

Brazilian cohort results of the PRECONNECT study: safety and efficacy of trifluridine/tipiracil in metastatic colorectal cancer

Resultados da coorte brasileira do estudo PRECONNECT: segurança e eficácia da trifluridina/tipiracil no câncer colorretal metastático

Celso Abdon Lopes de Mello¹, Felipe Melo Cruz², Fernando Meton de Alencar Camara Vieira³, Alan Arrieira Azambuja⁴, Luiz A Senna Leite⁵, Luciana Mardegan⁶, Andreia Gil⁶, Loïck Vidot⁷, Anelisa Coutinho⁸

ABSTRACT

PRECONNECT is a multicenter study demonstrating the efficacy and tolerability of trifluridine/tipiracil in adult patients with histologically confirmed adenocarcinoma of the colon or rectum and pretreated metastatic lesions. The current article describes the characteristics and outcomes of the Brazilian cohort of patients who underwent trifluridine/tipiracil therapy within PRECONNECT. Brazilian patients (n=55) received oral trifluridine/tipiracil 35mg/m² twice daily on days 1-5 and 8-12 of each 28-day cycle. The primary endpoint was safety including time to ECOG (Eastern Cooperative Oncology Group) PS (performance status) deterioration, and the secondary endpoints included progression-free survival (PFS) and quality of life (QoL). Baseline characteristics showed only 34.5% of patients underwent ≥ 3 lines of treatment, 29.1% presented ≥ 3 metastatic sites and 52.7% showed an ECOG PS of 0. The disease control rate (DCR) was 32.0% and 28.6% in patients with one and two metastatic sites, respectively, the median PFS was 3.0 months (95%CI: 2.5-3.4), and the time to ECOG PS deterioration (≥ 2) was 5.4 months. Drug-related treatment-emergent adverse events (TEAE) were observed at least once in 87.3% of patients, and the most common ($\geq 40\%$ of patients) hematological TEAEs were neutropenia and anemia; there was no febrile neutropenia case. The shorter time to ECOG PS deterioration showed in the Brazilian subset of patients is likely due to late diagnosis setting compared to the global population, despite that trifluridine/tipiracil showed good DCR results, including patients with two metastatic sites. In conclusion, safety and efficacy results provide confidence in routine practice use and are in line with the PRECONNECT study

Keywords: Trifluridine/tipiracil; Colorectal cancer; Metastatic colorectal cancer; Refractory disease.

1. A.C. Camargo Cancer Center, Department Of Medical Oncology - São Paulo - São Paulo - Brazil.
2. Núcleo de Ensino e Pesquisa da Rede São Camilo - São Paulo - São Paulo - Brazil.
3. Americas Oncology and Americas Institute - Rio de Janeiro - Rio de Janeiro - Brazil.
4. Mãe de Deus Hospital - Porto Alegre - Rio Grande do Sul - Brazil.
5. ICESP - Instituto do Câncer do Estado de São Paulo - São Paulo - São Paulo - Brazil.
6. Laboratório Servier do Brasil - Rio de Janeiro - Rio de Janeiro - Brazil.
7. Servier - Suresnes - France.
8. AMO Clinic - Salvador - Bahia - Brazil.

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Correspondence author: Luciana Mardegan.

