Thesis

Evaluation of palliative third line treatment in patients with metastatic colorectal cancer

Submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 27.08.2024 Lukas Raffael Wagner m.p.

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Zusammenfassung

Einleitung

Trotz der Entwicklung neuer zielgerichteter Behandlungsmöglichkeiten für das metastasierte kolorektale Karzinom (mCRC) ist die Prognose in fortgeschrittenen Stadien nach wie vor schlecht. In der palliativen Drittlinientherapie standen bis vor kurzem nur die beiden Monotherapien Regorafenib und TAS-102 zur Verfügung. In der rezent publizierten randomisierten Phase 3 „SUNLIGHT“ Studie wurde gezeigt, dass eine Kombinationstherapie aus TAS-102+Bevacizumab (TAS-102+Bev) einer Monotherapie mit TAS-102 überlegen ist. Bis dato gibt es jedoch nur sehr limitierte Daten zur Effizienz dieser Behandlungsstrategie außerhalb eines klinischen Studiensettings. [1]

Material und Methoden

Diese retrospektive Kohortenstudie verglich die klinische Wirksamkeit von TAS-102+Bev versus TAS-102 versus Regorafenib in der Behandlung des metastasierten kolorektalen Karzinoms hinsichtlich der klinischen Endpunkte Krankheitskontrolle (DCR), progressionsfreies Überleben (PFS) und Gesamtüberleben (OS). Dazu wurden sämtliche PatientInnen mit histologisch gesichertem, lokal fortgeschrittenem, metastasiertem kolorektalem Karzinom eingeschlossen, die zwischen 1. Januar 2016 bis 30. September 2023 an der klinischen Abteilung für Onkologie der Medizinischen Universität Graz mit TAS-102, TAS-102+Bev oder Regorafenib behandelt wurden. Die Daten wurden aus dem elektronischen Krankenhausinformationssystem MEDOCS, sowie handschriftlichen Notizen erfasst und in der Webbasierten Datenbank REDCap dokumentiert.

Ergebnisse

Insgesamt wurden 179 PatientInnen eingeschlossen, wovon 109 mit TAS-102, 20 mit TAS-102+Bev und 50 mit Regorafenib behandelt wurden. Die

Baselinecharakteristika zwischen den Gruppen unterschieden sich statistisch signifikant in Bezug auf Alter, ECOG Performance Status, RAS-Status und Substanzen der zuvor verabreichten palliativen Therapielinien.

Das mediane Gesamtüberleben (OS) betrug in der TAS-102 Gruppe (Kohorte A) 7,4 Monate (95%-KI: 5,6-8,7), in der TAS-102+Bev Gruppe (Kohorte B) 17,5 Monate (95%-KI: 6,3-nicht erreicht) und in der Regorafenib Gruppe (Kohorte C) 7,3 Monate (95%-KI: 5,1-9,6). Die TAS-102+Bev Gruppe zeigte einen signifikanten Überlebensvorteil gegenüber den TAS-102 und Regorafenib Gruppen (p=0,029). Auch nach multivariabler Adjustierung möglicher Störfaktoren wie dem ECOG Performance Status, Alter, Anzahl vorheriger Therapielinien und der Tumorlast zeigte sich eine signifikante Überlegenheit für die Kombinationstherapie aus TAS-102+Bev.

Das mediane progressionsfreie Überleben (PFS) betrug 3 Monate (95%-KI: 2,7-3,3) in der TAS-102 Gruppe, 3,2 Monate (95%-KI: 2,3-6,3) in der TAS-102+Bev Gruppe und 2,8 Monate (95%-KI: 2,0-3,9) in der Regorafenib Gruppe (p=0,09). Die Krankheitskontrollrate (DCR) betrug 45% in der TAS-102+Bev Gruppe, 16% in der TAS-102 Gruppe und 14% in der Regorafenib Gruppe (p=0,006).

Conclusio

Diese retrospektive Kohortenstudie hat gezeigt, dass die Kombination von TAS-102 (Trifluridin/Tipiracil) und Bevacizumab das Überleben von Patienten unter realen klinischen Bedingungen verlängern kann. Darüber hinaus erwies sich diese Therapie auch bei Patienten mit schlechtem Performance-Status, Therapierefraktärität und ungünstiger Tumorbiologie als wirksam. Diese Ergebnisse untermauern die Daten der „SUNLIGHT“-Studie, dass TAS-102+Bev als neuer Therapiestandard in der Drittlinientherapie des metastasierten kolorektalen Karzinoms zu sehen ist.[1]

Abstract

Introduction

Despite the development of new targeted therapy options for metastatic colorectal cancer (mCRC), the prognosis in advanced disease remains poor. Until recently, only two monotherapies, Regorafenib and TAS-102, were available for palliative third-line treatment. The recently published randomised phase 3 “SUNLIGHT” trial showed that the combination of TAS-102+Bevacizumab (TAS-102+Bev) was superior to TAS-102 monotherapy. However, there is very limited data on the efficacy of this treatment strategy outside of a clinical trial setting.[1]

Material and methods

This retrospective cohort study compared the clinical efficacy of TAS-102+Bev versus TAS-102 versus Regorafenib in the treatment of metastatic colorectal cancer with regard to the clinical endpoints of disease control (DCR), progression-free survival (PFS) and overall survival (OS). All patients with histologically confirmed, locally advanced, metastatic colorectal cancer who were treated with TAS-102+Bev, TAS-102 or Regorafenib at the Department of Oncology of the Medical University of Graz between 1 January 2016 and 30 September 2023 were included. The data were collected from the electronic hospital information system MEDOCS, as well as handwritten notes and documented in the web-based database REDCap.

Results

A total of 179 patients were included, of which 109 were treated with TAS-102, 20 with TAS-102+Bev and 50 with Regorafenib. The baseline characteristics between the groups differed significantly in terms of age, ECOG performance status, RAS-status and previously administered palliative therapy lines.

The median overall survival (OS) was 7.4 months (95% CI: 5.6-8.7) in the TAS-102 group (Cohort A), 17.5 months (95% CI: 6.3-not reached) in the TAS-102+Bev group (Cohort B) and 7.3 months (95% CI: 5.1-9.6) in the Regorafenib group (Cohort C).

The TAS-102+Bev group showed a significant survival advantage over the TAS-102 and Regorafenib groups (p=0.029). Even after multivariable adjustment for possible confounding factors such as ECOG performance status, age, number of previous lines of therapy and tumor burden, there was a significant superiority for the combination therapy of TAS-102+Bev.

The median progression-free survival (PFS) was 3 months (95% CI: 2.7-3.3) in the TAS-102 group, 3.2 months (95% CI: 2.3-6.3) in the TAS-102+Bev group and 2.8 months (95% CI: 2.0-3.9) in the Regorafenib group (p=0.09). The disease control rate (DCR) was 45% in the TAS-102+Bev group, 16% in the TAS-102 group and 14% in the Regorafenib group (p=0.006).

Conclusion

This retrospective cohort study has shown that the combination of TAS-102 (Trifluridine/Tipiracil) and Bevacizumab can prolong the survival of patients under routine clinic conditions. In addition, this therapy also proved to be effective in patients with poor performance status, treatment refractory and unfavourable tumor biology. These results support the data from the "SUNLIGHT" study that TAS-102+Bev should be seen as a new standard of care in the third-line treatment of metastatic colorectal cancer.[1]

Contents

Abbreviations

AE ..... *adverse event*
AJCC ..... American Joint Committee on Cancer
AKT ..... protein kinase B
AMWF ..... *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*
BRAF-V600E ..... amino acid substitution at position 600 in v-raf murine sarcoma viral oncogene homolog B1
BSC ..... *best supportive care, best supportive care*
CA-19 ..... carbohydrate antigen 19
CEA ..... *carcinoembryonic antigen*
CRC ..... *colorectal cancer*
CT ..... *computer tomography*
ctDNA ..... *circulating tumor DNA*
CTLA-4 ..... cytotoxic T-lymphocyte associated protein-4
dMMR ..... defective DNA mismatch repair
ECOG PS ..... Eastern Cooperative Oncology Group Performance Status
EGFR ..... anti-epidermal growth factor receptor
EORTC ..... *European Organisation for Research and Treatment of Cancer*
ErbB-1 ..... v-erb-b2 avian erythroblastic leukemia viral oncogene homolog
ERK ..... extracellular signal-regulated kinase
ESMO ..... *European Society for Medical Oncology*
FDG-PET ..... *Fluorodeoxyglucose-positron emission tomography*
FOLFIRI ..... *Folinic acid/Fluorouracil/Irinotecan*
FOLFOX4 ..... *Folinic acid/Fluorouracil/Oxaliplatin*
FOLFOXIRI ..... *Folinic acid/Fluorouracil/Oxaliplatin/Irinotecan*
GCO ..... *Global Cancer Observatory*
HER-1 ..... human epidermal growth factor receptor 1
HR ..... hazard ratio
ICI ..... immune checkpoint inhibitors
IgG-1R ..... insulin-like growth factor receptor
KPS ..... *Karnofsky Performance Status*
KRAS ..... *kirsten rat sarcoma viral oncogene*
LV ..... *Leucovorin*
mABs ..... monoclonal antibodies
MAPK ..... Mitogen-activated protein kinases
mCRC ..... *metastatic colorectal carcinoma*
MEK ..... mitogen-activated protein kinase
MLH1 ..... MutL Homolog of E. coli 1
MRI ..... *magnetic radiologic imaging*
MSI ..... microsatellite instability
mt ..... *mutated*
mTOR ..... mammalian target of rapamycin
NCCN ..... *National Comprehensive Cancer Network*
NMPA ..... National Medical Products Administration
PD ..... *progressive disease*
PD-1 ..... programmed cell death protein-1 receptor
PDGF ..... placental growth factor
PD-L1 ..... programmed cell death Ligand 1
PIGF ..... placental growth factor
PIK3 ..... phosphatidylinositol 3-kinase

pMMR ..... proficient (DNA-) mismatch repair
PS ..... *performance status*
QoL ..... *quality of life*
RAF ..... rapidly accelerated fibrosarcoma
RCT ..... *randomized controlled trial*
TTP ..... *time to tumor progression*
UICC ..... *Union for International Cancer Control*
VEGF ..... *vascular endothelial growth factor*, vascular endothelial growth factor
WHO ..... *World Health Organization*
wt ..... *wildtype*

Figures

Tables

Introduction

Epidemiology

Colorectal cancer (CRC) is a common disease, with 1- 2 million new cases per year worldwide. Approximately 600.000 patients die from this disease every year. The incidence varies widely between countries and is highly dependent on dietary and lifestyle factors.[2]

Regions with the most cases per year comprise the high-income countries of Europe, North America, and Oceania. By contrast, annual case numbers are the lowest in the poor-income countries of Asia and Africa.[3]

However, in several high-income countries the incidence of CRC either stabilized, or even decreased. Two measures are mainly responsible for this: first, the widespread promotion and implementation of preventive colonoscopy, and secondly, if precancerous polyps are detected, the endoscopic ablation of them. This has been observed in wide parts of North America and Europe.[3, 4]

Real life data incidence rates

The estimated numbers of cases and deaths from 2020 are accessible from the World Health Organization (WHO) database Global Cancer Observatory (GCO). Based on these numbers, current trends in recent cancer incidence rates can be calculated specifically for each country, region or global population.[5]

(Table 1) provides an overview of data on the population estimates, the incidence of colorectal cancer and the absolute colorectal cancer related mortality for the various continents. From these data, the probability of contracting the disease (risk) on a certain continent and the probability of dying from the disease if it occurs (lethality), were calculated.

Population data were taken from the “Worldometer” website at 13:37 MEZ Jan. 18th, 2022; colorectal cancer epidemiology data were taken from the WHO GCO website at 14:45 MEZ Jan. 18th, 2022.[5, 6]

Table 1: Continental incidences of 2020

	New cases of CRC (N1)	Habitants (N0)	Risk (CI)	Mortality	Lethality
Asia	975.000	4.641.054.775	0,00021	440.000	0,451
Africa	60.000	1.340.598.147	0,00004	38.800	0,647
Europe (Germany)	507.000 55.000	747.636.026 83.783.942	0,00068 0,00066	241.000 26.400	0,475 0,480
North America	171.000	368.869.647	0,00046	62,400	0,364
Latin America and Caribbean	129.000	653.962.331	0,00020	67.900	0,526
Oceania	19.800	42.677.813	0,00046	7.370	0,372
Global	1.879.900	7.794.798.739	0,00024	857.470	0,456

The calculation of this data implies that the risk of developing CRC in Europe, Oceania and North America is higher than in Latin America and the Caribbean or Asia. In Africa, the risk is lowest compared to all other continents. Lethality is the lowest in North America and Oceania. Europe and Asia balance each other out. In Latin America and the Caribbean, the lethality is highly increased, and in Africa it is by far the highest. In the case of Africa, on the one hand, it is least probable that one will develop CRC, but most probable that one will die from the disease.

