Trifluridine/Tipiracil in Metastatic Colorectal Cancer

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Title:

Trifluridine/tipiracil in metastatic colorectal cancer: a UK multicentre real-world analysis on efficacy, safety, predictive and prognostic factors.

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Conflict of interest summary

CS: travel accommodation expenses from Servier & Amgen and lecture honoraria from Servier ;VA: travel accommodation expenses from Servier & Amgen ; KKS : (as an individual) received honoraria or travel funding from, or has consulted for, Bristol-Myers Squibb, Guardant Health, Innovent Biologics, Merck, Merck KGaA, Mirati Therapeutics, Roche, and Servier; and has received research funding (institutional) from Bristol-Myers Squibb, Merck, Merck KGaA, and Roche; TI: consulting/advisory role with Servier; MH: lecture fees from Servier ; AT: advisory role for Bristol-Myers Squibb PJR: Research Funding – Bayer, Sanofi, Consulting or Advisory role: Sirtex Medical, Eisai, SERVIER, Pierre Fabre, Shire & Roche , Honoraria: Roche, Sirtex Medical, Eisai, SERVIER, Pierre Fabre, Shire & AstraZeneca Speakers Bureau: Servier, Roche, Amgen & Merck.Travel, Accommodation, Expenses: Bayer, Servier &Roche
The remaining authors have stated that they have no conflicts of interest.

Micro-abstract

This multicenter retrospective study assessed the safety and efficacy of trifluridine/tipiracil in the real-world setting in patients with chemotherapy refractory metastatic colorectal cancer (mCRC), while identifying predictive and prognostic clinicopathological factors. Our findings suggest that real-world safety and efficacy of trifluridine/tipiracil are in keeping with the pivotal clinical trial outcomes. Pre-treatment neutrophil to lymphocyte ratio (NLR) and carcinoembryonic antigen (CEA) were prognostic, while treatment-induced grade 3 neutropenia was predictive for response.

Abstract (250 words)

Background: The orally administered combination trifluridine/tipiracil has been approved as third line treatment in mCRC, demonstrating survival benefit and acceptable toxicity profile in the phase III RECOURSE study.

Patient and methods: We performed a multicentre retrospective real-world analysis of patients with mCRC receiving trifluridine/tipiracil between 2016 and 2019 in eight cancer centers across the United Kingdom.

Results: A total of 236 patients were included with median age of 69 years. All patients had received at least 2 lines of fluoropyrimidine-based chemotherapy doublet with oxaliplatin or irinotecan. About 10% of patients had ECOG $\geq$ 2. Median duration of trifluridine/tipiracil treatment was 3 months with an ORR of 2.1% and disease control rate of 21.6%. Median OS was 7.6 and median PFS 3.3 months. A dose reduction was required in 27% of patients, while 7.6% discontinued treatment due to toxicity. The most common grade 3 toxicities were neutropenia (34%), fatigue (10%), anaemia (9%) and febrile neutropenia (5%). Baseline NLR <5 and CEA <200 had favourable prognostic (HR: 0.52 and 0.39, $p \leq 0.001$) and predictive value (OR: 4.1 and 6.7, $p<0.05$). Development of grade 3 neutropenia predicted treatment response (OR: 0.32, $p<0.001$). Following treatment with trifluridine/tipiracil 41% were referred for phase I trial or rechallenged with chemotherapy.

Conclusions:

Trifluridine/tipiracil is well tolerated in refractory mCRC patients with comparable efficacy and toxicity profile to that of the phase III RECOURSE**.** Pre-treatment NLR and CEA could serve as potential markers for patient selection, while treatment-induced grade 3 neutropenia predicted response. Prospective validation is needed.

Keywords (not used in title): TAS-102, Lonsurf, real-world evidence, neutropenia, treatment outcomes

Introduction

Colorectal cancer (CRC) is the 4th most common malignancy and the second cause of cancer related deaths in the United Kingdom (UK). [1] More than half of the patients diagnosed with CRC will eventually develop metastatic disease which has a poor prognosis, with 5-year survival rates being around 14%. [1] The introduction of fluopyrimidine-based chemotherapy doublets with oxaliplatin and irinotecan and the use of targeted treatments such as anti-epidermal growth factor receptor (EGFR) antibodies (cetuximab/ panitumumab) and bevacizumab in the first- and second-line setting, have significantly improved the survival of mCRC patients over the past two decades. [2] However, patients ultimately develop resistance to these agents and their management remains a challenge due to limited treatment options.

