Factors associated with Trifluridine/Tipiracil (TAS-102) effectiveness in patients with refractory metastatic colorectal cancer: real-life data from the Czech Republic.

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Abstract

Background: Trifluridine/tipiracil (TAS-102) is effective in refractory metastatic colorectal cancer (mCRC). Currently, no predictive biomarkers are established and used in clinical practice.

Methods: We analyzed data of 160 patients treated with TAS-102 in real clinical practice in the Czech Republic. Different factors associated with progression-free survival (PFS) and overall survival (OS) were evaluated.

Results: Median PFS was 3.3 months, and median OS 10.2 months. Factors significantly associated with PFS and/or OS were: ECOG performance status (PS), time from diagnosis of mCRC > 24 months, initiation of treatment > 3 months from last fluoropyrimidine, number of metastatic sites, baseline CRP level, WBC count, neutrophils count, monocytes count, neutrophil to lymphocyte ratio, development of neutropenia, thrombocytopenia, diarrhea, required dose reduction and cycle delay. We developed a scoring system TAScore from factors available at the beginning of treatment. One point each was assigned to the following factors (PS, diagnosis of mCRC > 24 months, initiation of TAS-102 > 3 months from fluoropyrimidine, baseline CRP, WBC, monocytes count < 0.5 × 10 9 /L) and patients were divided into 3 groups: high risk group (0 to 1 point), intermediate (2 to 3), favorable with 4 or more points. OS according to risk group was: 5.7 months for high risk, 8.7 for intermediate, 12.8 for favorable (P < 0.001). TAScore was also associated with PFS (P < 0.001).

Conclusions : TAS-102 is effective in patients with refractory mCRC. We propose simple scoring system TAScore to help with precise patient selection at the beginning of TAS-102 treatment.

Background

Colorectal cancer is the third most common cancer and the fourth leading cause of cancer mortality worldwide [1]. In the last three decades the median survival of patients with metastatic colorectal cancer has dramatically improved from 6 months to more than 30 months [2].

This success was achieved by introducing new chemotherapies and targeted treatments and establishing the Continuum of Care whereby the patient is sequentially treated with all available treatment options including maintenance therapy, and retreatments. Approximately two thirds of patients have adequate performance status after two lines of treatment to be considered for further systemic therapy.

Trifluridine/tipiracil (TAS–102) is approved for the treatment of metastatic colorectal cancer (mCRC) progressing after other standard regimens (including 5-fluorouracil, oxaliplatin, irinotecan, and targeted therapies). TAS–102 is a fixed combination of trifluridine, a nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor. In the pivotal phase III trial RECOURSE TAS–102 significantly improved progression-free survival (PFS, median 2.0 months versus 1.7 months; HR 0.48; 95% CI, 0.41 to 0.57; P < 0.001) and overall survival (OS, median 7.1 months versus 5.3 months; HR 0.68; 95% CI, 0.58 to 0.81; P <

0.001) versus placebo in 800 heavily pretreated patients [3]. Most commonly reported adverse events were leukopenia, neutropenia, anemia, and diarrhea. However, the gains in PFS and OS were only modest.

Based on results from the RECOURSE study, the FDA approved TAS–102 in September 2015 and the EMA in April 2016 as new therapeutic option for patients with previously treated mCRC.

Currently, no predictive biomarkers associated with TAS–102 treatment efficacy are established and used in clinical practice. The objective of our retrospective multicenter analysis was to identify potentially predictive and prognostic factors in patients treated with TAS–102.

Materials And Methods

Patients and treatment

Data from 160 patients treated between 2016 and 2018 at 4 academic institutions (Department of Comprehensive Oncology Care, Masaryk Memorial Cancer Institute in Brno; Department of Oncology, Thomayer Hospital in Prague; Department of Oncology, General University Hospital in Prague; Department of Oncology, University Hospital in Hradec Kralove) in the Czech Republic were analyzed retrospectively. All patients receiving TAS–102 were pretreated with 5-fluorouracil or capecitabine, oxaliplatin, and irinotecan. All patients started TAS–102 treatment with dose of 35 mg/m^2 twice daily for day 1 to day 5 and day 7 to day 12, followed by a 2-week rest period in 28-day cycle.

Adverse events occurring during the treatment were categorized according to the Common Terminology Criteria for Adverse Events, version 4.0. Dose delays and dose reduction (reducing dose by 5 mg/m^2) were made according to physician discretion. Patient restaging with contrast enhanced imaging to assess treatment efficacy was performed every 2–3 months.

Informed consent was obtained from all individual participants included in the study. The study protocol was reviewed and approved by the institutional ethics committees.

Statistical analysis

Factors evaluated in association with PFS and OS included age at the onset of TAS–102 treatment, line of therapy, number of metastatic sites, site of metastatic disease, RAS mutational status, BRAF mutational status, location of primary tumor, time from diagnosis of metastatic disease, time from previous fluoropyrimidine treatment, previous biologic treatment, baseline laboratory values—white blood cell count, absolute neutrophil count, absolute monocyte count, absolute lymphocyte count, neutrophil to lymphocyte ratio (NLR), CEA level, CA19–9 level, C-reactive protein (CRP) level, lactate dehydrogenase (LDH) level, treatment toxicity—neutropenia, low platelets count, anemia, diarrhea, asthenia, adverse events requiring TAS–102 dose reduction, and adverse events requiring TAS–102 cycle delay.

