A Real-World Comparison of Regorafenib and Trifluridine/Tipiracil in Refractory Metastatic Colorectal Cancer in the United States

Christopher Nevala-Plagemann, MD, MSCI[1]; Shashank Sama, MD[1]; Jian Ying, PhD[2]; Jincheng Shen, PhD[2]; Benjamin Haaland, PhD[2]; Vaia Florou, MD[1]; and Ignacio Garrido-Laguna, MD, PhD[1]

ABSTRACT

Background: Trifluridine/Tipiracil (TAS-102) and regorafenib are FDA-approved in the United States for treatment of refractory metastatic colorectal cancer (mCRC). FDA approvals of these agents were based on modest improvements in overall survival (OS) compared with best supportive care + placebo in the RECOURSE and CORRECT trials, respectively. This study compared real-world clinical outcomes with the use of these agents. **Methods:** A nationwide deidentified electronic health record–derived database was reviewed for patients diagnosed with mCRC between 2015 and 2020. Patients who received at least 2 lines of standard systemic therapy followed by treatment with either TAS-102 or regorafenib were included for analysis. Kaplan-Meier and propensity score–weighted proportional hazards models were used to compare survival outcomes between groups. **Results:** The records of 22,078 patients with mCRC were reviewed. Of these, 1,937 patients received at least 2 lines of standard therapy followed by regorafenib and/or TAS-102. Median OS for the TAS-102 alone or prior regorafenib group (n=1,016) was 6.66 months (95% CI, 6.16–7.18 months) compared with 6.30 months (95% CI, 5.80–6.79 months) for regorafenib alone or prior to TAS-102 (n=921; *P*=.36). A propensity score–weighted analysis controlling for potential confounders did not demonstrate a significant difference in survival between groups (hazard ratio, 0.99; 95% CI, 0.90–1.09; *P*=.82). A subgroup analysis did not identify any significant differences in outcomes regarding age, performance status, tumor sidedness, microsatellite instability status, or *RAS/RAF* status. **Conclusions:** This analysis of real-world data found that OS was similar for patients with mCRC who were treated with TAS-102 compared with regorafenib. Median OS with both agents in a real-world setting was similar to that shown in the clinical trials that led to their approvals. A prospective trial comparing TAS-102 and regorafenib would unlikely change current management of patients with refractory mCRC.

J Natl Compr Canc Netw 2023;21(3):257–264
doi: 10.6004/jnccn.2022.7082

[1]Division of Medical Oncology, Department of Internal Medicine, Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah, and [2]Department of Population Health Sciences, University of Utah, Salt Lake City, Utah.

Background

Colorectal cancer (CRC) remains among the largest contributors of cancer mortality, with >50,000 projected deaths in 2022, making it the second leading cause of cancer death in the United States.[1] For patients with advanced or metastatic CRC (mCRC), fluoropyrimidine-based cytotoxic chemotherapy has long been the mainstay of treatment.[2,3] Improvements in clinical outcomes have been achieved by combining chemotherapy with an anti–vascular endothelial growth factor (anti-VEGF) monoclonal antibody or, if *RAS/RAF* wild-type disease, an epidermal growth factor receptor inhibitor,[4–6] and through increased use of immunotherapy or targeted therapy in those with actionable genetic alterations. Unfortunately, even with these improvements, most patients will eventually experience disease progression. Two oral therapies, regorafenib and trifluridine/tipiracil (TAS-102), are currently approved for use in this chemotherapy-refractory setting.

FDA approval of regorafenib in 2012 was based on results of the phase III CORRECT trial, which showed a modest improvement in median overall survival (OS) using regorafenib compared with best supportive care + placebo (6.4 vs 5 months; hazard ratio [HR], 0.77; 95% CI, 0.64–0.94).[7] Soon after, in 2015, an alternate third-line option became available with the FDA approval of TAS-102, a combination cytotoxic chemotherapy combining a thymidine-based nucleic acid analog (trifluridine) with a thymidine phosphorylase inhibitor (tipiracil hydrochloride). Approval of TAS-102 was based on results of the phase III RECOURSE trial, which showed a similarly modest overall survival benefit using TAS-102 compared with best supportive care + placebo (7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58–0.81).[8]