Trifluridine/tipiracil is an orally administered combination of the thymidine-based nucleic acid analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride at a 2:1 ratio. [3] Trifluridine's cytotoxic action is based on the incorporation of its phosphorylated form into the DNA, interfering with DNA synthesis and inhibiting cell proliferation. Tipiracil increases the bioavailability of trifluridine by preventing its degradation. [4]

Trifluridine/tipiracil has received regulatory approvals [5] and has been incorporated in the therapeutic armamentarium for mCRC following progression after at least two lines of oxaliplatin, irinotecan and fluoropyrimidine based chemotherapy. The approval was based on the results of the randomised, double-blind, placebo-controlled Phase III RECOURSE study which demonstrated survival benefit of 1.8 months compared to placebo with a tolerable toxicity profile.[6] The safety profile of trifluridine/tipiracil was further evaluated in the recent phase IIIb PRECONNECT trial, which confirmed the previously reported findings on its safety and efficacy profile while demonstrating that it maintained quality of life in heavily pre-treated mCRC patients. [7]

As there are significant differences between real-world and trial populations,[8] we performed a multicentre retrospective observational study to evaluate the safety and efficacy of trifluridine/tipiracil in the UK population. Furthermore, we explored clinicopathological factors of prognostic and predictive significance, which could potentially help clinicians identify patients who will derive the most benefit from trifluridine/tipiracil.

Patients and Methods

Study design and data source

We conducted a retrospective observational study to assess the real-world efficacy and safety profile of trifluridine/tipiracil in adult metastatic colorectal cancer patients at 8 cancer centres across the United Kingdom: Guy's and St Thomas' NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, University Hospitals of Leicester NHS Trust, Maidstone and Tunbridge Wells NHS Trust, Poole Hospital NHS Foundation Trust, Beatson West of Scotland Cancer Centre and Barking, Havering and Redbridge University Hospitals NHS Trust. A further objective of this study was to identify clinicopathological factors of predictive and prognostic significance. All data were extracted from electronic patient health records using a universal data collection protocol.

Patient population

Consecutive patients with refractory metastatic colorectal cancer who underwent treatment with trifludirine/tipiracil between January 2016 and January 2019 across 8 UK cancer centres were retrospectively identified. Patients included in this study were $\geq$ 18 years old, had a histologically confirmed diagnosis of mCRC and had received at least one dose of trifluridine/tipiracil as 3rd line treatment. The initiating dose of trifluridine/tipiracil treatment was 35 mg/m^2 twice daily, for 5 days per week with 2 days of rest for 2 weeks, followed by 2 weeks of rest.

Clinicopathological Characteristics

Complete demographic and clinical information were collected from electronic health records and included: age, gender, primary tumour location, metastatic sites, KRAS mutation status, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), prior CRC treatments and trifluridine/tipiracil treatment details (start and stop dates, number of cycles, dose modifications, adverse events). Baseline laboratory data collected included: haemoglobin, white blood cell and platelet counts, albumin and carcinoembryonic antigen (CEA). The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil to the absolute lymphocyte count, while the platelet to lymphocyte ratio (PLR) was calculated by dividing the absolute platelet to the absolute lymphocyte count.

Prespecified variables for the identification of potential prognostic and predictive factors were categorized based on clinical reasoning, existing literature and taking subgroup sizes into account as follows: age (<65 versus $\geq$ 65 years), ECOG PS (<2 versus $\geq$2), tumour sidedness (right colon versus left colon and rectum with splenic flexure as differentiation), number of metastatic sites (<2 versus $\geq$2),

time between first diagnosis of metastases and treatment initiation (<18 versus ≥ 18 months), albumin (<35 versus ≥35), NLR (<5 versus ≥5), PLR (<300 versus ≥300) and CEA (<200 versus ≥ 200).
Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Computed tomography (CT) based tumour assessments were carried out at various intervals as decided by patients' treating physicians.