E-mail: luciana.mardegan@servier.com

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RESUMO

O PRECONNECT é um estudo multicêntrico que demonstra a eficácia e tolerabilidade de trifluridina/tipiracil em pacientes adultos com adenocarcinoma de cólon ou reto confirmado histologicamente e lesões metastáticas pré-tratadas. O presente artigo descreve as características e os resultados da coorte brasileira de pacientes submetidos à terapia com trifluridina/tipiracil dentro do PRECONNECT. Pacientes brasileiros (n=55) receberam trifluridina/tipiracil oral 35mg/m² duas vezes ao dia, nos dias 1-5 e 8-12 de cada ciclo de 28 dias. O desfecho primário foi a segurança, incluindo o tempo até a deterioração do ECOG (*Eastern Cooperative Oncology Group*) SD (status de desempenho), e os desfechos secundários incluíram sobrevida livre de progressão (SLP) e qualidade de vida (QV). As características basais mostraram que apenas 34,5% dos pacientes foram submetidos a ≥3 linhas de tratamento, 29,1% apresentaram ≥3 sítios metastáticos e 52,7% apresentaram ECOG SD de 0. A taxa de controle da doença (TCD) foi de 32,0% e 28,6% em pacientes com um e dois sítios metastáticos, respectivamente, a PFS mediana foi de 3,0 meses (IC95%: 2,5-3,4) e o tempo para deterioração do ECOG SD (≥2) foi de 5,4 meses. Os eventos adversos emergentes do tratamento (EAET) relacionados ao medicamento foram observados pelo menos uma vez em 87,3% dos pacientes, e os EAETs hematológicos mais comuns (≥40% dos pacientes) foram neutropenia e anemia; não houve caso de neutropenia febril. O menor tempo para deterioração do ECOG SD mostrado no subgrupo brasileiro de pacientes é provavelmente devido ao diagnóstico tardio em comparação com a população global, apesar de que trifluridina/tipiracil mostrou bons resultados de TCD, incluindo pacientes com dois sítios metastáticos. Em conclusão, os resultados de segurança e eficácia fornecem confiança no uso da prática de rotina e estão de acordo com o estudo PRECONNECT.

Descritores: Trifluridina/tipiracil; Câncer colorretal; Câncer colorretal metastático; Doença refratária.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy and the second most deadly cancer worldwide. In 2020 the global estimated incidence of CRC cases was 1.9 million and there was 0.9 million deaths.⁽¹⁾ In Brazil, CRC is also the third most incident cancer, behind only prostate and breast cancer.⁽²⁾ The National Cancer Institute (INCA) has estimated 41.010 new annual cases of CRC for the three-year period 2020-2022, and predictions by Souza et al. (2014)⁽³⁾ estimate that between 2021-2025 there will be 100,706 deaths, number proportionally higher than the 137,242 deaths attributed to CRC between 1996 and 2010 in Brazil.^(2,3)

About 20-25% of patients with CRC have a synchronous diagnosis of liver metastasis at initial diagnosis, and in more than 40-50% of patients with CRC, liver metastasis occurs within the first three years of follow-up after resection of the primary tumor.⁽⁴⁾ New chemotherapies, therapeutic monoclonal antibodies and other targeted agents have been developed and approved for the treatment of CRC over the last two decades,⁽⁵⁾ and in the last 10 years, in particular, the median overall survival (OS) has improved, including patients with metastatic CRC (mCRC). Patients with mCRC treated in phase III studies and in large series of observational registries, the OS is around 30 months, more than double that of 20 years ago.⁽⁶⁾

However, it was estimated that only 28% of patients receive at least three lines of treatment,⁽⁷⁾ even though approximately 80% of these patients are considered fit (an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1) to receive a third line treatment.^(8,9) Therefore, especially for those patients who continue to have good performance status and are eligible for new therapies, or for those refractory or intolerant to all approved drugs, there was an unmet medical need.

In the phase III RECURSE trial, mCRC patients randomized to trifluridine/tipiracil showed extension of OS and progression-free survival (PFS), and the medication had an acceptable result for safety and efficacy.⁽¹⁰⁾ Trifluridine/tipiracil is a new antimetabolite agent consisting of the thymidine analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride.⁽¹¹⁾ This oral cytotoxic chemotherapy is recommended by the European Society of Medical Oncology, the National Comprehensive Cancer Network (NCCN) and the Brazilian Society of Clinical Oncology (SBOC) guideline as a third-line (or further) therapeutical option for eligible patients.^(6,12,13) PRECONNECT, an international and multicenter study, was conceived to provide adult patients with mCRC early access to trifluridine/tipiracil, in order to further assess safety, efficacy and quality of life (QoL) as measured by patient-reported outcomes (PROs).⁽¹⁴⁾

This study was conducted in eligible pretreated patients from 16 countries, and the current article aims to describe the characteristics and outcomes of Brazilian cohort patients with mCRC who underwent trifluridine/tipiracil therapy within the PRECONNECT.

PATIENTS AND METHODS

The Brazilian group of mCRC patients (n=55) is a subset from the international and multicenter PRECONNECT study.⁽¹⁴⁾ Briefly, the PRECONNECT study was an open-label, single-arm, phase IIIb study of trifluridine/tipiracil in patients (aged ≥ 18 years) with histologically confirmed adenocarcinoma of the colon or rectum and metastatic lesions pretreated with at least two prior regimens of standard chemotherapies and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 during the screening period.