Frequency analysis and summary statistics were used to characterize the sample data set.

Progression-free survival was defined as the time from the initiation of TAS–102 treatment to the date of first documented progression or death due to any cause and overall survival as the time from the initiation of TAS–102 treatment to death due to any cause. Survival curves were estimated using the Kaplan-Meier method. A log-rank test was used to test the difference between survival curves (PFS or OS) for different factors. All point estimates include 95% confidence intervals (CIs). Fisher's exact test or Chi-squared test were used for establishing the significance of the association between categorical variables. Univariate and multivariate analyses of predictive factors were performed using Cox proportional hazard regression. All tests were performed at a significance level of $\alpha = 0.05$.

Results

Baseline characteristics

Patient characteristics are summarized in Table 1. Median follow-up from the beginning of TAS–102 treatment was 12.4 months. The median age was 66 years (range 28–83), 106 patients were male (66.3%), ECOG performance status 0 and 1 was present in 38.1% and 61.9%, respectively, at the start of TAS–102 therapy. Primary tumor location was right colon in 15%, transversum in 5%, left colon in 50%, and rectum in 30% of patients. Almost 30% of patients had disease limited to one organ site, 48.8% had 2 metastatic sites and 21.8% had 3 or more metastatic sites. Ninety-five patients were diagnosed with synchronous metastatic colorectal cancer (59.4%). The median number of previous treatment lines for metastatic disease was 2 (range 1–7). One hundred two patients (63.8%) were treated for metastatic colorectal cancer for more than 24 months before they started TAS–102 treatment. All patients had previously received fluoropyrimidines, oxaliplatin, and irinotecan, and 28 (17.5%) had previously received regorafenib. A total of 72 (45%) patients had RAS wild-type cancers. Anti-VEGF treatment had been used in 133 (83.1%) patients and anti-EGFR treatment in 70 (43.8%) patients.

TAS–102 treatment

The median number of administered TAS–102 cycles was 3 (range 1—27). At the time of analysis 24 (15%) patients continued on TAS–102 treatment. One hundred eighteen (73.8%) patients discontinued treatment due to disease progression, 11 (6.9%) due to treatment toxicity, 6 patients (3.8%) decided to discontinue treatment (mostly for subjective poor treatment tolerance), in 1 (0.6%) patient was treatment changed per physician decision. After progression on TAS–102, about 50% of patients received another systemic oncologic treatment.

Outcomes and toxicity

The best overall response was stable disease in 34 patients (21.3%), disease progression as the best response was recorded in 108 patients (67.5%). In 18 (11.3%) patients, the response could not be precisely assessed. There were no partial or complete responses, ORR was 0%.

At the time of analysis, 90 patients had died (56.3%). Median PFS was 3.3 months (95% CI, 3.0 to 3.5), and the estimated 6-months PFS rate was 20.3% (Fig. 1). Median OS was 10.2 months (95% CI, 8.9 to 11.8), and the estimated 6-month and 12-month OS rate was 76.1% and 38.8%, respectively (Fig. 2).

Any grade toxicity was recorded in 88.1% of patients (Table 2). The most common toxicities included neutropenia, asthenia, and nausea. Any grade ≥ 3 toxicity was recorded in 65 patients (40.6%). Most common grade ≥ 3 toxicity was neutropenia in 56 patients (35%) (Table 2). Febrile neutropenie was recorded in 4 patients (2.5%). One patient died due to infectious complication during the treatment. TAS–102 dose reduction was performed in 48 (30%) and the next treatment cycle was delayed in 84 (52.5%) patients.

Prognostic and predictive factors

Various patient and tumor characteristics in association with survival parameters were analyzed (these results are summarized in Table 3). Factors significantly associated with prolonged PFS in univariate analysis were: patient's ECOG performance status 0, time from diagnosis of metastatic disease to initiation of TAS–102 treatment more than 24 months, initiation of TAS–102 treatment more than 3 months from last fluoropyrimidine therapy, normal baseline CRP level, baseline WBC, normal baseline neutrophils count, baseline monocytes count, NLR < 3, number of metastatic sites, neutropenia ≥ grade 2 during TAS–102 treatment, diarrhea grade ≥ 1 or more, required TAS–102 dose reduction, required TAS–102 next cycle delay.

Factors significantly associated with prolonged OS in univariate analysis were: time from diagnosis of metastatic disease to initiation of TAS–102 treatment more than 24 months, initiation of TAS–102 treatment more than 3 months from last fluoropyrimidine therapy, normal baseline CRP level, baseline WBC, baseline neutrophils count, NLR < 3, baseline monocytes count, neutropenia ≥ grade 2 during TAS–102 treatment, thrombocytopenia ≥ grade 2 during TAS–102 treatment, required TAS–102 dose reduction, required TAS–102 cycle delay. The trend to prolonged OS was in patients with ECOG performance status 0.

The main reason for TAS–102 dose reduction and the next cycle delay was neutropenia during TAS–102 treatment and dose reduction and cycle delay were significantly associated with the occurrence of neutropenia grade 2 ($P < 0.001$).

In multivariate analysis factors associated with prolonged PFS were ECOG performance status 0 (HR 2.16, $P = 0.005$), time from diagnosis of metastatic disease more than 24 months (HR 0.50, $P = 0.01$), baseline CRP level (HR 0.53, $P = 0.03$), baseline neutrophils count (HR 0.33, $P = 0.04$), neutropenia ≥

grade 2 during treatment (HR 0.38, P = 0.002, Table 4). Factors associated with prolonged OS in multivariate analysis were neutropenia ≥ grade 2 during treatment (HR 0.36, P < 0.001), and there was trend for significance for baseline CRP level (HR 0.58, P = 0.07, Table 5).