Clinical Outcomes

Clinical outcomes, including overall survival (OS) and progression free survival (PFS) were calculated from the time of treatment initiation with trifluridine/tipiracil. For those who were still alive by the time of the data analysis, OS was calculated based on their last recorded visit. For patients who did not experience disease progression or death until the data cut-off date, PFS was censored to the last tumour assessment date. Objective response rate was calculated as the proportion of patients whose best response was complete or partial response. Disease control rate was calculated as the proportion of patients whose best response was complete response, partial response and stable disease.

Statistical Analysis

For the purposes of this observational study, data were routinely collected with no formal sample size calculation. The cut-off date for data analysis was 3rd of May 2019.
Baseline demographics and patient characteristics were descriptively analysed. Continuous outcomes were presented as means (standard deviations [SD]) and medians (range, interquartile range [IQR]) while categorical outcomes were presented as frequencies and proportions. Median OS and PFS and 95% confidence intervals (95% CIs) were estimated by the Kaplan-Meier method.
Univariable logistic regression analysis was conducted to identify baseline clinicopathological factors predicting response to trifluridine/tipiracil. Multivariable analysis (MVA) with backward model selection was then performed to assess for independent predictors. Univariable Cox regression was used to identify clinicopathological factors associated with survival was. The independent prognostic value of each factor was explored with MVA according to the Cox-proportional hazard model with a stepwise backward selection approach. Only variables displaying a significance level below 0.05 (2-sided) in the univariable analyses were included in the multivariable models.
All analyses were two-tailed, and *p*-values ≤0.05 were considered significant. The SPSS statistical package version 25 (IBM SPSS Inc.) was used.

Ethical considerations

According to UK Health Research Authority guidance [9] formal ethical approval for this real-world analysis was not required. Approval was obtained from the participating institutions' institutional review boards. Data were handled in accordance with the Declaration of Helsinki.

Results

Patient characteristics

A total of 236 patients with metastatic colorectal cancer who met the eligibility criteria were included in this analysis. Baseline demographic and clinicopathological characteristics are summarised in **Table 1**. The median age at trifluridine/tipiracil initiation was 70 years (range 35-82). The majority of patients were ≥ 65 years of age (64%), were male (67%) and had a primary tumour at the colon (67%). Ninety per cent (90%) of patients had an ECOG-PS score of 0 or 1, while 10% had a PS of 2. Of the included patients, 70% had prior colorectal surgery, all had received at least 2 prior lines of treatment containing a fluoropyrimidine with oxaliplatin or irinotecan, 35% had also received an anti-EGFR monoclonocal antibody and 21% had been treated with bevacizumab.

Treatment outcomes

Median treatment duration for our patient cohort was 3 months (0.2 – 25.2) and the median number of administered trifluridine/tipiracil cycles was 3 (IQR 2-5). At the time of the analysis 66% (n=156) of the patients had died. Median OS was 7.6 months (95%CI 6.5 - 8.6) and median PFS was 3.3 months (95% CI 3.03 - 3.57). A total of 208 patients (88%) were evaluated for response. Five patients had partial response (2.4%) and 45 had stable disease (21.6%). The objective response rate (ORR) was 2.4%, while the disease control rate (DCR) was 24% (**Table 2**). At the time of the analysis 213 patients (90%) had discontinued treatment. Reasons for treatment discontinuation were progressive disease (n=175, 82%), toxicity (n=18, 8%) and other non-medical reasons (n=20, 9%). Of these patients, 140 (65.7%) received best supportive care, 33 (15%) were referred to a clinical trial while 25 (12%) were re-challenged with chemotherapy.

Safety and adverse events

All patients commenced treatment with trifluridine/tipiracil at the recommended dose. Of the patients receiving at least one dose, 98% (n= 220) experienced at least one adverse event of any grade. A summary of the adverse events observed in this patient cohort is provided in **Table 3.** The most frequently encountered toxicities were anaemia in 74% (n= 166) (≥ grade 3 9%, n= 21), fatigue 70% (n= 159) (≥ G3 10%, n=22) and neutropenia 62% (n=139) (≥ G3 37%, n=82). Although neutropenia was the most frequent grade 3 toxicity, febrile neutropenia was only observed in 5% of the patients.