Eligible patients received oral trifluridine/tipiracil 35mg/m² twice daily (after morning and evening meals) on days 1-5 and 8-12 of each 28-day cycle until they met one or more criteria for treatment discontinuation, such as disease progression, unacceptable toxicity, withdrawal of consent, physician decision, pregnancy, major protocol deviation or commercial availability of trifluridine/tipiracil. The study was approved by the Brazilian National Research Ethics Committee (CAAE: 94404418.2.1001.5328); all patients who participated in PRECONNECT study provided written informed consent.

Safety was the primary endpoint, including time to ECOG (Eastern Cooperative Oncology Group) PS (performance status) deterioration. Safety was assessed from baseline through to the end-of-treatment visit, which was up to 28 days after the last study drug administration. Safety assessments included treatment-emergent adverse events (TEAEs), graded according to the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.9. The adverse event is graded according to severity; grade 3 is considered severe or clinically significant, and at grade 4 there are life-threatening consequences and urgent intervention is indicated, for example. The time to ECOG (Eastern Cooperative Oncology Group) PS (performance status) deterioration was a safety criterion. Secondary endpoints included progression-free survival (PFS), disease control rate (DCR) and quality of life (QoL). QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) health questionnaire.

Statistical analysis

Safety and efficacy variables were evaluated in patients who had received at least one dose of trifluridine/tipiracil. Baseline disease and patient characteristics and AEs were summarized using descriptive statistics (mean \pm standard deviation [SD], and median and 95% confidence interval [CI]).

Survival functions were estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS 9.2 software under the responsibility of the Centre of Excellence Methodology and Valorisation of Data of the sponsor *Institut de Recherches Internationales Servier*.

RESULTS

Brazilian patients were selected for the PRECONNECT study between March 2019 and July 2020. A total of 55 patients (58.2% male; median age of 58 years; 14.5% of patients >70 years old) were enrolled into the global study. At baseline, 55.8% of patients had an ECOG PS of 0, 56.4% had a mutant global RAS tumor status and 61.8% had synchronous metastasis at diagnosis. Thirty-five percent of patients received at least three previous lines of treatment (median: 2) and only 12.7% was previously exposed to regorafenib (Table 1). All patients started treatment with the approved full dose, as recommended, and the treatment lasted on average 15.6 \pm 11.57 weeks, with the median number of cycles equal three (range: 1-13). Median relative dose intensity was 82.8% (Table 2). During treatment, seven patients (12.7%) received at least one dose of granulocyte colony-stimulating factor.

At the end of study, 45 patients (81.8%) had discontinued treatment because of disease progression, six (10.9%) because of AEs, two (3.6%) for non-medical reasons and two (3.6%) for other causes.

Safety

The TEAE incidence was 98.2% (affected 54 of 55 patients) in the Brazilian subset from the PRECONNECT study and the drug-related TEAE incidence was 87.3% (48 patients). Eighty per cent (44 patients) had severe TEAE, CTCAE grades ≥ 3 , and the TEAE led to trifluridine/tipiracil dose reduction and dose delay in 25.5% (14 patients) and 61.8% (34 patients) of cases, respectively. The most common hematological TEAEs were neutropenia (all grades: 32 patients [58.2%]; 95%CI: 44.1-71.4; grade ≥ 3 : 18 patients [32.7%]; 95%CI: 20.7-46.7), and anemia (all grades: 22 patients [40.0%]; 95%CI: 27.0-54.1); grade ≥ 3 : 8 patients [14.5%]; 95%CI: 6.5-26.7). There was no case of febrile neutropenia. Considering the extra-hematological toxicities, asthenia (22 patients [40.0%]; 95%CI: 27.0-54.1), diarrhea (21 patients [38.2%]; 95%CI: 25.4-52.3), and nausea (20 patients [36.4%]; 95%CI: 23.87-50.4) were the most common (Table 3).

Efficacy

Trifluridine/tipiracil was associated with a median PFS of 3.0 months (95%CI: 2.5-3.4), with a DCR of 23.6% (95%CI: 13.2-37.0). The time to treatment failure was 3.3 months (95%CI: 2.8-3.9) and the time to ECOG deterioration was 5.4 months (95%CI: 4.2-NC; NC = not computed). The median PFS for patients with ECOG PS of 0 at baseline was 3.3 months (N=29; 95%CI: 2.7-3.7) and the DCR was 34.5% (95%CI: 17.9-54.3); patients with ECOG PS of 1 showed PFS of 2.7 months (N=23; 95%CI: 1.7-3.3) and the DCR was 8.7% (95%CI: 1.1-28.0).