Although the approvals of regorafenib and TAS-102 have provided much needed additional treatment options for patients with mCRC, the choice of which agent to choose for an individual patient has thus far been left up to the discretion of treating oncologists. There have been no head-to-head prospective studies comparing outcomes

with regorafenib versus TAS-102. As such, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer (Version 1.2022) do not indicate a preference for one agent over the other.[9] There have been indirect comparisons through network meta-analyses[10] and small-scale retrospective studies of patients outside the United States that have attempted to determine whether one agent may be preferable over the other.[11–16] These studies have so far suggested similar clinical outcomes with TAS-102 and regorafenib, but whether these results can be applied to the larger US population is yet to be established.

In this study, we sought to use a large nationwide real-world database to compare clinical outcomes between patients receiving regorafenib or TAS-102 in the third-line or greater setting in the United States. We also evaluated patterns in the relative use of these drugs within US clinical practice over the years since their introduction and performed an exploratory subgroup analysis to identify potential predictors of response to these drugs.

Methods

Data Source

This study used the nationwide, deidentified, electronic health record (EHR)–derived Flatiron Health database. Deidentified data available during the study period originated from approximately 280 cancer clinics representing >800 sites of care, including both academic and community oncology settings. The longitudinal Flatiron Health database includes both structured and unstructured patient-level data curated using technology-enabled abstraction.[17,18] All data are subject to obligations to protect patient confidentiality. University of Utah Institutional Review Board approval was obtained prior to study conduct and included a waiver of informed consent.

Study Population

The deidentified database was reviewed for patients with de novo or recurrent mCRC diagnosed between 2015 and 2020 who received treatment with either TAS-102 or regorafenib. Patients who did not receive at least 2 lines of standard fluoropyrimidine-based chemotherapy with or without targeted therapy prior to treatment with TAS-102 or regorafenib were excluded from analysis. To ensure patients were engaged with the data-providing institution, only those with a visit or medication order documented within 90 days of metastatic diagnosis were included. Date of death in the Flatiron Health database is a consensus variable generated through review of the EHR, Social Security Death Index, and review of obituaries.[19]

Statistical Analysis

Baseline characteristics of patients who received TAS-102 alone or prior to receiving regorafenib (TAS-102 group) versus those who received regorafenib alone or prior to TAS-102 (regorafenib group) were compared using chi-square tests for categorical variables and a Wilcoxon test for continuous variables. Trends in the relative use of regorafenib versus TAS-102 over time were visually assessed using a stacked bar graph. A logistic regression model was used to test for statistically significant change in the annual percentage of patients receiving one treatment relative to the other.

Survival estimates for treatment groups were plotted according to the Kaplan-Meier method. OS as the primary endpoint of interest was defined as the time in months between TAS-102 or regorafenib treatment initiation and death. Patients without a confirmed date of death were censored at the time of last confirmed activity documented in the EHR. An inverse propensity weighted Cox proportional hazards model was used to minimize potential confounding. Propensity scores were based on a logistic regression prediction model for treatment group using the following potential confounders: age at metastatic diagnosis, gender, race, line of initiation (eg, third, fourth), ECOG performance status, stage at diagnosis, location of primary tumor, mismatch repair (MMR) status, *RAS/RAF* mutation status, CEA level, albumin level, and categorical year of initiation. For variables with values at multiple timepoints (performance status, CEA level, albumin level), the documented value closest to and within 90 days prior to the date of treatment initiation was used. To assess balance of potential confounders between groups, standardized mean differences (SMDs) were constructed. Potential confounders with SMD >0.1 (indicating imbalance) were included as covariates in the weighted Cox model. Statistical inference for the comparison of regorafenib versus TAS-102 was based on bootstrap standard errors, with both propensity construction and OS model fitting nested within each bootstrap iteration.

An exploratory subgroup analysis was conducted comparing OS between treatment groups stratified by age at metastatic diagnosis, performance status, *RAS/RAF* status, MMR status, tumor sidedness, and receipt of prior targeted therapy. In a separate subgroup analysis, patients treated with TAS-102 were stratified by development of neutropenia (neutrophil count <1,500/mcL) occurring during the first 4 weeks after initiation of treatment. To minimize immortal time bias, follow-up time in this analysis was defined as time in months starting 4 weeks after initiation of treatment. A final exploratory propensity score model was constructed to assess whether outcomes differed based on order of therapy in patients who received TAS-102 in line 3 followed by regorafenib in line 4 compared with the reverse sequence.

