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Original Article

Biweekly dosing of trifluridine-tipiracil reduces rates of myelosuppression while maintaining efficacy in patients with metastatic colorectal cancer

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Abstract

Background: Trifluridine-tipiracil (TAS-102) is approved as monotherapy and in combination with bevacizumab for refractory unresectable metastatic colorectal cancer (mCRC). The recommended dose is 35 mg/m^2 twice daily on days 1-5 and days 8-12 of 28-day cycles commonly resulting in grade 3-4 neutropenia, dose delays/reductions, and requiring GCSF support. To maintain efficacy and reduce toxicity, we analyzed a biweekly dosing schedule (days 1-5 and days 15-19 q28 days).

Patients and Methods: A retrospective analysis was performed in patients with mCRC and appendiceal cancer who completed >12 days of TAS-102 therapy and underwent surveillance imaging every 8-12 weeks. ECOG performance status (PS), prior lines of therapy, use of bevacizumab, CTCAE grade of treatment-related myelotoxicity, dose reductions/delays, and use of GCSF were assessed. Among patients with mCRC, survival analyses were performed.

Results: 61 patients met inclusion criteria, with mCRC:appendiceal CA ratio of 56:5. Median ECOG PS = 1; median number of prior therapies = 3; Reduction in grade ≥3 neutropenia (16.3%, 1 patient with grade 4) and grade ≥3 anemia (8.2%) relative to the historic controls of the RECOURSE and SUNLIGHT trials. No neutropenic fever was noted; GCSF was not required. Eight patients required a dose delay. In the mCRC patients, the median progression-free survival (PFS) was 4.2 months, with a median overall survival (OS) of 9.2 months.

Conclusions: Biweekly dosing of TAS-102 demonstrated a reduction in myelosuppression, with similar PFS and OS. With an improved toxicity profile, this alternative dosing schedule may potentially broaden the utilization of TAS-102 in patients with borderline PS and provide a favorable option for future combination studies.

Key words: trifluridine tipiracil; TAS-102; bevacizumab; colorectal cancer; neutropenia.

Implications for Practice

The use of a biweekly dosing schedule of Trifluridine-tipiracil (TAS-102) promotes the reduction of treatment-related toxicities, with similar therapeutic efficacy when used as monotherapy or in combination with bevacizumab when compared to historical controls. Biweekly dosing mitigated dose delays and importantly, eliminated the use of granulocyte-colony stimulating factor. Moreover, this dosing schedule aligns with biweekly dosing of bevacizumab potentially increasing patient compliance. Our findings indicate an improved toxicity profile which can provide support for the investigation use of TAS-102 in combination with other therapeutic agents.

Introduction

Colorectal cancer remains a significant source of morbidity and mortality within the United States, with an estimated 106 590 new diagnoses and nearly 462 200 deaths in 2024 alone.[1] Late-stage or metastatic disease (mCRC) is incurable, lending to a dismal 14% 5-year survival rate; however, advancements in chemotherapy have allowed for an estimated 50% of patients with mCRC to reach third-line therapy, making the choice of therapy in these later line settings all the more pivotal.[2-4]

Specifically, trifluridine and tipiracil (TAS-102), are incorporated into DNA in place of thymidine, co-formulated with a pharmacokinetic enhancer (tipiracil hydrochloride) which inhibits thymidine phosphorylase, the enzyme that degrades tipiracil.[5] Multiple dosing schedules of TAS-102 were evaluated in phase I trials, including once daily dosing over 14 days in a 21-day cycle, three times daily dosing, daily dosing on days 1-5 and 8-12 of a 21- or 28-day cycle, and twice daily dosing of days 1-5 and 8-12 of a 28-day cycle. Dosing was determined via a dose escalation study between 30 versus 35 mg/m^2.[6-10] Based on these results, and the efficacy shown in

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phase II placebo-controlled trial, the TAS-102 dosing schedule of 35 mg/m^2 twice PO daily (maximum dose 80 mg PO daily) on days 1-5 and days 8-12 of a 28-day cycle was used in phase III RECOURSE trial, resulting in approval of TAS-102 in refractory metastatic CRC.[11,12] Recently, the SUNLIGHT trial demonstrated that the addition of bevacizumab to TAS-102 demonstrated superior median overall survival (OS) versus TAS-102 alone (10.8 vs 7.5 months; HR 0.61).[13]

