

Original Article

Efficacy of Stivarga and Lonsurf in Metastatic Colorectal Cancer: A Comparative Analysis Involving the Monotherapy and Combination Therapy Approaches

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Key Words

Colorectal cancer;

Stivarga;

Regorafenib;

Lonsurf;

Metastatic colorectal cancer

Purpose. This study aimed to compare overall survival (OS) and progression-free survival (PFS) between Stivarga (regorafenib) and Lonsurf (trifluridine/tipiracil) in patients with metastatic colorectal cancer (mCRC), using propensity score matching (PSM) to adjust for age, sex, tumor sidedness, and RAS mutation status. The study also evaluated the impact of treatment sequence on outcomes.

Methods. We conducted a retrospective analysis of mCRC patients treated with either Stivarga or Lonsurf at Taichung Veterans General Hospital between 2018 and 2023. Patients were stratified into monotherapy and combination therapy groups. PSM was applied to balance baseline characteristics including RAS mutation status. Survival outcomes were evaluated using Kaplan-Meier curves and Cox proportional hazards regression. Treatment continuation rate was defined as the proportion of patients able to proceed to subsequent lines of therapy without premature discontinuation.

Results. Following PSM, 166 patients received Stivarga and 134 received Lonsurf. Baseline characteristics were well balanced across groups (Table 1). Combination therapy significantly improved PFS in both Stivarga (3.78 vs. 2.40 months, $p = 0.001$) and Lonsurf (4.86 vs. 3.02 months, $p = 0.008$) cohorts. OS was significantly prolonged in the Lonsurf combination group compared to monotherapy (12.68 vs. 6.41 months, $p = 0.026$), while no significant OS difference was observed for Stivarga (8.38 vs. 7.13 months, $p = 0.163$). Direct comparison demonstrated superior OS and PFS for Lonsurf over Stivarga (OS median 10.18 vs. 5.98 months, $p = 0.033$; PFS median 7.43 vs. 2.76 months, $p = 0.005$). Multivariate Cox regression identified treatment continuation and combination therapy as significant independent predictors of OS (HR 0.33, $p = 0.008$) and PFS (HR 0.43, $p = 0.005$). Treatment sequencing did not significantly affect OS.

Conclusions. Lonsurf, particularly in combination regimens, confers superior survival benefits compared to Stivarga in mCRC patients after adjustment for key prognostic factors including RAS mutation. Treatment continuation and combination therapy are critical factors associated with improved outcomes. These findings support personalized treatment strategies tailored to tumor biology and therapy sequencing.

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Metastatic colorectal cancer (mCRC) remains a leading cause of cancer-related mortality worldwide.¹ Regorafenib (Stivarga) and trifluridine/tipiracil (Lonsurf) are established third-line therapies demonstrating modest survival benefits.² RAS mutation status has emerged as important predictors of treatment response; however, real-world comparative data considering these variables are limited.³ Monotherapy with agents such as Stivarga or Lonsurf is widely used in refractory mCRC; however, combination therapy with other cytotoxic or targeted agents has been proposed to enhance efficacy. Despite increasing clinical adoption, comparative data between monotherapy and combination regimens remain limited, particularly in real-world settings. This study therefore aims to test the hypothesis that combination therapy with Lonsurf provides superior survival outcomes compared to Stivarga, using propensity score matching to minimize confounding.

Methods

Study design and patient population

This retrospective cohort study included mCRC patients treated at Taichung Veterans General Hospital between January 2018 and December 2023. Eligible patients received either Stivarga (regorafenib) or Lonsurf (trifluridine/tipiracil) as part of later-line therapy. Patients were classified into four groups based on treatment modality: Stivarga Combination Therapy, Stivarga Monotherapy, Lonsurf Combination Therapy, and Lonsurf Monotherapy. Combination therapy was defined as concurrent administration of either agent with other chemotherapeutic or targeted drugs.