Results

Patient Characteristics

A review of 22,078 patients with mCRC yielded 4,407 patients who had documented receipt of at least 3 lines of therapy, of which at least 2 were standard fluorouracil-based chemotherapy. Of these, 1,937 patients received either regorafenib or TAS-102 in the third-line setting or beyond and were included for further analysis. A total of 921 (47.5%) patients received TAS-102 alone or prior to regorafenib (TAS-102 group) and 1,016 (52.5%) received regorafenib alone or prior to TAS-102 (regorafenib group). A total of 111 patients received regorafenib after receiving TAS-102 and 99 patients received TAS-102 after receiving regorafenib (Figure 1). A comparison of baseline characteristics of the TAS-102 and regorafenib groups is shown in Table 1.

Survival Analysis

Median OS for patients treated in the TAS-102 group was 6.66 months (95% CI, 6.16–7.18 months) compared with 6.30 months (95% CI, 5.80–6.79 months) for those in the regorafenib group (P=.36) (Figure 2). A propensity score–weighted analysis controlling for potential confounding variables did not demonstrate a significant difference in survival between groups (HR, 0.99; 95% CI, 0.90–1.09; P=.82).

An exploratory subgroup analysis did not identify any significant differences in survival between groups when stratified by age, performance status, *RAS/RAF* status, microsatellite instability (MSI) status, tumor sidedness, or prior targeted therapy received (Figure 3). A decreased risk of death was observed in patients who received TAS-102 and who developed neutropenia within the first 4 weeks after initiation of therapy compared with those who did not (HR, 0.56; 95% CI, 0.37–0.84). An additional exploratory propensity score–weighted analysis comparing OS of patients who received third-line TAS-102 followed by fourth-line regorafenib (n=111) versus third-line regorafenib followed by fourth-line TAS-102 (n=99) showed similar outcomes regardless of sequence of therapy (HR, 0.98; 95% CI, 0.83–1.14).

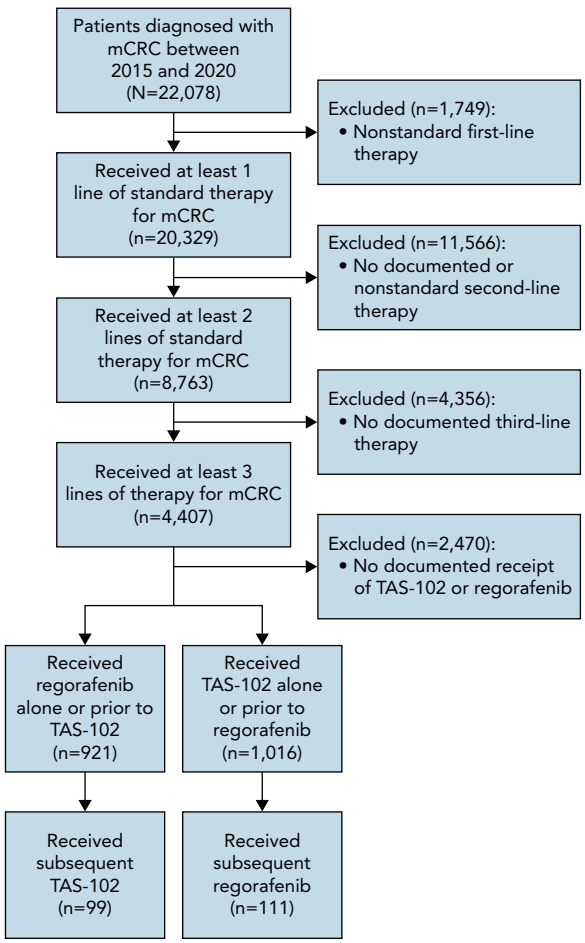

Figure 1. Study flowchart.
Abbreviations: mCRC, metastatic colorectal cancer; TAS-102, trifluridine/tipiracil.