Despite the apparent benefits of this drug combination, TAS-102 can result in significant adverse events. In the RECOURSE trial and SUNLIGHT trial, almost all (96.9%-99.4%; 98%) patients had at least one adverse event, and notably, most patients experienced hematologic abnormalities requiring dose reductions or delays. Specifically, 38% of patients in the RECOURSE trial, and 43.1% in the combination arm of the SUNLIGHT suffered grade 3-4 neutropenia.[14] These and other toxicities led to dose delays of 53% and 69.5%, in the RECOURSE and SUNLIGHT trials, respectively.

To mitigate the dose-limiting toxicities associated with TAS-102 to promote increased on-treatment effect and quality of life, we examined the use of an alternative dosing schedule. Compared to the RECOURSE and SUNLIGHT study dosing schedule of 35 mg/m^2 twice PO daily (maximum dose 80mg PO daily) on days 1-5 and days 8-12 of a 28-day cycle, we implemented an adjusted biweekly dosing regimen to reduce adverse effects. This dosing regimen consists of trifluridine-tipiracil 35 mg/m^2 (capped at 80 mg per dose) PO twice a day on days 1-5 and 15-19 of a 28-day cycle.

Methods

A retrospective analysis was completed at Vanderbilt-Ingram Cancer Center (2019-2023) and University of Wisconsin Carbone Cancer Center (2018-2022) in patients with refractory mCRC and appendiceal cancer who completed >12 days of TAS-102 therapy and underwent surveillance imaging every 8-12 weeks. Patient data was assessed for ECOG performance status (PS), prior lines of therapy, the addition of bevacizumab, CTCAE grade of treatment-related myelotoxicity, dose delays or reduction, and use of GCSF. Patients' adverse events data were summarized with frequency and percentage and compared between patients using TAS-102 and patients using TAS-102 plus bevacizumab in this alternative dosing trial. Additionally, the adverse event data were extracted from RECOURSE and SUNLIGHT trials, summarized in the same manner, and compared with the same treatment arm used in this alternative dosing trial. All the comparisons on the adverse events data were conducted using Fisher's exact test. Among patients with mCRC, survival analyses were performed for both progression-free survival (PFS) and OS. Median survival times and 1-year survival rates with 95% CI were reported for the overall cohort and by study arms separately. Survival data was also extracted from the RECOURSE and SUNLIGHT trials and compared with those in this analysis using confidence intervals. In the final analysis, patients with appendiceal cancer were excluded from PS and OS analyses for adequate comparison to the historical control arms. Due to the inaccessibility of the raw data, however, no formal tests were conducted. Kaplan–Meier plots were reported to depict the cohort's survival over time. Log-rank tests were used to compare the difference in survival between the study arms. A two-sided P-value < .05 was considered statistically significant. All analyses were conducted with R software version 4.3.[15]

Results:

A total of 61 patients were included in the analysis; 5 patients with appendiceal adenocarcinoma were excluded from the PS and OS analyses. The median age was 56.5 (range 30-80), male to a female ratio of 1.38:1. Patients with ECOG PS 0 represented 14% of the patient cohort, with 79% having an ECOG PS of 1. Median lines of prior therapy were 3. Please see **Table 1** for a detailed comparison of myelotoxicity associated with the biweekly dosing schedule compared to reported data from the RECOURSE and SUNLIGHT trials. Alternative biweekly dosing is associated with reduced neutropenia of any grade, less grade ≥3 neutropenia, anemia, and thrombocytopenia. With the biweekly dosing schedule, GCSF utilization was not required. Additionally, no episodes of febrile neutropenia or treatment-related deaths were noted, and there was a reduction in the amount of dose delays.