Based on the findings of factors associated with better survival of patients, we have developed a scoring system (TAScore) to select patients who will benefit most from TAS–102 treatment. One point each was assigned to the following criteria: ECOG performance status 0, time from diagnosis of metastatic disease to initiation of TAS–102 treatment more than 24 months, initiation of TAS–102 treatment more than 3 months from last fluoropyrimidine therapy, normal baseline CRP level, normal baseline WBC, baseline monocytes count < 0.5×10^9/L, Table 6). The overall score was the sum of these points. Based on the overall score patients were divided into 3 groups: high risk group with 0 to 1 point, intermediate risk group with 2 to 3 points and favorable risk group with 4 or more points. In our cohort the median OS according to risk group was: 5.7 months (95% CI, 2.4 to 6.5 months) for the high risk group (11 patients), 8.7 months (95% CI, 6.4 to 10.2 months) for the intermediate risk group (63 patients) and 12.8 months (95% CI, 10.6 to 19.1 months) for the favorable risk group (59 patients) (P < 0.001) (Fig. 3). TAScore was also significantly associated with prolonged median PFS: 2.4 months (95% CI, 1.2 to 2.7 months) for high risk, 2.9 months (95% CI, 2.7 to 3.4 months) for intermediate and 3.9 months (95% CI, 3.4 to 5.3 months) for the favorable risk group (P < 0.001).

Discussion

Our analysis confirmed the TAS–102 efficacy in heavily pretreated group of patients with metastatic colorectal cancer. The PFS and OS results in the present cohort were slightly better compared to outcomes in the RECOURSE study and to those reported in studies on “real-world” TAS–102 efficacy from Japan Spain, Italy, and Netherland [4–7]. The likely reason for these differences is conceivably patient selection. Patients in our cohort had less extensive disease with approximately 80% of patients in our study having only 1 or 2 metastatic sites compared to 61% in RECOURSE [3], 59% in the Spanish TERRA trial [5], or 38% and 23% in other studies [6,7]. Treatment-related toxicity in our analysis was similar to other studies with TAS–102 therapy and no new adverse events have emerged. The treatment has favorable toxicity profile with asymptomatic neutropenia as the most common adverse event.

We found several factors associated with better prognosis on TAS–102 treatment. Some of these factors are probably associated not only with the outcomes of TAS–102 therapy but with CRC prognosis in general. For example, lower monocyte count is associated with better prognosis of localized CRC and metastatic disease[8–11] and was also confirmed as positive prognostic factor for TAS–102 in a study published by Kwakman and collaborators [7]. Similarly, elevated CRP levels are associated with poor prognosis of non-metastatic and metastatic CRC [12–16]. In our analysis, normal white blood count, neutrophil count, monocyte count, and lower NLR were associated with better treatment results. In general, it can be proposed that the inflammatory state reflected in elevated CRP and high white blood counts is associated with higher disease burden and/or biologically aggressive disease and thus poor prognosis. It is possible that only group of patients with slowly progressing and less aggressive disease

can benefit from TAS–102 monotherapy. We did not confirm the association between LDH level and treatment outcomes reported in two previously published studies [6,7]. However different cut-off for LDH levels was used in these studies. Baseline tumor characteristic including RAS and BRAF mutational status or tumor localization were not prognostic in our analysis. Patients with or without previous regorafenib had similar results.

The TAS–102 component trifluridine is a fluoropyrimidine derivate. Currently available data of TAS–102 efficacy were acquired in clinical studies enrolling patients pretreated with, and refractory to 5-fluorouracil or capecitabine. It can be assumed that patients not pretreated with a fluoropyrimidine or with a longer interval from the last fluoropyrimidine treatment could have better response to TAS–102. Indeed, in our study, patients who started TAS–102 treatment more than 3 months from the last fluoropyrimidine had better outcomes.

TAS–102 has a relatively favorable toxicity profile. Several groups have described that the occurrence of toxicity, in particular neutropenia, was associated with better outcomes of TAS–102 therapy [17,18]. In our study, patients who developed grade 2 or higher neutropenia during the treatment had much better prognosis and more than doubled OS than those without this adverse event. Similarly, thrombocytopenia and diarrhea, although not as frequently observed, were also associated with longer OS and PFS. It is possible that slower drug metabolism or higher effective drug doses could lead to higher TAS–102 blood levels and higher drug concentrations in the tumor, resulting in better outcomes and simultaneously higher risk of toxicities.

Based on prognostic factors in univariate and multivariate analyses, we defined the TAScore which could be helpful for decision-making prior to TAS–102 therapy. The TAScore consists of six clinical and laboratory parameters that are measurable prior to treatment initiation: performance status, time from diagnosis of metastatic disease, time from last fluoropyrimidine therapy, normal baseline CRP level, normal baseline WBC, and baseline monocytes count. Using this very simple tool, we have been able to separate patients into 3 different prognostic groups. The high-risk group (score 0 or 1) achieved OS of only 5.4 months which is similar to the outcome in the placebo arm of phase III clinical trial with TAS–102. These patients may not benefit from TAS–102 and other treatment options or best supportive care should be considered. On the contrary, patients with TAScore of 4 or more have excellent outcomes with median OS of more than one year. If we take into account good toxicity profile, TAS–102 therapy could be the preferred regime for this group of patients.