Advanced colorectal cancer

Advanced colorectal cancer (stage IV) is defined as the spread of the tumor to tissues or organs remote from the colon. Tumor cells predominantly spread through blood and lymph vessels. Advanced colorectal carcinoma is frequently used as a synonym for metastatic colorectal carcinoma (mCRC).[7]

When colorectal cancer is diagnosed, around 25% of patients already have metastases, and a total of 50% of all patients develop metastases during the disease. This is one of the primary reasons for the high mortality rate and poor prognosis of CRC, with an overall survival (OS) rate of 13.1% within 5 years.[8]

The most common metastasized organ is the liver (70%), mainly due to the portal venous connection of the gastrointestinal tract with the liver. Thereafter, in

decreasing frequency affected are the lungs (24%), distant lymph nodes (16%) and peritoneum (10%). Less frequently observed (<5%) are metastases in bone marrow, the brain, or adrenal glands. However, advances in systemic therapy and the associated increase in survival have led to a higher incidence in these regions.[9, 10]

Tumor staging and grading

Tumor staging (0-IV) is conducted to assess the extent and severity of CRC. The basis for staging is the TNM system, used by both the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). UICC staging primarily considers the anatomic extent, while the AJCC additionally contemplates clinical properties of the tumor.[11]

The grading (G1-G4) of a tumor is always determined by a histopathological examination. It classifies how severely the tumor tissue has degenerated compared to the original specimen. Grading is an important indicator of the invasiveness of the tumor.[12]

TNM classification

The TNM system represents an internationally recognized tool for the consistent classification of the anatomical extent of colorectal cancer. The Dukes classification is considered obsolete and should no longer be applied. The TNM letters are each assigned to a clinical-pathological term. The T stands for primary tumor, the N for regional lymph node involvement and the M for distant metastases.[13, 14]

The TNM coding is usually preceded by prefixes of lowercase letters, which provide additional information. Most relevant are cTNM and pTNM. The cTNM classification is based on preliminary clinical findings before the start of therapy (clinical examination, imaging, and endoscopy). The pTNM classification, which is based on histopathological examination of a tumor specimen, offers more informative value. [13, 14]

A synopsis of the TNM classification, tumor staging, and grading of CRC is displayed in **(Table 2-Table 7).**

T) codes for the anatomical expansion of the primary tumor

Table 2: T- Primary tumor

T – Primary tumor	
TX	Primary tumor cannot be assessed
T0	No tumor found
Tis	Carcinoma in situ
T1	Tumor infiltrates submucosa
T2	Tumor infiltrates muscularis propria
T3	Tumor infiltrates in subserosa or visceral peritoneum
T4a	Tumor perforates the visceral peritoneum
T4b	Tumor infiltrates adjacent organs

[13]

N) codes for the number of affected lymph nodes in the regional lymphatic drainage area

Table 3: N- Regional lymph nodes

N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No affected lymph node
N1a	Metastatic dissemination in 1 lymph node
N1b	Metastatic dissemination in 2-3 lymph nodes
N2a	Metastatic dissemination in 4-6 lymph nodes
N2b	Metastatic dissemination in 7 or more lymph nodes

[13]

M) codes for the occurrence of distant metastasis

Table 4: M- distant metastasis

M – Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Distant metastasis, but in no more than 1 site, and not in the peritoneum
M1b	Distant metastasis, in more than one site
M1c	Distant metastasis in the peritoneum

[13]

Prefixes) provide additional information to TNM

Table 5: TNM prefixes

Prefixes	
c	Clinical evidence prior to treatment, no pTNM.
p	Histopathological examination
r	Recurrent cancer
y	After neoadjuvant therapy
a	Autopsy

[13]

Staging UICC)

Table 6: UICC staging

Staging based on TNM [UICC 2002]			
Stadium 0	Tis	N0	M0
Stadium I	T1, T2	N0	M0
Stadium IIA	T3	N0	M0
Stadium IIB	T4	N0	M0
Stadium IIIA	T1, T2	N1	M0
Stadium IIIB	T3, T4	N1	M0
Stadium IIIC	every T	N2	M0
Stadium IV	every T	every N	M1

[13]

Grading)

Table 7: Tumor grading

Grading	
GX	Grade cannot be assessed
G1	Well differentiated (low grade)
G2	Moderately differentiated (intermediate grade)
G3	Poorly differentiated (high grade)
G4	Undifferentiated (high grade)

[12]

Treatment planning of advanced colorectal carcinoma

Once the diagnosis of colorectal carcinoma has been confirmed, subsequent procedures should be coordinated in interdisciplinary collaboration and a full clinical

examination performed. This includes a medical history with age and comorbidities, a general clinical examination, performance status, blood tests, and liver/kidney blood parameters. To ensure optimal therapy from an oncological point of view, four key points always require clarification in advance: [15]

1) performance status (PS)
2) Disease extent and localization
3) Age and comorbidities
4) Molecular biology (possibility of targeted therapy)

Performance status: Karnofsky and ECOG status

In routine oncology practice, the patient's performance status (PS) is regularly assessed to make a treatment plan and to monitor overall health status during or after therapy. The PS can be quickly and easily obtained and quantified by using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) and the Karnofsky Performance Status (KPS). The disadvantage of these instruments is the subjective nature of the assessment, which entails large variability in results depending on the examiner. There is a large margin for bias along with poor reproducibility.[16]

Still, evaluations of the KPS and ECOG have been shown to hold clinical relevance; in a multivariate analysis of 3825 mCRC patients receiving systemic therapy with 5-fluorouracil (5-FU), patients with an ECOG of 0 or 1 were associated with distinctly longer survival than patients with an ECOG of 1 or higher.[17]

The classification of the Karnofsky score and EGOG performance status were obtained from the European Society for Medical Oncology (ESMO) website [18] as juxtaposed in **(Table 8):**

Table 8: Karnofsky and ECOG performance status

Karnofsky score	**Karnofsky grade**	**ECOG grade**	**ECOG status**
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction

Able to carry on normal activities. Minor signs or symptoms of disease	90	0	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Care for self. Unable to carry on normal activity or to do active work	70	1	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	2	Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours
Severely disabled. Hospitalization indicated though death non-imminent	30	3	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

The performance status defines the patient's eligibility for intensive therapy. Three patient subgroups can be distinguished: If the PS is good, the most effective tumor reduction is always targeted. In patients who cannot tolerate intensive treatment, a reduced regimen and/or targeted therapy is used. For patients who are no longer suitable for systemic therapy, the focus lies on sustaining quality of life (QoL) through best supportive care (BSC). Yet, this vaguely defined classification is reliant on subjective evaluation, hence consultation with the patient should be involved.[15, 19]

Disease extent and localization

Radiologic imaging of the tumor extent and distribution is essential for treatment planning. According to current guidelines, disease staging of advanced CRC should be obtained by a contrast enhanced computer tomography (CT) scan of the thorax, abdomen and pelvis. In special scenarios such as isolated liver metastasis, a magnetic radiologic imaging (MRI) scan may provide additional information. Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be helpful to further characterize and detect the extent of malignant lesions if the findings are not entirely clear. Detection of metastases by radiologic imaging critically influences the patient's therapeutic path and prognosis.[20]

Comorbidities

Comorbidities have a significant impact on treatment tolerability and are therefore crucial for treatment planning. While most relevant comorbidities increase mortality in general, it has been emphasized, that dementia, diabetes, peptic ulcer disease, chronic kidney disease and liver disease furthermore lead to colorectal cancer-specific mortality.[21]

Molecular biology

DNA sequencing of molecular gene alterations and biomarkers holds a high priority in modern time's therapy of mCRC. Based on the molecular profile, targeted tumor therapy provides individually tailored treatment for the patient. *This is addressed in further detail in the chapter "Role of targeted therapy in the first- and second-line treatment of mCRC".*[22]

Treatment management of advanced colorectal cancer

For metastatic colorectal disease, four different treatment scenarios condense across guidelines.[15, 19, 21]

Curative treatment goal:

- mCRC with primary resectable metastases
- mCRC with primary unresectable metastases, that might become resectable after neoadjuvant conversion therapy

Palliative treatment goal:

- mCRC with oligometastatic disease that potentially qualifies for local therapeutic procedures but do not enable a curative treatment approach
- mCRC with unresectable metastatic disease

Metastatic colorectal cancer with primary resectable metastasis

Surgery

At present the only curative treatment approach for patients with distant metastasis requires resection with tumor-free surgical margins. However, less than 20% of patients with liver metastases are amenable to metastasectomy.[23]

Eligible patients who have undergone a clean resection of liver metastases demonstrate significantly prolonged survival. Several retrospective reviews report a 5-year PFS for more than 50% of patients, with one-sixth even exceeding a 10-year PFS, which is essentially equivalent to cure. Yet, all these studies face ongoing allegations of selection bias, as these survival figures are certainly inflated by selecting patients with favorable metastatic situations. Regardless, the clinical relevance and rationale of the approach remains undeniable.[24–26]

In a retrospective analysis using data from the “SEER database” of 1325 patients with mCRC, it was calculated that the 3-year survival rate increased from 27.5% to 44.5% with surgery for suitable liver metastases. This effect applied only to lesions confined exclusively to the liver; no survival benefit was found for resection of pulmonary metastases.[27]

Perioperative systemic treatment

The evidence on whether perioperative chemotherapy should be added to liver metastasectomy is not entirely conclusive. One randomized controlled trial by the

European Organisation for Research and Treatment of Cancer (EORTC) compared the benefit of surgery alone and surgery + perioperative FOLFOX therapy in 364 patients with resectable liver metastases. Although 3-year progression-free survival (PFS) increased by 7.3%, there was no significant improvement in overall survival (OS).[28]

According to the ESMO guidelines, perioperative chemotherapy is a reasonable therapy option if the tumor characteristics are associated with poor surgical outcome. These include synchronous and multiple lesions, bilobar pulmonal disease and limited extrahepatic disease. Perioperative chemotherapy is particularly recommended for small metastases (10-15 mm) that are covered by systemic therapy and are likely to be missed by surgery.[20]

Currently, there is no recommendation for the perioperative use of targeted therapy in liver metastasis surgery. In the “EPOC” randomized controlled trial (RCT), 257 patients with kirsten rat sarcoma viral oncogene (KRAS) exon 2 wildtype mCRC were randomized to either Cetuximab or placebo during metastasectomy. The application of Cetuximab did not lead to any benefit, in fact shortened the PFS compared to the control group. Further investigations and molecular analysis will be necessary to clarify this contradictory result.[29]

Metastatic colorectal cancer with potentially resectable metastasis after conversion therapy

Conversion (neoadjuvant) tumor therapy is applied to patients, who show primary unresectable metastases, that might become resectable by systemic therapy. Consequently, it is pivotal to treat with an intensive regimen, to achieve maximum tumor reduction. To date, no uniform recommendation exists. Toxicity is increased with triplet (FOLFOXIRI) therapy, but it is more effective for quickly down-sizing tumor mass and thus represents a treatment option for fit patients and especially in those with right-sided tumors. In patients who do not qualify for triplet therapy, a chemotherapy doublet (FOLFOX/FOLFIRI) is preferred. Tumor biology (mutational tumor profile, localization of primary tumor, extent, and aggressiveness of the

disease) as well as the patient's PS and wishes must be factored into the treatment decision.[30]

Based on the ESMO guidelines, for left-sided RAS-wildtype (wt) CRC, anti-epidermal growth factor receptor monoclonal antibodies (EGFR-mABs) should be used for conversion therapy; if the tumor is right-sided and RAS-mutated (mt), a triplet therapy of FOLFOXIRI and Bevacizumab or, when intolerable, a doublet therapy with Bevacizumab should be considered.[20]

Metastatic colorectal cancer with oligometastatic disease

Oligometastasis refers to metastases that are limited in number and spread. However, no consensus has yet been reached on either the definition or the therapeutic approach due to lack of reliable data from randomized controlled trials in this setting.[15, 31]

This is a group of patients who may benefit from local therapy of metastases in addition to systemic therapy. The objective is thereby to prolong PFS and OS and reduce tumor mass, and in selected cases even achieve complete resectability. To accomplish this, local ablative procedures (thermoablation, radiotherapy, electroporation) or other local procedures (intra-arterial chemotherapy of the liver, stereotactic radiotherapy, hyperthermic chemotherapy) can be used in addition to standard surgery.[15, 32, 33]

Metastatic colorectal cancer with unresectable metastasis

If a patient with unresectable metastases is eligible for intensive therapy, the primary treatment aim is the prolongation of survival and a preservation of QoL. A sequential therapeutic approach using all available treatment options is recommended. The option of local tumor therapy and/or surgical resection should be reviewed at regular intervals in a multidisciplinary manner. In cases of reduced PS, that does not allow intensive chemotherapy, the focus should be set on best supportive care (BSC) and symptom control. Systemic therapy with reduced-dose Fluoropyrimidine+Bevacizumab, reduced-dose doublet therapy with or without

Bevacizumab may be considered in this patient subgroup. Anti-EGFR monotherapy is another option in RAS-wt tumors. More intensive therapy in poor PS (ECOG >1) may be considered if the tumor is directly responsible as major cause of severe symptomatology (tumor stenosis). [15, 34, 35]

Systemic treatment of mCRC

Systemic therapy for mCRC involves a broad selection of cytotoxic agents, biologics such as antibodies to cellular and vascular growth factors, immunotherapy, and combinations of these.[36] For most patients with mCRC, systemic therapy is the main treatment lever. 5-fluorouracil (5-FU) was the only agent available until Irinotecan was approved by the United States Food and Drug Administration (U.S. FDA) in 1996. From then on, a series of other drugs followed, steadily improving patient outcomes. A synopsis of FDA-approved antitumor agents against mCRC is shown in **(Table 9).** The underlying data sources from the U.S. FDA drug approval database.[37–39]

Table 9: overview of FDA approved systemic treatment options for mCRC

Drug name	Application	Drug class	Mechanism of action	FDA approval date for mCRC
5-fluorouracil (+Leucovorin)	i.v.	cytotoxic	pyrimidine-analogue + (folinic acid)	1962
Capecitabine	p.o.	cytotoxic	pyrimidine-analogue	2001
Irinotecan	i.v.	cytotoxic	topoisomerase I-inhibitor	1996
Oxaliplatin	i.v.	cytotoxic	anti-DNA, toxic platin compounds	2004
Regorafenib	p.o.	targeted, immunotherapy	multikinase-inhibitor, anti VEGF	2012
Tipiracil*	p.o.	targeted	thymidine phosphorylase inhibitor	2015
Trifluridine*	p.o.	cytotoxic	nucleoside-analogue	2015
Cetuximab	i.v.	targeted	anti EGFR	2004
Panitumumab	i.v.	targeted	anti EGFR	2006
Bevacizumab	i.v.	targeted	anti VEGF	2004
Ziv-Aflibercept	i.v.	targeted	anti VEGF-A, anti PlGF	2012