Of the 56 patients included in the PFS and OS analyses, 72% were treated with the combination of TAS-102 and bevacizumab, while 28% received TAS-102 alone. The median OS of all patients with mCRC using a biweekly dosing schedule was 9.2 months (95% CI 6.5-12.1), with a 1-year survival rate of 32.8% (95% CI 21.4%-50.1%). Specifically, the median OS of patients treated with combination therapy was 9.2 months (95% CI 6.4-12.1) and 8.8 months for TAS-102 alone (95% CI 5.4-NA). Median PFS was 4.2 months (95% CI 2.5-6.5) for all patients, with combination therapy demonstrating a median PFS of 4.2 months (95% CI 2.7-6.5) and 3.2 months with TAS-102 alone (95% CI 2.3-8.2). Please see **Table 2** for a comparison of survival data for biweekly dosing to standard dosing relative to the historic phase III RECOURSE and SUNLIGHT trials. Reference **Figure 1** for Kaplan–Meier plots depicting the probability of PFS and OS over time for all patients treated with biweekly dosing and separated by use of TAS-102 plus bevacizumab or TAS-102 alone.

Discussion

This is the first study in a US patient cohort demonstrating evidence of reduced myelotoxicity following biweekly dosing of TAS-102 in the treatment of mCRC or appendiceal cancer while maintaining treatment efficacy in mCRC patients. The patient cohort reflects a heavily pretreated patient population with metastatic disease, adequate PS, equivalent male:female ratio, and a median age slightly lower than the median age of patients diagnosed with CRC in the United States.

Regarding myelotoxicity, alternative biweekly dosing resulted in overall less treatment-related neutropenia and less grade ≥3 neutropenia compared to patients provided standard dosing, with notable statistical significance observed when comparing patients treated with TAS-102 and bevacizumab. Importantly, no patients required the use of GCSF with biweekly dosing in contrast to the 29.3% of patients receiving TAS-102 with bevacizumab and 19.5% receiving TAS-102 alone in the SUNLIGHT trial. Elimination of the granulocyte support allows patients to avoid commonly associated toxicities including ostealgia, thrombocytopenia, fever, in addition to rare, yet severe, toxicities including splenic rupture and pulmonary toxicity.[16] In our analysis, greater than

Table 1. Comparison of myelotoxicity and dose reduction or delay in the alternative biweekly dosing schedule to the RECOURSE and SUNLIGHT trials.

Adverse events	Alternative dosing			RECOURSE trial		SUNLIGHT trial			
	35 mg/m2 BID PO days 1-5, days 15-19 (*N* = 19)	35 mg/m2 BID PO days 1-5, days 15-19 + Bevacizumab (*N* = 42)		35 mg/m2 BID PO days 1-5, days 8-12 (*N* = 534)		35 mg/m2 BID PO days 1-5, days 8-12 (*N* = 246)		35 mg/m2 BID PO days 1-5, days 8-12 + Bevacizumab (*N* = 246)	
	N (%)[a]	*N* (%)[b]	*P*-value[g]	*N* (%)[c]	*P*-value[d]	*N* (%)[e]	*P*-value[d]	*N* (%)[e]	*P*-value[f]
Neutropenia									
Any grade	5 (26.3%)	19 (45.2%)	.258	353 (67%)	<.001	126 (51.2%)	.055	153 (62.2%)	.042
Grade ≥ 3	3 (15.8%)	7 (16.7%)	1	200 (38%)	.055	79 (32.1%)	.198	106 (43.1%)	.001
Grade 3	3 (15.8%)	6 (14.3%)		NA					
Grade 4	0 (0%)	1 (2.4%)							
Anemia									
Any grade	10 (52.6%)	16 (38.1%)	.403	404 (77%)	.027	78 (31.7%)	.077	71 (28.9%)	.275
Grade ≥ 3	2 (10.5%)	3 (7.1%)	.643	96 (18%)	.549	27 (11.0%)	1.00	15 (6.1%)	.734
Grade 3	2 (10.5%)	3 (7.1%)		NA					
Grade 4	0%	0%							
Thrombocytopenia									
Any grade	0%	11 (26.1%)	.013	223 (42%)	<.001	28 (11.4%)	.237	42 (17.1%)	.194
Grade ≥ 3	0%	1 (2.4%)	1	27 (5%)	.616	3 (1.2%)	1.00	7 (2.8%)	1.00
Grade 3	0%	1 (2.4%)		NA					
Grade 4	0%	0%							
Other AEs									
Use of GCSF	0%	0%	-	9%	NA	19.5%	NA	29.3%	NA
Dose delay	3 (15.8%)	5 (11.9%)	.695	53%	NA	53.3%	NA	69.5%	NA
Dose reduction	5 (26.3%)	7 (16.7%)	.489	14%	NA	12.2%	NA	16.3%	NA