Gastrointestinal toxicities such as nausea and diarrhoea were observed in 32% (n=72) and 26% (n=58) of the patients respectively but were mild in the vast majority of cases. Thrombocytopaenia was only seen in 12% (n=27) of patients with only 1.8% (n=4) of patients experiencing grade 3 severity.
A dose reduction was required in 27% (n=63) of the patients. Of those undergoing a dose reduction 89% (n=56) had one and 11% (n=7) had 2 dose reductions respectively. The majority of dose reductions were due to haematological toxicities (60%, n=38), followed by gastrointestinal toxicities (12%, n=8) (**Figure 1**), while only 8% (n=18) permanently discontinued. Reasons for treatment discontinuation were progressive disease, toxicity, other non-medical reason. There were no treatment related deaths.

Predictors of response to trifluridine/tipiracil

In univariable analysis, baseline neutrophil to lymphocyte ratio (NLR) <5 (odds ratio [OR] 5.69, 95%CI 1.67 - 19.34, p=0.005) and CEA <200 (OR 5.08, 95%CI 2.3 – 11.13, p<0.001) were associated with response to trifluridine/tipiracil. Furthermore, development of grade 3 neutropenia while on treatment was also associated with achieving a response (OR 3.08, 95%CI 1.58 – 5.99, p=0.001). No statistically significant association was observed with any of the other examined factors (**Table 4**). In multivariable logistic regression, baseline CEA <200 (OR 6.09, 95%CI 2.23 – 16.67, p<0.001) and development of G3 neutropenia (OR 2.147, 95%CI 1.03 – 4.48, p=0.042) maintained statistical significance as independent prognostic factors for treatment response. Baseline NLR<5 showed a trend towards predicting treatment response (OR 3.49, 95%CI 0.97 – 12.5, p= 0.056). These results are summarised in **Table 4.**

Prognostic factors for survival

Univariable analysis identified age $\geq$ 65, ECOG PS <2, baseline albumin >35, NLR<5 and CEA <200 as positive prognostic factors for OS. Furthermore, development of grade 3 neutropenia during treatment was also associated with favourable OS. In the multivariable analysis baseline NLR<5 and CEA<200 maintained statistical significance while $\geq$ grade 3 neutropenia was also identified as an independent favourable prognostic factor (**Table 5**). Patients with baseline ECOG PS <2 had a median OS of 8.1 months (95%CI 6.6 – 9.5) compared to 4.2 months (95%CI 2 – 6.3) in those with ECOG PS $\geq$ 2. Baseline NLR <5 was associated with a median OS of 9.2 months (95%CI 7.5 – 10.8), while NLR $\geq$5 with 5.4 months (95%CI 6.4 – 8.7). Patients who developed G3 neutropenia during treatment had a median OS of 10.6 months (95%CI 8 – 13), versus 6.3 months (95%CI 5.1 – 7.4) in those who did not develop this toxicity (**Figure 2**).

Discussion

In this retrospective multi-centre observational study, we evaluated the efficacy and safety of trifluridine and tipiracil in patients with refractory mCRC in the real-world setting involving 8 cancer centres across the United Kingdom. Furthermore, we identified clinicopathological factors of predictive and prognostic significance. Our data demonstrated that the efficacy and toxicity profile of trifluridine/tipiracil were consistent with the outcomes reported in the pivotal phase III RECOURSE trial [6] as well as with the more recent phase IIIb PRECONNECT trial. [7]

Although the demographic and clinicopathological characteristics of our patient cohort were comparable with these of the patients enrolled in both trials, there were several key differences which demonstrate the disparity between real-world and trial populations and underline the importance and complementary role of real-world data in the evaluation of drug safety and efficacy. Median age was higher in our patient population (70 years) compared to the trial populations (63 years) [6,7]. An important difference is the fact that 10% of our patient cohort had an ECOG PS of 2, whereas such patients were excluded in both RECOURSE and PRECONNECT trials. Several other real-world studies assessing trifluridine/tipiracil in mCRC have also included patients with ECOG PS 2.[10-15] Our findings are keeping with the existing literature showing that patients with borderline performance status do not experience added toxicity from trifluridine/tipiracil [12] but seem to have worse survival outcomes. [11,13,14]