Ramucirumab	i.v.	targeted	anti VEGF	2015
Pembrolizumab	i.v.	immunotherapy	anti PD-1	2017
Nivolumab	i.v.	immunotherapy	anti PD-L1	2018
Ipilimumab	i.v.	immunotherapy	anti CTLA-4	2018
Encorafenib**	p.o.	targeted	BRAF-V600E kinase inhibitor	2020

*: approved only as combination of Tipiracil+Trifluridine (TAS-102)

**: approved only in combination with Cetuximab

Role of cytotoxic chemotherapy in the first- and second-line treatment of mCRC

First line

Basis

The standard backbone of first line cytotoxic therapy are Fluoropyrimidines. The options include 5-fluorouracil (5-FU) + Leucovorin (LV), for intravenous administration, and the orally applicable Capecitabine. A phase III RCT enrolled 1207 previously untreated patients and randomized them to either 5-FU/LV or Capecitabine, to assess, whether the oral 5-FU-prodrug can rival its well-served predecessor. The results showed identical OS and time to tumor progression (TTP) in both treatment arms, whereas Capecitabine demonstrated a better objective response rate (ORR), less severe adverse events, and was reported to be more convenient to take.[40, 41]

Doublet chemotherapy

Depending on the patient's fitness, a Fluoropyrimidine should be supplemented with either Irinotecan in a 5-FU/LV/Irinotecan (FOLFIRI) regimen or Oxaliplatin in a 5-FU/LV/Oxaliplatin (FOLFOX) regimen. The ORR, OS and PFS can be significantly improved by these combinations in comparison to Fluoropyrimidine alone, as shown in several studies.[42, 43]

In the front-line setting, Irinotecan and Oxaliplatin based regimens have comparable efficacy. Studies comparing their synergistic effect with 5-FU, yielded comparable results. The "GERCOR" study reported for FOLFIRI versus FOLFOX an ORR of

56% versus 54%, a median PFS of 8.5 versus 8 months and an OS of 21.6 versus 20.6 months, respectively. Toxicity profiles differed, but not in severity.[44] Other phase II/III studies from Italy and Greece confirmed these results.[45, 46] Further therapeutic options are not limited with either agent; combinations with biologics are possible with both.[47]

5-FU can be substituted by Capecitabine in combination with Oxaliplatin (XELOX), however, the combination with Irinotecan (XELIRI) is not recommended due to an unfavorable side effect profile.[20]

Triplet chemotherapy

In patients with good PS, triplet therapy with a Fluoropyrimidine, Irinotecan and Oxaliplatin (FOLFOXIRI) can be considered. The “Gruppo Oncologico Nord Ovest” initiated a phase III trial, in which 244 mCRC patients were randomized to either FOLFIRI or the extended FOLFOXIRI regimen. Although toxicity increased in the triplet regimen, the magnitude was found to be less than anticipated. Response rate, as well as PFS and OS, increased considerably in the FOLFOXIRI arm.[48]

Subsequently, a 60.6-month follow-up was performed to investigate the long-term effects of FOLFOXIRI. The positive trend was repeated, as FOLFOXIRI emerged superior to FOLFIRI in PFS and OS endpoints in the long-term. The 5-year overall survival rose from 8% to 15% under triplet therapy.[49]

Side effects

The side effects of cytotoxic therapy often limit its efficacy. Classic chemotherapy associated symptoms that frequently occur include the following: myelosuppression, oral mucositis, diarrhea, acute cholinergic syndrome, nausea and emesis, neurotoxicity, hand-foot syndrome and other cutaneous adverse effects; ocular toxicity, cardiotoxicity, small bowel toxicity, asthenia, elevated liver transaminase levels and alopecia.[50]

Second line

Second-line chemotherapy for mCRC in general is less effective than the first line. QoL and side effect control now exert a stronger influence on treatment choice.[15]

Doublet therapy (FOLFOX/FOLFIRI) plus targeted therapy is the standard for patients with adequate organ function and performance and its choice depends on the previously administered chemotherapeutic drugs. The recommended approach envisages the interchange of Irinotecan and Oxaliplatin based on the assumption of resistant tumor cell line prevalence.[20, 51] If the patient progressed on an Irinotecan-based regimen in the first-line treatment, an Oxaliplatin-based regimen (FOLFOX) should be chosen for second line therapy. The same applies in reverse: if the response to an Oxaliplatin-based regimen was poor, Irinotecan can be newly introduced in second line treatment (Irinotecan monotherapy or FOLFIRI).[52]

Role of targeted therapy in the first- and second-line treatment of mCRC

In addition to chemotherapy, biologic antibodies have proven instrumental in improving clinical outcome of patients with advanced CRC. These biologics do not exert their effect via cell toxicity, but inhibit small molecular targets, like the vascular endothelial growth factor (VEGF), the epidermal growth factor receptors (EGFR) or immune checkpoints.[53, 54]

The introduction of targeted therapy has been a huge step towards individualized medicine, which requires detailed molecular profiling prior to its deployment for each patient.[20]

VEGF targeting agents

The vascular endothelial growth factor (VEGF) is a polypeptide with 5 members (VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF) and a key factor in regulating tumor angiogenesis. VEGF-inhibitors not only reduce the amount of tumor blood vessels, but also normalize vascular malformations, thereby improving drug uptake into tumor tissue and the effect of complementary applied cytostatic drugs.[55, 56]

FDA approval has so far been granted to 4 compounds in this drug class: Bevacizumab is being considered for all lines of therapy, Aflibercept and Ramucirumab serve as surrogates, and Regorafenib is being considered for the use of last reserve.[15, 57]

First Line

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor-A activity. FDA approval was granted in 2004. Since then, a wealth of clinical data has supported the safety and efficacy of Bevacizumab for first or later line treatment of mCRC.

The “AVF2107g” trial randomly assigned 813 mCRC patients without prior systemic therapy to FOLFIRI + Bevacizumab or FOLFIRI + placebo. The Bevacizumab study arm provided both statistically significant and clinically relevant improvement in all survival endpoints. OS increased from 15.6 to 20.3 months, PFS from 6.2 to 10.6 months, and the ORR from 34.8% to 44.8% when compared to placebo. Bevacizumab caused more serious adverse events (AEs), but rarely led to patient hospitalization or discontinuation of treatment.[58]

A subsequent meta-analysis supported the value of Bevacizumab for mCRC first line therapy. 5 large RCTs comparing chemotherapy with and without Bevacizumab resulted in improved RR, PFS and OS outcomes in favour of the combination. With 10 percentage points more Grade 3 or 4 AEs the safety profile of Bevacizumab stayed consistent to previously registered data.[59]

In contrast to EGFR-blockers, Bevacizumab also showed the ability to provide benefit in difficult-to-treat molecular subgroups RAS-mutated (mt). A subgroup stratified analysis of a phase lll study comparing chemotherapy +/- Bevacizumab in mCRC patients without prior therapy showed, that although survival parameters were lower in KRAS-mt than in KRAS-wt, Bevacizumab also improved survival in the KRAS-mt subgroup substantially.[60]

However, Bevacizumab displayed weaknesses and limitations. The “NO16966” RCT reported, that in non-Irinotecan chemotherapies (FOLFOX, CAPOX), Bevacizumab only offered a marginal survival advantage.[61] In combination with triplet chemotherapy, Bevacizumab led to a significant extension of PFS, but not OS

at the costs of increased toxicity.[62] Previous publications additionally suggest that toxicity may exceed previous expectations and recommend a more cautious usage of Bevacizumab.[63]

Second Line

Anti-VEGF agents in conjunction with chemotherapy are also effective after initial progression on systemic mCRC therapy. However, the gain in overall survival remains below that of first-line treatment, averaging 1-2 months. In addition to Bevacizumab, the fusion protein Ziv-Aflibercept and the monoclonal antibody Ramucirumab expand the treatment spectrum of VEGF targeting drugs for pre-treated mCRC.[15, 57]

The efficacy and safety of Bevacizumab in the palliative second line for mCRC is backed by multiple RCTs (“E2300”, “TML”, “BEBYP”) that provide consistent results across different settings. The “E2300” trial investigated a potential effect of Bevacizumab added to FOLFOX in a first-line Bevacizumab naïve patient selection. Both PFS and OS were superior in the combination arm, compared to chemotherapy alone (PFS was 7.3 months versus 4.7 months, hazard ratio (HR) = 0.6); OS was 12.9 months versus 10.8 months, HR = 0.75). The dosage was increased to 10mg/kg compared to first line standard yet was well tolerated.[64] The “TML” and “BEBYP” trials later examined the efficacy of Bevacizumab in patients who had already been treated with it in the first line. Both showed that continuation of Bevacizumab after first progression still provided a synergistic effect with chemotherapy. Treatment attempts with Bevacizumab alone were prematurely halted due to insufficient activity.[65, 66]

Ziv-Aflibercept is a recombinant fusion protein that targets tumor angiogenesis by binding VEGF-A, VEGF-B and placental growth factor (PIGF) and is used in advanced CRC after first line progression. The safe and effective use of Aflibercept was shown by the phase lll “VELOUR” study. 614 participants who had previously undergone a systemic Oxaliplatin-based first line treatment were randomly assigned to either FOLFIRI + Aflibercept or FOLFIRI + placebo. A survival benefit in the Aflibercept arm was observed in both Bevacizumab pre-treated (OS was 12.5 months versus 11.7 months) and Bevacizumab naïve patients (OS was 13.9 months

versus 12.4 months). The toxicity of Aflibercept was in accordance with what would be expected from anti-VEGF medication.[67, 68]

Another angiogenesis inhibitor used for second line mCRC treatment is the insulin-like growth factor receptor 1 (IgG-1R) monoclonal antibody Ramucirumab. By targeting the extracellular domain of VEGF receptor 2, ligand attachment is prevented, and the VEGF pathway is blocked. The approval of Ramucirumab in 2015 stems from the phase lll “RAISE” trial; 1072 patients, who showed progressive disease on a FOLFOX + Bevacizumab first-line treatment, were randomly assigned to either FOLFIRI or FOLFIRI + Ramucirumab. All survival parameters significantly increased under the combination therapy (OS was 13.3 months versus 11.7 months, HR = 0.84; PFS was 5.7 months versus 4.5 months, HR = 0.79). Ramucirumab toxicity met prior experience with anti-VEGF drugs.[57]

EGFR targeting agents

The epidermal growth factor receptor (EGFR, ErbB-1, HER-1) is a transmembrane glycoprotein classified as an ErbB receptor tyrosine kinase. Ligand-driven activation of EGFR activates the molecular RAS-RAF-MEK-ERK (MAPK) and PIK3/AKT/mTOR signaling pathways that govern key functions such as cellular growth, proliferation, transformation, motility, and angiogenesis.[69]

Cetuximab and Panitumumab are monoclonal antibodies that bind and block the EGF-receptor. Both substances are FDA approved for the therapy of metastatic colorectal carcinoma and showed efficacies in all lines of therapy in combination with chemotherapy or as sole agents.[15]

However, several genetic mutations and right-sided primary tumor localization limit EGRF-antibody efficacy. It is therefore imperative to test for RAS and BRAF mutations prior to drug administration, since a mutation in these genes represents the commonest source of anti-EGFR antibody resistance in mCRC.[70, 71]

First line

The chimeric monoclonal antibody Cetuximab occupies the EGFR and thus decreases downstream signal transduction. After approval in chemotherapy-

refractory mCRC patients in 2004, the highly inconsistent efficiency of Cetuximab raised questions about the presence of potential resistance mechanisms. Shortly thereafter, it became clear, that response to anti-EGFR antibodies is subject to underlying genetic etiology and a mutation in KRAS was shown to be a negative predictive biomarker.[72, 73]

The major “CRYSTAL” and “OPUS” randomized controlled trials are a sample of a variety of studies showing significant survival benefits for Cetuximab in combination with chemotherapy in first line mCRC treatment. The phase III “CRYSTAL” trial enrolled 1198 patients with mCRC who were randomized to either receive FOLFIRI+Cetuximab or FOLFIRI alone. During a subgroup analysis, tumor samples from 1063 individuals were tested for KRAS-status in codons 12 and 13, which showed a mutation in 37% of cases. In the presence of KRAS-wt, combination therapy with Cetuximab showed distinguishable advantages to FOLFIRI alone (ORR was 57.3% versus 39.7%; PFS was 9.9 months versus 8.4 months; OS was 23.5 months versus 20.0 months). Concurrently, the KRAS-mt group did not benefit from Cetuximab administration in any of these outcomes. The phase II “OPUS” trial demonstrated benefit for Cetuximab in an Oxaliplatin regimen (FOLFOX + Cetuximab). Again, genetic subgroup analyses were performed and underlined the missing efficacy of Cetuximab, if KRAS-mt was present. Furthermore, the same negative predictive value was proposed for the amino acid substitution at position 600 in v-raf murine sarcoma viral oncogene homolog B1 (BRAF-V600E) despite rarer occurrence. Increased toxicity was reported in both Cetuximab studies but was deemed tolerable.[74, 75]

The wholly human antibody Panitumumab was approved by the FDA two years after its pendant Cetuximab and shares similar mode of action, efficacy, and tolerability. Evidence for its efficacy is provided by the phase III “PRIME” trial, in which 1183 mCRC patients received FOLFOX + Panitumumab or FOLFOX + placebo. KRAS-status was subgroup stratified, with KRAS-mt present in 40% of patients. The KRAS-wt group receiving Panitumumab maintained longer survival than the placebo group (PFS was 9.6 months versus 8.0 months; OS was 23.9 months versus 19.7 months). In the KRAS-mt group, even a deterioration in results was observed. Overall toxicity was increased but lingered within expectations.[76]

Another limitation to the treatment with Cetuximab and Panitumumab is the localization of the primary. Even in the absence of RAS/BRAF-mt, patients with a right-sided primary CRC hardly benefit from anti-EGFR treatment. An expanded molecular profiling might further supply learnings into the underlying causes.[77]