Data collection

Clinical and demographic data including age at treatment initiation, sex, line of therapy (third/fourth line vs. fifth line or beyond), primary tumor location (right vs. left colon), and RAS gene mutation status were extracted from the hospital's electronic medical

records. RAS mutation status was determined by standard molecular diagnostic techniques, such as polymerase chain reaction (PCR) or next-generation sequencing (NGS). Patients with unknown RAS status were excluded from mutation-specific subgroup analyses.

Treatment details — including dosing regimens, duration, and concurrent agents such as irinotecan, 5-fluorouracil, oxaliplatin, and bevacizumab — were meticulously documented. The treatment continuation rate was defined as the proportion of patients who, despite disease progression or toxicity, were able to proceed to subsequent lines of systemic therapy. This measure reflects treatment feasibility in real-world settings and is conceptually inverse to the commonly reported treatment attrition rate, which indicates the proportion of patients who discontinue or do not receive further therapy.^{4,5}

Outcome measures

Primary endpoints were OS (time from treatment initiation to death) and PFS (time from treatment initiation to radiologically confirmed disease progression or death). Tumor progression was assessed by CT or MRI according to RECIST v1.1 criteria, typically every 8-12 weeks.

Statistical analysis

PSM was performed using a 1:1 nearest neighbor algorithm with a caliper width of 0.2 for age, sex, tumor sidedness, and RAS mutation status. Continuous variables were reported as median (IQR) and compared with Mann-Whitney U tests; categorical variables were compared by Chi-square or Fisher's exact tests. Survival was estimated by Kaplan-Meier method with group differences assessed via log-rank test. Multivariate Cox proportional hazards models adjusted for age, sex, tumor sidedness, RAS status, treatment type, and treatment continuation rate were used to identify independent predictors of OS and PFS. Statistical significance was set at $p < 0.05$. Analyses were conducted using SPSS v22.

Results

Baseline characteristics (Table 1)

In this study, age, sex, tumor sidedness, and RAS mutation status were selected as matching variables for propensity score matching due to their established association with clinical outcomes in metastatic colorectal cancer. These factors have been widely reported to influence overall survival (OS) and progression-

free survival (PFS), with age and sex affecting treatment tolerance and prognosis, tumor sidedness impacting biological behavior and response to targeted therapies, and RAS mutation serving as a key predictive biomarker for treatment efficacy.

Furthermore, these clinical and molecular characteristics may also influence treatment selection and response, representing potential confounders. By including these variables in the matching process, we aimed to minimize selection bias and achieve bal-

Table 1. Baseline characteristics

After PSM, N = 166			
	Stivarga combination therapy (N = 83)	Stivarga mono-use (N = 83)	<i>p</i> value
Age	62.0 (54.0-69.0)	62.0 (53.0-69.0)	0.948
Gender			0.631
Female	30 (36.1%)	33 (39.8%)	
Male	53 (63.9%)	50 (60.2%)	
Line of therapy			0.301
3-4th	61 (75.3%)	68 (81.9%)	
> 5th	20 (24.7%)	15 (18.1%)	
Primary tumor side			1.000
Right	73 (88.0%)	73 (88.0%)	
Left	10 (12.0%)	10 (12.0%)	
Ras mutation			0.874
No	32 (38.6%)	33 (39.8%)	
Yes	51 (61.4%)	50 (60.2%)	
Treatment continuation rate	58 (72.5%)	47 (56.6%)	0.034*
Dose	80.0 (80.0-120.0)	80.0 (80.0-80.0)	0.057
After PSM, N = 134			
	Lonsurf combination therapy (N = 67)	Lonsurf mono-use (N = 67)	<i>p</i> value
Age	61.0 (54.0-69.0)	59.0 (51.0-64.0)	0.153
Gender			0.287
Female	23 (34.3%)	29 (43.3%)	
Male	44 (65.7%)	38 (56.7%)	
Line of therapy			0.279
3-4th	43 (66.2%)	37 (56.9%)	
> 5th	22 (33.8%)	28 (43.1%)	
Primary tumor side			0.825
Right	54 (80.6%)	55 (82.1%)	
Left	13 (19.4%)	12 (17.9%)	
Ras mutation			0.727
No	28 (41.8%)	30 (44.8%)	
Yes	39 (58.2%)	37 (55.2%)	
Treatment continuation rate	39 (78.0%)	42 (63.6%)	0.095
Dose	110.0 (80.0-120.0)	110.0 (100.0-120.0)	0.707