Several tools for predicting the survival of patients with metastatic colorectal cancer have been proposed. A similar tool for predicting survival of patient with refractory metastatic CRC was created by Pietrantonio et al. by defining a nomogram for predicting of 12-week death probability (“Colon Life”) [19]. This nomogram includes performance status, primary tumor resection, LDH value, and peritoneal involvement and identify patients with a poor prognosis in general. This nomogram was validated by Cremolini et al. in patients treated with TAS–102. However, the nomogram is less practical to use than our TAScore scoring system that was validated specifically in patients with TAS–102 treatment and dividing patients

into 3 prognostic groups. Another group utilized modified a Glasgow prognostic score (mGPS) consisting of CRP and albumin values [20]. This score was prognostic for PFS an OS in patients with metastatic CRC treated with TAS–102 or regorafenib. No significant differences in OS and PFS were observed between treatment groups in each mGPS group. This mGPS is simple to use but it does not take into account previous patient treatment and the overall clinical condition of the patient which are important factors in physician decision making.

The present study has several limitations. The group of patients was relatively small for establishing robust prognostic factors. The retrospective character of our analysis can contribute to selection bias. We are currently analyzing the identified prognostic model for other therapies in later lines of treatment, such as regorafenib in order to select patients who will benefit from any treatment.

In summary, in the current study, we confirmed the moderate efficacy of TAS–102 in heavily pretreated patients with metastatic colorectal cancer. We found several factors associated with prolonged survival and defined the TAScore as a very simple and useful tool for patient selection before initiation of TAS–102 treatment.

Abbreviations

CI: Confidence interval; CRP: C-reactive protein; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; LDH: lactate dehydrogenase; NLR: Neutrophil-to-lymphocyte ratio; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors; TAS–102: trifluridine/tipiracil; ULN: Upper limit of normal

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

Peter Grell, Josef Dvorak, and Michal Vocka designed study. Peter Grell, Josef Dvorak, Michal Vocka, Stanislav John, Helena Pitauerova, and Simona Borilova collected data. Iveta Selingerova performed statistical analysis. Lubos Petruzelka, Radka Obermannova, Igor Kiss, Tomas Buchler, and Rostislav Vyzula took part in interpretation of the data. Peter Grell, Michal Vocka, and Tomas Buchler wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during the current study are not publicly available due to ethical restrictions, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This

retrospective study was approved by institutional review boards. This study involved retrospective analysis of de-identified data with no patient intervention. Informed consent was obtained from all individual participants included in the study.

Consent for publication

This manuscript contains no individual person's data

Competing interests:

Peter Grell received honoraria for lectures from Roche and institutional travel grants from Bayer, Roche, Novartis and Servier. Tomas Buchler received honoraria for advisory boards and/or lectures from Servier, Bayer, Roche and Amgen. Igor Kiss received honoraria and has advisory roles for Roche, Merck, Servier and Amgen.

Rostislav Vyzula received travel grants from Roche. Radka Obermannova has had consulting/advisory roles for Amgen, Roche, Servier and Bayer; served on speakers' bureaus for Amgen, Roche and Eli Lilly and Company and received research funding from Merck. Other authors have declared no conflict of interest.

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Tables

Table 1 Baseline patients characteristics

Patients characteristics	N = 160	% of patients
Age, median (range)	66 (28 – 83)	
Gender		
Male	106	66.3
Female	54	33.7
ECOG Performance status		
0	61	38.1
1	99	61.9
Previous therapy with fluoropyrimidine, oxaliplatin, irinotecan	160	100
Time from dg. of metastatic disease to TAS-102 treatment:		
< 24 months	58	36.2
≥ 24 months	102	63.8
Median time from last therapy (in months)	1	
Median time from last fluoropyrimidine therapy (in months)	2	
Previous targeted therapy:		
Anti-VEGF therapy	133	83.1
Anti-EGFR therapy	70	43,8
Previous regorafenib treatment	28	17.5
Site of metastatic disease		
liver	102	63.8
lung	97	60.6
other	96	60
Number of metastatic sites:		
1	47	29.4
2	78	48.8
3	25	15.6
4 or more	10	6.3
Metastatic disease:		
Synchronous	95	59.4
Metachronous	65	40.6
RAS wildtype status	72	45
Primary tumor location:		
right colon	24	15
transversum	8	5

left colon	80	50
rectum	48	30
Median previous lines of treatment (range)	2 (1 – 7)	
Median number of TAS-102 cycles (range)	3 (1 – 27)	

BRAF mutation was analyzed in 54 patients, 5 (9.3%) patients had BRAF mutation. Mismatch protein deficiency was analyzed in 33 patients, one (3%) had MMR deficient tumor.