Treatment Trends

Approximately 20% of patients in the overall CRC cohort (4,407/22,078) received third-line therapy after receiving at least 2 lines of standard chemotherapy. When excluding the year 2015, the year immediately after approval of TAS-102, use of TAS-102 and regorafenib in this population appeared to be relatively equal, ranging from 12% to 20% of therapies administered. A logistic regression model demonstrated no significant change in the use of either therapy between 2016 to 2021 (Figure 4).

Discussion

This study is the largest real-world comparison with date of clinical outcomes in patients receiving TAS-102 or regorafenib in the United States. Our results suggest relatively equal use of these agents since their approvals and demonstrate no significant difference in the OS of patients who receive either TAS-102 or regorafenib in the third-line or greater setting. The results of this study are important because these drugs will likely never be compared directly in a head-to-head prospective trial.

Current data supporting use of TAS-102 and regorafenib are derived from randomized controlled trials that used placebo + best supportive care as a control.[7,8,20,21] The OS benefit demonstrated in these trials was modest. In the CORRECT trial, regorafenib improved median OS to 6.4 months compared with 5.0 months with placebo + best supportive care (P=.005).[7] Similarly, in the RECOURSE trial, TAS-102 improved median OS to 7.1 months compared with 5.3 months in the best supportive care + placebo arm (P<.001).[8] Two additional placebo-controlled

Table 1. Baseline Characteristics

Variable	Regorafenib Group n (%)	TAS-102 Group n (%)	*P* Value
Total, n	921	1,016	
Age, median [SD], y	61.1 [11.0]	60.9 [11.2]	.73
Gender			.74
Female	404 (44)	438 (43)	
Male	517 (56)	578 (57)	
Race			.11
Asian	36 (4)	31 (3)	
Black	137 (15)	125 (12)	
Other[a]	137 (15)	127 (12)	
White	555 (60)	653 (64)	
Stage at diagnosis			.41
I	21 (2)	24 (2)	
II	87 (9)	97 (10)	
III	180 (20)	202 (20)	
IV	605 (66)	672 (66)	
ECOG PS			.26
0	212 (23)	263 (26)	
1	352 (38)	386 (38)	
2	120 (13)	131 (13)	
≥3	15 (2)	23 (2)	
BRAF status			<.001
Wild-type	555 (60)	687 (68)	
Mutated	36 (4)	47 (5)	
KRAS status			.15
Wild-type	380 (41)	440 (43)	
Mutated	513 (55)	558 (55)	
NRAS status			<.001
Wild-type	518 (56)	670 (66)	
Mutated	35 (4)	43 (4)	
MMR/MSI status			<.001
Proficient/MSI-S	660 (72)	819 (81)	
Deficient/MSI-H	14 (2)	19 (2)	
Primary tumor sidedness			.89
Left	481 (52)	534 (53)	
Right	263 (29)	300 (30)	
Prior anti-EGFR	239 (26)	249 (25)	.47
Prior bevacizumab	773 (84)	872 (86)	.24

Variables with sum of percentages not equal to 100 include missing data.
Abbreviations: MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-S, microsatellite instability-stable; PS, performance status; TAS-102, trifluridine/tipiracil.
[a]Includes Hispanic or Latino, American Indian or Alaska Native, Hawaiian or Pacific Islander, and Unknown.

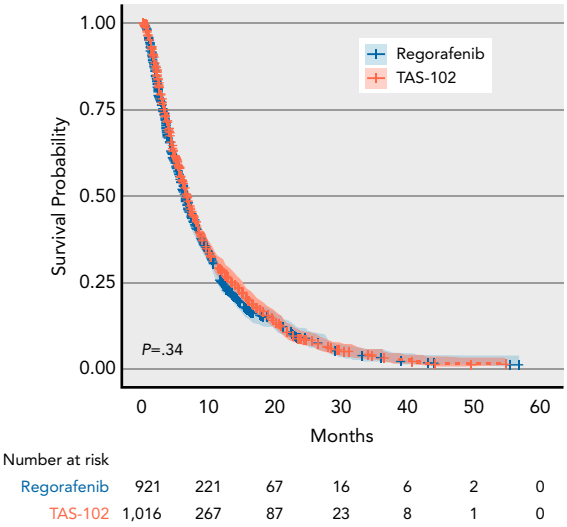

Figure 2. Kaplan-Meier curve comparing overall survival between patients in the regorafenib and TAS-102 groups.
Abbreviation: TAS-102, trifluridine/tipiracil.