Second line

Cetuximab and Panitumumab have shown efficacy across different settings in KRAS-wt CRC following disease progression on standard first line therapy. A positive impact on outcome for KRAS-mt was never evidenced in second line treatment.[78]

In conjunction with suitable chemotherapy for second-line treatment, both Cetuximab and Panitumumab showed improved ORR and PFS, albeit no significant OS benefit, compared with chemotherapy alone ("EPIC" and "191" phase lll RCTs).[79, 80]

Alternatively, EGFR antibodies can also be administered as monotherapy in pre-treated patients. In the "C0.17" phase lll study, a total of 572 mCRC patients with progressive disease (PD) were randomized to either Cetuximab or BSC alone. Cetuximab administration performed better than BSC, extending OS from 4.6 to 6.1 months, while showing manageable toxicity.[81]

The phase lll "20020408" study investigated the same for Panitumumab and included 463 mCRC patients to determine whether Panitumumab prolongs survival in a second line setting relative to BSC alone. PFS and ORR increased significantly with Panitumumab administration, while OS prolongation remained not significant. This is most likely due to the early performance of the study, whereby 76% of the BSC group were crossed over to Panitumumab treatment. Toxicity was deemed tolerable.[82]

BRAF targeting agents

V-raf murine sarcoma viral oncogene homolog B1 (BRAF) is a protooncogene and encodes the eponymous serine-threonine kinase BRAF. It is an integral link in the RAS-RAF-MEK-ERK (MAPK) pathway, which promotes cell proliferation, division,

and differentiation. The most common BRAF mutation in mCRC is the V600E mutation, which occurs in approximately 8-12% of patients with mCRC.[83] Resistance to EGFR blocker therapy forms analogously to RAS mutations, except that BRAF kinase ranks one link higher in the MAPK-cascade.[84, 85]

The prognosis of BRAF-mt mCRC is worse than in wildtype, which is attributed to the limited treatment options and more aggressive biology of the tumor. Studies comparing survival between BRAF-wt and BRAF-mt are abundant. The “PRIME” trial showed an OS of only 10.5 months for BRAF-mt, while patients with BRAF-wt achieved an OS of 28.3 months.[86] The “COIN” study and a pooled analysis of “CRYSTAL” and “OPUS” support this thesis; all demonstrated significant disadvantages in survival of patients with BRAF-mt.[87, 88]

Mutations in BRAF are considerably rarer than in RAS. In a test population of 138 patients with mCRC, in 6.5% BRAF-mt were detected. RAF+ KRAS-mutations co-occurred in 1.4% of cases.[89]

Since the BRAF-V600E mutation drastically limits the efficacy of chemotherapy, its targeted inhibition has been the subject of detailed investigation. Two drugs for BRAF-V600E inhibition have been approved for cancer therapy so far: Vemurafenib and Encorafenib.

Vemurafenib is an oral BRAF-V600E kinase inhibitor that has demonstrated efficacy and has gained approval for the treatment of metastatic melanoma.[90] Subsequently, the benefit of Vemurafenib in combination with EGFR-mABs has also been investigated for mCRC, but study results are inconsistent. Although pilot studies did show clinical activity, the benefit of Vemurafenib for mCRC could not be validated in clinical trials.[91–93]

More promising results were reported for the BRAF-V600E kinase-inhibitor Encorafenib, which was tested together with the mitogen-activated protein kinase (MEK)-inhibitor Binimetinib in the phase III “BEACON” trial in pre-treated patients with mCRC BRAF-V600E mutations. The study compared a control group receiving standard of care against a triplet therapy group with Encorafenib+Binimetinib+Cetuximab and a doublet therapy group with Encorafenib+Cetuximab. OS improved from 5.9 months in the control group to 9.3 months in both intervention groups. Response rates improved from 1.8% in the

control group to 26.8% in the triplet and 19.5% in the doublet therapy group. These results represent a major benefit for this subgroup and led to approval of Encorafenib in combination with Cetuximab for BRAF-V600E mt mCRC in 2020.[94]

Microsatellite instability

Microsatellite instability (MSI) is a genetic predisposition to develop new mutations, caused by a defective DNA mismatch repair (dMMR) protein system. Approximately 15% of early-stage CRC present with MSI, and in about one-fifth of these, the tumor presents as part of a hereditary Lynch syndrome. The remainder occurs sporadically, due to hypermethylation of the MLH1-gene.[95] In mCRC, the percentage drops to only 5% of cases harboring dMMR.[96, 97]

CRC with MMR-deficiency is associated with some clinically relevant specifics. It affects biological features, such as the enhanced occurrence in the proximal colon. The prognosis is also impacted by MSI, apparently depending on the degree of tumor spread. Better prognosis has been recorded for early stages of the disease (till stage lll), whereas the prognosis for mCRC with MSI has been reported to be poor; this is likely to improve in the future, based on the successful implementation of immunotherapy in patients with dMMR mCRC.[98–100]

In dMMR mCRC, optimal therapy requires adaptation since several studies have suggested limited response to chemotherapy and targeted drugs, in virtually all stages of the disease.[101]

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI) work by binding and blocking checkpoint proteins to their partner proteins. This basically suppresses the signal that protects the cancer cells from being targeted and killed by the T-cells.[102] There are three main types of immune checkpoints that are currently under investigation: Cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death protein-1 receptor (PD-1) and programmed cell death Ligand 1 (PD-L1). These proteins prevent an excessive immune response to components, such as native body tissue

and are commonly expressed on tumor cells which offers a rationale for the use of ICI drugs.[103]

Despite promising new insights into immunotherapy in mCRC, efficacy remains limited to a minority of patients, who present with MSI/dMMR. The importance of determining mismatch repair status prior to therapy with ICIs has been demonstrated in several studies. The phase II study “KEYNOTE 016” evaluated the efficacy of Pembrolizumab (anti-PD-1) in 41 mCRC patients with mixed microsatellite status. Study arm 1 included patients with dMMR, while study arm 2 accounted for those with proficient (DNA-) mismatch repair (pMMR). The ORR differed in arm 1 to arm 2 with 40% to 0% respectively.[104] An update from “KEYNOTE 016” with approximately twice the number of patients and an identical design, showed similar results in ORR, achieved a 2-year PFS of 59% and a 2-year OS of 72% under Pembrolizumab monotherapy in patients with dMMR tumors.[105]

Further randomized evidence for the efficacy of Pembrolizumab was obtained from the “KEYNOTE 177” phase lll trial; 307 MSI/dMMR mCRC patients were treated with either standard chemotherapy + Bevacizumab/Cetuximab or Pembrolizumab alone as palliative first line therapy. Importantly, Pembrolizumab led to a statistically significant and clinically relevant improvement of the primary endpoint PFS, making it the new standard of care in this setting.[97]

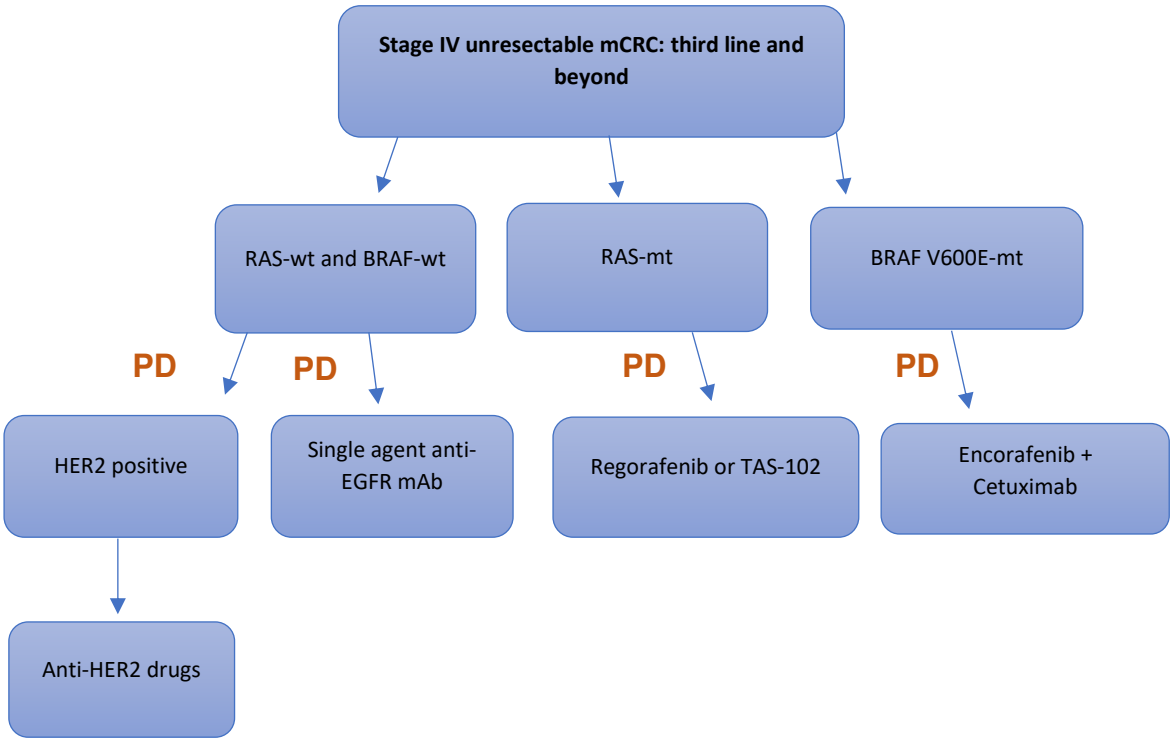
Immune checkpoint inhibitors approved to date by the U.S. FDA for the treatment of MSI/dMMR mCRC include Pembrolizumab and Nivolumab (anti-PD-L1) alone or a combination of Nivolumab with Ipilimumab (anti-CTLA-4).[106] The approval of Nivolumab with or without Ipilimumab is based on the phase II “CheckMate 142” study, in which 119 patients with MSI/dMMR mCRC received Nivolumab with or without Ipilimumab; this included unselected pre-treated and untreated patients, as well as patients with or without BRAF/RAS mt. In the final analysis, the ORR in the combination arm was 55%, which remarkably was also shown in the BRAF-mt subgroup. The 9-month PFS was 76%, and the 9-month OS 87%.[107]

Third and later line treatment

Due to increased treatment options with enhanced efficacy, an increasing number of patients with mCRC are considered for third and later line therapy. In this setting, patients usually have exhausted at least two prior lines of therapy, including a Fluoropyrimidine, Irinotecan, Oxaliplatin, an anti-VEG, and an anti-EGFR monoclonal antibody for patients with RAS-wt left sided CRC. At this stage, the importance of retaining QoL through BSC and the close surveillance of the patients' needs is crucial. Still, further antineoplastic therapy can be offered to fit patients, to prolong survival. The most relevant treatment options, which include Trifluridine/Tipiracil (TAS-102), Regorafenib, and a rechallenge of previously used agents as well as novel perspectives are each to be illuminated separately in this chapter.[15]

According to the ESMO Guidelines therapeutic algorithm for third line treatment, mutational status, once again, plays a decisive role for treatment selection. The ESMO therapy algorithm is shown in **(**Fehler! Verweisquelle konnte nicht gefunden werden.**.**[20]

Figure 1: unresectable mCRC therapy algorithm flowchart, adapted from ESMO guidelines



Regorafenib

Regorafenib is an oral administrable agent that inhibits multiple intra- and extracellular kinases and shows anti-angiogenic effects via blockade of vascular endothelial growth factor (VEGF), angiopoietin-1 receptor (TIE2) and placental growth factor (PDGF) receptors. In addition, Regorafenib intervenes with the MAPK signalling pathway and improves the immune response to tumor cells through macrophage modulation.[108]

Regorafenib was approved for patients with mCRC, who have exhausted palliative chemotherapy, anti-VEGF and anti-EGFR antibody treatment. Given its immunomodulatory properties, the extent to which synergism with immunotherapy may increase efficacy is currently under exploration.[15]

The efficacy of Regorafenib was demonstrated by the two phase lll studies, “CONCUR” and “CORRECT”. The “CORRECT” trial dates to 2012 and included over 1052 patients with mCRC from 114 different centres. These patients had exhausted all standard treatment options and were randomized to either Regorafenib or placebo. The major endpoint was defined OS, which at follow-up was 5 months for BSC alone and 6.4 months (HR 0,77) for Regorafenib. Most observed therapy-associated grade 3 or 4 AEs were in 17% hand-foot skin reaction, 10% fatigue, 7% hypertension, and 7% diarrhea (7%).[109]

The subsequent “CONCUR” trial pursued a similar objective in 2015. 243 patients in Asia were selected under similar criteria and were randomized to Regorafenib or placebo to substantiate the value of Regorafenib in end of line therapy for mCRC. Patients in the placebo group showed an OS of 6.3 months, while it increased to 8.8 months in the Regorafenib group (HR 0.55). Like in “CORRECT”, severe AEs were common, but would also remain within the expected safety profile of Regorafenib. [110]

Several other studies have been conducted on the same topic. Among them is the phase lllb “CONSIGN” study with 2827 patients or the prospective observational trial “CORRELATE”, which evaluated real world data from 1037 patients. In both cases, survival benefit and safety of Regorafenib were revalidated.[111, 112]

Limitations for Regorafenib to be considered are the low response rates. None of the studies achieved a complete response, “CORRECT” showed a 1% partial response rate and in “CONCUR” a 4% partial response rate was observed. This suggests that the survival benefit resulted from disease stabilization rather than tumor remission. Apart from that, Regorafenib showed robustness and reliability to improve survival despite exhausted chemotherapy and antibody treatment options. Simultaneously, it offers a predictable side effect profile and was well tolerated by most patients over the long-term.[113]

Trifluridine-Tipiracil (TAS-102)

TAS-102, also known by its trade name Lonsurf, is an oral administrable cytotoxic agent that can be offered to patients with mCRC, who have exhausted standard chemo/antibody therapy.[114]

It is composed of the cytotoxic Trifluridine, a thymidine nucleoside analogue, and Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, which prevents fast degradation of Trifluridine to maintain sufficient drug levels.[115, 116]

The efficacy and safety of TAS-102 has already been tested in a phase ll trial in 2012. The patient population comprised 169 Japanese patients with therapy-refractory mCRC. Compared to placebo, TAS-102 increased median survival from 6.6 to 9 months, with a hazard ratio for death of 0.56. Adverse effects of grade 3 or 4 occurred in more than 50% of patients under TAS-102 administration but were deemed manageable.[117]

Later in 2015, the pivotal phase lll “RECOURSE” trial was conducted and obtained similar results. About 800 patients with out-of-treatment mCRC were randomly assigned to either placebo or TAS-102. The primary endpoint was OS, which improved from 5.3 months in placebo to 7.1 months, the median 1-year OS improved from 18% to 27% with TAS-102 (HR 0,68). The ORR of 1.5% was rather poor though. Grade 3 or higher classified adverse events were observed in 52% of placebo patients and 69% of those who received TAS-102.[118]

Given the difficulty to provide feasible treatment in late stages of the disease, an average survival extension of 1.8 months may be regarded clinically relevant.

