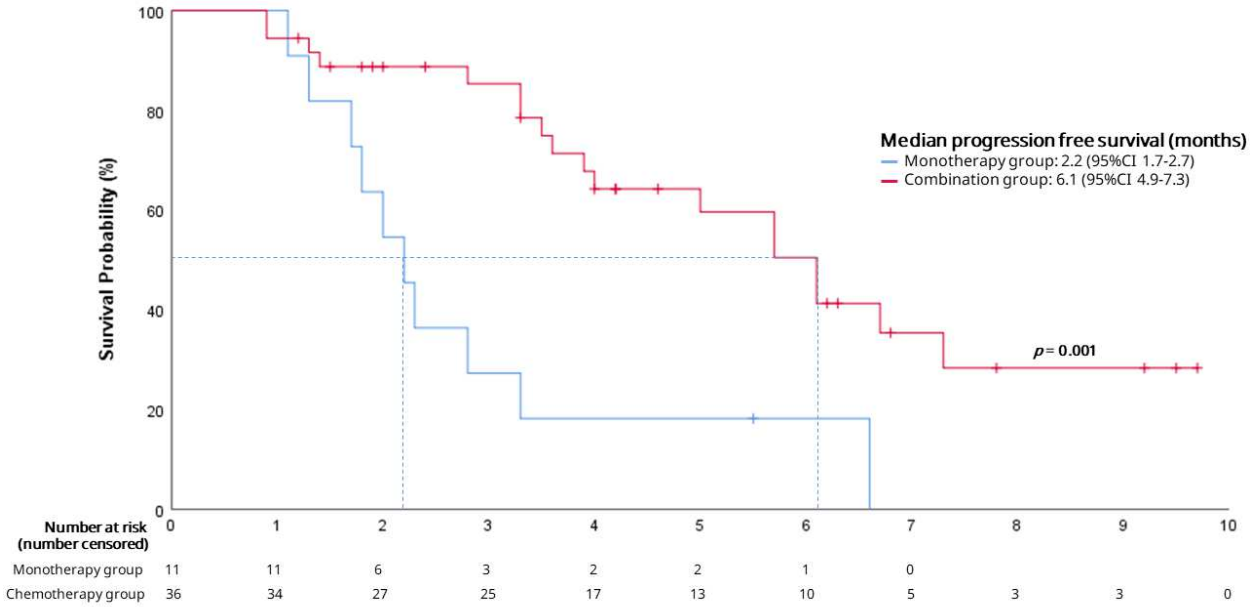


Figure 2. Forest plot of risk factors of progression for mCRC patients undergoing fruquintinib

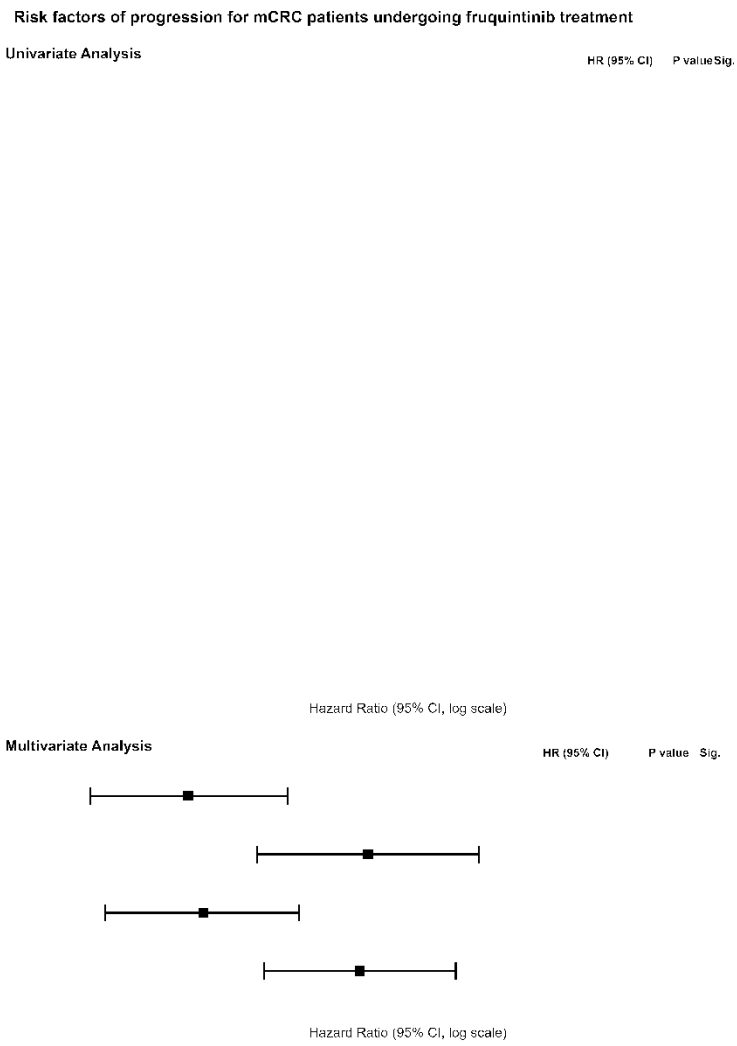


Figure 3. Kaplan–Meier Curves for Overall Survival by Treatment Group.