NA: When detailed data were not reported in the original trial article, no statistical test was attempted.
[a]: % were calculated against denominator 19.
[b]: % were calculated against denominator 42.
[c]: % were calculated against denominator 528 as reported in the original trial article.
[d]: Compared with Alternative Dosing 35 mg/m^2 BID arm. Fisher's exact test was used.
[e]: % were calculated against denominator 246 as reported in the original trial article.
[f]: Compared with Alternative Dosing 35 mg/m^2 BID + Bevacizumab arm.
[g]: Compared between Alternative Dosing Arms.
Myelotoxicity of biweekly dosing schedule versus standard dosing schedule.

80% of patients in the cohort remained at full therapeutic dose throughout their treatment course, and only 13.1% required dose delays. This is a significant reduction in dose delays relative to the standard dosing schedule, with 69.5% of patients with the combination of TAS-102 and bevacizumab in SUNLIGHT requiring delays, and 53% for TAS-102 alone in RECOURSE and SUNLIGHT.

This reduction in myelotoxicity and improvement in time on treatment was in conjunction with similar PFS and OS. Although the study population had improvement in PFS and OS when compared to the RECOURSE trial, the SUNLIGHT trial had about 1 month longer PFS and OS than our study cohort (Table 2). This slightly lower PFS and OS is in the setting of a more heavily treated patient population, as our study population had a median of 3 prior therapies whereas SUNLIGHT did not allow more than 2 lines of prior therapy onto the study.

Additionally, our study patient population was treated entirely at US academic cancers. In contrast, United States or North American patients only represented a minority of the patient population in the RECOURSE and SUNLIGHT trials, including a total of 99 (12.3%) and 16 patients (3.3%), respectively. These demographic differences could present variations in side effect profiles and possibly treatment effects between populations. The efficacy of this biweekly strategy has been studied in small cohorts of Japanese patients within the past decade. A case series using this dosing scheme at a single-center institution in Japan indicated improved rates of neutropenia and PFS relative to standard dosing, without deleterious effects on OS.[17] This was followed by the publication

Table 2. Survival data of biweekly dosing schedule versus standard dosing schedule.

	Alternative dosing			RECOURSE trial	SUNLIGHT trial	
	TAS-102 (*N* = 16)	TAS-102 + Bevacizumab (*N* = 40)	Total patient population (*N* = 56)	TAS-102 (*N* = 534)	TAS-102 (*N* = 246)	TAS-102 + Bevacizumab (*N* = 246)
Progression-free survival						
Median PS (95% CI)	3.2 months (CI 2.3-8.2)	4.2 months (CI 2.7-6.5)	4.2 months (CI 2.5-6.5)	2 months (CI 1.9-2.1)	2.4 months (CI 2.1-3.2)	5.6 months (CI 4.5-5.9)
Overall survival						
Median OS (95% CI)	8.8 months (CI 5.4-NA)	9.2 months (CI 6.4-12.1)	9.2 months (CI 6.5-12.1)	7.1 months (CI 6.5-7.8)	7.5 months (CI 6.3-8.6)	10.8 months (CI 9.4-11.8)
1-year survival rate	36.8% (CI 18.5%-73.4%)	30.6% (CI 17.7%-52.8%)	32.8% (CI 21.4%-50.1%)	27%	30%	43%

Comparison of median PFS, OS, and 1-year survival data for RECOURSE trial and SUNLIGHT trial relative to the alternative biweekly dosing schedule. Analyses excluded patients with appendiceal cancer for adequate comparison to historical control arms.