Table 2 Treatment related toxicity in patients treated with TAS-102

TAS-102 Treatment-related toxicity	
Total	N = 160
Any	141 (88.1%)
Neutropenia	95 (59.4%)
Asthenia	57 (35.6%)
Nausea	53 (33.1%)
Diarrhea	32 (20.0%)
Thrombocytopenia	31 (19.4%)
Anemia	31 (19.4%)
Vomiting	16 (10.0%)
Hepatopathy	9 (5.6%)
Infection	7 (4.4%)
Stomatitis	2 (1.3%)
Dyspnea	2 (1.3%)
Grade ≥ 3 toxicity	65 (40.6%)
Neutropenia	56 (35.0%)
Anemia	9 (5.6%)
Thrombocytopenia	7 (4.4%)
Infection	3 (1.9%)
Diarrhea	3 (1.9%)
Asthenia	3 (1.9%)
Nausea	2 (1.3%)
Hepatopathy	1 (0.6%)
Febrile neutropenie	4 (2.5%)
Discontinued due to treatment toxicity	11 (6.9%)

Table 3 Factors analyzed in relation to progression-free survival and overall survival

	Factors analyzed in relation to PFS					Factors analyzed in relation to OS				
		Median (months)	P value	HR	95% CI		Median (months)	P value	HR	95% CI
e at the beginning of TAS-102 treatment										
5 years	N = 65	3.1	P = 0.54	1.11	0.63 to 1.29	N = 68	8.7	P = 0.57	1.13	0.74 to 1.71
5 years	N = 88	3.5				N = 92	10.3			
ıe from dg. of metastatic disease to TAS-102 treatment										
4 nths	N = 97	3.5	**P = 0.001**	0.57	0.38 to 0.85	N = 102	10.6	**P = 0.02**	0.61	0.38 to 0.97
4 nths	N = 56	2.7				N = 58	8.9			
ıe from last fluoropyrimidine treatment										
months	N = 69	3.7	**P = 0.005**	0.61	0.43 to 0.87	N = 73	11.8	**P = 0.01**	0.59	0.39 to 0.89
months	N = 83	3.1				N = 86	9.3			
mary tumor location right vs. left colon										
ht colon	N = 30	3.3	P = 0.99	1.00	0.64 to 1.58	N = 32	7.4	P = 0.34	1.59	0.72 to 2.28
t colon	N = 123	3.3				N = 128	10.5			
rmal baseline CRP level (ULN 11 mg/L)										
rmal	N = 36	3.7	**P = 0.005**	0.52	0.33 to 0.82	N = 38	12.0	**P = 0.02**	0.56	0.35 to 0.91
JLN	N = 56	2.7				N = 60	7.3			
rmal baseline WBC (4 to 10 × 10^9/L)										
rmal	N = 124	3.4	P = 0.22	0.75	0.45 to 1.25	N = 131	10.6	**P < 0.001**	0.43	0.22 to 0.85
JLN	N = 28	2.7				N = 28	6.5			
seline WBC										
× /L	N = 93	3.5	**P = 0.007**	0.62	0.42 to 0.91	N = 98	11.8	**P < 0.001**	0.41	0.26 to 0.67
× /L	N = 59	2.8				N = 61	7.3			
rmal baseline neutrophils (2 to 7 ×10^9/L)										
mal	N = 117	3.5	**P < 0.001**	0.31	0.12 to 0.78	N = 124	10.5	**P < 0.001**	0.30	0.11 to 0.86
JLN	N = 18	2.5				N = 18	5.7			
seline neutrophils < 4 × 10^9/L										
× /L	N = 91	3.6	P = 0.75	0.94	0.63 to 1.40	N = 96	11.6	**P = 0.014**	0.55	0.36 to 0.86
× /L	N = 44	3.3				N = 46	8.9			

seline lymphocytes < 1.5 × 10^9/L										
.5 × /L	N = 65	3.3	P = 0.50	1.14	0.78 to 1.68	N = 65	9.6	P = 0.46	1.17	0.76 to 1.81
.5 × /L	N = 77	3.4				N = 77	11.1			
R < 3										
	N = 64	3.5	**P = 0.02**	0.65	0.44 to 0.95	N = 64	11.8	**P = 0.003**	0.53	0.34 to 0.81
	N = 71	3.0				N = 78	8.0			
rmal baseline monocytes count (0.08 to 1.2 x 10^9/L)										
mal	N = 122	3.4	**P = 0.007**	0.47	0.21 to 1.03	N = 129	10.5	**P = 0.03**	0.49	0.21 to 1.19
JLN	N = 13	2.7				N = 13	6.5			
seline monocytes count										
.5 × /L	N = 25	5.3	**P = 0.003**	0.47	0.31 to 0.71	N = 26	15.7	**P = 0.001**	0.38	0.24 to 0.61
.5 × /L	N = 110	3.1				N = 116	9.2			
rmal baseline platelets (150 to 400 x 10^9/L)										
mal	N = 142	1.2	P = 0.08	0.56	0.23 to 1.34	N = 149	10.3	P = 0.07	0.48	0.15 to 1.52
JLN	N = 10	3.4				N = 10	3.0			
seline platelets < 200 × 10^9/L										
00 × /L	N = 49	3.3	P = 0.95	0.99	0.68 to 1.45	N = 52	9.6	P = 0.08	0.67	0.43 to 1.02
00 × /L	N = 103	3.3				N = 107	10.6			
OG Performance status										
	N = 59	3.5	**P = 0.004**	0.59	0.42 to 0.84	N = 61	11.8	**P = 0.06**	0.66	0.44 to 1.01
	N = 94	3.0				N = 99	9.2			
AS wildtype										
	N = 70	3.6	P = 0.25	0.83	0.55 to 1.26	N = 72	10.1	P = 0.38	0.83	0.55 to 1.26
	N = 83	3.0				N = 88	10.2			
AF wildtype										
	N = 50	3.1	P = 0.09	0.44	0.10 to 1.91	N = 54	9.1	P = 0.21	0.42	0.05 to 3.53
	N = 5	2.5				N = 5	6.6			
seline LDH level (ULN 3.59 mcat/l)										
rmal	N = 24	3.5	P = 0.97	0.99	0.52 to 1.88	N = 26	13.8	P = 0.07	0.48	0.21 to 1.09
JLN	N =	3.2				N =	7.7			