Limitations of TAS-102 result from the low response rate, indicating that rather than tumor shrinkage, transient stabilization of the disease is achieved. Despite the increase in adverse events, the drug is considered safe and a valid option in fit patients to prolong survival alongside Regorafenib.[114]

Regorafenib versus TAS-102

A central question in this thesis is whether or when Regorafenib or TAS-102 should be preferred for the treatment of mCRC in third or later line of therapy in a real-world setting. According to the guidelines, the level of evidence for both agents is the same. Neither the 2019 AMWF S3 Guideline for CRC, nor the 2021 NCCN Clinical Practice Guidelines for CRC prescribe a general preference nor a recommendation for subgroups and specific sequence, making the approach challenging for physicians in the clinic.[119, 120]

Detailed results of meta-analyses and systematic reviews convey useful data on this topic. A first systematic review was published in 2018 by Abraho et al. to indirectly compare TAS-102 with Regorafenib. Only RCTs and therapy-refractory patient populations were included. These criteria were met by the earlier discussed “CORRECT”, “CONCUR”, and “RECOURSE” studies, amounting to 1764 patients. The result of the analysis revealed no significant distinguishable outcomes regarding OS, PFS, ORR or DCR. Yet, there was an elevated incidence of grade 3 to 5 AEs seen in the Regorafenib group.[121]

A subsequent systematic review published in 2019 delves further into the issue. The eligibility criteria involved RCTs testing TAS-102 or Regorafenib in therapy-refractory mCRC. Ultimately, 6 studies were included, expanding the total population size to 2445 patients. The emphasis of the comparison was on the endpoints OS, PFS, AEs, and QoL. Of the 6 RCTs, 3 compared TAS-102 with BSC, of which two were phase lll and one was a phase ll trial. Two other phase lll studies looked at Regorafenib 160 mg (full dose) vs BSC and the phase ll “ReDOS” study compared Regorafenib 80mg+ (dose escalation) with Regorafenib 160mg and BSC. The results did not yield a significant difference for Regorafenib 160mg vs. TAS-102 in OS and PFS outcomes. Astonishingly, no survival disadvantage was observed between the dose escalation strategies Regorafenib 80mg+ versus Regorafenib

160mg/TAS-102. The AE profiles of TAS-102 and Regorafenib were found different but with comparable magnitude, while less grave QoL impairment was identified for the Regorafenib 80mg+ dose escalation strategy.[122, 123]

TAS-102+Bevacizumab

TAS-102 in combination with Bevacizumab demonstrated the potential to become the new standard of care for advanced colorectal cancer in the 2023 “SUNLIGHT” study. This study assigned 246 patients each into a TAS-102 alone and a TAS-102+Bevacizumab (TAS-102+Bev) group. The combination group not only showed an extension in OS from 7.5 to 10.8 months, but also postponed a worsening of the ECOG by one or more points by an average of 3 months compared to the monotherapy group.[1]

Chemotherapeutic rechallenge

Since the response and efficacy of Regorafenib and TAS-102 are limited, a rechallenge of standard chemotherapeutics previously used in the course of the disease has been frequently tried in routine clinical practice. However, there is limited scientific evidence supporting the concept of chemotherapy rechallenge after previous progression. There were a few retrospective analyses performed in 2017-2019 suggesting an Oxaliplatin/Irinotecan+Fluoropyrimidine rechallenge to be equal or better than Regorafenib/TAS-102 in safety and efficacy endpoints. However, the purely retrospective nature and small sample size limit their significance, which is why prospective randomized trials are urgently needed to deliver more profound evidence.[124–126]

EGFR-mABs rechallenge

The phase II “CHRONOS” trial went a step further in 2019. Prior to administration of a rechallenge with EGFR-antibodies, a liquid biopsy (ctDNA) was taken and tested for RAS, BRAF and EGFR ectodomain wt. Thereupon, only patients who were considered sensitive to anti-EGFR rechallenge were treated.

The liquid biopsy of 52 patients were used for screening, of which 37 tested RAS/BRAF-wt. Of these, 27 patients received the EGFR-antibody Panitumumab. The primary endpoint ORR of 30% was met, DCR was obtained in 40% and the median PFS was 4 months. This suggests that liquid biopsy-driven rechallenge with anti-EGFR antibodies may improve objective responses compared with standard late line treatment of mCRC.[127]

Fruquintinib

Regorafenib and TAS-102 are still considered the standard of care in late-line therapy of mCRC, but ongoing research is still meticulously pursuing improvements in this field. One substance that could compete with the established agents is the highly specific VEFGR-blocker Fruquintinib.

The 2018 “FRESCO-1” study was conducted in China on 416 patients with mCRC, who had received at least two standard palliative treatment lines beforehand. Compared to placebo, OS improved from 6.6 months to 9.3 months, and PFS improved from 1.8 months to 3.7 months in the Fruquintinib group. Furthermore, the study provided an ORR of 4.7% and safety standards were adhered.[128]

Based on these findings, approval was cleared in the same year by the National Medical Products Administration (NMPA) in China, as was a fast-track designation grant by the FDA and the initiation of the “FRESCO-2” study brought under way.[129, 130]

The “FRESCO-2” study was tested under comparable conditions in a global population. It substantiated that Fruquintinib results in a significant survival benefit with manageable toxicities over placebo.[131, 132] Importantly, in this trial also patients with previous Regorafenib and/or TAS-102 treatment were included, which supports the use of Fruquintinib in last line setting.

In 2019, a systematic review assessed the efficacy and safety of Fruquintinib compared with the standard of care, Regorafenib and TAS-102. 5 RCTs with 2604 patients matched the inclusion criteria. However, only the first “FRESCO” trial, which was confined to China, provided data regarding Fruquintinib, as FRESCO-2 was still pending. Nonetheless, the network analysis showed, that Fruquintinib was

significantly superior to Regorafenib and TAS-102 in terms of PFS and DCR. ORR and OS, however, were comparable, while Fruquintinib led to more serious AEs.[133]

Based on these study results, Fruquintinib was approved by the FDA on November 8, 2023, for the treatment of mCRC for patients with exhausted standard pre-treatment.[134]

Material and Methods

Study Aim

The purpose of this retrospective cohort study was to compare the clinical efficacy of TAS-102, TAS-102+Bev and Regorafenib as palliative therapy for mCRC in a real-world setting. For this purpose, the medical records of all patients with metastatic adenocarcinoma of the colon who were treated with either TAS-102, TAS-102+Bev or Regorafenib at the Department of Oncology of the Medical University of Graz in the period from January 1, 2016, to September 30, 2023, were screened in depth to obtain all relevant data.

Endpoints

The primary endpoints of the study were the disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) under therapy with either TAS-102, TAS-102+Bev or Regorafenib. The OS was measured from start of treatment until death or last day of life. The PFS was defined as the time period from the start of treatment to radiographic disease progression, clinical progression or to death, whatever came first. The DCR was defined as a composite of radiographic complete or partial remission or stable disease, in analogy to current RECIST criteria.

Data acquisition & documentation

For data collection, the hospital's electronic health database MEDOCS, archived personal health records, and the in-house pharmacy prescription program were mined. Each patient's medical record was captured in an online database and documented in detail using REDCap software.

A total of 179 patients were documented, and 937 data points were queried per case. These included demographic data such as age, gender, comorbidities and performance status, tumor-specific data including the primary tumor localization,

histology, grading, and the molecular tumor profile, as well as comprehensive data on the treatment and disease course.

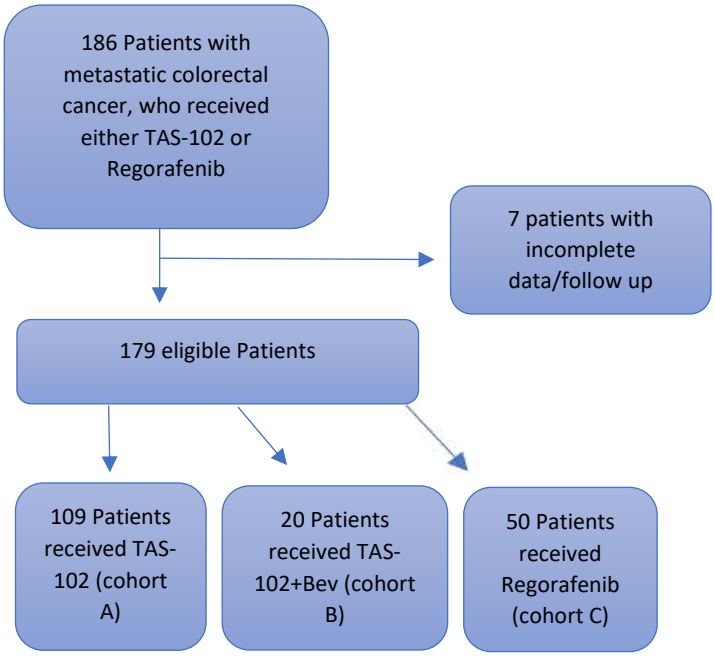
To keep these data sets organized, they were compartmentalized into 18 sub-forms to provide quick access to targeted sub-items. These are as follows:

→Baseline characteristics, Curative neoadjuvant CTX, Curative neoadjuvant RCTX, Cur. Induction CTX (primary metastasis), Cur. Surgery, Cur. Adjuvant CTX, Cur. pseudoadjuvant CTX, Recurrence, Recurrence 2, Molecular diagnostics, Palliative First Line Antineoplastic Therapy, Palliative Second Line Antineoplastic Therapy, Palliative Third Line Antineoplastic Therapy, Palliative Fourth Line Antineoplastic Therapy, Palliative Fifth Line Antineoplastic Therapy, Palliative Sixth Line Antineoplastic Therapy, Palliative surgery, End Of Life.

Study cohort

All patients with histologically confirmed, locally advanced metastatic colon or rectal cancer who were treated at the Department of Oncology at the Medical University of Graz in the period from January 1, 2016, to September 30, 2023, who have received at least one cycle of palliative therapy with either Regorafenib or TAS-102 (single agent or combined with Bevacizumab) were included. The minimum age was 18 years. Both men and women were eligible. Patients missing key treatment data (e.g. start date, end date) or who were lost to follow up were excluded. Baseline characteristics of the patient population were obtained from the start of treatment.

Figure 2: Flow chart study enrolment



Ethics declaration

Prior to data collection and patient-related analysis, this study was approved by the local ethics committee (Ethics Committee of the Medical University of Graz, Austria; EK number 33-380 ex 20/21). All investigations and analyses were performed in strict compliance with local, national, and international guidelines for ethical conduct in medical research involving human subjects.

Statistical analysis

Descriptive statistics of baseline characteristics were assessed for the overall population and the three treatment cohorts (TAS-102, TAS-102+Bev and Regorafenib). Absolute and relative frequencies of missing data for each variable were reported. Distributions of continuous variables were summarized by the median and corresponding 25^{th} and 75^{th} percentiles. Categorical variables were reported as absolute and relative frequencies. Analysis of Variance (ANOVA) was applied to evaluate differences of continuous variables with normal distribution between the three treatment cohorts, while the Kruskal-Wallis test was used for non-

parametric samples. Normality was assessed by graphical methods and normality tests such as the Shapiro Wilk test. Proportions of categorical variables were compared by the chi2 and fisher-exact tests depending on the sample size of each group. Survival estimates of the OS and PFS were assessed by the Kaplan Meier method and compared by log-rank tests. A uni- and multivariable Cox regression model was implemented to evaluate the association of clinicopathologic risk factors with the OS. Variables included in the multivariable model were selected based on clinical reasoning (established prognostic markers) and observed associations in the univariable model. All statistical analyses were conducted with Stata 17.0 (Stata Corp., Houston, TX, USA).

Results

Baseline characteristics of the study cohort

A total of 179 patients were included in the study **(Table 10)**. Of these, 109 were treated with TAS-102, 20 with TAS-102+Bev and 50 with Regorafenib.

60.9% of the study cohort were male and 39.1% were female. The median age was 65 years, with significant differences being observed between the three treatment cohorts. In detail, it was 67 years in the TAS-102 group, 66 years in the TAS-102+Bev group and 61 years in the Regorafenib group (p=0.006).

The Charlson Comorbidity Index was 4 or higher in more than 40% of patients. At 47.7%, the rate of these patients tended to be higher in the TAS-102 group than in the TAS-102+Bev (30%) and Regorafenib groups (28%), however the difference between the three groups did not reach statistical significance. (p=0.068). In terms of the ECOG performance status, significant differences were observed between the treatment groups. Patients treated with Regorafenib were more likely to have and ECOG performance status of 0 (64%), than patients treated with TAS-102+Bev (45%) and patients treated with TAS-102 (40%) (p=0.026).