Chi-square test or Mann-Whitney U test. Median (IQR) * $p < 0.05$.

anced comparison groups, thereby enabling a more accurate assessment of the efficacy between Stivarga and Lonsurf in both monotherapy and combination therapy settings.

After propensity score matching (PSM) was performed to adjust for potential confounding variables including age, sex, primary tumor sidedness, and RAS mutation status, the treatment groups were well balanced. The median age across groups ranged narrowly between 61 and 62 years. The distribution of sex was comparable, with a similar proportion of males and females in both the Stivarga and Lonsurf cohorts. Primary tumor location was predominantly right-sided, accounting for approximately 80% to 88% of cases in all groups, while RAS mutation prevalence ranged from 55% to 60%, reflecting the genetic profile typical of metastatic colorectal cancer populations. Importantly, the treatment continuation rate was significantly higher in the combination therapy groups compared to the monotherapy groups. Specifically, among patients treated with Stivarga, 72.5% in the combination therapy group continued treatment beyond disease progression or toxicity, versus 56.6% in the monotherapy group ($p = 0.034$), indicating a potential benefit of combination regimens in maintaining treatment adherence and possibly improving clinical outcomes.

Regimens (Tables 2 and 3)

Detailed analyses of treatment regimens revealed distinct patterns in combination therapies for the two agents. Patients receiving Stivarga in combination frequently received irinotecan-based regimens or other fluorouracil (5-FU)-based chemotherapy protocols,

which are standard components in colorectal cancer management.⁶ Conversely, in the Lonsurf group, the predominant combination agent was bevacizumab,⁷ an anti-angiogenic monoclonal antibody targeting VEGF, used either alone or alongside irinotecan. These regimen differences highlight varying therapeutic strategies tailored to each drug's mechanism of action and established clinical evidence supporting their use.

Survival outcomes

Our study demonstrated that Lonsurf (TAS-102) conferred a significant survival advantage over Stivarga (regorafenib). Specifically, Stivarga combination therapy significantly prolonged progression-free survival (PFS) compared to monotherapy (3.78 vs. 2.40 months, $p = 0.001$), although overall survival (OS) did not differ significantly (8.38 vs. 7.13 months, $p = 0.163$).^{8,9}

To further explore the heterogeneity of combination regimens within the Stivarga cohort, we performed a subgroup analysis comparing three common combination strategies: 5-fluorouracil (5-FU)-based, irinotecan or oxaliplatin-based (Irino/Oxa), and multi-agent regimens involving two or more cytotoxic agents.

As shown in the Kaplan-Meier survival curves (Fig. 4), there was no statistically significant difference in median progression-free survival (mPFS) among the three groups (5-FU: 5.4 months; Irino/Oxa: 4.1 months; two or more agents: 4.9 months; $p = 0.8926$). Similarly, the median overall survival (mOS) was not significantly different across regimens (5-FU: 5.4 months; Irino/Oxa: 11.8 months; two or more agents: 9.2 months; $p = 0.5563$) (Fig. 5).