The type of previous lines of treatment was another point of divergence between our study and the RECOURSE trial. Due to funding restrictions, only 21% of our patients had received bevacizumab as part of their prior treatment compared to 100% in the trial population. Similarly, only 1 patient had received regorafenib compared to 17% in the RECOURSE trial. The diversity in the type and number of previous lines of treatment in mCRC patients treated with trifluridine/tipiracil across different countries is apparent from existing real-world studies [11,12,16-18] and reflects not only the differences in cancer drug access but also the great variation in the treatment pathways beyond second line.

The efficacy of trifluridine/tipiracil in our real-world study was comparable to that observed in the RECOURSE trial. We observed a median OS of 7.6 months compared to 7.1 months in the clinical trial. Across the literature median OS was ranging from 5.4 months [11] up to 9 months.[19] This variation could be attributed to the differences observed among real-world patient cohorts as described above. Medial PFS in our study was 2.6 months with a DCR of 21.6%, compared to 2 months and 44% respectively in the RECOURSE study. This disparity could be justified by the different timings of radiologic tumour assessments in the clinical trial and the real-world setting. In the RECOURSE study patients underwent their first disease evaluation at 8 weeks whereas in clinical practise patients are evaluated at 12-14 weeks. This difference could positively distort the observed PFS while having a negative impact on DCR. It is of note that in the PRECONNECT study, where patients had their tumour assessments done as per investigator's usual practice and not at protocol defined intervals, the median

PFS was 2.8 months and DCR 34.4%. Other retrospective real-world studies reported disease control rates between 11.7% [17] and 37.6%.[19]

Trifluridine/tipiracil was generally well tolerated with a toxicity profile comparable to that observed in both RECOURSE and PRECONNECT trials. The most commonly noted grade 3 toxicity was neutropenia in 35% of our patients compared to 38% and 38.2% respectively in the trials. However, the incidence of febrile neutropenia was only 4.6% in our study compared to 4% and 1.4% in the above trials. These findings are consistent with several other real-world studies.[10-12,15,20] The use of granulocyte colony stimulating factor was found to vary among different centres and is at the discretion of the treating physician. The most frequent non-haematological toxicities were fatigue and gastrointestinal symptoms such as nausea, diarrhoea and vomiting and were mild in the vast majority of patients both in the real-world and trial setting. In our real-world analysis, 27% of patients underwent a dose reduction compared to 14% in the RECOURSE and 8.8% in the PRECONNECT trials. Treatment was discontinued due to toxicity in 8% of our patients compared to 4% and 5% in the trials respectively.

We evaluated the presence of factors that could predict response to trifluridine/tipiracil and identified pre-treatment NLR<5 and CEA<200 as well as the development of treatment induced $\geq$G3 neutropenia as independent predictors of treatment response. These factors were also found to have prognostic significance in the multivariable analysis and were associated with improved OS. The prognostic value of NLR was previously described in a small retrospective study [21], however we also demonstrated that it can also serve as a predictive marker for treatment response. The importance of grade 3 neutropenia as a predictive and prognostic marker in patients treated with trifluridine/tipiracil has been well established in the literature. [22-25] A recent *post hoc* pharmacokinetic/pharmacodynamic analysis of the RECOURSE study, attributed the development of treatment-induced neutropenia to a higher exposure to trifluridine and linked it to improved OS and PFS. [26] So far development of grade 3 neutropenia remains the most validated marker of response to trifluridine/tipiracil.

In an effort to optimise patient selection, several other prognostic factors have been identified. ECOG PS, time since diagnosis of first metastasis and number of metastatic sites were identified from the RECOURSE study.[6] In their retrospective study, Cremolini et al [13] identified ECOG PS, Lactate dehydrogenase (LDH) and time from diagnosis of metastases. However, in our analysis ECOG PS <2 was found to be a favourable prognostic factor in the univariable but not in the multivariable survival analysis.