	32					34				
ıtropenia ≥ G2 during TAS-102 treatment										
;2	N = 74	3.9	**P < 0.001**	0.39	0.25 to 0.62	N = 79	12.1	**P < 0.001**	0.34	0.20 to 0.57
;1	N = 55	2.7				N = 58	6.5			
ombocytopenia ≥ G2 during TAS-102 treatment										
;2	N = 12	3.7	P = 0.72	0.45	0.42 to 1.24	N = 14	19.1	**P = 0.03**	0.45	0.25 to 0.79
;1	N = 141	3.3				N = 146	9.7			
emia ≥ G2 during TAS-102 treatment										
;2	N = 29	2.9	P = 0.89	1.03	0.66 to 1.62	N = 31	8.7	P = 0.46	1.09	0.70 to 2.10
;1	N = 124	3.4				N = 129	10.5			
henia ≥ G1 during TAS-102 treatment										
;1	N = 55	3.4	P = 0.17	0.78	0.54 to 1.11	N = 57	11.8	P = 0.18	0.74	0.49 to 1.14
henia	N = 98	3.2				N = 103	9.7			
rrhea ≥ G1 during TAS-102 treatment										
;1	N = 35	3.7	**P = 0.05**	0.67	0.46 to 0.97	N = 35	11.8	P = 0.22	0.74	0.47 to 1.17
rrhea	N = 118	3.3				N = 125	9.6			
quired next TAS-102 cycle delay										
;	N = 79	3.9	**P < 0.001**	0.39	0.27 to 0.58	N = 84	12.1	**P < 0.001**	0.44	0.28 to 0.69
	N = 74	2.8				N = 76	6.6			
quired TAS-102 dose reduction										
;	N = 46	6.2	**P < 0.001**	0.36	0.26 to 0.52	N = 48	13.9	**P < 0.001**	0.40	0.26 to 0.60
	N = 107	3.0				N = 112	9.3			

Table 4 Multivariate analysis of factors associated with prolonged progression-free survival

Factors associated with prolonged PFS	P	HR	95% CI
ECOG Performance status 0 vs 1	**0.005**	2.16	1.26 to 3.69
Time from dg. of metastatic disease to TAS-102 treatment ≥ 24 months	**0.01**	0.50	0.29 to 0.87
Baseline CRP level (ULN ≤ 11 mg/L)	**0.03**	0.53	0.31 to 0.92
Normal baseline neutrophils (4 to 7 $\times 10^9$/L)	**0.04**	0.33	0.12 to 0.94
Neutropenia ≥ G2 during TAS-102 treatment	**0.002**	0.38	0.21 to 0.71

Table 5 Multivariate analysis of factors associated with prolonged overall survival

Factors associated with prolonged OS	P	HR	95% CI
Baseline CRP level (ULN ≤ 11 mg/L)	**0.07**	0.58	0.33 to 1.03
Neutropenia ≥ G2 during TAS-102 treatment	**< 0.001**	0.36	0.20 to 0.64

Table 6 Factors involved in TAScore scoring system in relation to progression-free survival and overall survival

1. Time from dg. of metastatic disease to TAS-102 treatment more than 24 months
2. Time from last fluoropyrimidine treatment more than 3 months
3. ECOG Performance status 0 vs 1
4. Normal baseline CRP level (ULN ≤ 11 mg/L)
5. Normal baseline WBC (4 to 10 × 10^9/L)
6. Baseline monocytes count (< 0.5 × 10^9/L)