Table 2. Regimen of the Stivarga group (N = 216)

Variables	N	%
Mono-use	132	61.10%
5-FU	15	6.90%
FOLFOX	11	5.10%
FOLFOXIRI	3	1.40%
Irinotecan	30	13.90%
Oxaplatin	7	3.20%
Irinotecan + Oxaplatin	10	4.60%
FOLFIRI	6	2.80%

Table 3. Regimen of the Lonsurf group (N = 172)

Variables	N	%
Mono-use	103	59.90%
Oxaplatin	4	2.30%
FOLFIRI	0	0.00%
Irinotecan + Oxaplatin	1	0.60%
Eribitux + Encorafenib	1	0.60%
Bevacizumab	52	30.20%
Irino + Bevacizumab	20	11.60%

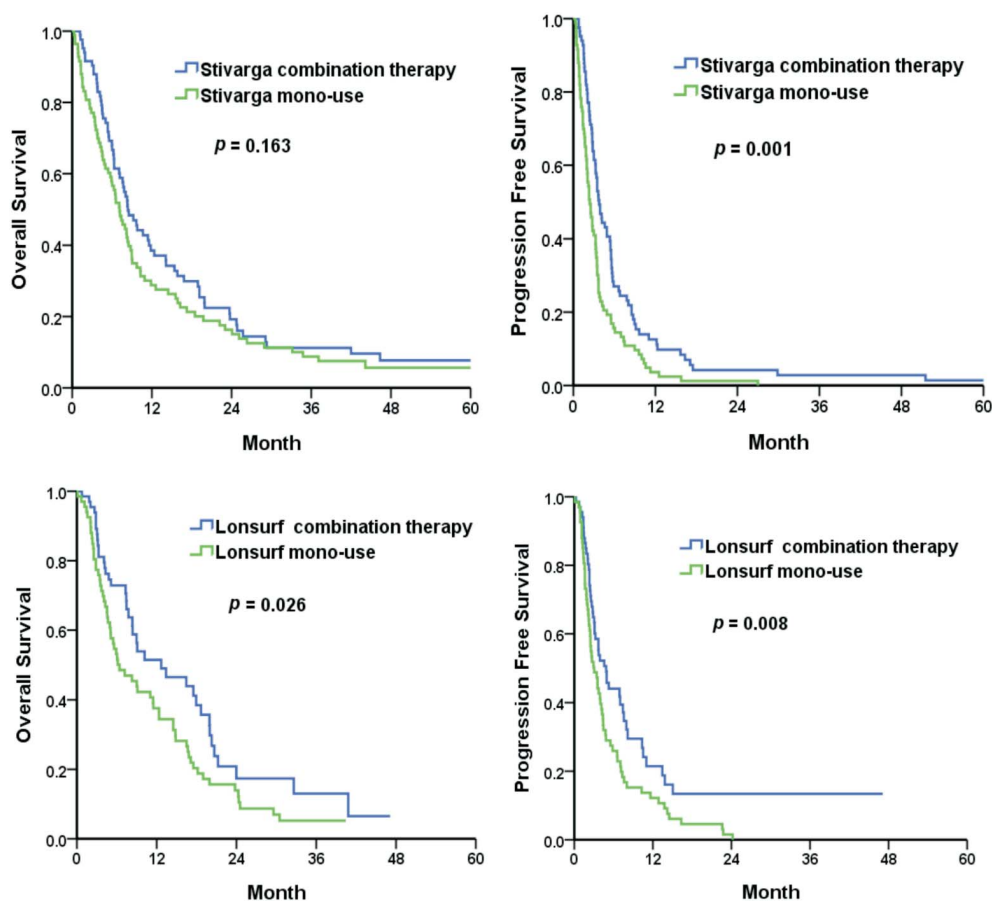


Fig. 1. Kaplan-Meier survival curves comparing overall survival (OS) and progression-free survival (PFS) between combination therapy and monotherapy in Stivarga and Lonsurf cohorts.