trials conducted in Asian populations have since offered further confirmation of these marginal OS benefits.[20,21] The small OS benefit may be due to a low objective response rate (<5%) across all 4 of these trials, suggesting that the treatment effect of TAS-102 and regorafenib is primarily related to disease stabilization. The median OS of patients in our study who received either regorafenib or TAS-102 (6.3 and 6.6 months, respectively) was similar to that demonstrated in the clinical trials that led to the FDA approvals. This suggests that the modest benefit of these agents is not lost in a real-world population.

The results of our study are also in line with other retrospective studies and meta-analyses comparing TAS-102 and regorafenib. At least 4 meta-analyses have been conducted comparing outcomes from patients receiving one of these drugs in a prospective trial.[10,22–25] None of these meta-analyses have identified a statistically significant difference in either OS or progression-free survival. Similarly, several small retrospective studies conducted in Asia[11–15] and Europe[26] using real-world populations have also failed to demonstrate any appreciable difference in efficacy between these 2 treatments. A small retrospective study in the United States suggested that tumor response and disease control rates may be better with TAS-102 compared with regorafenib; however, this study did not demonstrate a significant difference in OS.[16] To the best of our knowledge, the only study to date to suggest a difference in survival outcomes between TAS-102 and regorafenib was a large retrospective study in Japan that found a statistically significant increase in OS among patients receiving TAS-102.[27] Of note, the difference in survival in this study was limited to patients who received only TAS-102 or regorafenib and did not go on to receive the other agent sequentially.

There is clear interest in identifying potential clinical characteristics or biomarkers that may be predictive of response to these therapies. Previous studies have suggested clinical characteristics, such as age, primary tumor location, and prior targeted therapy receipt, as potential predictors of response to either TAS-102 or regorafenib.[11,13,25,28] However, in an exploratory subgroup analysis, our study identified no differences in survival when stratified by age, performance status, *RAS/RAF* status, MSI status, primary tumor sidedness, or prior targeted therapy receipt. Furthermore, sequence of therapy in patients who were fit enough to receive both TAS-102 and regorafenib did not appear to impact survival outcomes in our analysis.

Given what appears to be similar efficacy and lack of any clear clinical characteristics or biomarkers to predict response to treatment with TAS-102 or regorafenib, the choice of agent for eligible patients should be individualized, with an emphasis on the differences in toxicity and schedule of administration of each drug. Regorafenib, a multikinase inhibitor given daily for 21 days of a 28-day cycle, has been shown to lead to higher rates of grade 3 hand-foot syndrome, fatigue, hypertension, and hepatotoxicity compared with TAS-102.[10] On the other hand, TAS-102, a cytotoxic chemotherapy combination given on days 1–5 and 8–12 of a 28-day cycle, is associated with a higher incidence of hematologic toxicity, particularly neutropenia. When comparing the overall rate of any grade 3 toxicity, at least one meta-analysis has found no significant difference between TAS-102 and regorafenib.[23] Furthermore, since the initial approval, modified dosing strategies such as those studied in the ReDOS study have led to improved tolerability of regorafenib.[29]

Although TAS-102 and regorafenib appear to have activity in a real-world population, given the modest survival benefits of these agents, novel therapies or combinations are needed. A recent phase II study met its primary endpoint by showing improved progression-free survival with the combination of TAS-102/bevacizumab compared with TAS-102 alone in patients with refractory mCRC (HR, 0.45; 95% CI, 0.29–0.72).[30] This study also demonstrated a modest improvement in median OS with the combination (9.4 vs 6.7 months, respectively). Of note, patients in the TAS-102/bevacizumab arm had a higher rate of neutropenia. Interestingly, a subset analysis from the RECOURSE trial as well as a retrospective study of patients receiving TAS-102 have both shown that patients who developed neutropenia during TAS-102 treatment had improved outcomes.[31,32] Our analysis of real-world data demonstrated similar findings, showing a decreased risk of death in patients receiving TAS-102 who developed neutropenia during the first 4 weeks after