Table 1. Patients' baseline characteristics.

Baseline characteristics	Patients (N=55)
Age in years – median (range)	58 (40-79)
≤70	47 (85.5)
>70	8 (14.5)
Sex	
Male	32 (58.2)
Female	23 (41.8)
ECOG PS	
0	29 (55.8)
1	23 (44.2)
2	0
Primary tumor site†	
Right colon	13 (23.6)
Left colon	37 (67.3)
Not specified/data missing	5 (9.1)
Time since first diagnosis of metastatic disease to first trifluridine/tipiracil intake	
<18 months	9 (16.4)
≥18 months	46 (83.6)
Synchronous metastasis at diagnosis	34 (61.8)
Number of metastatic sites	
1	25 (45.5)
2	14 (25.4)
≥3	16 (29.1)
Liver metastases at study entry	34 (61.8)
RAS status	
Wild type	10 (18.2)
Mutant	31 (56.4)
NA	14 (25.45)
BRAF status for RAS wild type	
Wild type	1 (10.0)
Mutant	0 (0.0)
NA	9 (90.0)
Previous treatment	
Surgery	34 (61.8)
Radiotherapy	16 (29.1)
Anti-VEGF	40 (72.7)
Anti-EGFR	21 (38.2)
Regorafenib	7 (12.7)
Number of previous treatment lines	
≤2	36 (65.5)
3	12 (21.8)
4	5 (9.1)
≥5	2 (3.6)

Legend: All values presented as n (%), patients) unless otherwise specified; †Right colon includes transverse colon; left colon includes rectum. ECOG PS: Eastern Cooperative Oncology Group performance status; NA: Not available.

Table 2. Treatment exposure.

Characteristics	Patients (N=55)
Duration of treatments, weeks	
Mean (SD)	15.6 (11.57)
Median (range)	13.1 (2.4-59.1)
Relative dose intensity, † median (%), mean (SD)	82.8
Number of treatment cycles	
Mean (SD)	3.6 (2.45)
Median (range)	3 (1-13)
≥3 cycles, n (%)	34 (61.8)

Legend: †N=55; ‡Based on the total number of cycles; SD: Standard deviation.

Table 3. Treatment Emergent Adverse Effect (TEAE).

TEAE	n* (%)
Total	54 (98.2)
Severe	44 (80.0)
Drug related	48 (87.3)
Leading to drug dose reduction	14 (25.5)
Leading to drug dose delay	34 (61.8)
Most frequent TEAE	
Neutropenia (all grades)	32 (58.2)
Neutropenia (grade ≥3)	18 (32.7)
Asthenia	22 (40.0)
Asthenia (grade ≥3)	4 (7.3)
Anemia	22 (40.0)
Anemia (grade ≥3)	8 (14.5)
Diarrhea	21 (38.2)
Diarrhea (grade ≥3)	2 (3.6)
Nausea	20 (36.4)
Nausea (grade ≥3)	-

Legend: *Corresponds to the number of patients with at least one TEAE.

Median PFS analysis by metastatic sites was 3.3 months for one site (N=25; 95%CI: 2.3-3.9), 3.4 months for two sites (N=14; 95%CI: 2.8-7.3), 2.5 months for three or more sites (N=16; 95%CI: 1.6-3.0) and the DCR was 32.0% (95%CI: 14.95-53.5), 28.6% (95%CI: 8.4-58.1) and 6.3% (95%CI: 0.16-30.2), respectively. Patients who received up to two lines of treatment had PFS of 3.2 months (N=36; 95%CI: 2.4-3.7) and DCR of 30.6% (95%CI: 16.3-48.1); patients who received more than two lines of treatment had PFS of 2.9 months (N=19; 95%CI: 2.4-3.4) and DCR of 10.5% (95%CI: 1.3-33.1).

Quality of life

At baseline, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Global Health Status score was 68.3±19.9 (mean ± SD). At the time of study withdrawal, this score was 56.9±21.4 (mean ± SD) for 29 patients.