Figures

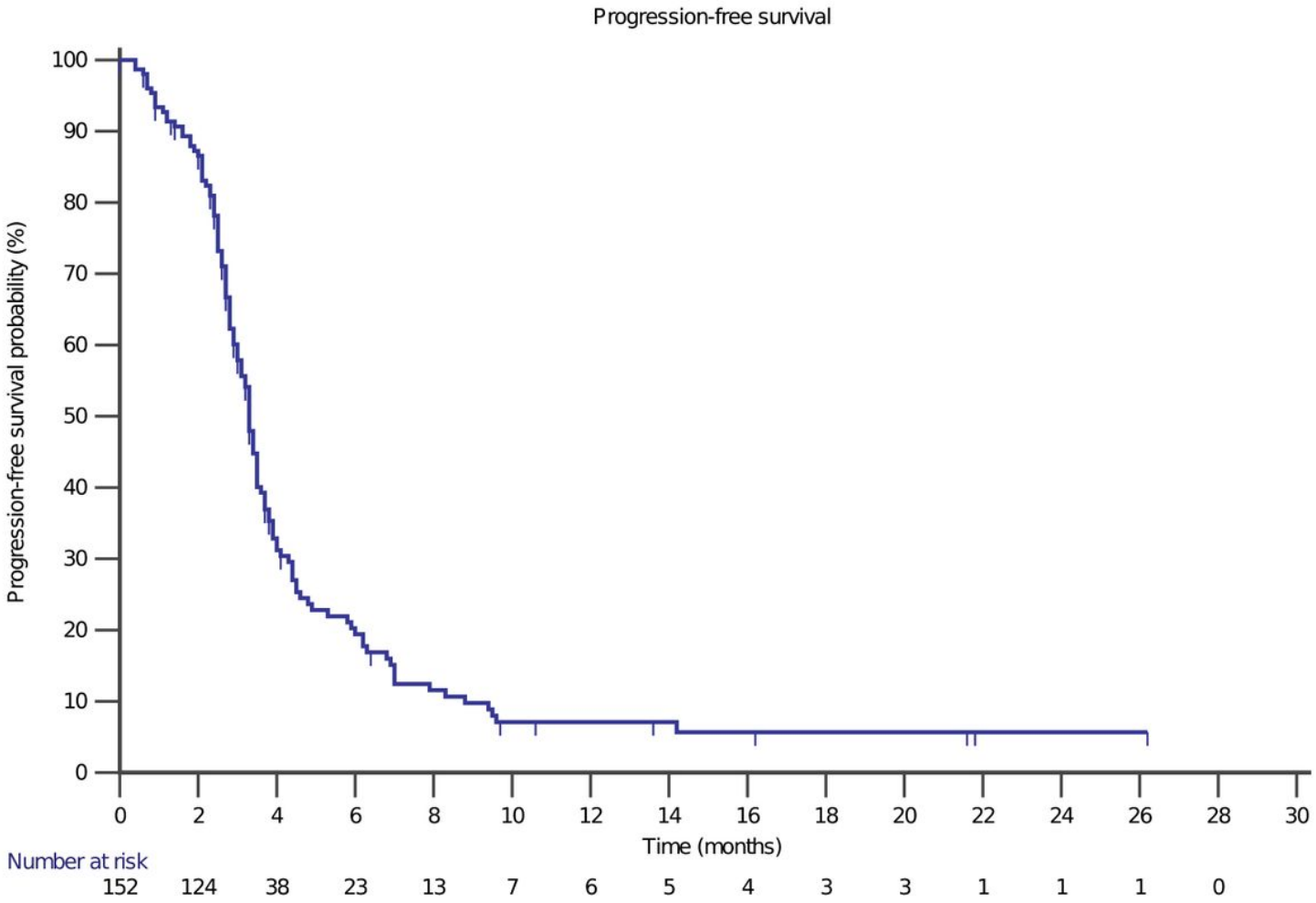

Figure 1

Progression-free survival Progression-free survival in patients treated with TAS-102. Median PFS for the whole group was 3.3 months (95% CI, 3.0 to 3.5), and the estimated 6-months PFS rate was 20.3%