The primary tumor was most commonly located in the rectum (36.9%), followed by the sigmoid (26.8%) and the ascending colon/cecum (11.7% each). Overall, there was a predominance of left sided tumors (72%). No significant differences of primary tumor location between the cohorts were observed.

Most patients had multiple metastatic organs at the time of treatment start. In detail, 37.4% of patients had metastases in two regions and 39.7% in three or more regions. The most common sites of metastasis were the liver (present in 76%) and the lung (present in 61.5%). Almost half of the patients had their primary tumor in situ and 21.2% presented with peritoneal carcinomatosis.

Biomolecular RAS-status was assessed in 177 patients (98.9%). Of these, 58.2% were KRAS mt and 2.8% NRAS mt, leaving 39% RAS wt. The prevalence of KRAS mt significantly differed between the treatment groups (p=0.01). At a rate of 66% it was highest in the Regorafenib group compared to 55% in the TAS-102 and TAS-102+Bev groups each. Similarly, out of a total of 5 NRAS-mutations, 4 were found

in the Regorafenib group. Additional subtyping of KRAS mutations revealed KRAS-G12 codon mt in 35.2% of all patients tested, followed by KRAS-G13 mt in 11.7%. Further sequencing results revealed a BRAF-V600E mt in 9 patients (5.8%), microsatellite instability in 3 patients (2.1%), a Tp53 mt in 50 patients (53.8%) and a PIK3CA mt in 18 patients (19.4%).

In 62% of patients, a primary curative treatment goal was set, while 38% of patients presented with unresectable advanced stage disease at time of diagnosis. 54.2% of patients received curative surgery of the primary tumor and 27.4% additionally underwent adjuvant chemotherapy. 15.1% of patients underwent local treatment of metastases such as surgical metastasectomy or local ablation. Induction chemotherapy, to achieve resectability, was carried out in 12.3% of patients. Neoadjuvant combined radio-chemotherapy was exclusively reserved for rectal cancer and was carried out in 14.5% of cases. No major differences of previous curative treatment approaches were observed between the three treatment cohorts.

All treatment groups were heavily pretreated, with 78.6% of patients having received two or more lines of palliative therapy and the remaining 22.4% having received at least one line of palliative therapy. The most commonly used agents in prior palliative therapy lines were Fluoropyrimidines (93.9%), Irinotecan (76%), VEGF-inhibitors (73.7%), Oxaliplatin (62%) and EGFR-inhibitors (36.9%). Patients treated with TAS-102+Bev were more likely of having received only one prior line of palliative therapy than the other treatment groups, however this did not reach statistical significance. Nevertheless, the three treatment groups showed significant differences regarding prior use of 5-FU ($p=0.004$), Oxaliplatin ($p=0.026$) and Irinotecan ($p=0.002$).

Other baseline characteristics including the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19 (CA-19) were equally distributed between the three treatment groups.

Table 10: Baseline characteristics of the study cohort (n=179). Distribution overall and by treatment cohorts. Values are medians [25-75th percentile] for continuous data and absolute frequencies (% column) for count data. n (%miss.) shows the number of patients with fully observed records for the respective variable (% missing).

Variable	n (% miss.)	Overall (n=179)	TAS-102 (n=109)	TAS-102+Bev (n=20)	Regorafenib (n=50)	p
Demographics at baseline						
Age [years]	179 (0%)	65 [57-72]	67 [59-73]	66 [56-72]	61 [52-67]	**0.006**
Gender	179 (0%)	/	/	/	/	/
Female gender	/	70 (39.1%)	48 (44%)	7 (35%)	15 (30%)	0.22
Male gender	/	109 (60.9%)	61 (56%)	13 (65%)	35 (70%)	
Weight [kg]	174 (2.8%)	72.5 [62-84]	71.5 [61-85]	72 [59.5-83.5]	75 [65-85]	0.54
BMI [kg/m²]	174 (2.8%)	24.6 [21.8-27.5]	24.5 [21.6-27.5]	24.5 [20.3-26.8]	24.6 [22.2-28.5]	0.71
Charleson Comorbidity Index (CCI)	179 (0%)	/	/	/	/	/
--CCI 0,1	/	35 (19.5%)	16 (14.7%)	4 (20%)	15 (30%)	0.068
--CCI 2,3	/	72 (40.2 %)	41 (37.6%)	10 (50%)	21 (42%)	
--CCI >=4	/	72 (40.2 %)	52 (47.7%)	6 (30%)	14 (28%)	
Performance status	175 (2.2%)					
--ECOG 0	/	83 (47.4%)	42 (40%)	9 (45%)	32 (64%)	**0.026**
--ECOG 1	/	82 (46.9%)	54 (51.4%)	10 (50%)	18 (36%)	
--ECOG 2-3	/	10 (5.7%)	9 (8.6%)	1 (5%)	0 (0%)	
Tumor variables						
Location of primary	179 (0%)	/	/	/	/	/
--Coecum	/	20 (11.2%)	11 (10.1%)	5 (25%)	4 (8%)	0.53
--C. ascendens	/	21 (11.7%)	14 12.8(%)	2 (10%)	5 (10%)	
--Flex. col. dex.	/	3 (1.7%)	3 (2.8%)	0 (0%)	0 (0%)	
--C. transversum	/	6 (3.4%)	3 (2.8%)	2 (10%)	1 (2%)	
--Flex. col. sin	/	4 (2.2%)	1 (1%)	1 (5%)	2 (4%)	
--Sigma	/	48 (26.8%)	28 (25.7%)	3 (15%)	17 (34%)	

--Rectum	/	66 (36.9%)	42 (38.5%)	7 (35%)	17 (34%)	
--C. descendens	/	3 (1.7%)	2 (1.8%)	0 (0%)	1 (2%)	
--Rectosigmoidal	/	8 (4.5%)	5 (4.6%)	0 (0%)	3 (6%)	
Tumor Side	179 (0%)	/	/	/	/	/
--right	/	50 (28%)	31 (28.4%)	9 (45%)	10 (20%)	0.11
--left	/	129 (72%)	78 (71.6%)	11 (55%)	40 (80%)	
Metastasis status	179 (0%)	/	/	/	/	/
--M0	/	77 (43%)	50 (45.9%)	8 (40%)	19 (38%)	0.62
--M1	/	102 (57%)	59 (54.1%)	12 (60%)	31 (62%)	
Molecular biological data						
RAS mutation testing performed?	177 (1.1%)	/	/	/	/	/
--wildtype	/	69 (39%)	48 (44.9%)	8 (40%)	13 (26%)	**0.01**
--KRAS mutation	/	103 (58.3%)	59 (55.1%)	11 (55%)	33 (66%)	
--NRAS mutation	/	5 (2.8%)	0 (0%)	1 (5%)	4 (8%)	
KRAS mutation type	177 (1.1%)	/	/	/	/	/
--wildtype	/	78 (43.6%)	52 (47.7%)	9 (45%)	17 (34%)	0.61
--g12	/	63 (35.2%)	34 (31.2%)	8 (40%)	21 (42%)	
--g13	/	21 (11.7%)	12 (11%)	1 (5%)	8 (16%)	
--other	/	17 (9.5%)	11 (10.1%)	2 (10%)	4 (8%)	
BRAF-V600E mutation	154 (14%)	9 (5.8%)	5 (5.2%)	3 (15%)	1 (2.6%)	0.16
MMR deficiency (MSI-H)	140 (21.8%)	3 (2.1%)	2 (2.4%)	0 (0%)	1 (2.7%)	1
Tp53 mutation	93 (48%)	50 (53.8%)	32 (55.2%)	5 (50%)	13 (52%)	0.95
PIC3CA mutation	93 (48%)	18 (19.4%)	13 (22.4%)	2 (20%)	3 (12%)	0.53
Disease extent						
Tumor burden at start of therapy	179 (0%)	/	/	/	/	/
--metastasis in 1 site	/	41 (22.9%)	26 (23.9%)	6 (30%)	9 (18%)	0.56
--metastasis in 2 sites	/	67 (37.4%)	44 (40.4%)	6 (30%)	17 (34%)	

--metastasis in >=3 sites	/	71 (39.7%)	39 (35.8%)	8 (40%)	24 (48%)	
Tumor sites at start of therapy						
--primary (colon)	179 (0%)	83 (46.4%)	52 (47.7%)	8 (40%)	23 (46%)	0.82
--peritoneum	179 (0%)	38 (21.2%)	22 (20.2%)	7 (35%)	9 (18%)	0.27
--liver	179 (0%)	136 (76%)	82 (75.2%)	13 (65%)	41 (82%)	0.31
--lung	179 (0%)	110 (61.5%)	66 (60.6%)	11 (55%)	33 (66%)	0.66
Previous curative treatment						
Primary treatment setting	179 (0%)	/	/	/	/	/
--curative	/	111 (62%)	65 (59.6%)	14 (70%)	32 (64%)	0.64
--palliative	/	68 (38%)	44 (40.4%)	6 (30%)	18 (36%)	
Neoadjuvant RCTX	179 (0%)	26 (14.5%)	12 (11%)	6 (30%)	8 (16%)	0.08
Induction CTX	179 (0%)	22 (12.3%)	14 (12.8%)	1 (5%)	7 (14%)	0.66
Surgery of primary	179 (0%)	97 (54.2%)	58 (53.2%)	12 (60%)	27 (54%)	0.85
Adjuvant CTX	179 (0%)	49 (27.4%)	28 (25.7%)	7 (35%)	14 (28%)	0.69
Local treatment of metastasis	179 (0%)	27 (15.1%)	12 (11%)	5 (25%)	10 (20%)	0.14
Pseudoadjuvant CTX	179 (0%)	16 (8.9%)	9 (8.3%)	3 (15%)	4 (8%)	0.54
Previous palliative treatment						
Previous lines of therapy	179 (0%)	/	/	/	/	/
--<=1	/	40 (22.4%)	24 (22%)	7 (35%)	9 (18%)	0.58
--2	/	67 (37.4%)	42 (38.5%)	7 (35%)	18 (36%)	
--3	/	46 (25.7%)	30 (27.5%)	4 (20%)	12 (24%)	
-->=4	/	26 (14.5%)	13 (12%)	2 (10%)	11 (22%)	
--5FU	179 (0%)	168 (93.9%)	104 (95.4%)	15 (74%)	49 (98%)	**0.004**
--Oxaliplatin	179 (0%)	111 (62%)	69 (63.3%)	7 (35%)	35 (70%)	**0.026**
--Irinotecan	179 (0%)	136 (76%)	81 (74.3%)	10 (50%)	45 (90%)	**0.002**
--VEGF	179 (0%)	132 (73.7%)	77 (70.6%)	11 (55%)	44 (88%)	**0.008**
--EGFR	179 (0%)	66 (36.9%)	46 (42.2%)	7 (35%)	13 26(%)	0.142

Laboratory parameters at baseline						
Neutrophil to lymphocyte ratio	173 (3.4%)	3.4 [2.3-5.1]	3.4 [2.2-4.9]	4.5 [3.3-5.6]	3.2 [2.3-5.5]	0.32
CEA	164 (19.6%)	52 [11-254]	65.4 [9.7-253]	42.8 [15.5-445]	44.9 [11.7-270]	0.94
CA-19	139 (22.4%)	102 [19-990]	166 [24-1015]	223 [10-3060]	60.4 [12-348]	0.15

Response rates

In the overall cohort the ORR was 2.3%, no patient showed a complete tumor remission. 81.3% of patients experienced primary disease progression either in form of radiographic disease progression (51.46%) or clinical deterioration (29.82%). TAS-102+Bev resulted in the highest ORR (10%) compared to TAS-102 (2%) and Regorafenib (0%) (p=0.033).