DISCUSSION

Our objective was to evaluate data from the Brazilian subset of the PRECONNECT Phase IIIb study to better understand the characteristics and impacts of management in this population on the outcomes obtained. Baseline characteristics showed that only 34.5% (n=19) of patients in the Brazilian subset underwent three or more lines of treatment, a lower proportion than observed in the global study (63.4%),⁽¹⁴⁾ whose patients were on more advanced lines of treatment. In addition, only 12.7% (n=7) of patients received regorafenib, compared to 33.4% in the global study.⁽¹⁴⁾ However, the proportions of patients treated with anti-VEGF and anti-EGFR were similar between the groups.⁽¹⁴⁾ Probably, the lower proportion of patients who received regorafenib in prior lines of treatment in the Brazilian subset was related to the non-availability of this drug in the Brazilian Public Unified Health System during the recruitment period of the PRECONNECT study; 80% of the Brazilian population depends exclusively on public services for any health care.⁽¹⁵⁾

Although the sample size of the Brazilian subset is a limiting factor for more robust statistical analysis, the higher proportion of patients with three or more metastatic sites (Brazilian: 29.1%; global: 19.2%) and the lower proportion of patients who underwent surgery (Brazilian: 61.8%; global: 79.0%) may indicate patients with more advanced disease at diagnosis due to delays in diagnosis.⁽¹⁴⁾ In this context, the shorter time to deterioration of the ECOG PS in the Brazilian subset (5.4 months, 4.2-NC) when compared to the global population (8.9 months, 0.03-14.7 months),⁽¹⁴⁾ the higher proportion of patients with the synchronous metastasis at diagnosis (Brazilian: 61.8%; global: 52.5%) and the change from baseline on EORTC QLQ-C30 global health status score at the time of study withdrawal (-14.1±20.1) support the late diagnosis hypothesis. Indeed, the median PFS was shorter (2.5 months) for patients with three or more metastatic sites when compared to patients with one (3.3 months) or two (3.4 months) metastatic sites. However, the time to ECOG PS deterioration (PS≥2) in the Brazilian subset is in line with the RECURSE study, whose time to ECOG PS deterioration was 5.7 months.⁽¹¹⁾

Trifluridine/tipiracil is a good option for eligible patients and shows encouraging results, including for mCRC patients with two metastatic sites. In these patients, the DCR was 28.6%, a value similar to that seen in patients with only one metastatic site (32.0%). Additionally, as expected, median PFS was longer in patients who had ECOG PS of 0 and in those who had received up to two lines of treatment at baseline. The safety profile of trifluridine/tipiracil has been previously evaluated^(10,11,16-19) and confirmed in the PRECONNECT study.⁽¹⁴⁾ As observed in these studies, hematological TEAEs (such as neutropenia and anemia) were relatively the most common.

In the Brazilian subset, 87.3% (n=48) of patients had drug-related TEAEs and in 25.5% (n=14) of patients, the TEAE led to dose reduction, a higher proportion than that observed in the global sample (8.8%). In addition, 10.9% (n=6) of patients discontinued treatment for AE, a much higher proportion than that observed in the global sample (5.0%).⁽¹⁴⁾ Post hoc pharmacokinetic and pharmacodynamic analyses on data from the RECURSE study and the J003 trial indicated that patients with higher exposure to the trifluridine/tipiracil drug had an increased risk of developing chemotherapy-induced neutropenia (CIN) and that patients who developed CIN during treatment had better OS and PFS when compared to patients treated with trifluridine/tipiracil who did not develop CIN or when compared to patients in the placebo group.⁽²⁰⁾ In the Brazilian subset, 58.2% (n=32) of patients developed neutropenia (any degree) compared to 53.0% of patients in the global sample. Furthermore, the median relative dose intensity was lower in the Brazilian subset (82.9%) when compared to the global sample, in which median relative dose intensity was 89.9%. In this context, it is possible that the dose reduction also contributed to the shorter time to ECOG PS deterioration in the Brazilian subset when compared to the global population.