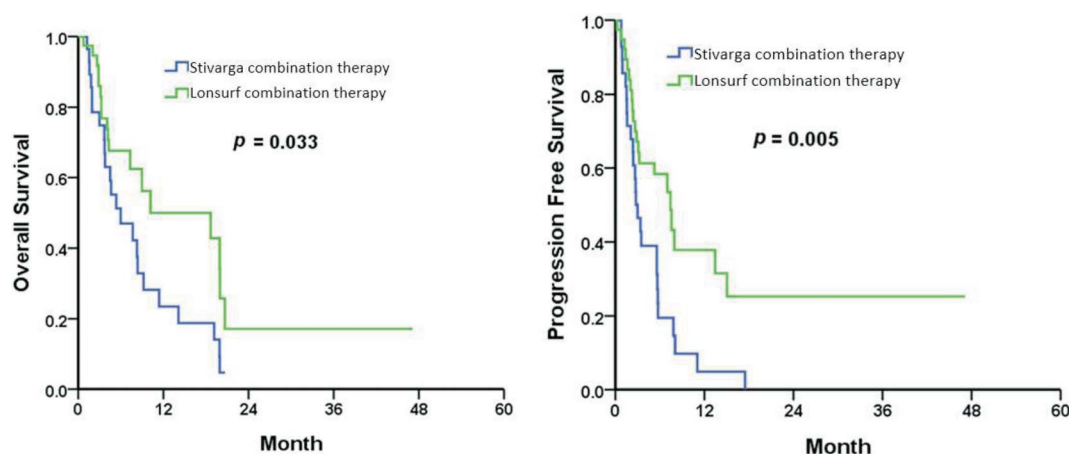


Fig. 2. Direct comparison of overall survival (OS) and progression-free survival (PFS) between Stivarga combination therapy and Lonsurf combination therapy.

These findings suggest that while multiple combination strategies are employed in real-world practice, no specific Stivarga-based combination regimen demonstrated a clear survival advantage in this cohort.

Meanwhile, Lonsurf combination therapy significantly improved both PFS (4.86 vs. 3.02 months, $p = 0.008$) and OS (12.68 vs. 6.41 months, $p = 0.026$).

Direct comparison further confirmed Lonsurf's

superiority, showing significantly longer OS (median 10.18 vs. 5.98 months, $p = 0.033$) and PFS (7.43 vs. 2.76 months, $p = 0.005$) compared to Stivarga.²

Cox regression analysis (Tables 4 and 5)

To identify independent predictors of survival out-

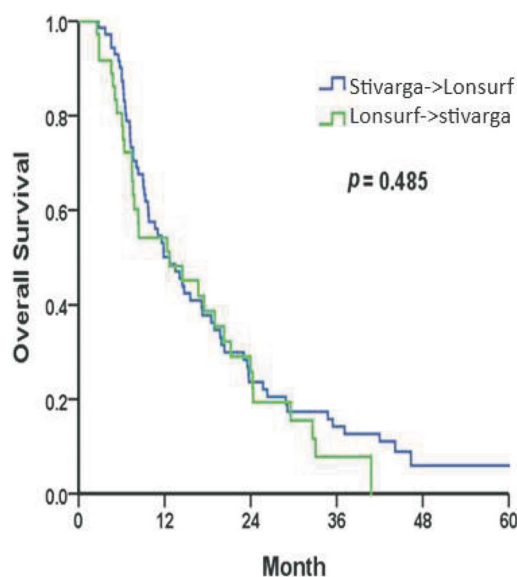


Fig. 3. Kaplan-Meier analysis of overall survival (OS) based on treatment sequencing (Stivarga followed by Lonsurf vs. Lonsurf followed by Stivarga).