Figure 3: Response rates: TAS-102

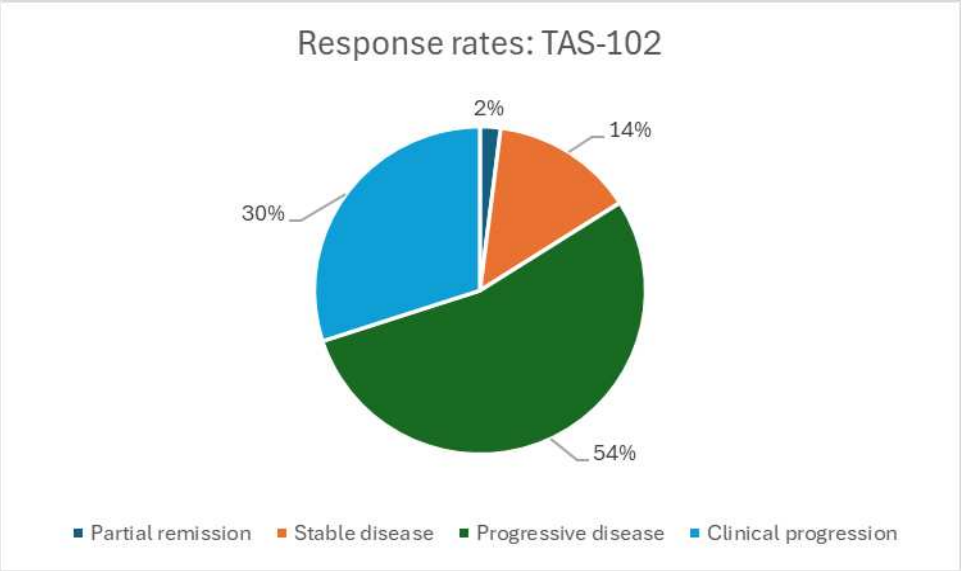


Figure 4: Response rates: TAS-102+Bev

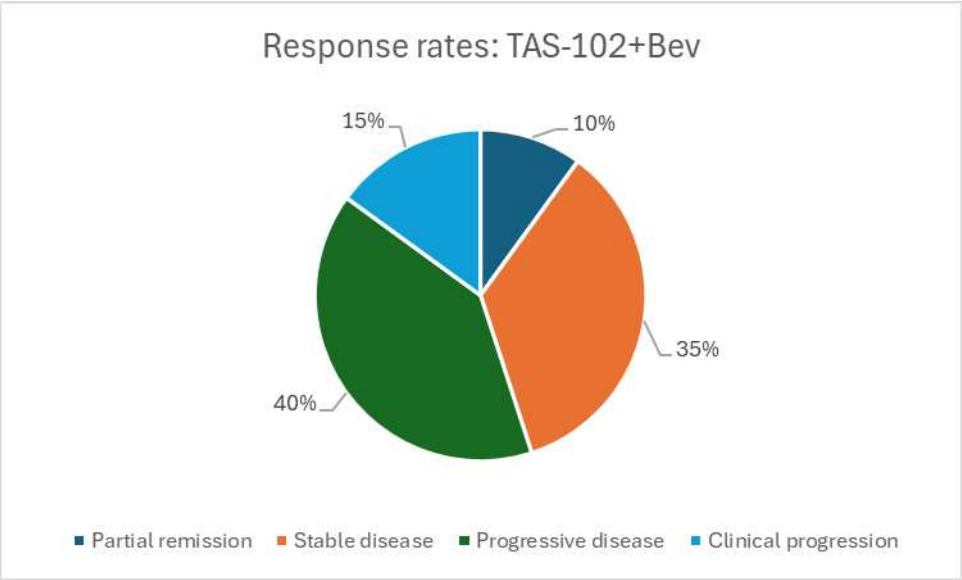
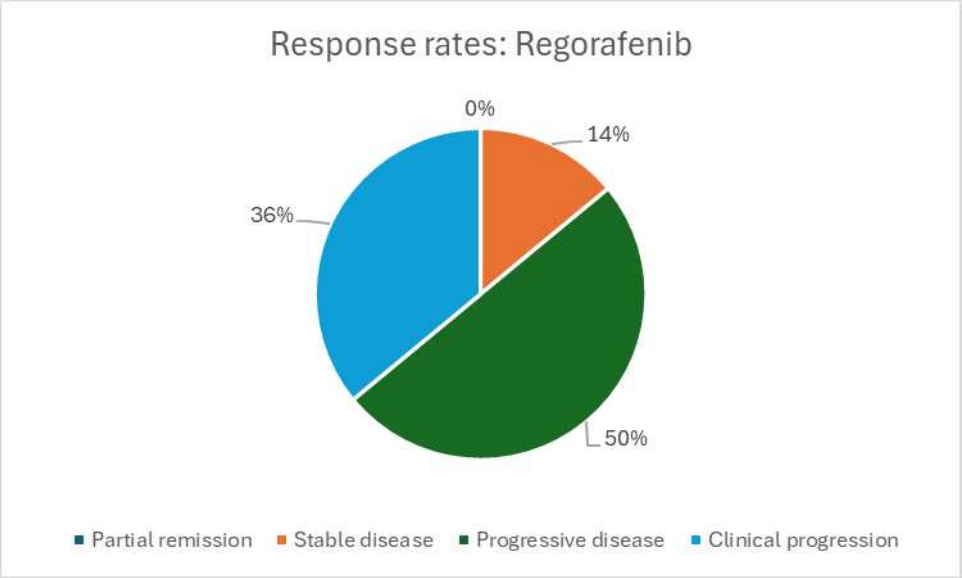


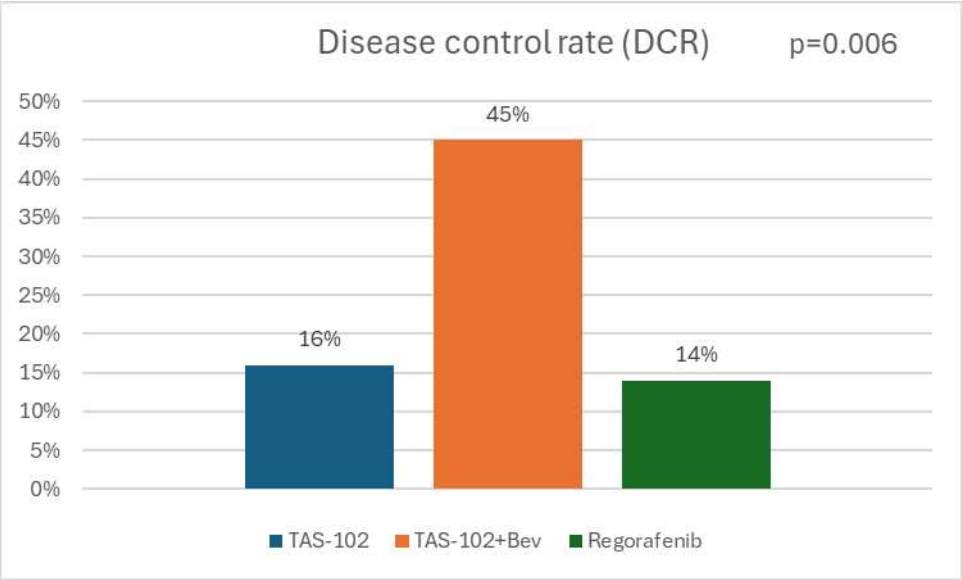
Figure 5: Response rates: Regorafenib



Disease control rate (DCR)

The DCR was highest for TAS-102+Bev at a rate of 45% compared to 16% for TAS-102 and 14% for Regorafenib (p=0.006).

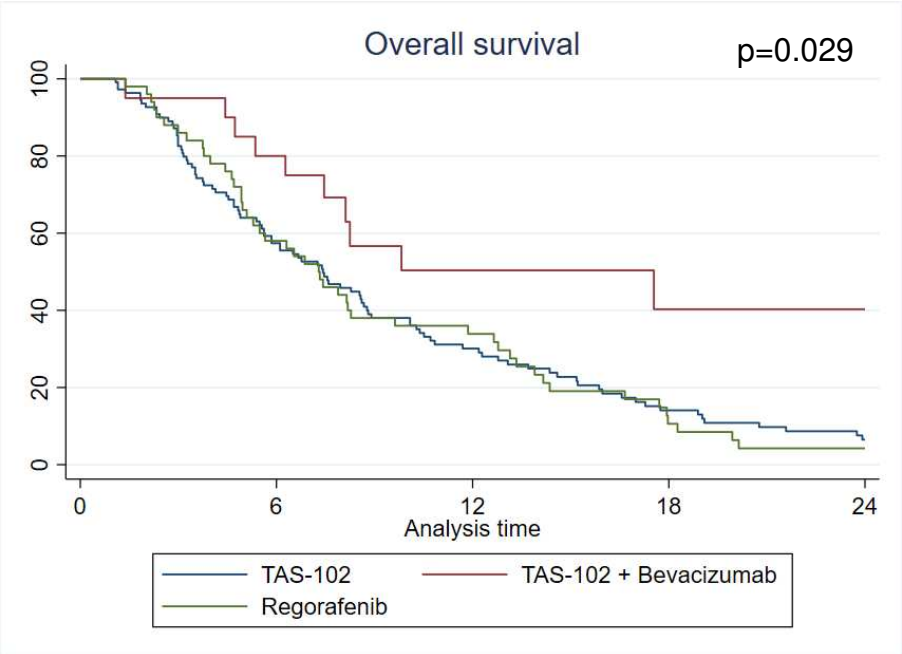
Figure 6: Disease control rate (DCR)



Overall survival (OS)

The median OS was 17.5 (95% CI: 6.3-not evaluated) months with TAS-102+Bev, 7.4 (95% CI: 5.6-8.7) months with TAS-102 and 7.3 (95% CI: 5.1-9.6) months with Regorafenib. Significant differences of OS were observed between the three treatment groups (p=0.029).

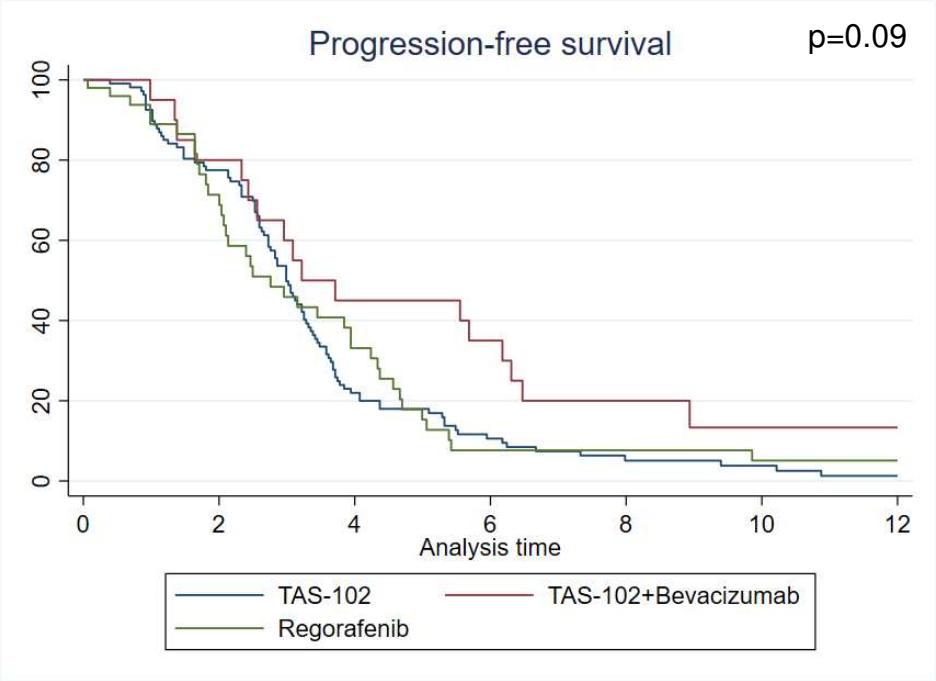
Figure 7: Overall survival of TAS-102, TAS-102+Bev and Regorafenib



Progression-free survival (PFS)

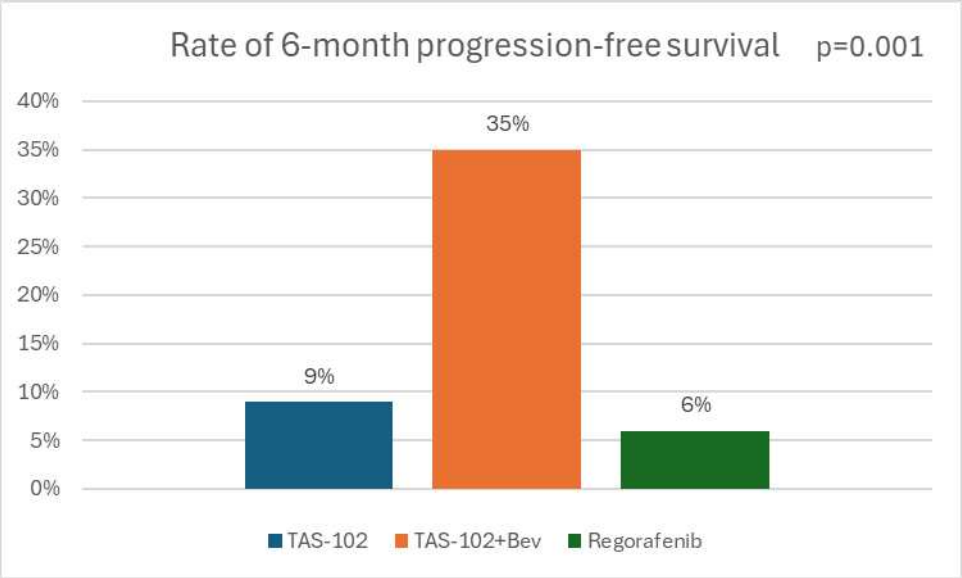
The median PFS was 3.2 (95% CI: 2.3-6.3) months in the TAS-102+Bev group, 3 (95% CI: 2.7.-3.3) months in the TAS-102 group and 2.8 (95% CI: 2-3.9) months in the Regorafenib group (p=0.09).

Figure 8: Progression-free survival of TAS-102, TAS-102+Bev and Regorafenib



The 6-month PFS rate was highest for the TAS-102+Bev group at a rate of 35% compared to 9% for TAS-102 and 6% for Regorafenib (p=0.001).

Figure 9: 6-months-PFS of TAS-102, TAS-102+Bev and Regorafenib



Uni- and multivariable Cox regression analysis of OS

A univariable and multivariable Cox proportional hazards model for OS was conducted to identify potential prognostic biomarkers and to account for confounding. The following variables were included: Treatment type (TAS-102, TAS-102+Bev, Regorafenib), age, ECOG performance status, side of primary tumor, number of previous therapy lines, metastasis status, tumorburden, prevalence of peritoneal and liver metastasis and level of the tumormarker CEA.

Univariable Cox regression analysis showed, that the type of treatment, the number of palliative therapy lines, the prevalence of synchronous metastases, the tumor burden, the presence of peritoneal and liver metastases and levels of CEA were significantly associated with OS. These variables were therefore subjected to the multivariable analysis to adjust for potential confounding **(Table 11).**

Accounting for imbalances between the three treatment groups in the multivariable analysis, the adverse outcome observed in patients treated with TAS-102 and

Regorafenib single agent therapy compared to TAS-102+Bev combination therapy was fully confirmed. In detail the risk of death was 2.9 times higher for TAS-102 alone (HR: 2.9; 95% CI: 1.3-6.5; p=0.009) and 3.2 times higher for Regorafenib (HR: 3.2; 95% CI: 1.4-7.3; p=0.008).