Our study is limited by its retrospective nature, which impacts on the reporting of non-laboratory toxicities. Furthermore, response to previous treatments was not explored as a predictive factor in our multivariate analyses. Despite its limitations, this is to the best of our knowledge the largest real-world

dataset for patients with refractory mCRC treated with trifluridine/tipiracil in the United Kingdom. The involvement of 8 cancer centres across the country enhanced the diversity of our patient cohort ensuring it represents real-life clinical practice. Our real-world analysis included patients with different characteristics compared to RECOURSE and PRECONNECT clinical trials, such as patients with different previous treatments as well as those with ECOG PS 2 providing valuable information on the safety and efficacy of trifluridine/tipiracil in these patient groups.

Conclusions

Our real-world analysis demonstrated that trifluridine/tipiracil is well tolerated in refractory mCRC patients with comparable efficacy and toxicity profile to that of the phase III RECOURSE and PRECONNECT clinical trials. Echoing the findings of other real-world studies, there were no safety concerns in patients with borderline ECOG performance status, but efficacy was limited in this patient cohort. We identified pre-treatment NLR<5 and CEA<200 as favourable predictive and prognostic factors and further validated the predictive and prognostic significance of treatment induced grade 3 neutropenia in our patient population. Prospective validation of these factors in warranted in order to optimize patient selection, maximising clinical benefit from trifluridine/tipiracil while avoiding unnecessary toxicity.

Clinical practice points

- The phase III RECOURSE and PRECONNECT clinical trials demonstrated a survival benefit and tolerable toxicity profile for trifluridine/tipiracil in patients with refractory mCRC
- In the real-world setting as reflected by mCRC patients from 8 cancer centres across the UK, trifluridine/tipiracil maintained comparable efficacy with no new safety signals
- Despite our limited data, patients with ECOG PS 2 did not experience added toxicities but did not benefit from trifluridine/tipiracil
- Pre-treatment NLR<5 and CEA<200 were favorable prognostic factors
- Development of treatment induced G3 neutropenia was predictive of treatment response and improved survival
- Prospective validation of these clinicopathological factors could optimize patient selection for trifluridine/tipiracil

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Tables

Table 1. Baseline patient demographics and clinical characteristics

Characteristic	N= 236 n (%)
Age- years	
Median (range)	70 (35-82)
< 65	85 (36)
≥ 65	156 (64)
Sex	
Male	135 (57)
Female	101 (43)
ECOG performance status	
0	48 (20)
1	165 (70)
2	23 (10)
Primary site of disease	
Colon	159 (67)
Rectum	77 (33)
Side of primary tumour	
Left	156 (66)
Right	80 (34)
Time from diagnosis of metastases	
< 18 months	159 (32)
≥ 18 months	74 (68)
Number of metastatic sites	
1-2	97 (42)
≥ 3	139 (58)
KRAS status	
Wild type	114 (48)
Mutant	80 (34)
Unknown	42 (18)
Previous chemotherapy	
Fluoropyrimidine doublet*	236 (100)
Bevacizumab	50 (21)
anti-EGFR	83 (35)
Regorafenib	1 (0.4)
Baseline albumin	
< 35	42 (18)
≥ 35	178 (75)
Unknown	16 (7)
Baseline NLR	
< 5	169 (72)
≥ 5	52 (22)
Unknown	15 (6)
Baseline PLR	
< 300	181 (77)
≥ 300	40 (17)
Unknown	15 (6)
Baseline CEA	
< 200	134 (57)

≥ 200	102 (43)

Abbreviations: ECOG= Eastern Cooperative Oncology Group, EGFR = Epithelial growth factor receptor, NLR= neutrophil to lymphocyte ratio, PLR= platelet to lymphocyte ratio, CEA= Carcinoembryonic antigen

Table 2. Treatment outcomes

Outcome	
Median treatment duration - months (range)	3 (0.2-25.2)
Objective Response Rate	2.1%
Disease Control Rate	24%
Median OS - months (95% CI)	7.6 (6.5 – 8.6)
Median PFS - months (95% CI)	3.3 (3.02 – 3.57)

Abbreviations: OS= overall survival, PFS= progression free survival, CI= confidence interval