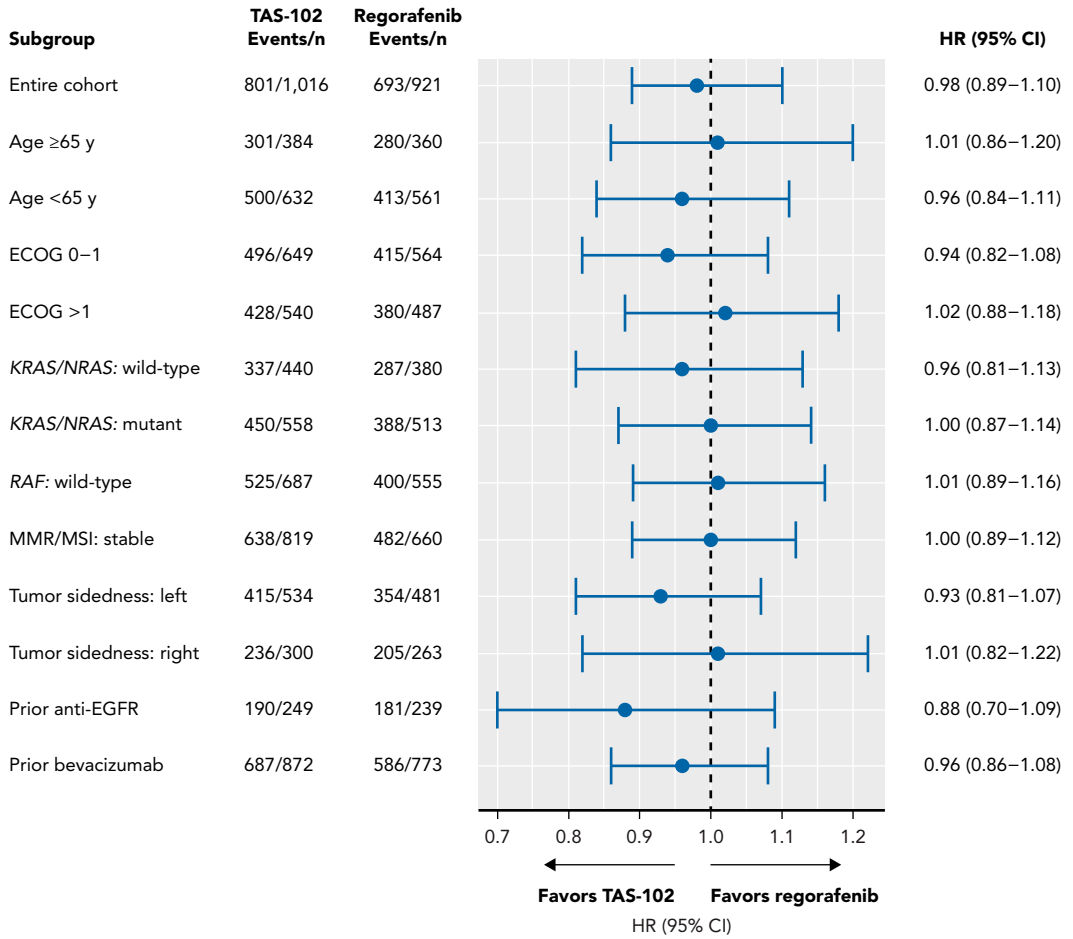

Figure 3. Subgroup analysis comparing overall survival between patients in the TAS-102 and regorafenib groups stratified by baseline characteristics.
Abbreviations: HR, hazard ratio; MMR, mismatch repair; MSI, microsatellite instability; PS, performance status; TAS-102, trifluridine/tipiracil.

initiation of treatment compared with those who did not develop neutropenia (HR, 0.56; 95% CI, 0.37–0.84). In the absence of better biomarkers, neutropenia during cycle 1 to 2 may help identify patients more likely to benefit from TAS-102. Maintaining dose intensity in these patients with use of treatment delays and/or growth factor support may be worth considering. A direct comparison of outcomes between patients receiving TAS-102/bevacizumab versus regorafenib could not be performed in this study due to the limited number of patients who received the combination at the time these data were collected. Additional trials confirming the benefit of TAS-102/bevacizumab and investigating the combination of TAS-102 or regorafenib with other targeted therapies or immunotherapy are ongoing. We are hopeful that these studies will lead to further improvements in outcomes of patients diagnosed with mCRC.