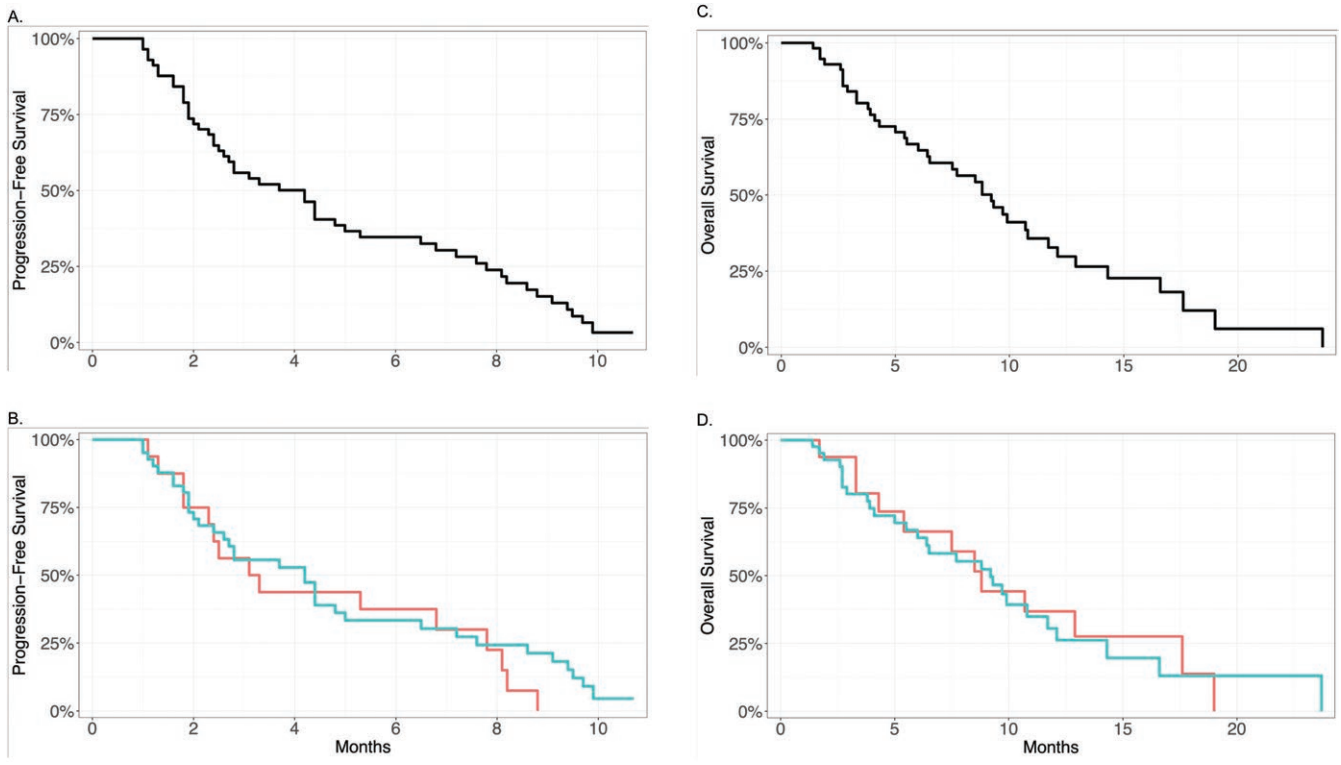

Figure 1. Survival analysis of biweekly dosing schedule with and without bevacizumab. Kaplan–Meier curves depicting survival curves for patients treated with alternative biweekly dosing. Progression-free survival for all patients and for those treated with TAS-102 versus TAS-102 with bevacizumab represented by A and B, respectively. OS for all patients and for those treated with TAS-102 versus TAS-102 with bevacizumab represented by C and D, respectively.

of three prospective studies, including the phase Ib/II BiTS study, redemonstrating a reduction in grade 3 or greater neutropenia, without compromising efficacy.[18-20] When comparing our results with the BiTS study, several differences emerge. First, our study only included patients with stage IV disease, unlike the BiTS study in which 11.3% of patients had stage III disease. This may have contributed to the slightly longer PFS and OS observed in this cohort (PFS 4.29 months, OS 10.49 months). These authors initiated a phase III study comparing standard dosing of TAS-102 versus biweekly dosing of TAS-102 plus bevacizumab; however, this was terminated early due to the results of the SUNLIGHT trial.[21]