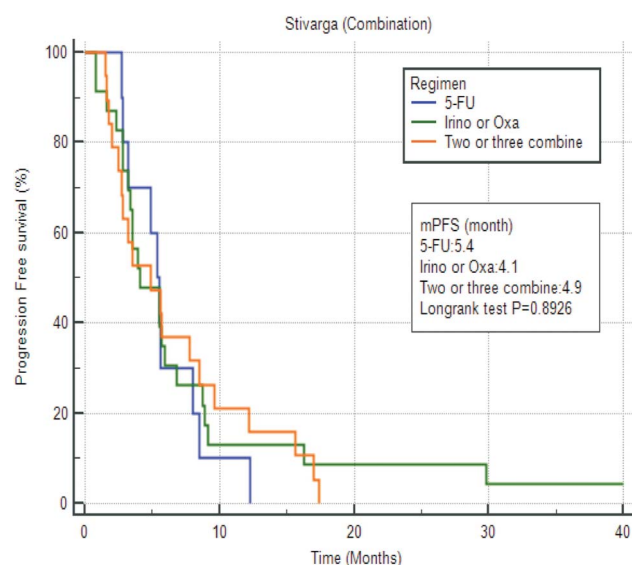


Fig. 4. Progression-free survival (PFS) across different Stivarga combination regimens (5-FU-based, Irinotecan or Oxaliplatin-based, and multi-agent regimens).

comes, multivariate Cox proportional hazards regression analyses were conducted. After adjusting for relevant clinical factors, treatment continuation rate and use of combination therapy emerged as significant independent predictors of improved OS and PFS. Specifically, patients who continued treatment beyond progression or toxicity had a 67% reduction in the hazard of death (HR 0.33, 95% CI 0.15-0.75, $p = 0.008$).¹⁰ Similarly, Lonsurf combination therapy comparing to Stivarga combination therapy was associated with a 57% reduction in risk of progression or death (HR 0.43, 95% CI 0.24-0.77, $p = 0.005$).¹¹ Notably, RAS mutation status was not independently associated with OS or PFS in the adjusted models, suggesting that its prognostic impact may be mitigated by treatment modality or other factors.¹²

Treatment sequencing (Fig. 3)

An analysis exploring the impact of treatment sequencing was performed to assess whether the order of drug administration influenced survival outcomes. Patients who received Stivarga followed by Lonsurf were compared with those who underwent the reverse sequence. The median OS was identical at 12.68 months in both groups, with no statistically significant difference observed ($p = 0.485$). This

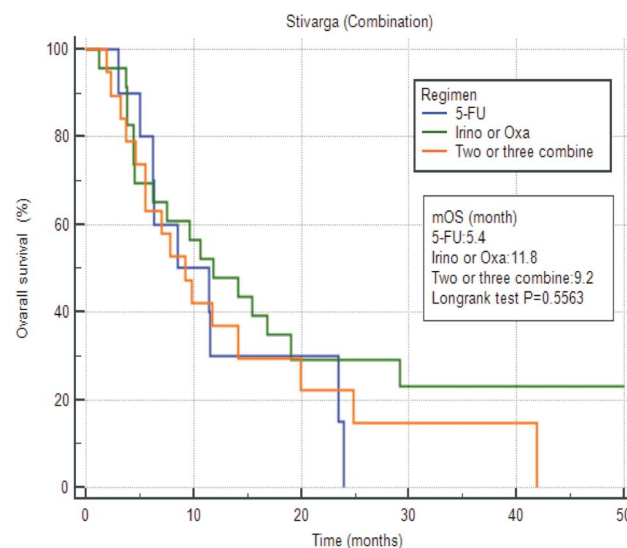


Fig. 5. Overall survival (OS) across different Stivarga combination regimens (5-FU-based, Irinotecan or Oxaliplatin-based, and multi-agent regimens).

Table 4. Cox regression -- OS (N = 66)

	Univariate			Multivariable		
	Hazard ratio	95% CI	<i>p</i> value	Hazard ratio	95% CI	<i>p</i> value
Age	1.02	(1.00-1.05)	0.066	0.98	(0.95-1.01)	0.243
Gender						
Female	Reference			Reference		
Male	1.94	(1.01-3.71)	0.046*	1.26	(0.61-2.58)	0.534
Line of therapy						
3-4th	Reference					
> 5th	0.71	(0.33-1.54)	0.387			
Primary tumor side						
Right	Reference					
Left	0.99	(0.46-2.16)	0.982			
Ras mutation						
No	Reference					
Yes	0.89	(0.46-1.70)	0.720			
Treatment continuation rate	0.37	(0.19-0.71)	0.003**	0.33	(0.15-0.75)	0.008**
Group						
Stivarga combination therapy	Reference			Reference		
Lonsurf combination therapy	0.52	(0.28-0.96)	0.037*	1.25	(0.60-2.64)	0.552

Cox proportional hazard regression. * $p < 0.05$, ** $p < 0.01$.