This study is limited by its retrospective nature. The propensity score models used for survival analysis were designed to control for potential confounding; however, it is possible that additional uncontrolled confounding may have been present. A significant amount of missing data was present for some variables, and although missingness was included as a variable in our analysis, this may have also impacted our results. Additionally, although we were able to compare survival outcomes between patients receiving TAS-102 and regorafenib, data regarding tolerability and rates of adverse events, an important piece of information when discussing options with patients, were not available for comparison. Our study was also limited by lack of data on site of metastatic disease, dose intensity of drug delivered, receipt of hematopoietic growth factor, and tumor mutational data beyond *RAS/RAF* and MMR status. Future studies accounting for these variables could provide further insight into potential predictors of response and dose optimization. Finally, in this dataset, Hispanic/Latinx patients are underrepresented, which limits the generalizability of our findings.

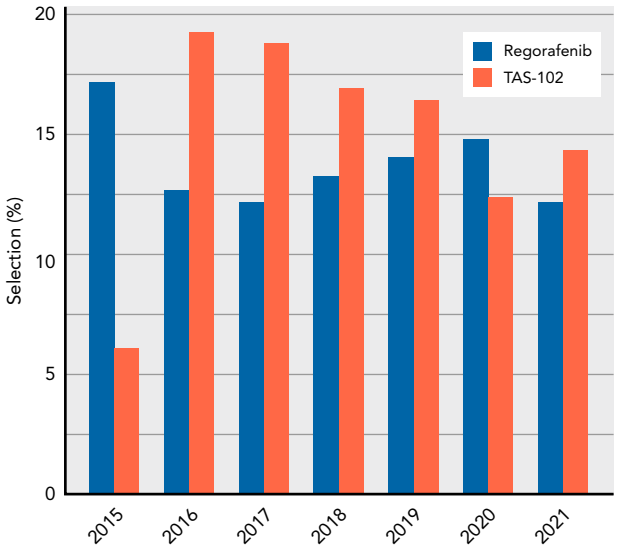

Figure 4. Trends in the use of regorafenib and TAS-102 over time as a percentage of therapies administered to patients with mCRC in the third-line or greater setting.
Abbreviations: mCRC, metastatic colorectal cancer; TAS-102, trifluridine/tipiracil.

Conclusions

This analysis of real-world data showed similar OS in patients with refractory mCRC who were treated with TAS-102 compared with regorafenib. Median OS with both agents in a real-world setting was comparable to that shown in the clinical trials that led to the FDA approvals. These data should be considered when discussing the risks and benefits of TAS-102 and regorafenib with patients who are eligible for third-line or greater treatment, and the findings demonstrate the need for novel therapeutic options in this patient population.

Submitted July 17, 2022; final revision received September 28, 2022; accepted for publication September 28, 2022. Published online February 22, 2023.

Author contributions: *Study concept and design:* Nevala-Plagemann, Sama, Garrido-Laguna. *Data analysis and interpretation:* All authors. *Manuscript preparation:* All authors.

Disclosures: Dr. Haaland has disclosed serving as a consultant for the National Kidney Foundation, Proxima Clinical Research, Value Analytics Labs, and Guidepoint Global. The remaining authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

Funding: Research reported in this publication was support by the Foundation for the National Institutes of Health under award number P30CA042014.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Correspondence: Christopher Nevala-Plagemann, MD, MSCI, Division of Medical Oncology, Department of Internal Medicine, Huntsman Cancer Institute at the University of Utah, 2000 Circle of Hope, Room 2143, Salt Lake City, UT 84112. Email: chris.nevala-plagemann@hci.utah.edu