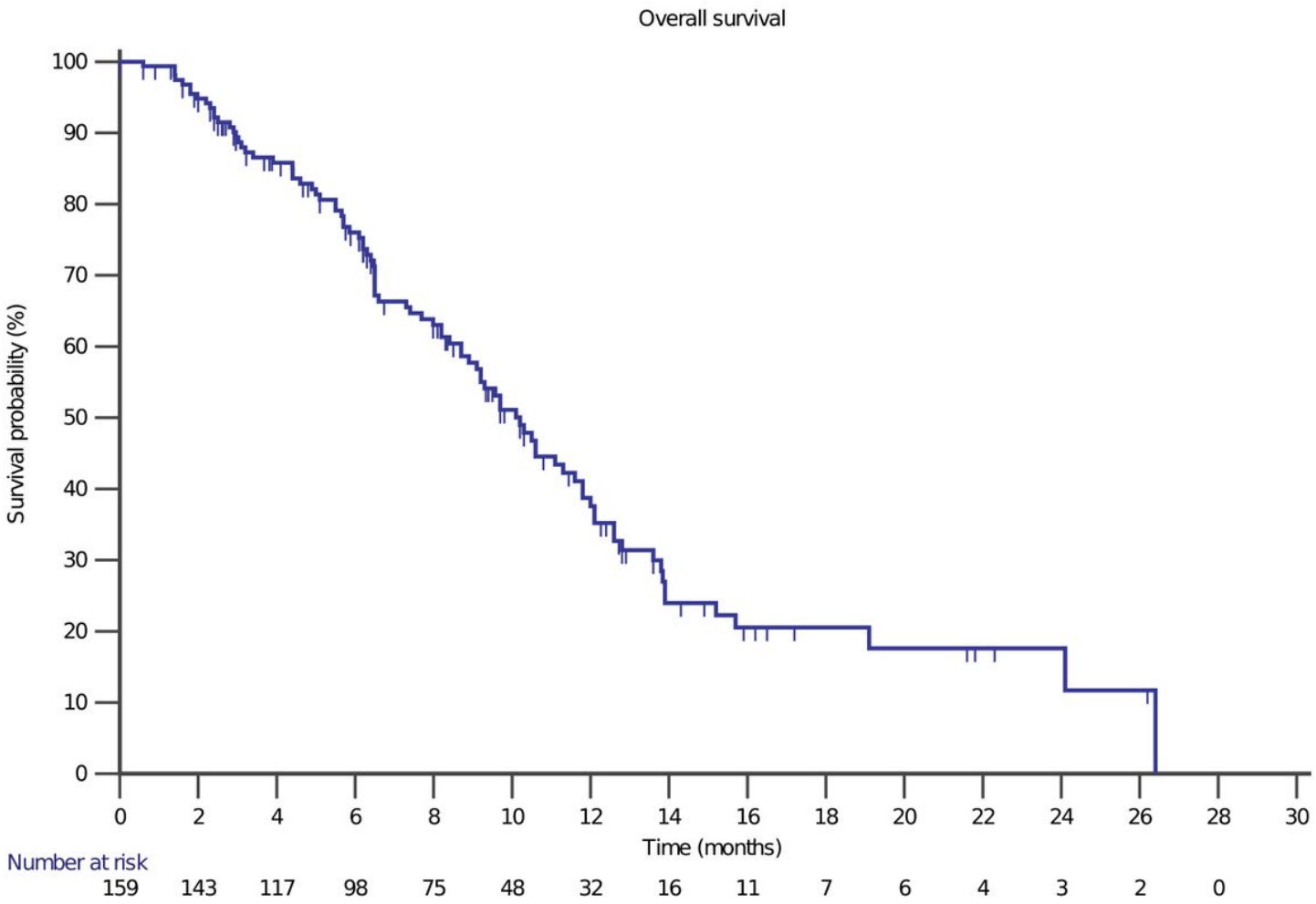

Figure 2

Overall survival Overall survival in patients treated with TAS-102. Median OS was 10.2 months (95% CI, 8.9 to 11.8), and the estimated 6-month and 12-month OS rate was 76.1% and 38.8%, respectively

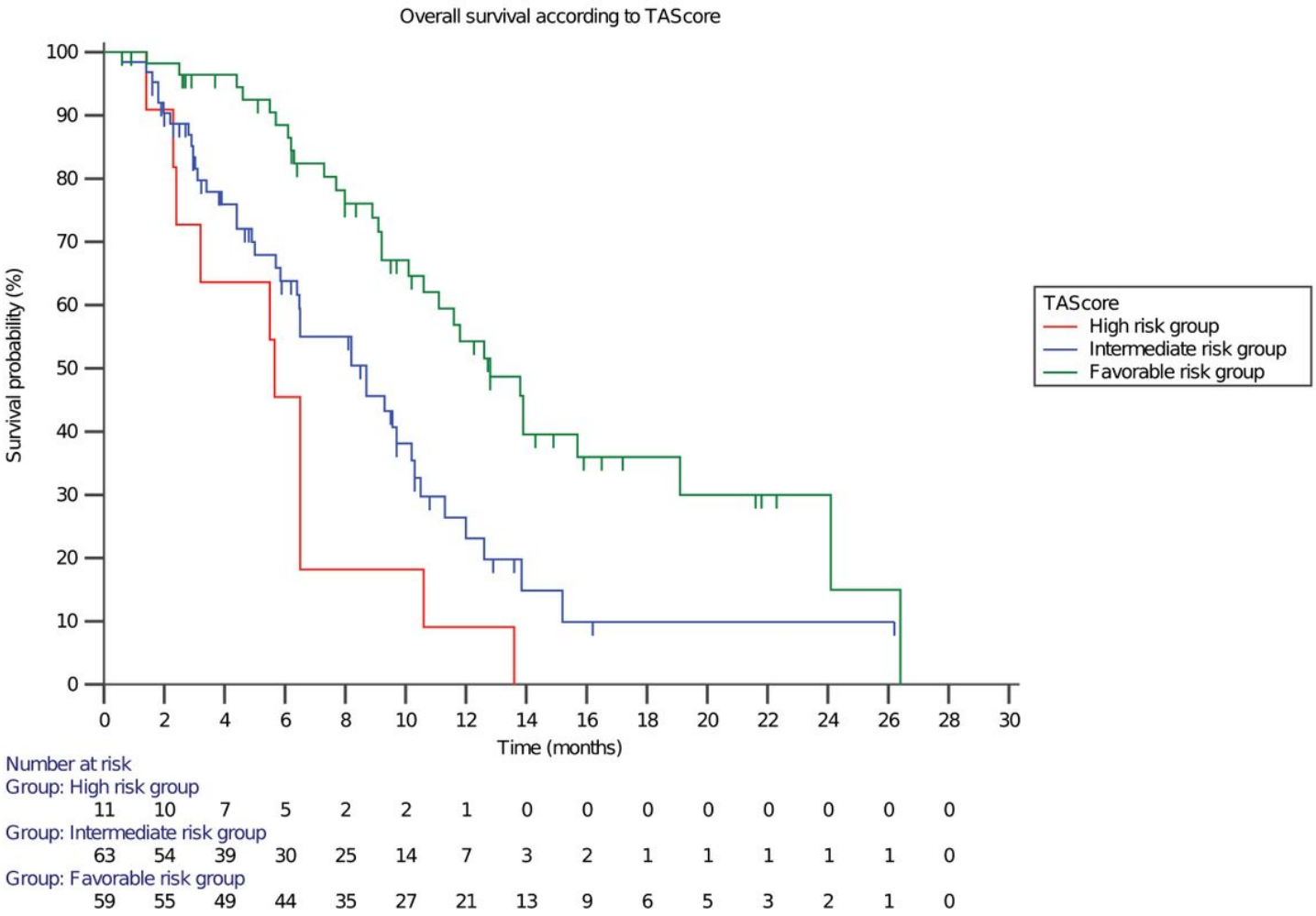

Figure 3

Overall survival according to TAScore Overall survival in patients treated with TAS-102 according to TAScore and corresponding risk group. OS was 5.7 months for high risk group (11 patients), 8.7 months for intermediate risk group (63 patients) and 12.8 months for favorable risk group (59 patients) ($P < 0.001$)