Table 5. Cox regression -- PFS (N = 66)

	Univariate			Multivariable		
	Hazard ratio	95% CI	<i>p</i> value	Hazard ratio	95% CI	<i>p</i> value
Age	1.02	(1.00-1.05)	0.084	1.02	(1.00-1.05)	0.070
Gender						
Female	Reference					
Male	1.24	(0.70-2.21)	0.465			
Line of therapy						
3-4th	Reference					
> 5th	0.66	(0.32-1.38)	0.273			
Primary tumor side						
Right	Reference					
Left	1.22	(0.60-2.46)	0.584			
Ras mutation						
No	Reference					
Yes	0.93	(0.51-1.68)	0.801			
Treatment continuation rate	0.86	(0.48-1.56)	0.621			
Group						
Stivarga combination therapy	Reference			Reference		
Lonsurf combination therapy	0.44	(0.25-0.79)	0.006**	0.43	(0.24-0.77)	0.005**

Cox proportional hazard regression. * $p < 0.05$, ** $p < 0.01$.

finding indicates that the sequencing of Stivarga and Lonsurf may not substantially affect overall survival,¹³ allowing clinicians flexibility in selecting treatment order based on patient-specific factors and tolerance.

Discussion

Our PSM-adjusted analysis confirms the prognostic importance of treatment continuous rate. Lonsurf combination therapy conferred superior OS and PFS

Table 6. Baseline characteristics before propensity score matching (PSM)

	Before PSM (N = 216)			Before PSM (N = 172)		
	Stivarga combination therapy (N = 84)	Stivarga mono-use (N = 132)	<i>p</i> value	Lonsurf combination therapy (N = 103)	Lonsurf mono-use (N = 69)	<i>p</i> value
Age	62.0 (54.3-69.0)	62.0 (54.3-68.8)	0.962	61.0 (53.5-69.0)	62.0 (53.0-69.0)	0.501
Gender			0.557			0.173
Female	31 (36.9%)	54 (40.9%)		23 (33.3%)	45 (43.7%)	
Male	53 (63.1%)	78 (59.1%)		46 (66.7%)	58 (56.3%)	
Line of therapy			0.803			0.540
3-4th	62 (75.6%)	101 (77.1%)		44 (65.7%)	61 (61.0%)	
> 5th	20 (24.4%)	30 (22.9%)		23 (34.3%)	39 (39.0%)	
Primary tumor side			0.066			0.495
Right	73 (86.9%)	99 (76.7%)		55 (80.9%)	78 (76.5%)	
Left	11 (13.1%)	30 (23.3%)		13 (19.1%)	24 (23.5%)	
Ras mutation			0.372			0.849
No	32 (38.6%)	56 (44.8%)		29 (42.6%)	42 (41.2%)	
Yes	51 (61.4%)	69 (55.2%)		39 (57.4%)	60 (58.8%)	
Treatment continuation rate	58 (71.6%)	75 (56.8%)	0.031*	41 (78.8%)	62 (62.0%)	0.035*
Dose	80.0(80.0-120.0)	80.0 (80.0-120.0)	0.067	62.0 (53.0-69.0)	110.0 (100.0-120.0)	0.666

Chi-square test or Mann-Whitney U test. Median (IQR) * $p < 0.05$, ** $p < 0.01$.

over Stivarga, consistent with emerging real-world data and meta-analyses.⁸ Treatment continuation rate was a critical factor associated with improved survival, underscoring the benefit of manageable toxicity and effective combination regimens.