Other independent factors associated with an increased risk of death included a higher tumor burden (HR for two metastatic organs compared to one metastatic organ : 2.7; 95% CI: 1-2.7; p=0.044), the prevalence of peritoneal (HR: 3.4; 95% CI: 1.9-5.9; p=<0.001) and liver (HR: 1.8; 95% CI: 1.1-2.9; p=0.011) metastases and higher baseline CEA levels (HR per doubling of CEA: 1.1; 95% CI: 1.1-1.3; p=<0.001) **(Table 11).**

Table 11: Uni- and multivariable predictors of OS

Variable	**Univariable analysis**		**Multivariable analysis**	
	HR (CI 95%)	**p**	**HR (CI 95%)**	**p**
Treatment cohort				
--TAS-102+Bevacizumab	1 (reference)	/		
--TAS-102)	2.3 (1.2-4.4)	**0.013**	2.9 (1.3-6.5)	**0.009**
--Regorafenib	2.4 (1.2-4.7)	**0.013**	3.2 (1.4-7.3)	**0.008**
Age (per 10 years increase)	0.99 (0.97-1.01)	0.3	1 (0.98-1.02)	0.825
ECOG				
--ECOG 0	1 (reference)	/		
--ECOG 1	1.2 (0.8-1.6)	0.36	1.2 (0.8-1.9)	0.321
--ECOG 2	1 (0.5-2.3)	0.92	0.8 (0.3-2.1)	0.626
Side of primary				
--right	1 (reference)	/		
--left	0.8	0.26	0.9 (0.6-1.5)	0.777
Previous therapy lines				
--0-1	1 (reference)	/		
--2	1.8 (1.2-2.8)	**0.008**	1.5 (0.9-2.5)	0.148
--3	1.3 (0.8-2.2)	0.22	1.3 (0.8-2.3)	0.306
-->=4	1.3 (0.7-2.2)	0.36	1.2 (0.7-2.3)	0.524

Metastasis status				
--M0	1 (reference)	/		
--M1	1.6 (1.1-2.2)	**0.006**	1.1 (0.8-1.7)	0.532
Tumorburden				
--1	1 (Reference)	/		
--2	1.7 (1.1-2.6)	**0.019**	1.7 (1-2.7)	**0.044**
-->=3	1.7 (1.1-2.7)	**0.012**	0.9 (0.5-1.6)	0.781
Location of metastasis				
peritoneum	2.2 (1.5-3.3)	**<0.001**	3.4 (1.9-5.9)	**<0.001**
liver	1.9 (1.3-2.9)	**0.001**	1.8 (1.1-2.9)	**0.011**
CEA laboratory levels (per doubling)	1.1 (1.1-1.2)	**<0.001**	1.1 (1.1-1.3)	**<0.001**

Further palliative therapy

After initial palliative treatment with either TAS-102, TAS-102+Bev or Regorafenib, a total of 84 (46.9%) patients received further palliative antineoplastic therapy. Of these, 60 (33.5%) received one further line of therapy and 24 (13.4%) received two or more additional therapy lines. TAS-102 single agent therapy was associated with the lowest rate of subsequent palliative therapy at a rate of 39% **(**Fehler! Verweisquelle konnte nicht gefunden werden.**).**

Almost half of the patients (48%) treated with Regorafenib received subsequent TAS-102, while Regorafenib was applied in 45% after TAS-102+Bev and in 23% after TAS-102 single agent therapy.

Figure 10: Amount of further therapy lines

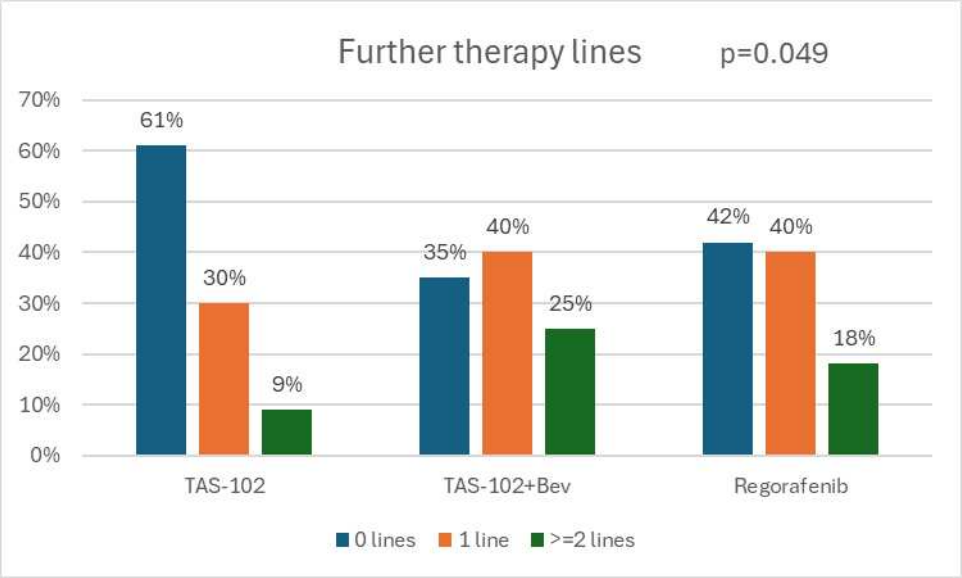
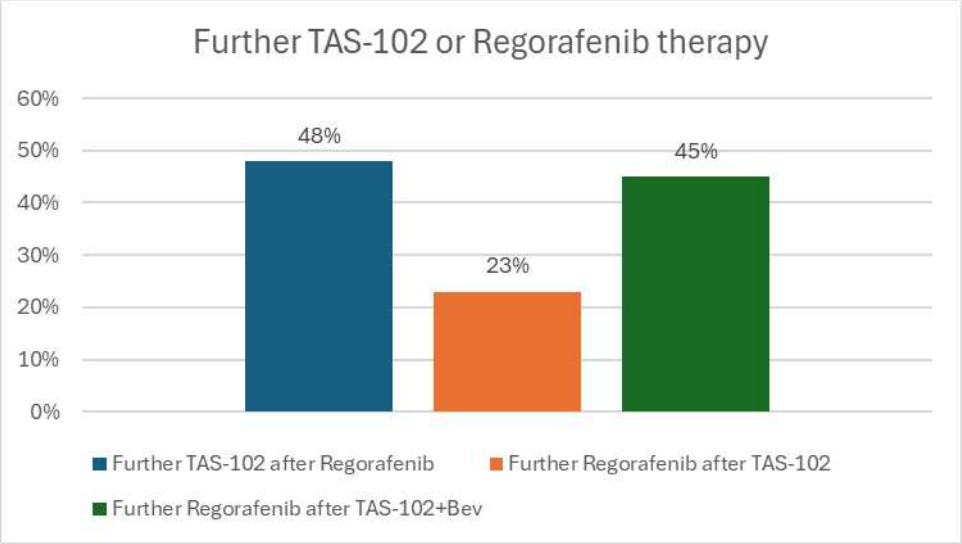


Figure 11: Further TAS-102 or Regorafenib therapy



Discussion

To date, there already exists a randomised controlled trial comparing TAS-102 with the combination therapy TAS-102+Bev in the salvage line treatment of mCRC.[1] In addition to strong evidence from RCTs, real-world data is essential to assess the effectiveness of this treatment in routine clinical practice. A significant proportion of patients with mCRC do not meet the inclusion criteria of the approval trials due to their age, multimorbidity, excessive tumor burden or their general unsuitability for standard therapy, but to date limited data exists on real-world treatment patterns and outcomes in patients with mCRC who have exhausted standard first and second line therapy options. In the present study, we sought to supplement the insufficient comparative data by performing a multivariate Cox regression-adjusted comparative effectiveness analysis of real-world outcomes of 179 patients treated with either TAS-102, TAS-102+Bev or Regorafenib.

In unadjusted analysis, the combination of TAS-102+Bev showed improved clinical effectiveness exemplified by a higher ORR and DCR and a significantly increased OS compared to the TAS-102 and Regorafenib single-agent groups. While the difference of the PFS between the treatment groups did not reach statistical significance, TAS-102+Bev was still associated with the best outcome among them. Notable, the baseline characteristics of the three treatment cohorts were not entirely congruent. In terms of age and ECOG, the Regorafenib group was favoured, while the TAS-102 group showed a higher rate of comorbidities. RAS mutations were observed more frequently in the Regorafenib group. The tumor burden was almost evenly distributed, with the TAS-102+Bev group exhibiting a larger number of patients with right-sided tumors. Crucially, TAS-102+Bev was administered more frequently to patients who had received only one prior palliative therapy line. Importantly, after adjustment for potential confounding factors including age, ECOG performance status, tumor side, previous therapy lines, metastasis status, tumor burden, location of metastasis and CEA levels using a multivariable Cox regression analysis, the positive treatment effect of TAS-102+Bev on OS was not attenuated and remained statistically significant.

At present the landmark 2023 “SUNLIGHT” study by Prager et al. is the only phase III trial to evaluate the survival benefit of the combination of TAS-102+Bev in

refractory mCRC, compared to third-line standard TAS-102. The results for OS in our study were almost identical to the “SUNLIGHT” study for the TAS-102 single agent group. Interestingly, for the TAS-102+Bev combination group, the OS estimate in our study exceeded the OS in the “SUNLIGHT” trial (17.5 vs. 10.8 months), while the PFS was shorter. The different survival times in the cross-study comparison are most likely related to different study inclusion criteria. While the “SUNLIGHT” trial only enrolled patients in the palliative third line or beyond, for our analysis we also included patients who were considered unsuitable for standard first and second line regimens and therefore received TAS-102±Bev or Regorafenib in earlier lines. Other factors that might have impacted the long OS estimate in the drug combination group in our study include the relatively small sample size for the combination group (20 versus 214 patients in "SUNLIGHT") and the retrospective nature of a cohort study which harbors the risk of loss of follow up.[1]

When comparing OS and DCR outcomes of TAS-102 and Regorafenib single agent therapy in our study to the respective approval trials, “RECOURSE” for TAS-102 and “CORRECT” for Regorafenib comparable outcomes are observed. The “RECOURSE” trial documented an OS of 7.1 months for TAS-102, which closely aligns with the 7.4 months in our study but reported a higher DCR (44% vs 16%). Similarly, the “CORRECT” trial showed an OS of 6.4 months for Regorafenib vs. 7.3 months in our study, while the DCR was 45% compared to 14% in our study. The higher DCR observed in the prospective clinical trials compared to our study can again be partly explained by the pre-selection of patients with favourable prognostic characteristics such as lower age within the setting of an RCT.[109, 118]

At the start of data acquisition for this study, there was very limited evidence on the clinical effectiveness of TAS-102+Bev in the treatment of mCRC. This changed with the publication of the randomized phase 3 “SUNLIGHT” trial, which demonstrated superiority of TAS-102+Bev over TAS-102 alone. Still, real-world clinical outcome data for this new regiment are highly relevant to validate the clinical robustness of the combination therapy.[135–137] Moreover, our study provides survival estimates separately for all three treatment groups (TAS-102, TAS-102+Bev and Regorafenib), evaluates their effectiveness also in patients not eligible for clinical trials and to the best of our knowledge is the first retrospective cohort study to investigate the subsequent use of TAS-102 and Regorafenib for this cohort.

A recently published retrospective cohort study by Kagawa et al. compared TAS-102+Bev versus TAS-102/Regorafenib utilizing an extensive Japanese real-world clinical dataset of 3574 patients who had received standard of care. The OS in the pooled TAS-102 and Regorafenib cohort was 11.6 months (versus 7.4 months for TAS-102 and 7.3 months for Regorafenib in our study), while survival in the TAS-102+Bev group (17 months) was almost identical to our study (17.5 months). Although baseline characteristics were not fully comparable to our study, the highly similar OS provides further support for the real-world effectiveness of TAS-102+Bev and underlines the validity of our data.[135] Similar studies from Arrichiello et al. analysed survival estimates of 31 patients who had received TAS-102+Bev, while Kotani et al. compared the effectiveness of TAS-102+Bev based on the outcomes of 60 patients against 66 who had received TAS-102 alone. Baseline characteristics of these studies were not entirely consistent with our data. TAS-102+Bev in these studies were more likely to have an ECOG performance status of 0 (100% (Arrichiello et al.) vs. 58% (Kotani et al.) vs. 45% (our study)) and had a lower rate of right sided tumors (23% (Arrichiello et al.) vs. 18% (Kotani et al.) 45% (our study)), which are both associated with a more favourable outcome. On the other hand, only our study included patients with early line therapy. In terms of the clinical outcomes, the OS in the TAS-102+Bev group measured 17.5 months in our study against 8.6 months in Arrichiello et al. and 14 months in Kotani et al., while the DCR was only 45% in our study, compared to 71% in Arrichiello and 87% in Kotani. This once again might be due to the inclusion of unfit patients in earlier therapy lines in our study. However, the clinical outcomes of these two studies must be scrutinized critically as to how DCR extending even a RCT could be achieved. [1, 136, 137] Take together, accumulating evidence supports the real-world clinical effectiveness of TAS-102+Bev and its superiority over single agent TAS-102 and Regorafenib therapy.

Ultimately, key limitations of our study need to be mentioned. In a retrospective cohort study, selection bias cannot be entirely excluded and the absence of randomization in retrospective studies increases the risk of potential bias. The small sample size (n=20) in the TAS-102+Bev group limits the external validity of the results, making them less generalizable to a larger population and increasing the risk of type II errors. Additionally, the severity of treatment-related adverse effects

as well as information on dose density for each line were not recorded, although they are therapy-limiting factors. Furthermore, long-term survival data in the TAS-102+Bev group had not been fully collected by the end of the study. Conducted as a single-centre study without external validation, our findings require further validation through studies in real-world settings.

Despite these limitations, the study presents several strengths. Data were collected and analysed over long periods of time, providing insights into long-term outcomes and trends. Reflecting real clinical conditions, the study is based on data from everyday practice, and the study population was well characterized.

Conclusion

This retrospective cohort study provides further evidence that the combination of TAS-102 (Trifluridine/Tipiracil) and Bevacizumab can prolong survival as later line therapy in patients with metastatic colorectal cancer in a real-world setting and reinforces the existing data, suggesting that TAS-102+Bev can be considered the new standard of care in this patient population and setting. Our study data also suggests that TAS-102+Bev can also be effectively used as early palliative lines of therapy in mCRC for patients unfit for standard therapy. However, it is important to emphasize that further studies are needed to better understand the optimal use of this therapy combination and sequence.

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