Given the reduction in toxicity observed with this alternative dosing schedule, studies of TAS-102 in combination with other cytotoxic agents may be more feasible and better tolerated. Furthermore, sequencing with agents that are provided

biweekly may allow for a less complicated treatment schedule. TAS-102 has been studied in combination with oxaliplatin plus bevacizumab and irinotecan plus bevacizumab in patients with previously treated mCRC. In these studies, TAS-102 was provided on days 1-5 of a 14-day cycle, in line with a biweekly dosing schedule. In both phase 1b and phase II studies analyzing TAS-102 with oxaliplatin, the combination was well tolerated overall, with limited grade 3 myelotoxicity.[22-24] In combination with irinotecan and bevacizumab, phase II studies suggest tolerable toxicity but potentially higher rates of neutropenia.[25,26] These early phase trials set a precedent that combination therapy with biweekly dosing of TAS-102 is feasible and well-tolerated, and the prospect of other novel combination therapies with this dosing schedule should be explored.

Despite our promising results, our analysis had some limitations. First, although our study is the largest population of patients evaluated with this dosing schedule to date in a US patient population, the sample size is still small, limiting the statistical power and statistical significance of some analyses. Our study was retrospective, non-randomized, and did not include the utilization of this dosing schedule in other GI histologies for which TAS-102 is approved including gastric or esophageal adenocarcinomas. The difference in pharmacokinetics and pharmacodynamics of biweekly dosing is also unknown. We recognize that although this dosing schedule aligns well for patients eligible to receive bevacizumab, with bevacizumab provided on days 1 and 15 of each cycle, a biweekly dosing schedule may increase treatment complexity for some patients. This complicacy may require additional patient education, dosing calendars, and may be further convoluted if dose reduction or delays are needed.

Conclusion

This retrospective analysis demonstrates a complementary dosing schedule of TAS-102 that results in similar therapeutic efficacy while reducing treatment-related toxicities in this palliative treatment setting. With this improved toxicity profile, future directions may include the use of TAS-102 in patients with borderline PS and the study of TAS-102 in combination with other therapeutic agents. Further, this dosing schedule aligns with the biweekly dosing of bevacizumab. Additional prospective, multicenter data is needed to validate our findings.

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None.

Author Contributions

Christopher Cann: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing-original. draft, Writing-review & editing. -Michael LaPelusa: Data curation, Writing-original draft, Writing-review & editing. -Sarah Cimino: Conceptualization, Data curation, Writing – review & editing. -Victoria Cancelliere: Data curation -Elizabeth Dow-Hillgartner: Data curation -Zhiguo Zhao: Data curation, Formal analysis, Methodology, Validation, Writing-original draft, Writing-review & editing. -Dustin Deming: Data curation, Investigation, Supervision, Validation, Writing-review & editing. -Cathy Eng: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing-review & editing.

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Conflicts of Interest

Christopher Cann: Corresponding author potential conflicts of interest are limited to payment for consulting and advisory board participation with Taiho Pharmaceutical, consulting payments from Targeted Oncology and Curio Science, and honoraria from MECC Global Meetings. Previous travel expenses were paid by PRECISCA and Association of American Cancer Institutes. -Michael LaPelusa: No conflicts of interest. -Sarah Cimino: No conflicts of interest. - Victoria Cancelliere: No conflicts of interest. - Elizabeth Dow-Hillgartner: Potential conflicts of interest are limited to speakers Bureau for AstraZeneca. - Dustin Deming: Potential conflicts of intereste are limited to consulting or advisory role for Pfizer, Seagen, Illumina, Foundation Medicine, Regeneron, Taiho Oncology, along with research funding from Merck, Bristol Myers Squibb, Genentech, Revolution Medicines, Millennium, Bayer, Lilly, Arcus Ventures, Curegenix, Natera, Promega, AADi, Strata Oncology, Ipsen. -Cathy Eng: Potential conflicts of interest are limited to grant, research or trial support from Arcus, Agenus, Gritstone, Janssen, Merk, Pfizer, Sumitomo, along with consulting/advisory boards for Abbvie, Amgen, Elevation, GE, GSK, IGM, Merck, Mirati, Natera, Pfizer, Seagen, Taiho.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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