Consistent with prior population-based findings in Taiwan by Chang et al. (2024)⁸ who reported superior survival outcomes with TAS-102 compared to regorafenib in mCRC patients, our study similarly demonstrated that Lonsurf (TAS-102) conferred a significant survival advantage over Stivarga (regorafenib).

The lack of OS benefit in Stivarga combination therapy may relate to dosing, sequencing, or patient selection, consistent with prior ReDOS study findings.¹⁴ Our analysis of treatment sequence found no significant survival difference, suggesting flexible clinical use based on patient factors.

Despite these promising findings, several limitations warrant caution. First, the retrospective design carries an inherent risk of selection bias and confounding variables that we could not entirely control. Second, our data reflects the experience of a single institution, which may not be generalized to broader mCRC populations with more diverse ge-

netic and clinical profiles. Third, heterogeneity in combination regimens — particularly within the Stivarga group — makes it challenging to draw definitive conclusions regarding the most effective co-therapies. Fourth, detailed adverse event data and toxicity profiles were not systematically collected, limiting our ability to assess the tolerability and safety of different regimens. Fifth, this study did not collect extended molecular profiling data, including BRAF mutation and microsatellite instability (MSI) status, which precluded subgroup analyses that might have revealed biomarker-specific treatment responses.¹⁵

Comparison with domestic data shows concordance with prior Taiwanese cohorts regarding survival trends and RAS mutation prevalence, supporting generalizability.⁸ Future prospective studies should focus on biomarker-guided therapy and sequencing optimization.

Conclusions

1. Lonsurf, particularly with combination therapy, provides superior OS and PFS in mCRC patients com-

pared to Stivarga after adjusting for age, sex, tumor side, and RAS mutation.

2. Treatment continuation and combination therapy are important predictors of improved survival.
3. No significant difference was found based on treatment sequencing order. Personalized treatment considering tumor biology and therapy tolerance is recommended.

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原 著

轉移性大腸癌第三線治療之藥物比較： Stivarga 與 Lonsurf 單獨與合併用藥療效分析

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目的 轉移性大腸直腸癌 (mCRC) 在臨床上為重大挑戰，晚期病患在經過標準化療與標靶治療後，仍需有效的後線藥物選擇。Stivarga (regorafenib) 與 Lonsurf (trifluridine/tipiracil) 是目前常用於第三線或更後線治療的口服藥物。本研究探討兩藥單用與合併療法在第四期 mCRC 病患中的療效，並進一步分析腫瘤部位 (左側或右側) 對治療結果的影響。

方法 本研究回顧 2018 至 2023 年間於臺中榮民總醫院接受 Stivarga 或 Lonsurf 治療之 mCRC 患者，將其依照單藥與合併療法分類。主要分析總存活期 (OS)、無惡化存活期 (PFS)、治療持續率以及藥物不良反應，並利用 Kaplan-Meier 法及 log-rank 檢定進行統計比較。

結果 共納入 216 位 Stivarga 與 172 位 Lonsurf 使用者。兩藥合併治療皆顯著延長 PFS (Stivarga：3.78 對 2.4 個月；Lonsurf：4.86 對 2.63 個月， p 值皆 < 0.001)。Lonsurf 合併治療顯著延長 OS (12.68 對 6.14 個月， $p = 0.007$)，而 Stivarga 則無統計差異。左側腫瘤患者整體存活優於右側者。毒性方面，Lonsurf 主要引起血液學毒性，Stivarga 則以疲憊與手足症候群為主。

結論 本研究結果指出，Lonsurf 在 mCRC 的疾病控制與存活方面表現優於 Stivarga，尤其在左側腫瘤病患中更為明顯。合併標靶藥物如 bevacizumab 可進一步提升療效。未來應持續透過前瞻性研究與生物標記導向策略，優化右側腫瘤患者的治療結果，實現更個人化的治療模式。

關鍵詞 轉移性大腸直腸癌、癌瑞格、朗斯弗。