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
2. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2000;343:905–914.
3. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938–2947.
4. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.
5. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–345.
6. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658–1664.
7. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303–312.
8. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909–1919.
9. Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 1.2022. Accessed September 20, 2022. To view the most recent version, visit https://www.nccn.org
10. Abrahao ABK, Ko YJ, Berry S, et al. A comparison of regorafenib and TAS-102 for metastatic colorectal cancer: a systematic review and network meta-analysis. Clin Colorectal Cancer 2018;17:113–120.
11. Moriwaki T, Fukuoka S, Taniguchi H, et al. Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): a Japanese Society for Cancer of the Colon and Rectum multicenter observational study. Oncologist 2018;23:7–15.
12. Masuishi T, Taniguchi H, Hamauchi S, et al. Regorafenib versus trifluridine/tipiracil for refractory metastatic colorectal cancer: a retrospective comparison. Clin Colorectal Cancer 2017;16:e15–22.
13. Tanaka A, Sadahiro S, Suzuki T, et al. Retrospective study of regorafenib and trifluridine/tipiracil efficacy as a third-line or later chemotherapy regimen for refractory metastatic colorectal cancer. Oncol Lett 2018;16:6589–6597.
14. Chiang CL, Choi HC, Lam KO, et al. Real-world treatment patterns and outcomes in refractory metastatic colorectal cancer. Asia Pac J Clin Oncol 2019;15(Suppl 2):5–13.
15. Ogata M, Kotaka M, Ogata T, et al. Regorafenib vs trifluridine/tipiracil for metastatic colorectal cancer refractory to standard chemotherapies: a multicenter retrospective comparison study in Japan. PLoS One 2020;15:e0234314.
16. Patel AK, Abhyankar R, Brais LK, et al. Trifluridine/tipiracil and regorafenib in patients with metastatic colorectal cancer: a retrospective study at a tertiary oncology center. Oncologist 2021;26:e2161–2169.
17. Ma X, Long L, Moon S, et al. Comparison of population characteristics in real-world clinical oncology databases in the US: Flatiron Health, SEER, and NPCR. bioRxiv. Preprint posted online May 30, 2020.
18. Birnbaum B, Nussbaum N, Seidl-Rathkopf, et al. Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. arXiv. Preprint posted online January 13, 2020.
19. Zhang Q, Gossai A, Monroe S, et al. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res 2021;56:1281–1287.
20. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2015;16:619–629.
21. Xu J, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102)

monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA Study. J Clin Oncol 2018;36:350–358.
22. Walter T, Hawkins NS, Pollock RF, et al. Systematic review and network meta-analyses of third-line treatments for metastatic colorectal cancer. J Cancer Res Clin Oncol 2020;146:2575–2587.
23. Chen J, Wang J, Lin H, et al. Comparison of regorafenib, fruquintinib, and TAS-102 in previously treated patients with metastatic colorectal cancer: a systematic review and network meta-analysis of five clinical trials. Med Sci Monit 2019;25:9179–9191.
24. Sonbol MB, Benkhadra R, Wang Z, et al. A systematic review and network meta-analysis of regorafenib and TAS-102 in refractory metastatic colorectal cancer. Oncologist 2019;24:1174–1179.
25. Casadei-Gardini A, Vagheggini A, Gelsomino F, et al. Is there an optimal choice in refractory colorectal cancer? A network meta-analysis. Clin Colorectal Cancer 2020;19:82–90.e9.
26. Vitale P, Zanaletti N, Famiglietti V, et al. Retrospective study of regorafenib versus TAS-102 efficacy and safety in chemorefractory metastatic colorectal cancer (mCRC) patients: a multi-institution real life clinical data. Clin Colorectal Cancer 2021;20:227–235.
27. Nakashima M, Takeuchi M, Kawakami K. Effectiveness and safety of regorafenib vs. trifluridine/tipiracil in unresectable colorectal cancer: a retrospective cohort study. Clin Colorectal Cancer 2020;19:e208–225.
28. Shitara K, Yamanaka T, Denda T, et al. REVERCE: a randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for previously treated metastatic colorectal cancer patients. Ann Oncol 2019;30:259–265.
29. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol 2019;20:1070–1082.
30. Pfeiffer P, Yilmaz M, Möller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:412–420.
31. Yoshino T, Cleary JM, Van Cutsem E, et al. Neutropenia and survival outcomes in metastatic colorectal cancer patients treated with trifluridine/tipiracil in the RECOURSE and J003 trials. Ann Oncol 2020;31:88–95.
32. Kasi PM, Kotani D, Cecchini M, et al. Chemotherapy induced neutropenia at 1-month mark is a predictor of overall survival in patients receiving TAS-102 for refractory metastatic colorectal cancer: a cohort study. BMC Cancer 2016;16:467.