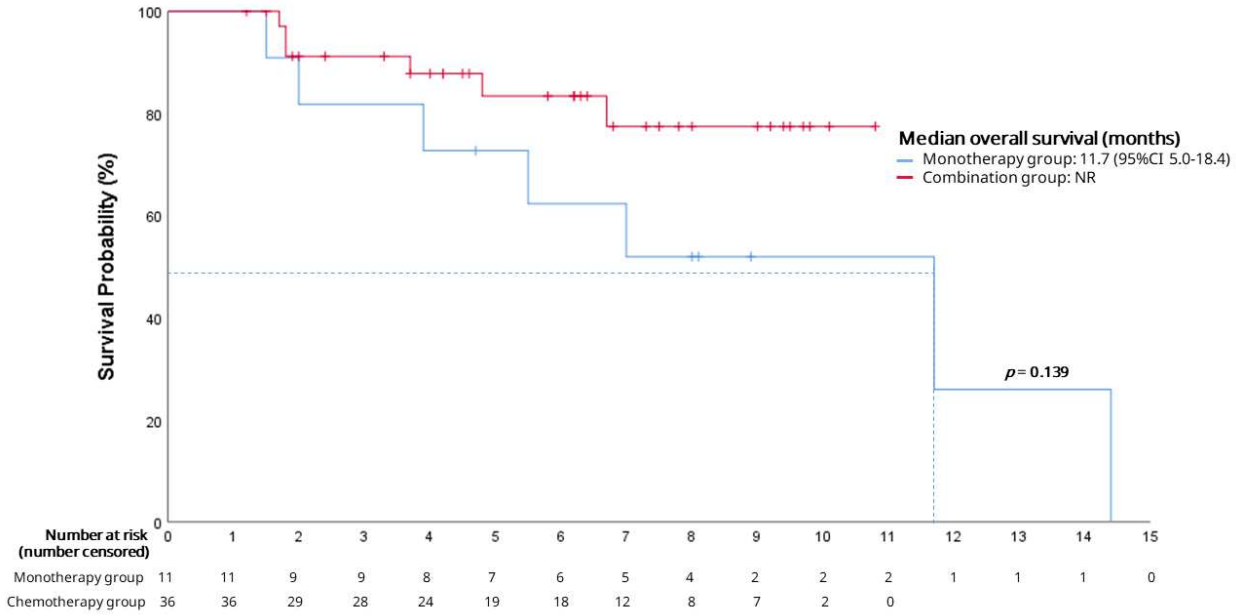
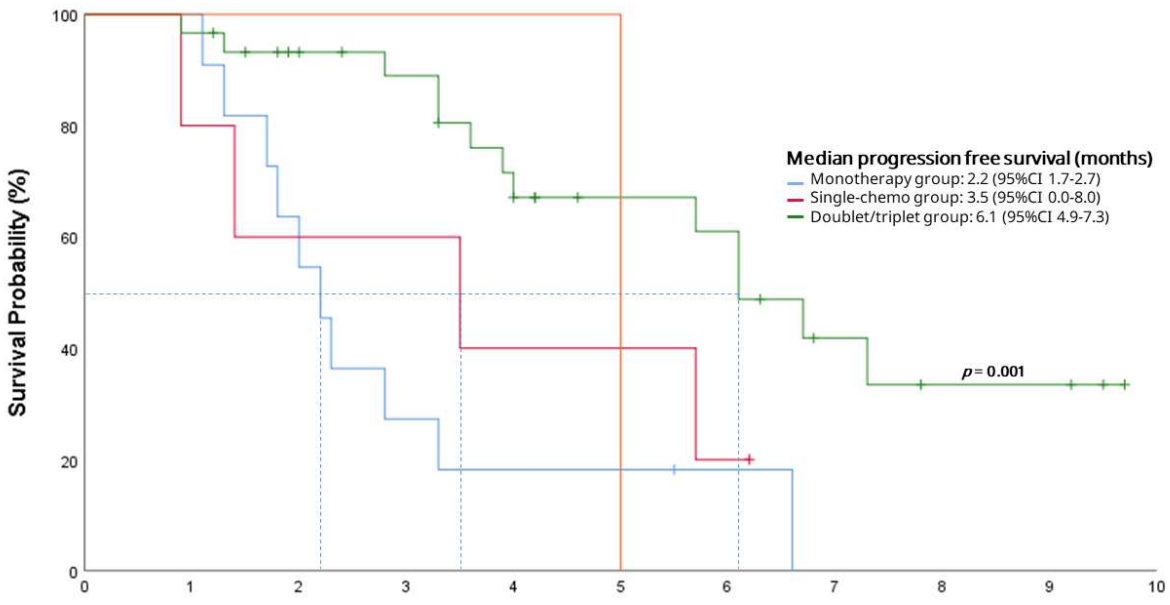


Figure 4. Kaplan–Meier Curves for progression-free survival by combination treatment choice



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