Yoshino et al. (2020)⁽²⁰⁾ point out that the RECURSE study and the J003 trial were not designed to specifically evaluate the efficacy of trifluridine/tipiracil dose maintenance or reduction in the context of CIN, but suggest that it is reasonable for clinicians to try to avoid unnecessary dose reductions. Therefore, the management of adverse events must follow the recommendations in the drug package insert. In case of hematological TEAE grades 2 and 3 (platelet count <75.000 and ≥25.000mm³; neutrophil count <1.500 and ≥500mm³), or grade 4 (platelet count <25.000mm³ and neutrophil count <500mm³) it is recommended to delay the start of the next cycle until toxicity returns to grade 1, or baseline. Resumption of treatment in the case of TEAE grades 2 and 3 will occur without dose adjustments. Resumption of treatment in case of TEAE grade 4 will occur without dose adjustments if the delay to the start of the next cycle is ≤1 week; if the delay is longer, a 5mg/m²/dose reduction from the previous dose is recommended. This dose reduction is also indicated in febrile neutropenia and in non-hematologic TEAE grades 3 and 4 (except nausea and vomiting grade 3, controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medications), and resumption of treatment should occur when toxicity returns to grade 1 or baseline.⁽²¹⁾ In addition, neutropenia can be managed with the use of granulocyte colony-stimulating factor. American Society of Clinical Oncology (ASCO) clinical practice guidelines recommend the use of granulocyte colony-stimulating factors as secondary prophylaxis in case of neutropenic complications, in which a reduced dose or delay in treatment may compromise the outcome.⁽²²⁾

In addition, this guideline recommends primary prophylaxis in patients who have a risk of febrile neutropenia of approximately 20% or more based on patient, disease, and treatment-related factors. In the PRECONNECT study, only 1.4% of patients in the global study had febrile neutropenia,⁽¹⁴⁾ but none of these events was observed in the Brazilian subgroup patients. Although ASCO recommends that granulocyte colony-stimulating factors should not be routinely used in patients with a febrile neutropenia,⁽²²⁾ meta-analysis studies point out that primary prophylaxis with CSFs reduces the risk of febrile neutropenia during chemotherapy for a solid tumor or lymphoma, and may also reduce the risk of hospitalization and infection.⁽²³⁾ In the Brazilian subset, 12.7% of patients (N=7) received at least one dose of granulocyte colony-stimulating factor, a proportion lower than that observed in the overall population (16.4%).

PRECONNECT study was designed to evaluate daily practice and did not include follow-up data collection. Therefore, among the limitations of the analysis in the present study are the lack of a comparator arm and the inability to evaluate OS data.

In conclusion, most patients recruited to the study were previously treated with one or two lines of treatment. However, a likely late diagnosis may have led to a shorter time to deterioration of the ECOG PS in the Brazilian subset when compared to the global population. Trifluridine/tipiracil showed good DCR results, including for patients with two metastatic sites, and the safety and efficacy results provide confidence in routine practice use and are in line with the global PRECONNECT study.

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AUTHORS' CONTRIBUTIONS

CALM: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

FMC: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

FMACV: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

AAA: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

LASL: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

LM: Data analysis and interpretation, Final approval of manuscript, Manuscript writing.

AG: Final approval of manuscript, Manuscript writing.

LV: Data analysis and interpretation, Final approval of manuscript, Manuscript writing.

AC: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

REFERENCES

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol*. 2021 Oct;14(10):101174. DOI: <https://doi.org/10.1016/j.tranon.2021.101174>
2. Kohlschutter A, Schulz A. CLN2 disease (classic late infantile neuronal ceroid lipofuscinosis). *Pediatr Endocrinol Rev*. 2016 Jun;13(Suppl 1):682-8.
3. Souza DL, Jerez-Roig J, Cabral FJ, Lima JR, Rotalira MK, Costa JA. Colorectal cancer mortality in Brazil: predictions until the year 2025 and cancer control implications. *Dis Colon Rectum*. 2014;57(9):1082-9. DOI: <https://doi.org/10.1097/DCR.0000000000000186>
4. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut*. 2006;55(Suppl 3):iii1-8. DOI: <https://doi.org/10.1136/gut.2006.098053>
5. Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Target Ther*. 2020;5(1):22. DOI: <https://doi.org/10.1038/s41392-020-0116-z>
6. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016 Aug;27(8):1386-422. DOI: <https://doi.org/10.1093/annonc/mdw235>
7. Abrams TA, Meyer G, Schrag D, Meyerhardt JA, Moloney J, Fuchs CS. Chemotherapy usage patterns in a US-wide cohort of patients with metastatic colorectal cancer. *J Natl Cancer Inst*. 2014 Feb;106(2):djt371. DOI: <https://doi.org/10.1093/jnci/djt371>
8. Calcagno F, Lenoble S, Lakkis Z, Nguyen T, Limat S, Borg C, et al. Efficacy, safety and cost of regorafenib in patients with metastatic colorectal cancer in french clinical practice. *Clin Med Insights Oncol*. 2016 Jul;10:59-66. DOI: <https://doi.org/10.4137/CMO.S38335>

9. Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO Randomized Clinical Trial. *JAMA*. 2018;319(24):2486-96. DOI: <https://doi.org/10.1001/jama.2018.7855>
10. Mayer RJ, Hochster HS, Cohen SJ, Winkler R, Makris L, Grothey A. Safety of trifluridine/tipiracil in an open-label expanded-access program in elderly and younger patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol*. 2018 Oct;82(6):961-9. DOI: <https://doi.org/10.1007/s00280-018-3686-5>
11. Van Cutsem E, Mayer RJ, Laurent S, Winkler R, Gravalos C, Benavides M, et al. The subgroups of the phase III RECURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer*. 2018 Feb;90:63-72. DOI: <https://doi.org/10.1016/j.ejca.2017.10.009>
12. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014 Apr;55(4):475-82. DOI: <https://doi.org/10.1111/epi.12550>
13. Fietz M, AlSayed M, Burke D, Cohen-Pfeffer J, Cooper JD, Dvorakova L, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): expert recommendations for early detection and laboratory diagnosis. *Mol Genet Metab*. 2016;119(1-2):160-7. DOI: <https://doi.org/10.1016/j.ymgme.2016.07.011>
14. Bachet JB, Wyrwicz L, Price T, Cremolini C, Phelip JM, Portales F, et al. Safety, efficacy and patient-reported outcomes with trifluridine/tipiracil in pretreated metastatic colorectal cancer: results of the PRECONNECT study. *ESMO Open*. 2020;5(3):e000698. DOI: <https://doi.org/10.1136/esmoopen-2020-000698>
15. Alsubaie L, Aloraini T, Amoudi M, Swaid A, Eyiad W, Al Mutairi F, et al. Genomic testing and counseling: The contribution of next-generation sequencing to epilepsy genetics. *Ann Hum Genet*. 2020 Jun;84(6):431-6. DOI: <https://doi.org/10.1111/ahg.12397>
16. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol*. 2012 Oct;13(10):993-1001. DOI: [https://doi.org/10.1016/S1470-2045\(12\)70345-5](https://doi.org/10.1016/S1470-2045(12)70345-5)
17. Ogata M, Kotaka M, Ogata T, Hatachi Y, Yasui H, Kato 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 Jun;15(6):e0234314. DOI: <https://doi.org/10.1371/journal.pone.0234314>
18. Cremolini C, Rossini D, Martinelli E, Pietrantonio F, Lonardi S, Noventa S, et al. Trifluridine/Tipiracil (TAS-102) in refractory metastatic colorectal cancer: a multicenter register in the frame of the Italian Compassionate Use Program. *Oncologist*. 2018;23(10):1178-87. DOI: <https://doi.org/10.1634/theoncologist.2017-0573>
19. Moriwaki T, Fukuoka S, Taniguchi H, Takashima A, Kumekawa Y, Kajiwara T, 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(1):7-15. DOI: <https://doi.org/10.1634/theoncologist.2017-0275>
20. Yoshino T, Cleary JM, Van Cutsem E, Mayer RJ, Ohtsu A, Shinozaki E, et al. Neutropenia and survival outcomes in metastatic colorectal cancer patients treated with trifluridine/tipiracil in the RECURSE and J003 trials. *Ann Oncol*. 2020;31(1):88-95. DOI: <https://doi.org/10.1016/j.annonc.2019.10.005>
21. Ireland PJ, McGill J, Zankl A, Ware RS, Pacey V, Ault J, et al. Functional performance in young Australian children with achondroplasia. *Dev Med Child Neurol*. 2011 Aug;53(10):944-50. DOI: <https://doi.org/10.1111/j.1469-8749.2011.04050.x>
22. Truty R, Patil N, Sankar R, Sullivan J, Millichap J, Carvill G, et al. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. *Epilepsia Open*. 2019 Jun;4(3):397-408. DOI: <https://doi.org/10.1002/epi4.12348>
23. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-212. DOI: <https://doi.org/10.1200/JCO.2015.62.3488>