Table 3: Adverse events in patients treated with trifluridine/tipiracil

Adverse event	**Any grade – N (%)**	**Grade ≥3 - N (%)**
Neutropenia	139/223 (62)	82/223 (37)
Anaemia	166/224 (74)	21/224 (9)
Thrombocytopenia	27/224 (12)	4/224 (2)
Fatigue	159/225 (70)	22/225 (10)
Diarrhea	58/225 (26)	5/225 (2)
Nausea & Vomiting	75/225 (34)	8/225 (3.5)
Anorexia	71/225 (31)	6/225 (3)
Febrile neutropenia		11/225 (5)

Table 4. Univariable and multivariable logistic regression to identify clinicopathological factors predicting response to trifluridine/tipiracil

	Univariable model		Multivariable model	
	OR (95%CI)	**p**	**OR (95%CI)**	**p**
Age <65 /≥ 65	0.75 (0.38 – 1.4)	0.4		
NLR <5/ ≥ 5	5.69 (1.68 – 19.34)	0.005*	3.49 (0.97- 12.5)	0.056
PLR <300/≥300	2.5 (0.84 – 7.67)	0.09		
Alb <35 /≥35	0.47 (0.187 – 1.21)	0.12		
CEA <200/≥200	13.68 (3.17 – 59.05)	<0.001*	6.09 (2.23 – 16.67)	<0.001*
ECOG PS <2 /≥ 2	2.043 (0.57 – 7.24)	0.26		
Time to metastases <18/≥ 18 months	0.61 (0.295 – 1.26)	0.182		
G3 neutropenia Yes/No	3.08 (1.58 – 5.99)	0.001*	2.14 (1.029 – 4.48)	0.04*
G3 thrombocytopenia Yes/No	1.02 (0.104 – 10.11)	0.98		
G3 Anaemia Yes/No	1.36 (0.49 – 3.77)	0.548		
Metastatic sites <2/≥2	1.00 (0.53- 1.90)	0.98		

Abbreviations: OR= odds ratio, NLR= neutrophil to lymphocyte ratio, PLR= platelet to lymphocyte ratio, Alb= albumin, CEA= carcinoembryonic antibody, ECOG PS= Eastern Cooperative Oncology Group performance status, G3= grade 3

Table 5. Univariable and multivariable Cox regression survival analysis of different prognostic clinicopathological factors in patients treated with trifluridine/tipiracil

	Univariable model		Multivariable model	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Age <65 /≥ 65	1.45 (1.59 – 2.0)	0.021		
NLR <5/ ≥ 5	0.45 (0.30 – 0.65)	<0.001*	0.56 (0.35 – 0.88)	0.01*
PLR <300/≥300	0.7 (0.466 – 1.05)	0.09		
Alb <35 /≥35	1.64 (1.10 – 2.44)	0.014		
CEA <200/≥200	0.45 (0.32 – 0.61)	<0.001*	0.34 (0.23 – 0.51)	<0.001*
ECOG PS <2 /≥ 2	0.396 (0.24 – 0.64)	<0.001*	0.58 (0.32 – 1.05)	0.07
Time to metastases <18/≥ 18 months	1.3 (0.93 – 1.83)	0.12		
G3 neutropenia Yes/No	0.44 (0.29 – 0.627)	<0.001*	0.43 (0.28 – 0.67)	<0.001*
G3 thrombocytopenia Yes/No	0.71 (0.17 – 2.9)	0.64		
G3 Anaemia Yes/No	0.77 (0.54- 1.1)	0.17		
Metastatic sites <2/≥2	1.29 (0.93 – 1.3)	0.13		

Abbreviations: HR= hazard ratio, NLR= neutrophil to lymphocyte ratio, PLR= platelet to lymphocyte ratio, Alb= albumin, CEA= carcinoembryonic antibody, ECOG PS= Eastern Cooperative Oncology Group performance status, G3= grade 3

Figure Legends

Figure 1. Reasons for dose reductions in our study population

Figure 2. Kaplan-Meier curve analysis showing that development of grade 3 neutropenia during treatment with trifluridine/tipiracil predicts for worse overall survival.